Towards a Total Synthesis of Mensacarcin

Dissertation
zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultäten
der Georg-August-Universität zu Göttingen

vorgelegt von
Marta Ewa Polomska
aus Gdansk

Göttingen 2004

D 7
Referent: Prof. Dr.Dr. h. c. L. F. Tietze
Korreferent: Prof. Dr. A. Zeeck
Tag der mündlichen Prüfung: 03.11.2004

Moim rodzicom

The material presented in this thesis represents the result of work carried out from October 2001 to August 2004 at the Institute of Organic and Biomolecular Chemistry, Georg-August University.

I would like to thank my supervisor, Professor Lutz Tietze, for his excellent supervision, guidance and the opportunity to undertake research within his group. His devotion to and knowledge of chemistry combined with the ability to share these traits with me is greatly appreciated.

Table of Contents

1 Introduction

"In organic chemistry there are many surprises and many disappointments; there are no miracles."

John C. Sheehan, 1982

In the last fifty years many chemical syntheses were developed which could not have been accomplished in the earlier part of the 20th century. Several very complex molecules have been synthesised, for example vitamin A (*O. Isler*, 1949), cortisone (*R. B. Woodward*, *R. Robinson*, 1951), morphine (*M. Gates*, 1956), penicillin (*J. C. Sheehan*, 1957) and chlorophyll (*R. B. Woodword*, 1960).[1] The break through in chemical synthesis, can be dated from the award of the Nobel Prize in Chemistry to *R. B. Woodword* in 1965. Since this time, organic synthesis has been developed to a high level. Advances have been possible by availability of new reagents and the discovery of new reactions. Improvement of methods for analysis, purification and determination of structure has made life easier for the organic chemist. Investigations of mechanistic aspects of transformation and a better understanding of synthetic processes has also led to great improvements in drug production.

In the past, synthetic success was mostly dependent on the choice of starting material, where currently it depends more on the planning of the synthesies. In 1957 *E. J. Corey* came up with the new idea of designing a chemical synthesis through retrosynthetic disconnections.[2] Today retrosynthetic analysis or a retrosynthetic way of thinking is a problem solving technique, which is the basis of all synthetic planning.

What is the role played by organic chemists in the discovery process? The answer is simple, organic chemistry is one of the backbones of science. However, chemical research is very expensive and very often research groups struggling with lack of funding find new discovery difficult. Today it is not enough to do only research for its beauty one has to know how to “sell” the project, that’s why all new target compounds have to have attractive biological properties. Specifically, in the drug discovery process academic laboratories provide basic research, which can provide novel ways of attacking diseases. The key to success is to organise research in a

multidisciplinary fashion as in the large pharmaceutical companies, where the drug discovery process is performed by teams, with chemistry as one of the key elements.

The work described within this thesis focuses upon developing total synthesis of mensacarcin (**1**) a new natural product displaying cytostatic and cytotoxic properties, which may have the potential of a new drug in the fight against cancer.

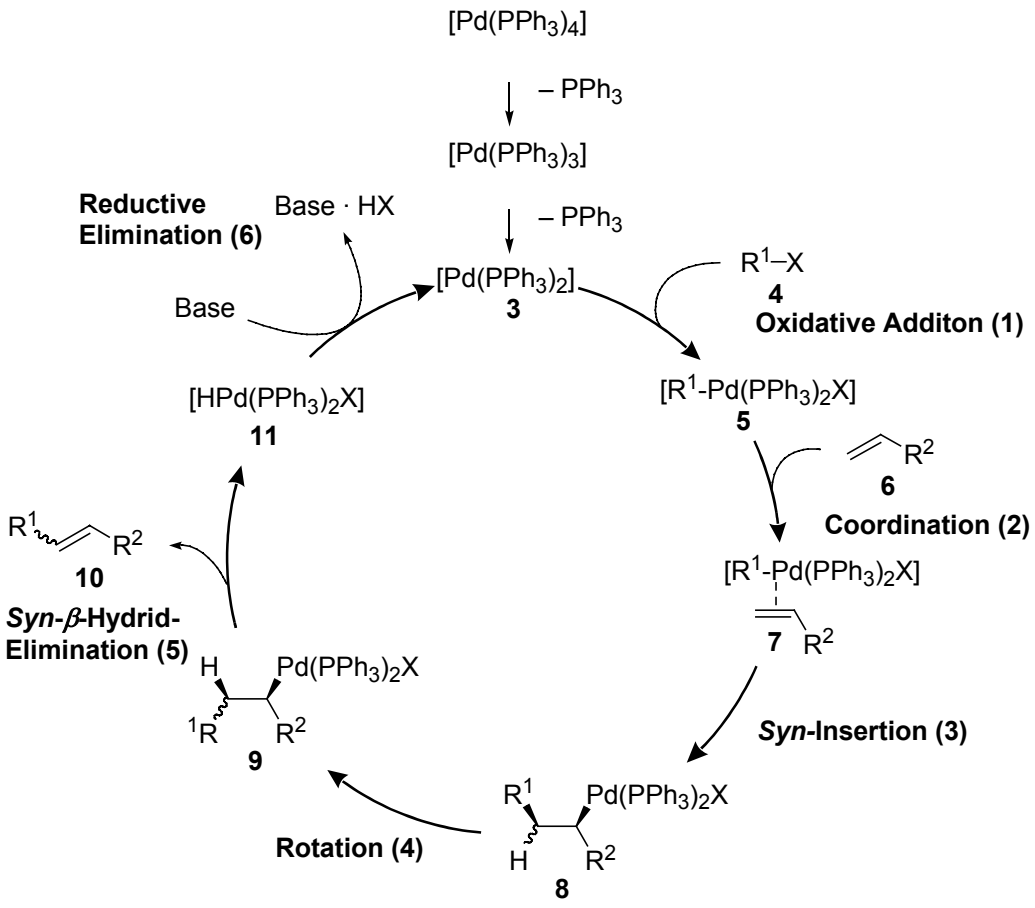
2 Theoretical Background

2.1 The *Heck* Reaction

Palladium-catalysed transformations have been developed very intensive in recent years. The advantage of Pd^0-catalysed reactions in formation of C–C, C–O, C–N bonds is the mildness of reaction conditions which allows for the tolerance of many functional groups. There are a number of excellent reviews covering different aspects of *Heck* chemistry.[3] The catalyst involved in the *Heck* transformation is often anything containing palladium where a small variation of substrate structure, ligands, nature of base, temperature, etc. often leads to different results. The term *Heck* chemistry is associated in the first place with the catalytic arylation and alkenylatioin of olefins, that is the original *Heck* or *Mizoroki-Heck* reaction, developed independently by *Mizoroki* and *Heck*.[3a]

Since its discovery in the early 1980s, the palladium-catalysed arylation of olefins has been applied to a diverse array of fields, from natural products synthesis and biomolecular chemistry to material science.[4] This powerful carbon-carbon bond forming process has been used on an industrial scale for the production of compounds such as naproxen[5] and octyl methoxycinnamate.[6] Functional group tolerance and the ready availability and low cost of simple olefins, compared to the vinylmetal compounds that are employed in the corresponding *Suzuki*, *Stille*, *Kumada* and other cross-coupling reactions, contribute to the exceptional utility of the *Heck* reaction.

2.1.1 The Heck Catalytic Cycle



R^1 = Alkenyl, Aryl, Benzyl, Alkinyl
R^2 = Alkenyl, Aryl, Alkyl, CO_2R', OR', SiR'_3 etc.
X = I, Br, Cl, OSO_2CF_3, SO_2Cl, COCl, $I^+(OAc)$
OSO_2F, $OSO_2C_nF_{2n+1}$, $OPO(OR)_2$

Scheme 2.1.1. Outline of the catalytic cycle for the *Heck* coupling reaction.

2.1.2 Preactivation Step

The catalytic species in the *Heck* reaction is a Pd(0) compound. The preactivation has been extensively studied by *Amatore* and *Jutand* et al.[7] If we use Pd(II) complex such as $Pd(OAc)_2$ the primary reduction of Pd(II) to Pd(0) is most likely accomplished by phosphine in the phosphin-assisted catalysis. The reduction is assisted by hard nucleophiles, of witch the most common are hydroxide[8] and alkoxide ions,[9] water,[10] in special cases even fluoride in the presence of water can play a role.[11] Donor phosphines are more susceptible for oxidation, in this process electron-

withdrawing groups in the phosphine increase the rate of reaction,[12] possibly because the nucleophilic attack at the more electrophilic phosphorus atom is facilitated. In phosphine free systems, the primary reduction of Pd(II) can be effected by amines, if these are used as a base, or an olefin. It is interesting to note that neither Et_3N nor olefins have any detectable influence on the reduction rate in the presence of phosphine. Indirect evidence tells that reduction can also be effected by quaternary ammonium and phosphonium salts,[13] possibly initiated by oxidative addition to C – P or C – N bonds. In the presence of excess ligand, the concentration of active species is strongly decreased, which leads to the inhibition of the catalytic process. However, if we take 2 equiv. of the ligand, the disproportionation of the dicoordinated complex to a stable tricoordinate complex occurs, which then undergo a fast agragation to clusters and further to give inactive metallic particles:

$$PdL_2 \rightleftharpoons PdL_3 + PdL \longrightarrow Pd_nL_m \longrightarrow \text{Pd-black}$$

This problem arises in all methods of the generation of catalytically active Pd complexes, either by reduction of PdL_2X_2 by means chemical reductants[14] or by reaction of $Pd(OAc)_2$ with 3 equiv. of phosphine:

$$Pd(OAc)_2 + 3PPh_3 \longrightarrow Pd(PPh_3)_2 + Ph_3PO$$

or by displacement of dba ligand:

$$Pd(dba)_2 + 2L \longrightarrow PdL_2 + 2dba$$

Full displacement of dba takes much more than 4 equiv. of phosphine.

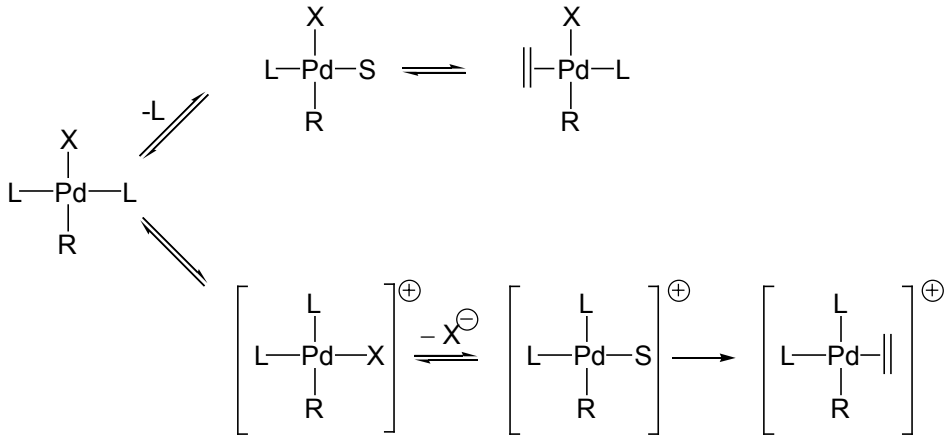
2.1.3 Oxidative Addition

The oxidative addition processes of a concentrated process in which C – X bond breaking is more or less perfectly synchronized with the formation of M – C and M – X bonds. The order of reactivity I >> OTf > Br >> Cl,[15] common to oxidative addition and has no precedence in nucleophilic substitution at sp^2-C. In most cases except for

the complexes with chelating ligands, the isolable products of the oxidative addition possesses *trans*-geometry, thought it is obvious that *cis*-complex must be formed first. Recent work by *Fu*[16] has proven that coupling using aryl chlorides can be accomplished in the presence of sterically hindered, electron-rich phosphines (e.g., P(*t*-Bu)$_3$). Explanation for the enhanced reactivity is that the oxidative addition of an aryl chloride is more facile with a more electron-rich palladium complex.

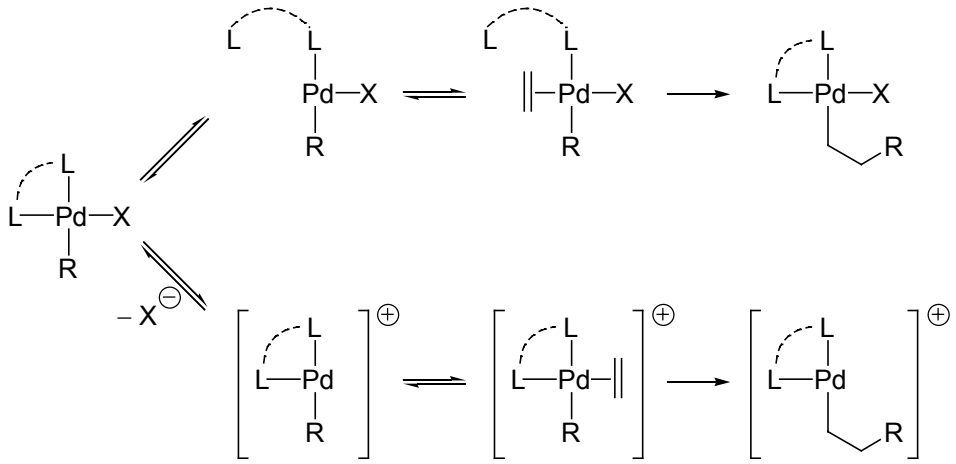
2.1.4 Insertion

Insertion is the product forming step of the *Heck* cycle, in which the new C – C bond is formed. It is the step responsible for regio- and stereoselectivity. The reaction of the product of oxidative addition requires that palladium gets rid of one of the ligands to free a coordination site for alkene. Two different routes have been proposed and proven for this process for phosphine-assisted reactions: the nonpolar route initiated by the deligation of neutral ligand and the cationic route initiate by the deligation of anionic ligand.[17] The most essential is the nature of the detached ligand. For monodentate phosphine complexes, both routes can be realized (Scheme 2.1.2).



Scheme 2.1.2. Monodentate phosphine complexes.

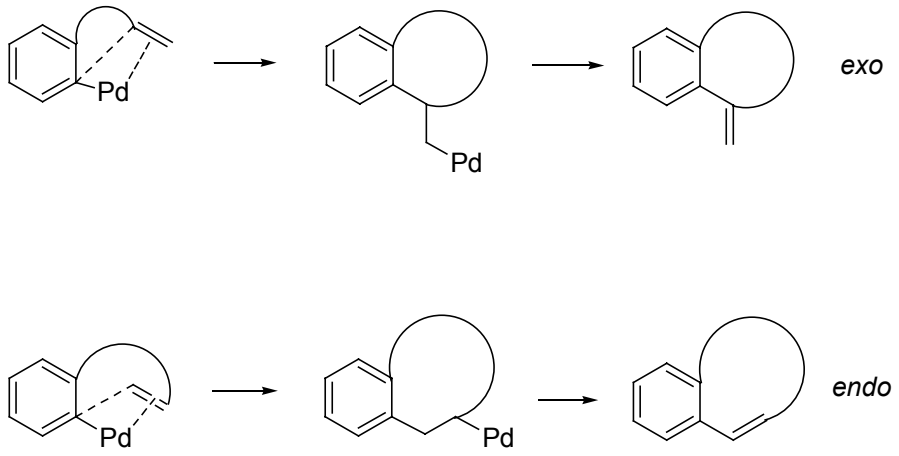
For bidentate phosphine complexes, the large bite-angle diphosphines in which phosphine residues are connected with more flexible spacer, the angel P – Pd – P is larger that 90° required by the squere-planar configuration the nonpolar route takes place (Scheme 2.1.3).[18]



Scheme 2.1.3. Bidentate phosphine complexes.

The insertion of cationic palladium intermediate into alkene is somethimes viewed as an electrophilic addition to double bond, which allows the regioselectivity of insertion based on the stability of carbocations.

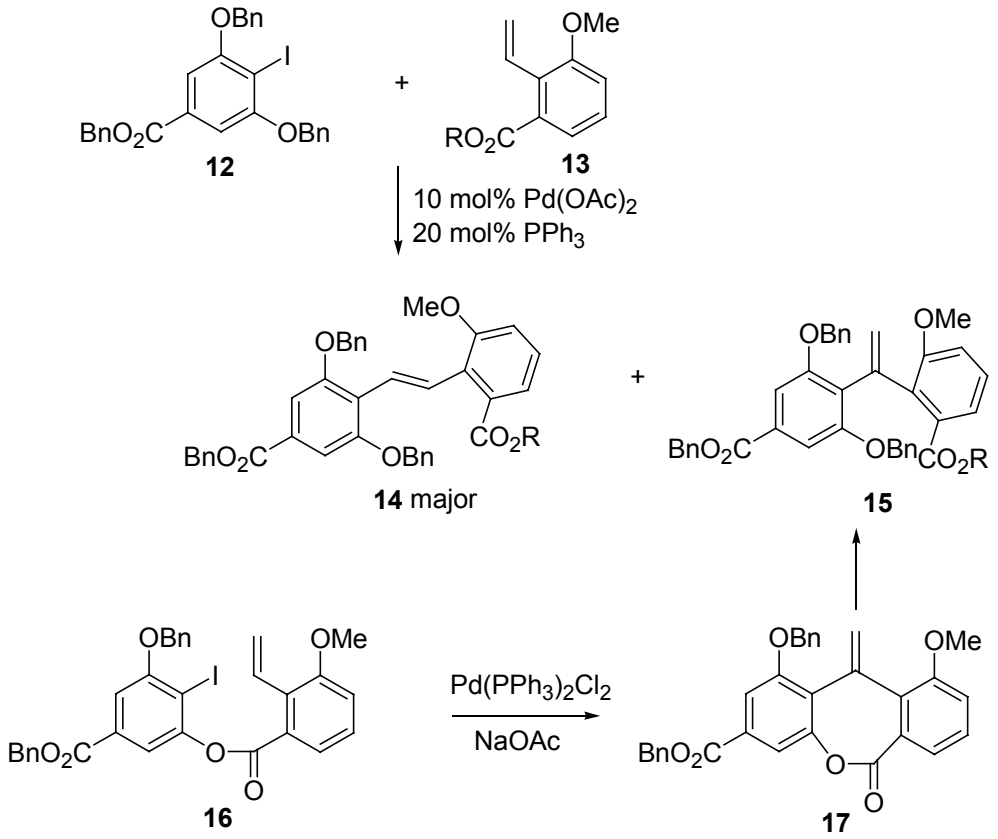
In the intramolecular reactions, entropic factors become dominant in determing the outcome. In the majority of studied cases, reactions proceed *via* the *exo-trig* mode, as this way is by far less sterically demanding. Five-memberd cycle formation is preferred. The *endo-trig* mode requires that the olefinic bond is moved inside the loop in the intermediate π-complex which is more sterically demanding (Scheme 2.1.4).



Scheme 2.1.4. Intramolecular cyclization - *endo, exo-trig.*

An aception the above rules is if the *endo* mode is favoured for electronic reasons (e.g., if the substrate contains a Michael-type olefinic fragment).

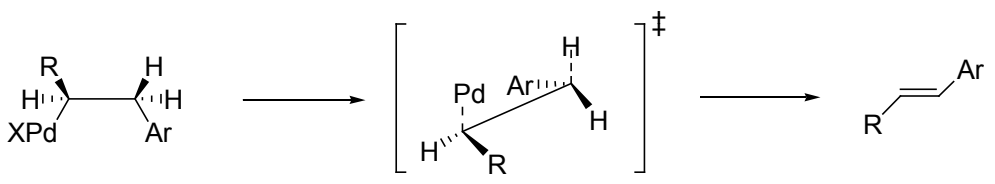
The different regioselectivity of the intra- and intermolecular *Heck* reactions was observed in the cyclisation of Balanol aryl core structure (Scheme 2.1.5).[19]



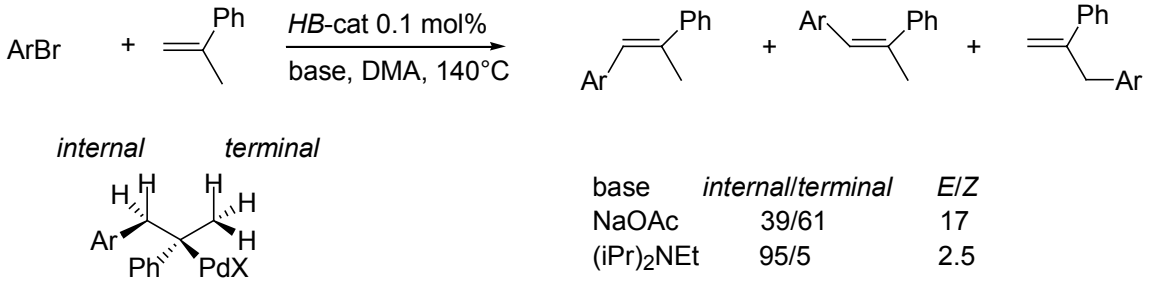
Scheme 2.1.5. Construction of the Balanol aryl core structure.

2.1.5 Palladium Hydride Elimination

The *syn*-Elimination of palladium hydride defines the stereoselectivity of the *Heck* reaction. The *E*-isomer product is predominant and the reaction is highly stereospecific even for very simple models.



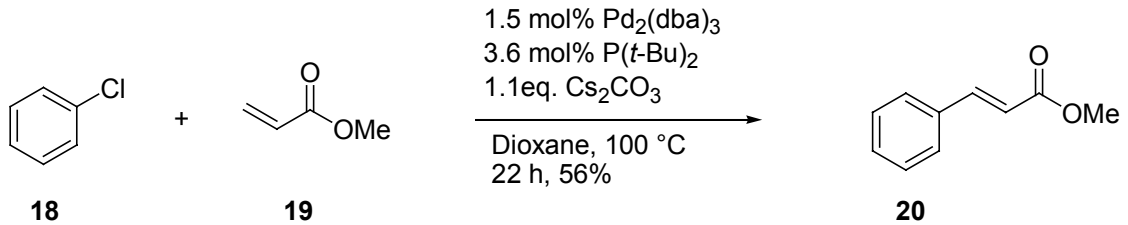
The arylation of disubstituted olefins has been investigated in the presence of Herrmann's palladacycle catalyst *HB* **24** (Scheme 6).[20] This process leads to the mixture of internal and terminal olefins with ratio depending on the nature of the base. The reaction in the presence of amine base gave almost exclusively the internal product.



Schme 2.1.6. The arylation of disubstituted olefins.

2.1.6 Phosphine-Assisted Catalysis

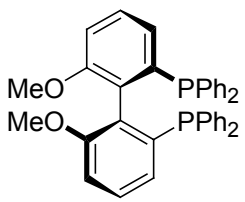
A pioneering effort in the *Heck* reaction was made in 1983 by *Spencer*,[21] who showed that the arylation of olefins with activated aryl bromides can be run with a low loads of catalyst and in solvents such as DMF, in the presence of NaOAc, and phosphine ligands, preferably P(*o*-Tol)$_3$. This result set an initial point for further improvements in developing *Heck* reactions protocols. Reactions of aryl chlorides and less reactive aryl bromides are thought to be dependet on the ability of given catalytic system to undergo oxidative addition to C – Cl or C – Br bonds, which requires highly donating phosphine ligands. In 1999 *Fu*[22] demonstrated that electron-rich phosphines P(*t*-Bu)$_3$ is an unusual but efective ligand for the $Pd_2(dba)_3$-catalyzed coupling of chlorobenzene with methyl acrylate (Scheme 2.1.7).



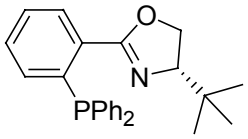
Scheme 2.1.7. P(*t*-Bu)$_3$/$Pd_2(dba)_3$-catalysed coupling.

Two years later the same authors established that a second generation Pd/P(*t*-Bu)$_3$-based catalyst, using Cy_2NMe rather than Cs_2CO_3 as the base, effects Heck reactions of a wide array of aryl bromides and chlorides under very mild conditions.[23] Trialkyl-phosphines are air-sensitive, which makes them more difficult to handle than triarylphosphines. The simple strategy for handling these phosphines is to transform them as their conjugate acid. Solution of phosphine in CH_2Cl_2 mixed with HBF_4 yields [(*t*-Bu)$_3$PH]BF_4 nearly quantitative. This new phosphonium salt is stable to oxygen and to moisture, can be stored in the air for long period of time. Most of palladium catalyzed couplings reactions that employ P(*t*-Bu)$_3$ as a ligand also require Brönsted-base additives, so substituting P(*t*-Bu)$_3$/Pd_2(dba)$_3$ in the original papers with [(*t*-Bu)$_3$PH]BF_4/Pd_2(dba)$_3$ leads to similar results. To understand the mechanism of action a series of ^{31}P NMR studies has been made. In the absence of a Brönsted base, the addition of Pd_2(dba)$_3$ to a solution of [(*t*-Bu)$_3$PH]BF_4 in THF (δ=52) leads to no change in the ^{31}P NMR spectrum. After adding KF, CyNMe or HN(*i*-Pr)$_2$ is added, the resonans for protonated phosphorus disappears and new signal appears (δ=86), corresponding to Pd(P(*t*-Bu)$_3$)$_2$.[24]

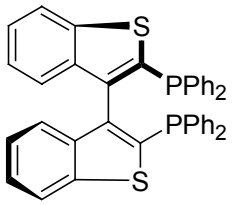
Chelating biphosphines play a major role in the processes in which an intimate control of the coordination sphere is vital, in the first place in enantioselective catalysis (Scheme 2.1.8).[25]



(*R*)-MeO-BIPHEP **21**



22

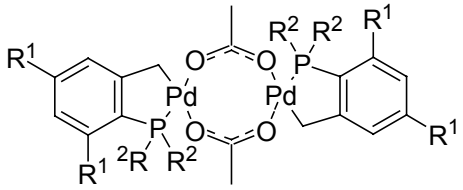


(*R*)-BITIANP **23**

Scheme 2.1.8. Chosen phosphine ligands for enantioselective *Heck* reactions.

2.1.7 Palladacycles

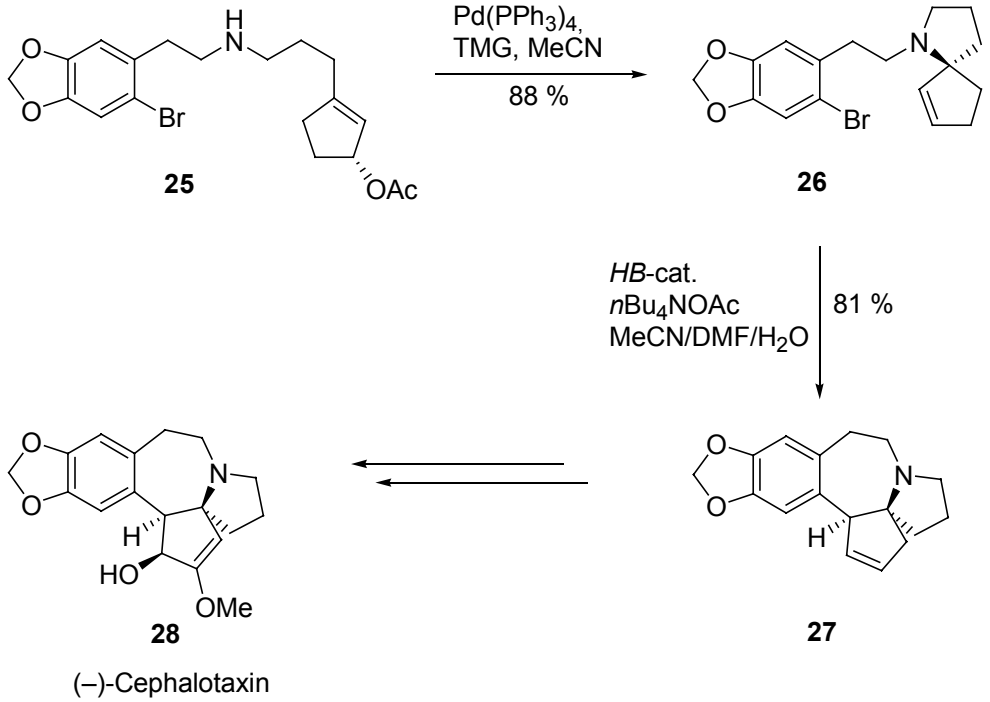
Discovery of the dimeric complex $Pd_2(P(o\text{-Tol})_3)_2(\mu\text{-OAc})_2$ by *Herrmann* and *Beller* et al. providing a unique catalytic activity is definitely one of the most convenient forms of palladium applied in homogeneous catalysis (Scheme 2.1.9).[26]



R^1 = H, R^2 = *o*-Tol
R^1 = Me, R^2 = Mesityl

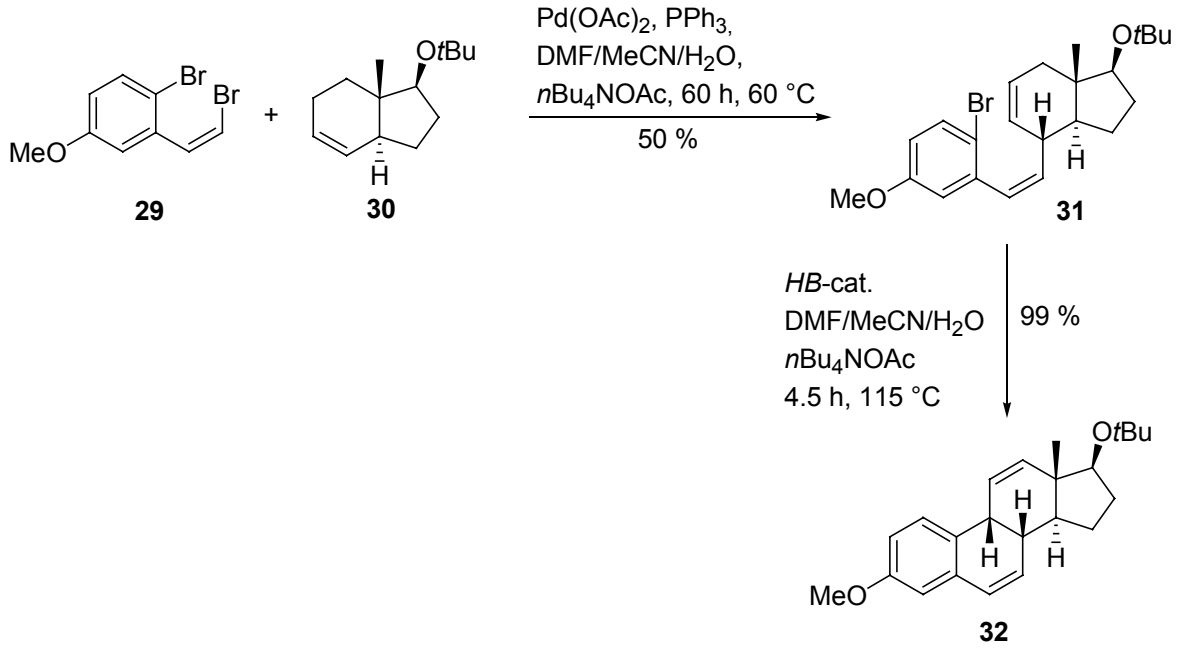
Scheme 2.1.9. *Herrmann-Beller* catalyst (*HB*-cat. **24**).

The so called *HB* catalyst **24** has been shown to be highly effective catalyst for the reaction with aryl bromides at 100-140 °C, particularly those with electron-withdrawing groups. *HB*-palladacycle **24** has been successfully applied in the synthesis of several complex molecules. An exemplary case of this is the intramolecular *exo* cyclisation by *Tietze* et al. (Scheme 2.1.10).[27] The palladacycle catalyzed the formation of a seven-member ring condensed with a *spiro*-system in high yield and stereoselectivity.



Scheme 2.1.10. Synthesis of (-)-Cephalotaxin by *Tietze*.

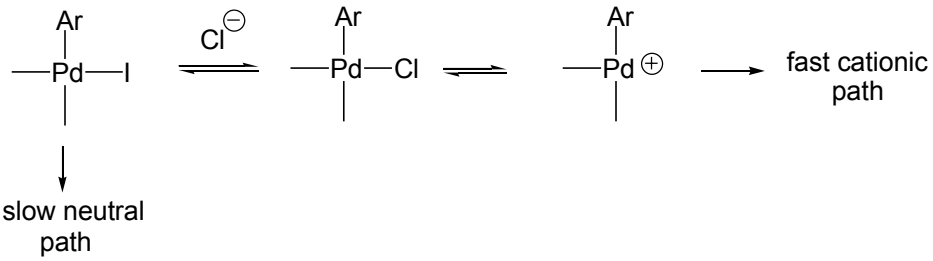
The *HB*-cat. showed spectacular efficiency for the enantioselective synthesis of steroid by intramolecular cyclization. Following an initial intremolecular *Heck* reaction the precursor **31** underwent a second transformation (Scheme 2.1.11).[28]



Scheme 2.1.11. Synthesis of steroid **32** by *Tietze*.

2.1.8 Phase-Transfer Agents in *Heck* Reaction.

The beneficial effect of a quaternary ammonium salts was first noted by *Jeffery*[29] and in further literature the *Heck* reaction in the presence of quaternary ammonium salts has been referred to as Jeffery's conditions. The stabilisation of catalytic system by halide salts has been demonstrated by extending the lifetime of the *HB*-cat. an effect very important for phosphine-free systems. Furthermore, the quaternary ammonium salts can act as an ion exchanger that is particularly important for the reactions with iodides. The exchange of iodide to chloride may lead to switching from the neutral to the cationic mechanism during the *Heck* cycle.



2.2 Organolithium Compounds in Organic Synthesis

A major factor responsible for the phenomenal rise in application of organolithium compounds in synthesis is that simple alkyl-lithium compounds can be used to prepare new organolithium derivatives. In the most important of the available methods, metallation,[30] the organolithium compound is strongly basic carboanion salt, which removes a proton from the substrate to give a new carboanion. Alkanes have pK_a *ca.* 40-45, and alkyl-lithium compounds readily metallate hydrocarbons acids with pK_a *ca.* 35. When the proton to be replaced is less acidic, the effective basicity of the alkyl-lithium compound may be increased by (a) the presence of electron-donating (cation-solvating) solvents or ligands such as TMEDA, THF, DABCO (b) conversion *in situ* into an organopotasium compound by the addition of a potasium alkoxide "superbase". Functional groups in the substrate influence metallation in various ways. (a) Potentially coordinating substituents on aromatic rings facilitate metallation and direct it to *ortho*-positions (b) Electronegative heteroatom able to delocalise negative charge, direct metallation in the *gem*-position. The heteroatom may be part of the ring or an open chain.

2.2.1 Halogen-Lithium Exchange Reaction

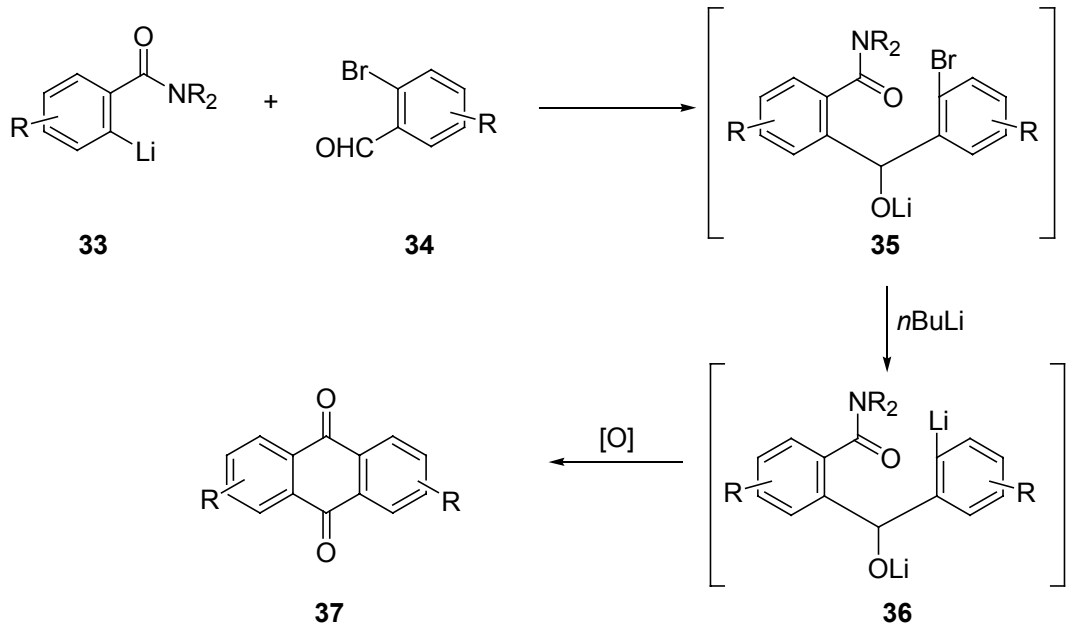
The metal-halogen exchange reaction is itself an extremely useful method for interconverting organolithium compounds. The main characteristics of this important reaction are: (a) it is reversible; (b) it takes place most readily with iodides and bromides, less readily with chlorides and rarely with fluorides; (c) the lithium becomes preferntialy attached to the organic group best able to accommodate a negative charge. The reaction is always in compatition with alkylation and/or metallation, as well as

reaction with functional groups. However, a further important feature is that lithium-halogen exchange proceeds readily at low temperatures (– 78 °C is common and sometimes – 100 °C) in order to supress competing reactions. A complication which sometimes arises is coupling between the desired organolithium compound or a subsequent product and the alkyl halide formed. Such side reaction may be avoided by the use of a one molar excess of *t*butyl-lithium, which reacts with the *t*butyl-halide.[31]

$$RX + t\text{BuLi} \rightleftharpoons RLi + t\text{BuX}$$

$$t\text{BuX} + t\text{BuLi} \longrightarrow Me_2CH{=}CH_2 + t\text{BuH} + LiX$$

Organo-lithium compounds display a strong anionic character that allows reactions with various electrophiles to take place. Asan example, benzamide *ortho*-metyllation, metal-halogen exchange may be used to effect one-pot regioselective synthesis of anthraquinones (Scheme 2.2.1).[32]

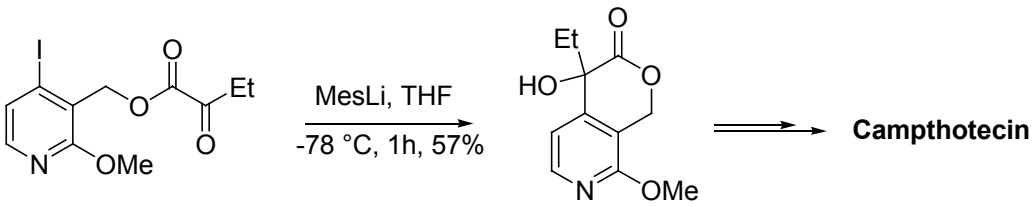


Scheme 2.2.1. Synthesis of Anthraquinones using an anionic cyclisation.

In this sequence of reactions, the initial *orto*-lithiated benzamide **33** is first added to a second aromatic system, which, after lithiation, undergoes an anionic cyclisation. Applied to the preparation of anthraquinones, a lithiated benzamide must first be reacted with a 2-bromobenzaldehyde. In the second step, bromine-lithium exchange

initiates an intramolecular nucleophilic attack to the amide functionality. Final air-oxidation gives a range of antraquinones.

An important precursor for the synthesis of camptothecin was prepared using a halogen-lithium exchange reaction.[33] Mesityllithium was found to be en excellent selective lithiating agent to prepare aryllithium compounds having alkoxycarbonyl groups.



38 **39**

Scheme 2.2.2. Synthesis of Campthothecin precursor.

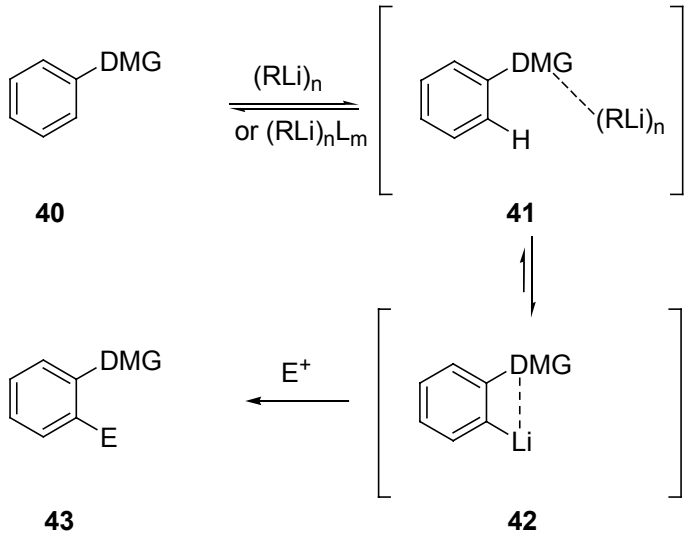
The chemoselective lithiation of iodopyridinylmethyl ketoester **38** was carried out using mesityl-lithium, accompanied by the spontaneous intramolecular 1,2-addition to give the hydroxylactone **39** (Scheme 2.2.2). The conversion of the lactone **39** to camptothecin has been well established by *Comins*, and is consiedered to be straightforword.[34]

2.2.2 Directed *ortho* Metalation Process

The regiospecific preparation and modification of polysubstituted aromatic compounds present many chellenges in synthetic chemistry both industrial and academic laboratories. Many modern synthetic targets, as well as starting materials, used by agrochemical or pharmaceutical industry, are aromatic or heteroaromatic components.[35] In 1939-1940, the independent discovery by *Gilman*, *Bebb,*[36] *Wittig*,[37] and *Fuhrman* of anisole *ortho* deprotonated by *n*BuLi was the beginning for a new concept in synthetic aromatic chemistry. Another laboratory technique of metal-halogen exchange reaction, also discovered by *Gilman*[38] and *Wittig*,[39] provided further development in this area.

The directed *ortho* metalation process may be described as a three-step sequence: coordination of the $(RLi)_n$ aggregate to the heteroatom-containing direct metalation

group (DMG), **40** → **41**; deprotonation to give the coordinated ortho-lithiated species, **41** → **42**; and reaction with electrophile to yield product, **42** → **43**. Crystal structure determination of *ortho*-lithiated species indicated complex tetrameric aggregates with a high degree of lithium-heteroatom coordination can be taken as evidence for existence of intermediate **42** (Scheme 2.2.3).

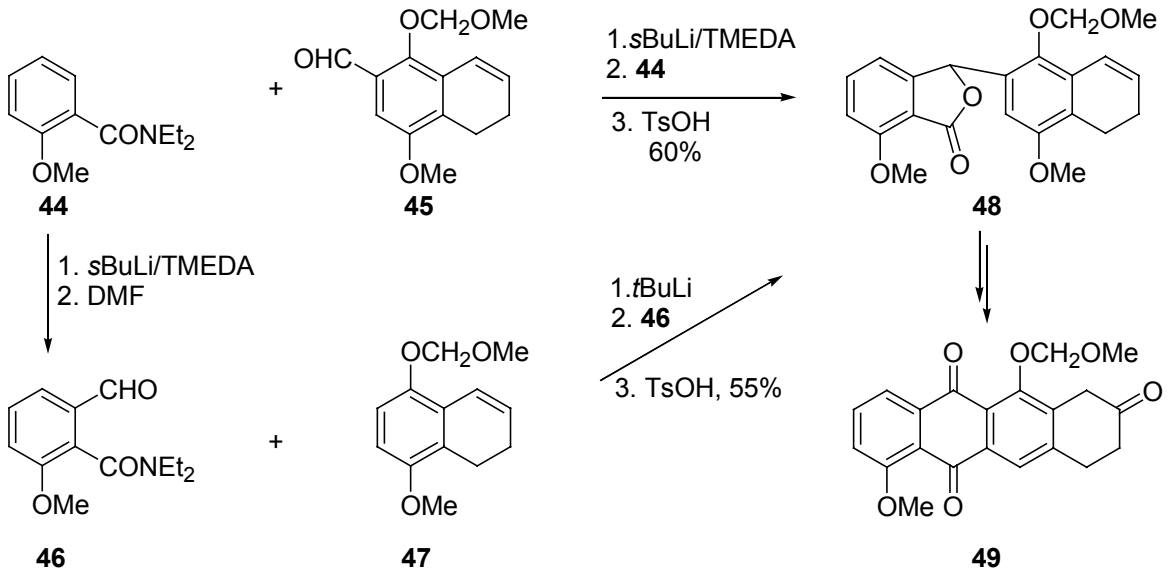


Scheme 2.2.3. Mechanistic aspects of directiong *ortho* metalation.

The process of directed metalation normally needs the use of powerfull alkyllithium bases in organic solvents in which they are high soluble due to association into aggregates, typically as hexamers (in hydrocarbons solvents) or tetramers-dimers (in basic solvents). Bidentate ligands, in particular TMEDA, which can break down alkyllithium aggregates, form monomers in solution and increase their basicity.[40] Generally, the *sec*BuLi•TMEDA combination appears to be a most potent metalating agent. For a successful deprotonation, the directing metalation group must have good coordinating properties for alkyllithium and a poor electrophilic sites for attack by this strong base. It must contain heteroatom. Steric hindrance ($CONEt_2$, oxazolino), charge deactivation (imidazolino, CON^-R), or both (CO_2N^--*t*Bu) are necessary in the *ortho* metalation process. The scope and limitations of wanted substitution will be determinate by combination of the DMG with the nature and position of other substituents that tolerate the RLi conditions. Steric and inductive effects that influence aggregation and complexation of alkyllitium reagents and formation of the *ortho*-lithiated species, must also be considered. A most powerfull synthetic method is the

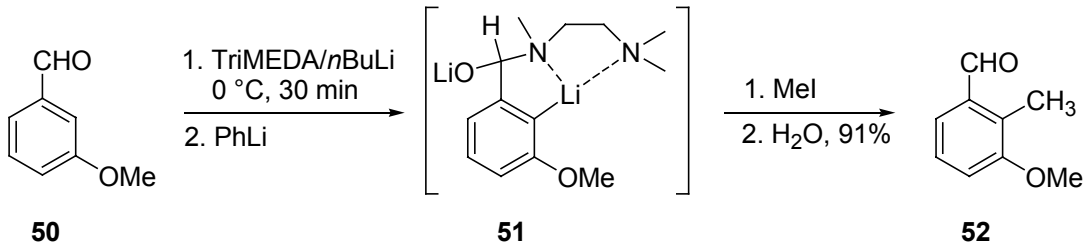
cooperative effect of 1,3-disubstituted DMGs in metalation at their common site. In the carbon based DMGs; $CON^{-}R$, $CONEt_2$ in meta relationship with OR, Cl, F, CH=NR, show exclusive metalation in the common site.[40]

Ketone **49**, a key intermediate in several synthesis of daunomycinone, has been prepared by a route that is initiated from **46** and **47** by amide directed ortho metalation tactics. Treatment of lithiated **44** with aldehyde **45,** and aldehyde **46** with lithiated **47**, led after TsOH cyclization, to the phtalide **48** in good overall yields (Scheme 2.2.4).[41]



Scheme 2.2.4. Synthesis of a key intermediate **49** towords Daunomycinone.

The addition of aromatic aldehydes to certain lithium alkylamides gives α-amino alkoxydes that can be lithiated in the ring with alkyllithiums.[42] Alkylation and hydrolysis provides *ortho*-substituted aryl aldehydes *via* a one-pot reaction (Scheme 2.2.5). This procedure works well for substitution of heterocyclic aromatic aldehydes as well as for benzaldehydes.[43]

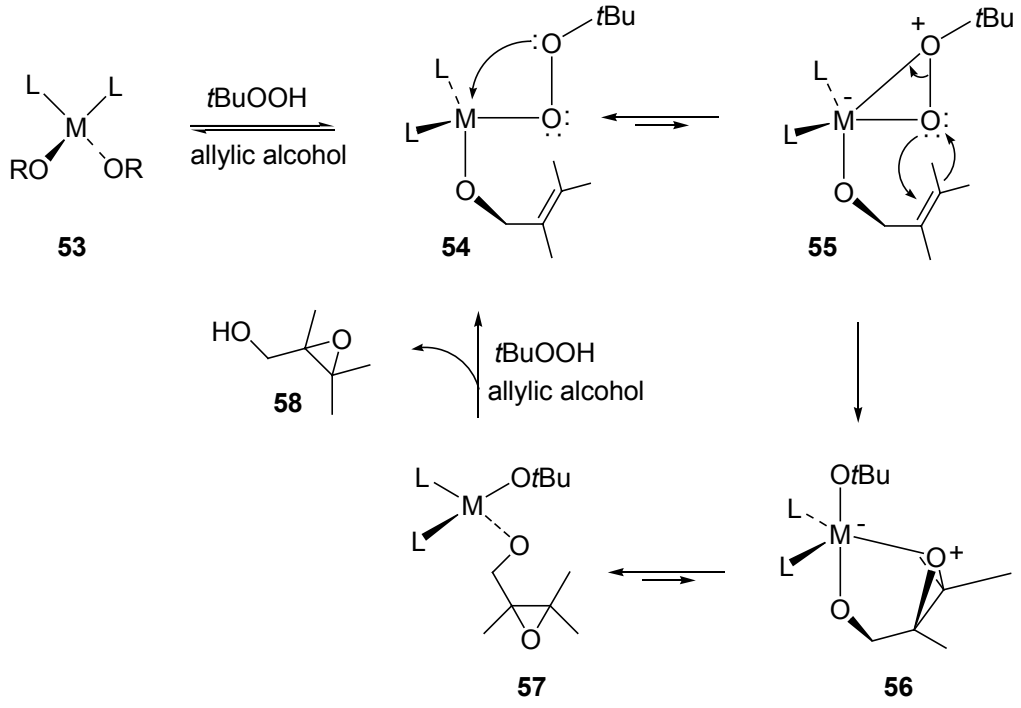


Scheme 2.2.5. Substitution of *m*-anisaldehyde.

Choice of proper base is very important. The use of PhLi allows deprotonating selectively in one position, in comparison *n*BuLi shows lower regioselectivity. The less basic nature of phenyllithium when compared to butyllithium seems to be the reason for this increase regioselectivity.

2.3 Asymmetric Epoxidation of Allylic Alcohols: The Sharpless Epoxidation.

Epoxides are versatile and important intermediates in organic synthesis. The strain of three-memberd heterocyclic ring makes them accessible to different reagents. Epoxidation is also attractive in the contests of asymmetric synthesis, as it can create two chiral centers in one reaction. This extremely useful and effective method was first reported in 1980 by *Katsuki* and *Sharpless*.[44] Since that time many applications of this reaction were reported.[45]

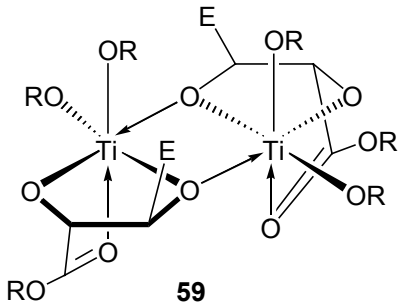


Scheme 2.3.1 *Sharpless* Mechanism for Metal-Catalysed Epoxidations with *tert*-Butyl Hydroperoxide.[46]

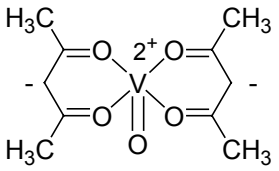
The asymmetric epoxidation reaction and kinetic resolution of allylic alcohols are similar to other early transition metal catalysed epoxidation (Scheme 2.3.1). The metal $ML_n(OR)_m$ (L = oxo ligands, OR = alkoxide ligands, depending on the metal), covalently binds with an alkyl hydroperoxide and an allylic alcohol, activating the

peroxide and organising the substrate for epoxidation *via* an intermediate complex **55**. The difference between the titanium catalysed epoxidation and other d^0 metal is that it is able to use successfully dialkyl tartrates as ligands to induce asymmetry in the reaction.

According to the mechanism proposed by *Sharpless*[47] the metal is a dimer consisting of two dialkyl tartrates covalently bound through the hydroxylic functions to two titaniums (Scheme 2.3.2).



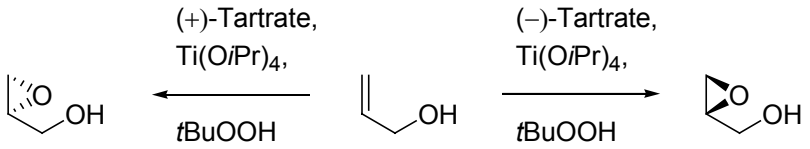
59



60

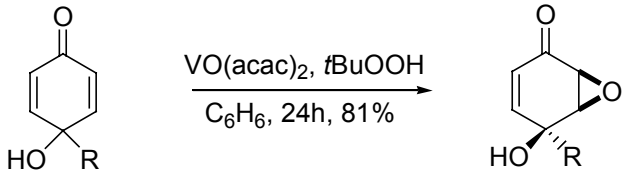
Scheme 2.3.2. Catalyst dimer proposed by *Sharpless* R = *i*Pr **59**, and $VO(acac)_2$ **60**

Two main advantages became clear from the first few examples of chiral epoxidation. The reaction gives higher asymetric induction for a wide range of primary alcohols. It seems that the epoxide oxygen is always delivered from the same enantioface of the olefin (given a specific tartrate isomer). The necessary compounds for this practical method are (–) or (+)-Diethyl tartrate (DET) or (–) or (+)-Diisopropyl tartrate (DIPT), and water free solution of *t*-butyl hydroperoxide. Additionally, racemic secondary alcohols can be kineticlly resolved by the asymmetric epoxidation.



Scheme 2.3.3. Stereochemistry of asymmetric epoxidation.

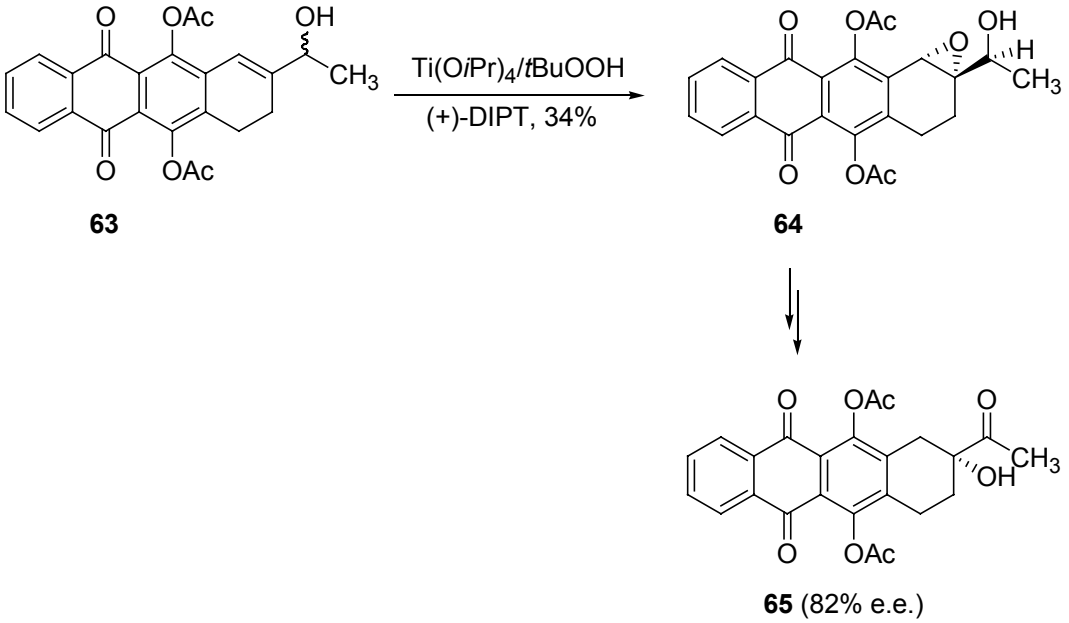
For an electron poor substrate $VO(acac)_2$ is a more effective catalyst for oxygen transfer (Scheme 2.3.4).[48]



61 **62**

Scheme 2.3.4

The *Sharpless* epoxidation has been used as a key transformation in many multi-step syntheses, especially of natural products.[49] The most important field for the application of the asymmetric epoxidation lies in carbohydrate chemistry.[50] Also, in the field of the anthracyclinones this method has been used several times. The racemic substrate **63** was knetically resolved using (+)-Diethyl tartrate (DET) in the asymmetric epoxidation step. Significantly, from epoxy alcohol **64**, (–)-4-demethoxy-7-deoxydaunomycinone **65** was obtained in 82% e.e (Scheme 2.3.4).[51]



63 **64**

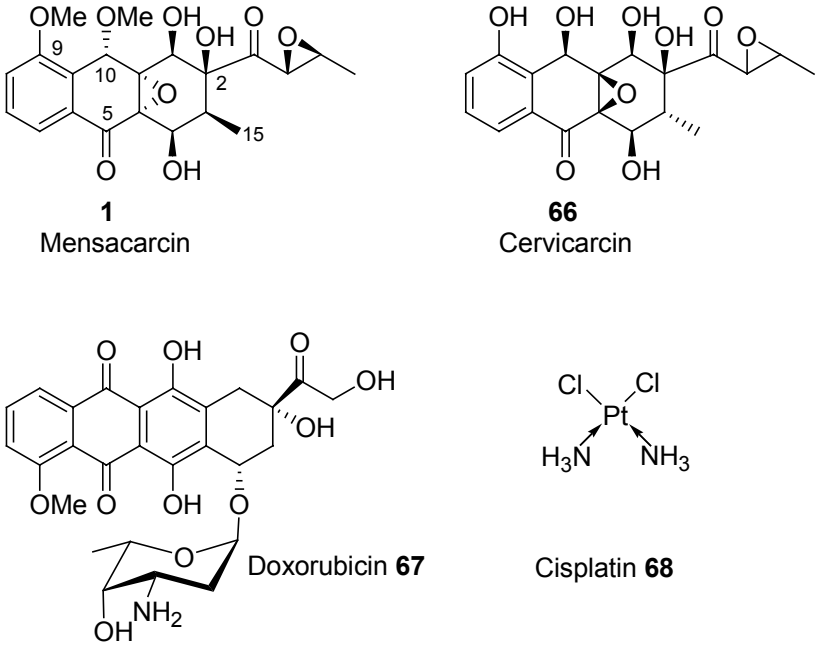
65 (82% e.e.)

Scheme 2.3.5

The main reasons which led to the success of this method is simplicity and all reagents are inexpensive easy to handle. Moreover, the absolute stereochemistry is easy to predict and in high optical purity, generally above 90% e.e.

3 Mensacarcin: Structure, Biosynthesis and Bioactivity

Mensacarcin (**1**) is a novel polyfunctionalised hexahydroanthracene with nine stereogenic centers and two epoxides which was isolated from a strain of *Streptomyces* (Gö C4/4) found next to the north canteen (mensa) of the Georg August University of Göttingen by Zeeck et al.[52] Extraction of a one litre broth containing the bacteria strain Gö C4/4 provided, after chromatographic separation/recrystalisation, 60 mg of **1**. Mensacarcin (**1**) shows cytostatic and cytotoxic activity comparable to those of doxorubicin (**67**) and cisplatin (**68**), other anticancer agents currently used in the treatment of malignant lymphomas and leukemias.[53] Interestingly, mensacarcin (**1**) has a high level of oxygenation as in compound **67**, along with some other structural similarities. At present, the only known natural product with a closely related structure to mensacarcin (**1**) is cervicarcin (**66**), which displays a much lower biological activity.[54]

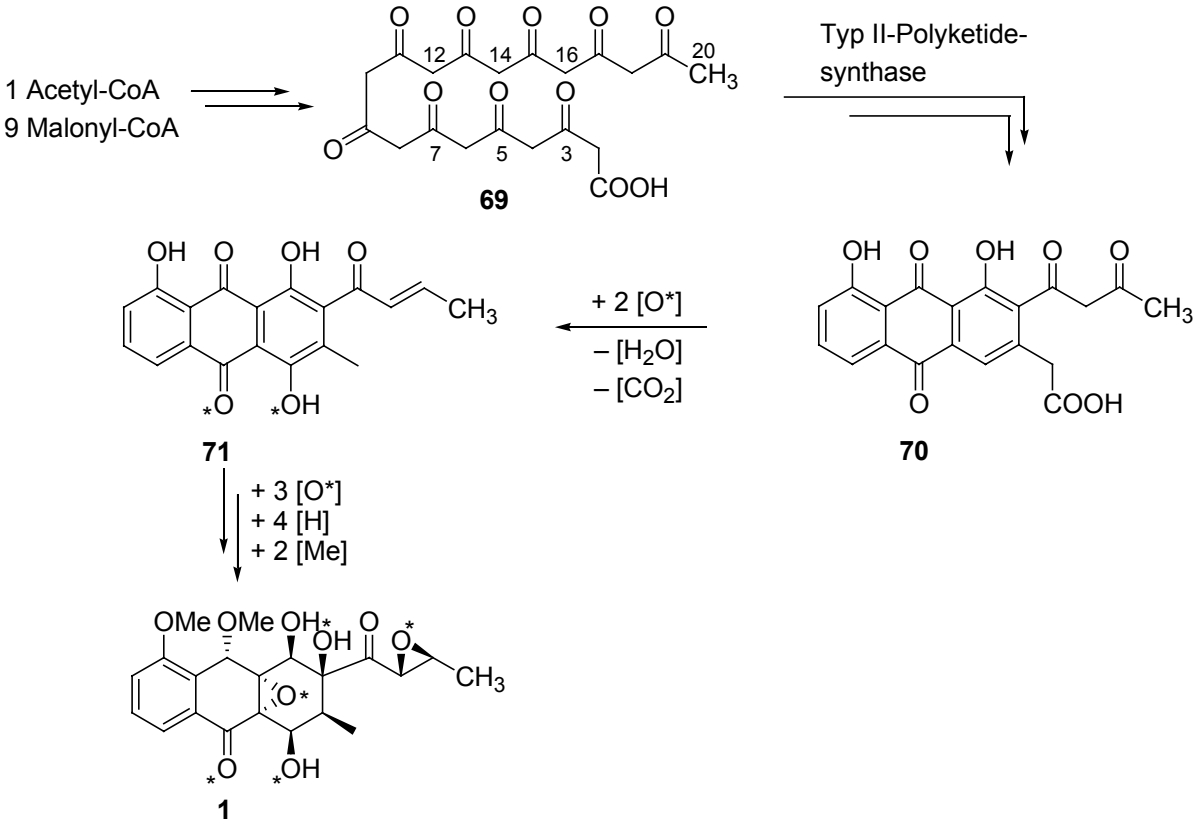


Scheme 3.1

The *in vitro* activity of this new anticancer agent was measured by *Beil* et al.[52] Cytostatic (TGI, Total Growth Inhibition) and cytotoxic (LC_{50}, Lethal Concentration) activity towards different tumour cells; HEP G2 (liver), HMO2 (stomach), MCF7 (breast) and Kato III (lung) were tested.

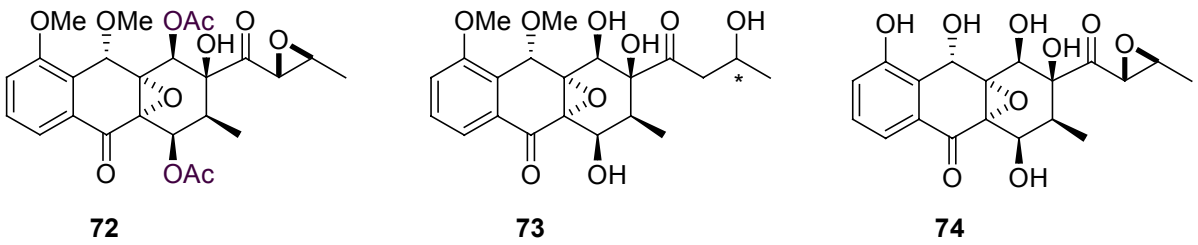
Compound	Conc. [µmol/l]	Tumor cells HMO 2	HEP G2	MCF 7	Kato III
Mensacarcin	TGI	0.55	5.0	0.24	< 0.5
	LC_{50}	2.44	> 50	0.4	1.6
Doxorubicin	TGI	0.14	1.0	0.2	> 50
	LC_{50}	0.4	> 50	> 10	> 50
Cisplatin	TGI	1.5	5.0	10	> 50
	LC_{50}	36	> 50	> 50	> 50

First experiments with ^{13}C-labelled acetate proved that mensacarcin (**1**) is a polyketide, which is probably synthesised through type II polyketide-synthase from the decaketide-precursor **69**. Following the formation of **69** an enzyme type II polyketidesynthase controlled cyclization takes place to assemble the anthraquinone skeleton **70** (Scheme 3.2). The final and complex biosynthetic pathways leading to the natural product mensacarcin **1** from antraquinone **71** have not as yet been revealed, but it is thought they include various oxidations, reductions and methylations. In an effort to determine the exact mechanism of biosynthesis a controlled fermentation was conducted under atmosphere of labelled [$^{18}O_2$] gas. This experiment proved that five oxygen atoms were introduced during biosynthesis from the atmophere. The ^{13}C-NMR spectrum displayed C-2, C-4, C-4a, C-5, C-10a, C-12 and C-13 signals shifted to a higher field, in comparison to the unlabeled compound, corresponding to an α-isotopshift.[55]



Scheme 3.2. Biosynthesis of Mensacarcin (**1**).

Important analogs of mensacarcin **1** have been tested by the group of *Zeek* providing a small but important structure-activity relationship. It was hoped that such analogs would provide a simpler and more active species to determine the mode of action of these class of compounds. Acetylation of the free hydroxyl groups at C4 and C11 results in the formation of **72**, which displayed a decreased activity when compared to mensacarcin (**1**). Similarly, opening the side chain epoxide led to a much less active compound **73**. Finally, di-desmethylmensacarcin **74** also isolated from the strain of *Streptomyces* (Gö C4/4) appeared to be slightly more active, proving that the methyl ether groups play no important role in the mode of action.

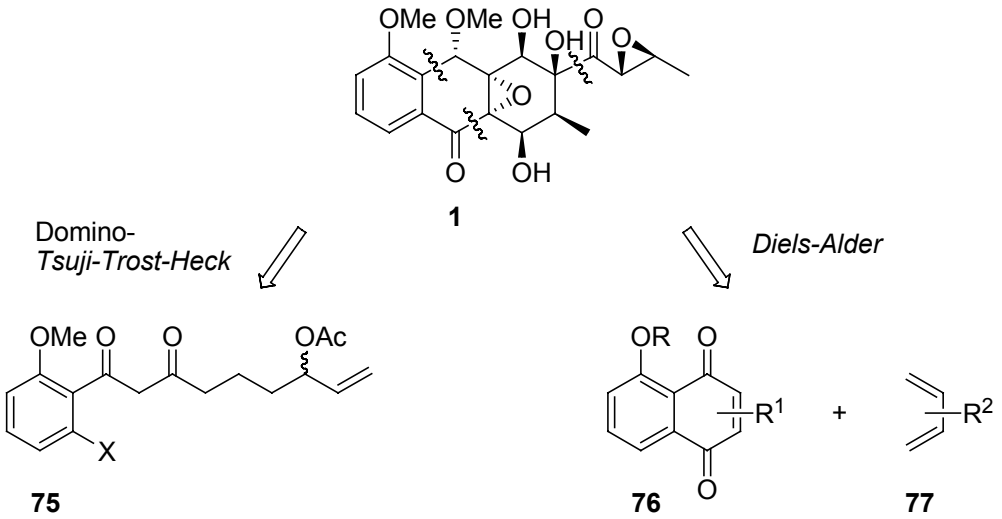


Scheme 3.3. Structure-activity relationship.

3.1 Aim of the Thesis

The structure of mensacarcin (**1**) is very complex with nine stereogenic centres together and a high level of oxygenation. These factors along with its biological activity make it an attractive and challenging target for organic synthesis. The aim of this thesis was the development of an efficient synthesis of the tricyclic core of **1**, with the intention to allow a total synthesis of mensacarcin (**1**) along with other biologically active analogs. Therefore most of the ring functionalities should be included in the initial formation of the core structure to minimize the amount of steps after formation of the tricycle (convergent approach). The project is part of the Sonderforschungsbereich SFB 416 "*Chemische und biologische Synthese und Transformation von Naturstoffen und Naturstoff-Analoga*". It should provide cytostatic and cytotoxic products to be tested at the cell laboratory within our institute.

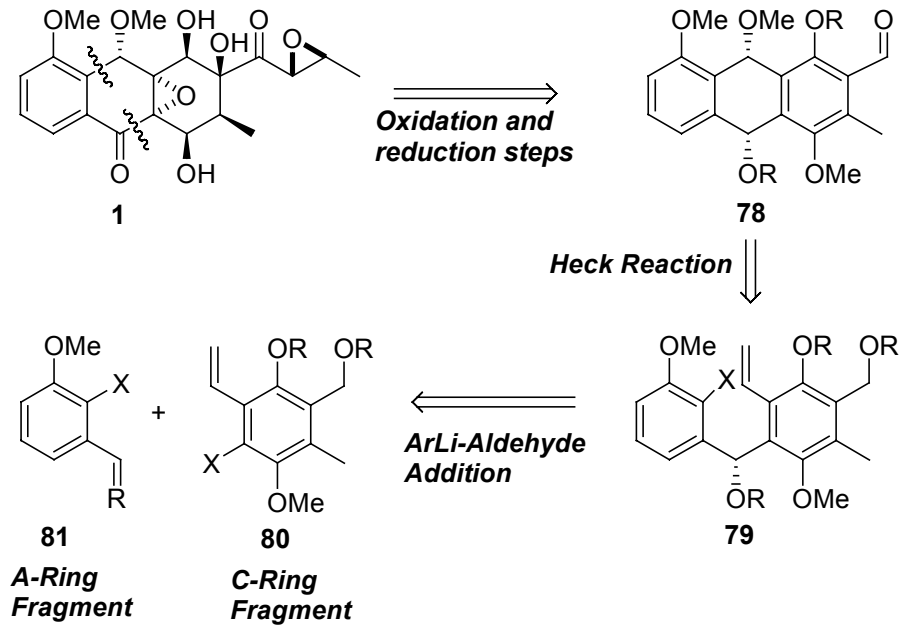
Two other approaches to carbocyclic framework of mensacarcin **1** have been also developed within this group (Scheme 3.4). An efficient synthesis of tricyclic system was achived using a palladium catalysed domino process.[56] Secondly, an approach involving the *Diels-Alder* cycloaddition reaction was also carried out.[57] Such approaches offer fast access to the tricyclic system, but without stereo or regio-control.



Scheme 3.4. Investigated retrosynthetic approaches towards Mensacarcin (**1**).

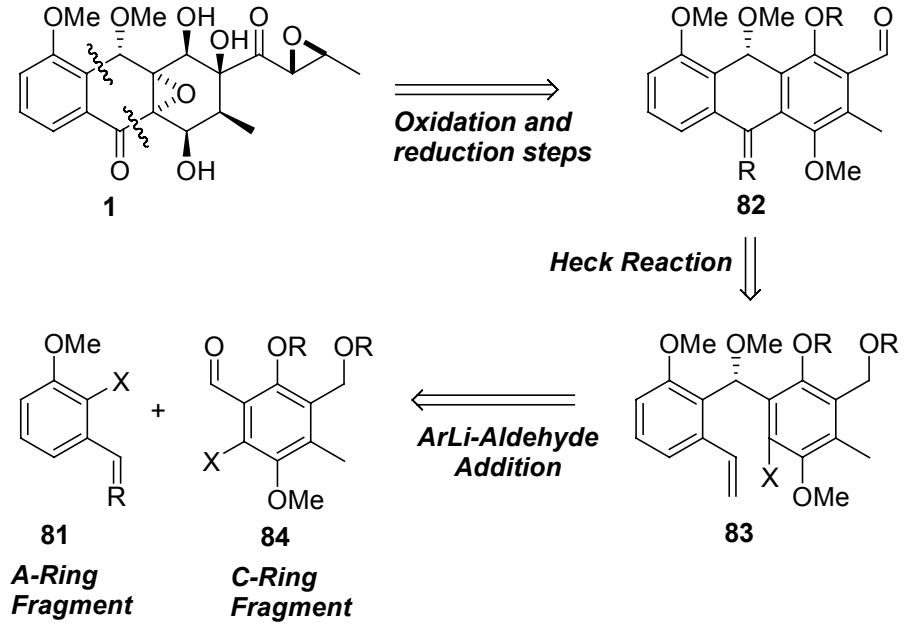
Considering the prevalence of anthraquinone type frameworks found in a variety of natural products it is not surprising that many approaches have been developed for their synthesis. However, only a few methods exist for the formation of the hydroxyl or methoxy dihydroanthracenone, either by regioselective reduction of anthraquinone or by other synthetic pathways. For this reason, and because of our interest in preparation of natural products *via* transition metal catalysed transformations,[58] a synthesis of the tricyclic core of **1** using an intramolecular *Heck* reaction was proposed. According to preliminary investigations by *Modi*[59] a fasable approach would be: the addition of a lithium species to an aldehyde containing a vinyl group followed by an intramolecular *Heck* reaction. The two key steps provide the tricyclic core in an efficient manner, but an additional feature of this pathway was the expectation that the methyl group in the C-ring could be introduced at the later stage of the synthesis. Unfortunately, difficulties arose when the required methyl group introduction was not possible using a simplified substrate. In the view of the complications of the initial approach to mensacarcin (**1**), a revised method for the preparation of this target compound was proposed.

It was envisioned that this tricyclic compound **1** could be broken up into two aromatic fragments, A **81** and C **80** (containing the necessary methyl group). The two fragments could be attached by a nucleophilic addition of the lithium species obtained from **80** to aldehyde. Intramolecular *Heck* reaction involving a protected diphenylocarbinol **79** should then give the required tricyclic core being considered as a good precursor for the tetrahydroanthracene **78** (Scheme 3.5).



Scheme 3.5. First retrosynthetic analysis of Mensacarcin (**1**).

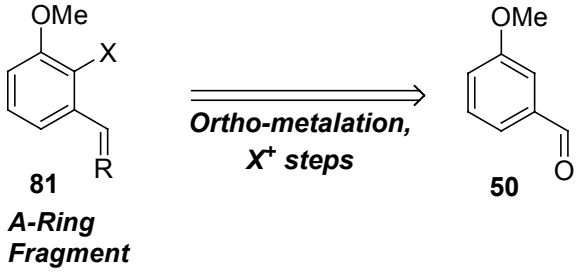
Similarly, an opposite connection sequence (Scheme 3.6) of the aromatic building blocks A **81** and C **84** should also provide a dihydroantracene of an equal importance as an intermediate towards synthesis of mensacarcin (**1**).



Scheme 3.6. Second retrosynthetic analysis of Mensacarcin **1**.

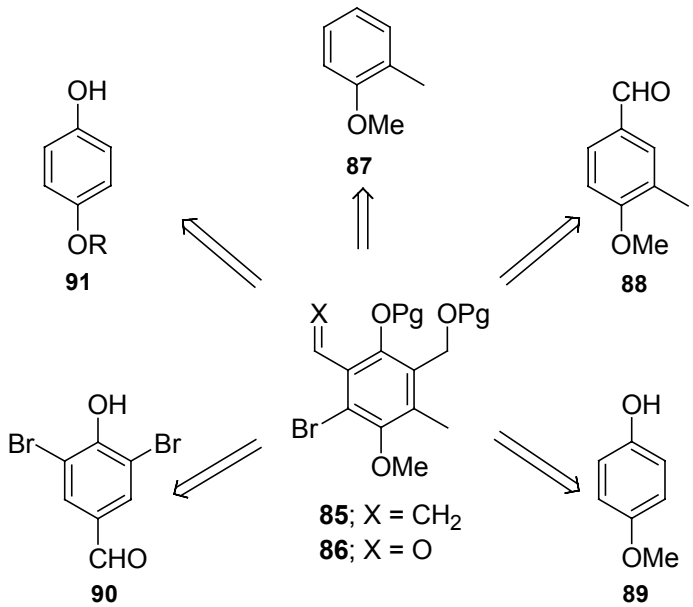
A wide-range of substituted benzaldehydes rings are described in the literature and many are commercially available. However, only a small proportion of these are 1,2,3-trisubstituted systems. A simple and general synthetic route to 2-halo-3-

methoxybenzaldehyde involves *ortho*-metalation followed by reaction with electrophile. Consequently, this approach (Scheme 3.7) to A-ring fragment was pursued.



Scheme 3.7. Rethrosynthesis of A-ring fragment **xx**.

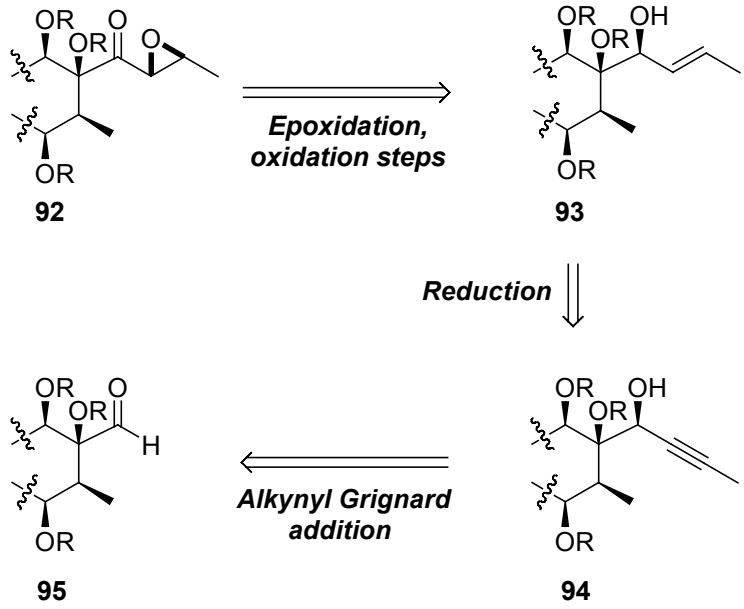
The various retrosynthetic approaches towards hexasubstituted aromatic compounds are outlined in Scheme 3.8. It was thought that a suitably protected phenol could be used as a starting material. Importantly, the chosen commercially available substrate needed to be cheap and the reaction sequences had to be efficient on a larger scale. Five different substituted aromatic rings as starting materials were taken into consideration.



Scheme 3.8. Retrosynthesis of C-ring fragments **85** and **86**.

Retrosynthetic analysis of the side chain associated with mensacarcin (**1**) (Scheme 3.9) indicated that the three carbon fragment, could be attached by applying a Grignard reagent. This retrosynthetic analysis highlighted the need for an aldehyde

group directly attached to the C-ring. It was also anticipated that a reduction of the triple bond within compound **94** followed by selective epoxidation should provide a method for establishing the required and biologically active side chain.

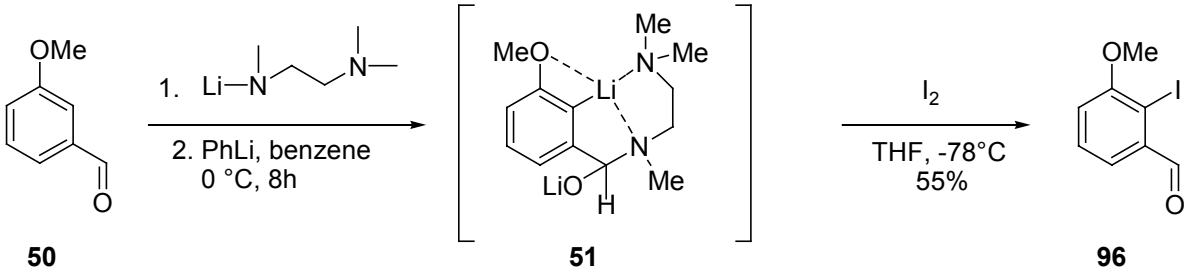


Scheme 3.9. Retrosynthesis of the Side Chain.

4 Synthesis of A-Ring Fragments

4.1 Synthesis

In both retrosynthetic analyses, it was envisaged that the A-ring fragments should be 1,2,3-trisubstituted benzalhehyde derivatives. The first such compounds was synthesised by a regioselective iodination of *m*-anisaldehyde using an *ortho*-lithiation strategy.[42] This lithiation-iodination sequence of an α-amino alkoxide **51** derived from 3-methoxybenzaldehyde **50** led to the desired 2-iodo-benzaldehyde **96** (Scheme 4.1.1). The intermediate α-amino alkoxide **51** was prepared by *in situ* protection when using *N*,*N*′,*N*′- trimethylethylenediamine and *n*BuLi in benzene at 0 °C then adding the 3-methoxybenzaldehyde **50**. Addition of phenyllithium in benzene to this mixture is thought to afford the intermediate **51**. Phenyllithium proved to be an effective base, although the reaction required longer times for regioselective deprotonation of the aromatic ring. Quenching of this proposed intermediate with iodine in THF at –78 °C furnished iodobenzene **96** in 55% yield. Unfortunately, this procedure gave a mixture of byproducts including the diphenylcarbinol (as product of addition of phenyllithium to benzaldehyde) and complete purification of **96** was only possible by recrystalization. The low yields of the above reaction were attributed to the fact that iodine is a poor electrophile and requires longer reaction times. Unfortunately, these extended reaction times were also responsible for the cleavage of amine moiety back to the aldehyde.

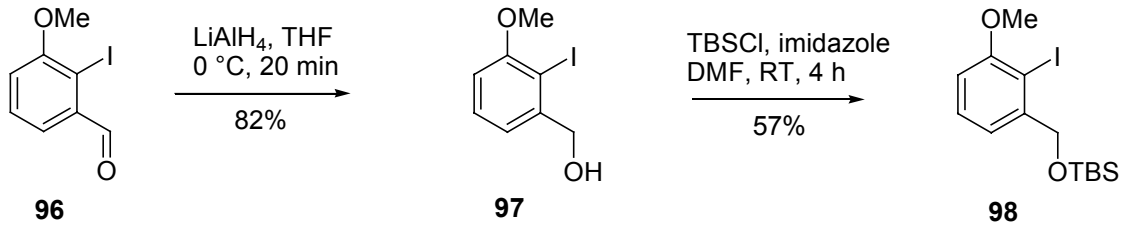


50 **51** **96**

Scheme 4.1.1

A second A-ring fragment was prepared by first treating of iodobenzene **96** (Scheme 4.1.2) with lithium aluminium hydride in THF to afford the benzylalcohol **97**

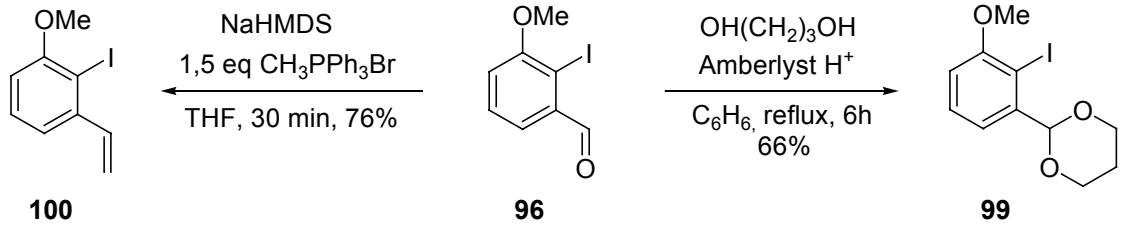
(82%). This alcohol was immediately protected upon treatment with TBSCl to produce the corresponding TBS-ether **98** in 57% yield. This latter compound was thought to be an excellent substrate for lithium-iodine exchange and a coupling partner for C-ring building blocks.



96 **97** **98**

Scheme 4.1.2

The final two A-ring fragments containing different functionalities in the 2-position were produced from the previously synthesised aldehyde **96** (Scheme 4.1.1). Firstly, *Wittig* reaction of compound **96** using triphenylmethyl-phosphonium bromide and sodium bis(trimethylsilyl) amide produced the styrene **100** in 76% yield (Scheme 4.1.3). Similarly, treatment of the aldehyde **96** with 1,3-propanodiol in acidic conditions afforded acetal-protected aldehyde **99** in reasonable yield (66%). In the strategy for the synthesis of the carbocyclic core of mensacarcin (**1**) an initial step in one of the retrosynthetic analyses should be a nucleophilic addition of the aryllithium species generated from these A-ring fragments to the various C-ring aldehydes. To develop an efficient version of this addition process the author has synthesised various A-ring building blocks.



100 **96** **99**

Scheme 4.1.3

4.2 Spectroscopic Data of the Presented Compounds.

*Iodo-benzaldehyde **96** and Iodo-styrene **100***

Characteristic features observed in the ^{1}H-NMR spectrum of compounds **96** and **100** included two singlets at δ = 3.95 (**96**) and δ = 3.87 (**100**) assigned to the respective methoxy groups. Resonances representing the aromatic protons included *meta*-doublets at δ = 7.05 (**96**) and δ = 6.71 (**100**) assigned to H6, *ortho*-coupled triplets at δ = 7.05 (*J* = 7.9 Hz) (**96**) and δ = 7.24 (*J* = 7.5 Hz) (**100**) assigned to H5 and *meta*-coupled doublets at δ = 7.50 (*J* = 7.9 Hz) (**96**) and δ = 7.12 (*J* = 7.5 Hz) (**100**) assigned to H4. A singlet corresponding to the aldehyde proton in **96** was observed at δ = 10.19. Resonance corresponding to the mono-substituted double bond was observed at δ = 7.00 (*J* = 7.9 Hz) as a doublet of doublets, δ = 5.30 (*cis J* = 11.0 Hz) doublet and δ = 5.62 (*trans J* = 17.3 Hz) doublet (**100**). The ^{13}C-NMR spectrum exhibited characteristic signals for methoxy groups at δ = 56.8 (**96**) and δ = 56.5 (**100**), carbonyl functionality at δ = 196.4 (**96**) and methylene unit δ = 116.9 (**100**). An accurate mass measurement on the molecular ion appearing at *m/z* 261.9 (**96**) and 260.0 (**100**) in the eV EI spectrum further confirmed the structure.

*Iodo-benzacetal **99***

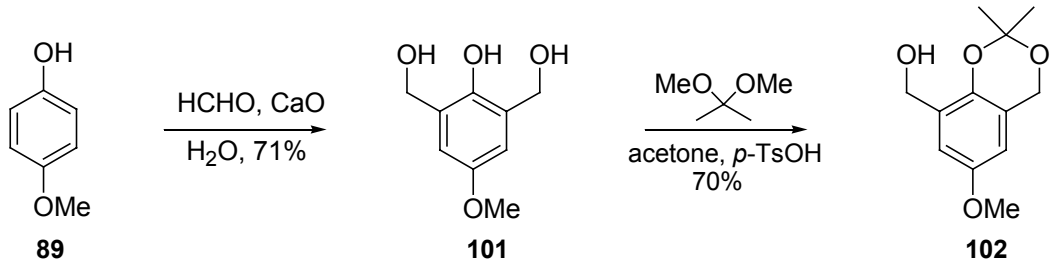
The ^{1}H-NMR spectrum of compound **99** displayed a resonance at δ = 5.79 assigned to the oxymethine proton and resonances appropriate for 1,2,3-substituted aromatic ring as observed in the previous iodo compounds. The ^{13}C-NMR spectrum exhibited characteristic signals for three methylene groups at δ = 25.6, 67.5. A molecular ion at *m/z* 320.1 in the eV EI spectrum confirmed the expected structure.

5 Synthesis of the C-Ring Fragments

This section describes various synthetic approaches to several novel and highly substituted aromatic building blocks used as C-ring fragments. Four routes starting with commercially available substrates were trailed resulting in one final and efficient synthesis.

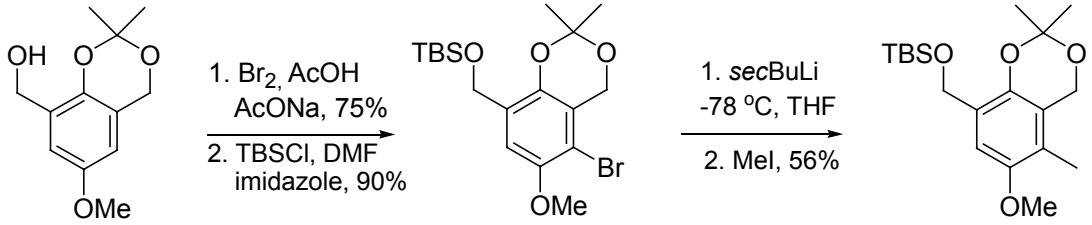
5.1 Synthesis with *p*-Methoxyphenol as Starting Material

Studies began with commercially available *p*-methoxyphenol (**89**) (Scheme 5.1.1), which was converted into the corresponding triol **101** (71%) using an aqueous solution of formaldehyde and calcium oxide.[60] This reaction required three days in the absence of light and purity of product depended on quality and age of the formaldehyde. The triol **101** was then converted into the corresponding acetal **102** (70%) using 2,2-dimethoxypropane/acetone mixture and a catalytic amount of *p*-toluenesulfonic acid.



Scheme 5.1.1

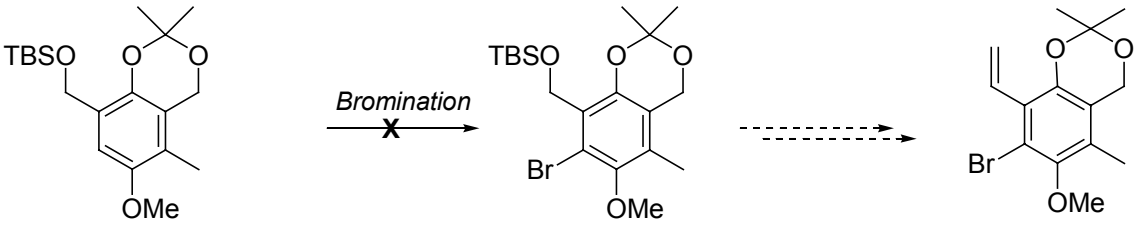
Previously a regioselective nitration of aromatic substrate had been described by *Nicolaou*,[61] however, in our case we required the introduction of a bromine atom. This halogenation was achieved using one equiv. of bromine in acetic acid (Scheme 5.1.2), which provide selectively the brominated compound **103** in 75% yield. Subsequent silylation under standard conditions, TBSCl and imidazole, afforded **104** in 90% yield. Requiring a methyl group in the 5-position found in mensacarcin (**1**) (C3) it was essential that the bromine was used as a handle for its introduction. Therefore, compound **104** was treated with *sec*BuLi at – 78 °C and quenched with methyliodide to give the required toluene **105** in 56% yield.



102 **104** **105**

Scheme 5.1.2

Further, attempts to introduce another bromine atom into the only unsubstituted position in the ring were unsuccessful. Many brominating reagents and reaction conditions were trailed such as tetraalkylammonium tribromides as well as others mild and selective brominating agents.[62] Unfortunately, neither using benzyltrimethylammonium tribromide (BTMA Br_3), or tetrabutylammonium tribromide ($TBABr_3$) in dichloromethane/methalol, gave the anticipated product **106**. Other more traditional and harsher reagents, bromine in acetic acid, also failed to produce the desired bromobenzene **106**.



105 **106** **85**

Reagents	Product 106
BTMA. Br_3, MeOH, CH_2Cl_2, 1 h, 20 °C	oxidation and decomposition
TBA Br_3, MeOH, CH_2Cl_2, 0.5 h, 0 °C	oxidation and decomposition
Br_2, AcOH, AcONa, 3 h, 20 °C	adduct
Br_2, CH_2Cl_2, AcONa, microwave, 15', 100 °C	decomposition
NBS, CH_2Cl_2, 2 h, 20 °C	oxidation and trace of adduct
1.*n*BuLi/TMEDA, Et_2O, -78 °C 2. Br_2, 2 h, 20 °C	brominaton of the benzylic position

Tabele 5.1. *Bromination reactions.*

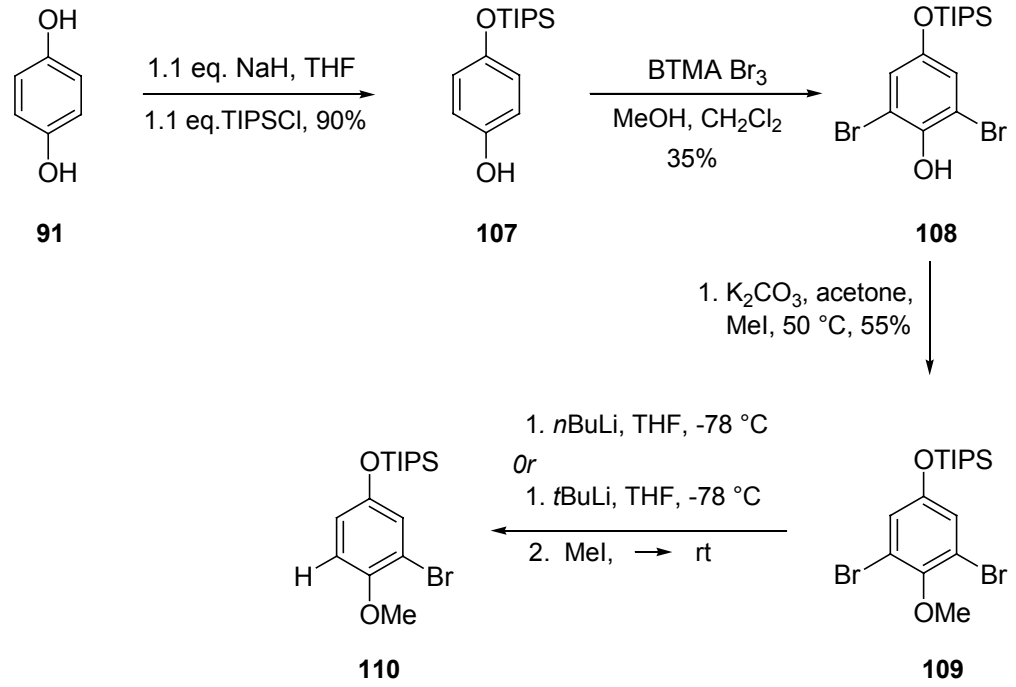
5.1.1 Discussion of Selected Spectroscopic Data

*Silyl ether **104** and toluene **105***

The ^{1}H-NMR spectrum of compound **104** displayed one signal at δ = 6.86 as a singlet, a molecular ion was observed at *m/z* 304.1 in the eV EI spectrum, while in the ^{1}H-NMR spectrum of compound **105** a new singlet resonance corresponding to the three protons found in the methyl group was located at δ = 1.82. A molecular ions were observed at *m/z* 418.3 and 352.0 in the eV EI spectrum.

5.2 Synthesis with Hydroquinone as Starting Material

Due to the previously explained bromination complications, a different approach was examined. An attractive feature of this newly considered pathway, involving a dibromination, was the low-cost of the starting material **91**. Preparation of monoprotected hydroquinone **107** (90%) was achieved using a method involving one equivalent of sodium hydride in THF and triisporopylsilyl chloride (Scheme 5.2.1). A wide range of reagents were trailed for the subsequent dibromination, the phenol moiety within **107** was used to direct this process. The best result was achieved with benzyltrimethylammonium tribromide in dichloromethane/methanol to give the dibromophenol **108** in 35% yield. A by-product observed was the expected monobrominated phenol. *O*-Methylation of dibromophenol **108** using methyliodide and potassium carbonate afforded the anisol **109** in 55% yield. Analogous with the previous procedure, it was necessary to introduce the methyl group into the ring for a total synthesis of mensacarcin (**1**). Thus, dibromophenol was subjected to a metal-halogen exchange using *n*- or *t*BuLi, followed by reaction with methyliodide. However, the desired methyl group wasn't introduced, only the dehalogenated product **110** was obtained.



Scheme 5.2.1

5.2.1 Discussion of Selected Spectroscopic Data

*TIPS-phenol **107***

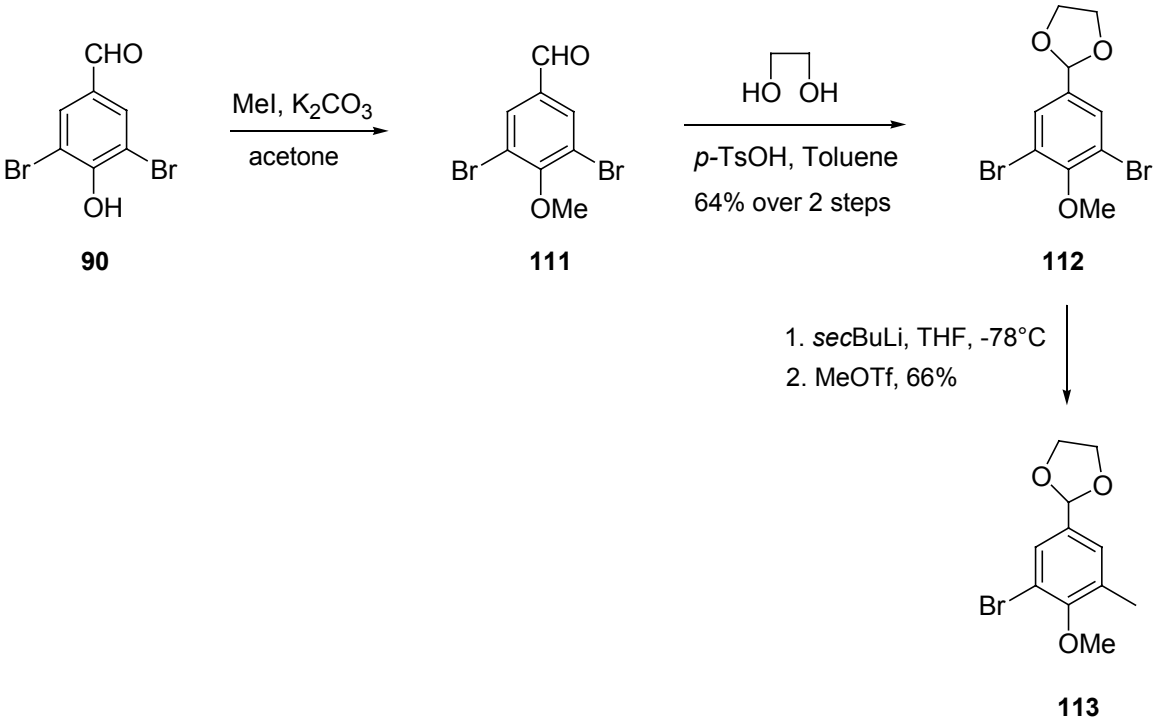
The ^{1}H-NMR spectrum of compound **107** included resonances at δ = 0.90-1.11 assigned to the newly introduced TIPS-ether moiety. A resonances assigned to the phenolic group at was found at δ = 9.87. EI mass spectrometric analysis of the compound revealed a molecular ion at *m/z* 266.2.

*Dibromoanisol **109***

Characteristic features in the ^{1}H-NMR spectrum of compound **109** included a singlet at δ = 7.01 corresponding to the aromatic proton. The phenolic signal found in **108** was not observed. Molecular ion was observed at *m/z* 424.0 in the eV EI spectrum.

5.3 Synthesis with Dibromo-*p*-hydroxybenzaldehyde as Starting Material

Following the same strategy as described in Section 5.2, a different starting material **90** was employed using an aldehyde in C1 position. Synthesis of methoxybenzaldehyde **111** was achieved by converting the commercially available phenol **90** into *O*-methyl-ether **111** using the conditions previously described. The aldehyde functionality within compound **111** was first protected as its acetal **112** using 1,2-ethanodiol and *p*-toluenesulfonic acid (*Dean-Stark* apparatus) in 64% yield over two steps (Scheme 5.3.1). Requiring a successful methyl group installation, dibromobenzene **112** was treated with *sec*BuLi at –78 °C and immediately quenched with excess of methyl trifluoromethanesulfonate, which resulted in formation of methyl-bromobenzene **113** in 66% yield. However, the reaction could only be conducted in small scales (~100 mg) and all attempts to increase the scale of this procedure failed. It should be noted, that using methyliodide as an electrophile gave an inseparable mixture of by-products. Considering the problems with scale up procedures coupled with the cost of starting materials and reagents (methyl trifluoromethanesulfonate) a new more efficient pathway was devised.



Scheme 5.3.1

5.3.1 Discussion of Selected Spectroscopic Data

*Dibromoanisol **112***

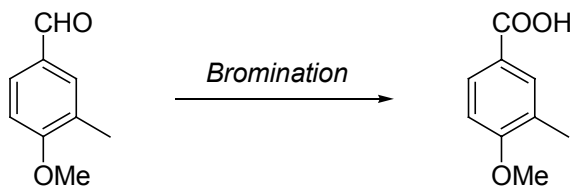
Characteristic features in the ^{1}H-NMR spectrum of compound **112** included two singlets at δ = 7.34 and δ = 7.65 attributed to the two aromatic protons . A Molecular ion was observed at *m/z* 336.9 in the eV EI spectrum.

*Methyl-bromobenzene **113***

The ^{1}H-NMR spectrum of compound **113** included a one signal at δ = 2.45 assigned to the new methyl group, as well as a resonance appropriate to the methylene groups at δ = 4.10-4-15 as a multiplet. The ^{13}C-NMR spectrum exhibited characteristic signals for methyl group at δ = 16.4, methoxy group δ = 60.2, methine moiety at δ = 103.8 and methylene unit at δ = 65.2. A molecular ion was observed at *m/z* 274.0 in the eV EI spectrum.

5.4 Synthesis with 3-Methyl-4-methoxybenzaldehyde as Starting Material

In respect of the previously described complications, the new compound benzaldehyde **88** was examined as a possible starting material. It was thought that aldehyde moiety within **88** would direct bromination to the *meta*-position. Furthermore, after such a bromination the carbonyl functionality could be transformed into hydroxyl group employing a *Bayer-Villiger* protocol.[63] The advantages of using such an aromatic system is the compatibility and the activation effects of the substituents. However, the tolerance of an aldehyde group to the bromination conditions was low. Hence, when the aldehyde **88** was treated with bromine under several conditions the benzoic acid **114** was isolated as the only product.

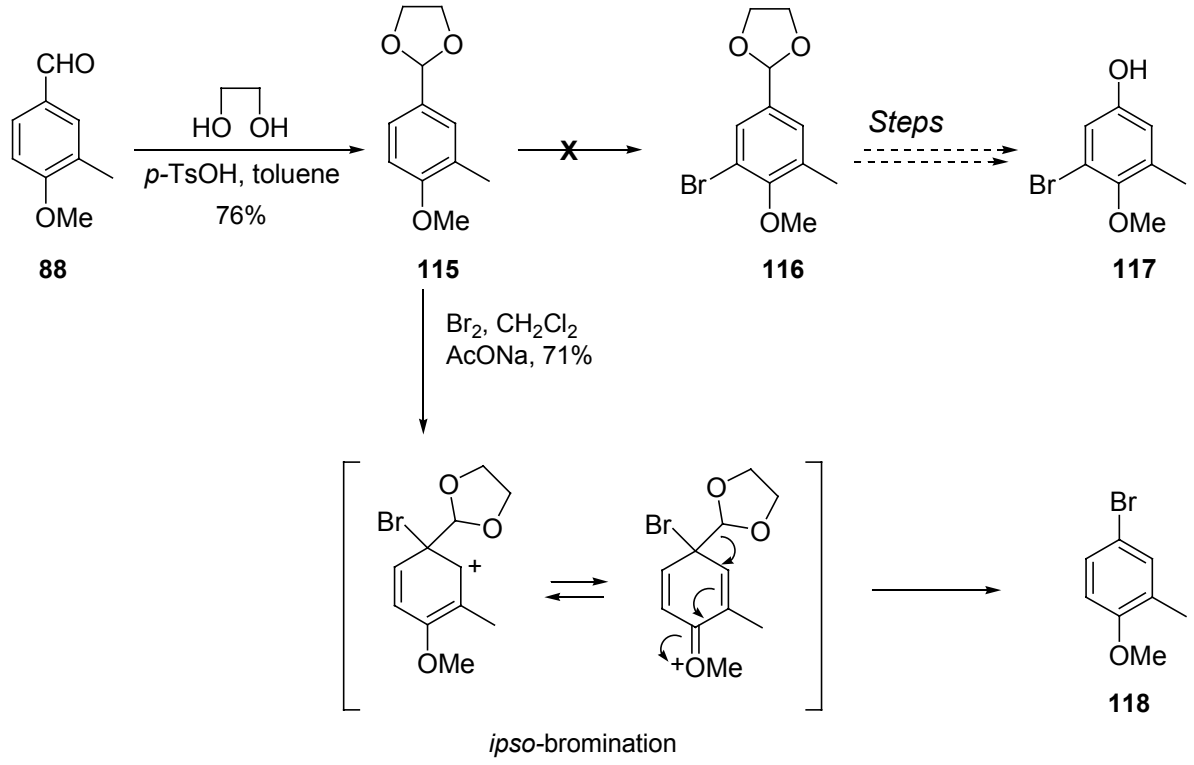


88 **114**

Bromination Reagents	**Yield (%) of 114**
Br_2, AcOH	decomposition
Br_2, CH_2Cl_2, AcONa	21
t-$BuNH_2$, Toluene, Br_2	35

Table 5.4. *Bromination of the benzaldehyde **88**.*

A solution to this problem might be to protect the aldehyde and avoid the harsh oxidative properties of bromine. Thus, aldehyde **88** was converted into acetal **115** (76%) using a *Dean-Stark* apparatus, 1,2-ethanodiol and *p*-toluenesulfonic acid. This latter product was then subjected to reaction with one equivalent of bromine in dichloromethane which, rather than brominating the aromatic ring at the 6-position, resulted in an *ipso* attack of the acetal C-position to afford bromobenzene **118** in 71% yield. It is believed that the reaction took place *via* arenium ion mechanism, and the leaving group was $[HC(CH_2O_2)]^+$.[64] It is hoped with further research that this new and exciting reaction can be exploited for other synthetic purposes.



Scheme 5.4

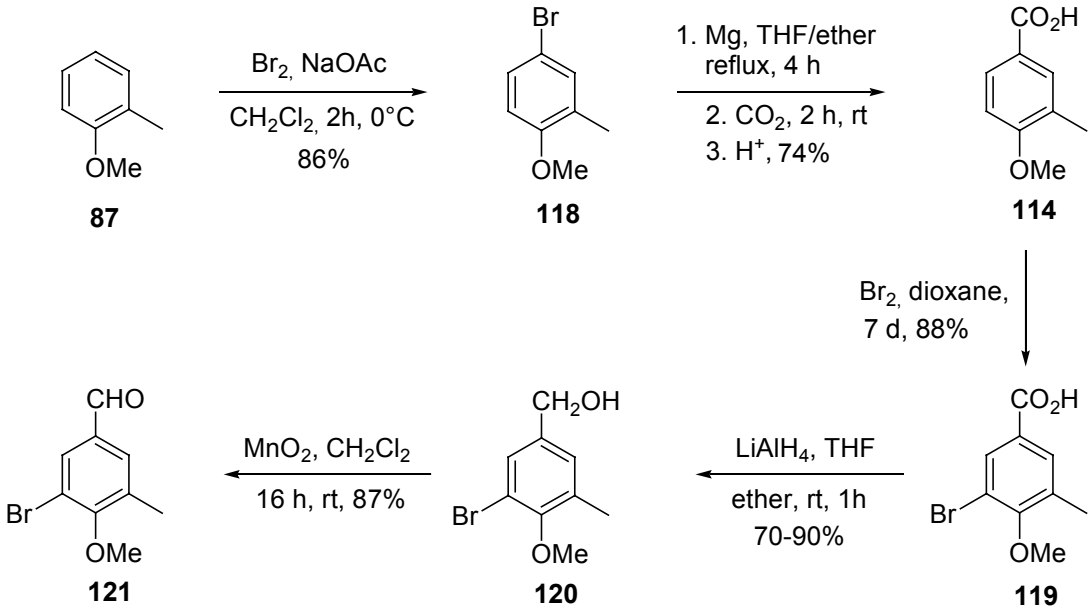
5.4.1 Discussion of Selected Spectroscopic Data

*Bromobenzene **118***

In the ^{1}H-NMR spectrum of compound **118** resonances corresponding to an acetal functionality were not longer observed. EI mass spectrometric analysis of the compound revealed a molecular ion at *m/z* 202.1 and 200.1 a pattern corresponding to the introduction of a bromine atom, the accurate mass measurement of one of these signals established the expected molecular formula C_8H_9OBr.

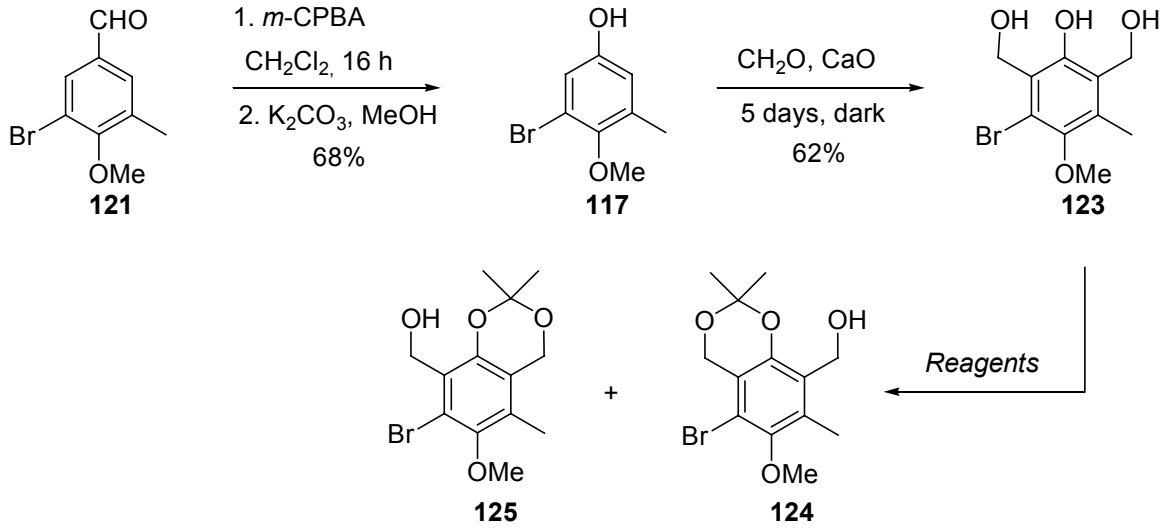
5.5 Synthesis of C-Ring Fragments with 2-Methoxytoluene as Starting Material

The final and ultimately successful pathway started with the commercially available anisol **87** by firstly brominating the *p*-position using bromine and NaOAc to give **118** in 86% yield (Scheme 5.5.1). This step was followed by preparation of the corresponding Grignard compound which in turn was CO_2 (dry) quenched to produce the carboxylic acid **114** in 70% yield over 2 steps.[65] Reaction of carboxylic acid **114** with 2.0 equiv. of Br_2 in dioxane furnished compound **119**, in 84% yield, containing a bromine atom in an *ortho* position to the methoxy substituent.[66] As intended, the carboxylic acid at C-1 in **114** was successful in directing the bromination and subsequently this functionality needed to be "unmasked" to the phenol to allow the introduction of two *ortho*-hydroxymethyl units.[67] This transformation first required an acid to aldehyde reduction which, was achieved in two steps by initial treatment of **119** with lithium aluminium hydride to give the alcohol **120**, in 72% yield. Subsequent oxidation with manganese dioxide afforded the aldehyde **121** in excellent yield (87%).



Scheme 5.5.1

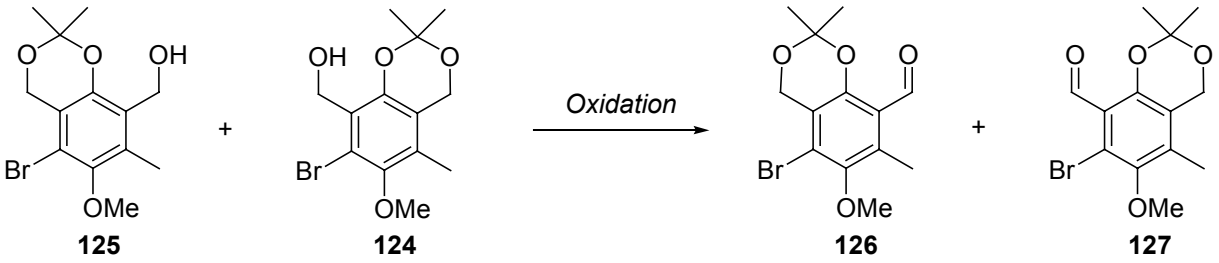
A *Baeyer-Villiger* oxidation of **121** to give the corresponding formate was followed by solvolysis using K_2CO_3, MeOH to furnish the phenol **117** in reasonable yields (68%) over two steps. It should be noted that best yields for this transformation were obtained up to a 2.0 g scale, larger batches resulted in lower yields. In a final transformation, the last two nonsubstituted positions within phenol **117** were hydroxymethylated upon exposure to formaldehyde and calcium oxide in water to give the novel hexasubstituted aromatic compound **123** in 69% yield. Acetonide protection of the triol **123** using acetone and catalytic amounts of *p*-TsOH gave a mixture of regioisomers **125** and **124** in a 1:1.1 ratio,[68] respectively and 91% overall yield (Scheme 5.5.2). Protection of triol **123** using other more common methods, i.e. 2,2-dimethoxypropane gave a preference for the regioisomer **124**, which can be transformed into another C-ring fragment (Scheme 5.5.2).



Conditions	T [°C]	Time [h]	Ratio 124	Ratio 125	Yield (%)
2,2 DMP, *p*-TsOH	20	16	1	1.3	75
2,2 DMP, *p*-TsOH	-10	16	1	4.3	73
2,2 DMP, *p*-TsOH	60	4	1	1.3	48
Acetone, *p*-TsOH	20	18	1.1	1	90

Scheme and Table 5.5.2. *Acetal protection of tiol* ***123***.

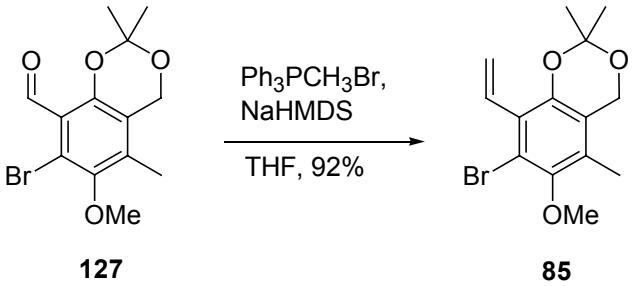
Unfortunately, at this stage alcohols **124** and **125** could not be separated by conventional chromatography therefore, the mixture was carried through the synthetic sequence and oxidised under *Dess-Martin* conditions, to give the corresponding aldehydes **126** and **127** in 92% overall yield. Thus, this procedure was suitable only for small scale. Oxidation using *Swern* conditions could be easily scaled up to five grams with a good yield of 83%. Here, the two aromatic regioisomers could be chromatographically separated and individually characterised, using standard spectroscopic techniques, as well as nOe difference measurements to determine their substitution pattern. Aldehyde **127**, which represented the desired C ring building block, was used for the anticipated ring coupling, while compound **126** was subjected to further transformations and used for another independent pathway to mensacarcin (**1**).



Scale	Conditions
Small (*ca*.100 mg)	Dess-Martin Periodinane, CH_2Cl_2, H_2O, 1h, 92%
Large (*ca*. 5 g)	DMSO, Oxalyl chloride, CH_2Cl_2, -78 °C, 2h, 83%

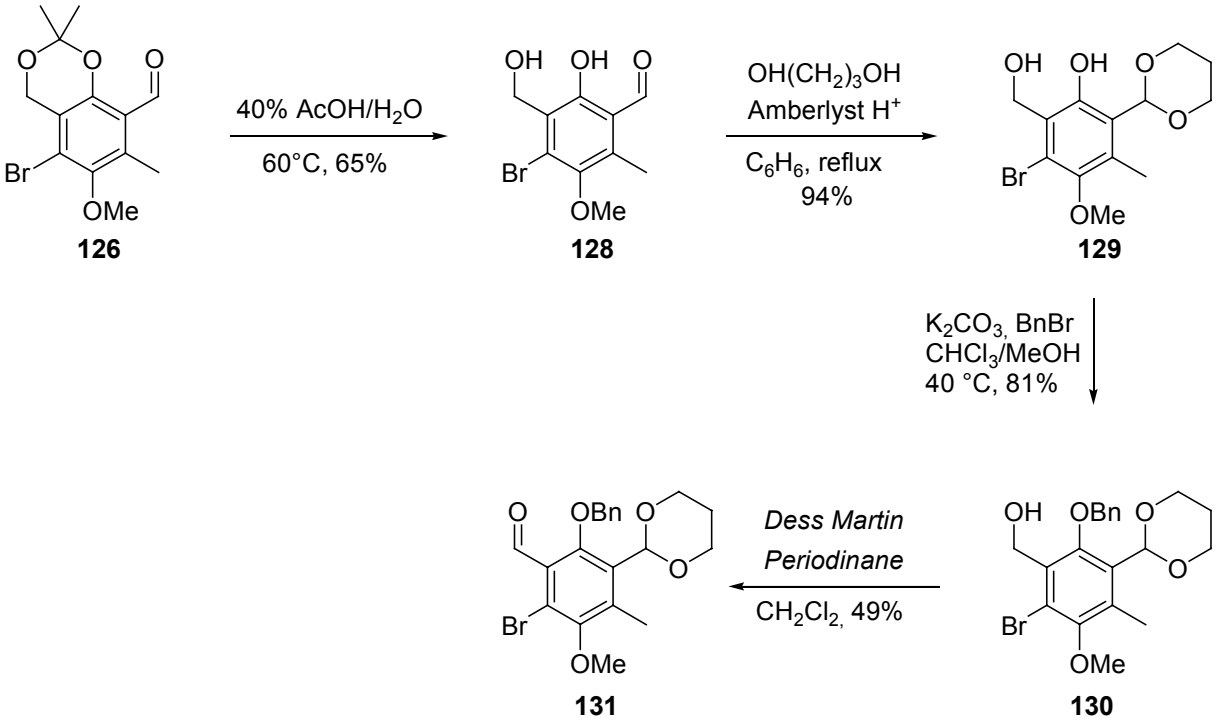
Scheme and Table 5.5.3. *Oxidation of alcohols **124** and **125**.*

A second C-ring building block was synthesised when aldehyde **127** was treated with 1.2 equivalent of phosphorus ylide to afford styrene **85** in 92% yield (Scheme 5.5.4).



Scheme 5.5.4

Aldehyde **126** obtained in the previous reactions sequence was used as a precursor for a third C-ring building block **131**. Deprotection of aldehyde **126** with acetic acid gave phenol **128** (Scheme 5.5.5) in 65% yield, which was then smoothly converted into the corresponding acetal **129** (94%) using 1,3-propanediol and Amberlyst as the acid catalyst. Selective protection of the phenol moiety over the benzylic hydroxyl group was achieved by deprotonation with potasium carbonate and reaction with benzyl bromide furnished the benzyl ether **130** in 81% yield. Standard *Dess-Martin* conditions only provided 49% yield of benzaldehyde **131**. A poor yield was also observed when benzyl alcohol **130** was treated with MnO_2, presumably these yields are due to the steric effect of the adjacent benzyl protecting group.



Scheme 5.5.5

5.5.1 Discussion of Selected Spectroscopic Data

*Phenol **117***

Characteristic features observed in the ^{1}H-NMR spectrum of compound **117** included two *meta*-couplet doublets at δ = 7.61 (*J* = 1.2 Hz) and 7.87 (*J* = 1.2 Hz) and phenolic resonance at δ = 9.82. An accurate mass measurement on the molecular ion observed at *m/z* 218.0 and 216.0 in the 70 eV EI mass spectrum together with elemental analysis established the molecular formula as C_8H_9BrO.

*Triol **123***

Characteristic features observed in the ^{1}H-NMR spectrum of compound **123** were the missing aromatic signals and a new appearance of two singlets at δ = 4.77 and δ = 4.96 assigned to the methylene group. Also, two broad signals at δ = 2.76 and δ = 2.81 assigned to the hydroxyl group, and a singlet appearing at δ = 8.89 assigned to the phenolic resonance. In the ^{13}C-NMR spectra, two signals corresponding to the CH_2 carbons, as well as eight signals corresponding to the remaining C and CH_3 carbons,

were observed. An accurate mass measurement on the molecular ion observed at *m/z* 278.1 and 276.1 in the 70 eV EI mass spectrum was confirmed.

*Aldehydes **126** and **127***

The ^{1}H-NMR spectroscopic studies, particularly nOe difference measurements, were used in characterising the structures of regioisomers **126** and **127**. Correlation between aldehyde proton of **126** with a methyl group in the ring was observed. Aldehydes **126** and **127** exhibited one resonance attributed to the aldehyde proton at δ = 10.32 (**126**) and δ = 10.49 (**127**), and a singlet at δ = 4.71 (**127**) and δ = 4.74 (**126**) assigned to the methylene protons. At δ = 1.55 (**127**) and δ = 1.56 (**126**) signals corresponding to the acetal oxymethylene protons were observed. The resonance at δ = 189.4 (**127**) and δ = 191.1 (**126**) in the ^{13}C-NMR spectrum are assigned to the aldehyde carbon. The IR spectrum shows the carbonyl stretching band at 1697 cm^{-1} (**127**) and 1685 (**126**), consistent with the presence aldehydes moieties. An accurate mass measurement on the molecular ion observed at *m/z* 316.1 in the 70 eV EI mass spectrum established molecular formula as $C_{13}H_{15}BrO_4$.

*Styrene **85***

Characteristic features observed in the ^{1}H-NMR spectrum of compound **85** included new doublets at δ = 5.42 (*J* = 11.0 Hz) and δ = 5.53 (*J* = 17.3 Hz) and doublet of doublets at δ = 7.11 (*J* = 17.3, 11.0 Hz) assigned to the olefinic group. In the ^{13}C-NMR spectra, two signals corresponding to the CH_2 carbons, as well as new signal at δ = 141.7 assigned to CH together with signals corresponding to the remaining C and CH_3 carbons, were observed. An accurate mass measurement on the molecular ion observed at *m/z* 314.0 and 312.0 in the 70 eV EI mass spectrum established molecular formula as $C_{14}H_{17}BrO_3$.

*Benzyl ether **131***

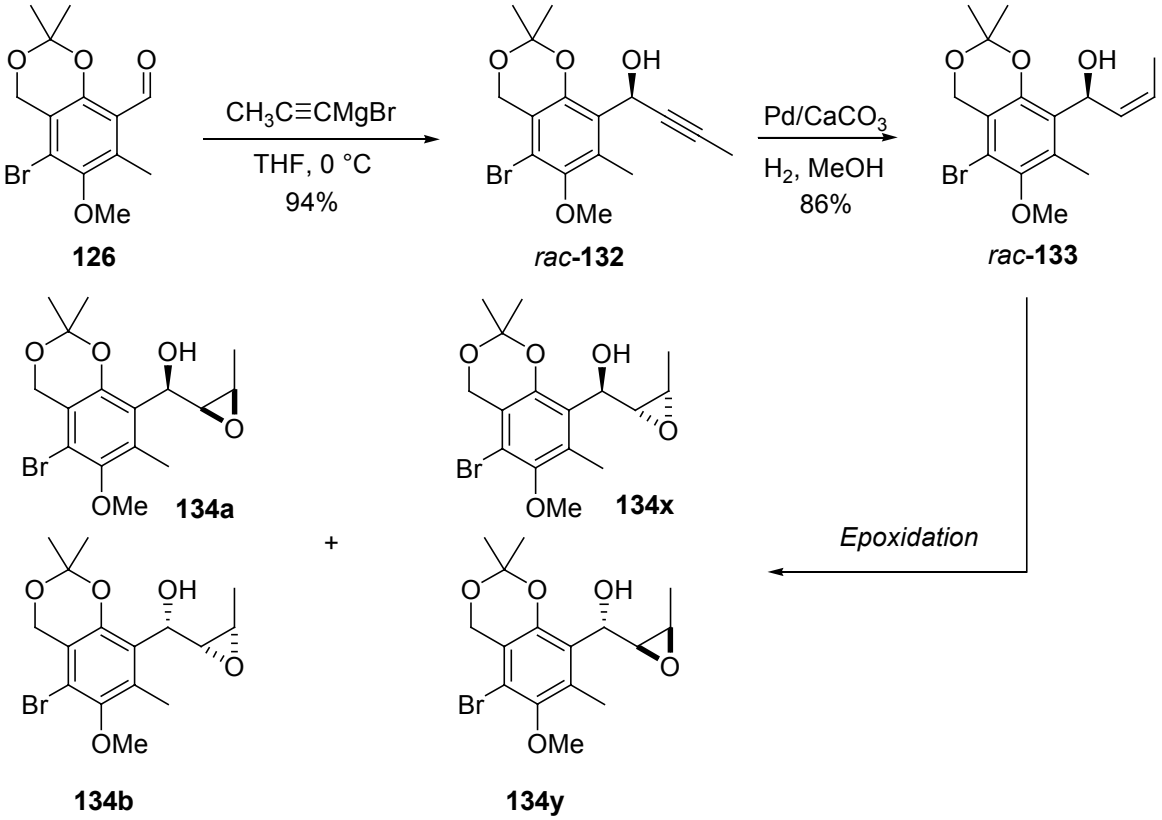
The ^{1}H-NMR spectrum of compound **131** shows a resonance at δ = 5.39 corresponding to oxymethine proton, five aromatic signals as a multiplet attributed to the benzyl protecting group, a new resonance at δ = 10.24 assigned to the aldehyde proton. The resonance at δ = 190.3 in the ^{13}C-NMR spectrum are assigned to the aldehyde carbon, as well as three signals corresponding to the CH_2 groups of the acetal. Twelve signals corresponding to the aromatic C carbons together with one assigned CH signal and two assigned CH_3 signals. The IR spectrum shows the carbonyl stretching band at

1703 cm^{-1}, consistent with the presence aldehyde moiety. An accurate mass measurement on the molecular ion observed at *m/z* 422.0 and 420.0 in the 70 eV EI mass spectrum established molecular formula as $C_{20}H_{21}BrO_5$.

6 Side Chain Development

6.1 Synthesis of the Side Chain Associated with Mensacarcin 1

As highlighted in the introduction an important fragment essential to any total synthesis of mensacarcin (**1**), because of its underlying connection to the biological activity, is the C-ring side chain. Hence, synthetic method for the installation this fragment was developed. To test this methodology a model system, C-ring **126**, was used not to waste any waluable tricyclic products. Compound **126** was treated with 1-propynyl magnesium bromide to give the racemic alcohol **132** in high yield (94%). This initial attachment provided the three carbons required for mensacarcin (**1**). Next, to test whether the triple bond could be reduced and epoxidised the alkyne **132** was treated with Lindlar's catalyst[69] ($Pd/CaCO_3/Pb$) resulting in the formation of the *Z*-olefin **133** in 86%.

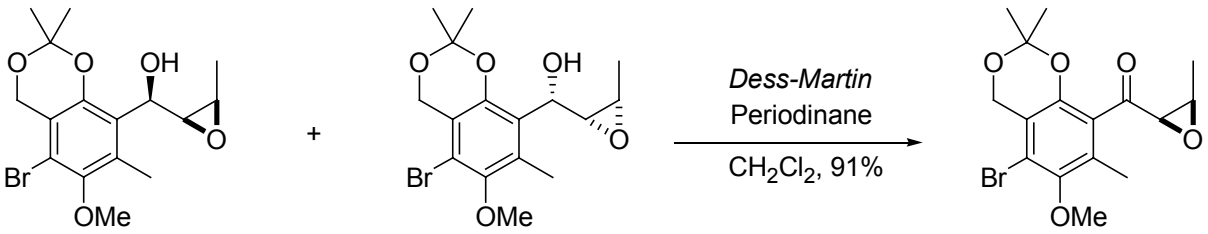


Conditions	Ratio of 134ab	to 134xy	Yield (%)
m-CPBA, CH_2Cl_2	1	0.3	76
$VO(acac)_2$, *t*-BuOOH	1	<0.1	64
t-BuOOH, CH_2Cl_2			

Table 6.1.1. *Epoxidation of alcohol rac-**133***.

A allylic hydroxyl directed epoxidation using either *m*-CPBA or $VO(acac)_2$ afforded epoxides **134ab** and **134xy** as two diastereoisomeric pairs, which could be separated by chromatography. Treatment of the olefin **133** with *m*-CPBA in dichloromethane gave a mixture of *syn*- and *anti*-diastereomers in ratio 3:1 (determined by ^{1}H-NMR) in good yield (76%). The *Sharpless* epoxidation[70] of olefin **133** using *tert*-butyl-hydroperoxide and catalytic amount of vanadyl(IV)-acetylacetonate provided the *syn*-diastereomer **134ab** almost exclusively, although in lower yields (64%).

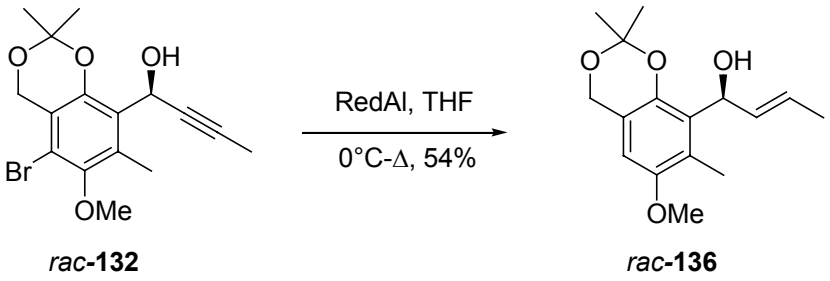
Finally oxidation of the secondary alcohol of compounds **134ab** using *Dess-Martin* periodinane[71] gave the desired ketone *rac*-**135** (91%) with the four carbon side chain containing an α,β epoxy ketone moiety similar to mensacarcin (**1**) (Scheme 6.1.2).



134a **134b** ***rac*-135**

Scheme 6.1.2

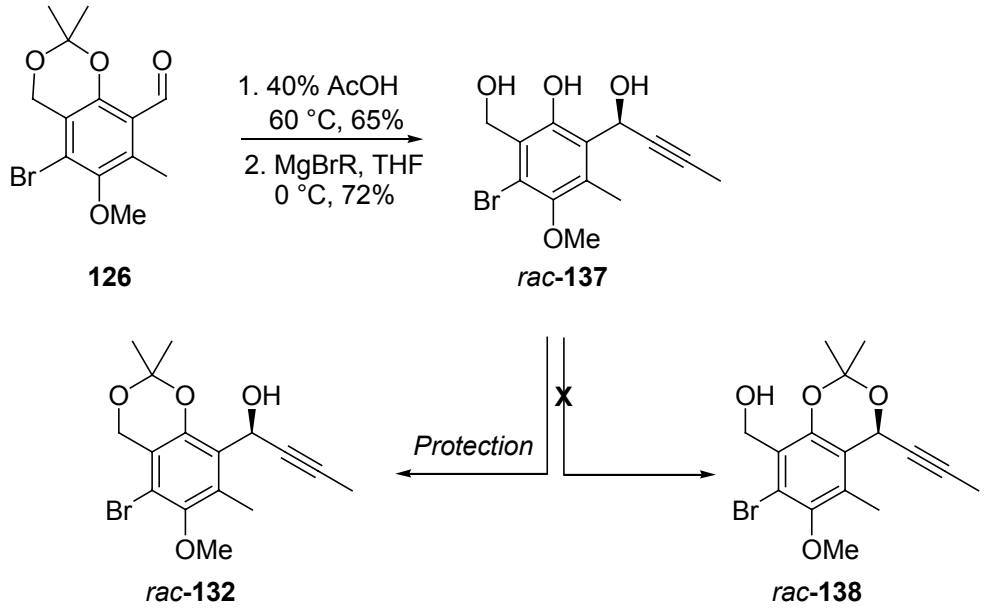
While it is important to test the stability of these compounds and the viability of this process, it is also important to note that the geometry of mensacarcin's side chain has been established as *anti*. Consequently, it was considered necessary to introduce correct *syn* geometry. Hence, the preparation of the *E*-configurated allylic alcohol *rac*-**136** (54%) was achieved by treatment of propalgyl alcohol *rac*-**132** with sodium bis(2-methoxyethoxy)-aluminium hydride (Red-Al).[72] Under these conditions debromination was observed in addition. However, the bromine atom was not expected to be present in the final anthraquinone structure. The route just described provides efficient access to ketone *rac*-**135** of which could be employed in the future synthesis using more complex tricyclic substrates.



rac-**132** *rac*-**136**

Scheme 6.1.3

Efforts towards the development of a C-ring unit already containing the four carbon side chain prior to coupling were made. C-ring building block **137** with a triple bond side chain and an acetal protecting group in the right section of the molecule i.e. *rac*-**138** was considered as an coupling fragment. Firstly, subjection of aldehyde **126** to deprotection with acetic acid gave phenol **128** in 65% yield. Other attempts to deprotect this acetal using HCl 1N in THF gave only small amount of product **128**, while Amberlist H^+ was not effective at all. Treatment of **128** with an excess of alkynyl Grignard reagent produced triol **137** in excellent yield (72%). In an attempt to prepare target acetal *rac*-**138** several conditions have been tried. However, using 2,2-dimethoxypropane and *p*-toluenesulfonic acid in different temperatures, always the undesired regioisomer *rac*-**132** was obtained as the only product. Formation of the acetal using acetone and *p*-toluenesulfonic acid gave also the undesired regioisomer *rac*-**132** (Scheme 6.1.4).



126 *rac*-**137**

rac-**132** *rac*-**138**

Scheme 6.1.4

Conditions	T [°C]	Time [h]	Yield (%)
2,2 DMP, *p*-TsOH	20	16	71
2,2 DMP, *p*-TsOH	-10	16	64
2,2 DMP, *p*-TsOH	60	4	55
Acetone, *p*-TsOH	20	18	82

Table 6.1.2. *Protection of triol rac-**137**.*

The alternative strategy could be protection of propalgylic alcohol group within compound *rac*-**137**, followed by deprotection of acetal moiety. In an effort to find right protecting group several conditions were evaluated. The alcohol *rac*-**137** was subjected to the protection reactions using TBSCl/imidazole or MeI/NaH. However, only starting material was isolated from these reactions, presumably due to the electronic influence of the triple bond.

6.2 Discussion of Selected Spectroscopic Data

*Alcohol **132***

The ^{1}H-NMR spectra of compound **132** showed two new resonances at δ = 1.75 and at δ = 3.50 assigned to the new methyl group and oxymethine proton respectively as doublet (*J* = 12.0 Hz). In the ^{13}C-NMR spectra a new CH_3 signal at δ = 3.7 together with signals corresponding to the remaining C and CH_3 carbons, were observed. The IR spectrum shows the OH stretching band at 3452 cm^{-1}, consistent with a vibration signal a alcohol moiety would give. An accurate mass measurement on the molecular ion was observed at *m/z* 356.2 and 354.2 in the 70 eV EI mass spectrum which with the aid of HRMS established molecular formula as $C_{16}H_{19}BrO_4$.

*Epoxides **134ab** and **134xy***

The olefinic signals found in compound *rac*-**133** in the region of δ = 5.50-5.81 were not seen in the^{1}H-NMR spectrum the of compounds *rac*-**134**. A new doublets of doubletes at δ = 3.48 (*J* = 11.6, 4.4 Hz) (**ab**) and δ = 3.32 (*J* = 12.6, 4.0 Hz) (**xy**) were observed and assined to the new CH epoxy protons. In the ^{13}C-NMR spectra, two new signals corresponding to the CH carbons at δ = 59.1, 59.6 (**ab**) δ = 59.0, 59.8 (**xy**) together with signals corresponding to the remaining C and CH_3 carbons, were observed. An accurate mass measurement on the molecular ion observed at *m/z* 374.0

and 372.0 in the 70 eV EI mass spectrum established molecular formula as $C_{16}H_{21}BrO_5$.

*Ketone rac-**135***

The ^{1}H-NMR spectrum of compound **135** exhibited resonance at δ = 3.45 (*J* = 4.5 Hz) assignet to the the H1 proton as a quartet and at δ = 3.99 (*J* = 4.5, 1.1 Hz) corresponding to and H2 proton as a doublet of doublets. The ^{13}C-NMR spectrum showed sixteen resonance including a peak at δ = 198.9 corresponding to the newly formed carbonyl group. The IR spectrum shows the carbonyl stretching band at 1720 cm^{-1}, consistent with the presence carbonyl moiety. An accurate mass measurement on the molecular ion observed at *m/z* 372.1 and 370.1 in the 70 eV EI mass spectrum established molecular formula as $C_{16}H_{19}BrO_5$.

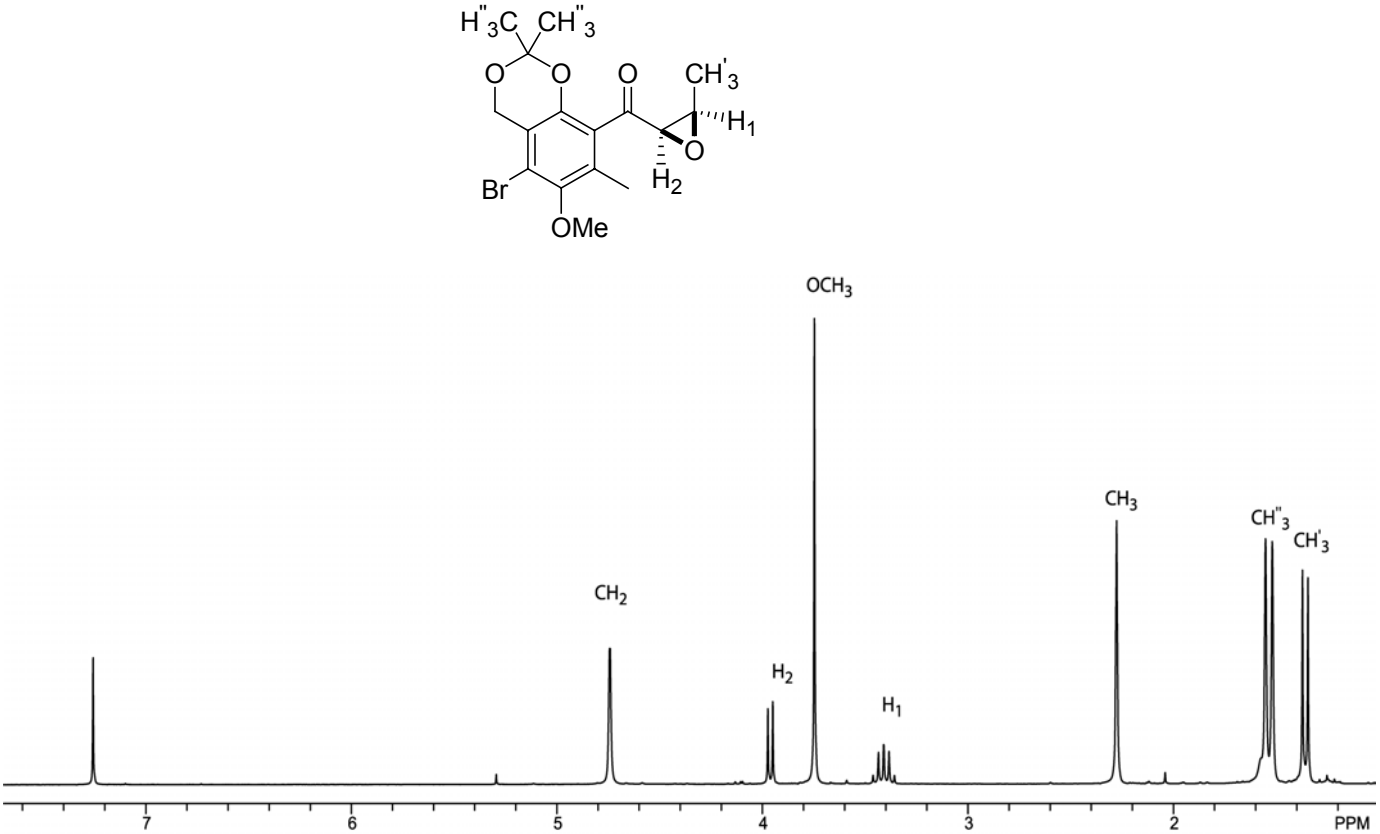
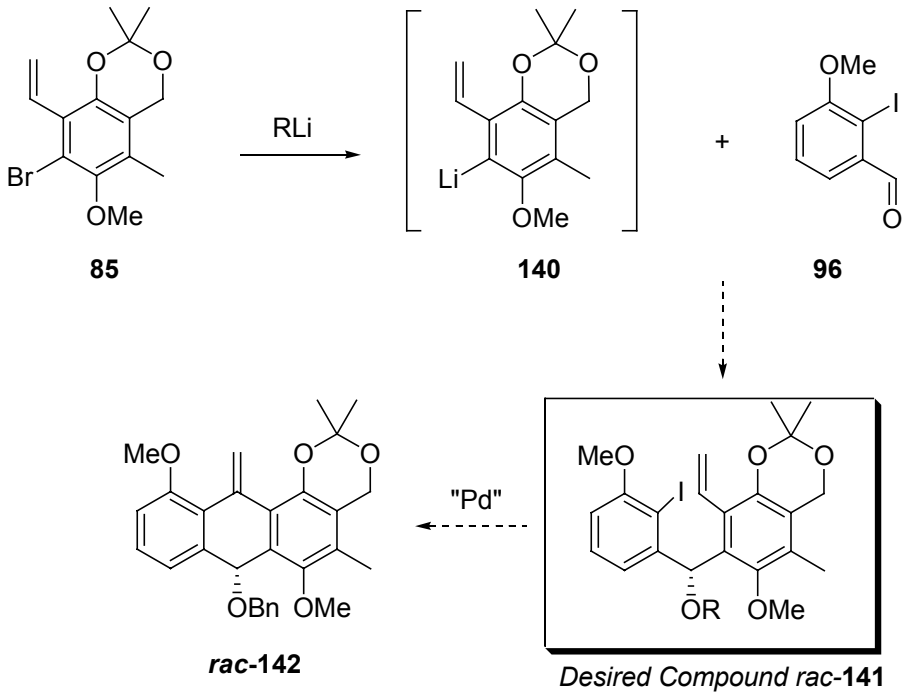


Figure xx. ^{1}H-NMR Spectrum of Ketone *rac*-**135** (300 MHz, $CDCl_3$).

7 Coupling of A- and C-Ring Fragments

7.1 Lithium-Halogen Exchange According to the First Retrosynthetic Analysis

This section describes studies based on the retrosynthetic analysis shown in Scheme 3.3. The initial plan was to use a nucleophilic aryllithium to aldehyde addition reaction to bring together the two aromatic fragments which is then followed by an intramolecular *Heck* reaction to afford the desired dihydroanthracene compound. The lithiation of bromostyrene **85** would produce aryllithium **140** which in turn, after addition, provide the corresponding diphenylcarbinol *rac*-**141** (Scheme 7.1.1). Such a compound could then be protected as its corresponding benzyl ether. Finally, the C-ring double bond together with A-ring iodide should undergo an intramolecular *Heck* cyclisation to furnish the key tricyclic product. The advantage of using such a highly substituted substrate for palladium catalysed transformation is to provide more advanced intermediates to mensacarcin (**1**) in a more convergent approach. To first evaluate whether such approach could be successfully carried out, coupling between nucleophile **140** with electrophile **96** was studied.

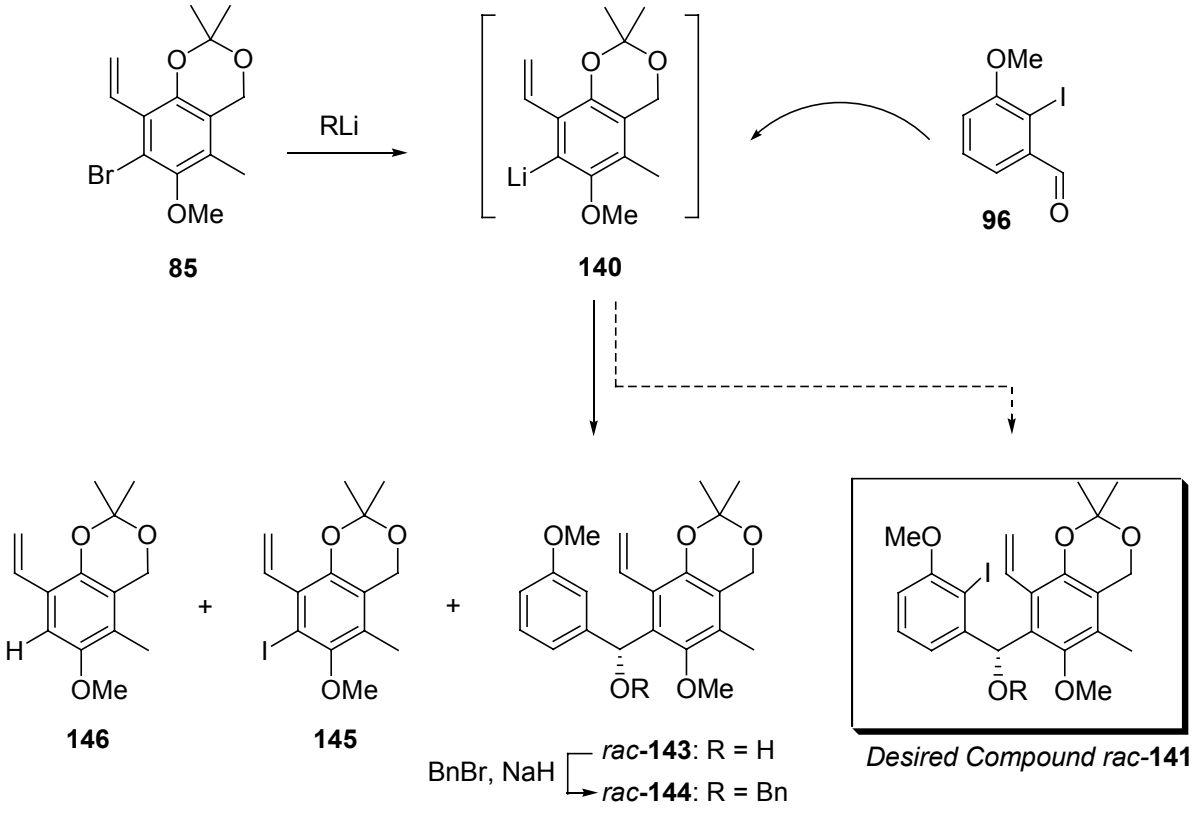


85 **140** **96**

***rac*-142** *Desired Compound rac*-**141**

Scheme 7.1.1

First, the lithiation of bromostyrene **85** using *t*BuLi was evaluated. Compound **85** was treated with 2.1 equiv. of *t*BuLi in Et_2O at –78 °C for 10 min, followed by addition of aldehyde **96** (Entry 1, Table 7.1). Unfortunately, the expected diphenylcarbinol was not obtained, but as a side reaction product, iodobenzene **145** (9%) was observed. Another compound isolated was the debrominated starting material **146** (13%). Because the diphenylcarbinol *rac*-**143** could not be isolated it was thought that this addition product could be highly unstable. Thus, the supposedly formed benzyl alcohol was immediately deprotonated with NaH and quenched with benzyl bromide to hopefully afford *rac*-**141** (Scheme 7.2).



Scheme 7.1.2

Unfortunately, the only product resulting from addition was the dehalogenated A-ring (observed only in traces >1%). Interestingly, when the reaction was carried out at lower temperatures (–100 °C), the main product was iodobenzene **145** 74% yield. This unique bromine/aryllithium to iodine exchange, is attributed to the low reactivity of the aldehyde moiety within **96**. It is believed that the sterically encumbered aryllithium

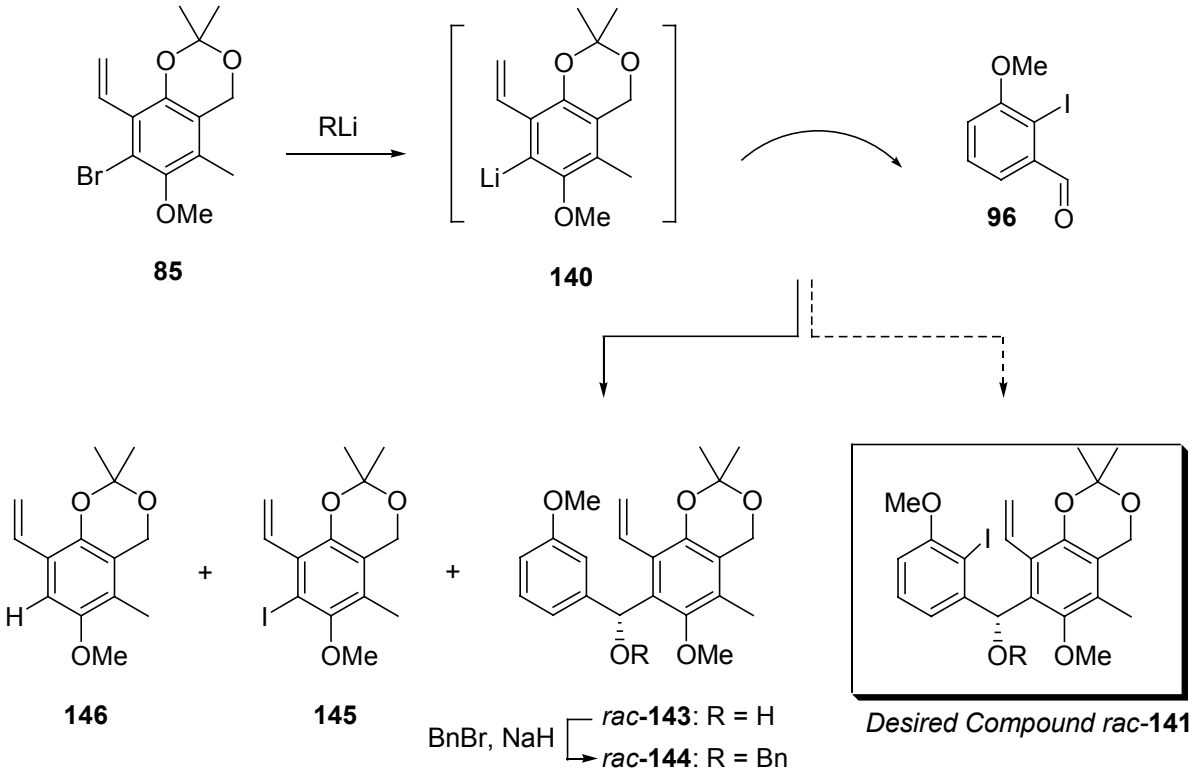
140 cannot approach the aldehyde moiety of **96**, instead the more accessible iodine is electrophilically removed. To overcome this problem, it was thought that the formation of organocerium reagent, generated from cerium chloride and an organolithium species, might give a softer and chemoselective addition to the aldehyde.[73] To examine such a possibility, bromostyrene **85** was treated with *t*BuLi and $CeCl_3$ in THF at –78 °C, after 30 min aldehyde **96** was added to the reaction.[74] Unfortunately, debrominated starting material **146** (44%) was the only product isolated (Entry 4, Table 7.1.1). Generation of the Grignard reagent derived from compound **85** was also not successful, presumably due to the electron rich nature of the aromatic C-ring.

Entry	RLi (eq.)	T [°C]	Time [min]*	Solvent	144 [%]	145 [%]	146 [%]
1	*t*BuLi (2.1)	-78	10	Et_2O	-	9	13
2	*t*BuLi (2.1)	-78	20	Et_2O	>1	32	22
3	*t*BuLi (1.1)	-100	30	Et_2O	-	74	4
4	*n*BuLi (2.1), $CeCl_3$	-78	30	THF	-	-	44
5	Mg	reflux	60	Et_2O	-	-	>1
6	*n*BuLi (1.1)	-78	1	Et_2O	5	-	-
7	*n*BuLi (1.1)	-78	10	Et_2O	9	-	11

Table 7.1.1. Lithium *via* bromine exchange, following aldehyde **96** addition.
* Time of lithiations.

Following the above negative results, attention was then directed towards reversed addition procedure for example the *in situ* organolithium compound **140**, derived from halide **85**, was added to aldehyde **96**. Hence, the bromostyrene **85** was treated with *t*BuLi (2.1 equiv.) at – 78 °C in Et_2O and the organolithum species **140** was added *via cannula* to aldehyde **96** dissolved in Et_2O at – 78 °C. The above procedure provided the desired diphenylcarbinol *rac*-**144** in 23% yield, however this compound did not contain the essential iodide for the intramolecular *Heck* reaction (Entry 2. Table 7.1.2).

Improving this procedure could not be achieved by employing of any of the literature known methods. This situation, forced the author to investigate other synthetic pathways, as described in the following chapters.



Entry	RLi (eq.)	T [°C]	Time [min]*	Solvent	144 [%]	145 [%]	146 [%]
1	*t*BuLi (2.1)	-78	10	Et_2O	10	>1	6
2	*t*BuLi (2.1)	-78	20	Et_2O	23	36	11
3	*n*BuLi (1.1)	-78	1	THF	-	-	8
4	*n*BuLi (1.1)	-78	10	Et_2O	>1	-	13

Tabele 7.1.2. Addition of the lithium species **xx** to the aldehyde **96**.
* Time of lithiations.

7.2 Discussion of Selected Spectroscopic Data

*Benzyl ether rac-**144***

The ^{1}H-NMR spectra of compound **144** shows a singlet at δ = 6.21 attributed to the oximethine proton. Furthermore, a new singlet at δ = 6.41 corresponding the new aromatic proton confirmed the outcome of the pre-described reaction. An accurate mass measurement on the molecular ion observed at *m/z* 460.4 in the 70 eV EI mass spectrum established molecular formula as $C_{29}H_{32}O_5$.

*Iodobenzene **145** and styrene **146***

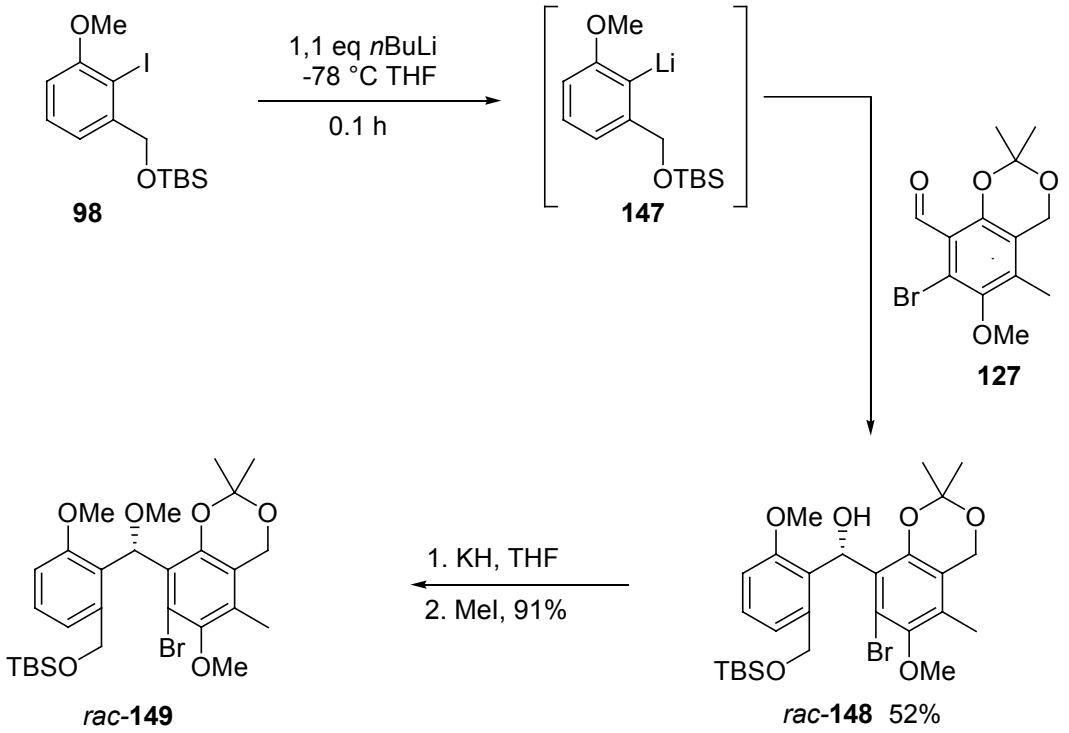
Characteristic features observed in the ^{1}H-NMR spectrum of compound **146** included a resonance at δ = 6.81 assigned to the newly formed aromatic proton. The ^{13}C-NMR

spectra of **145** displays all fourteen C resonances. An accurate mass measurement on the molecular ion observed at *m/z* 360.1 (**145**) in the 70 eV EI mass spectrum established molecular formula as $C_{14}H_{17}IO_3$.

7.2 Coupling of the A- and C-Ring Building Blocks According to the Second Retrosynthetic Analysis

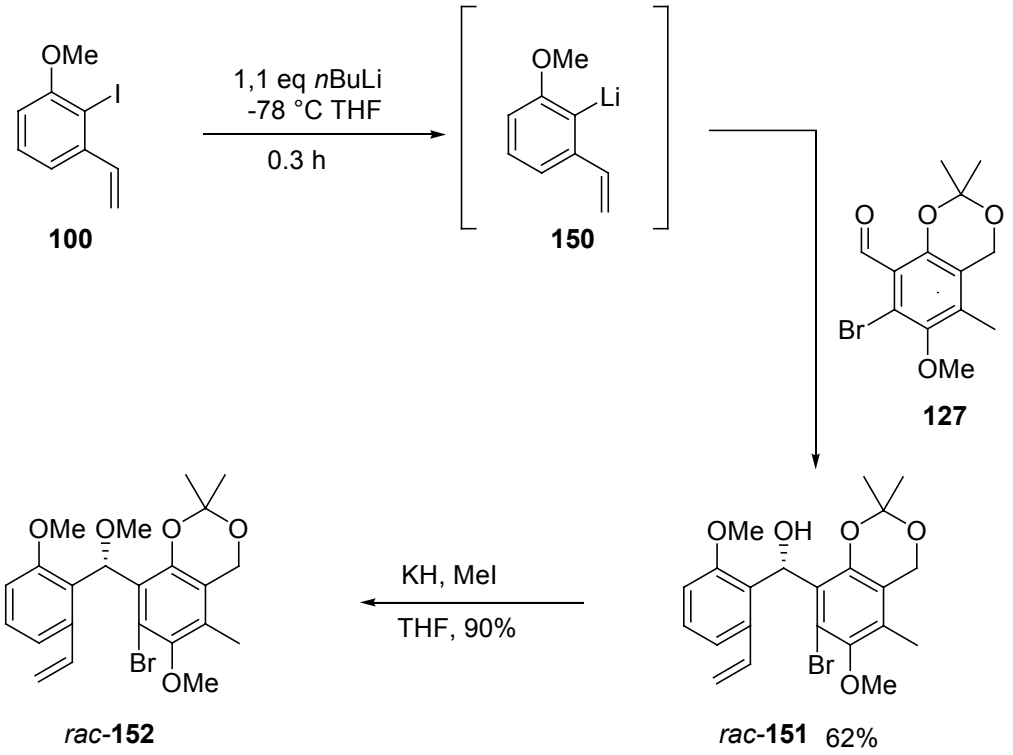
Investigation into an alternative synthetic pathway was carried out based on opposite retrosynthetic disconnection (Scheme 3.6). For this purpose, the aldehyde **127** was used as an electrophile, which could be nucleophilically attacked using a derived form of iodoarene **81** .

The preformed TBS-ether **98** first was subjected to metal/halogen exchange conditions using *n*BuLi in THF at – 78 °C to create the intermediate lithium species **147** as seen by TLC monitoring of the protonated arene. To this reaction mixture a solution containing aldehyde **127** was added to form the desired addition product diphenylcarbinol *rac*-**148** in 52% yield (Scheme 7.2.1). Due to the fact that neither of the starting materials were chiral and no chiral separation techniques were used **148** was isolated as a racemate. The rather moderate yield of this transformation may reflect the high steric hindrance within the *tert*-butyl dimethylsilyl ether interfering with the addition process. Subsequent, installation of what would become the C-10 methoxy substituent in mensacarcin (**1**) was achieved by treatment of this latter compound with potassium hydride and methyliodide. After this transformation the protected alcohol *rac*-**149** was isolated in 91% yield. However, due to the additional steps required for the installation of a double bond (deprotection, oxidation and *Wittig* reaction) which could react under *Heck* conditions a new substrate was investigated.



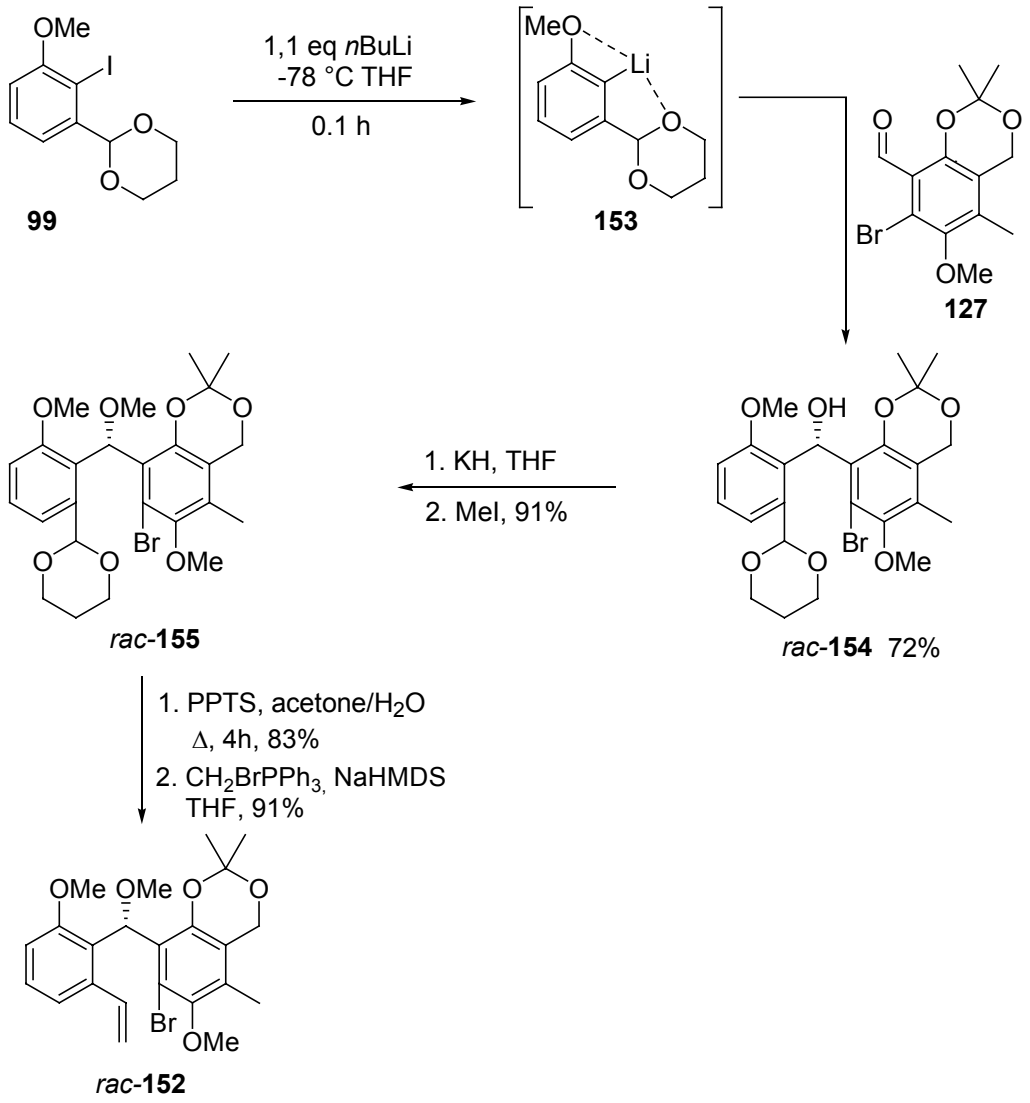
Scheme 7.2.1

In a more convergent approach (Scheme 7.2.2) aryllithim **150** was used as a new coupling partner. The new lithium species was prepared *in situ* from **100** once again using a lithium-iodine exchange with *n*BuLi. This was followed by addition of the hexasubstituted aldehyde **127** which led to formation of the diphenylcarbinol *rac*-**151** in a reasonable yield of 62%. Interestingly, the iodostyrene **100** was lithiated slower (t.l.c monitoring) than corresponding silylether **98**. On the other hand, the addition process gave superior results in both yield and amount of byproducts. Interestingly, a less efficient transformation resulted with *t*BuLi as lithiating reagent. The solvent (THF or Et_2O) does not seem to have a pronounced effect the metalations however, it was found that a higher concentration substrate during the lithiatuion increases the yield. Protection of the secondary alcohol to the required methoxy group furnished the first substrate *rac*-**152** (90%), set-up for the key transformation the intramolecular *Heck* reaction.



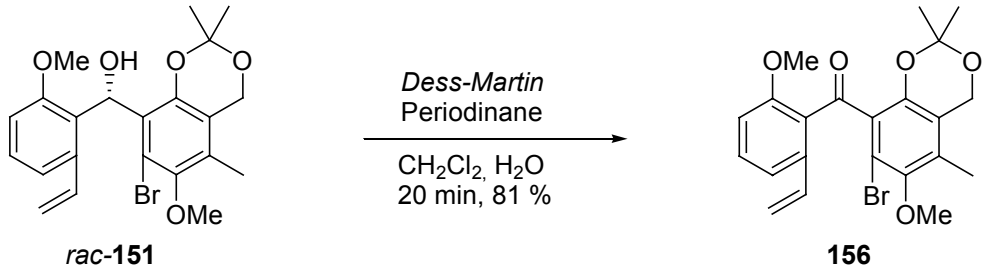
Scheme 7.2.2

In an effort to improve the aryllithium to aldehyde addition and hence the overall yields, an alternative pathway to compound *rac*-**152**, the intramolecular *Heck* reaction precursor, was devised. Thus, the aryllithium of acetal **153** (Scheme 7.2.3) was added to the aldehyde **127** to give the diphenylcarbinol *rac*-**154** in superior yields (74%). The reasons for the protected iodo compound **99** performing better under these conditions than its TBS ether **98** and styrene **100** counterparts are unknown however, one could assume that the oxygen atoms within the acetal moiety at the *ortho* position facilitates the lithiation and stabilises the formed metal organic compound. The alcohol moiety within compound *rac*-**154** was then methylated using KH and MeI to give *rac*-**xx** in 91% yield. Cleavage of the acetal moiety using pyridynium *p*-toluenesulfonate (83%) and olefination using PPh_3CH_3Br and NaHMDS (91%) gave the desired alkene *rac*-**152**, as synthesised previously. However, due to the additional steps the overall yield of this pathway does not exceed the direct previously mentioned approach to *rac*-**152** using compound **100** as a substrate.



Scheme 7.2.3

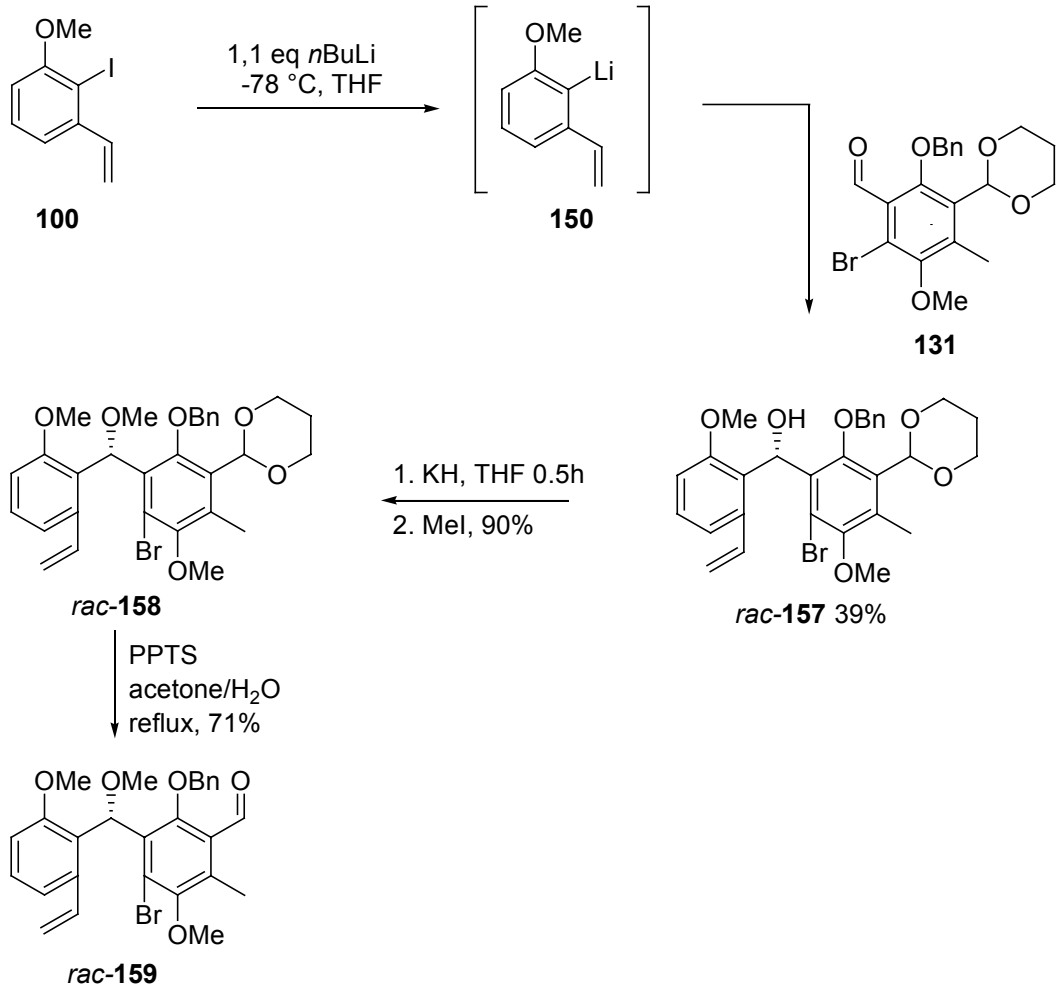
Having succeeded in preparing the first precursor for the cyclisation, investigations were focused on structural modifications, so the next *Heck* transformation could be accelerated. It was thought that conversion of hydroxyl group of compound *rac*-**151** into carbonyl functionality would lower the C ring aromatic electron density as well as bring the olefin and organopalladium intermediate in close proximity to each other through conjugation. With this in mind, benzophenone **156** was synthesised from *rac*-**151** using the *Dess-Martin* periodinane in 81% yield (Scheme 7.2.4).



rac-**151** **156**

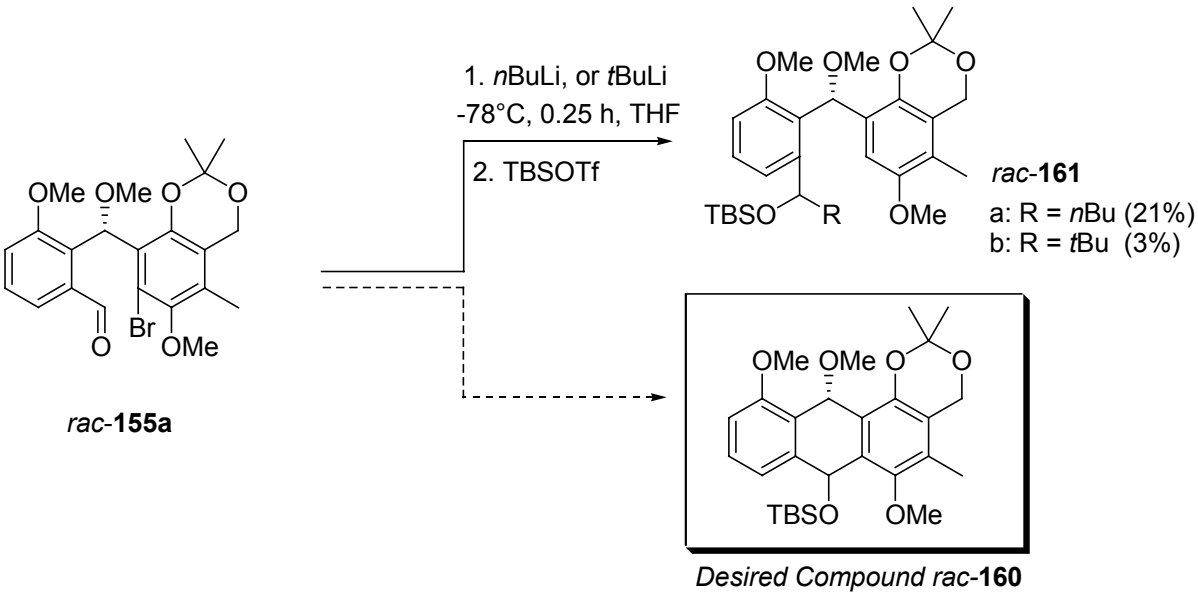
Scheme 7.2.4

Having established a successful pathway to diphenylcarbinol *rac*-**152** and benzophenone **156** it was now necessary to modify the overall system and trial coupling between another C-ring building block compound **131**. Thus, a third *Heck* reaction precursor was prepared *via* a three-step sequence (Scheme 7.2.5). This pathway was chosen for palladium catalysed cyclisation, because the bromine moiety would be activated towards oxidative addition step by the presence of a *para*-related electron withdrawing aldehyde substituent. The new aryllithium species **150** was added in the same manner as previously to aldehyde **131** to produce alcohol *rac*-**157** in 39% yield. This rather moderate addition yield when comparing to the previous couplings was attributed to a neighbourhood electronic effect of benzyl ether. All attempts to improve this yield by varying reaction time and reverse addition were unfortunately unsuccessful. Once again, the alcohol *rac*-**157** was converted into the corresponding methyl-ether **158** (90%). It is important to note that an excess of base (KH) was necessary to deprotonate the secondary hydroxyl group. Deprotection of compound *rac*-**158** was achieved using pirydynium *p*-toluenesulfonate in acetone/water mixture to afford benzaldehyde *rac*-**159** in 71% yield.



Scheme 7.2.5

During initial retrosynthetical analyses studies it was believed that compound *rac*-**155a** could be used for a one pot cyclisation and protection reaction. Using a lithium-bromine exchange, followed by an intramolecular addition to the aldehyde moiety the desired alcohol was produced (Scheme 7.2.6). Following, *in situ* protection to silyl ether, it should then give the stable *rac*-**160**. Reasons for carrying out this transformation were to investigate whether butyllithium would participate in halogen-metal exchange or an aldehyde addition reaction under these cold conditions. Aldehyde *rac*-**155a** was subjected to lithiation using 1.1 equiv. *n*BuLi in THF at – 78 °C and quenched with *tert*-butyl-dimethylsilyl triflate. Unfortunately, addition of butyllithium to the aldehyde occurred fated than metal for halogen exchange to give, after protection, *rac*-**161** (21%). To evaluate whether butyllithium to aldehyde addition could be avoided, *t*BuLi was also used, unfortunately the results were the same now forming the *t*butyl alcohol.



Scheme 7.2.6

7.3 Spectroscopic Data of Selected Compounds.

*Diphenylcarbinol (Heck substrate I) rac-**152***

The ^{1}H-NMR spectrum (Figure 7.3.1) of compound **152** showed a resonance at δ = 5.12 corresponding to the mono-substituted double bond (*J* = 10.8, 1.8 Hz) as a doublet of doublets *cis*, at δ = 5.43 (*J* = 17.5, 1.8 Hz) doublet of doublets *trans* and at δ = 7.81 (*J* = 17.5, 10.8 Hz) as a doublet of doublets. The *meta* and *ortho* values for resonances in the aromatic region of the ^{1}H-NMR spectrum were deemed appropriate for such tri-substituted aromatic rings. The ^{13}C-NMR spectrum exhibited twenty three signals, two methylene groups at δ = 60.0, 60.5, and two signals corresponding CH carbon at δ = 80.4 and 98.5. Molecular ion at *m/z* 464.2 in the eV EI spectrum together with elemental analysis established the expected structure.

*TBS-ether rac-**149***

Characteristic features observed in the ^{1}H-NMR spectrum of compound **149** included singlets at δ = 3.50, 3.59, 3.81 assigned to the three methoxy groups. Doublet and singlet resonances at δ = 0.10 (*J* = 8.5 Hz) and δ = 1.02 corresponding to the *tert*-butyl dimethylsilyl ether as were also observed. A singlet at δ = 6.21 was assigned to the oxymethine proton was also observed. The ^{13}C-NMR spectrum also exhibited characteristic signals at δ = 11.3 and δ = 22.0 assigned to the TBS-ether proton. An

accurate mass measurement on the molecular ion appearing at *m/z* 582.0 and 580.0 in the eV EI spectrum established the mass of the expected structure.

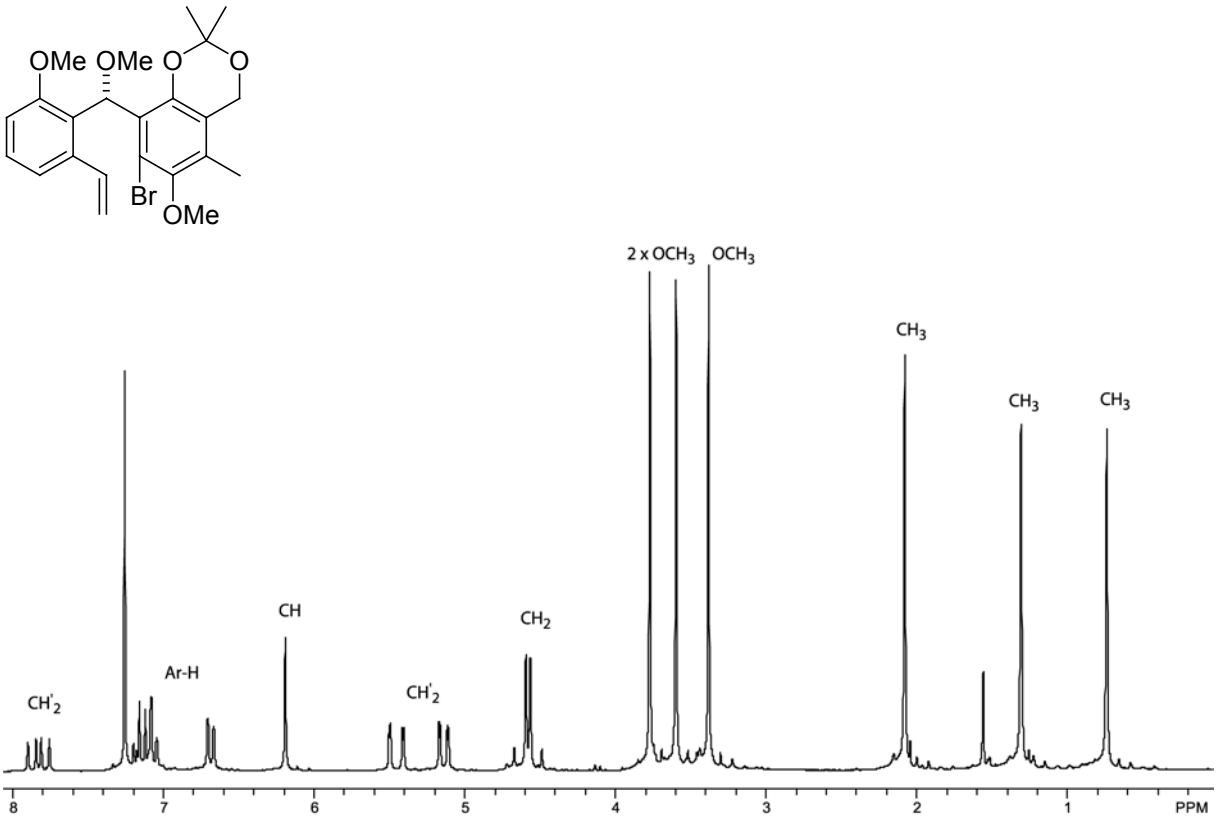


Figure 7.3.1. ^{1}H-NMR Spectrum of Diphenylcarbinol *rac*-**152** (300 MHz, $CDCl_3$).

Benzopheneone (Heck substrate II) ***156***

The ^{1}H-NMR spectrum of compound **156** (Figure 7.3.2) included no signal in the oxymethiene region as seen in compound *rac*-**152**. The appearance of a signal at δ = 195.4 in the ^{13}C-NMR spectra assigned to the new carbonyl was characeristic. The IR spectrum shows the carbonyl stretching band at 1680 cm^{-1}, also consistent with the presence carbonyl moiety. An accurate mass measurement on the molecular ion observed at *m/z* 448.3 and 446.3 in the 70 eV EI mass spectrum established molecular formula as $C_{22}H_{23}BrO_5$.

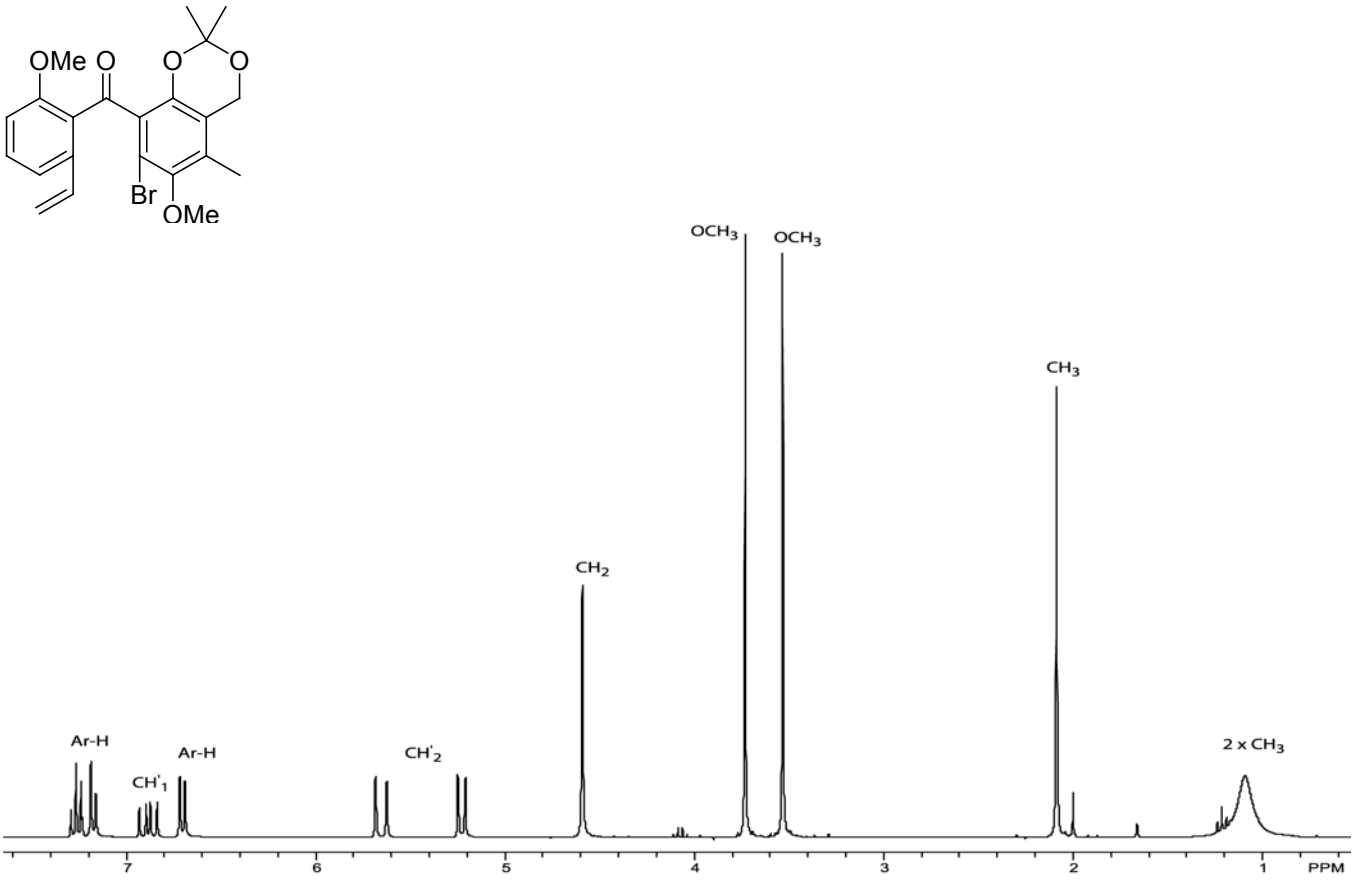


Figure 7.3.2. ^{1}H-NMR Spectrum of Benzophenon **156** (300 MHz, $CDCl_3$).

*Aldehyde (Heck substrate III) rac-**159***

The ^{1}H-NMR spectrum (Figure 7.3.3) of compound **159** shows resonance at δ = 6.25 corresponding oxymethine proton, five aromatic signals as multiplet is attributed to the benzyl protecting group, while a new resonance at δ = 10.16 is assigned to the aldehyde proton. The resonance at δ = 194.1 in the ^{13}C-NMR spectrum was assigned to the aldehyde carbon. Furthermore, two signals corresponding to the CH_2 of the benzyl group and olefin functionality were observed. The IR spectrum shows the stretching band at 1710 cm^{-1}, consistent with the presence of an aldehyde moiety. An accurate mass measurement on the molecular ion at *m/z* 512.2 and 510.2 in the 70 eV EI mass spectrum established molecular formula as $C_{27}H_{27}BrO_5$.

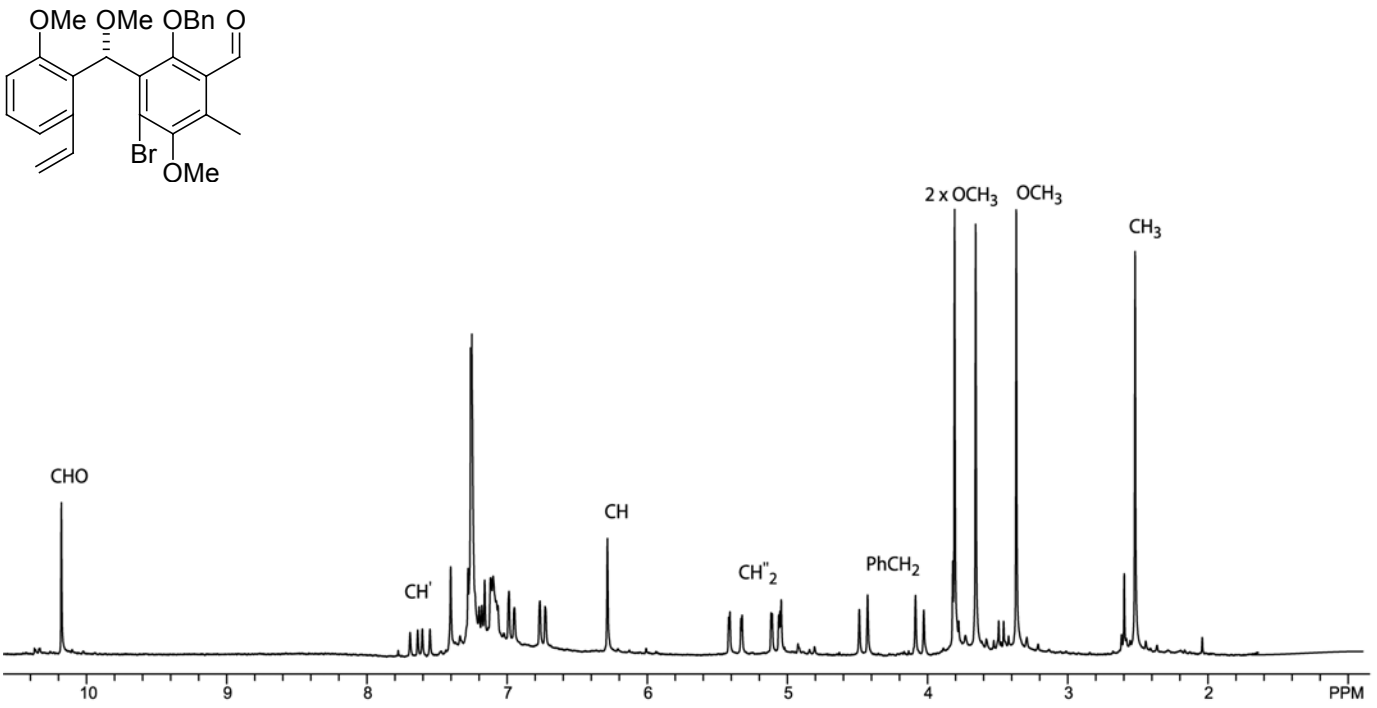


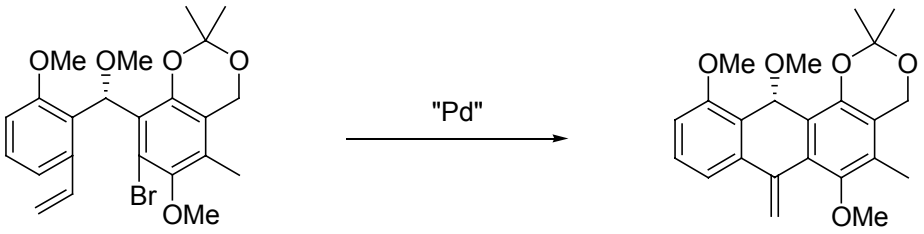
Figure 7.3.3. ^{1}H-NMR Spectrum of Aldehyde *rac*-**159** (300 MHz, $CDCl_3$).

8 Intramolecular *Heck* Reactions in the Synthesis of the Tricyclic Core of Mensacarcin

The key step during investigations towards synthesis of mensacarcin (**1**) was the construction of tricyclic framework by an intramolecular *Heck* reaction. Further requirements were that this reaction could be carried out quickly and under reasonably mild conditions, not to decompose the dihydroanthracene product. Palladium cross-coupling reactions have been utilized in the synthesis of a wide variety of biologically active and novel compounds.[75] Exploring the potential of reactions such as *Heck* type transformations is an important aspect in the refining of synthetic organic processes. The *Heck* coupling reaction, first observed in 1968, has advanced with discovery of a variety of different catalysts and catalytic systems. The improvements made for the intermolecular *Heck* reaction have also additionally advanced the intramolecular variant.[76]

Previous studies of both inter and intramolecular *Heck* reactions reveal that matching of the appropriate catalytic conditions with the electronic properties of the aryl or vinyl halide substrate is essential. Initial development of new catalysts and catalytic methodology by the groups of *Milstein* (bulky, electron-rich chelating bisphosphines),[77] *Herrmann* (palladacycles),[78] *Reetz* (tetraphenylphosphonium salts),[79] *Beller* (phosphites),[80] provided a variety of conditions for carrying out high yielding *Heck* transformation. Generally, from such studies electron poor aryl halides were considered essential for the oxidative addition to the Pd(0) species. More recently, *Fu* et. al. have developed systems [$Pd_2(dba)_3$, $HP(tBuP)_3BF_4$ and Cy_2NMe] that catalyse *Heck* couplings using less reactive electron rich aryl chlorides and bromides as substrates.[81] Sterically hindered, electron rich phosphine $(tBu)_3P$ have been found to be an effective ligand for the $Pd_2(dba)_3$-catalyzed *Heck* couplings.[82] Furthermore, the group of *Lautens* reported on intramolecular *Heck* reactions involving dihydronapthalene substrates with a variety of electronically diverse aryl bromides.[83] The following chapter of this thesis further examines if it is possible to match certain catalytic parameters with the electronic nature of the aryl bromide starting material for greater turnover numbers (TON).

To optimise these transformations three substrates from chapter 7 were synthesised containing varying electronic properties in the aryl bromide portion. These three substrates were subjected to a variety of palladium catalysis and conditions. The first substrate *rac*-**152** containing a highly electron rich aryl bromide moiety was initially trailed (Table 8.1) using two first generation catalysts $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$. At 90 °C for 5 hours both procedures afforded the product tetrahydroanthracene *rac*-**162**, however, only in poor yields 11 and 6% respectively (Entry 1,2, Table 8.1). Interestingly, in all cases large amounts of starting material remained which prompted the screening of second generation catalysts which could withstand higher temperatures and/or give better TON's. Next we performed *Heck* reaction using the palladacycle developed by *Herrmann* and *Beller*. A catalyst loading of 20 mol% $Pd_2(OAc)_2[P(o\text{-}Tol)_3]_2$ gave low yields of 27% after 5 hours at 120 °C with 42% of starting material remaining (Entry 3, Table 8.1). Unfortunately, longer reaction times (Entry 4, Table 8.1) only resulted in decomposed the remaining starting material and failed to dramatically increase the overall yield. Switching to a more electron rich palladium complex $Pd_2(dba)_3/P(t\text{BuP})_3$, provided such a system which was very effective for our electron rich substrate. Many laboratories also described the effectiveness of a bulky tertiary amine Cy_2NMe in *Heck* couplings.[84] Using a moderate catalyst loading (3 mol% Pd) and 6 mol% of phosphine (1:1 ratio of $Pd:P(t\text{Bu})_3$) and Cy_2NMe all that was needed to facilitate a 94% yield of the desired product (Entry 5, Table 8.1). Using the more stable and practical trialkylphosphonium salt $[(t\text{Bu})_3PH]BF_4$ gave similar yields of 92%. One of possible explanation for this enhanced reactivity could be that our extremely electron rich aryl bromide undergoes oxidative addition more facile with a similarly electron rich palladium species. The optimised temperature was 110-120 °C and as in the paper of *Fu* et. al. dioxane was solvent of choice. Longer reaction times once again resulted in a decomposition of tricyclic product (Entry 7, Table 8.1). This catalytic system is unreactive at ambient temperature.



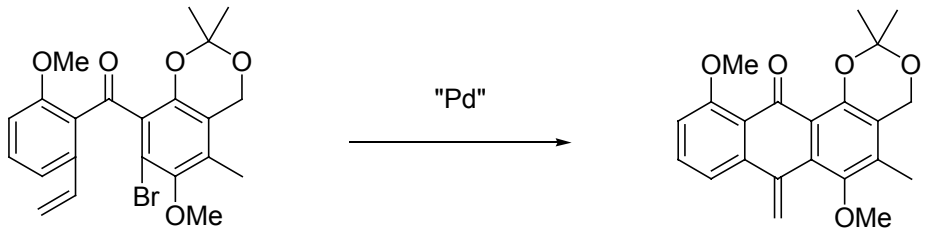
rac-**152** *rac*-**162**

Entry	Catalyst/Phosphine	Base	Solvent	Time [h]	T [°C]	%Yield (%Adduct)
1	10 mol% $Pd(PPh_3)_2Cl_2$	NaOAc	MeCN	5	90	**6**(58)
2*	10 mol% $Pd(OAc)_2$	nBu$_4$NOAc K_2CO_3	DMF	5	90	**11**(40)
3	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	5	120	**27**(42)
4	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	20	120	**33**(18)
5	3 mol% $Pd_2(dba)_3$/ 6 mol% P(tBuP)$_3$	Cy_2NMe	Dioxane	5	120	**94**(5)
6	3 mol% $Pd_2(dba)_3$/ 6 mol% HP(tBuP)$_3BF_4$	Cy_2NMe	Dioxane	5	120	**92**(5)
7	3 mol% $Pd_2(dba)_3$/ 6 mol% HP(tBuP)$_3BF_4$	Cy_2NMe	Dioxane	20	120	**78**(2)

Table 8.1. *Heck cyclisation of substrate rac-**152** to compound rac-**162**.*
* The Jeffery system requires K_2CO_3 and no phosphine[85]
$^{\xi}$ Herrmann-Beller catalyst is *trans*-di(μ-acetato)-bis[ortho-(di-*ortho*-tolylphosphino) benzyl]dipalladium (II)

The second olefin **156** examined contained an *ortho*-carbonyl group in relation to the bromine atom which, both lowered the electron richness of the aromatic ring and flattened the molecule through conjugation. It was found that the introduced carbonyl functionality had noticeable effects on the yields of reactions. A significant improvement, from 11% to 22% yield of desired product **163**, was observed when comparing results of the first substrate *rac*-**152** with the new substrate **156**, using $Pd(OAc)_2$ and K_2CO_3 as a base at 90 °C (Entry 2, Table 8.2). However, prolongation of the reaction time resulted in decomposition of both starting material and product (Entry 3, Table 8.2). Additionally, improvements were also made when the *HB* palladacycle at 90 °C was used (5 hours; 59% yield of anthracenone **163**). Greater

yields were also obtained when carrying out this reaction at higher temperatures (Entry 5, Table 8.2). As previously, longer reaction times result in lower yields of product and remaining starting material. Interestingly, when the $Pd_2(dba)_3$ with electron rich phosphine ligand were employed, a slight decrease of the product yield resulted when compared with substrate *rac*-**152**. These results suggest that the oxidative addition occurs more rapidly in this more electron poor substrate **156**. Extended reaction times at these temperatures only resulted in decomposition of substrate and product. These results agree with the theory that electronic properties of substrate must be compatible with the catalyst's electronic properties.

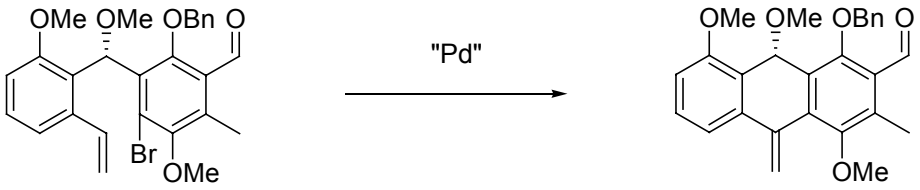


156 **163**

Entry	Catalyst/Phosphine	Base	Solvent	Time (h)	Temp (°C)	%Yield (%Adduct)
1	10 mol% $Pd(PPh_3)_2Cl_2$	NaOAc	MeCN	5	90	**7**(70)
2*	10 mol% $Pd(OAc)_2$	nBu$_4$NOAc K_2CO_3	DMF	5	90	**22**(61)
3*	10 mol% $Pd(OAc)_2$	nBu$_4$NOAc K_2CO_3	DMF	20	90	— (25)
4	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	5	90	**59**(20)
5	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	5	120	**73**(6)
6	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	20	120	**31**(6)
7	3 mol% $Pd_2(dba)_3$/ 6 mol%HP(tBuP)$_3$$BF_4$	Cy_2NMe	Dioxane	5	120	**78**(5)
8	3 mol% $Pd_2(dba)_3$/ 6 mol% HP(tBuP)$_3$$BF_4$	Cy_2NMe	Dioxane	5	20	— (93)

Table 8.2. *Heck cyclisation of substrate **156** to compound **163**.*
$^{\xi}$ Herrmann-Beller catalyst is *trans*-di(μ-acetato)-bis[ortho-(di-*ortho*-tolylphosphino) benzyl]dipalladium (II) * The Jeffery system requires K_2CO_3 and no phosphine

On the basis that electron poor aromatic bromides, in this case and others, are the most reactive towards the proposed oxidative addition step of most palladium catalysts, a third *Heck* precursor was prepared. The final substrate *rac*-**159**, containing a *para*-aldehyde moiety, was considered to be the least electron rich aryl ring of the three substrates. Introducing an aldehyde moiety, led to an increase reactivity when using $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and the Hermann-Beller catalyst (Entry 1-4, Table 8.3). The best result (Entrys 3 and 5, Table 8.3) using *HB* cat., 120 °C over 5 hours gave the desired tricyclic product *rac*-**164** in 82% yield. As expected, the conversion of *rac*-**159** to *rac*-**164** when using $Pd_2(dba)_3$ as a catalyst was lower yielding than the other two substrates *rac*-**152** and **156**.



rac-**159** *rac*-**164**

Entry	Catalyst/Phosphine	Base	Solvent	Time (h)	Temp (°C)	%Yield (%Adduct)
1	10 mol% $Pd(PPh_3)_2Cl_2$	NaOAc	MeCN	5	90	**12**(48)
2*	10 mol% $Pd(OAc)_2$	nBu$_4$NOAc K_2CO_3	DMF	5	90	**34** 52)
3	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	5	120	**82**(3)
4	20 mol% HB cat$^{\xi}$	nBu$_4$NOAc	DMF/MeCN/H_2O	20	120	**64**(—)
5	3 mol% $Pd_2(dba)_3$/ 6 mol% HP(tBuP)$_3$BF$_4$	Cy_2NMe	Dioxane	5	120	**77**(18)
6	3 mol% $Pd_2(dba)_3$/ 6 mol% HP(tBuP)$_3$BF$_4$	Cy_2NMe	Dioxane	20	120	**6** (4)

Table 8.3. *Heck cyclisation of substrate rac-**159** to compound rac-**164**.*
$^{\xi}$ Herrmann-Beller catalyst is *trans*-di(μ-acetato)-bis[ortho-(di-*ortho*-tolylphosphino) benzyl]dipalladium (II)
* The Jeffery system requires K_2CO_3 and no phosphine

In summary, an efficient pathway to tetrahydroanthracene compounds through an intramolecular *Heck* approach was developed. When carrying out these transformations on the first substrate *rac*-**152** the combination of $Pd_2(dba)_3/P(tBu)_3/Cy_2NMe$ was the most effective, providing the desired *rac*-**163** in an excellent yield of 94%. As expected a small variation of the substrate structure led to different results. Once a carbonyl moiety was introduced into the substrate (c.a. compound **156**), a clear enhanced reactivity towards a less electron rich palladium complex was observed. Altering the functionality occupying the *para*-position to the bromide to an electron poor substituent as in substrate *rac*-**159**, greatly influenced the reactivity towards $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ and the *Hermann-Beller* catalyst. These results suggest that there is obvious advantages when the electronic nature of substrates for intramolecular *Heck* transformation can be matched with the electronic nature of the catalytic system.

8.1 Spectroscopic Data of Chosen Compounds.

Heck product I rac- ***162***

The ^{1}H-NMR spectrum of compound **162** showed a resonance at $\delta = 5.95$ ($J = 1.2$ Hz) assigned to the exomethylene double bond as a doublet, at $\delta = 6.34$ ($J = 1.2$ Hz) and a resonance at $\delta = 6.16$ was assigned to oximethine proton. The *meta* and *ortho* values for resonances in the aromatic region of the ^{1}H-NMR spectrum were deemed to be appropriate for such tri-substituted aromatic rings. The ^{13}C-NMR spectrum exhibited twenty three signals, two methylene groups at $\delta = 60.2$, 64.0, and one signal corresponding CH carbon at $\delta = 98.9$. Molecular ion at *m/z* 382 in the eV EI spectrum together with elemental analysis established the expected structure.

Heck product II ***163***

The ^{1}H-NMR spectrum of compound **163** (Figure 8.1.1) included no signal in the oxymethiene region as seen in above compound *rac*-**162**. The resonances at $\delta = 6.07$ and 6.53 were assigned to the exomethylene double bond as two singlets were observed.
The signal at $\delta = 183.5$ in the ^{13}C-NMR spectra was assigned to the carbonyl together with resonance at $\delta = 67.0$ assigned to the new characteristic methylene group. The IR

spectrum shows the carbonyl stretching band at 1672 cm^{-1}, also consistent with the presence carbonyl moiety. An accurate mass measurement on the molecular ion observed at *m/z* 366.2 in the 70 eV EI mass spectrum established molecular formula as $C_{22}H_{22}O_5$.

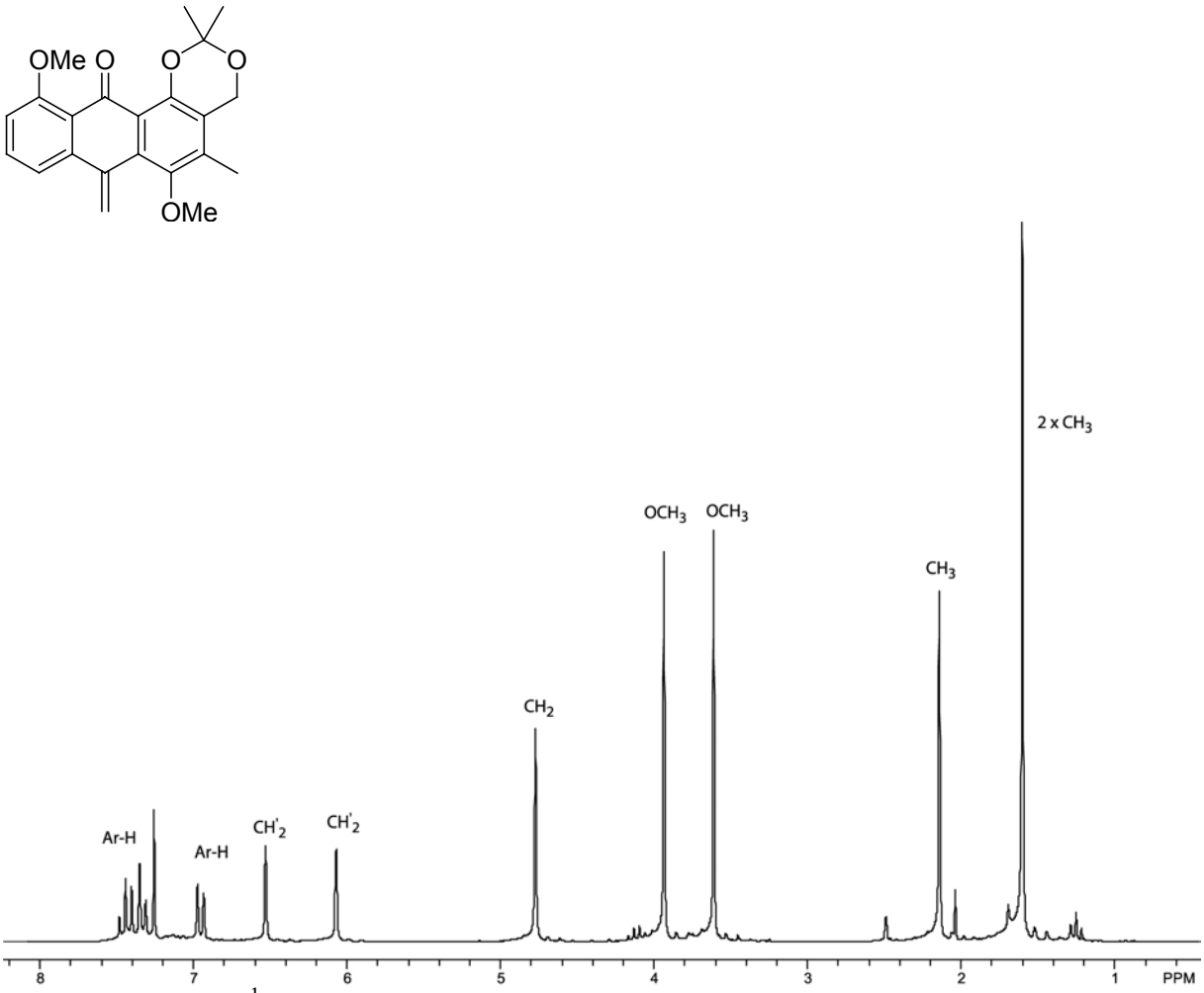


Figure 8.1.1. ^{1}H-NMR Spectrum of Dihydroantracene **163** (300 MHz, $CDCl_3$).

Heck product III rac- ***164***

The ^{1}H-NMR spectrum (Figure 8.1.2) of compound **164** shows resonance at δ = 6.31 correspond to an oxymethine proton, five aromatic signals as a multiplet is attributed to the benzyl protecting group and the resonances at δ = 6.08 and 6.49 were assigned to the exomethylene double bond. A singlet at δ = 10.50 was assigned to the aldehyde proton and a resonance at δ = 192.2 in the ^{13}C-NMR spectrum was assigned to the aldehyde carbon. Furthermore, two signals corresponding to the CH_2 of the benzyl group and olefin functionality were observed. The IR spectrum shows the stretching band at 1687 cm^{-1}, consistent with the presence of an aldehyde moiety. An accurate

mass measurement on the molecular ion at *m/z* 430.2 in the 70 eV EI mass spectrum established molecular formula as $C_{27}H_{26}O_5$.

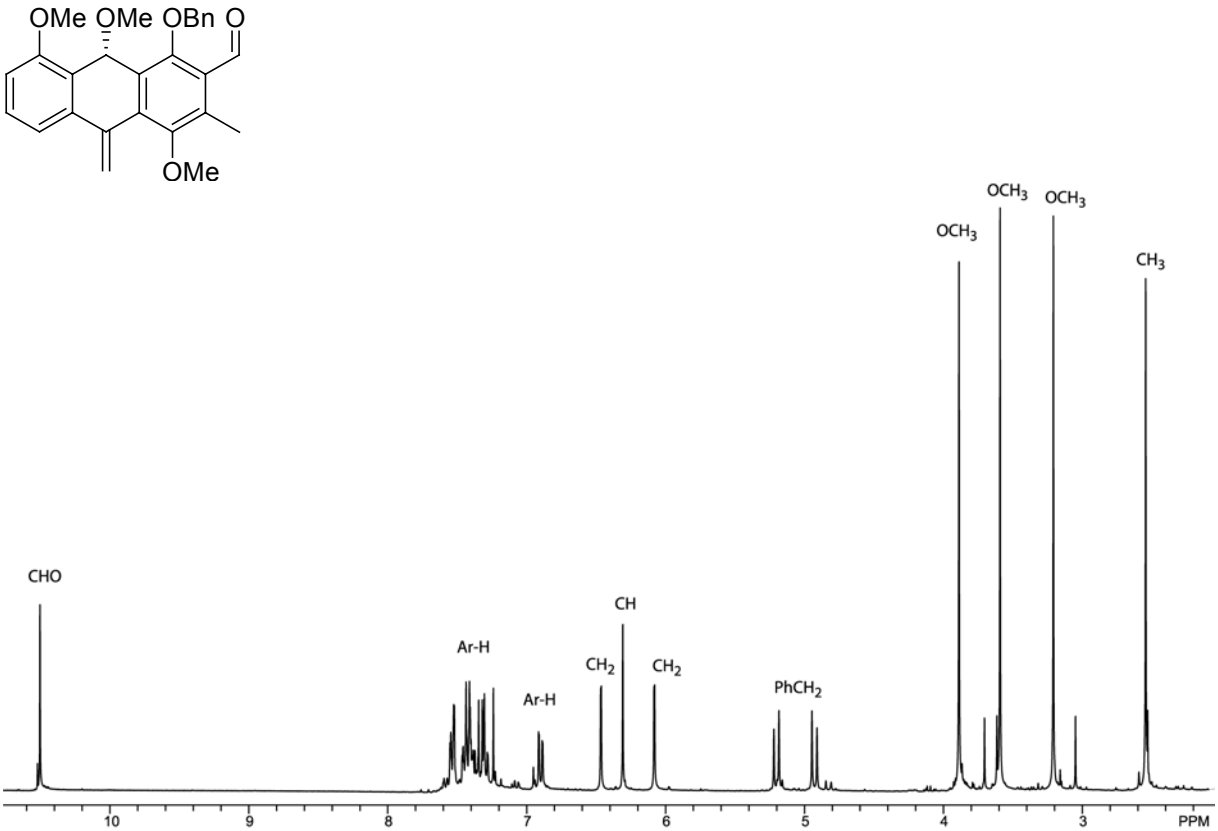
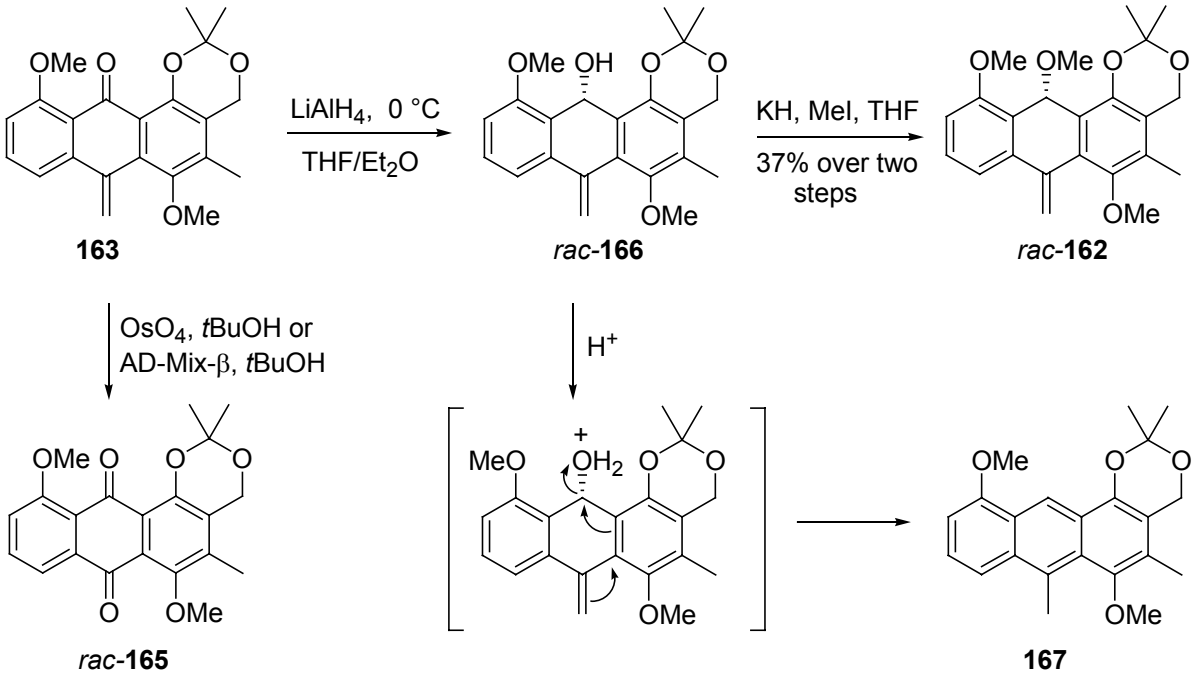


Figure 8.1.2. ^{1}H-NMR Spectrum of Tetrahydroanthracene *rac*-**164** (300 MHz,$CDCl_3$).

9 Further Transformations

9.1 Reduction and Oxidative Cleavage of the Exocyclic Double Bond

An attractive feature of the pathway using a substrate with carbonyl moiety in the B-ring, was the expectation that **163** could be stereoselectively reduced using literature procedures.[86] However, before such a transformation could be tested reduction had to be trailed using achiral reagent. Thus, preparation of tetrahydroanthracene *rac*-**166** was achieved by a reduction with $LiAlH_4$ (Scheme 9.1.1). Due to the instability of this compound the next step, installation of what would become the C-10 methoxy substituent in mensacarcin (**1**), the reaction was carried out immediately. These two aforementioned steps only gave a 37% yield of the desired methoxy compound *rac*-**162**. This low yield was due to the susceptibility of the intermediate tetrahydroanthracene *rac*-**166** to rearomatise, under presumably acidic conditions.



Conditions	Yield 165
OsO_4, tBuOH, Me_3N-O, , 24 h	72%
AD-Mix-β, H_2O/*t*BuOH, $CH_3SO_2NH_2$	45%

Table 9.1.1 *Oxidation of antrhracenone **163**.*

In an alternative approach, protection of the double bond by first converting it into the diol and subsequently to the acetonide, it was hoped the bottom part of the B-ring would then be unreactive to later oxidation. Hence, bishydroxylation of anthracenone **163** was attempted with either AD-mix-β or osmium tetroxide[87] (Table 9.1). Both cases where OsO_4 or AD-mix-β were used, complete oxidation took place and anthraquinone **165** (72% and 45% respectively) was obtained, as the only product.

In another transformation, treating the tricyclic intermediate *rac*-**162** with $RuCl_3/NaIO_4$ provided a smooth oxidative cleavage of the exocyclic double bond to afford benzophenone **168** in 69% yield (Scheme 9.1.2).[88] This fruitful reaction provides a compound containing the correct functionality for the AB-ring of mensacarcin **1** as well as much of C-ring oxygenation and methyl group. Compounds such as this analog *rac*-**168** are considered to be close to the natural product target.

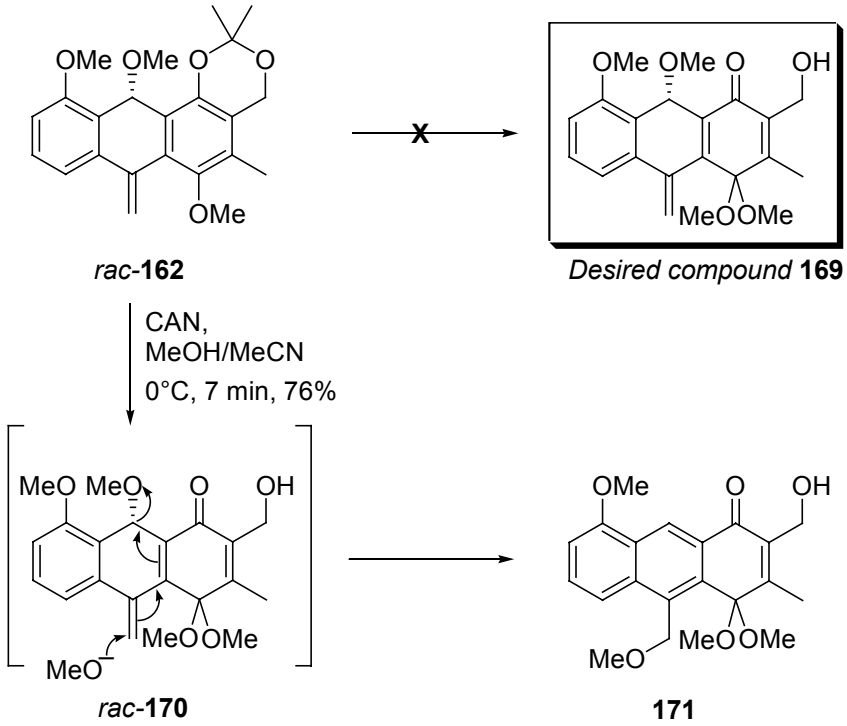
rac-**162** *rac*-**168**

Scheme 9.1.2.

9.2 Oxidation of the C-ring within the Tricyclic Core

When considering this research intends on finding a total synthesis of natural product mensacarcin (**1**) it is naturally obvious that a dearomatisation of the C-rings of *rac*-**162**, **163** or *rac*-**164** needed to be attempted. In principle, this could be achieved by using cerium (IV) ammonium nitrate (CAN),[89] or by hypervalent iodine oxidation.[90] In an effort to convert tetrahydroanthraquinine *rac*-**162** into benzoquinone monoketal *rac*-**169**, several oxidation conditions were evaluated. When compound *rac*-**162** was treated with 2 equiv. of CAN at 0 °C in CH_3CN/MeOH only compound **171** (76%) was isolated (Scheme 9.2.1).[91] Unfortunately, rearomatisation of the B-ring occurred as the only reaction. In contrast, oxidation by exposing *rac*-**162** to 1.2 equiv. of $PhI(OCOCF_3)_2$ in $MeOH/CH_2Cl_2$ (PIFA) led to decomposition. Two possible

solutions to these problems could be; removing the B-ring double bond followed by oxidation or anodic oxidation in non nucleophilic solvent.[92] Both of these options are currently being explored within the *Tietze* group.

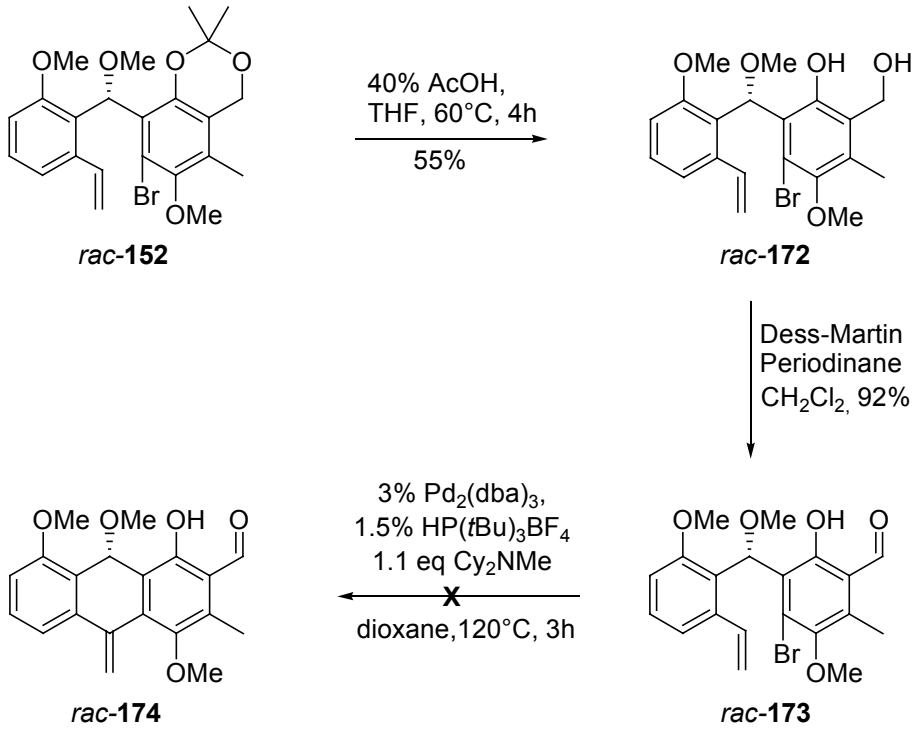


Scheme 9.2.1

9.3 Deprotection of the C-ring to Provide a New Substrate for the Intramolecular *Heck* Reaction

As shown in the previous section, tetrahydroanthraquinones in particular compound *rac*-**162** were very sensitive towards acidic, nucleophilic and oxidative conditions, which makes any further synthetic transformations difficult. Alternatively, deprotection of the acetal group was accomplished by treating the "open" substrate *rac*-**152** with acetic acid to successfully produce phenol *rac*-**172** in 55% yield (Scheme 9.3.1). Next, the primary alcohol within compound *rac*-**172** was oxidised under standard conditions, to afford aldehyde *rac*-**173** in excellent yield (92%). It was thought that this latter compound could be cyclised using the palladium based transformation described earlier. This would then give access to tricylic aldehydes that

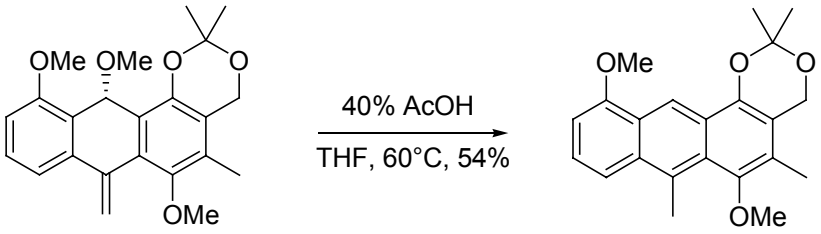
could act as electrophiles in order to attach the four carbon side chain (see Chapter 6). Due to time constraints, only one attempt to cyclise compound *rac*-**173**, (using $Pd_2(dba)_3$/HP(*t*Bu)BF_3,120 °C for 3 h) was attempted. Unfortunately, only decomposition resulted presumably due to the free hydroxyl groups within *rac*-**173** and their interaction with the catalyst at higher temperatures. Further optimisation of this *Heck* transformation is currently being explored, including using a phenolic protected version of *rac*-**173**.



Scheme 9.3.1

9.4 Installation of the Side Chain Associated with Mensacarcin 1

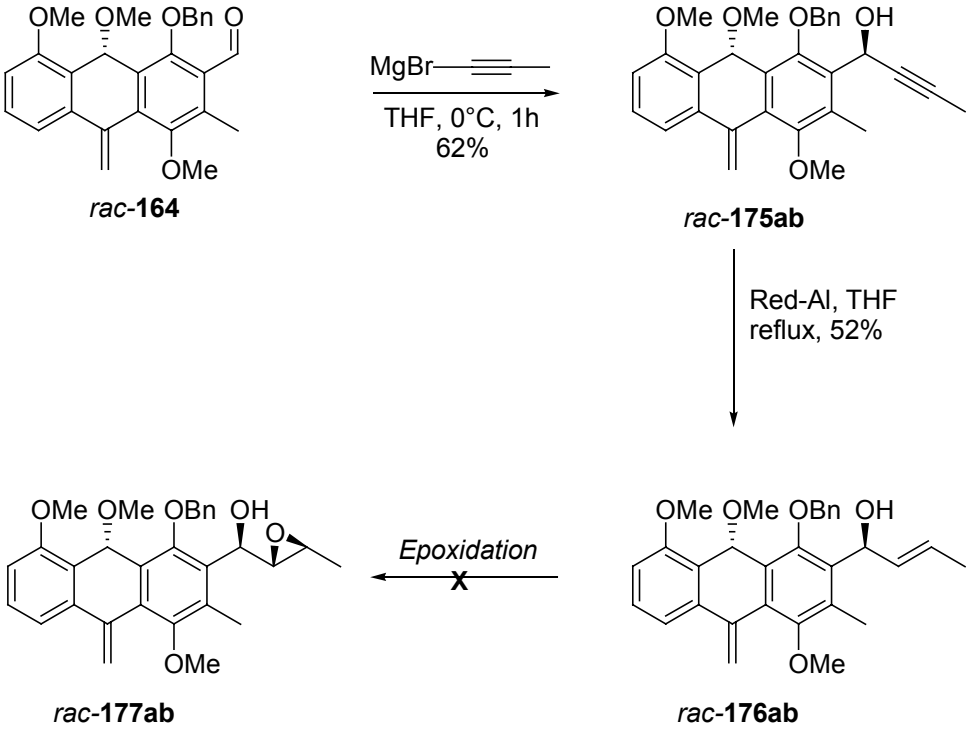
The author's intention of using the tricyclic compound *rac*-**162** in the further synthetic plans implied that the protecting group (acetonide) needed to be removed. Unfortunately, in order to deprotect this compound acidic conditions needed to be used (acetic acid and THF at 60 °C) which only produced the rearomatised anthracene **167** (Scheme 9.4.1).



rac-**162** **167**

Scheme 9.4.1

Planned introduction of the remaining three carbons that were needed for elaboration of the side chain was based on work described in the preliminary studies (chapter 6). The commercially available alkynyl Grignard reagent was reacted with aldehyde *rac*-**164** to afford a diastereoisomeric mixture of alcohols *rac*-**175ab** (55%). These two diastereomeric pairs were unseparable using chromatographic methods so further transformations were carried out on this mixture. In earlier work (Scheme 6.3) it was discovered that the reduction of the triple bond using Red-Al provided the essential *E*-geometical isomer. By employing the same procedure for the tricyclic substrate *rac*-**175ab**, the allylic alcohol *rac*-**176ab** was accessed in 52% yield. Also, previous work using single ring test substrate *rac*-**133** highlighted that both a catalytic amount of $VO(acac)_2$/*tert*-butyl hydroperoxide or *m*-CPBA, were effective in promoting a allylic hydroxyl-directed epoxidation. However, neither $VO(acac)_2$/*t*BuOOH or $Ti(OiPr)_4$/*t*BuOOH were satisfactory in inducing the analogous reaction of compounds *rac*-**176ab**. This could be attributed to the sterical influence of benzyl protection group. Possible solutions to this problem could be, deprotection the benzyl group, or use less bulky epoxidising agent such as dimethyldioxirane.[93] These reactions will be subject of future investigations within the *Tietze* laboratories.



Entry	Conditions	177
1	$VO(acac)_2$, *t*BuOOH, CH_2Cl_2, 20 °C, 16 h	no reaction
2	$Ti(OiPr)_4$, *t*BuOOH CH_2Cl_2, (-)-DIPT, 0 °C, 16 h	no reaction

Table 9.4. *Epoxidation of the olefin rac-**176ab**.*

9.5 Spectroscopic Data of the Chosen Compounds

*Anthraquinone **165***

In the ^{1}H-NMR spectrum of compound **165** characteristic feauters observed is missing resonance at δ = 6.07 and 6.53 assigned to the double bond. A resonance assigned to a 1,2,3-substituted aromatic ring was seen in three sections; δ = 6.90-7.19 as a multiplet, 7.57 (*J* = 8.4 Hz) as a triplet and 7.68 (*J* = 6.6 Hz) as a doublet. The ^{13}C-NMR spectrum exhibited all expected twenty signals, importantly two characteristic signals at δ = 182.1, 183.6 assigned to two carbonyl groups. The IR spectrum shows a stretching band at 1669 cm^{-1}, consistent with the presence carbonyl moiety. Molecular

ion at *m/z* 368.2 in the eV EI spectrum together with elemental analysis established the expected structure.

*Benzaldehyde rac-**173***

The ^{1}H-NMR spectrum of compound **173** shows a resonance at δ = 6.17 corresponding oxymethine proton, one signal at δ = 11.12 assigned to the phenolic group and a resonance at δ = 10.47 assigned to the newly formed aldehyde proton. Additionally, the resonance at δ = 193.8 in the ^{13}C-NMR spectrum was assigned again to the new aldehyde carbon. One signal at δ = 115.8 corresponding to the CH_2 olefin group, twelve signals corresponding aromatic C carbons together with four assigned CH_3 carbons, were observed. An accurate mass measurement on the molecular ion observed at *m/z* 424.2 and 422.0 in the 70 eV EI mass spectrum established molecular formula as $C_{20}H_{23}BrO_5$.

*Anthracenone rac-**168***

Characteristic features observed in the ^{1}H-NMR spectrum of compound **168** is missing signal in the δ = 6.5-5.5 region (assigned methylene region) and an appearance of new signal at δ = 184.4 in the ^{13}C-NMR spectra (assigned carbonyl region). The IR spectrum shows the carbonyl stretching band at 1673 cm^{-1}, consistent with the presence carbonyl moiety. An accurate mass measurement on the molecular ion observed at *m/z* 384.4 70 eV EI mass spectrum established molecular formula as $C_{22}H_{24}O_6$.

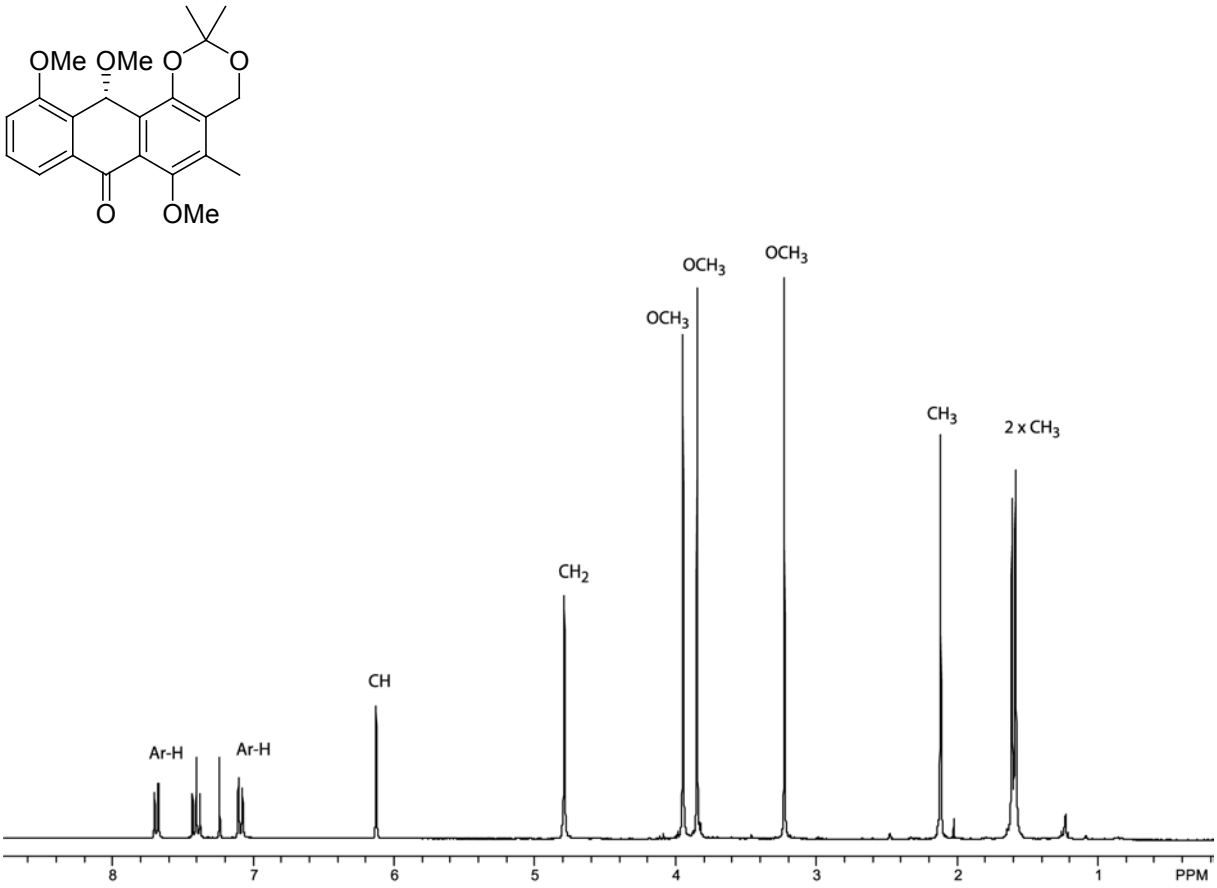
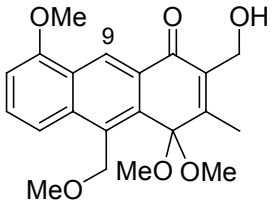


Figure xx. ^{1}H-NMR Spectrum of Anthracenone *rac*-**168** (300 MHz, $CDCl_3$).

*Dihydroanthracenone **171***

The ^{1}H-NMR spectrum of compound **171** shows a resonance at δ = 1.23 corresponding hydroxyl group proton, a singlet at δ = 2.93 characteristic for methoxy acetal protecting group, a resonance at δ = 5.32 assigned to the new methylene proton, and signal at δ = 9.21 assigned to the one B-ring aromatic proton appeareing after rearomatisation. The resonance at δ = 184.7 in the ^{13}C-NMR spectrum is assigned to the carbonyl moiety and two signals corresponding to the new OCH_3 at δ = 51.6, 58.2 and 58.7 were observed. Additionally, twelve signals corresponding to the aromatic carbons, two CH_2 signals for the of benzylic moiety and one signal for a CH_3 carbon resonance, were also observed in the ^{13}C-NMR. An accurate mass measurement on the molecular ion observed at *m/z* 372.2 in the 70 eV EI mass spectrum established molecular formula as $C_{21}H_{24}O_6$.



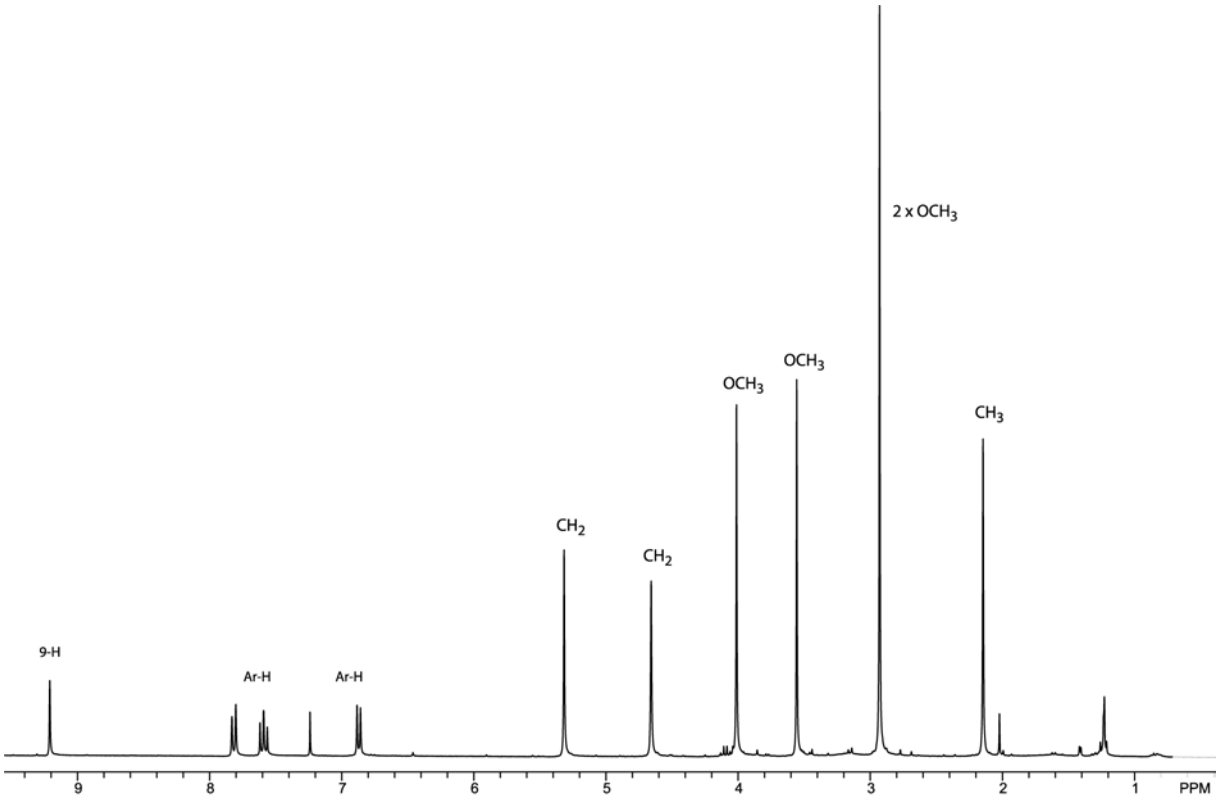
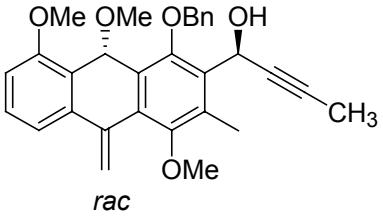


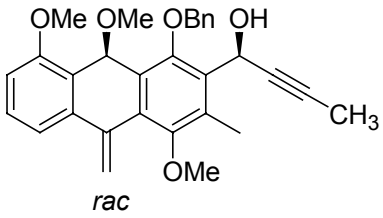
Figure xx. ^{1}H-NMR Spectrum of Dihydroanthracenone **171** (300 MHz, $CDCl_3$).

*Alcohols rac-**175ab***

Characteristic features observed in the ^{1}H-NMR spectrum of compounds **175ab** (which are two diastereomers) is appearance of two new methyl signal at δ = 2.40 and 2.45 assigned to the protons on the newly added side chain. Also, six methoxy group signals and two oximethine signals at δ = 5.98 (*J* = 1.2 Hz) and δ = 6.00 (*J* = 1.2 Hz) were displayed. The resonances at δ = 55.4, 55.6, 57.4, 57.9 60.1 in the ^{13}C-NMR spectrum are assigned to the OCH_3 groups and four signal at δ = 82.4, 82.5, 83.2, 83.8 correspond to the new alkynyl C carbons. The IR spectrum shows the hydroxyl stretching band at 3424 cm^{-1}, consistent with the presence alcohol moiety. An accurate mass measurement on the molecular ion observed at *m/z* 470.2 70 eV EI mass spectrum established molecular formula as $C_{30}H_{30}O_5$.



rac



rac

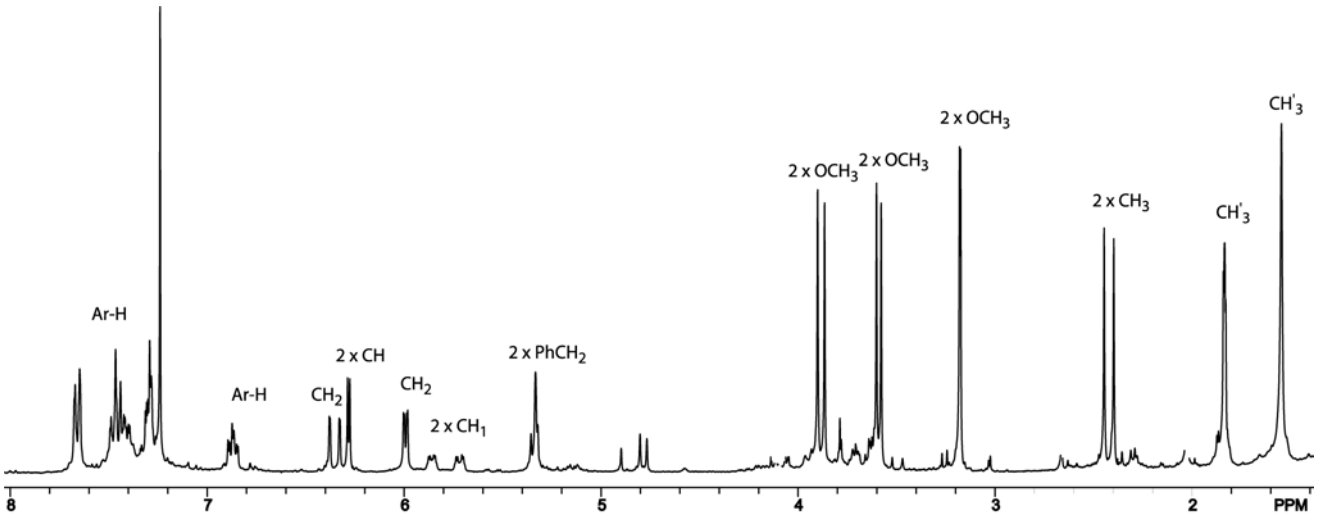
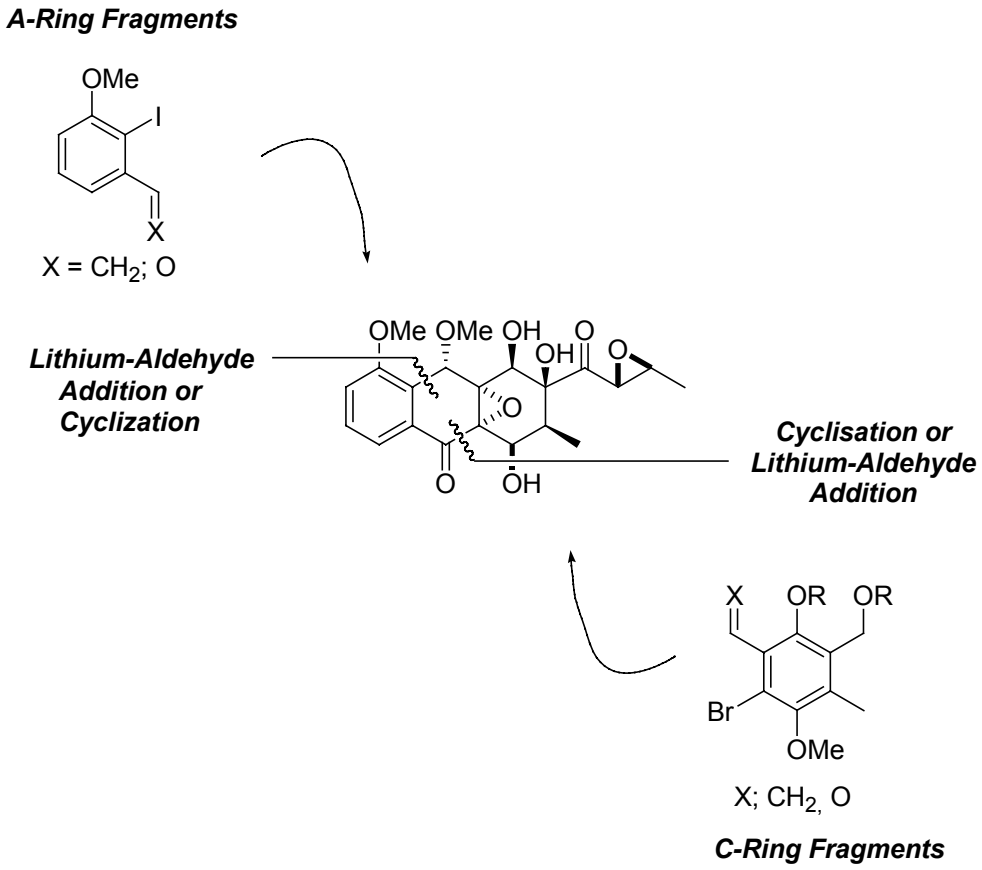


Figure xx. ^{1}H-NMR Spectrum of Alcohols *rac*-**175ab** (300 MHz, $CDCl_3$).

10 Summary

Mensacarcin (**1**) is a novel polyfunctionalised hexahydroanthracene with nine stereogenic centers isolated from a strain of *Streptomyces* (Gö C4/4) by Zeeck et al. It shows cytostatic and cytotoxic activity comparable to doxorubicin (**67**), another anticancer agent currently used in the treatment of malignant lymphomas and leukemias. Despite the pronounced bioactivity of mensacarcin **1**, its highly substituted tricyclic core makes it an attractive target for organic synthesis.

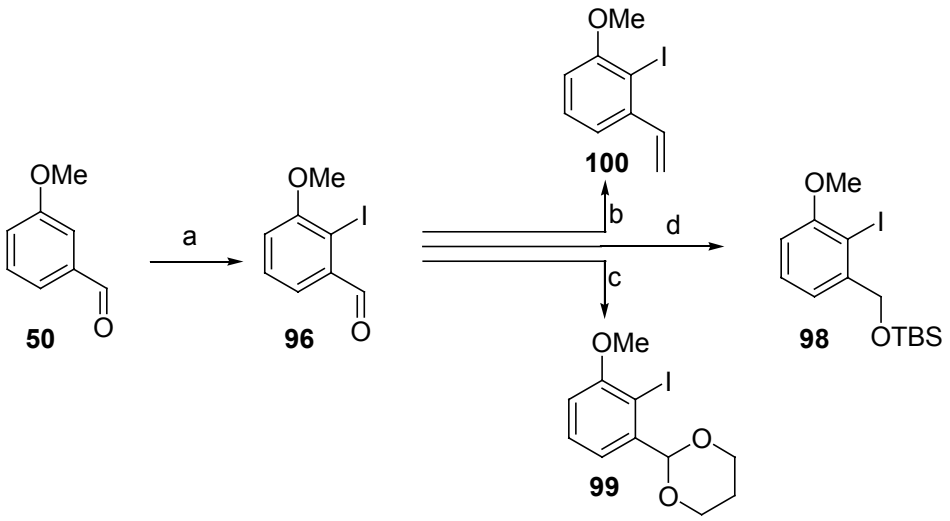


Scheme 10.1.1

Considering the prevalence of the anthraquinone type framework in a variety of natural products it is not surprising that many approaches have been developed for its synthesis. However, only a few methods exist for the formation of the hydroxyl or methoxy dihydroanthracenone, either by regioselective reduction of anthraquinone or by other synthetic pathways. For this reason, and because of our interest in preparation of natural products *via* transition metal catalysed transformations, we devised a synthesis of the tricyclic core of **1** using an intramolecular *Heck* reaction. The

strategy for the synthesis of the carbocyclic core of mensacarcin **1** is outlined above in Scheme 10.1.1. In the initial retrosynthetic analysis, it was envisaged that the tricyclic compound **1** could be broken up into the two aromatic fragments, A and C. The A-ring, used as a nucleophile, could be coupled to the benzaldehyde C-ring **80** and the resulting product protected. The latter compound was thought to be a reasonable precursor for an intramolecular *Heck* reaction to hopefully provide the required carbocyclic core of natural product **1**.

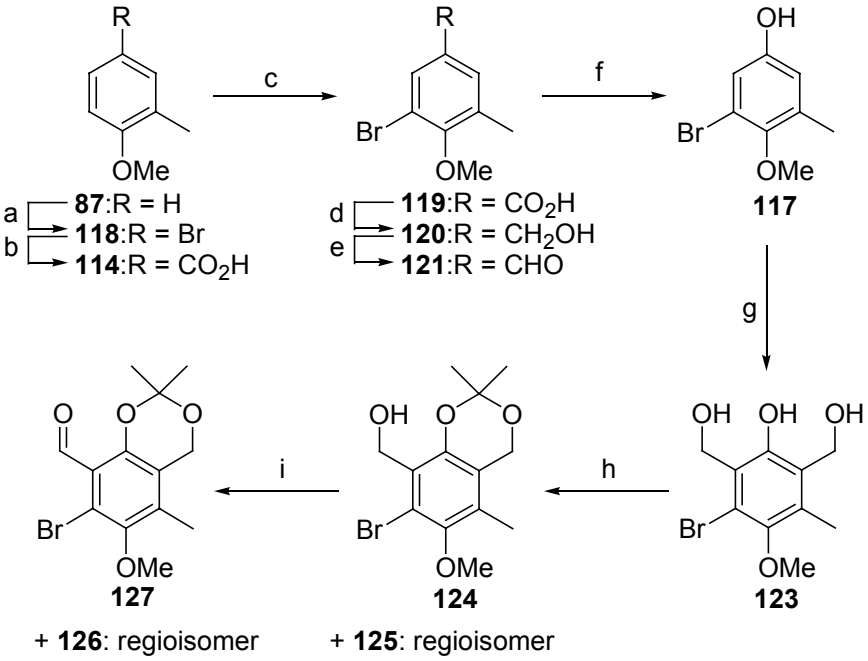
Before such retrosynthetic approaches were realised, the synthesis of the corresponding highly substituted aromatic building blocks had to be performed. The synthesis of 2-iodo-3-methoxybenzaldehyde (**96**) was achieved (Scheme 10.1.2) in 52% yield, by converting the commercially available benzaldehyde **50** into the corresponding *ortho*-aryllithium compound then quenching with iodine. The latter compound was either, subjected to a *Wittig* reaction to give **100** in 90% yield or protected as an acetal **99** (66%). Additionally, the reduction of aldehyde **96** to the corresponding alcohol, followed by TBS-ether protection give another C-ring fragment **98** in 94% yield.



Scheme 10.1.2

Reagents and conditions: (a) (i) *n*BuLi, TriMEDA, 0 °C → 20 °C, 15 min., (ii) **50**, 0.5 h, 20 °C, (iii) PhLi, 0 °C → 20 °C, 7h, (iv) I_2, THF, –78 °C → 20 °C, 2 h, 55%; (b) Ph_3PCH_3Br, NaHMDS, THF, 20 °C, 1 h, then **96**, 1 h, 90%; (c) 1,3-propandiol, Amberlyst 15 H^+, C_6H_6, reflux, 5 h, 66%; (d) $LiAlH_4$, THF, 0 °C, 0.5 h, then TBSCl, imidazole, DMAP cat., 12 h, 94%

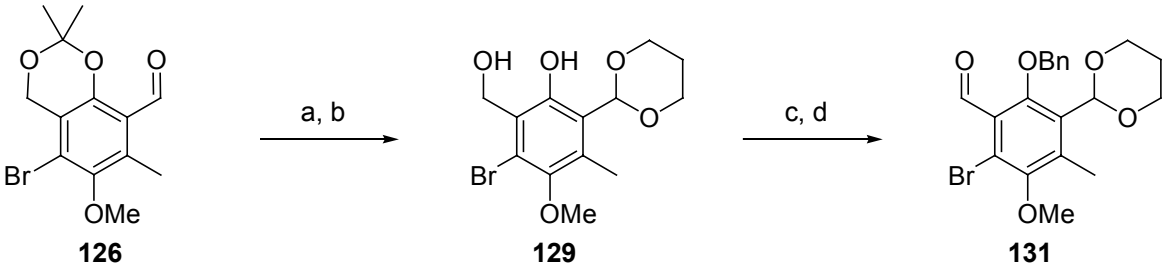
Synthesis of the more complex aldehydes **126** and **127** (Scheme 10.1.3) started with the commercially available anisol **87** which gave **118** by bromination in the *para*-position. This step was immediately followed by preparation of the corresponding magnesium compound which was CO_2 (dry) quenched to afford the carboxylic acid **114**. Reaction of carboxylic acid **114** with Br_2 in dioxane furnished compound **119** containing a bromine atom in an *ortho* position to the methoxy substituent. As intended, the carboxylic acid at C-1 in **114** was successful in directing the bromination and subsequently this functionality needed to be "unmasked" to the phenol to allow the introduction of two *ortho*-hydroxymethyl units. The complete transformation using formaldehyde for the introduction of the hydroxy-methyl moieties was achieved in a four-step sequence, from **119**, to produce the desired triol **123** (69%).



Scheme 10.1.3

Reagents and conditions:(a) Br_2, CH_2Cl_2, NaOAc, 0 °C, 2 h, 85%; (b) Mg, THF, Et_2O, reflux, 1 h 30 min then 20 °C, CO_2, 2 h, 82%; (c) Br_2, dioxane, 20 °C, 7 d, 84%; (d) $LiAlH_4$, THF, Et_2O, 0 °C, 1 h, 72%; (e) MnO_2, CH_2Cl_2, 20 °C, 12 h, 87%; (f) *m*-CPBA, CH_2Cl_2, 20 °C then K_2CO_3, MeOH, 20 °C, 15 min, 68%; (g) HCHO, H_2O, CaO, 20 °C, 5 d, 69%; (h) $(CH_3)_2CO$, *p*-TsOH, 20 °C, 18 h, 91%; (i) DMSO, ClCOCOCl, CH_2Cl_2, -78 °C, 30 min then **124**/**125**, -78 °C, 1.5 h then NEt_3, 5 min, 20 °C, 30 min, 83%.

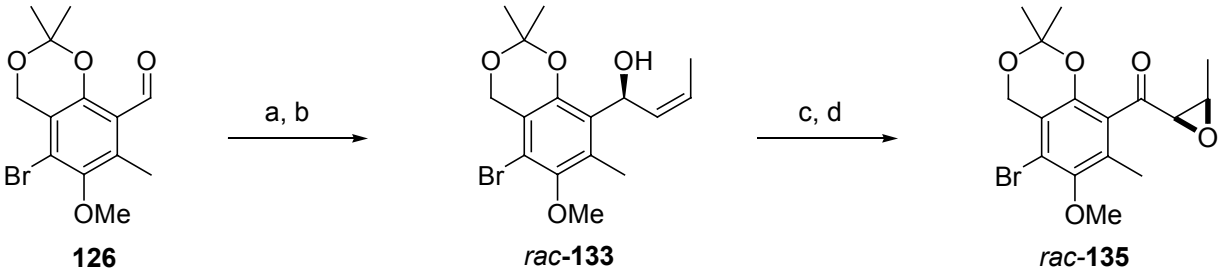
Acetonide protection of the latter compound gave a mixture of regioisomers **124** and **125** in a 1:1.1 ratio, respectively. Oxidation, under *Swern* conditions, provided the corresponding aldehydes **126** and **127**. Here, the two aromatic regioisomers were separated and used for independent synthetic pathways. Aldehyde **127**, which represented the desired C ring building block, was used for the anticipated ring coupling. When, compound **126** was subjected to four-step transformation another C-ring fragment **131** was furnished (Scheme 10.1.4).



Scheme 10.1.4

Reagents and conditions: (a) AcOH, 60 °C, 4 h, 66%; (b) 1,3-propandiol, Amberlyst 15 H^+, C_6H_6, reflux, 5 h, 98%; (c) BnBr, K_2CO_3, $CHCl_3$/MeOH, 40 °C, 12 h, 80%; (d) *Dess-Martin* periodinane, CH_2Cl_2, 1 h, 81%.

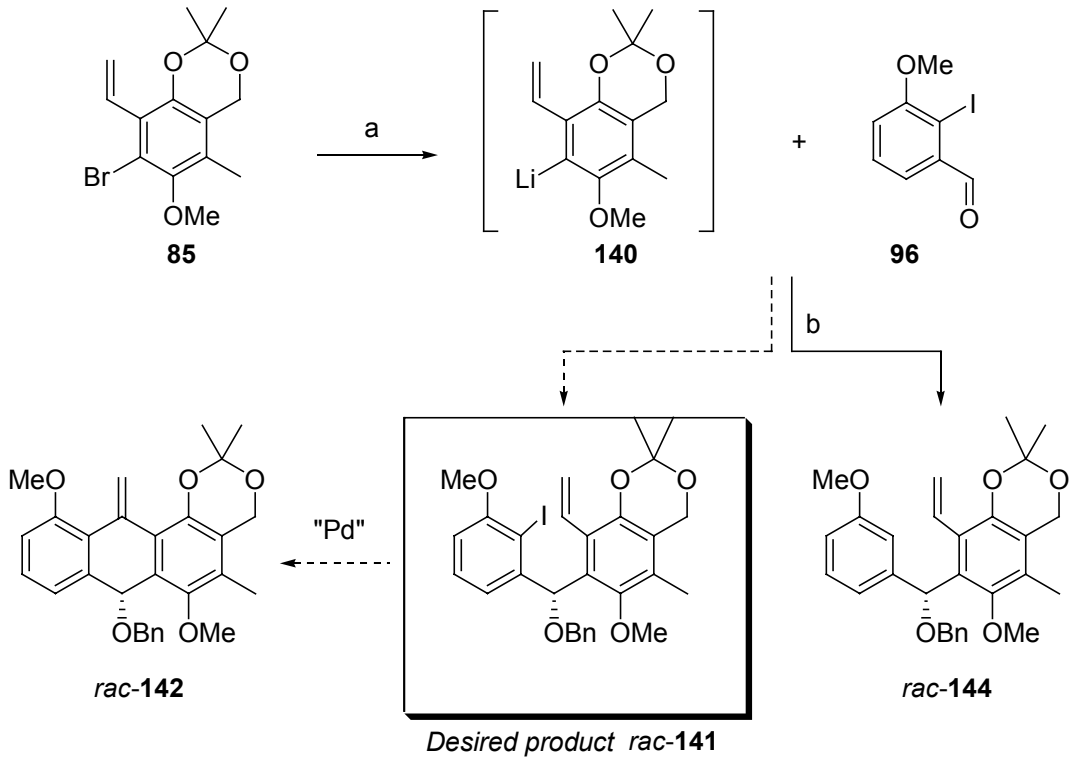
The side chain of mensacarcin (**1**) was initially installed using a test aromatic system. Subjection of aldehyde **126** to 1-propynyl magnesium bromide gave the alcohol *rac*-**132** in high yield (94%) containing the additional three carbons for the side chain (Scheme 10.1.5). Reduction of the triple bond within *rac*-**132** provided the *Z*-olefin *rac*-**133**. An allylic hydroxyl directed epoxidation using either *m*-CPBA or $VO(acac)_2$ afforded epoxides **134ab** and **134xy** as two diastereoisomeric pairs, which could be separated by chromatography. Treatment of the olefin *rac*-**133** with *m*-chloroperbenzoic acid in dichloromethane gave a mixture of *syn*- and *anti*-diastereomers in ratio of 3:1 respectively (determined by NMR) in 76% yield. The *Sharpless* epoxidation of olefin *rac*-**133** provided almost exclusively the *syn*-diastereomeric pair **134ab** (64%). Finally, *Dess-Martin* oxidation of the secondary alcohol of compounds **134ab** gave the desired ketone *rac*-**135** containing a similar side chain as that of mensacarcin (**1**).



Scheme 10.1.5

Reagents and conditions: (a) C_3H_3MgBr, THF, 0 °C → 20 °C, 20 min., 91%; (b) Lindlar's cat., H_2, 24 h, 96%; (c) *m*-CPBA, CH_2Cl_2, 12 h, 76% or $VO(acac)_2$, *t*BuOOH, CH_2Cl_2, 3 h, then Na_2SO_3, 1 h, 64%.

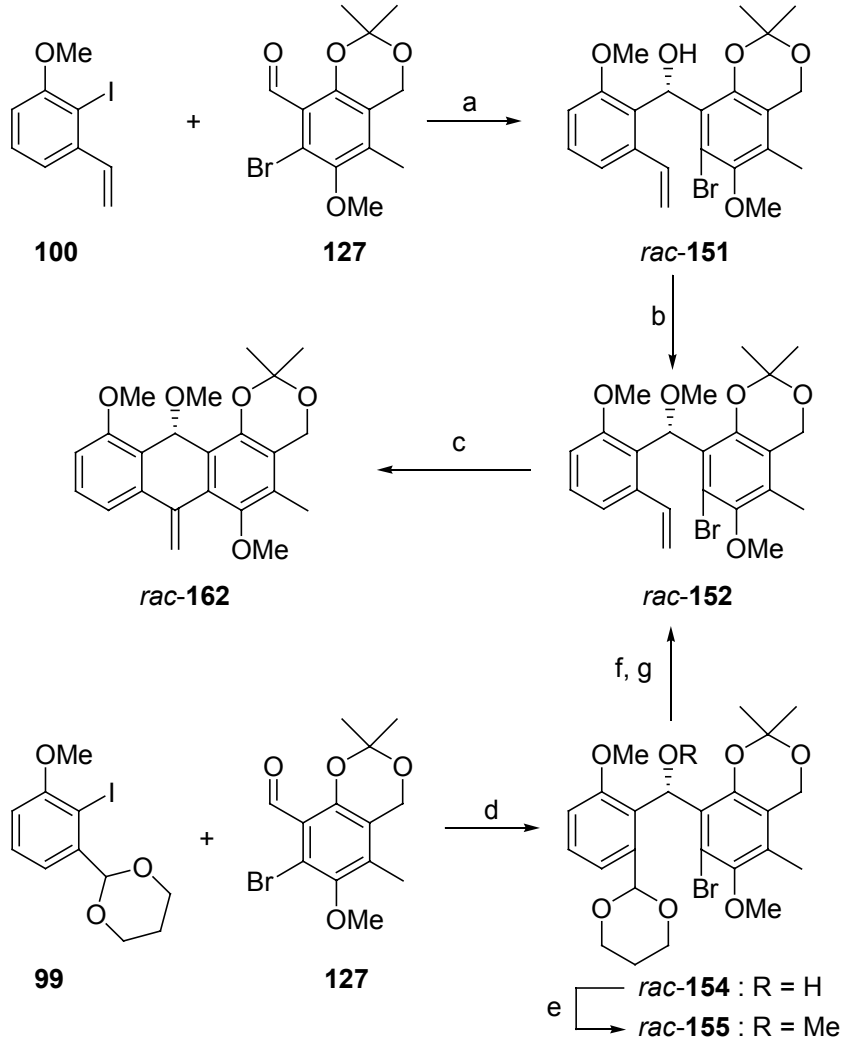
Connection of the two aromatic rings was firstly trailed by adding the lithium derivative of the hexasubstituted **85** to the trisubstituted benzaldehyde **96** to give the diphenylcarbinol *rac*-**144** (Scheme 10.1.6). Many reactions conditions were trailed, unfortunately, both *n*BuLi or *t*BuLi in THF/Et_2O did not give the anticipated product *rac*-**141**, but only the deiodinated compound *rac*-**144**.



Scheme 10.1.6

Reagents and conditions: (a) *n*BuLi, −78 °C, then **96**, −78 °C → 20 °C, 1 h; (b) BnBr, THF, 40 °C, 12 h.

To overcome this problem, the crucial connection of the two A and C ring aromatic fragments was performed following the second retrosynthetic analysis with **100** and **127** as substrates. The aryllithium was prepared *in situ* from **100** by a lithium-iodine exchange using *n*BuLi, this was followed by addition of the aldehyde **127** which led to formation of the diphenylcarbinol *rac*-**151** in a reasonable yield of 58% (Scheme 10.1.7). Subsequent, installation of what would become the C-10 methoxy substituent in mensacarcin (**1**) was achieved by subjection of *rac*-**151** to KH/MeI to furnish *rac*-**152**.

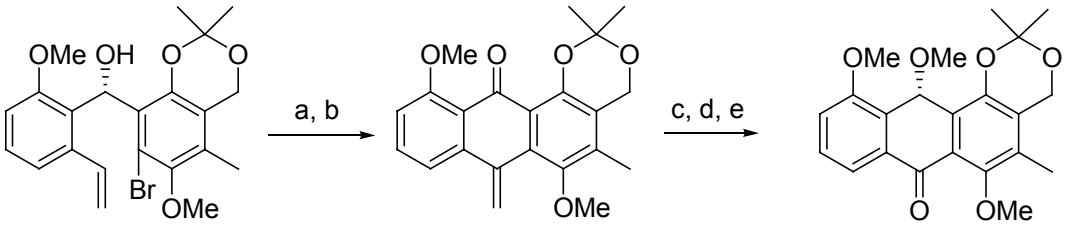


Scheme 10.1.7

Reagents and conditions: (a) *n*BuLi, THF, -78 °C, 20 min then **127**, THF, -78 °C, 20 min, 20 °C, 58%; (b) KH, THF, 0 °C, 40 min then MeI, 20 °C, 1 h, 87%; (c) $Pd_2(dba)_3$, $HP(tBu)_3BF_4$, Cy_2NMe, dioxane, 120 °C, 5 h, 94%; (d) *n*BuLi, THF, -78 °C, 10 min then **127**, THF, 20 °C, 35 min, 74%; (e) KH, THF, 0 °C, 40 min then MeI, 20 °C, 2 h, 91%; (f) PPTS, acetone/H_2O, 20 °C → reflux, 3 h, 81%; (g) Ph_3PCH_3Br, NaHMDS, THF, 20 °C, 1 h then aldehyde from f, 20 °C, 1 h, 81%.

In an effort to improve the aryllithium to aldehyde addition and hence the overall yields, an alternative pathway to compound *rac*-**152**, the intramolecular *Heck* reaction precursor, was devised. Thus, the aryllithium of acetal **99** was added in the same manner to the aldehyde **127** to give the diphenylcarbinol *rac*-**154** in superior yields (74%); it is believed that the acetal moiety in *ortho* position facilitates the lithiation and stabilises the formed metal organic compound. Alcohol **154** was then methylated to give *rac*-**155** (91%) followed by cleavage of the acetal moiety using PPTS in acetone/water (81%) and olefination gave the desired alkene *rac*-**152** (81%). However, due to the additional steps the overall yield of this pathway does not exceed the direct and shorter previously mentioned approach to *rac*-**152** using compound **100** as a substrate. The intramolecular *Heck* reaction of olefin *rac*-**152**, using the *Herrmann-Beller* catalyst, provided the desired methylene tetrahydroanthracene *rac*-**162** in a low yield of 24% (54% based on recovery of starting material). Following similar poor yields using several other palladium catalysts the highly electron donating C ring within substrate *rac*-**152** was deemed to negatively effect the initial insertion process of the *Heck* reaction cycle and hence lower the turnover rate of this transformation. However, a few solutions to this problem were discovered. Firstly, a new precursor, benzophenone **156**, was devised to allow a fast reaction rate of the palladium catalysed transformation. Secondly, a new catalytic system ($Pd_2(dba)_3$/HP(*t*Bu)$_3BF_4$/Cy_2NMe) was employed, the electron rich phosphine ligand appeared to be compatible with our substrate and gave tricyclic core *rac*-**162** in 94% yield.

Benzophenone **156** was synthesised from *rac*-**151** using the *Dess-Martin* periodinane in 81% yield (Scheme 10.1.8). As predicted, the intramolecular *Heck* reaction of this aforementioned compound proceeded smoothly under the previously described conditions to afford the anthracenone derivative **163** in 78% yield.



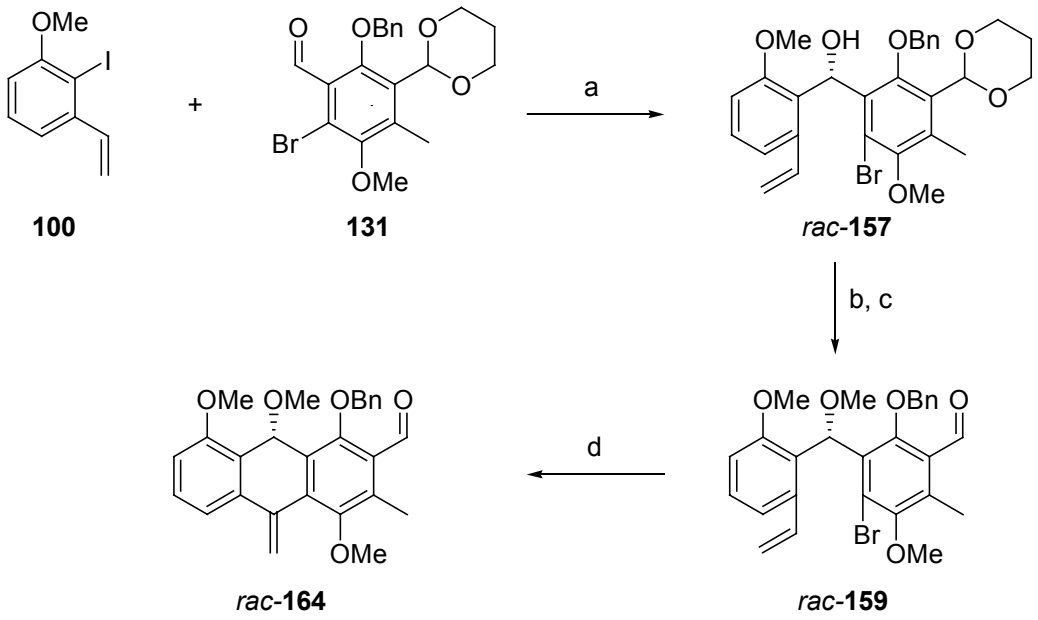
rac-**151** **163** *rac*-**168**

Scheme 10.1.8

Reagents and conditions: (a) *Dess-Martin* periodinane, CH_2Cl_2, 20 °C, 15 min, 81%; (b) $Pd_2(dba)_3$, $HP(tBu)_3BF_4$, Cy_2NMe, dioxane, 120 °C, 5 h, 78%; (c) $LiAlH_4$, THF, 0 °C, 10 min; (d) NaH, MeI, THF, 0 °C → 20 °C, 14 h 37% two steps; (e) $RuCl_3$, $NaIO_4$, CCl_4, MeCN, H_2O, 0 °C, 15 min, 69%.

This latter tricyclic derivative could be converted into the required previously prepared methoxy methylene compound *rac*-**162**. This conversion was achieved *via* a reduction with $LiAlH_4$ and methylation sequence in 37% overall yield. This poor yield was due to the susceptibility of the intermediate tetrahydroanthracene *rac*-**166** to rearomatise. Finally, an oxidative cleavage of the methylene moiety within anthracene *rac*-**162** using $RuCl_3$ (5 mol%) and $NaIO_4$ allowed for the formation *rac*-**168**, in 69% yield. This desired and key intermediate contains the correct ABC tricyclic core and the AB ring functionality as found in mensacarcin (**1**).

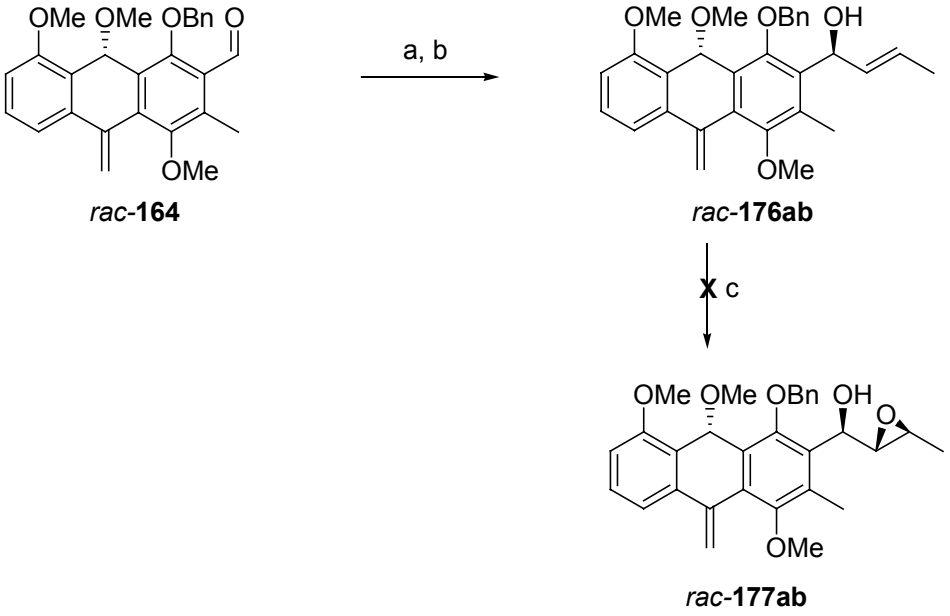
It was considered crucial that the synthetic strategy being employed would allow access to precursors for the intramolecular *Heck* reaction, which could be carried through the synthetic pathway to mensacarcin and analogs. This approach involved exploiting the available aldehyde **131** (Scheme 10.1.9), which after addition to corresponding lithium species, led to desired alcohol *rac*-**157**. This latter product was then methylated to give *rac*-**158** and the acetal moiety cleaved using PPTS to provide the alkene *rac*-**159**.



Scheme 10.1.9

Reagents and conditions: (a) *n*BuLi, THF, -78 °C, 20 min then **131**, THF, -78 °C, 20 min, 20 °C, 39%; (b) KH, THF, 0 °C, 40 min then MeI, 20 °C, 1 h, 91%; (c) PPTS, H_2O/acetone, reflux, 12 h, 71% (d) nBu_4NOAc, DMF/CH_3CN/H_2O, 60 °C then *HB* cat, 110 °C, 17 h, 82%

By enhancing the reactivity of alkene *rac*-**159** through a *para*-aldehyde moiety the palladium catalysed cyclisation was enhanced when using electron poor catalysts. The intramolecular *Heck* reaction of olefin *rac*-**159**, using the *Herrmann-Beller* catalyst, provided the desired methylene tetrahydroanthracene *rac*-**164** in an excellent yield of 82%. With a successful arrival at system *rac*-**164**, focus was then shifted to methodology for introduction of the side chain. Employing the same procedure as in chapter 6, the tricyclic substrate *rac*-**164** was treated with Grignard reagent to afford allylic alcohol *rac*-**175ab** (Scheme 10.1.9). Subsequent reduction of the triple bond furnished olefin *rac*-**176ab** in 52% yield. Further, attempts to introduce the epoxide moiety were unsuccessful, this may be attributed to the steric influence of benzyl protection group. Possible solution to this problem could be, deprotective cleavage of benzyl group, followed by epoxidation.



rac-**164** *rac*-**176ab** *rac*-**177ab**

Scheme 10.1.9

Reagents and conditions: (a) C_3H_3MgBr, THF, 0 °C → 20 °C, 20 min., 62%; (b) Red-Al, THF, reflux, 12 h, 52%; (c) $Ti(OiPr)_4$, *t*BuOOH , (-)-DIPT, 0 °C, 16 h, or $VO(acac)_2$, *t*BuOOH, CH_2Cl_2, 16 h, than Na_2SO_3, 1 h.

Conclusions and Future Work

Following a second retrosynthetic strategy towards mensacarcin (**1**), the preparation of various complex and new aromatic building blocks was achieved. The first key reaction involving aryllithium to aldehyde addition was successful after several procedure modifications. This transformation led to the way by connection of the A- and C-rings to the second ring forming step the intramolecular *Heck* reaction. After an investigation of several catalysts and conditions all three tested palladium catalyse transformations were optimised to over 90% yield. These new reactions, have followed the ideas to match the catalyst with the electronic properties of the arylbromide. Furthermore, methods have been developed for the addition of the four carbon associated with the biologically important side chain in **1**. Another important reaction advancing such intermediates was the oxidative cleavage of the exocyclic double bond in *rac*-**162**, which provided compounds with the same AB-ring system as mensacarcin (**1**). With these experiences in hand final dearomatisation of C-ring, epoxidation and installing tertiary hydroxyl group are remaining to complete the total syntheses of mensacarcin (**1**). When taking into account the studies it is evident that

simpler analogs, such as compound *rac*-**164**, are immediately accessible through the described synthesis. We hope that the developed strategies within this thesis and synthesised building blocks will prove their value for the synthesis of the natural product mensacarcin (**1**) and various biologically active analogues.

1 Experimental Protocol

1.1 Used instruments

1.1.1 Melting Points

Melting points were measured on a Mettler FP61 apparatus and stand uncorrected.

1.1.2 Infrared Spectra

Infrared spectra were recorded on IFS2 *Brucker* Instrument. Samples were analysed as KBr disks (for solides) or as thin films on KBr plates (for oils). Absorbtion maxima are recorded in wavenumbers (cm^{-1}).

1.1.3 UV/VIS Spectra

UV/VIS spectra were recorded on Perkin-Elmer Lambda 9 – *Perkin-Elmer* Instrument. Wavelengths were recorded in (nm).

1.1.4 ^{1}H-NMR Spectra

Proton (^{1}H) spectra were recorded on the *Varian* VXR-200 (200 MHz), Bruker AM-300 (300 MHz) spectrometers. Spectra were acquired in deuterochloroform and deuterobenzene at 20 °C. Chemical shifts were recorded as follows: Chemical shift (δ), multiplicity, coupling constant (*J*) (Hz = Hertz), where multiplicity is defined as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets) and br (broad)

1.1.5 ^{13}C-NMR Spectra

Carbon (^{13}C) spectra were recorded on the *Varian* XL-200 (50.3 MHz), VXR-200 (200 MHz), UNITY 300 (75.5 MHz), INOVA-500 (1255.7 MHz) and Bruker AM-300 (75.5 MHz) spectrometers. Spectra were acquired in deuterochloroform and deuterobenzene at 20 °C. Chemical shifts were recorded as follows: Chemical shift (δ), protonicity is defined as: Ar-C = aromatic; C = quaternary; CH = methine; CH_2 = methylene; CH_3 = methyl.

1.1.6 Mass Spectra

Low and high resolution mass spectra were recorded on a *Varian* MAT 731 spectrometer. Mass spectral data are listed as: mass-to-charge ratio (*m/z*) [assignment where possible), intensity relative to the base peak]. HRMS performed using a modified peak matching technique, error ± 2ppm, with a resolution of ca. 10,000.

1.1.7 Elemental Analyses

Elemental analyses were performed by Mikroanalytisches Labor des Institutes für Organische und Biomolekulare Chemie der Universität Göttingen.

1.2 Chromatography Methods

1.2.1 Analytical Thin Layer Chromatography

TLC chromatography was performed on precoated aluminium silica gel SIL G/UV254 plates *Macherey, Nagel & Co*. (0.2 mm thick silica gel). Visualisation of eluted plates was through use of 254 nm UV lamp and/or treatment with a reagent dip following by heating. Vaniline-sulfiric acid (5 g vaniline, 30 ml sulfuric acid, 850 ml methanol and 100 ml acetic acid).

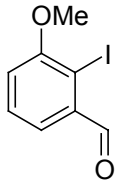
1.2.2. Flash Chromatography

Flash chromatography was performed using the anatytical grade solvents and silica gel 60 (0.032-0.064 mm) as supplied by *Macherey, Nagel & Co*

General: All reactions air and/or moisture sensitive were performed in flame dried glassware under an argon atmosphere. Solvents were dried and purified according to the method defined by Perin and Armarego.[94] Starting materials and reagents were generally available from either Aldrich, Merck, Acros or Lancaster Chemical Companies.

4 Synthesis of A-Ring Fragments

4.1 2-Iodo-3-methoxybenzaldehyde (96)



A solution of *N,N',N'*-trimethylethylenediamine (3.22 g, 31.5 mmol) in 100 mL of benzene was treated dropwise with *n*BuLi (12.6 mL, 2.5M in hexane, 31.5 mmol) at 0 °C. The resulting solution was warmed to 20 °C while continuously stirring for 15 min. The mixture was then again cooled to 0 °C and 3-methoxybenzaldehyde **50** (4.00 g, 29.4 mmol) was added in one portion. The resulting yellow solution was stirred for another 15 min at 20 °C before being cooled to 0 °C and treated with a solution of phenyllithium (44 mL, 2.0M solution in dibutyl ether, 88.2 mmol). After the mixture was stirred at 20 °C for 7 h, THF (50 mL) was added while the mixture was being cooled to –78 °C. This solution was then treated with freshly sublimed iodine (29.9 g, 118 mmol) in THF (50 mL), the cooling bath removed, and the reaction mixture allowed to warm to 20 °C. After stirring for a further 2 h the slurry was diluted with ethyl acetate (100 mL), and washed with HCl (1 x 20 ml, 1M), $Na_2S_2O_3$ (3 x 50 ml, saturated solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the resulting crude oil to flash chromatography (19:1 pentane/EtOAc) and concentration of appropriate fractions then afforded the iodobenzene **96** (4.23 g, 16.20 mmol, 55%) as a yellow solid.

R_f = 0.5

m.p. = 84 °C (recrystallised from EtOAc/hexane)

IR (KBr): $\tilde{\nu}$ = 2849 cm^{-1}, 1950, 1562, 1466, 1270, 1013, 787

UV (CH_3CN): λ_{max} = 222.0 nm (4.4167), 326.5 (3.7352)

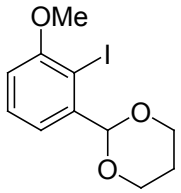
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 7.05 (d, *J* = 7.9 Hz, 1H, 4-H), 7.39 (t, *J* = 7.9 Hz, 1H, 5-H), 7.50 (d, *J* = 7.9 Hz, 1H, 6-H), 10.19 (s, 1H, CHO)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 56.8 (OCH_3), 93.9 (Ar-C), 116.0 (Ar-C), 122.2 (Ar-C), 129.4 (Ar-C), 136.7 (Ar-C), 158.2 (Ar-C), 196.4 (CHO)

MS (EI, 70 eV): m/z (%) = 261 (100) $[M]^+$, 133.0 (10), 104.0 (8), 76.0 (12)

$C_8H_7IO_2$ (262.04); **HRMS**: calcd: 261.9491; confirmed

4.2 2-(2'-Iodo-3'-methoxyphenyl)-[1,3]dioxane (99)



A magnetically stirred solution of aldehyde **96** (1.73 g, 6.65 mmol) in benzene (60 mL) was treated with 1,3-propandiol (961 µL, 13.30 mmol) and amberlyst 15 (192 mg) at 20 °C. The resulting mixture was heated to reflux for 5 h using a Dean-Stark apparatus. After cooling, the mixture was diluted with Et_2O (60 mL), washed with H_2O (4 x 10 mL), dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The resulting white solid was recrystallised (EtOAc/hexane) to afford acetal **99** (1.40 g, 4.39 mmol, 66%) as white solid.

R_f = 0.5 (1:19 EtOAc/pentane)

m.p. = 134 °C

IR (KBr): $\tilde{\nu}$ = 2972 cm^{-1}, 1571, 1433, 1379, 1267, 1105, 1065, 991, 781

UV (CH_3CN): λ_{max} = 204.5 nm (4.5436), 280.0 (3.5111), 287.0 (3.5195), 227.0 (0.3184)

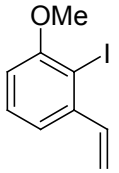
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.58-0.78 (m, 1H, 5-H), 1.70-2.00 (m, 1H, 5-H), 3.15 (s, 3H, OCH_3), 3.51-3.68 (m, 2H, 4-H/6-H), 3.33-3.97 (m, 2H, 4H/6-H), 5.79 (s, 1H, 2-H), 6.19 (d, *J* = 8.3 Hz, 1H, 4'-H), 6.99 (t, *J* = 8.0 Hz, 1H, 5'-H), 7.65 (d, *J* = 7.7 Hz, 1H, 6'-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 25.6 (CH_2), 56.6 (OCH_3), 67.5 (CH_2), 90.1 (CH_2), 105.2 (CH), 111.4 (Ar-C), 120.0 (Ar-C), 123.2 (Ar-C), 129.3 (Ar-C), 142.0 (Ar-C), 157.7 (Ar-C)

MS (EI, 70 eV): m/z (%) = 320.1 (100) $[M]^+$, 319.2 (76) $[M - H]^+$, 261.1 (17) $[M - C_3H_6O]^+$

$C_{11}H_{13}IO_3$ (320.12); **HRMS**: calcd: 319.0999; confirmed

4.3 2-Iodo-3-vinyl-anisole (100)



A solution of Ph_3PCH_3Br (1.38 g, 3.87 mmol) in THF (50 mL) was treated with sodium bis(trimethylsilyl) amide (3.87 mL of 1M solution in THF, 3.87 mmol) and stirred for 1 h at 20 °C. The reaction mixture was then treated with a solution of 2-iodo-3-methoxybenzaldehyde **96** (676 mg, 2.58 mmol) in THF (20 mL) and stirred for 1 h, before silica gel was added and the suspension concentrated under reduced pressure. Subjection of the resulting yellow solid to the flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded styrene **100** (601 mg, 2.31 mmol, 90 %) as a white solid .

R_f = 0.8

m.p. = 64 °C (recrystallised from EtOAc/hexane)

IR (KBr): $\tilde{\nu}$ = 3081 cm^{-1}, 2962, 2935, 1616, 1558, 1465, 1057, 786

UV (CH_3CN): λ_{max} = 222.0 nm (4.4427), 296.5 (3.3006), 249.0 (3.9419)

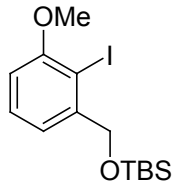
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.87 (s, 3H, OCH_3), 5.30 (d, *J* = 11.0 Hz, 1H, 2'-H), 5.62 (d, *J* = 17.3 Hz, 1H, 2'-H), 6.71 (d, *J* = 7.5 Hz, 1H, 6-H), 7.00 (dd, *J* = 17.3, 11.0 Hz, 1H, 1'-H), 7.12 (d, *J* = 7.5 Hz, 1H, 4-H), 7.24 (t, *J* = 7.5 Hz, 1H, 5-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 56.5 (CH_3), 92.0 (Ar-C), 100.7 (Ar-C), 116.9 (CH_2), 119.0 (Ar-C), 128.9 (Ar-C), 141.1 (CH), 142.7 (Ar-C), 158.2 (Ar-C)

MS (EI, 70 eV): m/z (%) = 260.0 (100) $[M]^+$, 245.0 (8) $[M - CH_3]^+$, 104.0 (8), 133.1 (4) $[M - I]^+$

C_9H_9IO (260.07); **HRMS**: calcd: 259.9698; confirmed

4.4 *tert*-Butyl-(2-iodo-3-methoxy-benzyloxy)-dimethyl-silane (98)



A magnetically stirred solution of aldehyde **96** (1.06 g, 4.00 mmol) in THF (50 mL) was treated in one portion with $LiAlH_4$ (114 mg, 3.00 mmol) at 0 °C. Stirring was continued for a further 0.5 h before the reaction mixture was treated with $MgSO_4$ (1.1 g) and dropwise with water (810 µL). The resulting suspension was filtered and washed thoroughly with Et_2O (6 x 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of the resulting crude oil to flash chromatography (9:1 pentane/EtOAc, R_f = 0.6) and concentration of the appropriate fractions afforded alcohol **97** (871 mg, 3.30 mmol, 82%) as a pale yellow oil.

The above alcohol **97** (160 mg, 0.60 mmol) in DMF (15 mL), imidazole (82 mg, 1.20 mmol), *tert*-butylsilyl chloride (135 mg, 0.90 mmol) was treated with dimethyl aminopyridine (cat.) at 20 °C. Stirring was continued for 12 h before being diluted with Et_2O (100 mL) and washed with water (5 x 20 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of appropriate fractions afforded iodobenzene **98** (212 mg, 0.56 mmol, 94%) as yellow oil.

R_f = 0.5

IR (KBr): $\tilde{\nu}$ = 2832 cm^{-1}, 1876, 1562, 1466, 1270, 787

UV (CH_3CN): λ_{max} = 222.0 nm (4.4167), 326.5 (3.7352)

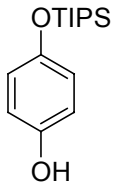
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 6H, 2 x $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 3.95 (s, 3H, OCH_3), 4.58 (s, 2H, CH_2), 6.85 (d, *J* = 7.9 Hz, 1H, 4-H), 7.19 (t, *J* = 7.9 Hz, 1H, 5-H), 7.33 (d, *J* = 7.9 Hz, 1H, 6-H)

MS (EI, 70 eV): m/z (%) = 378.0 (40) $[M]^+$, 263.0 (100) $[M - TBS]^+$

$C_{14}H_{23}IO_2Si$ (378.32); **HRMS**: calcd: 378.0512; confirmed

5 Synthesis of the C-Ring Fragments

5.1 4-Triisopropylsilanoxy-phenol (107)



A magnetically stirred solution of hydroxyquinone **91** (1.00 g, 9.00 mmol) in THF (100 mL) was treated in one portion with NaH (238 mg, 9.90 mmol of 60% in oil) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C before being treated dropwise over 5 min with triisopropylsilyl chloride (1.92 mL, 9.00 mmol). Stirring was continued for 12 h at 20 °C before being quenched with water (10 mL), extracted with Et_2O (3 x 50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of the resulting crude oil to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded monoprotected phenol **107** (2.15 g, 8.10 mmol, 90%) as a yellow oil.

R_f = 0.6

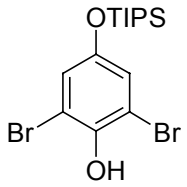
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.90-1.11 (m, 21 H, (*i*Pr)$_3$Si), 6.73 (m, 4H, Ar-H), 9.87 (s, 1H, OH)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.3 (Si<u>C</u>H(CH$_3$)$_2$), 18.1 (6 x SiCH(<u>C</u>H$_3$)$_2$), 114.6 (Ar-C), 120.5 (Ar-C), 151.5 (Ar-C), 152.7 (Ar-C)

MS (EI, 70 eV): m/z (%) = 266.2 (80) $[M]^+$, 223.1 (100) $[M - C_3H_7]^+$, 195.1 (41)

$C_{15}H_{26}O_2Si$ (266.45)

5.2 2,6-Dibromo-4-triisopropylsilanoxy-phenol (108)



A magnetically stirred solution of benzyltrimethylamonium tribromide (469 mg, 1.20 mmol) in MeOH/CH_2Cl_2 (3:3 mL) was treated dropwise with phenol **107** (160 mg, 0.60 mmol) over 15 min at 20 °C. The resulting reaction mixture was stirred over 4 h at 20 °C, before being diluted with CH_2Cl_2 (10 mL), washed with water (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Subjection of the resulting crude oil to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dibromophenol **108** (89.8 mg, 0.21 mmol, 35%) as a yellow oil.

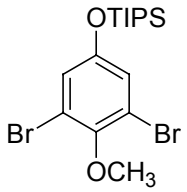
$\mathbf{R_f}$ = 0.5

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.90-1.11 (m, 21 H, (iPr)$_3$Si), 7.01 (s, 2H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.3 (Si<u>C</u>H(CH_3)$_2$), 18.1 (6 x SiCH(<u>C</u>H$_3$)$_2$), 110.5 (Ar-C), 118.0 (Ar-C), 147.1 (Ar-C), 157.4 (Ar-C)

MS (EI, 70 eV): m/z (%) = 424.0 (25) $[M]^+$, 381.0 (42) $[M - C_3H_7]^+$, 281.9 (100) [M – Br_2]

5.3 (3,5-Dibromo-4-methoxy-phenoxy)-triisopropyl-silane (109)



A magnetically stirred solution of dibromophenol **108** (60 mg, 0.14 mmol) in acetone (3 mL) was treated in one portion with K_2CO_3 (58 mg, 0.425 mmol) at 20 °C. The resulting reaction mixture was stirred for 5 min, before being treated with MeI (17 μL,

0.283 mmol) at 20 °C. Stirring was continued for 5 h, before being diluted with Et_2O (20 mL), washed with water (3 x 1 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Subjection of the resulting crude oil to flash chromatography (99:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dibromoanisole **109** (31 mg, 0.07 mmol, 55%) as a yellow oil.

R_f = 0.8

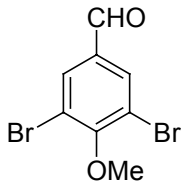
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.11-1.21 (m, 21H, *i*Pr), 3.87 (s, 3H, OMe), 7.01 (s, 2H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 12.3 (Si<u>C</u>H(CH_3)$_2$), 18.1 (6 x SiCH(<u>C</u>H_3)$_2$), 60.1 (OCH_3), 112.5 (Ar-C), 120.3 (Ar-C), 149.1 (Ar-C), 155.8 (Ar-C)

MS (EI, 70 eV): m/z (%) = 440. 0 (40), 438.0 (62) $[M]^+$, 395.0 (100) [M – C_3H_7], 338.9 (44), 284.0 (8) [M – Br_2]

$C_{16}H_{26}Br_2O_2Si$ (438.27)

5.4 3,5-Dibromo-4-methoxy-benzaldehyde (111)



A magnetically stirred solution of dibromophenol **90** (500 mg, 1.79 mmol) in acetone (60 mL) was treated in one portion with K_2CO_3 (497 mg, 3.58 mmol) and MeI (554 µL, 8.9 mmol) at 20 °C. The resulting reaction mixture was stirred over 12 h, at 50 °C, before being diluted with Et_2O (150 mL), washed with water (3 x 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford an orange oil. Subjection of the resulting crude oil to flash chromatography (2:1 pentane/methyl*t*butyl ether) and concentration of the appropriate fractions afforded anisol **111** (455 mg, 1.55 mmol, 86%) as a yellow oil.

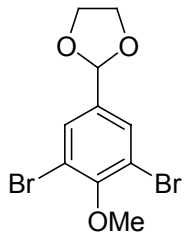
R_f = 0.9

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.12 – 1.25 (m, 21H, $(C_3H_7)_3$), 3.81 (s, 3H, OCH_3), 7.01 (s, 2H, Ar-H), 10.21 (s, 1H, CHO)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 60.6 (OCH_3), 116.7 (Ar-C), 136.2 (Ar-C), 137.9 (Ar-C), 156.0 (Ar-C), 190.8 (CHO)

$C_8H_6Br_2O_2$ (293.94)

5.5 2-(3,5-Dibromo-4-methoxy-phenyl)-[1,3]dioxolane (112)



A magnetically stirred solution of benzaldehyde **111** (520 mg, 1.76 mmol) and 1,2-propandiol (500 µL, 8.87 mmol) in benzene (50 mL) was treated in one portion with *p*-TsOH (cat) at 20 °C. The resulting mixture was heated to reflux for 5 h using a Dean-Stark apparatus. After cooling, the mixture was diluted with benzene (60 mL), washed with H_2O (4 x 10 mL), dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The resulting white solid was recrystallised (EtOAc/hexane) to afford acetal **112** (380 mg, 1.12 mmol, 64%) as white solid.

R_f = 0.6 (50:1 pentane/methyl*t*butyl ether)

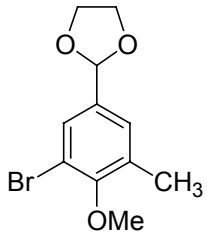
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.98 (s, 3H, OCH_3), 4.01-4.09 (m, 4H, 2-H/3-H), 5.87 (s, 1H, 5-H), 7.34 (s, 1H, Ar-H), 7.65 (s, 1H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 59.9 (OCH_3), 65.3 (CH_2), 102.2 (CH), 118.0 (Ar-C), 131.7 (Ar-C), 136.1 (Ar-C), 152.7 (Ar-C)

MS (EI, 70 eV): m/z (%) = 336.9 (100), 334.9 (60) $[M]^+$, 306.9 (42), 304.9 (20), 259.0 (78), 257.0 (80)

$C_{10}H_{10}Br_2O_3$ (337.99)

5.6 2-(3,5-Dibromo-4-methoxy-5-methyl-phenyl)-[1,3]dioxolane (113)



A magnetically stirred solution of acetal **112** (90 mg, 0.27 mmol) in THF (1 mL) was treated with *sec*-BuLi (190 µL, 0.32 mmol 1.7M solution in hexane) at −78 °C and stirred for 10 min before being treated with methyl trifluoromethanesulfonate (60 µL, 0.53 mmol). The resulting mixture was stirred for 1 h at 20 °C before being quenched with NH_4Cl (0.5 mL of a saturated aqueous solution). The resulting suspension was extracted with ether (3 x 20 mL) and washed with brine (1 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow solid. Subjection of the resulting solid to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded methylbenzene **113** (40 mg, 0.17 mmol, 66%) as a yellow solid.

R_f = 0.5

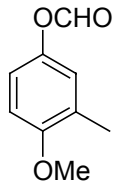
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), 4.10-4.15 (m, 4H, 2-H/3-H), 5.89 (s, 1H, 5-H), 7.61 (s, 1H, Ar-H), 7.82 (s, 1H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 16.4 (CH_3), 60.2 (OCH_3), 65.2 (CH_2), 103.8 (CH), 113.9 (Ar-C), 121.2 (Ar-H), 127.2 (Ar-C), 132.9 (Ar-C), 134.3 (Ar-C), 155.3 (Ar-C)

MS (EI, 70 eV): m/z (%) = 274.0 (12), 272.0 (22) $[M]^+$, 230.1 (70), 228.1 (85) $[M - C_2H_4O]^+$

$C_{11}H_{13}BrO_3$ (273.12)

5.7 Formic acid 4-methoxy-3-methyl-phenyl ester (88a)



A magnetically stirred solution of aldehyde **88** (1.00 g, 6.66 mmol) in CH_2Cl_2 (50 mL) was treated in one portion with *m*-CPBA (3.28 g of a 70% mixture in water, 19.0 mmol) at 20 °C. Stirring was continued for 12 h before the CH_2Cl_2 was removed under reduced pressure and subjected to flash chromatography (19:1 pentane/EtOAc). Concentration of the appropriate fractions afforded formate **88a** (829 mg, 4.99 mmol, 75%) as colourless oil.

R_f = 0.6

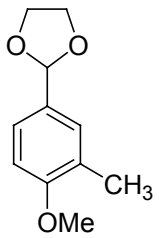
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.17 (s, 3H, CH_3), 3.94 (s, 3H, OCH_3), 6.91-6.99 (m, 3H, Ar-H), 8.18 (s, 1H, CHO)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 16.3 (CH_3), 55.4 (OCH_3), 111.0 (Ar-C), 117.1 (Ar-C), 117.3 (Ar-C), 124.2 (Ar-H), 154.7 (Ar-H), 162.3 (CHO)

MS (EI, 70 eV): m/z (%) = 166.0 (99) $[M]^+$

$C_9H_{10}O_3$ (166.17)

5.8 2-(4-Methoxy-3-methyl-phenyl)-[1,3]dioxolane (115)



A magnetically stirred solution of benzaldehyde **88** (500 mg, 3.30 mmol) and 1,2-propandiol (500 µL, 8.87 mmol) in benzene (50 mL) was treated in one portion with and *p*-TsOH (cat.) at 20 °C. The resulting mixture was heated at reflux for 5 h using a Dean-Stark apparatus. After cooling, the mixture was diluted with benzene (60 mL),

dried ($MgSO_4$), filtrated and concentrated under reduced pressure to afford acetal **115** (487 mg, 2.50 mol, 76%) as a white solid.

R_f = 0.5 (19:1 pentane/EtOAc)

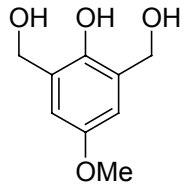
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.24 (s, 3H, CH_3), 3.97 (s, 3H, OCH_3), 4.01 (m, 4H, 2-H/3-H), 5.89 (s, 1H, 5-H), 6.97 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.01-7.06 (m, 2H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 16.9 (CH_3), 58.0 (OCH_3), 65.2 (CH_2), 103.6 (CH), 113.4 (Ar-C), 124.2 (Ar-C), 128.5 (Ar-C), 131.9 (Ar-C), 156.7 (Ar-C)

MS (EI, 70 eV): m/z (%) = 194.1 (6) $[M]^+$, 150.1 (99) $[M - C_2H_4O]^+$

$C_{11}H_{14}O_3$ (194.23)

5.9 2,6-Bis-hydroxymethyl-4-methoxy-phenol (101)



A magnetically stirred suspension of *p*-methoxyphenol **89** (124 g, 1.00 mol) in water (800 mL) was treated with formaldehyde (180 mL of 37% solution in water, 2.40 mol) and CaO (31.2 g, 0.48 mol) at 20 °C. The ensuing mixture was stirred for 1 h before being placed, unstirred, in the dark for 3 days. The resulting solution containing a yellow solid was diluted and dissolved using warm acetic acid (80 mL). The solution was then cooled in an ice bath to obtain the yellow crystals which were filtered and recrystallised from EtOAc to afford triol **101** (130 g, 704 mmol, 70%) as a pale white solid.

R_f = 0.5 (4:1 pentane/EtOAc)

m.p. = 125 °C

UV/VIS (CH_3CN): λ_{max} (lg ε) = 197.5 nm (4.4240), 230.5 (3.4963), 295.0 (3.4589)

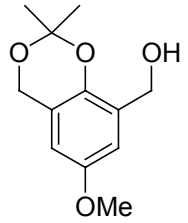
IR (KBr): $\tilde{\nu}$ = 2938 cm^{-1}, 1731, 1611, 1483, 1314, 860, 789

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.26 (s, 1H, OH), 2.33 (t, *J* = 6.5 Hz, 2H, OH), 3.75 (s, 3H, OCH_3), 4.77 (d, *J* = 6.5 Hz, 4H, 2 x CH_2OH), 6.65 (s, 2H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 56.0 (CH_2) , 58.9 (CH_2) , 129.3 (2 x Ar-C), 147.2 (Ar-C), 113.2 (Ar-C), 113.4 (Ar-C)

MS (EI, 70 eV): m/z (%) = 184 (64) $[M]^+$, 151 (38) $[M - CH_3OH]^+$, 137.1 (50) **$C_9H_{12}O_4$** (184.19); **HRMS**: calcd: 184.0736; confirmed

5.10 6-Methoxy-2,2-dimethyl-8-hydroxymethyl-4*H*-benzo[1,3]dioxine (102)



A magnetically stirred solution of triol **101** (14.30 g, 75.60 mmol) in acetone (70 mL) and dimethoxypropane (140 mL) at 20 °C was treated in one portion with Amberlyst 15™ (0.5 g). The resulting mixture was stirred for 1.5 h then concentrated under reduced pressure to afford a yellow oil. The mixture was diluted with Et_2O (70 mL) and washed with water (2 x 50 mL). The organic phase was treated with acetic acid (50 mL) and stirred at 20 °C for 0.5 h before being washed with $NaHCO_3$ (50 mL of a saturated aqueous solution). The combined organic fractions were dried ($MgSO_4$), filtered, concentrated under reduced pressure and recrystallised from hexane/CH_2Cl_2 to afford the benzyl alcohol **102** (12.70 g, 56.50 mmol, 73%) as a white solid.

R_f = 0.2 (2:1 pentane/methyl*t*butyl ether)

m.p. = 83 °C

IR (KBr): $\tilde{\nu}$ = 2991 cm^{-1}, 1613, 1477, 1385, 1284, 968, 879

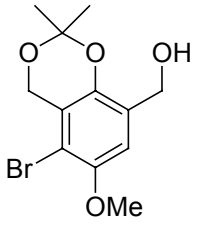
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.53 (s, 6H, 2 x CH_3), 2.90-3.30 (brs, 1H, OH), 3.74 (s, 3H, OCH_3), 4.62 (s, 2H, CH_2OH), 4.81 (s, 2H, CH_2OH), 6.44 (d, *J* = 2.9 Hz, 1H, Ar-H), 6.77 (d, *J* = 2.9 Hz, 1H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 24.7 (2 x CH_3), 55.6 (OCH_3), 60.9 (CH_2), 61.1(CH_2), 99.5 (C), 108.4 (Ar-C), 113.0 (Ar-C), 119.7 (Ar-C), 129.8 (Ar-C), 142.7 (Ar-C), 153.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 224.2 (18) $[M]^+$, 166.1 (100) $[M - C_3H_6O]^+$, 151.1 (24) $[M - C_3H_6O - CH_3]^+$, 137.1 (50)

$C_{12}H_{16}O_4$ (224.25); **HRMS**: calcd: 224.2530; confirmed

5.11 5-Bromo-8-hydroxymethyl-6-methoxy-2,2-dimethyl-4*H*-benzo[1,3]dioxine (103)



A magnetically stirred solution of benzyl alcohol **102** (12.70 g, 56.50 mmol) and KOAc (5.55 g, 56.50 mmol) in acetic acid (300 ml) was treated with bromine (9.48 g, 59.30 mmol) at 20 °C. Stirring was continued for 45 min before the reaction mixture was diluted with Et_2O (300 mL) and washed with $Na_2S_2O_3$ (aqueous saturated solution) until the colour of the solution changed from orange to yellow. The remaining organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was then recrystallised from hexane/CH_2Cl_2 to afford bromobenzene **103** (13.50 g, 44.60 mmol, 79%) as a white solid.

R_f = 0.3 (2:1 pentane/methyl*t*butyl ether)

m.p. = 117 °C

IR (KBr): $\tilde{\nu}$ = 2945 cm^{-1}, 1710, 1468, 1243, 965, 871, 792

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.52 (s, 6H, 2 x CH_3), 2.11 (t, *J* = 5.3 Hz, 1H, OH), 3.85 (s, 3H, OCH_3), 4.62 (d, *J* = 5.3 Hz, 2H, CH_2OH), 4.74 (s, 2H, CH_2OR), 6.86 (s, 1H, Ar-H)

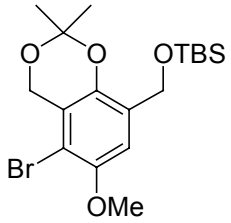
^{13}C-NMR (50 MHz, $CDCl_3$): δ = 24.7 (CH_3), 56.7 (CH_3), 60.6 (CH_2), 62.1 (OCH_3), 99.5(C), 107.8 (Ar-C), 110.6 (Ar-C), 120.2 (Ar-C), 128.3 (Ar-C), 143.4 (Ar-C), 149.5 (Ar-C)

MS (EI, 70 eV): m/z (%) = 304.1 (21), 302.1 (18) $[M]^+$, 246.0 (100), 244.0 (98) $[M - C_3H_6O]^+$, 217 (40), 215 (38)

$C_{12}H_{15}O_4$ (303.15); **HRMS**: calcd: 302.0154; confirmed

Elemental Analysis calcd (%) for $C_{12}H_{15}O_4Br$: C 47.54, H 4.99; found C 47.22, H 4.64.

5.12 (5-Bromo-6-methoxy-2,2-dimethyl-4*H*-benzo[1,3]dioxin-8-yl-methoxy)-*tert*-butyl-dimethyl silane (104)



A magnetically stirred solution of bromobenzene **103** (12.10 g, 40.20 mmol) in DMF (150 mL) was treated with imidazole (5.47 g, 80.40 mmol), TBSCl (6.67 g, 44.20 mmol) and DMAP (cat.) at 20 °C. Stirring was continued for 12 h before being diluted with Et_2O (200 mL) and washed with water (5 x 50 mL). The organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of this material to flash chromatography (40:1 pentane/methyl*t*butyl ether) and concentration of appropriate fractions afforded bromobenzene **104** (16.60 g, 39.80 mmol, 99%) as a yellow oil.

R_f = 0.4

UV/VIS (CH_3CN): λ_{max} (lg ε) = 197.0 nm (4.6176), 228.5 (3.8465), 294.5 (3.7166)

IR (KBr): $\tilde{\nu}$ = 2995 cm^{-1}, 1611, 1478, 1382, 1055, 881

^{1}H-NMR (200 MHz, C_6D_6): δ = 0.09 (s, 6H, 2 x $SiCH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.48 (s, 6H, 2 x CH_3), 3.13 (s, 3H, OCH_3), 4.64 (s, 2H, CH_2OR), 7.03 (s, 1H, Ar-H)

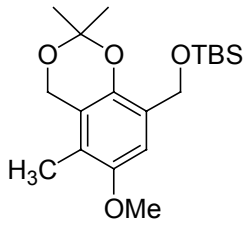
^{13}C-NMR (50 MHz, C_6D_6): δ = -5.3 (2 x $SiCH_3$), 18.3 ($SiC(CH_3)$, 24.5($SiC(CH_3)$, 25.9 (2 x CH_3), 56.6 (OCH_3), 59.3 (CH_2), 62.2 (CH_2), 99.2 (C), 106.6 (Ar-C), 109.4 (Ar-C), 119.5 (Ar-C), 129.3 (Ar-C), 142.2 (Ar-C), 149.5 (Ar-C)

MS (EI, 70 eV): m/z (%) = 418.3 (8), 416.3 (7) $[M]^+$, 303.2 (100), 301.2 (99) $[M - C_6H_{15}Si]^+$, 147.2 (10)

$C_{18}H_{29}O_4BrSi$ (417.41); **HRMS**: calcd: 416.1019; confirmed

Elemental Analysis calcd (%) for $C_{18}H_{29}O_4BrSi$: C 51.79, H 7.00; found C 51.55, H 6.82.

5.13 *tert*-Butyl-(6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl-methoxy)-dimethyl silane (105)



A magnetically stirred solution of acetonide **104** (100 mg, 0.24 mmol) in THF (1 mL) was treated with *sec*-BuLi (0.281 mL, 0.48 mmol 1.7M solution in hexane) at – 78 °C and stirred for 0.5 h before being treated with MeI (149 µL, 2.40 mmol). The resulting mixture was warmed to 20 °C and stirred for 2 h before being quenched with NH_4Cl (0.5 mL of a saturated aqueous solution). The resulting solution was extracted with ether (3 x 20 mL) and washed with brine (1 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Subjection of the resulting crude oil to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded toluene **105** (62 mg, 0.17 mmol, 73%) as a yellow oil.

R_f = 0.7

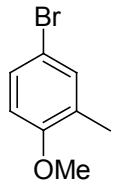
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 6H, 2 x $SiCH_3$), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.49 (s, 6H, 2 x CH_3), 1.82 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.59 (s, 2H, CH_2OR), 4.61 (s, 2H, CH_2OR), 6.82 (s, 1H, Ar-H)

^{13}C-NMR (50 MHz, $CDCl_3$): δ = -5.3 (2 x $SiCH_3$), 18.4 ($SiC(CH_3)$), 24.224.5($SiC(CH_3)$), 21.9 (CH_3), 25.9 (CH_3), 28.4 (CH_3), 55.6 (OCH_3), 59.7 (CH_2), 108.1 (Ar-C), 111.0 (Ar-C), 124.5 (Ar-C), 130.5 (Ar-C), 141.1 (Ar-C), 153.2 (Ar-C)

MS (EI, 70 eV): m/z (%) = 352.0 (8) $[M]^+$, 294.3 (4) $[M - C_3H_6O]^+$, 237.2 (100) $[M - C_6H_{15}Si]^+$

$C_{19}H_{32}O_4Si$ (352.54)

5.14 2-Methyl-3-methoxy-bromobenzene (118)



Procedure I

A magnetically stirred solution of bromobenzene **87** (40.00 g, 0.32 mol) in CH_2Cl_2 (400 mL) and NaOAc (26.20 g, 0.32 mol) was treated dropwise with bromine (16.4 mL, 0.32 mol) at 0 °C over 0.5 h. Stirring was continued at this temperature for 1.5 h, before the solution was washed with $Na_2S_2O_3$ (4 x 50 mL of saturated solution), brine (1 x 50 mL). The organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afforded bromobenzene **118** (50.80 g, 0.25 mol, 79%) as a white solid.

Procedure II

A magnetically stirred solution of acetale **115** (487 mg, 2.50 mmol) in CH_2Cl_2 (40 mL) and NaOAc (205 mg, 2.50 mmol) was treated dropwise with bromine (127 µL, 2.50 mmol) at 0 °C over 0.5 h. Stirring was continued at this temperature for 1 h, before the solution was washed with $Na_2S_2O_3$ (2 x 10 mL of saturated solution), brine (1 x 10 mL). The organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afforded bromobenzene **118** (357 mg, 1.78 mmol, 71%) as a white solid.

R_f = 0.6 (19:1 pentane/EtOAc)

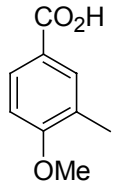
^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.14 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 6.62 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.31 (m, 2H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 16.0 (CH_3), 55.4 (OCH_3), 111.4 (Ar-C), 112.3 (Ar-C), 128.9 (Ar-C), 129.3 (Ar-C), 133.1 (Ar-C), 156.8 (Ar-C)

MS (EI, 70 eV): m/z (%) = 202.1 (97), 200.1 (100) $[M]^+$, 187.1 (42) 185.1 (45), 121.2 (20) $[M - Br]^+$

C_8H_9OBr (201.06)

5.15 2-Methyl-3-methoxy-benzoic acid



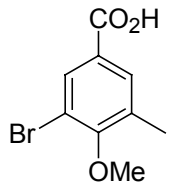
To the solution of magnesium turnings (6.80 g, 0.28 mol) and I_2 (cat.) in Et_2O (50 mL) was added dropwise bromobenzene **118** (52.0 g, 0.26 mol) in THF/ Et_2O (100/50 mL) exothermally self refluxing over 1 h. The resulting mixture was then heated to reflux over 1.5 h before being poured into dry ice (ca. 150 g), stirred vigorously and left standing over 2 h. Than crushed ice was added and conc. HCl (pH = 1), mixture was extracted with Et_2O (6 x 150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford benzoic acid **114** (34.50 g, 0.21 mol, 80%) as a white solid. The spectroscopic data for this compound matched those reported in lit.[95]

R_f = 0.2 (19:1 pentane/EtOAc)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2. 17 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 7.01 (d, *J* = 1.7 Hz, 1 H, Ar-H), 7.72 (s, 1H, Ar-H), 7.83 (d, *J* = 1.7 Hz, 1H, Ar-H)

MS (EI, 70 eV): m/z (%) = 166.0 (100) $[M]^+$, 149.0 (35) $[M - OH]^+$, 121.1 (30)

5.16 3-Bromo-4-methoxy-5-methylbenzoic acid (119)



A magnetically stirred solution of carboxylic acid **114** (88.0 g, 0.53 mol) in dioxane (850 mL) was treated dropwise with bromine (54.0 mL, 1.06 mol) at 20 °C. Stirring was continued for 7 days before the reaction mixture was diluted with ether (300 mL), transferred to a separating funnel and washed vigorously with an aqueous saturated solution of $Na_2S_2O_3$ until the solution changes from orange to yellow (ca 2 x 100 mL). The remaining organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give bromobenzene **119** (109.10 g, 0.44 mol, 84%) as a pale yellow solid.

m.p. = 160 °C (recrystallised from EtOAc/pentane)

IR (KBr): $\tilde{\upsilon}$ = 2950 cm^{-1}, 1603, 1416, 1104, 775, 661.

UV (CH_3CN): λ_{max} = 208 nm (4.4228), 245 (3.7995).

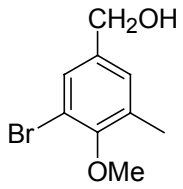
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 7.84 (d, *J* = 1.1 Hz, 1H, Ar-H), 8.11 (d, *J* = 1.1 Hz, 1H, Ar-H).

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 16.6 (CH_3), 61.5 (CH_2), 64.0 (OCH_3), 117.3 (Ar-C), 130.2 (Ar-C), 132.5 (Ar-C), 133.0 (Ar-C), 159.9 (Ar-C), 170.5 (Ar-C)

MS (EI, 70 eV): m/z (%) = 246.1 (96), 244.1 (100) $[M]^+$, 229.1 (68), 227.1 (55) $[M - H_2O]^+$ 166.1 (30) $[M - Br]^+$

$C_9H_9BrO_3$ (245.07); **HRMS**: calcd: 243.9735; confirmed

5.17 (3-Bromo-4-methoxy-5-methylphenyl)-methanol (120)



A magnetically stirred solution of carboxylic acid **119** (60.50 g, 0.25 mol) in THF/Et_2O (1:1, 300 mL) was treated, *via* cannula over 0.5 h with $LiAlH_4$ (70.0 mL of a 2.64M solution in Et_2O, 0.185 mol) at 0 °C. Stirring was continued for a further 0.5 h before the reaction mixture was treated with $MgSO_4$ (51.0 g) and dropwise with water (38 mL). The resulting suspension was filtered and washed thoroughly with Et_2O (6 x 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of the resulting crude oil to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded alcohol **120** (41.60 g, 0.18 mol, 72%) as a pale yellow oil.

R_f = 0.3

IR (KBr): $\tilde{\upsilon}$ = 2931 cm^{-1}, 1736, 1478, 1276, 821

UV (CH_3CN): λ_{max}(lg ε) = 201.5 nm (4.6209), 272.5 (2.8340)

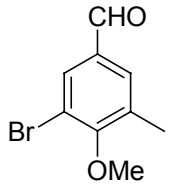
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.55 (s, 2H, 1'-H), 7.07 (d, *J* = 0.8 Hz, 1H, Ar-H), 7.35 (d, *J* = 0.8 Hz, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 16.6 (CH_3), 60.1 (OCH_3), 64.2 (CH_2), 117.2 (Ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 133.2 (Ar-C), 137.9 (Ar-C), 154.6 (Ar-C)

MS (EI, 70 eV): m/z (%) = 232.1 (98), 230.1 (100), $[M]^+$, 215.1 (25), 213.1 (20) [M - OH]$^+$, 153.2 (33), 151.2 (30) [M - Br]$^+$

$C_9H_{11}BrO_2$ (231.09); **HRMS**: calcd: 229.9943; confirmed

5.18 3-Bromo-4-methoxy-5-methylbenzaldehyde (121)



A magnetically stirred solution of alcohol **120** (17.80 g, 0.08 mol) in CH_2Cl_2 (400 mL) was treated in one portion with MnO_2 (67.0 g, 0.80 mol) at 20 °C. Stirring was continued for 12 h before the reaction mixture filtered and washed thoroughly with CH_2Cl_2 (3 x 100 mL). The organic filtrate was concentrated under reduced pressure to give a yellow oil. Subjection of the resulting crude oil to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded the aldehyde **121** (16.10 g, 0.07 mol, 87%) as a yellow oil.

R_f = 0.3

IR (KBr): $\tilde{\upsilon}$ = 1695 cm^{-1}, 1271, 1110, 740

UV (CH_3CN): λ_{max} = 217.0 nm (4.3877), 261 (4.0649)

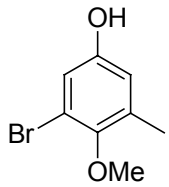
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.61 (d, *J* = 1.8 Hz, 1H, Ar-H), 7.87 (d, *J* = 1.8 Hz, 1H, Ar-H), 9.82 (s, 1H, CHO)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 16.5 (CH_3), 60.2 (OCH_3), 118.1 (Ar-C), 131.5 (Ar-C), 132.6 (Ar-C), 133.2 (Ar-C), 134.1 (Ar-C), 160.4 (Ar-C), 189.8 (CHO)

MS (EI, 70 eV): m/z (%) = 230.1 (100), 228.1 (97) $[M]^+$, 213.1 (8), 215.1 (6) $[M - CH_3]^+$, 187.1 (6), 185.0 (8), $[M - C_2H_3O]^+$, 171.0 (5), 77.1 (44) $[C_6H_5]^+$

$C_9H_9BrO_2$ (229.07); **HRMS**: calcd: 227.9786; confirmed

5.19 3-Bromo-4-methoxy-5-methylphenol (117)



A magnetically stirred solution of aldehyde **121** (2.60 g, 11.40 mmol) in CH_2Cl_2 (100 mL) was treated in one portion with *m*-CPBA (4.10 g of a 70% mixture in water, 17.0

mmol) at 20 °C. Stirring was continued for 12 h before the CH_2Cl_2 was removed under reduced pressure. The ensuing white solid was diluted with MeOH (150 mL), treated with K_2CO_3 (2.30 g, 17.0 mmol) and stirred at 20 °C for 15 min. The resulting mixture was treated with silica gel (3.5 g), concentrated under reduced pressure and subjected to flash chromatography (9:1 pentane/EtOAc). Concentration of the appropriate fractions afforded phenol **117** (1.68 g, 7.70 mmol, 68%) as colourless solid.

R_f = 0.2

m. p.= 114 °C (recrystalised from EtOAc/pentane)

IR (KBr): $\tilde{\upsilon}$ = 2951 cm^{-1}, 1602, 1456, 1418, 1225, 760

UV (CH_3CN): λ_{max} = 199.5 nm (4.6526), 289.0 (3.5079)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 7.61 (d, *J* = 1.2 Hz, 1H, Ar-H), 7.87 (d, *J* = 1.2 Hz, 1H, Ar-H), 9.82 (s, 1H, OH)

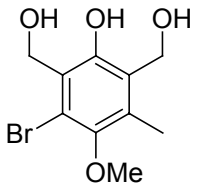
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 16.7 (CH_3), 60.5 (OCH_3), 117.1 (Ar-C), 117.2 (Ar-C), 117.5 (Ar-C), 133.6 (Ar-C), 148.8 (Ar-C), 152.2 (Ar-C)

MS (EI, 70 eV): m/z (%) = 218.0 (90), 216.0 (89) $[M]^+$, 203.0 (95), 201.0 (100) $[M - CH_3]^+$

$C_8H_9BrO_2$ (217.06); **HRMS**: calcd: 215.9786; confirmed

Elemental Analysis calcd (%): C 44.27, H 4.18; found C 44.27, H 3.95

5.20 3-Bromo-2,6-bishydroxymethyl-4-methoxy-5-methylphenol (123)



A magnetically stirred solution of phenol **117** (2.0 g, 9.20 mmol), formaldehyde (1.76 mL, 30% solution in water, 23.40 mmol) in water (7.6 mL) was treated with CaO (258 mg, 4.60 mmol) at 20°C. The resulting mixture was stirred for 0.5 h before being placed unstirred in the dark for 5 days. The resulting suspension was dissolved using warm $CHCl_3$ (50 mL) and acetic acid (10 mL) and then diluted two fold with $CHCl_3$. The organic phase was washed with $NaHCO_3$ (saturated aqueous solution) until the

acetic acid was removed and concentrated under reduced pressure to afford a yellow solid. This crude solid was washed with (4:1 pentane/EtOAc) to afford triol **123** (1.67 g, 6.40 mmol, 69%) as a colourless solid.

R_f = 0.4

m.p. = 132 °C (recrystalised from EtOAc/hexane)

IR (KBr): $\tilde{\upsilon}$ = 3384 cm^{-1}, 3259, 2959, 1453, 1005, 760

UV (CH_3CN): λ_{max} = 205.5 (4.6195) nm

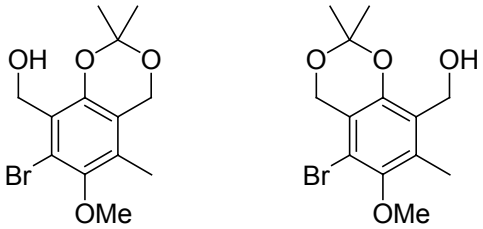
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3H, CH_3), 2.76 (brs, 1H, OH), 2.81 (brs, 1H, OH), 3.68 (s, 3H, OCH_3), 4.77 (s, 2H, CH_2), 4.96 (s, 2H, CH_2), 8.89 (s, 1H, OH);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 12.5 (CH_3), 58.2 (OCH_3), 60.5 (CH_2), 62.9 (CH_2), 109.9 (Ar-C), 117.7 (Ar-C), 124.2 (Ar-C), 126.7 (Ar-C), 131.5 (Ar-C), 153.2 (Ar-C)

MS (EI, 70 eV): m/z (%) = 278.1 (58), 276.1 (60) $[M]^+$, 260.1 (57), 258.1 (59) $[M - H_2O]^+$, 245.1 (100), 243.1 (90) $[M - H_2O - CH_3]^+$, 229.1 (45), 231 (40)

$C_{10}H_{13}BrO_4$ (277.11); **HRMS**: calcd: 275.9997; confirmed

5.21 7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)methanol (124) and 5-Bromo-6-methoxy-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)methanol (125)



A magnetically stirred solution of triol **123** (1.92 g, 7.00 mol) in acetone (100 mL) at 20 °C was treated with a few crystals of *p*-TsOH. The resulting mixture was stirred for 18 h then concentrated under reduced pressure to afford a colourless oil. Subjection of resulting crude oil to flash chromatography (4:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded a mixture of two regioisomeric acetonides **124** and **125** (2.02 g, 6.37 mmol, 91%) as a colourless oil.

R_f = 0.3

IR (KBr): $\tilde{\upsilon}$ = 3448 cm^{-1}, 2992, 1596, 1454, 1143

UV (CH_3CN): λ_{max} = 206.0 nm (4.5667), 293.0 (3.9987)

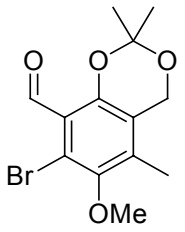
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 12H, CH_3), 2.08 (s, 6H, CH_3), 3.70 (s, 6H, OCH_3), 4.63 (s, 1H, CH_2OH), 4.65 (s, 1H, CH_2OH), 4.67 (s, 1H, CH_2OR), 4.79 (s, 1H, CH_2OR)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.3 (CH_3), 12.3 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 59.7 (CH_3), 59.8 (CH_3), 60.5 (OCH_3), 60.6 (OCH_3), 61.9 (2 x CH_2), 76.4 (2 x CH_2), 99.5 (C), 99.7 (C), 114.3 (Ar-C), 117.4 (Ar-C), 118.2 (Ar-C), 118.3 (Ar-C), 126.5 (Ar-C), 127.1 (Ar-C), 127.8 (Ar-C), 130.9 (Ar-C), 146.3 (Ar-C), 146.5 (Ar-C), 148.5 (Ar-C), 148.8 (Ar-C)

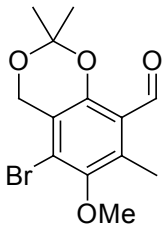
MS (EI, 70 eV): m/z (%) = 317.1 (50), 315.1 (48) $[M]^+$, 259.0 (96), 257.0 (100) $[M - C_3H_6O]^+$, 244.0 (30), 242.0 (34) $[M - C_3H_6O – CH_3]^+$

$C_{13}H_{13}BrO_4$ (317.18); **HRMS**: calcd: 316.0310; confirmed

5.22 7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-carbaldehyde (126) and 5-Bromo-6-methoxy-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-8-carbaldehyde (127)



127



126

A solution of oxalyl chloride (436 µL, 5.06 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added *via* cannula over 0.5 h to a magnetically stirred solution of DMSO (719 µL, 0.01 mol) in CH_2Cl_2 (20 mL) also maintained at –78 °C. The resulting clear solution was treated dropwise with a mixture of **124** and **125** (1.0 g, 3.16 mmol in 6 mL of CH_2Cl_2) from the above reaction and stirred at –78 °C for 1.5 h then treated dropwise with NEt_3 (1.9 mL). The solution was stirred at this temperature for 5 min before being warmed to 20 °C and stirred for a further 30 min. The ensuing solution was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic

fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale oil. Subjection of the crude oil to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded aldehydes **126** (420 mg, 1.33 mmol, 42%) as a colourless solid and **127** (410 mg, 1.30 mmol, 41%) as a colourless solid.

Aldehyde **127**:

R_f = 0.3

m.p. = 122 °C (recrystallised from pentane/EtOAc)

IR (KBr): $\tilde{\upsilon}$ = 2986 cm^{-1}, 1697, 1580, 1396, 1005

UV (CH_3CN): λ_{max} = 195.5 nm (4.3540), 268.5 (3.8656), 334.0 (0.1779)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.55 (s, 6H, 2 x CH_3), 2.17 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.71 (s, 2H, CH_2), 10.32 (s, 1H, CHO)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 12.1 (CH_3), 24.6 (2 x CH_3), 59.7 (CH_2), 60.7 (OCH_3), 100.1 (Ar-C), 117.3 (Ar-C), 118.9 (Ar-C), 121.4 (Ar-C), 134.4(Ar-C) , 149.1 (Ar-C), 150.7 (Ar-C), 189.4 (CHO)

MS (EI, 70 eV): m/z (%) = 316.1 (45), 314.1 (44) $[M]^+$, 258.0 (98), 256.0 (100) $[M - C_3H_6O]^+$, 243.0 (45), 241.0 (40) $[M - C_3H_6O – CH_3]^+$

$C_{13}H_{15}BrO_4$ (315.16); **HRMS**: calcd: 314.0154; confirmed

Elemental Analysis calcd (%): C 49.54, H 4.80; found C 49.68, H 4.62

Aldehyde **126**

R_f = 0.5 (19:1 pentane/EtOAc)

m.p. = 107 °C (recrystallised from pentane/EtOAc)

IR (KBr): $\tilde{\upsilon}$ = 2996 cm^{-1}, 2938, 1685, 1563, 1451, 839

UV (CH_3CN): λ_{max} = 220.0 nm (4.4725), 332.0 (4.3181)

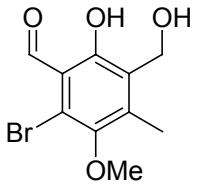
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 6H, 2 x CH_3), 2.53 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2), 10.49 (s, 1H, CHO)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 13.6 (CH_3), 24.5 (2 x CH_3), 60.6 (CH_2), 61.9 (OCH_3), 100.4 (Ar-C), 118.2 (Ar-C), 121.7 (Ar-C), 122.4 (Ar-C), 133.7 (Ar-C), 148.9 (Ar-C), 151.9 (Ar-C), 191.1 (CHO)

MS (EI, 70 eV): m/z (%) = = 316.1 (45), 314.1 (44) $[M]^+$, 258.0 (98), 256.0 (100) $[M - C_3H_6O]^+$, 243.0 (45), 241.0 (40) $[M - C_3H_6O – CH_3]^+$

$C_{13}H_{15}BrO_4$ (315.16); **HRMS**: calcd: 314.0154; confirmed

5.22 2-Bromo-6-hydroxy-5-hydroxymethyl-3-methoxy-4-methyl-benzaldehyde (128a)



A magnetically stirred solution of aldehyde **126** (100 mg, 0.32 mmol) in MeOH/dioxane 1:1 (2.5 mL) was treated in one portion with cerric ammonium nitrate (351 mg, 0.64 mmol in MeOH/dioxane 2.5 mL) at 0 °C. Stirring was continued at this temperature for 5 min before the mixture was diluted with ether (80 mL) and washed with water (1 x 10 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (1:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded phenol **128a** (21 mg, 76.3 μmol, 24%) as a white foam.

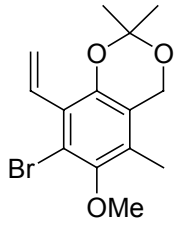
R_f = 0.5

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3H, CH_3), 3.72 (s, 6H, 2 x OCH_3), 4.77 (s, 2H, CH_2), 10.27 (s, 1H, CHO), 12.41 (s, 1H, OH)

MS (EI, 70 eV): m/z (%) = 276.1 (60), 274.1 (58) $[M]^+$, 258.0 (100), 256.0 (98) $[M - H_2O]^+$.

$C_{10}H_{11}BrO_4$ (275.11); **HRMS**: calcd: 273.9841; confirmed

5.23 7-Bromo-6-methoxy-2,2,5-trimethyl-8-vinyl-4*H*-benzo[1,3]dioxine (85)



A solution of Ph_3PCH_3Br (1.38 g, 3.87 mmol) in THF (50 mL) was treated with sodium bis(trimethylsilyl) amide (3.87 mL of 1M solution in THF, 3.87 mmol) and stirred for 1 h at 20 °C. The reaction mixture was then treated with a solution of aldehyde **127** (813 mg, 2.58 mmol) in THF (30 mL) and stirred for 1 h, before silica gel was added and the suspension concentrated under reduced pressure. Subjection of the resulting yellow solid to the flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded styrene **85** (821 mg, 2.62 mmol, 92 %) as a colourless solid.

R_f = 0.8 (19:1 pentane/EtOAc)

m.p. = 94 °C (recrystallised from pentane/EtOAc)

IR (KBr): $\tilde{\upsilon}$ = 2996 cm^{-1}, 2938, 1629, 1283, 1045, 883

UV (CH_3CN): λ_{max} = 220.0 nm (4.4725), 332.0 (4.3181)

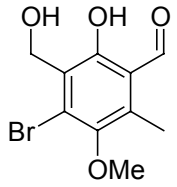
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56 (s, 6H, 2 x CH_3), 2.53 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.74 (s, 2H, CH_2OR), 5.42 (d, *J* = 11.0 Hz, 1H, 2'-H), 5.53 (d, *J* = 17.3 Hz, 1H, 2'-H), 7.11 (dd, *J* = 17.3, 11.0 Hz, 1H, 1'-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 13.6 (CH_3), 24.5 (CH_3), 60.6 (CH_2), 61.9 (OCH_3), 100.4 (Ar-C), 116.8 (CH_2), 118.2 (Ar-C), 121.7 (Ar-C), 122.4 (Ar-C), 133.7(Ar-C) , 141.7 (CH), 148.9 (Ar-C), 151.9 (Ar-C)

MS (EI, 70 eV): m/z (%) = 314.0 (10), 312.0 (9) $[M]^+$, 256.0 (50), 254.0 (48) $[M - C_3H_6O]^+$

$C_{14}H_{17}BrO_3$ (313.19); **HRMS**: calcd: 312.0361; confirmed

5.24 4-Bromo-2-hydroxy-3-hydroxymethyl-5-methoxy-6-methyl-benzaldehyde (128)



A magnetically stirred solution of aldehyde **126** (1.40 g, 4.44 mmol) in acetic acid (60 mL of 40% solution) was heated to 60 °C for 4 h. The resulting mixture was cooled to 20 °C, diluted with Et_2O (200 mL), washed with $NaHCO_3$ (5 x 30 mL saturated solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure and to afford a yellow solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of appropriate fractions afforded phenol **128** (803 mg, 2.92 mmol, 66%) as a colourless solid.

m.p. = 131 °C (recrystallised from hexane/EtOAc)

R_f = 0.4

UV/VIS (CH_3CN): λ_{max} (lg ε) = 194.5 nm (4.2829), 277.0 (4.1471), 355.5 (3.6208)

IR (KBr): $\tilde{\nu}$ = 1646 cm^{-1}, 1404, 1280, 1026, 787

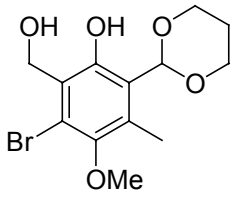
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.22 (s, 1H, OH), 2.59 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.95 (s, 2H, CH_2OH), 10.34 (s, 1H, CHO)

^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 11.2 (CH_3), 59.9 (CH_2), 60.4 (OCH_3), 117.6 (Ar-C), 128.1 (Ar-C), 130.9 (Ar-C), 134.5 (Ar-C), 158.2 (Ar-C), 195.2 (CHO)

MS (EI, 70 eV): m/z (%) = 276.1 (60), 274.1 (58) $[M]^+$, 258.0 (100), 256.0 (98) $[M - H_2O]^+$

$C_{10}H_{11}BrO_4$ (275.11); **HRMS**: calcd: 273.9841; confirmed

5.25 3-Bromo-6-[1,3]dioxan-2-yl-2-hydroxymethyl-4-methoxy-5-methyl-phenyl (129)



A magnetically stirred solution of phenol **128** (800 mg, 2.90 mmol) and 1,3-propandiol (634 µL, 8.76 mmol) in benzene (80 mL) was treated in one portion with Amberlyst 15™ (cat.) at 20 °C. The resulting mixture was heated to reflux for 5 h using a Dean-Stark apparatus. After cooling, the mixture was diluted with benzene (60 mL), washed with H_2O (4 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting white solid was recrystallised (EtOAc/hexane) to afford acetal **129** (955 mg, 2.86 mmol, 98%) as colourless solid.

m.p. = 128 °C (recrystallised from hexane/EtOAc)

R_f = 0.2 (9:1 pentane/EtOAc)

UV/VIS (CH_3CN): λ_{max} (lg ε) = 204.5 nm (4.5580), 286.0 (3.1993)

IR (KBr): $\tilde{\nu}$ = 3528 cm^{-1}, 2873, 1449, 1361, 1118, 988

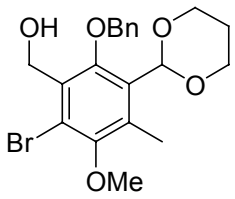
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.18 – 1.48 (m, 1H, 5-H), 2.16 – 2.27 (m, 1H, 5-H), 2.84 (brs, 1H, OH), 2.22 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 3.84 – 3.97 (m, 2H, 4-H/5-H), 4.19 – 4.27 (m, 1H, 2-H), 5.93 (s, 1H, 2-H), 9.01 (s, 1H, OH)

^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 13.7 (CH_3), 25.7 (CH_2), 60.4 (CH_3O), 67.7 (CH_2), 98.8 (CH), 122.5 (Ar-C), 127.6 (Ar-C), 128.2 (Ar-C), 128.6 (Ar-C), 134.7 (Ar-C), 136.9 (Ar-C), 152.9 (Ar-C)

MS (EI, 70 eV): m/z (%) = 333.1 (5) $[M]^+$, 316.1 (20) $[M - CH_3]^+$, 91.1 (100)

$C_{13}H_{17}BrO_5$ (333.18); **HRMS**: calcd: 333.1751; confirmed

5.26 (2-Benzyloxy-6-bromo-3-[1,3]dioxan-2-yl-5-methoxy-4-methyl-phenyl)-methanol (130)



A magnetically stirred solution of acetal **129** (1.10 g, 3.30 mmol) in $CHCl_3$/MeOH (30/15 mL) and K_2CO_3 (1.83 g, 13.20 mmol) was heated to 40 °C over 10 min. The resulting mixture was then treated in one portion with benzylbromide (470 μL, 3.96 mmol) and stirred at 40 °C for a further 12 h. After cooling to 20 °C, the mixture was diluted with CH_2Cl_2 (60 mL), washed with H_2O (2 x 10 mL), dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The resulting white solid was recrystallised (EtOAc/hexane) to afford alcohol **130** (1.12 g, 2.64 mmol, 80%) as white solid.

m.p. = 148 °C (recrystallised from hexane/EtOAc)

$\mathbf{R_f}$ = 0.4 (9:1 pentane/EtOAc)

UV/VIS (CH_3CN): λ_{max} (lg ε) = 205.0 nm (4.7277), 286.8 (3.3296)

IR (KBr): $\tilde{\nu}$ = 3489 cm^{-1}, 2852, 1448, 1365, 1005, 698

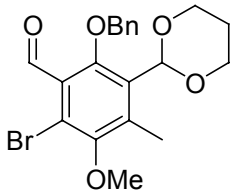
^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.20 – 1.24 (m, 1H, 5-H), 2.16 – 2.27 (m, 1H, 5-H), 2.25 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 3.89 – 4.17 (m, 2H, 4-H/5-H), 4.19 – 4.27 (m, 1H, 2-H), 4.81 (s, 2H, CH_2OH), 4.97 (s, 2H, CH_2OPh), 5.93 (s, 1H, 2-H), 7.41 – 7.55 (m, 5H, Ph)

^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 13.7 (CH_3), 25.8 (CH_3), 60.2 (OCH_3), 60.5 (CH_2), 67.8 (CH_2), 79.1 (CH_2), 98.8 (CH), 121.3 (Ar-C), 127.7 (Ar-C), 128.0 (Ar-C), 128.4 (Ar-C), 128.5(Ar-C), 128.7 (Ar-C), 130.6 (Ar-C), 132.6 (Ar-C), 134.4 (Ar-C), 136.6 (Ar-C), 152.4(Ar-C), 153.0 (Ar-C)

MS (EI, 70 eV): m/z (%) = 424.1 (24), 422.1 (25) $[M]^+$, 394.1 (5), 392.1 (7) $[M - CH_3OH]^+$, 318.1 (57), 316.1 (40) $[M - HOCH_2Ph]^+$

$C_{20}H_{23}BrO_5$ (423.30); **HRMS**: calcd: 422.0729; confirmed

5.27 2-Benzyloxy-6-bromo-3-[1,3]dioxan-2-yl-5-methoxy-4-methyl-benzaldehyde (131)



A magnetically stirred solution of alcohol **129** (625 mg, 1.48 mmol) in CH_2Cl_2 (60 mL) at 20 °C was treated in one portion with *Dess-Martin* periodinane (941 mg, 2.22 mmol). The resulting mixture was stirred for 1.5 h before being treated with $NaHCO_3$ (1 x 25 mL of a saturated solution) and $Na_2S_2O_3$ (1 x 25 mL of a 1M solution). Stirring was continued until the cloudy solution became clear (*ca.* 1 h). The resulting mixture was transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were subjected to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded benzaldehyde **131** (101 mg, 0.225 mmol, 81%) as a white solid.

m.p. = 123 °C (recrystallised from hexane/EtOAc)

R_f = 0.7

UV/VIS (CH_3CN): λ_{max} (lg ε) = 209.0 nm (4.4501), 264.0 (3.8917)

IR (KBr): $\tilde{\nu}$ = 2947 cm^{-1}, 2846, 1703, 1573, 1447, 1357, 994

^{1}H-NMR (200 MHz, $CDCl_3$) δ = 1.18 – 1.34 (m, 1H, 5-H), 2.16 – 2.27 (m, 1H, 5-H), 2.57 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.66 – 3.78 (m, 2H, 4-H/5-H), 4.09 – 4.17 (m, 1H, 2-H), 4.85 (s, 2H, CH_2OPh), 5.93 (s, 1H, 2-H), 7.31 – 7.45 (m, 5H, Ph), 10.24 (s, 1H, CHO)

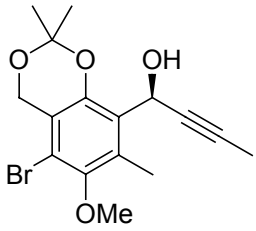
^{13}C-NMR (50.3 MHz, $CDCl_3$): δ = 14.4 (CH_3), 25.7 (CH_3), 60.3 (CH_2), 67.8 (CH_2), 79.8 (CH_2), 98.0 (CH), (Ar-C), 109.3 (Ar-C), 121.1 (Ar-C), 126.8 (Ar-C), 130.2 (Ar-C), 131.7 (Ar-C), 132.5 (Ar-C), 136.1 (Ar-C), 140.9 (Ar-C), 153.4 (Ar-C), 154.8 (Ar-C), 190.3 (CHO)

MS (EI, 70 eV): m/z (%) = 422.0 (10), 420.0 (9) $[M]^+$, 394.1 (5), 392.1 (7) $[M - CH_3OH]^+$, 316.1 (57), 314.1 (40) $[M - HOCH_2Ph]^+$

$C_{20}H_{21}BrO_5$ (421.28); **HRMS**: calcd: 420.0572; confirmed

6 Side Chain Development

6.1 5-Bromo-8-(1-*R*,*S*-hydroxy-but-2-ynyl)-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (132)



rac

A magnetically stirred solution of aldehyde **126** (40 mg, 127 μmol) in THF (1 mL) was treated dropwise with 1-propynylmagnesium bromide (255 μL, 127.5 μmol of 0.5 M solution in THF) at 0 °C. Stirring was continued for 20 min at 20 °C before the mixture was diluted with ether (30 mL) and washed with water (1 x 1 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **132** (41 mg, 116 μmol, 91%) as a colourless oil.

R_f = 0.2

IR (KBr): $\tilde{\nu}$ = 3452 cm^{-1}, 2838, 1457, 1280, 1006, 845

UV (CH_3CN): λ_{max} = 206.5 nm (4.5897), 293.0 (3.5241)

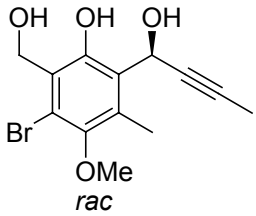
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.2 Hz, 6H, CH_3), 1.75 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.50 (d, *J* = 12.0 Hz, 1H, 1-H), 3.78 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2OR), 5.56 (d, *J* = 1.2 Hz, 1-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 3.7 (CH_3), 12.2 (CH_3), 23.5 (CH_3), 23.6 (CH_3), 59.2 (CH), 59.3 (OCH_3), 60.6 (CH_2), 78.7 (C), 80.8 (C), 100.4 (C), 114.5 (Ar-C), 116.4 (Ar-C), 117.9 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C),147.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 356.2 (60), 354.2 (58) $[M]^+$, 298.1 (90), 296.1 (91) $[M - C_3H_6O]^+$, 283.0 (94), 281.0 (100) $[M - C_3H_6O - CH_3]^+$

$C_{16}H_{19}BrO_4$ (355.22); **HRMS**: calcd: 354.0467; confirmed

6.2 3-Bromo-6-(1-*R*,*S*-hydroxy-but-2-ynyl)-2-hydroxymethyl-4-methoxy-5-methyl-phenol (137)



rac

A magnetically stirred solution of aldehyde **126** (329 mg, 1.21 mmol) in THF (30 mL) was treated dropwise with 1-propynylmagnesium bromide (8.4 mL, 4.22 mmol of 0.5 M solution in THF) at 0 °C. Stirring was continued for 30 min at 20 °C before the mixture was diluted with ether (100 mL) and washed with water (1 x 15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (1:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **137** (326 mg, 1.04 mmol, 86%) as a yellow oil.

R_f = 0.5

IR (KBr): $\tilde{\nu}$ = 3354 cm^{-1}, 2961, 2281, 1591, 1405, 998

UV (CH_3CN): λ_{max} = 207.0 nm (4.5492), 296.0 (3.5321)

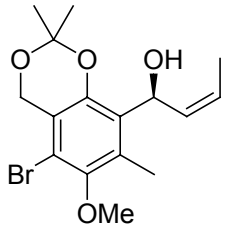
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.1 Hz, 6H, CH_3), 1.75 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.52 (d, J = 13.2 Hz, 1H, OH), 3.76 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2OR), 5.56 (d, *J* = 8.3 Hz, 1-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 3.8 (CH_3), 12.4 (CH_3), 60.6 (OCH_3), 61.2 (CH_2), 62.4 (CH_2), 76.4 (C), 82.5 (C), 118.3 (Ar-C), 124.4 (Ar-C), 124.8 (Ar-C), 129.4 (Ar-C), 147.9 (Ar-C), 151.5 (Ar-C)

MS (EI, 70 eV): m/z (%) = 316.0 (10), 314.0 (11) $[M]^+$, 298.1 (50), 296.1 (54) $[M - H_20]^+$, 283.0 (14), 281.0 (15) $[M - CH_3OH]^+$

$C_{13}H_{14}BrO_4$ (314.22); **HRMS**: calcd: 314.0154; confirmed

6.3 5-Bromo-8-(1-*R*,*S*-hydroxy-but-2-enyl)-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (133)



rac

A magnetically stirred solution of alcohol **132** (110 mg, 0.31 mmol) in MeOH (5 mL) was treated with Lindlar's catalyst (10 mg) at 20 °C and placed under an atmosphere hydrogen. Stirring was continued for 24 h at 20 °C before the mixture was filtered through a plug of silica gel and the filtrate concentrated under reduced pressure to afford a colourless oil. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **133** (106 mg, 0.28 mmol, 96%) as a colourless oil.

R_f = 0.2

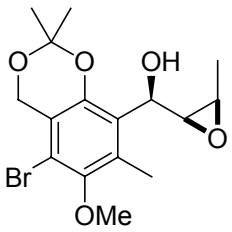
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.51 (d, *J* = 7.5 Hz, 6H, CH_3), 1.75 (dd, *J* = 5.0, 0.8 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.48 (d, *J* = 12.4 Hz, 1H, OH), 3.71 (s, 3H, OCH_3), 4.68 (s, 2H, CH_2OR), 5.50-5.81 (m, 3H, 1-H/2-H/3-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.1 (CH_3), 17.7 (CH_3), 23.5 (CH_3), 23.6 (CH_3), 56.0 (OCH_3), 59.3 (CH_2), 71.6 (CH), 99.5 (C), 105.1 (C), 116.8 (Ar-C), 123.7 (Ar-C), 126.2 (CH), 130.2 (CH), 132.3 (Ar-C), 142.6 (Ar-C), 151.8 (Ar-C)

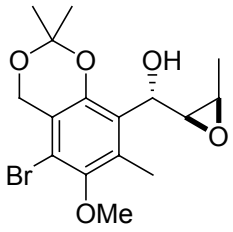
MS (EI, 70 eV): m/z (%) = 358.1 (5), 356.1 (7) $[M]^+$, 300.0 (35), 298.0 (30) $[M - C_3H_6O]^+$, 219.1 (100)

$C_{16}H_{21}BrO_4$ (357.24)

6.4 5-Bromo-8-[1-*R*-hydroxy-(3-methyl-2,3-*R*,*S*-oxiranyl)-methyl]-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (134a), 5-Bromo-8-[1-*R*-hydroxy-(3-methyl-*2,3-S,R*-oxiranyl)-methyl]-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (134b), 5-Bromo-8-[1-*S*-hydroxy-(3-methyl-*2,3-S,R*-oxiranyl)-methyl]-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (134x) and 5-Bromo-8-[1-*S*-hydroxy-(3-methyl-*2,3-R,S*-oxiranyl)-methyl]-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-6-ol (134y)



rac



rac

Procedure I

A magnetically stirred solution of alcohol **133** (60 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) was treated in one portion with *m*-CPBA (62 mg of a 70% mixture in water, 0.25 mmol) at 20 °C. Stirring was continued for 12 h before being diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$ (1 x 3 mL of sat. solution), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude white solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded epoxides **134ab** and **134xy** (36 mg, 0.097 mmol, 57%); R_f = 0.2 and epoxides **xx** and **xx** (12 mg, 0.032 mmol, 19%); R_f = 0.25 both as white solids.

Procedure II

A magnetically stirred solution of alcohol **133** (13 mg, 36.0 μmol), *tert*-butyl-hydroperoxide (8.5 μL of a 5.5 M solution in decane, 46.8 μmol) in CH_2Cl_2 (300 μL) was treated with Vanadyl(IV)-acetylacetonate (cat.) at 20 °C. Stirring was continued for 3 h before being diluted with Na_2SO_3 (300 μL of sat. solution) and stirred for another 1 h. The resulting mixture was extracted with CH_2Cl_2 (2 x 2 mL), dried

($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude white solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded epoxides **134ab** and **134xy** (8.6 mg, 23.0 μmol, 64%); R_f = 0.2 as a white solids.

Epoxides **134a** and **b**

IR (KBr): $\tilde{\nu}$ = 3418 cm^{-1}, 2936, 1452, 1280, 1006, 837

UV (CH_3CN): λ_{max} = 205.5 nm (4.6136), 293.5 (3.5429)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 5.6 Hz, 3H, CH_3), 1.55 (d, *J* = 3.8 Hz, 6H, CH_3), 2.39 (s, 3H, CH_3), 3.12 (q, *J* = 4.4 Hz, 1H, 3-H), 3.48 (dd, *J* = 11.6, 4.4 Hz, 1H, 2-H), 3.74 (s, 3H, OCH_3), 4.72 (s, 2H, CH_2OR), 4.82 (d, *J* = 7.6 Hz, 1H, 1-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 13.2 (CH_3), 14.2 (CH_2), 24.1, (CH_3), 25.0 (CH_3), 53.8 (OCH_3), 59.1 (CH), 59.6 (CH), 60.5 (CH_2), 62.0 (CH), 100.0 (C), 114.9 (Ar-C), 117.9 (Ar-C), 126.8 (Ar-C), 130.5 (Ar-C), 146.3 (Ar-C), 149.3 (Ar-C)

MS (EI, 70 eV): m/z (%) = 374.0 (40), 372.0 (42) $[M]^+$, 316.0 (56), 314.0 (60) $[M - C_3H_6O]^+$, 261.0 (100), 259.0 (98)

$C_{16}H_{21}BrO_5$ (373.24); **HRMS**: calcd: 372.0572; confirmed

Epoxides **134x** and **y** :

IR (KBr): $\tilde{\nu}$ = 3421 cm^{-1}, 2922, 1462, 1280, 1006, 831

UV (CH_3CN): λ_{max} = 204.5 nm (4.5925), 292.5 (3.5631)

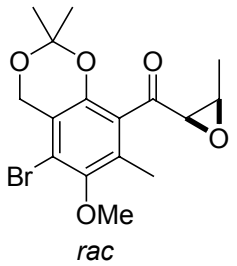
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, *J* = 4.8 Hz, 3H, CH_3), 1.60 (d, *J* = 4.8 Hz, 6H, CH_3), 2.30 (s, 3H, CH_3), 3.20 (q, *J* = 5.4 Hz, 1H, 3-H), 3.32 (dd, *J* = 12.6, 4.0 Hz, 1H, 2-H), 3.73 (s, 3H, OCH_3), 3.90 (d, *J* = 11.4, 1H, OH), 4.65 (dd, *J* = 19.8, 8.4 Hz, 1H, 1-H), 4.75 (s, 2H, CH_2OR)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 13.4 (CH_3), 14.0 (CH_2), 24.9, (CH_3), 25.1 (CH_3), 53.9 (OCH_3), 59.0 (CH), 59.8 (CH), 60.7 (CH_2), 62.7 (CH), 99.9 (C), 115.0 (Ar-C), 117.8 (Ar-C), 126.5 (Ar-C), 130.4 (Ar-C), 146.2 (Ar-C), 149.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 374.0 (40), 372.0 (42) $[M]^+$, 316.0 (56), 314.0 (60) $[M - C_3H_6O]^+$, 261.0 (100), 259.0 (98)

$C_{16}H_{21}BrO_5$ (373.24)

6.5 (5-Bromo-6-hydroxy-2,2,7-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-(3-methyl-2,3-*R,S* oxiranyl]-methanone (135)



rac

A magnetically stirred solution of alcohol **134ab** (12 mg, 32.3 μmol) in CH_2Cl_2 (2 mL) at 20 °C was treated in one portion with *Dess-Martin* periodinane (27 mg, 64.6 μmol). The resulting mixture was stirred for 1.5 h before being treated with $NaHCO_3$ (1 x 1 mL of a saturated solution) and $Na_2S_2O_3$ (1 x 1 mL of a 1M solution). Stirring was continued until the cloudy solution became clear (*ca.* 1 h). The resulting mixture was transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were subjected to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded ketone **135** (11 mg, 29.4 μmol, 91%) as a white solid.

R_f = 0.5

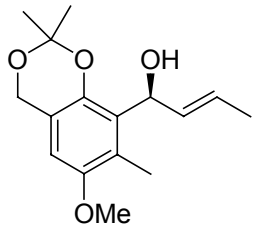
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.58 (d, *J* = 4.7 Hz, 3H, CH_3), 1.71 (d, *J* = 4.7 Hz, 6H, CH_3), 2.39 (s, 3H, CH_3), 3.45 (q, *J* = 4.5 Hz, 1H, 3-H), 3.98 (s, 3H, OCH_3), 3.99 (dd, *J* = 4.5, 1.1 Hz, 1H, 2-H), 4.75 (s, 2H, CH_2OR)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 12.9 (CH_3), 13.2 (CH_3), 24.3 (CH_3), 24.7 (CH_3), 56.0 (CH), 59.9 (CH), 60.5 (CH_3O), 61.9 (CH_2), 100.3 (C), 118.0 (Ar-C), 118.1 (Ar-C), 127.3 (Ar-C), 131.0 (Ar-C), 146.7 (Ar-C), 149.4 (Ar-C), 198.9 (CO)

MS (EI, 70 eV): m/z (%) = 372.1 (30), 370.1 (29) $[M]^+$, 314.0 (44), 312.0 (48) $[M - C_3H_6O]^+$, 259.0 (100), 257.0 (98)

$C_{16}H_{19}BrO_5$ (371.22); **HRMS**: calcd: 370.0416; confirmed

6.6 8-(1-*R*,*S*-Hydroxy-but-2-enyl)-2,2,7-trimethyl-4H-benzo[1,3]dioxin-6-ol (136)



rac

A magnetically stirred solution of alcohol **132** (108 mg, 0.32 mmol) in THF (5 mL) was treated with sodium bis-(2-methoxy-ethoxy)-aluminium-hydride (362 µL, 1.26 mmol of 3.5 M solution in toluene) at 0 °C. Stirring was continued for 24 h at 66 °C. The ensuing mixture was cooled to 0 °C and quenched with H_2O (0.5 mL). The reaction mixture was diluted with ether (20 mL) and washed with water (1 x 2 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **136** (189 mg, 0.68 mmol, 56%) as a yellow oil.

R_f = 0.5

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 5 Hz, 3H, CH_3), 1.55 (d, *J* = 5 Hz, 3H, CH_3), 2.15 (s, 3H, CH_3), 4.76 (s, 3H, OCH_3), 4.01 (d, *J* = 12 Hz, 1H, OH), 4.81 (s, 2H, CH_2OR), 5.21-5.30 (m, 1H, 1-H), 5.52-5.82 (m, 2H, 2-H/3-H), 6.39 (s, 1H, Ar-H)

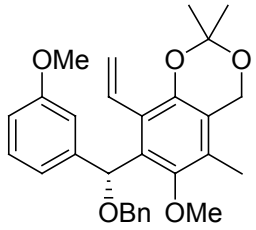
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.1 (CH_3), 17.7 (CH_3), 23.5 (CH_3), 23.6 (CH_3), 56.0 (OCH_3), 59.3 (CH_2), 71.6 (CH), 99.5 (C), 105.1 (C), 116.8 (Ar-C), 123.7 (Ar-C), 126.2 (CH), 130.2 (CH), 132.3 (Ar-C), 142.6 (Ar-C), 151.8 (Ar-C)

MS (EI, 70 eV): m/z (%) = 278.3 (20) $[M]^+$, 220.3 (92) $[M - C_3H_6O]^+$, 205.2 (100) $[M - C_3H_6O - CH_3]^+$, 191.2 (60)

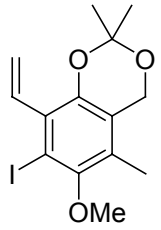
$C_{16}H_{22}O_4$ (278.34)

7 Coupling of A- and C-Building Blocks

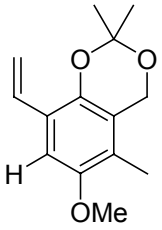
7.1 (7*RS*)-[Benzyloxy-(3-methoxy-phenyl)-methyl]-6-methoxy-2,2,5-trimethyl-8-vinyl-4*H*-benzo[1,3]dioxine (144), 7-Iodo-6-methoxy-2,2,5-trimethyl-8-vinyl-4*H*-benzo[1,3]dioxine (145) and 6-Methoxy-2,2,5-trimethyl-8-vinyl-4*H*-benzo[1,3]dioxine (146)



rac-**144**



145



146

A magnetically stirred solution of bromobenzene **85** (122 mg, 0.39 mmol) in Et_2O (1 mL) at -78 °C was treated dropwise with *t*BuLi (575 μL, 1.7M solution in hexane, 0.98 mmol). The resulting mixture was stirred at this temperature for 1 min before being added *via* cannula to a cooled (-78 °C) solution of benzaldehyde **96** (112 mg, 0.43 mmol) in Et_2O (1 mL). Stirring was continued at this temperature for 5 min then the solution was warmed to 20 °C and stirred for 0.5 h. The resulting mixture was quenched with NH_4Cl (1 mL of a saturated aqueous solution), extracted with ether (3 x 20 mL) and washed with brine (1 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford crude colourless oil alcohol xx (220 mg). A magnetically stirred solution of the afformentioned crude alcohol **143** in THF (5 mL) was treated with NaH (27 mg, 60% in oil, 0.88 mmol) and benzyl bromide (95 μL, 0.8 mmol) at 20 °C. The resulting mixture was then warmed to 40 °C and stirring was continued for 12 h. The ensuing cloudy solution was diluted with Et_2O (40 mL), washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale oil. Subjection of this material to flash chromatography (19:1 pentane/EtOAc → 9:1 pentane/EtOAc) and concentration of appropriate fractions afforded benzyl ether **144** (41 mg, 89.7 μmol, 23%) as white

foam; R_f = 0.3 (9:1 pentane/EtOAc), iodobenzene **145** (51 mg, 14.0 µmol, 36%) as yellow solid; R_f = 0.7 (9:1 pentane/EtOAc) and dehalogenated styrene **146** (10 mg, 42.9 µmol, 11%) as pale oil; R_f = 0.8 (9:1 pentane/EtOAc).

Benzyl ether **144**:

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.50 (s, 6H, 2 x CH_3), 3.64 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.41 (d, *J* = 18 Hz, 1H, CH_2Ph), 4.65 (d, *J* = 18.0 Hz, 1H, CH_2Ph), 5.38 (d, *J* = 11.0 Hz, 1H, 2'-H), 5.62 (d, *J* = 17.3 Hz, 1H, 2'-H), 6.21 (s, 1H, CHOBn), 6.41 (s, 1H, Ar-H), 6.78 (d, *J* = 12.0 Hz, 1H, 1'-H), 6.99-7.41 (m, 8H, Ar-H)

MS (EI, 70 eV): m/z (%) = 460.4 (14) $[M]^+$, 402.4 (16) $[M - C_3H_6O]^+$, 294.2 (90)

$C_{29}H_{32}O_5$ (460.56)

Iodobenzene **145**:

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 6H, 2 x CH_3), 2.12 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.73 (s, 2H, CH_2OR), 5.51 (d, *J* = 11.0 Hz, 1H, 2'-H), 5.92 (d, *J* = 17.3 Hz, 1H, 2'-H), 6.74 (dd, *J* = 17.3, 11.0 Hz, 1H, 1'-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.8 (CH_3), 24.6 (CH_3), 60.1 (CH_2), 60.5 (OCH_3), 99.0 (CH), 117.9 (CH_2), 119.2 (Ar-C), 120.9 (Ar-C), 124.3 (Ar-C), 126.5 (Ar-C), 131.6 (Ar-C) , 145.6 (Ar-C), 148.6 (Ar-C), 151.1 (Ar-C)

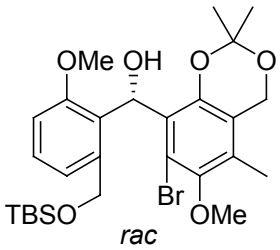
MS (EI, 70 eV): m/z (%) = 360.1 (10) $[M]^+$, 302.1 (70) $[M - C_3H_6O]^+$, 175.1 (100)

$C_{14}H_{17}IO_3$ (360.19)

Styrene **146**:

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.52 (s, 6H, 2 x CH_3), 1.98 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.75 (s, 2H, CH_2OR), 5.17 (d, *J* = 11.2 Hz, 1H, 2'-H), 5.52 (d, *J* = 16.7 Hz, 1H, 2'-H), 6.81 (s, 1H, Ar-H), 6.96 (dd, *J* = 16.9, 11.0 Hz, 1H, 1'-H)

7.2 (1'*RS*)-(7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-[2'-(*tert*-butyl-dimethyl-silanyloxymethyl)-6'-methoxy-phenyl]-methanol (148)



A magnetically stirred solution of iodobenzene **98** (173 mg, 0.47 mmol) in THF (1 mL) at -78 °C was treated dropwise with *n*BuLi (188 µL, 2.5M solution in hexane, 0.49 mmol). The resulting mixture was stirred at this temperature for 10 min before being treated dropwise with aldehyde **127** (147 mg, 0.47 mmol) in THF (1 mL). Stirring was continued at this temperature for 25 min then the solution was warmed to 20 °C and immediately quenched with NH_4Cl (1 mL of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 20 mL) and washed with brine (1 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear yellow oil. Subjection of the resulting crude oil to flash chromatography (19:1 pentane/EtOAc → 9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **148** (138 mg, 0.24 mmol, 52%) as a colourless oil.

R_f = 0.7 (9:1 pentane/EtOAc)

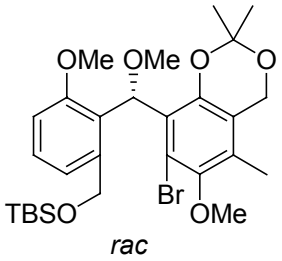
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.01 (d, *J* = 8.5 Hz, 6H, $Si(CH_3)_2$), 0.71 (s, 3H, CH_3), 0.82 (s, 9H, Si(*t*Bu)), 1.59 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.51-4.4.78 (m, 4H, CH_2), 5.42 (d, *J* = 11.4 Hz, 1H, OH), 6.41 (d, *J* = 13.2 Hz, 1H, CH), 6.70 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.09 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.20 (d, *J* = 4.8, 1H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.2 (CH_3), 18.3 (CH_3), 21.9 (CH_3), 25.3 (CH_3), 25.9 (3 x CH_3), 55.9 (OCH_3), 60.0 (CH_2), 60.5 (OCH_3), 63.6 (CH_2), 72.5 (CH), 98.4 (C), 110.5 (Ar-C), 118.6 (Ar-C), 119.5 (Ar-C), 126.8 (Ar-C), 128.9 (Ar-C), 139.9 (Ar-C) 146.1 (Ar-C), 148.6 (Ar-C), 157.5 (Ar-C)

MS (EI, 70 eV): m/z (%) = 566.2 (15) $[M]^+$, 600.1 (20), 508.1 (30) $[M - C_3H_6O]^+$, 451.1 (5), 453.1 (3) $[M - TBS]^+$, 297.1 (100)

$C_{27}H_{39}BrO_6Si$ (567.58)

7.3 {2'-[(7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-methoxy-methyl]-(3'*RS*)-methoxy-benzyloxy}-*tert*-butyl-dimethyl-silane (149)



rac

A magnetically stirred solution of alcohol **148** (138 mg, 0.24 mmol) in THF (2 mL) was treated in one portion with KH (19 mg, 0.48 mmol) at 0 °C. Stirring was continued for 2 h before the reaction mixture was treated with MeI (30 μL, 0.48 mmol) and stirred at 20 °C for a further 2 h. The resulting mixture was treated with water (5 mL), extracted with ether (3 x 15 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded olefin **149** (121 mg, 0.21 mmol, 87%) as colourless oil.

R_f = 0.6

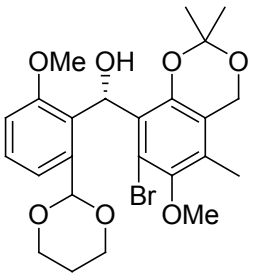
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.10 (d, *J* = 8.5 Hz, 6H, $Si(CH_3)_2$), 0.67 (s, 3H, CH_3), 1.02 (s, 9H, Si(*t*Bu)), 1.35 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.50 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.60 (d, *J* = 13.2 Hz, 2H, CH_2), 5.01 (d, *J* = 17.5 Hz, 1H, CH_2), 5.42 (d, *J* = 17.5 Hz, 1H, CH_2), 6.21 (s, 1H, CH), 6.62 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.22-7.41 (m, 2H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.3 (CH_3), 18.1 (CH_3), 22.0 (C), 25.6 (CH_3), 25.9 (3 x CH_3), 55.2 (OCH_3), 55.9 (OCH_3), 60.4 (CH_2), 60.5 (OCH_3), 63.5 (CH_2), 72.3 (CH), 98.2 (C), 110.9 (Ar-C), 118.9 (Ar-C), 119.6 (Ar-C), 127.0 (Ar-C), 129.2 (Ar-C), 141.6 , (Ar-C) 146.1 (Ar-C), 148.5 (Ar-C), 156.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 582.0 (25), 580.0 (20) $[M]^+$, 524.1 (44), 522.1 (42) $[M - C_3H_6O]^+$

$C_{28}H_{41}BrO_6Si$ (581.61)

7.4 (1'*RS*)-(7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-(7'-[1",3"]dioxan-2"-yl-2'-methoxyphenyl)-methanol (154)



A magnetically stirred solution of iodobenzene **99** (448 mg, 1.40 mmol) in THF (20 mL) at –78 °C was treated dropwise with *n*BuLi (560 µL, 2.5 M solution in hexane, 1.40 mmol). The resulting mixture was stirred at this temperature for 10 min before being treated dropwise with aldehyde **xx** (400 mg, 1.27 mmol) in THF (7 mL). Stirring was continued at this temperature for 35 min then the solution was warmed to 20 °C and immediately quenched with NH_4Cl (4 mL of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 20 mL) and washed with brine (1 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear yellow oil. Subjection of the resulting crude oil to flash chromatography (19:1 pentane/EtOAc → 9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **154** (481 mg, 0.945 mmol, 74%) as a colourless solid.

R_f = 0.3 (9:1 pentane/EtOAc)

IR (KBr): $\tilde{\upsilon}$ = 3455 cm^{-1}, 2991, 2960, 1456, 1257, 1046

UV (CH_3CN): λ_{max} = 285.0 nm (3.7282), 201.5 (4.7676)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.70 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.40 (m, 1H, 5"-H), 2.07 (s, 3H, CH_3), 2.10-2.32 (m, 1H, 5"-H), 3.64 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.80-4.02 (m, 2H, 4"-H/6"-H), 4.02-4.25 (m, 2H, 6"-H/4"-H), 4.58 (d, *J* = 4.6 Hz, 2H, 4-H), 4.78 (s, 1H, OH), 6.20 (s, 1H, 2"-H), 6.66 (d, *J* = 4.8 Hz, 1H, Ar-H), 6.76 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.20 (d, *J* = 4.8, 1H, Ar-H)

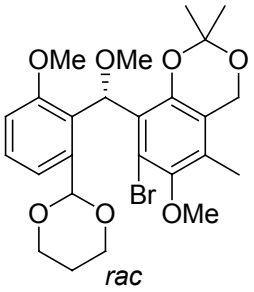
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.2 (CH_3), 21.4 (CH_3), 25.4(CH_3) , 25.5 (CH_3), 55.9 (OCH_3), 60.0 (OCH_3), 60.5 (CH_2), 67.2 (CH_2), 67.3 (CH_2), 72.5 (CH), 98.5 (CH), 99.3 (C), 111.7 (Ar-C), 118.4 (Ar-C), 118.7 (Ar-C), 119.8 (Ar-C), 126.9 (Ar-C), 127.2

(Ar-C), 128.9 (Ar-C), 129.3 (Ar-C), 137.6 (Ar-C), 146.2 (Ar-C), 148.6 (Ar-C), 157.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 510.3 (10) $[M]^+$, 508.0 (9), 452.0 (4) $[M - C_3H_6O]^+$, 450.2 (3), 374.1 (42), 371.3, (67) 312.3 (58), 295.2 (100), 222.2 (50), 163.1 (61)

$C_{24}H_{29}BrO_7$ (509.39); **HRMS**: calcd: 508.1097; confirmed

7.5 (1'*RS*)-7-Bromo-8-{[7'-(1",3")dioxan-2"-yl-3'-methoxyphenyl]-1'-methoxy-methyl}-6-methoxy-2,2,5-trimethyl-*4H*-benzo[1,3]dioxine (155)



A magnetically stirred solution of alcohol **154** (480 mg, 0.943 mmol) in THF (15 mL) was treated in one portion with KH (75 mg, 1.89 mmol) at 0 °C. Stirring was continued for 40 min before the reaction mixture was treated with Iodomethane (118 µL, 1.89 mmol) and stirred at 20 °C for a further 2 h. The resulting mixture was treated with water (5 mL), extracted with ether (3 x 15 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (17:3 pentane/EtOAc) and concentration of the appropriate fractions afforded olefin **155** (451 mg, 0.862 mmol, 91%) as colourless solid.

R_f = 0.3

IR (KBr): $\tilde{\upsilon}$ = 2942 cm^{-1}, 1456, 1255, 1074

UV (CH_3CN): λ_{max} = 285.5 nm (3.7228), 199.0 (4.7657)

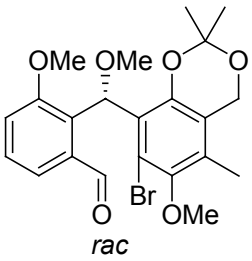
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3H, CH_3), 1.42 (m, 1H, H-5"), 1.55 (s, 3H, CH_3), 2.10-2.40 (m, 1H, H-5"), 2.30 (s, 3H, CH_3), 3.56 (s, 6H, 2 x OCH_3), 3.78 (s, 3H, OCH_3), 3.83-4.04 (m, 2H, 4"-H), 4.11-4.27 (m, 2H, 6"-H), 4.57 (d, *J* = 6.0, Hz, 2H, 4-H), 6.26 (s, 1H, 2"-H), 6.59 (s, 1H, 1'-H), 6.68 (d, *J* = 4.8 Hz, 1H, Ar-H), 7.19 (m, 1H, Ar-H), 7.45 (d, *J* = 8.2 Hz, 1H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.3 (CH_3), 21.3 (CH_3), 25.2 (CH_3), 26.0 (CH_3), 55.8 (OCH_3), 58.5 (OCH_3), 59.9 (OCH_3), 60.5 (CH_2), 67.1 (CH_2), 67.4 (CH_2), 80.7 (CH_2), 98.9 (CH), 99.8 (CH), 99.8 (C), 110.8 (Ar-C), 118.8 (Ar-C), 118.9 (Ar-C), 127.0 (Ar-C), 127.2 (Ar-C), 127.3 (Ar-C), 127.4 (Ar-C), 139.4 (Ar-C), 146.3 (Ar-C), 148.5 (Ar-C), 156.4 (Ar-C)

MS (EI, 70 eV): m/z (%) = 524.3 (24) 522.0 (20) $[M]^+$, 443.0 (14) $[M - Br]^+$, 385.3 (37) $[M – Br - C_3H_6O]^+$, 326.2 (25), 236 (38), 206.1 (100)

$C_{25}H_{31}BrO_7$ (523.41); **HRMS**: calcd: 464.0835; confirmed

7.6 (1'*RS*)-7-Bromo-6-methoxy-8-[1'-methoxy-(3'-methoxy-7'-vinyl-phenyl)-methyl]-2,2,5-trimethyl-4*H*-benzo[1,3]dioxine (155a)



rac

A magnetically stirred solution of acetal **155** (140 mg, 0.269 mmol) in a water/acetone mixture (2.5/5 mL) was treated in one portion with a few crystals of pyridinium *p*-toluenesulfonate at 20 °C. The resulting suspension was heated at reflux for 3 h before being extracted with ether (3 x 15 mL). The combined organic fractions were washed with brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude solid. Subjection of this material to flash chromatography (17:3 pentane/EtOAc) and concentration of the appropriate fractions afforded the corresponding aldehyde **155a** (101 mg, 0.217 mmol, 81%) as a colourless solid, recrystallised from EtOAc/hexane.

R_f = 0.3

m.p. = 140 °C

UV/VIS λ_{max} (lg ε) = 206.0 nm (4.7348), 296.0 (3.7415)

IR (KBr): $\tilde{\nu}$ = 1685 cm^{-1}, 1578, 1455, 1267, 1047

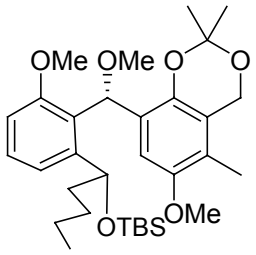
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.60 (dd, *J* = 28.8, 15.6 Hz, 2H, 4-H), 6.33 (s, 1H, 1'-H), 6.92 (d, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 7.30 (d, *J* = 8.1 Hz, 1-H, Ar-H), 7.42 (dd, *J* = 8.1, 1.2 Hz, 1H, Ar-H), 11.07 (s, 1H, CHO)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.4 (CH_3), 22.0 (CH_3), 25.3 (CH_3), 55.8 (OCH_3), 57.1 (OCH_3), 59.9 (OCH_3), 60.6 (CH_2), 80.6 (CH), 98.8 (C), 114.2 (Ar-C), 118.8 (Ar-C), 119.3 (Ar-C), 121.5 (Ar-C), 125.3 (Ar-C), 127.6 (Ar-C), 127.9 (Ar-C), 131.1 (Ar-C), 138.3 (Ar-C), 146.4 (Ar-C), 148.6 (Ar-C), 156.3 (Ar-C), 197.4 (CHO)

MS (EI, 70 eV): m/z (%) = 466.3 (5), 464.3 (5) $[M]^+$, 408.2 (7) 406.2 (6) $[M - C_3H_6O]^+$, 376.2 (100), 374.2 (97) $[M - C_7H_6]^+$, 295.3 (16) $[M - C_7H_6 - Br]^+$, 178.2 (7)

$C_{22}H_{25}BrO_6$ (465.33); **HRMS**: calcd: 465.0835; confirmed

7.7 *R,S-tert*-Butyl-(1-{3-methoxy-2-[methoxy-(6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-methyl]-phenyl}-pentyloxy)-dimethyl-silane (161)



rac

A magnetically stirred solution of aldehyde **155a** (40 mg, 86.0 μmol) in THF (0.5 mL) at –78 °C was treated dropwise with *n*BuLi (38 μL, 2.5M solution in hexane, 95.0 μmol). The resulting mixture was stirred at this temperature for 10 min before being treated dropwise with *tert*-Butyldimethylsilyl triflate (20 μL, 86.0 μmol). Stirring was continued at this temperature for 1 h then the solution was warmed to 20 °C and quenched with NH_4Cl (0.5 mL of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 20 mL) and washed with brine (1 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear yellow oil. Subjection of the resulting crude oil to flash

chromatography (19:1 pentane/EtOAc → 9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol **161** (10 mg, 17.9 μmol, 21%) as a colourless oil. Only one compound in NMR.

R_f = 0.8 (9:1 pentane/EtOAc)

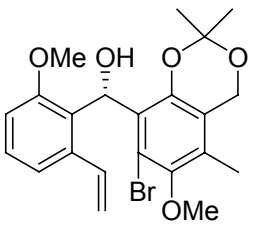
^{1}H-NMR (300 MHz, $CDCl_3$): δ = -0.25 (s, 3H, $SiCH_3$), 0.01 (s, 3H, CH_3), 1.14 (s, 9H, Si(*t*Bu)), 1.20-1.25 (m, 9H, Bu), 1.64 (s, 6H, 2 x CH_3), 2.37 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 4.18 (s, 3H, OCH_3), 4.21 (s, 3H, OCH_3), 5.01 (d, *J* = 13.2 Hz, 2H, CH_2), 5.31 (d, *J* = 17.5 Hz, 1H, CHOSi), 5.51 (s, 1H, CH), 7.13 (m, 2H, Ar-H), 7.54-7.62 (d, *J* = 4.8 Hz, 1H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = -5.3 (CH_3), 9.8 (CH_3), 14.1 (CH_3), 17.9 (C), 22.6 (CH_3), 23.6 (CH_3), 24.9 (CH_2), 25.7 (3 x CH_3), 25.9 (CH_2), 28.5 (CH_2), 40.7 (CH_2) 55.5 (OCH_3), 55.9 (OCH_3), 56.4 (OCH_3), 72.2 (CH), 97.8 (C), 107.8 (Ar-C), 108.9 (Ar-C), 118.5 (Ar-C), 119.3 (Ar-C), 119.9 (Ar-C), 124.5 , (Ar-C) 127.9 (Ar-C), 141.5 (Ar-C), 147.9 (Ar-C), 150.6 (Ar-C), 157.9 (Ar-C)

MS (EI, 70 eV): m/z (%) = 558.5 (10) $[M]^+$, 500.4 (4) $[M - C_3H_6O]^+$, 443.3 (42) $[M - C_4H_9]^+$, 349.3 (38), 231.2 (100)

$C_{32}H_{50}O_6Si$ (558.82)

7.8 (1'*RS*)(7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-(3'-methoxy-7'-vinylphenyl)-methanol (151)



rac

A magnetically stirred solution of iodobenzene **100** (240 mg, 0.92 mmol) in THF (10 mL) at –78 °C was treated dropwise with *n*BuLi (406 μL, 2.5M solution in hexane, 1.01 mmol). The resulting mixture was stirred at this temperature for 20 min before being treated with aldehyde **127** (264 mg, 0.84 mmol) in THF (5 mL). Stirring was

continued at this temperature for 20 min then the solution was warmed to 20 °C and quenched immediately with NH_4Cl (4 mL of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 10 mL), washed with brine (1 x 2 mL) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear yellow oil. Subjection of the resulting crude oil to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded diphenylcarbinol **151** (220 mg, 0.49 mmol, 58%) as a colourless solid.

R_f = 0.3

m.p. = 128 °C (recrystalised from EtOAc/hexane)

IR (KBr): $\tilde{\upsilon}$ = 3500 cm^{-1}, 1569, 1408, 1261, 1044

UV (CH_3CN): λ_{max} = 207.5 nm (4.7345), 293.5 (3.7238)

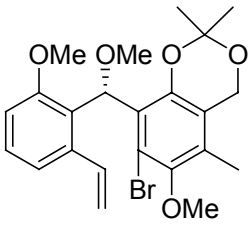
^{1}H-NMR (300 MHz, $CDCl_3$): δ =^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (s, 3H, Me) 1.33 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.61 (dd, *J* = 22.5, 7.2 Hz, 2H, 4-H), 5.15 (dd, *J* = 10.8, 1.8 Hz, 1H, 2”-H), 5.39 (dd, *J* = 17.1, 1.8 Hz, 1H, 2”-H), 6.48 (d, *J* = 9.0 Hz, 1H, Ar-H), 6.82 (d, *J* = 8.1 Hz, 1H, 1’-H), 6.92 (d, *J* = 17.1, 10.8 Hz, 1H, 1”-H), 7.00 (d, *J* = 7.5 Hz, 1H, Ar -H), 7.18 (t, *J* = 8.4 Hz, 1H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.3 (CH_3), 22.6 (CH_3), 25.0 (CH_3), 55.9 (OCH_3), 60.1 (OCH_3), 60.6 (CH_2), 73.0 (CH), 98.6 (CH_2), 110.9 (C), 116.2 (Ar-C), 118.4 (Ar-C), 119.1 (Ar-C), 120.0 (Ar-C), 126.8 (Ar-C), 127.5 (Ar-C), 128.2 (Ar-C), 129.1(Ar-C) , 135.8 (Ar-C), 138.4 (Ar-C), 146.2 (CH), 148.7 (Ar-C), 158.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 450.2 (1), 448.2 (1) $[M]^+$, 392.1 (88) $[M - C_3H_6O]^+$, 390.1 (92), 311.2 (100) $[M - C_3H_6O - Br]^+$, 293 (36), 148.1 (47)

$C_{22}H_{25}BrO_5$(449.33); **HRMS**: calcd : 448.0885; confirmed

7.9 (1'*RS*)-7-Bromo-6-methoxy-8-[1'-methoxy-(3'-methoxy-7'-vinyl-phenyl)-methyl]-2,2,5-trimethyl-4*H*-benzo[1,3]dioxine (152)



rac

Prosedure I

A magnetically stirred solution of diphenylcarbinol **151** (145 mg, 0.32 mmol) in THF (5 mL) was treated in one portion with KH (26 mg, 0.65 mmol) at 0 °C. Stirring was continued for 40 min before the reaction mixture was treated dropwise with Iodomethane (40 μL, 0.64 mmol). The ensuing solution was warmed to 20 °C and stirred for a further 1 h before being treated with water (2 mL) and extracted with ether (3 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded methyl ether **152** (130 mg, 0.28 mmol, 87%) as colourless solid.

Procedure II

A magnetically stirred solution of PPh_3CH_3Br (399 mg, 1.12 mmol) in THF (5 mL) at 20 °C was treated dropwise with sodium bis(trimethylsilyl) amide (1.12 mL, of a 1M solution in THF, 1.12 mmol). The resulting yellow suspension was stirred for 1 h before being treated with aldehyde **155a** (260 mg, 0.56 mol) in THF (5 mL). The resulting suspension was stirred for 1 h, treated with silica gel (*ca.* 1 g) and concentrated under reduced pressure. The resulting colourless solid was subjected to column chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded olefin **152** (210 mg, 0.45 mmol, 81%) as a colourless solid.

R_f = 0.4

m.p. = 202 °C.

UV/VIS λ_{max} (lg ε) = 294.5 nm (3.7312), 206.5 (4.5609)

IR (KBr): $\tilde{\nu}$ = 2937 cm^{-1}, 1408, 1071

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.65 (dd, *J* = 26.5, 15.6 Hz, 2H, 4-H), 5.12 (dd, *J* = 10.8, 1.8 Hz, 1H, 2"-H), 5.43 (dd, *J* = 17.5, 1.8 Hz, 1H, 2"-H), 6.17 (s, 1H, 1'-H), 6.67 (dd, *J* = 8.1, 0.9 Hz, 1H, 4'-H), 7.06 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.14 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.81 (dd, *J* = 17.5, 10.8 Hz, 1H, 1"-H)

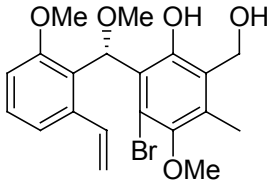
^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.3 (CH_3), 21.7 (CH_3), 25.4 (CH_3), 55.7 (OCH_3), 57.6 (CH_2), 60.0 (OCH_3), 60.5 (OCH_3), 80.4 (CH), 98.5 (CH_2), 109.6 (C), 112.5 (Ar-C), 118.6(Ar-C) , 120.0 (Ar-C), 121.2 (Ar-C), 126.7 (Ar-C), 127.0 (Ar-C), 127.1 (Ar-C), 127.2(Ar-C) , 139.9 (Ar-C), 140.1 (Ar-C), 146.2 (Ar-C), 148.5 (Ar-C), 156.9 (Ar-C)

MS (EI, 70 eV): m/z (%) = 464.2 (1), 462.0 (>1) $[M]^+$, 384.2 (12), 374.1 (13), 294.2 (100)

$C_{23}H_{27}BrO_5$ (463.36); **HRMS**: calcd: 462.1042; confirmed

Elemental Analysis calcd (%) for $C_{23}H_{27}BrO_5$: C 59.62, H 5.87; found C 59.38, H 5.71.

7.10 3-Bromo-6-hydroxymethyl-4-methoxy-(2'*RS*)-[methoxy-(2'-methoxy-6'-vinyl-phenyl)-methyl]-5-methyl-phenol (172)



rac

A magnetically stirred solution of acetonide **152** (160 mg, 0.35 mmol) in acetic acid (10 mL of 40% solution) and THF (5 mL) was heated to 60 °C over 12 h. The resulting mixture was cooled to 20 °C, diluted with Et_2O (100 mL), washed with H_2O (1 x 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure and to afford a yellow solid. Subjection of this material to flash chromatography (2:1 pentane/EtOAc) and concentration of appropriate fractions afforded phenol **172** (81 mg, 0.19 mmol, 55%) as a colourless solid.

R_f = 0.3

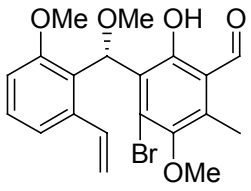
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.27 (s, 3H, CH_3), 2.81 (brs, 1H, OH), 3.42 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 4.69 (s, 2H, CH_2OH), 5.27 (dd, *J* = 10.5, 1.9 Hz, 1H, 2“-H), 5.48 (dd, *J* = 17.7, 1.7 Hz, 1H, 2”-H), 6.00 (s, 1H, 1’-H), 6.74 (dd, *J* = 8.1, 0.9 Hz, 1H, 4’-H), 6.98 (t, *J* = 8.2 Hz, 1H, Ar-H), 7.14 (t, *J* = 7.7 Hz, 1H, Ar-H), 7.76 (dd, *J* = 17.8, 10.2 Hz, 1H, 1”-H), 9.97 (s, 1H, Ph-OH)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.4 (CH_3), 55.1 (OCH_3), 57.6 (OCH_3), 60.7 (OCH_3), 82.1 (CH), 110.2 (Ar-C), 116.7 (CH_2), 119.8 (Ar-C), 121.2 (Ar-C), 124.2 (Ar-C), 127.3 (Ar-C), 128.6 (Ar-C), 129.5 (Ar-C), 134.2 (CH), 137.2 (Ar-C), 140.7 (Ar-C), 146.1 (Ar-C), 157.0 (Ar-C), 156.4 (Ar-C)

MS (EI, 70 eV): m/z (%) = 424.2 (28), 422.0 (30) $[M]^+$, 374.2 (84), 372.1 (90), 293.1 (100)

$C_{20}H_{23}BrO_5$ (423.30); **HRMS**: calcd : 422.0729; confirmed

7.11 4-Bromo-2-hydroxy-5-methoxy-(3’*RS*)-[methoxy-(2’-methoxy-6’-vinyl-phenyl)-methyl]-6-methyl-benzaldehyde (173)



rac

A magnetically stirred solution of alcohol **172** (25 mg, 59.1 μmol) in CH_2Cl_2 (2 mL) at 20 °C was treated in one portion with *Dess-Martin* periodinane (50 mg, 118.1 μmol). The resulting mixture was stirred for 1.5 h before being treated with $NaHCO_3$ (1 x 1 mL of a saturated solution) and $Na_2S_2O_3$ (1 x 1 mL of a 1M solution). Stirring was continued until the cloudy solution became clear (*ca.* 1 h). The resulting mixture was transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic fractions were subjected to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded aldehyde **173** (23 mg, 54.6 μmol, 92%) as a yellow solid.

R_f = 0.7 (9:1 pentane/EtOAc)

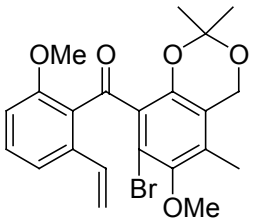
^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.55 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 5.30 (dd, *J* = 11.2, 1.9 Hz, 1H, 2“-H), 5.51 (dd, *J* = 18.0, 1.7 Hz, 1H, 2”-H), 6.17 (s, 1H, 1’-H), 6.74 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.21 (t, *J* = 8.7 Hz, 1H, Ar-H), 7.24 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.57 (dd, *J* = 17.9, 11.4 Hz, 1H, 1”-H), 10.47 (s, 1H, CHO), 11.12 (s, 1H, Ph-OH)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.5 (CH_3), 55.4 (OCH_3), 57.7 (OCH_3), 60.7 (OCH_3), 81.4 (CH), 110.2 (Ar-C), 115.8 (CH_2), 119.8 (Ar-C), 120.1 (Ar-C), 124.2 (Ar-C), 127.0 (Ar-C), 128.9 (Ar-C), 133.3 (CH), 137.2 (Ar-C), 140.7 (Ar-C), 147.9 (Ar-C), 157.6 (Ar-C), 158.8 (Ar-C), 193.8 (CHO)

MS (EI, 70 eV): m/z (%) = 424.2 (28), 422.0 (30) $[M]^+$, 374.2 (84), 372.1 (90), 293.1 (100)

$C_{20}H_{23}BrO_5$ (421.29)

7.12 (7-Bromo-6-methoxy-2,2,5-trimethyl-4*H*-benzo[1,3]dioxin-8-yl)-(3’-methoxy-7’-vinyl-phenyl)methanone (156)



A magnetically stirred solution of alcohol **151** (125 mg, 0.278 mmol) in CH_2Cl_2 (10 mL) at 20 °C was treated in one portion with *Dess-Martin* periodinane (177 mg, 0.417 mmol). The resulting mixture was stirred for 15 min before being treated with $NaHCO_3$ (1 x 2 mL of a saturated solution) and $Na_2S_2O_3$ (1 x 2 mL of a 1M solution). Stirring was continued until the cloudy solution became clear (*ca.* 1 h). The resulting mixture was transferred to a separating funnel and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were subjected to flash chromatography (10:1 pentane/EtOAc) and concentration of the appropriate fractions afforded benzophenone **156** (101 mg, 0.225 mmol, 81%) as a colourless solid.

R_f = 0.3

m.p. = 129 °C (recrystalised from EtOAc/hexane)

UV/VIS λ_{max} (lg ε) = 207.5 nm (4.6472), 313.0 (3.6938)

IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1}, 1471, 1400, 1271, 1045, 881

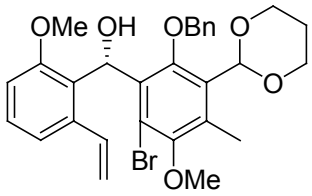
^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.14 (brs, 6H, 2 x CH_3), 2.13 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.64 (s, 2H, 4-H), 5.28 (dd, *J* =10.8, 1.2 Hz, 1H, 2"-H), 5.70 (dd, *J* = 17.4, 1.2 Hz, 1H, 2"-H), 6.75 (d, *J* = 8.1 Hz, 1H, Ar-H), 6.93 (dd, *J* = 17.4, 10.8 Hz, 1H, 1"-H), 7.22 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.31 (t, *J* = 7.8 Hz, 1H, Ar-H)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 11.5 (CH_3), 23.6 (CH_3), 24.0 (CH_3), 55.9 (CH_3O), 59.8 (CH_3O), 60.7 (CH_2), 98.9 (CH_2), 110.4 (C), 114.7 (Ar-C), 115.9 (Ar-C), 118.0 (Ar-C), 118.1(Ar-C), 129.4 (Ar-C), 129.9 (Ar-C), 130.2 (Ar-C), 130.8 (Ar-C), 135.1 (Ar-C), 138.8 (Ar-C), 145.9 (Ar-C), 148.9 (Ar-C), 157.8 , (Ar-C) 195.4 (CO)

MS (EI, 70 eV): m/z (%) = 448.3 (10) 446.3 (9) $[M]^+$, 390.2 (43), 388.2 (40) $[M - C_3H_6O]^+$, 309.3 (100) $[M - Br - C_3H_6O]^+$, 281.2 (20), 255.2 (24)

$C_{22}H_{23}BrO_5$ (447.32); **HRMS**: calcd: 446.0729; confirmed

7.13 (2-Benzyloxy-6-bromo-3-[1,3]dioxan-2-yl-5-methoxy-4-methyl-phenyl)-(2'-methoxy-6'-vinyl-phenyl)-methanol (157)



rac

Procedure I

A magnetically stirred solution of iodobenzene **100** (251.5 mg, 0.97 mmol) in THF (10 mL) at -78 °C was treated dropwise with *n*BuLi (425 µL, 1.06 mmol, 2.5 M solution in hexane, 1.01 mmol). The resulting mixture was stirred at this temperature for 20 min before being treated with aldehyde **131** (277 mg, 0.88 mmol) in THF (5 mL). Stirring was continued at this temperature for 20 min, the solution was warmed to 20 °C and quenched immediately with NH_4Cl (4 mL of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 10 mL), washed with brine (1 x 2 mL)

and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear yellow oil. Subjection of the resulting crude oil to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded diphenylcarbinol **157** (190 mg, 0.34 mmol, 39%) as a colourless solid.

Procedure II

A solution of iodobenzene **100** (59 mg, 0.23 mmol) in THF (2 mL) at –78 °C was treated dropwise with *n*BuLi (92 μL, 0.23 mmol, 2.5 M solution in hexane, 1.01 mmol). The resulting mixture was stirred at this temperature for 20 min before being treated *via* cannula over 5 min to a magnetically stirred solution of aldehyde **131** (60 mg, 0.19 mmol) in THF (2 mL) also maintained at –78 °C. Stirring was continued at this temperature for 20 min, the solution was warmed to 0 °C and quenched immediately with NH_4Cl (1 mL of a saturated aqueous solution). The resulting mixture was extracted with ether (3 x 10 mL), washed with brine (1 x 0.5 mL) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a clear yellow oil. Subjection of the resulting crude oil to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded diphenylcarbinol **157** (41 mg, 0.076 mmol, 40%) as a colourless solid.

R_f = 0.4

IR (KBr): $\tilde{\upsilon}$ = 3560 cm^{-1}, 2838, 1572, 1468, 1100, 993

UV (CH_3CN): λ_{max} = 203.5 nm (4.6397), 292.0 (3.5932)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.20-1.24 (m, 1H, 5'-H), 1.29-1.37 (m, 1H, 5'-H), 2.60 (s, 3H, CH_3), 3.52 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.62-3.82 (m, 2H, 4'-H/5'-H), 4.01- 4.21 (m, 2H, 4'-H/5'-H), 4.41 (d, *J* = 12 Hz, 1H, CH_2Ph), 4.81 (d, *J* = 12 Hz, 1H, CH_2Ph), 5.15 (dd, *J* = 12.4, 1.6 Hz, 1H, 2''-H), 5.21 (dd, *J* = 12.4, 1.6 Hz, 1H, 2''-H), 5.45 (d, *J* = 7.2 Hz, 1H, 1'-H), 5.93 (s, 1H, 2'-H), 6.54 (d, *J* = 9.2 Hz, 1H, 1''-H), 6.64 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.95-7.09 (m, 3H, Ar-H), 7.25-7.37 (m, 4H, Ar-H)

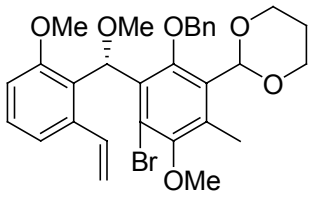
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 12.5 (CH_3), 14.1 (CH_2), 20.9 (CH_2) , 25.8 (CH_2), 55.5 (CH_3O), 55.8 (CH_3O), 60.3 (CH_2), 67.4 (CH_2), 67.8 (CH), 99.1 (CH), 110.4 (Ar-C), 111.4 (Ar-C), 116.7(Ar-C) , 119.9 (Ar-C), 127.1 (Ar-C), 127.6 (Ar-C), 127.8 (Ar-C), 127.9 (Ar-C), 128.2 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 130.6 (Ar-C), 133.5 (Ar-

C), 135.2 (Ar-C), 137.6 (Ar-C), 138.6 (Ar-C), 148.6 (Ar-C), 154.6 (Ar-C), 157.4 (Ar-C)

MS (EI, 70 eV): m/z (%) = 556.1 (5), 554.1 (4) $[M]^+$, 465.1 (43), 463.1 (42) [M - $C_7H_7]^+$, 417.1 (11), 415.1 (10)

$C_{29}H_{31}BrO_6$ (555.46) **HRMS**: calcd: 554.1304; confirmed

7.14 2''-{(2-Benzyloxy-4-bromo-5-methoxy-(3*RS*)-[methoxy-(2'-methoxy-6'-vinyl-phenyl)-methyl]-6-methyl-phenyl}-[1,3]dioxane (158)



rac

A magnetically stirred solution of diphenylcarbinol **157** (150 mg, 0.27 mmol) in THF (5 mL) was treated in one portion with KH (22 mg, 0.54 mmol) at 0 °C. Stirring was continued for 40 min before the reaction mixture was treated dropwise with MeI (34 µL, 0.54 mmol). The ensuing solution was warmed to 20 °C and stirred for a further 1 h before being treated with water (2 mL) and extracted with ether (3 x 5 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded methyl ether **158** (148 mg, 0.26 mmol, 91%) as colourless oil.

R_f = 0.2

IR (KBr): $\tilde{\upsilon}$ = 3543 cm^{-1}, 2812, 1589, 1467, 1201, 997

UV (CH_3CN): λ_{max} = 209.0 nm (4.7395), 294.5 (3.4654)

^{1}H-NMR (300 MHz, $CDCl_3$): δ =1.20-1.24 (m, 1H, 5'-H), 1.29-1.37 (m, 1H, 5'-H), 2.60 (s, 3H, CH_3), 3.32 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.62-3.82 (m, 2H, 4'-H/5'-H), 4.01- 4.21 (m, 2H, 4'-H/5'-H), 4.41 (d, *J* = 12 Hz, 1H, CH_2Ph), 4.81 (d, *J* = 12 Hz, 1H, CH_2Ph), 5.15 (dd, *J* = 12.4, 1.6 Hz, 1H, 2''-H), 5.21 (dd, *J* = 12.4, 1.6 Hz, 1H, 2''-H), 5.74 (s, 1H, 2'-H), 6.25 (s, 1H, 1'-H) 6.54 (d, *J* = 9.2

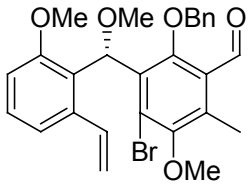
Hz, 1H, 1''-H), 6.64 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.95-7.09 (m, 3H, Ar-H), 7.25-7.37 (m, 4H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 13.7 (CH_3), 25.7 (CH_2), 55.4 (CH_3O), 57.4 (CH_3O), 60.0 (CH_2), 67.62 (CH_2), 67.64 (CH_2), 80.2 (CH_2), 80.79 (CH), 80.80 (CH), 98.8 (CH), 109.6 (Ar-C), 113.4 (Ar-C), 120.8 (Ar-C), 126.1 (Ar-C), 126.2 (Ar-C), 127.1 (Ar-C), 127.6 (Ar-C), 127.9 (Ar-C), 130.6 , (Ar-C) 132.6 (Ar-C), 133.6 (Ar-C), 137.9 (Ar-C), 138.6 (Ar-C), 139.9 (Ar-C), 152.8 (Ar-C), 153.1 (Ar-C), 157.2 (Ar-C)

MS (EI, 70 eV): m/z (%) = 570.3 (20), 568.2 (19) $[M]^+$, 479.2 (30), 477.2 (28), $[M - CH_2Ph]^+$, 447.2 (25), 445.2 (26), 91 (100)

$C_{30}H_{33}BrO_6$ (569.48) **HRMS**: calcd: 568.1461; confirmed

7.15 2-Benzyloxy-4-bromo-5-methoxy-(3*RS*)-[methoxy-(2'-methoxy-6'-vinyl-phenyl)-methyl]-6-methyl-benzaldehyde (159)



rac

A magnetically stirred solution of acetal **158** (100 mg, 0.18 mmol) in a water/acetone mixture (2.5/5 mL) was treated in one portion with a few crystals of pyridinium *p*-toluenesulfonate at 20 °C. The resulting suspension was heated at reflux for 12 h before being extracted with ether (3 x 15 mL). The combined organic fractions were washed with brine (1 x 2 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded the corresponding aldehyde **159** (65 mg, 0.13 mmol, 71%) as a colourless solid.

R_f = 0.3

IR (KBr): $\tilde{\upsilon}$ = 2941 cm^{-1}, 1710, 1597, 1450, 1113, 745

UV (CH_3CN): λ_{max} = 205.0 nm (4.6429), 292.0 (4.0995)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.63 (s, 3H, CH_3), 3.34 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.03 (d, *J* = 12 Hz, 1H, CH_2Ph), 4.55 (d, *J* = 12 Hz, 1H, CH_2Ph), 5.16 (dd, *J* = 12.4, 1.6 Hz, 1H, 2''-H), 5.41 (dd, *J* = 12.4, 1.6 Hz, 1H, 2''-H), 6.25 (s, 1H, 1'-H), 6.89 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.10-7.25 (m, 3H, Ar-H), 7.25-7.37 (m, 4H, Ar-H), 7.66 (d, *J* = 9.2 Hz, 1H, 1''-H), 10.16 (s, 1H, CHO)

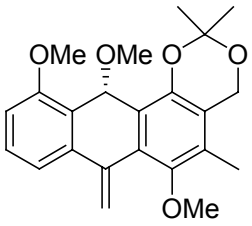
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 14.1 (CH_3), 55.8 (OCH_3), 55.3 (OCH_3), 59.2 (OCH_3), 65.0 (CH_2), 80.4 (C), 109.7 (Ar-C), 118.6 (Ar-C), 119.7 (Ar-C), 124.2 (CH_2), 127.6 (Ar-C), 127.2 (AR-C), 128.6 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 129.5 (Ar-C), 129.9 (Ar-C), 130.1 (Ar-C), 130.2 (Ar-C), 130.4 (Ar-C), 136.4 (Ar-C), 136.6 (Ar-C), 137.8 (Ar-C), 141.3 (Ar-C), 152.3 (Ar-C), 158.5 (Ar-C), 158.2 (Ar-C), 194.1 (CHO)

MS (EI, 70 eV): m/z (%) = 512.2 (38), 510.2 (42) $[M]^+$, 433.1 (12) $[M - Br]^+$

$C_{27}H_{27}BrO_5$ (511.40); **HRMS**: calcd: 510.1042; confirmed

8 *Heck* Reactions

8.1 (12*RS*)-6,11,12-Trimethoxy-2,2,5-trimethyl-7-methylene-7,12-dihydro-*4H*-1,3-dioxabenzo[a]anthracene (162)



rac

Procedure I

A magnetically stirred solution of olefin **152** (70 mg, 0.15 mmol), nBu$_4$NOAc (46 mg, 0.15 mmol), in pre-degassed mixture of DMF/CH_3CN/H_2O (2 mL of a 5:5:1 solution) at 60 °C was treated in one portion with *trans*-di(μ-acetato)-bis[ortho-(di-*ortho*-tolylphosphino)benzyl]-dipalladium(II) (14 mg, 0.015 mmol). The resulting suspension was heated to 120 °C and stirring was continued for 4 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **162** (14 mg, 0.004 mmol, 24%) as yellow solid and starting material **152** (40 mg, 0.086 mmol, 57%).

Procedure II

Cy_2NMe (12.5 μL, 59.3 μmol) in pre-degassed dioxane (0.5 mL) and P(*t-Bu*)$_3$ (5.2 μL, 2.58 μmol of 0.5M solution in hexane) were added, in a glovebox, to a magnetically stirred mixture of $Pd_2(dba)_3$ (1.18 mg, 1.29 μmol) and olefin **152** (20 mg, 43.0 μmol) at 20 °C. The resulting suspension was heated to 120 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate

fractions then afforded dihydroanthracene **162** (15.5 mg, 40.5 μmol, 94%) as yellow solid and starting material **152** (1.1 mg, 2.4 μmol, 5%).

Procedure III

$Pd_2(dba)_3$ (1.45 mg, 1.62 μmol) and $HP(t\text{-}Bu)_3BF_4$ (0.94 mg, 3.23 μmol) were transferred to a flask containing a magnetic stirrer bar, which was evacuated and then refilled with argon. The olefin **152** (25 mg, 53.9 μmol) and Cy_2NMe (12.5 μL, 59.3 μmol) in pre-degassed dioxane (0.5 mL) were then added in one portion at 20 °C. The resulting suspension was heated to 120 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **162** (18.8 mg, 49.3 μmol, 92%) as yellow solid and starting material **152** (1.5 mg, 3.2 μmol, 6%).

Procedure IV

A magnetically stirred solution of olefin **152** (25 mg, 53.9 μmol), $n Bu_4NOAc$ (29.5 mg, 107.8 μmol), K_2CO_3 (14.9 mg, 107.8 μmol) in pre-degassed DMF (0.5 mL) at 20 °C was treated in one portion with $Pd(OAc)_2$ (1.21 mg, 5.39 μmol). The resulting suspension was heated to 90 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **162** (2.3 mg, 5.9 μmol, 11%) as yellow solid and starting material **152** (10 mg, 21.6 μmol, 40%).

Procedure V

A magnetically stirred solution of olefin **152** (25 mg, 53.9 μmol), NaOAc (9.0 mg, 107.8 μmol) in pre-degassed CH_3CN (0.5 mL) at 20 °C was treated in one portion with $Pd(PPh_3)_2Cl_2$ catalyst (4.48 mg, 5.39 μmol). The resulting suspension was heated to 90 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried

($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **162** (1.2 mg, 3.23 μmol, 6%) as yellow solid; and starting material **152** (16 mg, 34.5 μmol, 58%).

R_f = 0.2

UV/VIS λ_{max} (lg ε) = 201.5 nm (4.4756), 290.5 (4.5398), 306.0 (3.5456)

IR (KBr): $\tilde{\nu}$ = 2929 cm^{-1}, 1456, 1269, 1065, 742

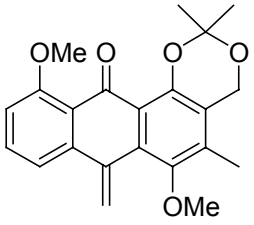
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 3.30 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 9.92 (s, 3H, OCH_3), 4.77 (s, 2H, 4-H), 5.95 (d, *J* = 1.2 Hz, 1H, 1'-H), 6.16 (s, 1H, 12-H), 6.34 (d, *J* = 1.2 Hz, 1H, 1'-H), 6.85 – 6.89 (m, 1H, Ar-H), 7.26–7.30 (m, 2H, Ar-H)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.7 (CH_3), 24.5 (CH_3), 25.0 (CH_3), 55.7 (OCH_3), 56.3 (OCH_3), 59.7 (OCH_3), 60.2 (CH_2), 64.0 (CH_2), 98.9 (C), 109.5 (C), 116.6 (Ar-C), 117.2 (Ar-C), 117.8 (Ar-C), 122.2 (Ar-C), 123.4 (Ar-C), 127.0 (Ar-C), 128.8 (Ar-C), 129.2 (Ar-C), 137.9 (Ar-C), 140.8 (Ar-C), 145.1 (Ar-C), 148.9 (Ar-C), 157.0 (Ar-C)

MS (EI, 70 eV): m/z (%) = 382 (32) $[M^+]$, 324 (100) $[M - C_3H_6O]^+$, 293 (86) $[M - C_3H_6O - CH_3O]^+$, 278 (65) $[M - C_3H_6O - CH_3O - CH_3]^+$, 265 (29)

$C_{23}H_{26}O_5$ (382.20); **HRMS**: calcd for $C_{23}H_{26}O_5$: 382.1780; confirmed.

8.2 6,11-Dimethoxy-2,2,5-trimethyl-7-methylene-4,7-dihydro-1,3-dioxabenzo[*a*]anthracen-12-one (163)



Procedure I

A magnetically stirred solution of benzophenone **156** (215 mg, 0.481 mmol), *n*Bu_4NOAc (290 mg, 0.961 mmol), in a pre-degassed mixture of DMF/CH_3CN/H_2O (10 mL of a 5:5:1 solution) at 60 °C was treated in one portion with *trans*-di(*μ*-acetato)-bis[ortho-(di-*ortho*-tolylphosphino) benzyl]dipalladium (II) (45 mg, 0.048

mmol). The resulting suspension was heated at 110 °C for 20 h, cooled, diluted with ether (30 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded anthracenone **163** (130 mg, 0.355 mmol, 74%) as yellow solid.

Procedure II

$Pd_2(dba)_3$ (1.53 mg, 1.68 μmol) and $HP(tBu)_3BF_4$ (0.97 mg, 3.35 μmol) were transfeered to a flask containing a magnetic stirrer bar, which was evacuated and then refilled with argon. The olefin **156** (25 mg, 55.9 μmol) and Cy_2NMe (13.0 μL, 61.0 μmol) in pre-degassed dioxane (0.5 mL) was added in one portion at 20 °C. The resulting suspension was heated to 120 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded anthracenone **163** (15.9 mg, 43.6 μmol, 78%) as yellow solid; and starting material **156** (1.2 mg, 2.7 μmol, 5%).

Procedure III

A magnetically stirred solution of olefin **156** (25 mg, 55.9 μmol), nBu_4NOAc (31.0 mg, 111.8 μmol), K_2CO_3 (15.0 mg, 111.8 μmol) in pre-degassed DMF (0.5 mL) at 20 °C was treated in one portion with $Pd(OAc)_2$ (1.25 mg, 5.59 μmol). The resulting suspension was heated to 90 °C and stirring was continued for 5 h. The ensuing brown mixture was diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded anthracenone **163** (4.2 mg, 11.5 μmol, 22%) as yellow solid and starting material **156** (15.3 mg, 34.2 μmol, 61%).

Procedure IV

A magnetically stirred solution of olefin **156** (25 mg, 55.9 μmol), NaOAc (9.1 mg, 111.8 μmol) in pre-degassed CH_3CN (0.5 mL) at 20 °C was treated in one portion with $Pd(PPh_3)_2Cl_2$ catalyst (4.60 mg, 5.59 μmol). The resulting suspension was heated to 90 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded anthracenone **163** (1.4 mg, 4.17 μmol, 7%) as yellow solid and starting material **156** (17.4 mg, 38.9 μmol, 70%).

R_f = 0.3

UV/VIS λ_{max} (lg ε) = 194.0 nm (4.6834), 229.0 (4.6089)

IR (KBr): $\tilde{\nu}$ = 1672 cm^{-1}, 1456, 1273, 1058, 842

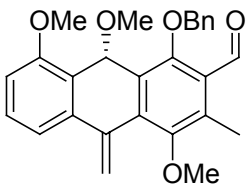
^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.60 (s, 6H, 2 x CH_3), 2.14 (s, 3H, CH_3), 3.61 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.77 (s, 2H, CH_2), 6.07 (s, 1H, 1'-H), 6.53 (s, 1H, 1'-H), 6.95 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.31-7.44 (m, 2H, Ar-H)

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 11.3 (CH_3), 24.7 (CH_3), 56.2 (CH_3O), 59.8 (CH_3O), 60.1 (CH_2), 67.0 (CH_2), 99.2 (C), 111.2 (Ar-C), 116.0 (Ar-C), 119.3 (Ar-C), 120.0 (Ar-C), 121.7 (Ar-C), 122.4 (Ar-C), 129.3 (Ar-C), 131.9 (Ar-C), 132.5 (Ar-C), 136.2 (Ar-C), 141.1 (Ar-C), 146.6 (Ar-C), 147.9 (Ar-C), 158.3 (Ar-C), 183.5 (CO)

MS (EI, 70 eV): m/z (%) = 366.2 (10) $[M]^+$, 308.1 (23) $[M - C_3H_6O]^+$, 293.1 (100) $[M - C_3H_6O - CH_3]^+$, 265.1 (6), 165.1 (6)

$C_{22}H_{22}O_5$ (366.41); **HRMS**: calcd: 366.1467; confirmed

8.3 1-Benzyloxy-4,8,(9*RS*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-carbaldehyde (164)



rac

Procedure I

A magnetically stirred solution of aldehyde **159** (20 mg, 39.1 μmol), *n*Bu_4NOAc (23.6 mg, 78.2 μmol), in a pre-degassed mixture of DMF/CH_3CN/H_2O (2 mL of a 5:5:1 solution) at 60 °C was treated in one portion with *trans*-di(*μ*-acetato)-bis[ortho-(di-*ortho*-tolylphosphino) benzyl]dipalladium (II) (7.3 mg, 7.82 μmol). The resulting suspension was heated at 120 °C for 5 h, cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions afforded dihydroanthracene **164** (13.8 mg, 32.1 μmol, 82%) as yellow solid and starting material **159** (5.9 mg, 1.17 μmol, 3%).

Procedure II

$Pd_2(dba)_3$ (1.00 mg, 1.17 μmol) and HP(*t*$Bu)_3BF_4$ (0.68 mg, 2.34 μmol) were transferred to a flask containing a magnetically stirrer bar, which was evacuated and then refilled with argon. The olefin **159** (20 mg, 39.1 μmol) and Cy_2NMe (9.0 μL, 43.0 μmol) in pre-degassed dioxane (0.5 mL) was added in one portion at 20 °C. The resulting suspension was heated to 120 °C and stirring was continued for 5 h. The ensuing brown mixture was diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **164** (13 mg, 30.2 μmol, 77%) as yellow solid and starting material **159** (3.5 mg, 6.8 μmol, 18%).

Procedure III

A magnetically stirred solution of olefin **159** (20 mg, 39.1 μmol), nBu_4NOAc (22 mg, 78.2 μmol), K_2CO_3 (10.5 mg, 78.2 μmol) in pre-degassed DMF (0.5 mL) at 20 °C was treated in one portion with $Pd(OAc)_2$ (1.2 mg, 5.4 μmol). The resulting suspension was heated to 90 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1

pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **164** (5.7 mg, 13.3 μmol, 34%) as yellow solid and starting material **159** (10.5 mg, 20.4 μmol, 52%).

Procedure IV

A magnetically stirred solution of olefin **159** (20 mg, 31.1 μmol), NaOAc (6.4 mg, 78.2 μmol) in pre-degassed CH_3CN (0.5 mL) at 20 °C was treated in one portion with $Pd(PPh_3)_2Cl_2$ catalyst (4.4 mg, 5.40 μmol). The resulting suspension was heated to 90 °C and stirring was continued for 5 h. The ensuing brown mixture was cooled, diluted with ether (20 mL) and washed with water (3 x 3 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracene **164** (1.6 mg, 4.73 μmol, 12%) as yellow solid and starting material **159** (13.4 mg, 26.4 μmol, 84%).

R_f = 0.8 (9:1 pentane/EtOAc)

IR (KBr): $\tilde{\upsilon}$ = 2932 cm^{-1}, 1687, 1584, 1453, 1264, 1062, 747

UV (CH_3CN): λ_{max} = 206.5 nm (4.6564), 283.0 (4.0785)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.53 (s, 3H, CH_3), 3.21 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.92 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 5.20 (d, *J* = 10.8 Hz, 1H, CH_2Ph), 6.08 (s, 1H, 1'-H), 6.31 (s, 1H, 9-H), 6.46 (s, 1H, 1'-H), 6.89 (dd, *J* = 9 Hz, 1.2 Hz, 1H, Ar-H), 7.24-7.53 (m, 6H, Ar-H), 7.55 (d, *J* = 1.5 Hz, 1H, Ar-H), 10.50 (s, 1H, CHO)

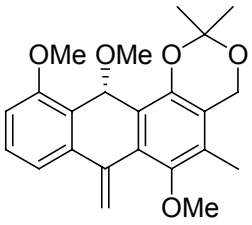
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 13.0 (CH_3), 55.7 (OCH_3), 55.8 (OCH_3), 59.7 (OCH_3), 64.6 (CH_2), 80.1 (C), 109.6 (Ar-C), 117.6 (Ar-C), 118.9 (Ar-C), 122.2 (CH_2), 127.2 (Ar-C), 127.7 (AR-C), 128.4 (Ar-C), 128.5 (Ar-C), 128.5 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 128.8 (Ar-C), 129.0 (Ar-C), 129.5 (Ar-C), 136.3 (Ar-C), 136.6 (Ar-C), 137.8 (Ar-C), 140.5 (Ar-C), 152.7 (Ar-C), 157.2 (Ar-C), 157.3 (Ar-C), 192.2 (CHO)

MS (EI, 70 eV): m/z (%) = 430.2 (20) $[M]^+$, 308.1 (58), 280.1 (100)

$C_{27}H_{26}O_5$ (430.49) **HRMS**: calcd: 430.1780; confirmed.

9 Further Transformations

9.1 (12*RS*)-6,11,12-Trimethoxy-2,2,5-trimethyl-7-methylene-7,12-dihydro-*4H*-1,3-dioxa-benzo[*a*]anthracene (162)

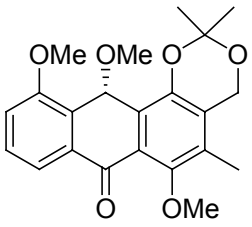


rac

A magnetically stirred solution of $LiAlH_4$ (2 mg, 0.05 mmol) in THF (1 mL) at 0 °C was treated dropwise with ketone **163** (20 mg, 0.05 mmol) in THF (0.5 mL). The resulting solution was stirred for 10 min before being treated with NH_4Cl (1 mL of a saturated aqueous solution) and extracted with ether (3 x mL). The combined organic fractions were dried $MgSO_4$, filtered and concentrated under reduced pressure to afford a yellow solid. The resulting alcohol was not isolated but immediately subjected to the next reaction.

The crude solid from the above reaction (ca. 20 mg) in THF (1 mL) at 0 °C was treated with KH (4 mg, 0.11 mmol) and immediately with MeI (6 μL, 0.11 mmol). The resulting solution was stirred at this temperature for 30 min before being warmed to 20 °C and stirred for a further 14 h. The resulting mixture was treated with water (1 mL), extracted with ether (3 x 3 mL) and the combined organic fractions dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a colourless solid. Subjection of this material to flash chromatography (19:1 pentane/EtOAc) and concentration of the appropriate fractions afforded **162** (7.7 mg, 0.02 mmol, 37%) as a yellow solid; R_f = 0.2. This material was identical in all respects with that obtained previously.

9.2 (12*RS*)-6,11,12-Trimethoxy-2,2,5-trimethyl-11a,12-dihydro-4H,7aH-1,3-dioxa-benzo[*a*]anthracen-7-one (168)



rac

A magnetically stirred solution of compound **162** (10 mg, 0.026 mmol) in 1:1:1.5 CCl_4/MeCN/H_2O (350 µL) at 20 °C was treated with a mixture of $RuCl_3$ (0.2 mg, 5 mol%, 1.3 x 10^{-3} mmol) and $NaIO_4$ (28 mg, 0.139 mmol). The ensuing solution was stirred for 15 min and the suspension was diluted with CH_2Cl_2 (10 mL). The organic layer was washed with water (2 x 1 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the resulting brown solid to flash chromatography using a small plug of silica (9:1 pentane/EtOAc) then afford crude anthracenone **168** (7 mg, 0.018 mmol, 69%) as a yellow foam.

R_f = 0.4

IR (KBr): $\tilde{\nu}$ = 2932 cm^{-1}, 1673, 1591, 1271, 1054, 861, 747

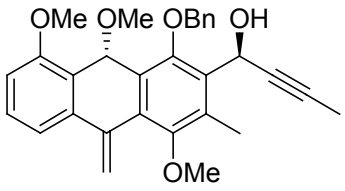
^{1}**H-NMR** (300 MHz, $CDCl_3$): δ = 1.60 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 2.14 (s, 3 H, CH_3), 3.25 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.81 (s, 2H, CH_2), 6.15 (s, 1H, 12-H), 7.10 (dd, *J* =8.4, 0.9 Hz, 1H, Ar-H), 7.43 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.64 (dd, *J* = 7.8, 0.9 Hz, 1H, Ar-H)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.3 (CH_3), 24.5 (CH_3), 24.9 (CH_3), 55.9 (CH_3O), 60.2 (CH_3O), 61.8 (CH_2), 62.6 (CH_3O), 99.4 (C), 114.3 (Ar-C), 119.0 (Ar-C), 124.6 (Ar-C), 125.6 (Ar-C), 126.6 (Ar-C), 127.0 (Ar-C), 129.1 (Ar-C), 129.5 (Ar-C), 136.4 (Ar-C), 145.2 (Ar-C), 151.3 (Ar-C), 157.0 (Ar-C), 184.8 (CO)

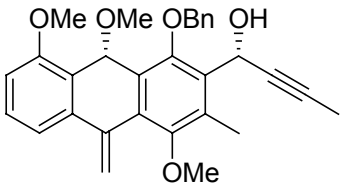
MS (EI, 70 eV): m/z (%) = 384.2 (14) $[M]^+$, 326.2 (100) $[M - C_3H_6O]^+$, 298.2 (25), 267.1 (24), 149.1 (40)

$C_{22}H_{24}O_6$ (384.42); **HRMS**: calcd: 384.1573; confirmed

9.3 1-(1-Benzyloxy-4,8,(9*R*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-yn-(1'*R*)-ol and 1-(1-Benzyloxy-4,8,(9*R*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-yn-(1'*S*)-ol and and 1-(1-Benzyloxy-4,8,(9*S*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-yn-(1'*S*)-ol and 1-(1-Benzyloxy-4,8,(9*S*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-yn-(1'*R*)-ol (175ab)



rac



rac

A magnetically stirred solution of aldehyde **164** (11 mg, 25.6 μmol) in THF (0.5 mL) was treated with 1-propynylmagnesium bromide (153 μL, 76.7 μmol of 0.5 M solution in THF) at 0 °C. Stirring was continued for 20 min at 20 °C. The ensuing mixture was diluted with ether (20 mL) and washed with water (1x 0.5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracenes **175ab** as two diastereomers (7.5 mg, 15.9 μmol, 62%) as yellow solids.

R_f = 0.5

IR (KBr): $\tilde{\upsilon}$ = 3424 cm^{-1}, 2924, 1455, 1261, 1063, 698

UV (CH_3CN): λ_{max} = 270.0 nm (4.4236), 392.5 (3.0649)

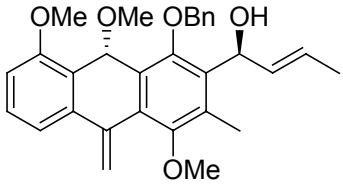
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 6H, CH_3), 2.40 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.18 (s, 6H, OCH_3), 3.60 (s, 3H, OCH_3), 3.63 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.78 (d, *J* = 10.8 Hz, 2H, CH_2Ph), 5.33 (d, *J* = 10.8 Hz, 2H, CH_2Ph), 5.66 (d, *J* = 10.0 Hz, 1H, 1-H), 5.86 (d, *J* = 10.0 Hz, 1H, 1-H), 5.98 (d, *J* = 1.2 Hz, 1H, 1'-H), 6.00 (d, *J* = 1.2 Hz, 1H, 1'-H), 6.30 (dd, *J* = 6.3, 1.2 Hz, 2H, 9-H), 6.27 (d, J = 1.2 Hz, 1H, 1'-H), 6.85 (d, *J* = 1.2 Hz, 1H, 1'-H), 6.89 (dd, *J* = 9 Hz, 1.2 Hz, 2H, Ar-H), 7.29-7.41 (m, 12H, Ar-H), 7.56 (d, *J* = 1.5 Hz, 2H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 3.0 (CH_3), 3.3 (CH_3), 14.5 (CH_3), 55.4 (OCH_3), 55.6 (OCH_3), 57.4 (OCH_3), 57.9 (OCH_3), 58.2 (OCH_3), 60.1 (OCH_3), 69.3 (CH), 70.1 (CH), 70.9 (CH), 71.0 (CH_2), 71.4 (CH_2), 82.4 (C), 82.5 (C), 83.2 (C), 83.8 (C), 108.4 (Ar-C), 108.6 (Ar-C), 109.3 (Ar-C), 110.3 (Ar-C), 111.2 (Ar-C), 114.2 (Ar-C), 114.8 (Ar-C), 119.2 (Ar-C), 119.5 (Ar-C), 119.7 (Ar-C), 120.3 (Ar-C), 120.9 (Ar-C), 121.7 (Ar-C), 122.1 (Ar-C), 122.4 (Ar-C), 122.4 (Ar-C), 127.2 (Ar-C), 127.3 (Ar-C), 127.4 (Ar-C), 128.4 (Ar-C), 128.8 (Ar-C), 128.9 (Ar-C), 134.3 (CH_2), 134.4 (CH_2), 136.7 (Ar-C), 143.2 (Ar-C), 143.3 (Ar-C), 144.1 (Ar-C), 144.5 (Ar-C), 150.2 (Ar-C), 150.6 (Ar-C), 152.4 (Ar-C), 152.5 (Ar-C), 162.1 (Ar-C), 162.6 (Ar-C)

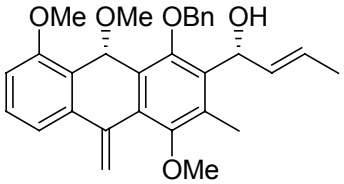
MS (EI, 70 eV): m/z (%) = 470.2 (20) $[M]^+$, 308.1 (58), 280.1 (100)

$C_{30}H_{30}O_5$ (470.54) **HRMS**: calcd: 470.2093; confirmed

9.4 1-(1-Benzyloxy-4,8,(9*R*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-en-(1'*R*)-ol and 1-(1-Benzyloxy-4,8,(9*R*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-en-(1'*S*)-ol and and 1-(1-Benzyloxy-4,8,(9*S*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-en-(1'*S*)-ol and 1-(1-Benzyloxy-4,8,(9*S*)-trimethoxy-3-methyl-10-methylene-9,10-dihydro-anthracene-2-yl)-but-2'-en-(1'*R*)-ol (176ab)



rac



rac

A magnetically stirred solution of dihydroanthracenes **175ab** (20 mg, 42.5 μmol) in THF (0.5 mL) was treated with sodium bis-(2-methoxy-ethoxy) aluminium hydride (24 μL, 84.4 μmol of 3.5 M solution in toluene) at 0 °C. Stirring was continued for 12 h at 65°C before the mixture was cooled to 0 °C and quenched with H_2O (0.1 mL). The reaction mixture was diluted with ether (20 mL) and washed with water (1 x 0.5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced

pressure to afford a crude brown solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded alcohol as a mixture of two diastereomers **176ab** (10 mg, 22.1 μmol, 52%) as a yellow oil.

R_f = 0.4

IR (KBr): $\tilde{\upsilon}$ = 3532 cm^{-1}, 2944, 1678, 1341, 1057, 702

UV (CH_3CN): λ_{max} = 268.5 nm (4.4117), 390.5 (3.0203)

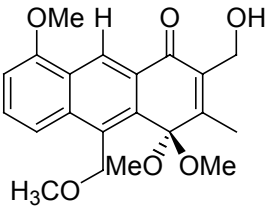
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.87 (s, 6H, CH_3), 2.35 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 3.222 (s, 6H, OCH_3), 3.63 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.81 (d, *J* = 11.2 Hz, 2H, CH_2Ph), 5.38 (d, *J* = 11.2 Hz, 2H, CH_2Ph), 5.51-5.72 (m, 6H, 1-H/2-H/3-H), 5.99 (d, *J* = 1.4 Hz, 1H, 1'-H), 6.22 (d, *J* = 1.4 Hz, 1H, 1'-H), 6.41 (dd, *J* = 6.3, 1.1 Hz, 2H, 9-H), 6.50 (d, *J* = 1.4 Hz, 1H, 1'-H), 6.89 (d, *J* = 1.4 Hz, 1H, 1'-H), 6.93 (dd, *J* = 8.5 Hz, 1.2 Hz, 2H, Ar-H), 7.30-7.42 (m, 12H, Ar-H), 7.60 (d, *J* = 1.5 Hz, 2H, Ar-H)

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 3.2 (CH_3), 3.6 (CH_3), 16.3 (CH_3), 55.6 (OCH_3), 55.7 (OCH_3), 57.9 (OCH_3), 58.1 (OCH_3), 58.3 (OCH_3), 60.2 (OCH_3), 69.7 (CH), 70.1 (CH), 71.0 (CH_2), 71.4 (CH_2), 72.3 (CH), 72.5 (CH), 74.1 (CH), 74.5 (CH), 74.8 (CH), 75.0 (CH), 108.2 (Ar-C), 108.4 (Ar-C), 110.1 (Ar-C), 110.5 (Ar-C), 111.7 (Ar-C), 114.6 (Ar-C), 115.0 (Ar-C), 115.2 (Ar-C), 119.4 (Ar-C), 119.9 (Ar-C), 120.1 (Ar-C), 120.5 (Ar-C), 120.9 (Ar-C), 121.4 (Ar-C), 122.8 (Ar-C), 122.3 (Ar-C), 127.6 (Ar-C), 127.7 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 128.9 (Ar-C), 129.4 (Ar-C), 129.8 (Ar-C), 129.9 (Ar-C), 134.2 (CH_2), 136.0 (Ar-C), 136.3 (Ar-C), 144.2 (Ar-C), 144.9 (Ar-C), 150.6 (Ar-C), 153.5 (Ar-C), 162.6 (Ar-C), 164.1 (Ar-C)

MS (EI, 70 eV): m/z (%) = 472.0 (34) $[M]^+$, 310.1 (60), 282.1 (99)

$C_{30}H_{32}O_5$ (472.56)

9.5 2-Hydroxymethyl-4,4,8-trimethoxy-10-methoxymethyl-3-methyl-4a,9a-dihydro-4*H*-anthracen-1-one (171)



A magnetically stirred solution of anthracene **162** (11 mg, 28.8 μmol) in MeOH/CH_3CN 5:1 (0.5 mL) was treated with cerric ammonium nitrate (32 mg, 57.6 μmol in CH_3CN 0.5 mL) at 0 °C. Stirring was continued for 7 min at 0 °C. The ensuing mixture was diluted with ether (20 mL) and washed with water (1 x 0.5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude brown solid. Subjection of this material to flash chromatography (1:1 pentane/EtOAc) and concentration of the appropriate fractions then afforded dihydroanthracenone **171** (8 mg, 21.9 μmol, 76%) as a colourless foam.

R_f = 0.5

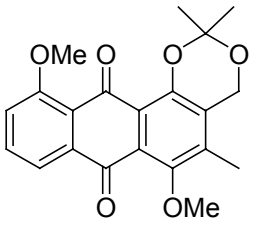
^{1}**H-NMR** (300 MHz, $CDCl_3$): δ = 1.23 (s, 1H, OH), 2.15 (s, 3H, CH_3), 2.93 (s, 6H, 2 x OCH_3), 3.56 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2OH), 5.32 (s, 2H, CH_2OMe), 6.87 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.59 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.82 (d, *J* = 7.5 Hz, 1H, Ar-H) , 9.21 (s, 1H, 9-H)

^{13}**C NMR** (75.5 MHz, C_6D_6): δ = 12.3 (CH_3), 51.6 (2 x OCH_3), 55.7 (CH_2), 58.2 (OCH_3), 58.7 (OCH_3), 67.2 (CH_2), 99.0 (C), 104.9 (Ar-C), 117.2 (Ar-C), 124.2 (Ar-C), 125.9 (Ar-C), 128.6 (Ar-C), 130.1 (Ar-C), 131.8 (Ar-C), 134.4 (Ar-C), 136.9 (Ar-C), 139.7 (Ar-C), 152.8 (Ar-C), 157.1 (Ar-C), 184.7 (CO)

MS (EI, 70 eV): m/z (%) = 372.2 (40) $[M]^+$, 340.2 (100) $[M - CH_3OH]^+$, 297.2 (25) $[M – C_3H_7O_2]$

$C_{21}H_{24}O_6$ (372.41)

9.6 6,11-Dimethoxy-2,2,5-trimethyl-4*H*-1,3-dioxa-benzo[*a*]anthracene-7,12-dione (165)



Procedure I

A magnetically stirred solution of anthracenone **163** (30 mg, 82.0 μmol), pyridine (5 μL), trimethylamine-*N*-oxide (29 mg, 0.27 mmol) and *t*BuOH (325 μL) was treated with osmium tetroxide (2 μL of 2.5 wt% solution in *t*BuOH) at 20 °C. The resulting mixture was heated to 85 °C for 24 h. The ensuing mixture was cooled, diluted with EtOAc (10 mL) and washed with water (1 x 0.5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude orange oil. Subjection of this material to flash chromatography (50:50 pentane/EtOAc) and concentration of the appropriate fractions then afforded anthraquinone **165** (22 mg, 59.7 μmol, 72%) as an orange oil.

Procedure II

A solution of AD-Mix-β (8.6 mg) in H_2O/*t*BuOH 1:1 (400 μL) was stirred for 15 min at 20 °, before being treated with $CH_3SO_2NH_2$ (3.5 mg, 0.04 mmol) and cooled to 0 °C. The resulting mixture was treated with anthracenone **163** (10 mg, 27.0 μmol), stirring was continued at 0 °C over 16 h. The ensuing mixture was diluted with EtOAc (5 mL) and washed with water (1 x 0.5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a crude orange oil. Subjection of this material to flash chromatography (50:50 pentane/EtOAc) and concentration of the appropriate fractions then afforded anthraquinone **165** (4.5 mg, 12.2 μmol, 45%) as an orange oil.

R_f = 0.4

UV/VIS λ_{max} (lg ε) = 195.5 nm (4.5955), 225.5 (4.4856)

IR (KBr): $\tilde{\nu}$ = 2938 cm^{-1}, 1669, 1451, 1270, 837

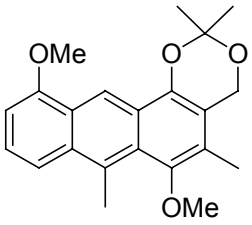
^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.56 (s, 6H, 2 x CH_3), 2.11 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.75 (s, 2H, CH_2OR), 6.90-7.19 (m, 1H, Ar-H), 7.57 (t, *J* = 8.4 Hz, 1H, Ar-H), 7.68 (d, *J* = 6.6 Hz, 1H, Ar-H)

^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 10.8 (CH_3), 24.7 (2 x CH_3), 56.5 (OCH_3), 60.3 (CH_2), 61.7 (OCH_3), 99.8 (C), 116.9 (Ar-C), 118.6 (Ar-C), 123.3 (Ar-C), 125.4 (Ar-C), 125.6 (Ar-C), 127.0 (Ar-C), 129.8 (Ar-C), 131.8 (Ar-C), 131.9 (Ar-C), 133.7 (Ar-C), 133.9 (Ar-C), 146.6 (Ar-C), 182.1 (CO), 183.6 (CO)

MS (EI, 70 eV): m/z (%) = 368.2 (20) $[M]^+$, 310.1 (100) $[M - C_3H_6O]^+$, 218.2 (19)

$C_{21}H_{20}O_5$ (368.38)

9.7 6,11-Dimethoxy-2,2,5,7-tetramethyl-4*H*-1,3-dioxa-benzo[*a*]anthracene (167)



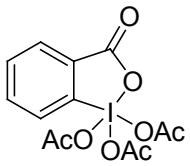
A magnetically stirred solution of dihydroanthracene **162** (16 mg, 42.0 μmol) in acetic acid (2 mL of 40% solution) and THF (0.5 mL) was heated to 60 °C over 3 h. The resulting mixture was cooled to 20 °C, diluted with Et_2O (40 mL), washed with H_2O (1 x 3 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure and to afford a yellow solid. Subjection of this material to flash chromatography (9:1 pentane/EtOAc) and concentration of appropriate fraction afforded anthracene **167** (11 mg, 31.2 μmol, 74%) as a brown oil.

R_f = 0.3

^{1}H NMR (300 MHz, $CDCl_3$) : δ = 1.57 (s, 3H, CH_3), 1.62 (s, 6H, 2 x CH_3), 2.26 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2OR), 6.89 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.55 (t, *J* = 8.1 Hz, 1H, Ar-H), 7.93 (d, *J* = 7.5 Hz, 1H, Ar-H) , 9.20 (s, 1H, 9-H)

$C_{22}H_{24}O_4$ (352.42)

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodioxol-3(1*H*)-one 178



A magnetically stirred solution of acetic anhydride (15.3 mL, 0.16 mol) was treated with Iodoxide (IBX) (13.0 g, 0.05 mol) (CAUTION explosive) at 20 °C. The resulting mixture was heated to 80 °C over 1 h and than stirred at this temperature for further 1.5 h, before being slowly cooled to 0 °C. The resulting colourless crystals were washed with ether (6 x 10 mL), than used a *Pasteur* pipet to remove excess solvent. Residual solvent was completely removed under reduced pressure to provide Dess-Martin periodinane **178** (13.9 g, 71%). The spectral data derived from this material matched those reportrd in the literature.[96]

10 References

[1] [a] N. Anand, J. S. Bindra, S. Ranganathan, *Art in Organic Synthesis*, Holden-Day, Inc., San Francisco, firs edition, **1970**; [b] F. Sondheimer, D. Taub, *J. Am. Chem. Soc.* **1951**, *73*, 3548; [c] F. Sondheimer, D. Taub, *J. Am. Chem. Soc.* **1951**, *73*, 4057; [d] M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749; [e] M. Gates, *J. Am. Chem. Soc.* **1956**, *78*, 1380.

[2] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, Inc., New York, **1989**.

[3] [a] L. F. Tietze, I. Hiriyakkanavar, H. P. Bell, *Chem. Rev.* **2004**, *104*, 3453 ; [b] A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473; [c] E. Negishi, C. Coperet, S. Ma, S.-Y. Liou, *Chem. Rev*. **1996**, *96*, 365; [d] W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2; [e] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; [f] S. Bräse, A. de Meijere in *Metal-Catalyzed Cross Coupling Reactions*, Ed. P. J. Stang, F. Diderich, Wiley-VCH, Weinheim **1997**.

[3a] [a] T. Mizoroki, K. Mori, A. Ozaki, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581;
[b] R. F. Heck, *J. Am. Chem. Soc*. **1968**, *90*, 5518. [a] R. F. Heck, J. P. Nolley Jr., *J. Org. Chem.* **1972**, *37*, 2320; [b] T. Jeffery, *Chem. Commun.* **1984**, 1287; [c] T. Hayashi, F. Ozawa, A. Kubo, *J. Am. Chem. Soc.* **1991**, *113*, 1417; [d] O. Loiseleur, P. Meier, A. Pfaltz, *Angew. Chem.* **1996**, *108*, 218; [e] W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2; [f] G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427; [g] A. Tenaglia, A. Heumann, *Angew. Chem.* **1999**, *111*, 2316; [h] C. Amatore, A. Jutand, *Acc. Chem. Res.* **2000**, *33*, 312; [i] M. T. Reetz, E. Westermann, *Angew. Chem.* **2000**, *112,* 170; L. F. Tietze, G. Kettschau, U. Heuschert, G. *Nordmann, Chem. Eur. J*. **2001**, *7*, 368

[4] A. Haberli, C. Leuman, *J. Org. Lett*. **2001**, *3*, 489.

[5] S. C. Stinson, *Chem. Eng. News* **1999**, January 18, 81.

[6] Octyl methoxycinnamate (OMC) is most common UV-B sunscreen that is on the market; A. Eisenstadt, In *Catalysis of Organic Reactions*; F. E. Herkes, Ed.; Marcel Dekker: New York, **1998**; Chapter 33.

[7] C. Amatore, A. Jutand, *J. Organomet. Chem*. **1999**, *576*, 254.

[8] M. Iole, G. Ortaggi, M. Scarsella, G. Sleiter, *Polyhedron* **1991**, *10*, 2475.

[9] P. Roffia, G. Gregorio, F. Conti, G. F. Pregaglia, *J. Mol. Catal.* **1977**, *2*, 191.

[10] C. Amatore, A. Jutand, M. J. Medeiros, *New J. Chem.*. **1996**, *20*, 1143.

[11] P. A. McLaughlin, J. G. Verkade, *Organometallics* **1998**, *17*, 5937.

[12] C. Amatore, E. Carre, A. Jutand, M. M'Barki, *Organometallics* **1995**, *14*, 1818.

[13] M. T. Reetz, G. Löhmer, R. Schwickardi, Angew. *Chem. Int. Ed. Engl*. **1998**, *37*, 481.

[14] E. Negishi, T. Takahashi, K. Akiyoshi, *J. Chem. Soc., Chem. Commun*. **1986**, *17*, 1338.

[15] A. Mosleh, A. Jutand, *Organometallics* **1995**, *14*, 1810.

[16] A. F. Littke, G. C. Fu, *J. Org. Chem*. **1999**, *64*, 10.

[17] Y. Sato, M. Sodeoka, M. Shibasaki, *Chem. Lett.* **1990**, *10*, 1953.

[18] M. Pportonoy, Y. Ben-David, I. Russo, D. Milstein, *Organometallics* **1995**, *14*, 5605.

[19] M. P. Danieul, T. Skrydstrup, *Tetrahedron Lett*. **1999**, *40*, 4901.

[20] M. Beller, T. H. Riermeier, *Eur. J. Inorg. Chem*. **1998**, 29.

[21] A. Spencer, *J. Organomet. Chem*. **1983**, *258*, 101.

[22] A. F. Littke, G. C. Fu, *J. Am. Chem*. *Soc*. **2001**, *123*, 6989.

[23] M. R. Netherton, G. C. Fu, *Org. Lett.*. **2001**, *26*, 4295.

[24] S. Otsuka, T. Yoshida, *Inorg. Synth*. **1990**, *28*, 113.

[25] M. Shibasaki, E. M. Vogl, *J. Organomet. Chem*. **1999**, *576*, 1.

[26] W. A. Herrmann, C. Brossmer, K. Öfele, C. P. Reisinger, T. Priermeier, M. Beller, H. Fisher, *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1844.

[27] L. F. Tietze, H. Schirok, M. Wöhrmann, *Eur. J. Org. Chem.* **2000**, *6*, 510; L. F. Tietze.

[28] L. F. Tietze, T. Nöbel, M. Spescha, *Angew. Chem.* **1997**, *108***,** 2385.

[29] [a] T. Jeffery, *Tetrahedron Lett*. **1885**, *26*, 2667.; [b] T. Jeffery, *Synthesis* **1987**, *1*, 70.

[30] G. E. Coates, M. L. H. Green, K. Wade, *Organometallic Compounds*, Methuen, London, **1968**, vol 2.

[31] J. P. Candlin, K. A. Taylor, D. T. Thompson, *Reaction of Transition Metal Complexes*, Elsevier, Amsterdam, **1968**.

[32] [a] M. Watanabe, V. Snieckus, *J. Am. Chem. Soc*. **1980**, *102*, 1457; [b] F. Keiser, L. Schwink, J. Velder, H.-G. Schmalz, *Tetrahedron* **2003**, *59*, 3201.

[33] Y. Kondo, M. Asai, T. Miura, M. Uchiyama, T. Sakamoto, *Org. Lett*. **2001**, *3*, 13.

[34] D. L. Comins, H. Hong, J. K. Saha, G. Jianhua, *J. Org. Chem.* **1994**, *59*, 5120.

[35] V. Snieckus, *Chem. Rev*. **1990**, *90*, 879.

[36] H. Gilman, R. L. Bebb, *J. Am. Chem. Soc*. **1939**, *61*, 109.

[37] G. Wittig, G. Fuhrman, *Chem. Ber*. **1940**, *73*, 1197.

[38] S. Harder, J. Boersma, L. Brandsma, J. A. Kanters, *J. Organomet. Chem*. **1988**, *339*, 7.

[39] B. J. Wakefield, *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, **1974**.

[40] [a] D. W. Slocum, C. A. Jennings, *J. Org. Chem*. **1976**, *41*, 3653; [b] J. E. Baldwin, K. W. Bair, *Tetrahedron Lett*. **1978**, *19*, 2559; [c] M. S. Newman, J. Kanakarajan, *J. Org. Chem*. **1980**, *45*, 2301.

[41] M. Watanabe, H. Maenosono, S. Furukawa, *Chem. Pharm. Bull. Jpn*. **1983**, *31*, 2662.

[42] D. L. Comins, J. D. Brown, *J. Org. Chem*. **1989**, *54*, 3730.

[43] [a] D. L. Comins, M. O. Killpack, *J. Org. Chem*. **1987**, *52*, 104; [b] D. L. Comins, J. D. Brown, *J. Org. Chem*. **1984**, *49*, 1078.

[44] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc*. **1980**, *102*, 5974.

[45] M. G. Finn, K. B. Sharpless in: J. D. Morrison (Ed.), *Assymmetric Synthesis* Vol. 5, Academic Press, Orlando, **1985**, 247-308.

[46] K. B. Sharpless, S. S. Woodard, M. G. Finn, *Pure Appl. Chem.* **1983**, *103*, 1823-1826.

[47] I. D. Williams, S. F. Pedersen, K. B. Sharpless, *J. Am. Chem. Soc.* **1984**, *106*, 6430-6431.

[48] W. Adam, P. Lupon, *Chem. Ber*. **1988**, *121*, 21.

[49] [a] A. K. Gosh, Y. Wang, *J. Org. Chem.* **1999**, *64*, 2789-2795; [b] A. F. Houri, Z. Xu,D. A. Cogan, A. H. Hoveyda, *J. Am. Chem. Soc.* **1995**, *117*, 2943-2944; [c] Z. Xu, W. Johannes, S. S. Salman, A. H. Hoveyda, *J. Am. Chem. Soc.* **1996**, *118*, 10926-10927.

[50] S. Y. Ko, A. W. M. Lee, S. Masamune, L. A. Reed III, K. B. Sharpless, F. J. Walker, *Science* **1983**, *220*, 949.

[51] D. Dominguez, M. P. Cava, *J. Org. Chem*. **1983**, *48*, 2820.

[52] A. Zeeck, M. Arnold, unpublished results.

[53] Antitumour activity was carried out by Prof. W. Beil at Medizinische Hochschule, Hannover, unpublished results. [a] W. Maison, J. V. Frangioni, *Angew. Chem.* **2003**, *115*, 4874; *Angew. Chem. Int. Ed. Engl*. **2003**, *42*, 4726; [b] D. Farquhar, A. Cherif, E. Bakina, A. J. Nelson, *J. Med. Chem*. **1998**, *41*, 965; [c] F. Arcamone, *Doxorubicin. Anticancer Antibiotics*; Academic Press: New. York. N. Y, **1981**.

[54] [a] C. Itakura, T. Sega, S. Suzukin, Y. Sumiki, *J. Antibiotics* **1963**, *16*, 231; [b] S. Marumo, K. Sasaki, S. Suzuki, *J. Am. Chem. Soc.* **1964**, *86*, 4507; [c] S. Marumo, K. Sasaki, K. Ohkuma, X. Anzai , S. Suzuki, *Ag. Biol. Chem.* **1968**, *32*, 209; [d] S. Marumo, K. Sasaki, S. Suzuki, *Ag. Biol. Chem.* **1971**, *35*, 1931.

[55] M. Arnold, *PhD Thesis*, Göttingen, **1998**.

[56] L. F. Tietze, G. Nordmann, *Eur. J. Org. Chem*. **2001**, *7*, 3247.

[57] C. Güntner, *PhD Thesis*, Göttingen, **2004**.

[58] [a] L. F. Tietze, W-R. Krahnert, *Chem. Eur. J.* **2002**, *8*, 2116; [b] L. F. Tietze, H. Schirok, M. Wöhrmann, *Eur. J. Org. Chem.* **2000**, *6*, 510; [c] L. F. Tietze, H. Schirok, M. Wöhrmann, K. Schrader, *Eur. J. Org. Chem.* **2000**, *6*, 2433.

[59] A. Modi, *PhD Thesis*, Göttingen, **2002**.

[60] W. J. Moran, E. C. Schreiber, D. Behn, J. L. Yamins, *J. Am. Chem. Soc.* **1952**, *74*, 127-129.

[61] D. A. Clark, F. De Riccardis, K. C. Nicolaou, Tetrahedron, **1994**, *50*, 11391-11426.

[62] S. Kajigaeshi, T. Kakinami, T. Okamoto, H. Nakamura, M. Fujikawa, *Bull. Chem. Soc. Jpn*. **1987**, *60*, 4187.

[63] T. Mino, S. Masuda, M. Nishio, M. Yamashita, *J. Org. Chem*. **1997**, *62*, 2633.

[64] C. L. Perrin, G. A. Skinner, *J. Am. Chem. Soc*. **1971**, *93*, 3389.

[65] [a] J. R. Vyvyan, R. E. Looper, *Tetrahedron Lett*, **2000**, *41*, 1151;[b] G. A. D. Holmberg, *Acta. Chem. Scand*, **1952**, *6*, 1137.

[66] L. Florvall, S. O. Ögren, *J. Med. Chem*. **1982**, 25, 1280.

[67] The bromination of the more accessible 3-bromo-4-methoxy-5-methyl-benzaldehyde was unsuccessful using several literature procedures.

[68] Ratio determined by crude ^{1}H NMR and upon later oxidation to aldehydes **126** and **127**.

[69] C. F. Thompson, T. F. Jamison, E. N. Jacobsen, *J. Am. Chem. Soc*. **2000**, *122*, 10482.

[70] K. B. Sharpless, R. C. Michaelson, *J. Am. Chem. Soc*. **1973**, *95*, 6136.

[71] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.

[72] L. Gentric, I. Hanna, L. Ricard, *Org. Lett*. **2003**, *5*, 1139.

[73] G. Bartoli, E. Marcantoni, M. Petrini, Angew. *Chem. Int. Ed. Engl*. **1993**, *32*, 1061.

[74] [a] L. A. Paquette, S. K. Huber, R. C. Thompson, *J. Org. Chem.* **1993**,*58*, 6874-6882; [b] T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, M. Yokoyama, *J. Org. Chem.* **1984**, *49*, 3904-3912.

[75] For aplication of the Heck reaction in natural synthesis, see: [a] L. F. Tietze, W-R. Krahnert, *Chem. Eur. J.* **2002**, *8*, 2116; [b] L. F. Tietze, H. Schirok, *J. Am. Chem. Soc.* **1999**, [c] L. F. Tietze, T. Nöbel, M. Spescha, *J. Am. Chem. Soc.* **1998**, *120*, 8971; [d] S. C. Stinson, *Chem. Eng. News* **1999**, January, 18, 81; for overviews see: [e] J. T. Link, L. E. Overman In *Metal-Catalyzed Cross-Coupling Reactions*; F. Diedrich, P. J. Eds. Wilea-VCH: New York, 1998.

[76] [a] R. F. Heck, *J. Am. Chem. Soc*. **1968**, *90*, 5518; [b] A. de Meijere, F. E. Meyer, *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 2379.

[77] M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein, *Organometallics* **1994**, *13*, 3465.

[78] W. A. Herrmann, C. B. Broßmer, K. Öfele, C-P. Reisinger, T. Priermeier, M. Beller, H. Fisher, *Angew. Chem.* **1995**, *107*, 1989; *Angew. Chem. Int. Ed*. *Engl*. **1995**, *34*, 1844.

[79] M. T. Reetz, G. Lohmer, R. Schwickardi, *Angew. Chem. Int. Ed*. *Engl*. **1998**, *37*, 481.

[80] M. Beller, H. Fisher, W. A. Herrmann, K. Öfele, C. Broßmer, *Angew. Chem.* **1995**, *107*, 1992; *Angew. Chem. Int. Ed*. *Engl*. **1995**, *34*, 1848.

[81] [a] M. R. Netherton, G. C. Fu, *Org*. *Lett.* **2001**, *3*, 4295; [b] A. F. Littke, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989.

[82] For example see: [a] D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722; [b] W. Shen, *Tetrahedron Lett.* **1997**, *38*, 5575; [c] Y. Ben-David, M. Portnoy, D. Milstein, *J. Am. Chem. Soc.* **1989**, *111*, 8742.

[83] M. Lautens, Y.-Q. Fang, *Org. Lett.* **2003**, *5*, 3679.

[84] [a] C. Gürtler, S. L. Buchwald, *Chem. Eur. J.* **1999**, *5*, 3107; [b] A. F. Littke, G. C. Fu, *J. Org. Chem.* **1999**, *64*, 10

[85] [a] T. Jeffery, *Tetrahedron Lett*. **1985**, *26*, 2667; [b] T. Jeffery, *Synthesis* **1987**, *1*, 70.

[86] E. J. Corey, C. J. Helal, Angew. Chem. **1998**, *110*, 2092.

[87] H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chm. Rev.* **1994**, *94*, 2483.

[88] P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936-3938.

[89] Y. Tanoue, A. Terada, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2039-2045.

[90] [a]Y. Tamura, T. Yakura, J. Haruta, Y. Kita, *J. Org. Chem*. **1987**, 52, 3927-3930; [b] A. Pelter, S. M. A. Elgendy, *J. Chem. Soc. Perkin Trans.1* **1993**, 1891-1896; [c] A. McKillop, L. McLaren, R. J. K. Taylor, *J. Chem Soc. Perkin Trans. 1* **1994**, 2047-2048.

[91] MeOH was added because of the limited solubility of CAN in organic solvents as well as a reagent form the desired monoacetal.

[92] J. S. Swenton, D. K. Anderson, C. E. Coburn, A. P. Haag, *Tetrahedron* **1984**, *40*, 4633.

[93] S. B. Cohen, R. L. Halcomb, *J. Org. Chem*. **2000**, *65*, 6145.

[94] D. D. Perrin, W. L. F. Armarego*, Purification of Laboratory Chemicals*; Pentagon Press: Oxford; **1988**, 3rd ed.

[95] [a] J. R. Vyvyan, R. E. Looper, *Tetrahedron Lett*, **2000**, *41*, 1151; [b] G. A. D. Holmberg, *Acta. Chem. Scand*, **1952**, *6*, 1137.

[96] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc*. **1991**, *113*, 7277.

11 Glossary

The following abbreviations have been used throughout this thesis:

Ac	acetyl
aq	aqueous
Bn	benzyl
Bu	butyl
*t*Bu	*tert*-Butyl
ca. *circa*	(approximately)
CAN	cerammoniumnitrate
cat.	catalyst
conc.	concentration
CSA	camphorsulfonic acid
Cy	cyclohexyl
δ	chemical shifts (parts per million)
d	days
dba	dibenzilideneacetone
Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2 benziodo -3(1*H*)-one –
DMF	*N, N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	Electron Impact
equiv.	equivalents
et al.	*et alia* (and others)
eV	electron volt
HB cat.	*trans*-di(μ-acetato)-bis[ortho-(di-*ortho*-tolylphosphino) benzyl]dipalladium (II)

HRMS	High Resolution Mass Spectroscopy
Hz	herz
IR	infrared
J	coupling constant (Hz)
m-CPBA	*m*-chloroperbenzoic acid
min	minutes
m.p.	melting point (°C)
MS	mass spectrum
m/z	mass-to-charge ratio
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
ν_{max}	infrared absorption maxima (cm^{-1})
Red-Al	sodium bis(2-methoxyethoxy)-aluminium hydride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TIPS	tri-isopropylsilyl
TLC	thin layer chromatography
p-TsOH	*p*-toluenesulfonic acid
UV	ultraviolet
via	by way of
TriMEDA	tri-methylethylendiamine
TMEDA	tetra-methylethylendiamine

12 Acknowledgments

Firstly and mostly, I would like to thank the love of my life, Scott Stewart for the most wonderful time in the lab and at home. Without Scott this work wouldn't be possible. There are no words which can express my gratitude and feelings.

Thanks to the members of Tietze's group, especially to Gordon Brasche and Kersten Gericke for true friendship and yummy dinners, to Felix Major for great time during übungen. To the members of lab 408, Carlos Güntner, Kasia Klapa, Dirk Spiegel, Deshan Liu, Michael Wöhrmann, Peter Steck. Dear nachbar labor Christian „Kleines", Holger Braun, Francisco Colunga and Oliver Elsner, Carsten Vock, Ilga Krimmelbein, who made my time in Göttingen enjoyable.

Thanks to all NMR abteilung, Mr. R. Machinek, Frau C. Sibet, Mr. Udvarnoki and Mr. H. Frauendorfer and E. Pfeil for very fast and good work.

A special thanks to my best friend Aleks Biarda for 27 years of friendship. I also would like to thank my friends from Gdansk, especially Slawek Walicki, Ania Naganowska, Agnieszka Wichrowska, Joanna Dziemidowicz, Beata & Kris Przeorscy, and last but not least Aga Komisarczyk. To my "new" Australian friends from Göttingen Linda & Duncan Wild, I'm lucky to have you guys!

I would like to thank my former supervisors Professor Janusz Rachon and Witold Przychodzen who helped me to begin my adventure in organic chemistry, furthermore, all members of Institute of Organic Chemistry at Technical University Gdansk for beautifull atmosphere for work.

I'm extremely grateful to my lovely mum Helena who was and will be inspiration for me, to my dad Wojtek for all of his love and support, special thanks to my "favorite" Aunty and Uncle, Ewa & Piotr Spychalowie for their constant generosity and friendship.

Curriculum Vitae

Personal Details :

Name:	Marta Polomska
Date of Birth:	04.10.1977
Place of Birth:	Gdansk
Marital Status:	Engaged
Nationality:	Polish

Education History:

1984-1992	Primary School
1992-1996	I Private High School in Gdansk
05/1996	Abitur (GCSE)

University:

10/1996-07/2001	Study of Chemistry at Technical University of Gdansk, Faculty of Chemistry
10/2000-07/2001	Master of Science at Technical University of Gdansk Department of Organic Chemistry Under the supervision of Prof. J. Rachon on the theme "Thionation of mixed *N*-hydeoxyamide-amide systems"
07.13.2001	Master of Science, Chemistry, Final Examination
10/2001-10/2003	Ph.D. completed at Georg-August Universität, Institut für Organische Chemie. Under the supervision of Prof. Dr. Dr. L. F. Tietze on the theme "Towords Total Synthesis of the Anti-Cancer Agent Mensacarcin"