Domino Reactions for the Syntheses of Chiral Chromanes

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Enantioselective Total Syntheses of (–)-Diversonol, (–)-Blennolide C, (–)-Gonytolide C and Formal Synthesis of Siccanin

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para

Mari Cruz

INDEX

A GENERAL SECTION

1 Introduction

By 2050, more than nine billion people are estimated to live on earth. Supplying this increasing world population with clean water, food, energy and medication thus represents a major challenge for the well-being of our society.[1]

In this regard, more efficient and environmentally friendly processes are highly sought after and catalysis is considered to provide chemical solutions to these pressing issues. Since the term was coined by Berzelius in 1835,[2] catalysis has emerged as an interdisciplinary key technology in numerous areas, ranging from the processing of raw materials to the manufacturing of chemical goods.[3] Catalytic reactions warrant higher yields and selectivities and reduce waste and energy at the same time. In fact, catalysis is one of the twelve green energy principles.[4] Its economic importance is reflected by the fact that, in industrialized countries, 15 to 20% of the economic activities directly depend on catalysis.[5] For instance, in 2005 the created value of goods produced with the help of catalysts amounted to 900 billion US$. Furthermore, it is estimated that over 85% of chemicals are produced by processes involving at least one catalytic transformation.[6]

In terms of volume, the by far most wildly used catalytic transformation is the fluid catalytic cracking (FCC) of crude oil. It accounts for the production of gasoline and feedstocks that are essential for the synthesis of other chemical products. However, catalysis is also pivotal for the conversion of biomass and in the storage of energy by batteries or fuel cells.

The development of heterogenic and homogenous catalytic processes has revolutionized the manufacturing of bulk and fine chemicals. Prominent examples of heterogenic catalytic reactions are the Haber-Bosch process for the production of ammonia, the Ziegler-Natta polymerization of α-olefins or the manufacturing of sulfuric acid by the contact process. As one of the earliest examples of homogenous catalysis, the Wacker process enabled the aerobic oxidative coupling of ethylene with water in order to yield acetaldehyde. Additionally, it can be regarded as the starting point for the development of diverse palladium-catalyzed cross-coupling reactions of aryl halides that were recently recognized with the Nobel Prize for Chemistry for Heck, Negishi and Suzuki in 2010.[7]

In their pursuit to emulate the perfect stereoselection of enzymes, the chemical community has devised asymmetric versions of almost every catalyzed reaction. In 2001, Knowles, Noyori and Sharpless were awarded with the Nobel Prize for Chemistry for their achievements in the field for asymmetric hydrogenation and oxidation methodologies.[8] These

reactions are also of tremendous importance for the agrochemical and pharmaceutical industry.[9] As the regulatory environment regarding the enantiopurity of drugs has become stricter over the past years, asymmetric catalysis is nowadays routinely used for the synthesis of active pharmaceutical ingredients (APIs).[10]

The domino concept introduced by Tietze is another approach that embeds into the fabric of efficient and environmentally benign syntheses. It allows the formation of several bonds under identical reaction conditions in a time-resolved manner, thereby significantly increasing the complexity of the targeted molecule. Good yields as well as high chemo-, regio- and stereoselectivities are among the typical advantages of domino reactions. Since the isolation of reaction intermediates is omitted and work-up and purification procedures are reduced, energy expenditures, chemicals and waste streams can be minimized equally. Additionally, its operational simplicity combined with its less labor-intensive workflow render the domino concept a powerful tool in organic synthesis.

The general objective of this thesis is to demonstrate the synthetic utility of the domino concept in the complex setting of natural product synthesis. Key step is a palladium-catalyzed domino Wacker/carbonylation/methoxylation reaction that was successfully applied in the enantioselective total syntheses of (–)-diversonol,[11] (–)-blennolide C and (–)-gonytolide C[12] as well as in the formal synthesis of siccanin.

2 Chromane Containing Natural Products

2.1 Tetrahydroxanthenone natural products

The most prominent class of tetrahydroxanthenones are the secalonic acids, first isolated from the extracts of *Claviceps purpurea* (ergot) by Kraft in 1906.[13] The secalonic acids and the structurally related ergoflavins and ergochrysins are summarized as ergochromes containing a dimeric structure.[14] In order to categorize the ergochromes, a nomenclature was introduced by Franck *et al*. which is based on seven monomers (Figure 1).[15]

ergochrome	original name
AA	secalonic acid A
BB	secalonic acid B
AB	secalonic acid C
CC	ergoflavin
AC	ergochrysin A
BC	ergochrysin B
AD	–
BD	–
CD	–
DD	–
EE	secalonic acid D
FF	secalonic acid E
BE	secalonic acid F
AF	secalonic acid G
CG	ergoxanthin

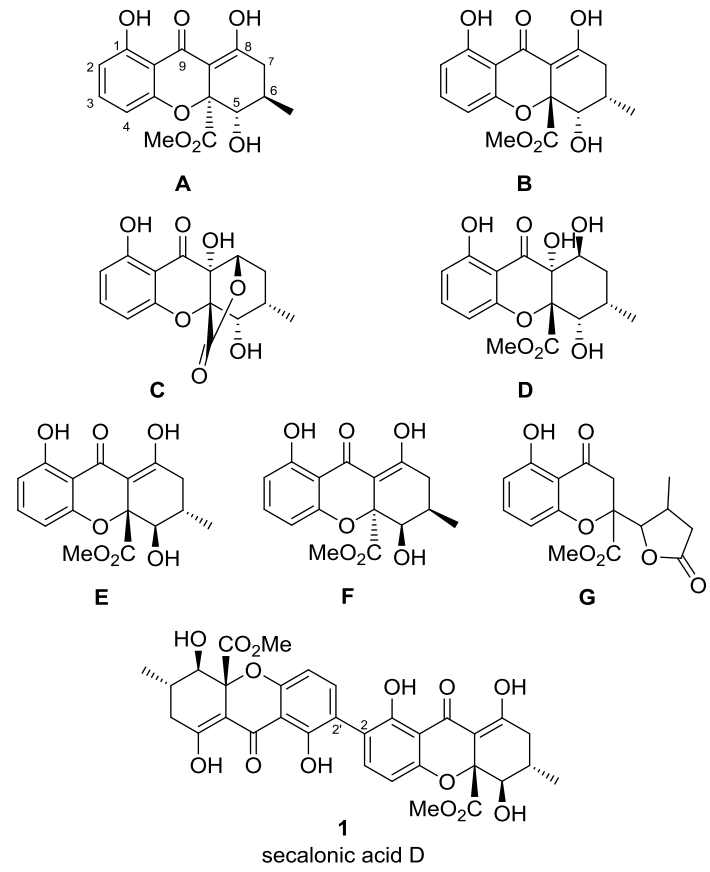


Figure 1: Structures of monomeric units **A**-**G** and secalonic acid D (**1**). The configuration of **G** is not known.

For instance, ergochrome **EE**, also known as secalonic acid D (**1**), is composed of two hemisecalonic acids **E**. The monomeric units possess different relative and absolute configurations and are linked by a 2,2'-biaryl connection to form homo- and heterodimers. Structure elucidation by NMR and X-ray analysis revealed that the biaryl moieties of the ergochromes are non-planar.[16]

Besides their intriguing structural complexity, the secalonic acids exhibit interesting biological properties. Secalonic acid B shows antialgal, antifungal and antimicrobial activity[17]

whereas secalonic acid A was reported to reduce colchicine cytotoxicity in rat cortical neurons.[18] Its enantiomer secalonic acid D (**1**) displays cytotoxic properties and is able to inhibit the DNA topoisomerase I and the HIV-I protease.[19] However, teratogenic effects on the development of rats were also observed upon exposure to **1**.[20]

The dicerandrols (**2a-c**), first isolated from the endophytic fungus *Phomopsis longifolia*, feature a 2,2'-biaryl linkage like the secalonic acids (Figure 2).[21] Their relative configuration corresponds to that of the secalonic acids B and E. However, their C-4a substituents are partly reduced to hydroxymethyl and acetoxymethyl groups. They show promising antimicrobial activity, which correlated to the degree of acylation (**2c** > **2b** > **2a**), and modest activity against colon and lung tumor cells.

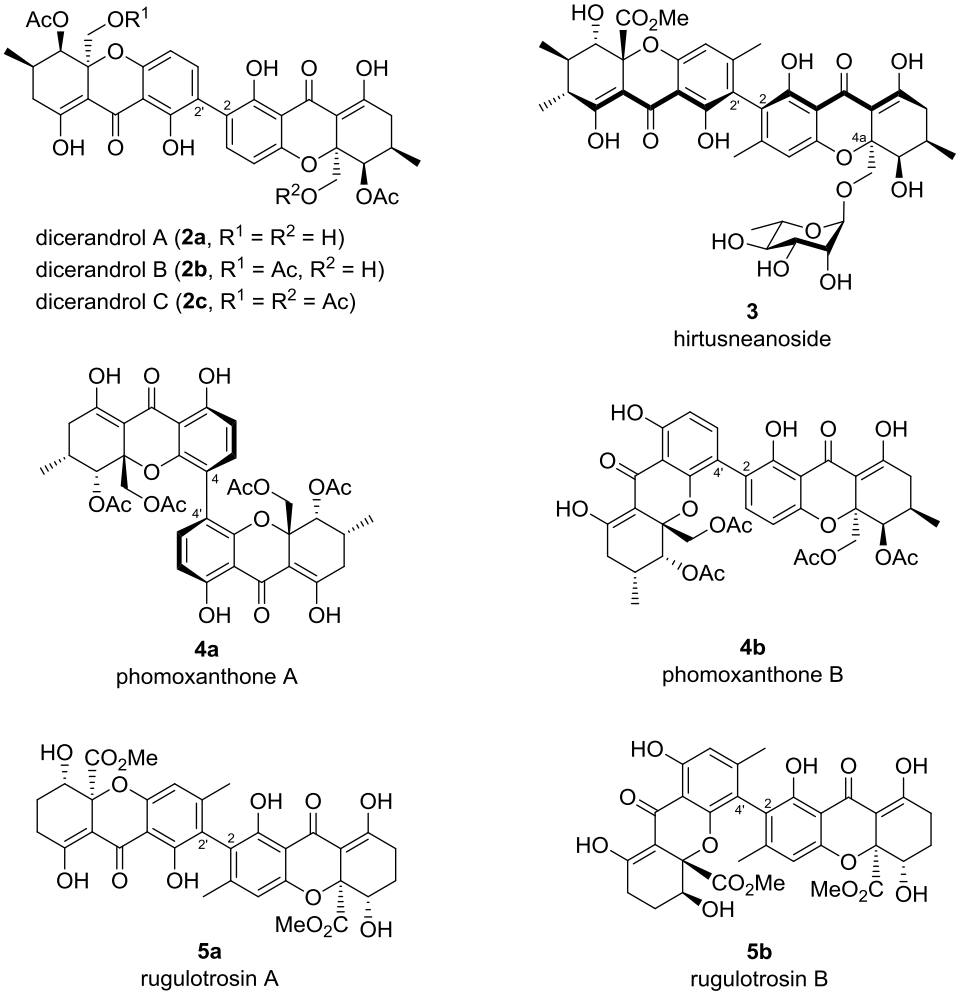
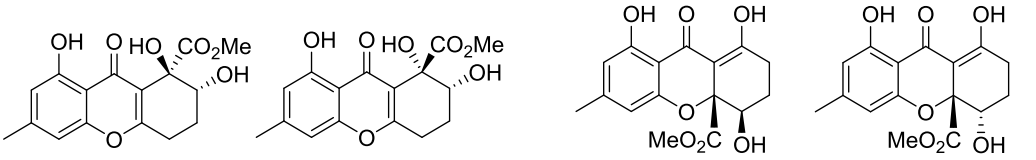


Figure 2: Structures of the dimeric tetrahydroxanthenones dicerandrol (**2a-c**), hirtusneanoside (**3**), the phomoxanthones A (**4a**) and B (**4b**) and the rugulotrosins A (**5a**) and B (**5b**). The absolute configuration of **2a-c**, **4b** and **5a**,**b** is not known.

Recently, Řezanaka and Sigler isolated the heterodimer hirtusneanoside (**3**) from the lichen *Usnea hirta* which exhibits antimicrobial properties against *Staphylococcus aureus* and

Bacillus subtilis.[22] As a unique feature, it contains an α-L-rhamnose moiety tethered with a hydroxymethyl substituent at C-4a. The rotation around the 2,2'-biaryl connection is restricted as a result of the additional methyl groups at the aromatic core, rendering **3** axially chiral. The absolute configuration was established by means of spectroscopic methods and enzymatic degradation studies.

The structurally related phomoxanthones A (**4a**) and B (**4b**) were first isolated from the endophytic fungus *Phomopsis sp.* and exhibit activity against the malaria- and tuberculosis-transmitting pathogens *Plasmodium falciparum* and *Mycobacterium tuberculosis*, respectively.[23] In contrast to the so far described compounds, the monomeric units of **4a** and **4b** are connected by distinctively different 4,4'- and 2,4'-biaryl linkages. The absolute configuration including the axial chirality of phomoxanthone A (**4a**) was determined by X-ray analysis and calculated CD-spectra by Krohn *et al*.[24] The unsymmetrical 2,4'-connection can also be found in rugulotrosin B (**5b**) whereas the monomers of rugulotrosin A (**5a**) are connected in the common 2,2'-manner. Both compounds were first isolated from *Penicillium sp.* showing antimicrobial activity.[25] The monomer of the rugulotrosins, formerly misassigned as α-diversonolic ester (**6a**), is the *syn*-diastereomer of blennolide C (**7c**) (Figure 3).[17,26]



6a α-diversonolic ester | **6b** β-diversonolic ester | ***epi*-7c** 4-*epi*-blennolide C formerly assigned as α-diversonolic ester | **7c** blennolide C formerly assigned as β-diversonolic ester

Figure 3: Structures of the α- and β-diversonolic esters (**6a**,**b**), blennolide C (**7c**) and 4-*epi*-blennolide C (*epi*-**7c**). The absolute configuration of *epi*-**7c** and **6a**,**b** is not known.

The blennolides A-G (**7a**-**g**) alongside secalonic acid B (**8**) were recently isolated by Krohn *et al*. from *Blennoria sp*. (Figure 4).[17] Preliminary studies showed antifungal, antibacterial and algicidal activities of these compounds. Furthermore, their absolute configuration was elucidated by CD-spectroscopy and time-dependent density functional theory (TDDF) calculations. The blennolides A (**7a**) and B (**7b**) represent the monomeric units of the secalonic acids B (**8**) and D (**1**), respectively. The spectroscopic data of blennolide C (**7c**) were previously incorrectly assigned to the structure of β-diversonolic ester (**6b**, Figure 3). The blennolides D-G (**7d**-**g**) result from **7a** and **7b** by rearrangement of the tetrahydroxanthenone ring into γ-lactonyl moieties.

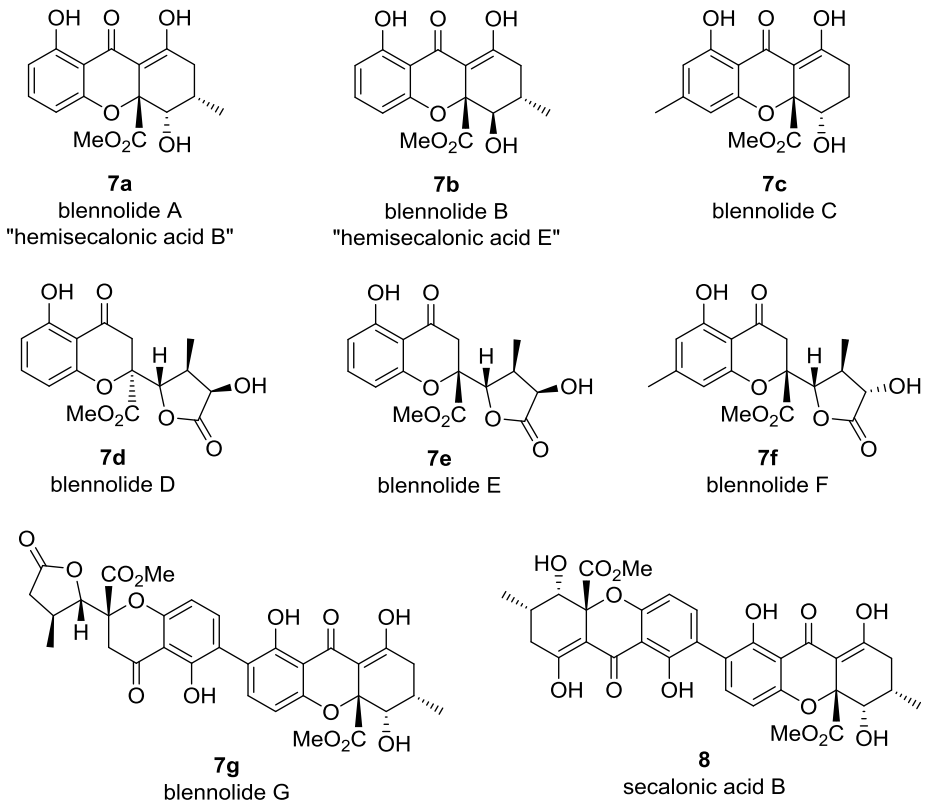


Figure 4: Structures of the blennolides A-G (**7a**-**g**) and secalonic acid B (**8**) isolated from *Blennoria sp*.

A similar rearrangement seems plausible for blennolide C (**7c**) leading to gonytolide C (**9c**), the monomeric unit of gonytolide A (**9a**).

The gonytolides A-C (**9a**-**c**) were isolated from the fungus *Gonytrichum sp*. by Kikuchi *et al*. (Figure 5).[27] Their structures were elucidated by NMR spectroscopy and the relative and absolute configurations of **9a** and **9c** established by X-ray analysis.

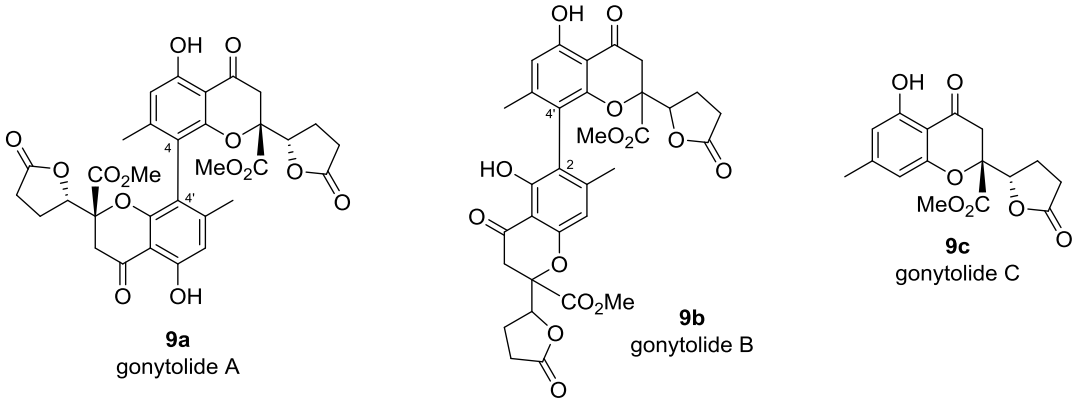
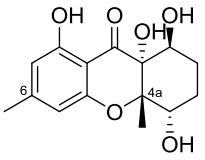


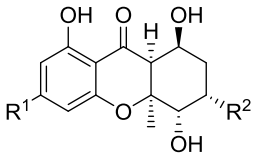
Figure 5: Structures of the gonytolides A-C (**9a**-**c**) from *Gonytrichum sp*. The relative configuration of **9b** is not known.

Whereas the 4,4'-dimer gonytolide A (**9a**) is a potent innate immune promoter, its 2,4'-linked isomer **9b** and its monomer **9c** show no innate immune response, indicating that the 4,4'-biaryl linkage is pivotal for the biological activity.

Diversonol (**10**), endowed with methyl groups at C-6 and C-4a (numbering as in **10**), is a fungal metabolite isolated from different fungi such as *Penicillium diversum*[28a] and *Microdiplodia sp*. (Figure 6).[28b] Its absolute configuration was recently determined by Krohn *et al*. using CD-spectroscopy and TDDF calculations.[28b] Up to now, no data were reported about the biological activities of **10**. However, the structurally related monodictysins A-C (**11a-c**), that also possess a methyl instead of a methoxycarbonyl group at C-4a, exhibit cancer chemopreventive potential.[29]



10
diversonol

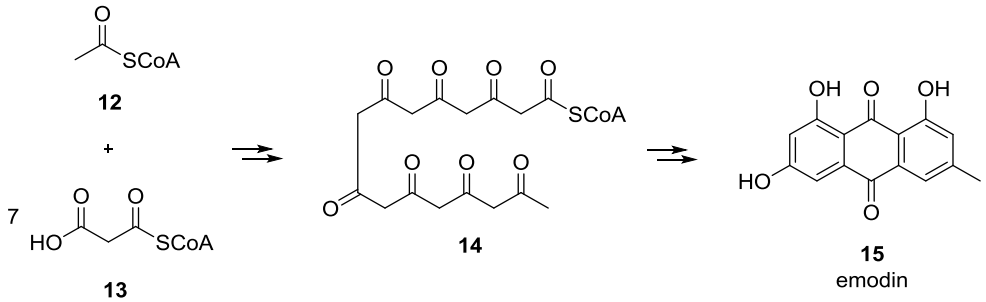


monodictysin A (**11a**, $R^1 = CH_3$, $R^2 = OH$)
monodictysin B (**11b**, $R^1 = H$, $R^2 = CH_3$)
monodictysin C (**11c**, $R^1 = OCH_3$, $R^2 = CH_3$)

Figure 6: Structures of diversonol (**10**) and the monodictysins A-C (**11a-c**).

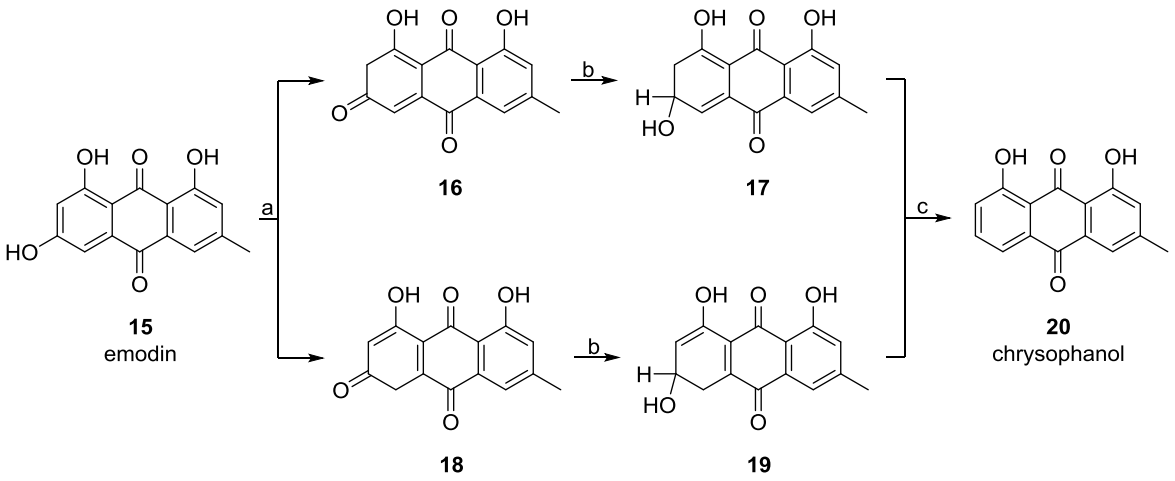
2.1.1 Biosyntheses of the tetrahydroxanthenones

Pioneering studies by Franck *et al*. revealed that the anthraquinone emodin (**15**) is a key intermediate in the biosynthesis of the ergochromes (Scheme 1).[30,31] The anthraquinone scaffold arises from octaketide **14**, which in turn results from condensation of one molecule acetyl-coenzyme A (**12**) and seven molecules malonyl-coenzyme A (**13**).



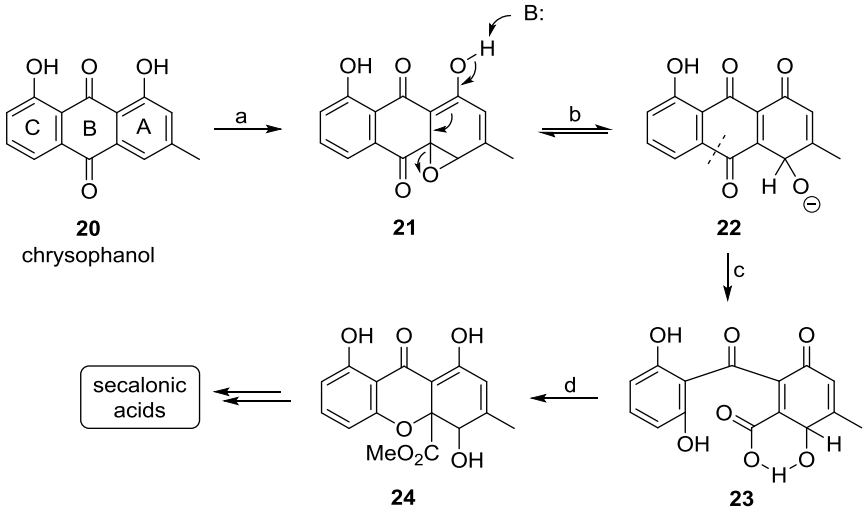
Scheme 1: Emodin (**15**) as a key intermediate in the biosynthesis of the ergochromes.

It was further shown that one phenolic hydroxyl group of **15** is cleaved yielding chrysophanol (**20**). On the basis of isotope labeling experiments, Anderson and Scott proposed a mechanism that accounts for the dehydroxylation of **15** comprising a keto/enol tautomerization and a reduction of **16** and **18** by NADPH followed by dehydration with concomitant rearomatization (Scheme 2).[32]



Scheme 2: Dehydroxylation of emodin (**15**) to chrysophanol (**20**): a) deprotonation/tautomerization; b) reduction with NADPH; c) elimination of H_2O and rearomatization.

According to Henry and Townsend, the A ring of chrysophanol (**20**) is next epoxidized by cytochrome P450 to give epoxide **21** which is in equilibrium with its ring-opened form **22** upon deprotonation (Scheme 3).[33]

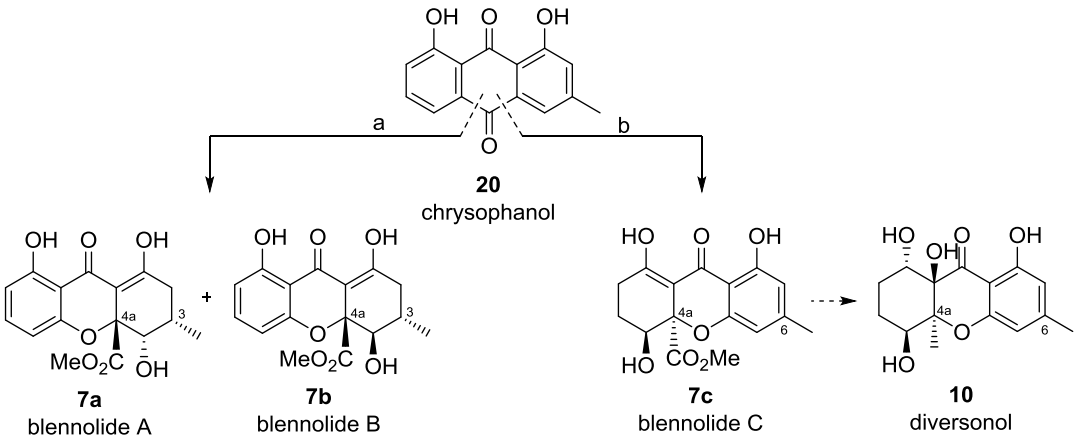


Scheme 3: Oxidative rearrangement of chrysophanol (**20**): a) aryl epoxidation; b) deprotonation; c) ring cleavage; d) conjugate addition.

The epoxidation of the anthraquinone core is envisioned to disrupt its planar structure and aromaticity rendering **22** more prone to the subsequent ring opening. A Baeyer-Villiger oxidation again by cytochrome P450 followed by lactone hydrolyses provides benzophenone **23** which is stabilized by a hydrogen bond. Methylation of the carboxylic acid and conjugate addition of a phenolic hydroxyl group provides dihydroxanthenone **24** which is a precursor of the secalonic acids.

Although no biosynthesis of diversonol (**10**) was put forward so far, it was reasoned that **10** and the ergochromes might arise from the same anthraquinone precursor chrysophanol (**20**)

(Scheme 4).[34] Oxidative opening of the anthraquinone ring by pathway a) or b) may lead to tetrahydroxanthenones bearing the methyl and the ester group on the same side or on opposite sides.[28a,35] Further support for this hypothesis was provided by Krohn *et al*. who isolated the blennolides A (**7a**) and B (**7b**) with a methyl group at C-3 and blennolide C (**7c**) with a C-6 methyl group from the same fungus *Blennoria sp*.[18] The carboxyl group at C-4a may be further reduced to the methyl stage present in diversonol (**10**).



Scheme 4: Putative biosynthetic relationship between the blennolides A (**7a**) and B (**7b**) (3-Me) and blennolide C (**7c**) and diversonol (**10**) (6-Me).

2.2 Siccanin and the siccanochomenes

Siccanin (**25**) and the structurally related siccanochromenes A-H (**26a**-**h**) were fist isolated from the culture broth of *Helminthosporium siccans* (Figure 7).[36,37] Siccanin (**25**) showed strong antifungal activity against several pathogenic fungi[38] and is clinically applied against surface mycosis.[39] Its structure and absolute configuration were disclosed by spectroscopic methods and X-ray crystallography unveiling the unusual *cis*-*syn*-*cis*-fused A/B/C-ring system (assignment as in **25**).[40] The siccanochromenes (**26**) possess potent antifungal, antibacterial cytotoxic and insecticidal activities.[41] Several compounds of this family were regarded as intermediates in the biosynthesis of **25**.

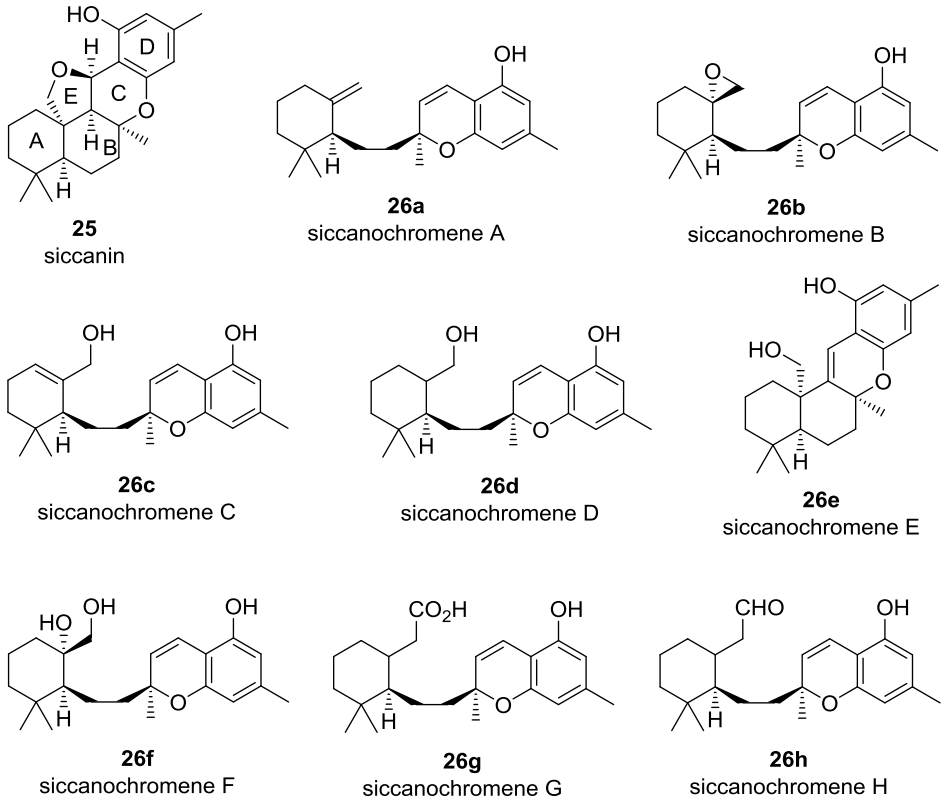
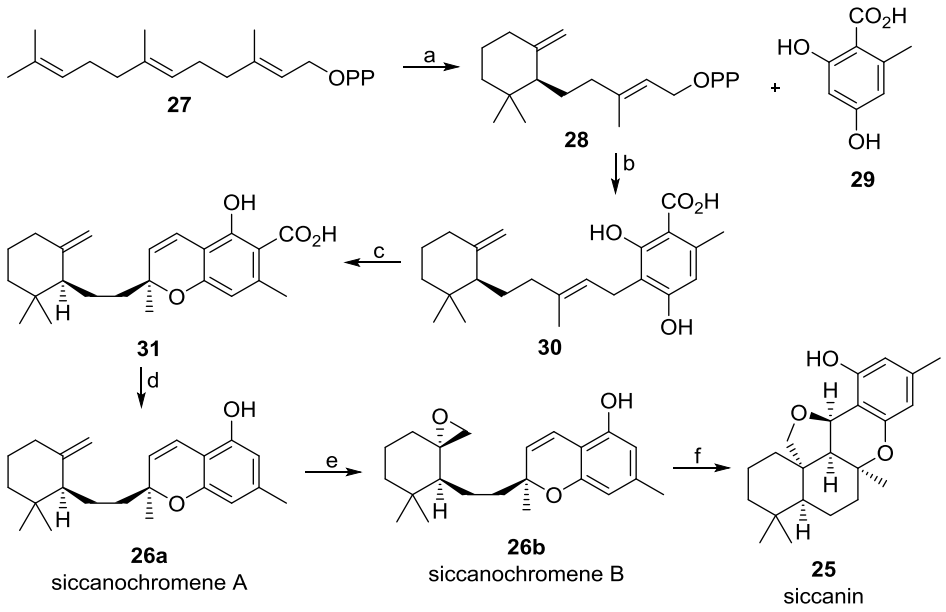


Figure 7: Structures of siccanin (**25**) and the siccanochromenes A-H (**26a**-**h**).

2.2.1 Biosynthesis of siccanin (25)

Nozoe *et al*. postulated a biosynthesis of siccanin (**25**) based on the isolation of minor metabolites from cell-free and intact cell systems of *Helminthosporium siccans* comprising at least six steps (Scheme 5).[42]



Scheme 5: Proposed biosynthesis of siccanin (**25**): a) cyclization of *trans*,*trans*-farnesyl pyrophosphate (**27**); b) coupling with orsellinic acid (**29**); c) oxidative cyclization; d) decarboxylation; e) epoxydation; f) epoxyolefin cyclization.

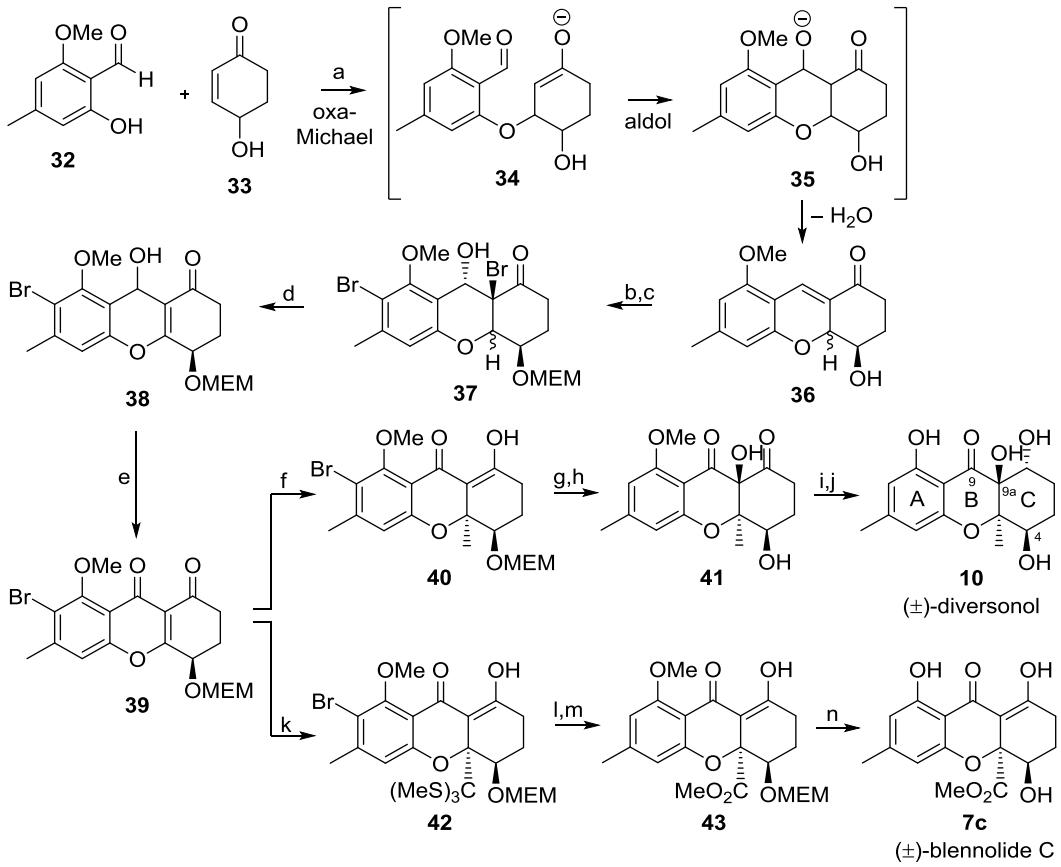
The biosynthetic pathway is believed to start with the formation of *trans*-γ–monocyclofarnesyl pyrophosphate (**28**) from *trans*,*trans*-farnesyl pyrophosphate (**27**). Coupling of the terpenic precursor with orsellinic acid (**29**) followed by cyclization leads to siccanochromenic acid (**31**) which subsequently undergoes decarboxylation to yield siccanochromene A (**26a**). Epoxydation of the exocylic alkene function of **26a** gives rise to siccanochromene B (**26b**) which engages in an epoxyolefin cyclization to yield siccanin (**25**).[43]

3 Syntheses of Diversonol, the Blennolides and Siccanin

3.1 Syntheses of Diversonol and the Blennolides

Natural products with a tetrahydroxanthenone structure possess a variety of interesting biological properties. In order to further evaluate their potential as novel promising lead structures, ample amounts of compound are required and a synthetic access to the tetrahydroxanthenone scaffold is therefore highly desirable. Although the first racemic synthesis of a hemisecalonic derivative was already reported by Franck *et al*. in 1973,[44] it was not until recently that successful syntheses of tetrahydroxanthenone natural products were accomplished.

The total synthesis of racemic diversonol (**10**), the first route to a naturally occurring tetrahydroxanthenone, was accomplished by Bräse *et al*. in 2005 (Scheme 6).[45] Based on this work, the same group also reported a total synthesis of racemic blennolide C (**7c**) in 2008.[46] The synthetic strategy towards **10** and **7c** was based on a domino oxa-Michael/aldol reaction of salicylic aldehyde **32** and 4-hydroxycyclohexenone (**33**) and imidazole as base to furnish racemic tetrahydroxanthenone **36** as a 1.5:1 mixture of epimers. MEM-protection of the hydroxyl group at C-4 (numbering as in **10**) then set the stage for the functionalization of ring B. The introduction of the hydroxyl group at C-9 was achieved by a bromohydrin formation with $TABr_3$. As a side reaction an undesired bromination of the aromatic ring A occurred. The intermediate bromohydrin **37** was eliminated with DABCO as base and subjected to a Ley oxidation to give key compound **39**. At this juncture, α,β-unsaturated diketone **39** underwent a diastereoselective conjugate addition with either the cyanocuprate MeCu(CN)Li leading to diversonol (**10**) or with a lithium species derived from thioorthoformiate paving the way to blennolide C (**7c**). Thus, after debromination of the aromatic A-ring by a bromine/lithium exchange with *t*BuLi and protonation, the tetrahydroxanthenone was hydroxylated with MMPP at C-9a and the unconjugated ketone diastereoselectively reduced with $NaBH_4$. The synthesis of diversonol (**10**) was completed with the cleavage of the aromatic methyl ether. The final steps to blennolide C (**7c**) involved the removal of the bromine atom, a Hg(II)-mediated oxidative methanolysis of the orthothioester and deprotection of the phenolic hydroxyl group.

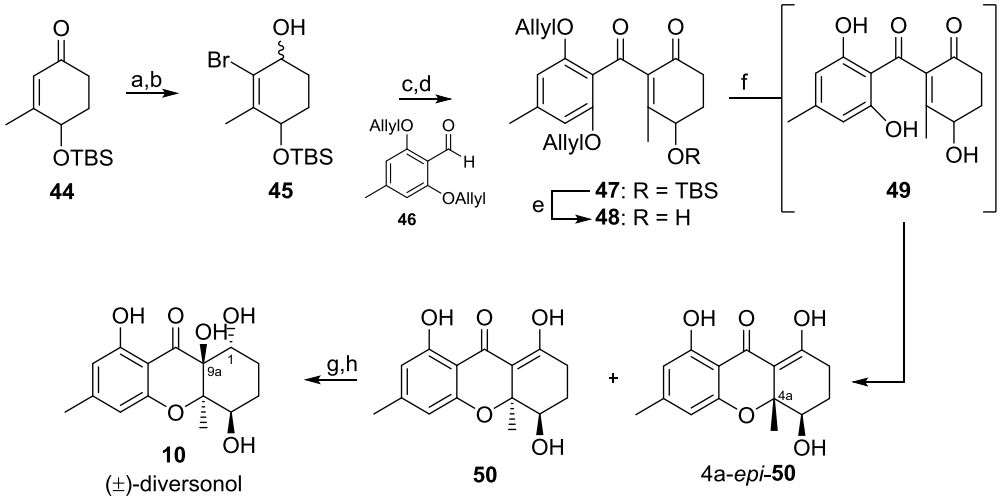


Scheme 6: Total syntheses of racemic diversonol (**10**) and blennolide C (**7c**) by Bräse *et al.*: a) imidazole, dioxane/H_2O, sonication, 7 d, 61%; b) MEMCl, *i*Pr_2NEt, CH_2Cl_2, RT, 3 h, 75%; c) $TBABr_3$, THF/H_2O, RT, 5 h, 52%; d) DABCO, dioxane, RT, 16 h, 53%; e) TPAP (10 mol%), NMO, CH_2Cl_2/CH_3CN, sonication, 40%; f) MeLi, CuCN, Et_2O, –78 °C, 5 h, 52%; g) *t*BuLi, THF, –78 °C, $NaHCO_3$, 4 h, 93%; h) MMPP, EtOH, RT, 5 h, 57%; i) BBr_3, CH_2Cl_2, RT, 7 h, 40%; j) $NaBH_4$, MeOH, –78 °C, 20 min, 66%; k) $LiC(SMe)_3$, THF, –78 °C, 12 h, 20%, l) *t*BuLi, THF, –78 °C, 30 min, then H_2O, 96%; m) $HgCl_2$, HgO, MeOH/H_2O, RT, 18 h, 100%; n) BBr_3, CH_2Cl_2, RT, 5 h, 23%.

Bräse's molular approach enabled the preparation of racemic diversonol (**10**) and blennolide C (**7c**) from easily accessible starting materials over nine and eight steps, respectively. However, the syntheses were plagued by low overall yields with only 0.4% for **10** and 0.2% for **7c**. Although an asymmetric version of the domino oxa-Michael/aldol reaction was reported by Córdova *et al.*,[47] the enantioselective synthesis of tetrahydroxanthenone **36** endowed with a hydroxy group at C-4 was not possible.

Based on the early work of Franck *et al.*,[44] the group of Nicolaou developed racemic total syntheses of diversonol (**10**), blennolide C (**7c**) and of the revised structures of α- and β-diversonolic esters (**6a**) and (**6b**) in 2008.[26] The key step represented an intramolecular oxa-Michael reaction to set up the tetrahydroxanthenone core.

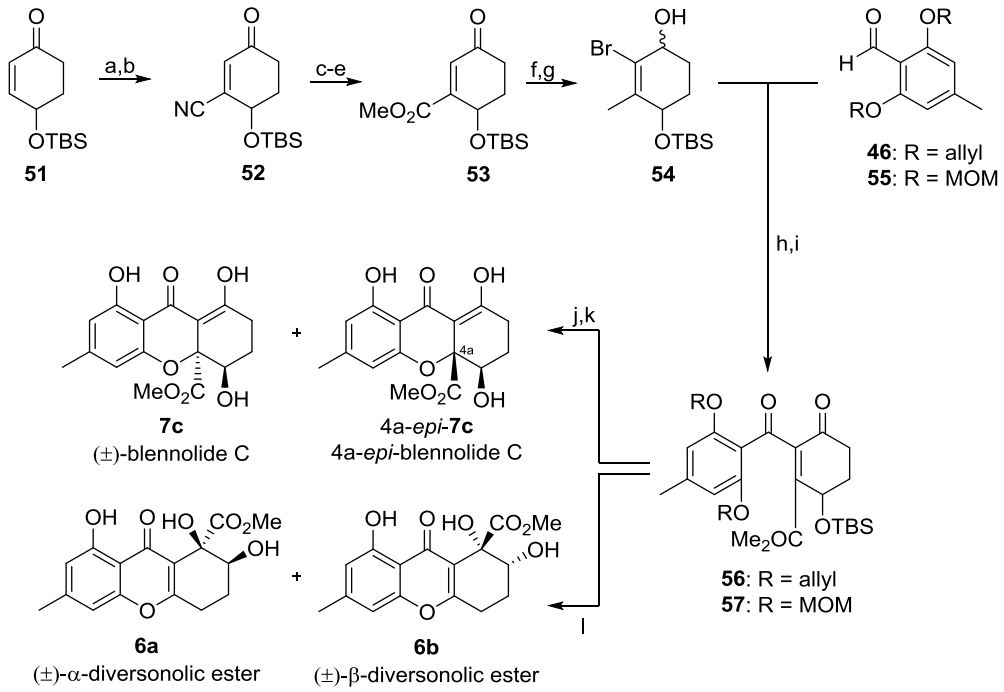
The synthesis towards diversonol (**10**) (Scheme 7) commenced with a bromination/elimination sequence of cyclohexenone **44** to furnish the corresponding mono-brominated cyclohexenone. Reduction of the ketone moiety with DIBAL-H to alcohol **45** set the stage for the coupling with the aromatic aldehyde **46**. Deprotonation of the hydroxyl group of **45** with MeLi followed by bromine/lithium exchange with *t*BuLi and anion trapping with **46** provided acetophenone **47** after oxidation with IBX. Cleavage of the TBS ether and a palladium(0)-catalyzed deallylation led to triol **49** which instantaneously underwent an oxa-Michael reaction to afford the tetrahydroxanthenones **50** and 4a-*epi*-**50** in a 2:1 ratio. The synthesis of diversonol (**10**) was completed employing Bräse's oxidation/reduction procedure to install the *anti*-diol moiety at C-1–C-9a.



Scheme 7: Total synthesis of racemic diveronol (**10**) by Nicolaou *et al.*: a) Br_2, CH_2Cl_2, 0 °C, 5 min, then NEt_3, 0 °C, 5 min, 90%; b) DIBAL-H, THF, –78 °C → 40 °C, 30 min, 95%, d.r. = 1:1; c) MeLi, Et_2O, –78 °C, 15 min, then *t*BuLi, –78 °C, 15 min, then **46**, –78 °C → 40 °C, 40 min; d) IBX, DMSO, RT, 1 h, 72% (2 steps); e) HF·pyridine, THF, RT, 12 h, 96%; f) $Pd(PPh_3)_4$ (5 mol%), $n$$Bu_3SnH$, AcOH, benzene, RT, 1 h, 90%, d.r. = 2:1 (**50**/4a-*epi*-**50**); g) MMPP, EtOH, RT, 30 min; h) $NaBH_4$, $MeOH/CH_2Cl_2$, –78 °C, 15 min, 73% (2 steps).

The syntheses of racemic blennolide C (**7c**) and α- and β-diversonolic esters (**6a**) and (**6b**) started with a Nagata hydrocyanation reaction of cyclohexenone **51** with Et_2AlCN (Scheme 8). The intermediate enolate was trapped with TMSCl and oxidized with IBX to enone **52**. In order to transform the nitrile into a methyl ester, **52** was first reduced with DIBAL-H and the corresponding hydroxy carbaldehyde subjected DMP and Pinnick conditions. The resulting keto acid was treated with TMS-diazomethane to provide ester **53**. Bromination of the double bond followed by elimination of HBr and a chemoselective Luche reduction furnished a diastereomeric mixture of bromides **54**. The final stages towards blennolide C (**8c**) resembled Nicolaou's endgame to diversonol (**10**). Fragment coupling of **54** with the allyl- and MOM-protected salicylic aldehydes **46** and **55** followed by subsequent

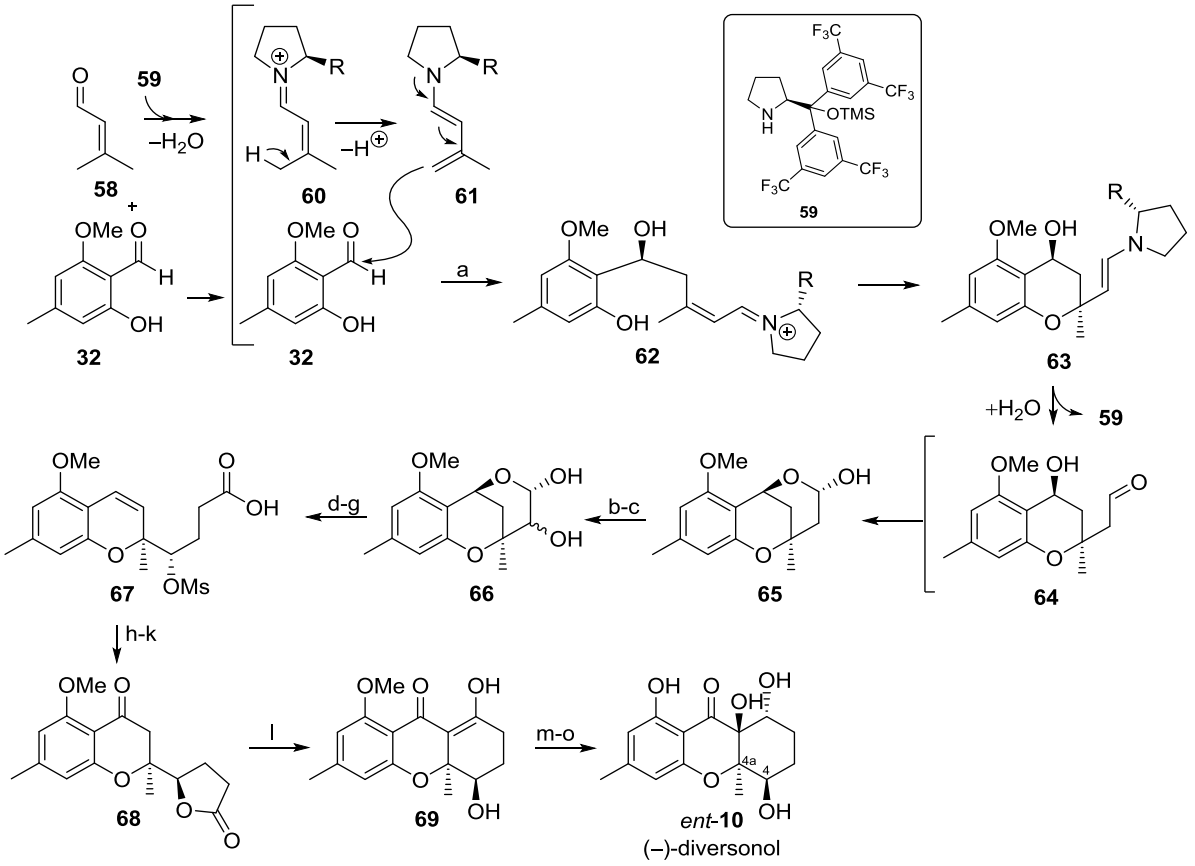
oxidation with IBX gave the acetophenones **56** and **57**. Desilylation and deallylation of **56** triggerd the ring closure leading to the tetrahydroxanthenones blennolide C (**7c**) and 4a-*epi*-blennolide C (4a-*epi*-**7c**) in a 2:1 ratio. Global deprotection of a similar MOM-protected acetophenone **57** with aq. perchloric acid gave rise to a 1:3 mixture of diastereomers whose spectroscopic data matched with those reported for α- and β-diversonolic ester (**6a**) and (**6b**).



Scheme 8: Racemic total syntheses of blennolide C (**7c**) and α- and β-diversonolic esters (**6a**) and (**6b**) by Nicolaou *et al.*: a) Et_2AlCN, toluene, RT, 30 min, then pyridine, TMSCl, 0 °C → RT, 1 h; b) IBX, MPO, DMSO, RT, 1 h, 62% (2 steps); c) DIBAL-H, toluene, –78 °C → 40 °C, 30 min, then DMP, CH_2Cl_2, RT, 45 min, 83%; d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*BuOH/H_2O (1:1), RT, 1 h; e) $TMSCHN_2$, MeOH, 0 °C, 20 min, 90% (2 steps); f) Br_2, CH_2Cl_2, 0 °C, 5 min, then NEt_3, 0 °C, 5 min, 94%; g) $CeCl_3 \cdot 7\,H_2O$, $NaBH_4$, MeOH, 0 °C, 30 min, 91% d.r. = 1.3:1; h) MeLi, Et_2O, –78 °C, 15 min, then *t*BuLi, –78 °C, 15 min, then **46** or **55**, –78 °C → 40 °C, 40 min; i) IBX, DMSO, RT, 1 h, for **56**: 41%; for **57**: 45% (2 steps); j) HF·pyridine, THF, RT, 12 h, 89%; k) *n*Bu_3SnH, AcOH, $Pd(PPh_3)_4$, benzene, RT, 1 h, 60%, d.r. = 2:1 (**7c**/4a-*epi*-**7c**); l) 1.0 M aq. $HClO_4$, THF, 50 °C, 2 h, 80%, d.r. = 1:3 (**6a**/**6b**).

Compared to Bräse's approach, Nicolaou's syntheses provided diversonol (**10**) and blennolide C (**7c**) in significantly improved yields of 26% and 6% over 8 and 11 steps, respectively. A decisive shortcoming represents the long and inelegant preparation of building block **54** whose oxidation state of carbon atom C-9 changes 4 times in the course of its synthesis.

The first asymmetric total synthesis of (–)-diversonol (*ent*-**10**) was accomplished by Bräse *et al*. in 2011 (Scheme 9).[48]



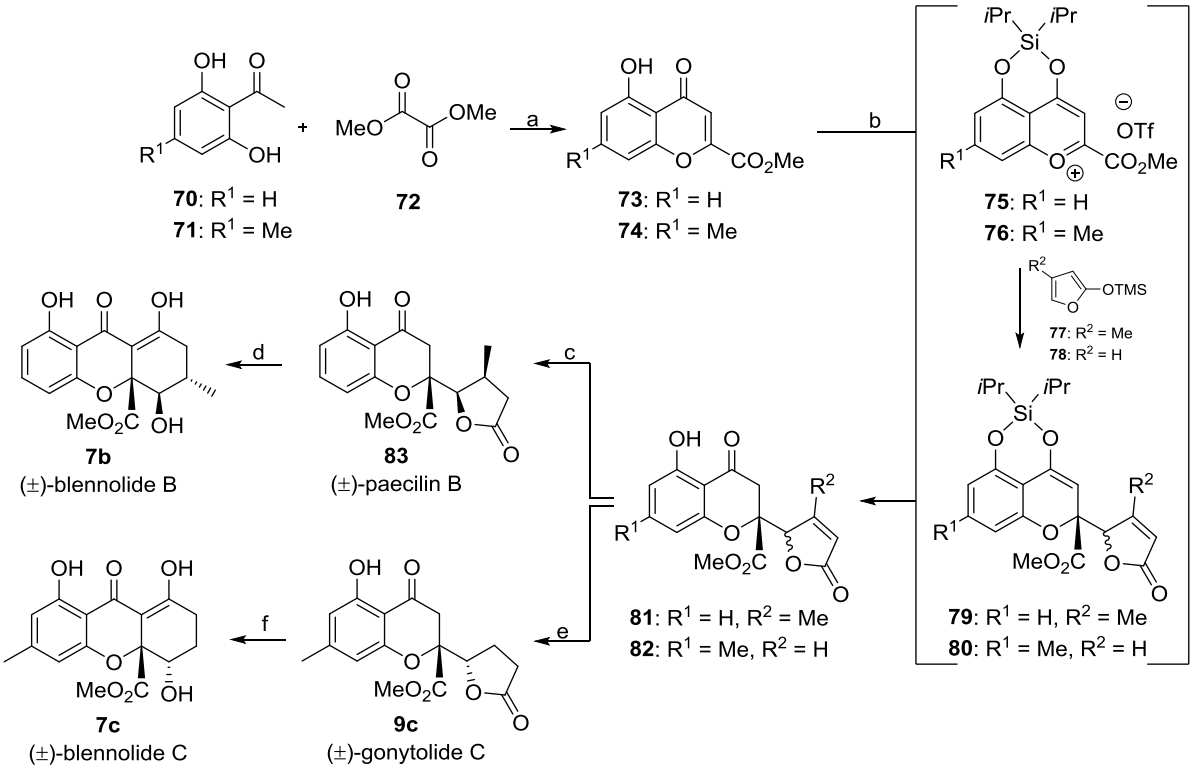
Scheme 9: Synthesis of (–)-diversonol (*ent*-**10**) by Bräse *et al*.: a) **59** (30 mol%), benzoic acid, toluene, RT, 72 h, 67%, 83% *ee*; b) MsCl, NEt_3, THF, 0 °C → RT, 3 h, 92%; c) OsO_4 (10 mol%), NMO, acetone/H_2O, RT, 4 d, 80%, d.r. = 4.7:1; d) $Ph_3P{=}CHCO_2Et$, THF, 60 °C, 12 h, 83%; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.5 h, 85%; f) Pd/$BaSO_4$ (5 mol%), H_2, EtOAc, RT, 12 h, 54%; g) MsCl, NEt_3, DMAP (10 mol%), CH_2Cl_2, 0 °C → RT, 3 h, 61%; h) LiOH, dioxane/H_2O, RT, 18 h, 72%; i) Cs_2CO_3, 18-crown-6, toluene, 90 °C, 79%; j) Pd/$BaSO_4$ (5 mol%), H_2, EtOAc, RT, 1 h, 79%; k) $Mn(OAc)_3$ (20 mol%), *t*BuOOH, 3 Å ms, EtOAc, RT, 4 d, 66%; l) NaOMe, THF, 0 °C, 1 h, 41%; m) BBr_3, CH_2Cl_2, RT, 16 h, 81%; n) MMPP, EtOH, RT, 30 min; o) $NaBH_4$, MeOH/CH_2Cl_2, –78 °C, 5 min, 52% (2 steps).

The enantioselective route started with a domino vinylogous aldol/oxa-Michael reaction, initially discovered by the same group and further developed by Woggon *et al*.,[49] of salicylaldehyde **32** and prenal (**58**) in the presence of Jørgensen's catalyst (**59**). The proposed mechanism involved the formation of iminium ion **60** which led to dienamine **61** after deprotonation. An enantioselective vinylogous aldol reaction of **61** with aldehyde **32** set the stage for the conjugate addition of the phenolic hydroxyl group of **62** to provide chromanol **63**. Release of the catalyst **59** and hemiacetal formation furnished tricyclic lactole **65** in 67% yield and 83% *ee*.

The hydroxyl group at C-4 (numbering as in *ent*-**10**) was introduced by a base-promoted elimination of the mesylate of **65** and a dihydroxylation of the double bond. The major diastereomer with the undesired *syn*-configuration between 4-OH and the methyl group at C-4a was further elaborated into lactonyl chromanone **68** by a Wittig ring-opening reaction to incorporate the side chain, hydrogenation of the double bond, lactonization with concomitant inversion of the stereocenter C-4, another hydrogenation and benzylic oxidation. Similar reactions were performed with the minor *anti*-diol to give lactonyl chromanone **68** (not shown). In the final steps of the synthesis, a Dieckmann condensation of **68**, developed by Porco *et al*. (*vide infra*), provided the tetrahydroxanthenone core of **69**. Oxidation of the enol double bond with MMPP, cleavage of the methyl aryl ether with BBr_3 and chemoselective reduction of the non-conjugated ketone gave (–)-diversonol (*ent*-**10**).

For the enantioselective total synthesis of 4-dehydroxy-diversonol (**199**) using a domino Wacker/carbonylation reaction by Tietze *et al*., see page 53.

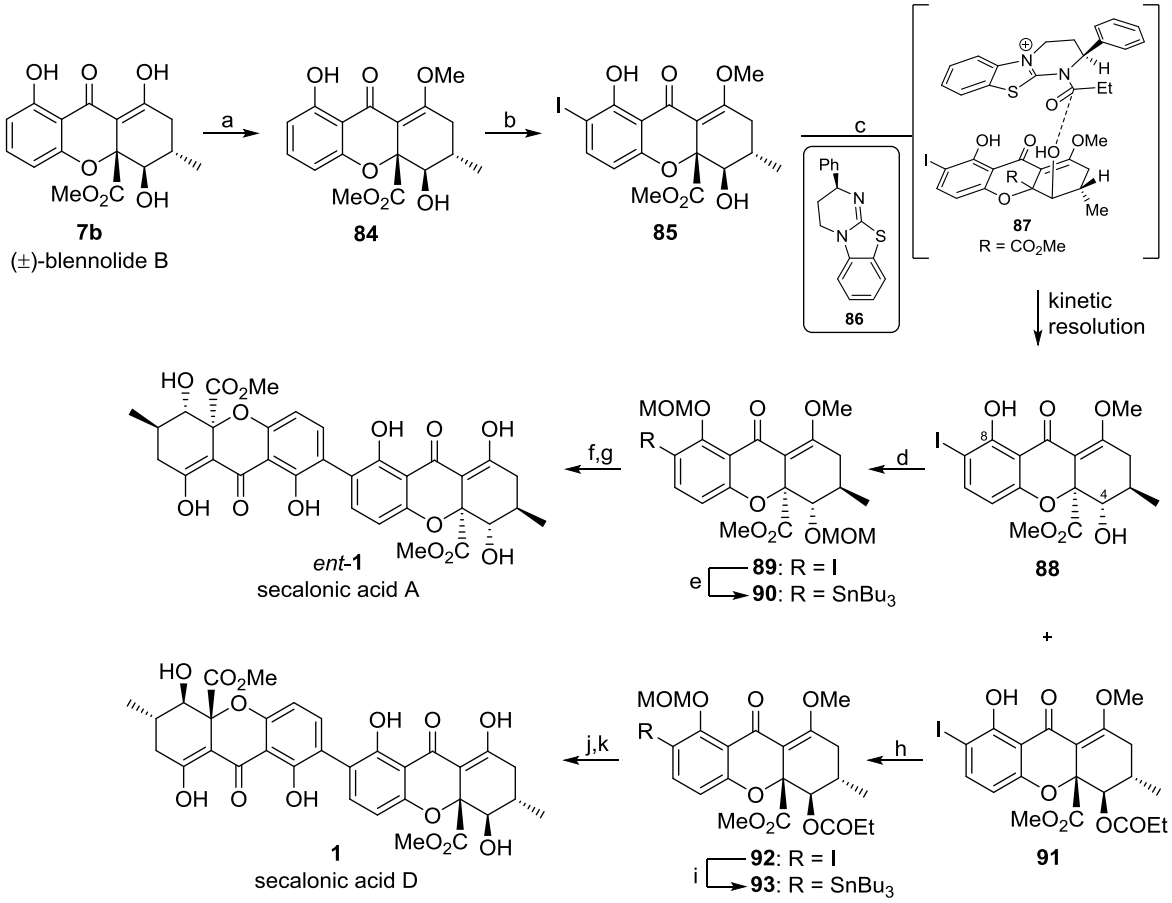
In 2011, Porco *et al*. published elegant racemic syntheses of the γ-lactonyl chromanones paecilin B (**83**) and gonytolide C (**9c**) and the tetrahydroxanthenones blennolides B (**7b**) and C (**7c**) using a "retrobiosynthetic" approach (Scheme 10).[50]



Scheme 10: Racemic total syntheses of paecilin B (**83**), gonytolide C (**9c**), blennolide B (**7b**) and C (**7c**): a) NaOMe, MeOH, reflux, overnight, for **73**: 48%; for **74**: 76%; b) *i*$Pr_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, RT, 30 min, for **79**: **77**, –78 °C,1 h, then 3 HF·NEt_3, 89%, d.r. = 2:1 (*syn*/*anti*); for **80**: **78**, 0 °C, 3 h, 97%, d.r. = 1:2 (*syn*/*anti*), then 3 HF·NEt_3; c) Rh/Al_2O_3 (10 mol%), H_2, MeOH, RT, 12 h, 37%; d) NaH, THF, 60 °C, 16 h, 76%; e) $NiCl_2$·6 H_2O, $NaBH_4$, THF/MeOH, 0 °C, 30 min; f) NaH, THF, 60 °C, 16 h, 37% (2 steps).

The chromanone core of **73** and **74** was efficiently assembled by condensation of the dihydroxyacetophenones **70** and **71** with dimethyl oxalate **72**. Silyl triflate activation provided the highly reactive siloxybenzpyrylium species **75** and **76** that readily engaged in vinylogous addition reactions with the siloxyfurans **77** and **78**. Computional studies suggested that the reaction proceeds by Diels-Alder-like transition states. Desilylation and conjugate reduction of the resulting butenolide double bond of **81** and **82** led to paecilin B (**83**) and gonytolide C (**9c**). The routes to blennolide B (**7b**) and C (**7c**) were completed by a Dieckmann cyclization.

The group of Porco also reported the first total syntheses of naturally ocurring ergochrome xanthenone dimers, namely the secalonic acid A (*ent*-**1**) and its enantiomer secalonic acid D (**1**) (Scheme 11).[51]



Scheme 11: Enantioselective total syntheses of secalonic acid A (*ent*-**1**) and D (**1**) by Porco *et al.*: a) $TMSCH_2N_2$, CH_2Cl_2/MeOH, 0 °C, 10 min, 63%; b) $CaCO_3$, $BnNMe_3ICl_2$, CH_2Cl_2/MeOH, RT, 12 h, 81%; c) **86** (10 mol%), Me_2NH, $(EtCO)_2O$, $CDCl_3$, 0 °C, 25 h, 41%, 99% *ee* (**88**); 40%, 99% *ee* (**91**); d) MOMCl, Me_2NH, DMAP, CH_2Cl_2, 40 °C, 12 h, 81%; e) $Pd_2(dba)_3$ (10 mol%), P*t*Bu_3 (40 mol%), *n*Bu_4NI (50 mol%), $(SnBu_3)_2$, 1,4-dioxane, 50 °C, 4 h, 51%; f) CuCl, DMA, air, RT, 12 h, 60%; g) 3 M HCl/MeCN, 60 °C, 30 min, 85%; h) MOMCl, Me_2NH, DMAP, CH_2Cl_2, RT, 12 h, 81%; i) $Pd_2(dba)_3$ (10 mol%), P*t*Bu_3 (40 mol%), *n*Bu_4NI (50 mol%), $(SnBu_3)_2$, 1,4-dioxane, 50 °C, 4 h, 56%; j) CuCl, DMA, air, RT, 12 h, 60%; k) 3 M HCl/acetone, 60 °C, 20 h, 81%.

Following up their concise approach to racemic tetrahydroxanthenones, blennolide B (**7b**) was methylated at the enol moiety with diazomethane and regioselectively iodinated with $BnNMe_3ICl_2$ to give racemic iodide **85**. A kinetic resolution of **85** in the presence of Birman's homobenzotetramisole (HMBT) catalyst **86** and acetic anhydride gave the unreacted and acylated iodides **88** and **91**, each in 99% *ee*. The excellent enantiodifferentiation between **85** and *ent*-**85** most likely results from π-stacking of the tetrahydroxanthenone core and the HMBT catalyst **86**, leading to a transition state **87** where the steric repulsion of the pendant phenyl ring is minimized. The iodides **89** and **92** were further elaborated into the stannanes **90** and **93** and unsuccessfully subjected to various Pd-catalyzed biaryl coupling methods. Key to the synthesis was an oxidative copper(I)-mediated C–C bond forming reaction to afford the secalonic acids A (*ent*-**1**) and D (**1**) after global deprotection.

3.2 Total Synthesis of Siccanin

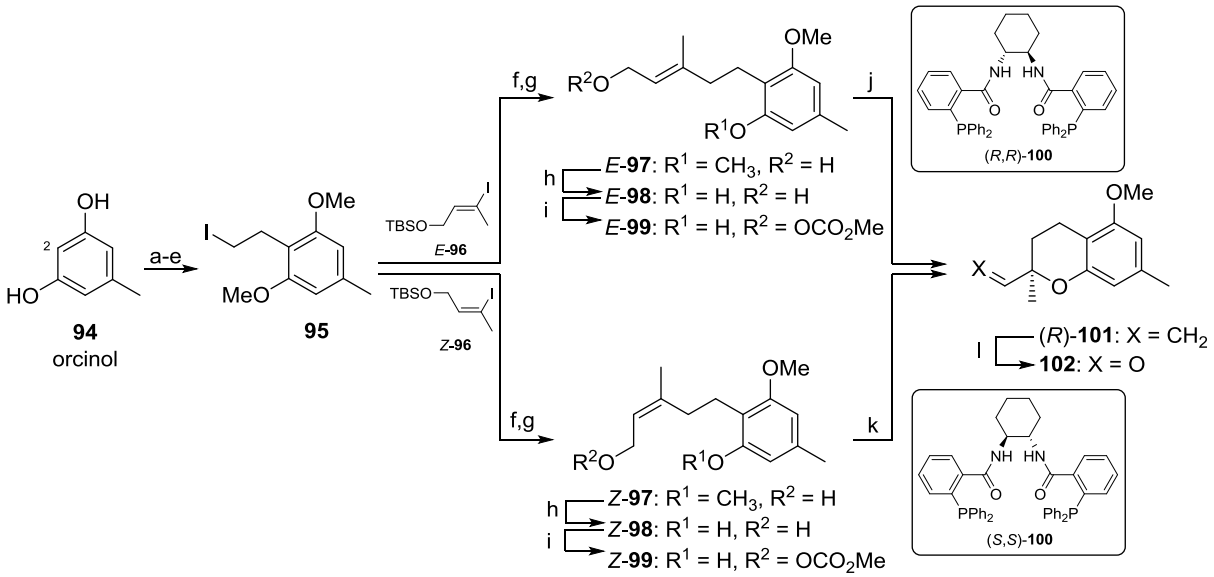
Siccanin (**25**, Scheme 13) is a potent antifungal agent and exhibits an unusual *cis*-*syn*-*cis*-fused A/B/C ring system endowed with two quaternary stereogenic centers, thus rendering it an interesting target for total synthesis. Besides several synthetic efforts towards **25**,[52] two racemic and one enantioselective total syntheses of siccanin (**25**) were reported to date.

The first synthesis was achieved by Yoshikoshi *et al*. featuring stereoselective formation of the *cis*-drimane scaffold and a Lewis-acid catalyzed olefin-phenol cyclization.[53] The racemic approach to **25** by Trost *et al*. relied on a Pd-catalyzed diyne reductive cycloisomerization to construct the B-ring.[54]

Inspired by the biosynthesis of siccanin, Trost *et al*. also accomplished the first enantioselective total synthesis of **25** using a Pd-catalyzed asymmetric allylic alkylation and a radical epoxy olefin cyclization as key steps. Trost's approach also enabled to access the siccanochromenes A (**26a**), B (**26b**), E (**26e**) and F (**26f**).[55]

The synthesis commenced with the preparation of the allylic carbonates *E*-**99** and *Z*-**99** in nine steps from commercially available orcinol (**94**) (Scheme 12). Methylation of both hydroxyl groups, formylation at C-2 (numbering as in **94**) and a sequence comprising a Wittig olefination, hydroborylation/oxidation and iodination gave alkyl iodide **95**. A Negishi coupling with the vinyl iodides *E*-**96** and *Z*-**96** followed by TBS- and methyl-ether cleavage and esterification provided the allylic carbonates *E*-**99** and *Z*-**99**. The introduction of the quaternary stereogenic center was accomplished by a Pd-catalyzed asymmetric alkylation of *E*-**99** and *Z*-**99** to provide vinyl chromane (*R*)-**101**. It should be noted that the use of acetic

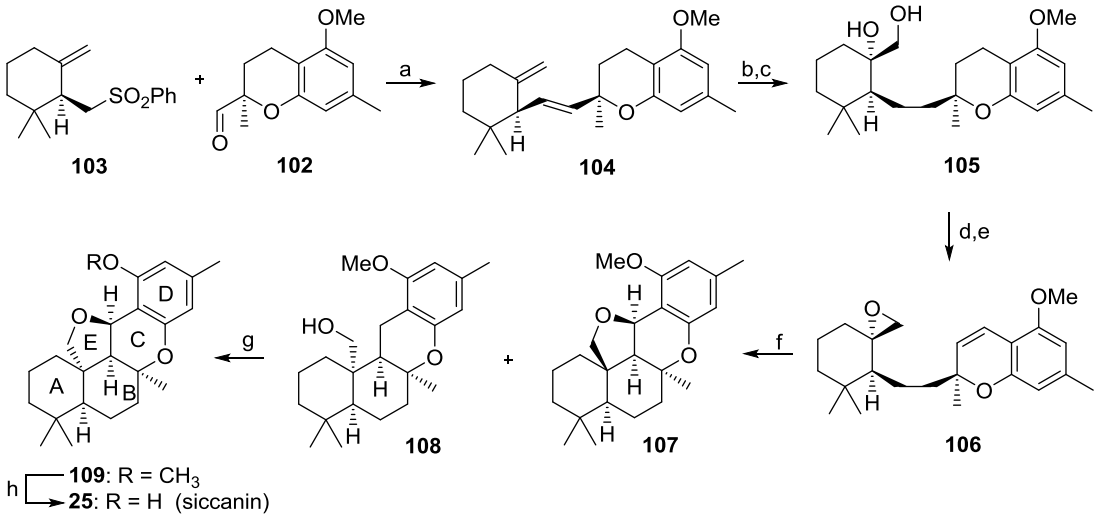
acid and the double bond geometry had a profound effect on the stereochemical outcome of the reaction.



Scheme 12: Syntheses of vinyl chromane (*R*)-**101** and aldehyde **102**: a) Me_2SO_4, K_2CO_3, acetone, reflux, 3 h, quant; b) *n*BuLi, TMEDA, Et_2O, 0 °C → reflux, 3 h, then DMF, 0 °C → RT, 2 h, 97%; c) *n*BuLi, CH_3PPh_3Br, THF, –78 °C, 3 h, then aldehyde, –78 °C → RT, over night, 98%; d) 1. $RhCl(PPh_3)_3$ (2 mol%), $(Bpin)_2$, 50 °C, 4.5 h; 2. 1 M NaOH, H_2O_2, THF, 50 °C, 1.5 h, quant; e) PPh_3, imidazole, I_2, THF, RT, 1 h, 97%; f) 1. $ZnCl_2$, *t*BuLi, THF, –78 °C → RT, 3 h; 2. $Pd(dppf)Cl_2$ (4 mol%), *n*BuLi, *Z*-**96** or *E*-**96**, THF, RT, over night; g) TBAF, THF, RT, 2 h, for *Z*-**97**: 32%, for *E*-**97**: 77% (2 steps); h) *n*PrSLi, HMPA, 120 °C, over night, for *Z*-**98**: 80%, for *E*-**98**: 87%; i) $MeCO_2Cl$, pyridine, CH_2Cl_2, 0 °C, 15 min, for *Z*-**99**: 95%, for *E*-**99**: > 95%; j) $Pd_2dba_3{\cdot}CHCl_3$ (2 mol%), (*R*,*R*)-**100** (6 mol%), HOAc, CH_2Cl_2, 0.2 M, RT, 1 h, 94%, 84% *ee*; k) $Pd_2dba_3{\cdot}CHCl_3$ (2 mol%), (*S*,*S*)-**100** (6 mol%), HOAc, CH_2Cl_2, 0.2 M, RT, 1 h, 79%, 97% *ee*; k) 1. aq. OsO_4 (5 mol%), NMO, CH_2Cl_2, RT, 5 h; 2. $NaIO_4$, acetone/H_2O, RT, 20 min, 94% (2 steps).

High *ee*-values were only observed when acetic acid was present in the reaction mixture. The authors postulated that it speeded up Pd-π-σ-π equilibration of which the more reactive π-allyl palladium species cyclized in the enantiodiscriminating step. Whereas *E*-**99** was transformed into (*R*)-**101** in the presence of ligand (*R*,*R*)-**100** in 94% yield and 84%% *ee*, the reaction of diastereomer *Z*-**99** with ligand (*S*,*S*)-**100**, bearing the opposite configuration, furnished (*R*)-**101** in 79% yield and 97% *ee*. Vinyl chromane (*R*)-**101** was dihydroxylated and the diol cleaved oxidatively giving rise to aldehyde **102**.[56]

A Julia olefination with of aldehyde **102** with chiral sulfone **103** gave diene **104** which subsequently underwent Sharpless dihydroxylation of the terminal alkene and hydrogenation of the internal double bond (Scheme 13). The resulting diol **105** was converted into epoxide **106**.

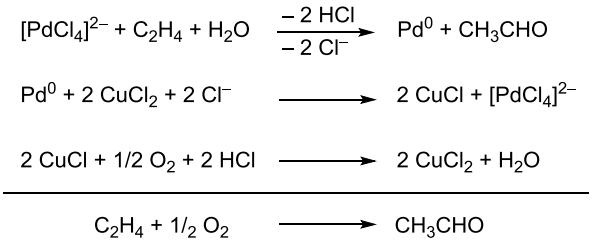


Scheme 13: Enantioselective total synthesis of siccanin (**25**) by Trost *et al.*: a) 1. *n*BuLi, then **102**; 2. *n*BuLi, then Ac_2O; 3. Na(Hg), Na_2HPO_4; 93% (3 steps); b) AD-mix β, $MeSO_2NH_2$, *t*BuOH/H_2O, 20 h, 94%, d.r. = 10:1; c) PtO_2 (20 mol%), H_2, EtOAc, 70 °C, 5 h, 82%; d) DDQ, benzene, 80 °C, 45 min, 91%; e) 1. *p*TsCl, DMAP; 2. NaH, 93% (2 steps); f) Cp_2TiCl_2, Mn, THF, RT, 10 h, 81%, **108**/**107** = 3:1; g) $PhI(OAc)_2$, I_2, benzene, 65%; h) NaSEt, DMF, 120 °C, 86%.

In the final steps of the synthesis, the B-ring was formed by a Ti^{III}-mediated radical cyclization to afford tetracyclic compound **108** and 5-*epi*-siccanin methyl ether (**107**) in a 3:1 ratio. The remaining tetrahydrofuran ring E was installed employing a Barton radical cyclization and cleaving the phenolic methyl ether to furnish siccanin (**25**).

4 Wacker Oxidation

The $PdCl_2$-catalyzed aerobic oxidative coupling of ethylene with water is referred to as Wacker or Wacker/Hoechst process. It was developed by Smidt and coworkers at the Consortium für elektrochemische Industrie, a subsidiary of Wacker Chemie, in 1959 to produce acetaldehyde, an important intermediate in the synthesis of acetic acid and C_4-products.[57] The origin of the Wacker reaction can be traced back to 1894 when Phillips oxidized ethylene with stoichiometric amounts of $PdCl_2$ in an aqueous solution.[58] Smidt and coworkers disclosed for the first that the formed Pd(0) metal can be reoxidized to the active Pd(II) species with $CuCl_2$ which in turn can be regenerated upon oxidation with molecular oxygen. The combination of the three reactions made it possible to use only catalytic amounts of the precious palladium and copper metals, rendering the overall process a highly efficient oxidation of ethylene to ethanal with air (Scheme 14). Additionally, Smidt *et al*. found that the carbonyl oxygen atom arises from water and not from O_2. It was thus reasoned that the active Pd(II)-species catalyzes the nucleophilic attack of water on ethylene by a hydroxypalladation step.



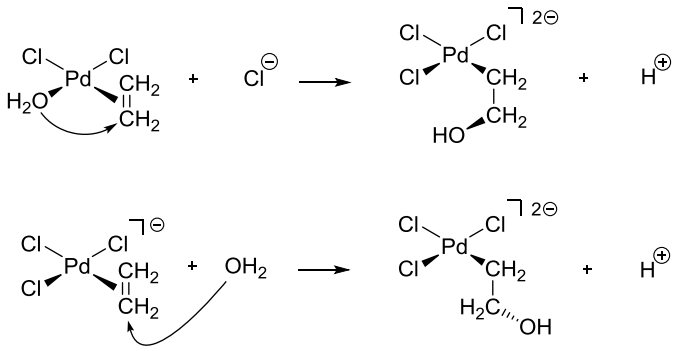
Scheme 14: Wacker reaction of ethylene comprising oxidative coupling with water and catalyst regeneration.

The Wacker process has lost some of its industrial relevance due to the increasing production of acetic acid by the carbonylation of methanol (Monsanto-process)[59] and the manufacturing of C_4-compounds by the hydroformylation of propylene (oxo synthesis).[60] However, it is still a very active area of research, fuelled by its various applications in organic synthesis.[61]

4.1 Mechanism of the Wacker oxidation

Since its discovery, the mechanism of the Wacker oxidation, in particular the nature of the hydroxypalladation step, has been heavily debated in the chemical community.[62] Depending on the reaction conditions, experimental and theoretical data were found to be consistent with either an intramolecular *syn*-attack of a coordinated water or hydroxy ligand (Scheme 15,

above) or with an intermolecular *anti*-attack of an exogenic oxygen nucleophile (Scheme 15, below).[63]



Scheme 15: Stereochemical pathways for the hydroxypalladation step: *syn*- (above) and *anti*-hydroxypalladation (below).

The analysis of this key question is hampered by the fact that the stereochemical information of the hydroxypalladation is lost in the course of the reaction. The oxidation of ethylene leads to achiral acetaldehyde whose sp^2-hybridized carbonyl carbon does not provide conclusive evidence for the one or the other pathway.

The numerous kinetic, stereochemical and theoretical studies that were performed to clarify this issue can be summarized as follows: High concentrations of Cl^- (> 3 M) and $CuCl_2$ (> 2.5 M) give rise to both acetaldehyde and chlorohydrin by an *anti*-attack of the oxygen nucleophile on ethylene. Under low concentrations of Cl^- and $CuCl_2$ (< 1 M), which are relevant for the industrial process, the hydroxypalladation proceeds most likely in a *syn*-fashion.[62]

A mechanism that describes the latter scenario (inner-sphere mechanism) was proposed by Goddard *et al*. (Figure 8).[64]

The catalytic cycle commences with the coordination of ethylene to $[PdCl_4]^{2-}$ (**I**) which is assumed to be the resting state of $PdCl_2$.[65] The resulting π-complex undergoes ligand exchange of a chloride ion with H_2O (**II**). An intramolecular *syn*-hydroxypalladation with concomitant deprotonation by a second water molecule leads to a 4-membered palladacycle (**III**). A 120° rotation around the C–C bond (**IV**) is followed by β-hydride elimination (**V**) and reinsertion into the double bond (**VI**). The chloride-mediated reductive elimination finally releases ethanal and Pd(0) (**VII**) which is reoxidized by the coupled $CuCl_2/O_2$-redox system (**VIII**).

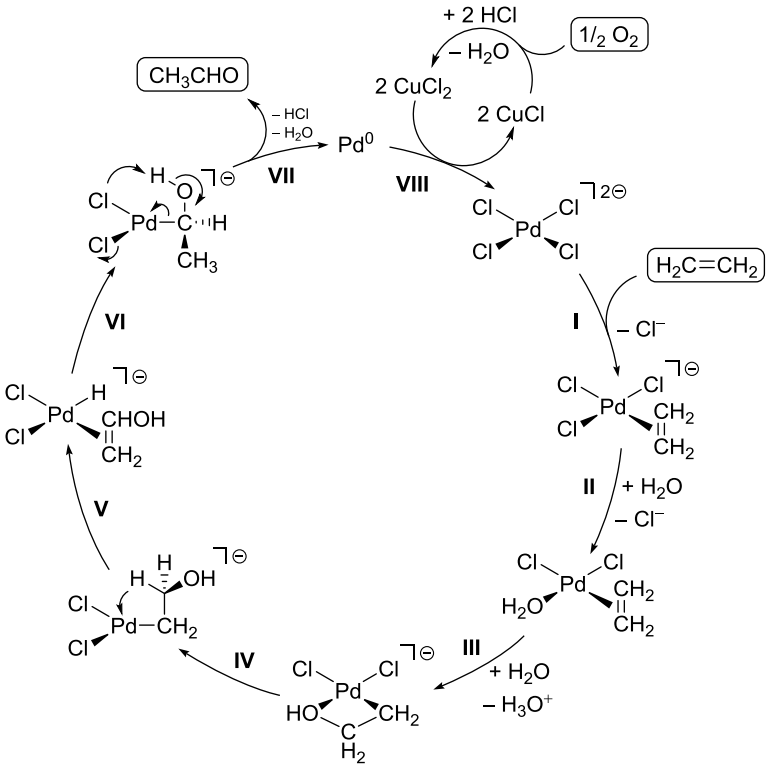


Figure 8: Inner-sphere catalytic cycle proposed by Goddard *et al.*

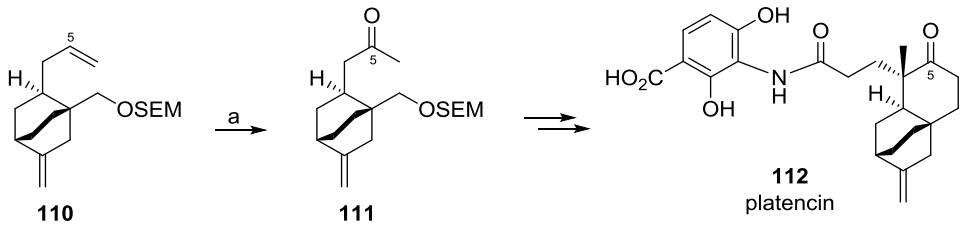
It should be noted that the role of $CuCl_2$ besides its ability to oxidize Pd(0) is not fully understood. Hosokawa *et al*. reported the formation of Pd-Cu bimetallic complexes as active species in the Wacker oxidation.[66] Surprisingly, recent experimental[67] and theoretical studies[68] showed that the hydroxypalladation occurs by an *anti*-pathway under copper-free conditions.

4.2 The Wacker oxidation in organic synthesis

Originating from the industrial production of acetaldehyde, the Wacker oxidation has emerged as an important method in organic synthesis. Its broad functional group compatibility combined with its air- and moisture tolerance also render it a versatile reaction in total synthesis.

The general reaction conditions involve the use of catalytic amounts of a palladium source and an optional ligand in a polar solvent such as DMF/H_2O, DMSO, dioxane or alcohol. The most commonly used oxidants for the regeneration of the active Pd(II)-catalyst are oxygen in combination with copper salts,[69] *p*-benzoquinone,[70] DMSO/oxygen[71] and AcOH/*tert*-butylhydroperoxide.[72] Whereas the regioselective oxidation of internal olefins requires the presence of an additional directing group,[73] terminal olefins are almost exclusively converted to the corresponding methyl ketones.

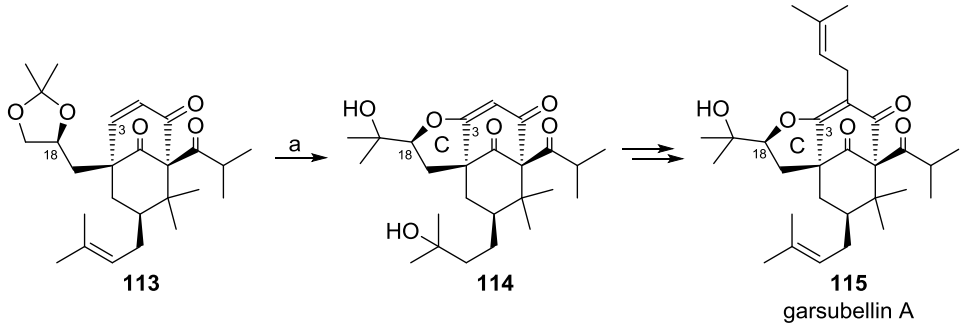
For example, Nicolaou *et al*. used a Wacker oxidation to introduce the ketone moiety at C-5 in the enantioselective total synthesis of the antibiotic platencin (**112**) (Scheme 16).[74]



Scheme 16: Wacker oxidation in the entantioselective total synthesis of platencin (**112**) by Nicolaou *et al*.: $PdCl_2$ (25 mol%), CuCl, O_2, DMF/H_2O, RT, 24 h, 50%.

More importantly, the intramolecular Wacker reaction is a useful method for the syntheses of oxygen- and nitrogen-containing heterocycles.[75] As in the Wacker reaction of ethylene, the intramolecular attack of the oxygen or the nitrogen nucleophile on the alkene can proceed by a *syn*- or an *anti*-pathway. Since the oxy- or aminopalladation is often accompanied by the generation of a new stereogenic center, this step has been the subject of tremendous research efforts for the last decades.[61a] The current mechanistic understanding is that in the majority of intramolecular Pd(II)-catalyzed alkene functionalizations, the nucleopalladation proceeds by a *syn*-pathway, however, minor variations of the substrate structure or the reaction conditions may alter the stereochemical outcome of the cyclization.

Shibasaki *et al*. used a Wacker cyclization to efficiently set up the tetrahydrofuran ring in the total synthesis of garsubellin A (**115**) (Scheme 17).[76] After removal of the acetonide protecting group, a palladium-mediated attack of the secondary hydroxyl group at C-18 provided the formation of the C-ring.



Scheme 17: Wacker cyclization of hydroxyenone **113** in the racemic total synthesis of garsubellin A (**115**) by Shibasaki *et al*.: a) 1. LiOH, THF, RT, 30 min; 2. Na_2PdCl_4 (4.9 eq.), TBHP, NaOAc, AcOH/H_2O/tBuOH, 75 °C, 3 h, 71% (2 steps)

In the context of domino reactions, the intramolecular nucleopalladation received increasing attention since the formed Pd(II)-σ-alkyl species **117** can engage in a variety of subsequent transformations (Figure 9). The simplest case represents the elimination of palladium and a hydrogen atom in β-position (Figure 9, a). If no such β-hydrogen is present in **117** or a *syn*-orientation to palladium is not feasible, the Pd(II)-σ-alkyl species **117** may participate in carbon-heteroatom and carbon-carbon bond forming reactions. For instance, **117** may be oxidized to the corresponding Pd(IV)-species. Attack from an external or internal heteroatom nucleophile and reductive displacement of palladium(II) then may give rise to diheterofunctionalizations such as amino acetoxylations,[77] dihydroxylations[78] and diaminations[79] (Figure 9, b).

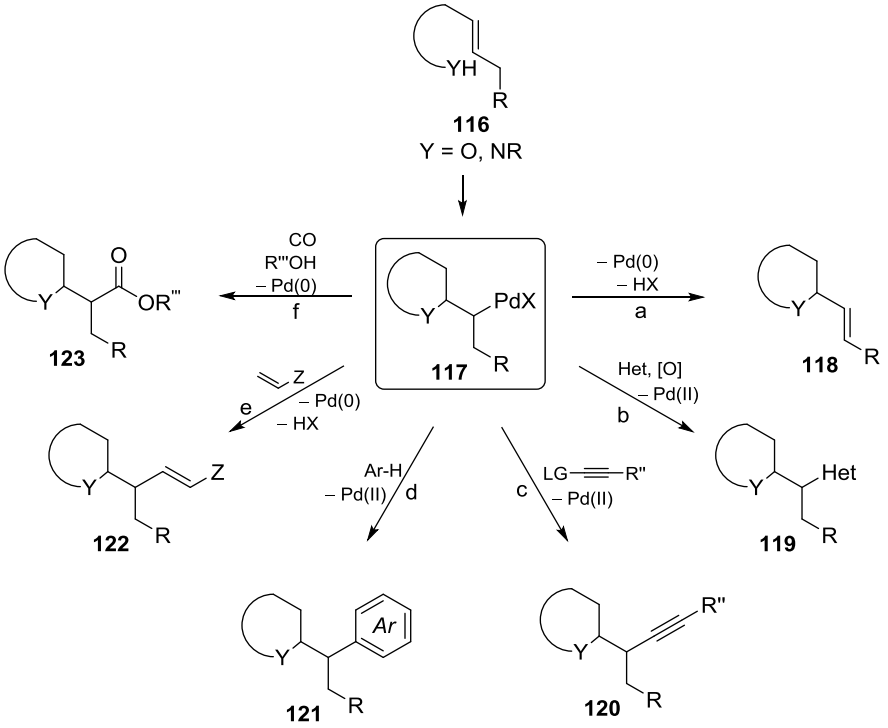
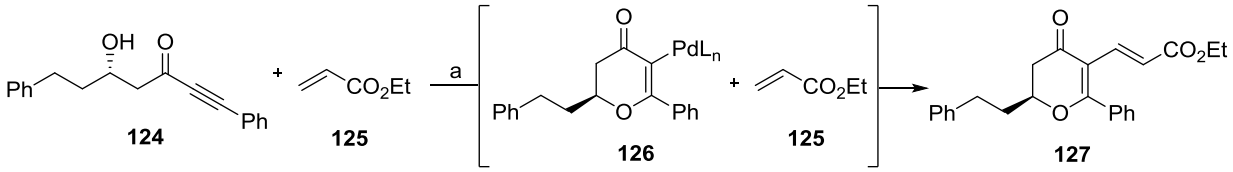


Figure 9: Subsequent transformations of the Pd(II)-σ-alkyl species **117** arising from intramolecular nucleopalladation.

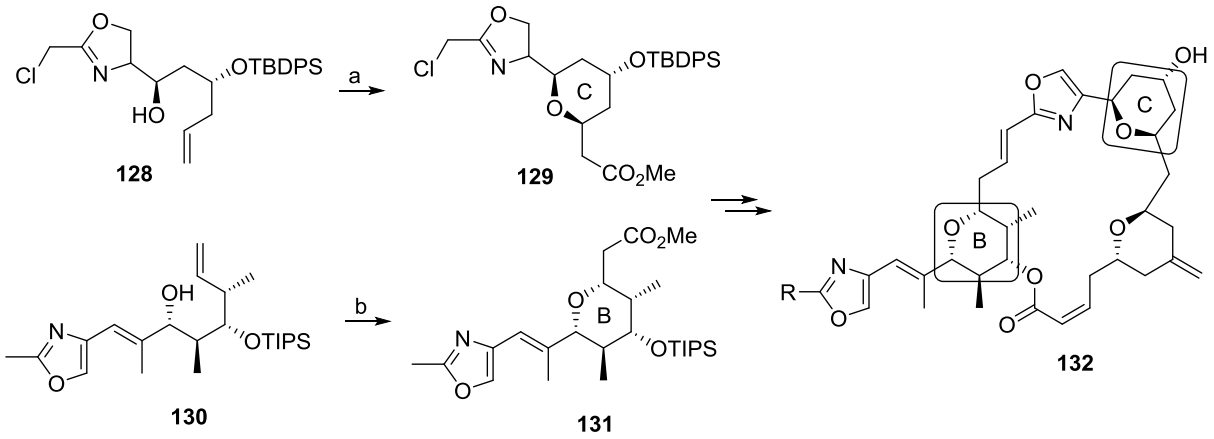
Carbon-carbon bond forming reactions that can follow nucleopalladation include for example alkynylation (Figure 9, c),[80] arylation[81] and indolyation reactions (Figure 9, d).[82]

Furthermore, capture of the transient Pd(II)-σ-alkyl **117** can be accomplished by the insertion into olefins followed by β-hydride elimination (Figure 9, e).[83] Tietze *et al*. developed such a domino Wacker/Heck reaction for the enantioselective total synthesis of vitamin E.[121b] Based on this work, Gouverneur *et al*. used a domino Wacker/Heck reaction of β-hydroxy ynone **124** and ethyl acrylate **125** to furnish dihydropyranone **127** in a moderate yield of 47% (Scheme 18).[84]



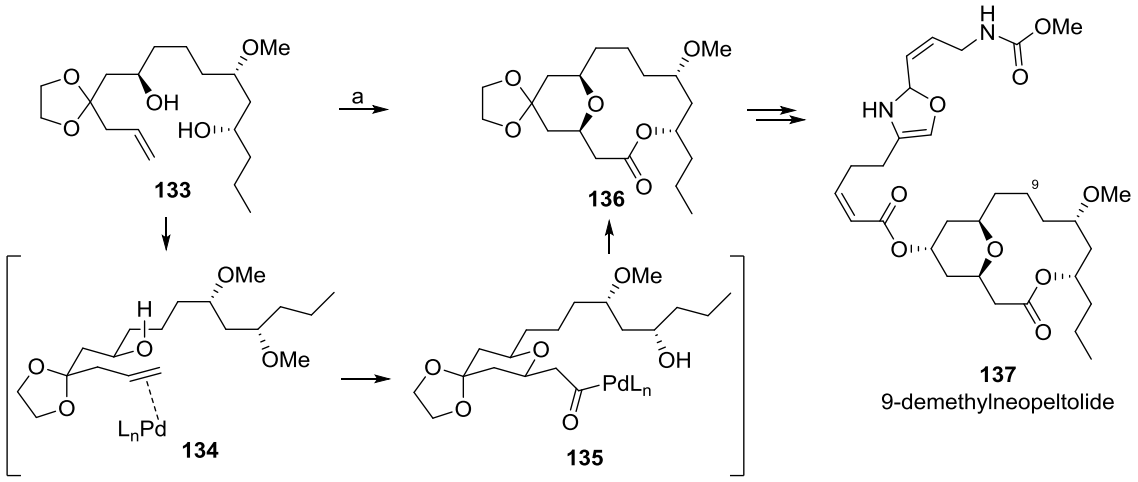
Scheme 18: Domino Wacker/Heck reaction of β-hydroxy ynone **124** with ethyl acrylate (**125**) by Gouverneur *et al*.: a) $Pd(MeCN)_2Cl_2$ (10 mol%), PPh_3 (10 mol%), LiBr (20 mol%), $Cu(OAc)_2$ (10 mol%), O_2, DME, 20 h, 65 °C, 47%.

In the presence of CO and an alcohol, **117** can also be trapped as a palladium-acyl intermediate which undergoes alcoholysis to yield an ester (Figure 9, f).[85a] This methodology was successfully applied in the total synthesis of the potent antitumor agent phorboxazole A (**132**) by White *et al*. (Scheme 19).[85b,c] Two domino Wacker/carbonylation/methoxylation reactions were employed for the formation of the tetrahydropyran rings B and C. In the case of tetrahydropyran C, 10 mol% of palladium chloride acetonitrile complex and stoichiometric amounts of the oxidant *p*-benzoquinone in MeOH under a CO-atmosphere provided the desired domino reaction in 58% yield and high diastereoselectivity. The synthesis of the B-ring proceeded in 86% using this domino reaction, however, requiring the addition of 3 equivalents of palladium acetate.



Scheme 19: Total synthesis of phorboxazole A (**132**) by White *et al*.: using intramolecular domino Wacker/carbonylation/methoxylation reactions for the formation of the tetrahydropyranes B and C: a) $PdCl_2(MeCN)_2$ (10 mol%), *p*-benzoquinone, MeOH/MeCN, RT, 24 h, 58%; b) $Pd(OAc)_2$ (3 eq.), CO, MeOH/MeCN, RT, 44 h, 86%. R = residue.

If a second hydroxyl group is present in the molecule, the terminating alcoholysis can occur intramolecularly to afford bicyclic lactones, particularly fused tetrahydropyran- and tetrahedrofuran-γ-lactones.[86]



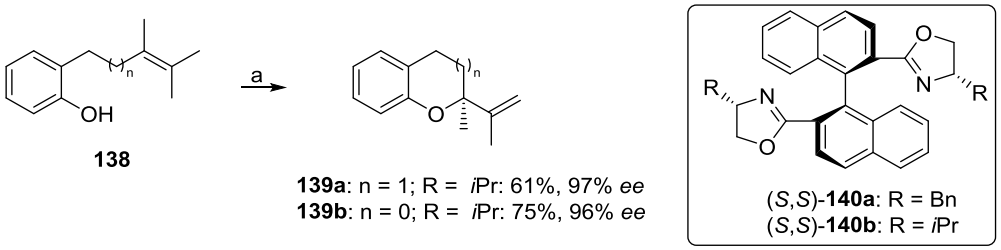
Scheme 20: Domino Wacker/carbonylation/macrolactonization reaction in the total synthesis of 9-demethyl-neopeltolide (**137**) by Dai *et al.*: $Pd(OAc)_2$ (10 mol%), $CuCl_2$, 4 Å ms, CO, DCE, RT, 20 h, 58%.

An impressive extension of this intramolecular domino Wacker/carbonylation/lactonization reaction was recently applied in the total synthesis of 9-demethylneopeltolide (**137**) by Dai *et al*. (Scheme 20).[87] A Pd-catalyzed alkoxycarbonylative macrolactonization installed the tetrahydropyran and the 11-membered macrolactone ring in 58% yield.

4.3 Enantioselective Wacker oxidations

Although the Wacker reaction has been subject of extensive investigation for more than 50 years, the development of highly enantioselective versions still remains not properly addressed.[61a] Firstly, chiral phosphine ligands that are commonly used in asymmetric Pd(0)-catalyzed reactions cannot be applied in Wacker-type transformations. Phosphines are usually inconsistent with the oxidizing reaction conditions and their σ-donor ability may deteriorate the electrophilic character of the metal center. Secondly, mechanistic studies revealed that the energy barriers between the enantiodetermining *syn*- and *anti*-nucleopalladation step may be very similar, rendering both pathways operative.

The first enantioselective Pd(II)-catalyzed alkene transformation was published by Hosokawa and Murahashi in 1978.[88] The cyclization of *ortho*-allyl phenols in the presence of the chiral ligand β-pinene, however, proceeded with only low *ee*-values (up to 29% *ee*).[66a,b] The first highly enantioselective Wacker procedure was reported by Uozumi and Hayashi using novel binaphthyl derived bisoxazoline ligands (BOXAX) **140** (Scheme 21).[89] The catalytic system comprising $Pd(TFA)_2$, BOXAX ligand (*S*,*S*)-**140a** or (*S*,*S*)-**140b** as well as *p*-benzoquinone as oxidant in MeOH provided the cyclization of tetrasubstituted *ortho*-allyl and homoallyl phenols **138** to dihydrobenzofuranes and chromanes with enantioselectivities up to 97% *ee*.

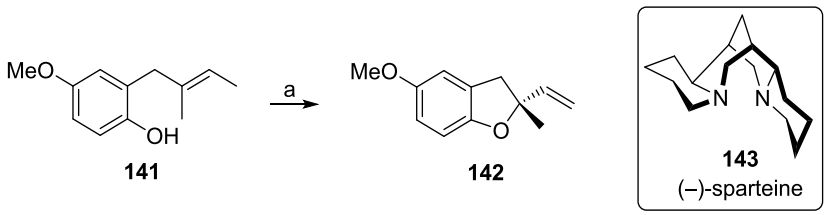


Scheme 21: Enantioselective Wacker oxidation of *ortho*-allyl and homoallyl phenols **138** by Uozumi and Hayashi: a) $Pd(TFA)_2$ (10 mol%), BOXAX ligand (*S*,*S*)-**140a** or (*S*,*S*)-**140b** (10 mol%), *p*-benzoquinone, MeOH, 60 °C, 24 h.

The BOXAX ligands were also employed by Tietze *et al*. for the domino Wacker/Heck and domino Wacker/carbonylation/methoxylation reaction to provide the chiral chromans with high *ee*-values (see page 53).[121]

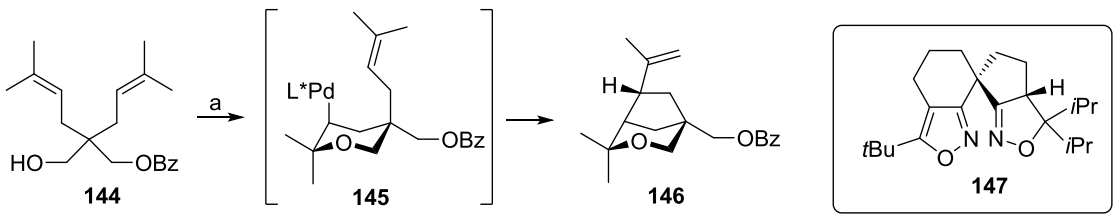
Zhang *et al*. used a series of structurally related, axially chiral biphenyl ligands with a tetraoxazoline backbone to induce enantioselectivity in the cyclization of tri- and tetrasubstituted *ortho*-allyl and homoallyl phenols.[90]

Stoltz *et al*. developed the first enantioselective Wacker cyclization under aerobic[91] reaction conditions (Scheme 22).[92] The cyclization of *ortho*-allyl phenol **141** with $Pd(TFA)_2$ and the C_1-symmetric natural product (–)-sparteine (**143**) as ligand under an O_2-atmosphere furnished the desired product **142** in moderate yield and high *ee*-value. Although, the scope of the reaction was plagued by moderate yields and the ligand's enantiomer (+)-sparteine (*ent*-**143**) is not easily accessible, the use of molecular oxygen as the sole oxidant represented a major improvement in terms of environmentally more benign transformations.



Scheme 22: Enantioselective Wacker oxidation of alkenyl phenol **141** by Stoltz *et al*.: a) (–)-sparteine-$Pd(TFA)_2$ (10 mol%), $Ca(OH)_2$, 3 Å ms, toluene, 60 °C, 55 h, 57%, 90% *ee*.

Aliphatic alcohols represent an interesting class of nucleophiles for the functionalization of alkenes. Under the oxidative conditions of the Wacker reaction, however, primary and secondary alcohols are prone to oxidation and thus require careful tuning of the catalytic system.



Scheme 23: Enantioselective desymmetrization by Sasai *et al.*: $Pd(TFA)_2$ (20 mol%), **147** (24 mol%), *p*-benzoquinone, CH_2Cl_2, 0 °C, 17 h, 74%, 95% *ee*.

The use of aliphatic alcohols as nucleophiles was first reported by Sasai *et al*. in the elegant desymmetrization of monoprotected diol **144** using catalytic amounts of $Pd(TFA)_2$ and novel spiro (isoxazol isoxazoline) ligand (SPRIX) (**147**) as well as *p*-benzoquinone as the stoichiometric oxidant (Scheme 23).[93] The oxypalladation of **144** led to the palladium species **145** that subsequently underwent insertion into the pendant alkene to furnish bicycle **146** in 74% yield and 95% *ee*.

5 Sharpless dihydroxylation

The OsO_4-catalyzed, asymmetric dihydroxylation developed by Sharpless *et al*. represents a powerful method to transform a large variety of prochiral olefins into chiral 1,2-diols.[94] The reaction combines operational simplicity with high enantioselectivity and excellent catalytic turn-over, the latter being based on the ligand acceleration effect (LAE) of the cinchona alkaloids dihydroquinine (DHQ) and dihydroquinidine (DHQD) used in the synthesis (Figure 10).[95]

The reaction is normally conducted with 0.2 mol% of an osmium(VI)-salt and 1 mol% of ligand in the presence of stoichiometric amounts of the base K_2CO_3 and the oxidant $K_3Fe(CN)_6$ in a biphasic solvent system (*t*BuOH/H_2O) or with the oxidant *N*-methylmorpholine *N*-oxide (NMO) in a homogeneous solution. Among the ligands studied, the phthalazine-based dimers $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL exhibit the highest enantioselectivities and the broadest substrate scope.[94b] Commercially available mixtures of non-volatile $K_2OsO_4 \cdot 2\ H_2O$, $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL, K_2CO_3 and $K_3Fe(CN)_6$, referred to as AD-mix-α and AD-mix-β, are routinely used for small-scale applications.[96]

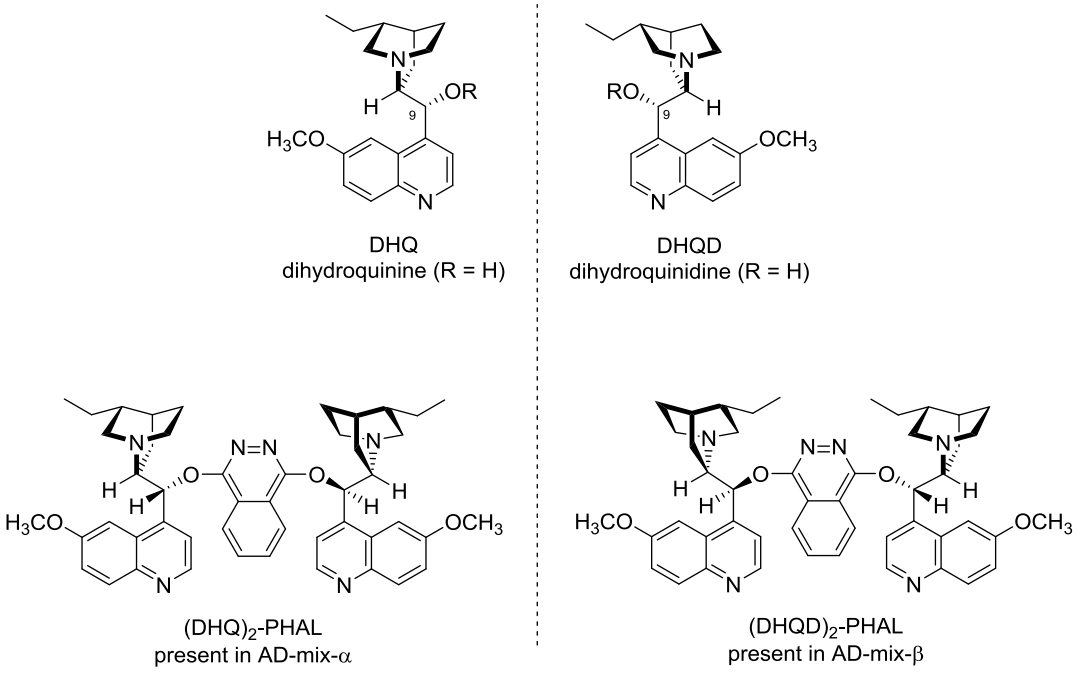


Figure 10: The cinchona alkaloids dihydroquinine (DHQ), dihydroquinidine (DHQD) and the phthalazine-based dimers $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL.

5.1 Mechanism of the Sharpless dihydroxylation

The initial catalytic system reported by Sharpless *et al*. relied on the use of cinchona alkaloids as ligands and stoichiometric amounts of the reoxidant NMO in a homogeneous acetone/H_2O mixture, constituting the very first example of this process with substoichiometric amounts of osmium.[94a] However, the reaction was plagued by low *ee*-values of only up to 8%. Mechanistic studies revealed that under these conditions two catalytic cycles are operative (Figure 11).[97]

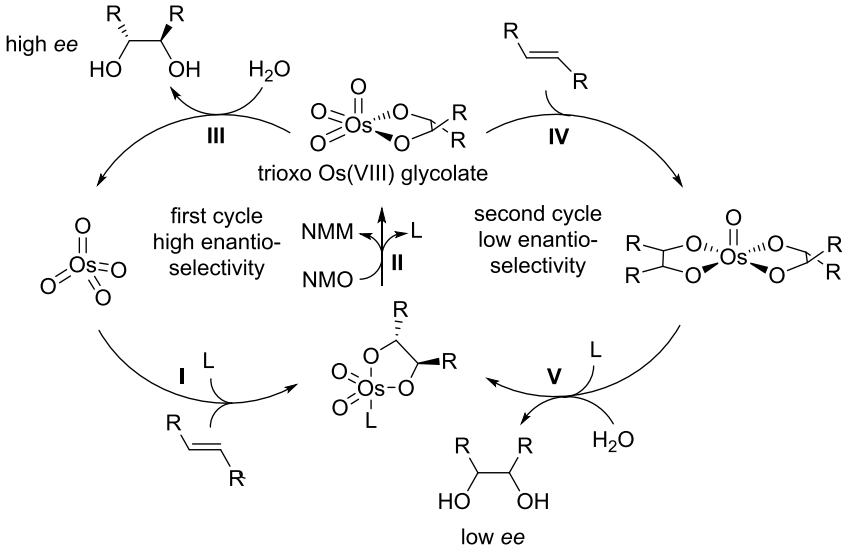


Figure 11: Mechanism of the asymmetric dihydroxylation with NMO as reoxidant in a monophasic solvent.

In the first cycle, osmylation of the olefin with OsO_4 gives an osmium(VI) monoglycolate species in a stereo-defined manner (**I**). Oxidation with NMO and release of the ligand then leads to a trioxo osmium(VIII) glycolate (**II**) that can undergo either of two subsequent reactions: upon hydrolysis the desired enantioenriched diol is released, alongside regenerated OsO_4 (**III**). Alternatively, the glycolate can add to a second olefin, this time however without asymmetric induction (**IV**). The resulting bisglycolate ester releases the diol with low enantioselectivity, thus lowering the overall enantiopurity of the dihydroxylation product (**V**).
When the reaction is performed in a biphasic solvent system with the water-soluble reoxidant $K_3Fe(CN)_6$, the second cycle can be completely suppressed (Figure 12). Since no oxidant is present in the organic layer, the monoglycolate ester undergoes hydrolysis liberating the diol and ligand to the organic phase and the Os(VI) species to the aqueous phase where it gets reoxidized to OsO_4.[98]

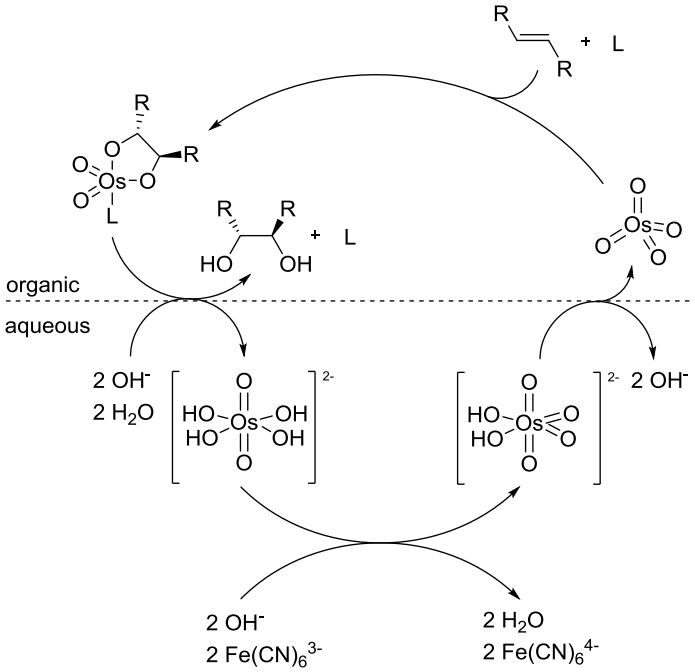


Figure 12: Mechanism of the asymmetric dihydroxylation with $K_3Fe(CN)_6$ as reoxidant in a biphasic solvent.

Although the Sharpless dihydroxylation has been subject of numerous mechanistic studies, the exact mechanism for the formation of the monoglycolate ester **150** was heavily debated (Figure 13). Sharpless *et al*. proposed a stepwise mechanism involving a [2+2]-addition to form osmaoxetane **148** which subsequently rearranges to **150**.[99] In contrast, Corey *et al*. suggested a [3+2]-cycloaddition of the olefin and the catalyst which directly leads to **150**.[100] The current mechanistic understanding favors the [3+2]-pathway.[101] Calculations showed that the activation energy for the [3+2]-addition is about 30 kcal/mol lower compared to the [2+2]-addition.[102]

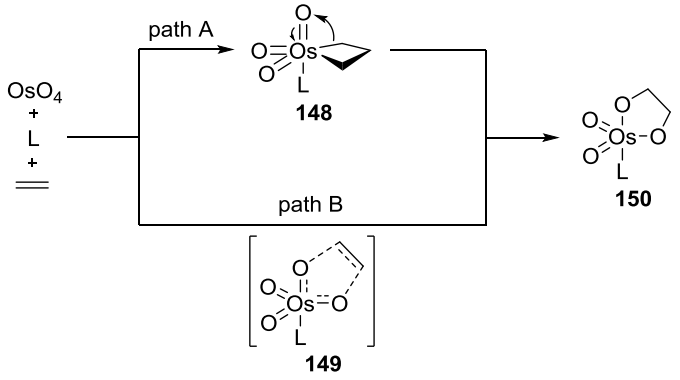


Figure 13: Formation of monoglycolate **150** by a stepwise [2+2]-cycloaddition/rearrangement (path A) or a concerted [3+2]-cycloaddition pathway (path B).

The hydrolysis of **150** was identified as the rate-determining step. It can be substantially accelerated by the addition of methanesulfonamide, also referred to as the "sulfonamide effect".[94b,c] Several substrates displayed rates that increased by a factor of 50 in the presence of this additive, even allowing the dihydroxylation of tetrasubstituted alkenes.[94b]

The excellent enantioinduction of the cinchona alkaloids can partly be attributed to the ligand acceleration effect. Binding of the quinuclidine nitrogen to OsO_4 greatly increases the rate for the enantioselectivity-determining formation of the osmium(VI) monoglycolate ester, rendering all non-accelerated osmylation pathways insignificant. Furthermore, extensive screening experiments revealed that ligands with O-9 substituents bearing extended aromatic systems gave the highest *ee*-values.[94c] This particularly holds true for the ligands $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL with two cinchona alkaloid units attached to a phthalazine spacer forming an enzyme-like binding pocket.[94b]

Sharpless *et al*. proposed a mnemonic device to predict the enantiofacial selectivity for the reaction of a prochiral olefin with AD-mix-α ($(DHQ)_2$-PHAL) or AD-mix-β ($(DHQD)_2$-PHAL) (Figure 14).[94c,95a] In this device, the south-east (SE) and to a minor extent the north-west (NW) corridor exert steric barriers whereas the north-east (NE) quadrant is open for the incoming olefin. The south-west (SW) corridor represents an "attractive area" which is best suited for flat, aromatic or large, aliphatic groups. Accordingly, the olefin is positioned in the device so that the smallest substituent, normally a proton, points to the south-east and the largest group to the south-west quadrant. AD-mix-β then approaches the olefin from the top face while AD-mix-α attacks from the bottom face.

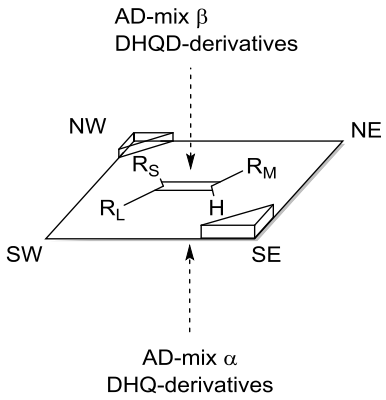
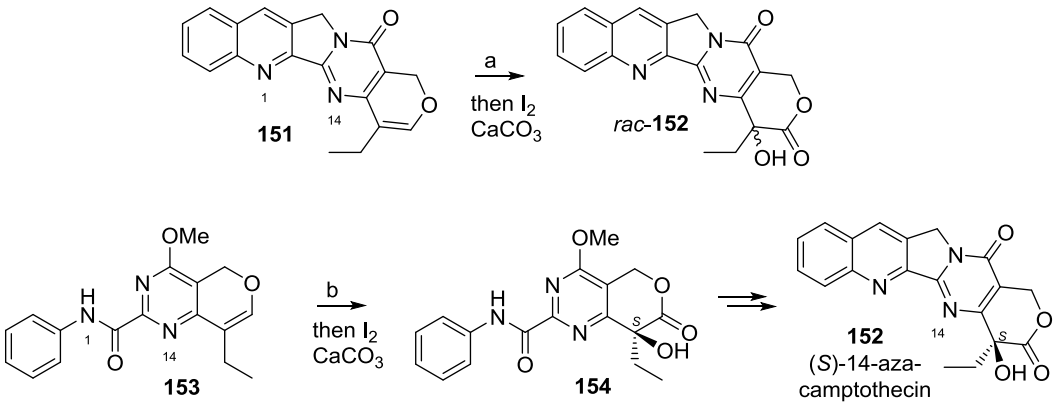


Figure 14: Mnemonic device for the prediction of the face selectivity.

5.2 Sharpless dihydroxylation in organic synthesis

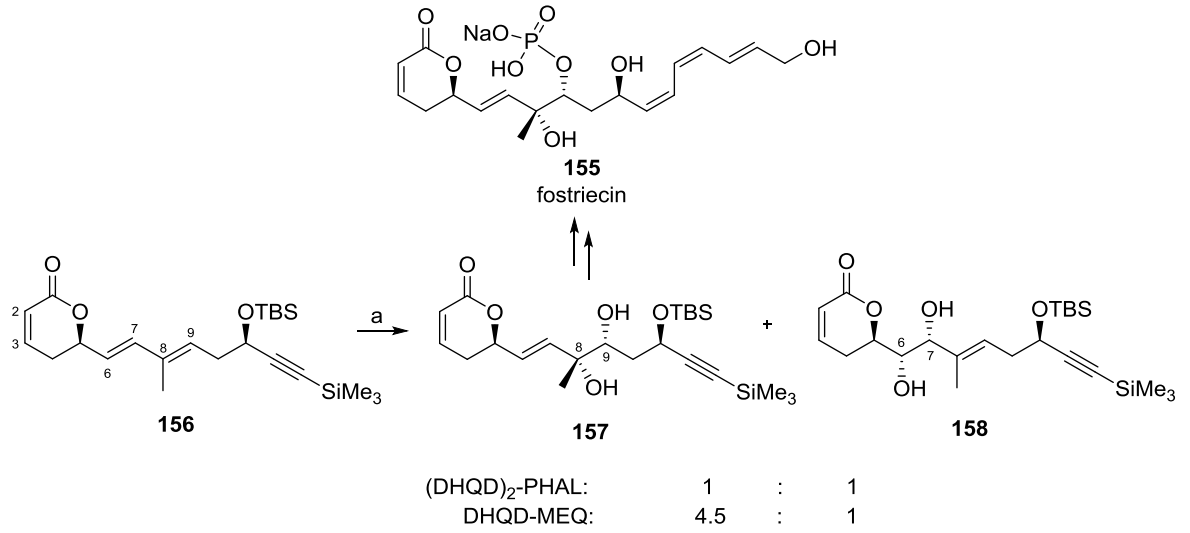
Given its wide substrate scope, mild reaction conditions and excellent performance in terms of yield and enantioinduction, the Sharpless dihydroxylation constitutes a powerful method to access chiral 1,2-diols. Not surprisingly, its synthetic utility led to numerous applications in the synthesis of complex target molecules.

In their asymmetric total synthesis of the water-soluble anticancer agent (*S*)-14-azacamptothecin (**152**) (Scheme 24), Yao *et al*. envisioned a late-stage Sharpless dihydroxylation to initiate formation of the α-hydroxyl lactone moiety.[103] Exposure of the pentacyclic intermediate **151** to standard conditions using $(DHQD)_2$-PHAL and subsequent iodine-mediated oxidation of the resulting hemiacetal gave the final compound in a good yield of 68%, however, without any enantioselectivity. It was reasoned that the two spatially close nitrogen atoms N-1 and N-14 interfere with the osmium-ligand complex, leading to the disruption of its chiral binding pocket. The authors thus resorted to enol ether **153** whose amide nitrogen atom N-1 exhibited no coordinating ability to the catalyst. Sharpless dihydroxylation of **153** in the presence of $(DHQD)_2$-PYR followed by hemiacetal oxidation furnished the desired α-hydroxyl lactone **154** in excellent 91% yield and 94% *ee*.



Scheme 24: Sharpless dihydroxylation reactions in the total synthesis of (*S*)-14-azacamptothecin (**152**) by Yao *et al*.: a) K_2OsO_4, $(DHQD)_2$-PHAL, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH/H_2O, 0 °C, 24 h, 68%, 0% *ee*; b) K_2OsO_4, $(DHQD)_2$-PYR, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 20 h, 91%, 94% *ee*.

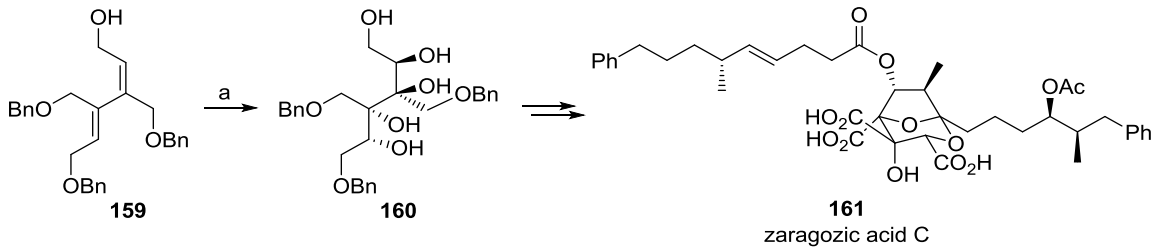
In the final steps of their total synthesis of the protein phosphatase inhibitor fostriencin (**155**), McDonald *et al*. were confronted with the regio- and stereoselective dihydroxylation of advanced intermediate **156** bearing three distinct olefin moieties (Scheme 25).[104] It was anticipated that the trisubstituted C-8–C-9 double bond would preferentially react as a result of the electronic deactivation of the C-2–C-3 and C-6–C-7 olefins.



Scheme 25: Regio- and stereoselective Sharpless dihydroxylation in the total synthesis of fostriecin (**155**) by McDonald *et al*.: a) K_2OsO_4, DHQD-MEQ, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH/H_2O, 0 °C, 36 h, 72%, **157**/**158** = 4.5:1.

Employing standard conditions with $(DHQD)_2$-PHAL resulted in the dihydroxylation of the C-6–C-7 and C-8–C-9 alkenes in an unsatisfying 1:1 ratio. The authors hypothesized that the binding pocket of the phthalazine-based dimer favors the accommodation of the disubstituted C-6–C-7 double bond, overriding the electronic preference for the C-8–C-9 alkene. Gratifyingly, substrate **156** reacted in the presence of the monomeric ligand DHQD-MEQ to the desired C-8–C-9 diol **157** in 59%, alongside 13% of its regioisomer **158**.

In their total synthesis of (+)-zaragozic acid C (**161**), Armstrong *et al*. used a double Sharpless dihydroxylation to simultaneously set up four contiguous stereocenters (Scheme 26).[105] While a one-pot procedure with AD-mix β was plagued by low yields, a two-step approach comprising two separate dihydroxylations was successful. In the first reaction, diene **159** was treated with Super-AD-mix β, a mixture of AD-mix β and additional osmium and ligand, in *t*BuOH/H_2O to give a regioisomeric triol mixture.



Scheme 26: Double Sharpless dihydroxylation of allyl alcohol **159** in the total synthesis of (+)-zaragozic acid C (**160**) by Armstrong *et al*.: a) 1. AD-mix β, OsO_4, $(DHQD)_2$-PHAL, $MeSO_2NH_2$, $K_2S_2O_8$, *t*BuOH/H_2O, 0 °C → RT, 4 d; 2. OsO_4, NMO, $(DHQD)_2$-PHAL, acetone/H_2O, 45%, 76% *ee*, d.r. = 9:1.

This was followed by a second dihydroxylation with catalytic amounts of OsO_4 and $(DHQD)_2$-PHAL in a homogeneous acetone/H_2O solution with NMO as the oxidant to furnish pentaol **160** in a moderate yield of 45% and good enantio- and diastereoselectivity of 76% *ee* and d.r. = 9:1, respectively.

6 Domino Reactions in Organic Synthesis

The increasing requirements for efficient and environmentally benign reactions constitute a major challenge to the synthetic community. An intriguing approach that meets these demands represents the domino concept which was first introduced by Tietze.[106,107] By definition, a domino reaction is "a process of two or more bond forming reactions under identical reaction conditions without adding additional reagents or catalysts, and in which the latter transformations take place at the functionalities obtained in the former bond forming reactions." On this basis, domino reactions can be classified according to the mechanism of the individual steps, which may be of the same (homo domino reaction) or of different type (hetero domino reaction) (Table 1). In most cases, the second and eventually the subsequent steps proceed intramolecularly. Domino reactions can take place in a single compound or between multiple reaction partners. Thus, multicomponent reactions are per definition a subgroup of domino transformations.

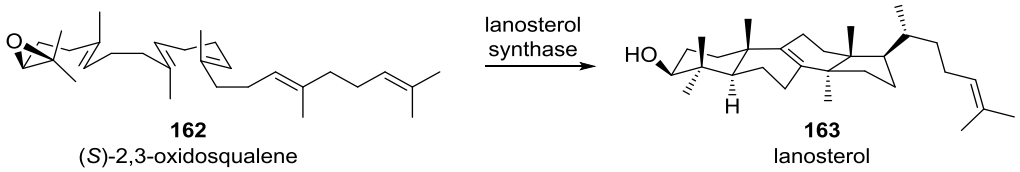
1st transformation	2nd transformation	…	nth transformation
cationic	cationic	…	cationic
anionic	anionic	…	anionic
radical	radical	…	radical
pericyclic	pericyclic	…	pericyclic
photochemical	photochemical	…	photochemical
transition metal induced	transition metal induced	…	transition metal induced
oxidative/reductive	oxidative/reductive	…	oxidative/reductive
enzymatic	enzymatic	…	enzymatic

Table 1: Classification of domino reactions by Tietze.

The terms tandem and cascade reaction were also introduced in the literature,[108,109] but they do not adequately describe the inherent characteristics of a domino reaction. A tandem reaction occurs in a substrate with several functionalities at different sites in a not necessarily time-resolved manner. The notion cascade should also be avoided, since it does not imply the picture of bond-formations that are based on functionalities arising from the previous step. Additionally, it is already used for photochemical or biochemical reaction cascades.

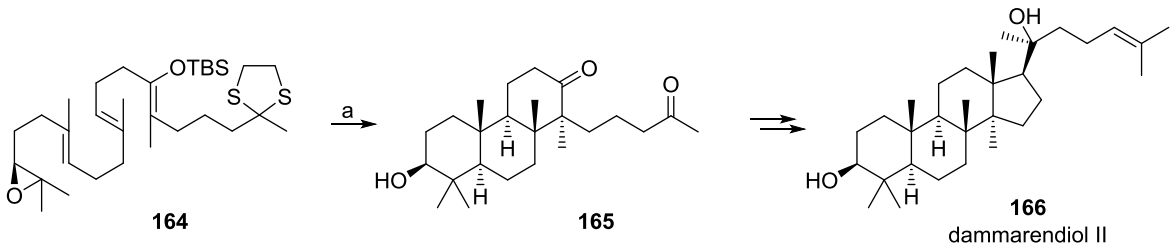
From a synthetic point of view, domino reactions normally exhibit good yields and high chemo-, regio- and stereoselectivities. Their usefulness can be attributed to the number of the created bonds and the significant increase in complexity of the reaction products. In fact, the domino concept may run even deeper as it paves the way for novel reaction profiles and allows access to chemical entities that are otherwise difficult to prepare. Since the domino approach omits the isolation of the reaction intermediates, tedious work-ups and purifications can be reduced to a minimum, thus reducing the amount of chemicals, waste and energy. The shortened production time and the less labor-intensive syntheses of compounds render domino reactions also well suited to industry.[110]

The domino approach is not an artificial concept; on the contrary, Nature provides numerous examples of domino reactions in the biosynthesis of alkaloids, terpenes and steroids. An intriguing example represents the biosynthesis of lanosterol (**163**) from (*S*)-2,3-oxidosqualene (**162**) comprising the formation of four new bonds and six stereogenic centers (Scheme 27).[111,112]



Scheme 27: Enzymatic cyclization of (*S*)-2,3-oxidosqualene (**162**) to lanosterol (**163**).

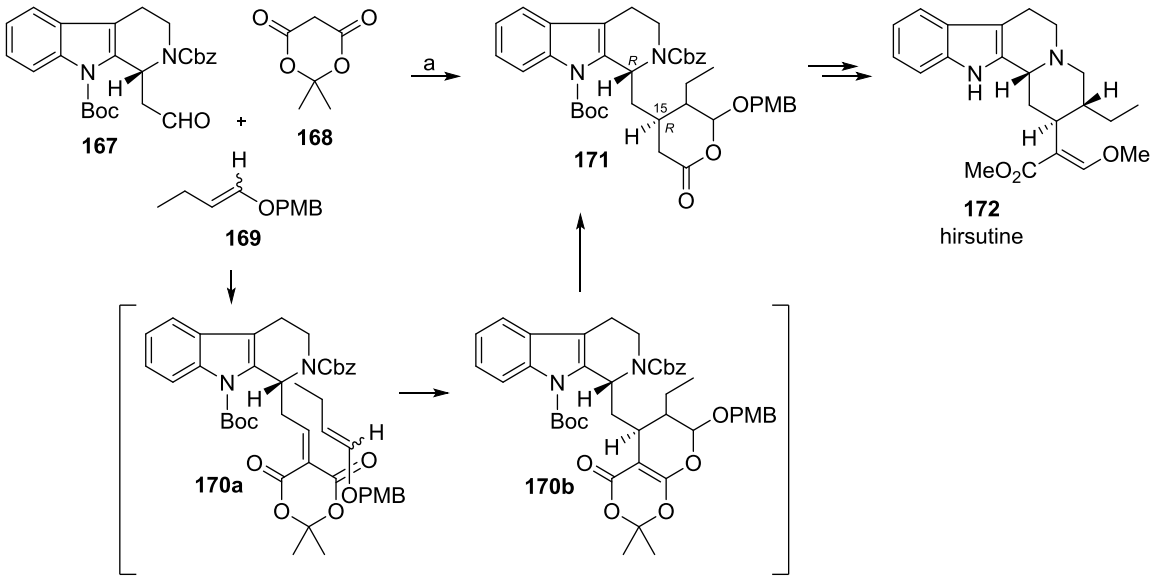
Attempts to emulate the reactivity of the lanosterol synthase by means of synthetic chemistry culminated in the biomimetic total synthesis of the antiviral drug dammarendiol II (**166**) by Corey *et al*. (Scheme 28).[113] A Lewis-acid initiated domino epoxide-ring-opening/ cyclotrimerization of acyclic epoxy triene **164**, a cationic-cationic-cationic transformation according to Tietze's classification, was followed by desilylation and thioacetal hydrolysis to provide diketone **165** in 42% yield over 3 steps. Intermediate **165** was further elaborated into **166** in 5 more steps involving an aldol reaction to form the cyclopentane ring.



Scheme 28: Domino epoxide-ring-opening/cyclotimerization reaction in the biomimetic total synthesis of dammarendiol II (**166**) by Corey *et al*.: a) 1. $MeAlCl_2$, CH_2Cl_2, –95 °C, 10 min; 2. aq. HF (cat.), MeCN, RT, 45 min; 3. $PhI(TFA)_2$, $MeOH/H_2O/i$PrOH, 0 °C, 45 min, 42% (3 steps).

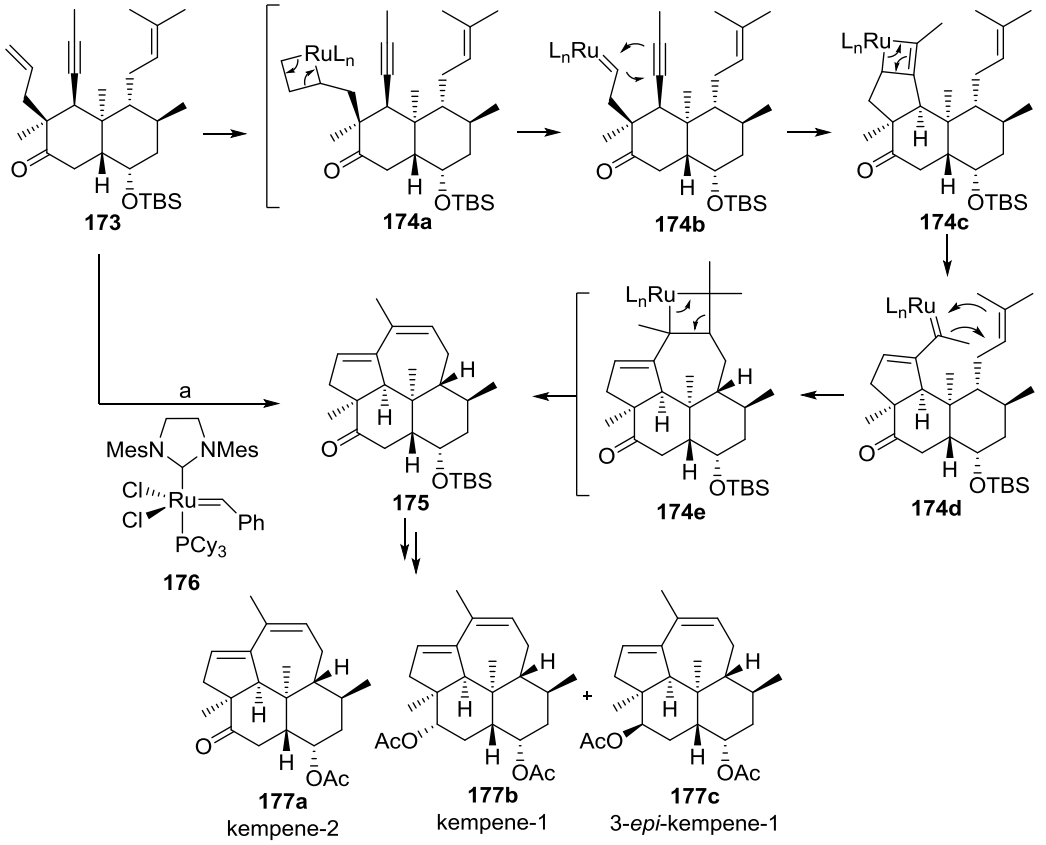
Various domino reactions were developed by Tietze *et al*., such as the domino Pictet-Spengler/ene reaction,[114] the domino amidation/*spiro*-cyclization/electrophilic aromatic substitution reaction[115] or the domino Knoevenagel/hetero-Diels-Alder reaction.[116]

The latter was used in the enantioselective total synthesis of the active anti-influenza A virus indole alkaloide hirsutine (**172**) (Scheme 29).[116c] Condensation of enantiopure β-carboline **167** with Meldrum's acid (**168**) and 4-methoxybenzyl butenyl ether (**169**) (*E*/*Z* = 1:1) gave rise to key intermediate **171** 84% yield and excellent diastereoselectivity of > 20:1. The domino reaction was proposed to proceed by a Knoevenagel condensation between aldehyde **167** and Meldrum's acid (**168**) in the presence of ethylenediamine diacetate (EDDA). The resulting 1,3-oxabutadiene **170a** then underwent a hetero-Diels-Alder reaction with enol ether **169** followed by decarboxylation and displacement of acetone to give stable lactone **171**.



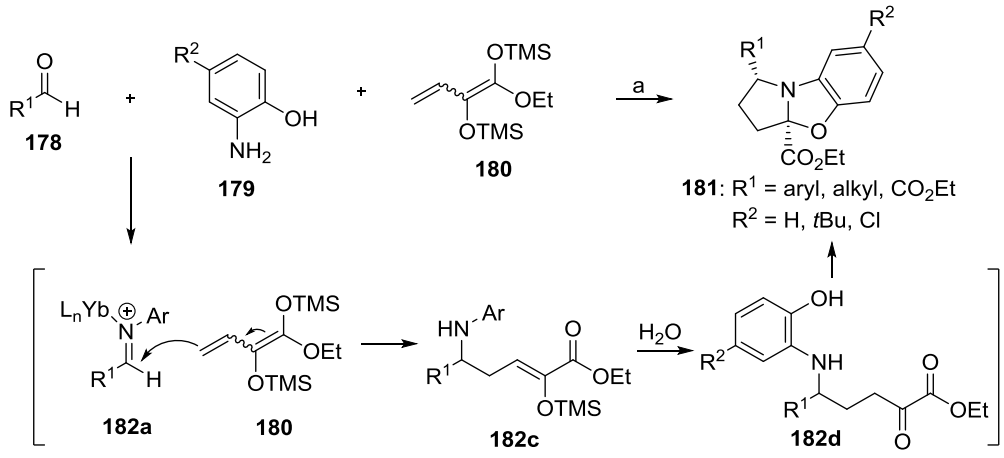
Scheme 29: Domino Knoevenagel/hetero-Diels-Alder reaction in the enantioselective total synthesis of hirsutine (**172**) by Tietze *et al*.: a) EDDA, benzene, sonification, 90%.

In 2011, Metz *et al*. reported the first enantioselective total syntheses of the structurally intriguing diterpenes kempene-2 (**177a**), kempene-1 (**177b**) and 3-*epi*-kempene-1 (**177c**) using a domino reaction as the key step (Scheme 30).[117a] Until then only one racemic synthesis of kempene-2 (**177a**) was accomplished by Dauben *et al*., the final steps of this route, however, were plagued by low yields.[117b] For this reason, Metz opted for a late-stage domino enyne metathesis reaction to assemble the tetracyclic scaffold. The ring-closing metathesis of dienyne **173** was efficiently catalyzed by the Hoveyda-Grubbs catalyst (**176**) in refluxing CH_2Cl_2 to provide **175** in excellent 92% yield. Compared to the stepwise synthesis of **177a**, the domino approach significantly improved the overall yield from 0.04% to 3.2%.



Scheme 30: Domino enyne metathesis reaction in the enantioselective total synthesis of kempene-2 (**177a**), kempene-1 (**177b**) and 3-*epi*-kempene-1 (**177c**) by Metz *et al.*: **176** (5 mol%), CH_2Cl_2, reflux, 3 h, 92%.

Domino reactions are particular attractive for the rapid generation of complex heterocycles. In 2012, Schneider *et al*. reported an elegant domino vinylogous Mannich/cyclocondensation reaction to furnish pyrrolobenzoxazoles in high yield and excellent diastereoselectivity (Scheme 31).[118]

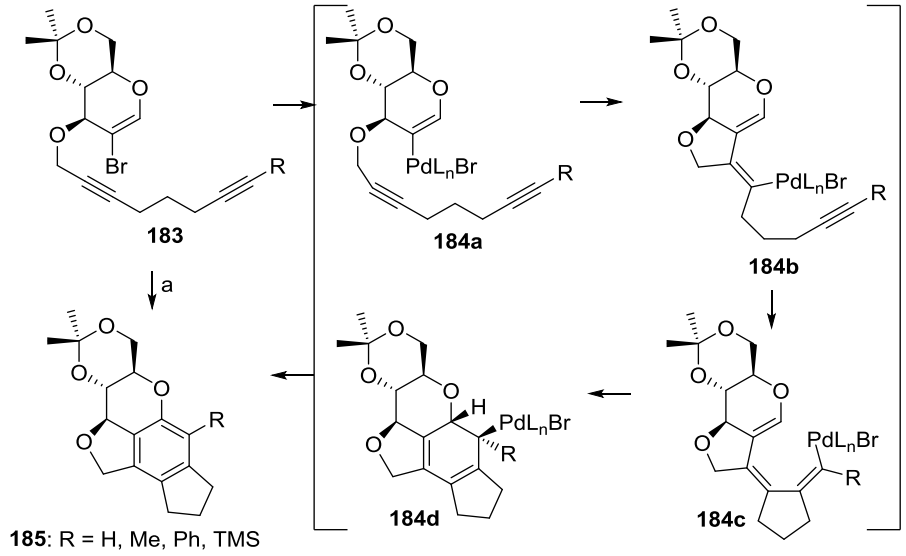


Scheme 31: Domino vinylogous Mannich/cyclocondensation reaction for the diastereoselective synthesis of pyrrolobenzoxazoles **181** by Scheider *et al.*: a) $Yb(OTf)_3$ (20 mol%), $MeCN/H_2O$ (9:1), RT, 1–4 h, 56–87%.

The three-component reaction of aliphatic, aromatic or unsaturated aldehydes **178** with 2-aminophenols **179** and bissilyldienolate **180** in the presence of catalytic amounts of $Yb(OTf)_3$ in a $MeCN/H_2O$ mixutre provided *N*,*O*-acetals **181**. The reaction commences with the condensation of aldehydes **178** and 2-aminophenols **179** to form imines **182a**. The latter undergo a vinylogous Mannich reaction with **180** followed by hydrolytic cleavage to provide highly reactive α-keto esters **182d**. The domino sequence is completed by a cyclocondensation of **182d** furnishing *N*,*O*-acetals **181** as single diastereomers. By employing a chiral scandium catalyst, the authers were also able to access **181** in up to 83% *ee*.

In 2011, Werz *et al*. used a domino approach for the synthesis of highly substituted chromanes and isochromanes.[119]

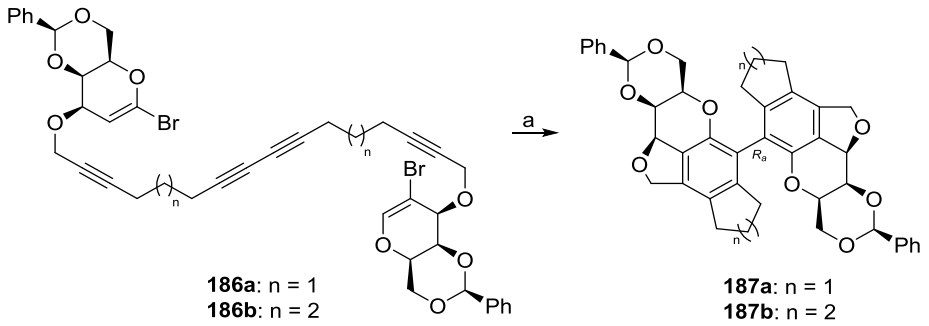
In the presence of a palladium source and an amine base, the 2-bromoglycals **183** underwent two consecutive carbopalladation steps followed by an electrocyclic ring closure and an aromatization reaction (Scheme 32). The domino sequence provided chromanes **185** with a variety of alkynyl substituents in excellent yields of up to 100%.



Scheme 32: Domino carbopalladation/carbopalladation/electrocyclic ring closure/aromatization for the synthesis of highly substituted chromanes **185** by Werz *et al*.: $Pd(PPh_3)_4$ (10 mol%),*i*Pr_2NH, DMF/MeCN/NMP (8:8:1), 120 °C, mw, 30 min, 70–100%.

Moreover, Werz *et al*. extended this process to C_2 symmetrical precursors **186**, where two domino reactions take place at both sides of the molecule (Scheme 33). With the formation of six C-C bonds, six rings and one chiral axis, the devised tandem-domino sequence enabled the

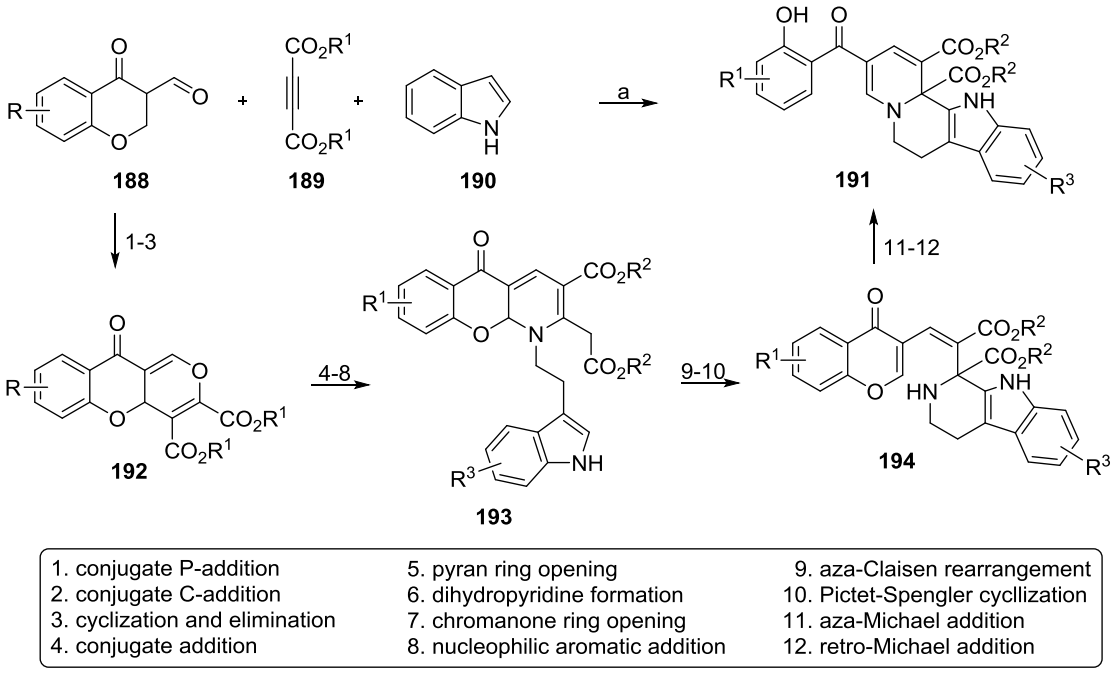
diastereoselective synthesis of sterically encumbered biphenyls **187** in excellent yields of up to 66%.



Scheme 33: Tandem-domino reaction for the synthesis of chiral biphenyls by Werz *et al.*: a) $Pd(PPh_3)_4$ (20 mol%), H*t*Bu_3PBF_4 (40 mol%), *i*Pr_2NH, DMF/MeCN/NMP (8:8:1), 120 °C, 2 h, for **187a**: 66%; for **187b**: 60%.

Apart from its indisputable relevance in organic synthesis, the domino concept has also the potential to foster research in neighboring fields.

In the context of drug discovery for example, domino reactions have proven to be powerful tools for the rapid generation of compound libraries with high levels of structural diversity and complexity. In 2012, the groups of Kumar and Waldmann developed a domino reaction for the synthesis of a library of complex indoloquinolizines (**191**) (Scheme 34).[120]



Scheme 34: 12-step domino sequence in the library synthesis of indoloquinolizines **191** by Waldmann *et al.*: PPh_3 (60 mol%), CSA, 5-30 min, 20-88%.

The compounds featured interesting biological activity such as the induction of delayed mitosis and chromosomal congressional defects and were therefore envisioned as potential anticancer agents. The domino reaction of highly substituted 3-formylchromanones **188**, acetylene dicarboxylates **189** and tryptamines **190** in the presence of triphenylphosphine and acid proceeded within 5 to 30 min and provided a 26-membered compound collection of indoloquinolizines in up to 88% yield. Mechanistic studies revealed that the domino reaction consists of 12 consecutive transformations, thus representing the longest domino sequence known to date.

B PLANNING OF THE THESIS

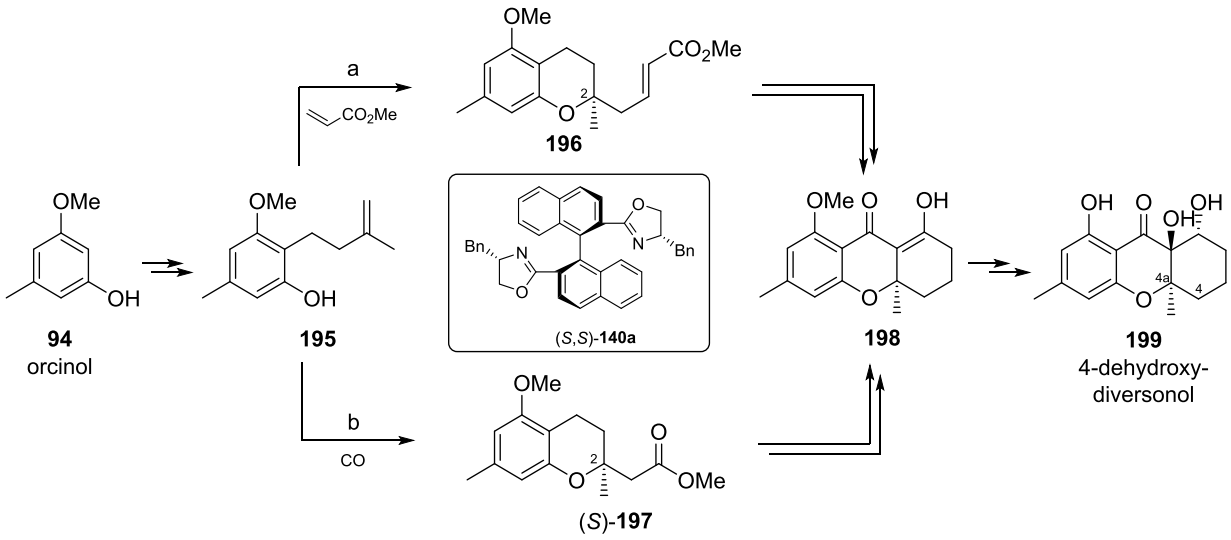
1 State of Research at the Beginning of the Thesis

The development of novel synthetic methods is of paramount importance for academia and industry. In particular, strategies that address efficiency and practicality as well as the environmental impact of a chemical process are nowadays in the focus of organic chemistry. The domino concept introduced by Tietze is an approach that meets the increasing requirements for more efficient and environmentally benign synthesis.[107,108] Domino reactions allow the formation of several bonds under identical reaction conditions in a time-resolved manner, thereby significantly increasing the complexity of the targeted molecule. Typical features are good yields and high chemo-, regio- and stereoselectivties. From an environmental and economic point of view, the domino concept reduces the amount of energy expenditures, chemicals and waste streams as well as the employment of labor and time.

Two examples from the Tietze research group of such domino reactions are the domino Wacker/Heck and the domino Wacker/carbonylation/methoxylation reaction.[121] These reactions enable an efficient access to the chiral chromane core endowed with a quaternary stereocenter at C-2 (numbering as in **196** and (*S*)-**197**, Scheme 35) in high yields and *ee*-values. Both reactions were successfully applied in the total synthesis of vitamin E, a member of the vitamin E family. The latter reaction was also used in the synthesis of dioxins and oxazins.[121f,122]

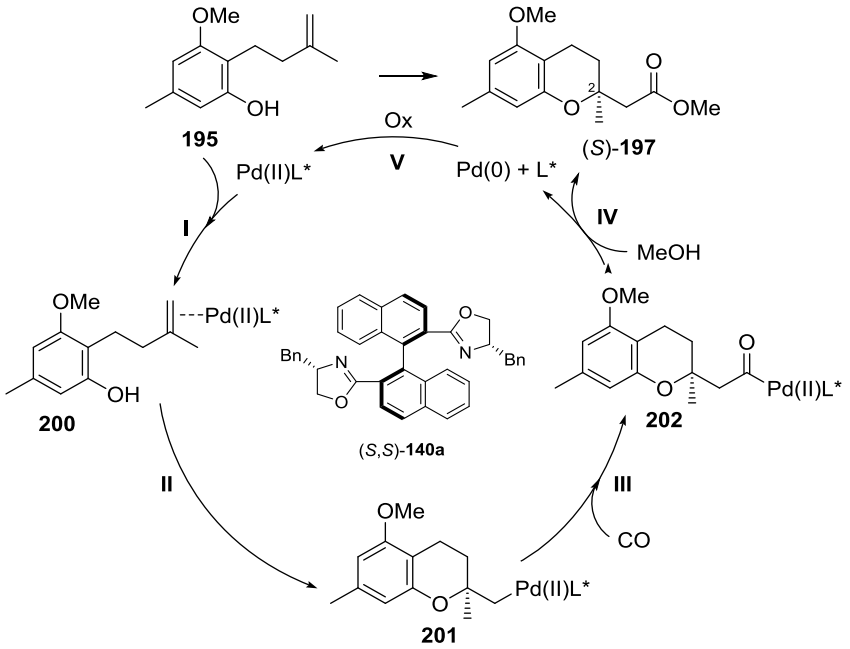
An interesting class of natural products that also contain a chromane scaffold are the tetrahydroxanthenones.[30] They exhibit a broad range of promising biological activities including, antiviral, antimicrobial and cytotoxic properties. In order to further investigate their mode of action and structure-activity relationships, ample amounts of these compounds are required and a general synthetic access to the tetrahydroxanthenone scaffold is therefore highly desirable.

The growing interest in these compounds by the synthetic community led to several racemic syntheses of tetrahydroxanthenones.[44-46,50] Bearing the importance to produce enantiopure drugs in mind, Tietze *et al*. presented the first enantioselective approach to the tetrahydroxanthenone core employing a domino Wacker/Heck and a domino Wacker/ carbonylation/methoxylation reaction (Scheme 33).[121] The domino strategy was applied by Tietze *et al*. in the synthesis of 4-dehydroxy-diversonol (**199**).[121e]



Scheme 35: Domino Wacker/Heck (a) and domino Wacker/carbonylation/methoxylation reaction (b) for the enantioselective synthesis of 4-dehydroxy-diversonol (**199**): a) $Pd(TFA)_2$ (10 mol%), Bn-BOXAX (*S*,*S*)-**140a** (40 mol%), methyl acrylate, *p*-benzoquinone, 1,2-dichloroethane, RT, 7 d, 55%, 88% *ee*; b) $Pd(TFA)_2$ (3 mol%), Bn-BOXAX (*S*,*S*)-**140a** (12 mol%), CO, *p*-benzoquinone, RT, 15 h, 80%, 96% *ee*.

Domino precursor **195** was synthesized in six steps from orcinol (**94**). It reacted in the presence of $Pd(TFA)_2$, chiral Bn-BOXAX ligand (*S*,*S*)-**140a**, the oxidant *p*-benzoquinone and either with (a) methyl acrylate or (b) CO. A postulated mechanism of the domino Wacker/carbonylation/ methoxylation reaction is depicted in Scheme 36.

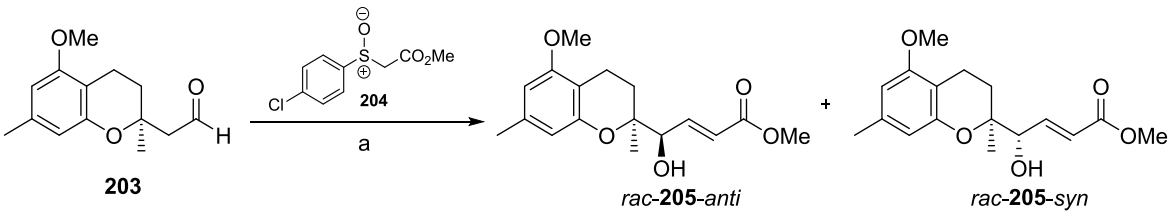


Scheme 36: Postulated mechanism of the domino Wacker/carbonylation/methoxylation reaction: I) enantiofacial coordination; II) oxypalladation; III) CO-insertion; IV) reductive elimination; V) reoxidation with *p*-benzoquinone.

The mechanism commences with the enantiofacial coordination of alkenyl phenol **195** by the chiral palladium-ligand complex of $Pd(TFA)_2$ and chiral Bn-BOXAX ligand (*S*,*S*)-**140a** (**I**). In the next step, the π-Pd-olefin species **200** is attacked by the phenolic hydroxyl group in an oxypalladation reaction (**II**). Mechanistic studies by Hayashi *et al*. revealed that under chloride-free conditions the cyclization proceeds *via* a *syn*-oxypalladation pathway.[123] With no hydrogen atom present in β-position, the resulting σ-Pd-alkyl species **201** is unable to undergo reductive elimination and instead inserts into carbon monoxide (**III**). Subsequent alcoholysis of the palladium-acyl intermediate **202** yields the domino product (*S*)-**197** and releases the chiral BOXAX ligand and Pd(0) (**IV**). Finally, oxidation of Pd(0) with *p*-benzoquinone regenerates the active Pd(II)-ligand species (**V**).

The domino products (*S*)-**197** and **196** were further elaborated into tetrahydroxanthenone **198** including a benzylic oxidation and a Ti-mediated intramolecular acylation. Diastereoselective functionalization of the tricyclic framework and cleavage of the phenolic methyl ether completed the synthesis of 4-dehydroxy-diversonol (**199**).

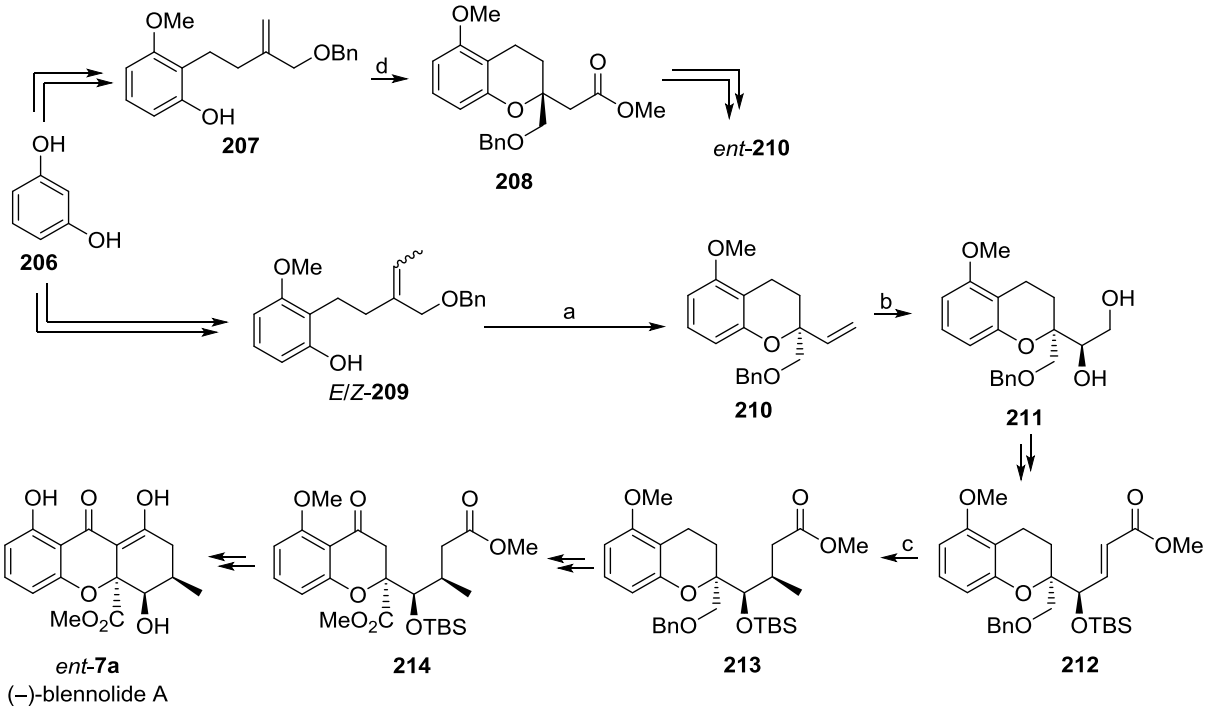
The introduction of the hydroxyl group at C-4 (numbering as in **199**) by a Rubottom-type oxidation of methyl ester (*S*)-**197** or allylic oxidation of the α,β-unsaturated ester **196** were not successful.[124] In a revised strategy a hydroxylating Knoevenagel reaction of the corresponding aldehyde indeed provided the hydroxylation at C-4. However, the steric integrity of the quaternary stereogenic center at C-4a (numbering as in **199**) was lost in this process. This result was explained assuming an opening of the chromane ring-system by a retro-1,6-Michael reaction (Scheme 37).[125]



Scheme 37: Hydroxylating Knoevenagel reaction of aldehyde **203** with concomitant epimerization of the stereogenic center at C-4a: piperidine, MeCN, RT, 6 h, 94%, d.r. = 1:1 (*anti*/*syn*).

Due to these unexpected difficulties, the introduction of the hydroxyl group at C-4 was envisaged by a Sharpless dihydroxylation of an appropriate vinyl chromane.

This strategy was successfully applied in the first total synthesis of (–)-blennolide A (*ent*-**7a**) by Tietze *et al*. (Scheme 38).[126]



Scheme 38: Total synthesis of (–)-blennolide A (*ent*-**7a**) using an enantioselective Wacker reaction by Tietze *et al.*: a) *E*/*Z*-**209** (*E*/*Z* = 1:1.7), $Pd(TFA)_2$ (10 mol%), Bn-BOXAX (*S*,*S*)-**140a** (10 mol%), *p*-benzoquinone, MeOH, 60 °C, 24 h, 82%, 85% *ee*; b) AD-mix-α, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 4 d, 95%, *anti*/*syn* = 2.4:1; c) $CuBr{\cdot}Me_2S$, MeLi, TMSCl, THF, –35 °C, 1 h; 91%; the enantiomeric vinyl chromane *ent*-**210** was accessible by a domino Wacker/carbonylation/ methoxylation reaction: d) $Pd(TFA)_2$ (5 mol%), Bn-BOXAX (*S*,*S*)-**140a** (20 mol%), CO, *p*-benzoquinone, MeOH, RT, 22 h, 74%, 96% *ee*.

The alkenyl phenols *E*/*Z*-**209** and **207** were accessed from resorcinol in six steps. An enantioselective Wacker reaction converted *E*/*Z*-**209** directly to vinyl chromane **210**. The enantiomer *ent*-**210** was also accessible by a domino Wacker/carbonylation/methoxylation reaction of alkenyl phenol **207** and subsequent elimination of the domino product **208**. For the introduction of the hydroxyl group at C-4 a Sharpless dihydroxylation of vinyl chromane **210** was used. Diol **211**, displaying the *anti*-configuration present in the natural product, was further converted to α,β-unsaturated ester **212** which underwent a diastereoselective conjugate addition. It followed a hydrogenolysis of the benzyl protecting group and oxidation of the resulting primary alcohol to the corresponding methyl ester. A benzylic oxidation to the chromanone **214** set the stage for an intramolecular acylation. Global deprotection of the resulting tetrahydroxanthenone furnished *ent*-**7a**.

2 Objectives

The general objective of this thesis is to illustrate the synthetic utility of the domino concept in the complex setting of natural product synthesis. With the domino Wacker/carbonylation/ methoxylation reaction in hand, a concise method for the formation of chiral chromanes with the concomitant introduction of the side-chain is available.

In order to achieve high catalytic activity and *ee*-values in this process, several (*S*,*S*)- and (*R*,*R*)-BOXAX ligands with varying substituents at the C-4 position of the oxazoline ring should be synthezised from 1-bromo-2-methylnaphtahline (**217**) according to literature procedures (Figure 15).

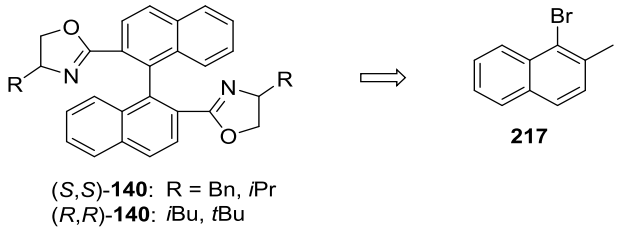


Figure 15: Synthesis of (*S*,*S*)- and (*R*,*R*)-BOXAX ligands **140**.

The first project of this PhD thesis deals with the completion of the enantioselective total synthesis of (–)-diversonol (*ent*-**10**). Due to the difficulties to introduce the hydroxyl group at C-4, it was planned to install this group by a Sharpless dihydroxylation of vinyl chromane (*S*)-**101** (Figure 16). This key compound should be directly accessible by a Wacker oxidation of the alkenyl phenols *E*/*Z*-**225** or by a domino Wacker/carbonylation/methoxylation reaction of **195** and subsequent elimination of (*S*)-**197**. The synthesis should furthermore involve a benzylic oxidation that would set the stage for an intramolecular acylation to yield the tetrahydroxanthenone core. Functionalization of the tricyclic framework should provide (–)-diversonol (*ent*-**10**).

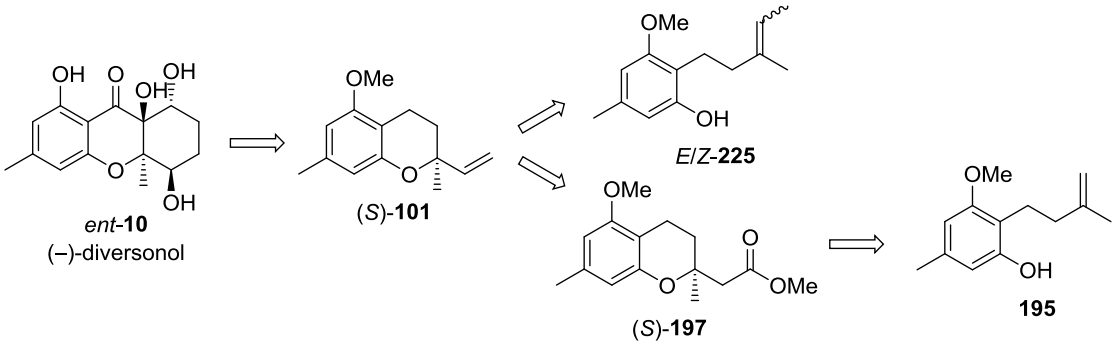


Figure 16: Key compound (*S*)-**101** accessible through a Wacker oxidation of *E*/*Z*-**225** or by a domino Wacker/carbonylation/methoxylation reaction of **195** and subsequent elimination.

In the second part of the thesis, the domino process will be used for a formal synthesis of the antifungal siccanin (**25**) (Figure 17). The strategy to **25** should intercept the enantioselective approach reported by Trost *et al*., in which diol **105** represented an advanced intermediate.[55] An aldol reaction between aldehyde **266** and enol ether **265** was intended as the key step of the synthesis. Functional group transformations should furnish **105**.

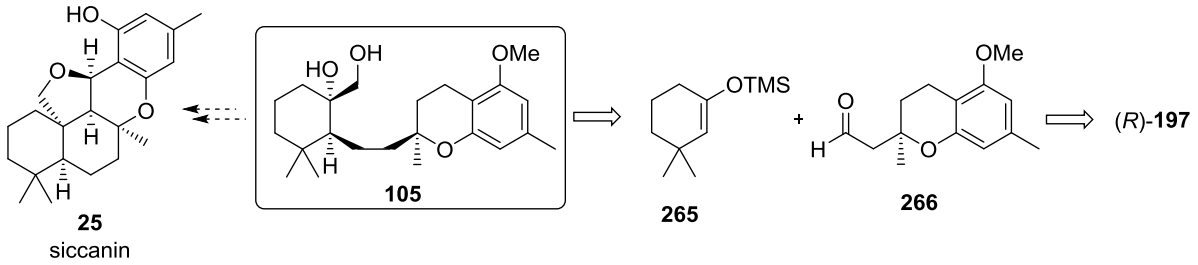


Figure 17: Formal synthesis of siccanin (**25**). Key compound **105** was envisioned to arise from aldehyde **266** and enol ether **265**.

The third part deals with the enantioselective total syntheses of (–)-blennolide C (*ent*-**7c**) and (–)-gonytolide C (*ent*-**7c**). The approach to these compounds would follow the general strategy towards tetrahydroxanthenones and γ-lactonyl chromanones developed by the Tietze research group (Figure 18).[126,127]

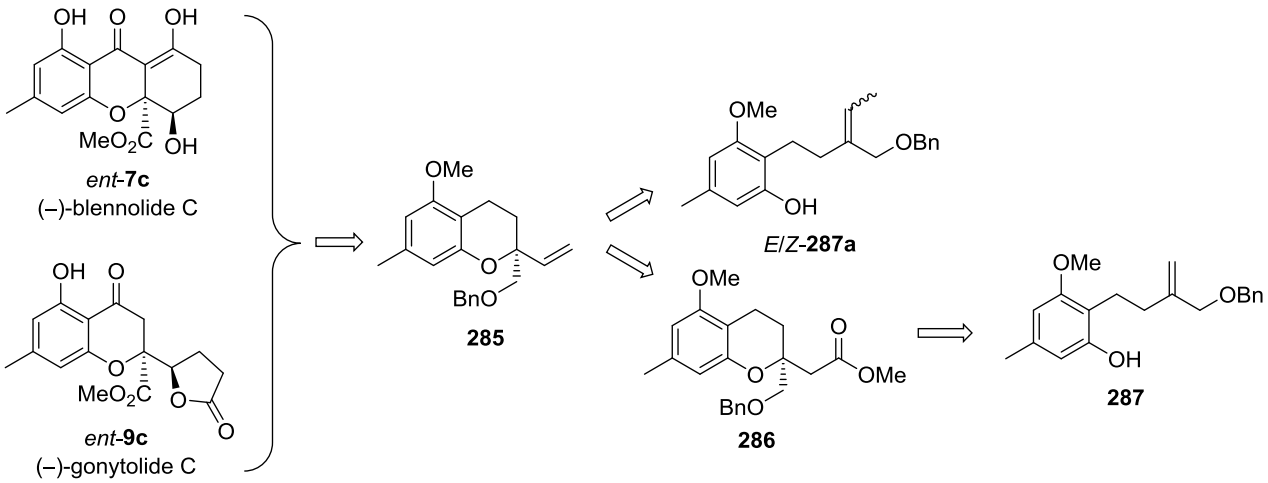


Figure 18: Synthesis of (–)-blennolide C (*ent*-**7c**) and (–)-gonytolide C (*ent*-**9c**). Vinyl chromane **285** should be accessible either by Wacker oxidation of **287a** or by a domino Wacker/carbonylation/methoxylation reaction of **287**.

In conclusion, this leads to the following specific objectives:

1) Synthesis of (*S*,*S*)- and (*R*,*R*)-BOXAX ligands with varying substituents at the C-4 position of the oxazoline ring.

2) Enantioselective total synthesis of (–)-diversonol (*ent*-**10**).
   a) Synthesis of vinyl chromane (*S*)-**101** by a Wacker oxidation of *E*-**225** and *Z*-**225** and/or by a domino Wacker/carbonylation/methoxylation reaction of **195**.
   b) Sharpless dihydroxylation of vinyl chromane (*S*)-**101**.
   c) Synthesis of the tetrahydroxanthenone framework and its diastereoselective functionalization.

3) Formal total synthesis of siccanin (**25**).
   a) Synthesis of aldehyde **266** by a domino Wacker/carbonylation/methoxylation reaction of **195** and reduction.
   b) Aldol reaction of **265** and **266**.
   c) Functionalization furnishing diol **105**.

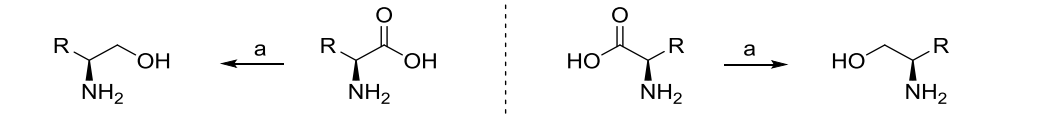
4) Enantioselective total synthesis of (–)-blennolide C (*ent*-**7c**) and (–)-gonytolide C (*ent*-**9c**).
   a) Synthesis of vinyl chromane **285** either by a Wacker oxidation of **287a** and/or by a domino Wacker/carbonylation/methoxylation reaction of **287**.
   b) Sharpless dihydroxylation of vinyl chromane **285**.
   c) Elaboration of **285** into *ent*-**7c** and *ent*-**9c**.

C RESULTS

1 Synthesis of the BOXAX Ligands

For the enantioselective Wacker and domino Wacker/carbonylation/methoxylation reactions utilized throughout this project, several chiral 2,2'-bis(oxazolin-2-yl)-1,1'-binaphthyl (BOXAX) ligands were synthesized according to literature procedures by Hayashi and Meyers and an optimized protocol by Tietze.[128,129,130] The (*S*,*S*)-BOXAX ligands substituted with benzyl-, *iso*-propyl, *iso*-butyl- and *tert*-butyl-groups at the C-4 position of the oxazoline ring (Scheme 39) were synthesized as well as the enantiomeric (*R*,*R*)-BOXAX ligands endowed with a benzyl- and an *iso*-propyl backbone.

The syntheses commenced with the reduction of the respective L-amino acids (*S*)-phenylalanine (*S*)-valine, (*S*)-leucine and (*S*)-*tert*-leucine (*S*)-**215a**-**d** to their corresponding amino alcohols (*S*)-**216a**-**d** using lithium aluminum hydride in refluxing THF, with yields of 70%, 75%, 66% and 75% respectively (Scheme 39).[131] Similarly, the reduction of the D-amino acids (*R*)-phenylalanine (*R*)-**215a** and (*R*)-valine (*R*)-**215b** afforded enantiomers (*R*)-**216a** and (*R*)-**216b** in 62% and 84% yield.

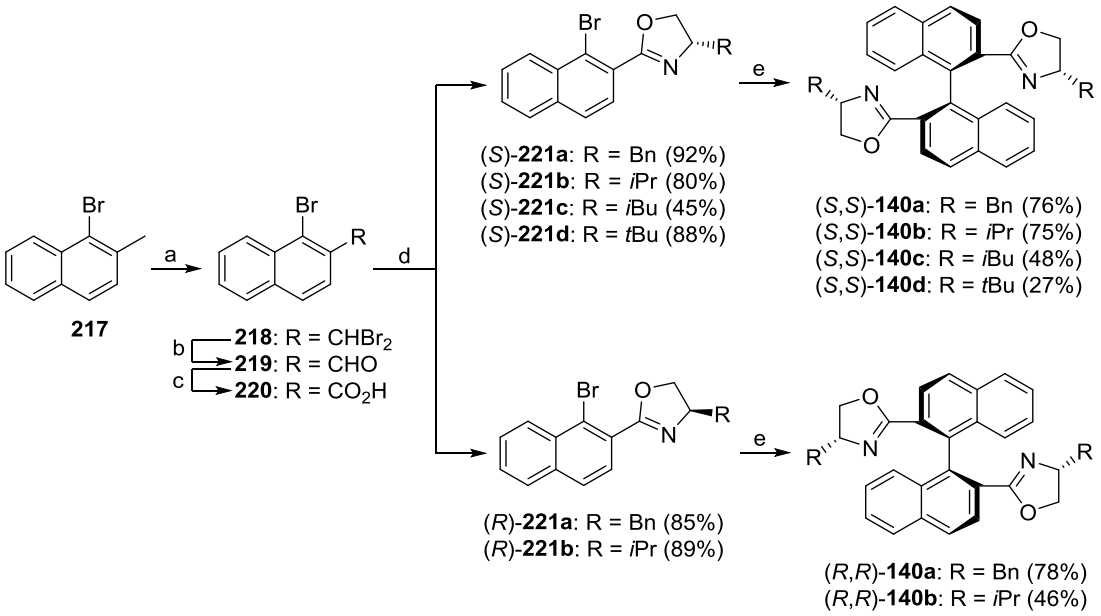


Scheme 39: Synthesis of the amino alcohols **216a**-**d**: a) $LiAlH_4$, THF, reflux, 16 h.

Commercially available 1-bromo-2-methylnaphthalene (**217**) was refluxed in the presence of excess *N*-bromosuccinimide and catalytic amounts of the initiator azobisisobutyronitrile in CCl_4 furnishing 1-bromo-2,2-dibromomethyl-naphthalene (**218**) in 87% yield (Scheme 40).[132] The dibromomethyl compound was subsequently converted to carbaldehyde **219** upon reflux in an aqueous formic acid solution, providing **219** in 87% yield.[133] This was followed by a Pinnick-oxidation with sodium chlorite in the presence of the scavenger 2-methyl-2-butene in a buffered aq. solution of *t*BuOH to give carboxylic acid **220** in 89% yield.[134]

With amino alcohols (*S*)-**216a**-**d** and (*R*)-**216a**-**b** and the carboxylic acid **220** in hand, a 4-step sequence then gave rise to the oxazoline core.[135] After *in situ* activation of the acid **220** with oxalyl chloride and catalytic amounts of DMF, the resultant acid chloride was reacted with the respective amino alcohols and triethylamine to yield the corresponding amides. Mesylation of

the primary hydroxyl group followed by a base-mediated intramolecular S_N-reaction afforded the (*S*)-oxazolines (*S*)-**221a-d** in 92%, 80%, 45% and 88% yield over four steps, respectively. The (*R*)-oxazolines (*R*)-**221a** and (*R*)-**221b** were obtained in a similar manner in 85% and 89% yield. No purification of the intermediates was required, rendering this reaction sequence remarkable in terms of overall yield and operational simplicity.



Scheme 40: Synthesis of the (*S*,*S*)- and (*R*,*R*)-BOXAX ligands: a) NBS (3.5 eq.), AIBN (10 mol%), CCl_4, reflux, 36 h, 87%; b) aq. HCOOH (88%), reflux, 20 h, 87%; c) $NaClO_2$ (9.0 eq.), 2-methyl-2-butene (7.0 eq.), NaH_2PO_4 (7.0 eq.), *t*BuOH/H_2O, RT, 19 h, 89%; d) 1. $(COCl)_2$, DMF (cat.), toluene, RT; 2. L-amino alcohols (*S*)-**216a-d** or D-amino alcohols (*R*)-**216a** or (*R*)-**216b**, NEt_3, CH_2Cl_2, RT; 3. MsCl, NEt_3, CH_2Cl_2, RT; 4. KOH, MeOH, RT; e) Cu, pyridine, reflux. For the equivalents and reaction times of d) and e) see Experimental Section.

A highly diastereoselective copper-mediated Ullmann reaction finally provided the desired biaryl ligands.[129b] To ensure good reproducibility and short reaction times, it was important to wash the copper powder consecutively with acetic acid, methanol and diethyl ether and dry it under high vacuum prior to use. Subjecting the coupling partners to stoichiometric amounts of the preactivated copper in freshly distilled, refluxing pyridine yielded the (*S*,*S*)-BOXAX ligands (*S*,*S*)-**140a-d** in 76%, 75%, 48% and 27%, respectively. The enantiomers (*R*,*R*)-**140a** and (*R*,*R*)-**140b** were synthesized in 78% and 46% yield, respectively.

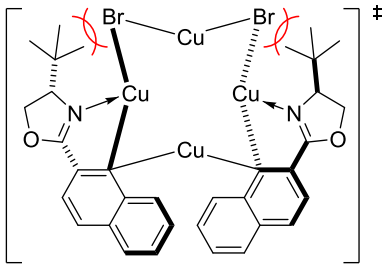


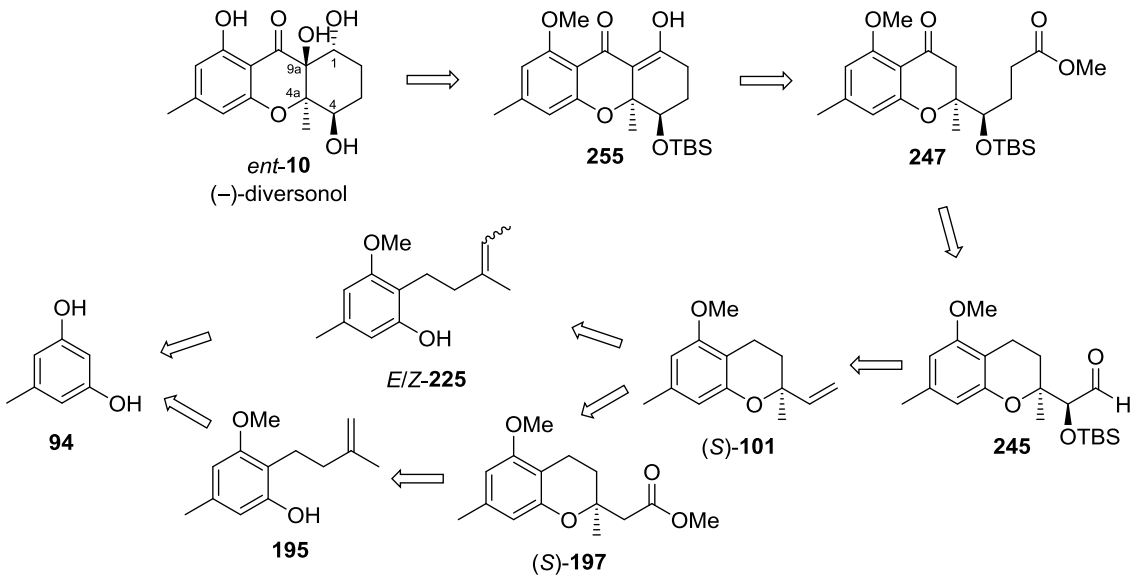
Figure 19: Transition state for the formation of the (*S*,*S*)-*t*Bu-BOXAX ligand proposed by M. B. Andrus.

Based on a model by M. B. Andrus for the formation of the (*S*,*S*)-*t*Bu-BOXAX ligand (Figure 19), the high level of diastereoselectivity in the Ullmann coupling can be explained with an 8-membered transition state comprising a diaryl-C_{ipso}-copper(I)-species and copper(I)bromide.[136] The configuration of the biaryl axis is proposed to arise from the minimization of steric repulsion between the oxazoline substituents and the bridging bromide ligands.

2 Enantioselective Total Synthesis of (–)-Diversonol

Central to the total synthesis of (–)-diversonol (*ent*-**10**) was the enantioselective formation of the quaternary stereocenter at C-4a (numbering as in *ent*-**10**, Scheme 41). Towards this goal, both an enantioselective Wacker oxidation and a domino Wacker/carbonylation/ methoxylation reaction were utilized to access key intermediate (*S*)-**101**. A second pivotal transformation was the diastereoselective hydroxylation of vinyl chromane (*S*)-**101** to set up the hydroxyl group at C-4, which was achieved using Sharpless chemistry.

2.1 Retrosynthetic analysis of (–)-diversonol (*ent*-10)



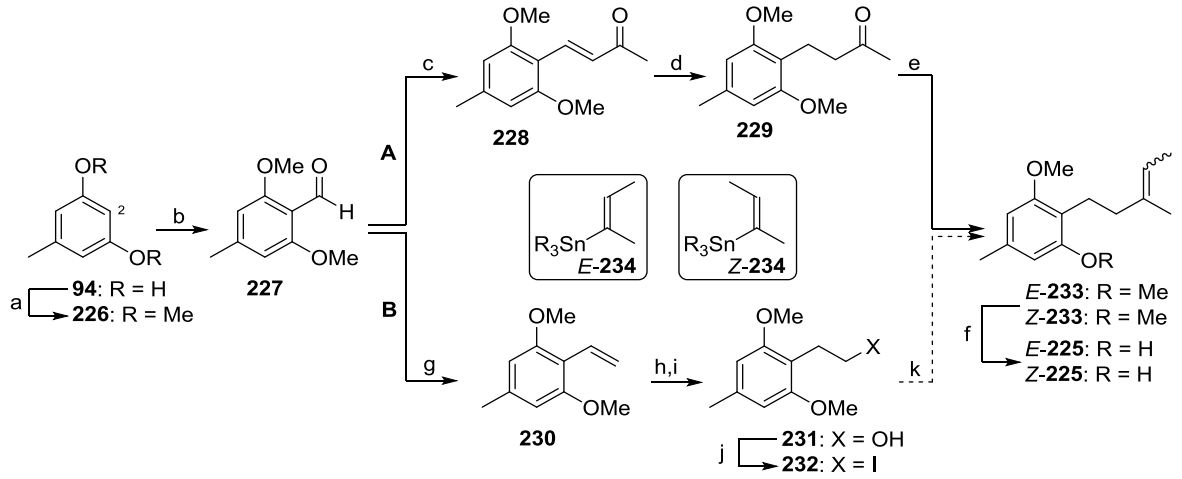
Scheme 41: Retrosynthetic analysis of (–)-diversonol (*ent*-**10**).

The retrosynthetic analysis of (–)-diversonol (*ent*-**10**) is outlined in Scheme 41. The 1,2-diol motif of *ent*-**10** can be formed by oxidation and subsequent reduction of the tetrahydroxanthenone core **255**, which in turn is accessible from methyl ester **247** by an intramolecular acylation. For the synthesis of **247**, a sequence comprising a Wittig/Horner reaction of aldehyde **245**, hydrogenation of the enone functionality and benzylic oxidation of the chromane was envisioned. Aldehyde **245** is accessable from vinyl chromane (*S*)-**101** by a Sharpless-dihydroxylation, a protection/deprotection sequence and oxidation. Vinyl chromane (*S*)-**101** can be traced back to the alkenyl phenols *E*/*Z*-**225** and **195**. The enantioselective formation of the chromane core was proposed to proceed by a Wacker oxidation of *E*/*Z*-**225** or by a domino Wacker/carbonylation/methoxylation reaction of **195**. The alkenyl phenols *E*/*Z*-**225** and **195** could be prepared from orcinol (**94**)

2.2 Enantioselective synthesis of vinyl chromane (*S*)-101

2.2.1 Synthesis and enantioselective Wacker oxidation of the alkenyl phenols *E*-225 and *Z*-225

The synthesis of the alkenyl phenols *E*-**225** and *Z*-**225** commenced with the methylation of commercially available orcinol (**94**) (Scheme 42).



Scheme 42: Synthesis of alkenyl phenols *E*-**225** and *Z*-**225**: a) Me_2SO_4 (2.3 eq.), K_2CO_3 (2.1 eq.), acetone, reflux, 23 h, 93%; b) *n*BuLi (1.2 eq.), TMEDA (2.0 eq.), Et_2O, 0 °C → reflux, 3 h, then DMF (3.0 eq.), 0 °C → RT, 2 h, 75%; A: c) 1 M NaOH, acetone/H_2O, RT, 3 h, then 1 M HCl, 81%; d) 1. H_2 (1 atm), Pd/C (3 mol%), EtOAc, RT, 3 h; 2. IBX (0.4 eq), CH_3CN, reflux, 1.5 h, 96% (2 steps); e) *n*BuLi (2.8 eq.), $CH_3CH_2PPh_3Br$ (3.0 eq.), THF, 0 °C → RT, 2.5 h, 90%, *E*/*Z* = 1:2.4; f) NaSEt (2.1 eq.), DMF, 120 °C, 20 h, 88%, *E*/*Z* = 1:2.4; B: g) *n*BuLi (2.2 eq.), CH_3PPh_3Br (2.0 eq.), THF, –78 °C → RT, 16 h, 94%; h) $RhCl(PPh_3)_3$ (2 mol%), $(Bpin)_2$ (4.0 eq), 50 °C, 20 h, 25%; i) 1 M NaOH (3.0 eq), H_2O_2 (15 eq.), THF, 50 °C, 1 h, 68%, j) PPh_3 (1.3 eq.), imidazole (1.4 eq.), I_2 (1.3 eq.), THF, RT, 4 h, 42%, (60% brsm); k) intended Stille coupling with vinyl stannanes *E*-**234** and *Z*-**234**.

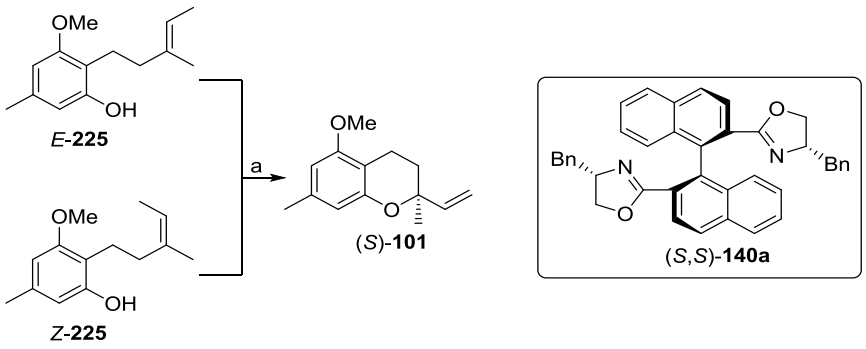
Refluxing **94** in acetone in the presence of dimethyl sulfate and potassium carbonate for 23 h gave dimethyl ether **226** in 93% yield.[137] Regioselective *ortho*-lithiation at C-2 (numbering as in **94**) with *n*BuLi and the deaggregating agent TMEDA in refluxing diethyl ether was followed by formylation of the phenyl anion with DMF, giving access to aldehyde **227** in 75%.[55] An aldol reaction using sodium hydroxide as base in acetone and acidic work-up led to the α,β-unsaturated ketone **228** in 81% yield. Hydrogenation of **228** with H_2 (1 atm) and 3 mol% of palladium on charcoal in EtOAc at ambient temperatures yielded the saturated ketone **229** alongside overreduced alcohol in a 4:1-ratio as determined by ^{1}H-NMR spectroscopy. Although the reaction products were readily separable by column chromatography, it proved to be more efficient to resubject the crude reaction mixture to

oxidation with IBX in refluxing MeCN to furnish ketone **229** in an excellent overall yield of 96%.

A Wittig reaction of ketone **229** with the ylide derived *in situ* from $CH_3CH_2PPh_3Br$ and *n*BuLi in THF provided olefins *E*-**233** and *Z*-**233** in 90% yield in a (*E*/*Z* = 1:2.4)-ratio. The *E*/*Z*-mixture was then subjected to mono-demethylation with NaSEt in DMF at 120 °C to furnish the Wacker precursors *E*-**225** and *Z*-**225** in a yield of 88% (*E*/*Z* = 1:2.4). All attempts to separate the two diastereomers by flash column chromatography on either standard or silver-doped silica gel were not successful. Fortunately, preparative HPLC on a chiral IA® phase provided small amounts of *E*-**225** and *Z*-**225**, whose double bond configuration was unambiguously assigned by NOE experiments.

To selectively access the diastereomers *E*-**225** and *Z*-**225**, a synthesis was devised based on a procedure by Trost *et al.*[55] A Wittig reaction of aldehyde **227** with the lithium ylide of CH_3PPh_3Br delivered styrene **230** in 94% yield, which was then hydroborated with bis(pinacolato)diboran $(Bpin)_2$ and Wilkinson's catalyst to afford the corresponding boronic ester in 25% yield. Oxidation and iodination gave alkyl iodide **232** in 29% yield over 2 steps. A Stille coupling with vinyl stannanes *E*-**234** and *Z*-**234**[138] was envisioned to selectively introduce the *E*- or *Z*-olefin moiety. Due to the low yield and limited amount of compound **232**, this route was not pursued any further.

With the *E*/*Z*-mixture of **225** and pure *E*-**225** and *Z*-**225** in hand, the stage was set for the pivotal enantioselective Wacker oxidation (Scheme 43). When the *E*/*Z*-mixture (*E*/*Z* = 1:2.4) was treated with catalytic amounts of $Pd(TFA)_2$ (10 mol%) and Bn-BOXAX ligand (*S*,*S*)-**140a** (20 mol%) in the presence of the reoxidant *p*-benzoquinone in MeOH at RT for 22 h, vinyl chromane (*S*)-**101** was obtained in 78% yield and 87% *ee*.

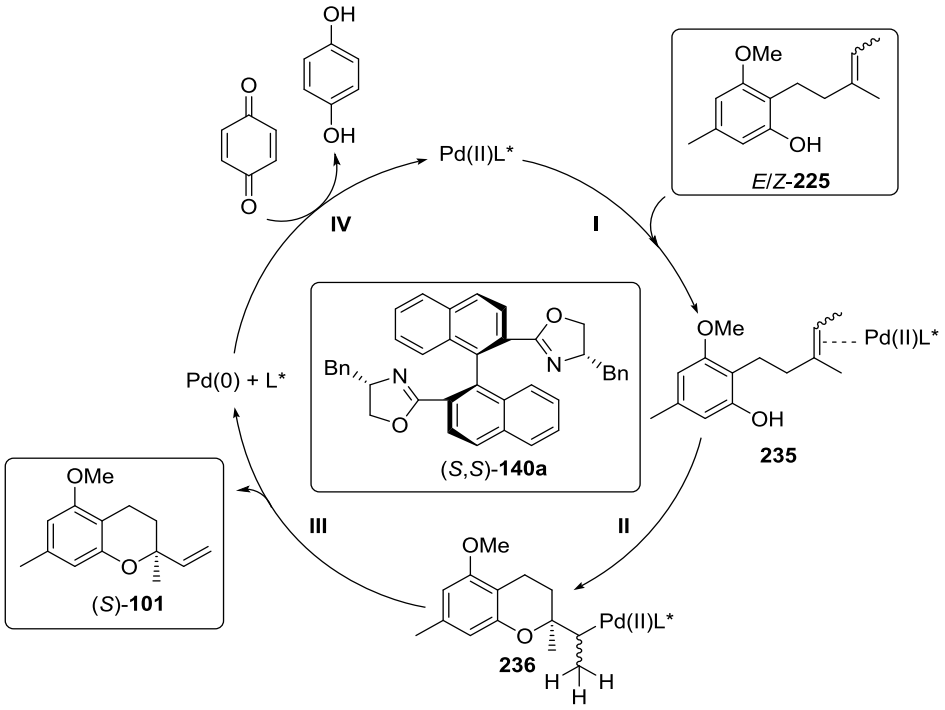


Scheme 43: Synthesis of vinyl chromane (*S*)-**101** by an enantioselective Wacker oxidation: a) $Pd(TFA)_2$ (10 mol%), Bn-BOXAX (*S*,*S*)-**140a** (20 mol%), *p*-benzoquinone (4.0 eq.), MeOH, RT, 22 h, for *E*-**225**: 75%, 93% *ee*; for *Z*-**225**: 79%, 83% *ee*; for the *E*/*Z*-mixture (*E*/*Z* = 1:2.4): 78%, 87% *ee*.

Employing the pure *E*-diastereomer *E*-**225**, the enantioselectivity has been improved to 93% with a slightly decreased yield of 75%. The pure *Z*-compound *Z*-**225**, the main product of the Wittig reaction, was converted to (*S*)-**101** with only 83% *ee* and 79%.

The mechanism postulated for the Wacker oxidation (Scheme 44) involves the enantiofacial coordination of the *in situ* formed chiral Pd(II)-BOXAX-complex to the trisubstituted alkene of *E*/*Z*-**225** (**I**). The resultant π-complex **235** undergoes an intramolecular oxypalladation (**II**) followed by a β-H elimination (**III**) to release vinyl chromane (*S*)-**101** and a palladium(0)-species. Regeneration of the active Pd(II)-catalyst by oxidation with *p*-benzoquinone completes the catalytic cycle (**IV**).

Based on this model, the significantly higher *ee*-value for *E*-**225** compared to *Z*-**225** might result from a sterically more rigid transition state in the enantioselectivity-determining oxypalladation step.



Scheme 44: Proposed mechanism for the enantioselective Wacker oxidation: I) enantiofacial coordination, II) oxypalladation, III) β-H elimination, IV) reoxidation.

Comparison of the optical rotation measured for (*S*)-**101** ($[\alpha]_D$ = –55.2, c = 0.50 in $CHCl_3$, 23 °C) with the value published by Trost *et al*. ($[\alpha]_D$ = +54.0, c = 2.18 in $CHCl_3$) confirmed its (*S*)-configuration.[55]

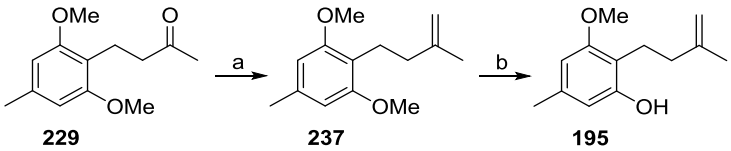
In conclusion, the Wacker oxidation of trisubstituted alkenyl phenols **225** gave direct access to the desired vinyl chromane (*S*)-**101** in 75% to 79% yield and enantioselectivities ranging from 83% to 93% *ee*. However, the shortcomings of this route, in particular the inefficient

HPLC separation of pure *E*-**225** and *Z*-**225** in combination with the modest *ee*-values, rendered this procedure not suitable for large amounts. An alternative route to vinyl chromane (*S*)-**101** was therefore derived, as discussed in the objectives chapter (Scheme 35).

2.2.2 Synthesis and enantioselective domino Wacker/ carbonylation/methoxylation reaction of alkenyl phenol 195

In order to gain access to vinyl chromane (*S*)-**101** on a larger scale, an alternative and more reliable route was investigated, utilizing an enantioselective domino Wacker/carbonylation/ methoxylation reaction. The synthesis of the precursor required for this transformation, i.e. alkenyl phenol **195**, started with the conversion of ketone **229** into terminal alkene **237**. In line with the preparation of olefin *E*/*Z*-**225**, a Wittig reaction was investigated first. Addition of **229** to the *in-situ* generated lithium ylide of CH_3PPh_3Br in THF gave olefin **237** in 98% yield. Upon scale-up, however, the more atom-economical Lombardo-methylenation[139] was employed to provide **237** in 87% on a 17 g scale.

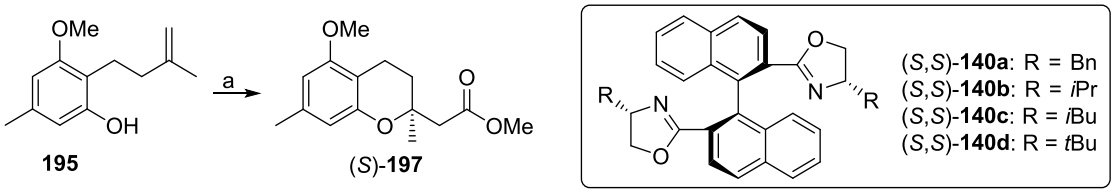
Finally, a mono-demethylation of **237** with NaSEt in DMF at 120 °C gave access to alkenyl phenol **195** in 88% yield, corresponding to 42% yield over six steps (Scheme 45).



Scheme 45: Synthesis of alkenyl phenol **195**: a) *n*BuLi (2.8 eq.), CH_3PPh_3Br (3.0 eq.), THF, 0 °C → RT, 4 h, 98% or Zn (4.5 eq), CH_2Br_2 (1.5 eq.), $TiCl_4$ (1.1 eq.), THF, 0 °C → RT, 75 min, 87%, b) NaSEt (2.2 eq.), DMF, 120 °C, 21.5 h, 88%.

The enantioselective domino Wacker/carbonylation/methoxylation reaction has previously been applied in the synthesis of 4-dehydroxy diversonol (**199**) reported by Tietze *et al*. (Scheme 35).[121e,124] Utilizing the optimized reaction conditions, it was found that exposure to alkenyl phenol **195** to 3 mol% of $Pd(TFA)_2$ and 12 mol% of the Bn-BOXAX ligand (*S*,*S*)-**140a** as well as to 4 equivalents of the reoxidant *p*-benzoquinone at RT under a CO-atmosphere (1 atm) gave the domino product (*S*)-**197** in excellent 61% yield and 93% *ee* (Table 2, entry 1).

Since steric tuning at the C-4 position of the oxazoline ring was reported to affect both the catalytic activity and the enantioselectivity,[89,140] a short screening was initiated to investigate the role of the ligand backbone (Table 2).



Scheme 46: Enantioselective synthesis of methyl ester (*S*)-**197**: a) $Pd(TFA)_2$, BOXAX ligand, *p*-benzoquinone (4.0 eq.), MeOH, CO (1 atm), RT, 24 h.

	$Pd(TFA)_2$	ligand	yield	*ee*[a]
1	3 mol%	Bn-BOXAX (*S*,*S*)-**140a** (12 mol%)	61%	93%
2	3 mol%	*i*Pr-BOXAX (*S*,*S*)-**140b** (12 mol%)	33%	99%
3	3 mol%	*i*Bu-BOXAX (*S*,*S*)-**140c** (12 mol%)	49%	99%
4	3 mol%	*t*Bu-BOXAX (*S*,*S*)-**140d** (12 mol%)	8%	60%
5[b]	3 mol%	Bn-BOXAX (*S*,*S*)-**140a** (12 mol%)	32%	-
6[c]	5 mol%	Bn-BOXAX (*S*,*S*)-**140a** (20 mol%)	76%	93%
7[d]	5 mol%	Bn-BOXAX (*R*,*R*)-**140a** (20 mol%)	71%	93%

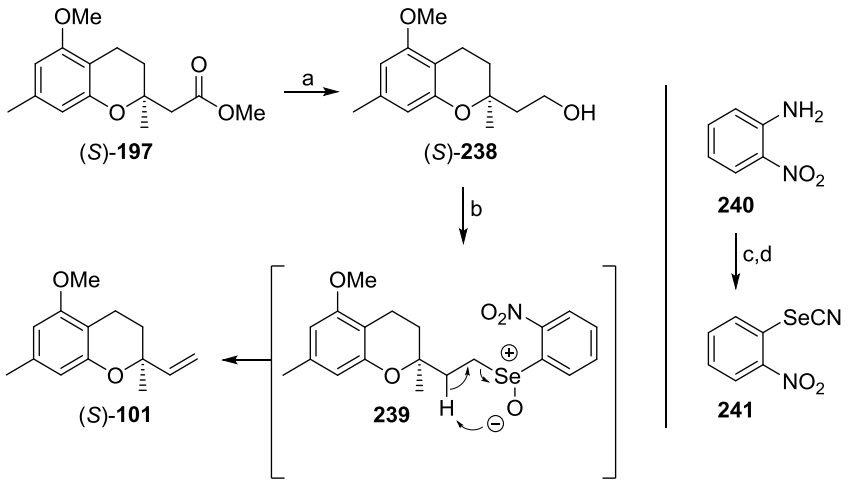
Table 2: Ligand screening for the enantioselective domino-Wacker/carbonylation/methoxylation reaction: [a] Determined by analytical HPLC (Chiracel IB®, *n*hexane/*i*PrOH = 98:2, 234 nm); [b] The reaction was run in MeOH/MeCN (1:1); *ee*-value not determined; [c] The reaction was stirred for 19 h; [d] The use of (*R*,*R*)-**140a** led to the formation of (*R*)-**197**.

The use of the *i*Pr-BOXAX ligand (*S*,*S*)-**140b**, the ligand of choice in Tietze's synthesis of vitamine E,[121f,122] resulted in an excellent *ee*-value of 99%, but at the expense of only 33% yield (entry 2). Employing ligand (*S*,*S*)-**140c** substituted with *iso*-butyl groups, the yield could be improved to 49% while preserving the high enantioselectivity of 99% *ee*. With 8% yield and 60% *ee*, the bulky *t*Bu-BOXAX ligand (*S*,*S*)-**140d** exhibited the lowest catalytic activity and selectivity. White *et al*. reported that the low conversion sometimes encountered in carbonylation reactions may arise from reduction of the Pd(II)-catalyst by CO.[85b,c] Using a MeOH/MeCN solvent system instead of MeOH, the authors were successful mitigating the undesired reduction. However, when the domino reaction of **195** was run in the presence of Bn-BOXAX ligand (*S*,*S*)-**140a** in a 1:1 mixture of MeOH/MeCN, the yield decreased to 32% (entry 5).

The comparatively high yield achieved with the Bn-BOXAX ligand (*S*,*S*)-**140a**, combined with the acceptable enantioselectivity (for further enrichment using chiral HPLC *vide infra*), resulted in the exclusive use of this ligand in the remainder of the synthesis. To ensure even

higher conversion especially upon scale-up, the domino reaction was conducted with an increased amount of catalyst (5 mol%) and ligand (20 mol%) . The yield of the reaction was thus increased to 76% while maintaining the enantioselectivity of 93% *ee* (entry 5). At this stage it was also shown that the synthetic route allows access to natural (+)-diversonol (**10**), as well as related natural products such as siccanin (**25**), whose quaternary stereocenter at C-4a display an (*R*)-configuration. Expectably, replacement of (*S*,*S*)-**140a** with the enantiomeric Bn-BOXAX ligand (*R*,*R*)-**140a** afforded (*R*)-**197** in comparable yield and enantioselectivity (entry 7).

Methyl ester (*S*)-**197** was then converted to the desired vinyl chromane (*S*)-**101** using a 3-step sequence starting with the reduction of (*S*)-**197** with $LiAlH_4$ in Et_2O, affording primary alcohol (*S*)-**238** in 98% yield (Scheme 47). At this stage, the enantiomeric excess was enriched to $\geq$ 99% by preparative HPLC on a chiral IA® phase eluting with *n*hexane/*i*PrOH = 99:1. Attempts to dehydrate enantiomerically pure (*S*)-**238** directly to vinyl chromane (*S*)-**101** with Martin's[141] or Burgess reagents[142] were not successful.



Scheme 47: Elimination of ester (*S*)-**197** to vinyl chromane (*S*)-**101**: a) $LiAlH_4$ (1.1 eq.), Et_2O, 0 °C → RT, 2 h, 98%; b) 1. *n*Bu_3P (2.0 eq.), **241** (2.0 eq.), THF, 0 °C, 1 h; 2. *m*CPBA (2.5 eq.), CH_2Cl_2, –40 °C, 1 h, *i*Pr_2NH (5.0 eq.), –40 °C → RT, 12 h, 98% (2 steps); c) $BF_3{\cdot}Et_2O$ (1.5 eq.), *t*$BuNO_2$ (1.2 eq.), CH_2Cl_2, –12 °C, 30 min → 0 °C, 30 min, quant.; KSCN (1.0 eq.), H_2O, 0 °C, 30 min, 55%.

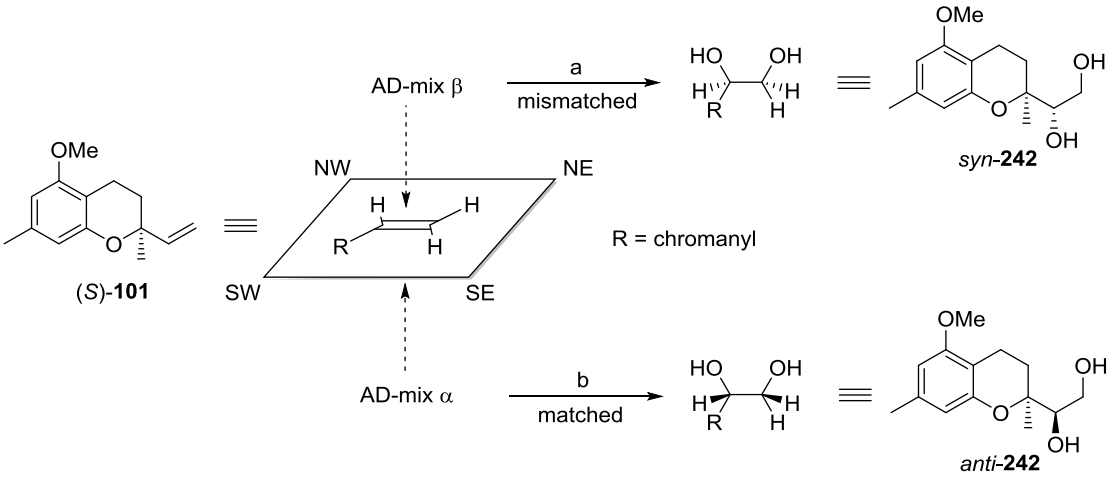
Instead, alcohol (*S*)-**238** was subjected to a Mukaiyama redox condensation followed by an oxidation/elimination sequence. Exposure of (*S*)-**238** to *ortho*-nitroselenocyanate (**241**), which was synthesized from *ortho*-nitroaniline (**240**) in 55% yield[143], and *n*Bu_3P gave rise to the corresponding seleno ether, which was then oxidized with *m*CPBA and eliminated with *i*Pr_2NH to give (*S*)-**101** in an excellent yield of 98% over 2 steps.[144]

2.3 Synthesis of the tetrahydroxanthenone core

2.3.1 Sharpless dihydroxylation of vinyl chromane (*S*)-101

Since previous attempts in the Tietze research group to introduce the hydroxyl group at C-4 (numbering as in *ent*-**10**, Scheme 41) were plagued by either low yields or epimerization at C-4a,[124,125] alternative methods were sought for the hydroxylation step while preserving the configurational integrity of the quaternary stereocenter.

Bearing these considerations in mind, a Sharpless dihydroxylation of the vinyl group adjacent to the chromane ring would constitute an elegant method to install the C-4 hydroxyl group with concomitant functionalization of the terminal carbon to elongate the side-chain (Scheme 48).



Scheme 48: Sharpless dihydroxylation of vinyl chromane (*S*)-**101** including prediction of the asymmetric induction: a) AD-mix β, $MeSO_2NH_2$ (1.0 eq.), *t*BuOH/H_2O (1:1), RT, 7 d, 73%, d.r. = 1:1.3 (*anti*/*syn*), mismatched; b) AD-mix α, $MeSO_2NH_2$ (1.0 eq.), *t*BuOH/H_2O (1:1), RT, 5 d, 93%, d.r. = 3.8:1 (*anti*/*syn*), matched.

When vinyl chromane (*S*)-**101** was subjected to AD-mix α and methanesulfonamide in *t*BuOH/H_2O (1:1) at RT, the diols *anti*-**242** and *syn*-**242** were obtained in an excellent yield of 93% and with a moderate diastereoselectivity of d.r. = 3.8:1 (*anti*/*syn*) after 5 d. The use of one equivalent of methanesulfonamide as additive and the two-fold amount of AD-mix α[145] were crucial for the successful outcome of the reaction. Otherwise, slow conversion and moderate yields were encountered.

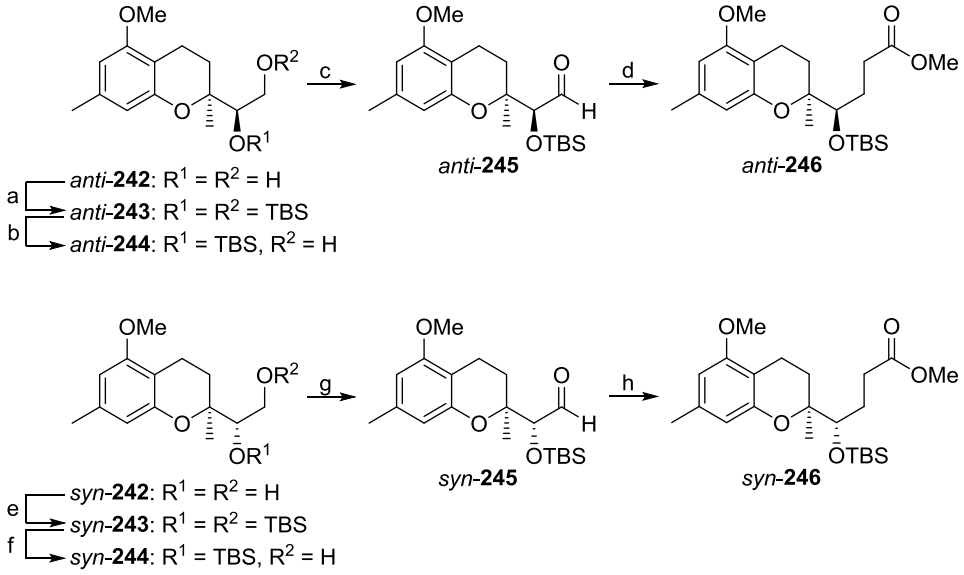
In the mismatched case, AD-mix β reacted significantly slower with the terminal double bond of (*S*)-**101**. After 4 d, additional AD-mix β was added to the reaction mixture to ensure complete conversion. The reaction was stirred at RT for further 3 d to give *anti*-**242** and

syn-**242** in a good yield of 73% as a 1:1.3 (*anti*/*syn*)-mixture. The decreased yield and the reversal of the diastereoselectivity can be explained using Sharpless's mnemonic. The attack of the catalyst occurs from the upper face pointing in the direction of the angular methyl group at C-4a. It seems that the increased bulk exerted by the methyl group disturbs the coordination of the catalyst to the olefin, thus lowering its catalytic activity.

The diols *anti*-**242** and *syn*-**242** were not separable by column chromatography on silica gel. As earlier studies indicated that the separation of the *anti*- and *syn*-epimers at a later stage of the synthesis was difficult, purification was undertaken using preparative HPLC. Under optimized conditions on a chiral IB® phase eluting with *n*hexane/*i*PrOH = 97:3, the diols *anti*-**242** and *syn*-**242** were obtained in pure form as vicious oils.

2.3.2 Chain-elongation of the diols *anti*-242 and *syn*-242

The transformation of *anti*-**242** and *syn*-**242** to the corresponding chromanes *anti*-**246** and *syn*-**246** endowed with the butyl side-chain necessary for construction of the final tetrahydroxanthenone ring commenced with a protection/deprotection sequence of the diol moiety (Scheme 49).



Scheme 49: Syntheses of the methyl esters *anti*-**246** and *syn*-**246**: a) TBSOTf (3.5 eq.), 2,6-lutidine (4.0 eq.), CH_2Cl_2, 0 °C → RT, 2.5 h, 99%; b) HF·pyridine (80 eq.), THF/pyridine (8:1), RT, 60 h, 70% (93% brsm); c) DMP (1.8 eq.), CH_2Cl_2, 0 °C → RT, 2 h, 95%; d) 1. $(MeO)_2P(O)CH_2CO_2Me$ (1.5 eq.), NaH (1.3 eq.), THF,0 °C → RT, 1.5 h; 2. H_2 (4 bar), Pd/C (10 mol%), EtOAc, RT, 15 h, 95% (2 steps); e) TBSOTf (3.5 eq.), 2,6-lutidine (4.0 eq.), CH_2Cl_2, 0 °C → RT, 2.5 h, quant.; f) HF·pyridine (80 eq.), THF/pyridine (8:1), RT, 52 h, 73% (98% brsm); g) DMP (2.5 eq.), CH_2Cl_2, 0 °C → RT, 2.5 h, 89%; h) 1. $(MeO)_2P(O)CH_2CO_2Me$ (1.7 eq.), NaH (1.3 eq.), THF, 0 °C → RT, 1.5 h; 2. H_2 (4 bar), Pd/C (10 mol%), EtOAc, RT, 15 h, 98% (2 steps).

Silylation of both hydroxyl groups in *anti*-**242** and *syn*-**242** with *tert*-butyldimethylsilyl methanesulfonate (TBSOTf) and 2,6-lutidine in CH_2Cl_2 was followed by the selective removal of the primary TBS group with HF·pyridine to yield the alcohols *anti*-**244** and *syn*-**244** in 69% (92% brsm) and 73% (98% brsm) over two steps. Oxidation with Dess-Martin periodinane (DMP) in CH_2Cl_2 to the corresponding aldehydes *anti*-**245** and *syn*-**245** in 95% and 89% yield then set the stage for the introduction of the required side-chain by a Wittig-Horner reaction. Deprotonation of $(MeO)_2P(O)CH_2CO_2Me$ with sodium hydride in THF and addition of the aldehydes *anti*-**245** and *syn*-**245** to the ylide provided the α,β-unsaturated esters as inconsequential mixtures of *E*/*Z*-isomers. The crude mixtures were hydrogenated in the presence of 10 mol% of palladium on charcoal (Pd/C) to yield the chromanes *anti*-**246** and *syn*-**246** in 95% and 98% yield over two steps.

It is interesting to note that no epimerization of the α-chiral aldehydes *anti*-**245** and *syn*-**245** was observed under both acidic (DMP oxidation) and basic conditions (Wittig-Horner reaction), which may be attributed to the high steric shielding through the adjacent OTBS group.

2.3.3 Benzylic oxidation of the chromanes *anti*-246 and *syn*-246

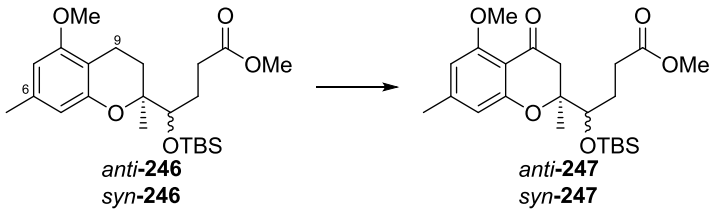
Following to the retrosynthetic analysis, the installation of the benzylic keto group was required next (Scheme 50).

First, a method developed by T. K. Shing,[146] which had been applied in the syntheses of (–)-4-dehydroxy diversonol (**199**) and racemic diversonol (*ent*-**10**),[124,124] was attempted. Thus, the chromanes *anti*-**246** and *syn*-**246** were treated with 10 mol% of manganese(III)-acetate and 5.2 eq. of *tert*-butyl hydroperoxide in the presence of 3 Å molecular sieves in ethyl acetate at RT (Table 3, entries 1 and 3).

Complete consumption of the starting materials, however, required further addition of the catalyst $Mn(OAc)_3$ (10 mol%) and the reoxidant *t*BuOOH (1.0 eq.) every 24 h. After 4 d, the chromanones *anti*-**247** and *syn*-**247** were formed in 51% and 42% yield, respectively. In the course of the reactions, the formation of various side-products was monitored by thin layer chromatography. The low yield and the slow conversion in combination with the necessity to use 40 mol% of catalyst rendered this method not suitable for large-scale synthesis.

Alternatively, the use of excess potassium permanganate ($KMnO_4$) and aq. $MgSO_4$ in acetone at RT furnished the desired chromanones *anti*-**247** in 55% (66% brsm) and *syn*-**247** in 33% (50% brsm) yield (Table 3, entries 2 and 4).[147] TLC monitoring of both reactions showed the

formation of polar side-products and signals of the chromane and chromanone core bearing a carboxylic acid function were found in the mass spectra of the crude reaction mixtures.



anti-**246** *anti*-**247**
syn-**246** *syn*-**247**

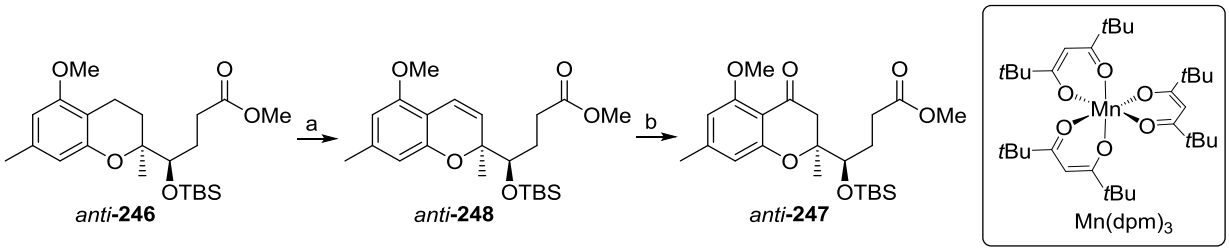
Scheme 50: Direct benzylic oxidation of the chromanes *anti*-**246** and *syn*-**246**.

	substrate	conditions	result
1	*anti*-**246**	$Mn(OAc)_3 \cdot 2\ H_2O$ (4 × 10 mol%), *t*BuOOH (5.2 eq. + 3 × 1 eq.), 3 Å ms, EtOAc, RT, 4 d	51%
2	*anti*-**246**	$KMnO_4$ (7.0 eq.), 15% aq. $MgSO_4$ solution, acetone, RT, 12 h	55% (66% brsm)
3	*syn*-**246**	$Mn(OAc)_3 \cdot 2\ H_2O$ (4 × 10 mol%), *t*BuOOH (5.2 eq. + 3 × 1 eq.), 3 Å ms, EtOAc, RT, 4 d	42%
4	*syn*-**246**	$KMnO_4$ (5.0 eq.), 15% aq. $MgSO_4$ solution, acetone, RT, 12 h	33% (50% brsm)

Table 3: Direct benzylic oxidation of the chromanes *anti*-**246** and *syn*-**246**.

Although the methylene position C-9 (numbering in as in **246**) should be more susceptible to oxidation due to electronic reasons and the coordinating ability of the adjacent methoxy group,[148] it stands to reason that the benzylic methyl group at C-6 was partially oxidized. Thus, an alternative route was sought that precludes the oxidation of the benzylic methyl group at C-6 and instead directs it exclusively to the methylene position at C-9.

To differentiate the two benzylic positions, chromane *anti*-**246** was first transformed to chromene *anti*-**248** upon exposure to 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing benzene, yielding *anti*-**248** in 95% after 2 h (Scheme 51).[55] Surprisingly, the yield for the dehydrogenation drastically decreased to 38% when microwave irradiation was used.
The next necessary step was the regioselective oxidation of chromene *anti*-**248** at C-9. While standard Wacker conditions gave no product,[149] a manganese(III)-catalyzed hydration of the double bond in *anti*-**248** was more successful. This reaction was first reported by Mukaiyama *et. al*. in the early 1990's for the hydration of α,β-unsaturated esters[150] and was extended to α,β-unsaturated ketones and nitriles by Magnus and coworkers.[151a,b]

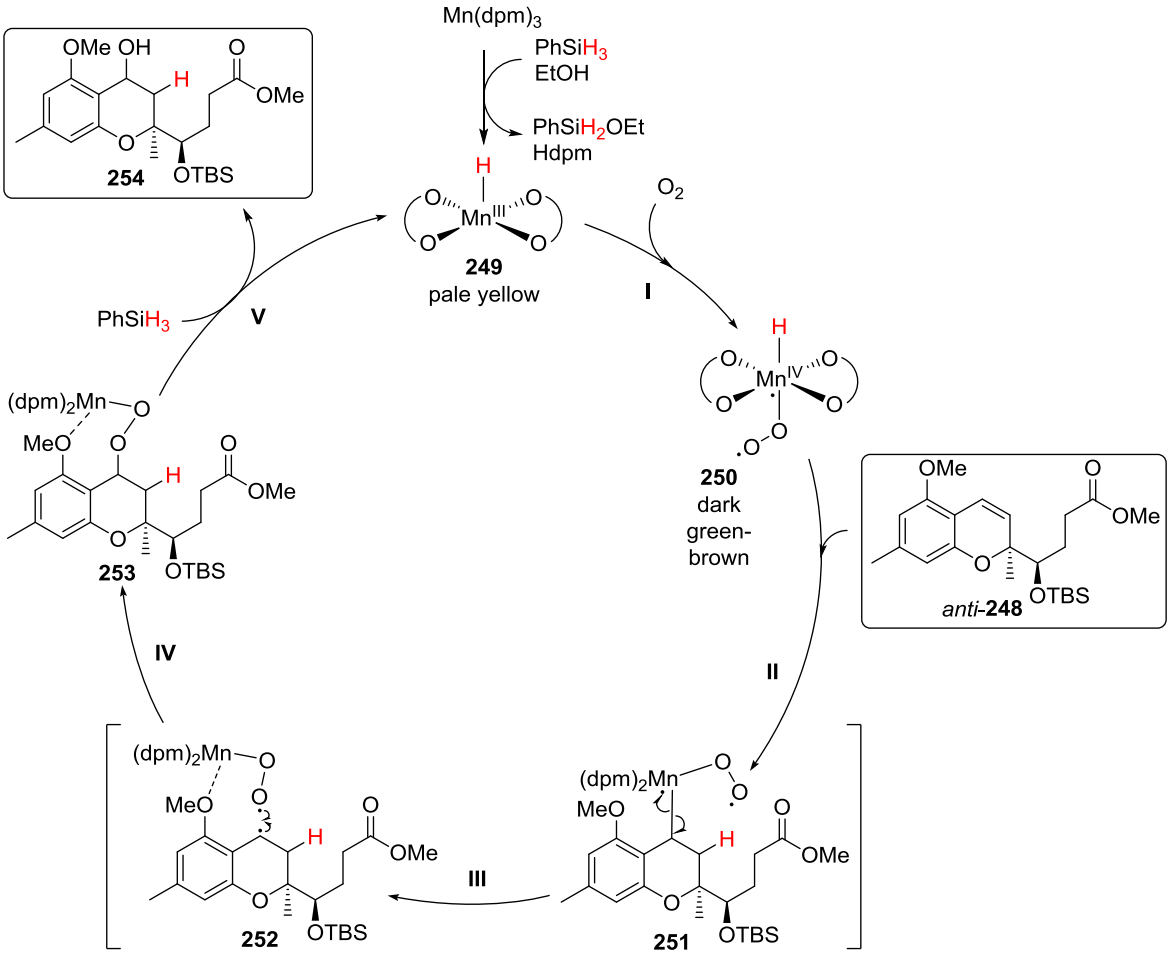


Scheme 51: Stepwise benzylic oxidation of chromane *anti*-**246** to chromanone *anti*-**247**: a) DDQ (2.00 eq.), benzene, reflux, 2 h, 95%; b) 1) $Mn(dpm)_3$ (10 mol%), $PhSiH_3$ (4.0 eq.), O_2 (1 atm), RT, 4.5 h; 2) MnO_2 (80 eq.), CH_2Cl_2, reflux, 4 d, 88% (2 steps).

Thus, chromene *anti*-**248** reacted in the presence of phenylsilane ($PhSiH_3$) and catalytic amounts of tris(dipivaloylmethanato)-manganese(III) $Mn(dpm)_3$ (10 mol%) under a oxygen atmosphere (1 atm) in ethanol at RT cleanly to an inconsequential mixture of diastereomeric alcohols along with minor amounts of chromanone *anti*-**247**. The alcohol mixture was subsequently oxidized with MnO_2 in refluxing CH_2Cl_2 to give chromanone *anti*-**247** in 88% yield over 2 steps.

From a mechanistic point of view, it is interesting to note that in the absence of $PhSiH_3$, no reaction was observed. A direct activation of dioxygen by $Mn(dpm)_3$ and subsequent addition of a manganese peroxy species to the double bond can therefore be excluded.

When $PhSiH_3$ was added to chromene *anti*-**248** and $Mn(dpm)_3$ in EtOH under a dioxygen atmosphere, the colorless solution immediately turned pale yellow and upon further stirring for less than 30 s to dark green-brown. These observations are in full agreement with mechanistic studies conducted by the groups of Mukaiyama,[150] Magnus[152] and Carreira,[153] revealing that the reaction proceeds by a stepwise introduction of the hydrogen atom and the peroxy group which is subsequently reduced to the hydroxy function (Scheme 52). The active species is most likely the hydridic manganese(III) complex $HMn(dpm)_2$ (**249**) which accounts for the pale yellow color of the solution. It is formed in the reaction of $Mn(dpm)_3$ with $PhSiH_3$ in the presence of an alcohol. Consequently, the use of a silane and an alcohol such as MeOH, EtOH or *i*PrOH as solvent or cosolvent is essential for the generation of the active catalyst. The hydridic complex $HMn(dpm)_2$ (**249**) then activates dioxygen, thus leading presumably to the manganese(IV) complex $HMnO_2(dpm)_2$ (**250**) which exhibits a dark green-brown color in solution. This peroxy-hydridic species then inserts into the double bond of chromene *anti*-**248**, giving rise to manganese radical **251** which can rearrange to benzylic radical **252**.

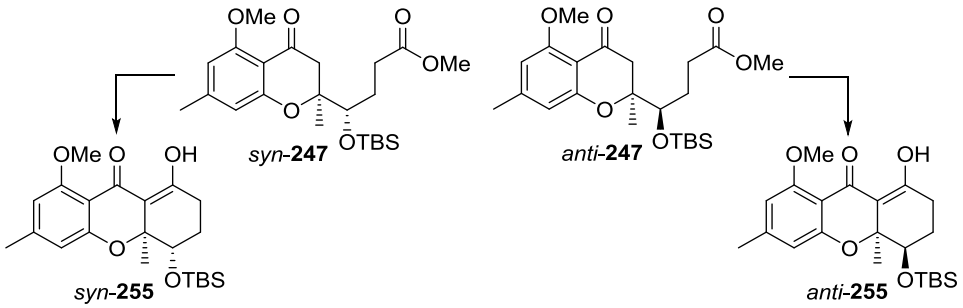


Scheme 52**:** Mechanism of the Mn(dpm)-catalyzed hydration of chromene *anti*-**248**.

In the case of chromene *anti*-**248**, the high level of regioselectivity of the reaction can be attributed to the diradical valence structure **252**. In addition to the coordination of the methoxy group to the metal center, it is stabilized by benzylic resonance. Recombination of the peroxy and the benzylic radical to form **253** followed by cleavage of the O-O bond by $PhSiH_3$ regenerates the active catalyst $HMn(dpm)_2$ and provides the benzylic alcohol **254**. Overall, this 3-step procedure comprising dehydrogenation, hydration and oxidation furnished chromanone *anti*-**247** in an excellent yield of 84%.

2.3.4 Synthesis of tetrahydroxanthenones *anti*-247 and *syn*-247

With the keto functionality installed, the stage was set for the closure of the final ring of the tetrahydroxanthenone scaffold. Tietze *et al*. found in their synthesis of (–)-4-dehydroxy diversonol (**199**) that the use of a Lewis acid in the presence of a tertiary amine base provided the tetrahydroxanthenone core in modest to good yields.[121f,124]



Scheme 53: Syntheses of the tetrahydroxanthenones *anti*-**255** and *syn*-**255**.

	substrate	conditions	result
1	*anti*-**247**	$TiCl_4$ (2.2 eq.), NEt_3 (2.5 eq.), CH_2Cl_2, 0 °C, 1 h	66%
2	*anti*-**247**	$TiCl_4$ (2.6 eq.), $Ti(OiPr)_4$ (0.9 eq.), 0 °C, 15 min → $Ti(OiPr)Cl_3$ (3.5 eq.), NEt_3 (2.8 eq.), CH_2Cl_2, 0 °C, 1 h	84%
3	*syn*-**247**	$TiCl_4$ (2.6 eq.), $Ti(OiPr)_4$ (0.9 eq.), 0 °C, 15 min → $Ti(OiPr)Cl_3$ (3.5 eq.), NEt_3 (2.8 eq.), CH_2Cl_2, 0 °C, 2.5 h	69%

Table 4: Syntheses of the tetrahydroxanthenones *anti*-**247** and *syn*-**247**.

Accordingly, titan tetrachloride (2.2 eq.) was added to a solution of chromanone *anti*-**255** and triethylamine (2.5 eq.) in CH_2Cl_2 at 0 °C, furnishing tetrahydroxanthenone *anti*-**255** in a good yield of 66% (Table 4, entry 1). The use of the *in-situ* formed Lewis acid $Ti(OiPr)Cl_3$ increased the yield to 84% (entry 2). This finding can be explained with the formation of a more nucleophilic Ti-enolate.[154] Employing the modified conditions, the $Ti(OiPr)Cl_3$-mediated acylation of methyl ester *syn*-**247** led to tetrahydroxanthenone *syn*-**255** in 69% yield (entry 3).

The relative configuration of the stereogenic centers in *anti*-**255** and *syn*-**255** was supported by comparison of the ^{1}H-NMR coupling constants of the proton at C-4 with the neighboring C-3 protons. For the *trans*-compound *anti*-**255**, the vicinal coupling constants J = 1.8 and 3.9 Hz for the signal at δ = 4.02 ppm corresponding to 4-H show that 4-H has an almost synclinal orientation to both hydrogen atoms at C-3; this requires an axial orientation of the OTBS-group. Similar spectroscopic investigations were performed with the *syn*-epimer *syn*-**255**. From the coupling constants J = 12.1 and 4.6 Hz for the signal corresponding to 4-H at δ = 4.11 ppm, it can be deduced that the OTBS-group has an equatorial orientation. These results were further confirmed by NOE experiments (Figure 20).

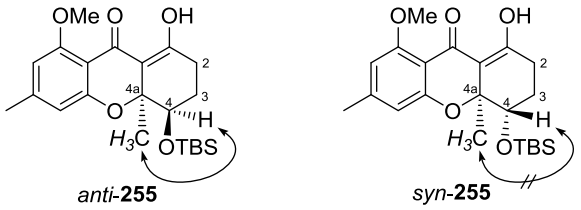


Figure 20: NOE experiments of *anti*-**255** and *syn*-**255**. The excited methyl groups are depicted in italic.

Bearing the liability of the chromane core to racemization in mind, tetrahydroxanthenone *anti*-**255** was subjected to analytical HPLC. Comparison of *anti*-**255** with the racemic sample *rac*-*anti*-**255** on chiral IA® and IB® phases gave an *ee*-value of ≥ 99%, indicating that the high enantiopurity was retained.

2.4 Functionalization of the tetrahydroxanthenone core

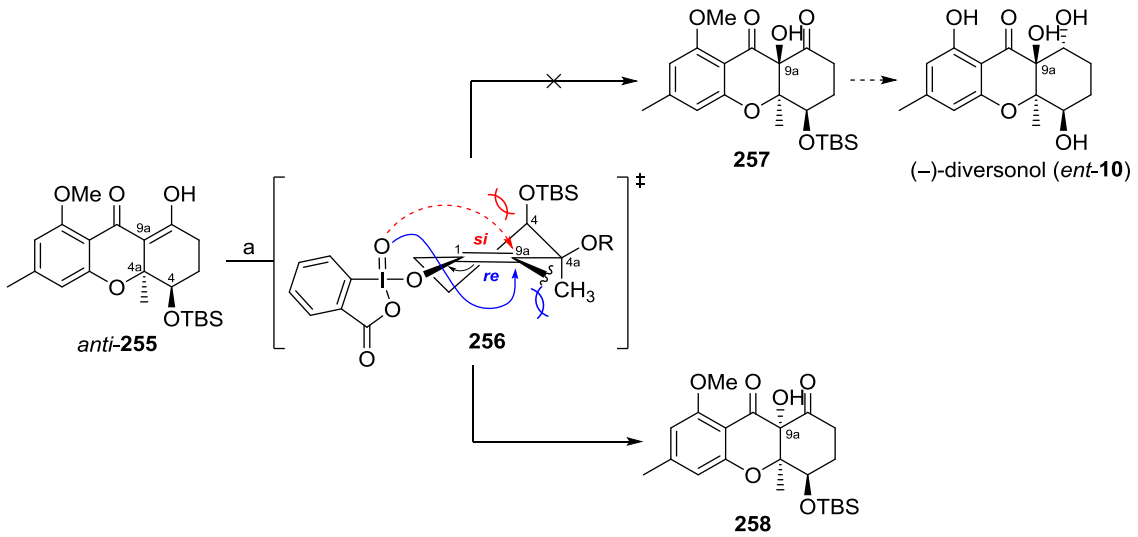
2.4.1 Hydroxylation of the tetrahydroxanthenone *anti*-255 at C-9a

Having the enantiopure tetrahydroxanthenone *anti*-**255** in hand, the stage was set for the diastereoselective introduction of the quaternary hydroxy group at C-9a.

For the synthesis of (–)-diversonol (*ent*-**10**) displaying a β-configuration at C-9a, it was anticipated that the steric shielding of the adjacent angular methyl group at C-4a would induce a strong 1,2-interaction and thus directs the hydroxylation from the *si*-face of the enol double bond.

Earlier studies in the Tietze research group with the TBS-protected tetrahydroxanthenone *rac*-*anti*-**255** employing magnesium monoperoxyphthalate (MMPP), dimethyldioxirane (DMDO) or *meta*-chloroperbenzoic acid (*m*CPBA) resulted in opening of the chromane ring or decomposition.[125] However, using a method developed by Kirsch *et al*.[155a] which was first applied on *rac*-*anti*-**255** by Raith,[125] the hydroxylation was successfully achieved upon exposure of *anti*-**255** to *o*-iodoxybenzoic acid (IBX) in a (3:1)-mixture of DMSO/H_2O at 55 °C, albeit in only 32% yield and with the undesired α-configuration at C-9a (Scheme 54).

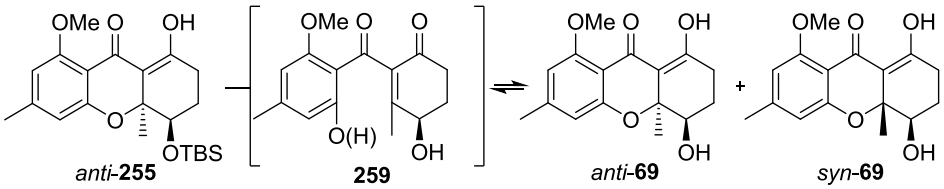
Mechanistically, the hydroxylation presumably proceeds by an intramolecular attack of one of the IBX-oxygen atoms to the carbon atom C-9a.[155b,c] The stereochemical outcome of the reaction can be rationalized with the steric bulk of the axially oriented OTBS-ether, which forces the oxidation to take place from the opposite side, the *re*-face.



Scheme 54: Hydroxylation of TBS-protected tetrahydroxanthenone *anti*-**255**: a) IBX (3.0 eq.), DMSO/H_2O (3:1), 55 °C, 12 h, 32%. For the transition state **256**, a half-chair with a pseudo-axial orientated OTBS-group was assumed.

Based on these considerations, the cleavage of the O-Si bond was investigated in order to facilitate the necessary hydroxylation at C-9a (Scheme 55). Initially, the deprotection was attempted under basic conditions by addition of a solution of tetra-*n*-butylammonium fluoride to tetrahydroxanthenone *anti*-**256** in THF at 0 °C. After stirring at RT and even heating at reflux for 2 d, no removal of the TBS-group was observed, instead the starting material slowly degraded (Table 5, entry 1).

While *anti*-**255** was incompatible with the presence of basic fluoride ions, efforts were directed to deprotect the OTBS-ether under mild acid conditions. Treatment of *anti*-**255** with 14 equivalents of HF·pyridine in THF at 30 °C for 3 d, however, gave no conversion (entry 2). Increasing the amount of HF·pyridine to 45 equivalents (3 × 15 eq., 15 eq. each at the start of the experiment and after 2 and 4 d) and stirring for 7 d at 30 °C provided the desired alcohol *anti*-**69** along with its C-4a epimer *syn*-**69** in a yield of 52% (86% brsm) as an inseparable (1.8:1)-mixture of diastereomers (entry 3).



Scheme 55: TBS deprotection of *anti*-**255** and postulated epimerization pathway.

	conditions	c [mol/L]	result
1	TBAF (5.0 eq.), THF, 0 °C → RT, 24 h, RT → reflux, 24 h	0.04	decomposition
2	HF·pyridine (14 eq.), THF, 0 °C → 30 °C, 3 d	0.02	no conversion
3	HF·pyridine (3 × 15 eq.), THF, 0 °C → 30 °C, 7 d	0.04	52% (86% brsm) epimerization
4	HF·pyridine (2 × 25 eq.), THF/pyridine (6:1), 0 °C → 30 °C, 5 d	0.035	20% (99% brsm)
5	HF·pyridine (2 × 25 eq.), THF, 0 °C → 30 °C, 5 d	0.04	72% (94% brsm)
6	HF·pyridine (2 × 25 eq.), THF, 0 °C → 30 °C, 5 d	0.045	32% (61% brsm) epimerization

Table 5: TBS deprotection of tetrahydroxanthenone *anti*-**255**.

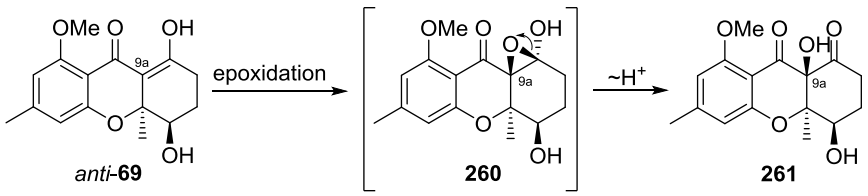
Fortunately, the starting material could be easily recovered by column chromatography and showed no loss of steric integrity. It was thus reasoned that under acidic conditions alcohol *anti*-**69** undergoes an opening of the chromane ring-system by a retro-oxa-Michael addition followed by the non-stereospecific readdition of the resultant phenol **259** to the α,β-unsaturated ketone.

Next, *anti*-**255** was subjected to 50 equivalents of HF·pyridine (2 × 25 eq., second addition of 25 eq. after 3 d) at a concentration of 0.035 M. In order to suppress the ring opening, the reaction time was reduced to 5 d and the acidity of the solution buffered using pyridine as cosolvent to selectively provide alcohol *anti*-**69** in 20 % yield (99% brsm) (entry 4). The best result in terms of yield and conversion was accomplished with 50 equivalents of HF·pyridine (2 × 25 eq.) and stirring at 30 °C for 5 d at a concentration of 0.04 M to yield alcohol *anti*-**69** in 72% (94% brsm) on a 26 mg scale (entry 5). Attempts to further improve the conversion by increasing the concentration to 0.045 M were not successful, instead leading to 32% of an epimeric mixture of *anti*-**69** and *syn*-**69** (entry 6).

The synthesis of *anti*-**69** with a free hydroxyl group at C-4 represented already a formal synthesis of (–)-diversonol (*ent*-**10**) by intercepting this key intermediate in Bräse's total synthesis of *ent*-**10**.

The unprotected alcohol *anti*-**69** was then subjected to hydroxylation conditions again. According to procedures of Nicolaou and Bräse,[26,48] densely functionalized alcohol *anti*-**69**

was first treated with MMPP in EtOH at RT leading to a complex reaction mixture (Table 6, entry 1). Therefore, the hydroxylation with MMPP was conducted at a reduced temperature of 0 °C. Full conversion of the starting material occurred after 2 h and the reaction was quenched by the addition of silica gel. However, all attempts to purify the reaction mixture by standard column chromatography met with failure. As a consequence of the polarity of the reaction products, the crude mixture was subjected to preparative reversed-phase HPLC eluting with H_2O/MeOH to provide the desired diketone *anti*-**261** along with its C-9a epimer in a 5:1 ratio and 46% yield (entry 2). Both the yield and diastereoselectivity were improved to 58% and d.r. = 6.4:1 by using a freshly prepared solution of DMDO at 0 °C in acetone (entry 3).



anti-**69** **260** **261**

Scheme 56: Hydroxylation comprising an epoxidation and a hydrolytic rearrangement of enol *anti*-**69**.

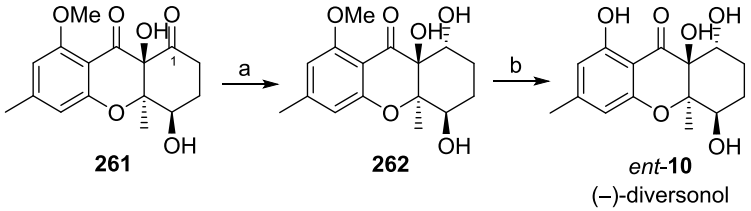
	conditions	result
1	MMPP (1.0 + 0.5 eq.), EtOH, RT, 5 h	decomposition
2	MMPP (0.5 + 0.05 eq.), EtOH, 0 °C, 2 h	46%, d.r. = 5:1
3	DMDO (2 × 0.5eq.), acetone, 0 °C, 1 h	58%, d.r. = 6.4:1

Table 6: Hydroxylation of enol *anti*-**69**.

Mechanistically, the formation of diketone *anti*-**261** is believed to involve an epoxidation of the enol double bond followed by a subsequent hydrolytic rearrangement.[156]

2.4.2 Synthesis of (–)-diversonol (*ent*-10)

The last steps of the synthesis involved the diastereoselective reduction of the C-1 carbonyl moiety and cleavage of the aryl methyl ether (Scheme 57).[45]



Scheme 57: Synthesis of (–)-diversonol (*ent*-**10**): a) $NaBH_4$ (1.3 eq.) , $MeOH/CH_2Cl_2$ (1:1), –78 °C, 2 h, 62%; b) BBr_3 (10 eq.), CH_2Cl_2, –78 °C → RT, 5.5 h, 75%.

Diketone **261** was first treated with one equivalent of sodium borohydride in a mixture of $MeOH/CH_2Cl_2$ (1:1) at –78 °C for 1.5 h. To reach completion, the reaction required the addition of further 0.3 eq of $NaBH_4$ followed by stirring for 30 min at –78 °C. Again the polarity of the reaction products hampered the purification by standard column chromatography and required preparative reversed-phase HPLC (H_2O/MeOH) to deliver **262** in 62% yield. Finally, demethylation of **262** with BBr_3 in CH_2Cl_2 occurred upon warming from –78 °C to RT to afford (–)-diversonol (*ent*-**10**) in 75% yield. No traces of the C-9a epimer, which had been formed as a side product in the hydroxylation step, were detected.
The spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, UV/Vis and MS) matched those published for the natural (+)-diversonol (**10**).[28b] Moreover, slow evaporation of a solution of *ent*-**10** in $CHCl_3$ gave suitable crystals for X-ray diffraction which confirmed the structure of *ent*-**10** (Figure 21).

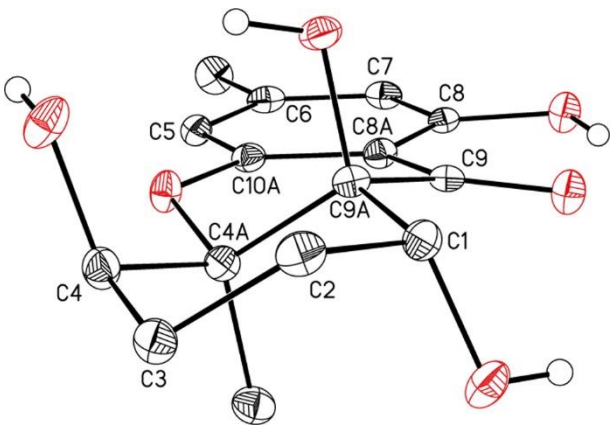
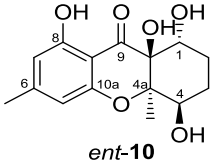


Figure 21: X-ray structure of (–)-diversonol (*ent*-**10**). The ellipsoids are set at 50% probability.

The optical rotation $[\alpha]_D$ was measured to be $\alpha = -62$ (c = 0.16, MeOH, 22 °C), which is slightly lower than the published value of $[\alpha]_D = +70$ (c = 0.33, MeOH, 29 °C). Since the Bn-BOXAX ligand (*S*,*S*)-**140a** used in both the enantioselective domino Wacker/carbonylation/methoxylation reaction of alkenyl phenol **195** and the enantioselective Wacker oxidation of *E*-**255** and *Z*-**225** is easily accessible in its enantiomeric form, the described procedure also allows for the synthesis of natural (+)-diversonol (**10**).

2.4.3 Spectroscopic data of (–)-diversonol (*ent*-10)



ent-**10**

The ^{1}H-NMR spectrum of (–)-diversonol (*ent*-**10**) (Figure 22) shows two characteristic singlets at $\delta = 1.40$ and 2.25 ppm, each integrating for three protons, which can be assigned to the methyl groups at C-4a and C-6. The diastereomeric methylene protons of the C-ring exhibit four distinct signals at 1.46, 1.69, 1.97 and 2.17 ppm.

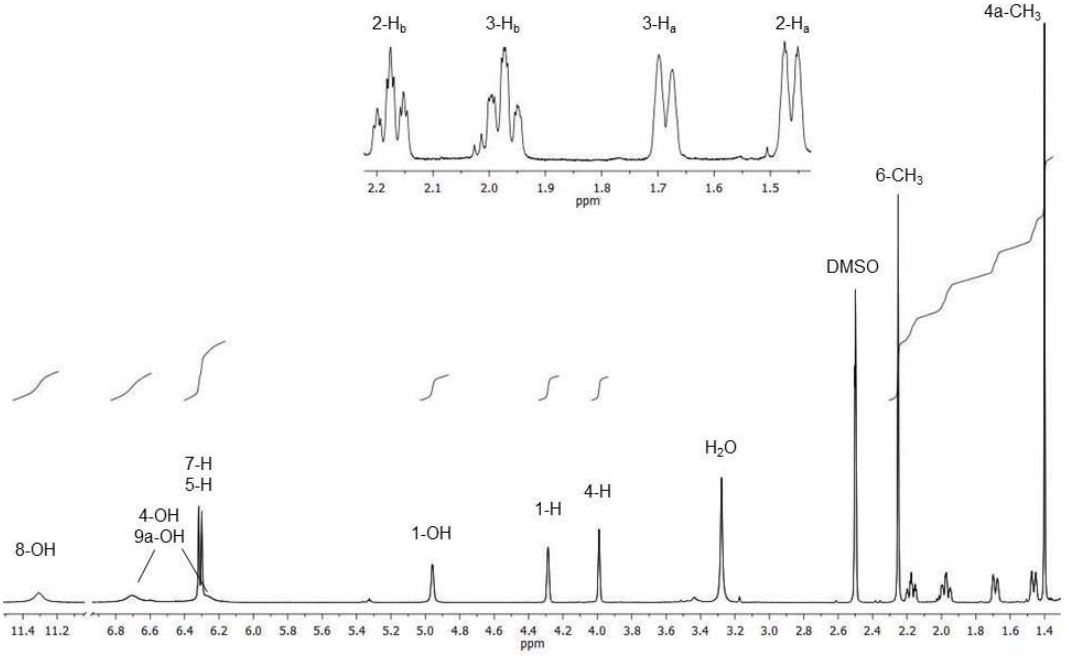


Figure 22: ^{1}H-NMR spectrum (600 MHz, DMSO-d_6) of (–)-diversonol (*ent*-**10**).

These protons at C-2 and C-3 share a similar chemical environment with respect to the adjacent hydroxyl groups 1-OH and 4-OH, the assignment therefore required the thorough analysis of the NOESY, COSY and HMBC spectra.

The 2D-NOESY experiment showed strong correlations of the angular methyl group at C-4a (δ = 1.40 ppm) to the protons 4-H (δ = 3.99 ppm) and 3-H_b (1.97 ppm), subsequently leading to the assignments of 2-H_a, 2-H_b and 3-H_a. Accordingly, 2-H_a resonates at δ = 1.46 ppm, as a doublet of doublet of triplets with the geminal and two vicinal coupling constants of ^2J = 14.0 and ^3J = 4.5 and 2.2 Hz. Based on these data, 2-H_a adopts a gauche conformation with respect to each 1-H, 3-H_a and 3-H_b, thus indicating an equatorial position. Similar reasoning revealed an equatorial orientation of 3-H_a which resonates at δ = 1.69 ppm as a broad doublet with ^2J = 14.1 Hz. Moreover these assignments are unambiguously confirmed by strong HMBC-correlations of 2-H_a to C-9_a and 3-H_a to C-4_a. The 3-H_b resonance at δ = 1.97 ppm appears as a triplet of doublet of doublets with the geminal and three vicinal coupling constants of ^2J = 14.0 and ^3J = 14.0, 4.5 and 2.4 Hz, respectively. As the last methylene proton of this spin system, 2-H_b resonates at δ = 2.17 ppm with ^2J = 14.1 and ^3J = 14.1 and 3.7 Hz. The large vicinal coupling constants of 2-H_b and 3-H_b indicate axial orientations of both protons. The chemical shifts of 4-H and 1-H at δ = 3.99 and 4.29 ppm both resonating as singlets are consistent with secondary protons adjacent to oxygen atoms. While the sharp doublet at δ = 4.96 ppm with J = 3.04 Hz unequivocally corresponds to the proton of 1-OH, the unambiguous assignment of 4-OH and 9a-OH to the broad singlets at δ = 6.27 and 6.71 ppm was ultimately not possible. The characteristic singlets at δ = 6.30 and 6.32 ppm correspond to the aromatic protons 5-H and 7-H. Finally, the proton of the phenolic 8-OH group is observed furthest downfield as a result of the intramolecular hydrogen bonding to the carbonyl moiety.

The upfield region of the ^{13}C-NMR spectrum (Figure 23) exhibits four signals which account for the methyl groups 4a-CH_3 and 6-CH_3 at δ = 19.4 and 21.9 ppm as well as for the methylene carbons C-2 and C-3 at δ = 22.6 and 24.8 ppm, respectively. The chemical shifts of the aliphatic methine (C-1, C-4) and quaternary carbon atoms (C-9a, C-4a) at δ = 66.2, 73.3, 75.5 and 81.0 ppm are in agreement with the inductive effect of the oxygen substituents. In the aromatic region of the spectrum, the carbon atoms C-8a, C-5 and C-7 resonate at δ = 104.4, 108.5 and 108.8 ppm followed by the downfield-shifted signals of C-6, C-10a and

C-8 at δ = 149.1, 158.3 and 161.5 ppm. The spectrum is completed by the carbonyl resonance of C-9 at δ = 194.0 ppm.

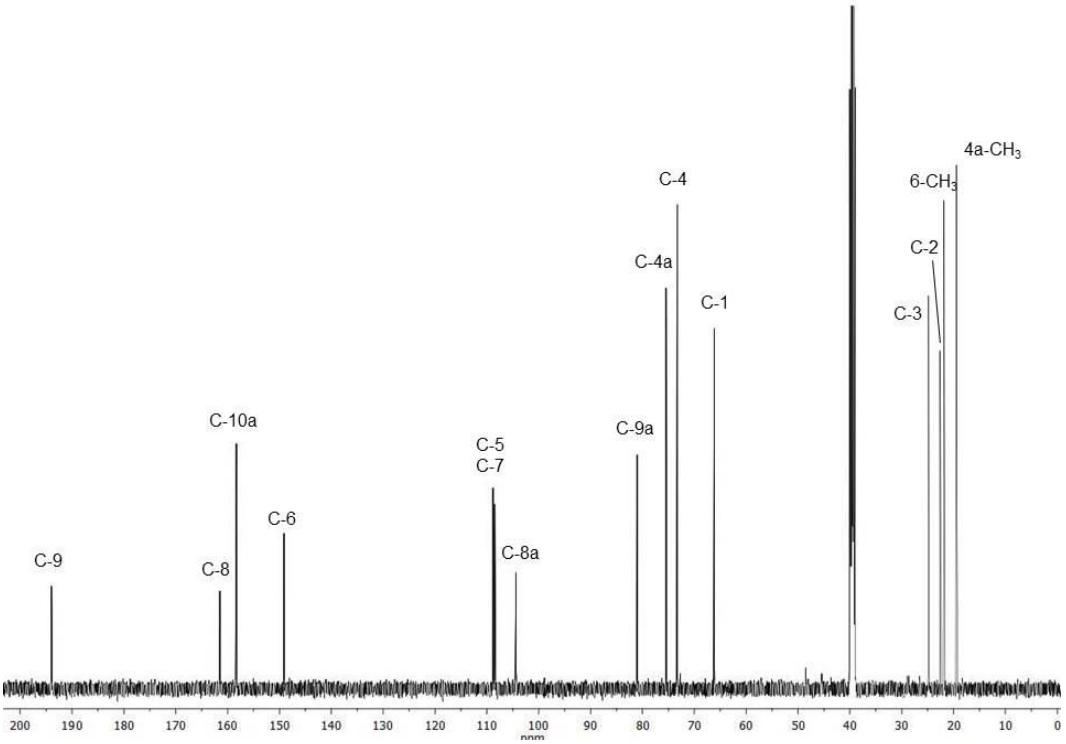


Figure 23: ^{13}C-NMR spectrum (125 MHz, DMSO-d_6) of (–)-diversonol (*ent*-**10**).

The IR spectrum of *ent*-**10** shows a sharp signal at 3554 cm^{-1} and two broad signals at 3410 and 3358 cm^{-1} which can be assigned to the hydroxyl groups. In addition to the CH-stretching band near 3000 cm^{-1}, the spectrum supports the presence of a carbonyl group resonating at 1655 cm^{-1}. The unusual low C=O stretching frequency results from conjugation of the carbonyl group with the aryl ring and the intramolecular hydrogen bonding to the aromatic 8-OH group. The sharp aromatic C-H out-of-plane bending vibration at 1630 cm^{-1} and in the finger print region at 883 and 850 cm^{-1} are typical for a 1,2,3,5- tetrasubstituted benzene ring.

In the ESI mass spectrum, the Na^+-adducts $[2M+Na]^+$ and $[M+Na]^+$ account for signals at *m*/*z* = 611.2 and 317.1 each with an intensity of 100%, while $[M+H]^+$ shows a signal at *m*/*z* = 295.1 with an intensity of 13%. Moreover, the measured high-resolution ESI-MS confirms the chemical formula $C_{15}H_{18}O_6$ for (–)-diversonol (*ent*-**10**).

The UV spectrum of *ent*-**10** displays bands at 349, 282 and 210 nm which correspond to π–π∗ and n-π∗ transitions of the chromanone chromophore. Comparison of the measured optical rotation ($[\alpha]_D$ = –62, c = 0.16 in MeOH, 22 °C) with the published value ($[\alpha]_D$ = +70, c = 0.33 in MeOH, 29 °C) supported the absolute configuration of (–)-diversonol (*ent*-**10**) to be (1*R*,4*R*,4a*R*,9a*S*).

3 Formal Synthesis of Siccanin

The mold metabolite siccanin (**25**), first isolated from *helminthosporium siccans*, is a potent antifungal and clinically applied against surface mycosis.[36-39] In addition to its biological activity, it features an interesting carbon framework comprising a chromanyl moiety embedded in an uncommon *cis*-*syn*-*cis*-fused alicyclic ring system. For these reasons, **25** represented an intriguing target to apply the asymmetric domino Wacker/carbonylation/ methoxylation reaction.

3.1 Retrosynthetic analysis of siccanin (25) and siccanochromene A (26a)

The retrosynthetic strategy to siccanin (**25**) intercepts the enantioselective approach reported by Trost *et al.* in which diol **105** was utilized as an advanced intermediate.[55] The same diol was identified as a ready target for the formal total synthesis as outlined in Figure 24. Retrosynthetic analysis revealed that dihydroxylation of alkene **263a** would lead to targeted diol **105**.

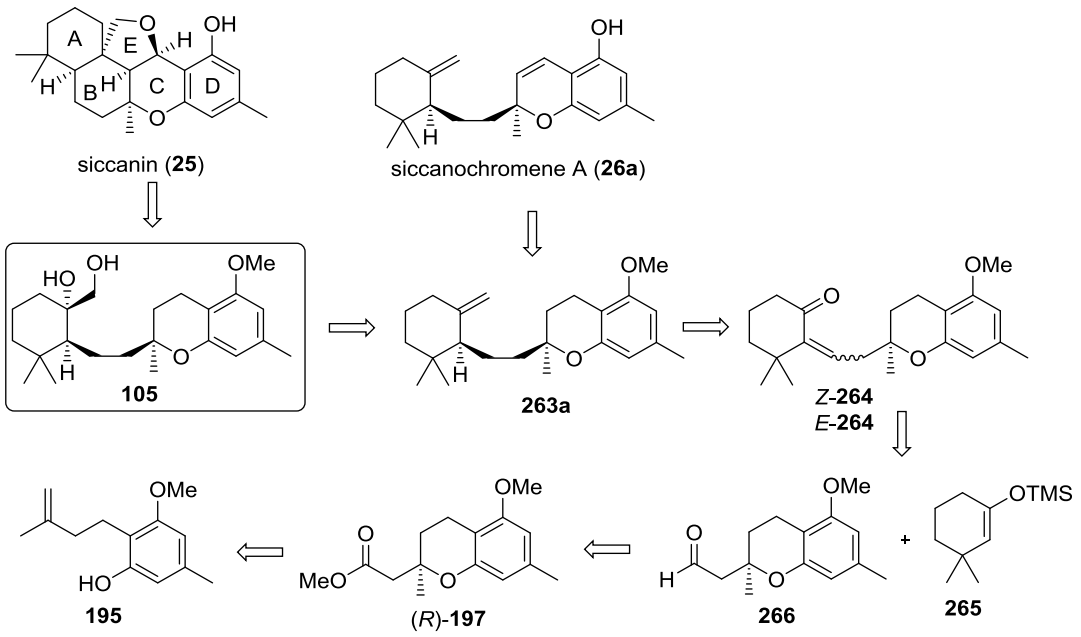


Figure 24: Retrosynthetic analysis of siccanin (**25**) by Trost's diol **105**, involving an aldol and a domino Wacker/carbonylation/methoxylation reaction as key steps.

In addition, alkene **263a** would enable access to the related natural product siccanochromene A (**26a**) following chromane oxidation and methyl ether cleavage. Alkene **264** was envisaged

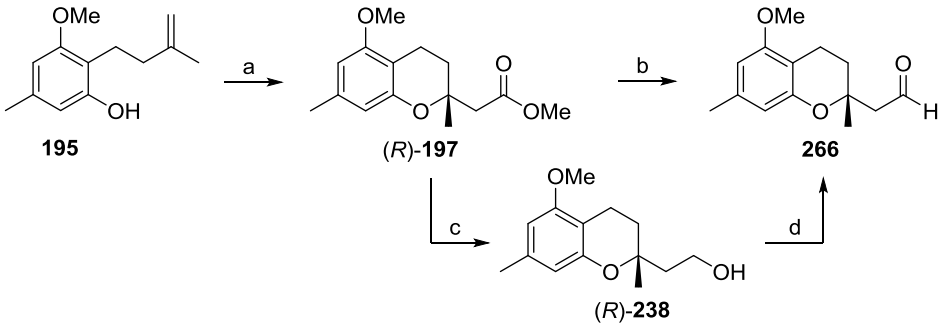
to derive from the α,β-unsaturated ketones *Z*-**264** or *E*-**264** by hydrogenation of the exocyclic double bond and methylenation of the carbonyl moiety.

The introduction of the cyclohexane ring may be achieved by an aldol reaction of silyl enol ether **265** and aldehyde **266** which in turn is accessible by reduction of methyl ester (*R*)-**197**. The efficient synthesis of (*R*)-**197** from phenolic precursor **195**, the key transformation of this PhD thesis, was proposed to proceed by an enantioselective domino Wacker/carbonylation/ methoxylation reaction.

3.2 Synthesis of alkene 263a

3.2.1 Syntheses of aldehyde 266 and silyl enol ether 265

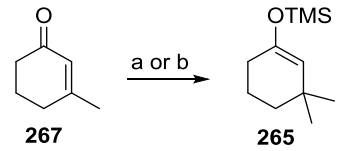
The synthesis of aldehyde **266** (Scheme 58) commenced with the enantioselective domino Wacker/carbonylation/methoxylation reaction of alkenyl phenol **195** (for the synthesis of **195**, Scheme 45) using the optimized conditions that were successfully applied in the total synthesis of (−)-diversonol (*ent*-**10**). To this end, alkenyl phenol **195** was treated with 5 mol% of $Pd(TFA)_2$, 20 mol% of the Bn-BOXAX ligand (*R*,*R*)-**140a** and four equivalents of the reoxidant *p*-benzoquinone in MeOH at RT under a CO-atmosphere (1 atm) to afford methyl ester (*R*)-**197** in 71% yield and 93% *ee* (see also Table 2).



Scheme 58: Synthesis of aldehyde **266**: a) $Pd(TFA)_2$, Bn-BOXAX (*R*,*R*)-**140a**, *p*-benzoquinone (4.0 eq.), MeOH, CO (1 atm), RT, 24 h, 71%, 93%; b) DIBAL-H (2.5 eq.), toluene, −78 °C, 20 min, 81% **267**, 16% (*R*)-**238**; c) $LiAlH_4$ (1.1 eq.), Et_2O, 0 °C → RT, 3 h, quant.; d) IBX (1.5 eq.), DMSO, RT, 2 h, 78%.

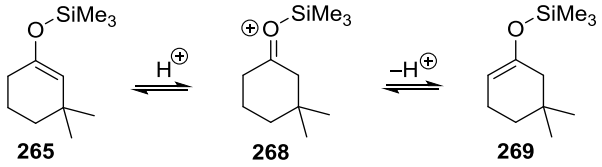
Careful reduction of (*R*)-**197** with DIBAL-H in toluene at −78 °C directly provided the desired aldehyde **266** in 81% yield, alongside overreduced alcohol (*R*)-**238** in 16%. On large scale, it proved to be more efficient to reduce ester (*R*)-**197** quantitatively to alcohol (*R*)-**238** using $LiAlH_4$, since it was possible to enrich the enantiomeric excess at the alcohol stage to ≥ 99% by preparative HPLC on a chiral IA® phase. The enantiopure alcohol (*R*)-**238** was subsequently oxidized with IBX to aldehyde **266** in 78% yield.

The enol coupling partner **265** was accessed by a methyl cuprate addition of 3-methyl-2-cyclohexanone (**267**) followed by trapping of the intermediate enolate as the TMS enol ether (Scheme 59). According to a standard procedure reported by Rubottom *et al*., cyclohexanone **267** was added to stoichiometric amounts of the preformed cuprate Me_2CuLi in Et_2O at −15 °C.[157] The reaction proceeded rapidly as evidenced by the instantaneous precipitation of polymeric $(MeCu)_n$. After stirring for further 15 min at −15 °C, a solution of trimethylsilyl chloride (3.2 eq.) and triethylamine (2.9 eq.) in Et_2O/HMPA (6:1) was added and the reaction mixture stirred at RT for further 4 h to give TMS enol ether **265** in 62% yield. While this method was successful in providing useful quantities of **265**, the use of stoichiometric amounts of copper iodide and carcinogenic HMPA made a change in the reaction conditions highly desirable.



Scheme 59: Synthesis of TMS enol ether **265**: method a: CuI (1.25 eq.), MeLi (2.5 eq.), Et_2O, −15 °C, 15 min, then TMSCl (3.2 eq.), NEt_3 (2.9 eq.), Et_2O/HMPA (6:1), −15 °C → RT, 4 h, 62%; method b: CuI (10 mol%), LiCl (20 mol%), MeMgCl (1.5 eq.), TMSCl (1.1 eq.), THF, −40 °C, 1 h, 84%.

Alternatively, Reetz *et al*. reported a Kharash-type conjugate addition of Grignard reagents catalyzed by CuI·2 LiCl.[158] When methyl magnesium chloride was added to a solution of 3-methyl-2-cyclohexanone (**267**), TMSCl and catalytic amounts of CuI (10 mol%) and LiCl (20 mol%) in THF at −40 °C, the desired silyl enol ether **265** was afforded in 84% yield after aqueous work-up.

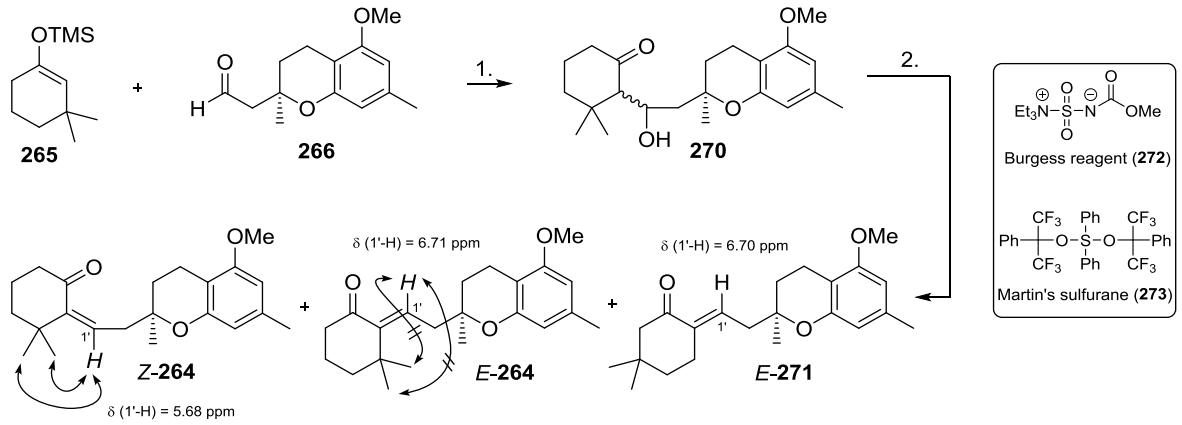


Scheme 60: Proposed isomerization of TMS enol ether **265**.

It should be noted that **265** was prone to isomerization of the enol double bond in the presence of acid to give an inseparable mixture of the regioisomers **265** and **269** (Scheme 60).[159] It was therefore crucial to distill all reagents and solvents prior to use and to perform the aqueous work-up quickly.

3.2.2 Aldol reaction of aldehyde 266 and silyl enol ether 265

With aldehyde **267** and silyl enol ether **265** in hand, the stage was set for the pivotal aldol reaction (Scheme 61). First, aldehyde **266** and TMS enol ether **265** were subjected to $BF_3 \cdot OEt_2$ in CH_2Cl_2/Et_2O (9:1) at −78 °C.[160] As the reaction progress was difficult to monitor by TLC, small aliquots were taken from the reaction mixture and analyzed by ^{1}H-NMR. Initially, all experiments seemed to indicate a very messy reaction with various unidentified side-products, however it was quickly identified that this happened only upon warming of the mixture to room temperature.



Scheme 61: Aldol reaction of aldehyde **266** and silyl enol ether **265** and NOE experiments of *Z*-**264** and *E*-**264**. The excited proton 1'-H is depicted in italic.

Accordingly, the reaction was quenched at −78 °C after TLC analysis indicated full conversion of aldehyde **266**. Attempts to promote the dehydration of the aldol adducts by acidic work-up or activation of the alcohol moiety and subsequent elimination using DEAD/PPh_3,[161] MsCl/DBU[162] or Ac_2O/pyridine were not successful. Conversely, subjection of the crude aldol adducts to Burgess reagent[142] at 80 °C in toluene under microwave irradiation afforded the α,β-unsaturated ketones *Z*-**264** and *E*-**264** in 20% and 13% yield, alongside 8% of the constitutional isomer *E*-**271** (*vide infra*) (Table 7, entry 1).

The double bond geometry of the α,β-unsaturated ketones *E*-**271**, *E*-**264** and *Z*-**264** was assigned by the different chemical shifts of the vinyl proton 1'-H. The magnetic anisotropy of the carbonyl group in *E*-**271** and the side-product *E*-**264** exerts a strong deshielding effect on 1'-H, whereas the carbonyl group in isomer *Z*-**264** is on the other side of the double bond and does not affect it. The assignments in *Z*-**264** and *E*-**264** were further supported by NOE experiments.

	conditions	*Z*-**264**	*E*-**264**	*E*-**271**
1	1. **266** (1.0 eq.), $BF_3 \cdot OEt_2$ (3 × 1.1 eq.), **265** (4 × 5.0 eq.), CH_2Cl_2/Et_2O (9:1), −78 °C, 23 h 2. **272** (3.0 eq.), toluene, 80 °C, mw, 30 min	20%	13%	8%
2	1. **265** (5.0 eq.), MeLi (5.0 eq.), THF 0 °C, 30 min, then **266** (1.0 eq.), −78 °C, 4 h 2. **274** (1.0 eq.), CH_2Cl_2, 0 °C → RT, 30 min	14%	21%	-
3	1. **265** (5.0 eq.), MeLi (5.0 eq.), Et_2O, 0 °C, 1 h, then $MgBr_2 \cdot OEt_2$ (5.0 eq.), 0 °C, 40 min, then **266** (1.0 eq.), −78 °C, 16 h 2. **273** (1.0 eq.), CH_2Cl_2, 0 °C → RT, 3 h	7%	47%	-
4	1. **265** (5.0 eq.), MeLi (5.0 eq.), THF, 0 °C, 30 min, then $ZnCl_2$ (5.0 eq.), −78 °C, 1 h, then **266** (1.0 eq.), −78 °C, 16 h 2. **273** (1.0 eq.), CH_2Cl_2, 0 °C → RT, 2 h	16%	44%	-

Table 7: Aldol condensation of aldehyde **266** and silyl enol ether **265**.

Thorough NMR analysis of *E*-**271** revealed that in this side product, the C-C bond formation occurred at the less hindered side of the cyclohexanone ring. Bearing the lability of silyl enol ether in mind, it was reasoned that the Lewis-acid $BF_3 \cdot OEt_2$ or the harsh dehydration conditions with Burgess reagent (**273**) might have triggered a retro-aldol reaction of the aldol adducts **271**, reflecting the relative stabilities of the kinetic and thermodynamic enolates as well as the steric congestion in **271**.[163]

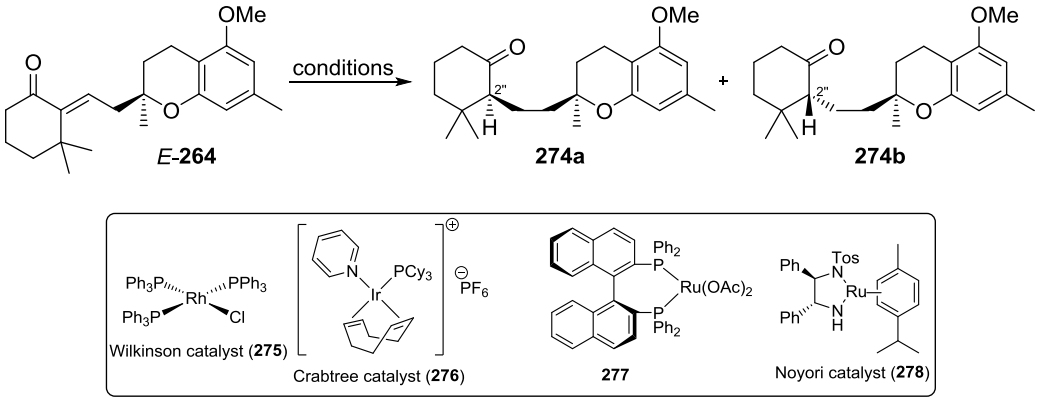
Efforts were therefore directed to suppress the formation of *E*-**271** by using milder conditions for both the aldol addition and the dehydration. Thus, TMS enol ether **265** was first transmetalated with methyl lithium and the resultant lithium enolate subsequently treated with aldehyde **266** at −78 °C (Table 7, entry 2). The crude aldol adducts were then treated with the mild dehydrating reagent Martin's sulfurane (**273**)[141] at room temperature to afford exclusively the desired isomers *Z*-**264** and *E*-**264** in 14% and 21% yield, respectively. The yield was further improved employing a second transmetalation of the lithium enolate of **265** with $MgBr_2 \cdot OEt_2$ (Table 7, entry 3). Addition of aldehyde **266** to the more nucleophilic Mg-enolate of **265** followed by dehydration of the aldol adducts with **273** led to 7% of *Z*-**264** and 47% of *E*-**264**. The best result in terms of yield were obtained with the Zn-enolate of **265** and

dehydration with **273** to give *Z*-**264** and *E*-**264** in an overall yield of 60% over 2 steps (Table 7, entry 4).

3.2.3 Hydrogenation of α,β-unsaturated ketone *E*-264

With the cyclohexane core in place, the hydrogenation of the α,β-unsaturated ketone was investigated (Scheme 62). For the stereoselective hydrogenation of exocyclic α,β-unsaturated ketones, only a few methods are known in the literature, most of which are limited to specific substitution patterns unlike the ones present in *E*-**264**.[164]

The hydrogenation of ketone *E*-**264**, the major diastereomer of the aldol reaction, was first attempted using homogenous reaction conditions. To this end, ketone *E*-**264** was exposed to the Wilkinson and Crabtree catalysts (**275**) and (**276**) at 50 psi of hydrogen in CH_2Cl_2 (Table 8, entries 1-2), however no product formation was observed in either reaction. Employing the ruthenium catalyst **277** endowed with a chiral BINAP backbone in CH_2Cl_2 at elevated pressure (50 psi) or temperature (50 °C) did not result in the reduction of the double bond either (Table 8, entries 3-4),[165] nor did Noyori's transfer hydrogenation catalyst (**278**) exhibit any reactivity towards *E*-**264** (Table 8, entry 5).



Scheme 62: Hydrogenation of α,β-unsaturated ketone *E*-**264**.

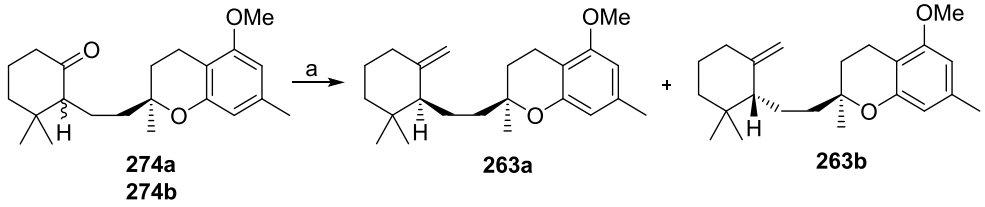
When *E*-**264** was subjected to catalytic amounts of palladium on charcoal (10 mol%) in CH_2Cl_2 at RT under a hydrogen atmosphere (1 atm), the reduction of the double bond occurred after 18 h as evidenced by the disappearance of the ^{1}H-NMR signal corresponding to the vinyl proton (Table 8, entry 6). Though the mixture of saturated ketones was not separable by column chromatography on silica gel, preparative HPLC on a chiral IB® phase provided the diastereomers **274a** and **274b** in 86% yield in a 1:1.1 ratio favoring the undesired epimer **274b**. The modest selectivity of the hydrogenation seems plausible considering the weak 1,4-stereoinduction of the remote chromanyl stereocenter.

	conditions	results
1	**275** (10 mol%), H_2 (50 psi), CH_2Cl_2, RT, 16 h	no conversion
2	**276** (10 mol%), H_2 (50 psi), CH_2Cl_2, RT, 24 h	no conversion
3	(*S*)-Ru(OAc)$_2$BINAP (**277**) (10 mol%), H_2 (1 atm), CH_2Cl_2, RT, 20 h, then 50 °C, 24 h	no conversion
4	(*S*)-Ru(OAc)$_2$BINAP (**277**) (10 mol%), H_2 (50 psi), CH_2Cl_2, RT, 25 h	no conversion
5	**278** (10 mol%), *i*PrOH, RT, 11 h, then 75 °C, mw, 9 h	no conversion
6	Pd/C (10 mol%), H_2 (1 atm), CH_2Cl_2, RT, 18 h	41% **274a**, 45% **274b**

Table 8: Hydrogenation of α,β-unsaturated ketone *E*-**264**.

3.2.4 Methylenation of the ketones 275a and 275b

The next step of the synthesis required the transformation of the carbonyl into an olefin moiety (Scheme 63).



274a
274b **263a** **263b**

Scheme 63: Methylenation of the ketones **274a** and **274b**.

The non-basic Lombardo methylenation, successfully applied in the synthesis of (−)-diversonol (*ent*-**10**), gave no conversion (Table 9, entry 1). The Wittig reaction of **274a** with the *in-situ* formed ylide of $MePPh_3Br$ and KO*t*Bu in THF did not bring about the olefination either (Table 9, entry 2). Nevertheless, the ^{1}H-NMR spectrum of the recovered starting material indicated that the stereochemical integrity of the α-chiral ketone **274a** was not affected under the basic reaction conditions. Replacing the base KO*t*Bu by *n*BuLi gave the more reactive lithium ylide which affected the desired methylenation as indicated by thin layer chromatography (Table 9, entry 3). However, the reaction showed incomplete conversion, even after reflux for 4 h leading to 38% of alkene **263a** and 57% of reisolated starting material. The inverse addition of a large excess (20 eq.) of the lithium ylide to ketone **274a** in THF by a syringe pump gave the desired alkene **263a** in 88% (Table 9, entry 4).

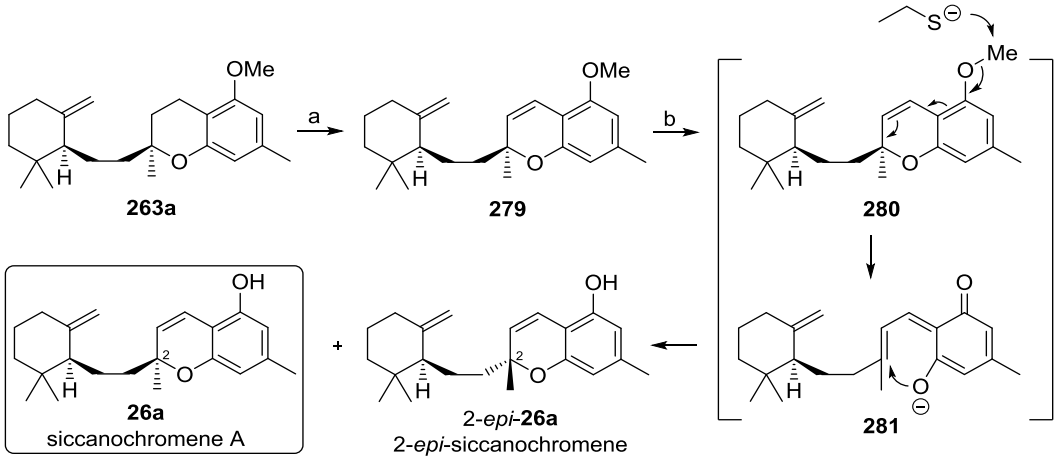
	substrate	conditions	results
1	**274a**	$TiCl_4$ (1.1 eq.), Zn (4.5 eq.), CH_2Br_2 (1.5 eq.), THF, 0 °C, 30 min, then **274a**, 0 °C → RT, 13 h	no conversion
2	**274a**	$MePPh_3Br$ (5.0 eq.), KO*t*Bu (5.0 eq.), THF, 0 °C → reflux, 1 h, then **274a**, 0 °C → RT, 4 h; RT → reflux, 4 h	no conversion
3	**274a**	$MePPh_3Br$ (5.0 eq.), *n*BuLi (5.0 eq.), THF, 0 °C → reflux, 1 h, then **274a**, 0 °C → RT, 4 h; RT → reflux, 4 h	38% **263a** (88% brsm)
4	**274a**	$MePPh_3Br$ (30 eq.), *n*BuLi (30 eq.), THF, 0 °C → RT, 30 min; ylide to **274a** by syringe pump, 0 °C → RT	88% **263a** (not pure)
5	**274a**	1. $TMSCH_2MgCl$, LiCl (2.0 eq.), Et_2O, 0 °C → RT, 20 h 2. NaH (9.9 eq.) THF, 100 °C, mw, 16 h	85% **263a**
6	**274b**	1. $TMSCH_2MgCl$, Et_2O, 0 °C → RT, 16 h 2. NaH (10 eq.) THF, 100 °C, mw, 19 h	78% **263b**

Table 9: Methylenation of the ketones **274a** and **274b**.

In spite of the excellent yield, the reaction was hampered by the tedious isolation of **263a** which exhibited a similar polarity as triphenylphosphine. Multiple column chromatographical separations on silica gel were necessary to purify **263a**, but substantial amounts of the phosphine remained in the product potentially affecting the intended osmium-catalyzed dihydroxylation in the next step. It was therefore decided to resort to a Peterson olefination (Table 9, entry 5).[166] In the first step, magnesium turnings were activated with catalytic amounts of 1,2-dibromoethane and refluxed in the presence of chloromethyltrimethylsilane in Et_2O for 1 h.[167] An excess of the stock solution and 2 equivalents of LiCl were added to ketone **274a** at 0 °C in Et_2O and the reaction stirred at RT for 20 h to give the diastereomeric alcohols in a 1:1 ratio. The alcohol mixture was then subjected to NaH in THF at 100 °C upon microwave irradiation to give alkene **263a** in 85% over 2 steps. A similar procedure furnished the epimeric alkene **274b** in 78% over 2 steps (Table 9, entry 6).

3.2.5 Synthesis of siccanochromene A (26a) and diol 105

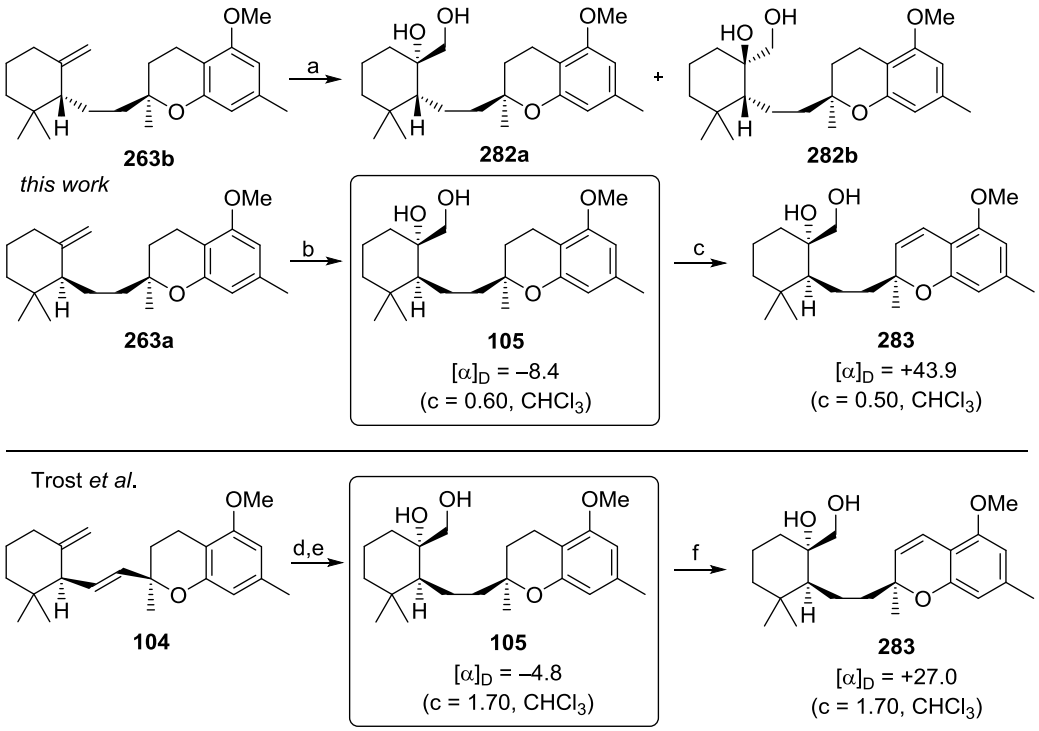
At this junction alkene **263a** was modified following 2 different pathways. Oxidation of the chromane to the chromene core and cleavage of the methyl ether gave access to the natural product siccanochromene A (**26a**) while a dihydroxylation of the terminal double bound of **263a** provided Trost's diol **105**, thus completing the formal synthesis of siccanin (**25**).



Scheme 64: Synthesis of siccanochromene A (**26a**) and proposed mechanism for the isomerization at C-2 by a retro 1,6-oxa-Michael addition: a) DDQ (3.0 eq.), benzene, reflux, 2 h, 83%; b) NaSEt (4.0 eq.), DMF, 120 °C, 10 h, 84%, **26a**/2-*epi*-**26a** = 1:1.

For the total synthesis of siccanochromene A (**26a**), **263a** was treated with 3 equivalents of DDQ in refluxing benzene for 2 h to give the corresponding chromene **279** in 83% yield (Scheme 64). The subsequent removal of the methyl group with NaSEt in DMF under microwave irradiation gave the demethylated product in 84% yield. Surprisingly, ^{1}H-NMR and analytical HPLC analysis of the isolated product indicated the formation of a 1:1 mixture of epimers at C-2 (numbering as in **26a**). Mechanistically, the epimerization at the quaternary stereocenter C-2 is proposed to proceed by a retro 1,6-oxa-Michael addition. The opening of the chromane ring system is most likely initiated by the nucleophilic attack of ethanethiolate. The resulting phenolate **281** can subsequently re-add to the α,β,γ,δ-unsaturated dienone in a non-stereospecific manner to give siccanochromene A (**26a**) and its C-2 epimer. A similar ring opening was also described by Trost *et al*.[55] A separation of **26a** and 2-*epi*-**26a** was not possible due to limited amount of time.

In order to complete the formal synthesis of siccanin (**25**), both chromane alkenes **263a** and **263b** were exposed to AD-mix β in the presence of methanesulfonamide in *t*BuOH/H_2O (1:1) at RT (Scheme 65).



Scheme 65: Synthesis of key compound **105**: a) AD-mix β, $MeSO_2NH_2$ (1.0 eq.), *t*BuOH/H_2O (1:1), 4 d, 91%, d.r. = 4:1; b) AD-mix β, $MeSO_2NH_2$ (1.0 eq.), *t*BuOH/H_2O (1:1), 5 d, 90%; c) DDQ (3.0 eq.), benzene, 80 °C, 2 h, 63%; d) AD-mix β, $MeSO_2NH_2$ (2.3 eq.), *t*BuOH/H_2O (1:1), 20 h, 94%, d.r. = 10:1; e) PtO_2 (20 mol%), H_2 (1 atm), EtOAc, 70 °C, 5 h, 82%; f) DDQ (1.7 eq.), benzene, 80 °C, 45 min, 91%.

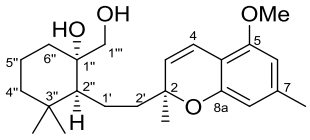
While the dihydroxylations of both compounds proceeded sluggishly and required multiple additions of AD-mix β to ensure complete conversion, the products were isolated in excellent yields. Conversion of **263b** afforded an unseparable 4:1 mixture of diastereoisomers **282a** and **282b** in 91% yield, while diol **105**, displaying the C-2 configuration present in siccanin (**25**), was obtained in 90% yield as the exclusive isomer.

The spectroscopic data of key compound **105** (^{1}H-NMR, ^{13}C-NMR, UV/VIS, IR, MS) were in agreement with those published for this intermediate.[55] However, the measured optical rotation of **105** $[\alpha]_D = –8.4$ (c = 0.60, $CHCl_3$, 24.0 °C) differed significantly from the value reported by Trost *et al*. $[\alpha]_D = –4.8$ (c = 1.70, $CHCl_3$). In order to clarify this ambiguity, the next step in Trost's synthesis of siccanin (**25**) was conducted as well. Diol **105** was oxidized with DDQ in refluxing benzene for 2 h to furnish chromene **283** in 63%. Again, the spectroscopic data of **283** (^{1}H-NMR, ^{13}C-NMR, UV/VIS, IR, MS) matched those reported by Trost *et al*. However, the measured optical rotation of chromene **283** $[\alpha]_D = +43.9$ (c = 0.50, $CHCl_3$, 24.6 °C) was again significantly higher than the published value of $[\alpha]_D = +27$ (c = 1.01, $CHCl_3$). A possible explanation for this mismatch may be seen in the purity of **105** and **283** in Trost's synthesis. The seminal paper states that the dihydroxylation proceeded

with a diastereoselectivity of 9:1, but from the experimental section is not clear if the optical rotation values correspond to pure **105** or the diastereomeric mixture.

In conclusion, as part of this doctoral project both the total synthesis of siccanochromene A (**26a**) and the formal synthesis of siccanin (**25**) were performed in a total of eight and seven steps, respectively. Key to the syntheses was the enantioselective domino Wacker/carbonylation/methoxylation to access chromane **195** and the two-step aldol condensation to install the pendant cyclohexyl moiety.

3.2.6 Spectroscopic data of diol 283



283

The ^{1}H-NMR spectrum of diol **283** (Figure 25) exhibits characteristic singlets at δ = 0.72 and 0.94 ppm, each integrating for 3 protons, which can be assigned to the geminal methyl groups at C-3".

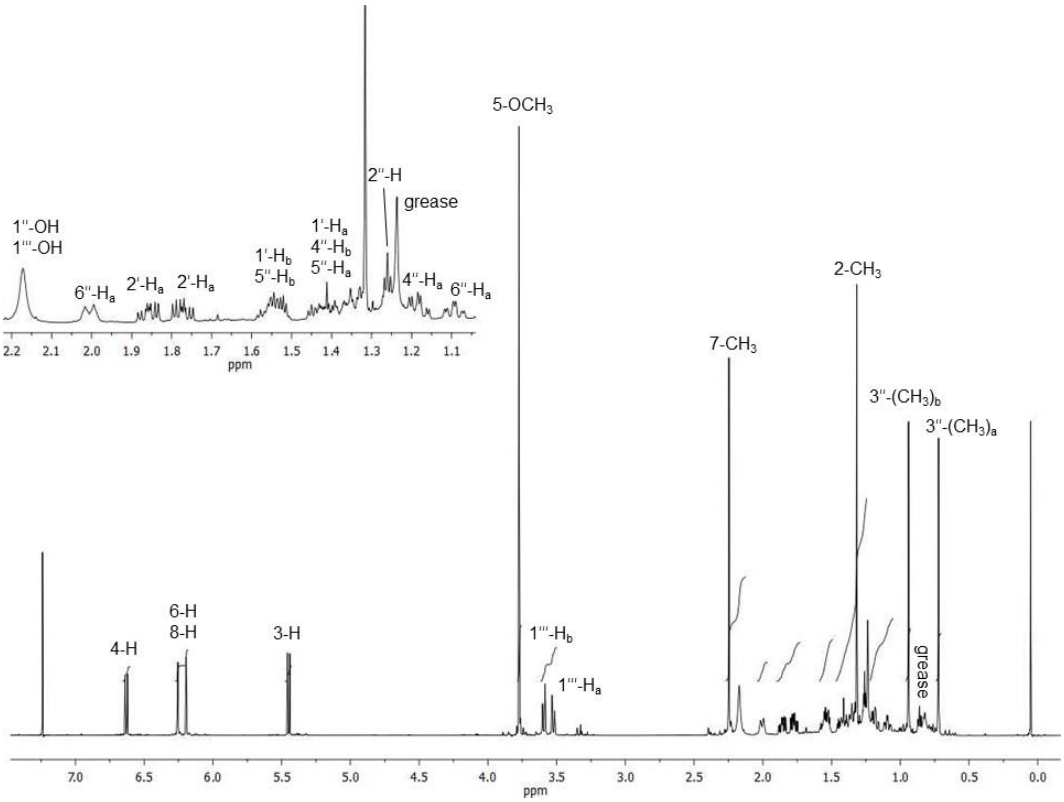


Figure 25: ^{1}H-NMR (600 MHz, $CDCl_3$) of diol **283**.

The methylene protons 6"-H_a and 4"-H_a resonate at δ = 1.09 and 1.18 ppm each as triplet of doublets with the geminal coupling constants of ^{2}J = 12.6 and 12.9 Hz, respectively. The

vicinal coupling constants of ^{3}J = 12.6 and 3.0 Hz for 6''-H_a and ^{3}J = 12.9 Hz and 4.0 Hz for 4''-H_a indicate that both protons adopt axial positions. The triplet at δ = 1.26 ppm with the coupling constant of J = 4.6 Hz for 2''-H is followed by the characteristic singlet at δ = 1.32 ppm which corresponds to the angular methyl group at C-2. The multiplets at δ = 1.32−1.46 ppm and δ = 1.50−1.59 ppm comprise the aliphatic protons 1'-H_2, 4''-H_b and 5''-H_2. The signals at δ = 1.77 and 1.86 ppm resonate each as doublet of doublet of doublets with the coupling constants of J = 13.8, 11.4, 5.3 Hz and J = 13.8, 11.5, 5.1 Hz, respectively. Both signals display strong HMBC correlations to the quaternary chromene carbon atom C-2 and can thus be assigned to the methylene protons 2'-H_a and 2'-H_b. According to the HSQC spectrum, the methylene proton 6''-H_b resonates at δ = 2.01 ppm as a broad doublet with the geminal coupling constant of ^{2}J = 12.9 Hz. It is interesting to note that the chemical shifts of the diastereotopic protons at C-6'' differ considerably (Δδ = 0.92 ppm) which can be attributed to the varying deshielding effect of the adjacent diol moiety on 6''-H_a and 6''-H_b. The broad singlet at δ = 2.17 ppm of the two hydroxyl groups and the sharp singlet at δ = 2.25 ppm of the C-7 methyl group complete the upfield region of the spectrum. The chemical shifts of the doublets at δ = 3.52 and 3.59 ppm and the sharp singlet at δ = 3.77 ppm are consistent with the diastereotopic protons 1'''-H_a and 1'''-H_b of the diol moiety and the methyl aryl ether. The chromene protons 3-H and 4-H resonate at δ = 5.45 and 6.63 ppm as doublets with the common vicinal coupling constant of ^{3}J = 10.0 Hz. The singlets at δ = 6.19 and 6.26 ppm of the aromatic protons 6-H and 8-H finally complete the spectrum.

The upfield region of the ^{13}C-NMR spectrum of diol **283** (Figure 26) exhibits in total 10 aliphatic signals which were assigned by HSQC and HMBC correlations. The methylene carbons C-1', C-5'', C-6'', C-4'' and C-2' were assigned to the resonances at δ = 19.7, 20.0, 35.5, 36.0, 40.7 and 43.8 ppm, respectively. In addition to the quaternary carbon C-3'' at δ = 36.0, the methyl groups 7-CH_3, 3''-$(CH_3)_a$, 2-CH_3, 3''-$(CH_3)_b$ resonate at δ = 22.0, 22.8, 26.1 and 32.4 ppm. The characteristic signal of the methoxy group at C-5 at δ = 55.5 is followed by the methine carbon C-2'' at 55.6 ppm. The chemical shifts of the carbon atoms C-1'', C-1''' and C-2 at δ = 63.6, 75.7 and 78.6 ppm are consistent with the inductive effect of the oxygen substituents.

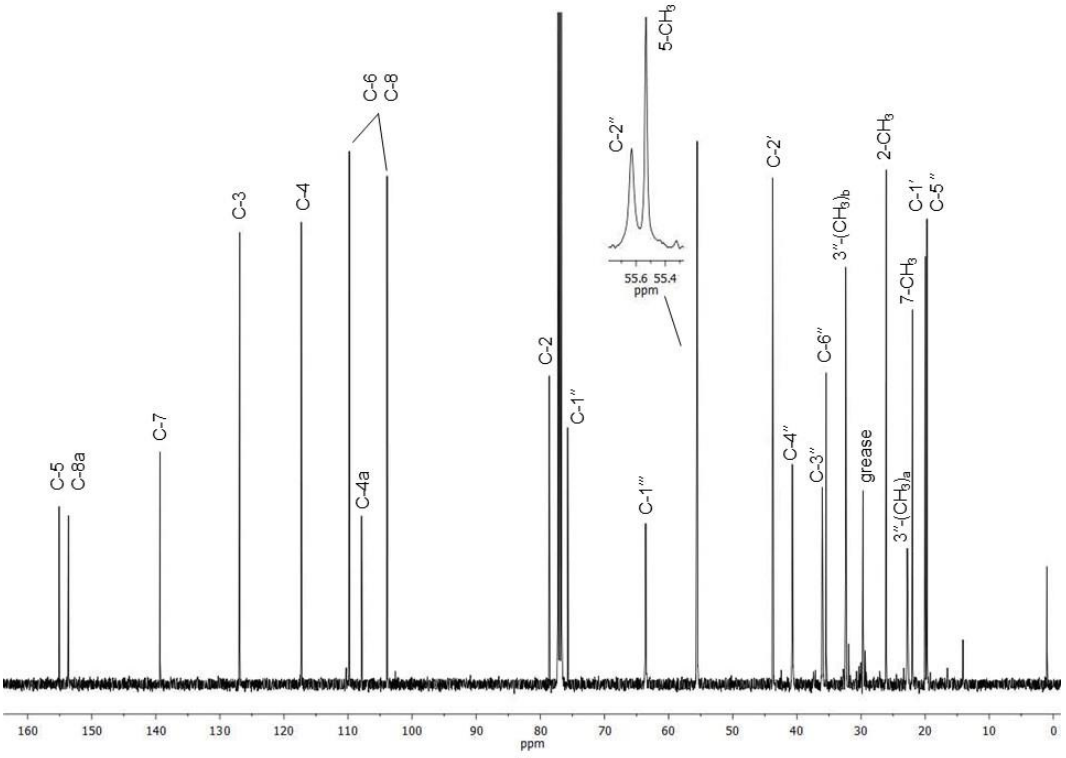


Figure 26: ^{13}C-NMR (125 MHz, $CDCl_3$) of diol **283**.

The unambiguous assignment of C-1‴ and C-2 was confirmed by strong HMBC correlations of C-2 to the adjacent protons 2-H_a, 3-H and 2-CH_3. The aromatic region of the spectrum exhibits the signals of the carbon atom C-6, C-4a and C-8 at δ = 103.9, 107.9 and 109.8 ppm. Further downfield-shifted are the resonances of C-3 and C-4 at δ = 117.3 and 126.9 ppm. The spectrum is completed by the signals of C-7, C-5 and C-8a at δ = 139.4, 153.6 and 155.1 ppm. In the ESI-mass spectrum of diol **283**, the dimer $[2M+Na]^+$ accounts for the base peak at *m*/*z* = 771.5. The signals of the adducts $[M+Na]^+$ and $[M+H]^+$ at *m*/*z* = 397.2 and *m*/*z* = 375.3 with the intensities of 73% and 21% are followed by the resonance of $[M-OH]^+$ at *m*/*z* = 357.2 (56%). The measured high-resolution ESI-MS confirms the chemical formula $C_{23}H_{34}O_4$ for diol **283**.

4 Enantioselective Total Synthesis of (–)-Blennolide C and (–)-Gonytolide C

For the first enantioselective total syntheses of the tetrahydroxanthenone (–)-blennolide C (*ent*-**7c**) and the structurally related γ-lactonyl chromanone (–)-gonytolide C (*ent*-**7c**) a stereodivergent strategy was employed using an enantioselective domino Wacker/ carbonylation/methoxylation reaction and a highly selective Sharpless dihydroxylation as key steps.

4.1 Retrosynthetic analysis of (–)-blennolide C (*ent*-7c) and (–)-gonytolide C (*ent*-9c)

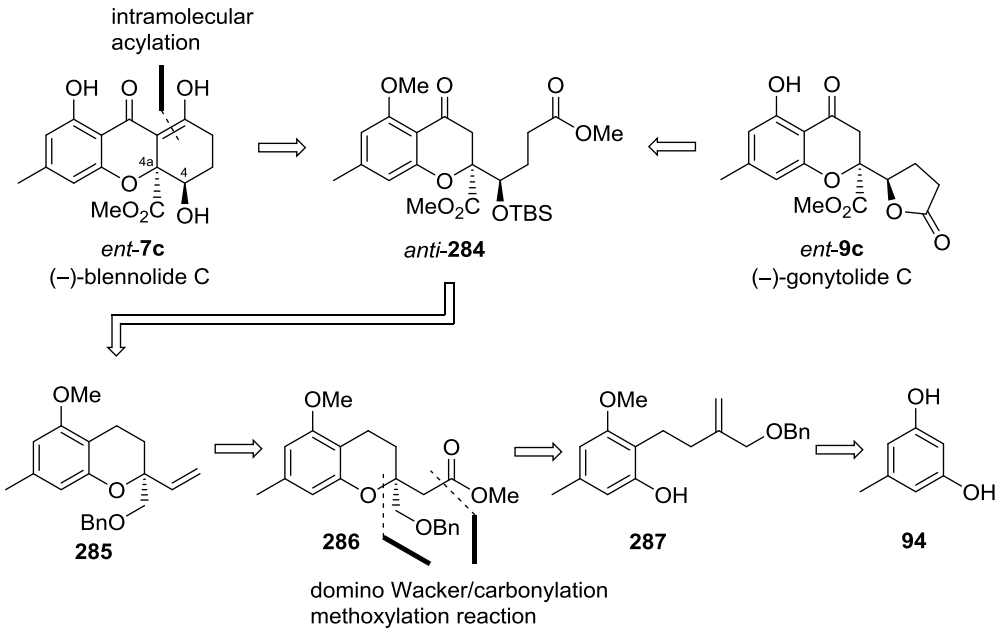


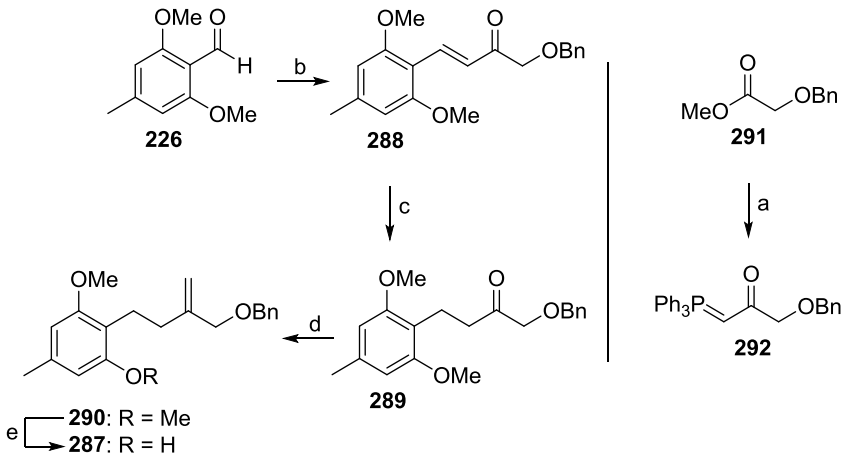
Figure 27: Retrosynthetic analysis of (–)-blennolide C (*ent*-**7c**) and (–)-gonytolide C (*ent*-**9c**).

Retrosynthetic analysis reveals that both *ent*-**7c** and *ent*-**9c** can be accessed from advanced intermediate *anti*-**284** (Figure 27). Chromanone *anti*-**284** can be transformed into *ent*-**7c** by intramolecular acylation and global deprotection, while a desilylating lactonisation followed by demethylation would enable access to *ent*-**9c**. Synthesis of *anti*-**284** may be achieved from **285** by C-4 hydroxylation (numbering as in *ent*-**7c**), chain elongation and benzylic oxidation. The efficient access of chromane **285** from phenolic precursor **287**, the key transformation in this PhD thesis, was proposed to proceed by the enantioselective domino-Wacker/carbonylation/methoxylation reaction. The devised strategy followed the successful synthesis of (–)-diversonol (*ent*-**10**) and (–)-blennolide A (*ent*-**7a**).[126]

4.2 Synthesis of (–)-blennolide C (*ent*-7c) and (–)-gonytolide C (*ent*-9c)

4.2.1 Synthesis of domino precursor 287

The synthesis of the domino precursor **287** (Scheme 66) commenced with the synthesis of phosphorane **292** which can be easily accessed from methyl glycolate **291** and the lithium ylide of Ph_3PCH_3Br. A high-temperature Wittig olefination of aldehyde **226** and phosphorane **292** yielded the α,β-unsaturated ketone **288** in 89%.



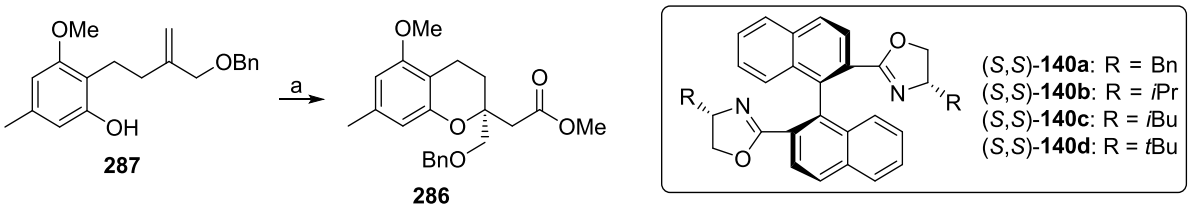
Scheme 66: Synthesis of domino precursor **287**: a) Ph_3PCH_3Br (2.2 eq.), *n*BuLi (2.2 eq.), THF, 0 °C, 20 h, 91%; b) **292** (1.3 eq.), toluene, reflux, 19.5 h, 89%; c) 1. PtO_2 (4 mol%), H_2 (1 atm), EtOAc, RT, 2 h; 2. IBX (0.4 eq.), CH_3CN, 80 °C, 1 h, 91% (2 steps); d) Ph_3PCH_3Br (3.0 eq.), *n*BuLi (2.8 eq.), THF, 0 °C → RT, 4 h, 93%; e) NaSEt (2.3 eq.), DMF, 120 °C, 21 h, 87% (92% brsm).

The subsequent reduction of **288** with catalytic amounts of platinum oxide (4 mol%) in EtOAc under a hydrogen atmosphere (1 atm)[168] and oxidation of the reaction intermediates with IBX in refluxing acetonitrile gave rise to saturated ketone **289** in 91%. The terminal alkene moiety was introduced by a second Wittig reaction with the lithium ylide of Ph_3PCH_3Br, providing olefin **290** in 93% yield. A chemoselective mono-demethylation with NaSEt finally afforded alkenyl phenol **287** in 87% yield (92% brsm).

4.2.2 Domino Wacker/carbonylation/methoxylation reaction of alkenyl phenol 287

The enantioselective synthesis of (–)-diversonol C (*ent*-**10**) illustrated that the domino Wacker/carbonylation/methoxylation reaction represents a powerful synthetic method to install the quaternary stereocenter of the chromane ring with the concomitant introduction of

the side-chain necessary to install the C-ring. Furthermore, it was shown that steric tuning at the C-4 position of the BOXAX-oxazoline ring has a major influence on the catalytic activity and the enantioselectivity of the reaction. A ligand survey was therefore conducted to optimally adjust the ligand structure to domino precursor **287** (Table 10).



Scheme 67: Enantioselective synthesis of methyl ester **286**: a) $Pd(TFA)_2$ (5 mol%), (*S*,*S*)-BOXAX ligand (20 mol%), *p*-benzoquinone (4.0 eq.), MeOH, CO (1 atm), RT, 24 h.

	ligand	yield [%]	*ee* [%][a]
1	Bn-BOXAX (*S*,*S*)-**140a**	68	93
2	*i*Pr-BOXAX (*S*,*S*)-**140b**	62	>99
3	*i*Bu-BOXAX (*S*,*S*)-**140c**	68	99
4	*t*Bu-BOXAX (*S*,*S*)-**140d**	7	-[b]

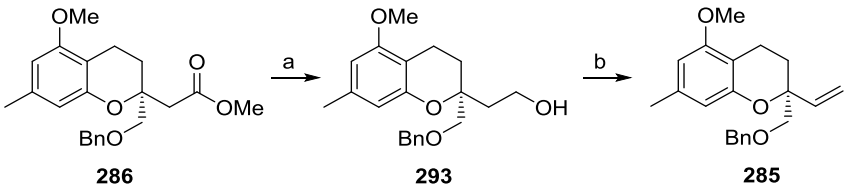
Table 10: Ligand screening for the enantioselective domino Wacker/carbonylation/methoxylation reaction: [a] Determined by analytical HPLC (Chiracel IB®, *n*hexane/*i*PrOH = 98:2, 234 nm); [b] Not determined.

Alkenyl phenol **287** was first treated with catalytic amounts of $Pd(TFA)_2$ (5 mol%) and Bn-BOXAX ligand (*S*,*S*)-**140a** (20 mol%) as well as 4 equivalents of the reoxidant *p*-benzoquinone. The reaction was run in MeOH under a CO-atmosphere (1 atm) at RT to provide methyl ester **268** in very good 68% yield and 93% *ee* (Table 10, entry 1). The use of ligand (*S*,*S*)-**140b** endowed with an *iso*-propyl group gave rise to the domino product **286** in a slightly decreased yield of 62% and excellent >99% *ee* (Table 10, entry 2). The *i*Bu-BOXAX ligand (*S*,*S*)-**140c** resulted in both a very good yield of 68% and an excellent enantioselectivity of 99% *ee* (Table 10, entry 3). With only 7% of **286** isolated, the bulky *t*Bu-BOXAX ligand (*S*,*S*)-**140d** exhibited the lowest catalytic activity which most likely originates from a weak coordination of the olefin to the catalyst (Table 10, entry 4).

It is interesting to note that the substitution pattern on the oxazoline ring seems to exert no or only little effect on domino precursor **287** with respect to the isolated yield (62–68%). Dependent on the BOXAX ligand, the corresponding alkenyl phenol **195** with a methyl group instead of a benzyloxymethyl group exhibited yields ranging from 8 to 76% yield (Table 2). A possible explanation for this discrepancy might involve a stabilizing interaction between the

catalyst and the pendant benzyloxymethyl group of **287**, thus leading to an increased catalytic activity.

Reduction of ester **286** with $LiAlH_4$ and subsequent elimination following the Grieco protocol gave vinyl chromane **285** in 90% over 3 steps (Scheme 68).[144]



Scheme 68: Synthesis of vinyl chromane **285**: a) $LiAlH_4$ (1.1 eq.), Et_2O, 0 °C → RT, 2 h, quant.; b) 1. *n*Bu_3P (2.4 eq.), *o*-NO_2-C_6H_4SeCN (**241**) (2.5 eq.), THF, 0 °C, 4 h; 2. *m*CPBA (2.5 eq.), CH_2Cl_2, –40 °C, 1 h, *i*Pr_2NH (5.0 eq.), –40 °C → RT, 15 h, 90% (2 steps).

4.2.3 Sharpless dihydroxylation of vinyl chromane 285

With vinyl chromane **285** in hand, the stage was set for the introduction of the C-4 hydroxyl group (numbering as in *ent*-**7c**). The targets blennolide C (*ent*-**7c**) and gonytolide C (*ent*-**9c**) display an *anti*-relationship between the oxygen at C-4 and the substituent at C-4a. On the other hand, an intermediate with a *syn*-orientated hydroxyl group at C-4 would lead to the monomeric unit of the rugulotrosins. In this regard, the Sharpless dihydoxylation was particularly intriguing as it allowed the stereoselective access of both C-4 epimers.[94]

According to the common mnemonic, the use of AD-mix α preferentially guides the dihydroxylation to the bottom face of the olefin leading to the diastereomer *anti*-**294**. The initial experiment with commercial AD-mix α and methansulfonamide (1 eq.) in a 1:1 mixture of *t*BuOH/H_2O at RT gave the diastereomeric diols *anti*-**294** and *syn*-**294** in a good combined yield of 64% and a modest *anti*/*syn* ratio of 2.4:1 (Table 11, entry 1). It is known that the catalytic activity and the stereoselectivity are considerably influenced by the O-9 substituent of the cinchona ligand backbone (Figure 28).

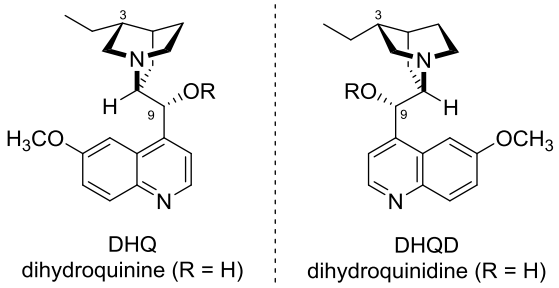
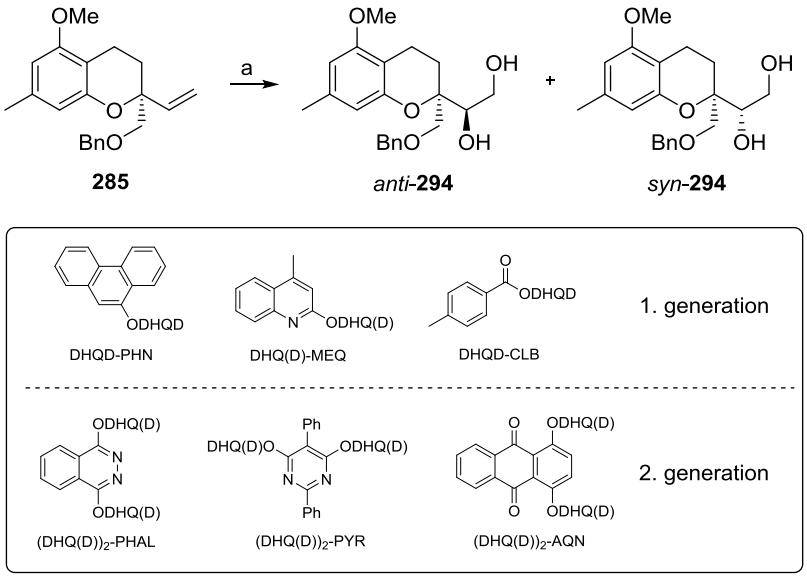


Figure 28: The cinchona alkaloids dihydroquinine (DHQ, left) and dihydroquinidine (DHQD, right) are diastereomers (pseudoenantiomers) as a result of the ethyl group at C-3.

A ligand survey was initiated to increase the catalyic performance using 5 mol% of potassium osmate(VI), 10 mol% of the ligand as well as stoichiometric amounts of potassium carbonate (6 eq.), potassium ferricyanide (6 eq.) and methansulfonamide (1 eq.) in a 1:1 mixture of *t*BuOH/H_2O at RT. When vinyl chromane **285** was treated with phthalazine-based $(DHQ)_2$-PHAL, the ligand present in the commercial AD-mix α, the diols *anti*-**294** and *syn*-**294** were obtained in a very good yield of 82%, albeit in a low 1.8:1 ratio (Table 11, entry 2). The use of $(DHQ)_2$-PYR, which is the ligand of choice for monosubstituted terminal olefins, resulted in an excellent yield of 90% and a diastereoselectivity of d.r. = 4.3:1 (Table 11, entry 3). The monomeric, "first generation" ligand DHQ-MEQ exerted an even higher selectivity with d.r. = 6.7:1, but at the expense of a slightly decreased yield of 84% (Table 11, entry 4). The best result in terms of diastereoselectivity was achieved with the $(DHQ)_2$-AQN ligand endowed with a anthraquinone spacer at O-9 to give *anti*-**294** and *syn*-**294** in 77% yield and an excellent 13.7:1 ratio (Table 11, entry 5).

For an entry to the C-4 epimer of blennolide C, ligands of the dihydroquinidine (DHQD) family were surveyed to selectively provide diol *syn*-**294**. In agreement with the mnemonic, commercial AD-mix-β was able to reverse the selectivity, furnishing *anti*-**294** and *syn*-**294** in combined yield of 93% and a 1:1.7 ratio (Table 11, entry 6). The use of AD-mix β and additional potassium osmate(VI) (5 mol%), $(DHQD)_2$-PHAL (10 mol%) and reoxidant potassium persulfate often referred to as "Super AD-mix" had no effect on the reaction outcome (Table 11, entry 7). However, subjecting vinyl chromane **285** to the individual components of AD-mix β increased the *anti*/*syn*-ratio to 1:2.2 (Table 11, entry 8). The ligands $(DHQD)_2$-PYR and DHQD-CLB exterted low stereoinduction (Table 11, entries 9-10) whereas DHQD-MEQ and $(DHQD)_2$-AQN gave increased selectivities of 1:3.1 and 1:3.0, respectively (Table 11, entry 11-12). Terminal olefins bearing an allylic heteroatom are known to be problematic for the Sharpless dihydroxylation. For these special substrates, the monomeric phenanthryl ether-based ligand DHQD-PHN was reported to give reasonable selectivies.[94c,169]



Scheme 69: Sharpless dihydroxylation of vinyl chromane **285**: a) $K_2OsO_4 \cdot 2\ H_2O$ (5 mol%), ligand (10 mol%), K_2CO_3 (6.0 eq.), $K_3Fe(CN)_6$, (6.0 eq.) $MeSO_2NH_2$ (1.0 eq.), *t*BuOH/H_2O (1:1), RT.

	ligand	time	yield [%]	*anti*-**294**:*syn*-**294** [a]
1	AD-mix-α[a]	4 d	64	2.4:1
2	$(DHQ)_2$-PHAL	2 d	82	1.8:1
3	$(DHQ)_2$-PYR	2 d	90	4.3:1
4	DHQ-MEQ	3 d	84	6.7:1
5	$(DHQ)_2$-AQN	3 d	77	13.7:1
6	AD-mix-β[b]	3 d	94	1:1.7
7	Super-AD-mix-β [c]	2 d	93	1:1.7
8	$(DHQD)_2$-PHAL	2 d	80	1:2.2
9	$(DHQD)_2$-PYR	2 d	90	1:1.9
10	(DHQD)-CLB	2 d	90	1:1.5
11	(DHQD)-MEQ	2 d	89	1:3.1
12	$(DHQD)_2$-AQN	3 d	93	1:3.0
13	(DHQD)-PHN	2 d	88	1:3.7

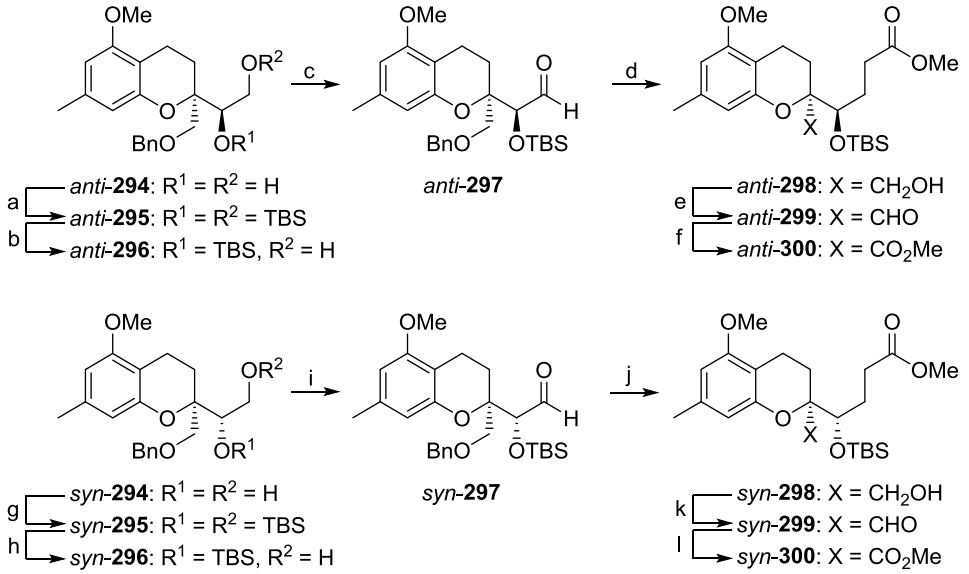
Table 11: Sharpless dihydroxylation of vinyl chromane **285**: [a] Commercial AD-mix α used; [b] Commercial AD-mix β used; [c] "Super AD-mix β": commercial AD-mix β, $K_2OsO_4 \cdot 2\ H_2O$ (1 mol%) $(DHQD)_2$-PHAL (5 mol), $K_2OsO_4 \cdot 2\ H_2O$ (1.0 eq), $MeSO_2NH_2$ (1.0 eq.).

Indeed, the use of DHQD-PHN gave *anti*-**294** and *syn*-**294** in 88% yield and a 1:3.7 ratio (Table 11, entry 13), the best result obtained in this optimization process.

It should be noted that the chiral ligand has to override the intrinsic diastereofacial preference of the olefin substrate. Moreover, calculations on the dihydroxylation of a related allylic olefin by Denmark *et al*. suggests a high degree of rotational freedom for the vinyl group.[169c] It was thus reasoned that many reactive conformations can engage in the coordination of the osmium-ligand complex leading to lower diasteroselectivities.

4.2.4 Syntheses of the chromanones *anti*-284 and *syn*-284

The syntheses of the chromanones *anti*-**284** and *syn*-**284** commenced with the protection of the respective enantiopure diols *anti*-**294** and *syn*-**294** (Scheme 70).



Scheme 70: Syntheses of chromanes *anti*-**300** and *syn*-**300**: a) TBSOTf (4.0 eq.), 2,6-lutidine (5.0 eq.), CH_2Cl_2, 0 °C, 2.5 h, 96%; b) HF·pyidine (40 eq.), THF/pyridine (5:1), 0 °C → RT, 24 h, 85% (98% brsm); c) DMP (2.0 eq.), CH_2Cl_2, 0 °C → RT, 2 h, 96%; d) 1. $(MeO)_2P(O)CH_2CO_2Me$ (1.7 eq.), NaH (1.3 eq.), THF, 0 °C, 30 min, then *anti*-**297**, THF, 0 °C → RT, 2 h; 2. Pd/C (10 mol%), H_2 (4 bar), MeOH, 2 d, 90% (2 steps); e) DMP (3.0 eq.), CH_2Cl_2, 0 °C → RT, 2 h, 92%; f) KOH (32 eq.), I_2 (14 eq.), MeOH, 0 °C → RT, 9 h, 100%; g) TBSOTf (4.0 eq.), 2,6-lutidine (5.0 eq.), CH_2Cl_2, 0 °C, 2.5 h, 98%; h) HF·pyridine (40 eq.), THF/pyridine (5:1), 0 °C → RT, 30 h, 81% (89% brsm); i) DMP (2.0 eq.), CH_2Cl_2, 0 °C → RT, 2 h, 98%; k) 1. $(MeO)_2P(O)CH_2CO_2Me$ (1.7 eq.), NaH (1.3 eq.), THF, 0 °C, 30 min, then *syn*-**297**, THF, 0 °C → RT, 2 h; 2. Pd/C (10 mol%), H_2 (4 bar), AcOH (10 eq.), MeOH, 3 d, 91% (2 steps); k) DMP (3.0 eq.), CH_2Cl_2, 0 °C → RT, 1.5 h, 93%; l) KOH (24 eq.), I_2 (11 eq.), MeOH, 0 °C → RT, 6.5 h, 96%.

The diol hydroxyl groups were silylated with TBSOTf and 2,6-lutidine as the base in CH_2Cl_2 at 0 °C in 96% and 98% yield, respectively. Selective mono-desilylation of the primary hydroxyl groups in *anti*-**295** and *syn*-**295** proceeded in 85% (98% brsm) and 81% (89% brsm)

yield. Oxidation of the alcohols *anti*-**296** and *syn*-**296** with DMP in CH_2Cl_2 gave the aldehydes *anti*-**297** and *syn*-**297** in excellent yields of 96% and 98%.

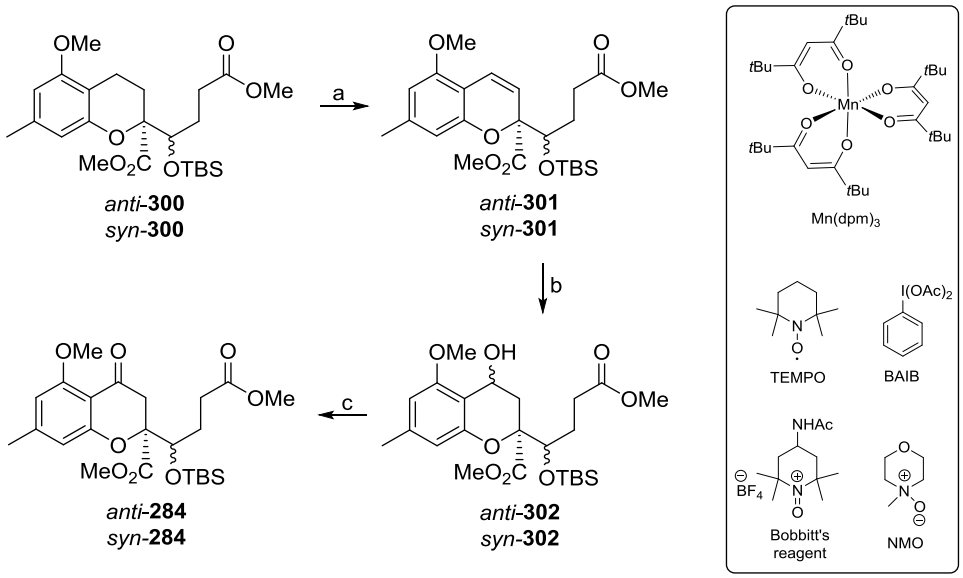
In regards to compound throughput upon scale-up, however, it proved to be more efficient to omit the time- and solvent-consuming HPLC-separation after the Sharpless-dihydroxylation. Instead, the diastereomeric alcohol mixture of *anti*-**294** and *syn*-**294** was carried on through the silylation/deprotection/oxidation sequence and readily separated at the aldehyde stage by standard column chromatography on silica gel to access enantiopure *anti*-**297** and *syn*-**297** in an overall yield of 77% over three steps.

Chain-elongation by a Wittig-Horner reaction of *anti*-**297** and *syn*-**297** with the sodium ylide of trimethyl phosphonoacetate in THF gave the corresponding α,β-unsaturated methyl esters as inconsequential mixtures of *E*/*Z*-isomers. The subsequent reduction of the double bond with concomitant cleavage of the benzyl group proceeded sluggishly and required high hydrogen pressure (4 bar) to afford the alcohols *anti*-**298** and *syn*-**298** in 90% and 91% yield after a reaction time of several days. It is important to note that the hydrogenation under these reaction conditions, but with another batch of Pd/C resulted in considerable reduced yields. It was thus reasoned that the strong acid HCl derived from residual $PdCl_2$, which is used to manufacture Pd/C, might have a some influence on the reaction.

Oxidation of the primary alcohols *anti*-**298** and *syn*-**298** with DMP and KOH/I_2 in MeOH[170] provided the methyl esters *anti*-**300** and *syn*-**300** in in 92% and 90% yield over two steps, respectively.

The next stage of the synthesis towards (–)-blennolide C (*ent*-**7c**) and (–)-gonytolide C (*ent*-**9c**) required the regioselective benzylic oxidation of the methylene position at C-9 (numbering as in *ent*-**7c**) without affecting the benzylic methyl group at C-6. For this purpose, a 3-step procedure was envisioned comprising a dehydration followed by a hydroxylation and an alcohol oxidation. This strategy was successfully applied in the synthesis of (–)-diversonol (*ent*-**10**) and showed superior results in terms of yield and selectivity compared to direct oxidation methods. To this end, the chromanes *anti*-**300** and *syn*-**300** were first dehydrated in the presence of DDQ to give the chromenes *anti*-**301** and *syn*-**301**. The reaction progress was difficult to monitor by TLC since the starting material and the corresponding chromenes possessed similar polarities. However, iterative addition of excess DDQ (2 × 1.5 eq.) and stirring under reflux for 3 h ensured complete conversion to yield *anti*-**301** and *syn*-**301** in 87% and 77%, respectively. With the chromenes *anti*-**301** and *syn*-**301** in hand, the stage was set for the hydroxylation of the double bond using the previously established conditions (Scheme 51). The reaction of *anti*-**301** in the presence of catalytic amounts of $Mn(dpm)_3$

(10 mol%) and $PhSiH_3$ (4.0 eq.) in MeOH under a O_2 atmosphere (1 atm) at RT, however, proceeded sluggishly. To increase the reaction rate, the temperature was elevated to 50 °C and silane $PhSiH_3$ (20 eq.) was added continuously by a syringe pumpe to provide *anti*-**302** in 96% yield as an inconsequential 2.5:1 mixture of diastereomers.



Scheme 71: Syntheses of the chromanones *anti*-**284** and *syn*-**284**: a) DDQ (4.0 eq.), benzene, reflux, 3 h: for *anti*-**301** (87%); for *syn*-**301** (77%); b) $Mn(dpm)_3$ (30 mol%), $PhSiH_3$ (20 eq., 0.06 mL/h), O_2 (1 atm), MeOH, 50 °C, *anti*-**302** (96%), yield for *syn*-**302** not determined, see Table 12, entry 6.

	substrate	conditions c)	result
1	*anti*-**302**	DMP (2.0 eq.), CH_2Cl_2, 0 °C, 30 min	*anti*-**284**/*anti*-**301**/*anti*-**302**[a]
2	*anti*-**302**	MnO_2 (50 eq.), CH_2Cl_2, reflux, 24 h	no conversion
3	*anti*-**302**	TEMPO (20 mol%), BAIB (1.2 eq.), CH_2Cl_2, RT, 24 h	no conversion
4	*anti*-**302**	Bobitt's reagent (3 × 1.5 eq.), CH_2Cl_2, 0 °C → RT, 39 h	62%
5	*anti*-**302**	TPAP (2 × 10 mol%), NMO (2 × 3 eq.), CH_2Cl_2/CH_3CN (1:1), 4 Å ms, RT, 24 h	95%
6	*syn*-**302**	TPAP (2 × 10 mol%), NMO (2 × 3 eq.), CH_2Cl_2/CH_3CN (1:1), 4 Å ms, RT, 24 h	85% (2 steps)

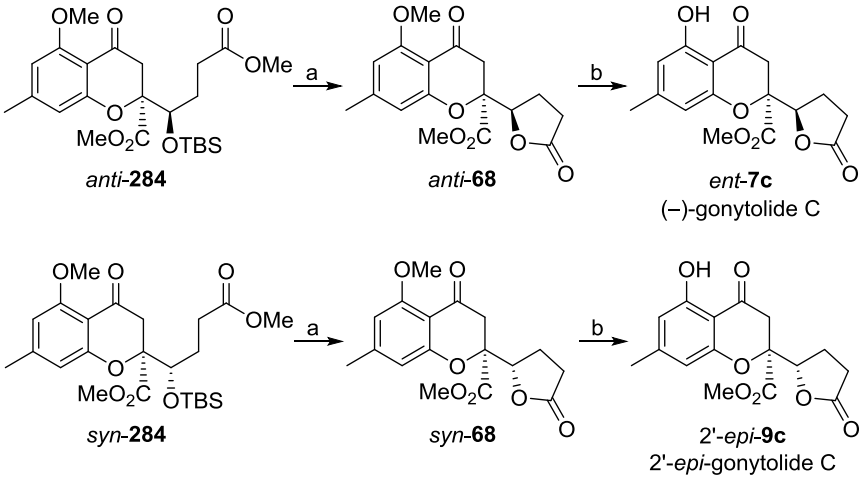
Table 12: Oxidation of the benzylic alcohols *anti*-**302** and *syn*-**302**: [a] Yield and ratio not determined.

The seemingly easy oxidation of the benzylic alcohol to the corresponding ketone proved to be troublesome. The addition of DMP to the inherently acid-sensitive alcohol *anti*-**302** at 0 °C

gave the chromanone *anti*-**284** alongside chromene *anti*-**301** in (Table 12, entry 1). In order to suppress the undesired dehydration, oxidation methods under neutral conditions were investigated. Exposure of *anti*-**302** to an excess of MnO_2 (50 eq.) in refluxing CH_2Cl_2, the method of choice in the synthesis of (–)-diversonol (*ent*-**10**), gave no conversion (Table 12, entry 2). Using catalytic amounts of tetramethylpiperidinyloxy (TEMPO) (20 mol%) and 1.2 equivalents of bis(acetoxy)iodobenzene (BAIB) as the reoxidant once again led only to the recovery of the unreacted starting material (Table 12, entry 3). Gratifyingly, a method of Porco *et al*. using of Bobbitt's reagent in CH_2Cl_2 at RT provided the desired chromanone *anti*-**284** in 62% (Table 12, entry 4).[50] Bräse *et al*. found that the yield of similar substrates can be further improved employing a Ley oxidation.[45] When the diastereomeric alcohol mixture *anti*-**302** was subjected to 20 mol% of tetrapropylammonium perruthenate (TPAP) and 6 equivalents of *N*-methylmorpholine *N*-oxide (NMO) in the presence of 4 Å molecular sieves in CH_2Cl_2/CH_3CN (1:1), the chromanone *anti*-**284** was isolated in excellent 95% yield (Table 12, entry 5). The optimized conditions for the hydroxylation/oxidation sequence were also applied to the corresponding chromene *syn*-**301** furnishing chromanone *syn*-**284** in a comparable yield of 85% over two steps (Table 12, entry 6).

4.2.5 Syntheses of (–)-gonytolide C (*ent*-9c) and 2'-*epi*-gonytolide C (2'-*epi*-9c)

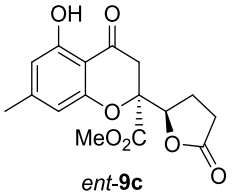
In order to complete the total syntheses of (–)-gonytolide C (*ent*-**9c**) and 2'-*epi*-gonytolide C (2'-*epi*-**9c**), the chromanones *anti*-**284** and *syn*-**284** were exposed to $NEt_3 \cdot 3$ HF in dioxane at 60 °C (Scheme 72).



Scheme 72: Syntheses of (–)-gonytolide C (*ent*-**9c**) and 2'-*epi*-gonytolide C (2'-*epi*-**9c**): a) $NEt_3 \cdot 3$ HF (50 eq.), dioxane, 60 °C, *anti*-**68** (87%), *syn*-**68** (84%); BBr_3 (10 eq.), CH_2Cl_2, –78 °C, 2 h, *ent*-**9c** (77%), 2'-*epi*-**9c** (86%).

The TBS-deprotection and subsequent γ–lactone formation proceeded uneventfully and furnished *anti*-**68** and *syn*-**68** in 86% and 84% yield, respectively. The remaining phenolic methyl ether was cleaved in the presence of 10 equivalents of BBr_3 in CH_2Cl_2 at –78 °C to give (–)-gonytolide C (*ent*-**9c**) and its 2'-epimer 2'-*epi*-**9c** in 77% and 86% yield, respectively. The spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, UV/Vis and MS) of *ent*-**9c** are in complete agreement with those published for the natural (+)-gonytolide C (**9c**).

4.2.6 Spectroscopic data (–)-gonytolide C (*ent*-9c)



ent-**9c**
(–)-gonytolide C

The ^{1}H-NMR spectrum of (–)-gonytolide C (*ent*-**9c**) (Figure 29) exhibits a singlet at δ = 2.29 ppm integrating for 3 protons which can be assigned to the methyl group at C-7.

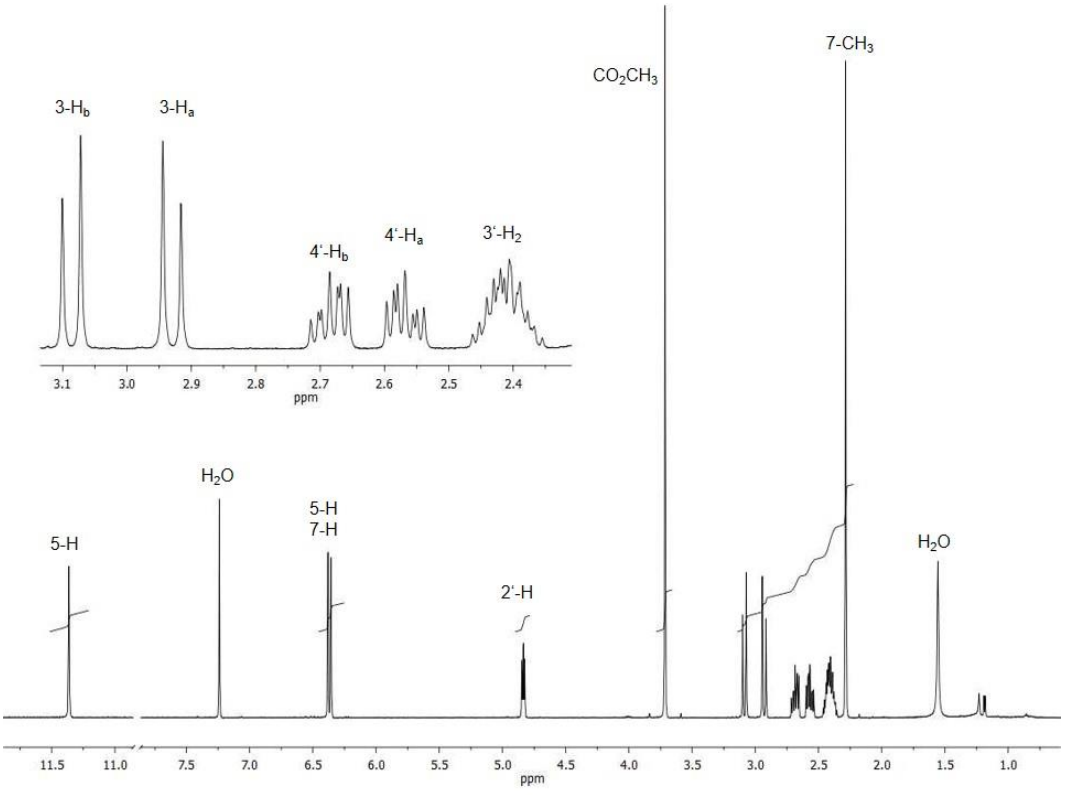


Figure 29: ^{1}H-NMR spectrum (600 MHz, $CDCl_3$) of (–)-gonytolide C (*ent*-**9c**).

The methylene protons 3'-H_2 account for the centered multiplet at δ = 2.41 ppm displaying strong vicinal couplings to the adjacent protons at C-4'.

The protons 4'-H_a and 4'-H_b resonate at δ = 2.57 and 2.69 ppm each as doublet of doublets of doublets with the geminal coupling of ^2J = 17.4 Hz and the vicinal couplings of ^3J_a = 10.2 and 6.6 Hz and ^3J_b = 9.9 and 7.1 Hz. The methylene protons at C-3 exhibit signals at δ = 2.93 and 3.09 ppm each resonating as doublets with the geminal coupling of ^2J = 16.9 Hz. The singlet at δ = 3.72 ppm integrating for 3 protons can be assigned to the methyl ester group at C-2 whereas the doublet of doublets at δ = 4.84 ppm with ^3J = 8.0 and 5.7 Hz is consistent with the lactonyl proton at C-2'. The chemical shift for the signals at δ = 6.36 and 6.38 ppm are characteristic for the aromatic protons 5-H and 7-H. The downfield-shifted singlet at δ = 11.36 ppm arises from the intramolecular hydrogen bonding of the aromatic 5-OH group to the adjacent carbonyl oxygen at C-4.

The ^{13}C-spectrum of *ent*-**9c** (Figure 30) exhibits the characteristic signal at δ = 22.6 ppm for the methyl group at C-6. The lactonyl carbons C-3' and C-4' resonating at δ = 22.0 and 27.6 ppm are followed by the signal of the methylene carbon C-3 at δ = 39.4 ppm. The chemical shift at δ = 53.6 ppm is in agreement with the methyl group of the ester moiety. The methine carbon C-2' resonates at δ = 80.9 ppm whereas the resonance of the quaternary stereocenter C-4a can be found at δ = 84.0 ppm.

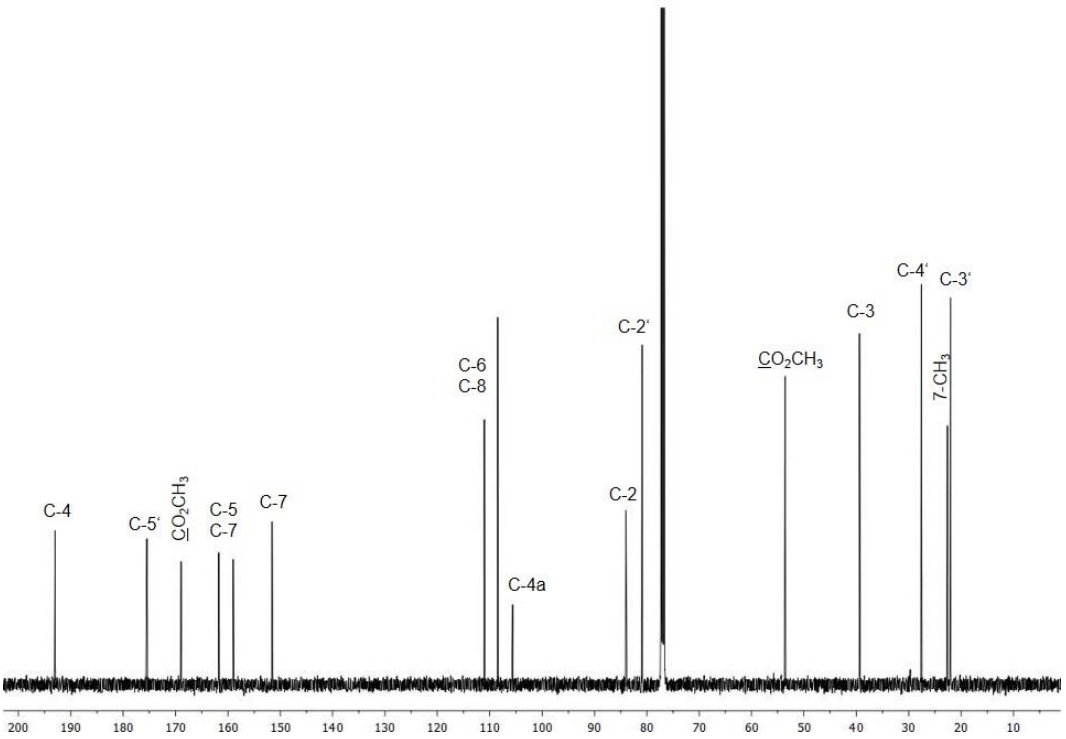


Figure 30: ^{13}C-NMR spectrum (125 MHz, $CDCl_3$) of (–)-gonytolide C (*ent*-**9c**).

In the aromatic region of the spectrum, the signal at δ = 105.6 ppm for the quaternary carbon C-4a is followed by the resonances of C-6 and C-8 at δ = 108.5 and 111.1 ppm, respectively. The further downfield-shifted signals at δ = 151.6, 159.0 and 161.8 ppm correspond to the remaining aromatic carbons C-5, C-7 and C-8a. The carboxyl carbons of the methyl ester and of the lactone (C-5') display resonances at δ = 169.0 and 175.5 ppm. The spectrum is completed by the characteristic carbonyl signal of C-4 at δ = 193.0 ppm.

In the IR-spectrum of *ent*-**9c**, the CH-stretching band near 3000 cm^{-1} is accompanied by the carbonyl absorption of the γ-lactone at 1785 cm^{-1}. The intense signal of 1644 cm^{-1} is characteristic for the enol form of the β-oxy-keto moiety.

The ESI-mass spectrum shows intense signals at 663.2 (50%), 343.1 (85%) and 321.1 (100%) which correspond to the adducts $[2M+Na]^+$, $[M+Na]^+$ and $[M+H]^+$. The high resolution ESI-MS confirms the chemical formula $C_{16}H_{16}O_7$.

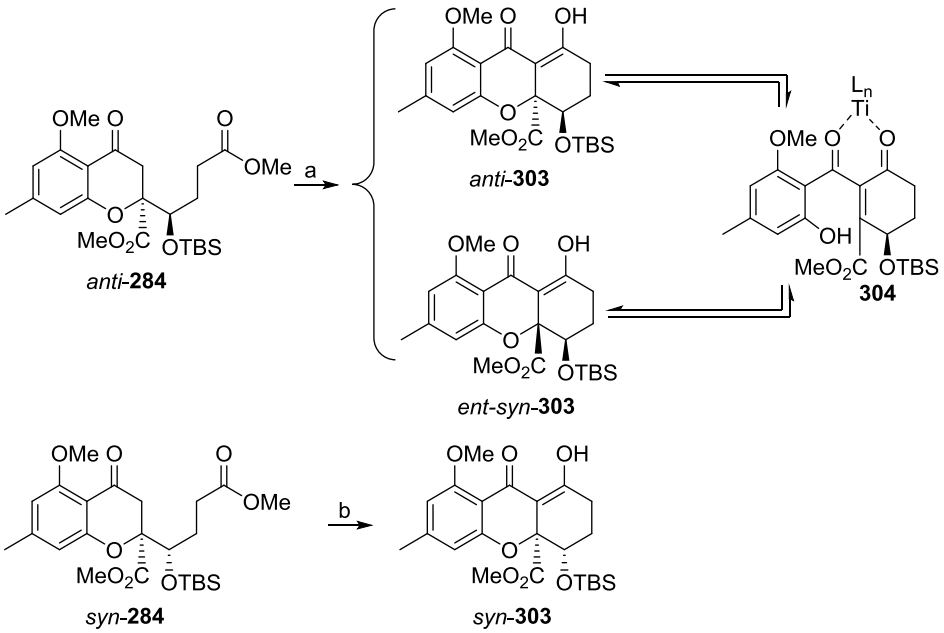
The UV spectrum of *ent*-**9c** displays absorption bands at 340 and 277 nm which are consistent with the π–π∗ and n-π∗ transitions of the chromanone chromophore.

Comparison of the measured optical rotation ($[\alpha]_D$ = –28.5, c = 0.10 in $CHCl_3$, 24.7 °C) with the published value ($[\alpha]_D$ = +25.1, c = 0.184 in $CHCl_3$) proved the absolute configuration of (–)-gonytolide C (*ent*-**9c**) to be (2*S*,2'*R*).

4.2.7 Synthesis of the tetrahydroxanthenone core of (–)-blennolide C (*ent*-7c) and acid (306)

The retrosynthetic approach towards (–)-blennolide C (*ent*-**7c**) required the formation of the tetrahydroxanthenone core by a Ti-mediated acylation of the chromanone *anti*-**284**. The modified reaction conditions using Ti(*i*OPr)Cl_3 instead of $TiCl_4$ showed superior results in the total synthesis of (–)-diversonol (*ent*-**10**) and were therefore investigated first.

Thus, the chromanones *anti*-**284** and, for the proposed synthesis epimer, *syn*-**284** were subjected to NEt_3 and Ti(*i*OPr)Cl_3 in CH_2Cl_2 at 0 °C (Scheme 73). While the latter was cleanly converted to the tetrahydroxanthenone *syn*-**303** in 73% yield after 2 h, the reaction of *anti*-**284** was plagued by epimerization. The reaction was quenched after 1 h leading to a 9.5:1 mixture of *anti*-**303** and *ent-syn*-**303** in an overall yield of 84%. It was possible to purify tetrahydroxanthenone *anti*-**303** by standard column chromatography. However, the procedure was tedious and did not allow the isolation of pure *ent-syn*-**303**.



Scheme 73: Syntheses of the tetrahydroxanthenones *anti*-**303** and *syn*-**303**: a) $TiCl_4$ (2.6 eq.), Ti(O*i*Pr)$_4$ (0.9 eq.), NEt_3 (2.8 eq.), CH_2Cl_2, 0 °C, 1 h, 59% of pure *anti*-**303**, 25% of a mixture of *anti*-**303**/*ent-syn*-**303** (2.2:1); b) $TiCl_4$ (2.6 eq.), Ti(O*i*Pr)$_4$ (0.9 eq.), NEt_3 (2.8 eq.), CH_2Cl_2, 0 °C, 2 h, 73%.

Mechanistically, the epimerization of the quaternary stereocenter C-4a is proposed to proceed after the ring-closing event. In the presence of a Lewis-acidic Ti-species, tetrahydroxanthenone *anti*-**303** can undergo a retro-oxa-Michael addition to form phenol **304**, which can subsequently re-add in a non-stereospecific manner to the double bond of α,β-unsaturated ketone **304** furnishing *anti*-**303** and *ent-syn*-**303**. A similar epimerization mechanism was proposed by Porco *et al*. in the synthesis of racemic blennolide C (*rac*-**7c**).[50] It is interesting to note that in the syntheses of structurally related (–)-blennolide A (*ent*-**7a**)[126] and (–)-diversonol (*ent*-**10**) by Tietze *et al*. no epimerization was observed in the acylation step. This highlights the fact that minor structural variations may already affect the course of this reaction.

4.2.8 Syntheses of (–)-blennolide C (*ent*-7c) and acid (*ent*-306)

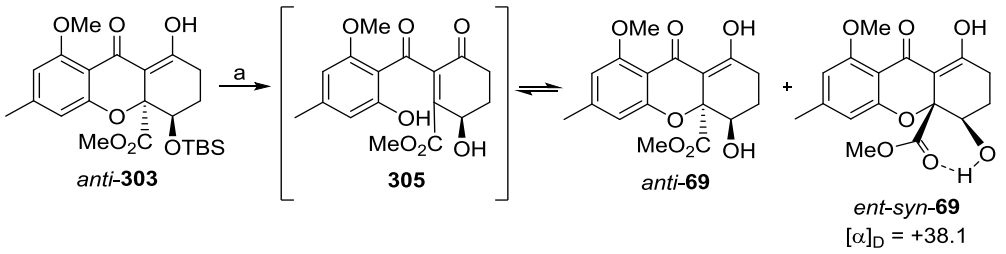
With the tetrahydroxanthenone backbone installed, the final deprotection of the TBS- and the phenolic methyl group of *anti*-**303** and *syn*-**303** was investigated. A sequence of TBS-deprotection followed by OCH_3-ether cleavage was initially envisioned (Scheme 74).

Preliminary experiments showed that *anti*-**303** was incompatible with basic conditions as the removal of the TBS group occurred neither with TBAF in THF nor with the mild desilylating reagent tris(dimethylamino)sulfonium difluorotrimethylsilicate (TSAF)[171] in DMF at 0 °C or

RT. Instead, *anti*-**303** gradually decomposed in both reactions presumably due to the basicity of the fluoride ion (Table 13, entries 1-2).

The reaction conditions that were successfully applied in the synthesis of (–)-diversonol (*ent*-**10**) were trialled next. To this end, tetrahydroxanthenone *anti*-**303** was treated with 25 equivalents of HF·pyridine in THF and the reaction mixture stirred at 30 °C. After 3 d little conversion was observed and additional 25 equivalents of HF·pyridine were added. The reaction was stirred for further 2 d at 30 °C furnishing a 1.5:1 mixture of *anti*-**69** and the C-4a epimer *ent-syn*-**69** in 26% (99% brsm) (Table 13, entry 3).

In the synthesis of (–)-blennolide A (*ent*-**7a**), the use of $NEt_3 \cdot 3$ HF showed superior results compared to HF·pyridine.[126,172] The OTBS-ether *anti*-**303** was therefore subjected to 25 equivalents of $NEt_3 \cdot 3$ HF in dioxane at 50 °C for 3 d. The reaction went to near completion after adding further 25 equivalents $NEt_3 \cdot 3$ HF and heating at 50 °C for 3 more days to give a 1.5:1 mixture of the diastereomers *anti*-**69** and *ent-syn*-**69** in 52% (55% brsm) (Table 13, entry 4).



Scheme 74: Cleavage of the TBS-ether in tetrahydroxanthenone *anti*-**303**.

	conditions a)	*anti*:*syn*	result
1	TBAF (5.0 eq.), THF, 0 °C → RT, 24 h, RT → reflux, 24 h	-	decomposition
2	TSAF (5.0 eq.), THF, 0 °C → RT, 24 h	-	decomposition
3	HF·pyridine (2 × 25 eq.), THF, 0 °C → 30 °C, 5 d	1.5:1	26% (99% brsm)
4	$NEt_3 \cdot 3$ HF (2 × 25 eq.), THF, 0 °C → 50 °C, 5 d	1.5:1	52% (55% brsm)
5	aq. H_2SiF_6 (2 × 25 eq.), DMF, 50 °C, 6 d	10.5:1	56% (60% brsm)

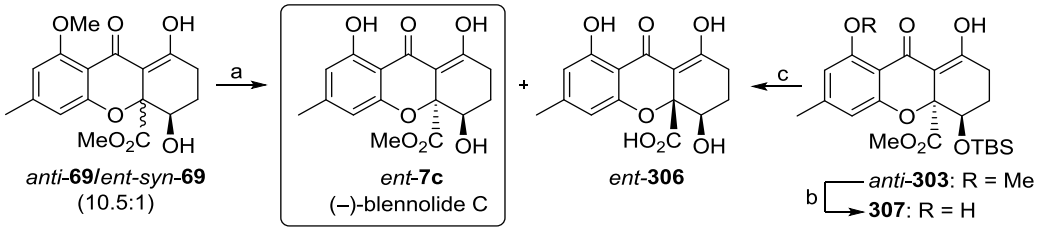
Table 13: TBS deprotection of tetrahydroxanthenone *anti*-**303**.

The starting material *anti*-**303** was easily recovered in both reactions by column chromatography on silica gel. Attempts to separate the two alcohols *anti*-**69** and *ent-syn*-**69** failed even when using normal-phase HPLC. However, a tedious HPLC purification on a reversed-phase (Kromasil C18) eluting with H_2O/MeOH gave small amounts of the epimer

ent-syn-**69**. Its ^{1}H-NMR data match with those of alcohol *syn*-**69** (*vide infra*) and both compounds display the comparable values of the optical rotation, but with different orientation (*syn*-**69**: $[\alpha]_D = -37.3$; *ent-syn*-**69**: $[\alpha]_D = +38.1$).

While the steric integrity of OTBS-protected starting material *anti*-**303** was not affected, the free alcohol *anti*-**69** was apparently susceptible to epimerization giving rise to *ent-syn*-**69**. The epimerization event most likely proceeds by an opening of the chroman ring-system by a retro-oxa-Michael addition followed by a sterically non-specific readdition of the phenol hydroxyl group to the α,β-unsaturated diketone moiety. In this regard, the assumption of a stabilizing intramolecular hydrogen bonding in *ent-syn*-**69** between the *syn*-orientated ester moiety at C-4a and the hydroxyl group at C-4 played a pivotal role. It was anticipated that addition of the cosolvent water acting as a hydrogen donor could suppress the epimerization. Indeed, treatment of *anti*-**303** with aq. fluorosilicic acid (2 × 25 eq.) in DMF at 50 °C for 6 d provided the alcohols *anti*-**69** and *ent-syn*-**69** in 56% as a 10.5:1 mixture (Table 13, entry 5).[173]

In the final step of the synthesis, the diastereomeric mixture *anti*-**69**/*ent-syn*-**69** (10.5:1) was subjected to 10 equivalents of BBr_3 in CH_2Cl_2 at RT for 1 h to provide (–)-blennolide C (*ent*-**7c**) alongside the *syn*-compound *ent*-**306** in 65% combined yield in a ratio of 10.2:1 (Scheme 75). Thorough analysis of the crude ^{1}H-NMR spectrum indicated that the minor isomer *ent*-**306** lacked the signals of the ester methyl group at C-4a (*vide infra*). Reversing the order of deprotection, i.e. cleavage of the methyl ether followed by desilylation was also investigated.

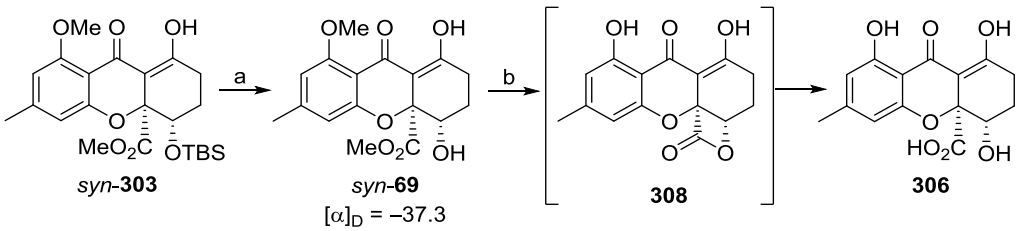


Scheme 75: Synthesis of (–)-blennolide C (*ent*-**7c**): a) *anti*-**69**/*ent-syn*-**69** (10.5:1), BBr_3 (10 eq.), CH_2Cl_2, RT, 1 h, 65%, *ent*-**7c**/*ent*-**306** (10.2:1); b) BBr_3 (10 eq.), CH_2Cl_2, –78 °C → RT, 4 h, 86%; c) aq. H_2SiF_6 (50 eq.) , DMF, 50 °C, 6 d, 67%, *syn*-**7c**/*ent*-**306** (3.0:1).

Exposure of *anti*-**303** to 10 equivalents of BBr_3 in CH_2Cl_2 and warming from –78 °C to 0 °C within 4 h cleanly provided phenol **307** in excellent 86% yield with no observable epimerization. The subsequent removal of the TBS group with aq. H_2SiF_6 in DMF at 50 °C gave 67% of (–)-blennolide C (*ent*-**7c**) and *ent*-**306** in a 3:1 ratio.

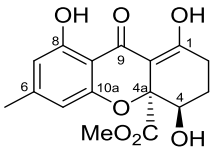
Separation attempts by column chromatography on silica gel were not successful. The detection by TLC was hampered as *ent*-**7c** and *ent*-**306** only display absorption bands at high concentrations and are not stainable. The latter is even more surprising taking the various functional groups in the molecule into account. The use of preparative RP HPLC did not lead to a separation either. However, multiple injections on the analytical RP HPLC provided 3 mg of pure (–)-blennolide C (*ent*-**7c**) as a white solid sufficient for a complete characterization. All spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, UV/Vis and MS) matched with those of the published natural (+)-blennolide C (**7c**). However, the measured optical rotation with $[\alpha]_D = -175.3$ (c = 0.2, $CHCl_3$, 22.7 °C) is slightly lower than the value of $[\alpha]_D = +181.7$ (c = 0.06, $CHCl_3$, 25 °C) reported by Krohn *et al.*[17] Since the (*S,S*)-BOXAX ligands used in the enantioselective domino Wacker/carbonylation/methoxylation reaction are easily accessible in the other enantiomeric form, the described procedure also allows the synthesis of (+)-blennolide C (**7c**) and (+)-gonytolide C (**9c**).

For an entry to the C-4 epimer of blennolide C (*ent*-**7c**), tetrahydroxanthenone *syn*-**303** was subjected to aq. H_2SiF_6 in DMF at 50 °C for 6 d to provide alcohol *syn*-**69** in an excellent yield of 96% as the only diastereomer. Finally, alcohol *syn*-**69** was exposed to 10 equivalents of BBr_3 in CH_2Cl_2 at RT for 1 h. Surprisingly, the phenolic ether cleavage was accompanied by ester hydrolysis furnishing acid *syn*-**306** in 44%, presumably arising from β-lactone intermediate **308**. It is reasonable to assume that the ester carbonyl oxygen was activated by the Lewis acid BBr_3, thus facilitating the attack of the *syn*-orientated hydroxyl group.



Scheme 76: Synthesis of acid **306**: a) aq. H_2SiF_6 (50 eq.) , DMF, 50 °C, 6 d, 96%; b) BBr_3 (10 eq.), CH_2Cl_2, RT, 1 h, 44%.

4.2.9 Spectroscopic data of (–)-blennolide C (*ent*-7c)



ent-**7c**
(–)-blennolide C

Basically, the tetrahydroxanthenone (–)-blennolide C (*ent*-**7c**) can adopt two different half-chair conformations. However, the ^{1}H-NMR data clearly reveals that only one is populated at room temperature.

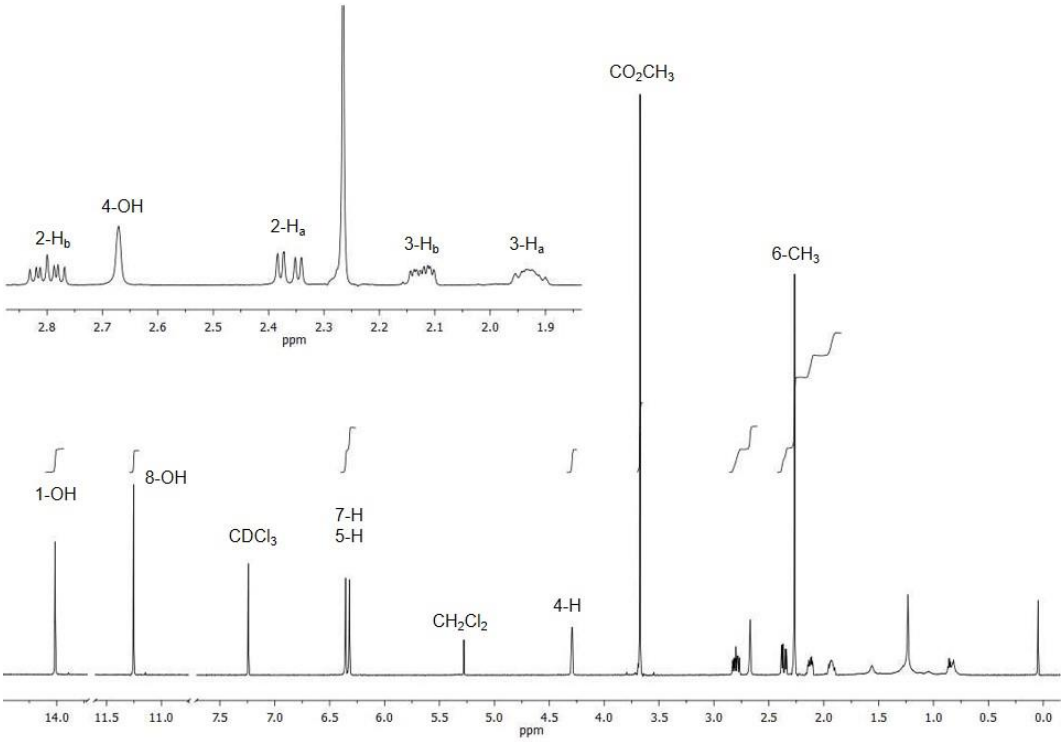


Figure 31: ^{1}H-NMR spectrum (600 MHz, $CDCl_3$) of (–)-blennolide C (*ent*-**7c**).

The ^{1}H-NMR spectrum of *ent*-**7c** (Figure 31) displays centered multiplets at $\delta = 1.93$ and 2.12 ppm which correspond to the methylene protons at C-3. The sharp singlet at $\delta = 2.27$, integrating for 3 protons, can be assigned to the methyl group at C-6. The protons at C-2 resonate at $\delta = 2.36$ and 2.80 ppm each as a doublet of doublet of doublets with the geminal coupling constant of $^{2}J = 19.0$ Hz. According to the Karplus correlation, the vicinal couplings of the signal at $\delta = 2.36$ ppm are consistent with a *gauche* conformation of 2-H_a with respect to 3-H_a ($^{3}J = 6.9$ Hz) and 3-H_b ($^{2}J = 1.3$ Hz), thus establishing a pseudoequatorial position. Proton 2-H_b exhibits the vicinal coupling constants $^{3}J = 11.3$ and 7.0 Hz and has consequently

adopted a pseudoaxial position. The upfield region is completed by the broad 4-OH resonance at δ = 2.67 ppm. The singlet at δ = 3.67 ppm, integrating for 3 protons, is in agreement with the methyl ester group. The singlet at δ = 4.29 ppm accounts for the proton 4-H. Although the COSY spectrum clearly shows a correlation to 3-H_b, no fine splitting was observed for the signal indicating a dihedral angle of 90° between 4-H and 3-H_b. The aromatic signals at δ = 6.32 and 6.36 ppm correspond to 5-H and 7-H whereas the sharp downfield-shifted signals at δ = 11.25 and 14.02 ppm are characteristic for the hydroxyl groups 8-OH and 1-OH as a result of the intramolecular hydrogen bonding to the adjacent carbonyl group.

The ^{13}C-NMR spectrum of *ent*-**7c** (Figure 32) shows the signals of the aliphatic methyl group at C-6 and the methylene carbons C-3 and C-2 at δ = 22.5, 23.1 and 24.3 ppm. In addition to the characteristic methyl signal of the ester group at δ = 53.4 ppm, the methine carbon C-4 and the quaternary stereocenter C-4a resonate at δ = 67.0 and 83.8 ppm, repectively. The aromatic region of the spectrum exhibits the resonances for the carbons C-9a, C-8a, C-5 and C-7 at δ = 101.1, 104.9, 108.7 and 111.7 ppm. The downfield-shifted aromatic signals at δ = 149.9, 157.6 and 161.9 ppm can be assigned to the carbons C-6, C-10a and C-8. The chemical shift of the ester resonance at δ = 171.2 ppm is complemented by the carbonyl signals of C-1 and C-9 at 179.1 and 186.9 ppm.

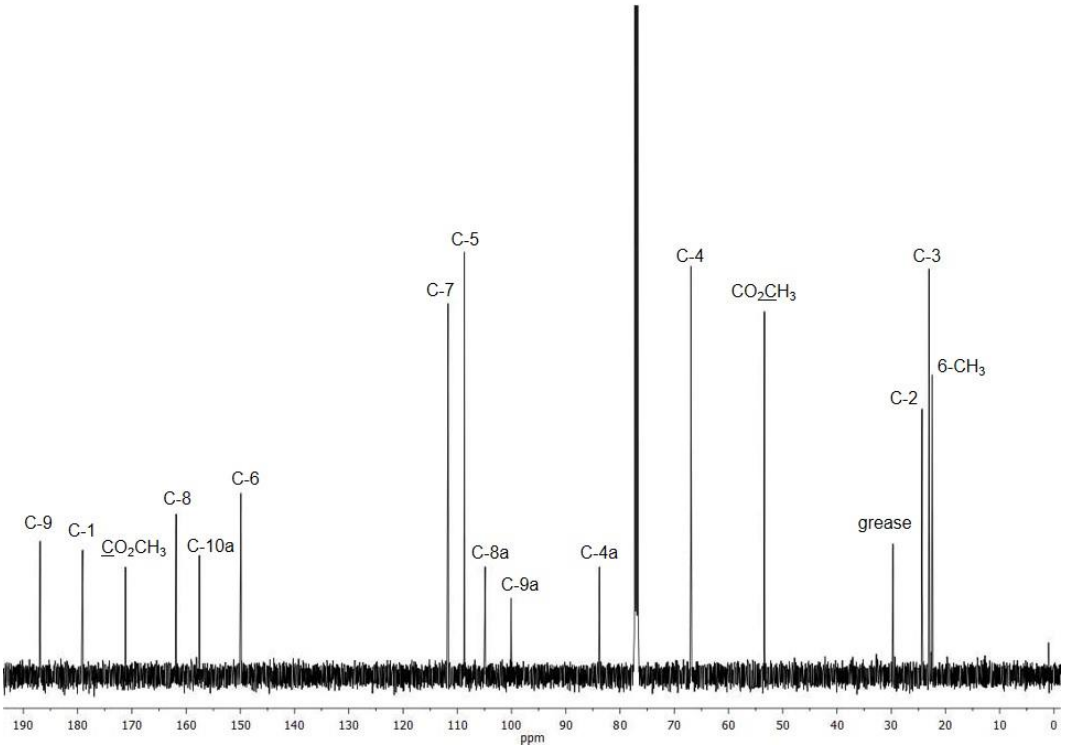


Figure 32: ^{13}C-NMR spectrum (125 MHz, $CDCl_3$) of (–)-blennolide C (*ent*-**7c**).

The IR spectrum of *ent*-**7c** shows a sharp and a broad signal at 3484 and 3131 cm^{-1} which can be assigned to the hydroxyl goups. The CH-streching band near 3000 cm^{-1} is followed by a sharp signal at 1740 cm^{-1} that is consistent with the presence of the methyl ester at C-2. The intense band at 1613 cm^{-1} can be assigned to the enol form of the β-oxy-keto moiety.

The signals in the ESI mass spectrum at 663.2 (44%), 343.1 (100%) and 321.1 (36%) can be assigned to the adducts $[2M+Na]^+$, $[M+Na]^+$ and $[M+H]^+$. In addition, the measured high-resolution ESI-MS proved the chemical formula $C_{16}H_{16}O_7$.

The absorption bands at 333 and 279 nm in the UV spectrum account for the π–π* and n-π* transitions of the chromanone chromophore. The measured optical rotation value was deteremined to be $[\alpha]_D = -175.3$ (c = 0.20 in $CHCl_3$, 23 °C). Comparison with the published value $[\alpha]_D = +181.7$ (c = 0.06 in $CHCl_3$, 25 °C) established the absolute configuration of *ent*-**7c** to be (4*R*,4a*S*).

D SUMMARY

In light of limited natural resources and a growing world population, the increasing demand for more efficient and environmentally benign syntheses represents a major challenge in organic chemistry.

An approach that addresses this pressing issue is the domino concept, first introduced by Tietze.[106,107] Domino reactions enable the formation and cleavage of several chemical bonds under identical reaction conditions, thereby shortening the synthetic routes to complex target molecules significantly. Good yields combined with high chemo-, regio- and stereoselectivities are among the typical advantages of domino reactions. Compared to classical step-wise strategies, the domino approach prevents the isolation, work-up and purification of intermediates which, on the other hand, reduces energy expenditures, chemicals and waste. An intriguing example of such a reaction is the enantioselective domino Wacker/carbonylation/methoxylation reaction for the formation of chiral chromanes, developed by Tietze *et al*.[121] In this regard, the synthesis of complex natural products provides an excellent testing ground to evaluate the synthetic utility of novel concepts and reactions.

Several natural products with a chiral chromane or tetrahydroxanthenone scaffold were shown to exhibit pronounced biological activities, including antiviral, antimicrobial and cytotoxic properties, and were thus envisioned as promising lead structures. However, the isolation of these secondary metabolites from fungi, lichens and bacteria is tedious and not feasible on large scale. In order to elucidate structure-activity relationships and to provide sufficient amounts for field testing, a smart synthetic access to these compounds is highly desirable.

The general objective of this thesis was to demonstrate the synthetic utility of the domino concept in the complex setting of natural product synthesis.

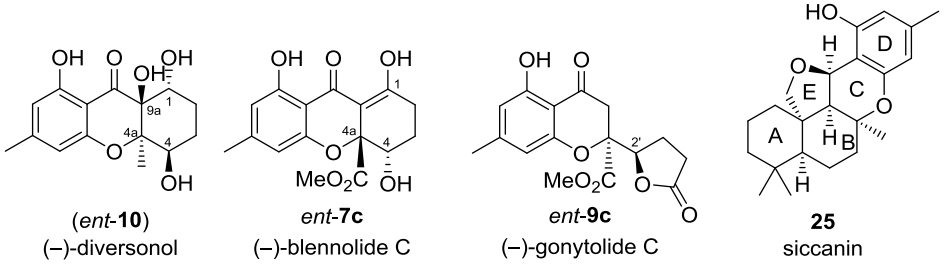
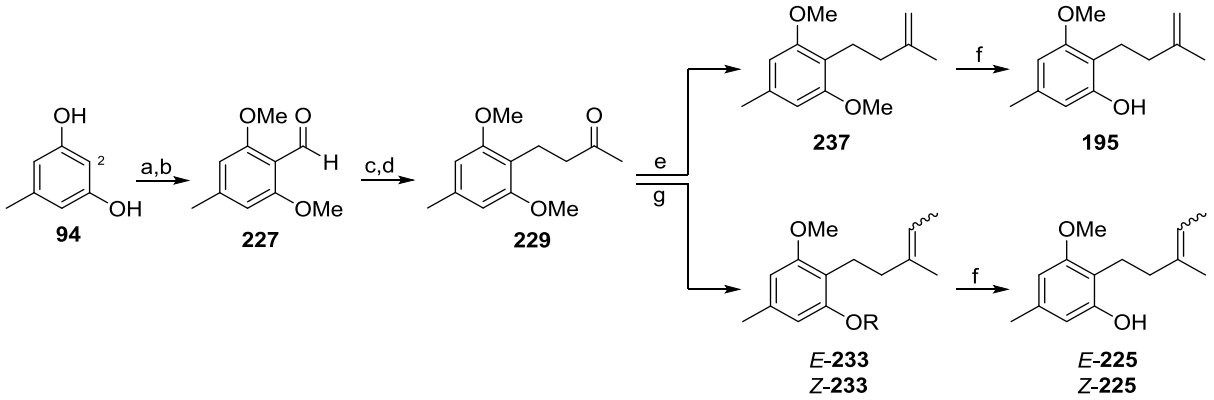


Figure 33: Target molecules of this PhD thesis.

By using the palladium-catalyzed domino Wacker/carbonylation/methoxylation reaction as a key step, it enabled the enantioselective total syntheses of (–)-diversonol (*ent*-**10**),

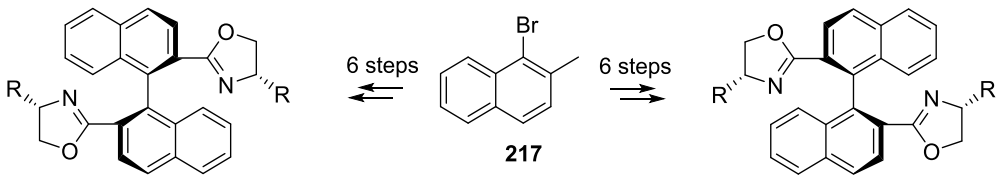
(–)-blennolide C (*ent*-**7c**) and (–)-gonytolide C (*ent*-**9c**) as well as the formal synthesis of siccanin (**25**) (Figure 33).

The first part of this PhD thesis focused on the total synthesis of the enantiomer of the fungal metabolite diversonol (**10**). Its intriguing structure, owing to the high density of functional groups and four adjacent stereocenters, rendered (–)-diversonol (*ent*-**10**) a challenging target. The preparation of *ent*-**10** commenced with the synthesis of the alkenyl phenols **195**, *E*-**225** and *Z*-**225** from commercially available orcinol (**94**) in six steps. The devised route required methylation of both hydroxyl groups of **94**, formylation at C-2 (numbering as in **94**), an aldol reaction to install the side chain, Wittig transformations to incorporate the alkene moieties and chemoselective cleavage of one of the methyl ethers to give **195** in 42% as well as *E*-**225** and *Z*-**225** in 43% (*E*/*Z* = 1:2.4) overall yield (Scheme 77).



Scheme 77: Syntheses of the alkenyl phenols **195**, *E*-**225** and *Z*-**225**: a) Me_2SO_4, K_2CO_3, acetone, reflux, 23 h, 93%; b) *n*BuLi, TMEDA, Et_2O, 0 °C → reflux, 3 h, then DMF, 0 °C → RT, 2 h, 75%; c) 1 M NaOH, acetone/H_2O, RT, 3 h, then 1 M HCl, 81%; d) 1. H_2, Pd/C (3 mol%), EtOAc, RT, 3 h; 2. IBX, CH_3CN, reflux, 1.5 h, 96% (2 steps); e) method A: *n*-BuLi, CH_3PPh_3Br, THF, 0 °C → RT, 4 h, 98%; method B: Zn, CH_2Br_2, $TiCl_4$, THF, 0 °C → RT, 75 min, 87%, f) NaSEt, DMF, 120 °C, 20–21.5 h, for **195**: 88%; for *E*-**225** and *Z*-**225**: 88%, *E*/*Z* = 1:2.4; g) *n*BuLi, $CH_3CH_2PPh_3Br$, THF, 0 °C → RT, 2.5 h, 90%, *E*/*Z* = 1:2.4.

Several (*S*,*S*)- and (*R*,*R*)-BOXAX ligands **140a-d** that induce enantioselectivity for the formation of chiral chromanes were synthesized over six steps according to literature procedures (Scheme 78).

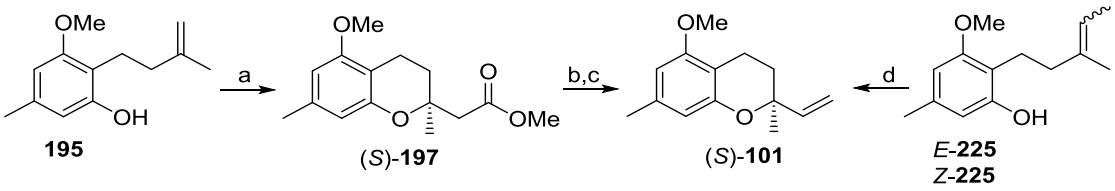


(*S*,*S*)-**140a**: R = Bn (47%)
(*S*,*S*)-**140b**: R = *i*Pr (40%)
(*S*,*S*)-**140c**: R = *i*Bu (15%)
(*S*,*S*)-**140d**: R = *t*Bu (16%)

(*R*,*R*)-**140a**: R = Bn (45%)
(*R*,*R*)-**140b**: R = *i*Pr (28%)

Scheme 78: Syntheses of the (*S*,*S*)- and (*R*,*R*)-BOXAX ligands. Yields over 6 steps are in parentheses.

The quaternary stereocenter of the chromane core at C-4a (numbering as in *ent*-**10**) was successfully installed by an enantioselective domino Wacker/carbonylation/methoxylation reaction of domino precursor **195** to give methyl ester (*S*)-**197** in 76% yield and 93% *ee*. Reduction of (*S*)-**197** followed by enantiomeric enrichment of the corresponding alcohol on a chiral IA phase and a dehydration gave vinyl chromane (*S*)-**101** in 73% over three steps in 99% *ee*. Compound (*S*)-**101** was also directly accessible by an enantioselective Wacker oxidation from the alkenyl phenols *E*-**225** and *Z*-**225** in 75% and 79% yield and 93% *ee* and 83% *ee*, respectively (Scheme 79).

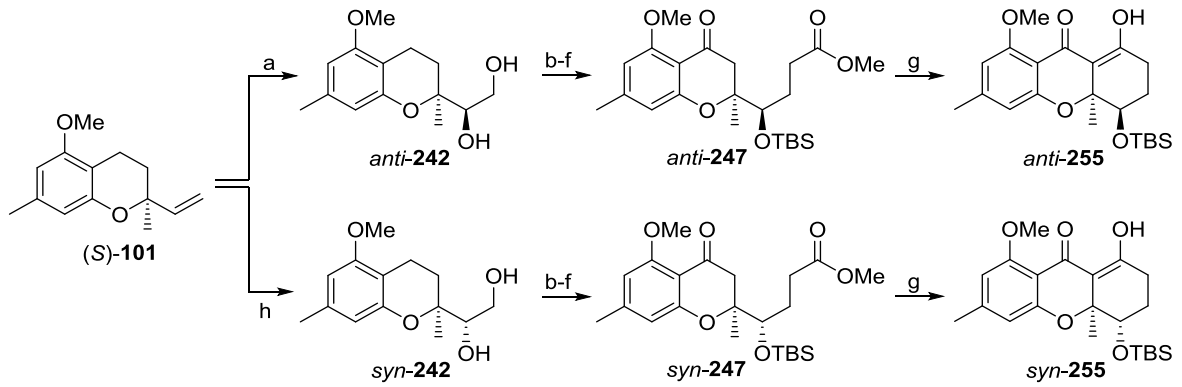


195 (*S*)-**197** (*S*)-**101** *E*-**225** *Z*-**225**

Scheme 79: Synthesis of vinyl chromane (*S*)-**101** by an enantioselective domino Wacker/carbonylation/methoxylation reaction or Wacker oxidation: a) $Pd(TFA)_2$ (5 mol%), Bn-BOXAX (*S*,*S*)-**140a** (20 mol%), *p*-benzoquinone, MeOH, CO, RT, 24 h, 76%, 93% *ee*; b) $LiAlH_4$, Et_2O, 0 °C → RT, 2 h, 98%; c) 1. nBu_3P, *o*-NO_2-C_6H_4SeCN (**241**), THF, RT, 1 h; 2. *m*CPBA, CH_2Cl_2, –40 °C, 1 h, iPr_2NH, –40 °C → RT, 12 h, 98% (2 steps); d) $Pd(TFA)_2$ (10 mol%), Bn-BOXAX (*S*,*S*)-**140a** (20 mol%), *p*-benzoquinone, MeOH, RT, 22 h, for (*E*)-**225**: 75%, 93% *ee*; for (*Z*)-**225**: 79%, 83% *ee*; for the *E*/*Z*-mixture (*E*/*Z*=1:2.4): 78%, 87% *ee*.

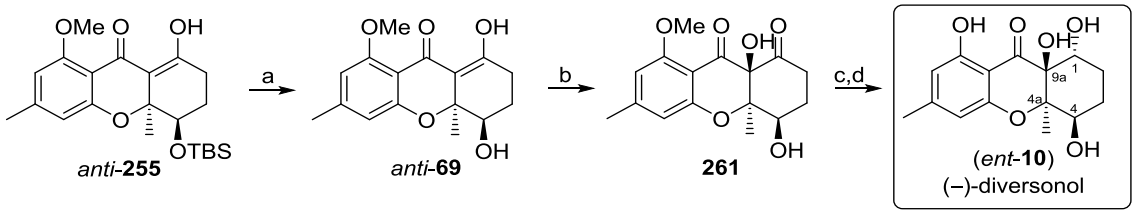
A Sharpless dihydroxylation of vinyl chromane (*S*)-**101** efficiently set up the hydroxyl group at C-4 (numbering as in *ent*-**10**) and at the same time provided a point of divergence (Scheme 80). Exposure of (*S*)-**101** to AD-mix α led to diol *anti*-**242** displaying the configuration at C-4 of (–)-diversonol (*ent*-**10**), whereas AD-mix β preferentially gave rise to its epimer *syn*-**242**. Both diols were further elaborated into the corresponding aldehydes comprising a TBS-protection of both hydroxyl groups, selective desilylation of the primary TBS group and subsequent oxidation with DMP.

A Wittig-Horner reaction to elongate the side-chain was followed by hydrogenation of the double bond. Benzylic oxidation at C-9 (numbering as in *ent*-**10**) then set the stage for a Ti-mediated acylation to afford the tetrahydroxanthenones *anti*-**255** and *syn*-**255** in yields of 32% and 8% over seven steps, respectively.



Scheme 80: Syntheses of the tetrahydroxanthenones *anti*-**255** and *syn*-**255**: a) AD-mix α, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 5 d, 93%, d.r. = 3.8:1 (*anti*-**242**/*syn*-**242**); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 2.5 h, for *anti*:99%; for *syn*: quant.; c) HF·pyridine, THF/pyridine, RT, 52–60 h, for *anti*: 70% (93% brsm); for *syn*: 73% (98% brsm); d) DMP, CH_2Cl_2, 0 °C → RT, 2–2.5 h, for *anti*: 95%; for *syn*: 89%; e) 1. $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF,0 °C, 30 min, then aldheyde, 0 °C → RT, 1.5 h; 2. H_2, Pd/C (10 mol%), EtOAc, RT, 15 h, for *anti*: 95% (2 steps); for *syn*: 98% (2 steps); f) method A: $Mn(OAc)_3 \cdot 2\ H_2O$ (40 mol%), *t*BuOOH, 3 Å ms, EtOAc, RT, 4 d, for *anti*-**247**: 51%; for *syn*-**247**: 42%; method B: 1. DDQ, benzene, reflux, 2 h, 95%; 2. $Mn(dpm)_3$ (10 mol%), $PhSiH_3$, O_2, RT, 4.5 h; 3. MnO_2, CH_2Cl_2, reflux, 4 d, for *anti*-**247**: 88% (2 steps); g) Ti(O*i*Pr)Cl_3, NEt_3, CH_2Cl_2, 0 °C, 1–2.5 h, for *anti*-**255**: 84%; for *syn*-**255**: 69%; h) AD-mix β, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 7 d, 73%, d.r. = 1:1.3 (*anti*-**242**/*syn*-**242**).

Completion of the total synthesis of (–)-diversonol (*ent*-**10**) was achieved by TBS-deprotection, diastereoselective epoxidation of the enol double bond, reduction of the resulting ketone and methyl ether cleavage (Scheme 81).

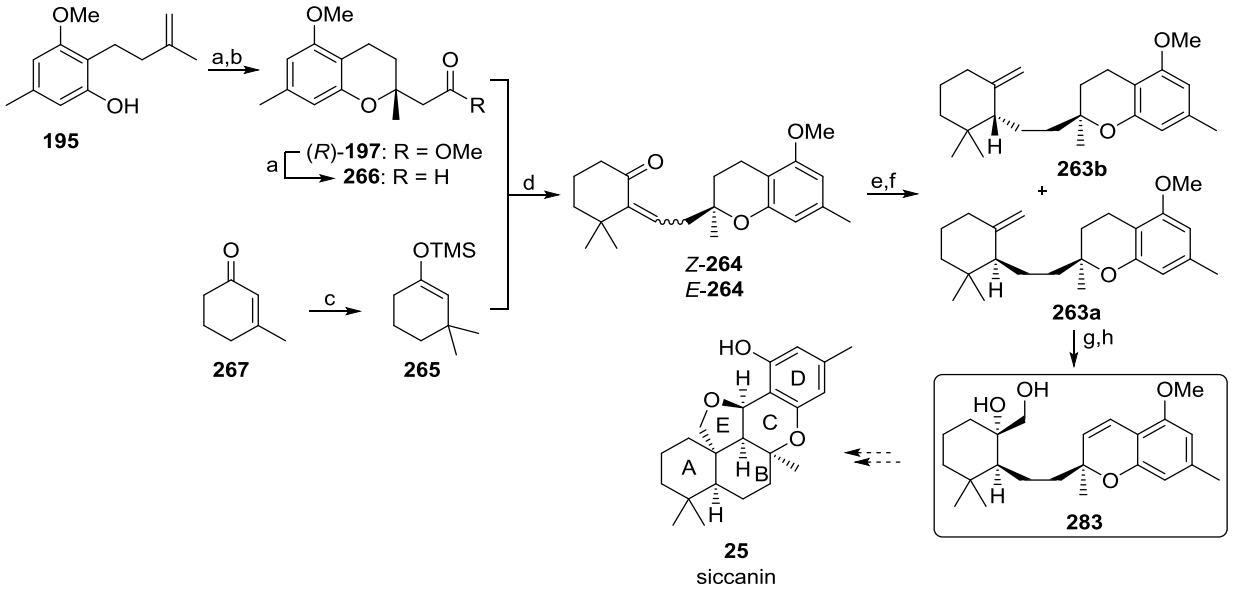


Scheme 81: Synthesis of (–)-diversonol (*ent*-**10**): a) HF·pyidine, THF, 30 °C, 5 d, 72% (94% brsm); b) DMDO, acetone, 0 °C, 1 h, 58%, d.r. = 6.4:1; c) $NaBH_4$, MeOH/CH_2Cl_2, –78 °C, 2 h, 62%; d) BBr_3, CH_2Cl_2, –78 °C → RT, 5.5 h, 75%.

In conclusion, (–)-diversonol (*ent*-**10**) was synthesized over 21 steps from commercially available orcinol (**94**) in 2% overall yield, rendering it the most efficient enantioselective route to this target to date. Key steps of the synthesis were the highly enantioselective access to the chromane core, accomplished either by a domino Wacker/carbonylation/methoxylation reaction or by a Wacker oxidation, a diastereoselective Sharpless dihydroxylation to install the C-4 hydroxyl group, a high yielding benzylic oxidation followed by an intramolecular acylation and a stereoselective oxidation/reduction sequence to furnish the *anti*-diol moiety at C-1/C-9.

The second project of this PhD thesis dealt with the formal synthesis of the antifungal siccanin (**25**). Diol **283**, being a key compound in Trost's synthetic route towards **25**, was identified as target (Scheme 82).

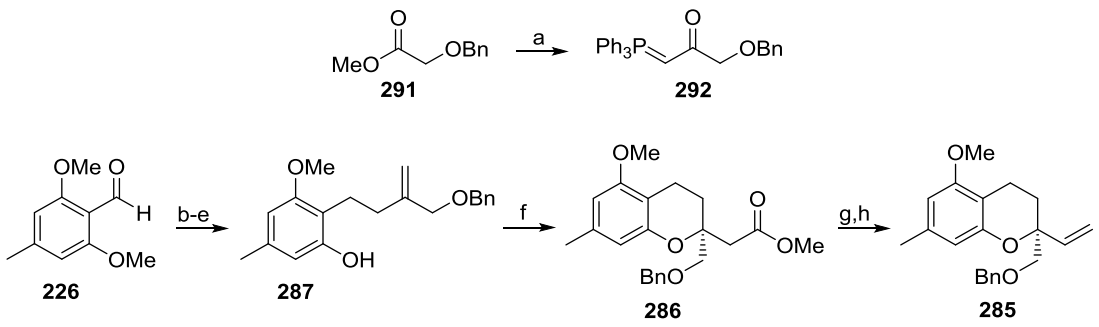
The enantioselective domino Wacker/carbonylation/ methoxylation reaction of alkenyl phenol **195** in the presence of a Bn-BOXAX (*R*,*R*)-**140a** ligand allowed the synthesis of methyl ester (*R*)-**197** in 71% yield and 93% *ee*. Reduction of the domino product to aldehyde **266** and formation of the TMS enol ether **265** by a conjugate addition of methyl Grignard to 3-methyl-2-cyclohexanone (**267**) set the stage for fragment coupling. An aldol addition of the transmetalated Zn-enolate of **265** with aldehyde **266** followed by dehydration gave rise to the α,β-unsaturated ketones *Z*-**264** and *E*-**264** in 60% yield. Subsequent hydrogenation of the double bond and a Peterson olefination to incorporate the methylene moiety furnished alkene **263a** and **263b** which could be separated. Finally, a highly selective Sharpless dihydroxylation of **263a** and oxidation to the chromene gave diol **283** in 3% over 13 steps from orcinol (**94**).



Scheme 82: Formal synthesis of siccanin (**25**): a) $Pd(TFA)_2$ (5 mol%), Bn-BOXAX (*R*,*R*)-**140a** (20 mol%), *p*-benzoquinone, MeOH, CO, RT, 24 h, 71%, 93% *ee*; b) DIBAL-H, toluene, –78 °C, 20 min, 81%; c) CuI (10 mol%), LiCl (20 mol%), MeMgCl (1.5 eq.), TMSCl (1.1 eq.), THF, –40 °C, 1 h, 84%; d) 1. **265**, MeLi, THF, 0 °C, 30 min, then $ZnCl_2$, –78 °C, 1 h, then **266**, –78 °C, 16 h; 2. Martin's sulfurane, CH_2Cl_2, 0 °C → RT, 2 h; *Z*-**264** 16%, *E*-**264** 44%; e) Pd/C (10 mol%), H_2, CH_2Cl_2, RT, 18 h, 86%; d.r. = 1:1.1 (**263a**/**263b**); f) 1. $TMSCH_2MgCl$, LiCl, Et_2O, 0 °C → RT, 20 h; 2. NaH, THF, 100 °C, mw, 16 h, 85%; g) AD-mix β, $MeSO_2NH_2$, *t*BuOH/H_2O, 5 d, 90%; h) DDQ, benzene, 80 °C, 2 h, 63%.

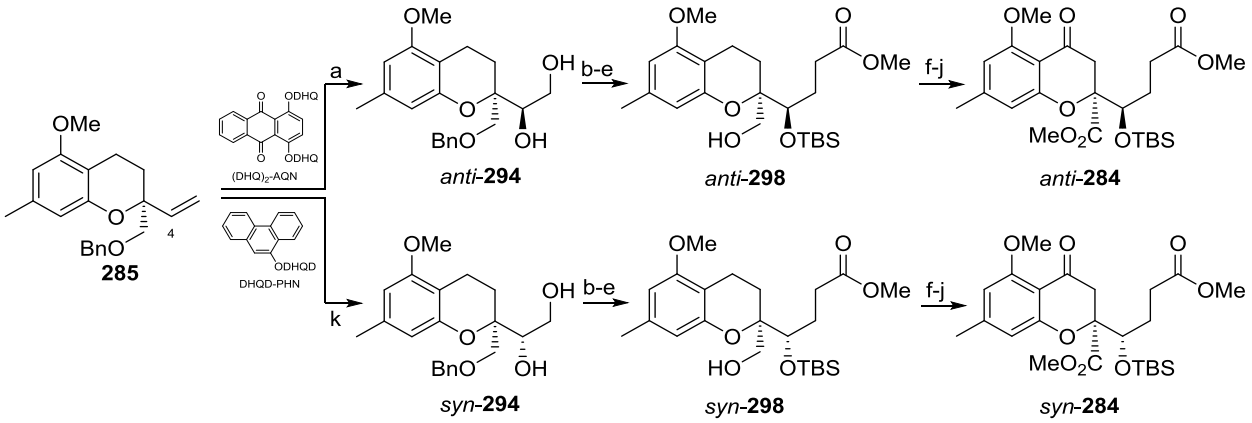
The third part of this thesis describes the enantioselective total syntheses of the tetrahydroxanthenone (–)-blennolide C (*ent*-**7c**) and its isomerized γ-lactonyl chromanone (–)-gonytolide C (*ent*-**9c**), highlighting the broad scope of the devised synthetic strategy.

The synthesis of *ent*-**7c** and *ent*-**9c** followed the successful route to (–)-diversonol (*ent*-**10**) to a large extent and started with the preparation of domino precursor **287** (Scheme 83). Aldehyde **226** reacted in a Wittig reaction with phosphorane **292** which in turn was easily accessible from methyl glycolate **291**. Hydrogenation of the resulting α,β-unsaturated ketone, a second Wittig reaction to install the olefin moiety and a mono-demethylation furnished alkenyl phenol **287** in 46% yield over six steps from orcinol (**94**). A ligand screening revealed that the novel *i*Bu-BOXAX ligand (*S*,*S*)-**140c** gave the best results in terms of yield and enantioselectivity (68%, 99% *ee*). Reduction of ester **286** followed by a stepwise elimination of the corresponding alcohol gave key compound **285** in 61% over three steps.



Scheme 83: Synthesis of vinyl chromane **285**: a) Ph_3PCH_3Br, *n*BuLi, THF, 0 °C, 20 h, 91%; b) **292**, toluene, reflux, 19.5 h, 89%; c) 1. PtO_2 (4 mol%), H_2, EtOAc, RT, 2 h; 2. IBX, CH_3CN, 80 °C, 1 h, 91% (2 steps); d) Ph_3PCH_3Br, *n*BuLi, THF, 0 °C → RT, 4 h, 93%; e) NaSEt, DMF, 120 °C, 21 h, 87% (92% brsm); f) $Pd(TFA)_2$ (5 mol%), *i*Bu-BOXAX (*S*,*S*)-**140c** (20 mol%), *p*-benzoquinone, MeOH, CO, RT, 24 h, 68%, 99% *ee*; g) $LiAlH_4$, Et_2O, 0 °C → RT, 2 h, quant.; h) 1. nBu_3P, *o*-NO_2-C_6H_4SeCN (**241**), THF, 0 °C, 4 h; 2. *m*CPBA, CH_2Cl_2, –40 °C, 1 h, iPr_2NH, –40 °C → RT, 15 h, 90% (2 steps).

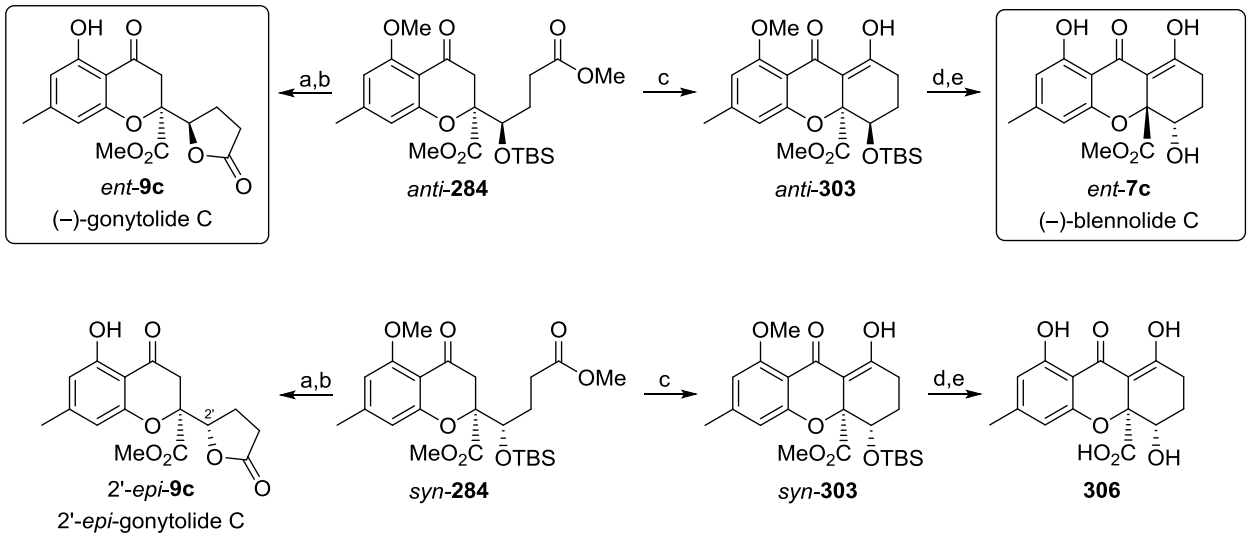
The second stereocenter, the hydroxyl group at C-4 (numbering as in **285**) was established employing a diastereoselective Sharpless dihydroxylation. An extensive survey of (DHQ)- and (DHQD)-based ligands enabled the preparation of both isomers *anti*-**294** and *syn*-**294** in very good selectivities of 13.8:1 and 1:3.7, respectively (Scheme 84). A sequence of TBS-protection, selective removal of the primary TBS group and DMP-oxidation set the stage for chain elongation.



Scheme 84: Syntheses of the chromanones *anti*-**284** and *syn*-**284**: a) $K_2OsO_4 \cdot 2\ H_2O$ (5 mol%), $(DHQ)_2$-AQN (10 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 3 d, 77%, d.r. = 13.7:1 (*anti*-**294**/*syn*-**294**); b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2.5 h, for *anti*: 96%; for *syn*: 98%; c) HF·pyidine, THF/pyridine, 0 °C → RT, 24–30 h, for *anti*: 85% (98% brsm); for *syn*: 81% (89% brsm); d) DMP, CH_2Cl_2, 0 °C → RT, 2 h, for *anti*: 96%; for *syn*: 98%; e) 1. $(MeO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C, 30 min, then aldehyde, THF, 0 °C → RT, 2 h; 2. Pd/C (10 mol%), H_2, MeOH, 2–3 d, for *anti*: 90% (2 steps); for *syn*: 91% (2 steps); f) DMP, CH_2Cl_2, 0 °C → RT, 1.5–2 h, for *anti*: 92%; for *syn*: 93%; g) KOH, I_2, MeOH, 0 °C → RT, 6.5–9 h, for *anti*: quant.; for *syn*: 96%; h) DDQ, benzene, reflux, 3 h, for *anti*: 87%; for *syn*: 77%; i) $Mn(dpm)_3$ (30 mol%), $PhSiH_3$, O_2, MeOH, 50 °C, 24–30 h; j) TPAP (20 mol%), NMO, CH_2Cl_2/CH_3CN, 4 Å ms, RT, 24 h, for *anti*: 91% (2 steps); *syn*: 85% (2 steps); k) $K_2OsO_4 \cdot 2\ H_2O$ (5 mol%), (DHQD)-PHN (10 mol%), K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*BuOH/H_2O, RT, 2 d, 88%, d.r = 1:3.7 (*anti*-**294**/*syn*-**294**).

The subsequent hydrogenation of the double bond with concomitant cleavage of the benzyl ether was followed by oxidation of the primary alcohol to the methyl ester. A 3-step benzylic oxidation procedure comprising dehydration to the chromene, hydroxylation and alcohol oxidation completed the syntheses of the chromanones *anti*-**284** and *syn*-**284** in 37% and 29% over 11 steps.

At this junction, the chromanones *anti*-**284** and *syn*-**284** were modified following two different pathways (Scheme 85). On the one hand, a desilylating lactonization and demethylation of *anti*-**284** and *syn*-**284** gave the natural product (–)-gonytolide C (*ent*-**9c**) and its epimer 2'-*epi*-**9c** in 66% and 72% yield over two steps, respectively. On the other hand, an intramolecular acylation of *anti*-**284** and *syn*-**284** provided the tetrahydroxanthenones *anti*-**303** and *syn*-**303** in 76% and 73% yield. Global deprotection finally led to the natural product (–)-blennolide C (*ent*-**7c**) and epimerized acid *ent*-**306** in 36% yield as a 10.2:1 mixture. Multiple injections on an analytical HPLC reversed phase provided 3 mg of pure (–)-blennolide C (*ent*-**7c**) as a white solid sufficient for a complete characterization. Similar reaction conditions gave rise to acid **306** in 42% over two steps.



Scheme 85: Syntheses of (–)-blennolide C (*ent*-**7c**), (–)-gonytolide C (*ent*-**9c**), 2'-*epi*-gonytolide C (2'-*epi*-**9c**) and acid **306**: a) 3 HF·Et_3N, dioxane, 60 °C, 6 d, for *anti*: 86%; for *syn*: 84%; b) BBr_3, CH_2Cl_2, –78 °C, 2 h, for *ent*-**9c**: 77%; for 2'-*epi*-**9c**: 86%; c) $TiCl_4$, $Ti(OiPr)_4$, NEt_3, CH_2Cl_2, 0 °C, 1–2 h, 59% of pure *anti*-**303**, 25% of a mixture of *anti*-**303**/*ent*-*syn*-**303** (2.2:1); for *syn*-**303**: 73%; d) aq. H_2SiF_6, DMF, 50 °C, 6 d, for *syn*: 96%;e) BBr_3, CH_2Cl_2, RT, 1 h, *ent*-**7c**/*ent*-**306** = 10.2:1, 36% (2 steps); for **306**: 44%.

In conclusion, the devised strategy enabled the first enantioselective total syntheses of (–)-blennolide C (*ent*-**7c**), (–)-gonytolide C (*ent*-**9c**) and their structural congeners 2'-*epi*-gonytolide C (2'-*epi*-**9c**) and acid **306**. The stereodivergent strategy featured several key transformations, namely the enantioselective domino Wacker/carbonylation/methoxylation reaction with a novel *i*Bu-BOXAX ligand **140c** to set up the stereocenter at C-4a and a diastereoselective Sharpless dihydroxylation. Moreover, a regioselective benzylic oxidation and an intramolecular acylation enabled an efficient access to the tetrahydroxanthenone scaffold.

E EXPERIMENTAL SECTION

1 General Methods

Experimental methods: All reactions (except reactions with HF·pyridine and H_2SiF_6) were performed under an argon atmosphere in flame-dried flasks and the reactants were introduced by syringe or transfer cannula with pressure using argon. All solvents were reagent grade and stored over molecular sieve. All reagents obtained from commercial sources were used without further purification.

Cooling: Short-term cooling was performed either with an ice/H_2O or with a dry ice/acetone bath. Long-term cooling was performed by using the cryostat EK 90 from the *Haake*.

Parr apparatus: Hydrogenations under elevated pressure were performed with a Parr hydrogenator in a 100 mL borosilicate glass bottle up to 60 psi (4 bar).

Microwave reactor: Reactions under microwave irradiation were performed in an Initiator 2.0 microwave reactor equipped with an autosampler from *Biotage* using microwave vials (0.5, 2, 5 and 20 mL).

Thin-layer chromatography (TLC): Thin-layer chromatography was performed on precoated silica gel plates TLC Silica gel F_{254} from *Merck*. UV detection at 254 and 365 nm was performed with an UV lamp VL-6.LC from Vilber Lourmat. Staining was accomplished using vanillin (900 mL MeOH, 100 mL acetic acid, 30 mL conc. H_2SO_4 and 5 g vanillin) and potassium permanganate solutions (5% in H_2O).

Column chromatography: Silica gel Geduran 60 (0.040–0.063 mm) from *Merck* was used for column chromatography. Technical grade solvents were distilled prior to use. Yields refer to isolated and purified compounds, unless stated otherwise.

Analytical HPLC: For analytical high performance liquid chromatography (HPLC) the samples were membrane-filtered (0.2 μm) and HPLC grade solvents were used. Analytical chromatograms were recorded with a HPLC system from *Jasco* equipped with a degasser DG 1580-54, a low-pressure gradient unit LG-1590-04, a pump PU-2080, a multiwavelength detector MD-2010 Plus, an operating unit LC-Net II/ADC and an autosampler AS-2055. The programs Borwin Chromatography and HSS-2000 was uses to operate the measurments and to analyze spectra. The chiral columns Chiralpak IA® (4.6 × 250 mm, 5 μm), Chiralpak IB® (4.6 × 250 mm, 5 μm) and Chiralpak OD® (4.6 × 250 mm, 5 μm) from *Daicel Chemical Industries Ltd.* were used for the determination of *ee*-values. The normal-phase LiChrosorb®

(4.6 × 250 mm, 5 μm) from *JASCO* was complemented by the reversed phase Kromasil® 100 C-18 (4.6 × 250 mm, 5 μm) from the the same company.

Preparative HPLC: Preparative HPLC-separations were performed on a *JASCO* system equipped with 2 pumps PU-2087 Plus, a mixing chamber (normal phase: 1000 μL, reversed phase: 5000 μL); an operating unit LC-Net II/ADC and a UV detector UV-2075 Plus. The programs Borwin Chromatography and HSS-2000 was uses to operate the measurments and to analyze spectra. The chiral columns Chiralpak IA® (20 × 250 mm, 7 μm) and Chiralpak IB® (10 × 250 mm, 7 μm) from *Daicel Chemical Industries Ltd.* and the reversed phase Kromasil® 100 C-18, (20 × 250 mm, 7 μm) from *JASCO* were used for preparative separations.

^{1}H-NMR spectroscopy: ^{1}H-NMR spectra were recorded with a Mercury-300 (300 MHz), Unity-300 (300 MHz) and Inova-600 (600 MHz) spectrometer from *Varian* and an AMX-300 (300 MHz) spectrometer from *Bruker* in deuterated solvents. Chemical shifts δ are given in ppm relative to tetramethylsilane (TMS) and coupling constants *J* in Hertz. The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CHCl_3$: δ_H = 7.24 ppm). The multiplicities of first order were assigned as: s (singlet), s_{br} (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), etc. Signals of higher orders were assigned as: m (multiplet) or m_c (centred multiplet).

^{13}C-NMR spectroscopy: ^{13}C-NMR spectra were recorded with a Mercury-300 (75 MHz), Unity-300 (75 MHz) and Inova-500 (125 MHz) spectrometer from *Varian*. The spectra were measured with complete proton decoupling. Chemical shifts δ_C are given in ppm relative to tetramethylsilane (TMS). The solvent signals were used as references and the chemical shifts converted to the TMS scale ($CHCl_3$: δ_C = 77.36 ppm). ^{13}C-NMR spectra with the Inova-500 (125 MHz) spectrometer were measured with the cryoprobe ^{13}C {^{1}H} PFG Cold Probe from *Varian* at 25 K.

IR spectroscopy: IR spectra were recorded with a FT/IR-4100 spectrometer from *Jasco* as thin films. The signals are reported in cm^{-1}. The measuring range is 500 to 4000 cm^{-1}.

OPR spectroscopy: Optical rotation values were recorded with a P-2000 polarimeter from *JASCO* at the sodium D line. The solvent, temperature and sample concentration (g/100 mL) are stated in all cases.

UV spectroscopy: UV spectra were recorded with a *JASCO* V-630 spectrometer. The measuring range was 190 to 600 nm.

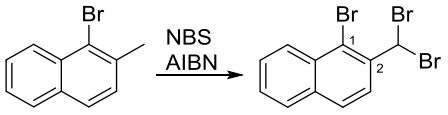
Mass spectrometry: EI-MS spectra were recorded with a double-focusing high-resolution instrument MAT 95 from *Finnigan*. ESI-MS spectra were recorded with a triple stage

quadrupole instrument TSQ 7000 and with an ion trap mass spectrometer LCQ from *Finnigan*. The data are reported in the form *m*/*z* (intensitiy relative to the base peak = 100). ESI-HRMS spectra were recorded with a 7 T Fourier Transform Ion Cyclotron Resonance (FTICR)-mass spectrometer Apex IV from *Bruker* equipped with an Apollo source from *Bruker* and a 74900 series syringe pump from *Cole-Parmer* (flow = 2 μL/min). The program XMASS was uses to operate the measurments and to analyze spectra.

2 BOXAX ligand and reagent syntheses

2.1 Synthesis of naphthoic acid (220)

2.1.1 1-Bromo-2-(dibromomethyl)naphthalene (218)



217 **218**

A solution of 1-bromo-2-methylnapthalene (**217**) (24.7 g, 112 mmol, 1.00 eq.) in CCl_4 (550 mL) was treated with AIBN (2.16 g, 13.2 mmol, 10 mol%) and NBS (68.9 g, 377 mmol, 3.50 eq.) at RT and refluxed for 36 h. The suspension was cooled to RT and filtered. The filtrate was washed with sat. aq. $NaHSO_3$ solution (500 mL), the organic phase dried over Na_2SO_4 and the solvent removed *in vacuo*. Recrystallization from petroleum ether and column chromatography on silica gel (petroleum ether) gave tribromide **218** as a colorless solid (37.0 g, 97.7 mmol 87%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.47 (s, 1 H, $CHBr_2$), 7.53–7.66 (m, 2 H, 6-H, 7-H), 7.82 (d, *J* = 7.2 Hz, 1 H, 5-H), 7.88 (d, *J* = 8.7 Hz, 1 H, 4-H), 8.05 (d, *J* = 8.7 Hz, 1 H, 3-H), 8.29 (d, *J* = 8.4 Hz, 1 H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 41.2 ($CHBr_2$), 119.5 (C-1), 126.7 (C-3), 127.9 (C-6), 128.2, 128.3, 128.4 (C-5, C-7, C-8), 129.0 (C-4), 131.2 (C-8a), 134.6 (C-4a), 137.9 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 2940, 1908, 1619, 1595, 1556, 1501, 1459, 1382, 1323, 1301, 1258, 1218, 1206, 1141, 1033, 973, 958, 906, 863, 804, 770, 747, 734, 677, 665, 646, 596, 528, 515.

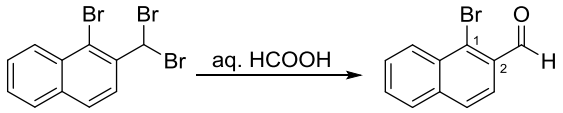
UV (CH_3CN): λ_{max} (nm) (lg ε) = 335 (3.522), 312 (3.481), 300 (4.771).

MS (EI, 70 eV): *m*/*z* (%) = 379.8 (5) $[M]^+$, 298.9 (95) $[M–Br]^+$, 219.0 (7) $[M–2Br]^+$, 139.1 (100) $[M–3Br]^+$.

$C_{11}H_7Br_3$ (378.89) calc.: 377.8078

found: 377.8071, $[M]^+$ (EI-HRMS).

2.1.2 1-Bromo-2-naphthaldehyde (219)

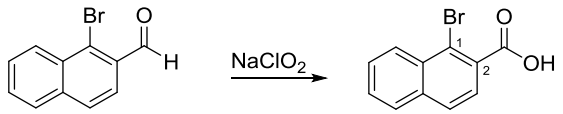


218 **219**

A suspension of tribromide **218** (37.0 g, 97.7 mmol, 1.00 eq.) in formic acid (1 L, 88%) was refluxed for 20 h. After cooling to RT, the solvent was removed *in vacuo* and the crude product taken up in H_2O (500 mL). The aq. phase was extracted with CH_2Cl_2 (3 × 250 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 30:1) gave aldehyde **219** as yellow needles (19.9 g, 84.7 mmol, 87%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.61–7.72 (m, 2 H, 6-H, 7-H), 7.77–7.97 (m, 3 H, 3-H, 4-H, 5-H), 8.43–8.56 (m, 1 H, 8-H), 10.66 (s, 1 H, CHO).
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 124.1 (C-3), 128.1, 128.2, 128.3, 128.5 (C-4, C-5, C-7, C-8), 129.7 (C-6), 131.2, 131.3, 132.1 (C-1, C-4a, C-8a), 137.2 (C-2), 192.8 (CHO).
IR: $\tilde{\nu}$ (cm^{-1}) = 3057, 1683, 1454, 1232, 1215, 969, 887, 869, 810, 751, 538.
UV (CH_3CN): λ_{max} (nm) (lg ε) = 213 (4.266), 228 (4.193), 248 (4.568), 254 (4.653), 290 (3.956), 300 (3.879), 344 (3.363), 353 (3.362).
MS (ESI): *m*/*z* (%) = 257.0 (100) $[M+Na]^+$.
$C_{11}H_7BrO$ (235.08) calc.: 256.9572
found: 256.9573 $[M+Na]^+$ (ESI-HRMS).

2.1.3 1-Bromo-2-naphtoic acid (220)



219 **220**

To a solution of 1-bromo-2-naphthaldehyde (**219**) (10.8 g, 45.9 mmol, 1.00 eq.) and 2-methyl-2-butene (36 mL) in *t*BuOH (750 mL) was added dropwise a solution of $NaH_2PO_4 \cdot H_2O$ (44.5 g, 323 mmol, 7.04 eq.) and $NaClO_2$ (46.9 g, 80%, 415 mmol, 9.04 eq.) in H_2O (1 L) at 0 °C (1.5 h) and the reaction mixture stirred at RT for 19 h. The organic solvent was removed *in vacuo*, the aq. phase acidified with conc. HCl (100 mL) to pH = 1 and extracted with MTBE (3 × 400 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Recrystallization of the crude product from EtOAc and column

chromatography of the mother liquor on silica gel (petroleum ether/EtOAc = 5:1, 1% AcOH) gave acid **220** as a yellow solid (10.3 g, 40.9 mmol, 89%).

^{1}H-NMR (300 MHz, acetone-d_6): δ (ppm) = 7.61–7.79 (m, 3 H, 5-H, 6-H, 7-H), 7.93–8.05 (m, 2 H, 3-H, 4-H), 8.39–8.43 (m, 1 H, 8-H).

^{13}C-NMR (125 MHz, acetone-d_6): δ (ppm) = 121.6 (C-1), 126.4 (C-3), 128.6, 128.8, 128.8, 129.1, 129.2 (C-4, C-5, C-6, C-7, C-8), 132.7, 133.3 (C-4a, C-8a), 135.8 (C-2), 168.2 (COOH).

IR: $\tilde{\nu}$ (cm^{-1}) = 2764, 2583, 1690, 1659, 1619, 1599, 1548, 1498, 1460, 1430, 1395, 1309, 1265, 1240, 1213, 1160, 1143, 1124, 1027, 954, 932, 883, 863, 822, 779, 755, 677, 663, 600, 564, 537.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 226 (4.706), 285 (3.840), 326 (3.049).

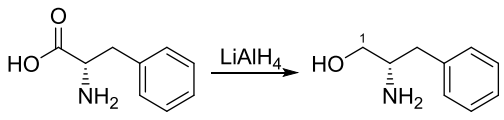
MS (ESI): *m/z* (%) = 251.0 $[M+H]^+$, 273.0 $[M+Na]^+$, 524.9 $[2M+Na]^+$.

$C_{11}H_7BrO_2$ (249.96) calc.: 248.9557

found: 248.9560 $[M–H]^-$ (ESI-HRMS).

2.2 Syntheses of the amino alcohols (*S*)-216a-d and (*R*)-216a-b

2.2.1 (2*S*)-2-Amino-3-phenylpropan-1-ol ((*S*)-216)



(*S*)-**215a** (*S*)-**216a**

To a suspension of $LiAlH_4$ (10.4 g, 276 mmol, 2.00 eq.) in THF (200 mL) was added L-phenylalanine ((*S*)-**215a**) (22.7 g, 138 mmol, 1.00 eq.) portionwise at 0 °C and the reaction mixture refluxed for 16 h. After cooling to RT, the reaction was quenched by careful addition of sat. aq. Na_2SO_4 solution (63 mL) at 0 °C and the suspension filtered. The precipitate was washed with THF (250 mL), the filtrate concentrated *in vacuo* and codistilled with toluene (2 × 85 mL). Recrystallization of the crude reaction product from EtOAc gave L-phenylalaninol ((*S*)-**216a**) as colorless crystals (14.4 g, 95.4 mmol, 70%). Using this procedure the enantiomer D-phenylalaninol ((*R*)-**216a**) was accessed in 62% yield.

Optical Rotation: $[\alpha]_D$ = –23.3 (c = 0.50, $CHCl_3$, 24.4 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (s_{br}, 3 H, 1-OH, 2-NH_2), 2.51 (dd, *J* = 13.5, 9.0 Hz, 1 H, 3-H_a), 2.78 (dd, *J* = 13.5, 4.5 Hz, 1 H, 3-H_b), 3.12 (m_c, 1 H, 2-H), 3.39 (dd, *J* = 10.5, 7.5 Hz, 1 H, 1-H_a), 3.62 (dd, *J* = 10.5, 3.0 Hz, 1 H, 1-H_b), 7.17–7.32 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 40.7 (C-3), 54.2 (C-2), 66.1 (C-1), 126.3 (Ph-C_p), 128.4 (Ph-C_o), 129.0 (Ph-C_m), 138.5 (Ph-C_i).

IR: $\tilde{\nu}$ (cm^{-1}) = 3354, 3296, 3021, 2938, 2916, 2874, 2817, 2782, 2736, 2697, 1575, 1492, 1465, 1453, 1435, 1380, 1360, 1337, 1226, 1154, 1121, 1089, 1064, 1030, 992, 973, 961, 905, 854, 832, 752, 697, 591, 553.

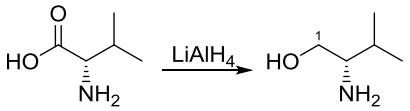
UV (CH_3CN): λ_{max} (nm) (lg ε) = 193 (4.285), 260 (2.206).

MS (ESI): *m/z* (%) = 152.1 (100) $[M+H]^+$.

$C_9H_{13}NO$ (151.21) calc.: 152.1070

found: 152.1072 $[M+H]^+$ (ESI-HRMS).

2.2.2 (2*S*)-2-Amino-3-methylbutan-1-ol ((*S*)-216b)



(*S*)-**215b** (*S*)-**215b**

To a suspension of $LiAlH_4$ (14.9 g, 392 mmol, 2.00 eq.) in THF (230 mL) was added L-valine ((*S*)-**215b**) (23.0 g, 196 mmol, 1.00 eq.) portionwise at 0 °C and the reaction mixture refluxed for 15.5 h. After cooling to RT, the reaction was quenched by careful addition of sat. aq. Na_2SO_4 solution (90 mL) at 0 °C and the suspension filtered. The precipitate was washed with THF (300 mL), the filtrate concentrated *in vacuo* and codistilled with toluene (2 × 85 mL). The crude product was dried in high vacuum to give L-valinol ((*S*)-**216b**) as a colorless solid (15.2 g, 148 mmol, 75%). Using this procedure the enantiomer D-valinol ((*R*)-**216b**) was accessed in 84% yield.

Optical Rotation: $[\alpha]_D$ = +23.3 (c = 0.50, $CHCl_3$, 22.6 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.85 (d, *J* = 3.0 Hz, 3 H, 3-CH_3), 0.86 (d, *J* = 3.0 Hz, 3 H, 4-H_3), 1.47–1.56 (m, 1 H, 3-H), 2.35 (s_{br}, 3 H, 1-OH, 2-NH_2), 2.48–2.54 (m, 1 H, 2-H), 3.24 (dd, *J* = 12.0, 9.0 Hz, 1 H, 1-H_a), 3.57 (dd, *J* = 9.0, 6.0 Hz, 1 H, 1-H_b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 18.4, 19.3 (C-4, 3-CH_3), 31.4 (C-3), 58.4 (C-2), 64.5 (C-1).

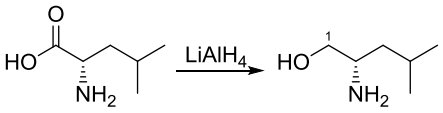
IR: $\tilde{\nu}$ (cm^{-1}) = 2995, 2945, 2888, 2835, 2361, 2332, 1690, 1585, 1559, 1513, 1458, 1440, 1417, 1397, 1353, 1242, 1202, 1177, 1162, 1115, 1066, 1033, 1014, 1000, 970, 904, 847, 824, 808, 759, 742, 724, 643, 587, 572, 554, 529, 503.

MS (ESI): *m/z* (%) = 104.1 (100) $[M+H]^+$, 189.2 (95) $[2M–H_2O+H]^+$.

$C_5H_{13}NO$ (103.10) calc.: 104.1070

found: 104.1071 $[M+H]^+$ (ESI-HRMS).

2.2.3 (2*S*)-2-Amino-4-methylpentan-1-ol ((*S*)-216c)



(*S*)-**215c** (*S*)-**216c**

To a suspension of $LiAlH_4$ (10.0 g, 256 mmol, 2.00 eq.) in THF (160 mL) was added L-leucine ((*S*)-**215c**) (17.1 g, 128 mmol, 1.00 eq.) portionwise at 0 °C and the reaction mixture refluxed for 16 h. After cooling to RT, the reaction was quenched by careful addition of sat. aq. Na_2SO_4 solution (60 mL) at 0 °C and the suspension filtered. The precipitate was washed with THF (200 mL), the filtrate concentrated *in vacuo* and codistilled with toluene (2 × 80 mL). The crude product was dried in high vacuum to give L-leucinol ((*S*)-**216c**) as a colorless oil (9.96g, 85.0 mmol, 66%).

Optical Rotation: $[\alpha]_D$ = +9.1 (c = 0.50, $CHCl_3$, 21.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.83 (d, *J* = 6.6 Hz, 3 H, 4-CH_3), 0.86 (d, *J* = 6.6 Hz, 3 H, 5-H_3), 1.10 (dd, *J* = 7.6, 0.8 Hz, 1 H, 3-H_a), 1.13 (d, *J* = 7.3 Hz, 1 H, 3-H_b), 1.63 (dp, *J* = 13.5, 6.7 Hz, 1 H, 4-H), 2.49 (s_{br}, 3 H, 1-OH, 2-NH_2), 2.84 (ddd, *J* = 13.9, 7.7, 3.7 Hz, 1 H, 2-H), 3.17 (dd, *J* = 10.7, 7.9 Hz, 1 H, 1-H_a), 3.48 (dd, *J* = 10.7, 3.7 Hz, 1 H, 1-H_b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.1 (4-CH_3), 23.2 (C-5), 24.6 (C-4), 43.3 (C-3), 50.5 (C-2), 66.8 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 3333, 3262, 3169, 2953, 2868, 1609, 1567, 1537, 1485, 1468, 1455, 1392, 1367, 1334, 1301, 1147, 1052, 944, 818, 654, 562.

MS (ESI): *m/z* (%) = 217.2 (45) $[2M–OH]^+$, 118.1 (100) $[M+H]^+$.

$C_6H_{15}NO$ (117.19) calc.: 118.1226

found: 118.1214 $[M+H]^+$ (ESI-HRMS).

2.2.4 (2*S*)-2-Amino-3,3-dimethylbutan-1-ol ((*S*)-215d)

(*S*)-**215d** (*S*)-**216d**

To a suspension of $LiAlH_4$ (10.0 g, 263 mmol, 2.00 eq.) in THF (160 mL) was added L-*tert*-leucine ((*S*)-**215d**) (17.3 g, 132 mmol, 1.00 eq.) portionwise at 0 °C and the reaction mixture refluxed for 16 h. After cooling to RT, the reaction was quenched by careful addition of sat. aq. Na_2SO_4 solution (57 mL) at 0 °C and the suspension filtered. The precipitate was washed with THF (180 mL), the filtrate concentrated *in vacuo* and codistilled with toluene (2 × 85 mL). The crude product was dried in high vacuum to give L-*tert*-leucinol ((*S*)-**216d**) as a colorless oil (11.5 g, 98.5 mmol, 75%).

Optical Rotation: $[\alpha]_D$ = +39.5 (c = 0.50, $CHCl_3$, 25.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.83 (s, 9 H, 3-$(CH_3)_3$), 2.47 (dd, *J* = 9.0, 3.0 Hz, 1 H, 2-H), 2.66 (s_{br}, 3 H, 1-OH, 2-NH_2), 3.18 (dd, *J* = 10.8, 9.0 Hz, 1 H, 1-H_a), 3.65 (dd, *J* = 10.8, 3.0 Hz, 1 H, 1-H_b).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 26.3 (3-$(CH_3)_3$), 33.1 (C-3), 61.6, 62.3 (C-1, C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3350, 3294, 2953, 2869, 2360, 2340, 1590, 1474, 1396, 1590, 1474, 1396, 1364, 1201, 1100, 1042, 995, 935, 909, 854, 669, 616, 547, 513.

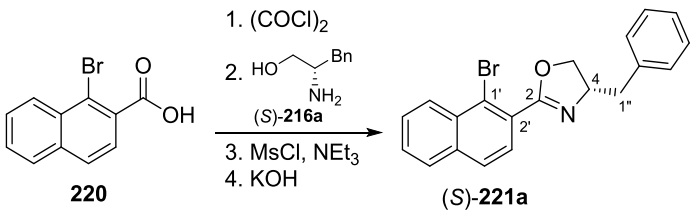
MS (ESI) : *m/z* (%) = 118.1 (100) $[M+H]^+$.

$C_6H_{15}NO$ (117.19) calc.: 118.1226

found: 118.1134 $[M+H]^+$ (ESI-HRMS).

2.3 Syntheses of the Oxazolines (*S*)-221a-d and (*R*)-221a-b

2.3.1 (4*S*)-4-Benzyl-2-(1-bromonaphthalene-2-yl)-4,5-dihydro-oxazole ((*S*)-221a)



220 (*S*)-**221a**

Oxalyl chloride (4.17 mL, 48.0 mmol, 2.00 eq.) and catalytic amounts of DMF (0.1 mL) were added dropwise to a solution of carboxylic acid **220** (6.00 g, 24.0 mmol, 1.00 eq.) in toluene

(50 mL) at 0 °C. The resulting mixture was stirred at RT for 4 h. The volatiles were removed under reduced pressure and the crude product was concentrated under high vacuum for 23 h. The acid chloride was dissolved in CH_2Cl_2 (50 mL) and subsequently added dropwise to a solution of L-phenylalaninol ((*S*)-**216a**) (3.96 g, 26.4 mmol, 1.10 eq.) and NEt_3 (6.98 mL, 49.7 mmol, 2.07 eq.) in CH_2Cl_2 (220 mL) followed by stirring at RT for 23 h. The reaction mixture was washed with 1 M HCl (130 mL) and brine (130 mL) and the combined aq. phases were extracted with EtOAc (5 × 80 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude carboxy amide was suspended in CH_2Cl_2 (360 mL), then NEt_3 (10.3 mL, 74.3 mmol, 3.00 eq.) and mesyl chloride (2.80 mL, 36.1 mmol, 1.50 eq.) were added at 0 °C and the reaction mixture stirred at RT for further 2.5 h. After the volatiles were removed under reduced pressure, the crude product was suspended in MeOH (300 mL), treated with KOH (6.70 g, 85%, 119 mmol, 5.00 eq.) and the resulting slurry stirred at RT for 19 h. The solvent was removed *in vacuo*, the residue taken up in H_2O (320 mL) and the aq. phase extracted with EtOAc (3 × 130 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (*n*-pentane/EtOAc = 6:1) furnished oxazoline (*S*)-**221a** as a yellow oil (8.07 g, 22.0 mmol, 92%). Using this procedure the enantiomer (*R*)-**221a** was accessed in 85% yield.

Optical Rotation: $[\alpha]_D$ = +4.3 (c = 0.50, $CHCl_3$, 25.6 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.87 (dd, *J* = 13.8, 8.4 Hz, 1 H, 1''-H_a), 3.27 (dd, *J* = 13.8, 8.4 Hz, 1 H, 1''-H_b) , 4.24 (dd, *J* = 8.4, 7.8 Hz, 1 H, 5-H_a), 4.44 (dd, *J* = 8.4, 7.8 Hz, 1 H, 5-H_b) , 4.67–4.72 (m, 1 H, 4-H), 7.22–7.33 (m, 5 H, 5 × Ph-H), 7.55–7.63 (m, 3 H, 5'-H, 6'-H, 7'-H), 7.80–7.83 (m, 2 H, 3'-H, 4'-H), 8.41 (d, *J* = 8.4 Hz, 1 H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) =41.6 (C-1''), 68.3 (C-4), 72.1 (C-5), 123.2 (C-1'), 126.5, 126.6, 127.6, 127.7, 127.8, 128.1, 128.2, 128.3, 128.5, 129.3 (C-3', C-4', C-5', C-6', C-7', C-8', C-8a', 5 × Ph-C), 132.2 (C-4a'), 134.5 (C-2'), 137.7 (Ph-C_i), 164.2 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3059, 3025, 2964, 2926, 2894, 2847, 2359, 2341, 1734, 1650, 1598, 1554, 1495, 1471, 1463, 1453, 1374, 1345, 1322, 1304, 1277, 1237, 1211, 1165, 1150, 1136, 1097, 1069, 1043, 1028, 974, 955, 928, 864, 813, 772, 747, 701, 662, 604, 581, 529, 511.

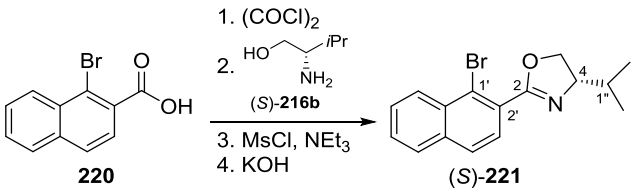
UV (CH_3CN): λ_{max} (nm) (lg ε) = 227 (4.769), 286 (3.836), 322 (2.954).

MS (ESI): *m/z* (%) = 366.1 (100) $[M+H]^+$, 388.0 (14) $[M+Na]^+$, 755.1 (16) $[2M+Na]^+$.

$C_{20}H_{16}BrNO$ (366.26) calc.: 366.0488

found: 366.0487 $[M+H]^+$ (ESI-HRMS).

2.3.2 (4*S*)-2-(1-Bromonaphthalene-2-yl)-4-(*iso*-propyl)-4,5-dihydro-oxazole ((*S*)-221b)



Oxalyl chloride (2.60 mL, 30.3 mmol, 2.00 eq.) and catalytic amounts of DMF (0.1 mL) were added dropwise to a solution of carboxylic acid **220** (3.72 g, 14.9 mmol, 1.00 eq.) in toluene (32 mL) at 0 °C. The resulting mixture was stirred at RT for 4.5 h. The volatiles were removed under reduced pressure and the crude product was concentrated under high vacuum for 12 h. The acid chloride was dissolved in CH_2Cl_2 (140 mL) and subsequently added dropwise to a solution of L-valinol ((*S*)-**216b**) (1.70 g, 16.4 mmol, 1.10 eq.) and NEt_3 (4.30 mL, 31.0 mmol, 2.08 eq.) in CH_2Cl_2 (30 mL) followed by stirring at RT for 19.5 h. The reaction mixture was washed with 1 M HCl (80 mL) and brine (80 mL) and the combined aq. phases were extracted with EtOAc (4 × 80 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude carboxy amide was suspended in CH_2Cl_2 (200 mL), then NEt_3 (6.20 mL, 44.7 mmol, 3.00 eq.) and mesyl chloride (1.73 mL, 22.3 mmol, 1.50 eq.) were added at 0 °C and the reaction mixture was stirred at RT for further 2 h. After the volatiles were removed under reduced pressure, the crude product was suspended in MeOH (190 mL), treated with KOH (4.18 g, 85%, 74.5 mmol, 5.00 eq.) and the resulting slurry stirred at RT for 19 h. The solvent was removed *in vacuo*, the residue taken up in H_2O (200 mL) and the aq. phase extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (*n*-pentane/EtOAc = 7:1 → 3:2) furnished oxazoline (*S*)-**221b** as a yellow oil (3.78 g, 11.9 mmol, 80%). Using this procedure the enantiomer (*R*)-**221b** was accessed in 89% yield.

Optical Rotation: $[\alpha]_D = -51.9$ (c = 0.50, $CHCl_3$, 23.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.01 (d, *J* = 6.0 Hz, 3 H, 1''-$(CH_3)_a$), 1.08 (d, *J* = 6.0 Hz, 3 H, 1''-$(CH_3)_b$), 1.88–2.03 (m, 1 H, 1''-H), 4.17–4.26 (m, 2 H, 4-H, 5-H_a), 4.44–4.53 (m, 1 H, 5-H_b), 7.52–7.63 (m, 3 H, 5'-H, 6'-H, 7'-H), 7.79–7.82 (m, 2 H, 3'-H, 4'-H), 8.40 (d, *J* = 9.0 Hz, 1 H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 18.4, 18.9 (1''-$(CH_3)_a$, 1''-$(CH_3)_b$), 32.7 (C-1''), 70.5 (C-5), 73.0 (C-4), 123.0 (C-1'), 126.7, 127.6, 127.6, 128.1, 128.2 (C-3', C-4', C-5', C-6', C-7', C-8'), 128.6 (C-8a'), 132.2 (C-4a'), 134.8 (C-2'), 163.7 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3058, 2956, 2926, 2895, 2871, 1657, 2895, 2871, 1657, 1596, 1555, 1498, 1463, 1425, 1374, 1344, 1323, 1300, 1282, 1256, 1237, 1211, 1165, 1149, 1137, 1094, 1029, 974, 952, 925, 894, 864, 816, 770, 748, 662, 600, 530.

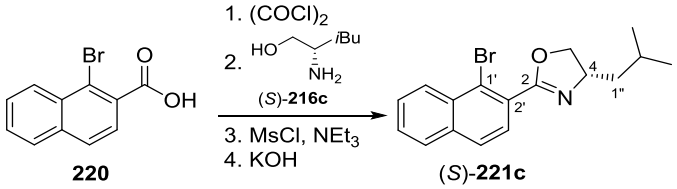
UV (CH_3CN): λ_{max} (nm) (lg ε) = 227 (4.767), 286 (3.849), 322 (2.944).

MS (EI): *m/z* (%) = 317.0 (13) $[M]^+$, 274.0 (100) $[M–C_3H_7]^+$, 126.0 (44) $[C_{10}H_6]^+$.

$C_{16}H_{16}BrNO$ (318.21) calc.: 317.0415

found: 317.0417 $[M]^+$(EI-HRMS).

2.3.3 (4*S*)-2-(1-Bromonaphthalene-2-yl)-4-(*iso*-butyl)-4,5-dihydro-oxazole ((*S*)-221c)



Oxalyl chloride (4.79 mL, 55.8 mmol, 2.00 eq.) was added dropwise to a solution of carboxylic acid **220** (7.00 g, 27.9 mmol, 1.00 eq.) in toluene (60 mL) and catalytic amounts of DMF (0.2 mL) at 0 °C. The resulting mixture was stirred at RT for 3 h. The volatiles were removed under reduced pressure and the crude product was concentrated under high vacuum for 2.5 h. The acid chloride was dissolved in CH_2Cl_2 (210 mL) and subsequently added dropwise to a solution of L-leucinol ((*S*)-**216c**) (4.12 g, 35.2 mmol, 1.26 eq.) and NEt_3 (7.40 mL, 57.7 mmol, 2.07 eq.) in CH_2Cl_2 (55 mL) followed by stirring at RT for 19 h. The reaction mixture was washed with 1 M HCl (200 mL) and brine (200 mL) and the combined aq. phases were extracted with EtOAc (4 × 100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent removed *in vacuo*. The crude carboxy amide was suspended in CH_2Cl_2 (500 mL), then NEt_3 (10.7 mL, 83.7 mmol, 3.00 eq.) and mesyl chloride (3.24 mL, 41.9 mmol, 1.50 eq.) were added at 0 °C and the reaction mixture was stirred at RT for further 2 h. After the volatiles were removed under reduced pressure, the crude product was suspended in MeOH (400 mL), treated with KOH (9.21 g, 85%, 140 mmol, 5.00 eq.) and the resulting slurry stirred at RT for 16 h. The solvent was removed *in vacuo*, the residue taken up in H_2O (500 mL) and the aqueous phase extracted with EtOAc (3 × 250 mL). The

combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (*n*-pentane/EtOAc = 10:1 → 7:3) furnished oxazoline (*S*)-**221c** as a yellow oil (4.17 g, 12.6 mmol, 45%).

Optical Rotation: $[\alpha]_D = -48.7$ (c = 0.50, $CHCl_3$, 21.3 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.98 (d, *J* = 6.2 Hz, 3 H, 2''-$(CH_3)_a$), 1.00 (d, *J* = 6.1 Hz, 3 H, 2''-$(CH_3)_b$), 1.45 (dt, *J* = 13.2, 7.1 Hz, 1 H, 1''-H_a), 1.84–1.93 (m, 2 H, 1''-H_b, 2''-H), 4.08 (t, *J* = 7.8 Hz, 1 H, 5-H_a), 4.42 (m_c, 1 H, 4-H), 4.57 (dd, *J* = 9.3, 7.9 Hz, 1 H, 5-H_b), 7.52–7.64 (m, 3 H, 3'-H, 4'-H, 5'-H), 7.79–7.83 (m, 2 H, 6'-H, 7'-H), 8.39 (d, *J* = 8.3 Hz, 1 H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 2 × 22.8 (2''-$(CH_3)_a$, 2''-$(CH_3)_b$), 25.4 (C-2''), 45.5 (C-1''), 65.6 (C-4), 73.5 (C-5), 123.2 (C-1'), 126.8, 127.7, 127.7, 127.9, 128.2, 128.2 (C-3', C-4', C-5', C-6', C-7', C-8'), 128.6, 132.3, 134.9 (C-2', C-4a', C-8a'), 163.6 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2868, 1658, 1597, 1555, 1498, 1465, 1374, 1366, 1346, 1339, 1304, 1242, 1100, 1079, 975, 962, 946, 814, 750, 662, 531.

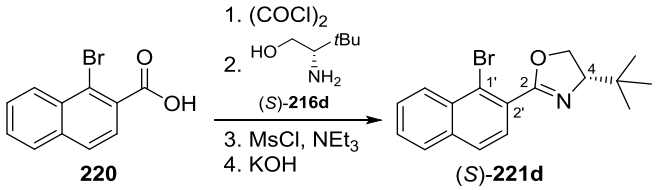
UV (CH_3CN): λ_{max} (nm) (lg ε) = 227 (4.772), 286 (3.849).

MS (ESI): *m*/*z* (%) = 332.1 (100) $[M+H]^+$.

$C_{17}H_{18}BrNO$ (332.24) calc.: 332.0645

found: 332.0649 $[M+H]^+$ (ESI-HRMS).

2.3.4 (4*S*)-2-(1-Bromonaphthalene-2-yl)-4-(*tert*-butyl)-4,5-dihydro-oxazole ((*S*)-221d)



Oxalyl chloride (2.69 mL, 30.5 mmol, 2.00 eq.) was added dropwise to a solution of carboxylic acid **220** (3.85 g, 15.3 mmol, 1.00 eq.) in toluene (33 mL) and catalytic amounts of DMF (0.1 mL) at 0 °C. The resulting mixture was stirred at RT for 4 h. The volatiles were removed under reduced pressure and the crude product was concentrated under high vacuum for 21 h. The acid chloride was dissolved in CH_2Cl_2 (140 mL) and subsequently added dropwise to a solution of L-*tert*-leucinol ((*S*)-**216d**) (1.98 g, 16.9 mmol, 1.10 eq.) and NEt_3 (4.46 mL, 32.2 mmol, 2.10 eq.) in CH_2Cl_2 (22 mL) followed by stirring at RT for 17.5 h. The

reaction mixture was washed with 1 M HCl (80 mL) and brine (80 mL) and the combined aq. phases were extracted with EtOAc (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude carboxy amide was suspended in CH_2Cl_2 (200 mL), then NEt_3 (6.34 mL, 45.7 mmol, 3.00 eq.) and mesyl chloride (1.78 mL, 23.0 mmol, 1.50 eq.) were added at 0 °C and the reaction mixture was stirred at RT for further 3.5 h. After the volatiles were removed under reduced pressure, the crude product was suspended in MeOH (190 mL), treated with KOH (4.28 g, 85%, 76.3 mmol, 5.00 eq.) and the resulting slurry stirred at RT for 2.5 h. The solvent was removed *in vacuo*, the residue taken up in H_2O (200 mL) and the aqueous phase extracted with EtOAc (3 × 125 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by column chromatography on silica gel (*n*-pentane/EtOAc = 6:1) furnished oxazoline (*S*)-**221d** as a yellow oil (4.45 g, 13.4 mmol, 88%).

Optical Rotation: $[\alpha]_D$ = –59.5 (c = 0.50, $CHCl_3$, 25.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.03 (s, 9 H, $C(CH_3)_3$), 4.15 (dd, *J* = 9.9, 7.8 Hz, 1 H, 4-H), 4.31 (t, *J* = 8.4 Hz, 1 H, 5-H_a), 4.44 (dd, 1 H, 5-H_b), 7.55–7.62 (m, 3 H, 5'-H, 6'-H, 7'-H), 7.81 (m_c, 2 H, 3'-H, 4'-H), 8.39 (d, *J* = 9.0 Hz, 1 H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 26.1 ($C(\underline{C}H_3)_3$), 34.1 ($\underline{C}(CH_3)_3$), 69.1 (C-5), 76.8 (C-4), 123.0 (C-1'), 126.7, 127.5, 127.6, 127.8, 128.0, 128.1 (C-3', C-4', C-5', C-6', C-7', C-8'), 128.6 (C-8a'), 132.2 (C-4a'), 134.7 (C-2'), 163.6 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2901, 2866, 2360, 2341, 1657, 1618, 1595, 1556, 1498, 1473, 1376, 1361, 1336, 1299, 1262, 1243, 1208, 1169, 1101, 1025, 975, 950, 924, 864, 833, 814, 768, 749, 662, 604, 542, 529.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 227 (4.581), 286 (3.652), 322 (2.718).

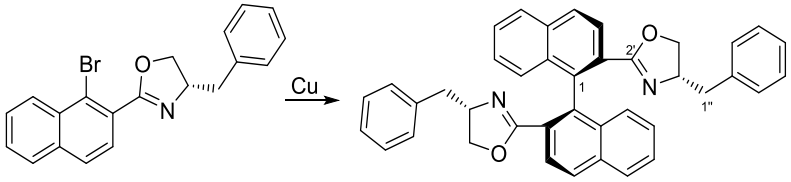
MS (ESI): *m/z* (%) = 332.1 (100) $[M+H]^+$, 354.1 (11) $[M+Na]^+$, 687.2 (11) $[2M+Na]^+$.

$C_{17}H_{18}BrNO$ (332.24) calc.: 332.0645

found: 332.0652 $[M+H]^+$ (ESI-HRMS).

2.4 Syntheses of the BOXAX ligands (*S*,*S*)-140a-d and (*R*,*R*)-140a-b

2.4.1 (*S*)-2,2'-Bis[(4*S*)-4-benzyl-4,5-dihydrooxazol-2-yl]-1,1'-binaphthalene ((*S*,*S*)-140a)



Bromide (*S*)-**221a** was divided into the two batches I (13.9 g, 38.0 mmol) and II (6.00 g, 16.4 mmol). To a solution of bromide (*S*)-**221a** (13.9 g, 38.0 mmol, 1.00 eq., batch I) in pyridine (300 mL, distilled over calcium hydride) was added activated copper powder (8.45 g, 133 mmol, 3.50 eq.) at RT and the reaction mixture heated at reflux for 15 h. To a solution of bromide (*S*)-**221a** (6.00 ,6.4 mmol, 1.00 eq., batch II) in pyridine (160 mL, distilled over calcium hydride) was added activated copper powder (3.64 g, 57.3 mmol, 2.00 eq.) at RT and the reaction mixture heated at reflux for 15.5 h. After cooling to RT, the batches I and II were unified and the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (1 L) and filtered over celite® (rinsing with CH_2Cl_2). The filtrate was washed with conc. NH_3 solution (3 × 300 mL) until the organic layer was colorless. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification of the residue by multiple column chromatography on silica gel (*n*-pentane/EtOAc = 100:1 → 9:1) gave the Bn-BOXAX-ligand (*S*,*S*)-**140a** as a white foam (11.8 g, 20.6 mmol, 76%). Using this procedure the enantiomer (*R*,*R*)-**140a** was accessed in 78% yield

Optical Rotation: $[\alpha]_D = -79.8$ (c = 0.50, $CHCl_3$, 26.6 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.87 (dd, *J* = 13.8, 9.0 Hz, 2 H, 2 × 1"-H_a), 2.58 (dd, *J* = 13.8, 5.4 Hz, 2 H, 2 × 1"-H_b), 3.60–3.65 (m, 4 H, 2 × 5'-H_2), 4.13 (m_c, 2 H, 2 × 4'-H), 6.94 (d, *J* = 7.2 Hz, 4 H, 2 × 6-H, 2 × 7-H), 7.11–7.20 (m, 6 H, 6 × Ph-H), 7.27–7.33 (m, 4 H, 4 × Ph-H), 7.48 (m_c, 2 H, 2 × 5-H), 7.89 (d, *J* = 7.8 Hz, 2 H, 2 × 3-H), 7.95 (d, *J* = 8.4 Hz, 2 H, 2 × 4-H), 8.06 (d, *J* = 8.4 Hz, 2 H, 2 × 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 41.0 (C-1"), 67.7 (C-4'), 71.5 (C-5'), 126.0 (C-8a), 126.0, 126.2, 126.4, 126.9, 126.9, 127.7, 127.9, 128.3, 129.0 (C-3, C-4, C-5, C-6, C-7, C-8, Ph-C), 132.8, 134.3 (C-2, C-4a), 137.8, 138.2 (C-1, Ph-C_i), 164.4 (C-2').

IR: $\tilde{\nu}$ (cm^{-1}) = 3058, 3023, 2891, 1735, 1638, 1597, 1494, 1472, 1453, 1360, 1307, 1277, 1237, 1212, 1148, 1119, 1094, 1056, 1028, 969, 949, 935, 916, 865, 822, 777, 750, 698, 635, 584, 560, 536.

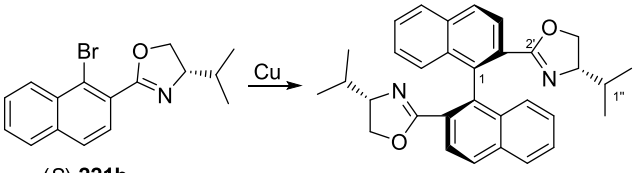
UV (CH_3CN): λ_{max} (nm) (lg ε) = 229 (4.805), 288 (4.083), 335 (3.217).

MS (ESI): *m/z* (%) = 573.3 (100) $[M+H]^+$.

$C_{40}H_{32}N_2O_2$ (572.25) calc.: 573.2537

found: 573.2537 $[M+H]^+$ (ESI-HRMS).

2.4.2 (*S*)-2,2'-Bis[(4*S*)-4-(*iso*-propyl)-4,5-dihydrooxazol-2-yl]-1,1'-binaphthalene ((*S*,*S*)-140b)



(*S*)-**221b** (*S*,*S*)-**140b**

To a solution of bromide (*S*)-**221b** (3.77 g, 11.9 mmol, 1.00 eq.) in pyridine (90 mL, distilled over calcium hydride) was added activated copper powder (2.26 g, 35.6 mmol, 3.00 eq.) at RT and the reaction mixture heated at reflux for 10 h. After cooling to RT, the solvent was removed *in vacuo*, the residue taken up in CH_2Cl_2 (100 mL) and filtered over celite® (rinsing with CH_2Cl_2). The filtrate was washed with conc. NH_3 solution (4 × 100 mL) until the organic layer was colorless. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc = 8:1 → 4:1) and recrystallization from EtOAc gave the *i*Pr-BOXAX-ligand (*S*,*S*)-**140b** as colorless crystals (2.12 g, 4.45 mmol, 75%). Using this procedure the enantiomer (*R*,*R*)-**140b** was accessed in 46% yield.

Optical Rotation: $[\alpha]_D$ = –219.9 (c = 0.50, $CHCl_3$, 23.2 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.57 (dd, *J* = 6.9, 5.4 Hz, 12 H, 4 × CH_3), 1.28 (m_c, 2 H, 2 × 1''-H), 3.56 (t, *J* = 7.8 Hz, 2 H, 2 × 4'-H), 3.62–3.72 (m, 4 H, 2 × 5'-H_2), 7.17–7.21 (m, 4 H, 2 × 6-H, 2 × 7-H), 7.43 (m_c, 2 H, 2 × 5-H), 7.87 (d, *J* = 7.8 Hz , 2 H, 2 × 3-H), 7.92 (d, *J* = 9.0 Hz, 2 H, 2 × 4-H), 8.08 (d, *J* = 9.0 Hz, 2 H, 2 × 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 18.1 ((CH_3)$_a$), 18.5 ((CH_3)$_b$), 32.7 (C-1''), 70.0 (C-5'), 72.4 (C-4'), 125.8 (C-8a), 126.1, 126.2, 126.7, 127.1, 127.5, 127.7 (C-3, C-4, C-5, C-6, C-7, C-8), 133.0, 134.2 (C-2, C-4a), 137.9 (C-1), 163.6 (C-2').

IR: $\tilde{\nu}$ (cm^{-1}) = 3043, 2953, 2896, 2867, 2364, 2335, 1645, 1597, 1560, 1505, 1464, 1425, 1381, 1363, 1337, 1316, 1292, 1273, 1258, 1230, 1165, 1147, 1027, 1012, 1057, 1027, 1012, 982, 948, 909, 857, 834, 822, 798, 758, 712, 690, 679, 571, 531, 522.

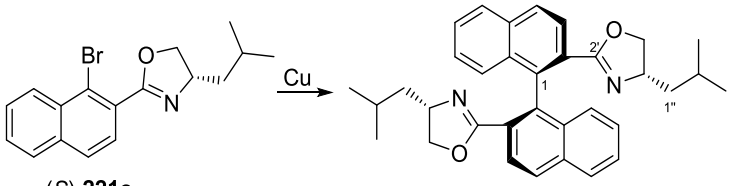
UV (CH_3CN): λ_{max} (nm) (lg ε) = 229 (4.753), 289 (4.036), 337 (3.150).

MS (ESI): *m*/*z* (%) = 477.5 (100) $[M+H]^+$, 975.8 (6) $[2M+Na]^+$.

$C_{32}H_{32}N_2O_2$ (476.25) calc.: 477.2537

found: 477.2543 $[M+H]^+$ (ESI-HRMS).

2.4.3 (*S*)-2,2'-Bis-[(4*S*)-4-(*iso*-butyl)-4,5-dihydrooxazol-2-yl]-1,1'-binaphthalene ((*S*,*S*)-140c)



(*S*)-**221c** (*S*,*S*)-**140c**

To a solution of bromide (*S*)-**221c** (2.00 g, 6.02 mmol, 1.00 eq.) in pyridine (46 mL, distilled over calcium hydride) was added activated copper powder (1.15 g, 18.1 mmol, 3.00 eq.) at RT and the reaction mixture heated at reflux for 11 h. After cooling to RT, the solvent was removed *in vacuo*, the residue taken up in CH_2Cl_2 (100 mL) and filtered over celite® (rinsing with CH_2Cl_2). The filtrate was washed with conc. NH_3 solution (3 × 100 mL) until the organic layer was colorless. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification of the residue by column chromatography on silica gel (*n*-pentane/EtOAc = 100:1→ 9:1) and preparative HPLC (*Jasco* LiChrosorb Si60®, 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH = 99:1, 10 mL/min, λ = 233 nm) furnished the (*S*,*S*)-*i*Bu-BOXAX-ligand (*S*,*S*)-**140c** (0.73 g, 1.45 mmol, 48%). Alternatively, (*S*,*S*)-**140c** can also be obtained by recrystallization from 2-PrOH.

Optical Rotation: $[\alpha]_D$ = –199.5 (c = 0.48, $CHCl_3$, 22.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.70 (d, *J* = 6.6 Hz, 6 H, 2 × 2"-$(CH_3)_a$), 0.74 (d, *J* = 6.6 Hz, 6 H, 2 × 2"-$(CH_3)_b$), 0.82 (dt, *J* = 13.3, 7.3 Hz, 2 H, 2 × 1"-H_a), 1.05 (dt, *J* = 13.6, 6.9 Hz, 2 H, 2 × 1"-H_b), 1.33 (dp, *J* = 13.4, 6.7 Hz, 2 H, 2 × 2"-H), 3.42 (t, *J* = 7.7 Hz, 2 H, 2 × 5'-H_a), 3.76 (dd, *J* = 9.2, 8.0 Hz, 2 H, 2 × 5'-H_b), 3.89 (dq, *J* = 9.2, 7.2 Hz, 2 H, 2 × 4'-H), 7.22 (m_c, 4 H, 2 × 6-H, 2 × 7-H), 7.44 (ddd, *J* = 8.0, 5.1, 2.8 Hz, 2 H, 2 × 5-H), 7.88 (d,

J = 8.2 Hz, 2 H, 2 × 8-H), 7.92 (d, J = 8.6 Hz, 2 H, 2 × 4-H), 8.03 (d, J = 8.7 Hz, 2 H, 2 × 3-H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = 22.5 (2"-$(CH_3)_a$), 22.6 (2"-$(CH_3)_b$), 25.0 (C-2"), 45.0 (C-1"), 64.7 (C-4'), 72.8 (C-5'), 126.0, 126.1, 126.3, 126.7, 127.0 (C-3, C-5, C-6, C-7, C-8), 127.5, 127.8 (C-4, C-8a), 132.9, 134.2 (C-2, C-4a), 137.8 (C-1), 163.7 (C-2').

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2916, 2891, 2866, 2360, 2341, 1656, 1505, 1468, 1379, 1364, 1296, 1243, 1233, 1103, 982, 951, 909, 854, 823, 753, 738, 569.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 228 (4.839), 288 (4.106), 336 (3.327), 370 (2.568).

Analytical HPLC (*Jasco* LiChrosorb Si60®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH = 99:1, 0.8 mL/min): t_R = 7.0 min.

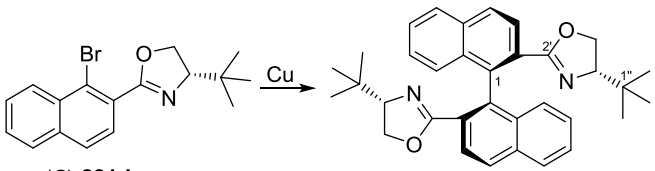
Preparative HPLC (*Jasco* LiChrosorb Si60®, 20 × 250 mm, 7 μm, *n*-hexane/2-PrOH = 99:1, 10 mL/min, 233 nm): t_R = 10.4 min.

MS (ESI): *m*/*z* (%) = 505.3 (100) $[M+H]^+$.

$C_{34}H_{36}N_2O_2$ (504.28) calc.: 505.2850

found: 505.2851 $[M+H]^+$ (ESI-HRMS).

2.4.4 (*S*)-2,2'-Bis[(4*S*)-4-(*tert*-butyl)-4,5-dihydrooxazol-2-yl]-1,1'-binaphthalene ((*S*,*S*)-140d)



(*S*)-**221d** (*S*,*S*)-**140d**

To a solution of bromide (*S*)-**221d** (4.45 g, 13.4 mmol, 1.00 eq.) in pyridine (100 mL, distilled over calcium hydride) was added activated copper powder (2.57 g, 40.2 mmol, 3.00 eq.) at RT and the reaction mixture heated at reflux for 16 h. Additional copper powder (19.7 g, 208 mmol, 23.0 eq.) was added at RT and refluxing continued for 22 h. After cooling to RT, the solvent was removed *in vacuo*, the residue taken up in CH_2Cl_2 (150 mL) and filtered over celite® (rinsing with CH_2Cl_2). The filtrate was washed with conc. NH_3 solution (4 × 250 mL) until the organic layer was colorless. The organic phase was dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification of the residue by two column chromatographies on silica gel (*n*-hexane/EtOAc = 20:1 → 5:1) and (*n*-hexane/EtOAc = 18:1 → 5:1) gave the *t*Bu-BOXAX-ligand (*S*,*S*)-**140d** as a yellow foam (0.93 g, 1.84 mmol, 27%).

Optical Rotation: $[\alpha]_D = -125.1$ (c = 0.50, $CHCl_3$, 23.7 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.48 (s, 18 H, 6 × CH_3), 3.59-3.72 (m, 6 H, 2 × 4'-H, 2 × 5'-H_2), 7.11-7.20 (m, 4 H, 2 × 6-H, 2 × 7-H), 7.41 (m_c, 2 H, 2 × 5-H), 7.86 (d, *J* = 8.1 Hz, 2 H, 2 × 4-H), 7.91 (d, *J* = 8.7 Hz, 2 H, 2 × 3-H), 8.11 (d, *J* = 8.7 Hz, 2 H, 2 × 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 25.4 (CH_3), 33.5 (C-1''), 68.1 (C-5'), 76.0 (C-4'), 125.6 (C-8a), 126.1, 126.2, 126.6, 127.2, 127.3, 127.6 (C-3, C-4, C-5, C-6, C-7, C-8), 133.1, 134.2 (C-2, C-4a), 138.3 (C-1), 163.2 (C-2').

IR: $\tilde{\nu}$ (cm^{-1}) = 3062, 2950, 2900, 2866, 2360, 2340, 1648, 1597, 1561, 1392, 1361, 1294, 1237, 1207, 1147, 1109, 1054, 1026, 975, 949, 931, 910, 859, 834, 821, 800, 752, 704, 573, 538, 517.

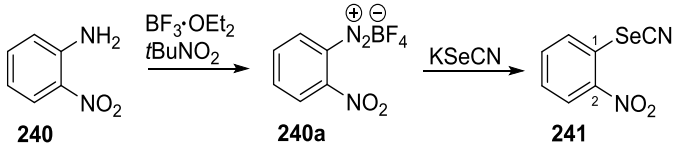
UV (CH_3CN): λ_{max} (nm) (lg ε) = 230 (4.777), 290 (4.038), 337 (3.172).

MS (ESI): *m/z* (%) = 505.3 (100) $[M+H]^+$.

$C_{34}H_{36}N_2O_2$ (504.28) calc.: 505.2851

found: 505.2850 $[M+H]^+$ (ESI-HRMS).

2.5 Synthesis of *ortho*-nitrophenyl selenocyanate (241)



A solution of *ortho*-nitroaniline (**240**) (12.0 g, 86.9 mmol, 1.00 eq.) in CH_2Cl_2 (120 mL) was treated with $BF_3{\cdot}OEt_2$ (16.5 mL, 130 mmol, 1.50 eq.) at –12 °C and the resulting brown suspension stirred at this temperature for 45 min. A solution of *tert*-butyl nitrite (12.8 mL, 95%, 104 mmol, 1.20 eq.) in CH_2Cl_2 (50 mL) was added within 30 min at –12 °C and the suspension stirred at this temperature for 30 min and at 0 °C for further 30 min. The reaction was quenched by addition of cold *n*-pentane (150 mL) at 0 °C. The precipitate was filtered off, washed with Et_2O (100 mL) and dried in high vacuum. The tetrafluoroborate **240a** was divided into two batches (9.90 g, 41.8 mmol).

To a solution of tetrafluoroborate **240a** (9.90 g, 41.8 mmol, 0.50 eq.) in H_2O (200 mL) was added dropwise a solution of potassium selenocyanate (6.00 g, 41.6 mmol, 0.50 eq.) in H_2O (50 mL) at 0 °C and the resulting reaction mixture stirred at 0 °C for 30 min. The precipitate was filtered off, washed with H_2O (200 mL) and dried under high vacuum. Column chromatography of the two batches on silica gel (petroleum ether/EtOAc = 10:1 → 5:1) and recrystallization from EtOH gave **241** as yellow crystals (11.3 g, 49.8 mmol, 60%).

Melting Point: 142 °C (lit. 142 °C).

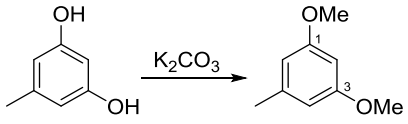
^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.59 (ddd, *J* = 8.4, 7.3, 1.2 Hz, 1 H, 4-H), 7.76 (ddd, *J* = 8.3, 7.3, 1.5 Hz, 2 H, 5-H), 8.20 (dd, *J* = 8.2, 1.2 Hz, 1 H, 6-H), 8.43 (dd, *J* = 8.2, 1.5 Hz, 1 H, 3-H).

$C_7H_4N_2O_2Se$ (227.08).

3 Enantioselective Total Synthesis of (–)-Diversonol

3.1 Syntheses of alkenyl phenols (*E*)-225 and (*Z*)-225

3.1.1 1,3-Dimethoxy-5-methylbenzene (226)



94 **226**

To a suspension of orcinol monohydrate (**94**) (40.0 g, 281 mmol, 1.00 eq.) and K_2CO_3 (81.6 g, 590 mmol, 2.10 eq.) in acetone was slowly added dimethyl sulfate (61.4 mL, 646 mmol, 2.30 eq.) at RT. The reaction mixture was refluxed for 23 h, cooled to RT and treated with conc. NH_3 solution (30 mL) and refluxed for further 15 min. After cooling to RT, the volatiles were removed *in vacuo*, the residue was suspended in H_2O (400 mL) and the aq. phase extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with H_2O (100 mL), 3 M aq. NaOH solution (200 mL) and brine (100 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Distillation (105 °C, 14 mbar) gave orcinol dimethyl ether (**226**) as a colorless liquid (39.3 g, 262 mmol, 93%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3 H, 5-CH_3), 3.78 (s, 6 H, 1-OCH_3, 3-OCH_3), 6.30 (s_{br}, 1 H, 2-H), 6.35 (s_{br}, 2 H, 4-H, 6-H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 21.8 (5-CH_3), 55.2 (1-OCH_3, 3-OCH_3), 97.5 (C-2), 107.1 (C-4, C-6), 140.2 (C-5), 160.7 (C-1, C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3059, 2955, 2838, 1597, 1461, 1321, 1295, 1205, 1151, 1070, 921, 828, 686.

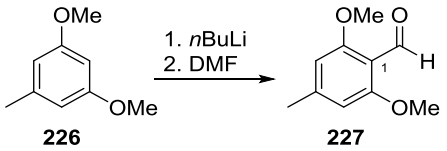
UV (CH_3CN): λ_{max} (nm) (lg ε) = 204 (4.645), 273 (3.181), 279 (3.182).

MS (EI, 70 eV): *m*/*z* (%) = 152.2 (100) $[M]^+$, 123.1 (37) $[M–2CH_3+H]^+$.

$C_9H_{12}O_2$ (152.19) calc.: 152.0837

found: 152.0841, $[M]^+$ (EI-HRMS).

3.1.2 2,6-Dimethoxy-4-methylbenzaldehyde (227)



226 **227**

A solution of orcinol dimethyl ether (**226**) (39.9 g, 262 mmol, 1.00 eq.) and TMEDA (78.9 mL, 524 mmol, 2.00 eq.) in Et_2O (400 mL) was treated with *n*BuLi (126 mL, 2.5 M in *n*-hexane, 315 mmol, 1.20 eq.) at 0 °C and refluxed for 3 h. After cooling to 0 °C, DMF (60.5 mL, 786 mL, 3.00 eq.) was added and the reaction mixture stirred at RT for 2 h before being quenched by addition of H_2O (500 mL). The aq. phase was extracted with EtOAc (5 × 200 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 9:1 → 8:2 → 7:3) gave aldehyde **227** as a colorless solid (35.5 g, 197 mmol, 75%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3 H, 4-CH_3), 3.82 (s, 6 H, 2-OCH_3, 6- OCH_3), 6.34 (s, 2 H, 3-H, 5-H), 10.39 (s, 1 H, CHO).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 22.6 (4-CH_3), 55.7 (2-OCH_3, 6-OCH_3), 104.6 (C-1), 111.9 (C-3, C-5), 147.7 (C-4), 162.2 (C-2, C-6), 189.0 (CHO).

IR: $\tilde{\nu}$ (cm^{-1}) = 3026, 2974, 2787, 1668, 1611, 1241, 1124, 814, 575.

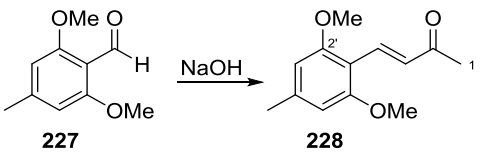
UV (CH_3CN): λ_{max} (nm) (lg ε) = 192 (4.375), 219 (4.274), 274 (4.125), 319 (3.587).

MS (EI, 70 eV): *m*/*z* (%) = 180.2 (100) $[M]^+$, 165.2 (11) $[M–CH_3]^+$.

$C_{10}H_{12}O_3$ (180.20) calc.: 180.0786

found: 180.0779 $[M]^+$ (EI-HRMS).

3.1.3 (4*E*)-(2,6-Dimethoxy-4-methylphenyl)-but-3-en-2-one (228)



227 **228**

To a solution of aldehyde **227** (35.5 g, 197 mmol, 1.00 eq.) in acetone (280 mL) was added dropwise 1 M aq. NaOH solution (125 mL) at 0 °C. The reaction mixture was stirred at RT for 3 h before being quenched by addition of 1 M HCl (140 mL) and H_2O (300 mL) at 0 °C. The aq. phase was extracted with EtOAc (3 × 100 mL), the combined organic phases were dried

over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 7:3) gave ketone **228** as a colorless solid (35.1 g, 159 mmol, 81%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.36 (s, 6 H, 1-H_3, 4'-CH_3), 3.86 (s, 6 H, 2'-OCH_3, 6'-OCH_3), 6.38 (s, 2 H, 3'-H, 5'-H), 7.12 (d, *J* = 16.7 Hz, 1 H, 3-H), 7.96 (d, *J* = 16.7 Hz, 1 H, 4-H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 22.5 (4'-CH_3), 26.9 (C-1), 55.7 (2'-OCH_3, 6'-OCH_3), 104.6 (C-1'), 109.4 (C-3', C-5'), 129.2 (C-3), 135.0 (C-4), 143.6 (C-4'), 159.9 (C-2', C-6'), 200.6 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3052, 3006, 2975, 2945, 2845, 1677, 1567, 1250, 1116, 994, 823, 549.

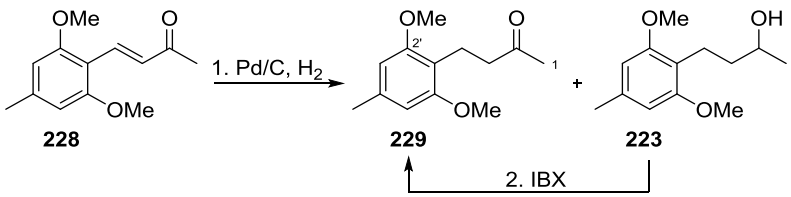
UV (CH_3CN): λ_{max} (nm) (lg ε) = 201 (4.384), 234 (3.940), 315 (4.367).

MS (EI, 70 eV): *m*/*z* (%) = 220.1 (15) $[M]^+$, 205.1 (21) $[M–CH_3]^+$, 189.1 (100) $[M–2CH_3–H]^+$.

$C_{13}H_{16}O_3$ (220.26) calc.: 221.1172

found: 221.1173 $[M+H]^+$ (ESI-HRMS).

3.1.4 4-(2,6-Dimethoxy-4-methylphenyl)-butan-2-one (229)



A solution of α,β-unsaturated ketone **228** (35.1 g, 159 mmol, 1.00 eq.) in EtOAc (900 mL) was treated with palladium on charcoal (5.08 g, 10% Pd, 4.78 mmol, 3 mol%) at RT and hydrogen passed through at RT for 30 min. The reaction mixture was stirred at RT for 3 h. Filtration through a pad of celite® (rinsing with CH_2Cl_2) and evaporation of the solvent *in vacuo* gave a mixture of ketone **229** and alcohol **223** (35.1 g, **229**/**223** = 4:1).

A solution of **229** and **223** (35.1 g, **229**/**223** = 4:1) in CH_3CN (280 mL) was treated with IBX (16.4 g, 58.6 mmol, 0.37 eq.) at RT. The reaction mixture was refluxed for 1.5 h and afterwards cooled to RT. After filtration, evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/MTBE = 9:1) saturated ketone **229** was obtained as a colorless solid (34.1 g, 153 mmol, 96%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.15 (s, 3 H, 1-H_3), 2.34 (s, 3 H, 4'-CH_3), 2.57–2.63 (m, 2 H, 3'-H_2), 2.83–2.93 (m, 2 H, 4'-H_2), 3.78 (s, 6 H, 2'-OCH_3, 6'-OCH_3), 6.36 (s, 2 H, 3'-H, 5'-H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 17.5 (C-4), 21.9 (4'-CH_3), 29.5 (C-1), 43.3 (C-3), 55.4 (2'-OCH_3, 6'-OCH_3), 104.4 (C-3', C-5'), 113.9 (C-1'), 137.1 (C-4'), 157.8 (C-2', C-6'), 209.6 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3064, 2994, 2938, 2838, 1704, 1589, 1466, 1246, 1127, 968, 814, 579.

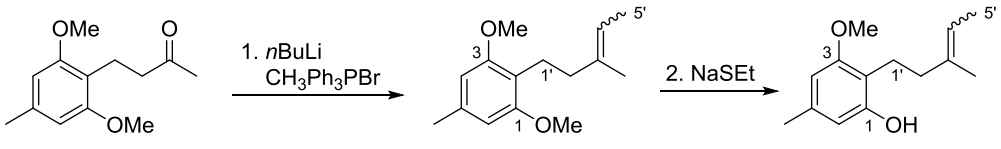
UV (CH_3CN): λ_{max} (nm) (lg ε) = 206.5 (4.650), 271.0 (2.924), 278.5 (2.880).

MS (ESI): *m*/*z* (%) = 245.1 (100) $[M+Na]^+$, 223.1 (27) $[M+H]^+$.

$C_{13}H_{18}O_3$ (222.28) calc.: 245.1148

found: 245.1148 $[M+Na]^+$ (ESI-HRMS).

3.1.5 (*E*)-3-Methoxy-5-methyl-2-(3-methylpent-3-en-1-yl)-phenol (*E*-225) and (*Z*)-3-Methoxy-5-methyl-2-(3-methylpent-3-en-1-yl)-phenol (*Z*-225)



229 *E*-**233** *Z*-**233** *E*-**225** *Z*-**225**

A suspension of ethyltriphenylphosphonium bromide (30.0 g, 80.8 mmol, 2.97 eq.) in THF (260 mL) was treated with *n*BuLi (30.2 mL, 2.5 M in *n*-hexane, 75.6 mmol, 2.80 eq.) at 0 °C and the reaction mixture stirred at 0 °C for 30 min and for further 30 min at RT. A solution of ketone **229** (6.00 g, 27.2 mmol, 1.00 eq.) in THF (160 mL) was added at 0 °C and the reaction mixture stirred at RT for 2.5 h before being quenched by addition of sat. aq. NH_4Cl solution (100 mL) and H_2O (100 mL) at 0 °C. The aq. layer was extracted with MTBE (3 × 100 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 50:1) furnished the alkenes *E*-**233** and *Z*-**233** as a colorless oil (5.67 g, 24.2 mmol, 90%, *E*/*Z* = 1:2.4).

A mixture of alkenes *E*-**233** and *Z*-**233** (5.67 g, 24.2 mmol, *E*/*Z* = 1:2.4, 1.00 eq.) in DMF (40 mL) was treated with NaSEt (4.27 g, 90%, 50.8 mmol, 2.10 eq.) and the resulting reaction mixture heated at 120 °C for 20 h before being quenched by addition of H_2O (200 mL) at RT. The aq. layer was extracted with MTBE (3 × 100 mL), the combined organic layers were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over Na_2SO_4 and the solvent was

removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 30:1) furnished a mixture of alkenes *E*-**225** and *Z*-**225** as a pale-yellow oil, which solidified upon storage at –30 °C (*E*/*Z* = 1:2.4). The two diastereomers were separated by chiral HPLC (*Daicel* Chiralpak IA®: 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH = 99:1, 18 mL/min, λ = 210 nm).

Analytical data of alkenyl phenol *Z*-**225**:

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.51 (dd, *J* = 6.6, 1.5 Hz, 3 H, 4'-CH_3), 1.74 (t, *J* = 1.4 Hz, 3 H, 3'-CH_3), 2.21 (dd, *J* = 8.8, 6.3 Hz, 2 H, 2'-H_2), 2.26 (s, 3 H, 5-CH_3), 2.66 (dd, *J* = 8.6, 7.0 Hz, 2 H, 1'-H_2), 3.78 (s, 3 H, 3-OCH_3), 4.79 (s_{br}, 1 H, OH), 5.22 (q, *J* = 6.8 Hz, 1 H, 4'-H), 6.26, 6.29 (2 × s, 2 H, 4-H, 6-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 13.0 (4'-CH_3), 21.5, 21.6 (C-1', 5-CH_3), 23.7 (3'-CH_3), 31.1 (C-2'), 55.6 (3-OCH_3), 104.3, 109.0 (C-4, C-6), 113.9 (C-2), 119.5 (C-4'), 136.8, 136.9 (C-3', C-5), 154.2, 158.5 (C-1, C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3435, 2959, 2923, 2857, 1617, 1591, 1454, 1416, 1219, 1154, 1099, 1070, 995, 973, 812, 584.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.577), 273 (2.946), 279 (2.938), 300 (2.595).

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 97:3, 0.8 mL/min): t_R = 17.5 min.

Preparative HPLC (*Daicel* Chiralpak IA®, 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH 99:1, 18 mL/min, 210 nm): t_R = 39.6 min.

MS (ESI): *m*/*z* (%) = 243.1 (100) $[M+Na]^+$, 221.2 (66) $[M+H]^+$.

$C_{14}H_{20}O_2$ (220.31) calc.: 243.1356

found: 243.1358 $[M+Na]^+$ (ESI-HRMS).

Analytical data of alkenyl phenol *E*-**225**:

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.56 (dd, *J* = 6.7, 1.0 Hz, 3 H, 4'-CH_3), 1.66 (s, 3 H, 3'-CH_3), 2.12 (t, *J* = 8.3 Hz, 2 H, 2'-H_2), 2.25 (s, 3 H, 5-CH_3), 2.66 (t, *J* = 8.0 Hz, 2 H, 1'-H_2), 3.77 (s, 3 H, 3-OCH_3), 4.71 (s_{br}, 1 H, OH), 5.25 (q, *J* = 6.6 Hz, 1 H, 4'-H), 6.26, 6.28 (2 × s, 2 H, 4-H, 6-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 13.4 (4'-CH_3), 15.9 (3'-CH_3), 21.5 (5-CH_3), 22.2 (C-1'), 38.9 (C-2'), 55.6 (3-OCH_3), 104.3, 109.0 (C-4, C-6), 113.8 (C-2), 118.5 (C-4'), 136.6, 136.8 (C-3', C-5), 154.1, 158.3 (C-1, C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3432, 2921, 2855, 1617, 1591, 1510, 1462, 1416, 1313, 1165, 1100, 1082, 973, 921, 812, 571.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.334), 271 (2.694).

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 97:3, 0.8 mL/min): t_R = 21.2 min.

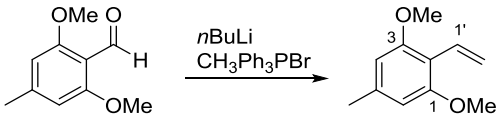
Preparative HPLC (*Daicel* Chiralpak IA®, 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH 99:1, 18 mL/min, 210 nm): t_R = 51.1 min.

MS (ESI): *m*/*z* (%) = 243.1 (100) $[M+Na]^+$, 221.2 (59) $[M+H]^+$.

$C_{14}H_{20}O_2$ (220.31) calc.: 243.1356

found: 243.1356 $[M+Na]^+$ (ESI-HRMS).

3.1.6 1,3-Dimethoxy-5-methyl-2-vinylbenzene (230)



A solution of *n*BuLi (24.2 mL, 2.5 M in *n*-hexane, 60.5 mmol, 2.18 eq.) was added dropwise to methyltriphenylphosponium bromide (20.2 g, 55.5 mmol, 2.00 eq.) in THF (150 mL) at 0 °C in 30 min. The ylide solution was stirred at RT for 4 h before being added dropwise to a solution of aldehyde **227** (5.00 g, 27.8 mmol, 1.00 eq.) in THF (150 mL) at –78 °C in 30 min. The reaction mixture was allowed to warm to RT in 16 h before being quenched by the addition of H_2O (300 mL) at 0 °C. The aq. phase was extracted with EtOAc (3 × 100 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 10:1) gave styrene **230** as a white solid (4.64 g, 26.0 mmol, 94%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (s, 3 H, 5-CH_3), 3.82 (s, 6 H, 1-OCH_3, 3-OCH_3), 5.38 (dd, *J* = 12.1, 2.9 Hz, 1 H, 2'-H_{cis}), 6.01 (dd, *J* = 18.0, 2.9 Hz, 1 H, 2'-H_{trans}), 6.37 (s, 2 H, 4-H, 6-H), 6.93 (dd, *J* = 18.0, 12.1 Hz, 1' H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.1 (5-CH_3), 55.6 (1-OCH_3, 3-OCH_3), 104.8 (C-4, C-6), 112.2 (C-2), 117.3 (C-2'), 127.3 (C-1'), 138.5 (C-5), 158.4 (C-1, C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 2936, 1618, 1605, 1572, 1460, 1404, 1313, 1240, 1196, 1160, 1117, 1045, 1004, 972, 905, 913, 774, 583, 560, 532.

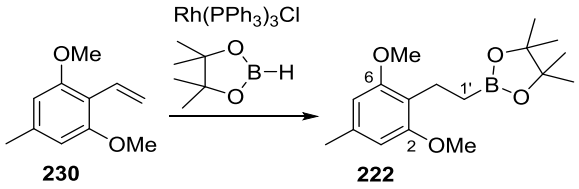
UV (CH_3CN): λ_{max} (nm) (lg ε) = 221 (4.450), 265 (4.194).

MS (ESI): *m*/*z* (%) = 201.1 (36) $[M+Na]^+$, 179.1 (100) $[M+H]^+$.

$C_{11}H_{14}O_2$ (178.23) calc.: 179.1067

found: 179.1068 $[M+H]^+$ (ESI-HRMS).

3.1.7 2-(2,6-Dimethoxy-4-methylphenethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (222)



230 **222**

A solution of styrene **230** (86 mg, 483 μmol, 1.00 eq.) in freshly distilled and degassed THF (1 mL) was treated with pinacolborane (144 μL, 965 μmol, 2.00 eq.) and rhodium tris(triphenylphosphine) chloride (8.0 mg, 8.7 μmol, 2 mol%) at RT. The reaction was heated at 50 °C for 10 h, additional pinacolborane (144 μL, 965 μmol, 2.00 eq.) was added at RT and stirring continued for futher 10 h at 50 °C. The reaction mixture was cooled to RT and adsorbed on silica gel. Column chromatography on silica gel (*n*-pentane/EtOAc = 30:1 → 20:1) gave boronate ester **222** (37.1 mg, 121 μmol, 25%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.97 (m_c, 2 H, 1'-H_2), 1.23 (s, 12 H, 4 × $(CH_3)_{Bpin}$), 2.31 (s, 3 H, 4-CH_3), 2.66 (m_c, 2 H, 2'-H_2), 3.76 (s, 6 H, 2-OCH_3, 6-OCH_3), 6.32 (s, 2 H, 3-H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 17.1 (C-2'), 21.9 (4-CH_3), 24.9 ($(CH_3)_{Bpin}$), 55.6 (2-OCH_3, 6-OCH_3), 82.8 (C_{Bpin}), 104.6 (C-3, C-5), 118.3 (C-1), 136.2 (C-4), 157.9 (C-2, C-6).

IR: $\tilde{\nu}$ (cm^{-1}) = 2976, 1607, 1586, 1463, 1412, 1368, 1314, 1238, 1144, 1112, 1093, 968, 886, 849, 813, 743, 674, 581.

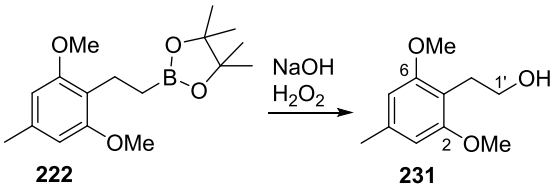
UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.677), 271 (3.091).

MS (ESI): *m*/*z* (%) = 635.4 (100) $[2M+Na]^+$, 329.2 (68) $[M+Na]^+$, 307.2 (83) $[M+H]^+$.

$C_{17}H_{27}BO_4$ (306.20) calc.: 307.2078

found: 307.2070 $[M+H]^+$ (ESI-HRMS).

3.1.8 2-(2,6-Dimethoxy-4-methylphenyl)-ethanol (231)



222 **231**

A solution of boronate ester **222** (221 mg, 722 μmol, 1.00 eq.) in THF (8.8 ml) was treated with 1 M aq. NaOH solution (2.2 mL, 2.16 mmol, 3.00 eq.) and 30% aq. H_2O_2 solution (1.1 mL, 11.0 mmol, 15.3 eq.) at RT. The reaction mixture was stirred at 50 °C for 1 h, cooled to RT and adsorbed on silica gel. Column chromatography on silica gel (*n*-pentane/EtOAc = 5:1 → 4:1) gave alcohol **231** (134 mg, 681 μmol, 68%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.94 (s_{br}, 1 H, 1'-OH), 2.32 (s, 3 H, 4-CH_3), 2.92 (t, *J* = 6.4 Hz, 2 H, 2'-H_2), 3.72 (t, *J* = 6.4 Hz, 2 H, 1'-H_2), 3.74 (s, 6 H, 2-OCH_3, 6-OCH_3), 6.37 (s, 2 H, 3-H, 5-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.0 (4-CH_3), 26.2 (C-2'), 55.6 (2-OCH_3, 6-OCH_3), 63.0 (C-1'), 104.7 (C-3, C-5), 112.2 (C-1), 137.6 (C-4), 158.3 (C-2, C-6).

IR: $\tilde{\nu}$ (cm^{-1}) = 3369, 2929, 1605, 1586, 1462, 1412, 1315, 1244, 1185, 1172, 1124, 1041, 1008, 970, 804, 736, 703, 615, 592, 580, 536, 526.

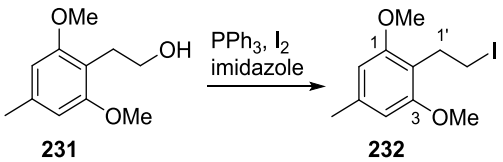
UV (CH_3CN): λ_{max} (nm) (lg ε) = 206 (4.636), 271 (2.984).

MS (ESI): *m*/*z* (%) = 415.2 (28) $[2M+Na]^+$, 219.1 (100) $[M+Na]^+$, 197.1 (75) $[M+H]^+$, 179.1 (98) $[M–OH]^+$.

$C_{11}H_{16}O_3$ (196.24) calc.: 197.1172

found: 197.1174 $[M+H]^+$ (ESI-HRMS).

3.1.9 2-(2-Iodoethyl)-1,3-dimethoxy-5-methylbenzene (232)



231 **232**

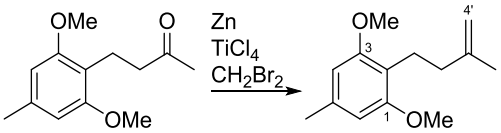
A solution of alcohol **231** (126 mg, 642 μmol, 1.00 eq.) in THF (6.4 mL) was treated with PPh_3 (202 mg, 770 μmol, 1.20 eq.), imidazole (61 mg, 896 μmol, 1.40 eq.) and I_2 (212 mg, 835 μmol, 1.30 eq.) at 0 °C and stirred at RT for 2 h. Additional PPh_3 (202 mg, 770 μmol, 1.20 eq.), imidazole (61 mg, 896 μmol, 1.40 eq.) and I_2 (212 mg, 835 μmol, 1.30 eq.) was

added at 0 °C and stirring continued for 2 h. The reaction was quenched by addition of sat. aq. Na_2SO_3 solution (12 mL). The aq. phase was extracted with MTBE (3 × 6 mL), the combined organic phases were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 40:1 → 5:1) gave iodide **232** (81 mg, 264 μmol, 41%, 60% brsm)

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.33 (s, 3 H, 5-CH_3), 3.21 (s, 4 H, 1'-H_2, 2'-H_2), 3.80 (s, 6 H, 1-OCH_3, 3-OCH_3), 6.35 (s, 2 H, 4-H, 6-H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 4.8 (C-1'), 22.2 (5-CH_3), 28.1 (C-2'), 55.6 (1-OCH_3, 3-OCH_3), 104.5 (C-4, C-6), 114.4 (C-2), 138.0 (C-5), 157.8 (C-1, C-3).
IR: $\tilde{\nu}$ (cm^{-1}) = 2931, 1604, 1585, 1462, 1410, 1320, 1301, 1237, 1168, 1141, 1081, 1042, 969, 735, 618, 583, 563, 525.
UV (CH_3CN): λ_{max} (nm) (lg ε) = 246 nm (3.929).
MS (ESI): *m*/*z* (%) = 329.0 (59) $[M+Na]^+$, 307.0 (100) $[M+H]^+$.
$C_{11}H_{15}IO_2$ (306.14) calc.: 307.0189
found: 307.0184 $[M+H]^+$ (ESI-HRMS).

3.2 Synthesis of alkenyl phenol 195

3.2.1 1,3-Dimethoxy-5-methyl-2-(3-methylbut-3-en-1-yl)-benzene (237)



229 **237**

To a suspension of zinc powder (26.5 g, 405 mmol, 4.50 eq.) and CH_2Br_2 (9.4 mL, 135 mmol, 1.50 eq.) in THF (440 mL) was added dropwise $TiCl_4$ (10.9 mL, 99.1 mmol, 1.10 eq.) at 0 °C and the resulting mixture stirred at 0 °C for 30 min. Ketone **229** (20.0 g, 90.0 mmol, 1.00 eq.) in THF (100 mL) was added at 0 °C and the reaction mixture stirred at RT for 75 min. After filtration through a pad of celite (rinsing with MTBE), the organic phase was washed with 1 M aq. HCl (500 mL) and sat. aq. $NaHCO_3$ solution (500 mL), dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 97:3) gave alkene **237** as a colorless oil (17.2 g, 78.1 mmol, 87%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.79 (s, 3 H, 3'-CH_3), 2.09–2.19 (m, 2 H, 2'-H_2), 2.33 (s, 3 H, 5-CH_3), 2.70–2.79 (m, 2 H, 1'-H_2), 3.79 (s, 6 H, 1-OCH_3, 3-OCH_3), 4.70 (d, *J* = 1.0 Hz, 2 H, 4'-H_2), 6.36 (s, 2 H, 4-H, 6-H).

^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) = 21.2 (C-1'), 21.8 (5-CH_3), 22.4 (3'-CH_3), 37.2 (C-2'), 55.5 (1-OCH_3, 3-OCH_3), 104.6 (C-4, C-6), 109.1 (C-4'), 115.9 (C-2), 136.7 (C-5), 147.0 (C-3'), 158.2 (C-1, C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3072, 2937, 2835, 1588, 1464, 1314, 1241, 1123, 970, 884, 813.

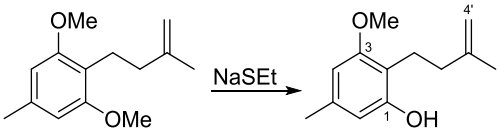
UV (CH_3CN): λ_{max} (nm) (lg ε) = 207.0 (4.682), 271.0 (2.924).

MS (EI, 70 eV): *m*/*z* (%) = 220.3 (13) $[M]^+$, 165.2 (100) $[M–C_4H_7]^+$.

$C_{14}H_{20}O_2$ (220.31) calc.: 220.1463

found: 220.1469 $[M]^+$ (EI-HRMS).

3.2.2 3-Methoxy-5-methyl-2-(3-methylbut-3-en-1-yl)-phenol (195)



237 **295**

A solution of dimethyl ether **237** (5.00 g, 22.7 mmol, 1.00 eq.) in DMF (35 mL) was treated with sodium thioethanolate (4.23 g, 90%, 45.4 mmol, 2.00 eq.) at RT and the resulting reaction mixture stirred at 120 h for 20 h. Additional sodium thioethanolate (531 mg, 5.68 mmol, 0.25 eq.) was added at RT and stirring at 120 °C continued for 1.5 h. The reaction was quenched by addition of H_2O (200 mL) at RT and the aq. phase extracted with MTBE (3 × 100 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 100:0 → 95:5) and Kugelrohr distillation (215 °C, 5 mbar) gave alkenyl phenol **195** as a colorless oil (4.14 g, 20.1 mmol, 88%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.82 (s, 3 H, 3'-CH_3), 2.17–2.27 (m, 2 H, 2'-H_2), 2.29 (s, 3 H, 5-CH_3), 2.73–2.82 (m, 2 H, 1'-H_2), 3.82 (s, 3 H, 3-OCH_3), 4.78 (m_c, 2 H, 4'-H_2), 4.93 (s, 1 H, OH), 6.29, 6.34 (2 × s, 2 H, 4-H, 6-H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 21.5 (5-CH_3), 21.7 (C-1'), 22.7 (3'-CH_3), 37.0 (C-2'), 55.6 (3-OCH_3), 104.3, 109.0 (C-4, C-6), 109.6 (C-4'), 113.6 (C-2), 136.9 (C-5), 146.8 (C-3'), 154.0 (C-1), 158.4 (C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3442, 3072, 2937, 1619, 1593, 1464, 1163, 1097, 886, 816.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 206.5 (4.639), 271.0 (2.898), 206.5 (4.639), 279.0 (2.847).

MS (EI, 70 eV): *m*/*z* (%) = 206.1 (28) $[M]^+$, 151.1 (100) $[M–C_4H_7]^+$.

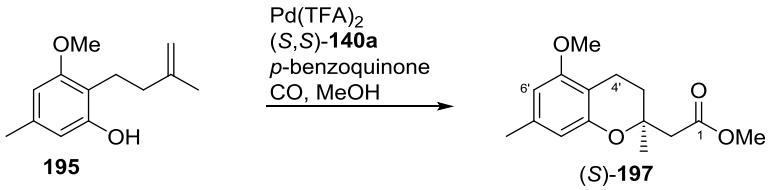
$C_{13}H_{18}O_2$ (206.28) calc.: 206.1307

found: 206.1302 $[M]^+$ (EI-HRMS).

3.3 Synthesis of vinyl chromane (*S*)-101

3.3.1 (2*R*)-2-Methyl-2-(5-methoxy-2,7-dimethylchroman-2-yl)-acetate ((*S*)-197)

Method A:



A solution of palladium(II)-trifluoroacetate (15 mg, 45.1 μmol, 5 mol%) and the Bn-BOXAX ligand (*S*,*S*)-**140a** (105 mg, 184 μmol, 20 mol%) in MeOH (2 mL) was stirred at RT for 15 min. Alkenyl phenol **195** (189 mg, 918 μmol, 1.00 eq.) in MeOH (4 mL) and *p*-benzoquinone (397 mg, 3.67 mmol, 4.00 eq.) were added at RT and CO gas (1 atm) was passed through the resulting reaction mixture for 5 min. After stirring at RT under an CO atmosphere (1 atm) for 19 h, the reaction was quenched by addition of 1 M aq. HCl solution (50 mL) at RT. The aq. phase was extracted with MTBE (3 × 10 mL) and the combined organic phases were washed with 1 M aq. NaOH solution (3 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/E_2O 10:1 → 8:2) gave ester (*S*)-**197** as a colorless oil (186 mg, 703 μmol, 76%).

Optical Rotation: $[\alpha]_D$ = –8.2 (c = 0.50, $CHCl_3$, 24.1 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.42 (s, 3 H, 2'-CH_3), 1.85 (dt, *J* = 13.8, 6.8 Hz, 1 H, 3'-H_a), 1.99 (dt, *J* = 13.8, 6.8 Hz, 1 H, 3'-H_b), 2.26 (s, 3 H, 7'-CH_3), 2.55–2.66 (m, 4 H, 2-H_2, 4'-H_2), 3.68 (s, 3 H, 1-OCH_3), 3.79 (s, 3 H, 5'-OCH_3), 6.24, 6.29 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.4 (C-4'), 21.5 (7'-CH_3), 24.6 (2'-CH_3), 30.3 (C-3'), 43.5 (C-2), 51.5 (1-OCH_3), 55.3 (5'-OCH_3), 74.2 (C-2'), 102.9, 110.4 (C-6', C-8'), 106.8 (C-4a'), 137.1 (C-7'), 153.5 (C-5'), 157.5 (C-8a'), 170.9 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 2949, 2856, 1738, 1619, 1586, 1354, 1227, 1108, 1023, 814.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207.5 (4.658), 271.5 (2.975), 280.0 (2.955).

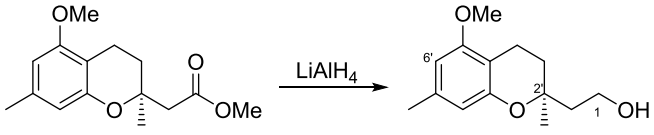
Analytical HPLC (*Daicel* Chiracel OD®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 98:2, 0.8 mL/min, 234 nm): t_R = 18.2 min (–)-(*S*)-**197**, 96.6%; 26.6 min (+)-(*R*)-**197**, 3.4%, 93% *ee*).

MS (EI, 70 eV): *m*/*z* (%) = 264.3 (58) $[M]^+$, 191.2 (49) $[M–CH_2CO_2Me]^+$, 151.2 (100).

$C_{15}H_{20}O_4$ (264.32) calc.: 265.1434

found: 265.1435 $[M+H]^+$ (ESI-HRMS).

3.3.2 (2*S*)-2-(5-Methoxy-2,7-dimethylchroman-2-yl)-ethan-1-ol ((*S*)-238)



(*S*)-**197** (*S*)-**238**

To a suspension of $LiAlH_4$ (1.36 g, 35.8 mmol, 2.45 eq.) in Et_2O (70 mL) was added chromanyl ester (*S*)-**197** (3.86 g, 14.6 mmol, 1.00 eq.) in Et_2O (10 mL) by a transfer cannula at –78 °C. The reaction mixture was stirred at RT for 3.5 h before being quenched by careful addition of H_2O (120 mL) at –78 °C. The suspension was slowly warmed to 0 °C. The aq. layer was extracted with MTBE (8 × 100 mL), the combined organic were layers dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 7:3) furnished chromanyl alcohol (*S*)-**238** as a colorless oil (3.79 g, 14.3 mmol, 98%). The enantiomeric alcohols (*S*)-**238** and (*R*)-**238** can be separated by chiral HPLC (*Daicel* Chiralpak IA®, 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH = 99:1, 18 mL/min, λ = 210 nm).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 3 H, 2'-CH_3), 1.68–2.05 (m, 4 H, 2-H_2, 3'-H_2), 2.27 (s, 3 H, 7'-CH_3), 2.44 (t, *J* = 4.9 Hz, 1 H, OH), 2.50–2.63 (m, 1 H, 4'-H_a), 2.69 (dt, *J* = 17.3, 6.0 Hz, 1 H, 4'-H_b), 3.77–3.99 (m, 2 H, 1-H_2), 3.80 (s, 3 H, 5'-OCH_3), 6.25, 6.28 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.3 (C-4'), 21.53 (7'-CH_3), 23.4 (2'-CH_3), 31.2 (C-3'), 41.8 (C-2), 55.3 (5'-OCH_3), 59.0 (C-1), 76.3 (C-2'), 102.9, 110.3 (C-6', C-8'), 106.9 (C-4a'), 137.1 (C-7'), 153.5, 157.6 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 3375, 2939, 2855, 1618, 1586, 1463, 1353, 1231, 1109, 1023, 880, 814.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207.5 (4.635), 272.0 (2.954), 280.0 (2.942).

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 97:3, 0.8 mL/min): t_R = 21.2 min).

Preparative HPLC (*Daicel* Chiralpak IA®, 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH 99:1, 18 mL/min, 210 nm): t_R = 24.1 min (*S*)-**238**; 47.0 min (*R*)-**238**).

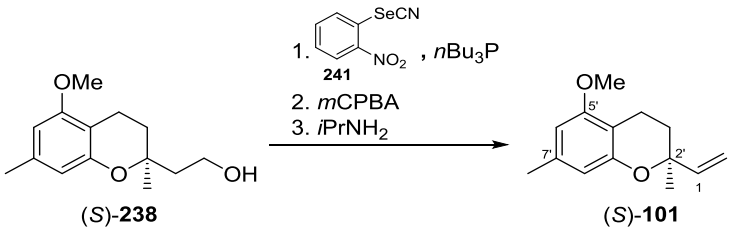
MS (ESI): *m*/*z* (%) = 495.2 (27) $[2M+Na]^+$, 259.1 (100) $[M+Na]^+$, 237.2 (8) $[M+H]^+$.

$C_{14}H_{20}O_3$ (236.31) calc.: 259.1305

found: 259.1305 [M+Na]+ (ESI-HRMS).

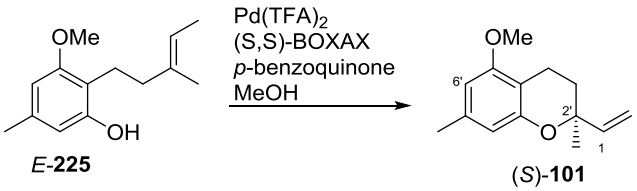
3.3.3 (2*S*)-5-Methoxy-2,7-dimethyl-2-vinylchromane ((*S*)-101)

Method A:



A solution of chromanyl alcohol (*S*)-**238** (1.00 g, 4.23 mmol, 1.00 eq.) in THF (70 mL) was treated with 2-nitrophenyl selenocyanate (**241**) (1.92 g, 8.46 mmol, 2.00 eq.) and nBu$_3$P (2.09 mL, 8.46 mmol, 2.00 eq.) in THF (10 mL) at 0 °C and stirred at 0 °C for 75 min. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (150 mL) at 0 °C and the aq. layer extracted with MTBE (4 × 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. A suspension of the crude product in CH_2Cl_2 (100 mL) was treated with $Na_2HPO_4 \cdot 2\,H_2O$ (3.76 g, 21.2 mmol, 5.00 eq.) and *m*CPBA (2.61 g, 70%, 10.6 mmol, 2.50 eq.) at –40 °C and stirred at at this temperature for 1 h. Additional *m*CPBA (521 mg, 70%, 2.12 mmol, 0.50 eq.) was added at –40 °C and stirring continued at this temperature for 1 h. Diisopropylamine (2.97 mL, 21.2 mmol, 5.00 eq.) was added at –40 °C and the reaction mixture allowed to warm to RT in 12 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (100 mL), the aq. layer extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 100:0 → 98:2) furnished vinyl chromane (*S*)-**101** as a yellow oil (902 mg, 4.13 mmol, 98%).

Method B:



E-**225** (*S*)-**101**

A solution of $Pd(TFA)_2$ (7.8 mg, 23.6 µmol, 10 mol%) and Bn-BOXAX (*S*,*S*)-**140a** (27.0 mg, 47.2 µmol, 20 mol%) in MeOH (0.5 mL) was stirred at RT for 15 min. After addition of a solution of phenol (*E*)-**225** (52.0 mg, 236 µmol, 1.00 eq.) in MeOH (1 mL) and *p*-benzoquinone (102 mg, 944 µmol, 4.00 eq.) stirring was continued for 22 h. The mixture was poured into 1 M aq. HCl (20 mL) and extracted with MTBE (4 × 10 mL). The combined extracts were washed with 1 M aq.NaOH (3 × 10 mL) and dried over Na_2SO_4. After evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 100:1 → 70:1) vinyl chromane (*S*)-**101** was obtained as a yellow oil (38.4 mg, 176 µmol, 75%, 93% *ee*).

Optical Rotation: $[\alpha]_D = -55.7$ (c = 0.50, $CHCl_3$, 23.0 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 (s, 3 H, 2'-CH_3), 1.76 (ddd, *J* = 13.5, 9.8, 5.9 Hz, 1 H, 3'-H_a), 1.90 (ddd, *J* = 13.5, 6.1, 5.0 Hz, 1 H, 3'-H_b), 2.28 (s, 3 H, 7'-CH_3), 2.44 (ddd, *J* = 16.7, 9.8, 6.0 Hz, 1 H, 4'-H_a), 2.65 (dt, *J* = 17.0, 5.4 Hz, 1 H, 4'-H_b), 3.78 (s, 3 H, 5'-OCH_3), 5.05 (dd, *J* = 10.8, 1.3 Hz, 1 H, 2-H_{cis}), 5.17 (dd, *J* = 17.3, 1.3 Hz, 1 H, 2-H_{trans}), 5.85 (dd, *J* = 17.3, 10.8 Hz, 1 H, 1-H), 6.22, 6.36 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.7 (C-4'), 21.6 (7'-CH_3), 26.8 (2'-CH_3), 31.3 (C-3'), 55.3 (5'-OCH_3), 76.2 (C-2'), 102.7, 110.1 (C-6', C-8'), 107.3 (C-4a'), 113.6 (C-2), 136.9 (C-7'), 141.4 (C-1), 154.4, 157.5 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 3082, 2952, 2927, 1615, 1583, 1459, 1409, 1350, 1261, 1229, 1209, 1126, 1091, 1023, 1013, 923, 814, 583.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.629), 273 (2.937), 280 (2.916), 333 (2.247).

Analytical HPLC (*Daicel* Chiracel OD®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 99.5:0.5, 0.8 mL/min): t_R = 10.1 min (–)-(*S*)-**101**, 96.3%; 11.9 min (+)-(*R*)-**101**, 3.7%, 93% *ee*).

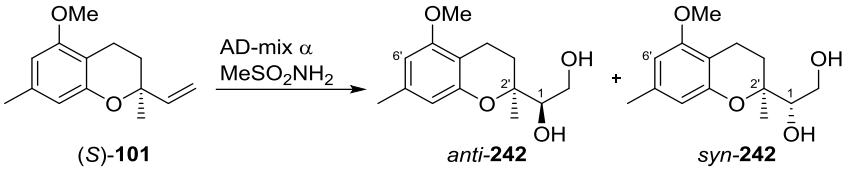
MS (ESI): *m*/*z* (%) = 241.1 (33) $[M+Na]^+$, 219.1 (100) $[M+H]^+$.

$C_{14}H_{18}O_2$ (218.29) calc.: 219.1380

found: 219.1378 $[M+H]^+$ (ESI-HRMS).

3.4 Syntheses of the tetrahydroxanthenones *anti*-255 and *syn*-255

3.4.1 (1*R*,2'*S*)-1-(5-Methoxy-2,7-dimethylchroman-2-yl)-ethan-1,2-diol (*anti*-242) and (1*S*,2'*S*)-1-(5-methoxy-2,7-dimethylchroman-2-yl)-ethan-1,2-diol (*syn*-242)



(*S*)-**101** *anti*-**242** *syn*-**242**

A solution of vinyl chromane (*S*)-**101** (2.93 g, 13.4 mmol, 1.00 eq.) in *t*BuOH/H_2O (60 mL/60 mL) was treated with AD-mix α (28.2 g) and $MeSO_2NH_2$ (1.29 g, 13.4 mmol, 1.00 eq.) at RT. After being stirred for 5 d the reaction was quenched by addition of sat. aq. $NaHSO_3$ solution (100 mL) at 0 °C and stirring continued at 0 °C for 30 min. The aq. layer was extracted with EtOAc (4 × 100 mL), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. After column chromatography on silica gel (petroleum ether/EtOAc = 6:4) and preparative HPLC (*Daicel* Chiralcel IB®: 10 × 250 mm, 5 µm, *n*-hexane/*i*PrOH = 97:3, 5 mL/min, λ = 210 nm) the diols *anti*-**242** (2.48 g, 9.81 mmol) and *syn*-**242** (654 mg, 2.59 mmol) were obtained as colorless oils (3.13 g, 12.4 mmol, 93%, d.r. = 3.8:1).

Analytical data of diol *anti*-**242**:

Optical Rotation: $[\alpha]_D$ = +16.7 (c = 0.50, $CHCl_3$, 26.2 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.22 (s, 3 H, 2'-CH_3), 1.68 (ddd, *J* = 13.5, 6.4, 3.9 Hz, 1 H, 3'-H_a), 1.96 (ddd, *J* = 13.5, 10.6, 6.3 Hz, 1 H, 3'-H_b), 2.25 (s, 3 H, 7'-CH_3), 2.49 (ddd, *J* = 17.3, 10.5, 6.5 Hz, 1 H, 4'-H_a), 2.72 (ddd, *J* = 17.4, 6.2, 4.0 Hz, 1 H, 4'-H_b), 2.86 (s_{br}, 1 H, OH), 3.66–3.86 (m, 3 H, 1-H, 2-H_2), 3.78 (s, 3 H, 5'-OCH_3), 6.23, 6.27 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = 15.8 (C-4'), 19.4 (2'-CH_3), 21.6 (7'-CH_3), 26.2 (C-3'), 55.4 (5'-OCH_3), 62.4 (C-2), 76.4 (C-1), 77.3 (C-2'), 103.0, 110.2 (C-6', C-8'), 107.2 (C-4a'), 137.2 (C-7'), 153.3, 157.5 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 3373, 2935, 1617, 1582, 1455, 1413, 1351, 1293, 1224, 1148, 1101, 1082, 1025, 992, 879, 810, 776.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.632), 272 (3.095), 280 (3.076).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH = 97:3, 0.8 mL/min): t_R = 25.6 min.

Preparative HPLC (*Daicel* Chiralpak IB®, 20 × 250 mm, 7 μm, *n*-hexane/2-PrOH = 97:3, 5 mL/min, 210 nm): t_R = 26.1 min.

MS (ESI): *m*/*z* (%) = 527.3 (100) $[2M+Na]^+$, 275.1 (15) $[M+Na]^+$, 253.2 (2) $[M+H]^+$.

$C_{14}H_{20}O_4$ (252.31) calc.: 275.1254

found: 275.1256 $[M+Na]^+$ (ESI-HRMS).

Analytical data of diol *syn*-**242**:

Optical Rotation: $[\alpha]_D$ = +20.6 (c = 0.50, $CHCl_3$, 26.7 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.21 (s, 3 H, 2'-CH_3), 1.74 (ddd, *J* = 13.7, 6.5, 4.1 Hz, 1 H, 3'-H_a), 1.82–2.01 (m, 1 H, 3'-H_b), 2.25 (s, 3 H, 7'-CH_3), 2.50 (ddd, *J* = 17.3, 10.3, 6.6 Hz, 1 H, 4'-H_a), 2.71 (dt, *J* = 17.2, 5.9 Hz, 1 H, 4'-H_b), 2.79 (s_{br}, 1 H, OH), 3.69–3.77 (m, 3 H, 1-H, 2-H_2), 3.78 (s, 3 H, 5'-OCH_3), 6.23, 6.28 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = 15.8 (C-4'), 18.6 (2'-CH_3), 21.6 (7'-CH_3), 27.5 (C-3'), 55.3 (5'-OCH_3), 62.5 (C-2), 76.4 (C-1), 77.5 (C-2'), 103.1, 110.2 (C-6', C-8'), 107.0 (C-4a'), 137.2 (C-7'), 153.0, 157.5 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 3383, 2933, 1617, 1584, 1455, 1414, 1351, 1227, 1159, 1139, 1104, 1079, 1024, 875, 812, 581.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.610), 272 (2.961), 280 (2.942).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH = 97:3, 0.8 mL/min): t_R = 36.0 min.

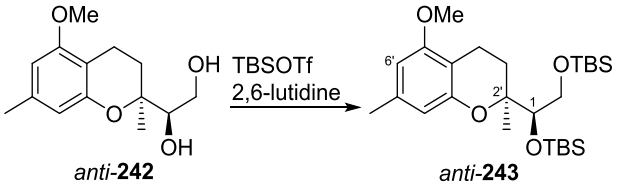
Preparative HPLC (*Daicel* Chiralpak IB®, 20 × 250 mm, 7 μm, *n*-hexane/2-PrOH = 97:3, 5 mL/min, 210 nm): t_R = 36.3 min.

MS (ESI): *m*/*z* (%) = 527.3 (100) $[2M+Na]^+$, 275.1 (9) $[M+Na]^+$.

$C_{14}H_{20}O_4$ (252.31) calc.: 275.1254

found: 275.1254 $[M+Na]^+$ (ESI-HRMS).

3.4.2 (1*R*,2'*S*)-1,2-Bis-(*tert*-butyldimethylsilyloxy)-2-(5-methoxy-2,7-dimethylchroman-2-yl)-ethane (*anti*-243)



anti-**242** *anti*-**243**

A solution of diol *anti*-**242** (1.34 g, 5.31 mmol, 1.00 eq.) in CH_2Cl_2 (50 mL) was treated with 2,6-lutidine (2.47 mL, 21.2 mmol, 4.00 eq.) and TBSOTf (4.27 mL, 18.6 mmol, 3.50 eq.) at 0 °C. After stirring at RT for 2.5 h, the reaction was quenched by careful addition of sat. aq. $NaHCO_3$ solution (50 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic extracts dried over $MgSO_4$ and the solvent removed *in vacuo*. After column chromatography on silica gel (petroleum ether/MTBE = 40:1) alcohol *anti*-**243** was obtained as a colorless oil (2.52 g, 5.24 mmol, 99%).

Optical Rotation: $[\alpha]_D$ = +17.9 (c = 0.51, $CHCl_3$, 24.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.00, 0.02, 0.04, 0.11 (4 × s, 12 H, 1-Si$(CH_3)_2$, 2-Si$(CH_3)_2$), 0.87 (s, 18 H, 1-SiC$(CH_3)_3$, 2-SiC$(CH_3)_3$), 1.15 (s, 3 H, 2'-CH_3), 1.70 (dt, *J* = 13.6, 6.2 Hz, 1 H, 3'-H_a), 1.95 (ddd, *J* = 13.6, 8.5, 6.3 Hz, 1 H, 3'-H_b), 2.24 (s, 3 H, 7'-CH_3), 2.47–2.52 (m, 1 H, 4'-H_a), 2.58 (dt, *J* = 17.3, 6.2 Hz, 1 H, 4'-H_b), 3.58 (dd, *J* = 10.6, 6.7 Hz, 1 H, 1-H_a), 3.67 (dd, *J* = 6.7, 2.2 Hz, 1 H, 2-H), 3.78 (s, 3 H, 5'-OCH_3), 3.98 (dd, *J* = 10.6, 2.2 Hz, 1 H, 1-H_b), 6.19, 6.22 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = –5.4, –5.3, –4.9, –3.9 (1-Si$(CH_3)_2$, 2-Si$(CH_3)_2$), 15.8 (C-4'), 18.3, 18.5 (1-SiC, 2-SiC), 19.6 (2'-CH_3), 21.6 (7'-CH_3), 26.0, 26.1 (1-SiC($\underline{C}H_3)_3$, 2-SiC($\underline{C}H_3)_3$), 27.6 (C-3'), 55.3 (5'-OCH_3), 65.2 (C-1), 77.4 (C-2'), 78.0 (C-2), 102.5, 110.3 (C-6', C-8'), 107.2 (C-4a'), 136.7 (C-7'), 153.9, 157.4 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2928, 2855, 1619, 1586, 1462, 1352, 1276, 1256, 1110, 1091, 1067, 1005, 965, 829, 811, 770, 747, 664.

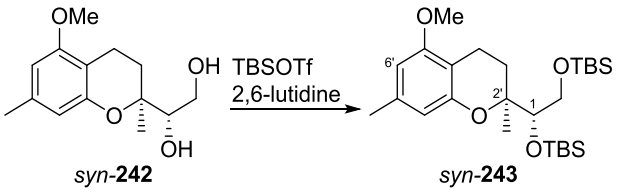
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.645), 272 (3.242), 280 (3.225).

MS (ESI): *m*/*z* (%) = 503.3 (100) $[M+Na]^+$, 481.3 (38) $[M+H]^+$.

$C_{26}H_{48}O_4Si_2$ (480.83) calc.: 503.2983

found: 503.2983 $[M+Na]^+$ (ESI-HRMS).

3.4.3 (1*S*,2'*S*)-1,2-(Bis-*tert*-butyldimethylsilyloxy)-2-(5-methoxy-2,7-dimethylchroman-2-yl)-ethane (*syn*-243)



syn-**242** *syn*-**243**

A solution of diol *syn*-**242** (638 mg, 2.53 mmol, 1.00 eq.) in CH_2Cl_2 (25 mL) was treated with 2,6-lutidine (1.18 mL, 10.1 mmol, 4.00 eq.) and TBSOTf (2.03 mL, 8.85 mmol, 3.50 eq.) at 0 °C. After stirring at RT for 2.5 h, the reaction mixture was quenched by careful addition of sat. aq. $NaHCO_3$ solution (30 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 20 mL), the combined organic extracts were dried over $MgSO_4$ and the solvent removed *in vacuo*. After column chromatography on silica gel (petroleum ether/MTBE = 40:1), *syn*-**243** was obtained as a colorless oil (1.22 g, 2.53 mmol, quant.).

Optical Rotation: $[\alpha]_D$ = +0.4 (c = 0.50, $CHCl_3$, 24.6 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.04, 0.05, 0.09, 0.10 (4 × s, 12 H, 1-Si$(CH_3)_2$, 2-Si$(CH_3)_2$), 0.89, 0.91 (2 × s, 18 H, 1-SiC$(CH_3)_3$, 2-SiC$(CH_3)_3$) 1.21 (s, 3 H, 2'-CH_3), 1.62 (ddd, *J* = 13.4, 11.1, 6.0 Hz, 1 H, 3'-H_a), 1.84 (ddd, *J* = 13.6, 6.1, 3.5 Hz, 1 H, 3'-H_b), 2.26 (s, 3 H, 7'-CH_3), 2.44 (ddd, *J* = 17.3, 11.2, 6.2 Hz, 1 H, 4'-H_a), 2.67 (ddd, *J* = 17.0, 5.6, 3.7 Hz, 1 H, 4'-H_b), 3.54 (dd, *J* = 10.6, 6.0 Hz, 1 H, 1-H_a), 3.71 (dd, *J* = 5.9, 3.3 Hz, 1 H, 2-H), 3.78 (s, 3 H, 5'-OCH_3), 3.82 (dd, *J* = 10.5, 3.3 Hz, 1 H, 1-H_b), 6.20, 6.26 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (150 MHz, $CDCl_3$): δ (ppm) = –5.3, –5.3, –4.7, –4.1 (1-Si$(CH_3)_2$, 2-Si$(CH_3)_2$), 16.1 (C-4'), 18.4, 18.5 (SiC), 19.6 (2'-CH_3), 21.7 (7'-CH_3), 26.1 (1-SiC($\underline{C}H_3)_3$, 2-SiC($\underline{C}H_3)_3$), 26.6 (C-3'), 55.4 (5'-OCH_3), 65.3 (C-1), 78.0 (C-2'), 79.5 (C-2), 102.4, 110.3 (C-6', C-8'), 107.3 (C-4a'), 136.9 (C-7'), 153.8, 157.5 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2928, 2855, 1618, 1586, 1462, 1352, 1252, 1137, 1109, 1059, 1003, 830, 811, 774, 663.

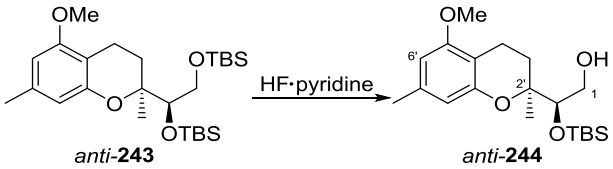
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.621), 273 (2.907), 280 (2.887).

MS (ESI): *m/z* (%) = 503.3 (100) $[M+Na]^+$, 481.3 (16) $[M+H]^+$.

$C_{26}H_{48}O_4Si_2$ (480.8279) calc.: 503.2983

found: 503.2982 $[M+Na]^+$ (ESI-HRMS).

3.4.4 (2*R*,2'*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(5-methoxy-2,7-dimethylchroman-2-yl)ethanol (*anti*-244)



A solution of *anti*-**243** (1.61 g, 3.35 mmol, 1.00 eq.) in THF (140 mL) and pyridine (17 mL) was treated with HF·pyridine (3.36 mL, 70% HF, 134 mmol, 40.0 eq.) at 0 °C and the resulting mixture stirred at RT. After 24 and 48 h additional HF·pyridine (1.68 mL, 70% HF, 67.0 mmol, 20.0 eq.) in THF/pyridine (70 mL/17 mL) was added at 0 °C. The reaction was quenched carefully with sat. aq. $NaHCO_3$ solution (250 mL) at 0 °C after 60 h. The aq. layer was extracted with EtOAc (3 × 100 mL), the combined organic extracts were washed with brine (100 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 100:0 → 50:50) yielded alcohol *anti*-**244** as a colorless oil (858 mg, 2.31 mmol, 70%, 93% brsm).

Optical Rotation: $[\alpha]_D$ = +6.8 (c = 0.50, $CHCl_3$, 25.0 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.07 (s, 3 H, $Si(CH_3)_a$), 0.14 (s, 3 H, $Si(CH_3)_b$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.19 (s, 3 H, 2'-CH_3), 1.77 (ddd, *J* = 13.6, 6.4, 4.6 Hz, 1 H, 3'-H_a), 1.90 (ddd, *J* = 13.6, 10.1, 6.2 Hz, 1 H, 3'-H_b), 2.22 (dd, *J* = 7.7, 4.6 Hz, 1 H, 1-OH), 2.25 (s, 3 H, 7'-CH_3), 2.49 (ddd, *J* = 16.9, 10.0, 6.5 Hz, 1 H, 4'-H_a), 2.65 (ddd, *J* = 17.2, 6.2, 4.6 Hz, 1 H, 4'-H_b), 3.65 (ddd, *J* = 10.8, 7.6, 5.0 Hz, 1 H, 1-H_a), 3.78 (s, 3 H, 5'-OCH_3), 3.79 (m, 1 H, 2-H), 3.83 (dt, *J* = 10.9, 4.6 Hz, 1 H, 1-H_b), 6.22, 6.23 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.5, –4.4 ($Si(CH_3)_a$, $Si(CH_3)_b$), 15.8 (C-4'), 18.2 (SiC), 19.0 (2'-CH_3), 21.6 (7'-CH_3), 25.9 ($SiC(\underline{C}H_3)_3$), 27.4 (C-3'), 55.3 (5'-OCH_3), 63.5 (C-1), 76.4 (C-2), 78.4 (C-2'), 102.9, 110.2 (C-6', C-8'), 107.2 (C-4a'), 137.1 (C-7'), 153.4, 157.6 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 3482, 2952, 2928, 2885, 2855, 1618, 1586, 1462, 1414, 1353, 1250, 1224, 1142, 1107, 1029, 1006, 951, 831, 812, 776.

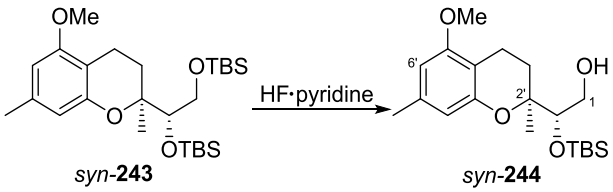
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.636), 273 (2.948), 280 (2.931).

MS (ESI): *m*/*z* (%) = 755.5 (100) $[2M+Na]^+$, 389.2 (50) $[M+Na]^+$, 367.3 (23) $[M+H]^+$.

$C_{20}H_{34}O_4Si$ (366.57) calc.: 367.2299

found: 367.2291 $[M+H]^+$ (ESI-HRMS)

3.4.5 (2*S*,2'*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(-5-methoxy-2,7-dimethylchroman-2-yl)-ethanol (*syn*-244)



syn-**243** *syn*-**244**

A solution of *syn*-**243** (1.36 g, 2.83 mmol, 1.00 eq.) in THF/pyridine (120 mL/14 mL) was treated with HF·pyridine (2.83 mL, 70% HF, 113 mmol, 40.0 eq.) at 0 °C and the resulting mixture stirred at RT. After 24 and 48 h additional HF·pyridine (1.68 mL, 70% HF, 56.0 mmol, 20.0 eq.) in THF/pyridine (70 mL/17 mL) was added at 0 °C. The reaction was quenched carefully with sat. aq. $NaHCO_3$ solution (250 mL) at 0 °C after 52 h. The aq. layer was extracted with EtOAc (3 × 100 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 100:0 → 50:50) yielded alcohol *syn*-**244** as a colorless oil (753 mg, 2.05 mmol, 73%, 98% brsm).

Optical Rotation: $[\alpha]_D$ = +6.2 (c = 0.50, $CHCl_3$, 19.4 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.11 (s, 3 H, $Si(CH_3)_a$), 0.18 (s, 3 H, $Si(CH_3)_b$), 0.94 (s, 9 H, $SiC(CH_3)_3$), 1.23 (s, 3 H, 2'-CH_3), 1.71–1.77 (m, 2 H, 3'-H_2), 2.17 (t, *J* = 6.1 Hz, 1 H, 1-OH), 2.26 (s, 3 H, 7'-CH_3), 2.47 (dt, *J* = 17.4, 8.5 Hz, 1 H, 4'-H_a), 2.69 (dt, *J* = 17.1, 4.9 Hz, 1 H, 4'-H_b), 3.59 (dt, *J* = 11.4, 6.0 Hz, 1 H, 1-H_a), 3.73 (dt, *J* = 10.3, 5.2 Hz, 1 H, 1-H_b), 3.79 (s, 3 H, 5'-OCH_3), 3.80 (m_c, 1 H, 2-H), 6.22, 6.27 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.5 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 16.0 (C-4'), 18.4 (SiC), 19.5 (2'-CH_3), 21.7 (7'-CH_3), 26.1 ($SiC(\underline{C}H_3)_3$), 26.7 (C-3'), 55.4 (5'-OCH_3), 63.2 (C-1), 77.7 (C-2), 78.3 (C-2'), 102.7, 110.2 (C-6', C-8'), 107.1 (C-4a'), 137.0 (C-7'), 153.2, 157.5 (C-5', C-8a').

IR: $\tilde{\nu}$ (cm^{-1}) = 3472, 2952, 2929, 2855, 1618, 1586, 1462, 1352, 1250, 1225, 1138, 1106, 1031, 955, 833, 812, 776.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.685), 272 (3.037), 280 (3.023).

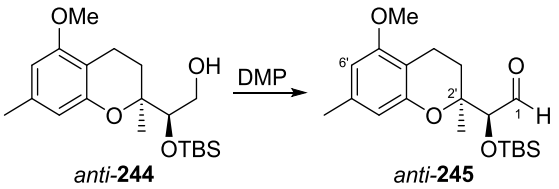
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 98:2, 0.8 mL/min): t_R = 7.0 min.

MS (ESI): *m*/*z* (%) = 755.4 (100) $[2M+Na]^+$, 389.2 (30) $[M+Na]^+$, 367.2 (14) $[M+H]^+$.

$C_{20}H_{34}O_4Si$ (366.57) calc.: 367.2299

found: 367.2297 $[M+H]^+$ (ESI-HRMS).

3.4.6 (2*S*,2'*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(5-methoxy-2,7-dimethylchroman-2-yl)-acetaldehyde (*anti*-245)



anti-**244** *anti*-**245**

A solution of alcohol *anti*-**244** (1.15 g, 3.14 mmol, 1.00 eq.) in CH_2Cl_2 (30 mL) was treated with DMP (2.33 g, 5.49 mmol, 1.75 eq.) at 0 °C and the reaction mixture stirred at RT for 2 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (20 mL) and H_2O (50 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the organic solvents and column chromatography on silica gel (petroleum ether/EtOAc = 20:1) aldehyde *anti*-**245** was obtained as a colorless oil (1.08 g, 2.97 mmol, 95%).

Optical Rotation: $[\alpha]_D$ = +57.7 (c = 0.51, $CHCl_3$, 26.3 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.02 (s, 3 H, $Si(CH_3)_a$), 0.09 (s, 3 H, $Si(CH_3)_b$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.26 (s, 3 H, 2'-CH_3), 1.72 (dt, *J* = 13.5, 6.6 Hz, 1 H, 3'-H_a), 2.04 (dt, *J* = 13.8, 7.0 Hz, 1 H, 3'-H_b), 2.26 (s, 3 H, 7'-CH_3), 2.59 (t, *J* = 6.8 Hz, 2 H, 4'-H_2), 3.79 (s, 3 H, 5'-OCH_3), 4.11 (d, *J* = 1.0 Hz, 1 H, 2-H), 6.24, 6.29 (2 × s, 2 H, 6'-H, 8'-H), 9.84 (d, *J* = 1.1 Hz, 1 H, CHO).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.1 ($Si(CH_3)_a$), –4.4 ($Si(CH_3)_b$), 15.8 (C-4'), 18.3 (SiC), 20.4 (2'-CH_3), 21.6 (7'-CH_3), 25.8 ($SiC(\underline{C}H_3)_3$), 28.2 (C-3'), 55.4 (5'-OCH_3), 77.9 (C-2'), 80.2 (C-2), 103.1, 110.2 (C-6', C-8'), 106.9 (C-4a'), 137.4 (C-7'), 153.3, 157.6 (C-5', C-8a'), 202.4 (CHO).

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2929, 2855, 1736, 1619, 1586, 1482, 1415, 1377, 1352, 1252, 1223, 1148, 1107, 885, 835, 813, 777.

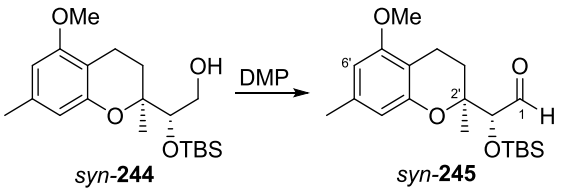
UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.218), 272 (2.529), 280 (2.504).

MS (ESI): *m*/*z* (%) = 387.2 (11) $[M+Na]^+$, 365.2 (6) $[M+H]^+$.

$C_{20}H_{32}O_4Si$ (364.55) calc.: 387.1962

found: 387.1965 $[M+Na]^+$ (ESI-HRMS).

3.4.7 (2*R*,2'*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-(5-methoxy-2,7-dimethylchroman-2-yl)-acetaldehyde (*syn*-245)



syn-**244** *syn*-**245**

A solution of alcohol *syn*-**244** (855 mg, 2.33 mmol, 1.00 eq.) in CH_2Cl_2 (20 mL) was treated with DMP (2.47 g, 5.83 mmol, 2.50 eq.) at 0 °C and the reaction mixture stirred at RT for 2.5 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (80 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 30 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the organic solvents and column chromatography on silica gel (petroleum ether/EtOAc = 65:1) aldehyde *syn*-**245** was obtained as a colorless oil (755 mg, 2.07 mmol, 89%).

Optical Rotation: $[\alpha]_D$ = –23.6 (c = 0.55, $CHCl_3$, 23.3 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 3 H, $Si(CH_3)_a$), 0.06 (s, 3 H, $Si(CH_3)_b$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 1.76 (ddd, *J* = 13.7, 10.1, 6.1 Hz, 1 H, 3'-H_a), 1.84 (ddd, *J* = 13.7, 6.4, 4.4 Hz, 1 H, 3'-H_b), 2.26 (s, 3 H, 7'-CH_3), 2.48 (ddd, *J* = 16.9, 10.1, 6.5 Hz, 1 H, 4'-H_a), 2.71 (ddd, *J* = 17.3, 6.2, 4.5 Hz, 1 H, 4'-H_b), 3.78 (s, 3 H, 5'-OCH_3), 4.04 (s, 1 H, 2-H), 6.23, 6.29 (2 × s, 2 H, 6'-H, 8'-H), 9.72 (s, 1 H, CHO).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.9 ($Si(CH_3)_a$), –4.6 ($Si(CH_3)_b$), 16.0 (C-4'), 18.4 (SiC), 20.7 (2'-CH_3), 21.7 (7'-CH_3), 25.8 ($SiC(\underline{C}H_3)_3$), 26.9 (C-3'), 55.4 (5'-OCH_3), 77.8 (C-2'), 81.9 (C-2), 103.0, 110.3 (C-6', C-8'), 107.1 (C-4a'), 137.1 (C-7'), 153.1, 157.4 (C-5', C-8a'), 202.4 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 2951, 2929, 2856, 1735, 1619, 1586, 1463, 1352, 1253, 1142, 1108, 1006, 837, 814, 780.

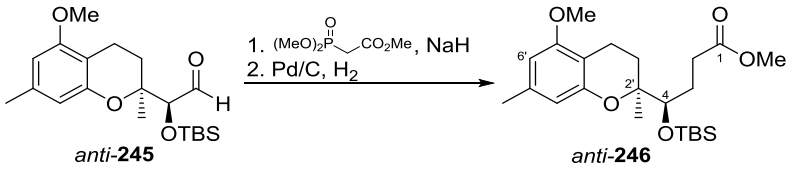
UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (3.948), 272 (2.377), 279 (2.353).

MS (ESI): *m*/*z* (%) = 751.4 (5) $[2M+Na]^+$, 387.2 (20) $[M+Na]^+$, 365.2 (25) $[M+H]^+$.

$C_{20}H_{32}O_4Si$ (364.55) calc.: 365.2143

found: 365.2134, $[M+H]^+$ (ESI-HRMS).

3.4.8 Methyl-(2'*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-4-(5-methoxy-2,7-dimethylchroman-2-yl)-butanoate (*anti*-246)



anti-**245** *anti*-**246**

A solution of trimethyl phosphonoacetate (0.71 mL, 4.32 mmol, 1.50 eq.) in THF (22 mL) was treated with sodium hydride (150 mg, 60% (w/w) in mineral oil, 3.75 mmol, 1.30 eq.) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before a solution of aldehyde *anti*-**245** (1.05 g, 2.88 mmol, 1.00 eq.) in THF (8.5 mL) was added dropwise at 0 °C. After complete addition the mixture was stirred at RT for further 1.5 h before being quenched with sat. aq. NH_4Cl solution (50 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Palladium on charcoal (307 mg, 10% Pd, 288 μmol, 10 mol%) was added to a solution of the unsaturated crude product (1.48 g, *E*/*Z* = 5:1) in EtOAc (25 mL) in a Parr-flask. Hydrogen was passed through the resulting mixture for 30 min before being shaken under a H_2 atmosphere (4 bar) in a Parr apparatus at RT for further 15 h. The catalyst was removed by filtration through a pad of silica gel (eluting with CH_2Cl_2). After evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 30:1 → 5:1), the saturated ester *anti*-**246** was obtained as a colorless oil (1.15 g, 2.72 mmol, 95%).

Optical Rotation: $[\alpha]_D$ = +15.9 (c = 0.50, $CHCl_3$, 27.0 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.02 (s, 3 H, $Si(CH_3)_a$), 0.11 (s, 3 H, $Si(CH_3)_b$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.13 (s, 3 H, 2'-CH_3), 1.69 (m_c, 2 H, 3-H_2), 1.85–2.04 (m, 2 H, 3'-H_2), 2.25 (s, 3 H, 7'-CH_3), 2.35–2.61 (m, 3 H, 2-H_2, 4'-H_a), 2.68 (ddd, *J* = 17.3, 6.2, 3.8 Hz, 1 H, 4'-H_b), 3.65 (s, 3 H, 1-OCH_3), 3.71 (dd, *J* = 8.7, 3.6 Hz, 1 H, 4-H), 3.78 (s, 3 H, 5'-OCH_3), 6.21, 6.22 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.4 ($Si(CH_3)_a$), –3.63 ($Si(CH_3)_b$), 16.0 (C-4'), 18.5 (SiC), 19.6 (2'-CH_3), 21.7 (7'-CH_3), 25.4 (C-3), 26.2 ($SiC(\underline{C}H_3)_3$), 27.8 (C-3'), 31.4 (C-2), 51.5 (1-OCH_3), 55.3 (5'-OCH_3), 76.7 (C-4), 78.7 (C-2'), 102.5, 110.5 (C-6', C-8'), 107.1 (C-4a'), 136.7 (C-7'), 153.8, 157.4 (C-5', C-8a'), 174.0 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 2930, 2855, 1738, 1618, 1585, 1462, 1352, 1225, 1167, 1140, 1105, 1087, 999, 985, 833, 811, 775, 734.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.226), 272 (2.633), 280 (2.615).

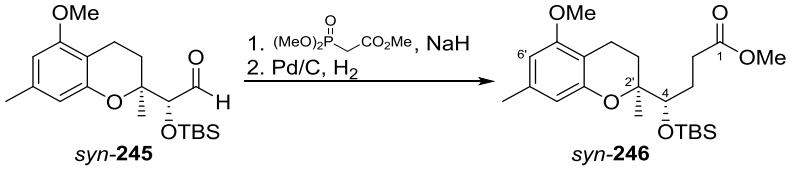
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 99:1, 0.8 mL/min): t_R = 5.7 min.

MS (ESI): *m*/*z* (%) = 867.5 (46) $[2M+Na]^+$, 445.3 (100) $[M+Na]^+$, 423.3 (6) $[M+H]^+$.

$C_{23}H_{38}O_5Si$ (422.63) calc.: 445.2381

found.: 445.2378 $[M+Na]^+$ (ESI-HRMS).

3.4.9 Methyl-(2'*S*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-4-(5-methoxy-2,7-dimethylchroman-2-yl)-butanoate (*syn*-246)



syn-**245** *syn*-**246**

A solution of trimethyl phosphonoacetate (0.57 mL, 3.52 mmol, 1.70 eq.) in THF (15 mL) was treated with sodium hydride (108 mg, 60% (w/w) in mineral oil, 2.70 mmol, 1.30 eq.) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before a solution of aldehyde *syn*-**245** (755 mg, 2.07 mmol, 1.00 eq.) in THF (8.0 mL) was added dropwise at 0 °C. After complete addition the mixture was stirred at RT for further 1.5 h before being quenched with sat. aq. NH_4Cl solution (30 mL) at 0 °C. The aq. layers were extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Palladium on charcoal (220 mg, 10% Pd, 207 µmol, 10 mol%) was added to a solution of the unsaturated crude product in EtOAc (20 mL) in a Parr-flask. Hydrogen was passed through the resulting mixture for 30 min before being shaken under a H_2 atmosphere (4 bar) in a Parr apparatus at RT for further 15 h. The catalyst was removed by filtration through a pad of silica gel (eluting with CH_2Cl_2). After evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc = 30:1 → 20:1) the saturated ester *syn*-**246** was obtained as a colorless oil (851 mg, 2.02 mmol, 98%).

Optical Rotation: $[\alpha]_D$ = +0.4 (c = 0.50, $CHCl_3$, 24.1 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.06 (s, 3 H, $Si(CH_3)_a$), 0.17 (s, 3 H, $Si(CH_3)_b$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 1.17 (s, 3 H, 2'-CH_3), 1.65 (m_c, 2 H, 3-H_a, 3'-H_a), 1.77 (ddd, *J* = 13.4, 6.3, 3.9 Hz, 1 H, 3'-H_b), 1.87–1.96 (m, 1 H, 3-H_b), 2.25 (s, 3 H, 7'-CH_3), 2.36 (ddd, *J* = 16.1, 9.7, 6.4 Hz, 1 H, 2-H_a), 2.47 (ddd, *J* = 17.2, 10.8, 6.4 Hz, 1 H, 4'-H_a), 2.56 (ddd, *J* = 16.2, 9.7, 5.5 Hz, 1 H, 2-H_b), 2.67 (ddd, *J* = 17.2, 5.7, 3.8 Hz, 1 H, 4'-H_b), 3.65 (s, 3 H, 1-OCH_3), 3.68 (dd, *J* = 9.3, 3.3 Hz, 1 H, 4-H), 3.78 (s, 3 H, 5'-OCH_3), 6.20, 6.27 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.5 ($Si(CH_3)_a$), –3.6 ($Si(CH_3)_b$), 16.1 (C-4'), 17.8 (2'-CH_3), 18.6 (SiC), 21.8 (7'-CH_3), 26.3 ($SiC(\underline{C}H_3)_3$), 27.6 (C-3), 27.9 (C-3'), 31.2 (C-2), 51.5 (1-OCH_3), 55.4 (5'-OCH_3), 77.1 (C-4), 79.0 (C-2'), 102.4, 110.2 (C-6', C-8'), 107.1 (C-4a'), 136.9 (C-7'), 153.6, 157.4 (C-5', C-8a'), 174.0 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 2951, 2929, 2855, 1739, 1617, 1585, 1462, 1352, 1248, 1160, 1141, 1102, 1002, 984, 833, 810, 775, 579.

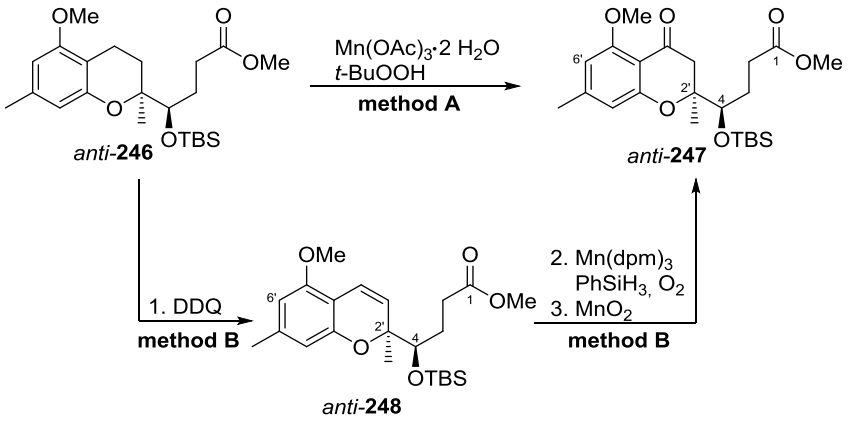
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.238), 273 (2.540), 280 (2.524).

MS (ESI): *m*/*z* (%) = 445.3 (100) $[M+Na]^+$, 423.3 (14) $[M+H]^+$.

$C_{23}H_{38}O_5Si$ (422.63) calc.: 423.2561

found: 423.2551 $[M+H]^+$ (ESI-HRMS).

3.4.10 Methyl-(2'*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-4-(5-methoxy-2,7-dimethyl-4-oxochroman-2-yl)-butanoate (*anti*-247) and Methyl-(2'*S*,4*R*)-4-(*tert*-butyldimethylsilyloxy)-4-(5-methoxy-2,7-dimethyl-2*H*-chromen-2-yl)-butanoate (*anti*-248)



Method A: A solution of chromane *anti*-**246** (1.32 g, 3.12 mmol, 1.00 eq.) and *tert*-butyl hydroperoxide (2.95 mL, 5.5 M in decane, 16.2 mmol, 5.20 eq.) in EtOAc (20 mL) was treated with powdered molecular sieve 3 Å (1.2 g) and the resulting mixture was stirred at RT for 30 min. Thereafter $Mn(OAc)_3 \cdot 2\ H_2O$ (86 mg, 312 μmol, 10 mol%) was added and the mixture stirred at RT for 4 d. Additional $Mn(OAc)_3 \cdot 2\ H_2O$ (86 mg, 312 μmol, 10 mol%) and *tert*-butyl hydroperoxide (0.57 mL, 3.12 mol, 1.00 eq.) were added after 24, 48 and 72 h. The mixture was then filtered through a pad of silica gel (eluting with EtOAc). Evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc 30:1 → 1:1) furnished chromanone *anti*-**247** as a yellow oil (701 mg, 1.60 mmol, 51%).

Method B: A mixture of *anti*-**246** (107 mg, 253 μmol, 1.00 eq.) and DDQ (115 mg, 507 μmol, 2.00 eq.) in benzene (10 mL) was heated at 80 °C for 2 h. After cooling to RT and filtration through a pad of silica gel (eluting with EtOAc) the solvent was removed *in vacuo*. Column chromatography of the residue on silica gel (petroleum ether/EtOAc = 30:1 → 10:1) furnished the corresponding chromene *anti*-**248** as a colorless oil (101 mg, 240 μmol, 95%).

A solution of the chromene *anti*-**248** (103 mg, 245 μmol, 1.00 eq.) in CH_2Cl_2 (6.1 mL) was treated with $Mn(dpm)_3$ (15 mg, 24.8 μmol, 10 mol%) and $PhSiH_3$ (125 μL, 980 μmol, 4.00 eq.). Oxygen was passed through the resulting mixture for 5 min before being stirred under an O_2 atmosphere (1 atm) at RT for further 4.5 h. After addition of silica gel, evaporation of the solvent *in vacuo* and column chromatography on silica gel (*n*-hexane/EtOAc = 9:1 → 1:1) the chromanone **251** and the diastereomeric alcohols were obtained.

A mixture of MnO_2 (48 mg, 490 μmol, 2.00 eq.) and the alcohols in CH_2Cl_2 (12 mL) was refluxed for 4 d (not at night). Additional MnO_2 (48 mg, 490 μmol, 2.00 eq.) was added every 3 h (4 additions per day, total amount of MnO_2: 1.92 g, 19.6 mmol, 80.0 eq.). After filtration through a pad of silica gel (eluting with EtOAc), evaporation of the solvent *in vacuo* and column chromatography on silica gel (*n*-hexane/EtOAc = 9:1 → 1:1) the chromanone *anti*-**247** was obtained as a colorless oil (combined yield: 94.7 mg, 217 μmol, 88%).

Analytical data of chromene *anti*-**248**:

Optical Rotation: $[\alpha]_D$ = –49.8 (c = 0.51, $CHCl_3$, 26.3 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = –0.04 (s, 3 H, $Si(CH_3)_a$), 0.03 (s, 3 H, $Si(CH_3)_b$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 1.27 (s, 3 H, 2'-CH_3), 1.77 (dddd, *J* = 13.9, 9.8, 8.3, 5.6 Hz, 1 H, 3-H_a), 2.01 (dddd, *J* = 14.0, 10.1, 6.3, 4.0 Hz, 1 H, 3-H_b), 2.25 (s, 3 H, 7'-CH_3), 2.39 (ddd, *J* = 16.2, 9.8, 6.3 Hz, 1 H, 2-H_a), 2.53 (ddd, *J* = 15.8, 9.9, 5.6 Hz, 1 H, 2-H_b), 3.64 (s, 1 H, 1-OCH_3), 3.77 (s, 3 H, 5'-OCH_3), 3.80 (dd, *J* = 8.3, 4.0 Hz, 1 H, 4-H), 5.55 (d, *J* = 10.1 Hz, 1 H, 3'-H), 6.19, 6.22 (2 × s, 1 H, 6'-H, 8'-H), 6.63 (d, *J* = 10.1 Hz, 1 H, 4'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.2 ($Si(CH_3)_a$), –3.9 ($Si(CH_3)_b$), 18.4 (SiC), 21.4 (2'-CH_3), 22.1 (7'-CH_3), 26.1 ($SiC(\underline{C}H_3)_3$), 27.7 (C-3), 31.0 (C-2), 51.5 (1-OCH_3), 55.6 (5'-OCH_3), 75.8 (C-4), 80.6 (C-2'), 104.0, 109.8 (C-6', C-8'), 108.0 (C-4a'), 117.3 (C-4'), 125.0 (C-3'), 139.2 (C-7'), 152.8, 155.0 (C-5', C-8a'), 174.0 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 2951, 2928, 2855, 1738, 1614, 1572, 1462, 1436, 1417, 1389, 1362, 1328, 1251, 1223, 1168, 1107, 1005, 991, 834, 814, 773, 713, 667.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 230 (4.343), 281 (3.979).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 90:10, 0.8 mL/min): t_R = 7.7 min.

MS (ESI): *m*/*z* (%) = 863.4 (70) $[2M+Na]^+$, 443.2 (100) $[M+Na]^+$.

$C_{23}H_{36}O_5Si$ (420.61) calc.: 443.2224

found: 443.2228 $[M+Na]^+$ (ESI-HRMS).

Analytical data of chromanone *anti*-**247**:

Optical Rotation: $[\alpha]_D$ = –19.4 (c = 0.49, $CHCl_3$, 25.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 3 H, $Si(CH_3)_a$), 0.10 (s, 3 H, $Si(CH_3)_b$), 0.84 (s, 9 H, $SiC(CH_3)_3$), 1.27 (s, 3 H, 2'-CH_3), 1.50–1.63 (m, 1 H, 3-H_a), 1.82–1.93 (m, 1 H, 3-H_b), 2.28 (s, 3 H, 7'-CH_3), 2.31 (d, *J* = 16.1 Hz, 1 H, 3'-H_a), 2.29–2.57 (m, 2 H, 2-H_2), 3.11 (d, *J* = 16.0 Hz, 1 H, 3'-H_b), 3.66 (s, 3 H, 1-OCH_3), 3.82 (dd, *J* = 9.3, 3.0 Hz, 1 H, 4-H), 3.86 (s, 3 H, 5'-OCH_3), 6.25, 6.27 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.5 ($Si(CH_3)_a$), –3.6 ($Si(CH_3)_b$), 18.4 (SiC), 19.9 (2'-CH_3), 22.5 (7'-CH_3), 26.1 ($SiC(\underline{C}H_3)_3$), 27.4 (C-3), 30.8 (C-2), 43.1 (C-3'), 51.6 (1-OCH_3), 56.0 (5'-OCH_3), 76.5 (C-4), 83.7 (C-2'), 104.4, 110.8 (C-6', C-8'), 108.3 (C-4a'), 147.3 (C-7'), 160.0, 160.7 (C-5', C-8a'), 173.6 (C-1), 190.9 (C-4').

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2930, 2855, 1737, 1682, 1613, 1568, 1463, 1416, 1351, 1250, 1221, 1169, 1142, 1104, 1081, 996, 833, 776.

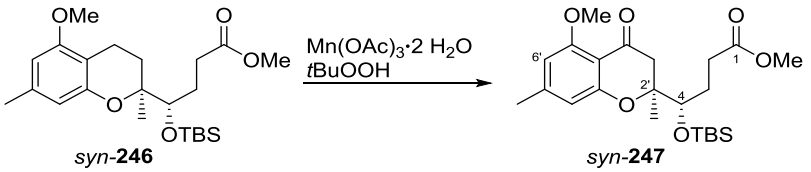
UV (CH_3CN): λ_{max} (nm) (lg ε) = 194 (4.343), 221 (4.254), 269 (3.991), 325 (3.539).

MS (ESI): *m*/*z* (%) = 895.4 (100) $[2M+Na]^+$, 459.2 (17) $[M+Na]^+$.

$C_{23}H_{36}O_6Si$ (436.61) calc.: 459.2173

found: 459.2168 $[M+Na]^+$ (ESI-HRMS).

3.4.11 Methyl-(2'*S*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-4-(5-methoxy-2,7-dimethyl-4-oxochroman-2-yl)-butanoate (*syn*-247)



syn-**246** *syn*-**247**

A solution of chromane *syn*-**246** (100 mg, 237 µmol, 1.00 eq.) and *tert*-butyl hydroperoxide (0.22 mL, 5.5 M in decane, 1.23 mmol, 5.20 eq.) in EtOAc (1.5 mL) was treated with powdered molecular sieve 3 Å (83 mg) and the resulting mixture was stirred at RT for 30 min.

$Mn(OAc)_3 \cdot 2\ H_2O$ (6.5 mg, 24 µmol, 10 mol%) was added and the resulting reaction mixture was stirred at RT for 4 d; additional $Mn(OAc)_3 \cdot 2\ H_2O$ (6.5 mg, 24 µmol, 10 mol%) and *tert*-butyl hydroperoxide (0.22 mL, 1.23 mmol, 5.20 eq.) were added after 24, 48 and 72 h. The mixture was filtered through a pad of silica gel (eluting with EtOAc). Evaporation of the solvent *in vacuo* and column chromatography on silica gel (petroleum ether/EtOAc 30:1 → 1:1) furnished chromanone *syn*-**247** as a yellow oil (43 mg, 98.5 µmol, 42%).

Optical Rotation: $[\alpha]_D = -42.6$ (c = 0.50, $CHCl_3$, 22.6 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.08 (s, 3 H, $Si(CH_3)_a$), 0.15 (s, 3 H, $Si(CH_3)_b$), 0.90 (s, 9 H, $SiC(CH_3)_3$), 1.28 (s, 3 H, 2'-CH_3), 1.64 (dtd, *J* = 14.3, 9.0, 5.5 Hz, 1 H, 3-H_a), 1.88 (m_c, 1 H, 3-H_b), 2.28 (s, 3 H, 7'-CH_3), 2.39 (ddd, *J* = 16.2, 9.1, 6.7 Hz, 1 H, 2-H_a), 2.46 (d, *J* = 15.6 Hz, 1 H, 3'-H_a), 2.54 (ddd, *J* = 16.4, 9.2, 5.5 Hz, 1 H, 2-H_b), 2.74 (d, *J* = 15.7 Hz, 1 H, 3'-H_b), 3.65 (s, 3 H, 1-OCH_3), 3.82 (dd, *J* = 8.8, 3.3 Hz, 1 H, 4-H), 3.86 (s, 3 H, 5'-OCH_3), 6.26, 6.32 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.3 ($Si(CH_3)_a$), –3.7 ($Si(CH_3)_b$), 17.6 (2'-CH_3), 18.5 (SiC), 22.5 (7'-CH_3), 26.1 ($SiC(\underline{C}H_3)_3$), 27.6 (C-3), 30.7 (C-2), 46.0 (C-3'), 51.6 (1-OCH_3), 56.1 (5'-OCH_3), 76.6 (C-4), 83.4 (C-2'), 104.3, 110.5 (C-6', C-8'), 108.4 (C-4a'), 147.4 (C-7'), 160.0 (C-5'), 160.7 (C-8a'), 173.6 (C-1), 190.1 (C-4').

IR: $\tilde{\nu}$ (cm^{-1}) = 2930, 2851, 1739, 1676, 1610, 1569, 1461, 1441, 1418, 1383, 1356, 1303, 1264, 1254, 1215, 1194, 1158, 1118, 1090, 985, 964, 834, 780.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 195 (4.407), 222 (4.300), 270 (4.047), 326 (3.632).

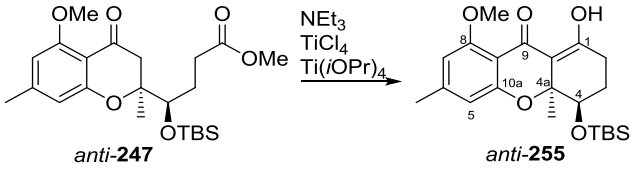
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 19.5 min.

MS (ESI): *m*/*z* (%) = 895.5 (100) $[2M+Na]^+$, 459.3 (24) $[M+Na]^+$, 437.2 (21) $[M+H]^+$.

$C_{23}H_{36}O_6Si$ (436.61) calc.: 437.2354

found: 437.2349 $[M+H]^+$ (ESI-HRMS).

3.4.12 (4*R*,4a*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydroxanthen-9-one (*anti*-255)



anti-**247** *anti*-**255**

$TiCl_4$ (2.86 mL, 1.0 M in CH_2Cl_2, 2.86 mmol, 2.60 eq.) was added slowly to $Ti(OiPr)_4$ (286 µL, 950 µmol, 0.87 eq.) in CH_2Cl_2 (5 mL) at 0 °C and the resulting mixture stirred for 15 min at 0 °C. NEt_3 (426 µL, 3.08 mmol, 2.80 eq.) was added to a solution of chromanone *anti*-**247** (480 mg, 1.10 mmol, 1.00 eq.) in CH_2Cl_2 (22 mL) at 0 °C. Subsequently, the solution of $Ti(OiPr)Cl_3$ was transferred slowly through a transfer cannula and the resulting reaction was stirred at 0 °C for 1 h (TLC monitoring) before being quenched with H_2O (100 mL). The aq. layer was extracted with EtOAc (6 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc = 9:1 → 5:1) yielded tetrahydroxanthenone *anti*-**255** as a pale-yellow solid (373 mg, 920 µmol, 84%).

Optical Rotation: $[\alpha]_D = -78.8$ (c = 0.50, $CHCl_3$, 25.1 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.00 (s, 3 H, $Si(CH_3)_a$), 0.13 (s, 3 H, $Si(CH_3)_b$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.37 (s, 3 H, 4a-CH_3), 1.87–1.96 (m, 2 H, 3-H_2), 2.24 (ddd, *J* = 18.7, 5.8, 1.9 Hz, 1 H, 2-H_a), 2.30 (s, 3 H, 6-CH_3), 2.74 (ddd, *J* = 18.9, 11.0, 8.0 Hz, 1 H, 2-H_b), 3.91 (s, 3 H, 8-OCH_3), 4.03 (dd, *J* = 3.8, 1.9 Hz, 1 H, 4-H), 6.28, 6.30 (2 × s, 2 H, 5-H, 7-H), 16.22 (s, 1 H, 1-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.0 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 18.3 (SiC), 22.4 (6-CH_3), 25.7 (4a-CH_3), 25.8, 25.8 (C-3, $SiC(\underline{C}H_3)_3$), 26.4 (C-2), 56.1 (8-OCH_3), 71.3 (C-4), 80.1 (C-4a), 105.1, 111.0 (C-5, C-7), 105.6 (C-9a), 107.0 (C-8a), 146.8 (C-6), 159.8, 160.4 (C-8, C-10a), 180.6 182.2 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2926, 2851, 1604, 1460, 1406, 1356, 1245, 1225, 1199, 1110, 1085, 995, 877, 834, 818, 772, 723, 683, 638.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 198 (4.280), 281 (3.484), 332 (4.061).

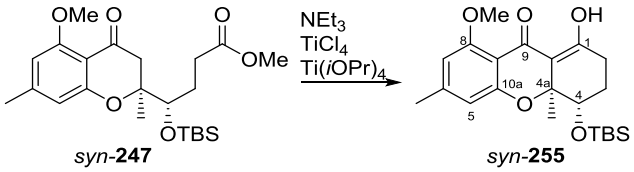
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 98:2, 0.8 mL/min): t_R = 11.6 min.

MS (ESI): *m*/*z* (%) = 1235.6 (46) $[3M+Na]^+$, 831.4 (100) $[2M+Na]^+$, 427.2 (36) $[M+Na]^+$, 405.2 (14) $[M+H]^+$.

$C_{22}H_{32}O_5Si$ (404.57) calc.: 427.1911

found: 427.1911 $[M+Na]^+$ (ESI-HRMS).

3.4.13 (4*S*,4a*S*)-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydroxanthen-9-one (*syn*-255)



syn-**247** *syn*-**255**

$TiCl_4$ (1.27 mL, 1.0 M in CH_2Cl_2, 1.27 mmol, 2.60 eq.) was added slowly to Ti(O*i*Pr)$_4$ (127 µL, 420 µmol, 0.86 eq.) in CH_2Cl_2 (2 mL) at 0 °C and the resulting mixture stirred for 15 min at 0 °C. NEt_3 (190 µL, 1.37 mmol, 2.80 eq.) was added to a solution of chromanone *syn*-**247** (213 mg, 490 µmol, 1.00 eq.) in CH_2Cl_2 (7.5 mL) at 0 °C. Subsequently, the solution of Ti(O*i*Pr)Cl_3 was transfered slowly through a transfer cannula into the solution of *syn*-**247**. The resulting reaction mixture was stirred at 0 °C for further 2.5 h (TLC monitoring) before being quenched with sat. aq. $NaHCO_3$ solution (25 mL) and H_2O (100 mL). The aq. layer was extracted with EtOAc (6 × 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 10:1 → 5:1) yielded tetrahydroxanthenone *syn*-**255** as a pale-yellow solid (137 mg, 340 µmol, 69%).

Optical Rotation: $[\alpha]_D = -37.6$ (c = 0.42, $CHCl_3$, 22.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.12 (s, 3 H, $Si(CH_3)_a$), 0.19 (s, 3 H, $Si(CH_3)_b$), 0.93 (s, 9 H, $SiC(CH_3)_3$), 1.36 (s, 3 H, 4a-CH_3), 1.73–1.85 (m, 2 H, 3-H_2), 2.30 (s, 3 H, 6-CH_3), 2.43 (ddd, *J* = 19.2, 6.6, 1.5 Hz, 1 H, 2-H_a), 2.55 (ddd, *J* = 19.3, 12.0, 7.3 Hz, 1 H, 2-H_b), 3.90 (s, 3 H, 8-OCH_3), 4.10 (dd, *J* = 12.1, 4.6 Hz, 1 H, 4-H), 6.29, 6.31 (2 × s, 2 H, 5-H, 7-H), 16.0 (s, 1 H, 1-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.7 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 18.3 (SiC), 19.2 (4a-CH_3), 22.5 (6-CH_3), 25.9 ($SiC(\underline{C}H_3)_3$), 27.1 (C-3), 29.3 (C-2), 56.1 (8-OCH_3), 73.2 (C-4), 80.9 (C-4a), 105.3, 111.0 (C-5, C7), 107.5 (C-9a), 107.9 (C-8a), 147.2 (C-6), 160.3, 160.5 (C-8, C-10a), 178.1, 182.7 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 2948, 2855, 1605, 1460, 1416, 1378, 1363, 1248, 1225, 1113, 911, 892, 877, 836, 824, 775, 691, 673.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 199 (4.528), 283 (3.799), 325 (4.297).

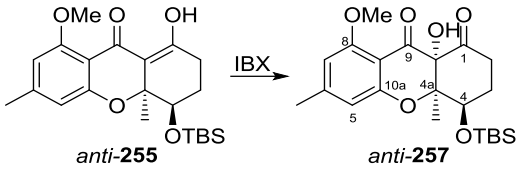
MS (ESI): *m*/*z* (%) = 1235.7 (13) $[3M+Na]^+$, 831.5 (88) $[2M+Na]^+$, 427.2 (100) $[M+Na]^+$.

$C_{22}H_{32}O_5Si$ (404.57) calc.: 427.1911

found: 427.1902 $[M+Na]^+$ (ESI-HRMS).

3.5 Functionalization of tetrahydroxanthenone *anti*-255

3.5.1 (4*R*,4a*R*,9a*S*)-4-(*tert*-Butyldimethylsilyloxy)-9a-hydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydro-1*H*-xanthene-1,9(9a*H*)-dione (*anti*-257)



anti-**255** *anti*-**257**

To a solution of tetrahydroxanthenone *anti*-**255** (325 mg, 803 μmol, 1.00 eq.) in DMSO (3.8 mL) and H_2O (1.2 mL) was added IBX (563 mg, 2.01 mmol, 2.50 eq.) and the resulting suspension heated at 55 °C for 9 h. Additional IBX (112 mg, 402 μmol, 0.50 eq.) was added at RT and stirring at 55 °C continued for further 3 h. The reaction mixture was cooled to RT, diluted with CH_2Cl_2 (20 mL) and stirred vigorously at RT for 30 min. The precipitate was removed by filtration, washed with CH_2Cl_2 (4 × 50 mL) and the combined organic phases were treated with sat. aq. $NaHCO_3$ solution (50 mL). The aq. layer was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic phases were washed with brine (100 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 4:1) furnished *anti*-**257** as a white solid (109 mg, 259 μmol, 32%).

Optical Rotation: $[\alpha]_D$ = +5.9 (c = 0.50, $CHCl_3$, 23.2 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = –0.07 (s, 3 H, $Si(CH_3)_a$), 0.07 (s, 3 H, $Si(CH_3)_b$), 0.80 (s, 9 H, $SiC(CH_3)_3$), 1.26 (s, 3 H, 4a-CH_3), 1.91–1.96 (m, 1 H, 3-H_a), 2.12–2.20 (m, 1 H, 3-H_b), 2.28 (s, 3 H, 6-CH_3), 2.67 (m_c, 1 H, 2-H_a), 2.74 (m_c, 1 H, 2-H_b), 3.86 (s, 3 H, 8-OCH_3), 4.18 (dd, *J* = 7.8, 3.6 Hz, 1 H, 4-H), 4.65 (s, 1 H, 9a-OH), 6.27, 6.35 (2 × s, 1 H, 5-H, 7-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.0 ($Si(CH_3)_a$), –4.6 ($Si(CH_3)_b$), 17.0 (4a-CH_3), 18.1 (SiC), 22.5 (6-CH_3), 25.7 ($SiC(\underline{C}H_3)_3$), 28.8 (C-3), 34.2 (C-2), 56.0 (8-OCH_3), 73.1 (C-4), 79.7 (C-4a), 86.6 (C-9a), 104.5, 110.6 (C-5, C-7), 107.1 (C-8a), 148.0 (C-6), 160.2, 161.0 (C-8, C-10a), 187.7 (C-9), 206.7 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 3432, 2928, 2852, 1718, 1683, 1618, 1575, 1466, 1414, 1387, 1360, 1248, 1224, 1128, 1088, 992, 892, 859, 834, 816, 783, 710, 595.

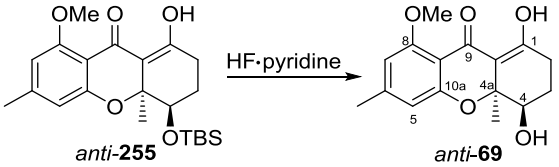
UV (CH_3CN): λ_{max} (nm) (lg ε) = 195 (4.333), 221 (4.194), 276 (3.998), 330 (3.494).

MS (ESI): *m*/*z* (%) = 863.5 (100) $[2M+Na]^+$, 443.2 (74) $[M+Na]^+$, 421.3 (12) $[M+H]^+$.

$C_{22}H_{32}O_6Si$ (420.57) calc.: 443.1860

found: 443.1859 $[M+Na]^+$ (ESI-HRMS).

3.5.2 (4*R*,4a*S*)-1,4-Dihydroxy-8-methoxy-4a,6-dimethyl-2,3,4,4a-tetrahydroxanthen-9-one (*anti*-69)



anti-**255** *anti*-**69**

HF·pyridine (78 µL, 70% HF, 3.09 mmol, 25.0 eq.) was added to a solution of *anti*-**255** (50 mg, 124 µmol, 1.00 eq.) in THF (3 mL) at 0 °C and the reaction mixture was stirred at 30 °C for 5 d; additionl HF·pyridine (78 µL, 70% HF, 3.09 mmol, 25.0 eq.) was added after 72 h at 0 °C. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (20 mL) and H_2O (20 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 9:1 → 1:1) furnished tetrahydroxanthenone **x** as a white solid (26 mg, 89.6 µmol, 72%, 94% brsm).

Optical Rotation: $[\alpha]_D$ = –42.8 (c = 0.41, $CHCl_3$, 23.9 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.41 (s, 3 H, 4a-CH_3), 1.90 (td, *J* = 13.3, 7.1 Hz, 1 H, 3-H_a), 2.14 (dddd, *J* = 14.6, 7.4, 4.2, 1.1 Hz, 1 H, 3-H_b), 2.28 (ddd, *J* = 19.1, 7.0, 1.1 Hz, 1 H, 2-H_a), 2.31 (s, 3 H, 6-CH_3), 2.71 (s, 1 H, 4-OH), 2.77 (ddd, *J* = 19.1, 11.7, 7.3 Hz, 1 H, 2-H_b), 3.92 (s, 3 H, 8-OCH_3), 4.05 (dd, *J* = 4.2, 1.8 Hz, 1 H, 4-H), 6.37 (s, 2 H, 5-H, 7-H), 16.09 (s, 1 H, 1-OH).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (ppm) = 22.3 (6-CH_3), 23.3 (C-3), 24.6 (4a-CH_3), 25.7 (C-2), 56.1 (8-OCH_3), 70.2 (C-4), 80.7 (C-4a), 105.0 (C-9a), 106.0, 111.3 (C-5, C-7), 107.7 (C-8a), 147.2 (C-6), 159.1, 160.6 (C-8, C-10a), 181.3, 181.9 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 3336, 2921, 1589, 1458, 1408, 1338, 1310, 1254, 1226, 1163, 1107, 1058, 941, 876, 826, 803, 689.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 281 (3.380), 330 (3.928).

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 83:17, 0.8 mL/min): t_R = 14.1 min.

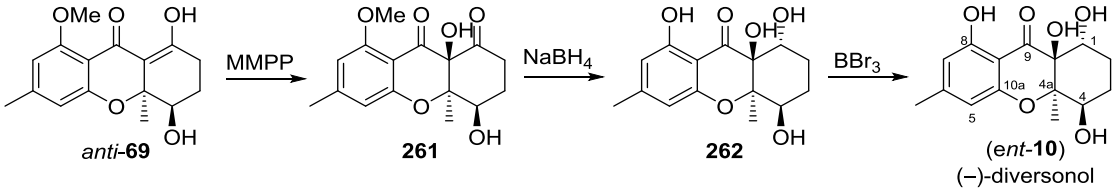
MS (ESI): *m*/*z* (%) = 893.3 (54) $[3M+Na]^+$, 603.2 (100) $[2M+Na]^+$, 313.1 (65) $[M+Na]^+$, 291.1 (4) $[M+H]^+$.

$C_{16}H_{18}O_5$ (290.31) calc.: 313.1046

found: 313.1047 $[M+Na]^+$ (ESI-HRMS).

3.6 Synthsis of (–)-diversonol (*ent*-10)

3.6.1 (–)-Diversonol (*ent*-10)



A stirred solution of enantiopure *anti*-**69** (33.0 mg, 114 µmol, 1.00 eq.) in EtOH (6.5 mL) was treated with MMPP (35.0 mg, 80%, 56.6 µmol, 0.50 eq.) at 0 °C and stirred at 0 °C. Additional MMPP (3.5 mg, 80%, 5.6 µmol, 0.05 eq.) was added after 1.5 h at 0 °C and stirring continued at this temperature for 30 min. The reaction was adsorbed on silica gel (1.5 g) at 0 °C and the mixture concentrated *in vacuo* at 0 °C. Filtration over silica gel (eluting with petroleum ether/EtOAc = 1:4) and purification by RP-HPLC with H_2O (A) and MeOH (B) as the eluent (*Jasco* Kromasil 100 C18®, 20 × 250 mm, 7 µm, gradient: 0–30 min: 70A/30B → 50A/50B, 30–40 min: 50A/50B → 0A/B100, 40–50 min: 0A/100B → 70A/30B, 18 mL/min, λ = 284 nm, t_R = 20.4 min) yielded diketone **261** as a white solid (16.0 mg, 52.2 µmol, 46%, d.r. = 5:1).

A solution of **261** (15.3 mg, 49.9 µmol, 1.00 eq.) in CH_2Cl_2 (0.5 mL) and MeOH (0.5 mL) was treated with powdered $NaBH_4$ (1.9 mg, 49.9 µmol, 1.00 eq.) at –78 °C. The reaction was stirred at this temperature for 1.5 h. Additional $NaBH_4$ (0.6 mg, 15.9 µmol, 0.32 eq.) was added at –78 °C and stirring at this temperature continued for 30 min. The reaction was

quenched by addition of sat. aq. NH_4Cl solution (2 mL) at –78 °C and the suspension poured into EtOAc (10 mL). The aq. layer was extracted with EtOAc (5 × 4 mL), the combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo*. Purification by RP-HPLC with H_2O (A) and MeOH (B) as the eluent (*Jasco* Kromasil 100 C18®, 20 × 250 mm, 7 µm, gradient: 0–30 min: 70A/30B → 50A/50B, 30–40 min: 50A/50B → 0A/B100, 40–50 min: 0A/100B → 70A/30B, 18 mL/min, λ = 284 nm, t_R = 23.1 min) yielded **262** as a white solid (9.5 mg, 30.8 µmol, 62%).

BBr_3 (0.31 mL, 1 M in CH_2Cl_2, 310 µmol, 10.1 eq.) was added slowly to a solution of **262** (9.5 mg, 30.8 µmol, 1.00 eq.) in CH_2Cl_2 (2 mL) at –78 °C. The resulting red solution was stirred for 30 min at –78 °C, 1.5 h at 0 °C and 3.5 h at RT before being quenched with H_2O (10 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by RP-HPLC with H_2O (A) and MeOH (B) as the eluent (*Jasco* Kromasil 100 C18®, 20 × 250 mm, 7 µm, gradient: 0–30 min: 70A/30B → 50A/50B, 30–40 min: 50A/50B → 0A/B100, 40–50 min: 0A/100B → 70A/30B, 18 mL/min, λ = 284 nm, t_R = 29.9 min) furnished (–)-diversonol (*ent*-**10**) as a white solid (6.8 mg, 23,1 µmol, 75%).

Optical Rotation: $[\alpha]_D$ = –62.0 (c = 0.16, $CHCl_3$, 22.0 °C).

^{1}H-NMR (600 MHz, DMSO-d_6): δ (ppm) = 1.40 (s, 3 H, 4a-CH_3), 1.46 (d, *J* = 14.2 Hz, 1 H, 2-H_a), 1.69 (d, *J* = 14.2 Hz, 1 H, 3-H_a), 1.97 (tdd, *J* = 14.2, 4.4, 2.4 Hz, 1 H, 3-H_b), 2.17 (ddd, *J* = 17.2, 8.7, 3.4 Hz, 1 H, 2-H_b), 2.25 (s, 3 H, 6-CH_3), 3.99 (s_{br}, 1 H, 1-H), 4.29 (s_{br}, 1 H, 4-H), 4.95 (s_{br}, 1 H, OH), 6.27 (s_{br}, 1 H, OH), 6.29, 6.31 (2 × s, 1 H, 5-H, 7-H), 6.59 (s_{br}, 1 H, OH), 11.29 (s_{br}, 1 H, OH).

^{13}C-NMR (125 MHz, DMSO-d_6): δ (ppm) = 19.4 (4a-CH_3), 21.9 (6-CH_3), 22.6 (C-2), 24.8 (C-3), 66.2 (C-4), 73.3 (C-1), 75.5 (C-4a), 81.0 (C-9a), 104.4 (C-8a), 108.5, 108.8 (C-5, (C-7), 149.1 (C-6), 158.3 (C-10a), 161.5 (C-8), 194.0 (C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 3554, 3358, 2978, 2942, 2879, 1655, 1630, 1570, 1439, 1387, 1352, 1327, 1252, 1197, 1093, 1056, 1022, 998, 883, 850, 829, 722, 675, 606, 575, 529.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 196 (4.236), 210 (4.174), 282 (3.958), 379 (4.340).

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 90:10, 0.8 mL/min): t_R = 16.0 min.

MS (ESI): *m*/*z* (%) = 611.2 (100) $[2M+Na]^+$, 317.1 (100) $[M+Na]^+$, 295.1 (13) $[M+H]^+$.

$C_{15}H_{18}O_6$ (294.30) calc.: 317.0995

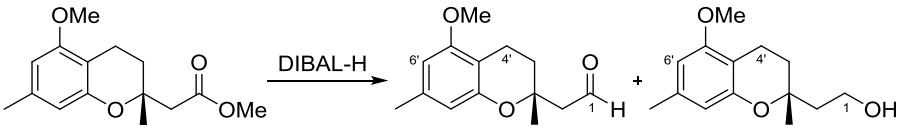
found: 317.0996 $[M+Na]^+$ (ESI-HRMS).

4 Formal Sythesis of Siccanin

4.1 Synthesis of aldehyde *R*-266 and TMS enol ether 265

4.1.1 (2*R*)-(5-Methoxy-2,7-dimethylchroman-2-yl)-acetaldehyde (*R*-266)

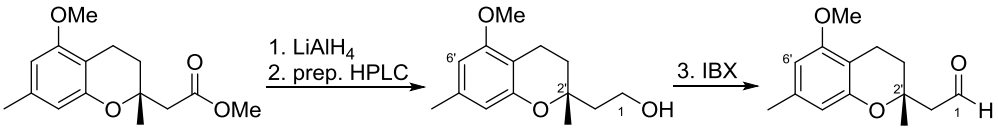
Method A:



(*R*)-**197** **266** (*R*)-**238**

To a solution of (*R*)-**197** (193 mg, 730 μmol, 1.00 eq.) in toluene (6 mL) was added DIBAL-H (1.52 mL, 1.2 M in toluene, 1.83 mmol, 2.50 eq.) by a syringe pump (3 mL/h) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 20 min before being quenched by addition of MeOH (1 mL) and H_2O (1 mL) at –78 °C. Additional H_2O (20 mL) was added at RT and the aq. phase extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 18:1 → 9:1) gave aldehyde **266** (139 mg, 593 μmol, 81%) and alcohol (*R*)-**238** (27 mg, 114 μmol, 16%) as colorless oils.

Method B:



(*R*)-**197** (*R*)-**238** **266**

To a suspension of $LiAlH_4$ (92 mg, 2.42 mmol, 1.10 eq.) in Et_2O (7 mL) was added chromanyl ester (*R*)-**197** (582 mg, 2.20 mmol, 1.00 eq.) in Et_2O (7 mL) by a transfer cannula at 0 °C. The reaction mixture was stirred at RT for 3 h before being quenched by careful addition of H_2O (20 mL) at 0 °C. The aq. layer was extracted with MTBE (4 × 20 mL), the combined organic layer dried over Na_2SO_4 and the volatiles were evaporated *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 5:1) furnished chromanyl alcohol (*R*)-**238** as a colorless oil (519 mg, 2.20 mmol, quant.). The enantiomeric alcohols (*S*)-**238** and (*R*)-**238** can be separated by chiral HPLC (*Daicel* Chiralpak IA®, 20 × 250 mm, 7 μm, *n*hexane/*i*PrOH = 99:1, 18 mL/min).

A solution of alcohol (*R*)-**238** (300 mg, 1.27 mmol, 1.00 eq.) in DMSO (10 mL) in the presence of 4 Å molecular sieves (700 mg) was treated with IBX (533 mg, 1.90 mmol, 1.50 eq.) at RT and stirred at RT for 2 h. The reaction was quenched by addition of brine (40 mL) at RT and the aq. phase extracted with MTBE (4 × 40 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ solution (40 mL) and brine (40 mL), dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 10:1) gave aldehyde **266** as a colorless oil (233 mg, 994 μmol, 78%).

Analytical data of aldehyde **266**:

Optical Rotation: $[\alpha]_D = -21.0$ (c = 0.50, $CHCl_3$, 25.1 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.40 (s, 3 H, 2'-CH_3), 1.83 (dt, *J* = 14.1, 6.8 Hz, 1 H, 3'-H_a), 1.89 (dt, *J* = 14.1, 6.8 Hz, 1 H, 3'-H_b), 2.28 (s, 3 H, 7'-CH_3), 2.57 (dd, *J* = 15.2, 3.1 Hz, 1 H, 2-H_a), 2.62 (t, *J* = 6.8 Hz, 2 H, 4'-H_2), 2.71 (dd, *J* = 15.2, 2.2 Hz, 1 H, 2-H_b), 3.80 (s, 3 H, 5'-OMe), 6.26, 6.31 (2 × s, 2 H, 6'-H, 8'-H), 9.89 (t, *J* = 2.7 Hz, 1 H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.4 (C-4'), 21.6 (7'-CH_3), 24.7 (2'-CH_3), 32.3 (C-3'), 52.2 (C-2), 55.3 (5'-OMe), 74.2 (C-2'), 103.1, 110.3 (C-6', C-8'), 106.6 (C-4a'), 137.4 (C-7'), 153.4 (C-5'), 157.6 (C-8a'), 201.6 (C-1).

IR: $\tilde{\nu}$ (cm^{-1}) = 2938, 2853, 1723, 1619, 1586, 1463, 1353, 1231, 1108, 816.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207.0 (4.634), 271.5 (2.951), 280.0 (2.937).

MS (ESI): *m*/*z* (%) = 235.1 (100) $[M+H]^+$, 257.1 (31) $[M+Na]^+$.

$C_{14}H_{18}O_3$ (234.29) calc.: 235.1329

found: 235.1330 $[M+H]^+$ (ESI-HRMS).

Analytical data of alcohol (*R*)-**238**:

Optical Rotation: $[\alpha]_D = +3.5$ (c = 1.0, $CHCl_3$, 25.7 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.31 (s, 3 H, 2-CH_3), 1.68–2.05 (m, 4 H, 2-H_2, 3'-H_2), 2.27 (s, 3 H, 7'-CH_3), 2.44 (t, *J* = 4.9 Hz, 1 H, OH), 2.50–2.63 (m, 1 H, 4'-H_a), 2.69 (dt, *J* = 17.3, 6.0 Hz, 1 H, 4'-H_b), 3.77–3.99 (m, 2 H, 1-H_2), 3.80 (s, 3 H, 5'-OCH_3), 6.25, 6.28 (2 × s, 2 H, 6'-H, 8'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.3 (C-4'), 21.5 (7'-CH_3), 23.4 (2'-CH_3), 31.2 (C-3'), 41.8 (C-2), 55.3 (5'-OCH_3), 59.0 (C-1), 76.3 (C-2'), 102.9, 110.3 (C-6', C-8'), 106.9 (C-4a'), 137.1 (C-7'), 153.5, 157.6 (C-5', C-8a').

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207.5 (4.635), 272.0 (2.954), 280.0 (2.942).

IR: $\tilde{\nu}$ (cm^{-1}) = 3375, 2939, 2855, 1618, 1586, 1463, 1353, 1231, 1109, 1023, 880, 814.

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 97:3, 0.8 mL/min): t_R = 60.1 min.

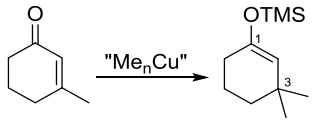
Preparative HPLC (*Daicel* Chiralpak IA®, 20 × 250 mm, 7 µm, *n*-hexane/2-PrOH 99:1, 18 mL/min, 210 nm): t_R = 24.1 min (*S*)-**238**; 47.0 min (*R*)-**238**.

MS (ESI): *m*/*z* (%) = 495.2 (27) $[2M+Na]^+$, 259.1 (100) $[M+Na]^+$, 237.2 (8) $[M+H]^+$.

$C_{14}H_{20}O_3$ (236.31) calc.: 259.1305

found: 259.1305 $[M+Na]^+$ (ESI-HRMS).

4.1.2 3,3-Dimethyl-1-(trimethylsilyloxy)cyclohexene (265)



267 **265**

Methode A: A suspension of LiCl (38 mg, 896 µmol, 20 mol%) and CuI (83 mg, 436 µmol, 10 mol%) in freshly distilled THF (24 mL) was treated with 3-methyl-2-cyclohexenone (**267**) (0.5 mL, 4.41 mmol, 1.00 eq.) and freshly distilled TMSCl (0.62 mL, 4.85 mmol, 1.10 eq.) at –40 °C. After stirring at –40 °C for 10 min MeMgCl solution (2.2 mL, 3 M in THF, 1.50 eq.) was added dropwise at –40 °C. The reaction mixture was stirred at –40 °C for 60 min before being quenched by addition of sat. aq. NH_4Cl solution (75 mL) at –40 °C. The aq. phase was extracted with EtOAc (3 × 50 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated *in vacuo* to give the TMS enol ether **265** as a colorless liquid (736 mg, 3.71 mmol, 84%).

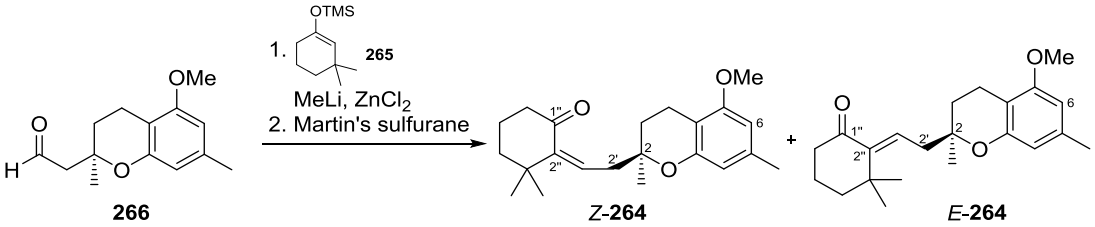
Methode B: MeLi (13.5 mL, 1.60 M in Et_2O, 2.50 eq.) was added dropwise to a suspension of CuI (2.06 g, 10.8 mmol, 1.25 eq.) in freshly distilled Et_2O (24 mL) at –15 °C. The resulting solution was stirred at –15 °C for 10 min until 3-methyl-2-cyclohexenone (**267**) (1.0 mL, 8.64 mmol, 1.00 eq.) was added dropwise. The reaction mixture was stirred at –15 °C for 15 min. A solution of TMSCl (3.5 mL, 27.2 mmol, 3.15 eq.) and NEt_3 (3.5 mL, 24.9 mmol, 2.90 eq.) in HMPA (0.86 mL) and Et_2O (5.4 mL) was added dropwise at –15 °C, the reaction mixture warmed to RT and stirred at RT for 4 h. After filtration and evaporation of the solvent *in vacuo*, the crude reaction mixture was dissolved in *n*-pentane (50 mL) and filtered once again. The filtrate was washed with sat. aq. $NaHCO_3$ solution (25 mL) and brine (25 mL) and

dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give **265** as a colorless liquid (1.06 g, 5.34 mmol, 62%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.17 (s, 9 H, $Si(CH_3)_3$), 0.97 (s, 6 H, 3-CH_3), 1.34 (m_c, 2 H, 4-H_2), 1.67 (m_c, 2 H, 5-H_2), 1.93 (td, *J* = 6.4, 1.4 Hz, 2 H, 6-H), 4.65 (s, 1 H, 2-H).
^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 0.3 ($Si(CH_3)_3$), 19.9 (C-5), 29.8 (C-6), 30.6 (3-CH_3), 31.7 (C-3), 37.0 (C-4), 115.7 (C-2), 148.7 (C-1).
IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 1660, 1454, 1363, 1261, 1251, 1212, 1184, 1141, 963, 835, 751, 689.
MS (ESI): *m*/*z* (%) = 183.2 (100) $[M–CH_3]^+$.
$C_{11}H_{22}OSi$ (198.38) calc: 198.1440
found: 198.1442 $[M]^+$ (EI-HRMS).

4.2 Synthesis of the alkenes 263a and 263b

4.2.1 (2*R*,2''*Z*)-2-(2-(5-methoxy-2,7-dimethylchroman-2-yl)-ethylidene)-3,3-dimethylcyclohexan-1-one (*Z*-264) and (2*R*,2''*E*)-2-(2-(5-methoxy-2,7-dimethylchroman-2-yl)-ethylidene)-3,3-dimethylcyclohexan-1-one (*E*-264)



A solution of 3,3-dimethyl-1-(trimethylsilyloxy)cyclohexene (**265**) (208 mg, 1.05 mmol, 4.93 eq.) in THF (5 mL) was treated with MeLi (0.6 mL, 1.6 M in Et_2O, 960 μmol, 4.51 eq.) at 0 °C and the reaction mixture stirred for 1.5 h. A solution of anhydrous $ZnCl_2$ in THF (1 mL, 1.25 M in THF, 1.25 mmol, 5.86 eq.) was added at –20 °C and stirring continued at –20 °C for 5 min. The reaction mixture was cooled to –78 °C and aldehyde **266** (50 mg, 213 μmol, 1.00 eq.) in THF (3 mL) added by a syringe pump (2 mL/h) at –78 °C. The reaction mixture was stirred for 16 h at –78 °C before being quenched by addition of sat. aq. NH_4Cl solution (5 mL) at –78 °C. The aq. phase was extracted with EtOAc (3 × 5mL), the combined organic phases were washed with brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated *in vacuo*.

The crude aldol products in CH_2Cl_2 (2 mL) were treated with Martin's sulfurane (**273**) (155 mg, 231 μmol, 1.08 eq.) in CH_2Cl_2 (2 mL) by a transfer cannula at 0 °C. The reaction mixture was stirred at RT for 2 h before being quenched by addition of sat. aq. $NaHCO_3$ solution (5 mL). The aq. phase was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 30:1) gave *Z*-**264** (11 mg, 32.1 μmol, 15%) and *E*-**264** (32 mg, 93.4 μmol, 44%) as colorless oils.

Analytical data of ketone *Z*-**264**:

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.05 (s, 3 H, 3''-$(CH_3)_a$), 1.07 (s, 3 H, 3''-$(CH_3)_b$), 1.20 (s, 3 H, 2-CH_3), 1.63 (m_c, 2 H, 4''-H_2), 1.71 (m_c, 2 H, 3-H_2), 1.89 (dt, *J* = 13.6, 6.8 Hz, 2 H, 5''-H_2), 2.25 (s, 3 H, 7-CH_3), 2.34 (m_c, 2 H, 6''-H_2), 2.46 (dd, *J* = 15.1, 7.2 Hz, 1 H, 2'-H_a), 2.52 (dd, *J* = 15.2, 7.2 Hz, 1 H, 2'-H_b), 2.54 (m_c, 1 H, 4-H_a), 2.60 (dt, *J* = 17.4, 6.3 Hz, 1 H, 4-H_b), 3.77 (s, 3 H, 5-OCH_3), 5.68 (t, *J* = 7.5 Hz, 1 H, 1'-H), 6.20, 6.28 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.5 (C-4), 21.1 (C-5''), 21.6 (7-CH_3), 24.0 (2-CH_3), 27.7 (3''-$(CH_3)_2$), 30.7 (C-3), 38.3 (C-2'), 39.8 (C-3''), 39.9 (C-4''), 43.4 (C-6''), 55.3 (5-OCH_3), 75.5 (C-2), 102.6 (C-8), 107.1 (C-4a), 110.4 (C-6), 124.6 (C-1'), 136.9 (C-7), 149.7 (C-2''), 154.2, 157.7 (C-5, C-8a), 206.6 (C-1'').

MS (ESI): *m/z* (%) = 707.4 (100) $[2M+Na]^+$, 365.2 (28) $[M+Na]^+$, 343.2 (2) $[M+H]^+$.

$C_{22}H_{30}O_3$ (342.47) calc.: 365.2087

found: 365.2089 $[M+Na]^+$ (ESI-HRMS).

Analytical data of ketone *E*-**264**:

Optical Rotation: $[\alpha]_D$ = –45.8 (c = 1.0, $CHCl_3$, 23.3 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.24 (s, 3 H, 3''-$(CH_3)_a$), 1.25 (s, 3 H, 3''-$(CH_3)_b$), 1.27 (s, 3 H, 2-CH_3), 1.55 (dd, *J* = 6.0, 3.3 Hz, 2 H, 4''-H_2), 1.77 (dq, *J* = 13.4, 6.5 Hz, 2 H, 3-H_2), 1.82 (m_c, 2 H, 5''-H_2), 2.25 (s, 3 H, 7-CH_3), 2.39 (t, *J* = 6.9 Hz, 2 H, 6''-H_2), 2.58 (m_c, 2 H, 4-H_2), 2.62 (dd, *J* = 16.2, 7.5 Hz, 1 H, 2'-H_a), 2.68 (dd, *J* = 16.2, 7.5 Hz, 1 H, 2'-H_b), 3.77 (s, 3 H, 5-OCH_3), 6.21, 6.30 (2 × s, 2 H, 6-H, 8-H), 6.72 (t, *J* = 7.5 Hz, 1 H, 1'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.4 (C-4), 18.5 (C-5''), 21.6 (7-CH_3), 24.0 (2-CH_3), 28.8 (3''-$(CH_3)_a$), 28.9 (3''-$(CH_3)_b$), 30.4 (C-3), 36.1 (C-3''), 39.2 (C-6''), 39.6 (C-2), 41.3 (C-4''), 55.3 (5-OCH_3), 75.3 (C-2), 102.7, 110.5 (C-6, C-8), 106.9 (C-4a), 136.2 (C-1'), 137.1 (C-7), 146.2 (C-2''), 153.9, 157.6 (C-5, C-8a), 202.4 (C-1'').

IR: $\tilde{\nu}$ (cm^{-1}) = 2934, 1682, 1617, 1585, 1461, 1415, 1352, 1228, 1153, 954, 882, 812, 567.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.6951), 228 (4.2358).

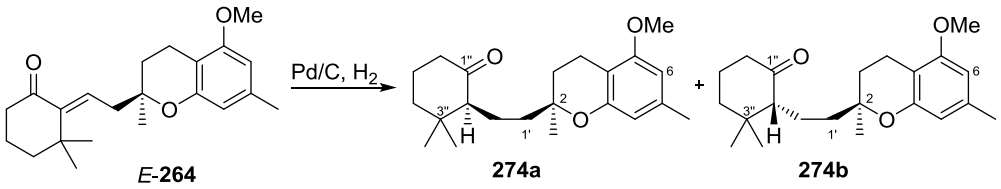
Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 99.5:0.5, 0.8 mL/min): t_R = 19.4 min.

MS (ESI): *m*/*z* (%) = 707.4 (100) $[2M+Na]^+$, 365.2 (23) $[M+Na]^+$.

$C_{22}H_{30}O_3$ (342.47) calc.: 365.2087

found: 365.2090 $[M+Na]^+$ (ESI-HRMS).

4.2.2 (2*S*,2''*S*)-2-(2-(5-Methoxy-2,7-dimethylchroman-2-yl)ethyl)-3,3-dimethylcyclohexan-1-one (274a) and (2*S*,2''*R*)-2-(2-(5-Methoxy-2,7-dimethylchroman-2-yl)ethyl)-3,3-dimethylcyclohexan-1-one (274b)



E-**264** **274a** **274b**

A solution of *E*-**264** (100 mg, 292 µmol, 1.00 eq.) in CH_2Cl_2 (8 mL) was treated with palladium on charcoal (32 mg, 10% Pd, 10 mol%) at RT and hydrogen (1 atm) passed through for 30 min. After stirring at RT under an H_2 atmosphere (1 atm) for 18 h, the reaction mixture was filtered through a pad of celite (rinsing with CH_2Cl_2). Column chromatography on silica gel (petroleum ether/EtOAc = 30:1) and preparative chiral HPLC (*Daicel* Chiralpak IB®, 10 × 250 mm, 7 µm, *n*-hexane/2-PrOH = 95:5, 3 mL/min, 210 nm) gave the diastereomeric ketones **274a** (41 mg, 119 µmol, 41%) and **274b** (45 mg, 131 µmol, 45%) as colorless oils.

Analytical data of ketone **274a**:

Optical Rotation: $[\alpha]_D$ = +3.2 (c = 0.14, $CHCl_3$, 24.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.76 (s, 3 H, 3''-$(CH_3)_a$), 1.02 (s, 3 H, 3''-$(CH_3)_b$), 1.24 (s, 3 H, 2-CH_3), 1.37–1.44 (m, 2 H, 1'-H_a, 2'-H_a), 1.55–1.60 (m, 3 H, 1'-H_b, 4''-H_2), 1.65–1.73 (m, 2 H, 2'-H_b, 3-H_a), 1.77–1.89 (m, 3 H, 3-H_b, 5''-H_2), 2.06 (dd, *J* = 10.4, 1.3 Hz, 1 H, 2''-H), 2.17–2.22 (m, 1 H, 6''-H_a), 2.24 (s, 3 H, 7-CH_3), 2.24–2.30 (m, 1 H, 6''-H_b), 2.49–2.61 (m, 2 H, 4-H_2), 3.77 (s, 3 H, 5-OCH_3), 6.19, 6.26 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.6 (C-4), 18.2 (C-2'), 21.6 (7-CH_3), 22.4 (3"-$(CH_3)_a$), 23.1 (C-5"), 24.0 (2-CH_3), 29.3 (3"-$(CH_3)_b$), 29.5 (C-3), 38.9 (C-4"), 39.1 (C-1'), 39.7 (C-3"), 41.0 (C-6"), 55.3 (5-OCH_3), 61.4 (C-2"), 75.8 (C-2), 102.4, 110.4 (C-6, C-8), 107.1 (C-4a), 136.9 (C-7), 154.4, 157.6 (C-5, C-8a), 213.3 (C-1").

IR: $\tilde{\nu}$ (cm^{-1}) = 2935, 1707, 1617, 1584, 1461, 1352, 1228, 1161, 878, 811.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.684), 273 (3.176).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 6.4.1 min.

Preparative HPLC (*Daicel* Chiralpak IB®, 10 × 250 mm, 7 µm, *n*-hexane/2-PrOH 96:4, 3 mL/min, 210 nm): t_R = 7.1 min.

MS (ESI): *m*/*z* (%) = 367.2 (19) $[M+Na]^+$, 711.5 (100) $[2M+Na]^+$.

$C_{22}H_{30}O_3$ (344.49) calc.: 367.2244

found: 367.2246, $[M+Na]^+$ (ESI-HRMS).

Analytical data of ketone **274b**:

Optical Rotation: $[\alpha]_D$ = –25.5 (c = 0.44, $CHCl_3$, 23.4 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.76 (s, 3 H, 3"-$(CH_3)_a$), 1.02 (s, 3 H, 3"-$(CH_3)_b$), 1.26 (s, 3 H, 2-CH_3), 1.35 (ddd, *J* = 12.8, 11.5, 4.2 Hz, 1 H, 1'-H_a), 1.45 (tdd, *J* = 12.2, 4.3, 2.3 Hz, 1 H, 2'-H_a), 1.52 (dd, *J* = 12.8, 4.4 Hz, 1 H, 1'-H_b), 1.54–1.62 (m, 2 H, 4"-H_2), 1.71 (dq, *J* = 13.6, 6.9 Hz, 1 H, 3-H_a), 1.73–1.81 (m, 3 H, 2'-H_b, 3-H_b, 5"-H_a), 1.86 (m, 1 H, 5"-H_b), 2.04 (dd, *J* = 10.4, 2.3 Hz, 1 H, 2"-H), 2.24 (s, 3 H, 7-CH_3), 2.20 (m_c, 1 H, 6"-H_a), 2.24 (s, 3 H, 7-CH_3), 2.29 (dt, *J* = 12.7, 4.3 Hz, 2.3 H, 6"-H_b), 2.54 (dt, *J* = 17.3, 6.8 Hz, 1 H, 4-H_a), 2.60 (dt, *J* = 17.2, 6.9 Hz, 1 H, 4-H_b), 3.77 (s, 3-H, 5-OCH_3), 6.19, 6.25 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.4 (C-4), 18.0 (C-2'), 21.6 (7-CH_3), 22.1 (3"-$(CH_3)_a$), 23.2 (C-5"), 23.7 (2-CH_3), 29.4 (3"-$(CH_3)_b$), 31.1 (C-3), 38.2 (C-1'), 39.2 (C-4"), 39.9 (C-3"), 41.3 (C-6"), 55.3 (5-OCH_3), 61.3 (C-2"), 75.7 (C-2), 102.5, 110.3 (C-6, C-8), 107.3 (C-4a), 136.8 (C-7), 154.2, 157.6 (C-5, C-8a), 213.3 (C-1").

IR: $\tilde{\nu}$ (cm^{-1}) = 2936, 1708, 1617, 1584, 1460, 1352, 1230, 1161, 879, 812.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.6628), 272 (3.1963).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 11.0 min.

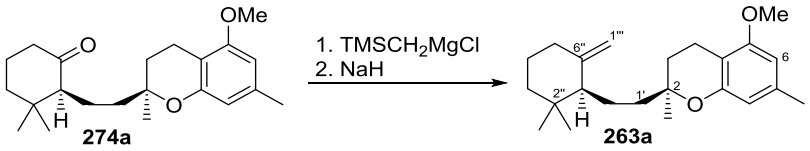
Preparative HPLC (*Daicel* Chiralpak IB®, 10 × 250 mm, 7 µm, *n*-hexane/2-PrOH 95:5, 3 mL/min, 210 nm): t_R = 11.8 min.

MS (ESI): *m*/*z* (%) = 711.5 (100) $[2M+Na]^+$, 367.2 (28) $[M+Na]^+$.

$C_{22}H_{32}O_3$ (344.49) calc.: 367.2244

found: 367.2243, $[M+Na]^+$ (ESI-HRMS).

4.2.3 (2*S*,2"*S*)-2-(2-(2,2-Dimethyl-6-methylenecyclohexyl)-ethyl)-5-methoxy-2,7-dimethylchromane (263a)



A suspension of magnesium turnings (500 mg, 20.6 mmol) in Et_2O (10 mL) was activated with 1,2-dibromoethane (50 µL, 578 µmol) at RT and stirred at RT for 1 h. Chloromethyltrimethylsilane (2.4 mL, 17.2 mmol) was added dropwise at RT, the reaction mixture refluxed for 1 h and then cooled to RT.

To a solution of ketone **263a** (31 mg, 90.0 µmol, 1.00 eq.) in Et_2O (3 mL) was added LiCl (8.0 mg, 189 µmol, 2.10 eq.) and $TMSCH_2MgCl$ stock solution (2 mL) at 0 °C. The reaction mixture was stirred at RT for 19.5 h. before being quenched by addition of H_2O (10 mL) at 0 °C. The aq. phase was extracted with MTBE (3 × 5 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 50:1) gave the (trimethylsilyl)methyl addition product as a colorless oil (36 mg, 83.2 µmol, 92%).

The (trimethylsilyl)methyl addition product (36 mg, 83.2 µmol, 1.00 eq.) in THF (5 mL) was treated with NaH (33 mg, 825 µmol, 9.92 eq.) and heated at 100 °C under microwave irradiation for 16 h. The reaction was quenched by addition of H_2O (5 mL) at 0 °C and the aq. phase extracted with MTBE (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 50:1 → 40:1) gave alkene **263a** as a colorless oil (26.2 mg, 76.5 µmol, 92%, 85% over 2 steps).

Optical Rotation: $[\alpha]_D = -2.4$ (c = 0.50, $CHCl_3$, 22.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.83 (s, 3 H, 2"-$(CH_3)_a$), 0.91 (s, 3 H, 2"-$(CH_3)_b$), 1.18–1.23 (m, 1 H, 3"-H_a), 1.23 (s, 3 H, 2-CH_3), 1.33-1.60 (m, 7 H, 1'-H_2, 2'-H_2, 3"-H_b, 4"-H_2), 1.63 (m_c, 1 H, 1"-H), 1.69 (m_c, 1 H, 3-H_a), 1.78 (ddd, *J* = 14.2, 8.2, 6.4 Hz, 1 H, 3-H_b), 1.94 (m, 1 H, 5"-H_a), 2.00 (m_c, 1 H, 5"-H_b), 2.25 (s, 3 H, 7-CH_3), 2.56 (m_c, 2 H, 4-H_2), 3.78 (s,

3 H, 5-OCH_3), 4.50 (d, *J* = 2.3 Hz, 1 H, 1'''-H_a), 4.70 (s, 1 H, 1'''-H_b), 6.20, 6.28 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.6 (C-4), 20.0 (C-1''), 21.6 (7-CH_3), 23.7, 23.9 (2-CH_3, C-4''), 26.1 (2''-$(CH_3)_a$), 28.5 (2''-$(CH_3)_b$), 30.2 (C-3), 32.6 (C-5''), 35.0 (C-2''), 36.5 (C-3''), 38.6 (C-2'), 54.3 (C-1') 55.3 (5-OCH_3), 75.9 (C-2), 102.3, 110.5 (C-6, C-8), 107.2 (C-4a), 109.0 (C-1'''), 136.9 (C-7), 149.1 (C-6''), 154.5, 157.6 (C-5, C-8a).

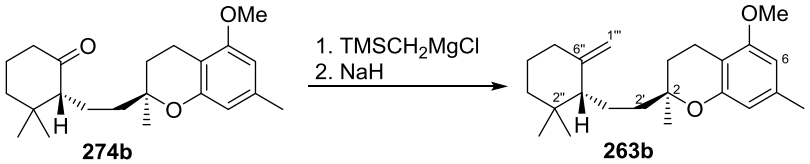
IR: $\tilde{\nu}$ (cm^{-1}) = 2926, 1618, 1585, 1462, 1352, 1228, 1160, 1109, 886, 810.

MS (ESI): *m*/*z* (%) = 707.5 (13) $[2M+Na]^+$, 365.3 (62) $[M+Na]^+$, 343.3 (100) $[M+H]^+$.

$C_{23}H_{34}O_2$ (342.51) calc.: 365.2451

found: 365.2447 $[M+Na]^+$ (ESI-HRMS).

4.2.4 (2*S*,2''*R*)-2-(2-(2,2-Dimethyl-6-methylenecyclohexyl)-ethyl)-5-methoxy-2,7-dimethylchromane (263b)



274b 263b

A suspension of magnesium turnings (250 mg, 10.3 mmol) in Et_2O (5 mL) was activated with 1,2-dibromoethane (30 μL, 347 μmol) at RT and stirred at RT for 15 min. (Trimethylsilyl)methyl chloride (1.2 mL, 8.56 mmol) was added dropwise at RT, the reaction mixture refluxed for 1 h and then stirred at RT for 20 min.

To a solution of ketone **274b** (36.1 mg, 105 μmol, 1.00 eq.) in $E_{t2}O$ (3 mL) was added $TMSCH_2MgCl$ stock solution (0.05 mL) at 0 °C and the reaction mixture stirred at 0 °C for 20 min. Additional $TMSCH_2MgCl$ solutiones were added after 40 min (0.25 mL), 60 min (0.75 mL), 100 min (1 mL) and 150 min (0.7 mL) and the reaction mixture stirred at 0 °C in the meantime. The reaction mixture was stirred at RT for 16 h before being quenched by addition of H_2O (10 mL) at 0 °C. The aq. phase was extracted with MTBE (3 × 5 mL), the combined organic phases were dried over Na_2SO_4 and the solvent evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/EtOAc = 30:1) gave the (trimethylsilyl)methyl addition product as a colorless oil (41 mg, 94.8 μmol, 90%).

The (trimethylsilyl)methyl addition product (41 mg, 94.8 μmol, 1.00 eq.) in THF (5 mL) was treated with NaH (38 mg, 950 μmol, 10.0 eq.) and heated at 100 °C under microwave irradiation for 19 h. The reaction was quenched by addition of H_2O (5 mL) at 0 °C and the aq.

phase extracted with MTBE (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (petroleum ether/MTBE = 50:1 → 40:1) gave alkene **263b** as a colorless oil (28 mg, 81.7 μmol, 86%, 78% over 2 steps).

Optical Rotation: $[\alpha]_D = -34.9$ (c = 0.10, $CHCl_3$, 23.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.83 (s, 3 H, 2"-$(CH_3)_a$), 0.89 (s, 3 H, 2"-$(CH_3)_b$), 1.18–1.20 (m, 1 H, 4"-H_a), 1.22 (s, 3 H, 2-CH_3), 1.32–1.61 (m, 7 H, 1'-H_2, 2'-H_2, 3"-H_b, 4"-H_2), 1.63 (dd, *J* = 11.0, 3.2 Hz, 1"-H), 1.67–1.72 (m, 1 H, 3-H_a), 1.73–1.78 (m, 1 H, 3-H_b), 1.95–1.99 (m, 1 H, 5"-H_a), 2.00–2.05 (m, 1 H, 5"-H_b), 2.25 (s 3 H, 7-CH_3), 2.56 (m_c, 2 H, 4-H_2), 3.78 (s, 3 H, 5-OCH_3), 4.52 (d, *J* = 2.4 Hz, 1'"-H_a), 4.72 (d, *J* = 2.3 Hz, 1'"-H_b), 6.20, 6.27 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.5 (C-4), 20.0 (C-1'), 21.6 (7-CH_3), 23.7, 23.7 (2-CH_3, C-4"), 26.3 (2"-$(CH_3)_a$), 28.4 (2"-$(CH_3)_b$), 30.7 (C-3), 32.4 (C-5"), 35.0 (C-2"), 36.3 (C-3"), 38.5 (C-2'), 54.3 (C-1"), 55.3 (5-OCH_3), 75.8 (C-2), 102.4, 110.4 (C-6, C-8), 107.1 (C-4a), 109.1 (C-1'"), 136.9 (C-7), 149.2 (C-6"), 154.4, 157.6 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 2982, 1617, 1584, 1462, 1416, 1352, 1229, 1159, 885, 810.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.6598).

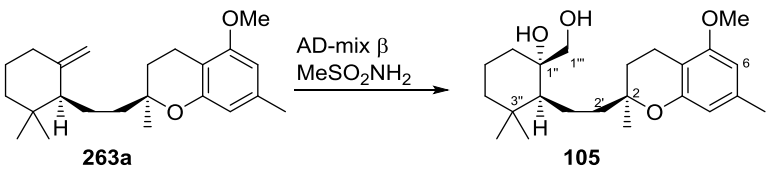
MS (ESI): *m*/*z* (%) = 707.5 (15) $[2M+Na]^+$, 365.3 (57) $[M+Na]^+$, 343.3 (100) $[M+H]^+$.

$C_{23}H_{34}O_2$ (342.51) calc.: 343.2632

found: 343.2627 $[M+H]^+$ (ESI-HRMS).

4.3 Synthesis of the diols 105 and 283 and chromene 279

4.3.1 (1'''*S*,2*S*,2''*S*)-1-(Hydroxymethyl)-2-(2-(5-methoxy-2,7-dimethylchroman-2-yl)-ethyl)-3,3-dimethylyclohexan-1-ol (105)



A solution of alkene **263a** (22.4, 65.4 μmol, 1.00 eq.) in *t*BuOH/H_2O (0.7 mL/0.7 mL) was treated with methanesulfonamide (6.3 mg, 65.4 μmol, 1.00 eq.) and AD-mix β (794 mg) at

RT and stirred at RT for 40 h. Additional AD-mix β (794 mg) and *t*BuOH/H_2O (0.7 mL/0.7 mL) were added at RT after 40 and 80 h and the reaction mixture was stirred at RT in the meantime. After 120 h, the reaction mixture was quenched by addition of sat. aq. $NaHSO_3$ solution (5 mL) at 0 °C and the aq. phase extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 10:1 → 7:3) gave diol **105** as a colorless oil (22.2 mg, 59.0 μmol, 90%).

Optical Rotation: $[\alpha]_D$ = –8.4 (c = 0.60, $CHCl_3$, 24.0 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.76 (s, 3 H, 3"-$(CH_3)_a$), 0.96 (s, 3 H, 3"-$(CH_3)_b$), 1.11 (td, *J* = 12.2, 3.1 Hz, 1 H, 6"-H_a), 1.19 (td, *J* = td, 12.5, 3.5 Hz, 1 H, 4"-H_a), 1.24 (s, 3 H, 2-CH_3), 1.27 (t, *J* = 4.4 Hz, 1 H, 2"-H), 1.34–1.43 (m, 3 H, 1'-H_a, 4"-H_b, 5"-H_a), 1.55 (dt, *J* = 14.5, 4.3 Hz, 1 H, 5"-H_b), 1.57–1.69 (m, 2 H, 1'-H_b, 2'-H_a), 1.72 (t, *J* = 6.2 Hz, 1 H, 3-H_a), 1.77 (ddd, *J* = 13.5, 8.5, 6.3 Hz, 1 H, 3-H_b), 1.84 (ddd, *J* = 12.6, 11.1, 4.5 Hz, 1 H, 2'-H_b), 2.00 (dt, *J* = 12.6, 3.9 Hz, 1 H, 6"-H_b), 2.25 (s, 3 H, 7-CH_3), 2.38 (s, 2 H, 1"-OH, 1'"-OH), 2.53 (ddd, *J* = 17.1, 8.6, 6.3 Hz, 1 H, 4-H_a), 2.61 (dt, *J* = 17.3, 6.1 Hz, 1 H, 4-H_b), 3.54 (dd, *J* = 10.9, 1.4 Hz, 1 H, 1'"-H_a), 3.59 (d, *J* = 11.0 Hz, 1 H, 1'"-H_b), 3.77 (s, 3 H, 5-OCH_3), 6.20, 6.27 (2 × s, 2 H, 6-H, 8-H).**^{13}C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 16.5 (C-4), 19.1 (C-1'), 19.6 (C-5"), 21.6 (7-CH_3), 22.9 (3"-$(CH_3)_a$), 23.3 (2-CH_3), 30.6 (C-3), 32.3 (3"-$(CH_3)_b$), 35.4 (C-6"), 35.8 (C-3"), 40.6 (C-4"), 42.5 (C-2'), 55.3 (5-OCH_3), 55.8 (C-2"), 63.7 (C-1'"), 75.7, 76.3 (C-1'", C-2), 102.6, 110.3 (C-6, C-8), 107.2 (C-4a), 137.0 (C-7), 154.1, 157.6 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3402, 2930, 1617, 1584, 1461, 1388, 1229, 1159 1105, 1040, 1022, 878, 811, 753.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.610), 273 (3.104).

MS (ESI): *m*/*z* (%) = 775.5 (100) $[2M+Na]^+$, 399.3 (69) $[M+Na]^+$, 359.3 (52) $[M+H]^+$.

$C_{23}H_{36}O_4$ (376.54) calc.: 399.2506

found: 399.2506 $[M+H]^+$ (ESI-HRMS).

4.3.2 (1'''*S*,2*S*,2''*S*)-1-(Hydroxymethyl)-2-(2-(5-methoxy-2,7-dimethyl-2*H*-chroman-2-yl)-ethyl)-3,3-dimethylyclohexan-1-ol (283)

105 **283**

A mixture of alcohol **105** (14.5 mg, 38.5 μmol, 1.00 eq.) and DDQ (4.9 mg, 57.7 μmol, 1.50 eq.) in benzene (2 mL) was heated at 80 °C for 1 h. Additional DDQ (4.9 mg, 57.7 μmol, 1.50 eq.) was added at RT and stirring continued at 80 °C for 1 h. The reaction mixture was cooled to RT and adsorbed on silica gel. Column chromatography on silica gel (*n*-pentane/EtOAc = 5:1 → 4:1) furnished the corresponding chromene **283** as a colorless oil (9.1 mg, 24.3 μmol, 63%).

Optical Rotation: $[\alpha]_D$ = +44.0 (c = 0.50, $CHCl_3$, 24.6 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.72 (s, 3 H, 3''-$(CH_3)_a$), 0.94 (s, 3 H, 3''-$(CH_3)_b$), 1.09 (td, *J* = 12.6, 3.0 Hz, 1 H, 6''-H_a), 1.18 (td, *J* = 12.9, 4.0 Hz, 1 H, 4''-H_a), 1.26 (t, *J* = 4.6 Hz, 1 H, 2''-H), 1.32–1.46 (m, 3 H, 1'-H_a, 4''-H_a, 5''-H_a), 1.50–1.59 (m, 2 H, 1-H', 5''-H_b), 1.77 (ddd, *J* = 13.8, 11.4, 5.3 Hz, 1 H, 2'-H_a), 1.86 (ddd, *J* = 13.8, 11.5, 5.1 Hz, 1 H, 2'-H_b), 2.01 (d, *J* = 12.9 Hz, 1 H, 6''-H_b), 2.17 (s_{br}, 2 H, 1''-OH, 1'''-OH), 2.25 (s, 3 H, 7-CH_3), 3.52 (dd, *J* = 10.9, 1.6 Hz, 1 Hz, 1'''-H_a), 3.59 (d, *J* = 10.8 Hz, 1 H, 1'''-H_b), 3.77 (s, 3 H, 5-OCH_3), 5.45 (d, *J* = 10.0 Hz, 1 H, 3-H), 6.19, 6.26 (2 × s, 2 H, 6-H, 8-H), 6.63 (d, J = 10.0 Hz, 1 H, 4-H), **^{13}C-NMR** (125 MHz, $CDCl_3$): δ (ppm) = 19.7, 20.0 (C-1', C-5''), 22.0 (7-CH_3), 22.8 (3''-$(CH_3)_a$), 26.1 (2-CH_3), 32.4 (3''-$(CH_3)_b$), 35.5 (C-6''), 36.0 (C-3''), 40.7 (C-4''), 43.8 (C-2'), 55.5 (5-OCH_3), 55.6 (C-2''), 63.6 (C-1'''), 75.7 (C-1''), 78.6 (C-2), 103.9, 109.8 (C-6, C-8), 107.9 (C-4a), 117.3 (C-4), 126.9 (C-3), 139.4 (C-7), 153.6, 155.1 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3385, 2923, 1613, 1573, 1462, 1388, 1261, 1208, 1109, 1037, 898, 814, 775, 738, 706.

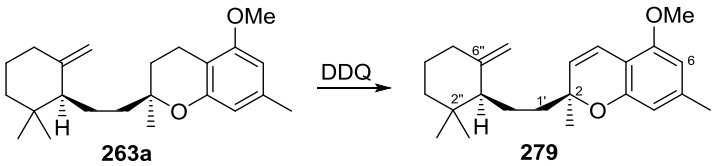
UV (CH_3CN): λ_{max} (nm) (lg ε) = 230 (4.297), 281 (3.862), 288 (3.851).

MS (ESI): *m*/*z* (%) = 771.5 (100) $[2M+Na]^+$, 397.2 (73) $[M+Na]^+$, 375.3 (21) $[M+H]^+$, 357.2 (56) $[M–OH]^+$.

$C_{23}H_{32}O_2$ (374.52) calc.: 397.2349

found: 397.2351 $[M+Na]^+$ (ESI-HRMS).

4.3.3 (1''*S*,2'*S*)-2-(2-(2,2-Dimethyl-6-methylenecyclohexyl)ethyl)-5-methoxy-2,7-dimethyl-2*H*-chromene (279)



263a **279**

A mixture of **263** (12.7 mg, 37.1 μmol, 1.00 eq.) and DDQ (9.6 mg, 111 μmol, 3.00 eq.) in benzene (1.85 mL) was heated at reflux for 2 h. After cooling to RT, the reaction mixture was adsorbed on silica gel and the solvent was evaporated *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 100:0 → 50:1) furnished the chromene **279** as a colorless oil (10.5 mg, 30.8 μmol, 83%).

Optical Rotation: $[\alpha]_D$ = +58.4 (c = 0.50, $CHCl_3$, 23.1 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.79 (s, 3 H, 2'-$(CH_3)_a$), 0.88 (s, 3 H, 2''-$(CH_3)_b$), 1.17 (m_c, 1 H, 3''-H_a), 1.32 (s, 3, 2-CH_3), 1.35–1.51 (m, 5 H, 1'-H_a, 2'-H_a, 3''-H_b, 4''-H_2), 1.55–1.66 (m, 3 H, 1'-H_b, 2'-H_b, 1''-H), 1.93–2.02 (m, 2 H, 5''-H_2), 2.25 (s, 3 H, 7-CH_3), 3.80 (s, 3 H, 5-OCH_3), 4.51 (s, 1-H, 1'''-H_a), 4.72 (s, 1 H, 1'''-H_b), 5.40 (d, *J* = 10.0 Hz, 1 H, 3-H), 6.19, 6.26 (2 × s, 2 H, 6-H, 8-H), 6.64 (d, *J* = 10.0 Hz, 4 H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 20.6 (C-2'), 22.0 (7-CH_3), 23.7 (C-4''), 26.4 (2-CH_3, 2''-$(CH_3)_a$), 28.4 (2''-$(CH_3)_b$), 32.4 (C-5''), 35.0 (C-2''), 36.2 (C-3''), 39.9 (C-1'), 54.2 (C-1''), 55.5 (5-OCH_3), 78.4 (C-2), 103.7, 109.9 (C-6, C-8), 107.9 (C-4a), 109.0 (C-1'''), 117.3 (C-4), 126.9 (C-3), 139.3 (C-7), 149.3 (C-6''), 153.9, 155.0 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 1638, 1613, 1573, 1463, 1387, 1229, 1204, 1042, 887, 814, 775, 708.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 229 (4.331), 281 (3.8871).

MS (ESI): *m*/*z* (%) = 363.4 (50) $[M+Na]^+$, 341.4 (100) $[M+H]^+$.

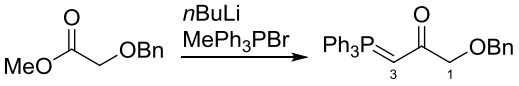
$C_{23}H_{32}O_2$ (340.50) calc.: 363.2295

found: 363.2285 $[M+Na]^+$ (ESI-HRMS).

5 Enantioselective Total Syntheses of (–)-Blennolide C and (–)-Gonytolide C

5.1 Synthesis of domino precursor 287

5.1.1 1-Benzyloxy-3-(triphenylphosphoranylidene)-propan-2-one (292)



291 **292**

A solution of *n*BuLi (20.0 mL, 2.5 M in *n*-hexane, 50.4 mmol, 2.21 eq.) was added dropwise to CH_3Ph_3PBr (18.4 g, 50.2 mmol, 2.20 eq.) in THF (190 mL) at 0 °C and the reaction mixture stirred at 0 °C for 1 h. A solution of methyl 2-(benzyloxy)-acetate (**291**) (4.11 g, 22.8 mmol, 1.00 eq.) in THF (20 mL) was added dropwise at 0 °C and stirring continued at 0 °C for 20 h. The solvent was removed *in vacuo* and the crude product suspended in H_2O (200 mL). The aq. phase was extracted with Et_2O (5 × 200 mL) and EtOAc (2 × 200 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Column chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) gave **292** as a colorless solid (6.60 g, 15.6 mmol, 68%).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.03 (s, 2 H, 1-H_2), 4.24 (d, J_{PH} = 25.4 Hz, 1 H, 3-H), 4.66 (s, 2 H, OCH_2Ph), 7.24–7.67 (m, 20 H, 20 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 49.5 (d, J_{PC} = 109 Hz, C-3), 73.2 (OCH_2Ph), 75.6 (d, J_{PC} = 13.3 Hz, C-1), 126.8 (d, J_{PC} = 90.7 Hz, PPh_3-C_i), 127.3 (OCH_2Ph-C_p), 127.7, 128.1 (OCH_2Ph-C_o, OCH_2Ph-C_m), 128.7 (d, J = 12.2 Hz, PPh_3-C_m), 132.0 (d, J = 2.9 Hz, PPh_3-C_p), 133.0 (d, J = 10.2 Hz, PPh_3-C_o), 138.4 (OCH_2Ph-C_i), 189.5 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3047, 2849, 2822, 1733, 1573, 1539, 1479, 1454, 1437, 1403, 1368, 1342, 1251, 1207, 1181, 1165, 1095, 1079, 1026, 1007, 992, 940, 920, 868, 750, 716, 692, 678, 667, 639, 594, 575, 543, 512.

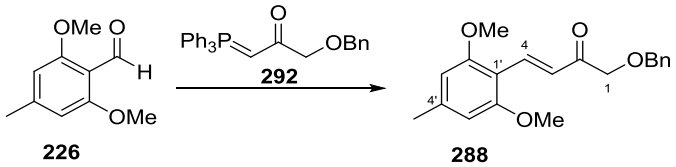
UV (CH_3CN): λ_{max} (nm) (lg ε) = 197 (4.804), 292 (3.515).

MS (ESI): *m/z* (%) = 849.3 (49) $[2M+H]^+$, 425.2 (100) $[M+H]^+$.

$C_{28}H_{25}O_2P$ (424.47) calc.: 425.1665

found: 425.1667 $[M+H]^+$ (ESI-HRMS).

5.1.2 (*E*)-1-Benzyloxy-4-(2,6-dimethoxy-4-methylphenyl)-but-3-en-2-one (288)



A solution of 2,6-dimethoxy-4-methylbenzaldehyde (**226**) (5.22 g, 29.0 mmol, 1.00 eq.) in toluene (100 mL) was treated with 1-(benzyloxy)-3-(triphenylphosphoranylidene)-propran-2-one (**292**) (16.0 g, 37.7 mmol, 1.30 eq.) at RT and refluxed for 19.5 h. After cooling to RT, the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc = 3:1 → 2:1) furnished α,β-unsaturated ketone **288** as a yellow solid (8.42 g, 25.8 mmol, 89%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.34 (s, 3 H, 4'-CH_3), 3.83 (s, 6 H, 2'-OCH_3, 6'-OCH_3), 4.33 (s, 2 H, 1-H_2), 4.64 (s, 2 H, OCH_2Ph), 6.35 (s, 2 H, 3'-H, 5'-H), 7.27–7.41 (m, 6 H, 3-H, 5 × Ph-H), 8.13 (d, *J* = 16.2 Hz, 1 H, 4-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.6 (4'-CH_3), 55.7 (2'-OCH_3, 6'-OCH_3), 73.2 (OCH_2Ph), 74.6 (C-1), 104.6 (C-3', C-5'), 109.6 (C-1'), 123.4 (C-3), 127.7 (Ph-C_p), 127.8, 128.4 (Ph-C_o, Ph-C_m), 134.6 (C-4), 137.6 (Ph-C_i), 142.8 (C-4'), 160.2 (C-2', C-6'), 198.5 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3057, 3028, 2975, 2948, 2919, 2867, 2828, 2730, 1694, 1593, 1563, 1468, 1456, 1414, 1382, 1326, 1283, 1243, 1202, 1181, 1163, 1117, 1068, 1034, 1005, 978, 959, 906, 862,

845, 825, 743, 696, 644, 603, 588, 553, 533, 502.

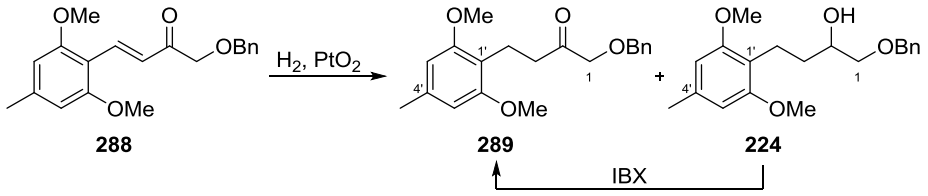
UV (CH_3CN): λ_{max} (nm) (lg ε) = 201 (3.784), 324 (3.612).

MS (ESI) : *m/z* (%) = 657.3 (100) $[2M+H]^+$, 349.1 (36) $[M+Na]^+$, 327.2 (51) $[M+H]^+$.

$C_{20}H_{22}O_4$ (326.15) calc.: 327.1591

found: 327.1592 $[M+H]^+$ (ESI-HRMS).

5.1.3 1-Benzyloxy-4-(2,6-dimethoxy-4-methylphenyl)-butan-2-one (289)



A solution of α,β-unsaturated ketone **288** (8.42 g, 25.8 mmol, 1.00 eq.) in EtOAc (235 mL) was treated with platinum dioxide (240 mg, 1.03 mmol, 4 mol%), flushed with hydrogen gas at RT for 15 min and stirred under a hydrogen atmosphere (1 atm) at RT for 2 h. After filtration through a pad of celite (rinsing with CH_2Cl_2), the solvent was removed *in vacuo*. A solution of the crude product in MeCN (175 mL) was treated with IBX (1.12 g, 10.3 mmol, 0.40 eq.) at RT and stirred at 80 °C for 1 h. After cooling to RT, the solvents were removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc = 7:1) furnished ketone **289** as a colorless oil that solidified under vacuum (7.62 g, 23.4 mmol, 91%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3 H, 4'-CH_3), 2.60 (t, *J* = 7.8 Hz, 2 H, 3-H_2), 2.89 (t, *J* = 7.8 Hz, 2 H, 4-H_2), 3.74 (s, 6 H, 2'-OCH_3, 6'-OCH_3), 4.07 (s, 2 H, 1-H_2), 4.56 (s, 2 H, OCH_2Ph), 6.33 (s, 2 H, 3'-H, 5'-H), 7.24–7.35 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 17.3 (C-4), 22.1 (4'-CH_3), 38.8 (C-3), 55.5 (2'-OCH_3, 6'-OCH_3), 73.2 (OCH_2Ph), 74.8 (C-1), 104.4 (C-3', C-5'), 113.8 (C-1'), 127.7, 127.8, 128.3 (Ph-C_p, Ph-C_o, Ph-C_m), 137.1, 137.3 (C-4', Ph-C_i), 157.8 (C-2', C-6'), 208.6 (C-2).

IR: $\tilde{\nu}$ (cm^{-1}) = 3067, 3010, 2985, 2927, 2897, 2828, 1721, 1605, 1584, 1498, 1463, 1407, 1354, 1326, 1312, 1277, 1242, 1182, 1160, 1119, 1077, 1038, 968, 919, 850, 812, 759, 734, 696, 610, 582, 525.

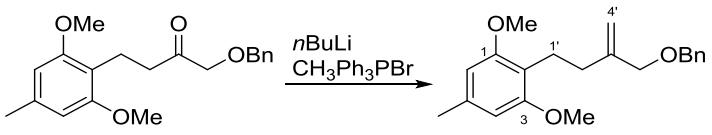
UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.420), 271 (2.634).

MS (ESI): *m/z* (%) = 679.5 (100) $[2M+Na]^+$, 351.3 (45) $[M+Na]^+$, 329.3 (36) $[M+H]^+$.

$C_{20}H_{24}O_4$ (328.17) calc.: 329.1747

found: 329.1747 $[M+H]^+$ (ESI-HRMS).

5.1.4 2-(3-(Benzyloxymethyl)-but-3-en-1-yl)-1,3-dimethoxy-5-methylbenzene (290)



289 **290**

A solution of methyltriphenylphosphonium bromide (26.0 g, 69.7 mmol, 3.00 eq.) in THF (220 mL) was treated with *n*BuLi (27.2 mL, 2.5 M in *n*-hexane, 65.0 mmol, 2.80 eq.). The suspension was stirred at 0 °C for 30 min, at RT for further 30 min and cooled to 0 °C again. A solution of ketone **289** (7.62 g, 23.2 mmol, 1.00 eq.) in THF (100 mL) was added to the ylide solution by a transfer cannula at 0 °C and the resulting reaction mixture stirred at RT for 4 h. The reaction was quenched by addition of sat. aq. NH_4Cl solution (375 mL) und H_2O (155 mL). The aq. layer was extracted with CH_2Cl_2 (3 × 100 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc = 20:1) furnished alkene **290** as a colorless oil (7.05 g, 21.6 mmol, 93%).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.23 (t, *J* = 7.8 Hz, 2 H, 2'-H_2), 2.32 (s, 3 H, 5-CH_3), 2.77 (t, *J* = 7.8 Hz, 2 H, 1'-H_2), 3.76 (s, 6 H, 1-OCH_3, 3-OCH_3), 4.03 (s, 2 H, CH_2OBn), 4.51 (s, 2 H, OCH_2Ph), 4.95 (s, 1 H, 4'-H_a), 5.05 (s, 1 H, 4'-H_b), 6.34 (s, 2 H, 4-H, 6-H), 7.24–7.37 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.7 (C-1'), 22.1 (5-CH_3), 32.7 (C-2'), 55.6 (1-OCH_3, 3-OCH_3), 71.9 (OCH_2Ph), 73.2 (CH_2OBn), 104.5 (C-4, C-6), 110.9 (C-4'), 115.4 (C-2), 127.3 (Ph-C_p), 127.5, 128.2 (Ph-C_o, Ph-C_m), 136.6 (C-5), 138.6 (Ph-C_i), 146.6 (C-3'), 157.9 (C-1, C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3089, 3064, 3029, 2994, 2935, 2835, 2328, 1650, 1607, 1586, 1497, 1453, 1412, 1362, 1313, 1239, 1183, 1161, 1116, 1073, 1028, 969, 899, 812, 734, 696, 612, 582, 525.

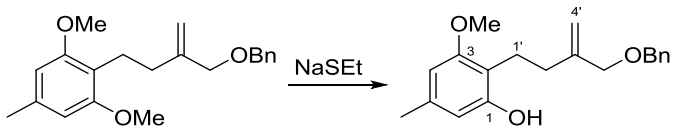
UV (CH_3CN): λ_{max} (nm) (lg ε) = 206 (4.756), 259 (3.103), 270 (3.148).

MS (ESI): *m/z* (%) = 349.2 (100) $[M+Na]^+$.

$C_{21}H_{26}O_3$ (326.19) calc.: 349.1774

found: 349.1772 $[M+Na]^+$ (ESI-HRMS).

5.1.5 2-(3-(Benzyloxymethyl)-but-3-en-1-yl)-3-methoxy-5-methylphenol (287)



290 **287**

A solution of alkene **290** (7.05 g, 21.6 mmol, 1.00 eq.) in DMF (33 mL) was treated with sodium thioethanolate (3.64 g, 90%, 38.9 mmol, 1.80 eq.) and the resulting reaction mixture stirred at 120 °C for 16 h. Additional sodium thioethanolate (0.90 g, 90%, 9.63 mmol, 0.45 eq.) was added and stirring continued at 120 °C for further 5 h. After cooling to RT, the reaction mixture was poured into H_2O (200 mL) and the aq. phase extracted with Et_2O (4 × 100 mL). The combined organic phases were washed with H_2O (330 mL) and brine (160 mL). The combined aq. phases were extracted with Et_2O (50 mL), the combined organic phases dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc = 7:1) furnished alkenylphenol **287** as a colorless oil (5.88 g, 18.9 mmol, 87%, 92% brsm).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.26 (s, 3 H, 5-CH_3), 2.31 (t, *J* = 7.5 Hz, 2 H, 2'-H_2), 2.79 (t, *J* = 7.5 Hz, 2 H, 1'-H_2), 3.77 (s, 3 H, 3-OCH_3), 4.03 (s, 2 H, CH_2OBn), 4.58 (s, 2 H, OCH_2Ph), 4.80 (s, 1 H, 4'-H_a), 4.97 (s, 1 H, 4'-H_b), 6.20 (s, 1 H, OH), 6.26, 6.30 (2 × s, 2 H, 4-H, 6-H), 7.26–7.37 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.6 (5-CH_3), 22.2 (C-1'), 33.9 (C-2'), 55.5 (3-OCH_3), 72.7 (OCH_2Ph), 74.4 (CH_2OBn), 103.7, 109.5 (C-4, C-6), 112.7 (C-2), 114.3 (C-4'), 127.8 (Ph-C_p), 128.0, 128.4 (Ph-C_o, Ph-C_m), 137.0 (C-5), 137.7 (Ph-C_i), 144.9 (C-3'), 154.9 (C-1), 158.2 (C-3).

IR: $\tilde{\nu}$ (cm^{-1}) = 3362, 3065, 3030, 2934, 2857, 1737, 1708, 1650, 1616, 1592, 1510, 1498, 1453, 1416, 1346, 1314, 1262, 1221, 1192, 1160, 1091, 1028, 979, 904, 813, 736, 696, 609, 584, 561, 533.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.696), 271 (2.928).

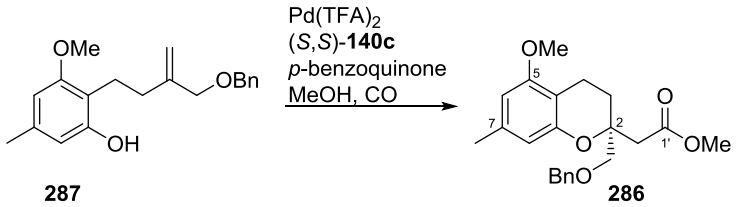
MS (ESI): *m/z* (%) = 313.2 (35) $[M+H]^+$, 335.2 (100) $[M+Na]^+$.

$C_{20}H_{24}O_3$ (312.41) calc.: 335.1618

found: 335.1616 $[M+Na]^+$ (ESI-HRMS).

5.2 Synthesis of vinyl chromane 285

5.2.1 Methyl-(2*S*)-2-(2-benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-acetate (286)



287 **286**

A solution of palladium(II)-trifluoracetate (2.7 mg, 8.1 μmol, 5 mol%) and *i*Bu-BOXAX (*S*,*S*)-**140c** (16.2 mg, 32.1 μmol, 20 mol%) in MeOH (0.5 mL) was stirred for 15 min at RT before being added to alkenylphenol **287** (50 mg, 160 μmol, 1.00 eq.) by a syringe (rinsing with 0.5 mL MeOH). *p*-Benzoquinone (71 mg. 640 μmol, 4.00 eq.) was added and the reaction mixture stirred under an CO atmosphere (1 atm) at RT for 24 h. The reaction mixture was poured into 1 M aq. HCl (10 mL) and the aq. layer extracted with MTBE (3 × 5 mL). The combined organic phases were washed with aq. 1 M NaOH (3 × 5 mL), dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc 25:1 → 10:1) furnished methyl ester **286** as a colorless oil that solidified under vacuum (40.5 mg, 109 μmol, 68%, 99% *ee*).

Optical Rotation: $[\alpha]_D$ = +0.9 (c = 0.18, $CHCl_3$, 22.9 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.01 (m_c, 2 H, 3-H_2), 2.26 (s, 3 H, 7-CH_3), 2.58 (m_c, 2 H, 4-H_2), 2.71 (d, *J* = 15.0 Hz, 1-H, 2'-H_a), 2.82 (d, *J* = 14.4 Hz, 1 H, 2'-H_b), 3.61 (s, 3 H, 1'-OCH_3), 3.65 (d, *J* = 3.0 Hz, 2 H, CH_2OBn), 3.78 (s, 3 H, 5-OCH_3), 4.53 (d, *J* = 12.0 Hz, 1 H, OCH_aPh), 4.61 (d, *J* = 12.0 Hz, 1 H, OCH_bPh), 6.23, 6.33 (2 × s, 2 H, 6-H, 8-H), 7.25–7.34 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.8 (C-4), 21.6 (7-CH_3), 26.2 (C-3), 39.3 (C-2'), 51.5 (1'-OCH_3), 55.4 (5-OCH_3), 72.7 (CH_2OBn), 73.6 (OCH_2Ph), 76.3 (C-2), 103.1, 110.4 (C-6, C-8), 107.2 (C-4a), 127.5, 127.6, 128.3 (Ph-C_o, Ph-C_m, Ph-C_p), 137.2 (C-7), 138.2 (Ph-C_i), 153.3, 157.5 (C-5, C-8a), 170.8 (C-1').

IR: $\tilde{\nu}$ (cm^{-1}) = 2923, 2885, 1728, 1579, 1316, 1223, 1094, 824, 750, 701.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.785), 272 (3.053), 279 (3.022).

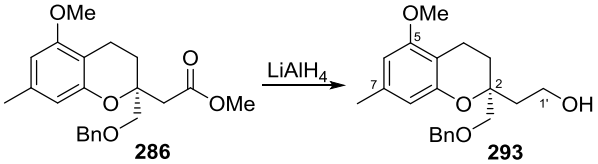
Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH = 98:2, 0.8 mL/min, 234 nm): t_R = 11.0 min (–)-(*R*)-**286**, 0.7%, t_R = 14.2 min (+)-(*S*)-**286**, 99.3%; 99% *ee*.

MS (ESI): *m/z* (%) = 763.3 (75) $[2M+Na]^+$, 393.2 (100) $[M+Na]^+$.

$C_{22}H_{26}O_5$ (370.44) calc.: 393.1672

found: 393.1677 $[M+Na]^+$ (ESI-HRMS).

5.2.2 (2*S*)-2-(2-Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-ethan-1-ol (293)



A solution of chromanyl ester **286** (1.48 g, 4.00 mmol, 1.00 eq.) in Et_2O (30 mL) was treated with $LiAlH_4$ (167 mg, 4.40 mmol, 1.10 eq.) at 0 °C. The reaction mixture was stirred at RT for 2 h before being quenched by careful addition of H_2O (100 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 50 mL), the combined organic layers were dried over Na_2SO_4 and the volatiles removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 5:1) furnished chromanyl alcohol **293** as a colorless oil (1.37 g, 3.99 mmol, quant.).

Optical Rotation: $[\alpha]_D$ = –2.3 (c = 0.50, $CHCl_3$, 24.4 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.83 (ddd, *J* = 14.2, 8.3, 6.5 Hz, 1 H, 3-H_a), 1.93–2.08 (m, 3 H, 2'-H_2, 3-H_b), 2.25 (s, 3 H, 7-CH_3), 2.44–2.66 (m, 3 H, 4-H_2, 1'-OH), 3.51 (d, *J* = 9.6 Hz, 1 H, CH_aOBn), 3.56 (d, *J* = 9.6 Hz, 1 H, CH_bOBn), 3.76–3.80 (m, 2 H, 1'-H_2), 3.78 (s, 3 H, 5-OCH_3), 4.56 (d, *J* = 12.0 Hz, 1 H, OCH_aPh), 4.57 (d, *J* = 12.0 Hz, 1 H, OCH_bPh), 6.23, 6.28 (2 × s, 2 H, 6-H, 8-H), 7.25–7.36 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.8 (C-4), 21.6 (7-CH_3), 27.0 (C-3), 38.7 (C-2'), 55.4 (5-OCH_3), 58.6 (C-1'), 72.4 (CH_2OBn), 73.8 (OCH_2Ph), 77.4 (C-2), 103.1, 110.2 (C-6, C-8), 107.2 (C-4a), 127.7, 128.4 (Ph-C_o, Ph-C_m), 127.8 (Ph-C_p), 137.3, 137.7 (C-7, Ph-C_i), 153.3, 157.6 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3395, 2930, 2856, 1617, 1584, 1497, 1454, 1413, 1352, 1291, 1228, 1136, 1101, 1025, 813, 736, 697, 578.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.721), 272 (3.048).

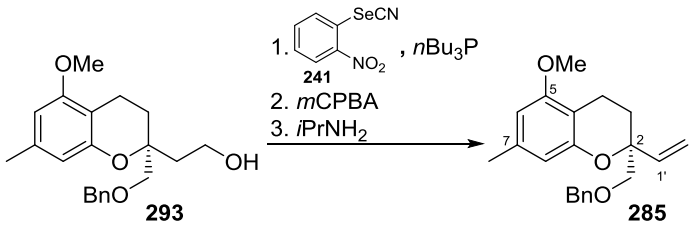
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 99:1, 0.8 mL/min): t_R = 13.0 min.

MS (ESI): *m*/*z* (%) = 707.4 (100) $[2M+Na]^+$, 685.4 (15) $[2M+H]^+$, 365.2 (91) $[M+Na]^+$, 343.2 (58) $[M+H]^+$.

$C_{21}H_{26}O_4$ (342.43) calc.: 343.1904

found: 343.1899 $[M+H]^+$ (ESI-HRMS).

5.2.3 (2*S*)-2-Benzyloxymethyl-5-methoxy-7-methyl-2-vinyl chromane (285)



A solution of chromanyl alcohol **293** (1.38 g, 4.03 mmol, 1.00 eq.) in THF (50 mL) was treated with *o*-nitrophenyl selenocyanate (**241**) (1.83 g, 8.06 mmol, 2.00 eq.) and nBu$_3$P (2.00 mL, 7.70 mmol, 1.91 eq.) at 0 °C and stirred at this temperature for 1.5 h. Additional 2-nitrophenyl selenocyanate (**241**) (458 mg, 2.02 mmol, 0.50 eq.) and nBu$_3$P (0.50 mL, 1.93 mmol, 0.48 eq.) was added at 0 °C and stirring continued at this temperature for 2.5 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (180 mL) at 0 °C and the aq. layer extracted with MTBE (5 × 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. A suspension of the crude product in CH_2Cl_2 (80 mL) was treated with $Na_2HPO_4 \cdot 2\ H_2O$ (3.59 g, 20.2 mmol, 5.00 eq.) and *m*CPBA (2.48 g, 70%, 10.1 mmol, 2.50 eq.) at –40 °C and stirred at this temperature for 1 h. Diisopropylamine (2.82 mL, 20.2 mmol, 5.00 eq.) was added at –40 °C and the reaction mixture warmed to RT in 15 h. The reaction mixture was adsorbed on silica gel and the solvent removed under reduced pressure. Column chromatography on silica gel (*n*-pentane/EtOAc = 100:0 → 90:10) furnished vinyl chromane **285** as a yellow oil (1.18 g, 3.62 mmol, 90%).

Optical Rotation: $[\alpha]_D$ = –72.0 (c = 0.50, $CHCl_3$, 23.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.91 (ddd, *J* = 13.6, 6.1, 4.0 Hz, 1 H, 3-H_a), 1.99 (ddd, *J* = 13.6, 11.0, 5.6 Hz, 1 H, 3-H_b), 2.28 (s, 3 H, 7-CH_3), 2.39 (ddd, *J* = 17.1, 10.9, 6.2 Hz, 1 H, 4-H_a), 2.68 (dt, *J* = 16.8, 4.8 Hz, 1 H, 4-H_b), 3.52 (d, *J* = 10.0 Hz, 1 H, CH_aOBn), 3.57 (d, *J* = 10.0 Hz, 1 H, CH_bOBn), 3.77 (s, 3 H, 5-OCH_3), 4.60 (d, *J* = 12.3 Hz, 1 H,

OCH_aPh), 4.63 (d, *J* = 12.3 Hz, 1 H, OCH_bPh), 5.16 (dd, *J* = 10.9, 1.4 Hz, 1 H, 2'-H_{cis}), 5.25 (dd, *J* = 17.3, 1.4 Hz, 1 H, 2'-H_{trans}), 5.84 (dd, *J* = 17.3, 10.9 Hz, 1 H, 1'-H), 6.22, 6.41 (2 × s, 2 H, 6-H, 8-H), 7.27 (m_c, 1 H, Ph-H_p), 7.32 (m_c, 4 H, Ph-H_o, Ph-H_m).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 16.0 (C-4), 21.6 (7-CH_3), 26.6 (C-3), 55.3 (5-OCH_3), 73.6 (OCH_2Ph), 75.5 (CH_2OBn), 78.7 (C-2), 102.8, 110.0 (C-6, C-8), 107.7 (C-4a), 116.1 (C-2'), 127.5 (Ph-C_p), 127.6, 128.3 (Ph-C_o, Ph-C_m), 136.9 (C-7), 137.9 (C-1'), 138.4 (Ph-C_i), 154.1, 157.4 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 2932, 2854, 1616, 1584, 1497, 1453, 1410, 1351, 1320, 1291, 1227, 1196, 1135, 1099, 1026, 991, 927, 812, 734, 696, 580, 550.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.690), 271 (2.978).

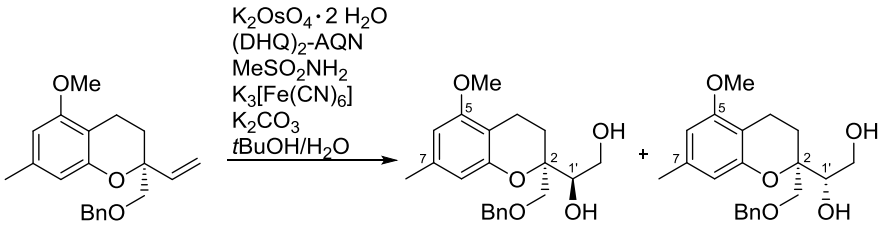
MS (ESI): *m*/*z* (%) = 671.3 (86) $[2M+Na]^+$, 666.4 (56) $[2M+NH_4]^+$, 347.2 (48) $[M+Na]^+$, 342.2 (13) $[M+NH_4]^+$, 325.2 (100) $[M+H]^+$.

$C_{21}H_{24}O_3$ (324.41) calc.: 325.1798

found: 325.1796 $[M+H]^+$ (ESI-HRMS).

5.3 Syntheses of the chromanones *anti*-284 and *syn*-284

5.3.1 (1'*R*,2*R*)-1-(2-Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-ethan-1,2-diol (*anti*-294) and (1'*S*,2*R*)-1-(2-Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-ethan-1,2-diol (*syn*-294)



A solution of **285** (376 mg, 1.16 mmol, 1.00 eq.) in *t*BuOH/H_2O (5.8 mL/5.8 mL) was treated with $K_2OsO_4 \cdot 2\ H_2O$ (21.3 mg, 58.0 µmol, 5 mol%), $(DHQ)_2$-AQN (143 mg, 159 µmol, 10 mol%), $K_3[Fe(CN)_6]$ (2.29 g, 6.95 mmol, 6.00 eq.) and K_2CO_3 (961 mg, 6.95 mmol, 6.00 eq.) at RT. After stirring at RT for 3 d, the reaction was quenched by addition of sat. aq. $NaHSO_3$ solution (20 mL) at 0 °C and stirring was continued at RT for 30 min. The aq. layer was extracted with EtOAc (3 × 10 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. After column chromatography on silica gel

(*n*-pentane/EtOAc = 5:1 → 1:1) the diastereomeric mixture was obtained as a colorless oil (320 mg, 894 μmol, 77%, d.r. = 13.7:1 (*anti*/*syn*)). The diastereomeric alcohols *anti*-**294** and *syn*-**294** can be separated by chiral HPLC (*Daicel* Chiralpak IB®, 10 × 250 mm, 7 μm, *n*-hexane/2-PrOH = 96:4, 7 mL/min).

Analytical data of *anti*-**294**:

Optical Rotation: $[\alpha]_D$ = +2.8 (c = 0.50, $CHCl_3$, 23.0 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.00 (m_c, 2 H, 3-H_2), 2.26 (s, 3 H, 7-CH_3), 2.47 (dt, *J* = 16.8, 7.9 Hz, 1 H, 4-H_a), 2.69 (dt, *J* = 17.4, 5.7 Hz, 1 H, 4-H_b), 2.74 (s_{br}, 1 H, 2'-OH), 2.99 (d, *J* = 6.8 Hz, 1 H, 1'-OH), 3.57 (d, *J* = 10.0 Hz, 1 H, CH_aOBn), 3.64 (d, *J* = 10.0 Hz, 1 H, CH_bOBn), 3.76–3.83 (m, 2 H, 2'-H_2), 3.78 (s, 3 H, 5-OCH_3), 3.85 (q, *J* = 5.8 Hz, 1 H, 1'-H), 4.47 (d, *J* = 11.8 Hz, 1 H, OCH_aPh), 4.56 (d, *J* = 11.8 Hz, 1 H, OCH_bPh), 6.24, 6.30 (2 × s, 2 H, 6-H, 8-H), 7.27–7.34 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.4 (C-4), 21.6 (7-CH_3), 23.5 (C-3), 55.4 (5-OCH_3), 61.9 (C-2'), 70.2 (CH_2OBn), 74.0 (OCH_2Ph), 74.2 (C-1'), 77.6 (C-2), 103.3, 110.0 (C-6, C-8), 107.4 (C-4a), 127.7, 128.5 (Ph-C_o, Ph-C_m), 127.9 (Ph-C_p), 137.2, 137.3 (C-7, Ph-C_i), 153.1, 157.5 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3399, 2924, 2855, 1618, 1584, 1497, 1453, 1413, 1352, 1291, 1223, 1139, 1098, 1073, 1026, 951, 814, 775, 736, 697, 576.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.743), 271 (3.095).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 22.6 min.

Preparative HPLC (*Daicel* Chiralpak IB®, 10 × 250 mm, 7 μm, *n*-hexane/2-PrOH 96:4, 7 mL/min, 210 nm): t_R = 14.7 min.

MS (ESI): *m*/*z* (%) = 739.4 (100) $[2M+Na]^+$, 717.4 (6) $[2M+H]^+$, 381.2 (32) $[M+Na]^+$, 359.2 (48) $[M+H]^+$.

$C_{21}H_{26}O_5$ (358.43) calc.: 359.1853

found: 359.1852 $[M+H]^+$ (ESI-HRMS).

Analytical data of *syn*-**294**:

Optical Rotation: $[\alpha]_D$ = +7.5 (c = 0.50, $CHCl_3$, 22.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.83 (ddd, *J* = 13.8, 11.0, 6.1 Hz, 1 H, 3-H_a), 2.13 (ddd, *J* = 13.9, 6.3, 3.6 Hz, 1 H, 3-H_b), 2.25 (s, 3 H, 7-CH_3), 2.41 (ddd, *J* = 17.3, 11.0, 6.3 Hz, 1 H, 4-H_a), 2.56 (s_{br}, 1 H, 2'-OH), 2.69 (ddd, *J* = 17.3, 6.2, 3.7 Hz, 1 H, 4-H_b), 2.96 (s_{br}, 1 H,

1'-OH), 3.52 (d, J = 9.7 Hz, 1 H, CH_aOBn), 3.66 (d, J = 9.7 Hz, 1 H, CH_bOBn), 3.75 (dd, J = 11.9, 4.1 Hz, 1 H, 2'-H_a), 3.78 (s, 3 H, 5-OCH_3), 3.80 (dd, J = 11.7, 6.2 Hz, 1 H, 2'-H_b), 3.91 (dd, J = 6.1, 3.9 Hz, 1 H, 1'-H), 4.46 (d, J = 11.8 Hz, 1 H, OCH_aPh), 4.52 (d, J = 11.8 Hz, 1 H, OCH_bPh), 6.24, 6.31 (2 × s, 2 H, 6-H, 8-H), 7.26–7.34 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 15.5 (C-4), 21.6 (7-CH_3), 23.1 (C-3), 55.4 (5-OCH_3), 62.3 (C-2'), 69.1 (CH_2OBn), 73.9 (OCH_2Ph), 75.4 (C-1'), 78.2 (C-2), 103.3, 110.1 (C-6, C-8), 107.2 (C-4a), 127.7, 128.5 (Ph-C_o, Ph-C_m), 128.0 (Ph-C_p), 137.3, 137.4 (C-7, Ph-C_i), 153.0, 157.5 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3385, 2923, 2855, 1618, 1585, 1497, 1454, 1413, 1353, 1292, 1224, 1197, 1149, 1100, 1074, 1026, 952, 815, 736, 698, 577.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.748), 271 (3.344).

Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 27.5 min.

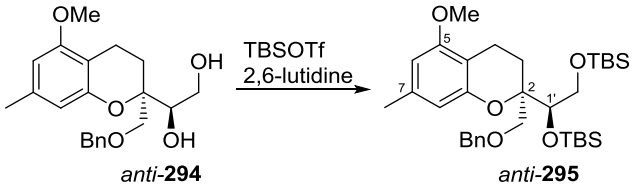
Preparative HPLC (*Daicel* Chiralpak IB®, 10 × 250 mm, 7 µm, *n*-hexane/2-PrOH 96:4, 7 mL/min, 210 nm): t_R = 19.7 min.

MS (ESI): *m*/*z* (%) = 739.4 (100) $[2M+Na]^+$, 717.4 (3) $[2M+H]^+$, 381.2 (38) $[M+Na]^+$, 359.2 (40) $[M+H]^+$.

$C_{21}H_{26}O_5$ (358.43) calc.: 359.1853

found: 359.1856 $[M+H]^+$ (ESI-HRMS).

5.3.2 (1'*R*,2*R*)-1-(2-Benzyloxymethyl-5-methoxy-7-methyl-chroman-2-yl)-1,2-(bis-*tert*-butyldimethylsilyloxy)-ethane (*anti*-295)



anti-**294** *anti*-**295**

A solution of diol *anti*-**294** (158 mg, 441 µmol, 1.00 eq.) in CH_2Cl_2 (9 mL) was treated with 2,6-lutidine (0.21 mL, 2.21 mmol, 5.00 eq.) and TBSOTf (0.42 mL, 76.0 mmol, 4.00 eq.) at 0 °C. After stirring at 0 °C for 2.5 h, the reaction was quenched by careful addition of sat. aq. $NaHCO_3$ solution (30 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. After column chromatography on silica gel (*n*-pentane/EtOAc = 50:1) *anti*-**295** was obtained as a colorless oil (249 mg, 424 µmol, 96%).

Optical Rotation: $[\alpha]_D$ = +9.5 (c = 0.50, $CHCl_3$, 22.8 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = –0.04, –0.03, 0.04, 0.09 (4 × s, 12 H, 1'-Si(CH_3)$_2$, 2'-Si(CH_3)$_2$), 0.84 (s, 18 H, 1'-SiC(CH_3)$_3$, 2'-SiC(CH_3)$_3$), 1.96 (dt, *J* = 13.8, 6.8 Hz, 1 H, 3-H_a), 2.01 (dt, *J* = 13.9, 6.9 Hz, 1 H, 3-H_b), 2.25 (s, 3 H, 7-CH_3), 2.52 (q, *J* = 6.9 Hz, 2 H, 4-H_2), 3.60 (s, 2 H, CH_2OBn), 3.61 (dd, *J* = 10.8, 6.6 Hz, 1 H, 2'-H_a), 3.78 (s, 3 H, 5-OCH_3), 3.87 (dd, *J* = 6.6, 2.0 Hz, 1 H, 1'-H), 3.97 (dd, *J* = 10.7, 2.0 Hz, 1 H, 2'-H_b), 4.48 (d, *J* = 12.1 Hz, 1 H, OCH_aPh), 4.52 (d, *J* = 12.1 Hz, 1 H, OCH_bPh), 6.20, 6.31 (2 × s, 2 H, 6-H, 8-H), 7.22–7.30 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.4, –5.4, –4.9, –4.0 (1'-Si(CH_3)$_2$, 2'-Si(CH_3)$_2$), 15.6 (C-4), 18.3, 18.4 (1'-SiC, 2'-SiC), 21.6 (7-CH_3), 22.2 (C-3), 26.0, 26.1 (1'-SiC($\underline{C}H_3$)$_3$, 2'-SiC($\underline{C}H_3$)$_3$), 55.4 (5-OCH_3), 64.9 (C-2'), 70.8 (CH_2OBn), 73.6 (OCH_2Ph), 76.4 (C-1'), 79.7 (C-2), 102.7, 110.5 (C-6, C-8), 107.4 (C-4a), 127.4 (Ph-C_p), 127.5, 128.2 (Ph-C_o, Ph-C_m), 136.8, 138.5 (C-7, Ph-C_i), 153.9, 157.4 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 2927, 2854, 1619, 1586, 1462, 1414, 1354, 1251, 1226, 1107, 1005, 830, 812, 775, 733, 696, 664, 576.

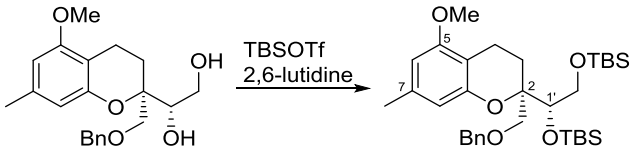
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.766), 272 (3.369).

MS (ESI): *m*/*z* (%) = 1195.6 (16) $[2M+Na]^+$, 609.4 (100) $[M+Na]^+$, 604.4 (64) $[M+NH_4]^+$, 587.4 (77) $[M+H]^+$.

$C_{33}H_{54}O_5Si_2$ (586.95) calc.: 587.3583

found: 587.3583 $[M+H]^+$ (ESI-HRMS).

5.3.3 (1'*S*,2*R*)-1-(2-Benzyloxymethyl-5-methoxy-7-methoxy-chroman-2-yl)-1,2-(bis-*tert*-butyldimethylsilyloxy)-ethane (*syn*-294)



syn-**294** *syn*-**295**

A solution of diol *syn*-**294** (239 mg, 667 μmol, 1.00 eq.) in CH_2Cl_2 (13 mL) was treated with 2,6-lutidine (0.39 mL, 3.33 mmol, 5.00 eq.) and TBSOTf (0.63 mL, 2.67 mmol, 4.00 eq.) at 0 °C. After stirring at 0 °C for 2.5 h, the reaction was quenched by careful addition of sat. aq. $NaHCO_3$ solution (30 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*.

After column chromatography on silica gel (*n*-pentane/EtOAc = 50:1) *syn*-**295** was obtained as a colorless oil (385 mg, 656 μmol, 98%).

Optical Rotation: $[\alpha]_D = -10.1$ (c = 0.51, $CHCl_3$, 22.8 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.02, 0.06, 0.07 (3 × s, 12 H, 1'-Si(CH_3)$_2$, 2'-Si(CH_3)$_2$), 0.87, 0.88 (2 × s, 18 H, 1'-SiC(CH_3)$_3$, 2'-SiC(CH_3)$_3$), 1.70 (ddd, *J* = 13.8, 10.5, 6.1 Hz, 1 H, 3-H_a), 2.10 (ddd, *J* = 13.9, 6.2, 4.5 Hz, 1 H, 3-H_b), 2.25 (s, 3 H, 7-CH_3), 2.42 (ddd, *J* = 17.0, 10.3, 6.3 Hz, 1 H, 4-H_a), 2.62 (dt, *J* = 17.1, 5.3 Hz, 1 H, 4-H_b), 3.49 (d, *J* = 9.9 Hz, 1 H, CH_aOBn), 3.61 (dd, *J* = 10.6, 6.7 Hz, 1 H, 2'-H_a), 3.73 (d, *J* = 9.8 Hz, 1 H, CH_bOBn), 3.77 (s, 3 H, 5-OCH_3), 3.90 (dd, *J* = 10.6, 3.0 Hz, 1 H, 2'-H_b), 3.97 (dd, *J* = 6.7, 3.0 Hz, 1 H, 1'-H), 4.46 (s, 2 H, OCH_2Ph), 6.20, 6.29 (2 × s, 2 H, 6-H, 8-H), 7.20–7.28 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.3, –4.9, –4.2, –3.0 (1'-Si(CH_3)$_2$, 2'-Si(CH_3)$_2$), 15.8 (C-4), 18.4, 18.5 (1'-SiC, 2'-SiC), 21.7 (7-CH_3), 23.3 (C-3), 26.1 (1'-SiC($\underline{C}H_3$)$_3$, 2'-SiC($\underline{C}H_3$)$_3$), 55.4 (5-OCH_3), 65.3 (C-2'), 68.9 (CH_2OBn), 73.4 (OCH_2Ph), 77.0 (C-1'), 79.3 (C-2), 102.6, 110.3 (C-6, C-8), 107.6 (C-4a), 127.2 (Ph-C_p), 127.3, 128.2 (Ph-C_o, Ph-C_m), 136.9, 138.6 (C-7, Ph-C_i), 153.8, 157.4 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 2928, 2855, 1619, 1586, 1462, 1353, 1253, 1101, 960, 833, 813, 777, 735, 697, 666.

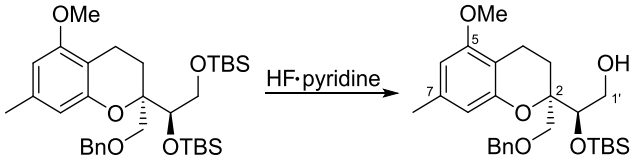
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.764), 272 (3.253).

MS (ESI): *m*/*z* (%) = 1195.7 (20) $[2M+Na]^+$, 1190.8 (20) $[2M+NH_4]^+$, 609.4 (100) $[M+Na]^+$, 604.8 (26) $[M+NH_4]^+$, 587.4 (61) $[M+H]^+$.

$C_{33}H_{54}O_5Si_2$ (586.95) calc.: 587.3583

found: 587.3583 $[M+H]^+$ (ESI-HRMS).

5.3.4 (2*R*,2'*R*)-2-(2-Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-2-(*tert*-butyldimethylsilyloxy)-ethan-1-ol (*anti*-296)



anti-**295** *anti*-**296**

A solution of *anti*-**295** (235 mg, 400 μmol, 1.00 eq.) in THF (7 mL) and pyridine (1.5 mL) was treated with HF·pyridine (0.42 mL, 70% HF, 16.0 mmol, 40.0 eq.) at 0 °C and the

resulting mixture stirred at RT for 24 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ solution (10 mL) and H_2O (20 mL) at 0 °C. The aq. layer was extracted with EtOAc (3×10 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 10:1 → 1:1) yielded alcohol *anti*-**296** as a colorless oil (160 mg, 338 μmol, 85%, 97% brsm).

Optical Rotation: $[\alpha]_D$ = +0.9 (c = 0.51, $CHCl_3$, 22.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.05 (s, 3 H, $Si(CH_3)_a$), 0.14 (s, 3 H, $Si(CH_3)_b$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.96 (d, *J* = 5.7 Hz, 1 H, 3-H_a), 1.97 (d, *J* = 5.4 Hz, 1 H, 3-H_b), 2.26 (s, 3 H, 7-CH_3), 2.42 (dt, *J* = 17.0, 8.4 Hz, 1 H, 4-H_a), 2.59 (s_{br}, 1 H, 1'-OH), 2.63 (dt, *J* = 17.3, 5.5 Hz, 1 H, 4-H_b), 3.54 (d, *J* = 10.7 Hz, 1 H, CH_aOBn), 3.59 (d, *J* = 10.7 Hz, 1 H, CH_bOBn), 3.67 (dd, *J* = 11.4, 4.2 Hz, 1 H, 1'-H_a), 3.75 (dd, *J* = 11.8, 4.6 Hz, 1 H, 1'-H_b), 3.78 (s, 3 H, 5-OCH_3), 3.99 (t, *J* = 5.0 Hz, 1 H, 2'-H), 4.45 (d, *J* = 11.9 Hz, 1 H, OCH_aPh), 4.52 (d, *J* = 11.9 Hz, 1 H, OCH_bPh), 6.22, 6.30 (2 × s, 2 H, 6-H, 8-H), 7.25–7.31 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.6 ($Si(CH_3)_a$), –4.4 ($Si(CH_3)_b$), 15.5 (C-4), 18.2 (SiC), 21.7 (7-CH_3), 21.8 (C-3), 25.9 ($SiC(CH_3)_3$), 55.3 (5-OCH_3), 63.1 (C-1'), 70.1 (CH_2OBn), 73.9 (OCH_2Ph), 75.6 (C-2'), 79.7 (C-2), 102.9, 110.3 (C-6, C-8), 107.2 (C-4a), 127.7, 128.4 (Ph-C_o, Ph-C_m), 127.7 (Ph-C_p), 137.0, 137.7 (C-7, Ph-C_i), 153.5, 157.4 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3462, 2927, 1618, 1585, 1461, 1413, 1353, 1249, 1225, 1027, 955, 831, 813, 776, 736, 697, 577.

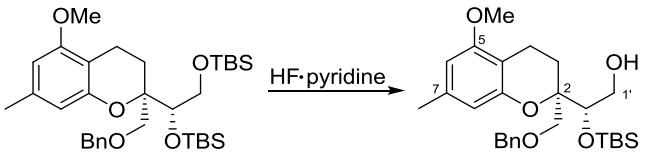
UV (CH_3CN): λ_{max} (nm) (lg ε) = 272 (3.065).

MS (ESI): *m*/*z* (%) = 967.6 (100) $[2M+Na]^+$, 945.6 (35) $[2M+H]^+$, 495.3 (90) $[M+Na]^+$, 473.3 (84) $[M+H]^+$.

$C_{27}H_{40}O_5Si$ (472.69) calc.: 473.2718

found: 473.2711 $[M+H]^+$ (ESI-HRMS).

5.3.5 (2*R*,2'*S*)-2-(2-Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-2-(*tert*-butyldimethylsilyloxy)-ethan-1-ol (*syn*-296)



syn-**295** *syn*-**296**

A solution of *syn*-**295** (374 mg, 637 μmol, 1.00 eq.) in THF (11 mL) and pyridine (2.4 mL) was treated with HF·pyridine (0.64 mL, 70% HF, 25.5 mmol, 40.0 eq.) at 0 °C and the resulting mixture stirred at RT for 30 h. The reaction was quenched carefully with sat. aq. $NaHCO_3$ solution (10 mL) and H_2O (20 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 10 mL), the combined organic extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 10:1 → 1:1) yielded alcohol *syn*-**296** as a colorless oil (244 mg, 516 μmol, 81%, 89% brsm).

Optical Rotation: $[\alpha]_D$ = –1.5 (c = 0.51, $CHCl_3$, 22.6 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, $Si(CH_3)_a$), 0.12 (s, 3 H, $Si(CH_3)_b$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.76 (ddd, *J* = 13.8, 10.7, 6.2 Hz, 1 H, 3-H_a), 2.08 (ddd, *J* = 13.7, 6.2, 4.0 Hz, 1 H, 3-H_b), 2.26 (s, 3 H, 7-CH_3), 2.42 (ddd, *J* = 17.2, 10.7, 6.2 Hz, 1 H, 4-H_a), 2.65 (ddd, *J* = 17.4, 5.9, 4.3 Hz, 1 H, 4-H_b), 3.41 (d, *J* = 9.6 Hz, 1 H, CH_aOBn), 3.69 (dd, *J* = 11.8, 4.3 Hz, 1 H, 1'-H_a), 3.69–3.81 (m, 2 H, 1'-H_b, CH_bOBn), 3.76 (s, 3 H, 5-OCH_3), 3.99 (t, *J* = 4.7 Hz, 1 H, 2'-H), 4.48 (s, 2 H, OCH_2Ph), 6.22, 6.28 (2 × s, 2 H, 6-H, 8-H), 7.21–7.32 (m, 5 H, 5 × Ph-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = –4.7, ($Si(CH_3)_a$), –4.5 ($Si(CH_3)_b$), 15.7 (C-4), 18.3 (SiC), 21.7 (7-CH_3), 23.3 (C-3), 26.0 ($SiC(\underline{C}H_3)_3$), 55.4 (5-OCH_3), 63.2 (C-1'), 67.9 (CH_2OBn), 73.6 (OCH_2Ph), 75.9 (C-2'), 79.6 (C-2), 103.0, 110.1 (C-6, C-8), 107.3 (C-4a), 127.5, 128.3 (Ph-C_o, Ph-C_m), 127.6 (Ph-C_p), 137.2, 137.8 (C-7, Ph-C_i), 153.3, 157.5 (C-5, C-8a).

IR: $\tilde{\nu}$ (cm^{-1}) = 3446, 2927, 2854, 1618, 1585, 1497, 1461, 1413, 1353, 1248, 1221, 1104, 1027, 952, 831, 813, 776, 734, 696, 576.

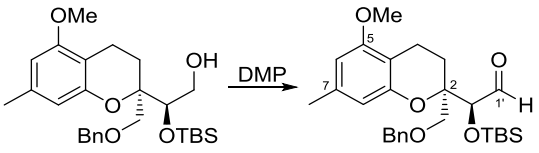
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.762).

MS (ESI): *m*/*z* (%) = 967.6 (70) $[2M+Na]^+$, 495.3 (58) $[M+Na]^+$, 473.3 (100) $[M+H]^+$.

$C_{27}H_{40}O_5Si$ (472.69) calc.: 473.2718

found: 473.2719 $[M+H]^+$ (ESI-HRMS).

5.3.6 (2*S*,2'*R*)-2-(2-Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-2-(*tert*-butyldimethylsilyloxy)-acetaldehyde (*anti*-297)



anti-**296** *anti*-**297**

A solution of alcohol *anti*-**296** (157 mg, 332 μmol, 1.00 eq.) in CH_2Cl_2 (6.6 mL) was treated with DMP (282 mg, 664 μmol, 2.00 eq.) at 0 °C and the reaction mixture stirred at RT for 2 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (25 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 8 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the organic solvent and column chromatography on silica gel (*n*-pentane/EtOAc = 10:1) aldehyde *anti*-**297** was obtained as a colorless oil (150 mg, 319 μmol, 96%).

Optical Rotation: $[\alpha]_D$ = +39.8 (c = 0.50, $CHCl_3$, 23.7 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.03 (s, 3 H, $Si(CH_3)_a$), 0.15 (s, 3 H, $Si(CH_3)_b$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.82 (dt, *J* = 13.9, 7.1 Hz, 1 H, 3-H_a), 1.96 (dt, *J* = 13.3, 6.5 Hz, 1 H, 3-H_b), 2.28 (s, 3 H, 7-CH_3), 2.56 (t, *J* = 6.8 Hz, 2 H, 4-H_2), 3.53 (d, *J* = 10.5 Hz, 1 H, CH_aOBn), 3.62 (d, *J* = 10.5 Hz, 1 H, CH_bOBn), 3.78 (s, 3 H, 5-OCH_3), 4.07 (s, 1 H, 2'-H), 4.43 (d, *J* = 12.2 Hz, 1 H, OCH_aPh), 4.52 (d, *J* = 12.2 Hz, 1 H, OCH_bPh), 6.25, 6.40 (2 × s, 2 H, 6-H, 8-H), 7.21–7.35 (m, 5 H, 5 × Ph-H), 9.83 (d, *J* = 0.7 Hz, 1 H, 1'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.2 ($Si(CH_3)_a$), –4.1, $Si(CH_3)_b$), 15.4 (C–4), 18.3 (SiC), 21.6 (7-CH_3), 23.7 (C-3), 25.8 ($SiC(\underline{C}H_3)_3$), 55.4 (5-OCH), 70.4 (CH_2OBn), 73.7 (OCH_2Ph), 78.1 (C-2'), 80.8 (C-2), 103.3, 110.3 (C-6, C-8), 106.8 (C-4a), 127.5 (Ph-C_p), 127.8, 128.3 (Ph-C_o, Ph-C_m), 137.5, 137.9 (C-7, Ph-C_i), 153.1, 157.5 (C-5, C-8a), 200.0 (C-1').

IR: $\tilde{\nu}$ (cm^{-1}) = 2927, 2854, 1732, 1619, 1586, 1497, 1462, 1414, 1353, 1252, 1219, 1158, 1100, 1005, 892, 836, 815, 778, 735, 697, 577.

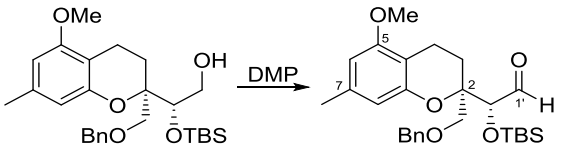
UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.751), 271 (3.185).

MS (ESI): *m*/*z* (%) = 963.5 (55) $[2M+Na]^+$, 493.3 (100) $[M+Na]^+$, 488.3 (48) $[M+NH4]^+$, 471.3 (97) $[M+H]^+$.

$C_{27}H_{38}O_5Si$ (470.67) calc.: 471.2561

found: 471.2557 $[M+H]^+$ (ESI-HRMS).

5.3.7 (2*R*,2'*R*)-2-(Benzyloxymethyl-5-methoxy-7-methylchroman-2-yl)-2-(*tert*-butyldimethylsilyloxy)-acetaldehyde (*syn*-297)



syn-**296** *syn*-**297**

A solution of alcohol *syn*-**296** (243 mg, 514 μmol, 1.00 eq.) in CH_2Cl_2 (10.3 mL) was treated with DMP (436 mg, 1.03 mmol, 2.00 eq.) at 0 °C and the reaction mixture stirred at RT for 2 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (25 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 8 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the organic solvents *in vacuo* and column chromatography on silica gel (*n*-pentane/EtOAc = 10:1) aldehyde *syn*-**297** was obtained as a colorless oil (236 mg, 501 μmol, 98%).

Optical Rotation: $[\alpha]_D$ = –23.5 (c = 0.51, $CHCl_3$, 23.5 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 0.01 (s, 3 H, $Si(CH_3)_a$), 0.04 (s, 3 H, $Si(CH_3)_b$), 0.92 (s, 9 H, $SiC(CH_3)_3$), 1.90–2.07 (m, 2 H, 3-H_2), 2.25 (s, 3 H, 7-CH_3), 2.41–2.51 (m, 1 H, 4-H_a), 2.70 (dt, *J* = 17.5, 6.1 Hz, 1 H, 4-H_b), 3.38 (d, *J* = 9.0 Hz, 1 H, CH_aOBn), 3.77 (s, 3 H, 5-OCH_3), 3.79 (d, *J* = 9.0 Hz, 1 H, CH_bOBn), 4.15 (d, *J* = 1.8 Hz, 1 H, 2'-H), 4.51 (s, 2 H, OCH_2Ph), 6.22, 6.26 (2 × s, 2 H, 6-H, 8-H), 7.22–7.36 (m, 5 H, 5 × Ph-H), 9.57 (d, *J* = 1.7 Hz, 1 H, 1'-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.9 ($Si(CH_3)_a$, –4.9 ($Si(CH_3)_b$), 15.5 (C-4), 18.3 (SiC), 21.6 (7-CH_3), 23.7 (C-3), 25.8 ($SiC(\underline{C}H_3)_3$), 55.4 (5-OCH_3), 68.4 (CH_2OBn), 73.6 (OCH_2Ph), 79.5 (C-2'), 79.6 (C-2), 103.2, 110.1 (C-6, C-8), 107.4 (C-4a), 127.4, 128.4 (Ph-C_o, Ph-C_m), 127.6 (Ph-C_p), 137.2, 137.9 (C-7, Ph-C_i), 153.1, 157.5 (C-5, C-8a), 202.0 (C-1').

IR: $\tilde{\nu}$ (cm^{-1}) = 2927, 2855, 1732, 1619, 1586, 1462, 1413, 1354, 1253, 1218, 1105, 1026, 1006, 864, 836, 814, 779, 735, 697, 577.

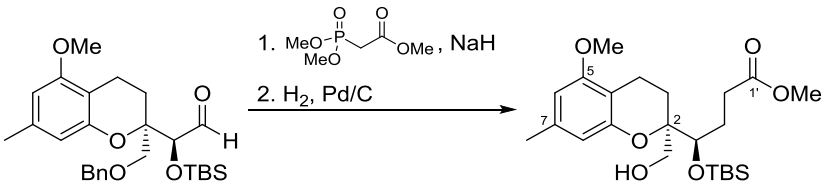
UV (CH_3CN): λ_{max} (nm) (lg ε) = 206 (4.747), 271 (3.139).

MS (ESI): *m*/*z* (%) = 963.5 (38) $[2M+Na]^+$, 493.3 (47) $[M+Na]^+$, 471.3 (100) $[M+H]^+$.

$C_{27}H_{38}O_5Si$ (470.67) calc.: 471.2561

found: 471.2560 $[M+H]^+$ (ESI-HRMS).

5.3.8 (2*R*,4'*R*)-4-(*tert*-Butyldimethysilyloxy)-4-(2-hydroxymethyl-5-methoxy-7-methylchroman-2-yl)-methyl butanoate (*anti*-298)



anti-**297** *anti*-**298**

A solution of trimethyl phosphonoacetate (0.20 mL, 1.21 mmol, 1.68 eq.) in THF (4 mL) was treated with sodium hydride (37.6 mg, 60% (w/w) in mineral oil, 939 μmol, 1.30 eq.) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before a solution of aldehyde *anti*-**297** (340 mg, 722 μmol, 1.00 eq.) in THF (10 mL) was added dropwise at 0 °C. After complete addition the mixture was stirred at RT for further 2 h before being quenched with sat. aq. NH_4Cl solution (50 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 20 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude product was filtered through a pad of silica gel (*n*-pentane/EtOAc = 9:1) and the solvent removed *in vacuo*. Palladium on charcoal (77 mg, 10% Pd, 72.2 μmol, 10 mol%) was added to a solution of the unsaturated crude product in MeOH (7 mL) in a *Parr*-flask. Hydrogen was passed through the resulting mixture for 30 min before being shaken under a H_2 atmosphere (4 bar) in a *Parr* apparatus at RT for further 48 h. The catalyst was removed by filtration through a syringe filter (rinsing with MeOH). After evaporation of the solvent *in vacuo* and column chromatography on silica gel (*n*-pentane/EtOAc = 9:1), the saturated ester *anti*-**298** was obtained as a colorless oil (284 mg, 647 μmol, 90%).

Optical Rotation: $[\alpha]_D$ = +6.9 (c = 0.50, $CHCl_3$, 21.3 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.05 (s, 3 H, $Si(CH_3)_a$), 0.11 (s, 3 H, $Si(CH_3)_b$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.72–1.84 (m, 1 H, 3'-H_a), 1.87–2.01 (m, 2 H, 3-H_2), 2.04–2.16 (m, 1 H, 3'-H_b), 2.24 (s_{br}, 1 H, OH), 2.25 (s, 3 H, 7-CH_3), 2.37–2.57 (m, 3 H, 2'-H_2, 4-H_a), 2.63 (dt, *J* = 18.2, 6.0 Hz, 1 H, 4-H_b), 3.58 (dd, *J* = 12.1, 4.4 Hz, 1 H, CH_aOH), 3.63 (s, 3 H, 1'-OCH_3), 3.77 (s, 3 H, 5-OCH_3), 3.82 (dd, *J* = 12.3, 3.5 Hz, 1 H, CH_bOH), 3.97 (dd, *J* = 7.9, 4.2 Hz, 1 H, 4'-H), 6.21, 6.26 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.5 ($Si(CH_3)_a$), –4.0 ($Si(CH_3)_b$), 15.4 (C-4), 18.2 (SiC), 21.6 (7-CH_3), 22.1 (C-3), 23.0 ($SiC(\underline{C}H_3)_3$), 27.7 (C-3'), 31.1 (C-2'), 51.5 (1'-OCH_3), 55.3 (5-OCH_3), 63.2 (CH_2OH), 74.4 (C-4'), 79.4 (C-2), 103.0, 110.2 (C-6, C-8), 107.2 (C-4a), 137.0 (C-7), 153.3, 157.4 (C-5, C-8a), 174.1 (C-1').

IR: $\tilde{\nu}$ (cm^{-1}) = 3483, 2952, 2855, 1738, 1618, 1586, 1462, 1416, 1354, 1252, 1226, 1197, 1171, 1124, 1106, 1052, 986, 835, 813, 777, 674.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.660), 272 (3.186).

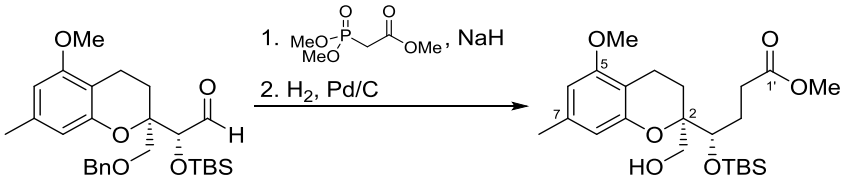
Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 10.8 min.

MS (ESI): *m*/*z* (%) = 899.5 (100) $[2M+Na]^+$, 461.2 (91) $[M+Na]^+$, 439.3 (94) $[M+H]^+$.

$C_{23}H_{38}O_6Si$ (438.63) calc.: 439.2510

found: 439.2510 $[M+H]^+$ (ESI-HRMS).

5.3.9 (2*R*,4'*S*)-4-(*tert*-Butyldimethysilyloxy)-4-(2-hydroxymethyl-5-methoxy-7-methylchroman-2-yl)-methyl butanoate (*syn*-298)



syn-**297** *syn*-**298**

A solution of trimethyl phosphonoacetate (0.14 mL, 848 µmol, 1.73 eq.) in THF (5 mL) was treated with sodium hydride (25.5 mg, 60% (w/w) in mineral oil, 635 µmol, 1.30 eq.) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min before a solution of aldehyde *syn*-**297** (230 mg, 489 µmol, 1.00 eq.) in THF (5 mL) was added dropwise at 0 °C. After complete addition the mixture was stirred at RT for further 2 h before being quenched with sat. aq. NH_4Cl solution (15 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 10 mL), the combined organic phases were dried over Na_2SO_4 and the was solvent removed *in vacuo*. Palladium on charcoal (52 mg, 10% Pd, 48.9 µmol, 10 mol%) and AcOH (0.28 mL, 489 µmol, 10.0 eq.) were added to a solution of the unsaturated crude product in MeOH (10 mL) in a *Parr*-flask. Hydrogen was passed through the resulting mixture for 30 min before being shaken under a H_2 atmosphere (4 bar) in a *Parr* apparatus at RT for further 80 h. The catalyst was removed by filtration through a syringe filter (rinsing with MeOH). After evaporation of the solvent *in vacuo* and column chromatography on silica gel (*n*-pentane/EtOAc = 9:1) the saturated ester *syn*-**298** was obtained as a colorless oil (195 mg, 445 µmol, 91%).

Optical Rotation: $[\alpha]_D$ = –11.6 (c = 0.50, $CHCl_3$, 22.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.03 (s, 3 H, $Si(CH_3)_a$), 0.16 (s, 3 H, $Si(CH_3)_b$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 1.74 (ddd, *J* = 13.9, 9.5, 6.2 Hz, 1 H, 3-H_a), 1.80 (ddd, *J* = 14.1, 8.6, 3.1 Hz, 1 H, 3'-H_a), 1.95 (dt, *J* = 13.8, 5.9 Hz, 1 H, 3-H_b), 1.92–2.04 (m, 1 H, 3'-H_b), 2.26 (s, 3 H, 7-CH_3), 2.32 (s_{br}, 1 H, OH), 2.37 (ddd, *J* = 16.2, 9.2, 6.7 Hz, 1 H, 2'-H_a), 2.46 (ddd, *J* = 16.8, 9.6, 6.4 Hz, 1 H, 4-H_a), 2.53 (ddd, *J* = 16.2, 9.4, 5.7 Hz, 1 H, 2'-H_b), 2.61 (dt, *J* = 17.3, 5.9 Hz, 1 H, 4-H_b), 3.64 (s, 3 H, 1'-OCH_3), 3.69 (d, *J* = 11.5 Hz, 1 H, CH_aOH), 3.76 (d, *J* = 11.7 Hz, 1 H, CH_bOH), 3.77 (s, 3 H, 5-OCH_3), 3.97 (dd, *J* = 8.4, 4.0 Hz, 1 H, 4'-H), 6.22, 6.32 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.7 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 15.6 (C-4), 18.3 (SiC), 21.7 (7-CH_3), 22.8 (C-3), 26.1 ($SiC(\underline{C}H_3)_3$), 27.7 (C-3'), 31.1 (C-2'), 51.5 (1'-OCH_3), 55.4 (5-OCH_3), 63.1 (CH_2OH), 74.7 (C-4'), 79.7 (C-2), 103.0, 110.3 (C-6, C-8), 107.4 (C-4a), 137.2 (C-7), 153.2, 157.5 (C-5, C-8a), 173.8 (C-1').

IR: $\tilde{\nu}$ (cm^{-1}) = 3511, 2951, 1738, 1618, 1585, 1462, 1415, 1353, 1252, 1102, 1002, 834, 812, 775, 671, 578.

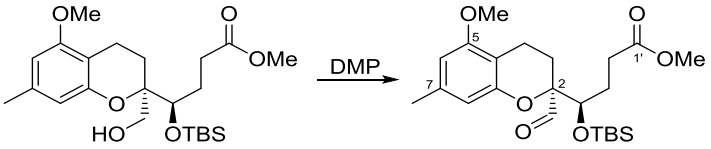
UV (CH_3CN): λ_{max} (nm) (lg ε) = 208 (4.688), 272 (3.081).

MS (ESI): *m*/*z* (%) = 899.5 (100) $[2M+Na]^+$, 461.3 (23) $[M+Na]^+$, 439.3 (29) $[M+H]^+$.

$C_{23}H_{38}O_6Si$ (438.63) calc.: 439.2510

found: 439.2514 $[M+H]^+$ (ESI-HRMS).

5.3.10 (2*S*,4'*R*)-4-(*tert*-Butyldimethylsilyloxy)-4-(2-formyl-5-methoxy-7-methylchroman-2-yl)-methyl butanoate (*anti*-299)



anti-**298** *anti*-**299**

A solution of alcohol *anti*-**298** (233 mg, 531 μmol, 1.00 eq.) in CH_2Cl_2 (5.3 mL) was treated with DMP (676 mg, 1.59 mmol, 3.00 eq.) at 0 °C and the reaction mixture stirred at RT for 2 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (15 mL) and H_2O (15 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the solvent and column chromatography on silica gel (*n*-pentane/EtOAc = 30:1 → 20:1) aldehyde *anti*-**299** was obtained as a colorless oil (214 mg, 490 μmol, 92%).

Optical Rotation: $[\alpha]_D$ = +13.8 (c = 0.50, $CHCl_3$, 23.3 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.07 (s, 3 H, $Si(CH_3)_a$), 0.11 (s, 3 H, $Si(CH_3)_b$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.81–1.90 (m, 2 H, 3'-H_a, 3-H_a), 1.91–1.97 (m, 1 H, 3'-H_b), 2.22–2.29 (m, 1 H, 4-H_a), 2.27 (s, 3 H, 7-CH_3), 2.32 (ddd, *J* = 13.2, 6.6, 2.1 Hz, 1 H, 3-H_b), 2.43 (ddd, *J* = 16.4, 9.0, 6.4 Hz, 1 H, 2'-H_a), 2.56 (ddd, *J* = 16.5, 9.1, 6.1 Hz, 1 H, 2'-H_b), 2.67 (ddd, *J* = 17.3, 6.4, 2.0 Hz, 1 H, 4-H_b), 3.64 (s, 3 H, 1'-OCH_3), 3.74 (s, 3 H, 5-OCH_3), 4.00 (dd, *J* = 6.9, 4.3 Hz, 1 H, 4'-H), 6.22, 6.43 (2 × s, 2 H, 6-H, 8-H), 9.62 (d, *J* = 1.2 Hz, 1 H, CHO).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.4 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 15.8 (C-4), 18.2 (SiC), 21.6 (7-CH_3), 22.0 (C-3), 25.9 ($SiC(\underline{C}H_3)_3$), 27.7 (C-3'), 30.1 (C-2'), 51.6 (1'-OCH_3), 55.3 (5-OCH_3), 74.3 (C-4'), 85.8 (C-2), 103.6, 110.0 (C-6, C-8), 107.3 (C-4a), 137.4 (C-7), 153.6, 157.5 (C-5, C-8a), 173.7 (C-1'), 203.1 (CHO).

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 2856, 1736, 1620, 1462, 1436, 1415, 1354, 1252, 1226, 1124, 1097, 996, 834, 815, 776, 667, 578, 545.

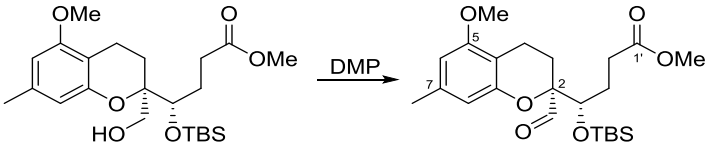
UV (CH_3CN): λ_{max} (nm) (lg ε) = 206 (4.666), 272 (3.108).

MS (ESI): *m*/*z* (%) = 895.5 (26) $[2M+Na]^+$, 459.2 (37) $[M+Na]^+$, 454.3 (46) $[M+NH_4]^+$, 437.2 (100) $[M+H]^+$.

$C_{23}H_{36}O_6Si$ (436.61) calc.: 437.2354

found: 437.2354 $[M+H]^+$ (ESI-HRMS).

5.3.11 (2*S*,4'*S*)-4-(*tert*-Butyldimethylsilyloxy)-4-(2-formyl-5-methoxy-7-methylchroman-2-yl)methyl butanoate (*syn*-299)



syn-**298** *syn*-**299**

A solution of alcohol *syn*-**298** (480 mg, 1.09 mmol, 1.00 eq.) in CH_2Cl_2 (12 mL) was treated with DMP (1.39 g, 3.28 mmol, 3.00 eq.) at 0 °C and the reaction mixture stirred at RT for 1.5 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (30 mL) at 0 °C. The aq. layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phases were dried over Na_2SO_4. After evaporation of the organic solvents and column chromatography on silica gel (*n*-pentane/EtOAc = 30:1 → 5:1) aldehyde *syn*-**299** was obtained as a colorless oil (443 mg, 1.01 mmol, 93%).

Optical Rotation: $[\alpha]_D$ = –8.9 (c = 0.50, $CHCl_3$, 26.0 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.07 (s, 3 H, $Si(CH_3)_a$), 0.22 (s, 3 H, $Si(CH_3)_b$), 0.89 (s, 9 H, $SiC(CH_3)_3$), 1.71 (m_c, 1 H, 3-H_a), 1.84 (dtd, *J* = 14.4, 8.9, 5.6 Hz, 1 H, 3'-H_a), 1.99 (m_c, 1 H, 3'-H_b), 2.25–2.33 (m, 2 H, 3-H_b, 4-H_a), 2.28 (s, 3 H, 7-CH_3), 2.35 (ddd, *J* = 16.4, 8.7, 7.2 Hz, 1 H, 2'-H_a), 2.51 (ddd, *J* = 16.5, 8.8, 5.6 Hz, 1 H, 2'-H_b), 2.60–2.65 (m, 1 H, 4-H_b), 3.65 (s, 3 H, 1'-OCH_3), 3.75 (s, 3 H, 5-OCH_3), 3.98 (dd, *J* = 9.1, 3.3 Hz, 1 H, 4'-H), 6.24, 6.45 (2 × s, 2 H, 6-H, 8-H), 9.62 (s, 1 H, CHO).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.7 ($Si(CH_3)_a$), 3.9 ($Si(CH_3)_b$), 15.8 (C-4), 18.4 (SiC), 21.7 (7-CH_3), 22.9 (C-3), 26.0 ($SiC(\underline{C}H_3)_3$), 27.3 (C-3'), 30.1 (C-2'), 51.6 (1'-OCH_3), 55.4 (5-OCH_3), 76.3 (C-4'), 85.8 (C-2), 103.6, 109.9 (C-6, C-8), 107.5 (C-4a), 137.4 (C-7), 153.5, 157.5 (C-5, C-8a), 173.7 (C-1'), 204.4 (CHO).

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 2856, 1737, 1620, 1587, 1462, 1436, 1415, 1353, 1251, 1223, 1199, 1170, 1130, 1098, 998, 974, 835, 815, 777, 670.

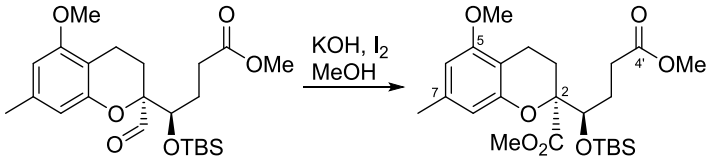
UV (CH_3CN): λ_{max} (nm) (lg ε) = 271 (3.167).

MS (ESI): *m*/*z* (%) = 895.4 (100) $[2M+Na]^+$, 459.2 (53) $[M+Na]^+$, 454.3 (62) $[M+NH_4]^+$, 437.2 (41) $[M+H]^+$.

$C_{23}H_{36}O_6Si$ (436.61) calc.: 437.2354

found: 437.2355 $[M+H]^+$ (ESI-HRMS).

5.3.12 (2*S*,1'*R*)-2-(1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-4-oxobutyl)-5-methoxy-7-methylchroman-2-methyl carboxylate (*anti*-300)



anti-**299** *anti*-**300**

A solution of KOH (220 mg, 3.92 mmol, 8.00 eq.) and I_2 (435 mg, 1.72 mmol, 3.50 eq.) in MeOH (3.5 mL) was stirred at RT for 5 min and added to aldehyde *anti*-**299** (214 mg, 490 μmol, 1.00 eq.) in MeOH (3 mL) at 0 °C followed by stirring at RT. Additional solutions of KOH (220 mg, 3.92 mmol, 8.00 eq.) and I_2 (435 mg, 1.72 mmol, 3.50 eq.) in MeOH (3.5 mL) were added at 0 °C after 1.5, 4.5 and 8 h; the reaction mixture was stirred at RT in the meantime. After stirring at RT for further 1 h after the last addition (9 h overall), sat. aq. $Na_2S_2O_3$ solution (50 mL) was added. The aq. phase was extracted with MTBE (3 × 20 mL),

the comined organic phases were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc 15:1 → 10:1) furnished methyl ester *anti*-**300** (229 mg, 491 μmol, quant.) as a colorless oil.

Optical Rotation: $[\alpha]_D$ = +4.7 (c = 0.50, $CHCl_3$, 22.4 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 3 H, $Si(CH_3)_a$), 0.12 (s, 3 H, $Si(CH_3)_b$), 0.86 (s, 9 H, $SiC(CH_3)_3$), 1.79–1.87 (m, 2 H, 2'-H_2), 1.89 (td, *J* = 12.3, 5.9 Hz, 1 H, 3-H_a), 2.25 (s, 3 H, 7-CH_3), 2.32–2.39 (m, 2 H, 3-H_b, 4-H_a), 2.41 (ddd, *J* = 16.2, 8.9, 7.0 Hz, 1 H, 3'-H_a), 2.58 (ddd, *J* = 16.2, 8.7, 6.3 Hz, 1 H, 3'-H_b), 2.70 (dd, *J* = 16.8, 6.1 Hz, 1 H, 4-H_b), 3.64 (s, 3 H, 4'-OCH_3), 3.64 (s, 3 H, 2-CO_2CH_3), 3.75 (s, 3 H, 5-OCH_3), 4.03 (dd, *J* = 7.1, 4.3 Hz, 1 H, 1'-H), 6.20, 6.36 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.6 ($Si(CH_3)_a$), –3.9 ($Si(CH_3)_b$), 16.3 (C-4), 18.3 (SiC), 21.6 (7-CH_3), 22.9 (C-3), 26.0 ($SiC(\underline{C}H_3)_3$), 27.7 (C-2'), 30.3 (C-3'), 51.5 (4'-OCH_3), 52.3 (2-$CO_2\underline{C}H_3$), 55.3 (5-OCH_3), 75.0 (C-1'), 84.1 (C-2), 103.4, 110.1 (C-6, C-8), 107.3 (C-4a), 137.0 (C-7), 153.7, 157.4 (C-5, C-8a), 172.1 (2-$\underline{C}O_2CH_3$), 173.9 (C-4').

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 2855, 1736, 1621, 1587, 1462, 1436, 1354, 1278, 1252, 1233, 1194, 1170, 1109, 1074, 991, 835, 815, 776, 704, 579.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 207 (4.602), 272 (3.120).

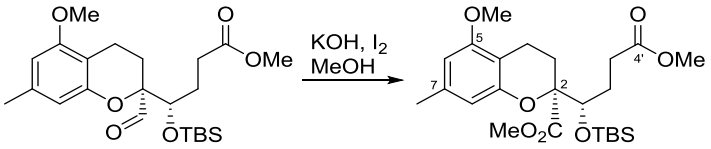
Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH 99:1, 0.8 mL/min): t_R = 8.4 min.

MS (ESI): *m*/*z* (%) = 955.5 (58) $[2M+Na]^+$, 489.2 (81) $[M+Na]^+$, 484.3 (100) $[M+NH_4]^+$, 467.2 (65) $[M+H]^+$.

$C_{24}H_{38}O_7Si$ (466.64) calc.: 467.2460

found: 467.2460 $[M+H]^+$ (ESI-HRMS).

5.3.13 (2*S*,1'*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-4-oxobutyl)-5-methoxy-7-methylchroman-2-methyl carboxylate (*syn*-300)



syn-**299** *syn*-**300**

A solution of KOH (452 mg, 8.06 mmol, 8.00 eq.) and I_2 (895 mg, 3.53 mmol, 3.50 eq.) in MeOH (4 mL) was stirred at RT for 5 min and added to a solution of aldehyde *syn*-**299** (440 mg, 1.01 mmol, 1.00 eq.) in MeOH (20 mL) at 0 °C followed by stirring at RT. Additional solutions of KOH (452 mg, 8.06 mmol, 8.00 eq.) and I_2 (895 mg, 3.53 mmol, 3.50 eq.) in MeOH (4 mL) were added at 0 °C after 4 and 6 h and the reaction mixture was stirred at RT in the meanwhile. After stirring at RT for further 30 min after the last addition (overall 6.5 h), sat. aq. $KHSO_3$ solution (30 mL) was added. The aq. phase was extracted with MTBE (3 × 50 mL), the comined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc 20:1 → 10:1) furnished methyl ester *syn*-**300** (451 mg, 966 µmol, 96%) as a colorless oil.

Optical Rotation: $[\alpha]_D$ = +39.1 (c = 0.50, $CHCl_3$, 27.6 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.07 (s, 3 H, $Si(CH_3)_a$), 0.18 (s, 3 H, $Si(CH_3)_b$), 0.88 (s, 9 H, $SiC(CH_3)_3$), 1.80 (td, *J* = 12.6, 5.7 Hz, 1 H, 3-H_a), 1.97–2.07 (m, 2 H, 2'-H_2), 2.23–2.29 (m, 1 H, 4-H_a), 2.26 (s, 3 H, 7-CH_3), 2.34 (ddd, *J* = 12.9, 6.1, 2.1 Hz, 1 H, 3-H_b), 2.39 (ddd, *J* = 16.2, 9.0, 6.8 Hz, 1 H, 3'-H_a), 2.57 (ddd, *J* = 16.5, 8.9, 6.0 Hz, 1 H, 3'-H_b), 2.73 (ddd, *J* = 16.8, 5.7, 1.7 Hz, 1 H, 4-H_b), 3.36, 3.65 (2 × s, 6 H, 4'-OCH_3, 2-CO_2CH_3), 3.75 (s, 3 H, 5-OCH_3), 3.96 (dd, *J* = 8.1, 4.2 Hz, 1 H, 1'-H), 6.21, 6.38 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.6 ($Si(CH_3)_a$), –4.0 ($Si(CH_3)_b$), 16.4 (C-4), 18.2 (SiC), 21.6 (7-CH_3), 25.3 (C-3), 25.9 ($SiC(\underline{C}H_3)_3$), 27.6 (C-2'), 30.4 (C-3'), 51.4, 52.0 (4'-OCH_3, 2-$CO_2\underline{C}H_3$), 55.2 (5-OCH_3), 76.2 (C-1'), 84.3 (C-2), 103.2, 109.7 (C-6, C-8), 106.8 (C-4a), 137.1 (C-7), 153.8, 157.2 (C-5, C-8a), 171.7, 173.9 (C-4', 2-$\underline{C}O_2CH_3$).

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 2929, 2855, 1736, 1620, 1588, 1462, 1437, 1354, 1235, 1196, 1170, 1134, 1093, 995, 835, 776, 681, 579.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 194 (4.891), 206 (4.677), 271 (3.202).

MS (ESI): *m*/*z* (%) = 955.5 (82) $[3M+Na]^+$, 489.2 (100) $[M+Na]^+$, 484.3 (95) $[M+NH_4]^+$, 467.3 (55) $[M+H]^+$.

$C_{24}H_{38}O_7Si$ (466.64) calc.: 489.2279

found: 489.2275, $[M+Na]^+$ (ESI-HRMS).

5.3.14 (2*S*,1'*R*)-2-(1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-4-oxobutyl)-5-methoxy-7-methyl-2*H*-chromene-2-methyl carboxylate (*anti*-301)

anti-**300** *anti*-**301**

A mixture of ester *anti*-**300** (229 mg, 491 μmol, 1.00 eq.) and DDQ (228 mg, 983 μmol, 2.00 eq.) in benzene (10 mL) was heated at reflux for 1.5 h. Additional DDQ (228 mg, 983 μmol, 2.00 eq.) was added and heating at reflux continued for 1.5 h. After cooling to RT and filtration through silica gel (eluting with EtOAc) the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-hexane/EtOAc = 5:1) furnished the chromene *anti*-**301** as a colorless oil (198 mg, 426 μmol, 87%).

Optical Rotation: $[\alpha]_D$ = +138.9 (c = 0.36, $CHCl_3$, 24.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = –0.01 (s, 3 H, $Si(CH_3)_a$), 0.08 (s, 3 H, $Si(CH_3)_b$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.90–2.02 (m, 2 H, 2'-H_2), 2.26 (s, 3 H, 7-CH_3), 2.45 (ddd, *J* = 16.2, 9.1, 6.3 Hz, 1 H, 3'-H_a), 2.54 (ddd, *J* = 16.8, 9.2, 6.3 Hz, 1 H, 3'-H_b), 3.61 (s, 3 H, 4'-OCH_3), 3.65 (s, 3 H, 2-CO_2CH_3), 3.76 (s, 3 H, 5-OCH_3), 4.21 (dd, *J* = 6.6, 4.6 Hz, 1 H, 1'-H), 5.54 (d, *J* = 9.9 Hz, 1 H, 3-H), 6.20, 6.40 (2 × s, 2 H, 6-H, 8-H), 6.76 (d, *J* = 10.0 Hz, 1 H, 4-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.4 ($Si(CH_3)_a$), –4.1 ($Si(CH_3)_b$), 18.3 (SiC), 22.1 (7-CH_3), 25.9 ($SiC(\underline{C}H_3)_3$), 27.8 (C-2'), 30.0 (C-3'), 51.5 (4'-OCH_3), 52.3 (2-$CO_2\underline{C}H_3$), 55.5 (5-OCH_3), 75.1 (C-1'), 84.8 (C-2), 104.6, 109.6 (C-6, C-8), 106.9 (C-4a), 118.4 (C-3), 120.1 (C-4), 140.3 (C-7), 152.9, 155.1 (C-5, C-8a), 171.1 (2-$\underline{C}O_2CH_3$), 173.8 (C-4').

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 1736, 1616, 1463, 1435, 1385, 1325, 1253, 1231, 1212, 1197, 1129, 1092, 1037, 837, 799, 776, 579.

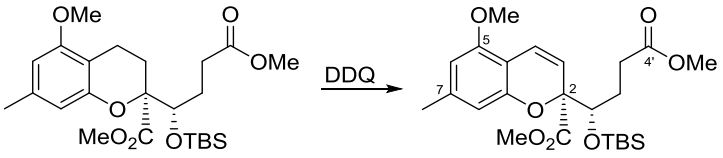
UV (CH_3CN): λ_{max} (nm) (lg ε) = 229 (4.303), 288 (3.961).

MS (ESI): *m*/*z* (%) = 951.4 (77) $[2M+Na]^+$, 487.2 (59) $[M+Na]^+$, 482.3 (100) $[M+NH_4]^+$, 465.2 (81) $[M+H]^+$.

$C_{24}H_{36}O_7Si$ (464.62) calc.: 465.2303

found: 465.2302 $[M+H]^+$ (ESI-HRMS).

5.3.15 (2*S*,1'*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-4-oxobutyl)-5-methoxy-7-methyl-2*H*-chromene-2-methyl carboxylate (*syn*-301)



syn-**300** *syn*-**301**

A mixture of ester *syn*-**300** (352 mg, 754 μmol, 1.00 eq.) and DDQ (349 mg, 1.51 mmol, 2.00 eq.) in benzene (15 mL) was heated at reflux for 1.5 h. Additional DDQ (349 mg, 1.51 mmol, 2.00 eq.) was added and heating continued for 1.5 h. After cooling to RT and filtration through silica gel (eluting with EtOAc) the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 15:1 → 5:1) furnished the corresponding chromene *syn*-**301** as a colorless oil (271 mg, 584 μmol, 77%).

Optical Rotation: $[\alpha]_D$ = +40.1 (c = 0.51, $CHCl_3$, 28.2 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.05 (s, 3 H, $Si(CH_3)_a$), 0.06 (s, 3 H, $Si(CH_3)_b$), 0.82 (s, 9 H, $SiC(CH_3)_3$), 1.92–2.05 (m, 2 H, 2'-H_2), 2.25 (s, 3 H, 7-CH_3), 2.36 (ddd, *J* = 16.2, 10.0, 5.8 Hz, 1 H, 3'-H_a), 2.52 (ddd, *J* = 16.2, 9.9, 6.1 Hz, 1 H, 3'-H_b), 3.62 (s, 3 H, 4'-OCH_3), 3.68 (s, 3 H, 2-CO_2CH_3), 3.76 (s, 3 H, 5-OCH_3), 4.16 (dd, *J* = 6.3, 5.1 Hz, 1 H, 1'-H), 5.70 (d, *J* = 10.1 Hz, 1 H, 3-H), 6.21, 6.35 (2 × s, 2 H, 6-H, 8-H), 6.81 (d, *J* = 10.1 Hz, 1 H, 4-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.4 ($Si(CH_3)_a$), –4.3 ($Si(CH_3)_b$), 18.1 (SiC), 22.0 (7-CH_3), 25.8 ($SiC(\underline{C}H_3)_3$), 28.2 (C-2'), 30.2 (C-3'), 51.5 (4'-OCH_3), 52.4 (2-$CO_2\underline{C}H_3$), 55.5 (5-OCH_3), 75.0 (C-1'), 84.2 (C-2), 104.7, 109.5 (C-6, C-8), 107.2 (C-4a), 118.4 (C-3), 120.1 (C-4), 140.0 (C-7), 152.6, 155.2 (C-5, C-8a), 171.3 (2-$\underline{C}O_2CH_3$), 173.9 (C-4').

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 1737, 1616, 1574, 1462, 1435, 1251, 1213, 1122, 1090, 836, 775, 581.

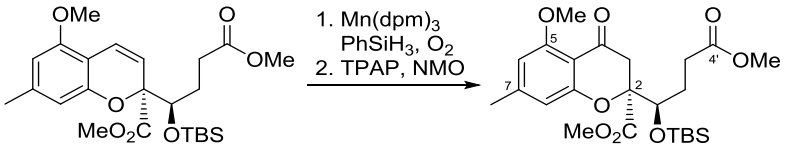
UV (CH_3CN): λ_{max} (nm) (lg ε) = 229 (4.311), 287 (3.935).

MS (ESI): *m*/*z* (%) = 951.5 (100) $[2M+Na]^+$, 487.2 (71) $[M+Na]^+$, 482.3 (79) $[M+NH_4]^+$, 465.2 (24) $[M+H]^+$.

$C_{24}H_{36}O_7Si$ (464.62) calc.: 465.2303

found: 465.2302 $[M+H]^+$ (ESI-HRMS).

5.3.16 (2*S*,1'*R*)-2-(1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-4-oxobutyl)-5-methoxy-7-methyl-4-oxochroman-2-methyl carboxylate (*anti*-284)



anti-**301** *anti*-**284**

A solution of chromene *anti*-**301** (240 mg, 517 µmol, 1.00 eq.) in MeOH (12 mL) was treated with $Mn(dpm)_3$ (32 mg, 51.7 µmol, 10 mol%) at RT and oxygen was passed through the resulting mixture at RT for 20 min. $PhSiH_3$ (1.30 mL, 10.3 mmol, 20.0 eq.) was added by a syringe pump (0.06 mL/h) while the reaction mixture was stirred under an O_2 atmosphere (1 atm) at 50 °C. Additional $Mn(dpm)_3$ (32 mg, 51.7 µmol, 10 mol%) was added after 8 and 16 h. After stirring at 50 °C for further 8 h (overall 24 h) the reaction was quenched by adsorption on silica gel. Evaporation of the solvent and column chromatography on silica gel (*n*-pentane/EtOAc = 10:1 → 1:1) furnished two diastereomeric alcohols (157 mg, 325 µmol, 63%) and (83 mg, 172 µmol, 33%) as colorless oils.

A solution of the diastereomeric alcohols (157 mg, 325 µmol, 0.65 eq.) and (83 mg, 172 µmol, 0.35 eq.) in CH_2Cl_2 (22.5 mL) and CH_3CN (7.5 mL) in the presence of 4 Å molecular sieve (400 mg) was treated with NMO (150 mg, 1.24 mmol, 2.50 eq.) at 0 °C and stirred at 0 °C for further 5 min. TPAP (17.5 mg, 47.9 µmol, 10 mol%) was added at 0 °C and the resulting reaction mixture stirred at RT for 12 h. Additional NMO (150 mg, 1.24 mmol, 2.50 eq.) and TPAP (17.5 mg, 47.9 µmol, 10 mol%) were added at 0 °C and the resulting reaction mixture was stirred at RT for further 12 h. After adsorption on silica gel, evaporation of the solvent and column chromatography on silica gel (*n*-pentane/EtOAc = 4:1 → 3:1) chromanone *anti*-**284** was obtained as a colorless oil (228 mg, 474 µmol, 95%, 92% over 2 steps).

Optical Rotation: $[\alpha]_D = -71.3$ (c = 0.20, $CHCl_3$, 25.0 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.08 (s, 3 H, $Si(CH_3)_a$), 0.14 (s, 3 H, $Si(CH_3)_b$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.66 (m_c, 2 H, 2'-H_2), 2.30 (s, 3 H, 7-CH_3), 2.36 (dt, *J* = 16.2, 7.9 Hz, 1 H, 3'-H_a), 2.52 (ddd, *J* = 16.2, 7.6, 6.4 Hz, 1 H, 3'-H_b), 2.96 (d, *J* = 16.6 Hz, 1 H, 3-H_a), 3.10 (d, *J* = 16.6 Hz, 1 H, 3-H_b), 3.65 (s, 6 H, 4'-OCH_3, 2-CO_2CH_3), 3.85 (s, 3 H, 5-OCH_3), 4.13 (dd, *J* = 6.8, 5.3 Hz, 1 H, 1'-H), 6.30, 6.42 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.7 ($Si(CH_3)_a$), –3.7 ($Si(CH_3)_b$), 18.3 (SiC), 22.4 (7-CH_3), 26.0 ($SiC(\underline{C}H_3)_3$), 27.4 (C-2'), 30.3 (C-3'), 39.2 (C-3), 51.6 (4'-OCH_3), 53.0 (2-$CO_2\underline{C}H_3$), 56.1 (5-OCH_3), 74.3 (C-1'), 87.2 (C-2), 105.8, 110.5 (C-6, C-8), 108.6 (C-4a), 147.9 (C-7), 160.4, 160.8 (C-5, C-8a), 170.6 (2-$\underline{C}O_2CH_3$), 173.3 (C-4'), 188.7 (C-4).

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2928, 2855, 1738, 1686, 1614, 1568, 1463, 1436, 1415, 1389, 1251, 1222, 1124, 1107, 1055, 993, 833, 777, 689.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 219 (4.270), 268 (3.988), 324 (3.623).

Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 95:5, 0.8 mL/min): t_R = 21.3 min.

MS (ESI): *m*/*z* (%) = 983.4 (24) $[2M+Na]^+$, 503.2 (49) $[M+Na]^+$, 481.2 (100) $[M+H]^+$.

$C_{24}H_{36}O_8Si$ (480.62) calc.: 481.2252

found: 481.2247 $[M+H]^+$ (ESI-HRMS).

5.3.17 (2*S*,1'*S*)-2-(1-(*tert*-Butyldimethylsilyloxy)-4-methoxy-4-oxobutyl)-5-methoxy-7-methyl-4-oxochroman-2-methyl carboxylate (*syn*-284)

syn-**301** *syn*-**284**

A solution of the chromene *syn*-**301** (333 mg, 717 µmol, 1.00 eq.) in MeOH (15 mL) was treated with $Mn(dpm)_3$ (45 mg, 71.7 µmol, 10 mol%) at RT and oxygen was passed through the resulting mixture at RT for 20 min. $PhSiH_3$ (1.77 mL, 14.3 mmol, 20.0 eq.) was added by a syringe pump (0.06 mL/h) while the reaction mixture was stirred under an O_2 atmosphere (1 atm) at 50 °C. Additional $Mn(dpm)_3$ (45 mg, 71.7 µmol, 10 mol%) was added after 10 and 22 h. After stirring at 50 °C for further 8 h (overall 30 h) the reaction was quenched by adsorption on silica gel. Evaporation of the solvent and chromatography over silica gel (*n*-pentane/EtOAc = 10:1 → 1:1) furnished the diastereomeric alcohols as a colorless oil.

A solution of the diastereomeric alcohols in CH_2Cl_2 (24.5 mL) and CH_3CN (8.5 mL) in the presence of 4 Å molecular sieve (500 mg) was treated with NMO (208 mg, 1.72 mmol, 2.50 eq.) at 0 °C and stirred for further 5 min at 0 °C. TPAP (24.3 mg, 67.0 µmol, 10 mol%) was added at 0 °C and the resulting reaction mixture was stirred at RT for 12 h. Additional NMO (208 mg, 1.72 mmol, 2.50 eq.) and TPAP (24.3 mg, 67.0 µmol, 10 mol%) were added

at 0 °C and the resulting reaction mixture stirred at RT for further 12 h. After adsorption on silica gel, evaporation of the solvent and column chromatography on silica gel (*n*-pentane/EtOAc = 4:1 → 2:1) chromanone *syn*-**284** (292 mg, 608 μmol, 85% over 2 steps) was obtained as a colorless oil.

Optical Rotation: $[\alpha]_D = -13.8$ (c = 0.44, $CHCl_3$, 26.4 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.08 (s, 3 H, $Si(CH_3)_a$), 0.15 (s, 3 H, $Si(CH_3)_b$), 0.87 (s, 9 H, $SiC(CH_3)_3$), 1.91 (dtd, *J* = 14.2, 8.4, 6.0 Hz, 1 H, 2'-H_a), 2.00–2.06 (m, 1 H, 2'-H_b), 2.34 (s, 3 H, 7-CH_3), 2.43 (ddd, *J* = 16.3, 8.8, 6.9 Hz, 1 H, 3'-H_a), 2.56 (ddd, *J* = 16.6, 8.9, 5.9 Hz, 1 H, 3'-H_b), 2.94 (d, *J* = 16.2 Hz, 1 H, 3-H_a), 2.99 (d, *J* = 16.2 Hz, 1 H, 3-H_b), 3.61 (s, 3 H, 2-CO_2CH_3), 3.65 (s, 3 H, 4'-OCH_3), 3.85 (s, 3 H, 5-OCH_3), 4.10 (dd, *J* = 7.8, 4.1 Hz, 1 H, 1'-H), 6.29, 6.47 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.4, –4.1 ($Si(CH_3)_a$, $Si(CH_3)_b$), 18.2 (SiC), 22.5 (7-CH_3), 25.8 ($SiC(\underline{C}H_3)_3$), 27.5 (C-2'), 30.0 (C-3'), 42.3 (C-3), 51.6 (4'-OCH_3), 52.7 (2-$CO_2\underline{C}H_3$), 56.1 (5-OCH_3), 75.0 (C-1'), 86.8 (C-2), 105.4, 110.4 (C-6, C-8), 108.7 (C-4a), 148.1 (C-7), 160.3, 161.5 (C-5, C-8a), 170.2 (2-$\underline{C}O_2CH_3$), 173.6 (C-4'), 188.0 (C-4).

IR: $\tilde{\nu}$ (cm^{-1}) = 2953, 2856, 1737, 1686, 1615, 1569, 1464, 1434, 1416, 1349, 1257, 1222, 1123, 1099, 836, 778, 699.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 269 (3.957), 325 (3.508).

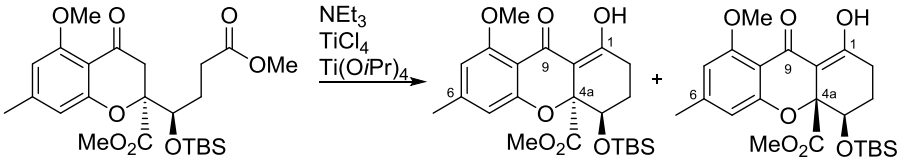
MS (ESI): *m*/*z* (%) = 983.4 (48) $[2M+Na]^+$, 503.2 (55) $[M+Na]^+$, 481.2 (100) $[M+H]^+$.

$C_{24}H_{36}O_8Si$ (480.62) calc.: 481.2252

found: 481.2253 $[M+H]^+$ (ESI-HRMS).

5.4 Synthesis of (–)-blennolide C (*ent*-7c) and acid 306

5.4.1 (4*R*,4a*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-8-methoxy-6-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-methyl carboxylate (*anti*-303)



$TiCl_4$ (1.23 mL, 1.0 M in CH_2Cl_2, 1.23 mmol, 2.60 eq.) was added slowly to $Ti(OiPr)_4$ (123 µL, 413 µmol, 0.87 eq.) in CH_2Cl_2 (1 mL) at RT and the resulting mixture was stirred for 15 min at RT. NEt_3 (184 µL, 1.33 mmol, 2.80 eq.) was added to a solution of chromanone *anti*-**284** (228 mg, 474 µmol, 1.00 eq.) in CH_2Cl_2 (8.5 mL) at 0 °C and it was stirred at 0 °C for 5 min. Subsequently, the solution of $Ti(OiPr)Cl_3$ was added slowly through a transfer cannula and the resulting solution was stirred at 0 °C for 1 h (TLC monitoring) before being quenched with H_2O (30 mL). The aq. layer was extracted with MTBE (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 5:1 → 2:1) furnished tetrahydroxanthenone *anti*-**303** as a brown solid (125 mg, 279 µmol, 59%) along with a mixture of *anti*-**303** and *ent-syn*-**303** (54 mg, 120 µmol, 25%, 2.2:1)

Optical Rotation: $[\alpha]_D = -156.9$ (c = 0.50, $CHCl_3$, 28.1 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.04 (s, 3 H, $Si(CH_3)_a$), 0.15 (s, 3 H, $Si(CH_3)_b$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.87 (m_c, 2 H, 3-H_2), 2.25–2.33 (m, 1 H, 2-H_a), 2.30 (s 3 H, 6-CH_3), 2.74 (ddd, *J* = 18.6, 10.1, 8.0 Hz, 1 H, 2-H_b), 3.61 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, 8-OCH_3), 4.31 (t, *J* = 2.9 Hz, 1 H, 4-H), 6.32, 6.40 (2 × s, 2 H, 5-H, 7-H), 16.22 (s_{br}, 1 H, 1-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.1 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 18.2 (SiC), 22.4 (6-CH_3), 25.4 (C-3), 25.7 ($SiC(\underline{C}H_3)_3$), 26.2 (C-2), 53.0 ($CO_2\underline{C}H_3$), 56.1 (8-OCH_3), 68.1 (C-4), 83.7 (C-4a), 101.6 (C-9a), 106.2, 110.6 (C-5, C-7), 107.3 (C-8a), 147.3 (C-6), 159.5, 160.4 (C-8, C-10a), 172.3 ($\underline{C}O_2CH_3$), 180.4, 184.7 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 2951, 2928, 2854, 1734, 1608, 1461, 1408, 1359, 1313, 1246, 1221, 1192, 1115, 1092, 1029, 1001, 887, 834, 777, 736, 676, 579, 543.

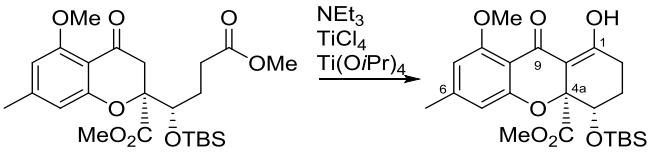
UV (CH_3CN): λ_{max} (nm) (lg ε) = 281 (3.637), 331 (4.145).

MS (ESI): *m*/*z* (%) = 1367.6 (4) $[3M+Na]^+$, 919.4 (22) $[2M+Na]^+$, 471.2 (24) $[M+Na]^+$, 449.2 (100) $[M+H]^+$.

$C_{23}H_{32}O_7Si$ (448.58) calc.: 471.1810

found: 471.1810 $[M+Na]^+$ (ESI-HRMS).

5.4.2 (4*S*,4a*S*)-4-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-8-methoxy-6-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-methyl carboxylate (*syn*-303)



syn-**284** *syn*-**303**

$TiCl_4$ (0.58 mL, 1.0 M in CH_2Cl_2, 580 µmol, 2.60 eq.) was added slowly to Ti(O*i*Pr)$_4$ (58 µL, 195 µmol, 0.87 eq.) in CH_2Cl_2 (1 mL) at RT. The resulting mixture was stirred at RT for 15 min. NEt_3 (87 µL, 630 µmol, 2.80 eq.) was added to a solution of chromanone *syn*-**284** (108 mg, 225 µmol, 1.00 eq.) in CH_2Cl_2 (4.5 mL) at 0 °C and stirring continued at 0 °C for 5 min. Subsequently, the solution of Ti(O*i*Pr)Cl_3 was added slowly through a transfer cannula and the resulting reaction mixture stirred at 0 °C for 2 h (TLC monitoring) before being quenched with H_2O (20 mL). The aq. layer was extracted with EtOAc (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 4:1) yielded tetrahydroxanthenone *syn*-**303** as a white solid (74 mg, 165 µmol, 73%).

Optical Rotation: $[\alpha]_D = -73.5$ (c = 0.33, $CHCl_3$, 24.8 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.11 (s, 3 H, Si(CH_3)$_a$), 0.21 (s, 3 H, Si(CH_3)$_b$), 0.89 (s, 9 H, SiC(CH_3)$_3$), 1.84 (m_c, 1 H, 3-H_a), 2.28–2.35 (m, 1 H, 3-H_b), 2.32 (s, 3 H, 6-CH_3), 2.53–2.63 (m, 2 H, 2-H_2), 3.58 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, 8-OCH_3), 4.21 (dd, *J* = 12.1, 5.0 Hz, 1 H, 4-H), 6.31, 6.45 (2 × s, 2 H, 5-H, 7-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –4.9 (Si(CH_3)$_a$), –4.5 (Si(CH_3)$_b$), 18.0 (SiC), 22.6 (6-CH_3), 25.6 (SiC($\underline{C}H_3$)$_3$), 26.4 (C-3), 29.0 (C-2), 52.3 ($CO_2\underline{C}H_3$), 56.1 (8-OCH_3), 72.8 (C-4), 84.6 (C-4a), 102.5 (C-9a), 105.8, 110.7 (C-5, C-7), 107.8 (C-8a), 147.8 (C-6), 160.5, 161.2 (C-8, C-10a), 170.2 ($\underline{C}O_2CH_3$), 181.5, 181.7 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 2951, 2928, 2887, 2855, 1754, 1735, 1608, 1462, 1415, 1371, 1249, 1216, 1099, 1010, 974, 906, 879, 834, 777, 736, 700, 671, 554, 501.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 282 (3.603), 322 (4.042).

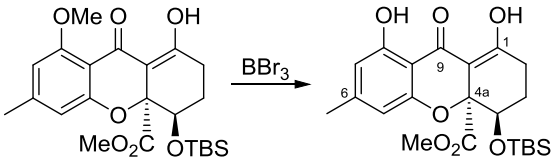
Analytical HPLC (*Daicel* Chiralpak IB®, 4.6 × 250 mm, 5 µm, *n*-hexane/2-PrOH 97:3, 0.8 mL/min): t_R = 21.6 min.

MS (ESI): *m*/*z* (%) = 1367.6 (28) $[3M+Na]^+$, 919.4 (61) $[2M+Na]^+$, 471.2 (20) $[M+Na]^+$, 449.2 (100) $[M+H]^+$.

$C_{23}H_{32}O_7Si$ (448.58) calc.: 471.1810

found: 471.1816 $[M+Na]^+$ (ESI-HRMS).

5.4.3 (4*R*,4a*S*)-4-(*tert*-Butyldimethylsilyloxy)-1,8-hydroxy-6-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-methyl carboxylate (307)



anti-**303** **307**

BBr_3 (0.76 mL, 1.0 M in CH_2Cl_2, 760 µmol, 10.0 eq.) was added slowly to a solution of tetrahydroxanthenone *anti*-**303** (34 mg, 75.8 µmol, 1.00 eq.) in CH_2Cl_2 (3 mL) at –78 °C. The resulting red solution was warmed to 0 °C in 4 h before being quenched with sat. aq. $NaHCO_3$ solution (10 mL) at 0 °C. The aq. layer was extracted with EtOAc (3 × 5 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 10:1) provided phenol *anti*-**307** as a white solid (28.4 mg, 65.4 µmol, 86%).

Optical Rotation: $[\alpha]_D$ = –190.1 (c = 1.6, $CHCl_3$, 24.4 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 0.03 (s, 3 H, $Si(CH_3)_a$), 0.15 (s, 3 H, $Si(CH_3)_b$), 0.83 (s, 9 H, $SiC(CH_3)_3$), 1.88 (m_c, 2 H, 3-H_2), 2.25 (s, 3 H, 6-CH_3), 2.31 (ddd, *J* = 18.9, 6.2, 1.5 Hz, 1 H, 2-H_a), 2.76 (ddd, *J* = 18.6, 11.2, 7.1 Hz, 1 H, 2-H_b), 3.66 (s, 3 H, CO_2CH_3), 4.34 (dd, *J* = 4.1, 1.7 Hz, 1 H, 4-H), 6.23, 6.30 (2 × s, 2 H, 5-H, 7-H), 11.30 (s, 1 H, 8-OH), 14.11 (s, 1 H, 1-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = –5.2 ($Si(CH_3)_a$), –4.2 ($Si(CH_3)_b$), 18.2 (SiC), 22.4 (6-CH_3), 24.8 (C-2), 25.4 (C-3), 25.7 ($SiC(\underline{C}H_3)_3$), 53.2 ($CO_2\underline{C}H_3$), 67.9 (C-4), 83.8 (C-4a),

100.7 (C-9a), 104.5 (C-8a), 108.4, 110.9 (C-5, C-7), 149.7 (C-6), 158.1, 161.8 (C-8, C-10a), 171.8 ($\underline{C}O_2CH_3$), 178.8, 187.1 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 2952, 2855, 1740, 1612, 1579, 1462, 1363, 1298, 1241, 1200, 1147, 1115, 1081, 1030, 1003, 890, 833, 815, 779.

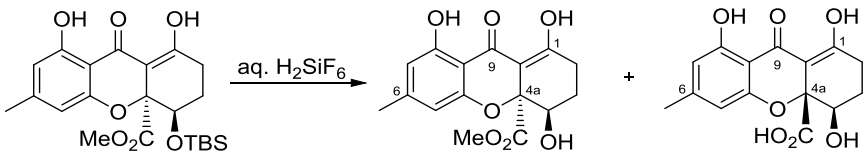
UV (CH_3CN): λ_{max} (nm) (lg ε) = 223 (4.199), 279 (3.621), 334 (4.193).

MS (ESI): *m*/*z* (%) = 891.4 (8) $[2M+Na]^+$, 457.2 (59) $[M+Na]^+$, 435.2 (100) $[M+H]^+$.

$C_{22}H_{30}O_7Si$ (434.55) calc.: 435.1834

found: 435.1836, $[M+H]^+$ (ESI-HRMS).

5.4.4 (–)-Blennolide C (*ent*-7c)



307 *ent*-**7c** (–)-blennolide C *ent-syn*-**306**

A solution of phenol **307** (28.4 mg, 65.4 μmol, 1.00 eq.) in DMF (2.3 mL) was treated with H_2SiF_6 (0.84 mL, 23 wt% in H_2O, 1.63 mmol, 25.0 eq.) at RT and stirred at 50 °C for 3 d. Additional H_2SiF_6 (0.84 mL, 23 wt% in H_2O, 1.63 mmol, 25.0 eq.) was added at RT and the mixture stirred at 50 °C for further 3 d. The reaction was quenched by addition of H_2O (10 mL) at 0 °C, the aq. layer extracted with MTBE (3 × 5 mL) and the combined organic phases were dried over Na_2SO_4. After column chromatography on silica gel (CH_2Cl_2/MeOH = 100:1 → 5:1), (–)-blennolide C (*ent*-**7c**) was obtained alongside *ent-syn*-**306** as a white solid (13.7 mg, 43.3 μmol, 66%, *ent*-**7c**/*ent-syn*-**306** = 3:1). Purification by analytical RP-HPLC with H_2O (A) and MeOH (B) as the eluent (*Jasco* Kromasil® 100-C18, 4.6 × 250 mm, 5 μm, gradient: 0–30 min: 50A/50B → 0A/100B, 30–40 min: 0A/100B → 50A/B50, flow: 0.8 mL/min, t_R = 16.4 min) furnished (–)-blennolide C (*ent*-**7c**) as a white solid.

Analytical data of (–)-blennolide C (*ent*-**7c**):

Optical Rotation: $[\alpha]_D$ = –175.3 (c = 0.20, $CHCl_3$, 22.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 1.93 (m_c, 1 H, 3-H_a), 2.12 (m_c, 1 H, 3-H_b), 2.27 (s, 3 H, 6-CH_3), 2.36 (ddd, *J* = 19.2, 6.9, 1.3 Hz, 1 H, 2-H_a), 2.67 (s, 1 H, 4-OH), 2.80 (ddd, *J* = 18.8, 11.3, 7.0 Hz, 1 H, 2-H_b), 3.67 (s, 3 H, CO_2CH_3), 4.29 (s, 1 H, 4-H), 6.32, 6.36 (2 × s, 2 H, 5-H, 7-H), 11.25 (s, 1 H, 8-OH), 14.02 (s, 1 H, 1-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 22.5 (6-CH_3), 23.1 (C-3), 24.3 (C-2), 53.4 ($CO_2\underline{C}H_3$), 67.0 (C-4), 83.8 (C-4a), 100.1 (C-9a), 104.9 (C-8a), 108.7, 111.7 (C-5, C-7), 149.9 (C-6), 157.6 (C-10a), 161.9 (C-8), 171.2 ($\underline{C}O_2CH_3$), 179.1, 186.9 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 3484, 2922, 2852, 1740, 1613, 1571, 1456, 1416, 1363, 1298, 1256, 1239, 1206, 1149, 1111, 1078, 1051, 957, 879, 837, 819, 736, 568.

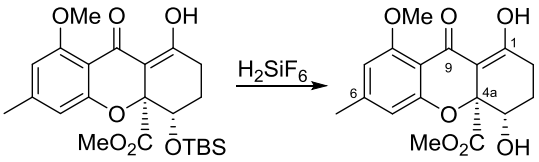
UV (MeOH): λ_{max} (nm) (lg ε) = 279 (3.496), 333 (4.072).

MS (ESI): *m*/*z* (%) = 663.2 (44) $[2M+Na]^+$, 343.1 (100) $[M+Na]^+$, 321.1 (36) $[M+H]^+$.

$C_{16}H_{16}O_7$ (320.29) calc.: 321.0969

found: 321.0966 $[M+H]^+$ (ESI-HRMS).

5.4.5 (4*S*,4a*S*)-1,4-Dihydroxy-8-methoxy-6-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-methyl carboxylate (*syn*-69)



syn-**303** *syn*-**69**

A solution of tetrahydroxanthenone *syn*-**303** (25.2 mg, 56.2 μmol, 1.00 eq.) in DMF (2.0 mL) was treated with H_2SiF_6 (0.72 mL, 23 wt% in H_2O, 1.40 mmol, 25.0 eq.) at RT and stirred at 50 °C for 3 d; additional H_2SiF_6 (0.72 mL, 23 wt% in H_2O, 1.40 mmol, 25.0 eq.) was added at RT and the mixture stirred at 50 °C for further 3 d. The reaction was quenched by addition of H_2O (10 mL) at 0 °C and the aq. layer extracted with MTBE (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. After column chromatography on silica gel (CH_2Cl_2/MeOH = 150:1 → 100:1 → 75:1) *syn*-**69** was obtained as a white solid (18.1 mg, 54.1 μmol, 96%).

Optical Rotation: $[\alpha]_D$ = –37.3 (c = 0.25, $CHCl_3$, 21.7 °C).

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) = 1.99–2.08 (m, 1 H, 3-H_a), 2.10–2.25 (m, 1 H, 3-H_b), 2.23 (s, 3 H, 6-CH_3), 2.59–2.64 (m, 2 H, 2-H_2), 2.81 (d, *J* = 2.6 Hz, 1 H, 4-OH), 3.65 (s, 3 H, CO_2CH_3), 3.88 (s, 3 H, 8-OCH_3), 4.29 (ddd, *J* = 12.5, 5.1, 2.4 Hz, 1 H, 4-H), 6.36, 6.53 (2 × s, 2 H, 5-H, 7-H), 16.0 (s, 1 H, 1-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.5 (6-CH_3), 24.0 (C-3), 28.8 (C-2), 52.9 ($CO_2\underline{C}H_3$), 56.1 (8-OCH_3), 72.1 (C-4), 84.5 (C-4a), 102.2 (C-9a), 106.4, 110.7 (C-5, C-7),

107.8 (C-8a), 148.0 (C-6), 160.4, 160.6 (C-8, C-10a), 170.1 ($\underline{C}O_2CH_3$), 181.3, 181.7 (C-1, C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 3450, 2953, 2852, 1749, 1733, 1607, 1481, 1461, 1416, 1352, 1257, 1217, 1165, 1107, 1066, 1011, 969, 826, 733, 576.

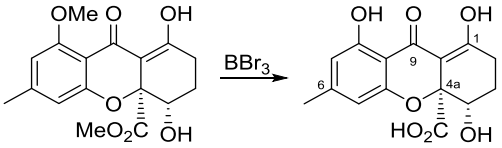
UV (CH_3CN): λ_{max} (nm) (lg ε) = 281 (3.667), 323 (4.116).

MS (ESI): *m*/*z* (%) = 691.2 (100) $[2M+Na]^+$, 357.1 (64) $[M+Na]^+$, 335.1 (35) $[M+H]^+$.

$C_{17}H_{18}O_7$ (334.32) calc.: 335.1125

found: 33.1127 $[M+H]^+$ (ESI-HRMS).

5.4.6 (4*S*,4a*S*)-1,4,8-Trihydroxy-6-methyl-9-oxo-2,3,4,4a-tetrahydroxanthene-4a-carboxylate (306)



syn-**69** **306**

A solution of tetrahydroxanthenone *syn*-**303** (18.0 mg, 54.0 μmol, 1.00 eq.) in CH_2Cl_2 (2.2 mL) was treated with BBr_3 (0.54 mL, 1.0 M in CH_2Cl_2, 0.54 mmol, 10.0 eq.) at 0 °C and stirred at RT for 1 h. The reaction was quenched by dropwise addition of H_2O (10 mL) at 0 °C and the aq. layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. After column chromatography on RP silica gel (H_2O/MeOH 50:50 → 0:100) carboxylic acid *syn*-**306** was obtained as a white solide (7.2 mg, 23.5 μmol, 44%).

Optical Rotation: $[\alpha]_D$ = –166.9 (c = 0.40, MeOH, 23.6 °C).

^{1}H-NMR (600 MHz, CD_3OD): δ (ppm) = 1.98 (ddd, *J* = 12.2, 8.8, 5.2 Hz, 1 H, 3-H_a), 2.23–2.30 (m, 1 H, 3-H_b), 2.26 (s, 3 H, 6-CH_3), 2.53 (dd, *J* = 19.4, 6.7 Hz, 1 H, 2-H_a), 2.70 (ddd, *J* = 19.0, 11.3, 7.2 Hz, 1 H, 2-H_b), 4.21 (dd, *J* = 12.4, 4.6 Hz, 1 H, 4-H), 6.27, 6.41 (2 × s, 2 H, 5-H, 7-H).

^{13}C-NMR (125 MHz, CD_3OD): δ (ppm) = 22.5 (6-CH_3), 26.2 (C-3), 28.6 (C-2), 72.4 (C-4), 85.9 (C-4a), 103.8 (C-9a), 106.2 (C-8a), 110.1, 111.1 (C-5, C-7), 151.2 (C-6), 161.1 (C-8), 162.9 (C-10a), 173.8 (CO_2H), 178.5 (C-1), 188.7 (C-9).

IR: $\tilde{\nu}$ (cm^{-1}) = 3358, 2925, 1726, 1612, 1579, 1459, 1418, 1363, 1297, 1247, 1202, 1065, 834, 728.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 220 (4.078), 279 (3.595), 334 (3.943).

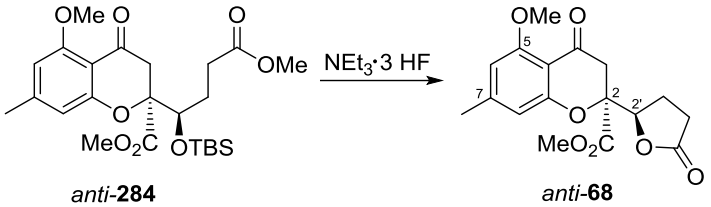
MS (ESI): *m*/*z* (%) = 611.1 (7) $[2M–H]^-$, 305.1 (100) $[M–H]^-$.

$C_{15}H_{14}O_7$ (306.27) calc.: 305.0667

found: 305.0667 $[M–H]^-$ (ESI-HRMS).

5.5 Syntheses of (–)-gonytolide C (*ent*-9c) and 2'-*epi*-gonytolide C (2'-*epi*-9c)

5.5.1 (2*S*,2'*R*)-2-(5-Oxotetrahydrofuran-2-yl)-5-methoxy-7-methyl-4-oxochroman-2-methyl carboxylate (*anti*-68)



anti-**284** *anti*-**68**

A solution ester of *anti*-**284** (30.0 mg, 62.4 μmol, 1.00 eq.) in dioxane (1.5 mL) was treated with NEt_3·3 HF (260 μL, 1.56 mmol, 25.0 eq.) at RT. The resulting reaction mixture was stirred at 60 °C for 3 d. Additional NEt_3·3 HF (260 μL, 1.56 mmol, 25.0 eq.) was added and the reaction heated at 60 °C for further 3 d. The reaction mixture was quenched by the addition of sat. aq. $NaHCO_3$ solution (10 mL), the aq. phase extracted with EtOAc (3 × 10 mL), the combined organic phases were dried over Na_2SO_4 and the solvent removed *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 1:1 → 1:2) provided chromanyl lactone *anti*-**68** as a white solid (18.2 mg, 54.4 μmol, 87%).

Optical Rotation: $[\alpha]_D$ = –24.9 (c = 0.50, $CHCl_3$, 22.2 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.32 (s, 3 H, 7-CH_3), 2.34–2.46 (m, 2 H, 3'-H_2), 2.55 (ddd, *J* = 17.9, 10.3, 6.3 Hz, 1 H, 4'-H_a), 2.69 (ddd, *J* = 17.9, 10.1, 7.0 Hz, 1 H, 4'-H_b), 2.85 (d, *J* = 16.3 Hz, 1 H, 3-H_a), 2.98 (d, *J* = 16.2 Hz, 1 H, 3-H_b), 3.68 (s, 3 H, CO_2CH_3), 3.86 (s, 3 H, 5-OCH_3), 4.83 (dd, *J* = 8.2, 5.5 Hz, 1 H, 2'-H), 6.34, 6.51 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.9 (C-3'), 22.5 (7-CH_3), 27.7 (C-4'), 41.3 (C-3), 53.4 ($CO_2\underline{C}H_3$), 56.1 (5-OCH_3), 81.1 (C-2'), 83.9 (C-2), 105.9, 110.5 (C-6, C-8), 108.7 (C-4a), 148.7 (C-7), 160.4 (C-8a), 161.1 (C-5), 169.0 ($\underline{C}O_2CH_3$), 175.7 (C-5'), 185.9 (C-4).

IR: $\tilde{\nu}$ (cm^{-1}) = 2955, 2851, 1781, 1757, 1736, 1680, 1614, 1567, 1462, 1414, 1347, 1259, 1225, 1179, 1121, 1098, 1072, 1048, 821, 729, 545.

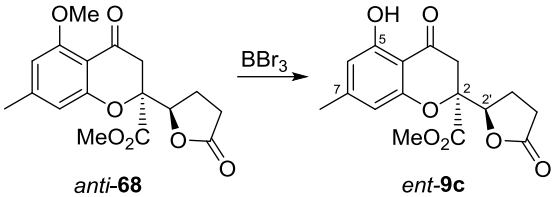
UV (CH_3CN): λ_{max} (nm) (lg ε) = 219 (4.252), 270 (4.040), 326 (3.569).

MS (ESI): *m/z* (%) = 691.2 (100) $[2M+Na]^+$, 357.1 (74) $[M+Na]^+$, 335.1 (45) $[M+H]^+$.

$C_{17}H_{18}O_7$ (334.32) calc.: 335.1125

found: 335.1127 $[M+H]^+$ (ESI-HRMS).

5.5.2 (–)-Gonytolide C (*ent*-9c)



A solution of chromanyl lactone *anti*-**68** (14.7 mg, 44.0 μmol, 1.00 eq.) in CH_2Cl_2 (2.2 mL) was treated with BBr_3 (0.44 mL, 1.0 M in CH_2Cl_2, 440 μmol, 10.0 eq.) at –78 °C and stirred at this temperature for 2 h. The reaction was quenched by dropwise addition of sat. aq. $NaHCO_3$ solution (10 mL) at –78 °C and the aq. layer extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. After column chromatography on silica gel (*n*-pentane/EtOAc = 2:1 → 1:2) (–)-gonytolide C (*ent*-**9c**) was obtained as a white solid (10.9 mg, 34.0 μmol, 77%).

Optical Rotation: $[\alpha]_D$ = –28.5 (c = 0.10, $CHCl_3$, 24.7 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.29 (s, 3 H, 7-CH_3), 2.41 (m_c, 2 H, 3'-H_2), 2.57 (ddd, *J* = 17.7, 10.2, 6.6 Hz, 1 H, 4'-H_a), 2.69 (ddd, *J* = 17.2, 9.9, 7.1 Hz, 1 H, 4'-H_b), 2.93 (d, *J* = 16.9 Hz, 1 H, 3-H_a), 3.09 (d, *J* = 16.9 Hz, 1 H, 3-H_b), 3.72 (s, 3 H, CO_2CH_3), 4.84 (dd, *J* = 8.0, 5.7 Hz, 1 H, 2'-H), 6.36, 6.38 (2 × s, 2 H, 6-H, 8-H), 11.36 (s, 1 H, 5-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 22.0 (C-3'), 22.6 (7-CH_3), 27.6 (C-4'), 39.4 (C-3), 53.6 ($CO_2\underline{C}H_3$), 80.9 (C-2'), 84.0 (C-2), 105.6 (C-4a), 108.5, 111.1 (C-6, C-8), 151.6 (C-7), 159.0 (C-8a), 161.8 (C-5), 169.0 ($\underline{C}O_2CH_3$), 175.5 (C-5'), 193.0 (C-4).

IR: $\tilde{\nu}$ (cm^{-1}) = 2924, 2853, 1785, 1759, 1738, 1644, 1570, 1455, 1366, 1262, 1220, 1131, 1074, 1055, 1033, 935, 837, 800, 734, 702, 555.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 277 (3.970), 344 (3.392).

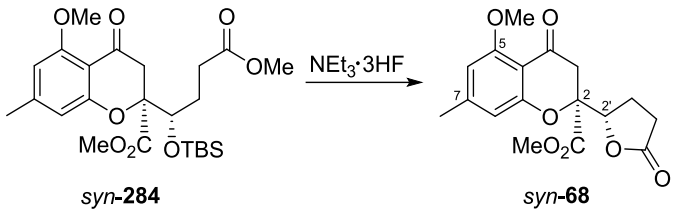
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH 75:25, 0.8 mL/min): t_R = 16.0 min.

MS (ESI): *m/z* (%) = 663.2 (50) $[2M+Na]^+$, 658.2 (10) $[2M+NH_4]^+$, 343.1 (85) $[M+Na]^+$, 338.1 (29) $[M+NH_4]^+$, 321.1 (100) $[M+H]^+$.

$C_{16}H_{16}O_7$ (320.29) calc.: 321.0969

found: 321.0970 $[M+H]^+$ (ESI-HRMS).

5.5.3 (2*S*,2'*S*)-2-(5-Oxotetrahydrofuran-2-yl)-5-methoxy-4-oxochroman-2-methyl carboxylate (*syn*-68)



syn-**284** *syn*-**68**

A solution of ketone *syn*-**284** (140 mg, 291 μmol, 1.00 eq.) in dioxane (7.3 mL) was treated with $NEt_3 \cdot 3$ HF (1.19 mL, 7.28 mmol, 25.0 eq.) at RT. The resulting reaction mixture was stirred at 60 °C for 3 d. Additional $NEt_3 \cdot 3$ HF (1.19 mL, 7.28 mmol, 25.0 eq) was added and the reaction mixture heated at 60 °C for further 3 d. The reaction mixture was quenched by addition of sat. aq. $NaHCO_3$ solution (10 mL) and H_2O (10 mL), the aq. phase extracted with EtOAc (3 × 10 mL) and the solvent evaporated *in vacuo*. Column chromatography on silica gel (*n*-pentane/EtOAc = 1:1 → 1:2) provided chromanyl lactone *syn*-**68** (81.4 mg, 244 μmol, 84%).

Optical Rotation: $[\alpha]_D = -26.4$ (c = 0.21, $CHCl_3$, 22.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.26–2.33 (m, 1 H, 3'-H_a), 2.31 (s, 3 H, 7-CH_3), 2.43 (dddd, *J* = 13.2, 10.3, 5.1, 4.2 Hz, 1 H, 3'-H_b), 2.53 (ddd, *J* = 17.9, 10.6, 5.0 Hz, 1 H, 4'-H_a), 2.78 (ddd, *J* = 18.2, 10.4, 8.0 Hz, 1 H, 4'-H_b), 2.94 (d, *J* = 16.3 Hz, 1 H, 3-H_a), 3.33 (d, *J* = 16.3 Hz, 1 H, 3-H_b), 3.68 (s, 3 H, CO_2CH_3), 3.85 (s, 3 H, 5-OCH_3), 4.76 (dd, *J* = 8.6, 4.2 Hz, 1 H, 2'-H), 6.32, 6.45 (2 × s, 2 H, 6-H, 8-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.7 (C-3'), 22.4 (7-CH_3), 27.8 (C-4'), 42.2 (C-3), 53.4 ($CO_2\underline{C}H_3$), 56.1 (5-OCH_3), 79.8 (C-2'), 84.5 (C-2), 105.9 110.3 (C-6, C-8), 108.5 (C-4a), 148.3 (C-7), 160.2 (C-8a), 160.8 (C-5), 169.2 ($\underline{C}O_2CH_3$), 176.2 (C-5'), 187.0 (C-4).

IR: $\tilde{\nu}$ (cm^{-1}) = 2955, 2850, 1781, 1749, 1682, 1614, 1567, 1463, 1413, 1346, 1258, 1225, 1163, 1123, 1058, 1028, 1006, 954, 929, 834, 822, 700, 575.

UV (CH_3CN): λ_{max} (nm) (lg ε) = 219 (4.3297), 269 (4.0995), 325 (3.6446).

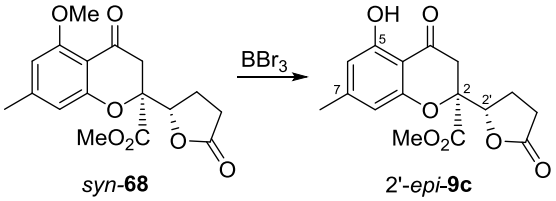
Analytical HPLC (*Daicel* Chiralpak IA®, 4.6 × 250 mm, 5 μm, *n*-hexane/2-PrOH 85:15, 0.8 mL/min): t_R = 15.9 min.

MS (ESI): *m*/*z* (%) = 691.2 (10) $[2M+Na]^+$, 357.1 (32) $[M+Na]^+$, 335.1 (100) $[M+H]^+$.

$C_{17}H_{18}O_7$ (334.32) calc.: 335.1125

found: 335.1125 $[M+H]^+$ (ESI-HRMS).

5.5.4 2'-*epi*-gonitolyde C (2'-*epi*-9c)



A solution of chromanyl lactone *syn*-**68** (16.0 mg, 47.9 μmol, 1.00 eq.) in CH_2Cl_2 (2.4 mL) was treated with BBr_3 (0.48 mL, 1 M in CH_2Cl_2, 479 μmol, 10.0 eq.) at –78 °C and stirred at –78 °C for 2 h. The reaction was quenched by dropwise addition of sat. aq. $NaHCO_3$ solution (10 mL) at –78 °C and the aq. layer extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. After column chromatography on silica gel (*n*-pentane/EtOAc = 2:1 → 1:3) 2'-*epi*-gonytolide C (2'-*epi*-**9c**) was obtained as a white solid (13.2 mg, 41.2 μmol, 86%).

Optical Rotation: $[\alpha]_D$ = –32.4 (c = 0.10, $CHCl_3$, 22.5 °C).

^{1}H-NMR (600 MHz, $CDCl_3$): δ (ppm) = 2.28 (s, 3 H, 7-CH_3), 2.28–2.35 (m, 1 H, 3'-H_a), 2.47 (m_c, 1 H, 3'-H_b), 2.55 (ddd, *J* = 17.7, 10.5, 4.9 Hz, 1 H, 4'-H_a), 2.79 (ddd, *J* = 17.9, 10.2, 4.9 Hz, 1 H, 4'-H_b), 3.04 (d, *J* = 17.2 Hz, 1 H, 3-H_a), 3.43 (d, *J* = 17.3 Hz, 1 H, 3-H_b), 3.72 (s, 3 H, CO_2CH_3), 4.75 (dd, *J* = 8.5, 4.1 Hz, 1 H, 2'-H), 6.34, 6.35 (2 × s, 2 H, 6-H, 8-H), 11.39 (s, 1 H, 5-OH).

^{13}C-NMR (125 MHz, $CDCl_3$): δ (ppm) = 21.7 (C-3'), 22.6 (7-CH), 27.8 (C-4'), 40.3 (C-3), 53.7 ($CO_2\underline{C}H_3$), 79.7 (C-2'), 84.6 (C-2), 105.5 (C-4a), 108.3, 111.0 (C-6, C-8), 151.2 (C-7), 158.9 (C-8a), 161.7 (C-5), 169.1 ($\underline{C}O_2CH_3$), 176.0 (C-5'), 194.0 (C-4).

IR: $\tilde{\nu}$ (cm^{-1}) = 3358, 2955, 1773, 1741, 1636, 1568, 1455, 1359, 1288, 1263, 1207, 1181, 1120, 1087, 1064, 1030, 837, 807, 743, 704.

UV (MeOH): λ_{max} (nm) (lg ε) = 224 (3.9672), 276 (3.8614), 343 (3.2846).

MS (ESI): *m*/*z* (%) = 663.2 (71) $[2M+Na]^+$, 343.1 (67) $[M+Na]^+$, 338.1 (25) $[M+NH_4]^+$, 321.1 (100) $[M+H]^+$.

$C_{16}H_{16}O_7$ (320.29) calc.: 343.0788

found: 343.0787 $[M+Na]^+$ (ESI-HRMS).

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2 List of Abbrevations

Å	Ångström (10^{-10} m)
Ac	acetyl
Ac_2O	acetanhydrid
aq.	aqueous
Ar	aryl
atm	atmophäre = 1013.25 hPa
Bn	benzyl
BOXAX	BisOXazolin ligand with AXial chirality
Bu	butyl
br	broad
C	concentration
cat.	Catalytic
conc.	concentrated
COSY	correlated spectroscopy
calc	calculated
CD	circular dichroism
d	day, doublet
dba	(*E*,*E*)-dibenzylidenacetone
DABCO	1,4-diazabicyclo[2.2.2]-octane
DBU	1,8-diazabicyclo[5.4.0]un-dec-7-en
DDQ	2,3-dichlor-5,6-dicyano-benzoquinone
DIBAL-H	diisobutylaluminiumhydride
DMAP	4-(*N*,*N*-dimethylamino)pyri-dine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DHQ	dihydroquinine
DHQD	dihydroquinidine
d.r.	diastereomeric ratio
EDDA	ethylenediamine diacetate
ee	*enantiomeric excess*
EI	elektron ionization
eq.	equivalent(s)
ESI	electron spray ionization
Et	ethyl
Et_2O	diethylether
EtOAc	ethyl acetate
EtOH	ethanol
gem	geminal
h	hour
HI(V)	human immunodeficiency (virus)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoramide
AcOH	acetic acid
HPLC	high performance chromate-graphie
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	Hertz (m^{-1})
i	*iso*-, *ipso*-
IBX	2-iodoxybenzoic acid
*i*Bu	*iso*-butyl
*i*Pr	*iso*-propyl
IR	infrared spectroscopy

L	ligand
m	*meta*
M	molar, mol/L
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
MEM	2-(methoxyethoxy)methyl
MeOH	methanol
min	minute
MMPP	magnesium monoperoxy-phthalate
MOM	methoxymethyl
MS	mass spectrometry
ms	molecular sieves
Ms	methansulfonyl, mesyl
MTBE	methyl *tert*-butyl ether
MW	microwave irradiation
NADP	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholin-*N*-oxide
NMP	1-methyl-2-pyrrolidone
NMR	nuclear magnetic resonace
NOE	nuclear Overhauser effect
NOESY	NOE-spektroscopy
Nu	nucleophile
o	*ortho*
OAc	acetate
OMe	methoxy
OTf	trifluorosulfonate, triflate
OTFA	trifluoroacetate
p	*para*
PG	protecting group
Ph	phenyl
Pr	propyl
p-TsO	*para*-toluolsulfonic acid
quant.	quantitative
R	residue
rac	racemic
R_f	ratio of fronts
RT	room temperature
t	tertiary
TASF	tris(dimethylamino)sul-fonium difluorotrimethyl-silicate
TBA	tetrabutylammonium
TBS	*tert*-butlyldimethylsilyl
TDDF	time-dependent density functional theory
Tf	trifluoromethansulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethyl-ethylendiamine
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium-perruthenate
t_R	retention time
UV	Ultraviolett spectroscopy
vic	vicinal

3 Crystal Data and Structure Refinement for (–)-Diversonol

Identification code of *ent*-**10**	p212121	
Empirical formula	$C_{15}\ H_{18}\ O_6$	
Formula weight	294.29	
Temperature	100(2) K	
Wavelength	0.56086 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.683(2) Å	α= 90°.
	b = 10.096(2) Å	β= 90°.
	c = 19.475(3) Å	γ = 90°.
Volume	1313.9(5) $Å^3$	
Z	4	
Density (calculated)	1.488 Mg/m^3	
Absorption coefficient	0.071 mm^{-1}	
F(000)	624	
Theta range for data collection	1.650 to 20.535°.	
Index ranges	-8<=h<=8, -12<=k<=12, -23<=l<=24	
Reflections collected	14565	
Independent reflections	2678 [R(int) = 0.0306]	
Completeness to theta = 19.665°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2678 / 0 / 197	
Goodness-of-fit on F^2	1.049	
Final R indices [I>2sigma(I)]	R1 = 0.0278, wR2 = 0.0667	
R indices (all data)	R1 = 0.0301, wR2 = 0.0679	
Absolute structure parameter	0.3(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.254 and -0.174 $e.Å^{-3}$	

Bruker Smart APEX II Quazar
INCOATEC Ag-Microfocus Source

Bond lengths [Å] and angles [°] for *ent*-**10**.

O(1)-C(10A)	1.370(2)
O(1)-C(4A)	1.454(2)
O(2)-C(4)	1.437(2)
O(3)-C(1)	1.434(2)
O(4)-C(9A)	1.432(2)
O(5)-C(9)	1.225(2)
O(6)-C(8)	1.353(2)
C(1)-C(2)	1.522(3)
C(1)-C(9A)	1.542(2)
C(2)-C(3)	1.534(3)
C(3)-C(4)	1.523(3)
C(4)-C(4A)	1.538(3)
C(4A)-C(11)	1.526(3)
C(4A)-C(9A)	1.544(2)
C(5)-C(10A)	1.382(3)
C(5)-C(6)	1.396(3)
C(6)-C(7)	1.390(3)
C(6)-C(12)	1.504(3)
C(7)-C(8)	1.388(3)
C(8)-C(8A)	1.411(3)
C(8A)-C(10A)	1.412(3)
C(8A)-C(9)	1.459(3)
C(9)-C(9A)	1.534(3)

C(10A)-O(1)-C(4A)	116.80(14)
O(3)-C(1)-C(2)	108.59(15)
O(3)-C(1)-C(9A)	112.22(14)
C(2)-C(1)-C(9A)	110.35(15)
C(1)-C(2)-C(3)	113.28(15)
C(4)-C(3)-C(2)	111.91(15)
O(2)-C(4)-C(3)	107.89(15)
O(2)-C(4)-C(4A)	111.55(14)
C(3)-C(4)-C(4A)	109.90(15)
O(1)-C(4A)-C(11)	107.56(14)
O(1)-C(4A)-C(4)	104.95(14)
C(11)-C(4A)-C(4)	110.25(15)
O(1)-C(4A)-C(9A)	108.65(14)

C(11)-C(4A)-C(9A)	114.45(15)
C(4)-C(4A)-C(9A)	110.49(15)
C(10A)-C(5)-C(6)	119.69(18)
C(7)-C(6)-C(5)	119.95(18)
C(7)-C(6)-C(12)	119.96(17)
C(5)-C(6)-C(12)	120.08(18)
C(8)-C(7)-C(6)	120.45(17)
O(6)-C(8)-C(7)	117.63(16)
O(6)-C(8)-C(8A)	121.61(17)
C(7)-C(8)-C(8A)	120.75(18)
C(8)-C(8A)-C(10A)	117.52(17)
C(8)-C(8A)-C(9)	121.97(17)
C(10A)-C(8A)-C(9)	120.42(16)
O(5)-C(9)-C(8A)	123.70(16)
O(5)-C(9)-C(9A)	122.35(17)
C(8A)-C(9)-C(9A)	113.88(16)
O(4)-C(9A)-C(9)	102.22(14)
O(4)-C(9A)-C(1)	107.52(14)
C(9)-C(9A)-C(1)	114.31(15)
O(4)-C(9A)-C(4A)	111.82(15)
C(9)-C(9A)-C(4A)	107.81(14)
C(1)-C(9A)-C(4A)	112.73(15)
O(1)-C(10A)-C(5)	116.32(16)
O(1)-C(10A)-C(8A)	122.04(16)
C(5)-C(10A)-C(8A)	121.64(16)

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