Catalytic Insertion Reactions into the Cyclopropane Ring

Syntheses of Various Belactosin C Congeners and Analogues

DISSERTATION

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

vorgelegt von

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aus

Sankt-Petersburg (Russland)

Göttingen 2008

D7

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Tag der mündlichen Prüfung: 2. Juli 2008

Die vorliegende Arbeit wurde in der Zeit von Oktober 2004 bis Juli 2008 im Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen unter der wissenschaftlichen Anleitung von Prof. Dr. Armin de Meijere angefertigt.

Für die Überlassung des Themas, die hilfreichen Diskussionen und Anregungen, sowie die ständige Unterstützung während der Arbeit möchte ich meinem Lehrer, Herrn Prof. Dr. Armin de Meijere, ganz herzlich danken.

Der Degussa-Stiftung danke ich für die Gewährung eines Promotionsstipendiums.

Meinen Eltern

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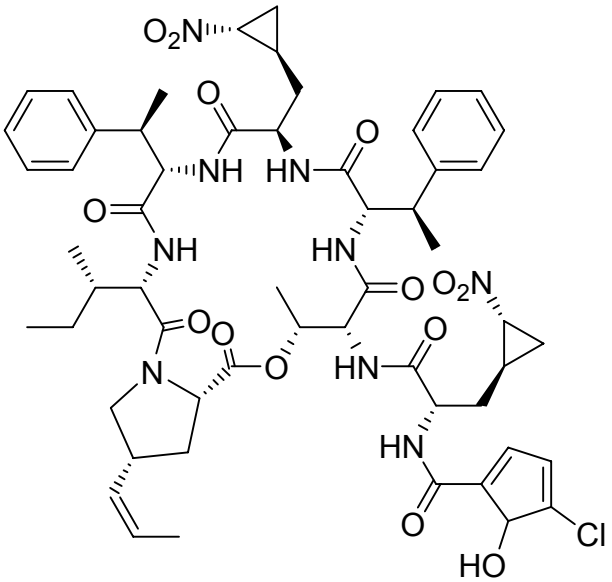
Abbreviations

Ac	=	acetyl
Bn	=	benzyl
Boc	=	*tert*-butyloxycarbonyl
BOP	=	benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
BOP-Cl	=	bis(2-oxo-3-oxazolidinyl)phosphonic chloride
Bz	=	benzoate
Cbz	=	benzyloxycarbonyl
de	=	diastereomeric excess
DMAP	=	4-dimethylaminopyridine
DMF	=	*N,N*-dimethylformamide
DMSO	=	dimethyl sulfoxide
EDC	=	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	=	enantiomeric excess
Fmoc	=	9*H*-fluoren-9-ylmethoxycarbonyl
HATU	=	(2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HOAt	=	1-hydroxy-7-azabenzotriazole
Ms	=	methanesulfonyl (mesyl)
PG	=	protective group
THF	=	tetrahydrofuran
TMP	=	2,4,6-trimethylpyridine

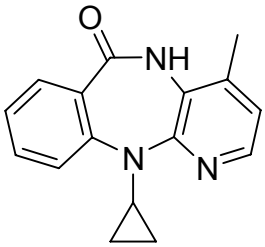
Introduction and Background

1. Cyclopropane Opening Reactions

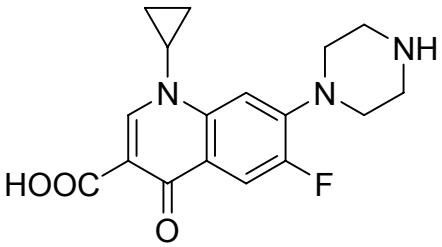
The chemistry of cyclopropane-containing substances has attracted great attention since the first synthesis of cyclopropane in 1882.[1] At first, cyclopropane and its derivatives were conceived as laboratory curiosities due to their relatively late first syntheses, but soon thereafter substituted cyclopropanes were discovered as subunits in natural products and biologically active substances. In the meantime, detailed investigations of the biological activities of such compounds have disclosed the significance of the cyclopropane moiety for many biological activities. Some recent examples are Hormaomicyn **1,** a secondary metabolite isolated from *Streptomyces griseoflavus*, the anti-HIV Nevirapine **2** and the potent antibiotic Ciprofloxacin **3**.



1 (Hormaomycin)



2 (Nevirapine)

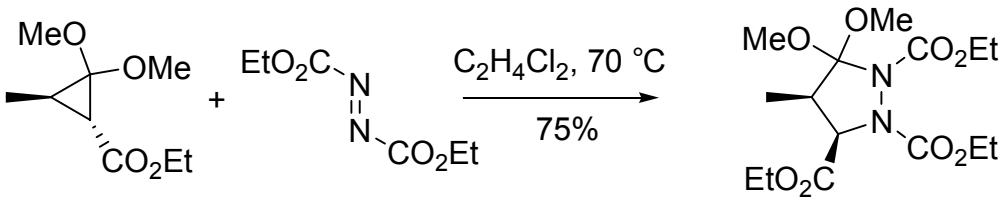


3 (Ciprofloxacin)

Figure 1. Recent examples of cyclopropane-containing biologically active compounds.

Detailed investigations of their transformations in biological systems have shown that cyclopropane moieties often undergo ring opening reactions, thus leading to a variety of other groups.[2] Bearing in mind that many highly efficient methods for the preparation of cyclopropanes have been developed, it has become attractive to use cyclopropane-containing compounds as intermediates en route to other types of targets. On the other hand, the selective catalytic activation of C-C σ-bonds has emerged as one of the most challenging problems in modern organic synthesis. The bonds in a cyclopropane ring, due to their inherent strain and unique electronic features,[3] undergo such an activation much more easily than those in alkanes and cycloalkanes of larger ring size. The bonds in cyclopropane derivatives with donor and acceptor substituents on the same ring are even more reactive.

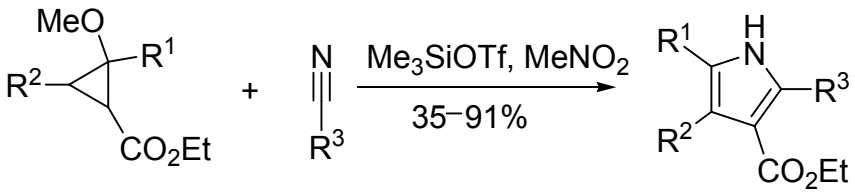
Many opening reactions of donor-acceptor substituted cyclopropanes have been studied so far. The most important achievements in this field before 2003 have been reviewed.[4] Most of the cases described in this review deal with the capability of cyclopropanols to undergo ring-opening rearrangements. One of the exceptions is the thermal reaction of cyclopropropanes with azodicarboxylates described by Graziano et al. (Scheme 1).[5]



4 **5** **6**

Scheme 1. Thermal reaction of diethyl azodicarboxylate **5** with donor-acceptor-substituted cyclopropane.[5]

After 2003, an important new type of cyclopropane opening reaction, namely, catalyzed enlargement reactions of three-membered rings, has been reported. The first example to mention here is the pyrrole synthesis of Pagenkopf et al (Scheme 2).[6]

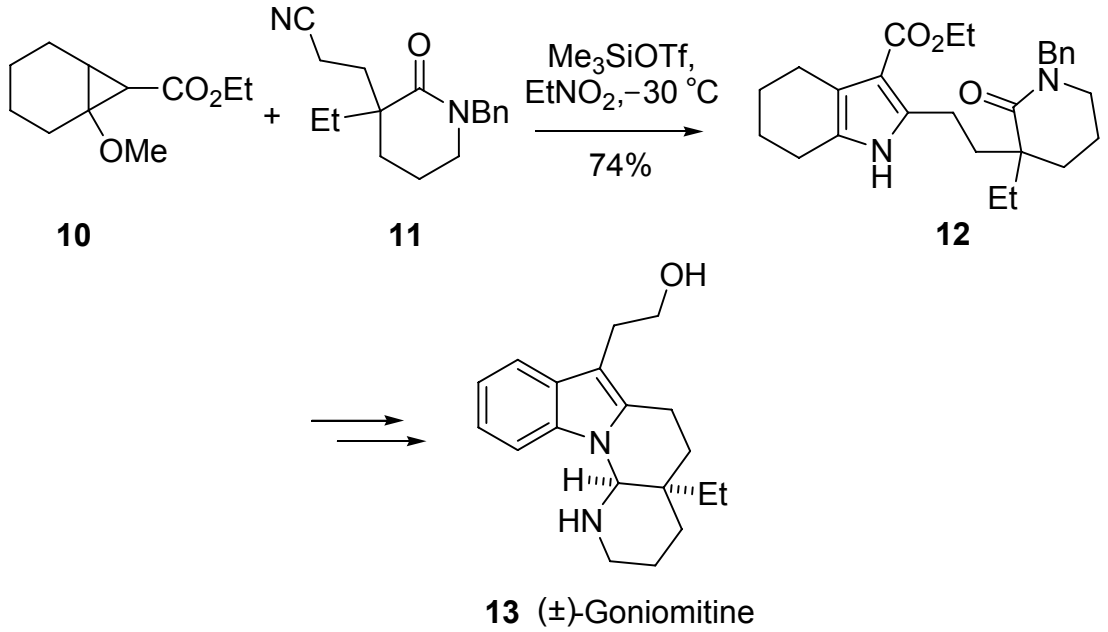


7 **8** **9**

Scheme 2. Formation of pyrroles by the insertion of a nitrile into a cyclopropane ring.[6]

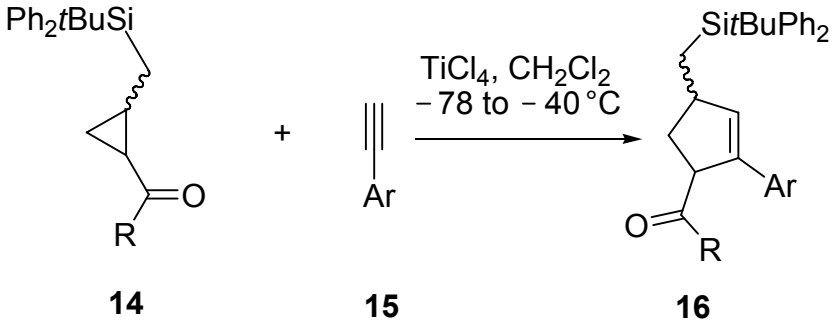
Here the insertion into the cyclopropane ring is followed by an elimination of methanol. However, if the starting cyclopropanes are chosen in such a way, that the elimination becomes impossible, the reaction ends up in a pyrroline formation.[7] Other types of the annelation partners can be also employed in this reaction, for example, pyridines[8] and indoles.[9]

This reaction was also successfully used in a key step of the total synthesis of the indole alkaloid goniomitine (Scheme 3).[10]



Scheme 3. Application of the insertion reaction to the total synthesis of (±)-Goniomitine **13**.[10]

Arylacetylenes[11] and allenes[12] also turned out to be appropriate partners for the reactions with cyclopropanes. Their insertions led to the formation of five- (in the case of arylacetylenes) or a mixture of six- and five-membered rings (in the case of allenes).

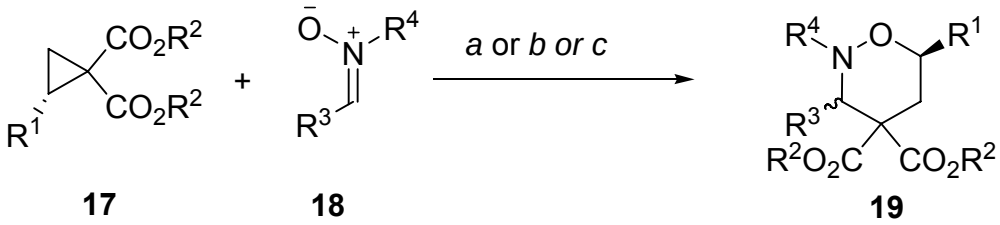


Scheme 4. Insertions of acetylenes into the cyclopropane ring.[11]

One of the most widely employed types of cyclopropanes are the cyclopropane-1,1-

dicarboxylates **17**. The presence of two carboxylate groups activates the C-C bonds of these compounds. The coordination of these groups to the catalyst ions can lead to an additional activation and even to a cleavage of the C-C bond. A donor aryl or vinyl substituent makes the cyclopropanes even more reactive.

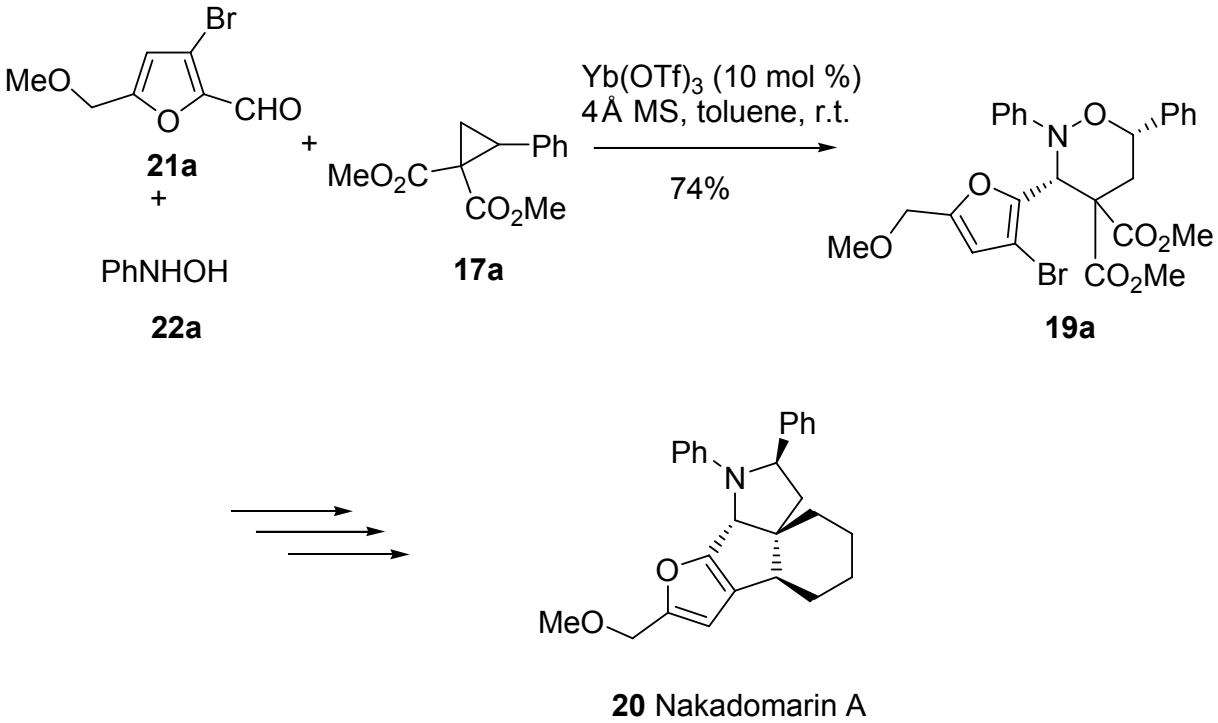
Another thoroughly studied insertion process is the reaction of cyclopropane-1,1-dicarboxylates **17** with nitrones **18**. The latter, being very reactive substances, even participate in reactions with cyclopropanes that do not even bear donor substituents. Nonstereospecific as well as enantioselective variants of this reaction have been developed (Scheme 5).[13]



Scheme 5. Reaction of cyclopropane-1,1-dicarboxylates **17** with nitrones **18**.[13] Reagents and conditions: (*a*) R^1 = H, $Ni(ClO_4)_2$ (30 mol.%), BOX-type ligand, CH_2Cl_2, 2 d, r. t., 39–99%[14], (b) R^1 = Ar, $Yb(OTf)_3$ (10 mol.%), CH_2Cl_2, r. t., 90–97%[15, 16] (c) (b) R^1 = Ar, MgI_2 (10 mol.%), THF, r. t., 45–99%[17]

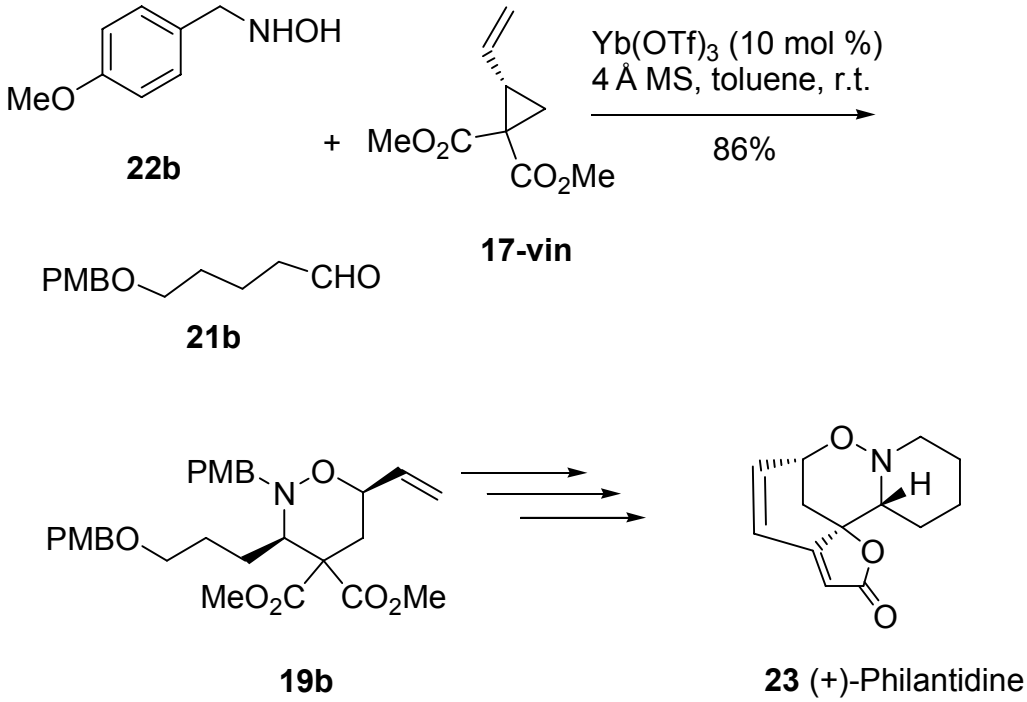
The interest in this reaction has been enhanced because the antitumor, antibiotic natural products FR9004821 and FR66979, related to the anticancer drug mitomycin C, have a structural motif similar to the products of this transformation.

This reaction turned out to be useful in some total syntheses. For example, it was employed in the construction of the tetracyclic core of Nakadomarin A (**20**) (Scheme 6).[18]



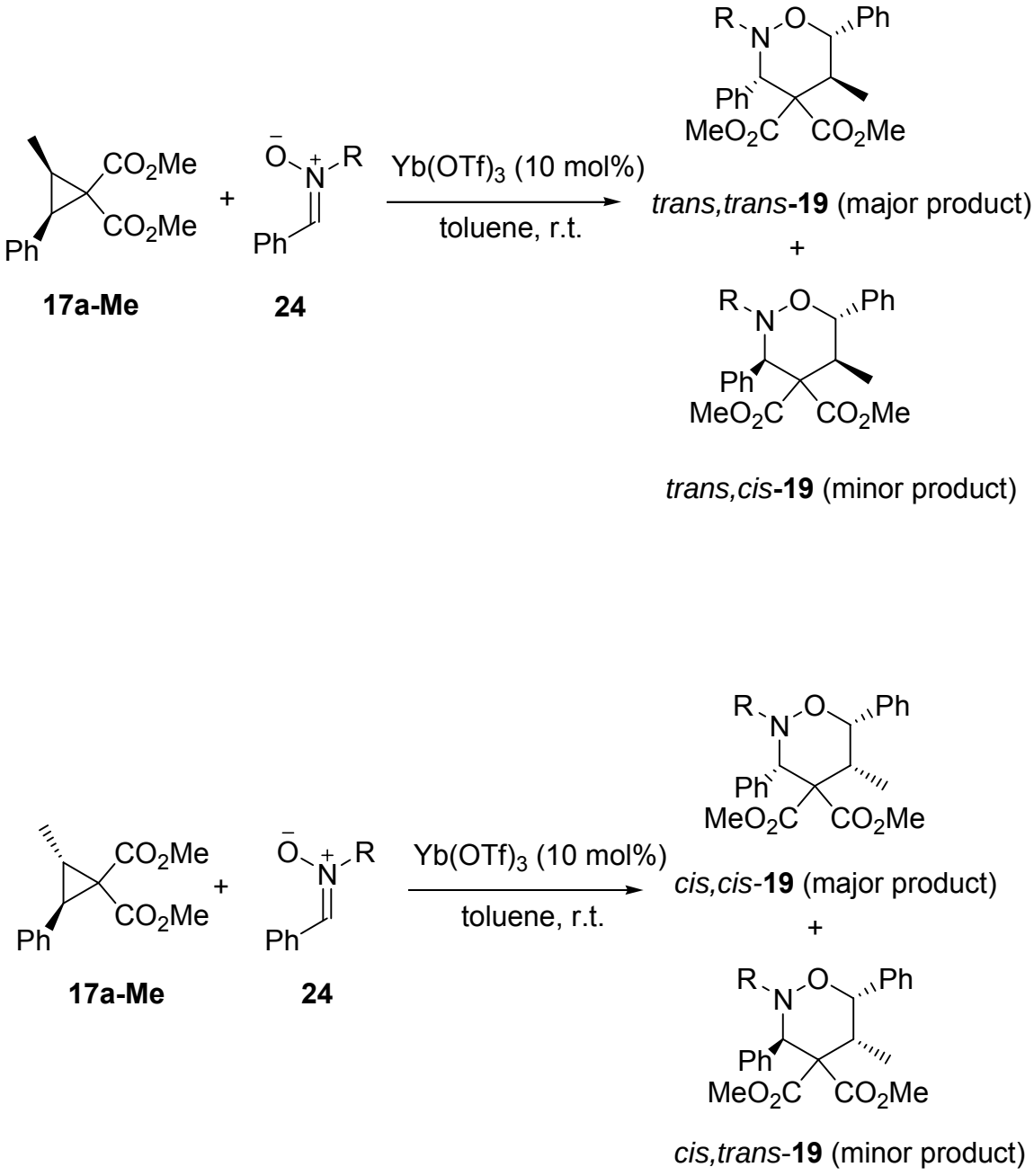
Scheme 6. Use of an insertion reaction in the total synthesis of the tetracyclic core of Nakadomarin A.[18]

It has also been employed in the synthesis of (+)-Philantidine (**23**) (Scheme 7).[19]



Scheme 7. Application of an insertion reaction in the total synthesis of (+)-Philantidine **23**.[19]

The mechanism of this reaction has also been studied. The most fundamental question is, whether this reaction proceeds stepwise or in a concerted fashion. Therefore the reaction of enantiomerically enriched 3-methyl-2-phenylcyclopropane-1,1-dicarboxylates with nitrones was performed (Scheme 8).[20]

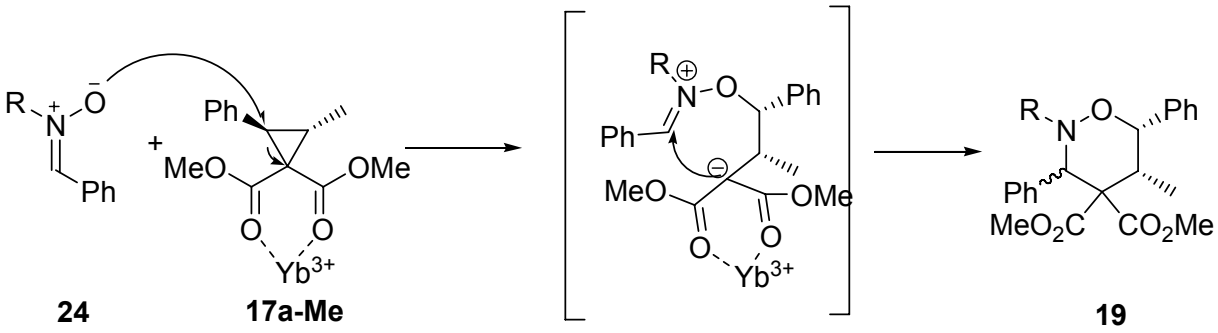


Scheme 8. Study of the mechanism of the insertion.[20]

The main conclusion to be drawn from the results is that the cyclopropane-ring enlargement proceeds with inversion of the configuration at C2. An analogous behavior

was observed for the *trans*-diastereomer of the starting cyclopropane derivative (Scheme 8).

These results ruled out the possibility of a concerted reaction mode and at the same time supported a stepwise one. The first step of this reaction is thought to be the formation of the complex with the catalyst metal ion. The next step is then an attack of the negatively charged nitrone O-terminus onto the carbon atom of the cyclopropane moiety bearing the aryl substituent with the formation of a 1,6-zwitterion that readily undergoes ring closure (Scheme 9).

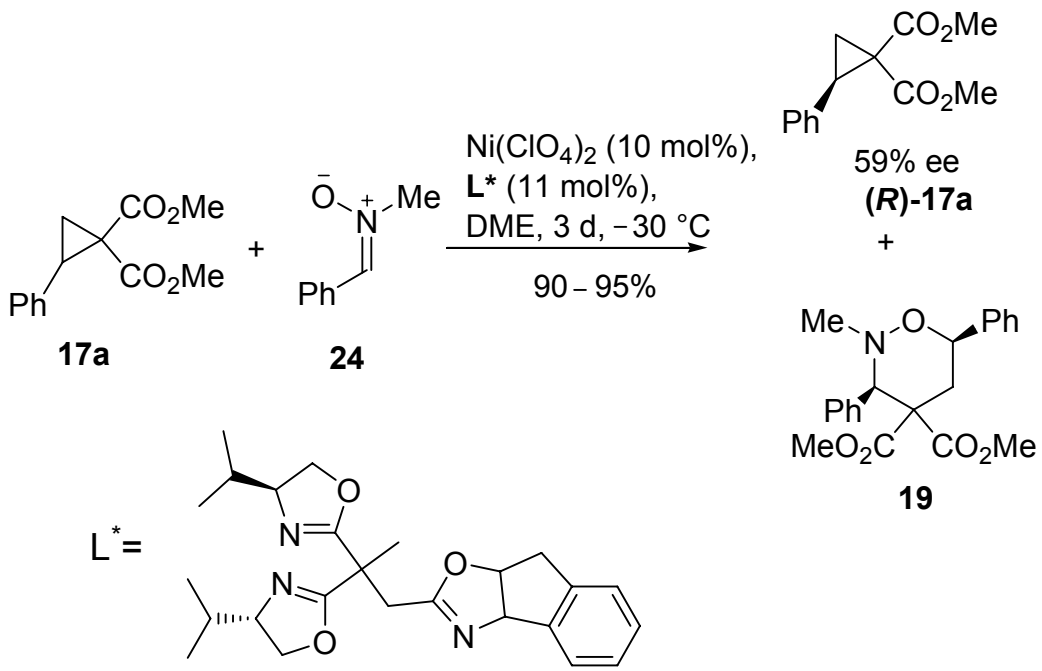


Scheme 9. The proposed mechanism of the nitrone insertion into the cyclopropane ring.[20]

This mechanism can be considered to some extent as an analogue of an S_N2 nucleophilic substitution, with the carbon atom bearing two carboxylates as a leaving group. The sterical outcome strongly supports this similarity.

The mechanism of the cyclopropane opening analogous to S_N1, proceeding *via* the initial dissociation of the C1-C2 cyclopropane bond with the formation of the zwitterion, also appears to be possible. For this path a stabilization of the zwitterion (by a stronger Lewis acid, for example) would be required.

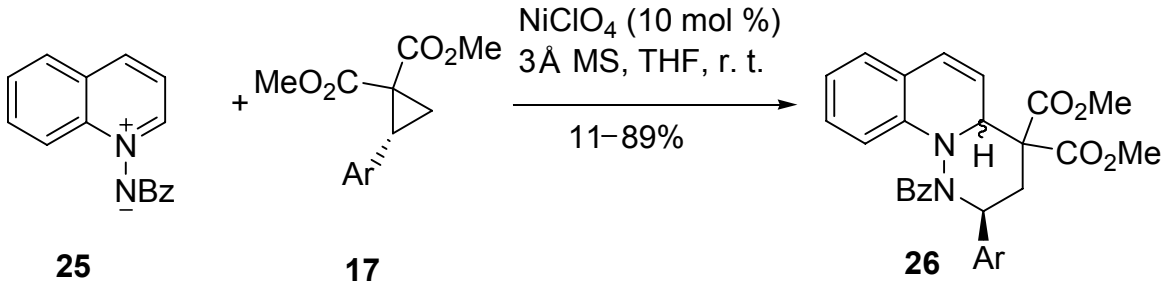
The same reaction with a chiral catalyst prepared *in situ* from $Ni(ClO_4)_2$ and a BOX-type trisoxazolidine ligand **L*** was shown to be applicable for the kinetic resolution of the starting cyclopropanedicarboxylates (Scheme 10).[21]



Scheme 10. Asymmetric variant of the insertion of nitrones into the cyclopropane ring and its application to the separation of cyclopropane enantiomers.

After two to three cycles an *ee* value of up to 91% could be achieved.

Since azomethineimines are also 1,3-dipoles and thus can be regarded as nitrone analogues, they consequently can also take part in enlargement reactions of cyclopropanes (Scheme 11).[22]

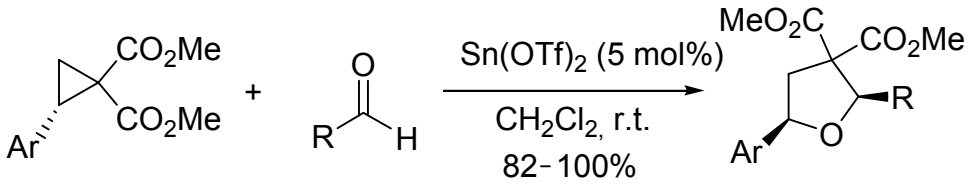


Scheme 11. Insertion of azomethineimines into the cyclopropane ring.[22]

It would be logical to expect that the mechanism of this reaction is analogous to that with nitrones, and the observations of the stereochemical outcome, the inversion of configuration of the C2 atom of the cyclopropane as well as the complete loss of the stereochemical information at the C1 atom, strongly support this assumption.

The same types of cyclopropanes were involved in other reactions. It was shown that they can react with aldehydes regioselectively giving substituted tetrahydrofurans

(Scheme 12).[23]

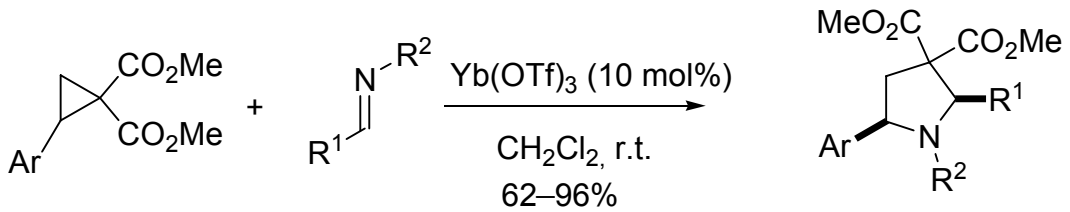


17 **20** **27**

Scheme 12. Insertion of aldehydes into the cyclopropane ring.

This reaction also proceeds with inversion of the configuration of the cyclopropane C2 atom (Scheme 12). This fact is in a good agreement with the mechanism described above.

A completely analogous reaction has been observed with *in situ* formed imines (Scheme 13).[24]



17 **28** **29**

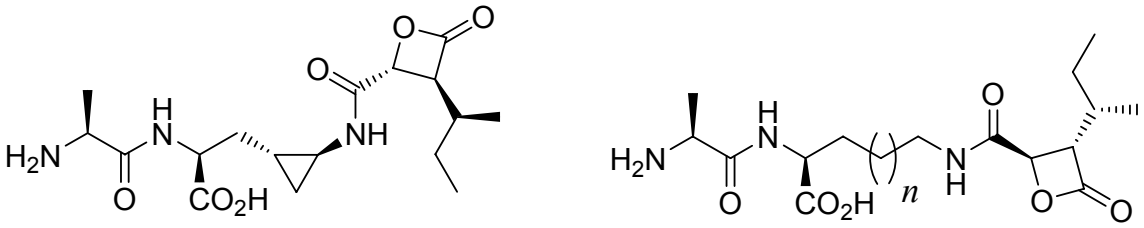
Scheme 13. Insertion of imines into the cyclopropane ring.

Since no such reactions with enantiomerically pure cyclopropanes were performed, the stereochemical features of this reaction cannot be discussed in detail.

All these results demonstrate that cyclopropane ring enlargement reactions have already become a versatile tool towards the assembly of more complex molecules. Yet, the potential of such reactions is certainly much greater than presented here, and much more is to be done. Other types of unsaturated compounds that deserve to be tried are diazenes, isocyanides as well as nitroso, and even nitro compounds.

2. Syntheses of Belactosin Analogues

As was already mentioned above, many natural compounds contain a cyclopropane moiety. A particularly interesting example is the so-called Belactosin A containing a 3-*trans*-(2-aminocyclopropyl)alanine residue.



30 (Belactosin A)

31 *n*=1 (Belactosin C)
32 *n*=2 (Homobelactosin C)

Figure 2. Members of the Belactosin family of natural products and analogues.[25]

Belactosin A and its non-cyclopropyl analogue Belactosin C were isolated from the fermentation broth of *Streptomyces* sp. UCK14[25] and were found to be highly potent proteasome inhibitors. As it turned out, the β-lactone moiety is crucial for the biological activity observed. The chemistry of β-lactones has attracted a great deal of attention from various research groups during the last 10 years. Among them, (–)-Panclicin D,[26] Omuralide,[27] Vibralactone,[28] Salinosporamide A,[29] Cinnabaramide[30] and others have been isolated, synthesized and intensively investigated.

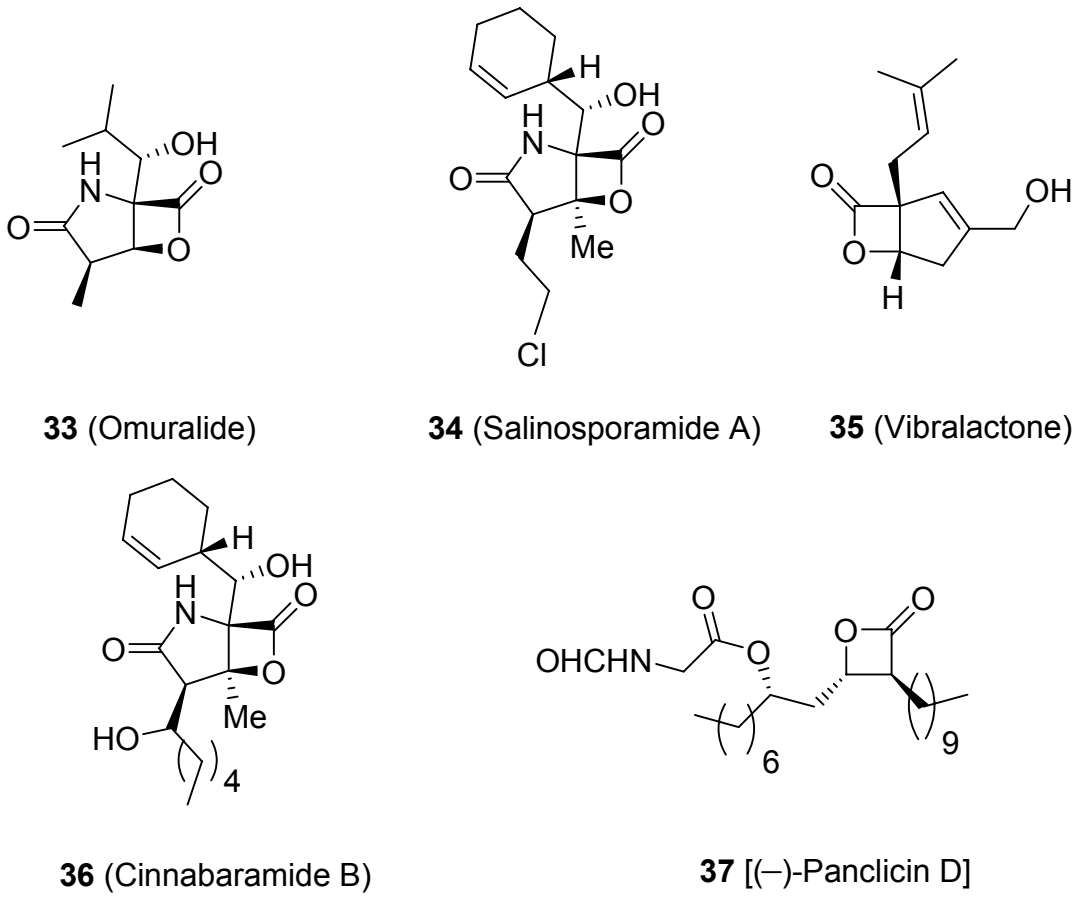
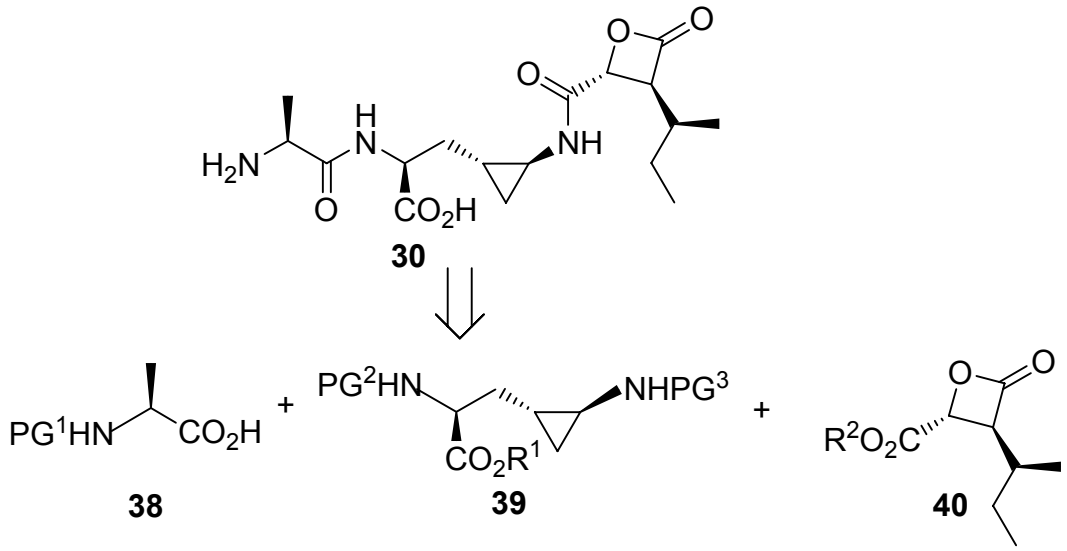


Figure 3. Natural products containing β-lactone moieties.

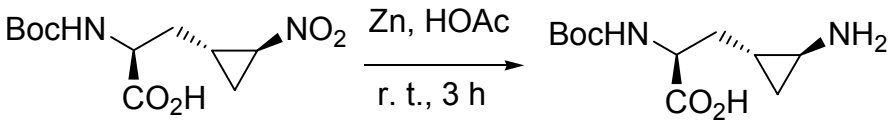
Accordingly, the results of these investigations can be compared with those obtained for the Belactosins, and molecular modelling can lead to hybrid structures with improved activities.[31] All the previously developed syntheses of Belactosines are essentially variants of the same retrosynthetic strategy (Scheme 14).



Scheme 14. Retrosynthetic analysis of the Belactosin A molecule.

The Belactosin molecule is composed of an (*L*)-alanine residue **38**, a *trans*-2-(aminocyclopropyl)alanine unit **39** [(*L*)-ornithine in the case of Belactosin C] and a β-lactonecarboxylate **40**. Both the synthesis of 3-(*trans*-2-aminocyclopropyl)alanine **39** and of the β-lactone had to be newly developed.

Larionov and de Meijere made 3-(*trans*-2-aminocyclopropyl)alanine **42** accessible by reduction of the nitro group in the previously prepared 3-(*trans*-2-nitrocyclopropyl)alanine (**41**) (Scheme 15).[32]

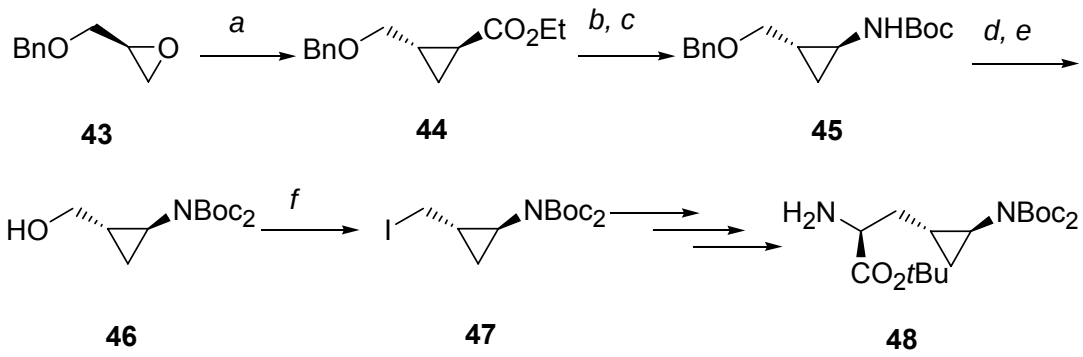


41 **42**

Scheme 15. Synthesis of protected 3-(*trans*-2-aminocyclopropyl)alanine (**42)** according to de Meijere et al.[15]

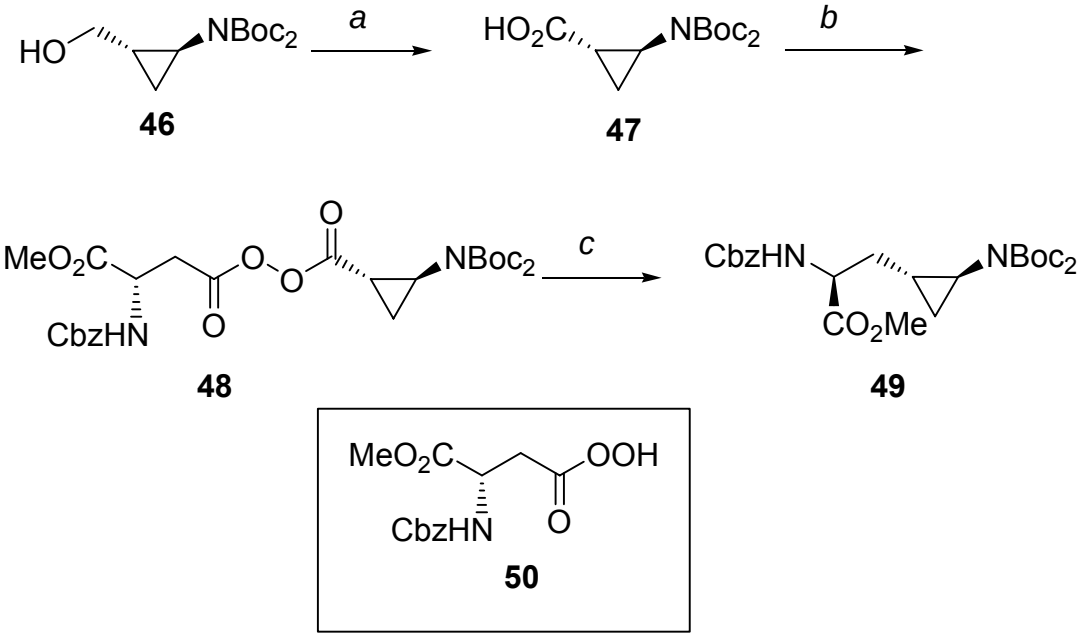
The synthesis of the starting material **41** is a bit tricky, but nevertheless the access to **42** via **41** appears to be the best one to date.

Another synthesis of this building block for Belactosin A was developed by Armstrong and Scutt. It is based on the transformation of (*R*)-glycidol benzyl ether into ethyl 2-(benzyloxymethyl)cyclopropanecarboxylate, which is subsequently subjected to a Curtius degradation. The product obtained was further transformed into the bis-Boc-protected 2-(iodomethyl)cyclopropylamine **47** which was employed in an enantioselective alkylation of a glycine enolate (Scheme 16).[33,34]



Scheme 16. Synthesis of protected 3-(*trans*-2-aminocyclopropyl)alanine **48** according to Armstong et al.[33,34] Reagents and conditions: (*a*) Triethyl phosphonoacetate, Na, toluene, 110 °C, 14 h, 63% (*b*) NaOH (aq.), EtOH, 96% (*c*) DPPA, *t*BuOH, NEt_3, reflux, 53% (*d*) Boc_2O, DMAP, MeCN, 95%, (*e*) Pd/C, H_2, HOAc, THF, 98%. (*f*) Bu_4NI, DDQ, PPh_3, $CHCl_3$, r.t.

Yet another route from the 2-(hydroxymethyl)cyclopropylamine **46** to the tris-protected (aminocyclopropyl)alanine **49** was reported by Vederas et al. (Scheme 17).[35]

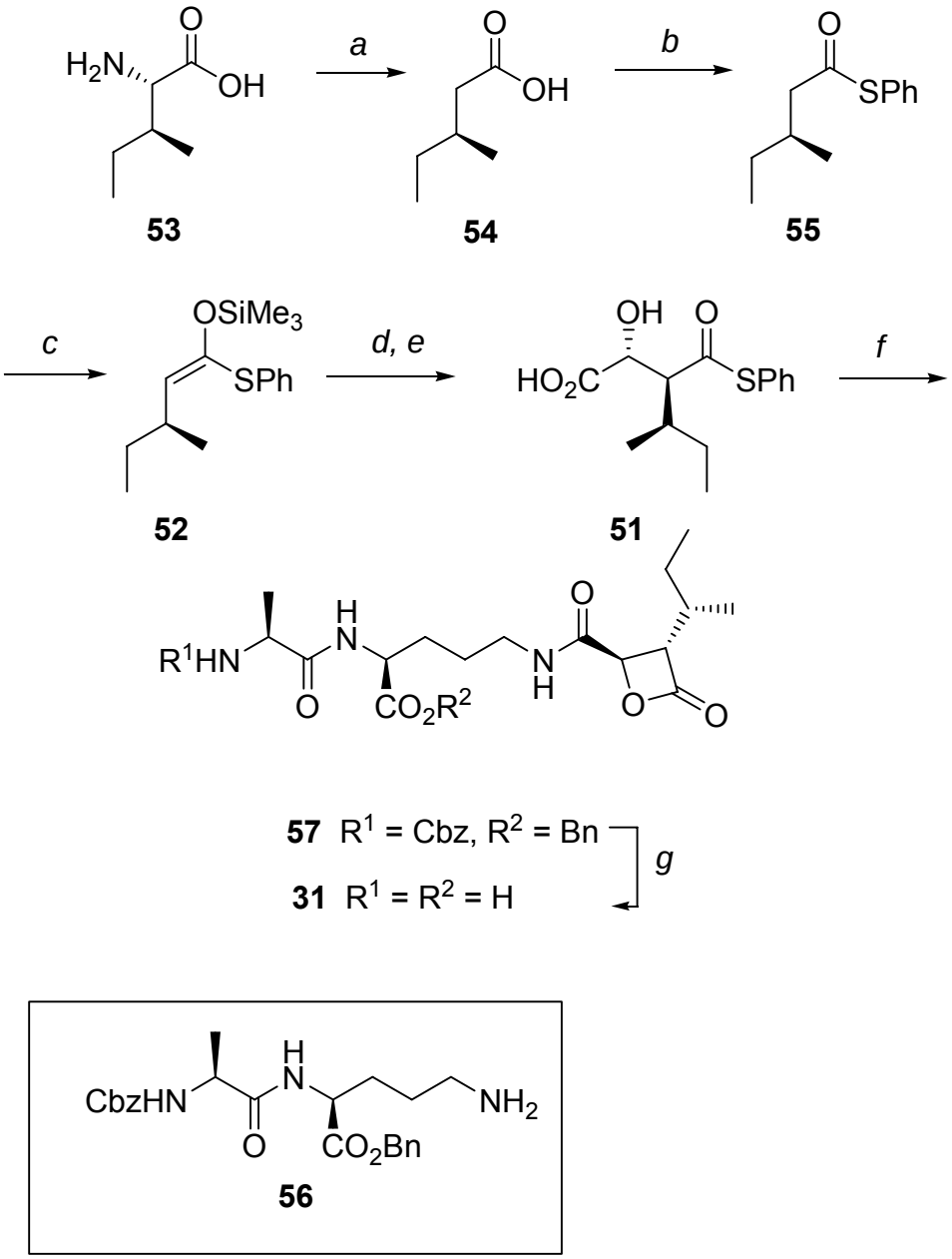


Scheme 17. Synthesis of trisprotected methyl 3-(*trans*-2-aminocyclopropyl)alanine according to Vederas et al.[35] Reagents and conditions: (*a*) $RuCl_3$, $NaIO_4$, 74% (*b*) **50**, DCC, 83% (*c*) hν, 254, 36 h, 47%

In this synthesis, the center of chirality in the side chain is introduced with the

derivative **50** of peroxyaspartic acid by photochemical extrusion of two CO_2 molecules. This synthesis has fewer steps, but the obvious disadvantage of having to deal with thermally labile and explosive peroxides limits the scale of this synthesis.

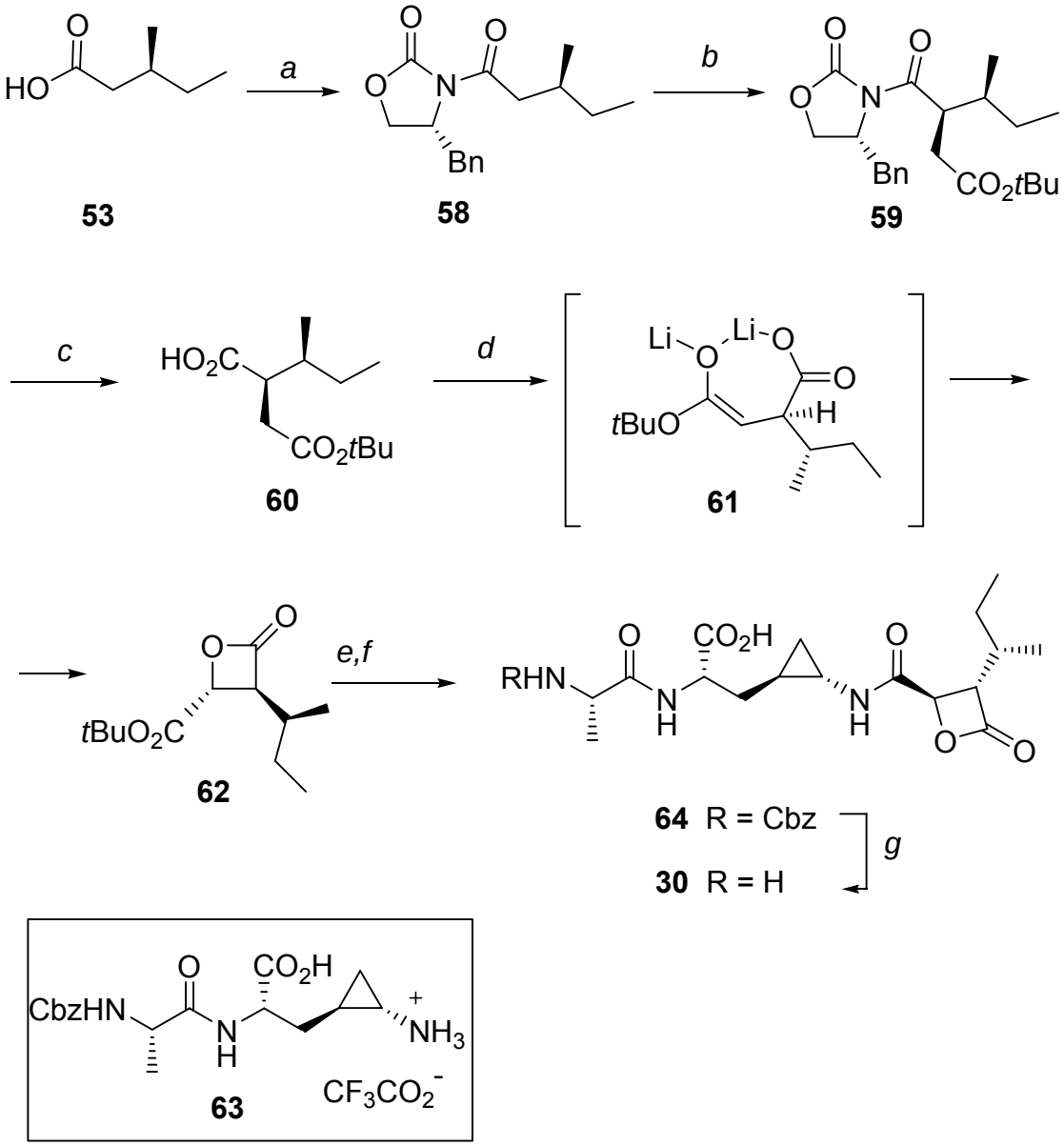
For the construction of the β-lactone moiety in the Belactosins, Larionov and de Meijere[36] employed a cascade peptide coupling/β-lactonization sequence of the substituted malic acid derivative **51**. The latter was obtained by chemoselective ester hydrolysis of the product of a tin triflate-BOX-catalyzed enantioselective aldol reaction of ethyl glyoxylate with the ketene *O*, *S*-acetal **52** (Scheme 18).



Scheme 18. Synthesis of Belactosin C according to de Meijere and Larionov.[36] Conditions: (*a*) H_2NOSO_3H, NaOH, H_2O, 0 °C, 6 h, reflux, 3 h, 87%; (*b*) DCC, PhSH,

DMAP, CH_2Cl_2, 0 °C to rt, 7 h, 92%; (*c*) LiTMP, Me_3SiCl, THF, –78 °C, 16 h, 90%; (*d*) EtO_2CCHO, $Sn(Otf)_2$ (10 mol %)/**BOX** (11 mol %), CH_2Cl_2, –78 °C, 20 h, then 2 N HCl, THF, rt, 2 h, 96%; (*e*) 10% aq HCl, dioxane (1 : 6), 60 °C, 51 h, 90%. (*h*) H_2, Pd/C, AcOH, r. t., 15 h, 80%.

The synthesis of Belactosin C in seven steps proceeds with an overall yield of 35%. Analogously, Belactosin A was obtained in an overall yield of 32% from the acid **41.** Armstrong and Scutt employed another possibility in that they established the first stereocenter by a diastereoselective alkylation of the Evans amide **58** and the second by diastereoselective chlorination of the substituted succinic acid monoester **60** followed by cyclization to the β-lactone (Scheme 19).[34]

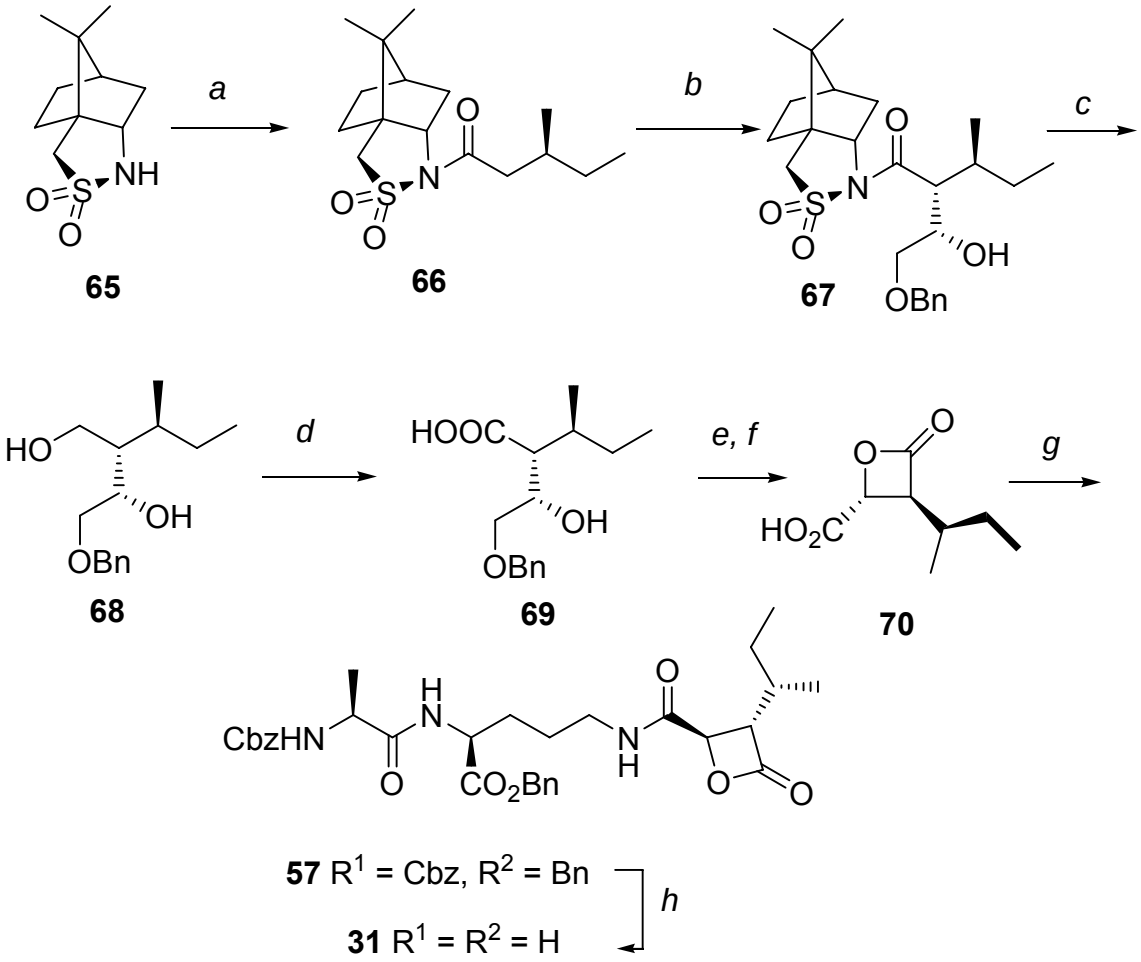


Scheme 19. Synthesis of Belactosin A according to Armstrong and Scutt.[34] Reagents and conditions: (*a*) (1) $(COCl)_2$, CH_2Cl_2, 0 to 20 °C, 80% (2) (4*R*)-benzyl-2-oxazolidinone, BuLi, –78 °C, 79% (*b*) *tert*-butyl bromoacetate, $NaN(SiMe_3)_2$, –78 °C, 82% (*c*) LiOH (aq), H_2O_2, 0 to 20 °C, 92% (*d*) $LiN(SiMe_3)_2$, CCl_4, –78 to 20 °C; then ether/$NaHCO_3$, 55% (*e*) TFA, CH_2Cl_2, 0 °C, 20 h, 90%. (*f*) (1) EDC, HOBt, CH_2Cl_2, 0 °C, (2) **63**, $EtNiPr_2$, DMF, 0 °C, 50% (*g*) H_2, Pd/C, THF/HCO_2H (3 : 2), r. t., 15 h, 96%.

The chlorination of **60** proceeds in a stereoselective manner *via* the stabilized lithium enolate chelate **61**. The overall yield in this synthesis was 15%.

For the route of Kumaraswamy et al.,[37] an analogous idea for the establishment of the

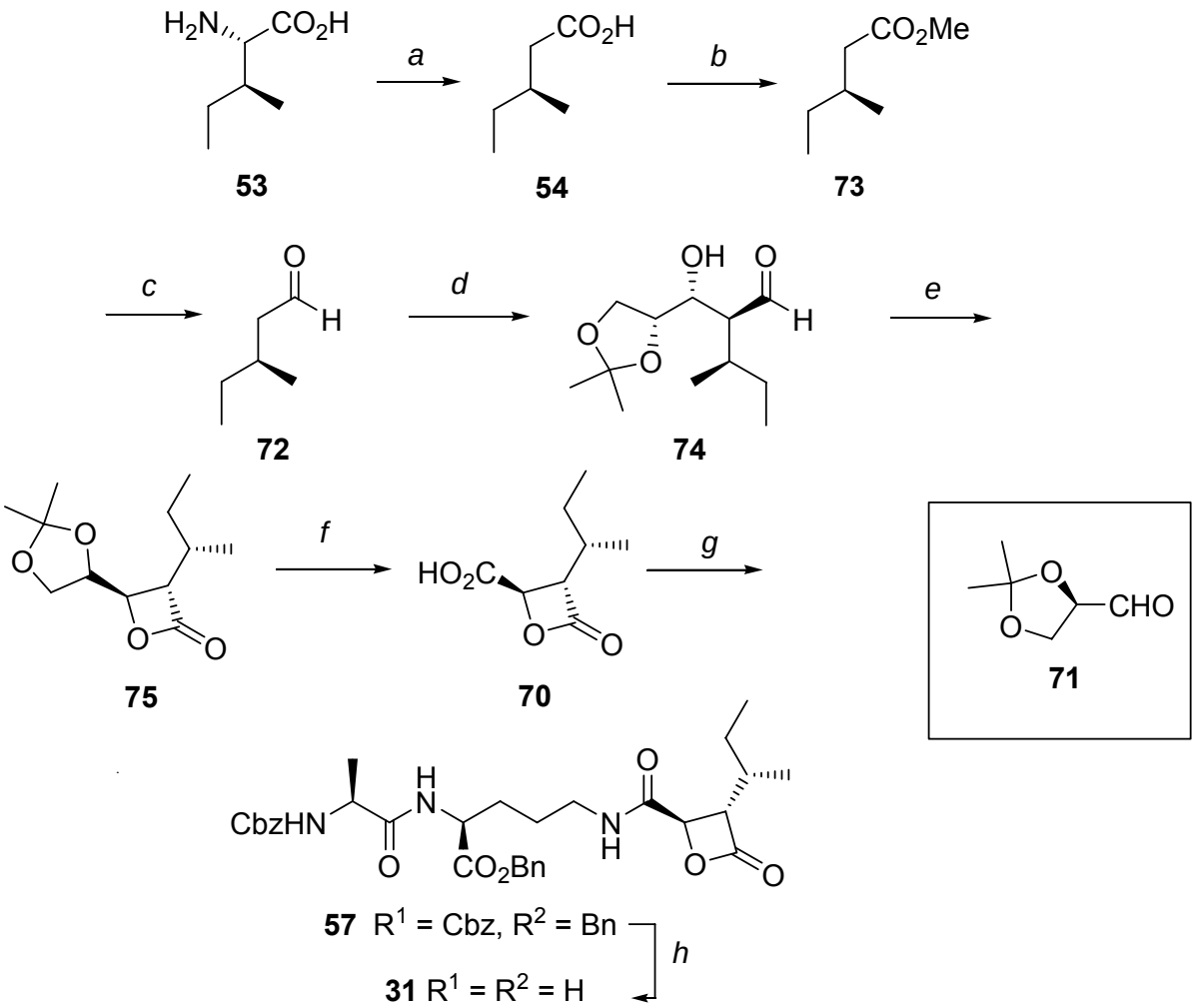
stereogenic centers employing chiral auxiliaries was used. These authors applied the $TiCl_4$-catalyzed aldol reaction of the Oppolzer (2*R*)-sultam derivative **66** (Scheme 20).



Scheme 20. Synthesis of Belactosin C according to Kumaraswamy et al.[37] Reagents and conditions: (*a*) (3*S*)-methylpentanoyl chloride, $CuCl_2$, benzene, reflux, 1 h, 80% (*b*) 2-(benzyloxy)acetaldehyde, $TiCl_4$, $(iPr)_2NEt$, –10 to 0 °C, 67% (*c*) $LiAlH_4$, ether, 0 °C to r. t., 3 h, 40% (*d*) (1) Dess-Martin oxidation (2) $NaClO_2$, NaH_2PO_4, 40% (*e*) BOPCl, Et_3N, CH_2Cl_2, 23 °C, 75% (*f*) (1) H_2, Pd/C (10%), EtOH : EtOAc (1 : 9) (2) $RuCl_3$*$3H_2O$, $NaIO_4$, 60% (*g*) **56**, DCC, HOBt, EtOAc : H_2O (1 : 1), 2 h, r. t., 50 %. (*h*) H_2, Pd/C, AcOH, r. t., 15 h, 80%.

This synthesis has many obvious disadvantages as it consists of 11 steps (starting from isoleucine) and furnishes an overall yield of only 1.5%. Some transformations are not as efficient as they could be. For example, the carboxamide **67** first had to be reduced to the alcohol **68** and the latter then oxidized back to the carboxylic acid **69**, apparently because the direct hydrolysis of **67** could not be brought about.

Another synthesis of Kumaraswamy et al.[38] employed an organocatalytic aldol reaction of the chiral Garner aldehyde **71** with the aldehyde **72** derived from the acid **54** (Scheme 21).

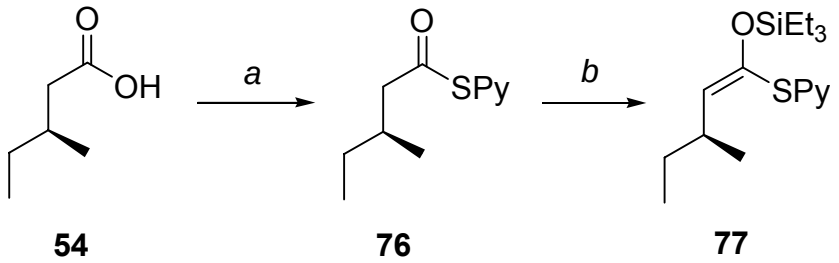


Scheme 21. Synthesis of Belactosin C according to Kumaraswamy et al.[38] Reagents and conditions: (*a*) (1) $NaNO_2$, HBr, 0 °C – r. t., 12 h, (2) Zn, H_2SO_4, 0 °C – r. t., 12 h, 65% (*b*) MeOH, H_2SO_4, reflux, 12 h, 70% (*c*) (1) $LiAlH_4$, ether, 3 h, (2) PCC, CH_2Cl_2, 1 h, 59% (*d*) **71**, (*S*)-proline (10%), DMF, 72 h, 4 °C (*e*) (1) $NaClO_2$, 20% NaH_2PO_4*2 H_2O, *t*BuOH, 0 °C – r. t., 4 h (2) BOPCl, Et_3N, CH_2Cl_2, 23 °C, 1 h, 46% (*f*) (1) 1 N HCl : THF (1 : 1), 0 °C – r. t., 3 h (2) $NaIO_4$, 1,4-dioxane / H_2O (1 : 2), 20 °C, 3 h (3) $NaClO_2$, 20% NaH_2PO_4*2H_2O, *t*BuOH, 0 °C – r. t., 4 h, 83% (*g*) **56**, DCC, HOBt, EtOAc / H_2O (1 : 1), 1 h, r. t., 50 %. (*h*) H_2, Pd/C, AcOH, r. t., 15 h, 80%.

This synthesis is interesting mostly because of the employment of the organocatalytic variant of the aldol reaction. Its disadvantages are also obvious: use of inefficient

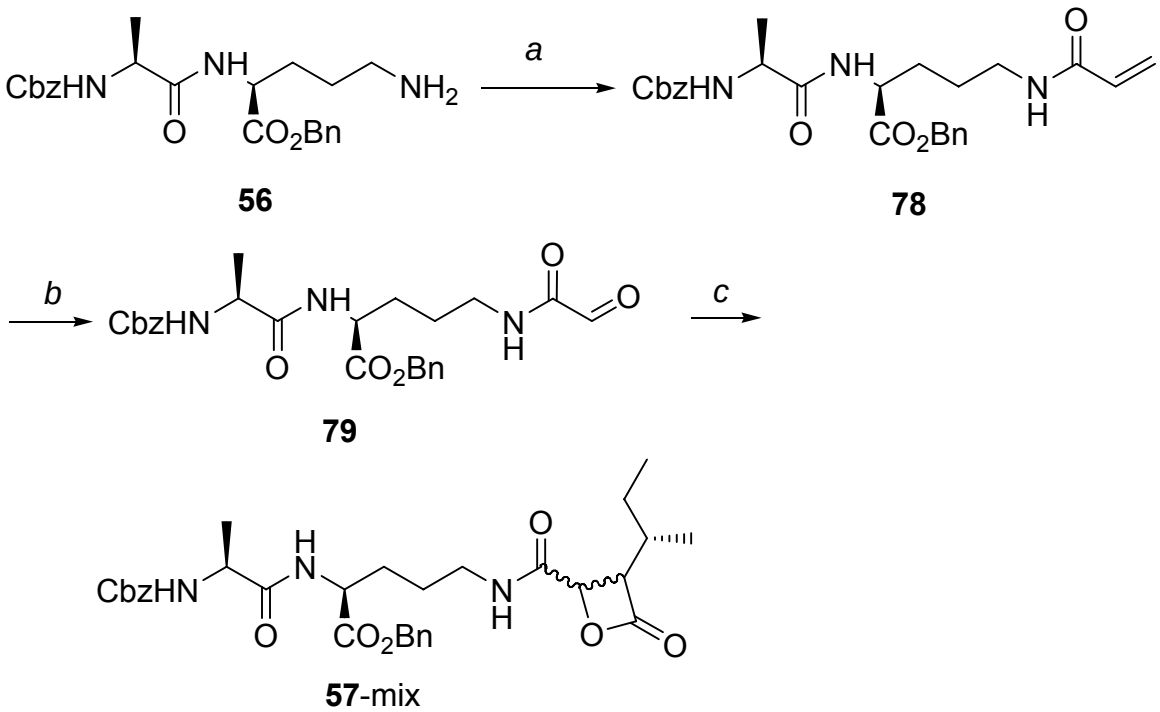
protocols, for example, the synthesis of **54** can be achieved in 87 instead of the reported 65% yield. The aldehyde **72** can be obtained directly from the acid **54**. The sequence is also not optimal. The acid **54** was first transformed into the aldehyde **72** in two steps and then back to the acid, although an aldol reaction could be achieved even with derivatives of the acid **52**. This synthesis comprises 12 steps with an overall yield of 4.8%.

The last reported synthesis of Belactosin C by Romo et al.[39] is based on the diastereoselective domino Mukaiyama aldol/lactonization process that leads to the simultaneous formation of both new bonds. First, a ketene silyl acetal was synthesized in a similar way as reported by de Meijere and Larionov for **52**.



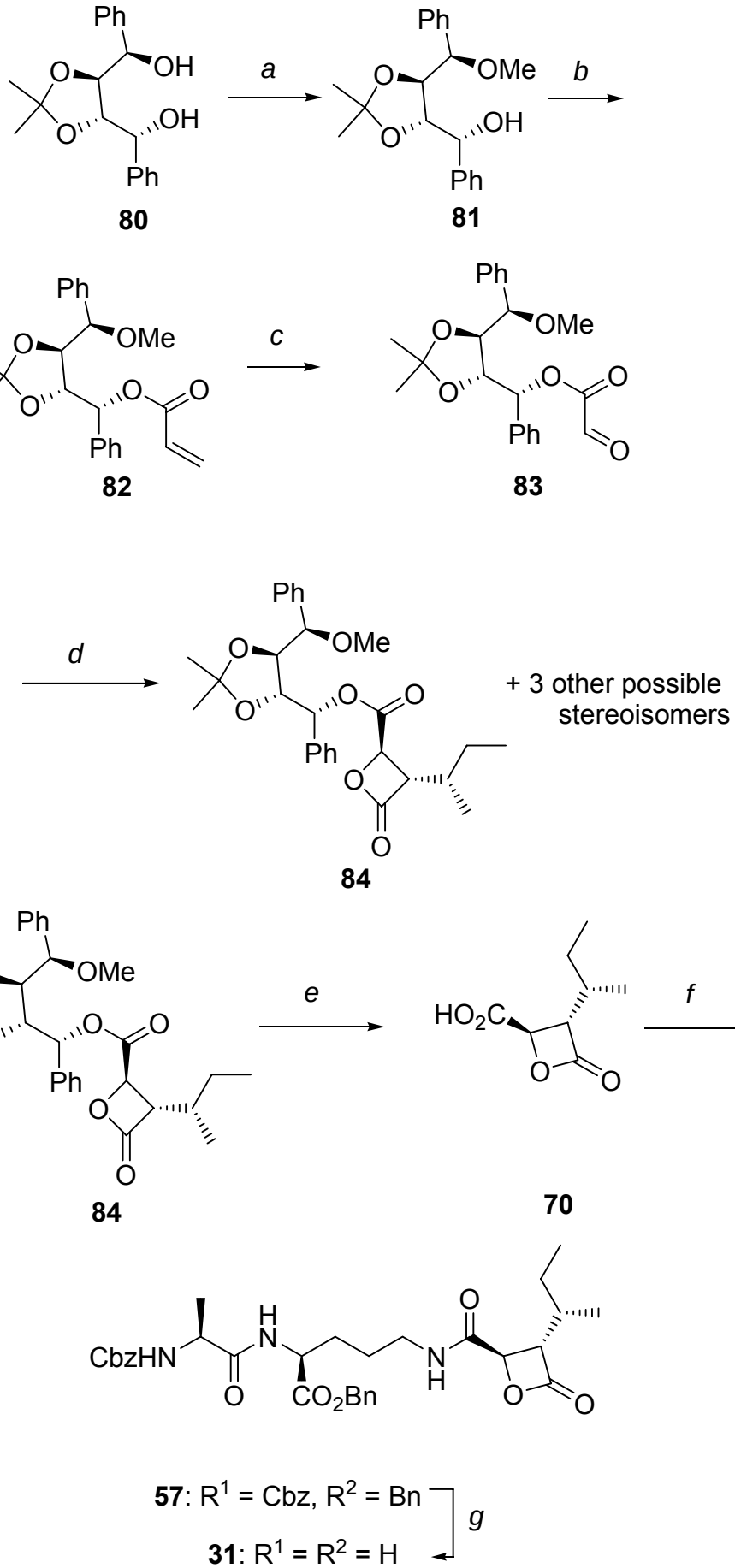
Scheme 22. Synthesis of a ketene *O*,*S*-acetal. Reagents and conditions: (*a*) (1) $(COCl)_2$, DMF, CH_2Cl_2, 22 °C, 1 h (2) PySH, Et_3N, CH_2Cl_2, 0 °C, 2 h, 98%; (*b*) (1) LiHMDS, THF, DMF, –78 °C, (2) Et_3SiCl, 2.5 h, 94%;

In the first variant of the synthesis, the peptide-containing glyoxamide **79** obtained by oxidation of the acrylamide **78** was coupled with the ketene silyl acetal **77** to form Belactosin C as a mixture of four diastereomers (Scheme 23).



Scheme 23. Synthesis of mixture of isomers of Belactosin C according to Romo et al.[39] Reagents and conditions: (*a*) (1) acryloyl chloride, HTMP, CH_2Cl_2, 93% (*b*) (1) O_3, MeOH/CH_2Cl_2 (2) DMS, 50% (3) molecular sieves 4 Å, CH_2Cl_2 (*c*) **77**, $ZnCl_2$, CH_2Cl_2, 30%.

Although the *trans*-isomers can be separated from the *cis*-isomers by column chromatography, the two *trans*-diastereomers could not be separated from each other. Experiments with a derivative of butyric acid instead of **77** showed that the stereogenic centers of the peptide moiety did not influence the diastereoselectivity of the reaction. The influence of the stereogenic center in the *sec*-butyl group in **77** was not sufficient to bring about any diastereoselectivity. Therefore another variant employing the chiral tartaric acid derivative **80** was tested (Scheme 24).

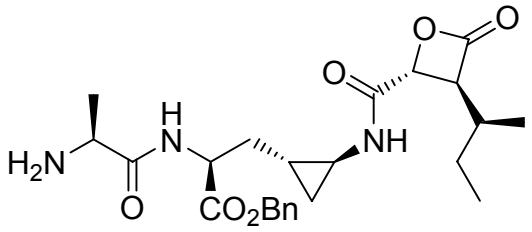

Ph
OH
OH
Ph
80
a
Ph
OMe
OH
Ph
81
b
Ph
OMe
Ph
82
c
Ph
OMe
Ph
83
d
Ph
OMe
Ph
84
+ 3 other possible stereoisomers
Ph
OMe
Ph
84
e
HO2C
70
f
CbzHN
CO2Bn
57: R1 = Cbz, R2 = Bn
31: R1 = R2 = H
g

Scheme 24. Synthesis of the asymmetric β-lactone derivative **84** according to Romo et al.[39] Reagents and conditions: (*a*) MeI, K_2CO_3, acetone, 90% (*b*) acryloyl chloride, *i*Pr_2NEt, CH_2Cl_2, 83% (*c*) $OsO_4/NaIO_4$, THF/H_2O, 98% (*d*) **77**, $ZnCl_2$, CH_2Cl_2, 73% (of the mixture containing 40% of the desired isomer) (*e*) H_2, Pd/C, THF, HCO_2H, 77% (*f*) **56**, EDC, HOBt, DMF, CH_2Cl_2, 51%. (*g*) H_2, Pd/C, AcOH, r. t., 15 h, 80%.

The monohydroxyether **81** was converted into the acrylate **82** which was oxidized to the glyoxylate **83**. The latter was further transformed into the β-lactone derivative **84**. In this case again all four possible diastereomers were formed, but in this case they could easily be separated by column chromatography because of the presence of the chiral auxiliary groups. The latter were cleaved off hydrogenolytically.

A disadvantage of this synthesis is the formation of a mixture of four stereoisomers of **84**. This decreases the overall yield of the target product. But to a certain extent this can even be seen as an advantage, because it enables one to determine the biological activities of Belactosin analogues containing all possible β-lactone configurations. This synthesis comprises seven steps with an overall yield of 8.4%.

The Belactosins have attracted such a lot of attention mostly because of their biological activities. First of all they showed an inhibition of the growth of HeLa S3 human uterine cervix carcinoma (IC_{50} 51 and 200 μM for Belactosin A and C, respectively).[24] They also showed a rabbit proteasome inhibition activity (IC_{50} 0.21 μM for both Belactosin A and C).[40] Surprisingly, a Belactosin A benzyl ester KF33955 showed better inhibitory activity against both HeLa and the rabbit proteasome (0.46 and 0.048 μM, respectively).



85 (KF33955)

Figure 4. The Belactosin A derivative KF 33955.

A possible explanation of this effect is that the introduction of a hydrophobic benzyl group may improve the capability of permeating the walls of human tumor cells. Further increase of the activity was achieved by acylation of the *N*-ternimus of the

Belactosin molecule.

The mechanism of the proteasome inhibition by Belactosins has been investigated in detail by X-ray diffraction of cocrystallizates with the 20S proteasome of Saccharomyces Cerevisiae. The cocrystallizate of Homobelactosin C bearing a benzyl ester moiety and a Cbz protective group on the *N*-terminus disclosed an acylation of a threonine hydroxy function of the β5-subunit of the proteasome by the β-lactone.[41] Similar results were obtained for the cocrystallizate of Omuralid **33** (Figure 5).[42]

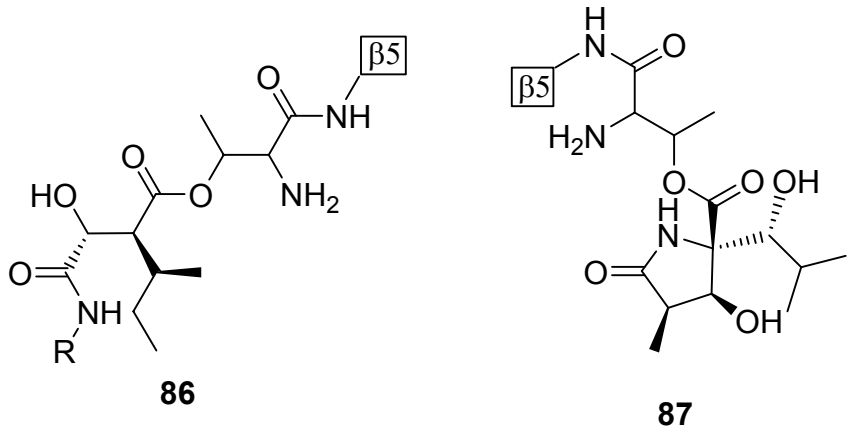
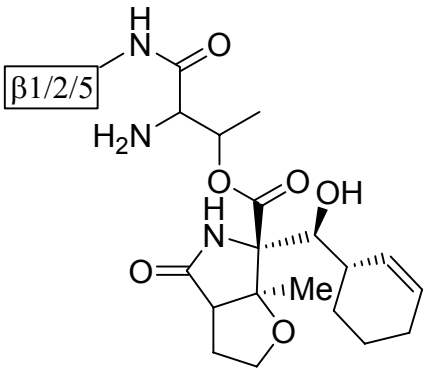


Figure 5. Product of the cocrystallization of the 20 S proteasome of Saccharomyces Cerevisiae with the Homobelactosin C **86** derivative (R stands for the peptide moiety) and Omuralid **87**.[42]

It would be very interesting to compare the mechanism of the proteasome inhibition by Belactosin and other β-lactones. For example, covalent binding of Omuralid **33** to the proteasome turned out to be similar to that of Homobelactosin C. But although both proteasome inhibitors are identically linked to the threonine part, they follow unique mechanisms to prevent cleavage of their newly formed ester bonds. In the case of Omuralide, the generated C4-hydroxy group, which is fixed in its orientation by the γ-lactam ring, cannot attack the ThrO-CO ester bond. In the bisprotected Homobelactosin C, the peptide residue assumes this role.

The binding modes of the Belactosin molecules and Salinosporamide differ more dramatically. Salinosporamide A **34** can form bonds not only with the β5-subunit of the proteasome, but also with β1 and β2,[42] thus being more potent as a proteasome inhibitor. This fact can be explained using the observation that Salinosporamide A **34** not only acylates the hydroxyl function of threonine, but also forms a tetrahydrofuran ring from the 2-chloroethyl moiety and the liberated hydroxyl group.[43]



87

Figure 6. Product of the cocrystallization of the proteasome with Salinosporamide A.[43]

This formation of the tetrahydrofuran ring makes this process favorable both entropically and enthalpically.

The analysis of the data obtained for the mechanism of interactions of various β-lactones with the proteasome can be used for the design of new substances with improved activities. For example, the acylated Belactosin esters showed better activity than Belactosin itself. But the choice of the acyl group was casual, as well as the choice of the alcohol residue in the ester. Molecular modelling based on such X-ray diffraction data would help to choose the optimal groups.

The goals of this doctoral dissertation can be summarized as follows:

- Investigation of new catalyzed insertion reactions of diazene derivatives into donor-acceptor substituted cyclopropanes.
- Investigation of the catalyzed reactions of isocyanides with donor-acceptor-substituted cyclopropanes.
- Synthesis of Belactosin congeners with various acyl groups on the *N*-terminus and alcohol moieties in the ester groups.
- Practical syntheses of Belactosin analogues without a peptide residue.
- Synthesis of Belactosin analogues with a hydroxyl function in the side chain.

Main Part

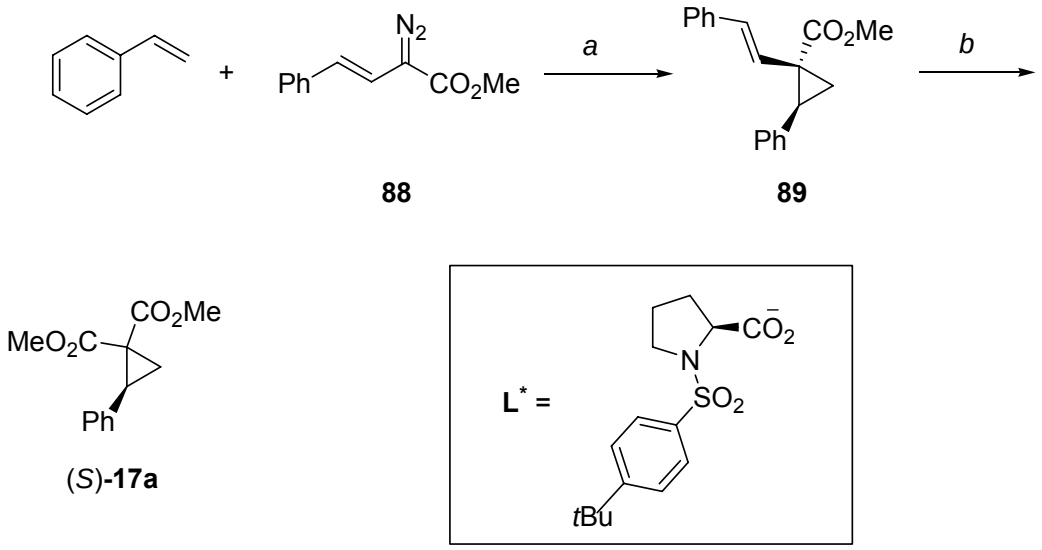
1. $GaCl_3$-catalyzed Insertions into Cyclopropane Rings

As mentioned above, many cyclopropane opening reactions have been studied in the past five years. It was decided to try out insertion reactions of other unsaturated compounds into cyclopropane rings. Thus, after aldehydes and imines, the reactions with azo compounds were tested.

Synthesis of the starting material

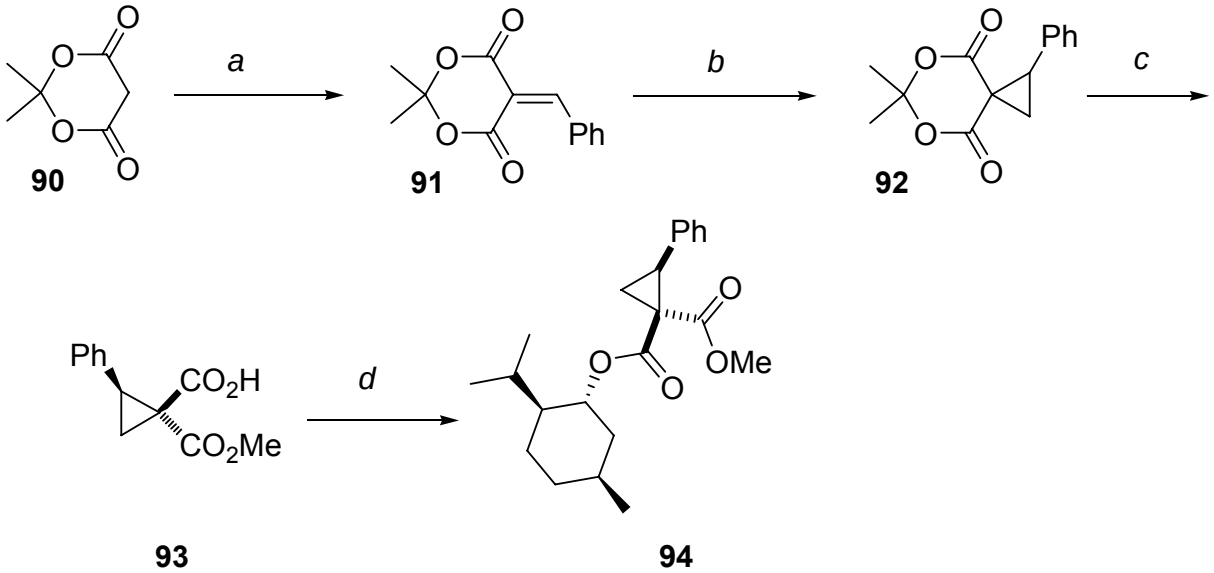
Racemic 2-arylcyclopropane-1,1-dicarboxylates can easily be synthesized according to several methods, including catalyzed cyclopropanations of unsaturated compounds with diazo compounds,[44] and by the Corey-Chaykovsky method.[45] The latter was chosen for the synthesis of racemic cyclopropane derivatives in this study.

The synthesis of enantiomerically pure starting materials turned out to be a separate problem. The known enantioselective synthesis of such cyclopropanes has many obvious disadvantages: it has many steps (including the preparation of the catalyst and the starting diazo compound **88**) and one has to use very expensive asymmetric rhodium catalysts, which also have to be prepared (see Scheme 25).[46]



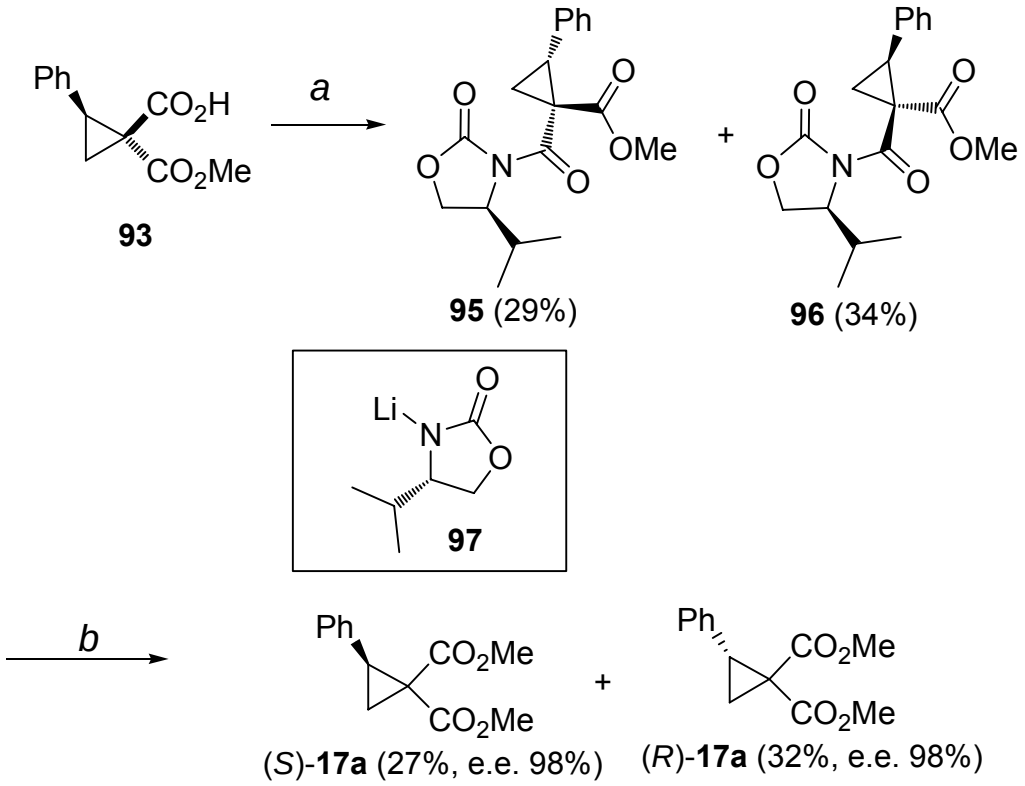
Scheme 25. Synthesis of enantiomerically pure cyclopropane (*S*)-**17a** according to Corey.[46] Reagents and conditions: (*a*) $Rh_2L^*_2$, pentane, 0 °C, 18 h, 79%, *ee* 94%. (*b*) (1) $KMnO_4$, $NaIO_4$, *t*BuOH, H_2O, 83%. (2) Me_2SO_4, K_2CO_3, acetone, 97%

Therefore, it was decided to perform some kind of enantiomer separation using a chiral reagent. For this purpose the diacid monoester **93** was synthesized from Meldrum's acid **90** (Scheme 26). The Knoevenagel product **91** from **90** and benzaldehyde was subjected to a Corey-Chaykovsky cyclopropanation, followed by base-catalyzed methanolysis to give the desired monoester **93**. The acid function of it was then further converted into a menthyl ester **94** using a DCC-mediated condensation (see Scheme 26).



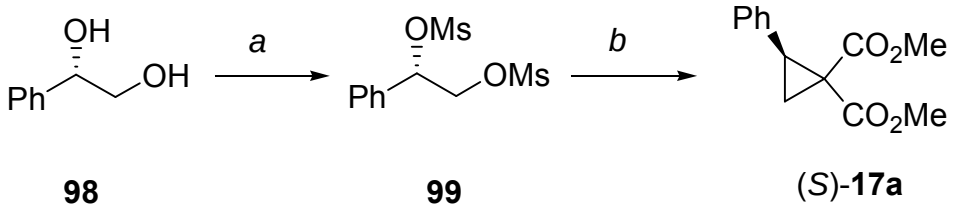
Scheme 26. Synthesis of the menthyl ester derivative **94**.[47] Reagents and conditions: (*a*) PhCHO, HOAc, morpholine, toluene, reflux, 4 h, 86%. (*b*) $Me_3SO^+I^-$, NaH, DMF, r. t. 3 h, 72%. (*c*) KOH, MeOH, 95%. (*d*) (1*R,* 2*S,* 5*R)*-2-isopropyl-5-methylcyclohexanol, DCC, DMAP, CH_2Cl_2, 0 to 20 °C, 4 h, 53%

Appropriate chromatographic conditions, under which the diastereomers would be separable, could not be found, and therefore another chiral auxiliary was employed. The Evans auxiliary has many obvious advantages for this purpose: it is inexpensive; it can be reused after the hydrolysis, and the prepared diacid monoester **93** can be used as well. Thus, the diacid monoester **93** was transformed into the chromatographically separable diastereomeric oxazolidinones **95** and **96**, which were hydrolyzed, and finally reesterified with diazomethane (Scheme 27).



Scheme 27. Synthesis of both enantiomers of the cyclopropanedicarboxylate **17a**. Reagents and conditions: (*a*) (1) PivCl, THF, Et_3N (2) **97** (*b*) (1) separation. (2) NaOH, H_2O_2 (3) HCl (4) CH_2N_2

This synthesis has some obvious disadvantages: it is not simple and requires seven steps. After its publication,[47] another elegant sequence was suggested starting from the enantiomerically pure commercially available alcohol (*S*)–**98** (Scheme 28).

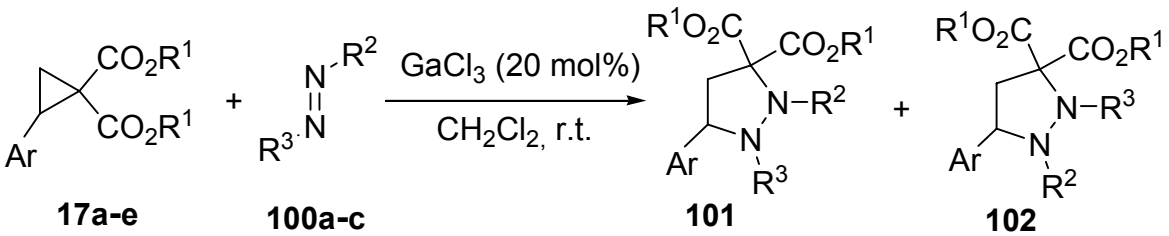


Scheme 28. Synthesis of enantiomerically pure cyclopropane (*S*)-**17a**. Reagents and conditions: (*a*) MsCl, CH_2Cl_2, Et_3N, 0 °C to r.t., 4 h, 84% (*b*) $CH_2(CO_2Me)_2$, NaH, THF, 67 °C, 24 h, 49%.

In view of the fact that both enantiomers of the starting diol **98** are commercially available and also can easily be obtained by reduction of mandelic acid, this synthesis really appears to be the best at this time.

Reactions of 2-Arylcyclopropane-1,1-dicarboxylates with Diazene Derivatives[47]

With the 2-arylcyclopropane-1,1-dicarboxylates in both racemic and enantiomerically pure form in hand, their reactions with diazene derivatives were initiated. Diisopropyl azodicarboxylate (**100a)** (R^2 = R^3 = CO_2iPr) and dimethyl 2-phenylcyclopropanedicarboxylate (**17a,** Ar=Ph, R^1=Me) were chosen as convenient reaction partners for initial experiments.



Scheme 29. Reaction of 2-arylcyclopropane-1,1-dicarboxylates **17** with diazenes **100a–c**. For details see Table 1.

Several Lewis acids ($Bi(OTf)_3$, $Sn(OTf)_2$, $InCl_3$) completely failed to catalyze the reaction, and with $Yb(OTf)_3$ only a trace of the desired product was isolated. Gratifyingly, the reaction was successful with added $GaCl_3$, with an optimum loading of 20 mol% (Figure 7). Further variations of the reaction conditions (solvent, concentrations and ratio of reagents, temperature, etc.) had little effect on the outcome of the reaction.

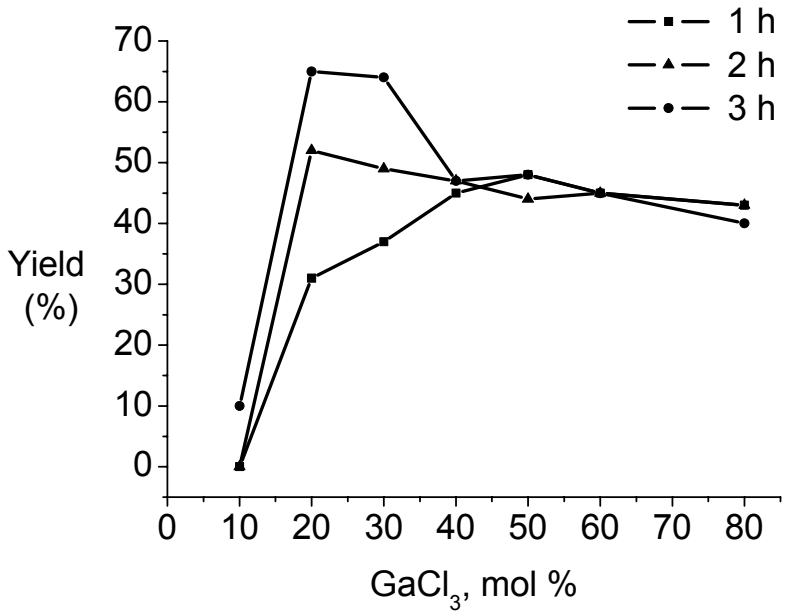


Figure 7. Dependence of the yields in the reaction of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**17a**) and diisopropyl azodicarboxylate (**100a**) in CH_2Cl_2 at r.t. on the loading of $GaCl_3$.

Under the optimized conditions, a number of 2-aryl-substituted cyclopropane-1,1-dicarboxylates **17b–f** were treated with diisopropyl azodicarboxylate (**100a**), ethyl phenyldiazenecarboxylate (**100b**) and azobenzene (**100c**) to give the correspondingly substituted pyrazolidine derivatives **101** in yields ranging from 41 to 67% (Table 1) except for the product from **17b** and the unsymmetrically substituted diazene **100b**, which was obtained as a mixture of the two regioisomers **101bb** and **102bb** in a total yield of 23% (Table 1, entry 8).

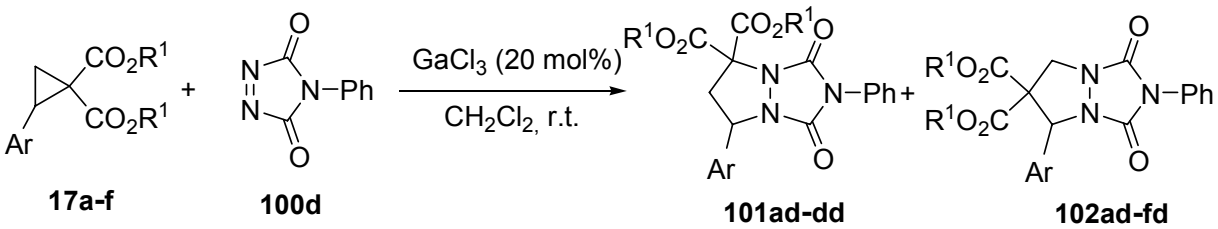
Table 1. Scope of the $GaCl_3$-Catalyzed Formal Cycloaddition of Various 2-Arylcyclopropane-1,1-dicarboxylates onto Different Diazene Derivatives[a]

Entry	Cyclo-propane	R^1, R^1	Ar	R^2-N=N-R^3	R^2	R^3	Product	Yield (%)
1	**17a**	Me, Me	Ph	**100a**	CO_2iPr	CO_2iPr	**101aa**	63
2	**17b**	Me, Me	4-MeC_6H_4	**100a**	CO_2iPr	CO_2iPr	**101ba**	52
3	**17c**	Me, Me	4-BrC_6H_4	**100a**	CO_2iPr	CO_2iPr	**101ca**	46
4	**17d**	Me, Me	4-ClC_6H_4	**100a**	CO_2iPr	CO_2iPr	**101da**	67
5	**17e**	Me, Me	4-$MeOC_6H_4$	**100a**	CO_2iPr	CO_2iPr	**101ea**	43
6	**17f**	CMe_2	Ph	**100a**	CO_2iPr	CO_2iPr	**101fa**	53
8	**17b**	Me, Me	4-MeC_6H_4	**100b**	CO_2Et	Ph	**101bb** +**102bb**	17 +6
9	**17a**	Me, Me	Ph	**100c**	Ph	Ph	**101ac**	42
10	**17b**	Me, Me	4-MeC_6H_4	**100c**	Ph	Ph	**101bc**	44
11	**17c**	Me, Me	4-BrC_6H_4	**100c**	Ph	Ph	**101cc**	41

[a] Reaction conditions: 20 mol% $GaCl_3$, CH_2Cl_2, r.t., 3 h.

However, all the diazene derivatives used above were naturally existing mixtures of minor amounts of *cis*- and major amounts of the thermodynamically favored *trans*-diastereomers. It was of particular interest to also investigate the reactivity of the cyclopropanes (**17a–e**) towards substances with fixed *cis*-configuration of the N,N double bond, as in 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**100d**).

Surprisingly, the reactions of cyclopropanes **17a–e** with PTAD **100d** led to separable mixtures of the expected products of insertion into the C(1)-C(2) cyclopropane bond (compounds **101ad–dd**), and the anomalous products of insertion into the C(2)-C(3) bond (compounds **102ad–dd**) in ratios varying from 1 : 1.5 to 1 : 3 (Table 2).



Scheme 30. Reaction of 2-arylcyclopropane-1,1-dicarboxylates **17** with PTAD **100d**. For details see Tables 1 and 2.

Actually, the products of type **102** were favored in all cases except for that of the spirocyclic diester **17f**, in which not even a trace of the anomalous product of type **102** was observed in the ^{1}H NMR spectrum of the crude reaction mixture. The structures of products **101bd** and **102bd** were unambiguously established by means of X-ray crystallographic analyses[48] (See Figure 8 and 9).

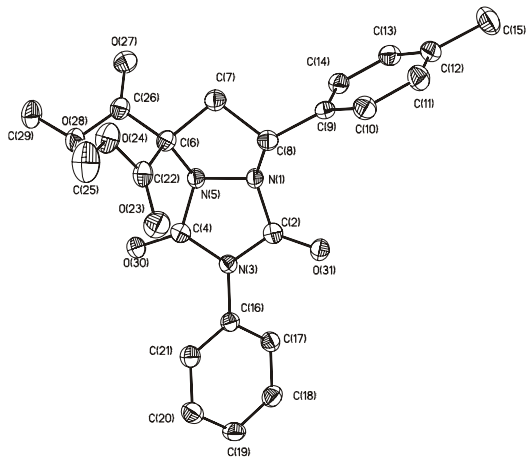


Figure 8. Structure of compound **101bd** in the crystal.[48]

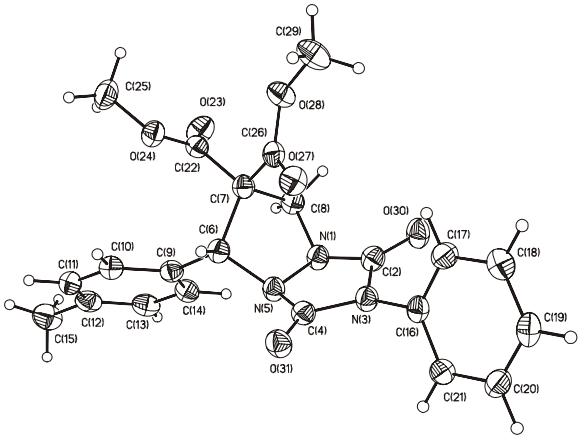


Figure 9. Structure of compound **102bd** in the crystal.[48]

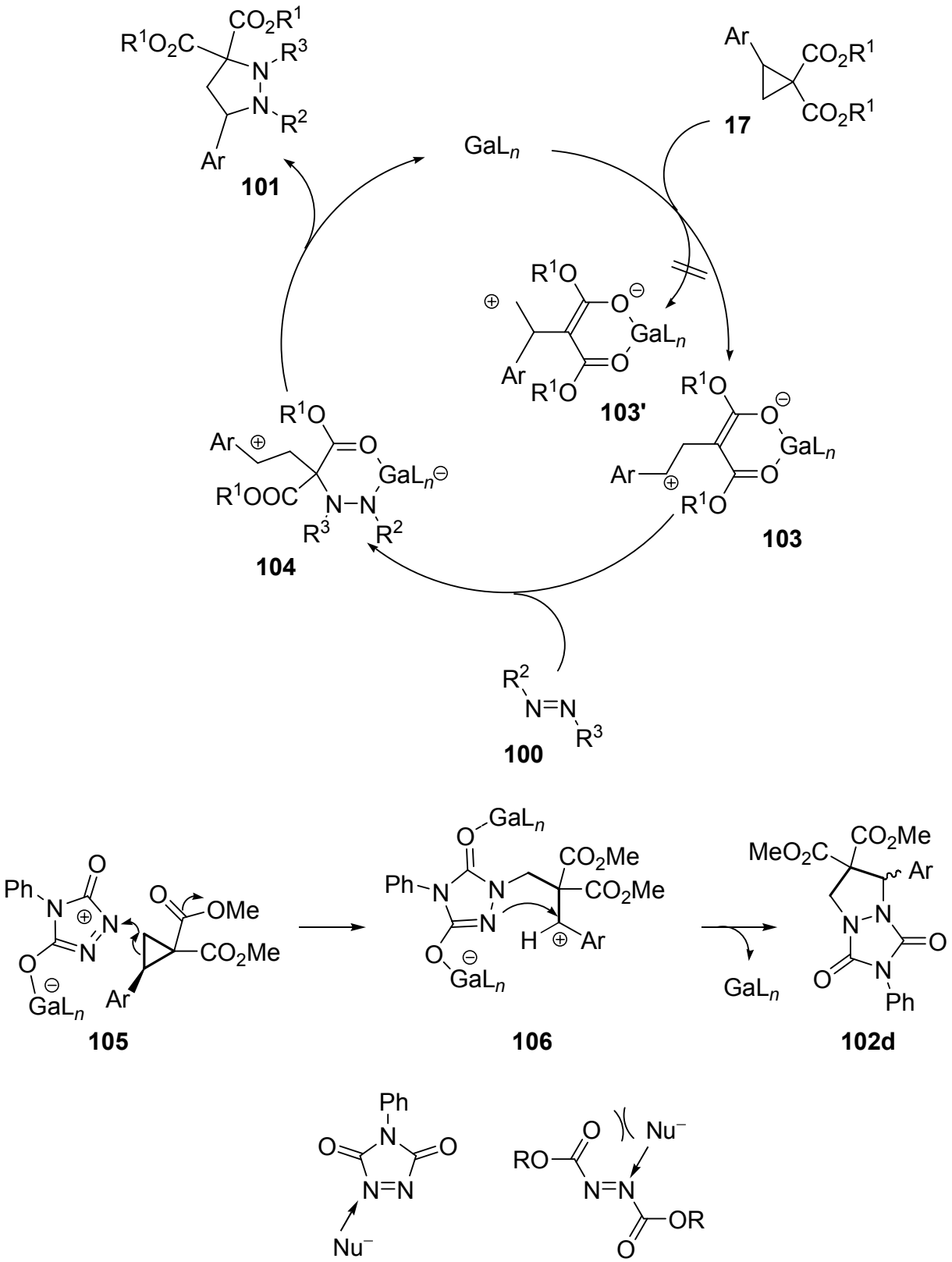
Table 2. Reaction of 2-Arylcyclopropane-1,1-dicarboxylates 17 with *N*-Phenyltriazolinedione (PTAD, 100d).

Entry	Cyclo-propane	R^1, R^1	Ar	Products	Yield (%) (**101**/**102** Ratio)
1	**17a**	Me, Me	Ph	**101ad + 102ad**	66 (1 : 3)
2	**17b**	Me, Me	4-MeC_6H_4	**101bd + 102bd**	67 (1 : 1.7)
3	**17c**	Me, Me	4-BrC_6H_4	**101cd + 102cd**	56 (1 : 1.5)
4	**17d**	Me, Me	4-ClC_6H_4	**101dd + 102dd**	55 (1 : 2.2)
6	**17f**	CMe_2	Ph	**102fd**	34

In order to unveil the reason for the formation of the anomalous products **102ad–dd,** further experiments were carried out. Thus, $GaCl_3$ was added to solutions of pure **101ad** and **102ad,** respectively. No interconversion of **101ad** and **102ad** was observed according to the ^{1}H-NMR spectra of solutions after 1, 2, 3 and even 24 h. This result is in accordance with the assumption that the insertions into the C(1)-C(2) and C(2)-C(3) bonds proceed along independent pathways under the reaction conditions.

The reaction of the enantiomerically pure 2-phenylcyclopropane-1,1-dicarboxylate (*R*)-**17a** with diisopropyl azodicarboxylate (**100a**) afforded the racemic product *rac*-**101aa**, according to HPLC analysis on a chiral phase column. Both, the regular **101ad** as well as the anomalous **102ad** product of the reaction of (*S*)-**17a** with PTAD **100d** also proved to be racemic. Thus, these reactions must proceed via an achiral dipolar intermediate of type **103**. Apparently, diazene dipolarophiles possess a much lower nucleophilicity than imines as well as aldehydes, and therefore fail to attack the cyclopropanes **17** at the C(2)-atom in the presence of mild Lewis acids [Sn(II), Cu(II), Bi(III), etc.]. Gallium trichloride, on the other hand, being a powerful Lewis acid, may effect formation of the achiral dipolar ring-opened intermediate of type **103** (see Scheme 31), which can add, with its negatively charged terminus coming in first, onto the electron-deficient N,N double bond. This would then be succeeded by a ring closure

leading to the racemic product **101**. In accordance with this hypothesis, addition of gallium trichloride to a solution of the enantiomerically pure cyclopropane derivative (*R*)-**17a** in the absence of any diazene did not lead to any racemization (according to an HPLC analysis) of the residual **17a**, while the net amount of available **17a** significantly decreased in the course of the experiment. Thus, the ring-opening event appears to be irreversible. Since formation of an intermediate of type **103'** featuring a primary carbocation is deemed highly unlikely, the anomalous by-product **102d** must emerge along a different pathway.



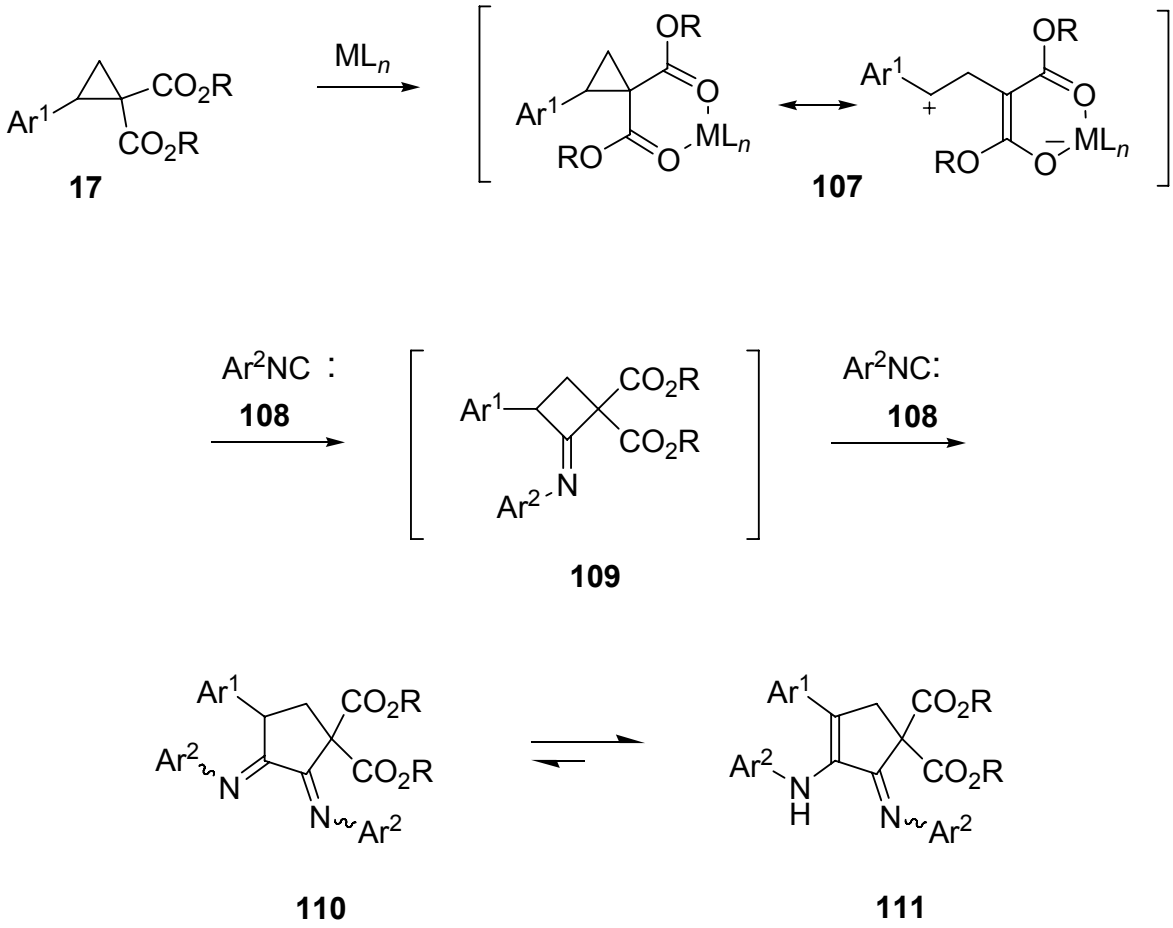
Scheme 31. Proposed mechanism for the $GaCl_3$-catalyzed formal cycloaddition of diazene derivatives **100** to cyclopropanes **17** and the rationale for the formation of the anomalous products of type **102d**.

Control experiments with **17a,** *N*-phenyltriazolinedione (PTAD) and azobisisobutyronitrile (AIBN) in the absence of $GaCl_3$ at elevated temperatures failed to elicit the formation of cycloaddition products, which rules out the possibility of a radical avenue. Therefore, the higher reactivity of the *cis*-configured PTAD **100d** over the *trans* counterparts allows it to add to the least sterically congested methylene group of the cyclopropane **17**, so that the nucleophilic nitrogen of the PTAD further attacks the achiral benzylic carbocation center in the intermediate **106**, and this would account for the formation of the racemic product **102**. This pathway is less favorable for the *trans*-configured diazene derivatives due to the steric interaction between the substituent in **100** and the incoming nucleophile.

2. Reactions with Isocyanides[49]

Next, the same cyclopropanes derivatives were subjected to catalyzed reactions with isocyanides. Being formally a special type of carbenes, isocyanides appeared to be interesting reagents for the insertion reactions into cyclopropanes. Although Lewis acid-catalyzed reactions of isocyanides with α,β-unsaturated carbonyl compounds,[50] epoxides[51] and, very recently, acetals[52] have been described, no records on such reactions with cyclopropanes have been found.

One would expect that a suitable Lewis acid and an appropriately substituted cyclopropane **17** might form a polarized complex **107**, which would be able to insert an isocyanide **108** to give a 2-iminocyclobutane-1,1-dicarboxylate **109.** The latter might be prone to undergo insertion of a second isocyanide molecule furnishing a more stable 2,3-diiminocyclopentane-1,1-dicarboxylate **110** or its tautomer **111** (Scheme 32).



Scheme 32. Proposed Lewis acid-catalyzed insertion of isocyanides into 2-arylcyclopropane-1,1-dicarboxylates **17**.

Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**17a**) and *p*-methoxyphenyl isocyanide (**108a**) were chosen to screen and optimize the reaction conditions. No formation of the expected products **109aa** or **111aa** was observed with $GaCl_3$, $AuCl_3$, $Zn(OTf)_2$, $Cu(OTf)_2$, and $Sc(OTf)_3$ as catalysts. On the other hand, with the triflates of lanthanide-like metals and of lanthanides $Ln(OTf)_3$ (Ln = Yb, Pr or Gd) as catalysts, only the double insertion product, 3-(arylamino)-2-(arylimino)cyclopent-3-ene-1,1-dicarboxylate **111aa** was obtained, at best in 64% yield with $Pr(OTf)_3$ in 1,2-dichloroethane at 70 °C (Table 1). Other variations of the reaction conditions, e.g. solvent, concentration, temperature, and ratio of the reagents, did not further improve

the efficiency of this new formal [3+1+1] cycloaddition. At higher concentrations, presumably, the product **111aa** may undergo further insertions of the isocyanide **108a**. Notably, no four-membered ring product **109aa** was observed, in contrast to the analogous reaction of isocyanides with epoxides.[51]

Table 3. Screening of reaction conditions for the insertion of *p*-methoxyphenyl isocyanide (108a) into the three-membered ring of dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (17a) (see Scheme 32).[a]

Entry	Catalyst (mol %)	Conc. mol/1	Yield of **111aa**,[b] (%)
1	$Yb(OTf)_3$ (20)	0.17 M	50
2	$Yb(OTf)_3$ (20)	0.09 M	27
3	$Yb(OTf)_3$ (20)	0.05 M	31
4	$Yb(OTf)_3$ (20)	0.04 M	27
5	$Yb(OTf)_3$ (30)	0.17 M	51
6	$Pr(OTf)_3$ (20)	0.17 M	64
7	$Gd(OTf)_3$ (20)	0.17 M	36

[a] The reactions were run in 1,2-dichloroethane at 70 °C for 24 h. [b] The yields were determined from ^{1}H NMR spectra of the reaction mixtures with hexamethylbenzene as an internal standard.

To test the scope and limitations of this new transformation, various 2-arylcyclopropane-1,1-dicarboxylates **17a-g** and donor-substituted aryl isocyanides **108a-c** were employed under the best conditions, i.e. with $Pr(OTf)_3$ in 1,2-dichloroethane at 70 °C. The correspondingly substituted cyclopentenedicarboxylates **111** were isolated in yields ranging from 19 to 62%. Neither did acceptor-substituted aryl isocyanides nor *tert*-butyl isocyanide, the latter probably for steric reasons, furnish any product of type **111**. The observation that 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione **112** did not react with *p*-methoxyphenyl isocyanide **108a** under these conditions, may be taken to indicate that for an efficient Lewis acid activation the two

carbonyl moieties have to be *syn*-oriented as in **107** (Scheme 32).

Table 4. Insertion of aryl isocyanides 108 into 2-arylsubstituted dimethyl cyclopropane-1,1-dicarboxylates 17 (see Scheme 32).

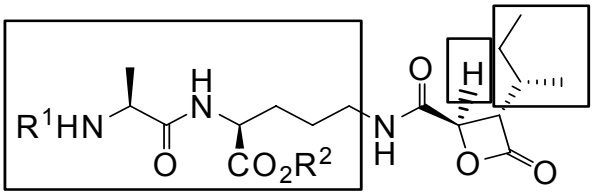
Entry	Cyclopropane Substrate	Ar^1	Ar^2NC	Ar^2	Product	Yield[a] (%)
1	**17a**	Ph	**3c**	4-$MeSC_6H_4$	**111ac**	60
2	**17a**	Ph	**3a**	4-$MeOC_6H_4$	**111aa**	57
3	**17e**	4-$MeOC_6H_4$	**3c**	4-$MeSC_6H_4$	**111ec**	63
4	**17e**	4-$MeOC_6H_4$	**3b**	3-Cl-4-$MeOC_6H_3$	**111eb**	48
5	**17e**	4-$MeOC_6H_4$	**3a**	4-$MeOC_6H_4$	**111ea**	36
6	**17g**	2-Furyl	**3a**	4-$MeOC_6H_4$	**111ga**	32
7	**17b**	4-MeC_6H_4	**3c**	4-$MeSC_6H_4$	**111bc**	62
8	**17b**-Et	4-MeC_6H_4	**3a**	4-$MeOC_6H_4$	**111ba**-Et	24
9	**17g**	2-Furyl	**3b**	3-Cl-4-$MeOC_6H_3$	**111gb**	23
10	**17h**	2-Thiophenyl	**3a**	4-$MeOC_6H_4$	**111ha**	21

[a] Isolated yields.

In conclusion, a new twofold insertion of isonitriles into the three-membered ring of 2-arylcyclopropane-1,1-dicarboxylates promoted by $Pr(OTf)_3$ has been developed. This formal [3+1+1] cycloaddition leads to oligofunctional cyclopentene derivatives **111** which not only may be of interest as ligands for transition metals[53] but also for pharmacological screenings after appropriate modification of the substituents.

3. Synthesis of Belactosin Congeners and Analogues

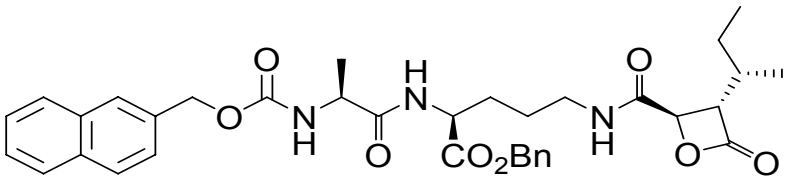
Although the total syntheses of the Belactosins A, C and Homo-C have already been achieved, the problem of improving the biological activity remained. One of the possibilities to do this in a directed way is by analysis of the important interactions in the proteasome-substrate complex and appropriate computer modelling. A cocrystal of a protected Homobelactosin C with the 20S-proteasome from Saccharomices Cerevisiae was investigated by X-ray diffraction, and the interactions responsible for the inhibition were determined. On the basis of this analysis it was decided which groups in the inhibitor are important and which are less important and should be modified accordingly. Of course, the β-lactone ring is the active toxiphore in all of these compounds. As the structure of the complex disclosed, an amide function (namely, NH) standing next to the β-lactone moiety also takes part in the bonding with the proteasome. As long as Belactosin A **30**, Belactosin C **31** and Homobelactosin C **32** showed biological activities in the same range, and Belactosin C **31** is most easy synthesized, the structure of Belactosin C **31** was chosen for the further modification. The parts that ought to be modified are outlined in Figure 10.



113

Figure 10. Common structure of Belactosin C congeners and analogues.

It had already been shown that the biological activity of the substituted Belactosin derivatives (**57**, R^1 = Cbz, R^2 = Bn) is higher than that of the unprotected Belactosin itself (**31**, R^1 = R^2 = H). Since the substituents R^1 and R^2 only served as protective groups en route to the unsubstituted Belactosin, there was no guarantee that this particular set of substituents would be the best. According to molecular modelling studies, some new derivatives were proposed for synthesis (see Figure 11).



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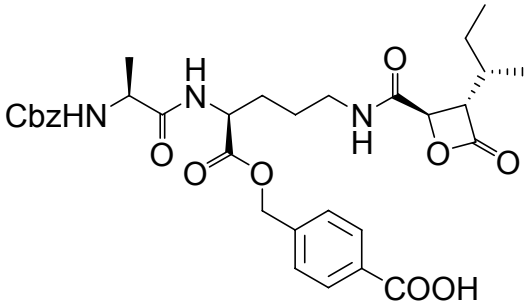

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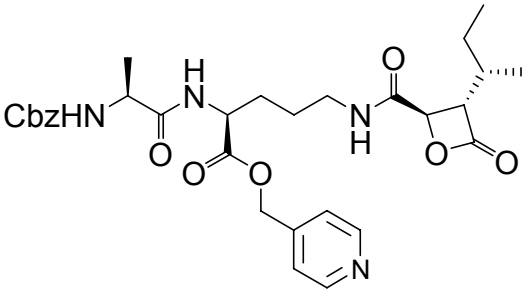

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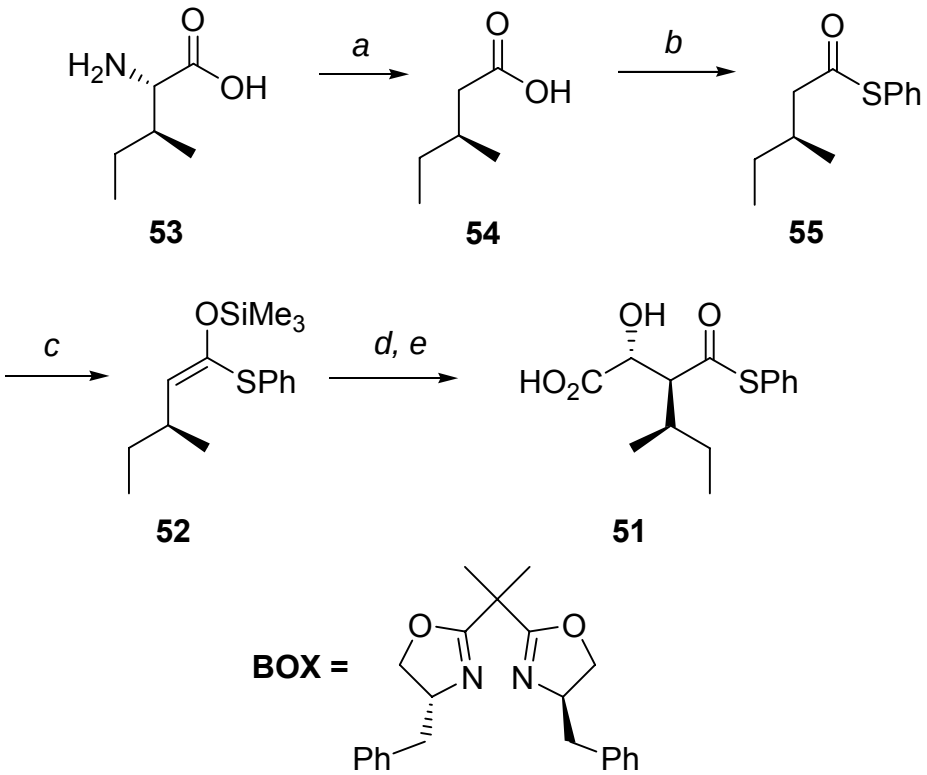
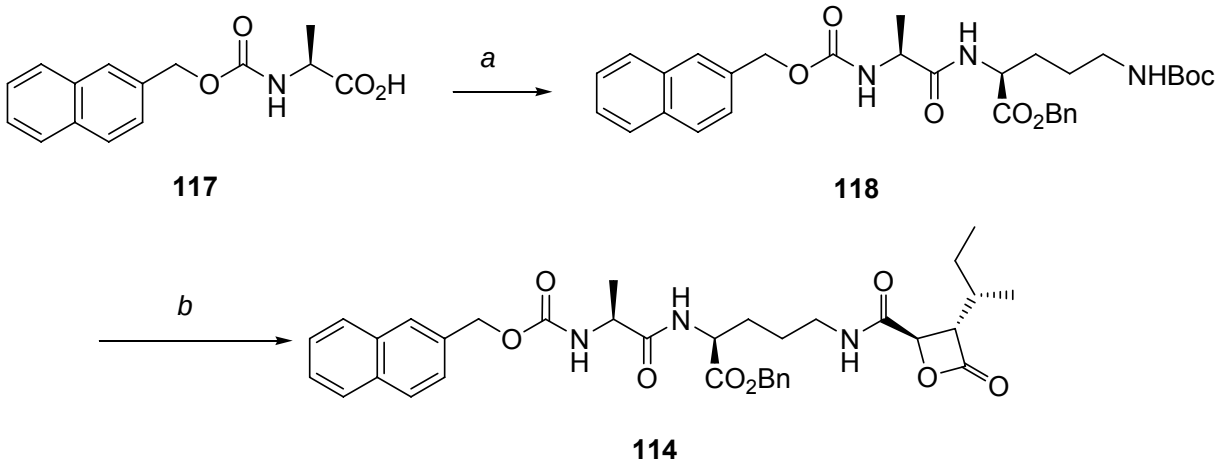
Figure 11. Suggested constitutions of Belactosin derivatives with potentially improved biological activity.

For the synthesis of the derivatives **114**–**116** the known sequence was employed. The key precursor **51** was obtained along the known route.[36] This sequence was performed on a one mole scale for the first time to demonstrate the feasibility of a large-scale synthesis of the Belactosins. All steps could be reproduced on this scale without a significant decrease in the yields.



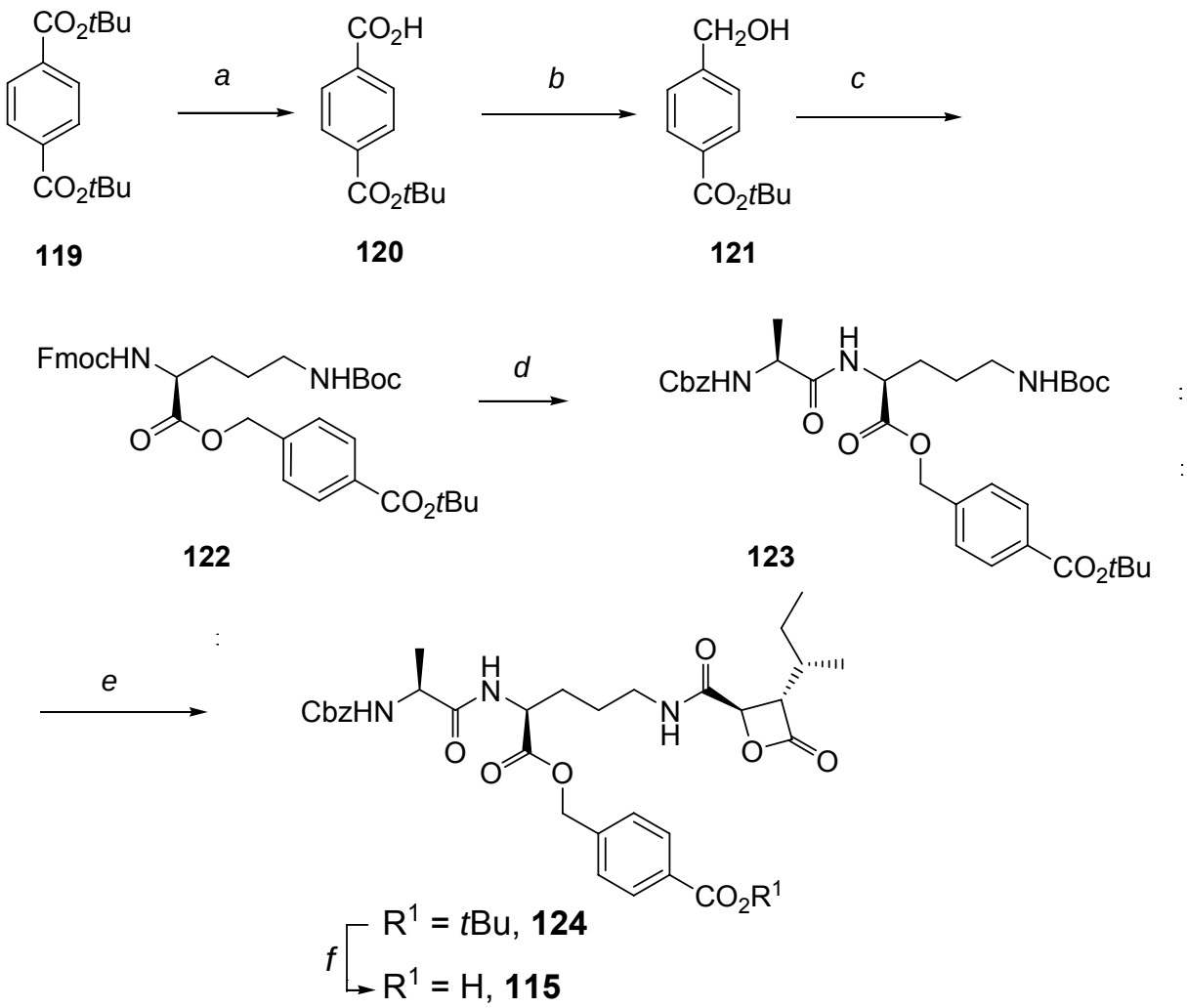
Scheme 33. Synthesis of the key building block **51** for the Belactosins according to de Meijere and Larionov.[36] Reagents and conditions: (*a*) H_2NOSO_3H, NaOH, H_2O, 0 °C, 6 h, reflux, 3 h, 87%; (*b*) DCC, PhSH, DMAP, CH_2Cl_2, 0 °C to rt, 7 h, 92%; (*c*) LiTMP, Me_3SiCl, THF, –78 °C, 16 h, 90%; (*d*) EtO_2CCHO, $Sn(OTf)_2$ (10 mol %)/**BOX** (11 mol %), CH_2Cl_2, –78 °C, 20 h, then 2 N HCl, THF, rt, 2 h, 96%; (*e*) 10% aq HCl, dioxane (1 : 6), 60 °C, 51 h, 90%.

According to the previously developed methodology, the naphthylmethoxycarbonyl-(CNAP) protected Belactosin congener was synthesized without any problems (see Scheme 34).



Scheme 34. Synthesis of the new Belactosin C derivative **114** with a (2-naphthylmethoxy)carbonyl substituent on the amino terminus. Reagents and conditions: (*a*) H_2N-Orn(Boc)-OBn, EDC, HOAt, TMP, 0 to 20 °C, 24 h, 77%. (*b*) (1) HCl, EtOAc, r.t., 12 h (2) **51**, TMP, HOAt, EDC, –20 to 20 °C, 48 h, 33%.

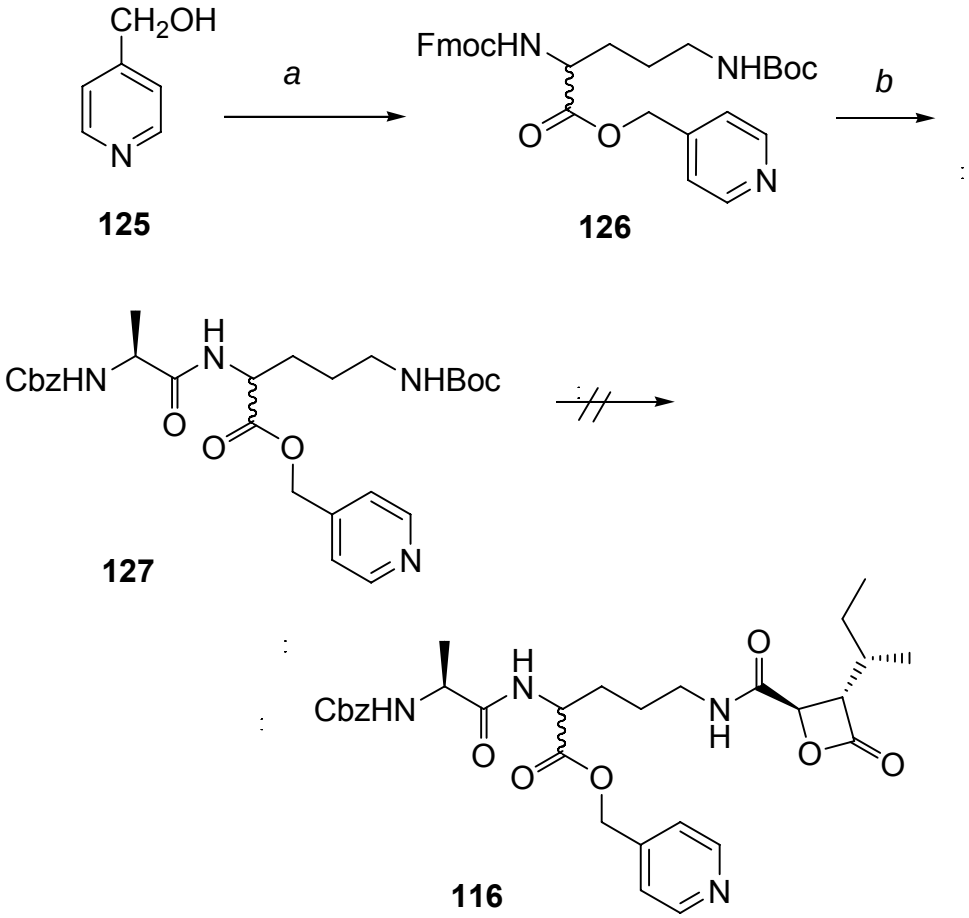
More difficulties were met in the synthesis of the congener with a carboxylate group in the benzyl ester moiety. First, a corresponding benzyl alcohol was synthesized from di-*tert*-butyl terephthalate by hydrolysis of one ester group and subsequent chemoselective reduction of the carboxylic acid functionality. Then, DCC-mediated esterification was employed for the condensation of this alcohol with a protected ornithine. The product was then coupled with the protected alanine and gave the corresponding dipeptide. In the subsequent step a selective removal of the Boc in the presence of a *tert*-butyl ester group had to be achieved. After many unsuccessful attempts, suitable conditions were found so that the synthesis of the Belactosin derivative **124** with a *tert*-butyl ester group in the benzyl moiety was achieved. Finally, the *tert*-butyl ester was cleaved under acidic conditions giving rise to the derivative **115** with a carboxylic acid function in the benzyl moiety (see Scheme 35).



Scheme 35. Synthesis of the Belactosin C analogues **115** and **124** with functionally substituted benzyl ester moieties. Reagents and conditions: (*a*) KOH, *t*BuOH, 50 °C, 3 h, 63%. (*b*) Bu_4NBH_4, r.t., 18 h, 75%. (*c*) Fmoc-Orn(Boc)-OH, DCC, CH_2Cl_2, 0 °C, 6 h, 74%. (*d*) (1) Et_2NH, THF, 3 h; (2) Cbz-Ala-OH, EDC, TMP, HOAt, 0 to 20 °C, 24 h, 65%. (*e*) (1) HCl, EtOAc, r.t., 3 h; (2) **51**, TMP, HOAt, EDC, –20 to 20 °C, 48 h, 37%. (*f*) CF_3CO_2H, CH_2Cl_2, –18 °C, 18 h, 99%.

Great difficulties were encountered during the synthesis of a congener with a pyridyl residue. First of all, the DCC-mediated preparation of ornithine 4-pyridylmethyl ester from enantiomerically pure protected (*L*)-ornithine ended up with complete racemization. Most probably, the basicity of the pyridyl moiety is responsible for this result. The mixture of two diastereomeric dipeptides obtained from this ornithine ester was employed in the synthesis of the corresponding Belactosin analogues. The first attempt was made under the usual conditions (3 N HCl in EtOAc followed by peptide

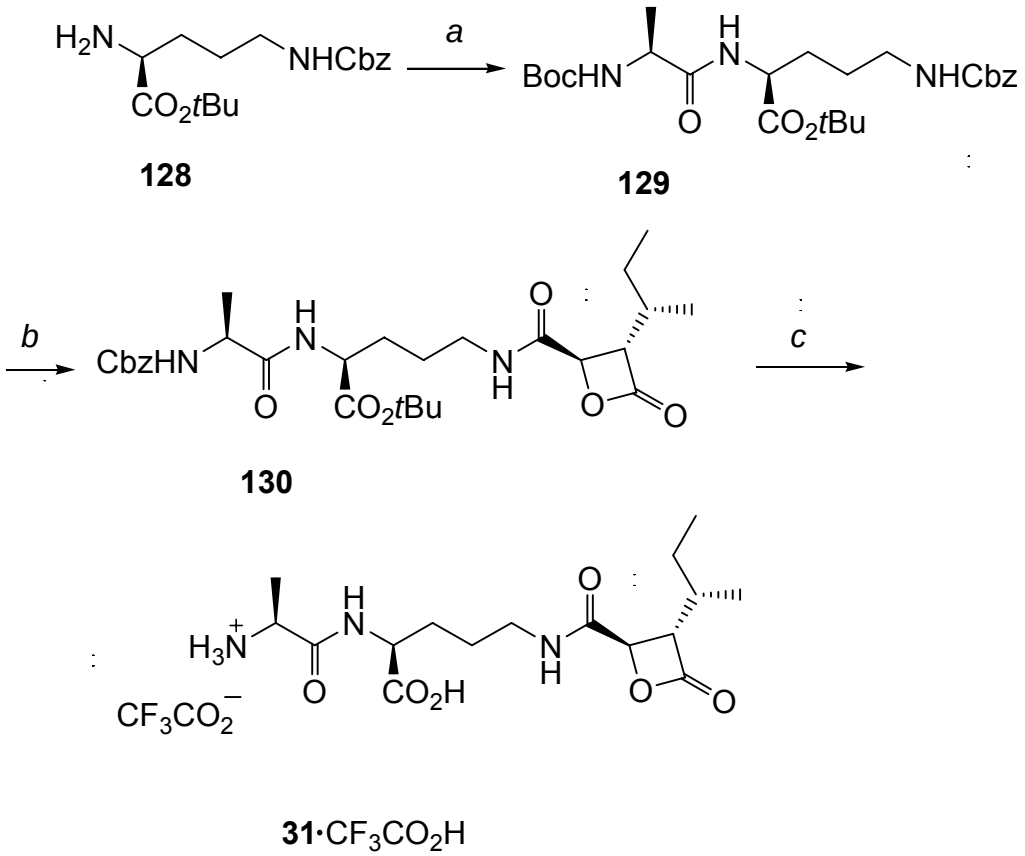
coupling / β-lactonization sequence), but after the addition of HCl, an unsoluble hydrochloride precipitated that could not be converted any further. In the next attempt a mixture of EtOAc and DMF was used as a solvent. Although the compounds stayed in solution, none of the desired Belactosin analogue was obtained. No formation of the target product **116** was observed upon attempted removal of the Boc protective group with trifluoroacetic acid in dichloromethane (see Scheme 36).



Scheme 36. Attempted synthesis of the Belactosin C analogue with a (4-pyridyl)methyl ester moiety. Reagents and conditions: (*a*) Fmoc-Orn(Boc)-OH, DCC, CH_2Cl_2, 0 °C, 6 h, 51%. (*b*) (1) Et_2NH, THF, 3 h; (2) Cbz-Ala-OH, EDC, TMP, HOAt, 0 to 20 °C, 24 h, 43%.

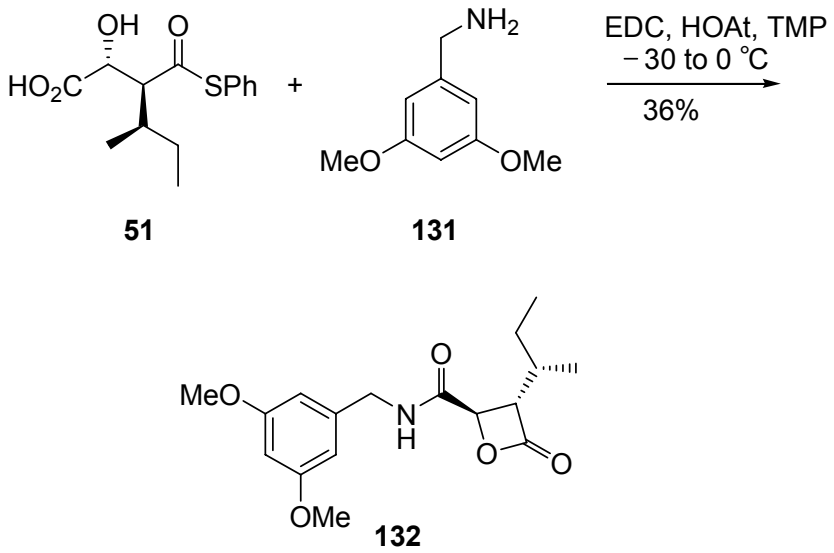
Another problem was the synthesis of an unprotected Belactosin directly as a salt. The reported results show that Belactosin is unstable under neutral conditions, but as a salt under acidic conditions it should be more stable. This salt could then be used as a reference compound in the screening for biological activities. However, the published route leads to the formation of Belactosin in free form that immediately starts to decompose. The original sequence was therefore modified by changing the set of

protective groups. Boc and *tert*-butyl ester groups were employed instead of Cbz and benzyl ester, respectively. Using this route one more interesting Belactosin C derivative was obtained (see Scheme 37).



Scheme 37. Preparation of the Belactosin C trifluoroacetate salt. Reagents and conditions: (*a*) Boc-Ala-OH, EDC, HOAt, TMP, 0 to 20 °C, 24 h, 87%. (*b*) (1) H_2/Pd/C, r.t., 16 h; (2) **51**, EDC, HOAt, TMP, –20 to 20 °C, 48 h, 57%. (*c*) CF_3CO_2H, CH_2Cl_2, –18 °C, 18 h, 99%.

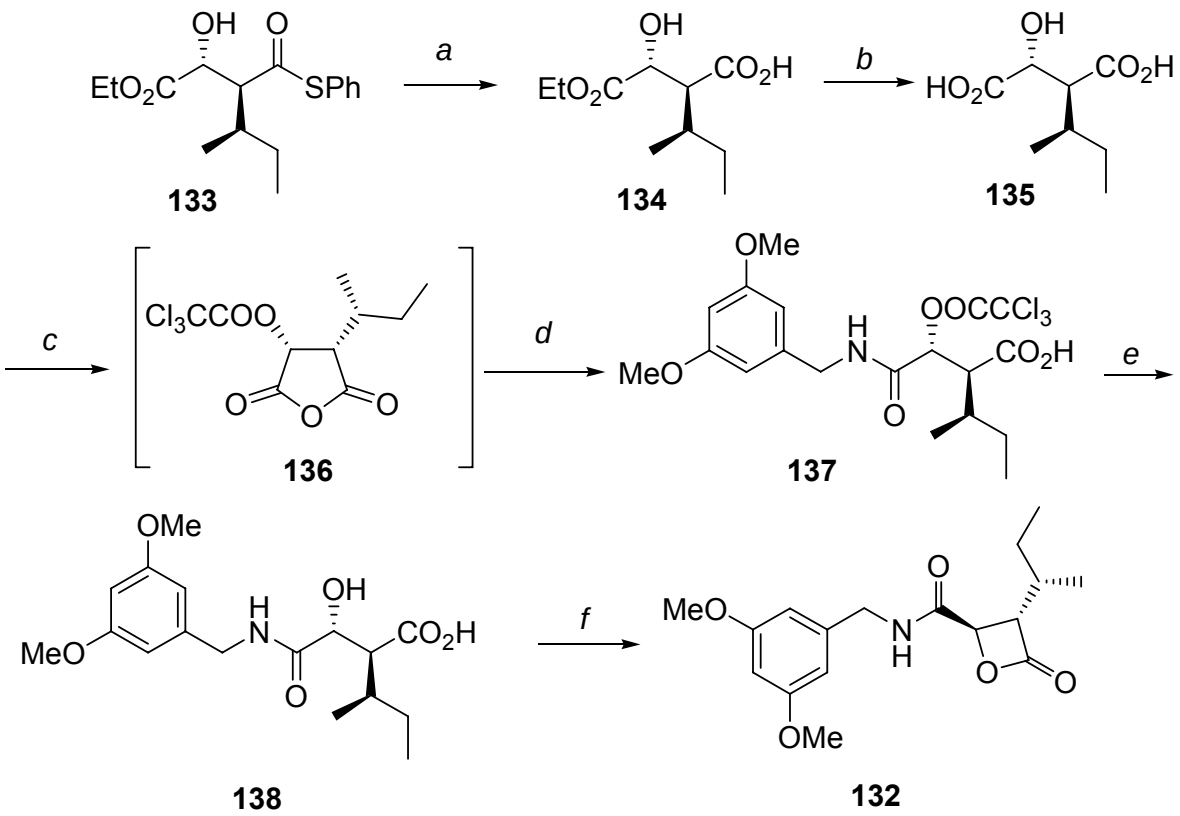
Yet another modification was the replacement of the whole dipeptide residue on the β-lactone by a relatively small and easily accessible amide moiety because it would considerably decrease the price of the synthesis. Of course, this modification should not go along without a loss, but with an increase of biological activity. Many possibilities were tried, and various substituted benzylamines turned out to be the best mimics of the dipeptide group. *N*-(3,5-dimethoxyphenyl)methyl-(3*S*)-((1*S*)-methylpropyl)-4-oxo-oxetane-(2*R*)-carboxamide (**132**) indeed showed an increased activity at least in a fungicidal test. Compound **132** was obtained using the common protocol for the condensation of the dipeptide with the malic acid derivative **51** with immediately ensuing β-lactonization (see Scheme 38).[54]



Scheme 38. Synthesis of amide **132** according to the common procedure.

Regarding the structural similarity of this oxetanonecarboxamide with the head group of Homobelactosin C it is assumed that this molecule binds the β5-subnits of the proteasome the same way as Homobelactosin C. This assumption matches the observed higher biological activity.

For the potential utilization of this amide in industry a new simple and scalable synthesis of **132** had to be developed. Towards this goal, the sequence depicted in Scheme 39 was proposed.

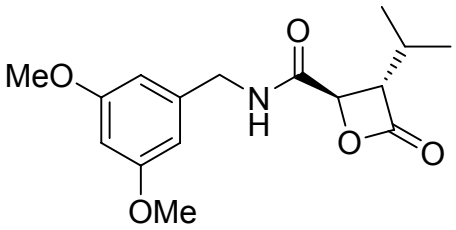


Scheme 39. New methodology for the preparation of the oxetanonecarboxamide **132**. Reagents and conditions: (*a*) $AgCF_3CO_2$, THF /H_2O (4 : 1), 55 °C, 16 h, 89%. (*b*) 10% aq HCl, dioxane (1 : 6), 60 °C, 51 h, 90%. (*c*) $(CCl_3CO)_2O$, dioxane, 75 °C, 3 h. (*d*) **131**, THF, 0 °C, 1 h. (*e*) aq. NaOH, 16 h, r. t. (*f*) BOP, Et_3N, CH_2Cl_2, 0 °C to r. t., 3 h, 51% over 3 steps.

In this case, both the phenyl thioester and ethyl ester moieties of the malic acid derivative **133** were hydrolyzed to yield the substituted malic acid **135** that was regioselectively converted into its monoamide **137** via the cyclic anhydride **136**, followed by the opening reaction with the benzylamine **131**. The trichloroacetyl group in **137** was cleaved off, and the hydroxyacid **138** was cyclized into the β-lactone **132**. This sequence has obvious advantages, but also disadvantages. It does not require to work at low temperatures for the cyclization, and the overall yield is better (41% vs. 36%). But it requires more steps and the use of the quite expensive BOP condensation reagent (although the price of BOP is comparable to that of EDC used in the other sequence). Comparing these two routes, one can conclude that if there were a simpler way to access the substituted malic acid **135** directly, the last route would be the most favorable one.

The hydrogen atom at the C-4 position of the β-lactone ring had previously been replaced by a methyl group, but this modification did not increase the biological activity.[55]

The last substituent that can possibly be modified is the *sec*-butyl group. The analogue **139** bearing an isopropyl group was prepared, but this compound turned out to be less active than one with the *sec*-butyl group.[56]



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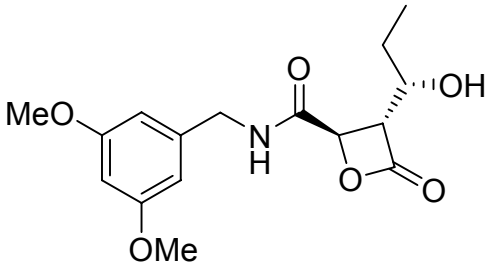

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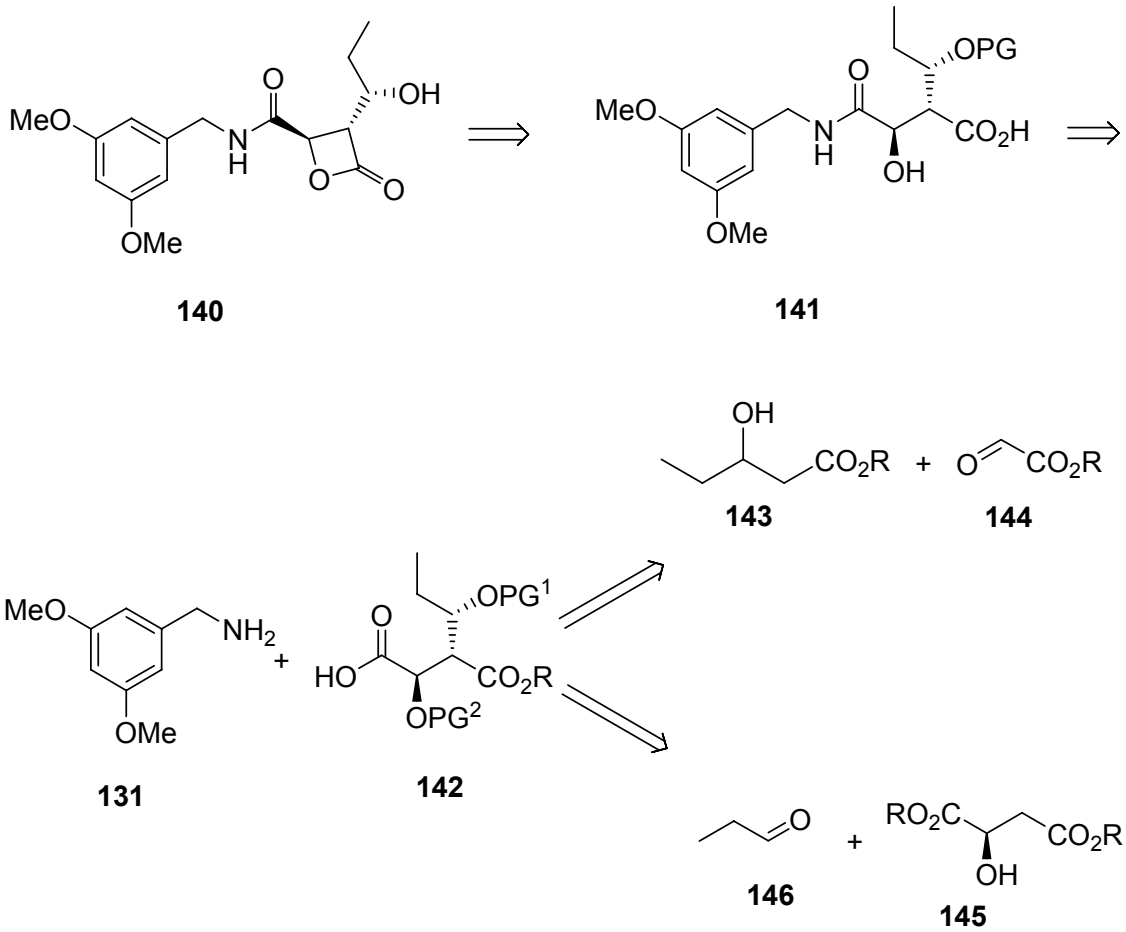
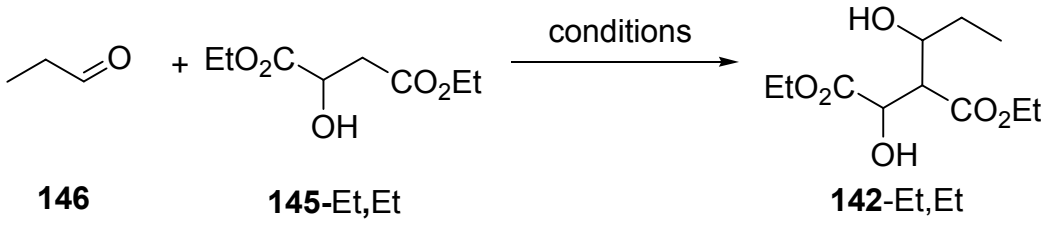
Another idea resulting from the molecular modelling studies was to modify the *sec*-butyl group replacing the α-methyl with a hydroxyl group. Although this target compound **140** does not look too different from the previous one, the synthetic strategy had to be changed dramatically. The retrosynthetic strategy depicted in Scheme 40 was envisaged.



Scheme 40. Retrosynthetic analysis of **140**.

The key intermediate in this sequence would be an appropriately bisprotected malic acid monoester derivative **142**. One can conceive two ways of preparing it: the reaction of a 3-hydroxyvalerianic acid ester **143** (or an *O*-protected derivative thereof) with the glyoxylate **144** or the reaction of the malic acid diester (maybe, in an *O*-protected form) **145** with propanal **146**. The last possibility would be preferable because it could allow one to achieve the desired configuration of at least two stereocenters.[57] However, numerous attempts to carry out such a transformation were unsuccessful (Scheme 41). This is probably due to the higher C,H acidity of the α-methylene group in the aldehyde than of that in the malic acid derivative.



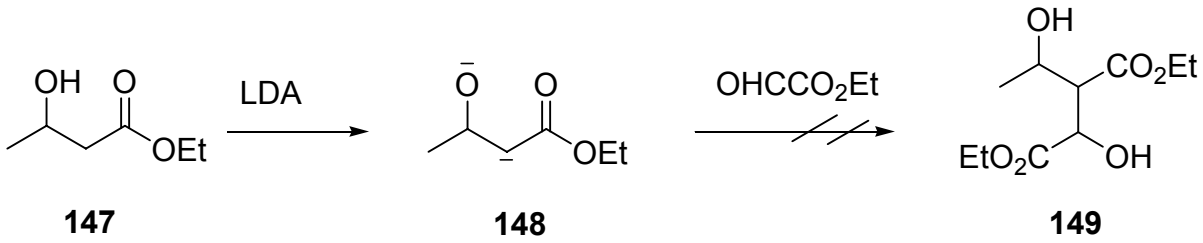
Scheme 41. Reaction of propanal **146** with diethyl malate **145-Et,Et**. For details see

Table 5.

Table 5. **Reaction of propanal 146 with diethyl malate 145-Et,Et (see Scheme 41).**

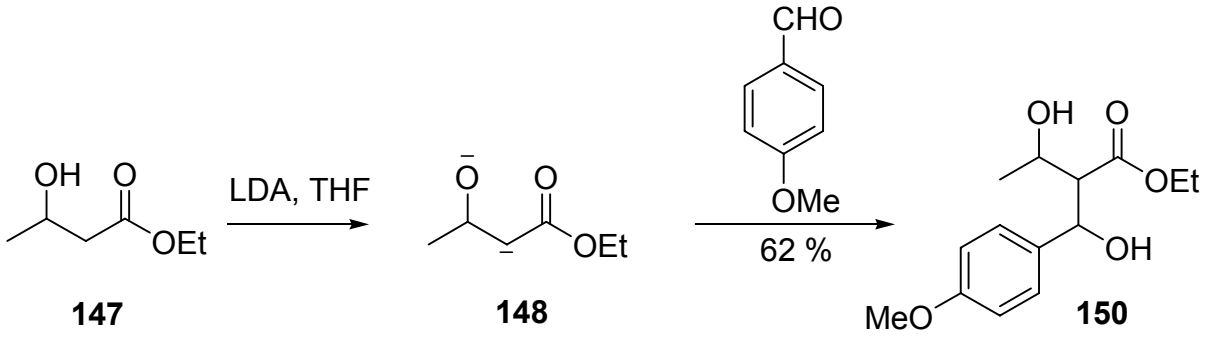
Entry	Conditions	Yield of **142**-Et,Et
1	LDA (2.1 eq.), **145-Et,Et**, THF, –78 °C, 3 h, then **146,** –78 °C, 3 h	0
2	LDA (2.1 eq.), **145-Et,Et**, THF, –78 °C, 3 h, then **146,** –78 to 0 °C, 6 h	0
3	LDA (2.1 eq.), **145-Et,Et**, THF, –78 to –30 °C, 3 h, then **146,** –78 to 0 °C, 6 h	0
4	LDA (2.1 eq.), **145-Et,Et**, $ZnCl_2$, THF, –78 to –30 °C, 3 h, then **146,** –78 to 0 °C, 6 h	0

Because of this failure an alternative possibility was tried out. Racemic ethyl 3-hydroxybutyrate was chosen as a cheap and easily accessible model compound. Many attempts were made to perform an aldol reaction of ethyl glyoxylate with 3-hydroxybutyric acid derivatives. The first difficulty was that eliminations readily occurred in ethyl 3-hydroxybutyrate derivatives with a protected hydroxyl group (employing benzyl and trimethylsilyl as protective groups). In order to avoid such an elimination, the unprotected ethyl 3-hydroxybutyrate was used in the hope that it would undergo condensation with ethyl glyoxylate using protocols referring to dianion chemistry. Unfortunately, this attempt was also unsuccessful (Scheme 42).



Scheme 42. Attempted aldol reaction of ethyl 3-hydroxybutyrate with ethyl glyoxylate.

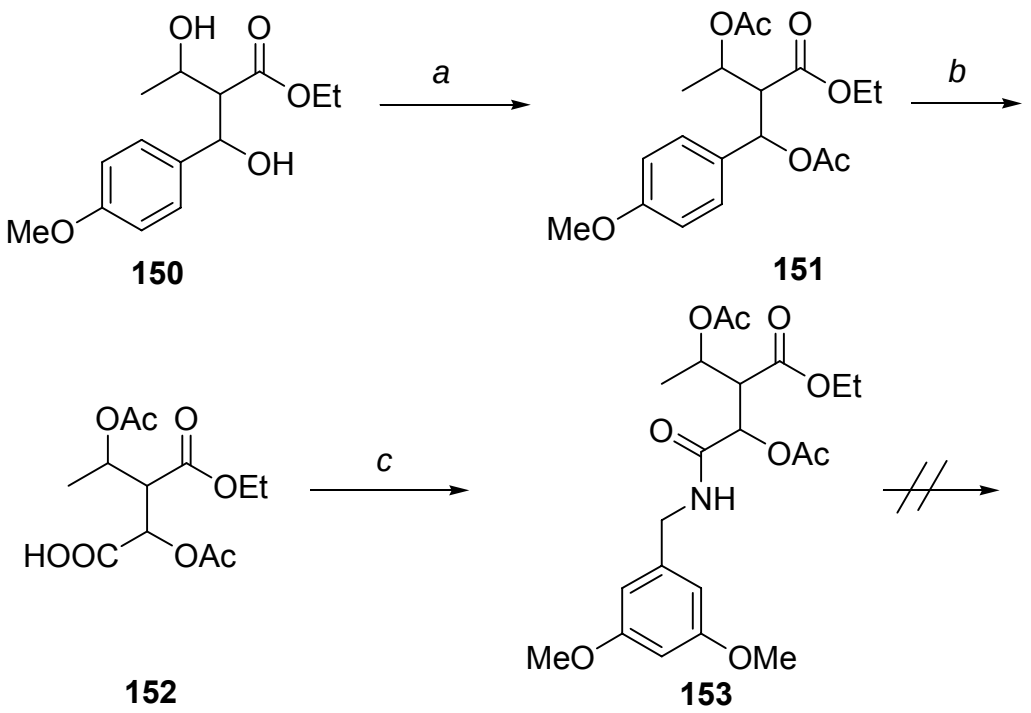
Since an aryl group, especially one bearing electron-donating substituents, can easily be converted into a carboxyl group by ruthenium-mediated oxidation, donor-substituted benzaldehydes can be used as glyoxylate equivalents. Indeed, the dianion generated from ethyl 3-hydroxybutyrate (**147**) upon treatment with 4-methoxybenzaldehyde did yield the expected product **150** (see Scheme 43).



Scheme 43. Aldol reaction of ethyl 3-hydroxybutyrate with 4-methoxybenzaldehyde.

Despite this partial success new problems turned up. The main difficulty that arose was the differentiation of the two hydroxy groups. The electronic and steric environments of these groups are very similar, and therefore it appeared to be impossible to protect one of them selectively. A second problem is the fact that this dianion aldol reaction cannot be performed with diastereocontrol like the Mukaiyama variant of the aldol reaction.

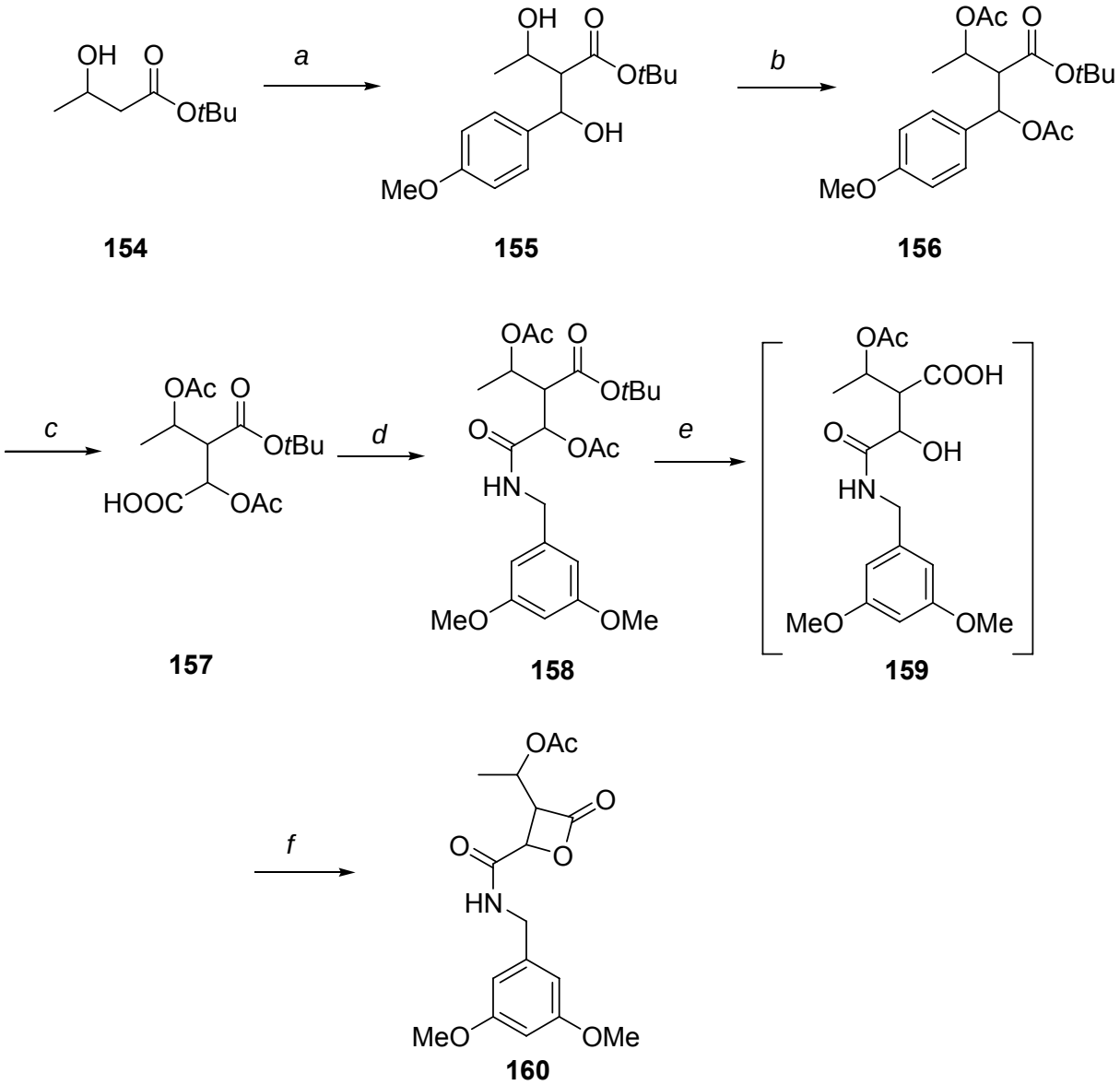
Nevertheless it was decided to go on with this route. The diol **150** was converted into the diacetate **151** under the usual conditions (acetic anhydride/pyridine). Then the malic acid monoester **152** was prepared from **151** by Ru-mediated oxidation. The carboxy function was converted into the 3,5-dimethoxybenzylamide according to the usual protocol of the peptide coupling (usage of EDC/HOAt). Here an advantage of this route comes to play, as the two carboxylate moieties are different from the beginning and can therefore selectively be converted into the respective derivatives (Scheme 44).



Scheme 44. An approach to a potential precursor of the hydroxyethyl-substituted oxetanonecarboxamide analogous to **140**. Reagents and conditions: (*a*) Ac_2O, py, r. t., 16 h, 52%. (*b*) $NaIO_4$, $RuCl_3$*xH_2O, CCl_4, H_2O, CH_3CN, r. t., 16 h, 89%. (*c*) **131**, EDC, HOAt, TMP, CH_2Cl_2.

An attempted hydrolysis of the product under basic conditions led to cleavage of both acetoxy groups as well as the ethyl ester. Therefore the cyclization to the desired β-lactone could not be achieved regioselectively. An attempted selective hydrolysis of only one acetoxy group under mildly acidic conditions (10% aq. HCl in dioxane) led to cleavage of both of them leaving the ethyl ester intact.

In view of the fact that *tert*-butyl esters are very easily cleaved under acidic conditions, a sequence employing the *tert*-butyl **154** instead of the ethyl ester **147** was executed in order to overcome this difficulty (Scheme 45).



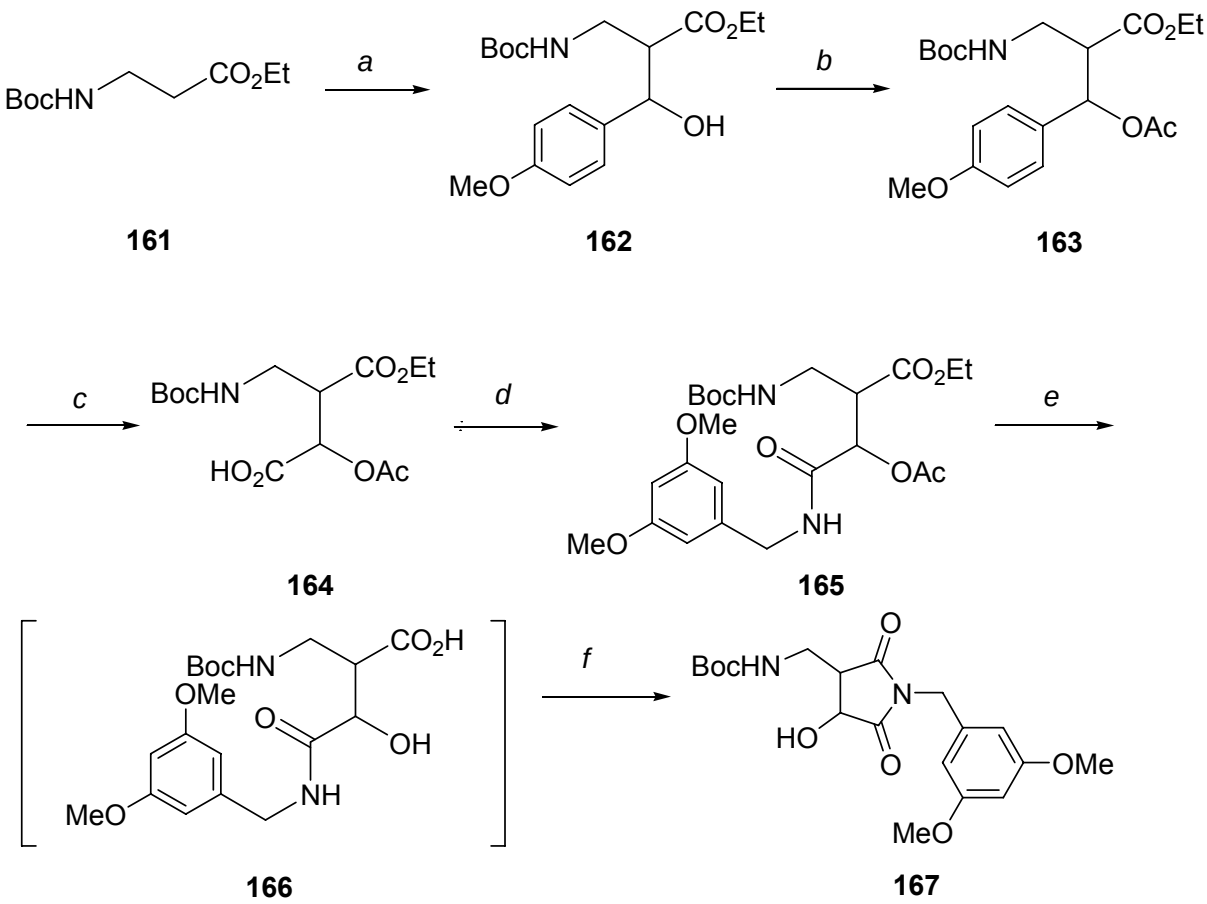
Scheme 45. Attempted preparation of the hydroxyethyl-substituted oxetanecarboxamide analogous **140**. Reagents and conditions: (*a*) (1) LDA, THF, –78 °C, 2 h (2) 4-methoxybenzaldehyde, –78 °C, 4 h, 34% (*b*) Ac_2O, py, r. t., 16 h, 62%. (*c*) $NaIO_4$, $RuCl_3$*xH_2O, CCl_4, H_2O, MeCN, r. t., 16 h, 87%. (*d*) **131**, EDC, HOAt, TMP, CH_2Cl_2, 62% (*e*) 10% aq HCl, dioxane (1 : 6), r. t., 48 h, (*f*) BOP, Et_3N, CH_2Cl_2, 0 °C to r. t., 3 h, 3%.

When the diacetate **158** was treated with HCl in dioxane, the *tert*-butyl ester was cleaved first, and the two acetoxy groups were hydrolyzed at different rates to yield the monoacetate **159** selectively. According to the ^{1}H-NMR spectrum, the hydroxyl group at C-3 was deprotected first. The crude product **159** was treated with BOP in the

presence of triethylamine to furnish the acetoxyethyl-substituted β-lactone **160**, yet in very low yield (3%).

Another idea to solve the problem of differentiating the two hydroxy groups in an aldol product of type **155** was to bring in one hydroxy group in the form of a carbonyl function and subsequently reduce it. However, the attempted aldol reaction of ethyl 3-oxobutyrate with 4-methoxybenzaldehyde only led to ethyl 2-(4-methoxybenzylidene)-3-oxobutyrate, i.e. the Knoevenagel condensation product.

Yet another proposal was to use a protected amino group and later convert that into the desired hydroxy function. The β-alanine derivative **161** was chosen to test this possibility. The aldol reaction of **161** with 4-methoxybenzaldehyde gave the product **162** in 52% yield. This is the first example of an aldol reaction involving a dianion bearing a negatively charge on a nitrogen atom. The hydroxy group in **162** was acetylated under standard conditions and the resulting acetoxy derivative (75% yield) was oxidatively degraded to the carboxylic acid **164**. This acid was further converted into the amide **165** (40%) according to the standard protocol. The acetoxy and ethyl ester groups in **165** were hydrolyzed and the resulting hydroxyacid **166** was treated with BOP in the presence of triethylamine. This, however, did not lead to the Boc-aminomethyl-substituted oxetanonecarboxamide, but to the hydroxyl-substituted succinimide **167** in 34% yield (Scheme 46).

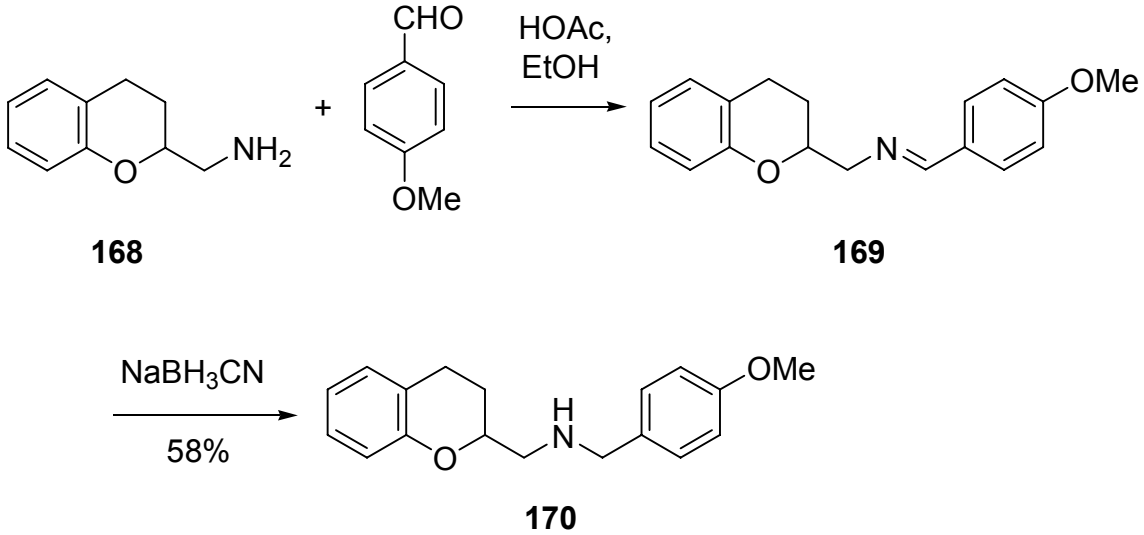


Scheme 46. Another attempted preparation of the hydroxyethyl-substituted oxetanonecarboxamide analogous to **140**. Reagents and conditions: (*a*) (1) LDA, THF, –78 °C, 2 h (2) 4-methoxybenzaldehyde, –78 °C, 4 h, 52% (*b*) Ac_2O, Py, r. t., 16 h, 75%. (*c*) $NaIO_4$, $RuCl_3$*xH_2O, CCl_4, H_2O, MeCN, r. t., 16 h, 83%. (*d*) **131**, EDC, HOAt, TMP, CH_2Cl_2, 40% (*e*) LiOH*H_2O, H_2O / THF (1 : 3), 16 h, 70% (*f*) BOP, Et_3N, CH_2Cl_2, 0 °C to r. t., 3 h, 34%.

Employing cyclization reagents like BOP-Cl or HATU also gave this imide **167** and traces of the corresponding unsaturated maleimide formed by elimination of water from **167**. In no case was the desired β-lactone obtained. It is obvious that the formation of the five-membered ring is favored thermodynamically.

In order to rule out the possibility of forming a five-membered ring, the amido group in **165** should be bis-protected. For this purpose a 4-methoxybenzyl group was chosen, because it can easily be cleaved off by oxidation with cerium ammonium nitrate. The problem in this case is that the 3,5-dimethoxybenzyl residue will be also cleaved under such oxidative conditions. In order to avoid that, another residue was chosen and a

secondary amine **170** bearing 4-methoxybenzyl residue was synthesized by reductive amination of 4-methoxybenzaldehyde (see Scheme 47).



Scheme 47. Synthesis of the secondary amine **170**.

However, all attempts to condense **170** with the acid **164** were unsuccessful.

Other modifications can be conceived in order to synthesize the target β-lactone in a better way, but their development will have to be a future endeavor.

Experimental Section

1. General Remarks

^{1}H and ^{13}C NMR spectra were recorded at 250, 300, 500, 600 (^{1}H), and 75.5, 151 MHz (^{13}C), additional APT (Attached Proton Test)] on Bruker AM 250, Bruker AMX 300, Varian VXR 500 S and Inova 600 instruments in $CDCl_3$ solutions if not otherwise specified, δ in ppm, *J* in Hz. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr pellets or as films between KBr plates. MS (EI): Finnigan MAT 95 spectrometer. Optical rotations: Perkin-Elmer 241 digital polarimeter, 1 dm cell. The enantiomeric purities of the dimethyl 2-phenylcyclopropanedicarboxylates (*S*)-**17a** and (*R*)-**17a** were determined by HPLC on the chiral-phase column 1A-Daicel, eluting with 2% isopropanol in hexane (0.8 mL/min)]. The HPLC chromatograms of the diisopropyl 3,3-di(methoxycarbonyl)-5-phenylpyrazolidine-1,2-dicarboxylate **(101aa),** dimethyl 5-(4-bromophenyl)-1,2-diphenylpyrazolidine-3,3-dicarboxylate **(101cc)** and dimethyl 2,4-dioxo-6-(4-methylphenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-7,7-dicarboxylate (**101bd**) were determined with the column Luna RP18, eluting with 40% water in methanol. M. p.: Büchi 540 capillary melting point apparatus, values are uncorrected. TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230–240 mesh. Starting materials: CH_2Cl_2 was distilled from P_4O_{10}, THF from sodium benzophenone ketyl, $HN(iPr)_2$ and DMF from CaH_2. Ethyl glyoxylate was obtained by the fractional distillation of the commercial 50% solution in toluene.[58]

2. Preparation of the Known Compounds

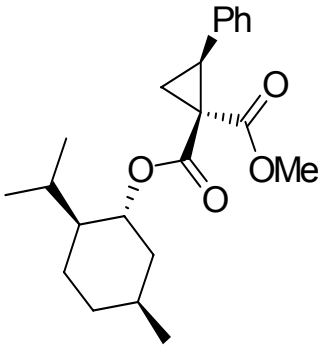
2-Arylcyclopropane-1,1-dicarboxylates **17** were prepared according to Fraser et al.,[45] *(E)*-1-methoxycarbonyl-2-phenylcyclopropanecarboxylic acid **93** was prepared according to Izquerdo.[59] 4-Phenyl-1,2,4-triazolin-3,5-dione (PTAD) **100d** was prepared according to Stickler[60] and Bautsch.[61] Ethyl phenyldiazenecarboxylate **100b** was prepared according to Kisseljova.[62] Aryl isocyanides **108** were prepared according to Ugi.[63] 2-Naphthylmethyl chloroformate was prepared according to Papageorgiou.[64] (N^{δ}-Benzyloxycarbonyl)-(*S*)-ornithine was prepared according to Lloyd.[65] (N^{δ}-Benzyloxycarbonyl)-(*S*)-ornithine *tert*-butyl ester **128** was prepared according to Widmer[66] and Wallace.[67] N^{δ}-(*tert*-Butyloxycarbonyl)-N^{α}-(9*H*-9-fluorenyloxycarbonyl)-L-ornithine benzyl ester was prepared according to Wiejak[68] and de Meijere.[36] (2*R*)-Hydroxy-(4*S*)-methyl-(3*S*)-phenylsulfanylcarbonylhexanoic acid ethyl ester **133** and (2*R*)-hydroxy-(4*S*)-methyl-(3*S*)-phenylsulfanylcarbonylhexanoic acid **51** were prepared according to published procedures.[36]

All other chemicals were used as commercially available. All reactions were conducted under an atmosphere of nitrogen. Organic extracts were dried over Na_2SO_4.

3. Experimental Procedures

3.1 Experimental Procedures for the Compounds from Chapter 1

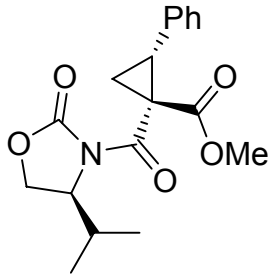
(E)-1-methoxycarbonyl-2-phenylcyclopropanecarboxylic acid (1R, 2S, 5R)-Isopropyl-5-methylcyclohexyl ester (94): DCC (5.4 g, 26 mmol) was added to an ice-cold solution of (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexanol (3.4 g, 23 mmol), (E)-1-methoxycarbonyl-2-phenylcyclopropanecarboxylic acid **93** (4.7 g, 22 mmol) and DMAP (0.52 g, 4 mmol) in CH_2Cl_2 (71 mL). The reaction mixture was stirred at r. t. for 4 h. Then the volatiles were distilled off under reduced pressure, and the residue was separated by column chromatography (eluent Et_2O / pentane 1 : 16), yielding 4.6 g (53%) of the desired product as a mixture of 2



diastereomers. Colorless solid, R_f = 0.45 (Et_2O /pentane (1 : 16)). ^{1}H NMR (300 MHz): 0.29 (1.5 H, d, J = 7 Hz), 0.61 (1.5 H, d, J = 7 Hz), 0.65 (1.5 H, d, J = 7 Hz), 0.66 (1.5 H, d, J = 7 Hz), 0.69– 0.94 (7 H, m), 1.04–1.24 (1.5 H, m), 1.26–1.36 (0.5 H), 1.46–1.59 (2 H, m), 1.66 (1 H, dd, J = 9, 5 Hz), 1.70–1.79 (0.5 H, m), 1.90–2.00 (0.5 H, m), 2.12–2.20 (1 H, m), 3.20 (1 H, t, J = 9 Hz), 3.73 (1.5 H, s), 3.75 (1.5 H, s), 4.32–4.47 (1 H, m), 7.10–7.26 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 15.5 (CH_3), 15.6 (CH_3), 18.3 (CH_2), 18.6 (CH_2), 20.8 (CH_3), 20.9 (CH_3), 21.8 (CH), 22.0 (CH), 22.6 (CH_2), 22.8 (CH_2), 24.9 (CH), 25.2 (CH), 31.0 (CH), 31.1 (CH), 32.1 (CH), 32.2 (CH), 33.9 (CH_2), 34.0 (CH_2), 37.9 (CH_2), 38.2 (CH_2), 39.5 (C), 39.9 (C), 52.4 (CH_3), 52.5 (CH_3), 75.4 (CH), 75.5 (CH), 127.26 (CH), 127.28 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 134.2 (C), 134.5 (C), 166.06 (C), 166.14 (C), 170.42 (C), 170.49 (C) ppm. IR (film): $\tilde{\nu}$ = 3041 cm^{-1}, 2945, 1720, 1430, 1276, 1179, 1162, 1110. MS (ESI): m/z = 739 ([2 M + Na$^+$], 7), 381 ([M + Na$^+$], 100). Calcd. for $C_{22}H_{30}O_4$: C 73.71%, H 8.44%; found: C 73.42%, H 8.13%.

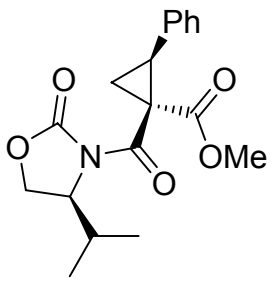
***(1'S,2'R,4S)*-4-Isopropyl-3-(1'-methoxycarbonyl-2'-phenylcyclopropylcarbonyl)-oxazolidin-2-one (95) and *(1'R,2'S,4S*-4-Isopropyl-3-(1'-methoxycarbonyl-2'-phenylcyclopropylcarbonyl)oxazolidin-2-one (96):** A mixture of **95** and **96** was obtained from *(E)*-1-methoxycarbonyl-2-phenylcyclopropane-carboxylic acid (**93**) (3.15 g, 14.3 mmol) and *(4S)*-4-isopropyloxazolidin-2-one (**97**) (1.85 g, 14.3 mmol) according to a published procedure.[69] This mixture was separated by column chromatography on silica gel, eluting with diethyl ether/pentane 1 : 4.

***(1'S,2'R,4S)*-4-Isopropyl-3-(1'-methoxycarbonyl-2'-phenylcyclopropylcarbonyl)-oxazolidin-2-one (95):** Colorless solid, yield 1.4 g (29%), R_f = 0.08 (diethyl ether/pentane 1 : 4), m. p. 129–130 °C. ^{1}H NMR (300 MHz): –0.07 (3 H, d, *J* = 7 Hz), 0.64 (3 H, d, *J* = 7 Hz), 0.92 (1 H, dd, *J* = 7, 8 Hz), 1.66–1.74 (1 H, m), 1.78 (1 H, dd, *J* = 5, 9 Hz), 2.36 (1 H, dd, *J* = 5, 8 Hz), 3.42 (1 H, t, *J* = 8 Hz), 3.72 (3 H, s), 4.01 (1 H, dd, *J* = 1, 8 Hz), 4.17 (1 H, t, *J* = 8 Hz), 7.16–7.30 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 13.3 (CH_3), 17.8 (CH_3), 18.6

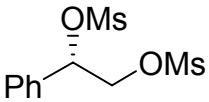


(CH_2), 26.2 (CH), 33.0 (CH), 39.9 (C), 52.6 (CH_3), 58.8 (CH), 63.3 (CH_2), 127.5 (CH), 128.2 (CH), 128.4 (CH), 133.6 (C), 153.3 (C), 165.0 (C), 169.7 (C) ppm. IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 1787, 1736, 1690, 1388, 1366, 1279, 1209, 1151, 1104, 1052, 1012, 975, 752, 699. $[\alpha]_D^{20}$ = +212.0 (*c* = 1.0, $CHCl_3$). MS (ESI): m/z = 685 ([2 M + Na^+], 15), 354 ([M + Na^+], 100). Calcd. for $C_{18}H_{21}N_2O_5$: C 65.24%, H 6.39%, N 4.23%; found: C 65.59%, H 6.26%, N 4.36%.

***(1'R,2'S,4S)*-4-Isopropyl-3-(1'-methoxycarbonyl-2'-phenylcyclopropylcarbonyl)-oxazolidin-2-one (96):** Colorless solid, yield 1.6 g (34%), R_f = 0.25 (diethyl ether/pentane 1 : 4), m. p. 128–129 °C. ^{1}H NMR (300 MHz): 0.80 (3 H, d, *J* = 7 Hz), 0.82 (3 H, d, *J* = 7 Hz), 1.79 (1 H, dd, *J* = 6, 9 Hz), 2.14–2.24 (1 H, m), 2.28 (1 H, dd, *J* = 6, 8 Hz), 3.24–3.36 (2 H, m), 3.71 (3 H, s), 3.74 (1 H, m), 3.87 (1 H, dd, *J* = 2, 9 Hz), 7.06–7.32 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 15.1 (CH_3), 17.6 (CH_3), 18.5 (CH_2), 28.9 (CH), 32.1 (CH), 39.7 (C), 52.5 (CH_3), 58.5 (CH), 63.7 (CH_2), 127.3 (CH), 127.6 (CH), 128.1 (CH), 133.9 (C), 152.8 (C), 165.3 (C), 169.8 (C) ppm. IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 1772, 1734, 1700, 1684, 1653, 1506, 1457, 1280, 1195, 1107, 870, 797, 758, 704. $[\alpha]_D^{20}$= – 73.2 (*c* = 1.0, $CHCl_3$). LRMS (ESI) m/z = 685 ([2 M + Na^+], 26), 413 (25), 385 (32), 354 ([M + Na^+], 100). Calcd. for $C_{18}H_{21}N_2O_5$: C 65.24%, H 6.39%, N 4.23%; found: C 65.41%, H 6.72%, N 4.01%.



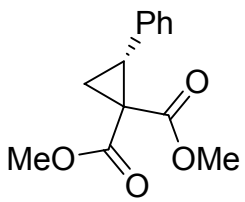
Synthesis of (*S*)-1,2-Dimesyloxyphenylethane (99): To an ice-cold solution of (*S*)-phenylethanediol **98** (1g, 7.2 mmol) and Et_3N (2.5 mL) in CH_2Cl_2 (25 mL) was added a solution of mesyl chloride (1.3 mL) in CH_2Cl_2 (12.5 mL) within 1 h, and the mixture was stirred at 0 °C for an additional 1 h and at r. t. for another 2 h. Then 1N aq. HCl was added to this solution, the phases were separated, the organic phase was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated $NaHCO_3$, aq. HCl, and dried. The volatiles were removed under reduced pressure yielding 1.8 g (84%) of a yellow solid. R_f = 0.45 (EtOAc / hexane (1 : 1)), m. p. 92–3 °C. $[\alpha]_D^{20}$= +82.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO–d_6): 3.15 (3 H, s), 3.24 (3 H, s), 4.50–4.56 (1 H, m), 4.59–4.65 (1 H, m), 5.96 (1 H, dd, *J* = 3, 7 Hz), 7.44–7.60 (5 H, m) ppm. ^{13}C NMR (90.58 MHz): 36.9 (CH_3), 38.3 (CH_3), 70.5



(CH_2), 79.8 (CH), 127.1 (CH), 128.7 (CH), 129.3 (CH), 134.3 (C) ppm. IR (film): $\tilde{\nu}$ = 2982 cm^{-1}, 1750, 1708, 1457, 1375, 1276, 1181, 1107, 1020, 913, 750. MS (ESI): m/z = 611 ([2 M + Na^+], 5), 317 ([M + Na^+], 100).

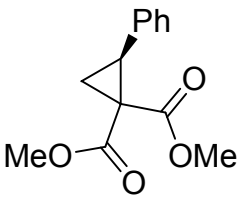
Synthesis of Both Enantiomers of Dimethyl 2-Phenylcyclopropane-1,1-dicarboxylate (17a) from Evans' Oxazolidines: A solution of *(*1'*S*,2'*R*,4*S)*-4-isopropyl-3-(1'-methoxycarbonyl-2'-phenylcyclopropylcarbonyl)oxazolidin-2-one (**96**) (200 mg, 0.6 mmol) in a mixture of NaOH (4 g, 100 mmol), THF (21 mL), H_2O_2 (6 mL, 30%) and H_2O (14 mL) was heated at reflux for 48 h, then the THF was distilled off under reduced pressure. Saturated aqueous $NaHCO_3$ was added to this mixture, and the solution obtained was washed twice with ethyl acetate (10 mL each), then the aqueous phase was acidified with diluted HCl, extracted with ethyl acetate (3×20 mL) and the organic phase was dried over Na_2SO_4. Then the solvent was distilled off, and an ethereal solution of CH_2N_2 (20 mL), obtained from *N*-nitroso-*N*-methylurea (1.0 g, 9.7 mmol) was added to the residue. After 24 h, the solvent was distilled off, and the residue was purified by the column chromatography on silica gel, eluting with diethyl ether/pentane 1 : 4.

Dimethyl (*R*)-2-Phenylcyclopropane-1,1-dicarboxylate ((*R*)-17a): Yield: 45 mg



(32%), $[\alpha]_D^{20}$= +93.4 (*c* = 0.8, benzene). ^{1}H NMR (300 MHz): 1.74 (1 H, dd, *J* = 4, 3 Hz), 2.20 (1 H, dd, *J* = 4, 3 Hz), 3.21 (1 H, t, *J* = 4 Hz), 3.40 (3 H, s), 3.80 (3 H, s), 7.20–7.30 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 19.0 (CH_2), 32.4 (CH), 36.8 (C), 52.1 (CH_3), 52.6 (CH_3), 127.2 (CH), 128.5 (CH), 128.9 (CH), 134.5 (C), 164.9 (C), 169.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3041 cm^{-1}, 2950, 1721, 1435, 1279, 1180, 1162, 1109.

Dimethyl (*S*)-2-Phenylcyclopropane-1,1-dicarboxylate ((*S*)-17a): Yield: 38 mg



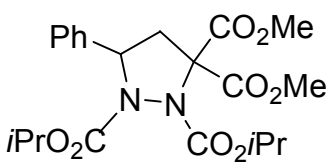
(27%), $[\alpha]_D^{20}$= –111.8 (*c* = 1.1, benzene). Lit.[70]: $[\alpha]_D^{20}$ = –124 (*c* = 2.23, benzene). ^{1}H NMR (300 MHz): 1.70 (1 H, dd, *J* = 4, 3 Hz), 2.24 (1 H, dd, *J* = 4, 3 Hz), 3.23 (1 H, t, *J* = 4 Hz), 3.45 (3 H, s), 3.80 (3 H, s), 7.20–7.30 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 18.9 (CH_2), 32.6 (CH), 36.9 (C), 52.4 (CH_3), 52.7 (CH_3), 127.3 (CH), 128.5 (CH), 128.8 (CH),

134.6 (C), 164.6 (C), 169.1 (C) ppm. IR (film): $\tilde{\nu}$ = 3042 cm^{-1}, 2953, 1726, 1435, 1281, 1180, 1160, 1110.

Synthesis of (*S*)-Dimethyl 2-Phenylcyclopropane-1,1-dicarboxylate ((*S*)-17a) from (*S*)-1,2-Dimesyloxyphenylethane (99): To an ice–cold suspension of NaH (0.5 g, 60% suspension in oil, 12.5 mmol) in THF (12 mL) was added dropwise a solution of dimethyl malonate (1.4 mL, 1.6 g, 12.2 mmol) in THF (12 mL). The mixture was stirred at 0 °C for an additional 1 h, then a solution of **99** (1.8 g, 6 mmol) in THF (12 mL) was added dropwise. The resulting mixture was stirred at 67 °C for 24 h, then poured into water (100 mL), extracted with EtOAc (3×20 mL), and dried. The volatiles were removed *in vacuo* and the residue was purified by column chromatography (eluent: pentane / Et_2O (4 : 1)), yielding 620 mg (49%) of (*S*)-**17a**. $[\alpha]_D^{20}$= –132.8 (*c* = 1.0, benzene)

General Procedure for the Synthesis of Diisopropyl 5-Aryl-3,3-di(methoxycarbonyl)-pyrazolidine-1,2-dicarboxylates (GP1): To a mixture of the respective dimethyl 2-arylcyclopropane-1,1-dicarboxylate **17** (0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of $GaCl_3$ (30 mg, 0.17 mmol, 20 mol%) in CH_2Cl_2 (3.5 mL). The mixture was stirred at rt for 3 h, while monitoring the progress of the reaction by TLC, then directly applied onto a chromatographic column (silica gel) and eluted with diethyl ether/pentane (1 : 1) to give the desired substituted pyrazolidine **101**.

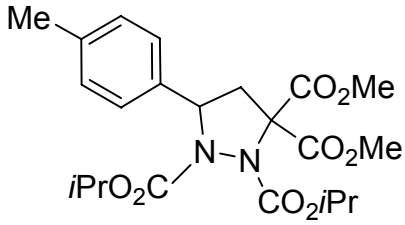
Diisopropyl 3,3-Di(methoxycarbonyl)-5-phenylpyrazolidine-1,2-dicarboxylate (101aa):



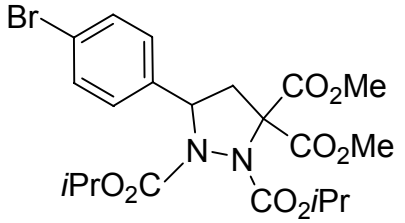
According to GP1, dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**17a**) (200 mg, 0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) gave 233 mg (63%) of the pyrazolidine **101aa** as a colorless oil. R_f = 0.33 (diethyl ether/pentane 1 : 1). ^{1}H NMR (250 MHz): 1.24–1.31 (12 H, m), 2.92 (1 H, dd, *J* = 14, 4 Hz), 3.31 (1 H, dd, *J* = 8, 14 Hz), 3.48 (3 H, s), 3.83 (3 H, s), 4.92–5.06 (2 H, m), 5.47 (1 H, dd, 4 Hz, 8 Hz), 7.23–7.45 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 21.8 (CH_3), 21.9 (CH_3), 44.6 (CH_2), 53.0 (CH), 53.4 (CH),

61.2 (CH), 70.5 (CH_3), 70.8 (CH_3), 72.3 (C), 125.8 (CH), 127.3 (CH), 128.3 (CH), 139.5 (C), 153.3 (C), 156.9 (C), 166.5 (C), 168.9 (C) ppm. IR (film): $\tilde{\nu}$ = 2983 cm^{-1}, 1751, 1707, 1456, 1375, 1276, 1180, 1107, 1020, 750, 701. MS (DCI) m/z = 890 ([2 M + NH_4^+], 8), 454 ([M + NH_4^+], 100), 437 ([M + H^+], 20), 222 (8). HRMS (APCI) [M + H^+] – calcd. for $C_{21}H_{29}N_2O_8$ 437.1924, found 437.1918.

Diisopropyl 3,3-Di(methoxycarbonyl)-5-(4-methylphenyl)-pyrazolidine-1,2-dicarboxylate (101ba): According to GP1, dimethyl 2-(4-methylphenyl)cyclopropane-1,1-dicarboxylate (**17b**) (211 mg, 0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) gave 198 mg (52%) of the pyrazolydine (**101ba**) as a colorless oil, R_f = 0.30 (diethyl ether/pentane 1 : 1). ^{1}H NMR (300 MHz): 1.20–1.30 (12 H, m), 2.31 (3 H, s), 2.90 (1 H, dd, J = 4, 13 Hz), 3.27 (1 H, dd, J = 8, 13 Hz), 3.51 (3 H, s), 3.82 (3 H, s), 4.90–5.05 (2 H, m), 5.40 (1 H, dd, J = 4, 8 Hz), 7.12 (2 H, d, J = 8 Hz), 7.26 (2 H, d, J = 8 Hz) ppm. ^{13}C NMR (90.58 MHz): 21.8 (CH_3), 21.9 (CH_3), 22.1 (CH_3), 44.6 (CH_2), 53.0 (CH), 53.4 (CH), 61.0 (CH), 70.5 (CH_3), 70.7 (CH_3), 72.4 (C), 125.8 (CH), 129.0 (CH), 136.5 (C), 136.9 (C), 153.3 (C), 156.8 (C), 166.4 (C), 168.8 (C) ppm. IR (film): $\tilde{\nu}$ = 2982 cm^{-1}, 1750, 1708, 1457, 1375, 1276, 1181, 1107, 1020, 913, 750. MS (ESI): m/z = 993 ([2 M + Na^+], 100), 473 ([M + Na^+], 36). Calcd. for $C_{22}H_{30}N_2O_8$: C 58.66%, H 6.71%, N 6.22%, found: C 58.46%, H 6.78%, N 5.98%.

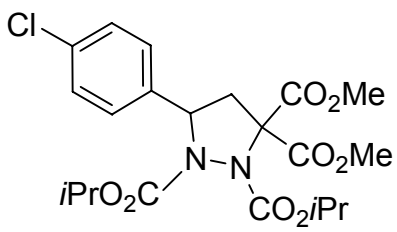


Diisopropyl 5-(4-Bromophenyl)-3,3-di(methoxycarbonyl)-pyrazolidine-1,2-dicarboxylate (101ca): According to GP1, dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (**17c**) (266 mg, 0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) gave 201 mg (46%) of the pyrazolidine (**101ca**) as a colorless oil, R_f = 0.24 (diethyl ether/pentane 1 : 2). ^{1}H NMR (300 MHz): 1.22–1.29 (12 H, m), 2.81 (1 H, dd, J = 4, 13 Hz), 3.27 (1 H, dd, J = 8; 13 Hz), 3.47 (3 H, s), 3.89 (3 H, s), 4.88–5.00 (2 H, m), 5.37 (1 H, dd, J = 4, 8 Hz), 7.27 (2 H, d, J = 8 Hz), 7.76 (2 H, d, J = 8 Hz) ppm. ^{13}C NMR (75.5 MHz): 21.86 (CH_3), 21.90 (CH_3), 21.93 (CH_3), 22.10 (CH_3), 44.6 (CH_2), 53.4 (CH), 53.7 (CH), 54.1 (CH), 71.0 (CH_3), 71.2 (CH_3), 72.8 (C), 121.2 (C),

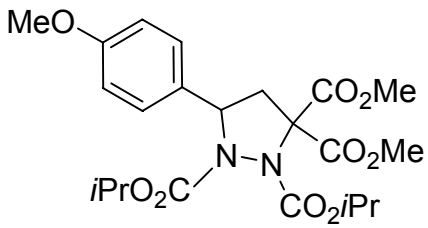


128.0 (CH), 131.6 (CH), 139.4 (C), 153.6 (C), 156.7 (C), 166.5 (C), 168.7 (C) ppm. IR (film): $\tilde{\nu}$ = 2983 cm^{-1}, 1750, 1707, 1635, 1559, 1540, 1456, 1374, 1106. MS (ESI) m/z = 1055 ([2 M + Na$^+$], 50), 1053 ([2 M + Na$^+$], 100), 1051 ([2 M + Na$^+$], 50), 539 ([M + Na$^+$], 30), 537 ([M + Na$^+$], 30). Calcd. for $C_{21}H_{27}BrN_2O_8$: C 48.94%, H 5.28%, N 5.44%, found: C 48.73%, H 5.36%, N 5.21%.

Diisopropyl 5-(4-Chlorophenyl)-3,3-di(methoxycarbonyl)-pyrazolidine-1,2-dicarboxylate (101da): According to GP1, dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate (**17d**) (228 mg, 0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) gave 268 mg (67%) of the pyrazolidine **101da** as a colorless oil, R_f = 0.27 (diethyl ether/pentane 1 : 1). ^{1}H NMR (300 MHz): 1.24–1.32 (12 H, m), 2.86 (1 H, dd, J = 4, 13 Hz), 3.30 (1 H, dd, J = 8, 13 Hz), 3.52 (3 H, s), 3.82 (3 H, s), 4.94–5.06 (2 H, m), 5.43 (1 H, dd, J = 4, 8 Hz), 7.28–7.40 (4 H, m) ppm. ^{13}C NMR (75.5 MHz): 21.82 (CH$_3$), 21.86 (CH$_3$), 21.88 (CH$_3$), 22.05 (CH$_3$), 44.6 (CH$_2$), 53.1 (CH), 53.4 (CH), 60.7 (CH), 70.6 (CH$_3$), 71.0 (CH$_3$), 72.3 (C), 127.1 (C), 127.3 (CH), 128.4 (CH), 133.1 (C), 153.1 (C), 156.8 (C), 166.4 (C), 168.6 (C) ppm. IR (film): $\tilde{\nu}$ = 2983 cm^{-1}, 1749, 1708, 1640, 1494, 1454, 1375, 1282, 1179, 1106, 1015, 736. MS (ESI) m/z = 963 ([2 M + Na$^+$], 100), 493 ([M + Na$^+$], 24). Calcd. for $C_{21}H_{27}ClN_2O_8$: C 53.56%, H 5.78%, N 5.95%, found: C 53.57%, H 5.50%, N 5.57%.

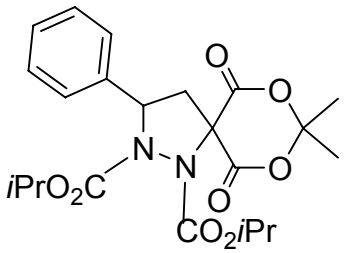


Diisopropyl 3,3-Di(methoxycarbonyl)-5-(4-methoxyphenyl)-pyrazolidine-1,2-dicarboxylate (101ea): According to GP1, dimethyl 2-(4-methoxyphenyl)cyclopropane-1,1-dicarboxylate (**17e**) (225 mg, 0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) gave 170 mg (43%) of the pyrazolidine **101ea** as a colorless oil, R_f = 0.48 (diethyl ether/pentane 1 : 5). ^{1}H NMR (300 MHz): 1.23–1.30 (12 H, m), 2.89 (1 H, dd, J = 4, 13 Hz), 3.25 (1 H, dd, J = 8, 13 Hz), 3.52 (3 H, s), 3.78 (3 H, s), 3.81 (3 H, s), 4.92–5.04 (2 H, m), 5.38 (1 H, dd, J = 4, 8 Hz), 6.84 (2 H, d, J = 9 Hz), 7.29 (2 H, d, J = 9 Hz) ppm. ^{13}C NMR (75.5 MHz): 21.80 (CH$_3$), 21.87 (CH$_3$), 21.89 (CH$_3$), 22.05 (CH$_3$), 44.6 (CH$_2$), 53.0 (CH), 53.3 (CH), 55.2 (CH), 60.7 (CH$_3$),



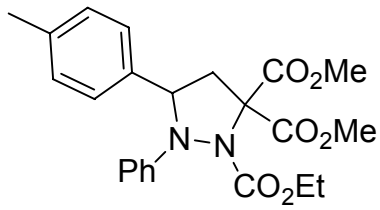
70.4 (CH_3), 70.7 (CH_3), 72.4 (C), 113.7 (CH), 127.1 (CH), 131.5 (C), 153.3 (C), 156.8 (C), 158.8 (C), 166.5 (C), 168.8 (C) ppm. IR (film): $\tilde{\nu}$ = 2984 cm^{-1}, 1749, 1636, 1516, 1437, 1374, 1249, 1177, 1106. LRMS (ESI): m/z = 954 ([2 M + Na^+], 100), 489 ([M + Na^+], 12). Calcd. for $C_{22}H_{30}N_2O_9$: C 56.64%, H 6.48%, N 6.01%, found: C 56.87%, H 6.20%, N 5.78%.

Diisopropyl 8,8-Dimethyl-6,10-dioxo-3-phenyl-1,2-diaza-7,9-dioxaspiro[4.5]decane-1,2-dicarboxylate (101fa): According to GP1, 3,3-dimethyl-7-phenyl-2,4-dioxaspiro[2.5]octan-1,5-dione (**17f**) (210 mg, 0.85 mmol) and diisopropyl azodicarboxylate (**100a**) (242 mg, 1.2 mmol) gave 203 mg (53%) of the pyrazolidine **101fa** as a colorless oil, R_f = 0.34 (diethyl ether/pentane 1 : 1). ^1H NMR (300 MHz): 1.12–1.30 (12 H, m), 1.73 (3 H, s), 1.86 (3 H, s), 2.96 (1 H, dd, J = 4, 13 Hz), 3.13 (1 H, dd, J = 8, 13 Hz), 4.94–5.06 (2 H, m), 5.78 (1 H, dd, J = 4, 8 Hz), 7.22–7.42 (5 H, m) ppm. ^{13}C NMR (90.58 MHz): 21.6 (CH_3), 21.7 (CH_3), 21.8 (CH_3), 21.9 (CH_3), 27.7 (CH_3), 29.0 (CH_3), 46.9 (CH_2), 61.8 (CH), 65.0 (C), 71.2 (CH), 71.6 (CH), 72.4 (C), 125.8 (CH), 127.4 (CH), 128.3 (CH), 139.3 (C), 152.5 (C), 157.0 (C), 162.2 (C), 166.0 (C) ppm. IR (film): $\tilde{\nu}$ = 2983 cm^{-1}, 1751, 1700, 1375, 1300, 1205, 1105, 961, 740, 701. MS (ESI): m/z = 919 ([2 M + Na^+], 48), 471 ([M + Na^+], 100), 401 (92). HRMS (ESI) [M + H^+]: calcd. for $C_{22}H_{29}N_2O_8$ 449.1924, found 449.1918.



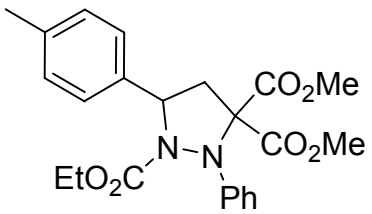
Dimethyl 2-Ethoxycarbonyl-5-(4-methylphenyl)-1-phenylpyrazolidine-3,3-dicarboxylate (101bb) and Dimethyl 1-Ethoxycarbonyl-5-(4-methylphenyl)-2-phenylpyrazolidine-3,3-dicarboxylate (102bb): According to GP1 dimethyl 2-(4-methylphenyl)cyclopropane-1,1-dicarboxylate (**17b**) (211 mg, 0.85 mmol) and ethyl phenyl diazenecarboxylate (**100b**) (213 mg, 1.2 mmol) gave a mixture of **101bb** and **102bb** which were separated by column chromatography on silica gel (70 g, column 3×30 cm) eluting with pentane/diethyl ether 4 : 1 to 2 : 1)

Dimethyl 2-Ethoxycarbonyl-5-(4-methylphenyl)-1-phenyl-pyrazolidine-3,3-dicarboxylate (101bb): Light yellow oil, yield: 60 mg (17%), R_f = 0.19 (diethyl ether/pentane 1 : 2). ^1H NMR (600 MHz): 1.13 (3 H, t, J



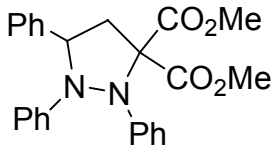
= 7 Hz), 2.28 (3 H, s), 2.94 (1 H, dd, J =10, 7 Hz), 3.14 (1 H, dd, J = 10, 2 Hz), 3.30 (3 H, s), 3.76 (3 H, s), 4.04–4.20 (2 H, m), 4.93 (1 H, dd, J = 7, 2 Hz), 6.80–7.40 (9 H, m). ^{13}C NMR (151 MHz): 14.4 (CH_3), 21.1 (CH_3), 43.4 (CH_2), 52.7 (CH_3), 53.3 (CH_3), 62.3 (CH_2), 69.2 (CH), 72.3 (C), 116.4 (CH), 122.2 (CH), 126.0 (CH), 128.7 (CH), 129.0 (CH), 136.9 (C), 150.3 (C), 154.0 (C), 167.4 (C), 169.3 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2954 cm^{-1}, 1740, 1436, 1261, 1177, 1066, 1034, 802, 752, 697, 668. LRMS (ESI) m/z = 875 ([2 M + Na$^+$], 100), 449 ([M + Na$^+$], 35). MS (ESI) [M + H$^+$]: Calcd. for $C_{23}H_{27}N_2O_6$ 427.1869, found 427.1864. Calcd. for $C_{23}H_{26}N_2O_6$: C 64.78%, H 6.15%, N 6.57%, found: C 64.48%, H 6.00%, N 6.29%.

Dimethyl 1-Ethoxycarbonyl-5-(4-methylphenyl)-2-phenyl-pyrazolidine-3,3-dicarboxylate (102bb): Light yellow oil, yield: 20 mg (6%), R_f= 0.15 (diethyl ether/pentane 1 : 2). ^{1}H NMR (600 MHz): 1.19 (3 H, t, J = 7 Hz), 2.35 (3 H, s), 3.08 (1 H, dd, J =10, 13 Hz), 3.21 (1 H, dd, J =8, 13 Hz), 3.51 (3 H, s), 3.86 (3 H, s), 4.13–4.20 (2 H, m), 5.14 (1 H, dd, J = 8, 10 Hz), 7.04–7.07 (1 H, m), 7.11–7.14 (2 H, m), 7.16–7.22 (4 H, m), 7.31 (2 H, d, J = 8 Hz). ^{13}C NMR (151 MHz): 14.5 (CH_3), 21.1 (CH_3), 41.8 (CH_2), 53.0 (CH_3), 53.4 (CH_3), 60.7 (CH), 62.2 (CH_2), 78.3 (C), 121.9 (CH), 124.6 (CH), 126.7 (CH), 128.5 (CH), 129.2 (CH), 136.6 (C), 137.1 (C), 147.1 (C), 165.7 (C), 169.4 (C) ppm. IR (film): $\tilde{\nu}$ = 2953 cm^{-1}, 1748, 1700, 1496, 1457, 1436, 1374, 1276, 1127, 1022, 912, 731. MS (ESI): m/z = 875 ([2 M + Na$^+$], 100), 449 ([M + Na$^+$], 13). HRMS (ESI) [M + H$^+$]: Calcd. for $C_{23}H_{27}N_2O_6$ 427.1869, found 427.1864.



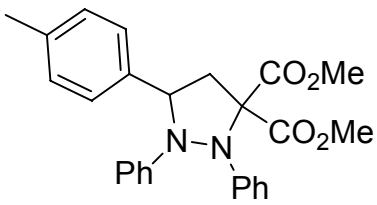
General Procedure for the Preparation of Dimethyl 5-Aryl-1,2-triphenylpyrazolidine-3,3-dicarboxylate (101ac–101cc) (GP2): A solution of $GaCl_3$ (30 mg, 0.17 mmol, 20 mol%) in CH_2Cl_2 (2 mL) was added dropwise to a solution of the respective dimethyl 2-arylcyclopropane-1,1-dicarboxylate (**17**) (0.85 mmol) and of azobenzene (**100c**) (309 mg, 1.7 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred for 2–3 h while monitoring the reaction progress by TLC, and the products were purified by column chromatography on silica gel, eluting with diethyl ether/pentane 1 : 4.

Dimethyl 1,2,5-Triphenylpyrazolidine-3,3-dicarboxylate (101ac): According to GP2,



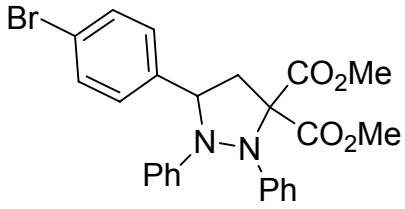
17a (200 mg, 0.85 mmol) and azobenzene (**100c**) (309 mg, 1.7 mmol) gave 150 mg (42%) of the pyrazolidine **101ac** as a colorless solid, R_f = 0.38 (diethyl ether/pentane 1 : 4), m. p. 127–128 °C. ^{1}H NMR (300 MHz): 3.14 (1 H, dd, *J* =7, 13 Hz), 3.39 (3 H, s), 3.48 (1 H, dd, *J* = 8, 13 Hz), 3.85 (3 H, s), 4.92 (1 H, t, *J* = 7 Hz), 6.88–7.61 (15 H, m) ppm. ^{13}C NMR (75.5 MHz): 44.8 (CH_2), 52.7 (CH_3), 53.1 (CH_3), 67.8 (CH), 76.4 (C), 116 (CH), 117.8 (CH), 121.2 (CH), 121.5 (CH), 126.4 (CH), 127.3 (CH), 128.56 (CH), 128.62 (CH), 146.7 (C), 167.7 (C), 170.5 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2955 cm^{-1}, 2852, 1759, 1736, 1594, 1490, 1448, 1431, 1258, 1192, 1087, 756, 694, 518. MS (ESI): m/z = 855 ([2 M + Na$^+$], 4), 439 ([M + Na$^+$], 100). Calcd. for $C_{25}H_{24}N_2O_4$: C 72.10%, H 5.81%, N 6.73%, found: C 71.81%, H 5.77%, N 6.58%.

Dimethyl 5-(4-Methylphenyl)-1,2-diphenylpyrazolidine-3,3-dicarboxylate (101bc):



According to GP2, dimethyl 2-(4-methylphenyl)cyclopropane-1,1-dicarboxylate (**17b**) (211 mg, 0.85 mmol) and azobenzene (**100c)** (309 mg, 1.7 mmol) gave 160 mg (44%) of the pyrazolidine **101bc** as a light yellow solid, R_f = 0.60 (diethyl ether/pentane 1 : 2), m. p. 104–105 °C (dec.). ^{1}H NMR (300 MHz): 2.37 (3 H, s), 3.06 (1 H, dd, *J* = 8, 13 Hz), 3.39 (3 H, s), 3.40–3.43 (1 H, m), 3.80 (3 H, s), 4.81 (1 H, t, *J* =8 Hz), 6.82–7.00 (4 H, m), 7.12 (2 H, d, *J* = 8 Hz), 7.15–7.24 (6 H, m), 7.41 (2 H, d, *J* = 8 Hz) ppm. ^{13}C NMR (75.5 MHz): 21.1 (CH_3), 44.8 (CH_2), 52.8 (CH_3), 53.2 (CH_3), 67.5 (CH), 76.7 (C), 115.9 (CH), 118.0 (CH), 121.0 (CH), 121.7 (CH), 126.5 (CH), 127.3 (CH), 128.55 (CH), 128.64 (CH), 129.3 (CH), 137.0 (C), 146.9 (C), 170.6 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3025 cm^{-1}, 2952, 1734, 1595, 1496, 1490, 1436, 1260, 1172, 1088, 812, 749, 695, 668. MS (ESI): m/z = 883 ([2 M + Na$^+$], 5), 453 ([M + Na$^+$], 100). HRMS (ESI): [M + H$^+$] calcd. for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1965. Calcd. for $C_{26}H_{26}N_2O_4$: C 72.54%, H 6.09%, N 6.51%, found: C 72.36%, H 5.83%, N 6.30%.

Dimethyl 5-(4-Bromophenyl)-1,2-diphenylpyrazolidine-3,3-dicarboxylate (101cc):



According to GP2, dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (**17c**) (266 mg, 0.85 mmol) and azobenzene (**100c**) (309 mg, 1.7 mmol) gave 172 mg (41%) of the pyrazolidine **101cc** as a light yellow solid, yield 172 mg (41%). R_f = 0.32 (diethyl ether/pentane 1 : 4), m. p. 144–145 °C. ^{1}H NMR (600 MHz): 3.04 (1 H, dd, J = 7, 13 Hz), 3.38 (3 H, s), 3.44 (1 H, dd, J = 8, 13 Hz), 3.81 (3 H, s), 4.84 (1 H, t, J =8 Hz), 6.87–6.98 (4 H, m), 7.10–7.24 (6 H, m), 7.40 (2 H, d, J = 8 Hz), 7.51 (2 H, m) ppm. ^{13}C NMR (151 MHz): 44.6 (CH_2), 52.8 (CH_3), 53.2 (CH_3), 67.4 (CH), 76.3 (C), 116.0 (CH), 117.5 (CH), 121.2 (CH), 121.5 (CH), 121.6 (CH), 128.3 (CH), 128.7 (CH), 129. 6 (C), 130.2 (C), 131.7 (CH), 167.7 (C) 170.4 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3025 cm^{-1}, 2953, 1772, 1749, 1594, 1490, 1436, 1263, 1168, 1102, 1009, 822, 790, 695. LRMS (ESI): m/z = 517 ([M + Na$^+$], 100). HRMS (ESI): [M + H$^+$] calcd. for $C_{25}H_{24}BrN_2O_4$ 495.0919, found 495.0914, [M + K$^+$] calcd. for $C_{25}H_{23}BrKN_2O_4$ 533.0478, found 533.0473.

General Procedure for the Preparation of Dimethyl 8-Aryl-2,4-dioxo-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicarboxylates (101ad-fd) and Dimethyl 6-Aryl-2,4-dioxo-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-7,7-dicarboxylates (102ad-ed) (GP3): A mixture of the respective dimethyl 2-arylcyclopropane-1,1-dicarboxylate (0.85 mmol) (**17**) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**100d**) (298 mg (1.7 mmol)) in CH_2Cl_2 (4 mL) was added dropwise to a solution of $GaCl_3$ (30 mg, 0.17 mmol, 20 mol%) in CH_2Cl_2 (1 mL). The mixture was stirred for 1–2 h, monitoring the progress of the reaction by TLC, and then subjected to column chromatography on silica gel, eluting with diethyl ether/pentane 1 : 2 to 5 : 1.

Dimethyl 2,4-Dioxo-8-(4-methylphenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicar-boxylate (101ad) and Dimethyl 2,4-Dioxo-3,6-diphenyl-1,3,5-triaza-bicyclo[3.3.0]octane-7,7-dicarboxylate (102ad): According to GP3, dimethyl 2-phenylcyclopropane-1,1-dicarboxylate (**17a**) (200 mg, 0.85 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**100d**) (298 mg, 1.7 mmol) gave a mixture, which was separated by chromatography on silica gel (70 g, column 3 × 30 cm).

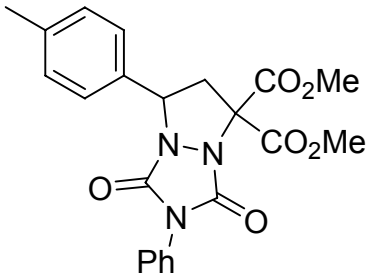
Dimethyl 2,4-Dioxo-3,8-diphenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicarboxylate (101ad): Colorless solid, yield 60 mg (17%), R_f = 0.47 (diethyl ether/pentane 5 : 1), m. p. 192–193 °C (dec.). ^{1}H NMR (300 MHz): 3.25 (1 H, m), 3.28 (1 H, m), 3.87 (3 H, s), 3.92 (3 H, s), 5.19 (1 H, dd, J = 8, 9Hz), 7.30–7.55 (10 H, m) ppm. ^{13}C NMR (75.5 MHz): 46.9 (CH_2), 54.0 (CH_3), 54.4 (CH_3), 59.2 (CH), 70.6 (C), 125.7 (CH), 126.2 (CH), 128.3 (CH), 128.7 (CH), 129.0 (CH), 129.1 (CH), 131.5 (C), 136.6 (C), 153.2 (CO), 153.5 (CO), 165.7 (COO), 167.0 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 3052 cm^{-1}, 2953, 2900, 1792, 1743, 1718, 1497, 1457, 1418, 1308, 1247, 1165, 758. LRMS (ESI): m/z = 1250 ([3 M + Na$^+$], 5), 841 ([2 M + Na$^+$], 100), 432 ([M + Na$^+$], 60). Calcd. for $C_{21}H_{19}N_3O_6$: C 61.61%, H 4.68%, N 10.26%, found: C 61.33%, H 4.46%, N 10.15%.

Dimethyl 2,4-Dioxo-3,6-diphenyl-1,3,5-triazabicyclo[3.3.0]octane-7,7-dicarboxylate (102ad): Colorless solid, yield: 170 mg (49%). R_f = 0.57 (diethyl ether/pentane 5 : 1), m. p. 179 °C. ^{1}H NMR (300 MHz): 3.44 (3 H, s), 3.78 (3 H, s), 4.28 (1 H, d, J =13 Hz), 4.46 (1 H, d, J = 13 Hz), 5.83 (1 H, s), 7.32–7.50 (m, 10 H) ppm. ^{13}C NMR (75.5 MHz): 49.7 (CH_2), 52.8 (CH_3), 54.0 (CH_3), 65.1 (C), 65.9 (CH), 125.9 (CH), 127.2 (CH), 128.4 (CH), 128.6 (CH), 129.0 (CH), 129.2 (CH), 131.5 (C), 134.8 (C), 156.2 (CO), 156.5 (CO), 164.7 (COO), 169.6 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 3014 cm^{-1}, 2953, 2871, 1734, 1653, 1506, 1409, 1318, 1260, 1140, 1098, 872, 769, 690. MS (ESI): m/z = 1250 ([3 M + Na$^+$], 15), 841 ([2 M + Na$^+$], 100), 432 ([M + Na$^+$], 95). Calcd. for $C_{21}H_{19}N_3O_6$: C 61.61%, H 4.68%, N 10.26%; found: C 61.62%, H 4.44%, N 10.08%.

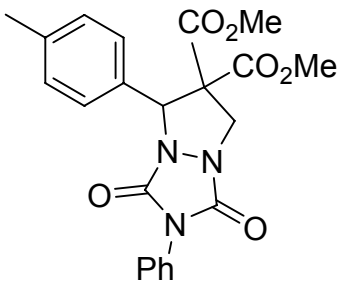
Dimethyl 2,4-Dioxo-8-(4-methylphenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicarbo-xylate (101bd) and Dimethyl 2,4-Dioxo-6-(4-methylphenyl)-3-phenyl-1,3,5-triazabicyclo-[3.3.0]octane-7,7-dicarboxylate (102bd): According to GP3, dimethyl 2-(4-methylphenyl)-cyclopropane-1,1-dicarboxylate (**17b**) (211 mg, 0.85 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**100d**) (298 mg, 1.7 mmol)

gave a mixture, which was separated by chromatography on silica gel (70 g, column 3 × 30 cm).

Dimethyl 2,4-Dioxo-8-(4-methylphenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicar-boxylate (101bd): Colorless solid, yield 90 mg (25%), R_f = 0.36 (diethyl ether/pentane 5 : 1), m. p. 166–167 °C (dec.). ^{1}H NMR (300 MHz): 2.35 (3 H, s), 3.25 (2 H, d, J = 8 Hz), 3.88 (3 H, s), 3.92 (3 H, s), 5.15 (1 H, t, J = 8 Hz), 7.21 (2 H, d, J = 8 Hz), 7.33 (2 H, d, J = 8 Hz), 7.34–7.54 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 21.1 (CH_3), 46.9 (CH_2), 54.0 (CH_3), 54.3 (CH_3), 59.2 (CH), 70.6 (C), 125.7 (CH), 126.2 (CH), 128.2 (CH), 129.0 (CH), 129.7 (CH), 131.5 (C), 133.5 (C), 138.6 (C), 153.2 (CO), 153.5 (CO), 165.8 (COO), 167.0 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 3038 cm^{-1}, 2958, 1885, 1718, 1497, 1457, 1436, 1410, 1313, 1277, 1247, 1164, 770. MS (ESI): m/z = 1291 (5), 869 ([2 M + Na$^+$], 100), 446 ([M + Na$^+$], 30). HRMS (ESI): [M + H$^+$] calcd. for $C_{22}H_{22}N_3O_6$ 424.1509, found 424.1503.



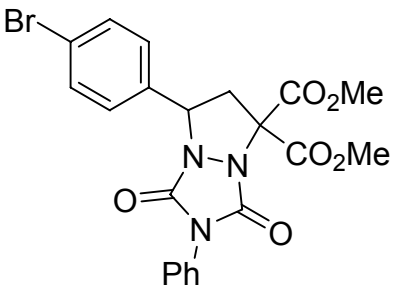
Dimethyl 2,4-Dioxo-6-(4-methylphenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-7,7-dicarboxylate (102bd): Colorless solid, yield 150 mg (42%), R_f = 0.62 (diethyl ether/pentane 5 : 1), m. p. 185–186 °C. ^{1}H NMR (300 MHz): 2.34 (3 H, s), 3.49 (3 H, s), 3.80 (3 H, s), 4.29 (1 H, d, 13 Hz), 4.46 (1 H, d, 13 Hz), 5.81 (1 H, s), 7.14–7.24 (4 H, m), 7.44–7.52 (5 H, m) ppm. ^{13}C NMR (75.5 MHz): 21.1 (CH_3), 49.7 (CH_2), 52.8 (CH_3), 54.0 (CH_3), 65.1 (C), 65.8 (CH), 125.9 (CH), 127.1 (CH), 128.4 (CH), 129.2 (CH), 129.3 (CH), 131.5 (C), 131.8 (C), 138.9 (C), 156.2 (CO), 156.5 (CO), 164.8 (COO), 169.7 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 3057 cm^{-1}, 2962, 1772, 1734, 1718, 1506, 1410, 1261, 1096, 1019, 804, 701. MS (ESI): m/z = 1291 (20), 869 ([2 M + Na$^+$], 100), 446 ([M + Na$^+$], 70). Calcd. for $C_{22}H_{21}N_3O_6$: C 62.41%, H 5.00%, N 9.92%; found: C 62.26%, H 4.94%, N 9.82%.



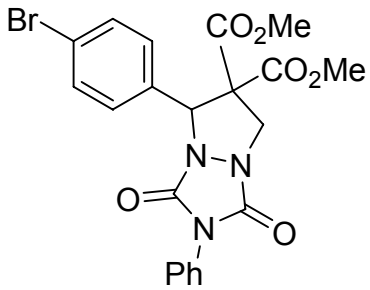
Dimethyl 2,4-Dioxo-8-(4-bromophenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicarbo-xylate (101cd) and Dimethyl 2,4-Dioxo-6-(4-bromophenyl)-3-phenyl-

1,3,5-triazabicyclo[3.3.0]oc-tane-7,7-dicarboxylate (102cd): According to GP3, dimethyl 2-(4-bromophenyl)cyclopropane-1,1-dicarboxylate (**17c**) (266 mg, 0.85 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**100d**) (298 mg, 1.7 mmol) gave a mixture, which was separated by chromatography on silica gel (70 g, column 3×30 cm).

Dimethyl 2,4-Dioxo-8-(4-bromophenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicarbo-xylate (101cd): Colorless solid, yield: 140 mg (34%), R_f = 0.46 (diethyl ether / pentane 5 : 1), m. p. 179–180 °C. ^{1}H NMR (300 MHz): 3.23 (2 H, m), 3.87 (3 H, s), 3.90 (3 H, s), 5.12 (1 H, dd, J = 7, 9 Hz), 7.30–7.56 (9 H, m) ppm. ^{13}C NMR (75.5 MHz): 46.6 (CH_2), 54.1 (CH_3), 54.4 (CH_3), 58.8 (CH), 70.6 (C), 122.7 (C), 125.7 (CH), 127.9 (CH), 128.4 (CH), 129.1 (CH), 131.3 (C), 132.2 (CH), 135.7 (C), 153.2 (CO), 153.8 (CO), 165.6 (COO), 166.9 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1}, 1718, 1506, 1410, 1313, 1258, 1164, 769, 732. MS (ESI): m/z = 999 ([2 M + Na$^+$], 100), 510 ([M + Na$^+$], 76), 488 ([M + H$^+$], 6). HRMS (ESI): [M + H$^+$] calcd. for $C_{21}H_{19}BrN_3O_6$ 488.0457, found 488.0452.

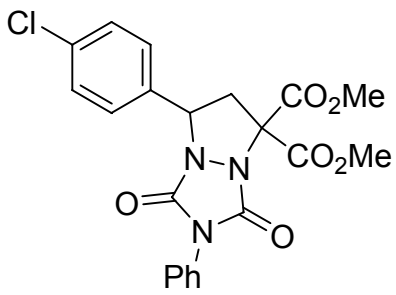


Dimethyl 2,4-Dioxo-6-(4-bromophenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-7,7-dicarboxylate (102cd): Colorless solid, yield 90 mg (22 %), R_f = 0.63 (diethyl ether/pentane 5 : 1), m. p. 167–168 °C. ^{1}H NMR (300 MHz): 3.52 (3 H, s), 3.81 (3 H, s), 4.24 (1 H, d, 13 Hz), 4.47 (1 H, d, 13 Hz), 5.80 (1 H, s), 7.20–7.24 (2 H, m), 7.28–7.32 (2 H, m), 7.46–7.54 (5H, m) ppm. ^{13}C NMR (75.5 MHz): 49.7 (CH_2), 53.0 (CH_3), 54.2 (CH_3), 65.0 (C), 65.4 (CH), 123.4 (C), 126.0 (CH), 128.6 (CH), 129.0 (CH), 129.3 (CH), 131.4 (C), 131.9 (CH), 134.0 (C), 156.3 (C), 156.5 (C), 164.7 (C), 169.5 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3328 cm^{-1}, 3000, 2950, 1727, 1653, 1594, 1559, 1496, 1437, 1412, 1301, 1232, 1100, 753, 694, 509. MS (ESI): m/z = 1487 ([3 M + Na$^+$], 35), 999 ([2 M + Na$^+$], 100), 550 (74), 510 ([M + Na$^+$], 13). HRMS (ESI): [M + H$^+$] calcd. for $C_{21}H_{19}BrN_3O_6$ 488.0457, found 488.0452.

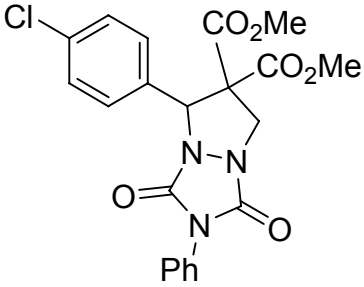


Dimethyl 2,4-Dioxo-8-(4-chlorophenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicar-boxylate (101dd) and Dimethyl 2,4-Dioxo-6-(4-chlorophenyl)-3-phenyl-1,3,5-triazabicyclo-[3.3.0]octane-7,7-dicarboxylate (102dd): According to the GP3, from dimethyl 2-(4-chlorphenyl)cyclopropane-1,1-dicarboxylate (**17d**) (228 mg, 0.85 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (**100d**) (298 mg, 1.7 mmol), gave a mixture which was separated by column chromatography on silica gel (70 g, column 3 × 30 cm).

Dimethyl 2,4-Dioxo-8-(4-chlorophenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-6,6-dicarbo-xylate (101dd): Colorless solid, yield 64 mg (17%), R_f = 0.43 (diethyl ether/pentane 5 : 1), m. p. 195–196 °C (dec.). ^{1}H NMR (300 MHz): 3.23 (2 H, m), 3.86 (3 H, s), 3.90 (3 H, s), 5.13 (1 H, dd, J = 7, 9 Hz), 7.30–7.56 (9 H, m) ppm. ^{13}C NMR (75.5 MHz): 46.7 (CH_2), 54.1 (CH_3), 54.4 (CH_3), 58.7 (CH), 70.6 (C), 125.7 (CH), 126.2 (CH), 127.6 (CH), 128.4 (CH), 129.1 (CH), 129.2 (CH), 131.3 (C), 133.5 (C), 134.6 (C), 135.1 (C), 153.3 (CO), 153.8 (CO), 165.6 (COO), 167.0 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 2959 cm^{-1}, 1786, 1718, 1497, 1412, 1313, 1258, 1092, 769, 691. MS (ESI): m/z = 461 ([M + NH_4^+], 44), 444 ([M + H^+], 3), 162 (100). Calcd. for $C_{21}H_{18}ClN_3O_6$: C 56.83%, H 4.09%, N 9.47%; found: C 56.83%, H 4.21%, N 9.23%.

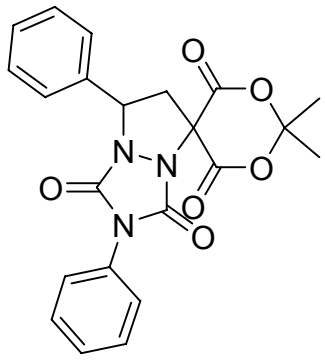


Dimethyl 2,4-Dioxo-6-(4-chlorophenyl)-3-phenyl-1,3,5-triazabicyclo[3.3.0]octane-7,7-dicarboxylate (102dd): Colorless solid, yield 150 mg (38%), R_f = 0.68 (diethyl ether/pentane 5 : 1), m. p. 166 °C. ^{1}H NMR (300 MHz): 3.51 (3 H, s), 3.80 (3 H, s), 4.23 (1 H, d, 13 Hz), 4.47 (1 H, d, 13 Hz), 5.82 (1 H, s), 7.24–7.49 (9 H, m) ppm. ^{13}C NMR (75.5 MHz): 49.6 (CH_2), 52.9 (CH_3), 54.1 (CH_3), 65.0 (C), 65.3 (CH), 125.9 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.2 (CH), 131.3 (C), 131.4 (C), 135.1 (C), 156.2 (CO), 156.4 (CO), 164.6 (COO), 169.5 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 3013 cm^{-1}, 1734,



1506, 1419, 1300, 1260, 1091, 668. MS (DCI): m/z = 478 ([M + NH_3 + NH_4^+], 12), 461 ([M + NH_4^+], 100), 231 (44), 179 (84), 162 (100). Calcd. for $C_{21}H_{18}ClN_3O_6$: C 56.83%, H 4.09 %, N 9.47 %; found: C 56.64%, H 4.30%, N 9.31%.

2,2-Dimethyl-3,8-diphenyl-1,5,2',4'-tetraoxospiro[(1,3-dioxane)-5,6'-(1',3',5'-triazabicyclo-[3.3.0]octane] (101fd): According to GP3, 3,3-dimethyl-7-phenyl-2,4-dioxaspiro[2.5]octane-1,5-dione (**17f**) (210 mg, 0.85 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (298 mg, 1.7 mmol)) (**100d**) gave 120 mg (34%) of **101fd** as a colorless solid, R_f = 0.49 (diethyl ether/pentane 5 : 1), m. p. 178–179 °C (dec.). ^{1}H NMR (300 MHz): 1.83 (3 H, s), 1.98 (3 H, s), 3.13 (1 H, dd, J =11, 13 Hz), 3.31 (1 H, dd, J =7, 13 Hz), 5.34 (1 H, dd, J = 7, 11 Hz), 7.34–7.52 (10 H, m) ppm. ^{13}C NMR (75.5 MHz): 28.1 (CH_3), 29.3 (CH_3), 50.7 (CH_2), 60.6 (CH), 64.0 (C), 108.3 (C), 125.8 (CH), 126.5 (CH), 128.7 (CH), 129.1 (CH), 129.2 (CH), 131.0 (C), 135.4 (C), 154.3 (CO), 154.4 (CO), 163.7 (COO), 165.8 (COO) ppm. IR (KBr): $\tilde{\nu}$ = 3010 cm^{-1}, 1787, 1717, 1491, 1411, 1315, 1267, 764, 747. MS (DCI): m/z = 860 ([2 M + NH_4^+], 3), 439 ([M + NH_4^+], 100). Calcd. for $C_{22}H_{19}N_3O_6$: C 62.70%, H 4.54%, N 9.97%; found: C 62.42%, H 4.43%, N 10.06%.



Reaction of Dimethyl (*R*)-2-Phenylcyclopropane-1,1-dicarboxylate (*R*)-17a with Diisopropyl Azodicarboxylate (100a): According to GP1, dimethyl (*R*)-2-phenylcyclopropane-1,1-dicarboxylate ((*R*)-**17a**) (20 mg, 0.085 mmol), diisopropyl azodicarboxylate (**100a**) (30 mg, 0.15 mmol) and $GaCl_3$ (3 mg, 0.017 mmol, 20 mol%) in CH_2Cl_2 (0.5 mL) after purification by column chromatography on silica gel (3 g, column 1×10 cm) gave 18 mg (49%) of the pyrazolidine **101aa,** which was subjected to HPLC analysis on a chiral-phase column.

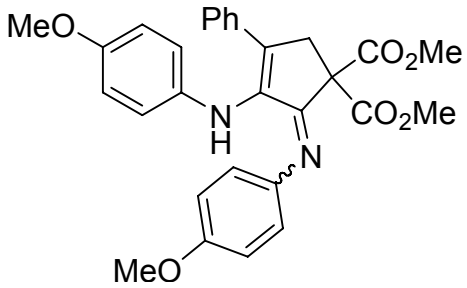
Reaction of Dimethyl (*S*)-2-Phenylcyclopropane-1,1-dicarboxylate (*S*)-17a with 4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) (100d): According to GP3, dimethyl (*S*)-2-phenylcyclopropane-1,1-dicarboxylate ((*S*)-**17a**) (15 mg, 0.064 mmol), 4-phenyl-1,2,4-

triazoline-3,5-dione (PTAD) (**100d**) (23 mg, 0.13 mmol) and $GaCl_3$ (2.5 mg, 0.014 mmol, 22 mol%) in CH_2Cl_2 (0.3 mL), gave a mixture, which was separated by chromatography on silica gel (3 g, column 1×10 cm). The isolated 3 mg (12%) of the pyrazolidine **101ad** and 5 mg (19%) of the pyrazolidine **102ad** were subjected to HPLC on a chiral-phase column 1A-Daicel.

3.2 Experimental Procedures for the Compounds from Chapter 2

General Procedure for the Preparation Dimethyl 3-Arylamino-2-arylimino-4-arylcyclopent-3-ene-1,1-dicarboxylate (GP4): A mixture of the respective aryl isocyanide **108** (4.5 mmol), the respective dimethyl 2-arylcyclopropane-1,1-dicarboxylate **17** (0.9 mmol) and $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%) in 1,2-dichloroethane (4 mL) was stirred under nitrogen at 70 °C for 24 h, monitoring the progress of the reaction by TLC. The reaction mixture was concentrated under reduced pressure and the product **111** was purified by column chromatography on silica gel, eluting with diethyl ether / pentane 2 : 1.

Dimethyl 3-(4-Methoxy-phenylamino)-2-(4-methoxyphenylimino)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (111aa): From **17a** (210 mg, 0.9 mmol) and



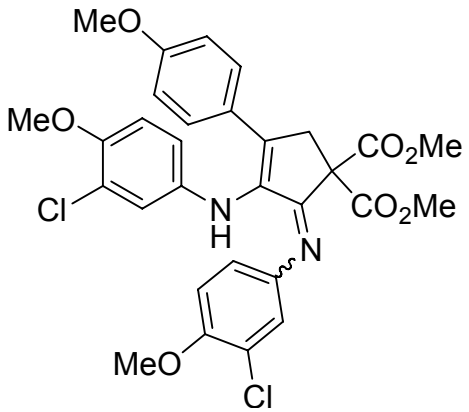
108a (600 mg, 4.5 mmol) with $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111aa** (258 mg, 57%) as a light yellow solid. R_f = 0.2 (Et_2O : pentane = 1 : 1); m. p. 54–55 °C. – ^1H NMR (300 MHz): 3.57 (6 H, s), 3.61 (2 H, s), 3.69 (3 H, s), 3.79 (3 H, s), 6.60 (4 H, s), 6.69 (1 H, s), 6.83 (4 H, s), 7.17–7.30 (5 H, m) ppm. – ^{13}C NMR (90.6 MHz): 42.1 (CH_2), 53.0 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 59.9 (C), 113.6 (CH), 115.6 (CH), 119.7 (CH), 126.5 (CH), 127.6 (C), 127.7 (CH), 129.0 (CH), 129.1 (CH), 134.2 (C), 134.4 (C), 134.8 (C), 141.9 (C), 154.0 (C), 156.0 (C), 164.2 (C), 168.9 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3313 cm^{-1}, 2950, 1734, 1653, 1617, 1559, 1506, 1437, 1352, 1240, 1175, 1061, 1031, 824, 756, 694, 515. – MS (DCI): m/z = 501 ([M + H^+], 100), 238 (28), 150 (44), 141 (16). – HRMS (ESI) [M + H^+] calcd. for $C_{29}H_{29}N_2O_6$ 501.2026, found 501.2020.

Dimethyl 3-(4-Methoxyphenylamino)-2-(4-methoxy-phenylimino)-4-(4-methoxyphenyl)cyclopent-3-ene-1,1-dicarboxylate (111ea): From **17e** (238 mg, 0.9 mmol) and **108a** (600 mg, 4.5 mmol) with $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111ea** (173 mg, 36%) as a yellow solid. R_f = 0.42 (Et_2O / pentane 1 : 1); m. p. 48–50 °C. – ^{1}H NMR (300 MHz): 3.54 (6 H, s), 3.58 (2 H, s), 3.71 (3 H, s), 3.77 (3 H, s), 3.79 (3 H, s), 3.86 (1 H, br s), 6.59–6.63 (4 H, m), 6.75 (2 H, d, J = 9 Hz), 6.81 (4 H, s), 7.27 (2 H, d, J = 9 Hz) ppm. – ^{13}C NMR (90.6 MHz): 42.0 (CH_2), 53.0 (CH_3), 55.2 (CH_3), 55.4 (CH_3) , 55.5 (CH_3), 59.8 (C), 113.2 (CH), 113.6 (CH), 113.8 (CH), 119.2 (CH), 120.7 (CH), 127.3 (C), 128.2 (C), 129.3 (CH), 133.3 (C), 134.7 (C), 142.1 (C), 153.8 (C), 155.9 (C), 159.2 (C), 164.2 (C), 169.0 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3416 cm^{-1}, 2954, 1732, 1662, 1624, 1563, 1505, 1436, 1367, 1247, 1210, 1123, 1019, 836, 785, 741, 510. – MS (ESI): m/z = 1084 (50), 1083 (([2 M + Na$^+$], 100), 559 (10), 553 ([M + Na$^+$], 28), 529 (18). – HRMS (ESI) [M + H$^+$] calcd. for $C_{30}H_{31}N_2O_7$ 531.2131, found 531.2126. – calcd. for $C_{30}H_{30}N_2O_7$: C 67.91%, H 5.70%, found: C 68.25%, H 6.04%.

Diethyl 3-(4-Methoxyphenylamino)-2-(4-methoxyphenylimino)-4-(4-methyl-phenyl)cyclo-pent-3-ene-1,1-dicarboxylate (111ba-Et): From **17b**-Et (248 mg, 0.9 mmol) and **108a** (600 mg, 4.5 mmol) with $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111ba**-Et (118 mg, 24%) as a yellow solid. R_f = 0.41 (Et_2O / pentane 1 : 1). m. p. 141–142 °C. – ^{1}H NMR (250 MHz): 1.11 (6 H, t, J = 7 Hz), 2.29 (3 H, s), 3.60 (2 H, s), 3.70 (3 H, s), 3.78 (3 H, s), 3.98 (4 H, q, J = 7 Hz), 6.61 (4 H, s), 6.80 (2 H, d, J = 8 Hz), 6.86 (2 H, d, J = 8 Hz), 7.01 (2 H, d, J = 8 Hz), 7.20 (2 H, d, J = 8 Hz) ppm. – ^{13}C NMR (75.5 MHz): 13.7 (CH_3), 21.3 (CH_3), 42.0 (CH_2), 55.4 (CH_3), 55.5 (CH_3), 60.4 (C), 62.1 (CH_2), 113.4 (CH), 113.6 (CH), 119.3 (CH), 121.0 (CH), 127.7 (CH), 127.8 (C), 128.5 (CH), 129.4 (C), 132.0 (C), 134.0 (C), 134.6 (C), 137.7 (C), 142.0 (C),

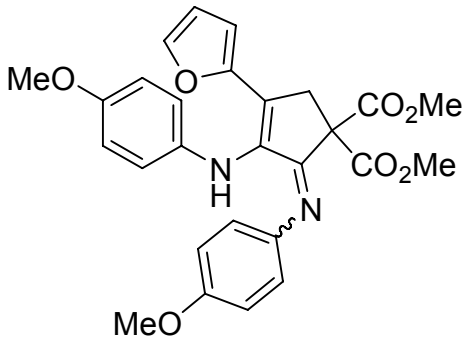
153.8 (C), 156.0 (C), 168.6 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3331 cm^{-1}, 2925, 2834, 1753, 1706, 1648, 1618, 1512, 1502, 1458, 1370, 1287, 1234, 1182, 1070, 1030, 841, 821, 515. – MS (ESI): m/z = 1107 ([2 M + Na$^+$], 60), 543 ([M + H$^+$], 86), 422 (100). – calcd. for $C_{32}H_{34}N_2O_6$: C 70.83%, H 6.32%, N 5.16%, found: C 70.61%, H 6.27%, N 5.03%.

Dimethyl 3-(3-Chloro-4-methoxyphenylamino)-2-(3-chloro-4-methoxyphenylimino)-4-(4-methoxyphenyl)cyclo-pent-3-ene-1,1-dicarboxylate (111eb): From



17e (238 mg, 0.9 mmol) and **108b** (750 mg, 4.5 mmol) with Pr(OTf)$_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111eb** (259 mg, 48%) as a brownish oil. R_f = 0.29 (Et$_2$O / pentane 1 : 1); – ^{1}H NMR (250 MHz): 3.60 (2 H, s), 3.61 (3 H, s), 3.79 (6 H, s), 3.83 (3 H, s), 3.88 (3 H, s), 6.44–7.32 (10 H, m) ppm. – ^{13}C NMR (75.5 MHz): 41.8 (CH$_2$), 53.1 (CH$_3$), 55.3 (CH$_3$), 56.3 (CH$_3$), 56.5 (CH$_3$), 59.8 (C), 111.7 (CH), 112.3 (CH), 113.4 (CH), 113.7 (CH), 114.1 (CH), 116.8 (CH), 118.9 (CH), 120.1 (CH), 121.8 (C), 126.8 (C), 129.0 (C), 129.3 (C), 129.7 (C), 130.9 (C), 132.6 (C), 142.4 (C), 149.2 (C), 151.2 (C), 159.6 (C), 168.7 (C) ppm. – IR (film): $\tilde{\nu}$ = 3313 cm^{-1}, 2924, 1732, 1603, 1496, 1440, 1256, 1180, 1061, 1022, 807, 732. – MS (ESI): m/z = 1104 (20), 599 ([M + H$^+$], 100). – HRMS (ESI) [M + H$^+$] calcd. for $C_{30}H_{29}Cl_2N_2O_7$ 599.1352, found 599.1346.

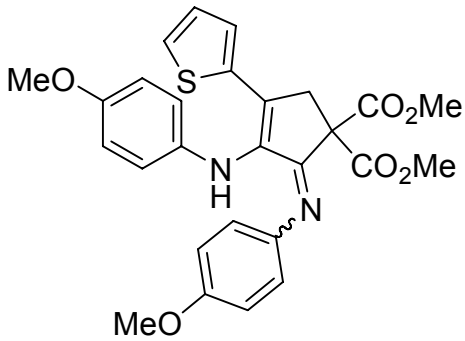
Dimethyl 3-(Methoxyphenylamino)-2-(4-methoxyphenylimino)-4-(2-furyl)cyclopent-3-ene-1,1-dicarboxylate (111ga, mixture of (E)- and (Z)-diastereomers): From



17g (202 mg, 0.9 mmol) and **108a** (600 mg, 4.5 mmol) with Pr(OTf)$_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111ga** (141 mg, 32%) as a light yellow solid. R_f = 0.25 (Et$_2$O / pentane 1 : 1); m. p. 123–124 °C. – ^{1}H NMR (300 MHz):

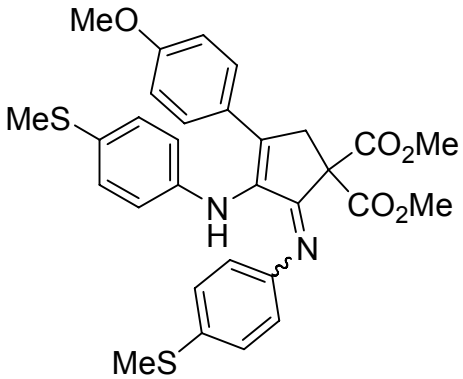
3.57 (4.47 H, s), 3.58 (0.94 H, s), 3.70 (0.73 H, s), 3.72 (0.73 H, s), 3.76 (2.80 H, s), 3.78 (2.80 H, s), 3.87 (1.05 H, s), 5.88 (0.66 H, q, *J* = 2 Hz), 6.24–6.28 (0.34 H, m), 6.34–6.40 (0.91 H, m), 6.53 (1H, d, *J* = 2 Hz), 6.44–6.45 (0.18 H, m), 6.56–6.57 (0.34 H, m), 6.68–6.70 (0.34 H, m), 6.76 (2.85 H, s), 6.80 (3.23 H, s), 7.38 (0.73 H, d, J = 2 Hz), 7.47–7.49 (0.27 H, m) ppm. – ^{13}C NMR (90.6 MHz): 39.6 (CH_2), 53.0 (CH_3), 53.4 (CH_3), 55.4 (CH_3), 55.6 (CH_3), 59.8 (C), 112.0 (CH), 112.1 (CH), 112.2 (CH), 112.9 (CH), 113.0 (CH), 113.5 (CH), 113.7 (CH), 113.8 (CH), 118.3 (CH), 120.2 (CH), 120.3 (CH), 120.7 (CH), 132.9 (C), 134.3 (C), 141.9 (CH), 142.6 (CH), 149.4 (C), 154.3 (C), 156.0 (C), 168.8 (C), 169.6 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3416 cm^{-1}, 2954, 1732, 1662, 1624, 1563, 1505, 1436, 1394, 1367, 1247, 1175, 1123, 1059, 1019, 994, 955, 881, 835, 785, 741, 590, 510. – LRMS (ESI): m/z = 1003 ([2 M + Na$^+$], 22), 491 ([M + H$^+$], 100). – HRMS (ESI) [M + H$^+$] calcd. for $C_{27}H_{27}N_2O_7$ 491.1818, found 491.1815. – calcd. for $C_{27}H_{26}N_2O_7$: C 66.11%, H 5.34%, N 5.71%, found: C 65.95%, H 5.64%, N 5.88%.

Dimethyl 3-(Methoxyphenylamino)-2-(4-methoxyphenylimino)-4-(2-thiophenyl)cyclopent-3-ene-1,1-dicarboxylate (111ha) (Two or More Rotamers and/or (E)- and (Z)-Diastereomers): From **17h** (216 mg, 0.9 mmol) and **108a** (600 mg, 4.5 mmol) with Pr(OTf)$_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111ha** (96 mg, 21%) as a light red solid. R_f = 0.58 (Et_2O / pentane 2 : 1); m. p. 127–128 °C. – ^{1}H NMR (300 MHz): 3.57 (3.7 H, s), 3.61 (1.4 H, s), 3.66 (0.3 H, s), 3.68 (1 H, s), 3.73 (2.1 H, s), 3.74 (1.6 H, s), 3.77 (2.3 H, s), 3.87 (1.7 H, s), 4.40 (1 H, br s), 6.08 (0.6 H, d, *J* = 9 Hz,), 6.50 (0.6 H, s), 6.54 (0.5 H, d, *J* = 2 Hz,), 6.57 (0.7 H, d, *J* = 2 Hz,), 6.62 (0.4 H , s), 6.71 (2.2 H, d, *J* = 2 Hz), 6.80 (2.2 H, d, *J* = 2 Hz), 6.86 (0.7 H, d, *J* = 3 Hz), 6.96 (1 H. dd, *J* = 5, 4 Hz), 7.04 (0.7 H, t, *J* = 4 Hz), 7.28 (0.4 H, d, *J* = 3 Hz), 7.32 (0.77 H, d, *J* = 5 Hz), 7.40 (0.3 H, d, *J* = 4 Hz) ppm. – ^{13}C NMR (90.6 MHz): 37.3 (CH_2), 42.0 (CH_2), 52.7 (CH_3), 53.0 (CH_3), 53.4 (CH_3), 55.3 (CH_3), 55.4 (CH_3), 59.8 (C), 113.5 (CH), 113.9 (CH), 114.0 (CH), 115.8 (CH), 119.4 (CH), 120.7 (CH), 125.7 (C), 125.9 (CH), 126.4 (CH), 126.7 (CH), 126.8 (CH), 126.9 (CH), 127.1 (CH), 127.6 (CH), 127.9 (C), 128.5 (C), 129.9 (C), 130.7 (CH), 133.5

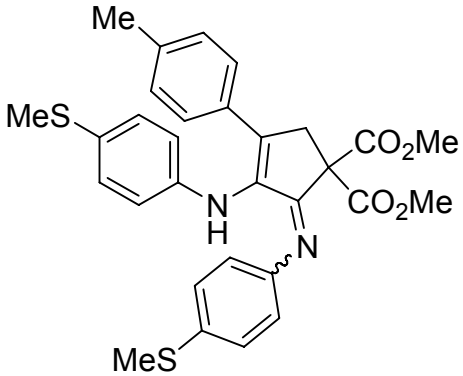


(C), 134.4 (C), 135.6 (C), 135.9 (C), 136.8 (C), 142.0 (C), 143.1 (C), 153.4 (C), 154.1 (C), 155.8 (C), 155.9 (C), 163.4 (C), 164.9(C), 168.6 (C), 168.7 (C), 168.9 (C), 169.1 (C), 169.4 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3313 cm^{-1}, 2952, 1772, 1734, 1717, 1616, 1559, 1506, 1472, 1457, 1437, 1352, 1242, 1175, 1064, 824, 751, 690, 515. – LRMS (ESI): m/z=1035 ([2 M + Na^+], 100), 535 (16), 529 ([M + Na^+], 15). – calcd. for $C_{27}H_{26}N_2O_6S$: C 64.02%, H 5.17%, N 5.53%, found: C 63.96%, H 5.46%, N 5.25%.

Dimethyl 3-(4-(Methylthio)phenylamino)-2-(4-(methylthio)-phenylimino)-4-(4-methoxyphenyl)cyclopent-3-ene-1,1-dicarboxylate (111ec): From **17e** (238 mg, 0.9 mmol) and **108c** (670 mg, 4.5 mmol) with $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111ec** (330 mg, 63%) as a brown solid. R_f = 0.36 (Et_2O / pentane 1 : 1); m. p. 71–72 °C. – ^1H NMR (300 MHz): 2.37 (2 H, s), 2.45 (3 H, s), 2.63 (1 H, s), 3.48 (0.6 H, s), 3.54 (3 H, s), 3.61 (2 H, s), 3.70 (1 H, s), 3.77 (3 H, s), 3.86 (1.4 H, s), 6.55–6.64 (2 H, m), 6.78 (4 H, d, J = 7 Hz), 7.04 (1 H, d, J = 8 Hz), 7.19 (1 H, d, J = 8 Hz), 7.30–7.36 (3 H, m), 7.49–7.55 (1 H, m) ppm. – ^{13}C NMR (90.6 MHz): 16.9 (CH_3), 17.9 (CH_3), 41.9 (CH_2), 53.2 (CH_3), 55.4 (CH_3), 59.9 (C), 113.6 (CH), 117.6 (C), 118.2 (CH), 119.2 (C), 120.3 (CH), 124.8 (C), 127.0 (C) 127.6 (CH), 128.3 (C), 129.1 (CH), 129.5 (CH), 132.4 (C), 139.6 (C), 146.6 (C), 159.6 (C), 164.1 (C), 168.8 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3228 cm^{-1}, 3016, 2948, 2887, 2831, 2120, 1734, 1653, 1506, 1473, 1457, 1340, 1251, 1176, 1031, 822, 668. – MS (ESI): m/z = 1147 (([2 M + Na^+], 100). – HRMS (ESI) [M + H^+] calcd. for $C_{30}H_{31}N_2O_5S_2$ 563.1674, found 563.1669.

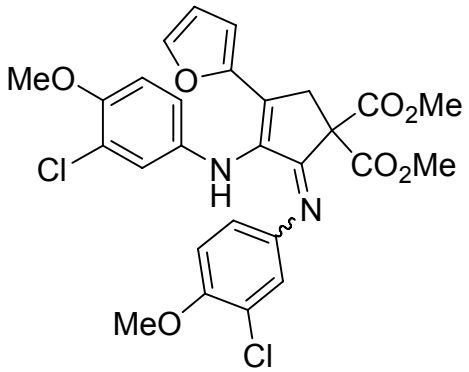


Dimethyl 3-(4-(Methylthio)phenylamino)-2-(4-(methylthio)-phenylimino)-4-(4-methylphenyl)cyclopent-3-ene-1,1-dicarboxylate (111bc): From **17b** (223 mg, 0.9 mmol) and **108c** (670 mg, 4.5 mmol) with $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111bc** (300 mg, 61%) as an orange solid. R_f = 0.21 (Et_2O / pentane 1 : 2); m. p.



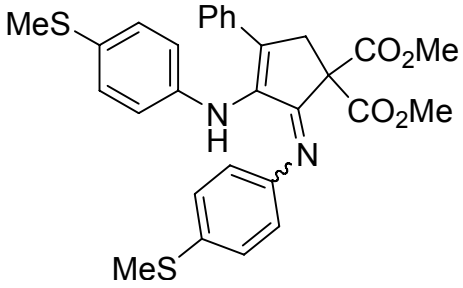
62–64 °C. – ^{1}H NMR (300 MHz): 2.29 (3 H, s), 2.36 (3 H, s), 2.44 (3 H, s), 3.53 (6 H, s), 3.61 (2 H, s), 6.55 (2 H, d, J = 7 Hz), 6.78 (2 H, d, J = 7 Hz), 7.00–7.26 (8 H, m) ppm. – ^{13}C NMR (90.6 MHz): 16.8 (CH_3), 17.7 (CH_3), 21.3 (CH_3), 41.8 (CH_2), 53.0 (CH_3), 59.8 (C), 118.2 (CH), 120.1 (CH), 127.4 (CH), 127.7 (CH) 128.7 (CH), 128.8 (CH), 129.1 (C), 129.5 (C), 131.1 (C),132.4 (C), 132.9 (C), 138.3 (C), 139.3 (C), 146.4 (C), 164.1 (C), 168.7 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3502 cm^{-1}, 2949, 2913, 1734, 1653, 1559, 1266, 1171, 815, 668, 506. – LRMS (ESI): m/z = 1115 (([2 M + Na^{+}], 100), 547 ([M + H^{+}], 56). – HRMS (ESI) [M + H^{+}] calcd. for $C_{30}H_{31}N_2O_4S_2$ 547.1725, found 547.1720.

Dimethyl 3-(3-Chloro-4-methoxyphenylamino)-2-(3-chloro-4-methoxyphenylimino)-4-(2-furyl)cyclopent-3-ene-1,1-dicarboxylate (111gb, Mixture of (E)- and (Z)-Diastereomers): From **17g** (202 mg, 0.9 mmol) and **108b** (750 mg, 4.5 mmol) with Pr(OTf)$_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111gb** (116 mg, 23 %) as a red solid. R_f = 0.25 (Et$_2$O / pentane 1 : 1); m. p. 131–132 °C. –^{1}H NMR (300 MHz)**:** 3.55 (1 H, s), 3.57 (1 H, s), 3.61 (3 H, s), 3.67 (0.18 H, s), 3.71 (0.33 H, s), 3.80 (2.8 H, s), 3.83 (1.6 H, s), 3.86 (1.4 H, s), 3.89 (2.67 H, s), 6.04 (0.56 H, d, J = 3 Hz), 6.13 (0.5 H, s), 6.26 (0.27 H, d, J = 2 Hz), 6.27 (0.33 H, d, J = 3 Hz), 6.34 (0.26 H, d, J = 2 Hz), 6.37 (0.37 H, d, J = 2 Hz), 6.40 (0.49 H, m), 6.42 (0.37 H, d, J = 3 Hz), 6.47 (0.23H, s), 6.50 (0.64 H, m), 6.55 (0.58 H, s), 6.57 (0.77 H, d, J = 2 Hz), 6.68 (0.79 H, td, J = 9, 2 Hz), 6.76 (0.76 H, m), 6.79 (0.14 H, m), 6.81 (0.23 H, s), 6.86 (0.82 H, s), 7.42 (0.35 H, s), 7.51 (0.24 H, s) ppm. – ^{13}C NMR (75.5 Hz): 35.1 (CH_2), 39.3 (CH_2), 53.2 (CH_3), 53.5 (CH_3), 56.3 (CH_3), 56.4 (CH_3) , 56.5 (CH_3), 56.6 (CH_3), 60.0 (C), 64.8 (C), 110.6 (CH), 111.7 (CH), 111.72 (CH), 112.1 (CH), 112.2 (CH), 112.4 (CH), 113.3 (CH), 117.1 (CH), 117.7 (CH), 118.7 (CH), 119.0 (CH), 119.9 (C), 120.8 (CH), 121.2 (C), 121.4 (C), 121.7 (C), 121.8 (C), 122.1 (C), 122.2 (C), 126.1 (C), 128.7 (C), 132.3 (C), 135.1 (C), 135.7 (C), 142.0 (CH), 142.3 (CH), 143.3 (C), 143.8 (C), 149.2 (C), 149.7 (C), 149.9 (C), 151.0 (C), 151.1 (C), 151.2 (C), 163.6 (C), 168.5 (C), 169.5 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3326 cm^{-1}, 2955, 1726, 1662, 1623, 1559, 1506, 1441,



1367, 1252, 1202, 1061, 1018, 957, 880, 808, 739, 588. – LRMS (ESI**):** m/z=1141 (100), 1139 ([2 M + Na^+], 70), 581 ([M + Na^+], 22), 559 ([M + H^+], 8). – calcd. for $C_{27}H_{24}Cl_2N_2O_7$: C 57.97%, H 4.32 %, N 5.01 %. Found: C 58.24%, H 4.60%, N 4.74%.

Dimethyl 3-(4-(Methylthio)phenylamino)-2-(4-(methylthio)-phenylimino)-4-phenylcyclopent-3-ene-1,1-dicarboxylate (111ac): From **17a** (210 mg, 0.9 mmol) and **108c** (670 mg, 4.5 mmol) with $Pr(OTf)_3$ (106 mg, 0.18 mmol, 20 mol%), was obtained **111ac** (287 mg, 60%) as a brown oil. R_f = 0.30 (Et_2O / pentane 1 : 2). – ^{1}H NMR (300 MHz): 2.37 (3 H, s), 2.46 (3 H, s), 3.55 (6 H, s), 3.64 (2 H, s), 3.87 (1 H, br s), 6.56 (2 H, d, J = 8 Hz), 6.80 (2 H, d, J = 8 Hz), 7.18–7.56 (9 H, m) ppm. – ^{13}C NMR (75.5 MHz): 16.7 (CH_3), 17.7 (CH_3), 41.8 (CH_2), 53.0 (CH_3), 59.9 (C), 118.4 (CH), 120.0 (CH), 127.4 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.67 (CH), 128.69 (C), 132.5 (C), 133.4 (C), 134.4 (C), 138.9 (C), 139.3 (C), 146.2 (C), 164.0 (C), 169.2 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3501cm^{-1}, 2951, 2915, 1732, 1650, 1561, 1264, 1171, 813, 667, 503. – MS (ESI): m/z = 1087 ([2 M + Na^+], 100), 533 ([M + H^+], 62). – MS (ESI) [M + H^+] calcd. for $C_{29}H_{29}N_2O_4S_2$ 533.1569, found 533.1563.



3.3 Experimental Procedures for the Compounds from Chapter 3

((2*S*)-Naphthylmethoxycarbonylamino))propionic Acid (CNAP-Ala) (117): To a stirred ice-cold solution of L-alanine (1.8 g, 20 mmol) and NaOH (1.6 g, 40 mmol) in H_2O (10 mL) was added 2-naphthylmethyl chloroformate (CNAP–Cl) (6.3 g, 29 mmol). Then water (10 mL) and THF (10 mL) were added, upon which the solution became clear. The reaction mixture was stirred at r.t. for 2 h, and the reaction was then quenched by adding a saturated solution of $NaHCO_3$ (20 mL). The mixture was extracted with Et_2O (1 × 30 mL), the ethereal phases were discarded, and the pH value of the aqueous phase was adjusted to 2–3 with 12 M aqueous HCl. Then it was extracted EtOAc (3 × 30 mL), and the combined organic phases were dried. Evaporation of the solvent gave 4.4 g (80%) of the acid **5** as a colorless solid, m. p. 132–3 °C. – ^{1}H NMR (500 MHz, CD_3OD): 1.48 (3 H, d, J = 7 Hz), 4.31 (1 H, q, J = 7 Hz), 5.32 (2 H, s), 7.50–7.56 (3 H, m), 7.86–7.92 (4 H, m) ppm. – ^{13}C NMR (125.7 MHz): 17.8 (CH_3), 50.8 (CH), 67.6 (CH_2), 126.5 (CH), 127.1 (CH), 127.2 (CH), 127.6 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 134.4 (C), 134.6 (C), 135.6 (C), 158.4 (C), 176.5 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3329 cm^{-1}, 3048, 1692, 1535, 1461, 1253, 1076, 820, 737, 623. – $[\alpha]_D^{20}$ = –8.1 (*c* 1.0, MeOH). – MS (DCI) m/z = 564 ([2 M + NH_4^+], 4), 291 ([M + NH_4^+], 100). – Calcd. for $C_{15}H_{15}NO_4$: C 65.92%, H 5.53%, N 5.13%, found: C 65.65%, H 5.31%, N 4.89%.

General Procedure (GP5) for Fmoc-Deprotection of the Benzyl Esters and Subsequent Peptide Condensation: To a solution of the respective benzyl ester (1.70 mmol) in THF (3.3 mL) was added at r. t. Et_2NH (3.3 mL). The mixture was stirred at r. t. for 1 h, then another 2 mL of Et_2NH was added, and the mixture was stirred for an additional 2 h. The volatiles were removed under reduced pressure at 35 °C. The oily residue was azeotropically distilled off with toluene (2 × 8 mL) under reduced pressure at 45–50 °C, and the crude amine was taken up in CH_2Cl_2 (5 mL).

A separate flask was charged with the corresponding protected alanine (2.06 mmol),

CH_2Cl_2 (7.5 mL) and HOAt (0.26 g, 1.92 mmol). EDC (0.32 g, 2.04 mmol) was added dropwise within 10 min at 0 °C, and the resulting mixture was stirred at 0 °C for 20 min. To the solution of the prepared crude amine in CH_2Cl_2 was added TMP (0.66 g, 0.72 mL, 5.43 mmol), and the resulting suspension was added via a cannula to the stirred reaction mixture. This was left to attain r.t. within 16 h and then concentrated under reduced pressure. The residue was taken up in EtOAc (30 mL). The cloudy solution was washed with 1 N aqueous $KHSO_4$ solution (2 × 30 mL), and saturated aqueous $NaHCO_3$ solution (2 × 30 mL), then dried and concentrated under reduced pressure. The oily residue was taken up in EtOAc (5 mL) and purified by column chromatography [SiO_2 (50 g), hexane / EtOAc 1 : 1] to give the desired dipeptide.

2-Naphthylmethoxycarbonyl-(*S*)-alanyl-(*S*)-(N^{δ}-*tert*-butyloxycarbonyl)ornithine Benzyl Ester [CNAP-Ala-Orn(Boc)-OBn] (118): 2-Naphthylmethoxycarbonyl-(*S*)-alanyl-(*S*)-(N^{δ}-*tert*-butyloxycarbonyl)ornithine benzyl ester (756 mg, 77%) was prepared from **117** (560 mg, 2.06 mmol) and N^{δ}-(*tert*-butyloxycarbonyl)-N^{α}-(9*H*-9-fluorenyloxycarbonyl)-L-ornithine benzyl ester (900 mg, 1.70 mmol) according to GP5 as a colorless solid. R_f = 0.40 [hexane / EtOAc (1 : 1)], m. p. 112–113 °C. – ^{1}H NMR (300 MHz): 1.30–1.50 (2 H, m), 1.38 (3 H, d, J = 7 Hz), 1.41 (9 H, s), 1.60–1.92 (2 H, m), 2.90–3.11 (2 H, m), 4.26–4.40 (1 H, m), 4.53–4.64 (1 H, m), 4.65–4.80 (1 H, m), 5.07–5.20 (2 H, m), 5.21–5.32 (2 H, m), 5.64–5.77 (1 H, br m), 7.05–7.12 (1 H, m), 7.28–7.40 (4 H, m), 7.40–7.52 (3 H, m), 7.75–7.85 (4 H, m) ppm. – ^{13}C NMR (75.5 MHz): 18.6 (CH_3), 26.0 (CH_2), 28.3 (CH_3), 28.9 (CH_2), 39.7 (CH_2), 50.4 (CH), 52.1 (CH), 67.0 (CH_2), 67.1 (CH_2), 79.2 (C), 125.7 (CH), 126.1 (CH), 126.2 (CH), 127.0 (CH), 127.6 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 133.0 (C), 133.1 (C), 133.6 (C), 135.1 (C), 155.9 (C), 156.1 (C), 171.7 (C), 172.3 (C) ppm. – IR (film): $\tilde{\nu}$ = 3336 cm^{-1}, 2926, 1718, 1700, 1685, 1669, 1653, 1521, 1507, 1457, 1368, 1251, 1159, 1027, 912, 738. – $[\alpha]_D^{20}$ = –6.0 (c 1.0, $CHCl_3$). – MS (ESI) positive ion mode: m/z = 1177 ([2 M + Na$^+$], 100), 600 ([M + Na], 40). Negative ion mode: m/z = 622 ([M + CH_3COO^-], 100). – HRMS (ESI) [M + H$^+$]. – Calcd. for $C_{33}H_{40}N_3O_7$ 578.2866, found 494.2861. – Calcd. for $C_{32}H_{39}N_3O_7$: C 66.53%, H 6.80%, N 7.27%,

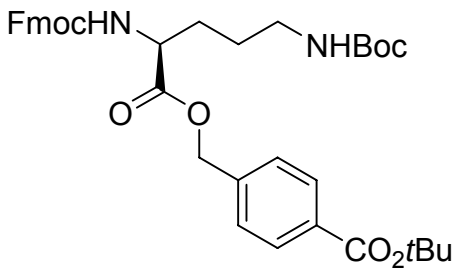
found: C 60.44%, H 6.65%, N 7.08%.

General Procedure (GP6) for Boc-Removal and Subsequent Sequential Acylation/β-Lactonization: To a solution of the respective dipeptide (1.56 mmol) in EtOAc (3 mL) was added 3 N HCl in EtOAc (12 mL). The mixture was stirred at r. t. for 12 h, then concentrated under reduced pressure at 40 °C. The resulting crude solid product was dried *in vacuo* (0.05 mbar) at r. t. for 3 h, then dissolved in DMF (6 mL), and the solution cooled to –30 °C. A solution of the thioester **51** (440 mg, 1.57 mmol) in CH_2Cl_2 (20.6 mL) was first added, then HOAt (255 mg, 1.54 mmol), TMP (377 mg, 3.11 mmol), as well as EDC (561 mg, 3.11 mmol), and the resulting mixture was stirred at –30 °C for 6 h, then at r. t. for 30 h. It was then washed with 1 N aqueous $KHSO_4$ (80 mL), dried and concentrated under reduced pressure. The oily residue was purified by column chromatography [SiO_2 (60 g), hexane / EtOAc (1 : 2)] to give the desired product.

(2*S*)-[(2*S*)-(2-Naphthyl)methoxycarbonylaminopropionylamino]-5-{[(3*S*)-((1*S*)-methylpropyl)-4-oxo-oxetane-(2*R*)-carbonyl]amino}pentanoic Acid Benzyl Ester (114): Compound **114** was prepared according to GP6 from 2-naphthylmethoxycarbonyl-(*S*)-alanyl-(*S*)-(N^{δ}-*tert*-butyloxycarbonyl)ornithine benzyl ester **118** (900 mg, 1.56 mmol), the thioester **51** (440 mg, 1.57 mmol), TMP (377 mg, 3.11 mmol), HOAt (255 mg, 1.54 mmol) and EDC (561 mg, 3.11 mmol) in dichloromethane (20.6 mL). Yield 320 mg (33%), R_f = 0.46 [hexane / EtOAc (1 : 2)]. – ^{1}H NMR (300 MHz): 0.88 (3 H, t, *J* = 7 Hz), 0.97 (3 H, d, *J* = 7 Hz), 1.20–1.27 (1 H, m), 1.37 (3 H, d, *J* = 7 Hz), 1.35–1.48 (2 H, m), 1.54–1.64 (2 H, m), 1.78–1.92 (2 H, m), 3.05–3.12 (1 H, m), 3.20–3.28 (1 H, m), 3.53 (1 H, dd, *J* = 8, 5 Hz), 4.33–4.40 (1 H, m), 4.48 (1 H, d, *J* = 5 Hz), 4.57–4.62 (1 H, m), 5.09–5.18

(2 H, m), 5.20–5.27 (2 H, m), 5.66–5.70 (1 H, d, J = 8 Hz), 6.82 (1 H, m), 7.03 (1 H, d, J = 8 Hz), 7.29–7.37 (4 H, m), 7.40–7.44 (1 H, m), 7.46–7.49 (2 H, m), 7.78–7.84 (4 H, m) ppm. – ^{13}C NMR (75.5 MHz): 18.2 (CH_3), 25.5 (CH_2), 27.9 (CH_3), 28.2 (CH_3), 29.6 (CH_2), 40.4 (CH_2), 50.1 (CH), 52.3 (CH), 66.5 (C), 80.0 (C), 82.2 (CH_2), 128.0 (CH), 128.4 (CH), 136.5 (CH), 155.4 (C), 156.5 (C), 171.0 (C), 172.5 (C) ppm. – IR (film): $\tilde{\nu}$ = 3306 cm^{-1}, 3059, 2964, 2877, 1830, 1734, 1717, 1700, 1696, 1684, 1669, 1653, 1539, 1250, 1098, 1072, 908, 734. – $[\alpha]_D^{20}$ = +5.4 (c 0.96, $CHCl_3$). – MS (ESI) positive ion mode: m/z = 1285 ([2 M + Na$^+$], 100), 654 ([M + Na$^+$], 90). Negative ion mode: m/z = 676 ([M + HCOO$^-$], 100), 630 ([M – H$^+$], 30). – HRMS (ESI) [M + H$^+$]. – Calcd. for $C_{35}H_{42}N_3O_8$ 632.2972, found 632.2966.

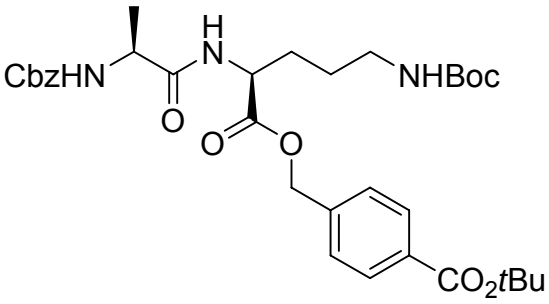
5-*tert*-Butyloxycarbonylamino-(*2S*)-(9*H*-fluoren-9-ylmethoxycarbonyl-amino)pentanoic Acid (4-*tert*-Butyloxycarbonylphenyl)methyl Ester (122):



Dicyclohexylcarbodiimide (1360 mg, 6.60 mmol) was added at 0 °C to a mixture of 5-*tert*-butoxycarbonylamino- (*2S*)-(9*H*)-fluoren-9-ylmethoxycarbonylamino)pentanoic acid (1530 mg, 3.37 mmol) and 4-(*tert*-butyloxycarbonyl)-phenylmethanol **121** (700 mg, 3.37 mmol) in CH_2Cl_2 (6.5 mL) and DMF (3.5 mL). The reaction mixture was stirred at r. t. for 3 h then the solvent was distilled off under reduced pressure, and the residue was purified by column chromatography, to yield 800 mg (37%) of the product (R_f = 0.28 [hexane / Et_2O (1 : 1)]) along with 350 mg (50%) of starting alcohol (R_f = 0.45 [hexane / Et_2O (1 : 1)]). – ^{1}H NMR (300 MHz): 1.43 (9 H, s), 1.58 (9 H, s), 1.88–2.00 (4 H, m), 3.04–3.20 (2 H, m), 3.40–3.54 (1 H, m), 4.08–4.24 (1 H, m), 4.30–4.44 (2 H, m), 5.07 (2 H, s), 5.19–5.22 (2 H, m), 7.26–7.44 (6 H, m), 7.56–7.64 (2 H, m), 7.76 (2 H, d, J = 8 Hz), 7.96 (2 H, d, J = 8 Hz) ppm. – ^{13}C NMR (75.5 MHz): 24.9 (CH_2), 25.6 (CH_2), 28.1 (CH_3), 28.4 (CH_3), 29.6 (CH_2), 33.9 (CH_2), 47.0 (CH), 47.1 (CH), 66.5 (CH_2), 66.9 (CH_2), 81.2 (C), 120.0 (CH), 127.0 (CH), 127.7 (CH), 129.7 (CH), 141.2 (C), 141.3 (C), 141.1 (C), 143.6 (C), 156.7 (CO), 165.2 (CO), 167.6 (CO), 172.1 (CO) ppm. – IR (film): $\tilde{\nu}$ = 3334 cm^{-1}, 2923, 1710, 1700, 1685, 1669, 1653, 1521, 1507, 1457, 1368,

1251, 1159, 1027, 912, 738. – $[\alpha]_D^{20}$ = –6.0 (*c* 1.0, $CHCl_3$). – MS (ESI) m/z = 683 ([M + K^+], 100), 622 ([M + Na^+], 80). – Calcd. for $C_{32}H_{39}N_3O_7$: C 66.53%, H 6.80%, N 7.27%, found: C 60.44%, H 6.65%, N 7.08%.

(*S*)-Benzyloxycarbonylalanyl-(*S*)-(N^{δ}-*tert*-butyloxycarbonyl)ornithine 4-(*tert*-Butoxycarbonyl)phenylmethyl Ester (123): (*S*)-Benzyloxycarbonylalanyl-(*S*)-(N^{δ}-*tert*-butyloxycarbonyl)ornithine 4-(*tert*-butoxycarbonyl)phenylmethyl ester **123** (343 mg, 44%) was prepared from **122** (800 mg, 1.24 mmol) and Cbz-Ala (330 mg, 1.42 mmol) according to GP5 as a colorless solid.



R_f = 0.11 [hexane / EtOAc (2 : 1)], m. p. 118–9 °C. – ^{1}H NMR (300 MHz): 1.38 (3 H, d, *J* = 7 Hz), 1.41 (7.7 H, s), 1.43 (1.3 H, s), 1.37 (9 H, s), 1.38–1.76 (2 H, m), 1.87–1.96 (2 H, m), 3.00–3.17 (2 H, m), 3.80–3.96 (1 H, m), 4.10–4.32 (1 H, m), 4.55–4.69 (1 H, m), 5.05–5.11 (2 H, m), 5.15–5.19 (2 H, m), 5.47–5.57 (1 H, br m), 6.93–7.02 (1 H, br m), 7.30–7.40 (7 H, m), 7.97 (2 H, d, *J* = 8 Hz) ppm. – ^{13}C NMR (75.5 MHz): 18.4 (CH_3), 25.8 (CH_2), 28.1 (CH_3), 28.3 (CH_3), 29.3 (CH_2), 39.7 (CH_2), 50.5 (CH), 52.2 (CH), 66.5 (CH_2), 67.0 (CH_2), 79.4 (C), 81.2 (C), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.9 (CH), 129.7 (CH), 132.0 (C), 136.2 (C), 139.6 (C), 156.2 (C), 156.7 (C), 157.3 (C), 165.3 (C), 172.3 (C) ppm. – IR (film): $\tilde{\nu}$ = 3336 cm^{-1}, 2926, 1718, 1700, 1685, 1669, 1653, 1521, 1507, 1457, 1368, 1251, 1159, 1027, 912, 738. – $[\alpha]_D^{20}$ = –6.0 (*c* 1.0, $CHCl_3$). – MS (ESI) positive ion mode: m/z = 1177 ([2 M + Na^+], 100), 600 ([M + Na], 40). Negative ion mode: m/z = 622 ([M + CH_3COO^-], 100). – HRMS (ESI) [M + H^+]. – Calcd. for $C_{33}H_{46}N_3O_9$ 628.3234, found 628.3229.

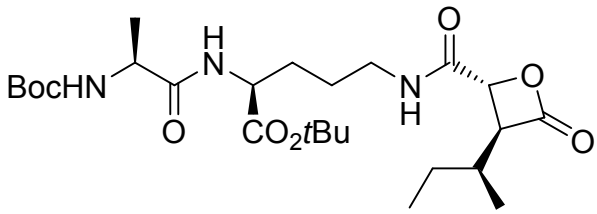
(2*S*)-[(2*S*)-Benzyloxycarbonylaminopropionylamino]-5-{[(3*S*)-((1*S*)-methylpropyl)-4-oxo-oxetane-(2*R*)-carbonyl]amino}pentanoic Acid 4-(*tert*-Butyloxycarbonyl)-phenylmethyl Ester (124): A solution of (*S*)-benzyloxycarbonylalanyl-(*S*)-(N^{δ}-*tert*-butyloxycarbonyl)ornithine 4-(*tert*-butoxycarbonyl)phenylmethyl ester **123** (340 mg, 0.54 mmol) and triethylsilane (316 mg, 2.70 mmol) in EtOAc (6 mL) was added to a saturated solution of HCl in EtOAc (5 mL) and the mixture was stirred for 3 h. The volatiles were distilled off, and the residue was dried in vacuo (0.05 mbar). The solution of the dry solid in DMF (3 mL) was treated with a solution of the thioester **4** (157 mg, 0.56 mmol) in CH_2Cl_2 (6 mL), TMP (146 mg, 1.21 mmol), HOAt (100 mg, 0.60 mmol) and EDC (200 mg, 1.11 mmol) in CH_2Cl_2 (2 mL) according to GP6 to yield 130 mg (35%) of the product **124** as a glassy colorless solid, R_f = 0.30 [hexane / EtOAc (1 : 2)]. – ^{1}H NMR (300 MHz): 0.90 (3 H, t, *J* = 7 Hz), 1.01 (3 H, d, *J* = 7 Hz) 1.20–1.30 (2 H, m), 1.35 (3 H, d, *J* = 7 Hz), 1.44–1.53 (1 H, m), 1.59 (9 H, s), 1.58–1.68 (2 H, m), 1.82–1.95 (2 H, m), 3.14–3.21 (1 H, m), 3.25–3.33 (1 H, m), 3.40–3.46 (1 H, m), 3.54 (1 H, dd, *J* = 8, 5), 4.28–4.34 (1 H, m), 4.52 (1 H, d, *J* = 5 Hz), 4.57–4.63 (1 H, m), 5.00–5.10 (2 H, m), 5.12–5.22 (1 H, m), 5.50–5.54 (1 H, m), 6.71–6.77 (1 H, m), 6.90–6.95 (1 H, m), 7.27–7.40 (7 H, m), 7.95 (2 H, d, *J* = 8 Hz) ppm. – ^{13}C NMR (75.5 MHz): 10.9 (CH_3), 16.2 (CH_3), 18.3 (CH_3), 25.3 (CH_2), 26.5 (CH_2), 28.1 (CH_3), 29.6 (CH_2), 38.3 (CH_2), 50.4 (CH), 51.7 (CH), 62.8 (C), 66.6 (CH), 66.9 (CH), 70.6 (CH), 81.18 (C), 127.7 (CH), 128.0 (CH), 128.1 (CH), 128.5 (CH), 129.7 (CH), 132.0 (C), 136.0 (C), 139.3 (C), 168.2 (C), 169.2 (C), 171.5 (C), 172.5 (C) ppm. – IR (film): $\tilde{\nu}$ = 3297 cm^{-1}, 2933, 2877, 1836, 1734, 1717, 1700, 1684, 1669, 1653, 1559, 1540, 1293, 1256, 1167, 1112, 756. – $[\alpha]_D^{20}$ = +1.6 (*c* 1.8, $CHCl_3$). – MS (ESI): m/z = 1385 ([2 M + Na$^+$], 48), 704 ([M + Na$^+$], 100), 682 ([M + H$^+$], 7). – HRMS (ESI) [M + NH_4^+]. – Calcd. for $C_{36}H_{51}N_4O_{10}$ 699.3605, found 699.3600.

(2*S*)-[(2*S*)-Benzyloxycarbonylaminopropionylamino]-5-{[(3*S*)-((1*S*)-methylpropyl)-4-oxo-oxetane-(2*R*)-carbonyl]amino}pentanoic Acid 4-(Hydroxycarbonyl)phenylmethyl Ester (115): To the solution of the product **124** (15 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (1 mL). The mixture was left overnight at –15 °C in the freezer. All the volatiles were distilled off under reduced pressure, and the residue was dried in vacuo. Yield 13 mg (99 %). – ^{1}H NMR (300 MHz): 0.91 (3 H, t, *J* = 7 Hz), 1.02 (3 H, d, *J* = 7 Hz) 1.20–1.30 (2 H, m), 1.37 (3 H, d, *J* = 7 Hz), 1.44–1.53 (1 H, m), 1.58–1.68 (2 H, m), 1.82–1.95 (2 H, m), 3.15–3.35 (2 H, m), 3.54 (1 H, dd, *J* = 8, 5), 4.28–4.38 (1 H, m), 4.57–4.63 (1 H, m), 4.59 (1 H, d, *J* = 5 Hz), 5.02–5.12 (2 H, m), 5.15–.25 (1 H, m), 5.84–5.90 (1 H, m), 6.71–6.77 (1 H, m), 6.90–7.00 (1 H, m), 7.27–7.43 (7 H, m), 8.05 (2 H, d, *J* = 8 Hz), 9.00–9.40 (1 H, br s) ppm. – ^{13}C NMR (75.5 MHz): 11.0 (CH_3), 16.2 (CH_3), 25.2 (CH_2), 26.5 (CH_2), 29.7 (CH_2), 33.7 (CH), 38.6 (CH_2), 50.6 (CH), 52.1 (CH), 63.0 (CH_2), 66.5 (CH_2), 67.3 (CH), 70.6 (CH), 127.8 (CH), 127.9 (CH), 128.5 (CH), 129.4 (C), 130.5 (CH), 132.0 (C), 135.9 (C), 140.8 (C), 169.0 (C), 169.2 (C), 170.1 (C), 171.3 (C) ppm. – IR (film): $\tilde{\nu}$ = 3022 cm^{-1}, 1844, 1792, 1772, 1734, 1717, 1700, 1696, 1684, 1669, 1653, 1559, 1539, 1457, 1250, 1098, 734. – $[\alpha]_D^{20}$ = –5.5 (c 0.65, $CHCl_3$). – MS (ESI): m/z = 1273 ([2 M + Na$^+$], 100), 648 ([M + Na$^+$], 90). HRMS (ESI) [M + H$^+$]. – Calcd. for $C_{32}H_{40}N_3O_{10}$ 626.2714, found 626.2708.

(*S*)-*tert*–Butyloxycarbonyl-alanyl-(*S*)-(N^δ-benzyloxycarbonyl)ornitine *tert*-Butyl Ester [Boc-Ala-Orn(Cbz)-OtBu] (129): The dipeptide **129** (2.60 g, 84%) was prepared from *N*-*tert*-butyloxycarbonyl-(*S*)-alanine (1.44 g, 7.62 mmol) and (N^δ-benzyloxycarbonyl)-(*S*)-ornithine *tert*-butyl ester **128** (2.00 g, 6.30 mmol) according to GP5 as a yellow viscous oil. R_f = 0.25

[hexane/EtOAc (1 : 1)] – ^{1}H NMR (300 MHz): 1.26 (3 H, d, J = 7 Hz), 1.34 (9 H, s), 1.37 (9 H, s), 1.38–1.76 (4 H, m), 3.14–3.22 (2 H, m), 4.10–4.20 (2 H, br m), 4.38–4.47 (1 H, m), 5.07 (2 H, s), 5.09–5.19 (1 H, br m), 6.80 (1 H, d, J = 6 Hz), 7.30–7.34 (5 H, m) ppm. – ^{13}C NMR (75.5 MHz): 18.2 (CH_3), 25.5 (CH_2), 27.9 (CH_3), 28.2 (CH_3), 29.6 (CH_2), 40.4 (CH_2), 50.1 (CH), 52.3 (CH), 66.5 (C), 80.0 (C), 82.2 (CH_2), 128.0 (CH), 128.4 (CH), 136.5 (CH), 155.4 (C), 156.5 (C), 171.0 (C), 172.5 (C) ppm. – IR (film): $\tilde{\nu}$ = 3336 cm^{-1}, 2926, 1718, 1700, 1685, 1669, 1653, 1521, 1507, 1457, 1368, 1251, 1159, 1027, 912, 738. – $[\alpha]_D^{20}$ = –3.0 (c 1.0, $CHCl_3$). – MS (ESI) positive ion mode: m/z = 1009 ([2 M + Na$^+$], 100), 516 ([M + Na$^+$], 34). Negative ion mode: m/z = 552 ([M + CH_3COO^-], 70), 538 ([M + $HCOO^-$], 100), 492 ([M - H], 48). – HRMS (ESI) [M + H$^+$] – calcd. for $C_{25}H_{40}N_3O_7$ 494.2866, found 494.2861. – Calcd. for $C_{25}H_{40}N_3O_7$: C 60.83%, H 7.96%, N 8.51%, found: C 60.60%, H 7.86%, N 8.29%.

(2*S*)-[(2*S*)-*tert*-Butyloxycarbonylaminopropionylamino]-5-{[(3*S*)-((1*S*)-methyl-propyl)-4-oxo-oxetane-(2*R*)-carbonyl]amino}pentanoic Acid *tert*-Butyl Ester (130):



A mixture of the dipeptide **129** (1.0 g, 2.1 mmol) and Pd/C (50 mg, 10%) in methanol (50 mL) was stirred overnight under an atmosphere of hydrogen, then it was filtered through a pad of Celite, the volatiles were removed in vacuo. The crude amine obtained was treated with the thioester **51** (510 mg, 1.83 mmol), TMP (438 mg, 3.6 mmol), HOAt (255 mg, 1.8 mmol) and EDC (561 mg, 3.6 mmol) according to GP2 to give 400 mg (38%) of **130**. R_f = 0.28 [hexane / EtOAc (1 : 1)]. – ^{1}H NMR (300 MHz): 0.91 (3 H, t, J = 7 Hz), 1.03 (3 H, d, J = 7 Hz), 1.32 (3 H, d, J = 7 Hz), 1.40 (9 H, s), 1.42 (9 H, s), 1.48–1.64 (4 H, m), 1.78–1.86 (1 H, m), 1.88–2.00 (1 H, m), 3.20–3.40 (2 H, m), 3.58 (1 H, dd, J = 9, 5 Hz), 4.10–4.20 (1 H, m), 4.36–4.44 (1 H, m), 4.57 (1 H, d, J = 5 Hz), 5.16–5.22 (1 H, m), 6.80–6.88 (1 H, m) ppm. – ^{13}C NMR (75.5 MHz): 10.9 (CH_3), 16.3 (CH_3), 18.2 (CH), 25.0 (CH_3), 28.2 (CH_3), 29.6 (CH_2), 33.7 (CH_3), 38.5 (CH_2), 50.0 (CH), 52.1 (CH), 62.8 (CH), 70.7 (CH), 80.0 (C), 82.3 (C), 155.5 (C), 168.1 (C), 169.2 (C), 170.8 (C), 172.6 (C) ppm. – IR (film): $\tilde{\nu}$ = 3318 cm^{-1}, 2976, 2934, 2878, 1837, 1669, 1540, 1507, 1457, 1368, 1251, 1161, 1098, 738. – $[\alpha]_D^{20}$

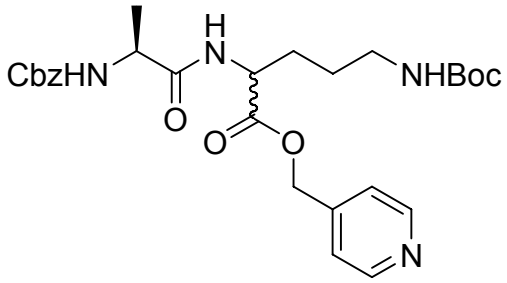
= +9.7 (c 1.5, $CHCl_3$). – MS (ESI) positive ion mode: m/z = 1049 ([2 M + Na^+], 100), 536 ([M + Na^+], 64). Negative ion mode: m/z = 558 ([M + $HCOO^-$], 100), 512 ([M – H], 26). – HRMS (ESI) [M + H^+]. – Calcd. for $C_{25}H_{44}N_3O_8$ 514.3128, found 514.3123.

(2*S*)-[(2*S*)-Aminopropionylamino]-5-{[(3*S*)-((1*S*)-methylpropyl)-4-oxo-oxetane-(2*R*)-carbonyl]amino}pentanoic Acid (31*CF_3COOH): The tripeptide **130** (75 mg, 0.15 mmol) was mixed with CH_2Cl_2 (2 mL) and trifluoroacetic acid (2 mL) at 0 °C, and this mixture was kept at –15 °C overnight. The volatiles were distilled off, and the obtained trifluoroacetic acid salt was dried in vacuo. Yield: 71 mg (99%). – ^{1}H NMR (CD_3OD, 300 MHz): 0.94 (3 H, t, *J* = 7 Hz), 1.03 (3 H, d, *J* = 7 Hz), 1.25–1.32 (1 H, m), 1.52 (3 H, d, *J* = 7 Hz), 1.60–1.71 (2 H, m), 1.90–2.00 (2 H, m), 3.25–3.32 (2 H, m), 3.65 (1 H, dd, *J* = 8, 4 Hz), 3.93–4.00 (1 H, m), 4.40–4.46 (1 H, m), 4.70 (1 H, d, *J* = 4 Hz) ppm. ^{13}C NMR (75.5 MHz): 11.3 (CH_3), 16.6 (CH_3) 17.5 (CH_3), 26.7 (CH_2), 27.7 (CH_2), 29.6 (CH_2), 36.9 (CH), 39.7 (CH_2), 50.2 (CH), 53.4 (CH), 63.8 (CH), 72.9 (CH), 170.7 (C), 171.0 (C), 171.1 (C), 174.5 (C) ppm. – IR (film): $\tilde{\nu}$ = 3420 cm^{-1}, 2967, 2934, 1830, 1684, 1540, 1457, 1362, 1203, 1140. – $[\alpha]_D^{20}$ = –3.6 (c 1.1, MeOH). – MS (ESI) positive ion mode: m/z = 715 ([2 M + H^+], 14), 358 ([M + H^+], 100). Negative ion mode: m/z = 713 ([2 M – H], 96), 356 ([M – H], 100). – HRMS (ESI) [M + H^+]. – Calcd. for $C_{16}H_{28}N_3O_6$ 358.1978, found 358.1973.

***rac*-5-*tert*-Butyloxycarbonylamino-(9*H*-fluoren-9-ylmethoxycarbonyl-amino)pentanoic Acid (Pyridyl-4)methyl Ester (126):** Dicyclohexylcarbodiimide (2.0 g, 9.7 mmol) was added at 0 °C to a mixture of 5-*tert*-butoxycarbonylamino-(*2S*)-(9*H*)-fluoren-9-ylmethoxycarbonylamino)pentanoic acid (4.0 g, 8.8 mmol) and 4-pyridylmethanol **125** (1 g, 9.1 mmol) in CH_2Cl_2 (10 mL) and DMF (2 mL). The reaction mixture was stirred at r. t. for 4 h, then the volatiles were distilled off under reduced pressure, and the residue was purified by column chromatography, to yield 2.4 g (51%) of the product as

a colorless solid, R_f = 0.28 [hexane / Et_2O (1 : 1)], m. p. 119–120 °C. – ^{1}H NMR (300 MHz): 1.41 (9 H, s), 1.46–1.60 (2 H, m), 1.65–1.80 (1 H, m), 1.85–2.00 (1 H, m), 3.09–3.21 (2 H, m), 4.21 (1 H, t, *J* = 7 Hz), 4.41 (2 H, d, *J* = 7 Hz), 4.40–4.50 (1 H, m), 4.60–4.69 (1 H, m), 5.17 (2 H, s), 5.69 (1 H, d, *J* = 7 Hz), 7.22 (2 H, d, *J* = 6 Hz), 7.30 (2 H, d, *J* = 6 Hz), 7.37–7.41 (2 H, m), 7.59 (2 H, d, *J* = 6 Hz), 7.75 (2 H, d, *J* = 8 Hz), 8.57 (2 H, m) ppm. – ^{13}C NMR (75.5 MHz): 26.3 (CH_2), 28.3 (CH_3), 29.4 (CH_2), 39.8 (CH_2), 47.1 (CH), 53.8 (CH), 65.0 (CH_2), 66.9 (CH_2), 79.3 (C), 119.9 (CH), 120.0 (CH), 121.8 (CH), 125.0 (CH), 127.0 (CH), 127.7 (CH), 141.3 (C), 141.6 (C), 141.7 (C), 150.1 (C), 156.0 (C), 172.0 (C) ppm. IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1}, 2922, 1719, 1690, 1680, 1676, 1646, 1519, 1500, 1460, 1366, 1250, 1169, 1023, 910, 736. – $[\alpha]_D^{20}$ = 0.0 (*c* 1.0, $CHCl_3$). – MS (ESI) positive ion mode m/z = 1113 ([2 M + Na^+], 80), 568 ([M + Na^+], 100). Negative ion mode: m/z = 590 ([M + $HCOO^-$], 100). – HRMS (ESI) [M + Na^+] – calcd. for $C_{31}H_{36}N_3O_6$ 546.2604, found 546.2598.

(*S*)-Benzyloxycarbonylalanyl-*rac*-(N^δ-*tert*-butyloxycarbonyl)ornithine (4-Pyridyl)methyl Ester (127): (*S*)-Benzyloxycarbonylalanyl-(*S*)-(N^δ-*tert*-butyloxycarbonyl)ornithine 4-pyridylmethyl ester **127** (315 mg, 43%) was prepared from **126** (750 mg, 1.38 mmol) and Cbz-Ala (380 mg, 1.64 mmol) according to GP5 as a colorless solid.



R_f = 0.34 [CH_2Cl_2 / MeOH (20 : 1)]. – ^{1}H NMR (300 MHz): 1.33 (3 H, d, *J* = 7 Hz), 1.36 (9 H, s), 1.40–1.52 (2 H, m), 1.60–1.73 (1 H, m), 1.80–1.92 (1 H, m), 2.98–3.11 (2 H, m), 4.24–4.36 (1 H, m), 4.53–4.63 (1 H, m), 5.02–5.07 (2 H, m), 5.08–5.14 (2 H, m), 5.74–5.83 (1 H, m), 7.18 (2 H, d, *J* = 5 Hz), 7.23–7.32 (7 H, m), 8.54 (2 H, d, *J* = 5 Hz) ppm. – ^{13}C NMR (75.5 MHz): 18.5 (CH_3), 26.3 (CH_2), 28.3 (CH_3), 28.5 (CH_2), 39.6 (CH_2), 50.3 (CH), 52.1 (CH), 64.9 (CH_2), 66.9 (CH_2), 79.3 (C), 121.8 (CH), 127.9 (CH), 128.0 (CH), 128.4 (CH), 136.1 (C), 144.2 (C), 149.9 (CH), 156.0 (C), 156.2 (C), 171.6 (C), 172.6 (C) ppm. – IR (film): $\tilde{\nu}$ = 3330 cm^{-1}, 2930, 1716, 1701, 1687, 1660, 1651, 1521, 1506, 1454, 1366, 1250, 1160, 1022, 910, 748. – MS (ESI) positive ion mode: m/z = 1079 ([2 M + Na^+], 100), 1057 ([2 M + Na^+], 30), 551 ([M + Na], 64), 529 ([M + H], 44). Negative ion mode: m/z = 573 ([M + $HCOO^-$], 100 – Calcd. for

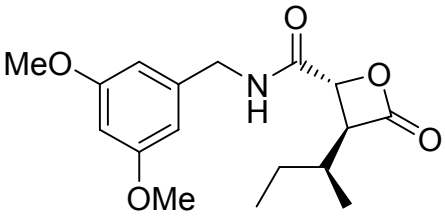
$C_8H_{14}O_5$: C 61.35%, H 6.86%, N 10.60%, found: C 60.99%, H 6.82%, N 10.46%.

Ethyl (2*R*)-Hydroxy-(4*S*)-methyl-(3*S*)-carboxylhexanoate (134): Silver trifluoroacetate (7.7 g, 35 mmol) was added to a solution of the malic acid derivative **133** (5 g, 17.5 mmol) in THF (20 mL) and H_2O (5 mL). The mixture was stirred at 55 °C for 16 h. Then the precipitate was filtered off and washed with THF. Then the volatiles were removed from the filtrate under reduced pressure. Water (20 mL) was added to the residue and this mixture was extracted with CH_2Cl_2. The solution was dried, and the solvent was distilled off to yield 3.0 g (89%) of the product. – ^{1}H NMR (300 MHz): 0.92 (3 H, t, *J* = 7 Hz), 1.03 (3 H, d, *J* = 7 Hz), 1.20 – 1.30 (1 H, m), 1.27 (3 H, t, *J* = 7 Hz), 1.44 – 1.56 (1 H, m), 1.98 – 2.09 (1 H, m), 2.74 (1 H, dd, *J* = 8, 3 Hz), 4.17 – 4.29 (2 H, m), 4.38 (1 H, d, *J* = 3 Hz) ppm. – ^{13}C NMR (125.7 MHz): 11.2(CH_3), 14.0 (CH_3), 16.1 (CH_3), 27.3 (CH_2), 33.5 (CH), 53.1 (CH), 62.0 (CH_2), 69.3 (CH), 173.8 (C), 178.2 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 2967 cm^{-1}, 2937, 1734, 1465, 1386, 1202, 1141, 1096, 1027. – $[\alpha]_D^{20}$ = +0.0 (*c* 1.0, $CHCl_3$). – MS (ESI): positive ion mode: m/z = 241 ([M + Na^+], 100). Negative ion mode: m/z = 217 ([M – H^+], 100).

(2*R*)-Hydroxy-(3*S*)-((1*S*)-methylpropyl)butandioic Acid (135): A solution of **134** (1.6 g, 7.3 mmol) in the dioxane (95 mL) and 10% aq. HCl (15 mL) was stirred at 60 °C for 50 h. Then the volatiles were removed under reduced pressure and the solid residue was recrystallized from hexane/EtOAc 1 : 2. Yield 1.2 g (86%), m. p. 140–1 °C. – ^{1}H NMR (300 MHz, DMSO – d_6): 0.84 (3 H, t, *J* = 7 Hz), 0.93 (3 H, d, *J* = 7 Hz), 1.02–1.21 (1 H, m), 1.39–1.53 (1 H, m), 1.66 – 1.80 (1 H, m), 2.48 – 2.55 (1 H, m), 4.16 (1 H, d, *J* = 6 Hz), 12.20 – 12.40 (2 H, br m) ppm. – ^{13}C NMR (125.7 MHz): 11.2 (CH_3), 116.3 (CH_3), 26.7 (CH_2), 33.8 (CH), 43.4 (CH_2), 55.4 (CH_3), 63.0 (CH), 70.7 (CH), 99.6 (CH), 105.8 (CH), 139.3 (C), 161.1 (C), 167.8 (C), 169.1 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 2964 cm^{-1}, 1702, 1289, 1090, 914. $[\alpha]_D^{20}$ = –11.5 (*c* 1.0, $CHCl_3$). – MS (ESI): positive ion mode: m/z = 235 ([M – H^+ + 2 Na^+], 100), 213 ([M + Na^+], 40). Negative ion mode: m/z = 189 ([M – H^+], 100). – Calcd. for $C_8H_{14}O_5$: C 50.52%, H

7.42%, found: C 50.35%, H 7.55%.

***N*-(3,5-Dimethoxyphenyl)methyl-(3*S*)-((1*S*)-methylpropyl)-4-oxo-oxetane-(2*R*)-carboxamide (132):** A mixture of (*2R*)-hydroxy-(3*S*)-((1*S*)-methylpropyl)butanedioic acid **135** (0.7 g, 3.7 mmol), trichloroacetic acid anhydride (2.3 g, 7.4 mmol) and dioxane (2 mL) was stirred at 75 °C for 3 h. Then the volatiles were removed in high vacuum at rt and the rest was dissolved in THF (10 mL) and cooled to 0 °C. 3,5-Dimethoxyphenylmethylamine (1.4 g, 8.4 mmol) was added, and the reaction mixture was stirred first at 0 °C for 1 h and then at r. t. for 16 h. The volatiles were removed *in vacuo,* and the residue was taken up in an aq. solution of NaOH (1.5 mL, 6 N), and the mixture was stirred at r. t. for 16 h. Then the solution was neutralized with conc. HCl, dichloromethane (20 mL) was added, and the mixture was washed with 1 N HCl (2×5 mL). The organic phase was dried over Na_2SO_4. The solvent was distilled off, the residue was purified by flash chromatography on silica; by-products were removed by eluting with pentane/diethyl ether (1 : 4), and the desired product was eluted with MeOH. The solvent was distilled off in vacuo and the malic acid monoamide was directly taken into the next step.



The crude malic acid monoamide (0.5 g, 1.5 mmol) was taken up in CH_2Cl_2 (40 mL), the solution cooled to 0 °C and treated with Et_3N (0.45 g, 4.5 mmol) followed by BOP (0.92 g, 2.1 mmol). The cooling bath was removed, and the reaction mixture was stirred at r. t. for 3 h. Then the solvent was distilled off in vacuo and the residue subjected to column chromatography (eluent pentane / diethyl ether 1 : 1) to give **132** as a colorless solid. Yield 240 mg (51%), R_f = 0.16 [pentane / diethyl ether (1 :1)], m. p. 104-5 °C. – ^{1}H NMR (300 MHz): 0.94 (3 H, t, *J* = 7 Hz), 1.07 (3 H, d, *J* = 7 Hz), 1.22–1.40 (1 H, m), 1.57–1.72 (1 H, m), 1.91 – 2.06 (1 H, m), 3.61 (1 H, dd, *J* = 4, 8 Hz), 3.77 (6 H, s), 4.29–4.50 (2 H, m), 4.63 (1 H, d, *J* = 4 Hz), 6.35–6.43 (3 H, m), 6.70–6.78 (1 H, m) ppm. – ^{13}C NMR (125.7 MHz): 11.0 (CH_3), 16.3 (CH_3), 26.7 (CH_2), 33.8 (CH), 43.4

(CH_2), 55.4 (CH_3), 63.0 (CH), 70.7 (CH), 99.6 (CH), 105.8 (CH), 139.3 (C), 161.1 (C), 167.8 (C), 169.1 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3302 cm^{-1}, 2958, 1828, 1651, 1601, 1473, 1206, 1151, 915, 838. – $[\alpha]_D^{20}$ = +2.2 (*c* 1.0, $CHCl_3$). – MS (ESI) m/z =366 ([M + $HCOO^-$], 68), 320 ([M – H^+], 100). – calcd. for $C_{17}H_{23}NO_5$: C 63.54%, H 7.21%, N 4.36%, found: C 63.34%, H 7.05%, N 4.24%.

General Procedure (GP7) for the Aldol Reaction: *n*-Butyllithium (34 mL, 2.5 M, 85 mmol) was added to a stirred solution of diisopropylamine (12.6 mL, 9.1 g, 90 mmol) in anhydrous THF (34 mL) at 0 °C under an atmosphere of nitrogen. After 10 min of stirring, the solution was cooled to -78 °C (dry ice / acetone bath) and stirred for additional 5 min. To this solution was added ethyl 3-hydroxybutanoate (**147)** (5.5 g, 42 mmol) in THF (23 mL), and the mixture was stirred at –78 °C for 1 h. A solution of 4-methoxybenzaldehyde (6.4 g, 47 mmol) in THF (23 mL) was then added, and the mixture was stirred at the same temperature for 4.5 h. The reaction was quenched by the addition of saturated aq. NH_4Cl, the reaction mixture was allowed to warm to r. t., extracted with ethyl acetate, dried over Na_2SO_4. The solvent was distilled off under the reduced pressure, and the residue was subjected to column chromatography (hexane / ethyl acetate (3 : 2)) on silica gel to yield 7.0 g (62%) of the product **150**.

Ethyl 3-Hydroxy-2-(hydroxy(4-methoxyphenyl)methyl)butyrate (150): The reaction of ethyl 3-hydroxybutyrate (**147)** (5.5 g, 42.0 mmol), 4-methoxybenzaldehyde (6.4 g, 47.0 mmol) and lithium diisopropyl amide, obtained from butyllithium (34 mL, 85.0 mmol, 2.5 M solution in hexane) and diisopropylamine (12.6 mL, 9.1 g, 91 mmol), according to GP7 gave 7.0 g, (62%) of **150** as a yellow oil comprising a mixture of three major diastereomers. R_f = 0.57 [hexane / EtOAc (3 : 2)]. – ^{1}H NMR (300 MHz): 1.00 (1.3 H, t, *J* = 7 Hz), 1.03–1.07 (1.7 H, m), 1.10–1.23 (3 H, m), 2.61 (0.25 H, dd, *J* = 8, 4 Hz), 2.68 (0.48 H, dd, *J* = 8, 3 Hz), 2.73 (0.23 H, dd, *J* = 8, 5 Hz), 3.11 (0.24 H, d, *J* = 9 Hz), 3.46 (0.24 H, d, *J* = 5 Hz), 3.52 (0.48 H, d, *J* = 9 Hz), 3.73 (3 H, s), 3.88–4.03 (2 H, m), 4.10–4.20 (1 H, m), 4.97 – 5.03 (0.28 H, m), 5.04–5.10 (0.69 H, m), 6.78–6.85 (2 H, m),

7.15 – 7.28 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 13.8 (CH_3), 14.0 (CH_3), 20.9 (CH_3), 21.4 (CH_3), 22.0 (CH_3), 55.1 (CH_3), 58.2 (CH), 59.1 (CH), 59.3 (CH), 60.4 (CH_2), 60.5 (CH_2), 60.7 (CH_2), 65.8 (CH), 66.2 (CH), 66.9 (CH), 71.2 (CH), 72.4 (CH), 73.4 (CH), 113.6 (CH), 126.7 (CH), 127.4 (CH), 134.0 (C), 159.1 (C), 173.1 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3444 cm^{-1}, 2976, 2936, 2837, 1726, 1612, 1514, 1464, 1377, 1249, 1178, 1033, 832. – MS (ESI) m/z =291 ([M + Na$^+$], 100). – calcd. for $C_{14}H_{20}O_5$: C 62.67%, H 7.51%, found: C 62.42%, H 7.29%.

***tert*-Butyl 3-Hydroxy-2-(hydroxy(4-methoxyphenyl)methyl)butyrate (155):** The reaction of *tert*-butyl 3-hydroxybutyrate (8 g, 50.0 mmol), 4-methoxybenzaldehyde (7.7 g, 56.4 mmol) and lithium diisopropylamide, obtained from butyllithium (41 mL, 102.5 mmol, 2.5 M solution in hexane) and diisopropylamine (13.5 mL, 9.8 g, 98 mmol), according to GP7 gave 3.8 g (34%) of **154** as a yellow oil comprising a mixture of two diastereomers. R_f = 0.57 (hexane / EtOAc 3 : 2). – ^{1}H NMR (300 MHz): 1.18 (9 H, s), 1.10–1.23 (3 H, m), 2.60–2.80 (1 H, m), 3.20–3.40 (1 H, m), 3.75 (3 H, s), 4.10–4.20 (1 H, m), 4.97 – 5.03 (0.3 H, m), 5.04–5.10 (0.7 H, m), 6.75–6.85 (2 H, m), 7.15 – 7.30 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 21.9 (CH_3), 21.4 (CH_3), 22.0 (CH_3), 27.8 (CH_3), 55.1 (CH_3), 58.2 (CH), 59.1 (CH), 59.3 (CH), 65.8 (CH), 66.2 (CH), 66.9 (CH), 71.2 (CH), 72.4 (CH), 73.4 (CH), 81.2 (C), 113.6 (CH), 126.7 (CH), 127.4 (CH), 134.0 (C), 159.1 (C), 173.1 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3447 cm^{-1}, 2982, 2930, 1728, 1612, 1510, 1460, 1385, 1250, 1030, 837. – MS (ESI) m/z =319 ([M + Na$^+$], 100).

Ethyl 2-(*tert*-Butyloxycarbonylaminomethyl)-3-hydroxy-3-(4-methoxyphenyl)-propionate (162): The reaction of **161** (3.8 g, 18 mmol), 4-methoxybenzaldehyde (4.6 g, 33.8 mmol) and lithium diisopropylamide, obtained from butyllithium (16 mL, 40 mmol, 2.5 M solution in hexane) and diisopropylamine (4.4 g, 44 mmol), according to GP7 gave **162** as a colorless solid comprising a mixture of two diastereomers. Yield 3.2 g (52%). R_f = 0.59 [hexane / EtOAc 3 : 2]. – ^{1}H NMR (300

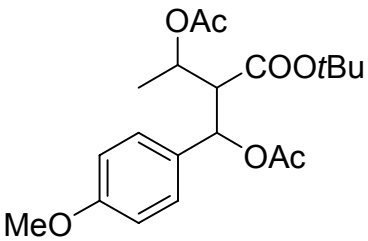
MHz): 1.12 (3 H, t, J = 7 Hz), 1.32 (7.2 H, s), 1.32 (1.8 H, s), 2.93 (1 H, q, J = 7 Hz), 3.14 (1 H, m), 3.69 (3 H, s), 3.87 (1 H, q, J = 7 Hz), 4.04 (2 H, q, J = 7 Hz), 4.46 (1 H, d, J = 4 Hz), 4.76 (1 H, t, J = 6 Hz), 4.96 (1 H, t, J = 6 Hz), 6.72 – 6.82 (2 H, m), 7.12 – 7.20 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 13.7 (CH_3), 13.9 (CH_3), 28.1 (CH_3), 38.9 (CH_2), 39.5 (CH_2), 52.6 (CH), 53.2 (CH), 55.0 (CH_3), 60.6 (CH_2), 64.3 (CH_2), 72.0 (CH), 72.5 (CH), 79.1 (C), 79.4 (C), 113.57 (CH), 113.62 (CH), 127.4 (CH), 128.3 (CH), 133.3 (C), 133.5 (C), 155.6 (C), 158.8 (C), 158.9 (C), 159.0 (C), 172.6 (C), 173.2 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3425 cm^{-1}, 2976, 1720, 1612, 1250, 834. – HRMS (ESI) [M + Na$^+$] – calcd. for $C_{18}H_{27}NNaO_6$ 376.1736, found 376.1731. – calcd. for $C_{18}H_{27}NO_6$: C 61.17%, H 7.70%, N 3.96%, found: C 61.44%, H 7.43%, N 4.20%.

General Procedure (GP8) for the Acetylation of the Aldol Reaction Products: To a solution of ethyl 3-hydroxy-2-(hydroxy-(4-methoxyphenyl)methyl)butanoate **150** (3.8 g, 14.2 mmol) in pyridine (26 mL) was added acetic anhydride (14.3 g, 13 mL, 140 mmol) and a catalytic amount of DMAP (ca. 30 mg). The mixture was stirred at r. t. for 16 h, then the solvent was distilled off under reduced pressure, and the residue was subjected to column chromatography (hexane / Et_2O 3 : 1) to yield 2.6 g (52%) of the desired product as a yellow oil.

Ethyl 3-Acetyloxy-2-(acetoxy(4-methoxyphenyl)methyl)butanoate (151): The product **151** was obtained from **150** (3.8g, 14.2 mmol), acetic anhydride (14.3g, 13 mL, 140 mmol) in pyridine (13 mL) according to GP8. Yield 2.6 g (52%) as a colorless solid comprising three major diastereomers, R_f = 0.33 [hexane / Et_2O (1 : 1)]. – ^{1}H NMR (300 MHz): 1.04 (1.5 H, t, J = 7 Hz), 1.12 – 1.24 (1.5 H, m), 1.27 (1.5 H, t, J = 7 Hz), 1.31 (1.5 H, d, J = 6 Hz), 1.96 (1.5 H, s), 2.00 (1.5 H, s), 2.01 (1.5 H, s), 2.06 (1.5 H, s), 3.03 (0.5 H, dd, J = 10, 4 Hz), 3.09 (0.5 H, dd, J = 10, 4 Hz), 3.76 (1.5 H, s), 3.77 (1.5 H, s), 3.95 (1 H, q, J = 7 Hz), 4.14–4.24 (1 H, m), 4.64 – 4.72 (0.5 H, m), 5.38 (0.5 H, dd, J = 7, 4 Hz), 5.97–6.01 (1 H, m), 6.79–6.89 (2 H, m), 7.20–7.32 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 14.0 (CH_3), 14.3 (CH_3), 18.45 (CH_3), 18.50 (CH_3), 20.90 (CH_3), 20.95 (CH_3), 21.01 (CH_3), 21.04 (CH_3), 55.2 (CH_3), 55.9 (CH), 56.1 (CH), 60.6 (CH_2), 60.7 (CH_2), 66.8 (CH), 67.8 (CH),72.0 (CH), 73.6 (CH), 113.7 (CH), 114.0 (CH), 128.6 (CH), 129.0

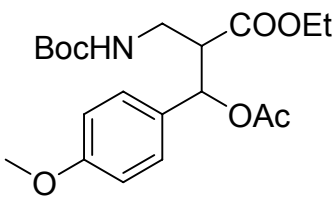
(CH), 129.3 (C), 130.1 (C), 159.6 (C), 159.8(C), 168.1 (C), 168.9 (C), 169.3 (C), 169.6 (C), 170.1 (C), 171.9 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3045 cm^{-1}, 2958, 1726, 1651, 1465, 1203, 1156, 842. MS (ESI) m/z =375 ([M + Na^+], 100). – calcd. for $C_{18}H_{24}O_7$: C 61.35%, H 6.86%, found: C 61.16%, H 6.65%.

***tert*-Butyl 3-Acetoxy-2-(acetoxy(4-methoxyphenyl)methyl)butanoate (156):**



Compound **156** was prepared from **155** (9 g, 30 mmol), acetic anhydride (30.3 g, 27.5 mL, 296 mmol) in pyridine (55 mL) according to GP8 as a coloroless solid comprising two major diastereomers. Yield 7.2 g (62%), R_f = 0.44 [hexane / diethyl ether 3 : 1]. – ^{1}H NMR (300 MHz): 1.18 (9 H, s), 1.30 (3 H, d, *J* = 6 Hz), 1.96 (3 H, s), 2.04 (3 H, s), 2.98 (1 H, dd, *J* = 10, 4 Hz), 3.74 (3 H, s), 5.31 (1 H, dd, *J* = 6, 4 Hz), 5.88 (1 H, d, *J* = 10 Hz), 6.81 (2 H, d, *J* = 7 Hz), 7.29 (2 H, d, *J* = 7 Hz) ppm. – ^{13}C NMR (125.7 MHz): 18.4 (CH_3), 21.0(CH_3), 27.6 (CH_3), 55.2 (CH_3), 56.6 (CH), 57.1 (CH), 67.1 (CH), 72.3 (CH), 81.2 (C), 113.5 (CH), 128.7 (CH), 129.3 (C), 159.6 (C), 168.9(C), 169.7(C), 171.9 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3040 cm^{-1}, 2950, 1728, 1649, 1467, 1203. – MS (ESI) m/z =783 ([2 M + Na^+], 10), 403 ([M + Na^+], 100).

Ethyl 3-Acetyloxy-2-(*tert*-butyloxycarbonylaminomethyl)-3-(4-methoxyphenyl)-propionate (163): A solution of **162** (3.2 g, 9 mmol) in pyridine (18 mL) and acetic

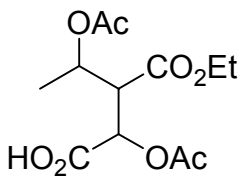


anhydride (9 mL) was treated with DMAP (ca. 20 mg) according to GP8 to yield after column chromatography (hexan / Et_2O 3 : 1 to 1 : 1) 2.7 g (75%) of **163**, R_f = 0.28 (hexane – diethyl ether 1 : 1) as a colorless solid comprising a mixture of two 2 : 1 diastereomers. – ^{1}H NMR (300 MHz): 0.80 – 0.84 (1 H, m), 1.00 (1 H, t, *J* = 7 Hz), 1.23 (2 H, t, *J* = 7 Hz), 1.36 (6 H, s), 1.37 (3 H, s), 1.96 (2 H, s), 2.02 (1 H, s), 3.02 – 3.18 (2 H, m), 3.73 (1 H, s), 3.74 (2 H, s), 3.93 (1 H, q, *J* = 7 Hz), 4.15 (2 H, qd, *J* = 7, 2 Hz), 4.70 – 4.76 (0.7 H, m), 4.90 – 4.96 (0.3 H, m), 5.86 – 5.96 (1 H, m), 6.80 – 6.86 (2 H, m), 7.20 – 7.26 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 13.9 (CH_3), 14.2 (CH_3), 21.0 (CH_3), 21.1 (CH_3), 28.3 (CH_3), 39.0 (CH_2), 39.2 (CH_2), 51.1 (CH), 51.4 (CH), 55.2 (CH_3), 60.9 (CH_2), 61.1 (CH_2), 73.4 (CH), 74.3 (CH), 79.4 (C), 113.9

(CH), 114.1 (CH), 128.4 (CH), 128.5 (CH), 129.2 (C), 155.5 (C), 159.6 (C), 159.9 (C), 171.9 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3308 cm^{-1}, 2968, 1745, 1650, 1475, 1208, 915. MS (ESI) m/z =813 ([2 M + Na^+], 100), 418 ([M + Na^+], 48). – calcd. for $C_{20}H_{29}NO_7$: C 60.74%, H 7.39%, N 3.54%, found: C 60.58%, H 7.19%, N 3.41%.

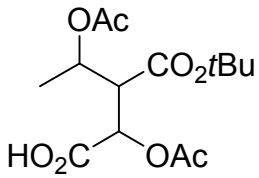
General Procedure (GP9) for the Ruthenium-Catalyzed Oxidative Degradation of Aromatic Rings: Compound **151** (2.6 g, 7.4 mmol) was added to a mixture of acetonitrile (19 mL), tetrachloromethane (19 mL) and water (28.5 mL). Sodium metaperiodate (22 g, 103 mmol) was added to this two-phase system under vigorous stirring followed by a catalytic amount of ruthenium(III) chloride hydrate (5–10 mg), and this mixture was vigorously stirred at r. t. for 16 h. Then a great amount of water (500 mL) was added to the reaction mixture in order to dissolve salts. The aqueous mixture was extracted with dichloromethane (3×150 mL). The combined organic phases were dried over Na_2SO_4. Volatiles were removed in vacuo to leave 1.9 g (89%) of the crude acid **152** as a black oil. Nevertheless it was pure according to its ^{1}H-NMR spectrum, and it was directly used in the next step without further purification.

2,4-Diacetoxy-3-(ethoxycarbonyl)pentanoic Acid (152): Compound **152** was prepared

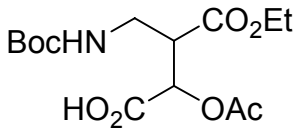


from **151** (2.6 g, 7.4 mmol), sodium metaperiodate (22 g, 103 mmol) and a catalytic amount of ruthenium(III) chloride hydrate in a mixture of acetonitrile (19 mL), tetrachloromethane (19 mL) and water (28.5 mL) according to GP9 and further used without purification. Yield 1.9 g (89%) as a black oil. – ^{1}H NMR (300 MHz): 1.20–1.29 (3 H, m), 1.30 – 1.37 (3 H, m), 1.98–2.03 (3 H, m), 2.11 (1 H, s), 3.15–3.33 (1 H, m), 4.18 (2 H, q, J = 7 Hz), 5.27–5.50 (2 H, m), 6.30 – 6.70 (1 H, br.m) ppm. MS (ESI) positive ion mode: m/z =625 ([2 M – H + 2 Na^+], 46), 603 ([M + Na^+], 12), 313 ([M + Na^+], 100). Negative ion mode: m/z =601 ([2 M – 2 H + Na^+], 100), 289 ([M + Na^+], 5).

2,4-Diacetoxy-3-(*tert*-butyloxycarbonyl)pentanoic Acid (157): Compound **157** was prepared from **156** (5 g, 13 mmol), sodium metaperiodate (44 g, 206 mmol) and a catalytic amount of ruthenium(III) chloride hydrate in a mixture of acetonitrile (38 mL), tetrachloromethane (38 mL) and water (57 mL) according to GP9 and used without further purification. Yield 3.6 g (87%) as a black oil.– ^{1}H NMR (300 MHz): 1.39 (3 H, d, J = 6 Hz), 1.43 (9 H, s), 2.00 (3 H, s), 2.13 (1 H, s), 3.19 (1 H, dd, J = 8, 3 Hz), 4.34 – 4.39 (1 H, m), 5.33–5.40 (1 H, m), 6.30 – 6.70 (1 H, br. m) ppm.

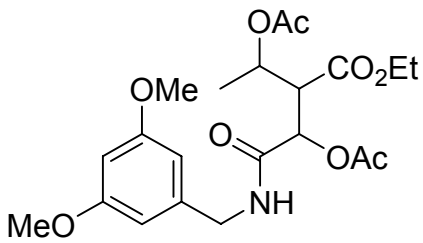


2-Acetoxy-4-(*tert*-butyloxycarbonylaminomethyl)-4-ethoxy-4-oxobutanoic Acid (164): Compound **164** was prepared from **163** (2.7 g, 6.8 mmol), sodium metaperiodate (22 g, 103 mmol) and a catalytic amount of ruthenium(III) chloride hydrate in the mixture of acetonitrile (19 mL), tetrachloromethane (19 mL) and water (28 mL) according to GP9 and used further without purification. Yield 1.9 g (83%), as a black oil.



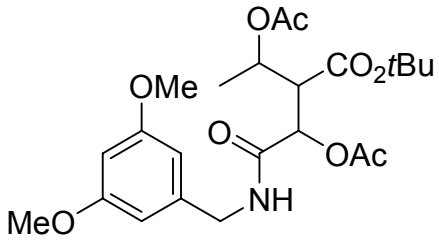
General Procedure (GP10) for the Synthesis of Amides: To an ice-cold solution of the acid **152** (1.9 g, 6.6 mmol), TMP (2.3 g, 18.8 mmol) and HOAt (1.0 g, 7.5 mmol) in dichloromethane (30 mL) was added EDC (1.2 g, 7.5 mmol) then, after 5 min, a solution of 3,5-dimethoxybenzylamine (**131)** (1.3 g, 7.5 mmol) in dichloromethane (15 mL), and the mixture was stirred at r. t. for 16 h. The reaction mixture was washed with water (20 mL) and 1 N $KHSO_4$ (20 mL). The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subjected to column chromatography (ethyl acetate / hexane 1 : 2), to yield 1.0 g (35%) of the amide **153** as a yellow oil.

***N*-3,5-Dimethoxybenzyl 2,4-Diacetoxy-3-ethoxycarbonylpentanamide (153):** Compound **153** was prepared from the acid **152** (1.9 g, 6.6 mmol), 3,5-dimethoxybenzylamine (1.3 g, 7.5 mmol), EDC (1.2 g, 7.5 mmol), TMP (2.3 g, 18.8 mmol) and HOAt (1.0 g, 7.5 mmol) in CH_2Cl_2 (45 mL) according to GP10. Yield 1.0 g (35%) as a



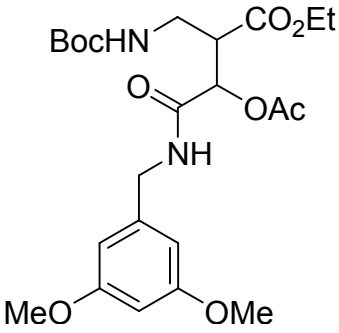
yellow oil comprising a mixture of two diastereomers, R_f = 0.47 (hexane – ethyl acetate 1 : 1). – ^{1}H NMR (300 MHz): 1.20 (0.6 H, t, J = 6 Hz), 1.21–1.23 (0.9 H, m), 1.25 (1.5 H, t, J = 6 Hz), 1.31 (0.6 H, d, J = 6 Hz), 1.35 (0.9 H, d, J = 6 Hz), 1.37 (1.5 H, d, J = 6 Hz), 1.99 (1.5 H, s), 2.00 (0.9 H, s), 2.01 (0.6 H, s), 2.10 (0.9 H, s), 2.12 (0.6 H, s), 2.13 (1.5 H, s), 3.28 (0.5 H, dd, J = 9, 4 Hz), 3.36 (0.3 H, dd, J = 6, 5 Hz), 3.42 (0.2 H, dd, J = 9, 4 Hz), 3.76 (3 H, s), 3.77 (1.8 H, s), 3.78 (1.2 H, s), 4.14–4.20 (2 H, m), 4.29–4.33 (1 H, m), 4.38 – 4.44 (2 H, m), 5.19–5.26 (1 H, m), 5.42–5.48 (1 H, m), 5.40 (1 H, d, J = 9 Hz), 6.37 – 6.42 (3 H, m) ppm. – ^{13}C NMR (125.7 MHz): 14.1 (CH_3), 14.2 (CH_3), 18.4 (CH_3), 18.6 (CH_3), 20.71 (CH_3), 20.73 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 43.46 (CH_2), 43.53 (CH_2), 50.5(CH), 51.7 (CH), 55.3 (CH_3), 61.0 (CH_2), 61.1 (CH_2), 66.5 (CH), 67.6 (CH), 70.8 (CH), 71.5 (CH), 99.5 (CH), 99.6 (CH), 105.3 (CH), 105.5 (CH), 139.9 (C), 161.01 (C), 161.03 (C), 167.6 (C), 167.7 (C), 169.3 (C), 169.7 (C), 170.1 (C), 170.4 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3302 cm^{-1}, 2958, 1828, 1651, 1601, 1473, 1206, 1151, 915, 838. MS (ESI) m/z =901 ([2 M + Na$^+$], 100), 462 ([M + Na$^+$], 38). – HRMS (ESI) [M + Na$^+$] – calcd. for $C_{21}H_{29}NNaO_9$ 462.1740, found 462.1734.

***N*-3,5-Dimethoxybenzyl 2,4-Diacetoxy-3-*tert*-butoxycarbonylpentanamide (158):**



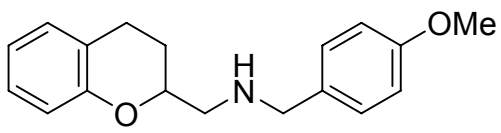
Compound **158** was prepared from the acid **157** (4.2 g, 13 mmol), 3,5-dimethoxybenzylamine **131** (2.6 g, 15 mmol), EDC (2.4 g, 15 mmol), TMP (4.6 g, 37.6 mmol) and HOAt (2.0 g, 15 mmol) in CH_2Cl_2 (90 mL) according to GP10. Yield 7.2 g (62%), as a yellow oil comprising a mixture of two major diastereomers. R_f = 0.62 (hexane – ethyl acetate 1 : 1). – ^{1}H NMR (300 MHz): 1.38 (3 H, t, J = 6 Hz), 1.43 (9 H, s), 1.99 (3 H, s), 2.12 (1 H, s), 3.18 (1 H, dd, J = 9, 4 Hz), 3.76 (6 H, s), 4.34 – 4.40 (2 H, m), 5.34 (1 H, dd, J = 7, 4 Hz) 5.37 (1 H, d, J = 7 Hz), 5.40 (1 H, d, J = 9 Hz), 6.31 – 6.33 (1 H, m), 6.38 – 6.40 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 18.7 (CH_3), 20.7 (CH_3), 20.9(CH_3), 27.9 (CH_3), 43.5 (CH_2), 51.3 (CH), 55.3 (CH_3), 66.8 (CH), 71.0 (CH_2), 82.0 (C), 99.6 (CH), 105.3 (CH), 139.9 (C), 161.0 (C), 167.8 (C), 168.3 (C), 171.9 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3366 cm^{-1}, 2979, 2938, 2840, 1734, 1684, 1598, 1533, 1457, 1373, 1159, 1049, 844. MS (ESI) m/z =783 ([2 M + Na$^+$], 10), 403 ([M + Na$^+$], 100).

Ethyl 3-Acetyloxy-2-(*tert*-butyloxycarbonylaminomethyl)-4-(3,5-dimethoxy-phenyl)methylamino-4-oxobutanoate (165): A solution of 3,5-



dimethoxybenzylamine (1.1 g, 6.7 mmol) in CH_2Cl_2 (13 mL) was added to a solution of **164** (1.9 g, 5.7 mmol), TMP (2.0 g, mmol), HOAt (0.87 g, 6.5 mmol) and EDC (1.0 g, 6.5 mmol) in CH_2Cl_2 (25 mL) and according to the GP10 gave 1.1 g (40%) of **165** as a colorless solid comprising a mixture of two major diastereomers, R_f = 0.23 (hexane – EtOAc 1 : 1). – ^{1}H NMR (500 MHz): 1.22 (3 H, t, J = 7 Hz), 1.41 (5.4 H, s), 1.63 (3.6 H, s), 2.10 – 2.16 (3 H, m), 3.20 – 3.40 (1 H, m), 3.44 – 3.56 (1 H, m), 3.76 (6 H, s), 3.92 – 3.98 (1 H, m), 4.10 – 4.20 (2 H, m), 4.37 – 4.44 (2 H, m), 4.99 – 5.05 (0.4 H, m), 5.09 – 5.17 (0.6 H, m), 5.26 (0.4 H, d, J = 4 Hz), 5.53 (0.6 H, d, J = 4 Hz), 6.34 – 6.36 (1 H, m), 6.40 – 6.44 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 13.97 (CH_3), 14.03 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 27.9 (CH_3), 28.3 (CH_3), 37.8 (CH_2), 37.9 (CH_2), 43.3 (CH_2), 43.4 (CH_2), 45.0 (CH), 47.3 (CH), 55.3 (CH_3), 61.25 (CH_2), 61.28 (CH_2), 71.5 (CH), 71.7 (CH), 79.6 (C), 84.9 (C), 99.6 (CH), 105.3 (CH), 140.0 (C), 155.8 (C), 162.9 (C), 167.7 (C), 169.6 (C), 170.3 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3302 cm^{-1}, 2958, 1828, 1651, 1601, 1473, 1206, 1151, 915, 838. LRMS (ESI) m/z =987 ([2 M + Na$^+$], 100), 505 ([M + Na$^+$], 96). – calcd. for $C_{23}H_{34}N_2O_9$: C 57.25%, H 7.10%, N 5.81%, found: C 57.01%, H 6.86%, N 5.59%

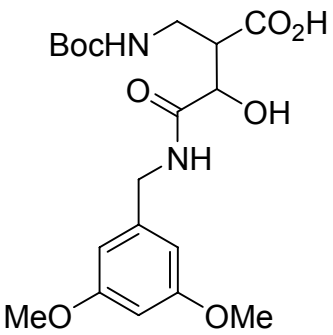
Chroman-2-ylmethyl-(4-methoxybenzyl)amine (170): Molecular sieve (1.60 g, 4 Å)



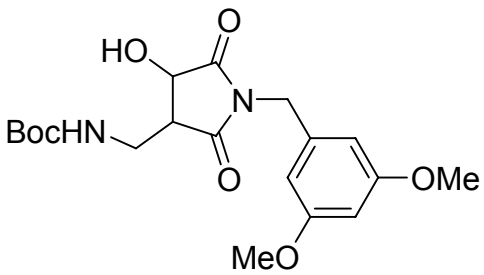
was added to the mixture of 4-methoxybenzaldehyde (0.86 g, 6.3 mmol), chroman-2-ylmethylamine (**168)** (1.00 g, 6.1 mmol) and acetic acid (60 mg) in EtOH (10 mL). This mixture was stirred at r. t. for 45 min. Then a solution of $NaBH_3CN$ (0.76 g, 12 mmol) in EtOH (6 mL) was added and the mixture was stirred at r. t. for 2.5 h. The reaction was quenched by addition of water, and the aqueous mixture was extracted with EtOAc (3×50 mL). The combined organic extracts were dried over Na_2SO_4. The solvent was distilled off and the residue was subjected to column chromatography (hexane / EtOAc 1 : 2), to yield 1.0 g (58%) of **170** as a colorless oil, R_f = 0.33 (hexane / ethyl acetate 1 : 2). – ^{1}H NMR (00 MHz, CD_3COCD_3): 1.56–1.72 (1 H, m), 1.87–1.97 (1 H, m), 2.60–2.84 (2 H, m), 2.87–3.02

(2 H, m), 3.76 (3 H, s), 3.96 – 4.00 (2 H, m), 4.15 – 4.25 (1 H, m), 6.51–6.55 (1 H, m), 6.79–6.90 (4 H, m), 6.96–7.08 (2 H, m), 7.30 – 7.35 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 23.9 (CH_2), 25.1 (CH_2), 51.2 (CH_2), 51.7 (CH_2), 55.1 (CH_3), 72.4 (CH), 114.2 (CH), 116.6 (CH), 120.7 (CH), 121.5 (C), 125.6 (C), 127.2 (CH), 129.4 (CH), 130.6 (CH), 153.4 (C), 159.7 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1}, 2970, 1844, 1734, 1653, 1559, 1457, 1205, 1159, 843. MS (ESI) m/z =567 ([2 M + H$^+$], 60), 284 ([M + H$^+$], 100).–

***N*-(3,5-Dimethoxybenzyl) 2-hydroxy-3-(*tert*-butyloxycarbonylaminomethyl)succin-imide (167): a) 3-Hydroxy-2-(*tert*-butyloxycarbonylaminomethyl)-4-(3,5-dimethoxyphenyl)methylamino-4-oxobutanoic Acid (166):** To a solution of **165** (500 mg, 1.0 mmol) in THF (42 mL) was added with a solution of LiOH*H_2O (336 mg, 8 mmol) in H_2O (14 mL), and the mixture was stirred at r. t. overnight. Then the pH value of the solution was adjusted to 5–6 by the addition of 10% aq. $KHSO_4$. The mixture was extracted with EtOAc (3×30 mL), the combined organic extracts were dried. Volatiles were removed yielding 300 mg (70%) of a crude product **166** that was used in the next step without further purification.

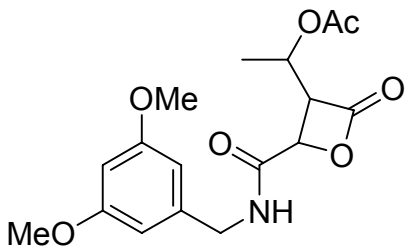


b) BOP-Induced Cyclization: To an ice-cold solution of a hydroxyacid **166** (300 mg, 0.73 mmol) in CH_2Cl_2 (17 mL) and Et_3N (0.5 mL) was added BOP (500 mg, 0.9 mmol), and the mixture was stirred at r. t. for 3 h. The volatiles were distilled off under reduced pressure and the residue was subjected to column chromatography (hexane / EtOAc 1 : 1), to yield 140 mg (34%) of **167** as a colorless solid comprising a mixture of two diastereomers, R_f = 0.44 [hexane / EtOAc (1 : 1)]. – ^{1}H NMR (600 MHz): 1.34 (9 H, s), 3.02–3.04 (1 H, m), 3.54–3.60 (2 H, m), 3.72 (6 H, s), 4.48–4.56 (2 H, m), 4.60–4.64 (1 H, m), 4.94–4.98 (1 H, m), 6.30–6.34 (1 H, m), 6.46–6.50 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): ppm. – IR (KBr): $\tilde{\nu}$ = 3453 cm^{-1}, 1717, 1653, 1635, 1161, 910. – MS (ESI) m/z =811 ([2 M + Na$^+$], 100), 417 ([M + Na$^+$], 76). – HRMS (ESI) [M + Na$^+$] –



calcd. for $C_{19}H_{26}N_2NaO_7$ 417.1638, found 417.1632 – calcd. for $C_{19}H_{26}N_2O_7$: C 57.86%, H 6.64%, N 7.10%, found: C 57.86%, H 6.34%, N 7.20%.

***N*-(3,5-Dimethoxybenzyl) 3-(1-acetoxyethyl)-4-oxo-oxetane-2-carboxamide (160):**



To a solution of **158** (1.0 g, 2.1 mmol) in dioxane (32 mL) was added 12% aq. HCl (5 mL) and the mixture was stirred for 48 h, monitoring the reaction by ^{1}H NMR. The volatiles were removed in vacuo. The residue was dissolved in CH_2Cl_2 (60 mL), the solution was cooled to 0 °C, $Et(iPr)_2N$ (1.2 mL) was added to it, and the mixture was treated with HATU (940 mg, 2.44 mmol), then stirred at r. t. for 4 h. The volatiles were distilled off under reduced pressure and the residue was subjected to column chromatography to yield 51 mg (6%) as a colorless foam, R_f = 0.41 (hexane / ethyl acetate 1 : 2). – ^{1}H NMR (600 MHz, CD_3COCD_3): 1.33 (3 H, d, J = 7 Hz), 2.04 (3 H, s), 3.27 (1 H, dd, J = 10, 9 Hz), 3.74 (6 H, s), 4.32 – 4.40 (2 H, m), 5.04 (1 H, d, J = 7 Hz), 5.21 (1 H, m), 6.42–6.44 (1 H, m), 6.46 – 6.49 (2 H, m) ppm. – ^{13}C NMR (125.7 MHz): 18.3 (CH_3), 20.8 (CH_3), 43.4 (CH_2), 52.9 (CH), 55.5 (CH_3), 66.0 (CH), 70.2 (CH_2), 99.7 (CH), 106.6 (CH), 141.9 (C), 161.9 (C), 162.0 (C), 167.1 (C), 169.7 (C) ppm. – IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1}, 2970, 1844, 1734, 1653, 1559, 1457, 1205, 1159, 843. MS (ESI) positive ion mode m/z =725 ([2 M + Na$^+$], 30), 374 ([M + Na$^+$], 100). Negative ion mode: 396 ([M + HCOO$^-$], 100). – HRMS (ESI) [M + H$^+$] – calcd. for $C_{17}H_{22}NO_7$ 352.1396, found 352.1391.

Summary and Outlook

Compounds containing a cyclopropane ring have attracted a great deal of interest during the last 60 years, because this moiety was found to be present in many biologically active substances. At the same time, cyclopropane derivatives have intensively been studied because of their unique bonding properties. Over the years, a large variety of synthetic accesses to various cyclopropane derivatives have been developed.

The next step in the development of cyclopropane chemistry has been the ever increasing employment of cyclopropanes in the syntheses of other classes of compounds. During the last 5 years, quite a few reactions of cyclopropane-ring enlargements have been reported. Inter alia, cyclopropanes have frequently been applied towards the syntheses of natural compounds, which demonstrates their wide potential. Yet, much more has to be done in this field.

Thus, certain insertion reactions of unsaturated compounds into the C,C bond of donor-acceptor-substituted cyclopropanes **17** were investigated. As a part of this study, two new syntheses of enantiomerically pure dimethyl 2-phenylcyclopropane-1,1-dicarboxylates **17a** were developed. The first one was conceived to proceed by the connection of the monoacid **93** with enantiomerically pure Evans auxiliary and subsequent separation of the resulting diastereomeric derivatives **95** and **96**. The latter after hydrolysis and reesterification with diazomethane gave the target cyclopropanes (*S*)- and (*R*)-**17a** in enantiomerically pure form in 27% and 32%, respectively, yield.

(*S*)-Phenylethanediol was chosen as the starting material for the second synthesis. It was converted into the bismesylate **99** and further into the (*S*)-**17a** (49% yield) by reaction with dimethyl malonate enolate.

With the starting cyclopropanes **17** both in racemic and enantiomerically pure form in hand, their insertion reactions with diazene derivatives were studied. The $GaCl_3$-catalyzed reaction of cyclopropanes **17** with diisopropyl azodicarboxylate **100a** led to pyrazolidines **101** in yields ranging from 41 to 67%. Screening of the reaction conditions and catalyst loadings showed that the best results are obtained at ambient temperature using 20 mol% of $GaCl_3$.

Analogously, the respective pyrazolidines **101** were obtained with azobenzene **100c** (41–44%). In the reaction of the cyclopropane **17b** with the non-symmetric ethyl phenyldiazenecarboxylate **100b** both possible regioisomers **101bb** and **102bb** were

formed in a ratio of 3 : 1 (23% yield).

Surprisingly, the reaction of cyclopropanes **17** with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) **100d** led to the unexpected products of insertion into the C2-C3 bond, i. e. products of type **102**, along with the normal products of type **101** resulting from insertion into the C1-C2 bond (ratios **101 : 102** ranging from 1 :1.5 to 1 : 3). The structures of the products **101bd** and **102bd** were verified by X-ray crystal structure analyses.

The mechanism of such insertions of diazene derivatives was studied employing the enantiomerically pure cyclopropane **(*R*)-17a** and diisopropyl azodicarboxylate **100a.** The fact that this reaction proceeded with complete racemization indicates a two-step mechanism via the zwitterionic intermediate **103** with a cationic center at the former C2 carbon.

The mechanism for the formation of type **102** products could not be elucidated. The possibility of a rearrangement of the type **101** products was ruled out and so was the possibility of this reaction to proceed via a radical path. The reaction of (*S*)-**17a** in this case also led to completely racemic products. Bearing all these facts in mind, a mechanism via an intermediate **106** bearing a cationic center at C2 was suggested.

Insertions of aryl isocyanides **108** into the cyclopropane ring of **17** were studied as well. Screening of a variety of catalysts showed that only lanthanide triflates were able to catalyze this reaction. Products of the insertion of two molecules of an isocyanide, namely dimethyl 3-arylamino-2-arylimino-4-arylcyclopent-3-ene-1,1-dicarboxylates (**111)**, were isolated in yields ranging from 21 to 62%, and not even traces of products of a single insertion were detected.

The second part of this thesis is concerned with the synthesis of Belactosin C analogues and congeners. Compounds of the Belactosin family were found to inhibit proteasomes including the 20S-proteasome from *Saccharomyces Cerevisiae*. All the previous investigations had shown that the activity of Belactosins can be improved by the esterification of its carboxylic acid group as well as by acylation of the nitrogen terminus. But the choice of these groups was casual.

Using the experimentally determined structure of a cocrystallizate of Homobelactosin C with the 20S-proteasome from *Saccharomyces Cerevisiae*, a computer modelling study was initiated to identify Belactosin C congeners that would be even better ligands for

this proteasome and possibly come along with improved biological activities. Thus, several new Belactosin C congeners were suggested for synthesis.

First, the Belactosin C congener **114** bearing a 2-naphthylmethyloxycarbonyl group on the *N*-terminus was prepared from 2-naphthylmethyloxycarbonylalanine **117** via the dipeptide **118** with subsequent peptide condensation with the substituted malic acid derivative **51** and ensuing β-lactonization. Compound **51** was synthesized according to the published sequence on a 1 mol scale, which proved the possibility of employing this route in industry.

An analogous route was chosen to synthesize the Belactosin C congener bearing a carboxyl group in its benzyl ester residue. The sequence started from di-*tert*-butyl terephthalate (**119)**, which was hydrolyzed to its monoester, and the latter was chemoselectively reduced to the alcohol **121**. This alcohol was used for the DCC-mediated esterification of *N*-protected ornithine. The resulting ester was coupled with Cbz-protected alanine, and the obtained dipeptide **123** was condensed with **51** after the selective cleavage of the *N*-Boc group in the presence of the *tert*-butyl ester group. Finally, the tripeptide **124** containing a β-lactone moiety was obtained, and in this the *tert*-butyl ester group was cleaved to furnish the Belactosin C congener **115**.

The attempted synthesis of the congener **116** with a pyridylmethyl residue was not successful. First, an *N*-protected ornithine was esterified with 4-pyridylmethanol **125** providing a completely racemized product **126**. This product was condensed with Cbz-alanine, but the dipeptide **127** could not be converted to the target compound **116** under various sets of conditions.

Another target of synthesis was the completely deprotected Belactosin C as a salt in order to increase its storage stability. Towards this end, the dipeptide **129** was synthesized according to the established procedure. It was then further converted into the tripeptide **130**. Both the *N*-Boc and the *tert*-butyl ester groups were cleaved by treatment with trifluoroacetic acid to yield the Belactosin C hydrotrifluoroacetate.

The next goal of this study was to develop a scalable synthesis of the Belactosin analogue **132**. This analogue had shown the best biological activity among all the Belactosin analogues bearing substituted benzylamide residues instead of the dipeptide moiety. This type of amide was therefore used as the lead structure in the development of a possible industrial application, and thus an inexpensive synthesis was required. Towards this goal, the malic acid derivative **133** was hydrolyzed stepwise to the

substituted malic acid **135** that was converted to the monoamide **138**. BOP-mediated cyclization of the latter led to the desired β-lactone **132**.

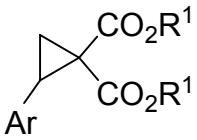
Finally, the Belactosin analogue **140** carrying a hydroxy function in the side chain of the β-lactone moiety was targeted. Towards this, a completely new synthetic approach had to be developed. The racemic ethyl 3-hydroxybutyrate **147** was chosen as a model compound instead of enantiomerically pure 3-hydroxyvalerate for this development. The only possible way to perform an aldol reaction with **147** turned out to be by applying dianion chemistry. All other attempted approaches led to eliminations. Unfortunately, an attempted aldol reaction of the dianion of **147** with ethyl glyoxylate did not give any product. For this reason, 4-methoxybenzaldehyde was used as a synthetic equivalent of ethyl glyoxylate. After the acylation of both hydroxy groups, the aryl moiety of the resulting **151** was oxidatively removed to provide the acid **152** that was further converted into the amide **153**. Attempts to selectively hydrolyze the ethyl ester and one acetoxy group were not successful. Under basic conditions, the ethyl ester as well as both acetoxy groups were cleaved, and under acidic conditions the ester group was not cleaved at all.

For this reason an analogous sequence with a *tert*-butyl instead of an ethyl ester group was carried out. *tert*-Butyl esters are known to be easily cleaved under acidic conditions. Thus, the ester **154** was coupled with 4-methoxybenzaldehyde, the product **155** was acylated and the 4-methoxyphenyl group was oxidatively fragmented employing $NaIO_4$ / $RuCl_3$. The resulting acid was coupled with the amine **131,** and the amide obtained was hydrolyzed under acidic conditions. Under optimized conditions, the *tert*-butyl ester and one of the acetoxy groups were cleaved selectively. Yet, the cyclization of the hydroxyacid **159** to the β-lactone **160** could only be achieved in a yield of 3%.

In order to overcome the difficulty with the differentiation of two hydroxy groups, *N*-Boc β-alanine ethyl ester **161** was chosen as the starting material. After the aldol reaction, acylation of the product **162**, oxidative fragmentation of the 4-methoxyphenyl group to the carboxylic acid and amide formation with the amine **131**, the amide **165** was obtained. However, after the simultaneous hydrolysis of the ester and the acetoxy group followed by BOP-mediated intramolecular condensation, the imide **167** was isolated instead of the desired β-lactone.

An attempted approach to the desired β-lactone with protection of the nitrogen in the

amide residue with 4-methoxybenzyl group also was not successful.



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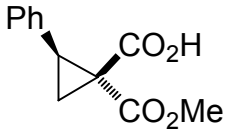

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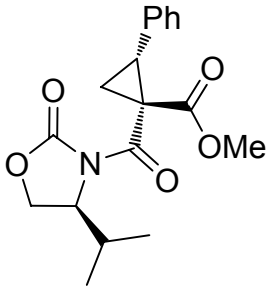

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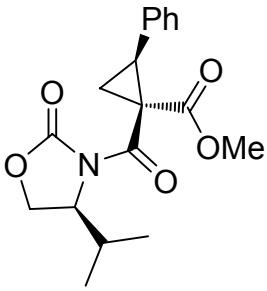

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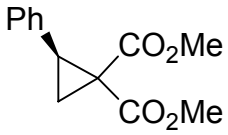
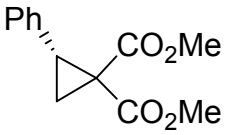
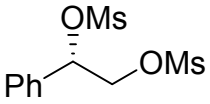


(*S*)-**17a**



(*R*)-**17a**



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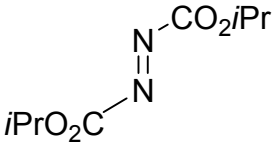
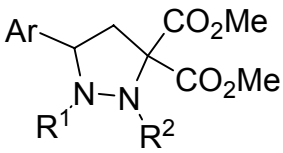


100a



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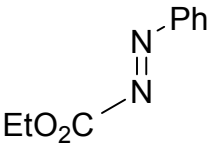

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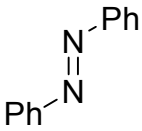

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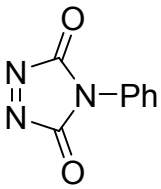

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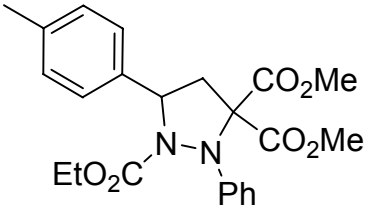

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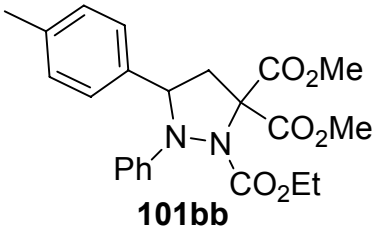

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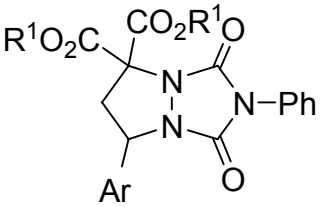

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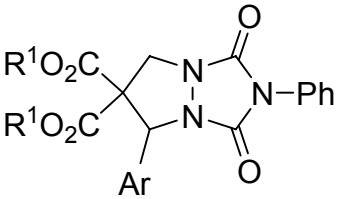

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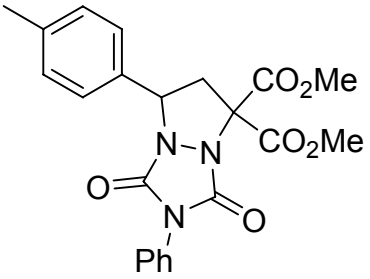

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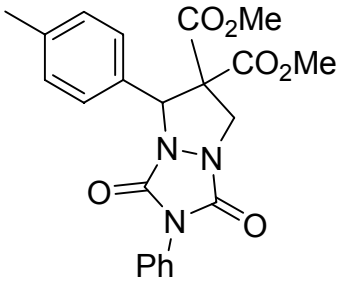

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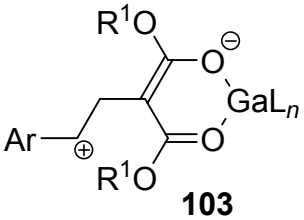

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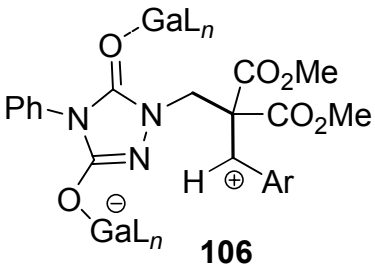
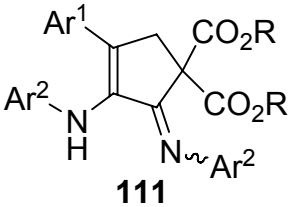


106

Ar^2NC:

108



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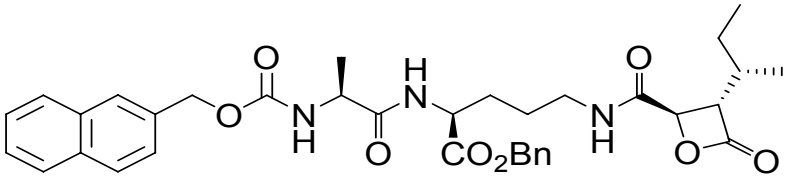

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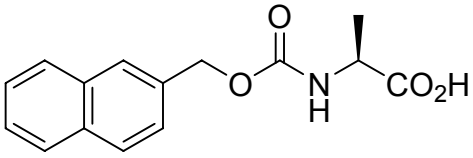

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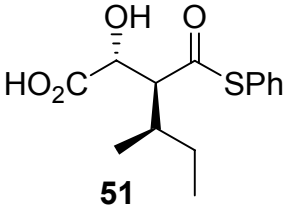

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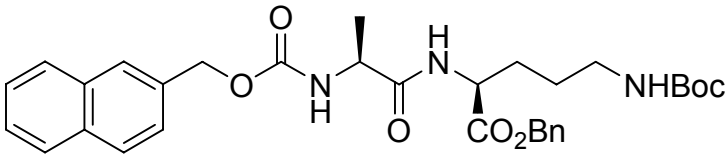

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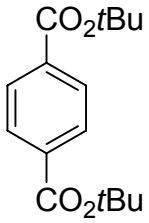

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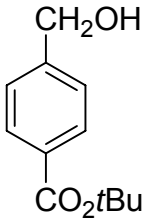

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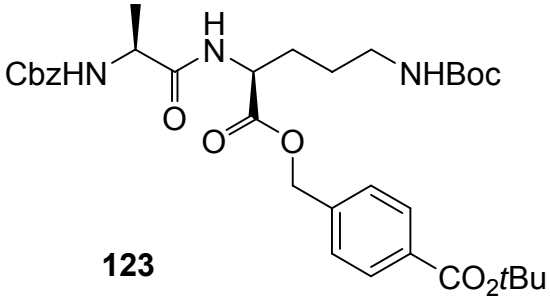

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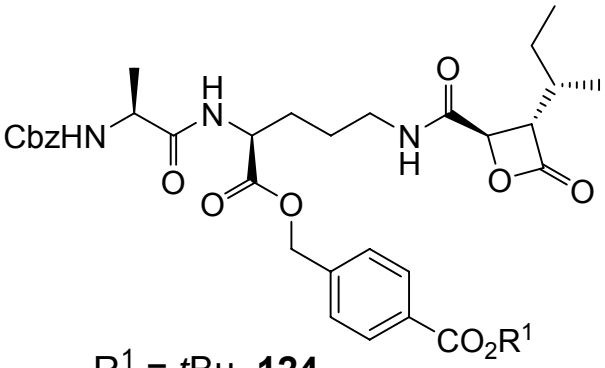
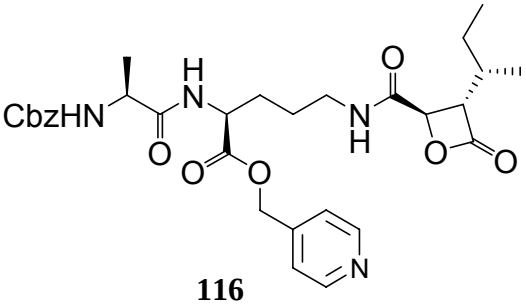


R^1 = *t*Bu, **124**

R^1 = H, **115**



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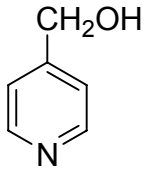

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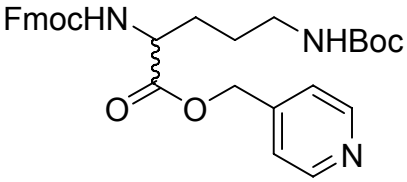

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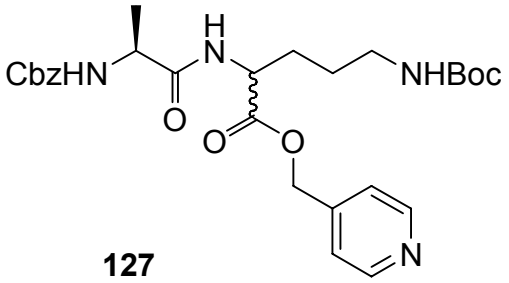

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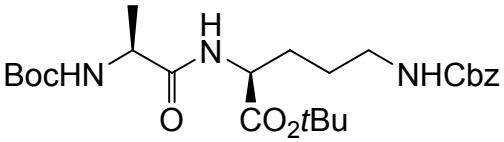

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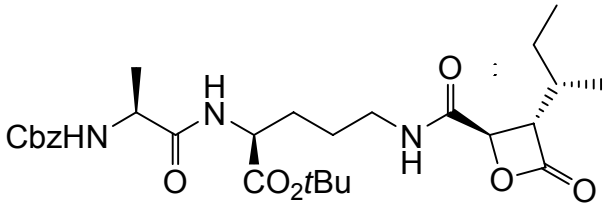

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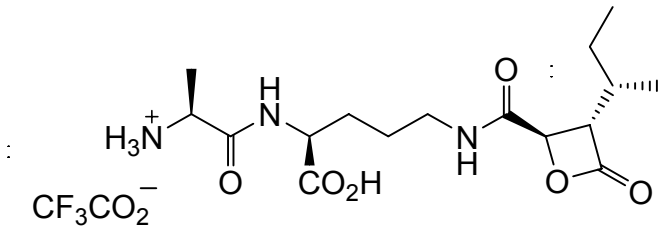

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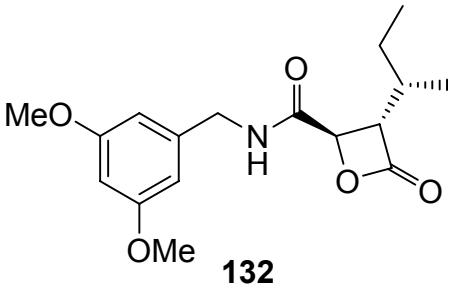

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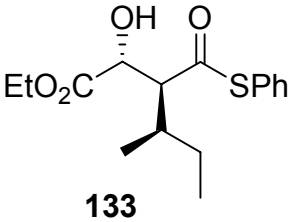

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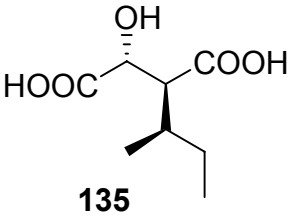

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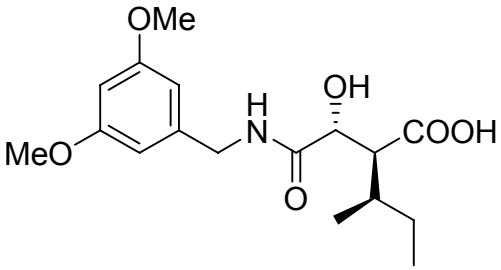

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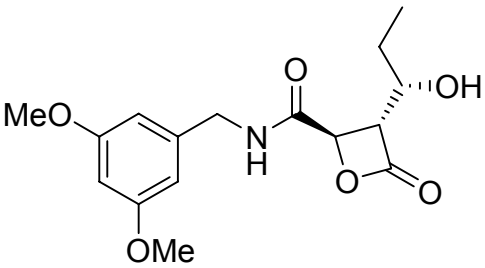

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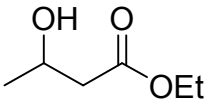

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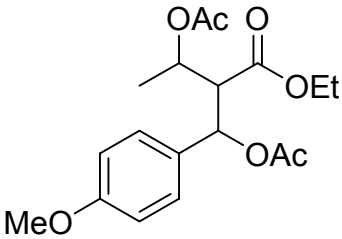

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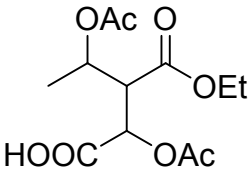

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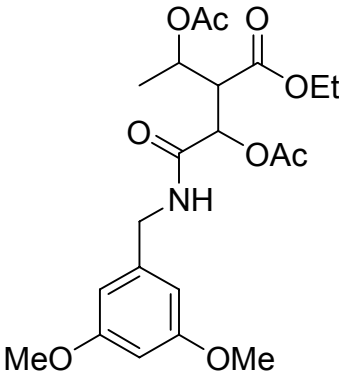

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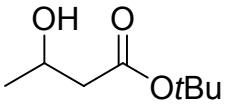

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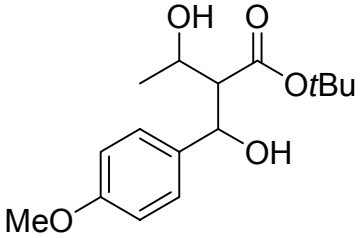

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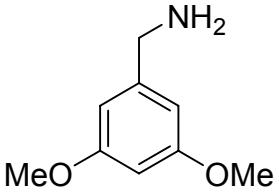

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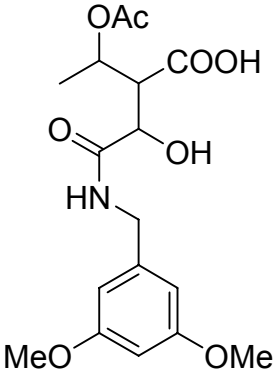

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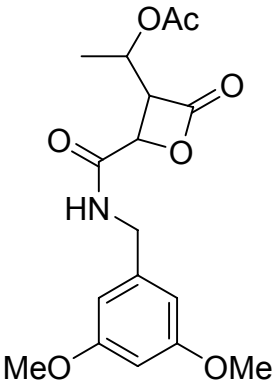

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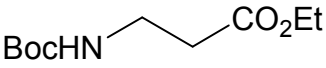

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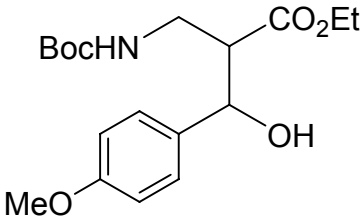

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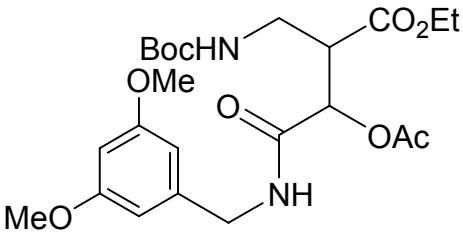

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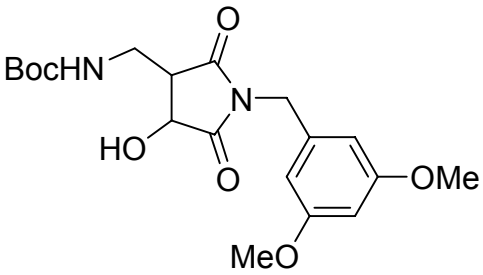

167

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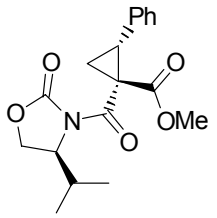
Spectral Data



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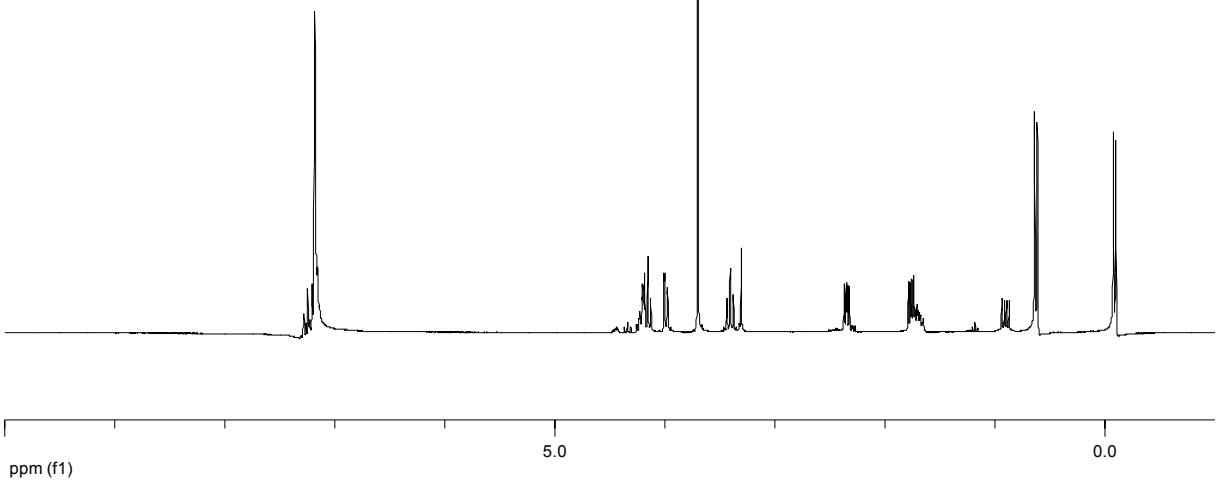

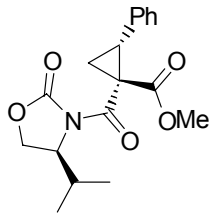

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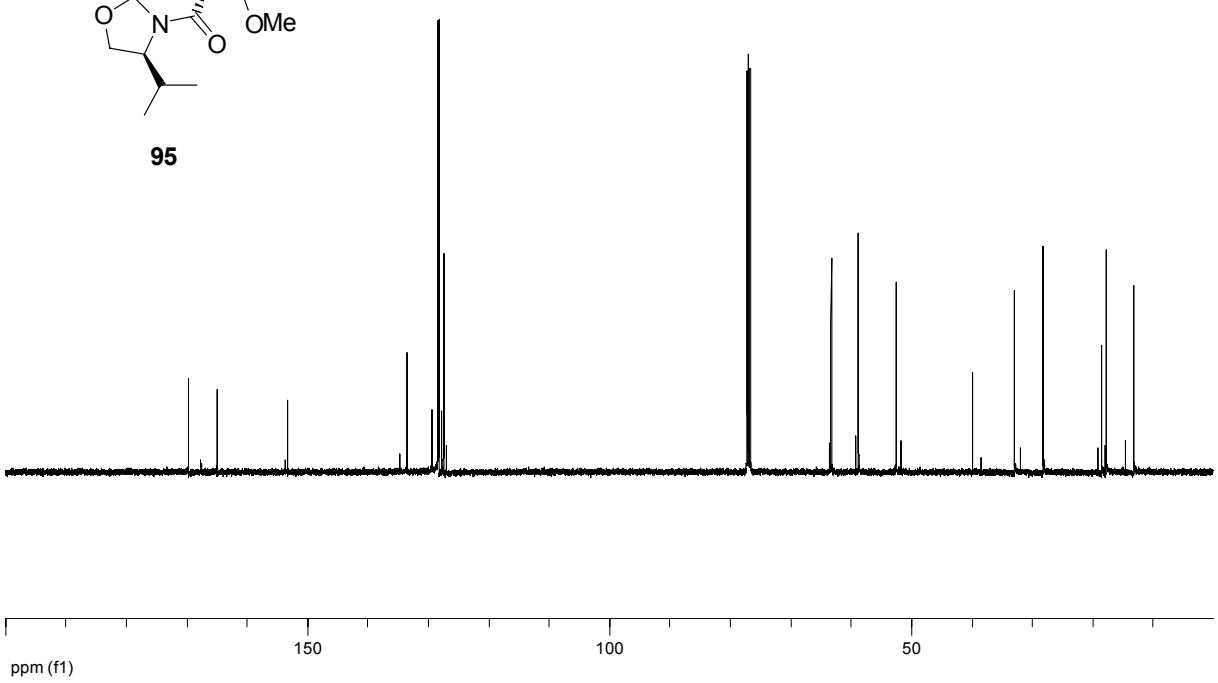

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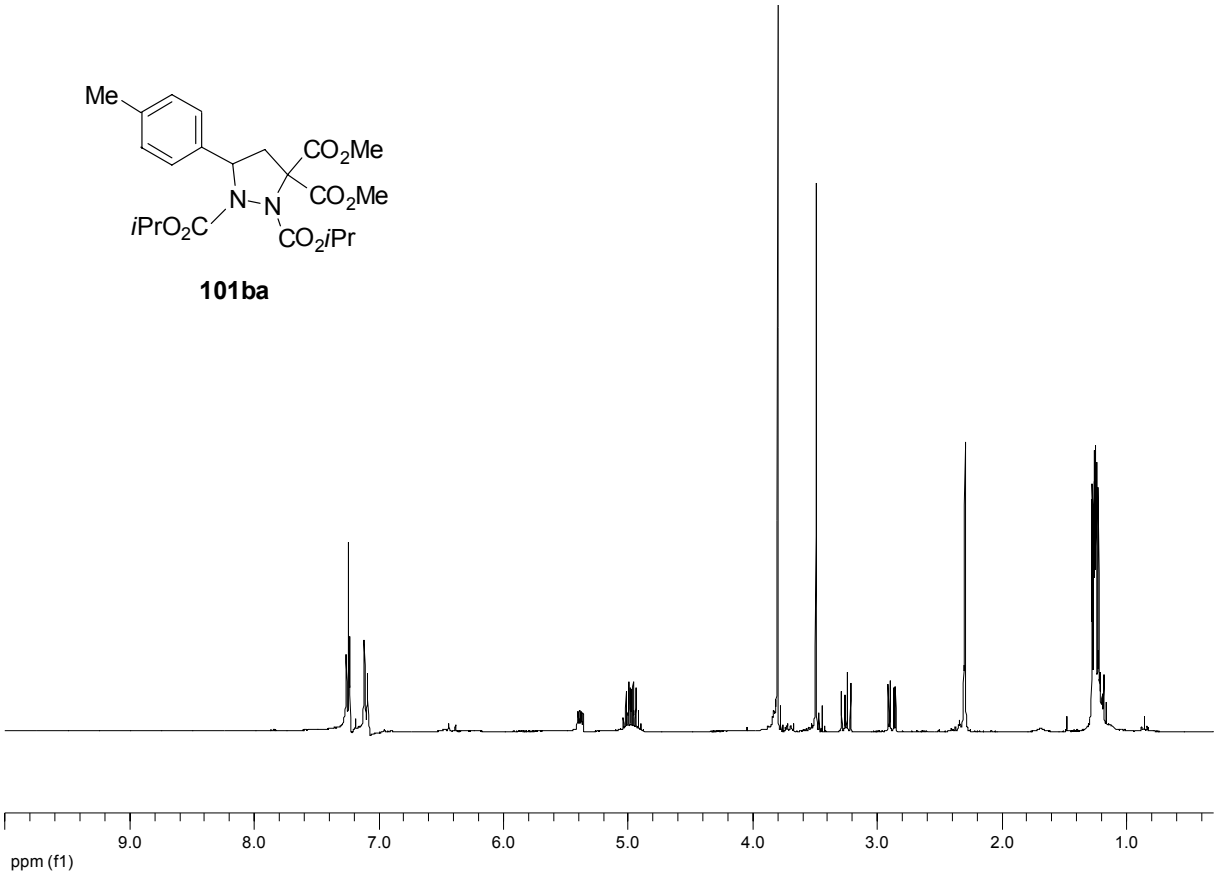
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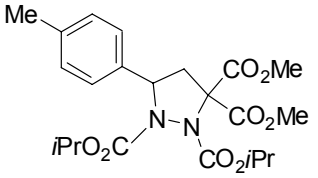
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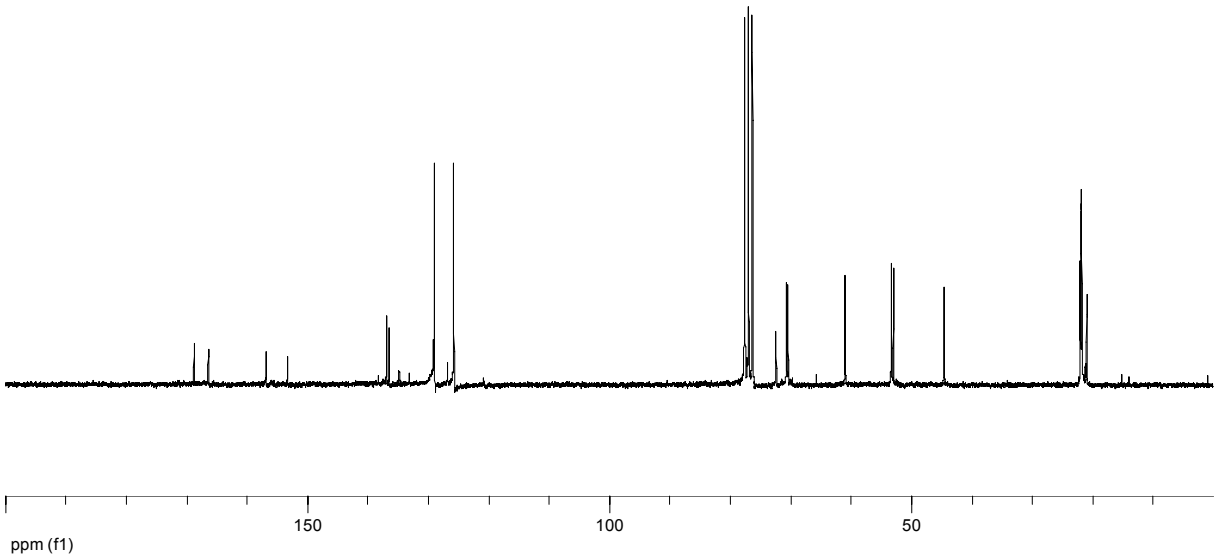
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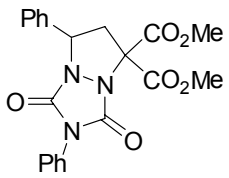
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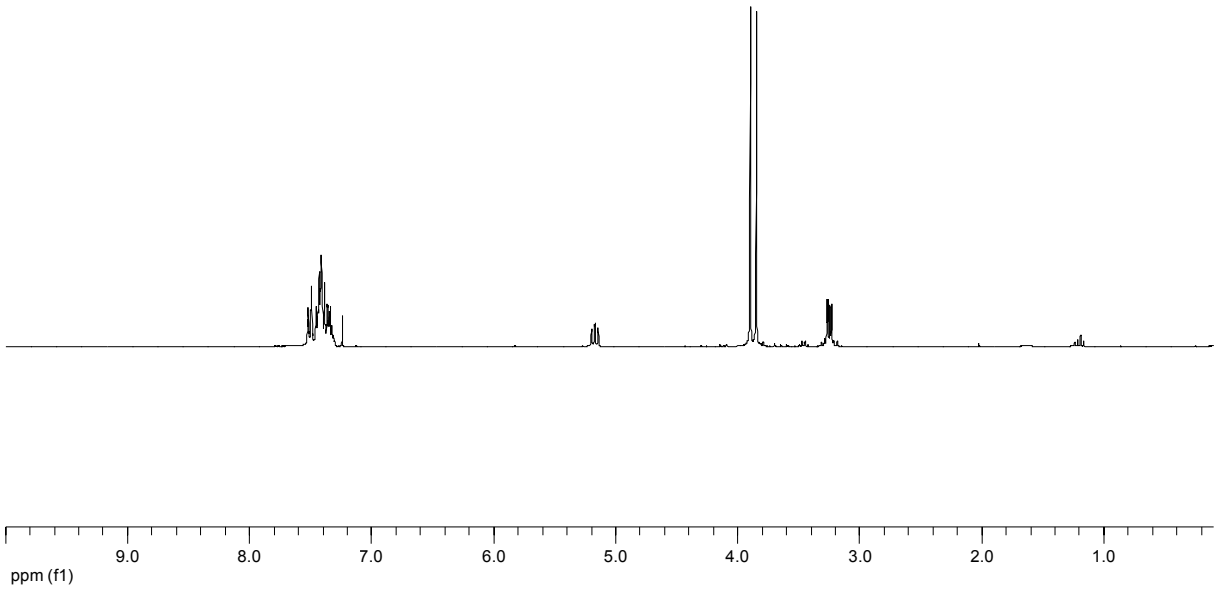
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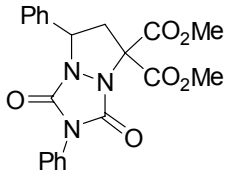
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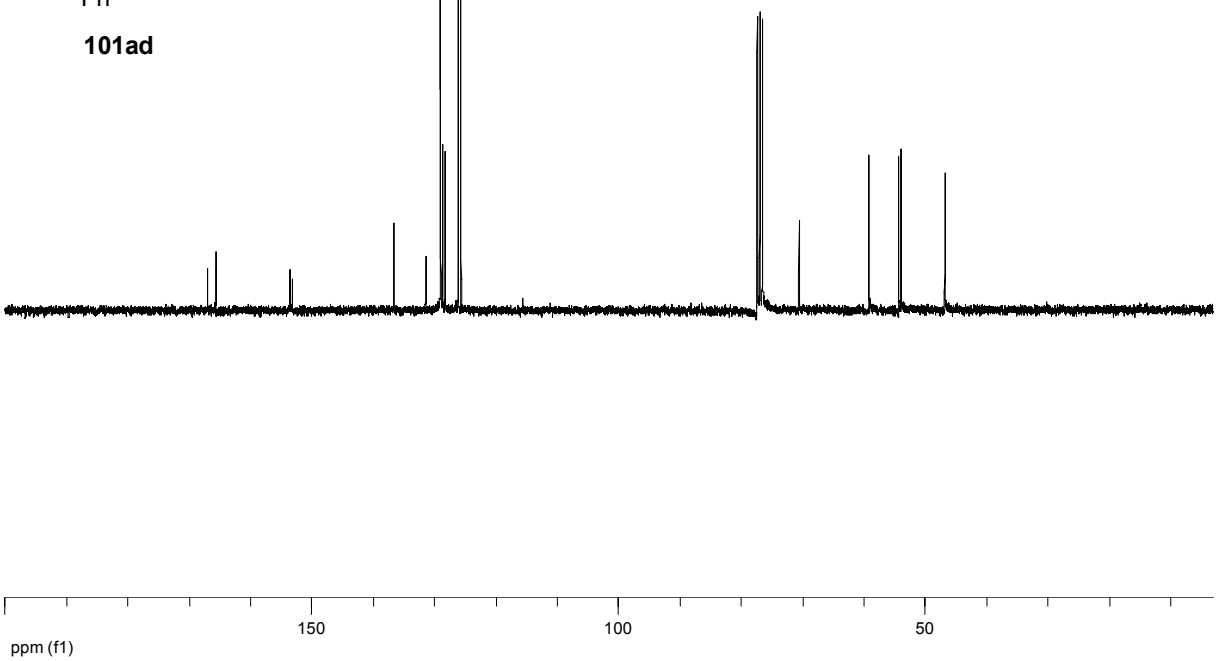
101ad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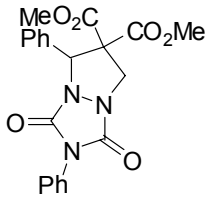
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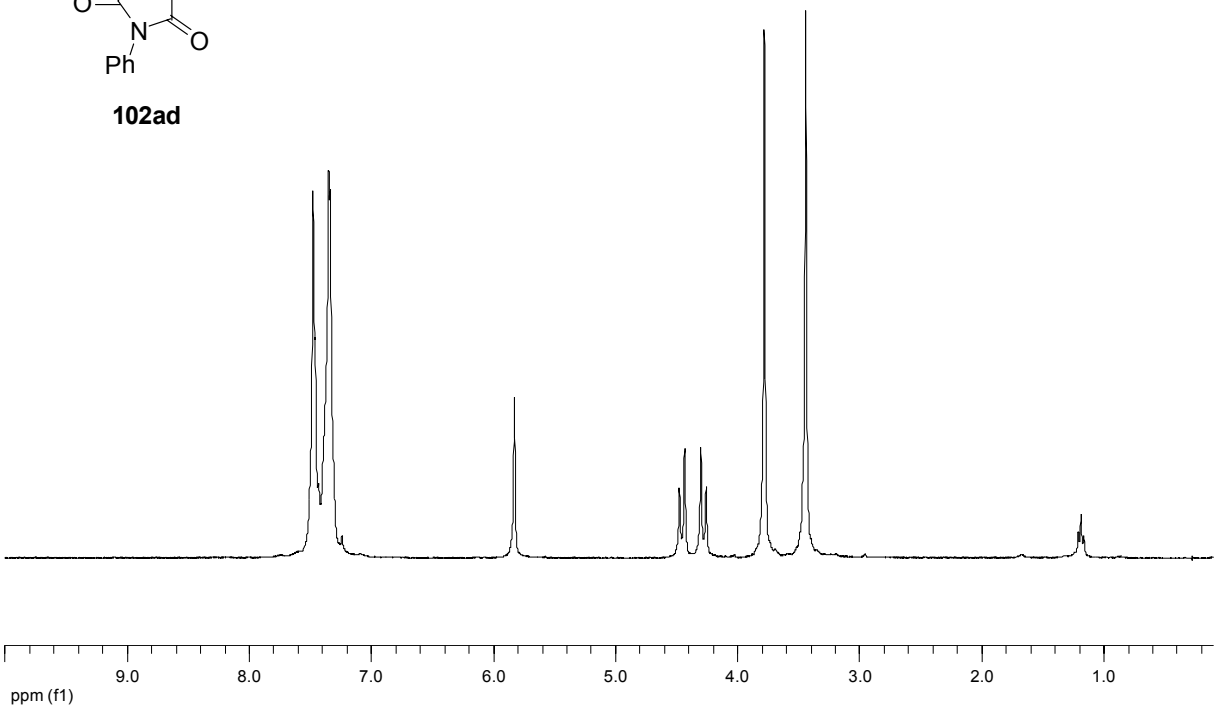
Ph
CO2Me
N
N
O
N
O
Ph

102ad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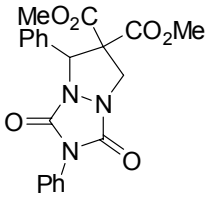
ppm (f1)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Ph
CO2Me
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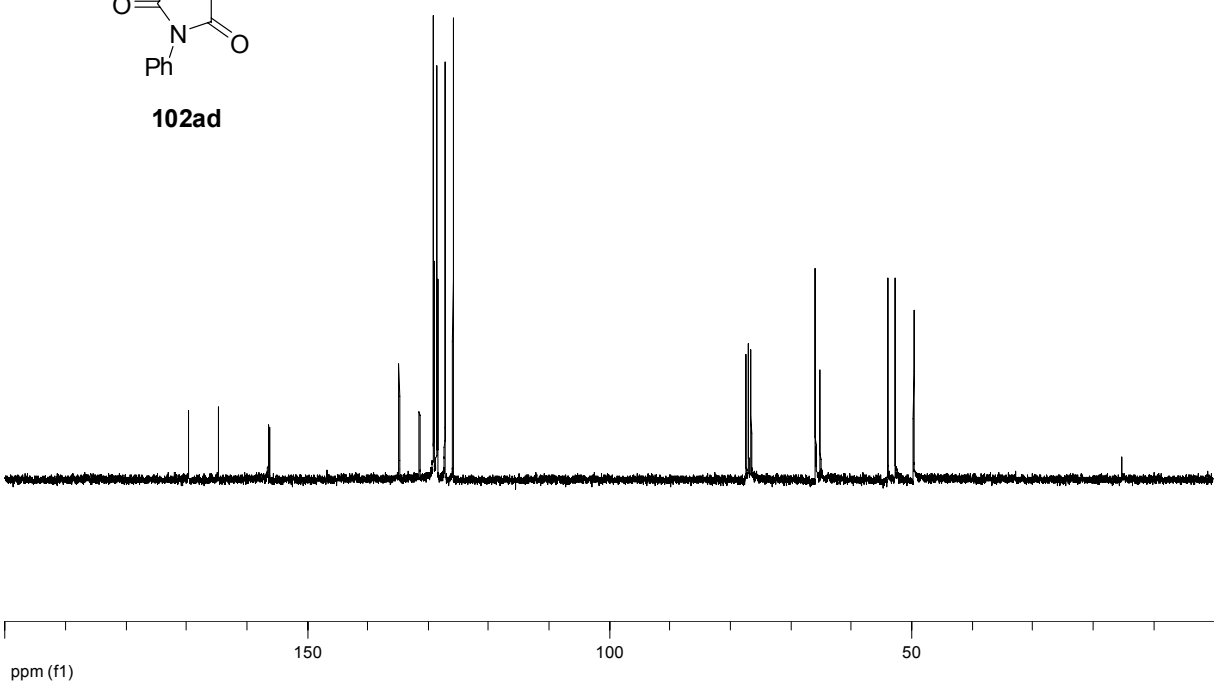
N
O
N
O
Ph

102ad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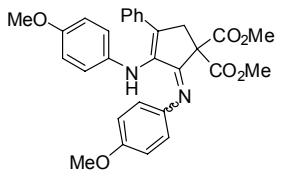
ppm (f1)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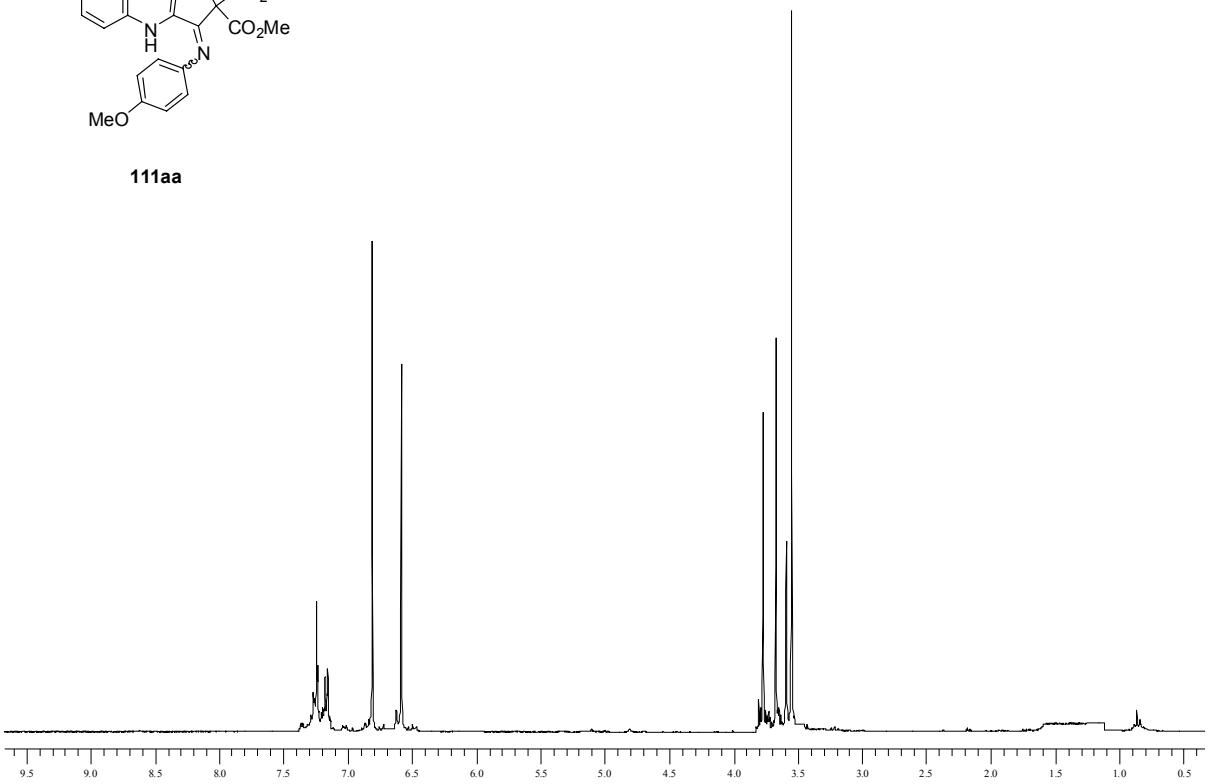
Ph
CO2Me
CO2Me
N
H
N
MeO

111aa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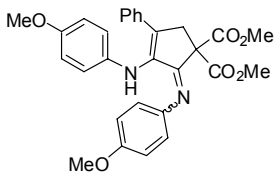
1.0
0.5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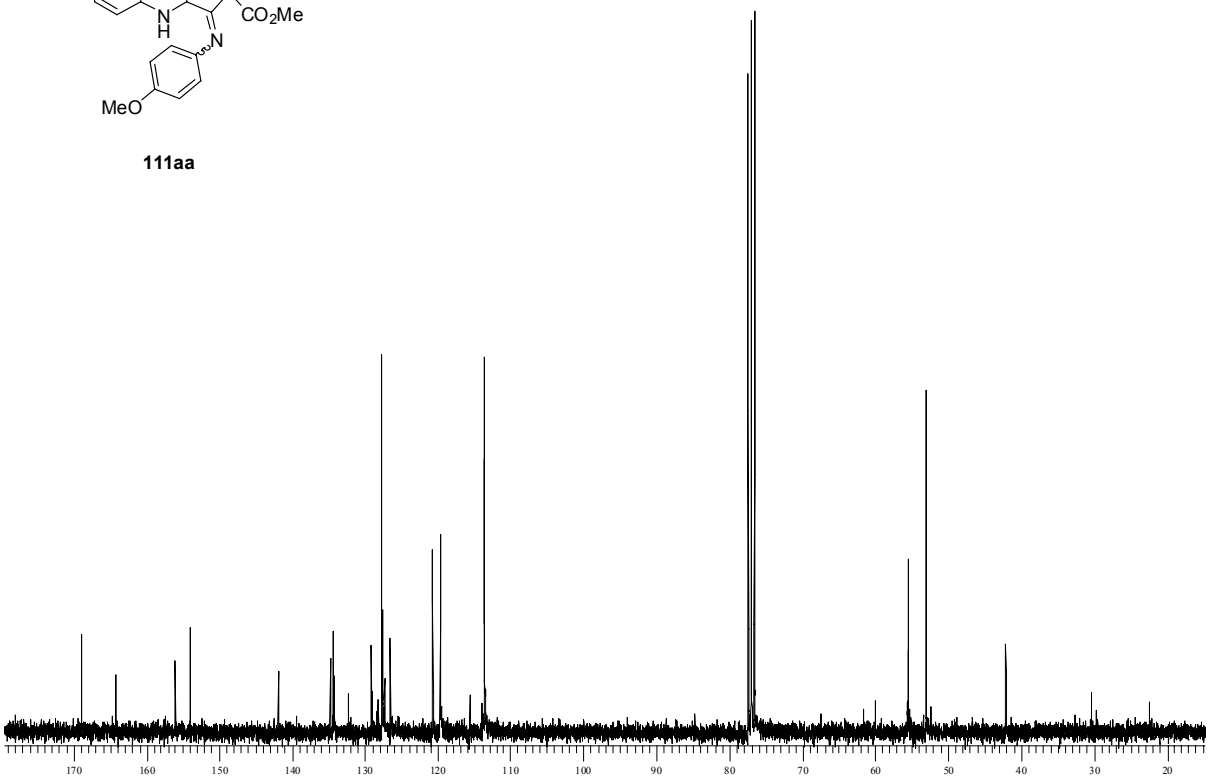
Ph
CO2Me
CO2Me
N
H
N
MeO

111aa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160
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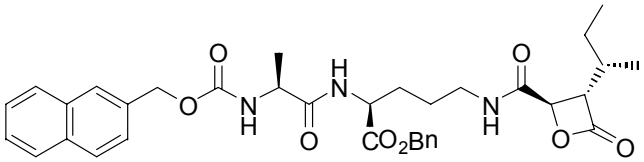
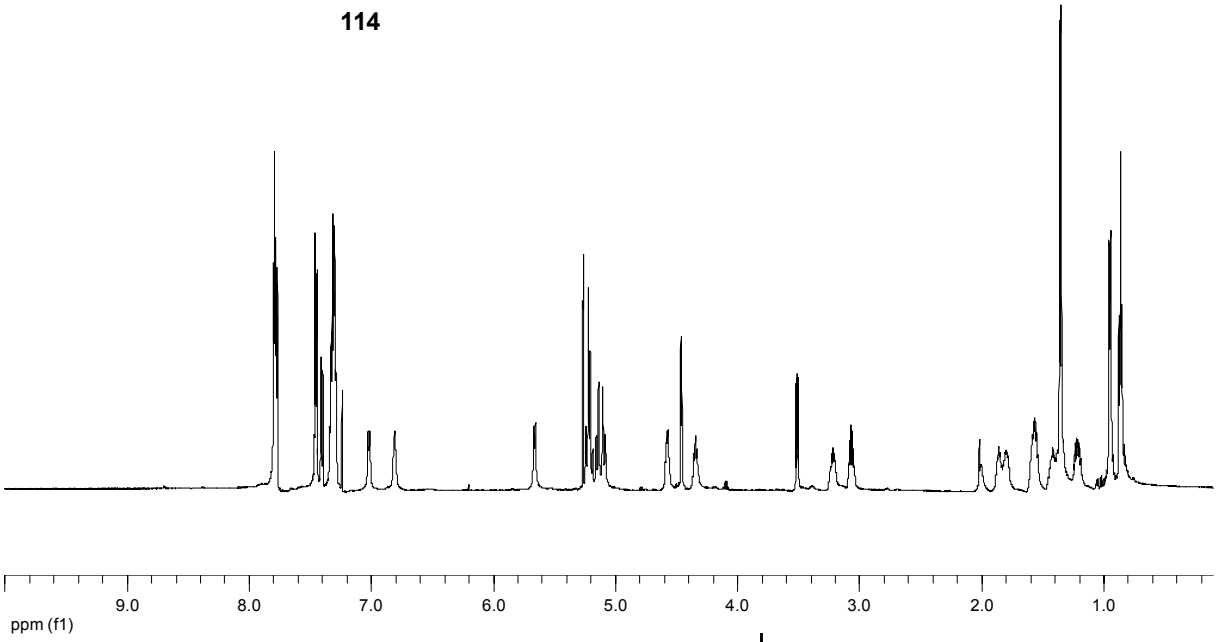
110
100
90
80
70
60
50
40
30
20


O
O
H
N
N
O
O
N
H
H
O
CO2Bn
O
O

114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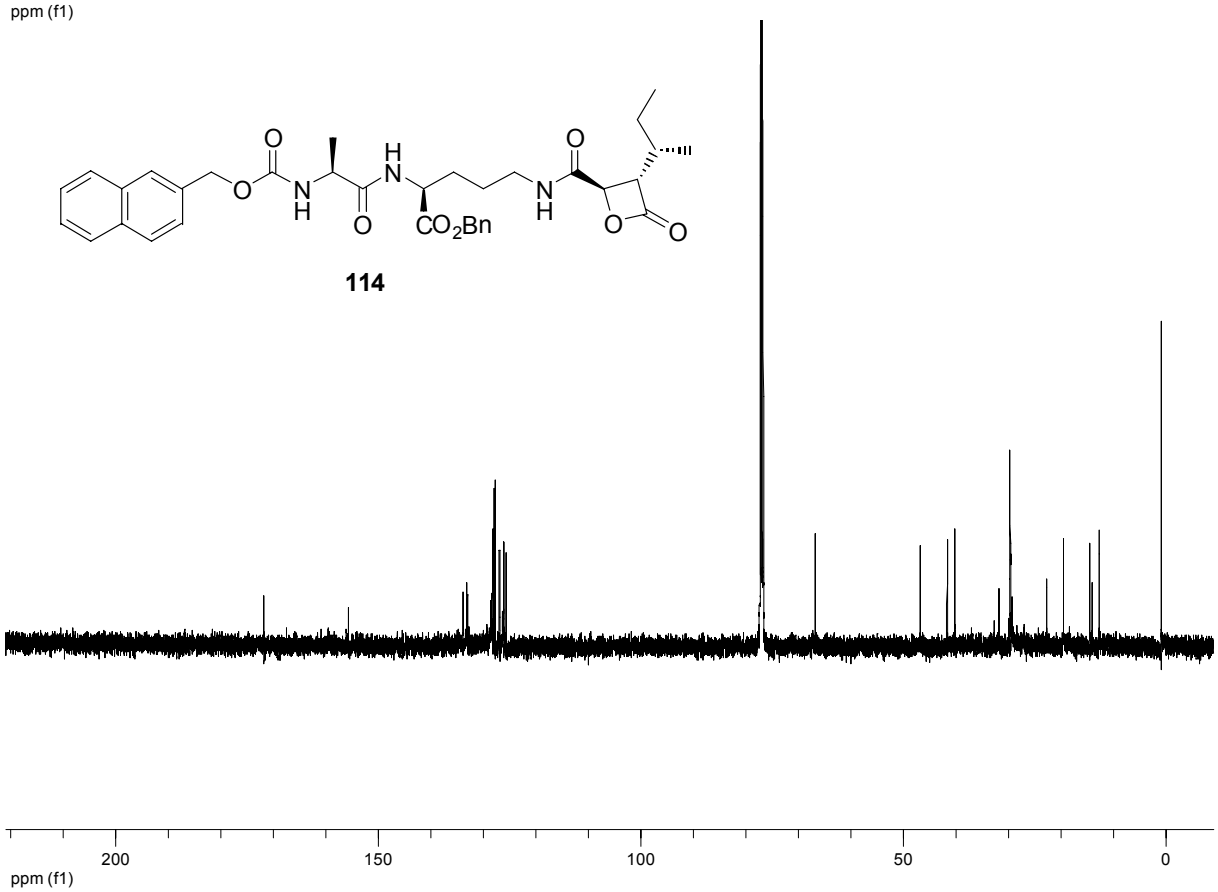
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)

O
O
H
N
N
O
O
N
H
H
O
CO2Bn
O
O

114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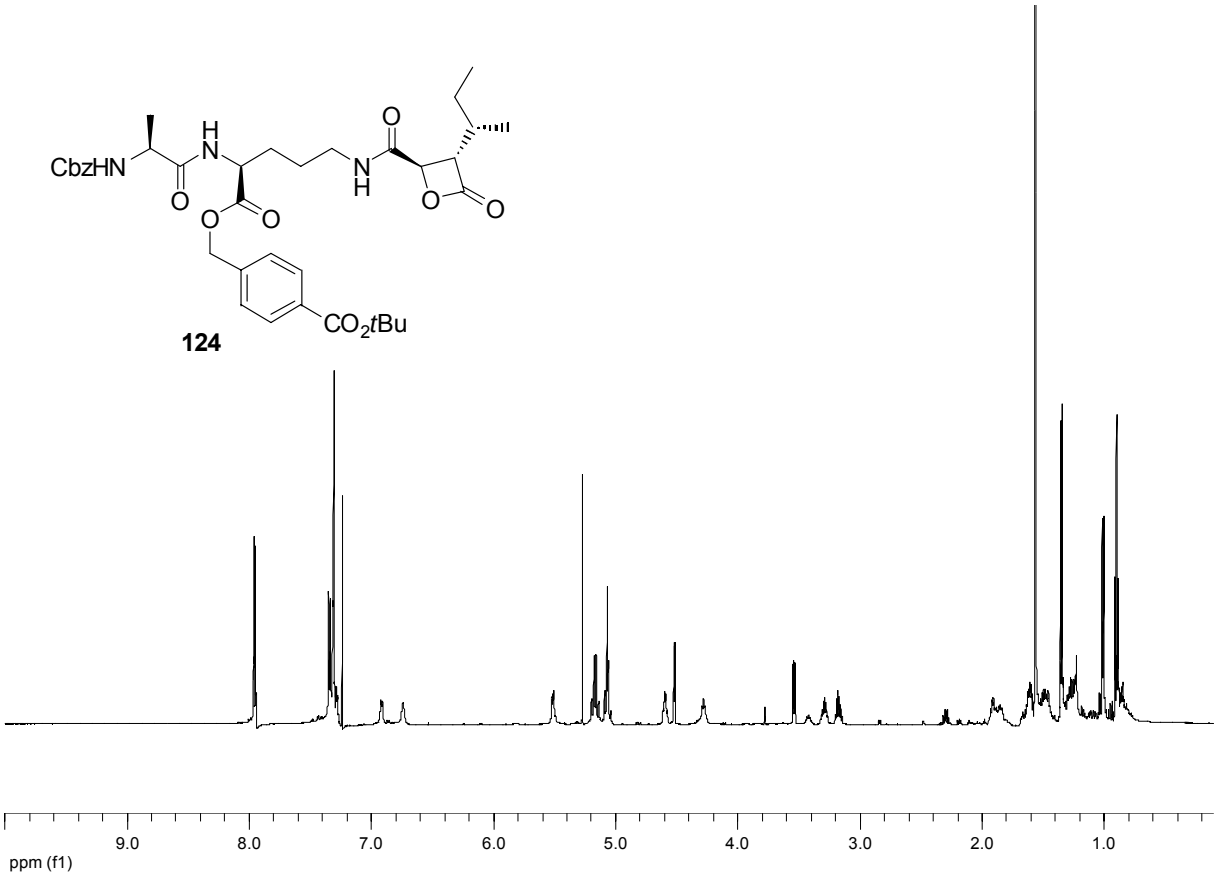
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N
O
O
O
O
N
H
O
O
O
CO2tBu
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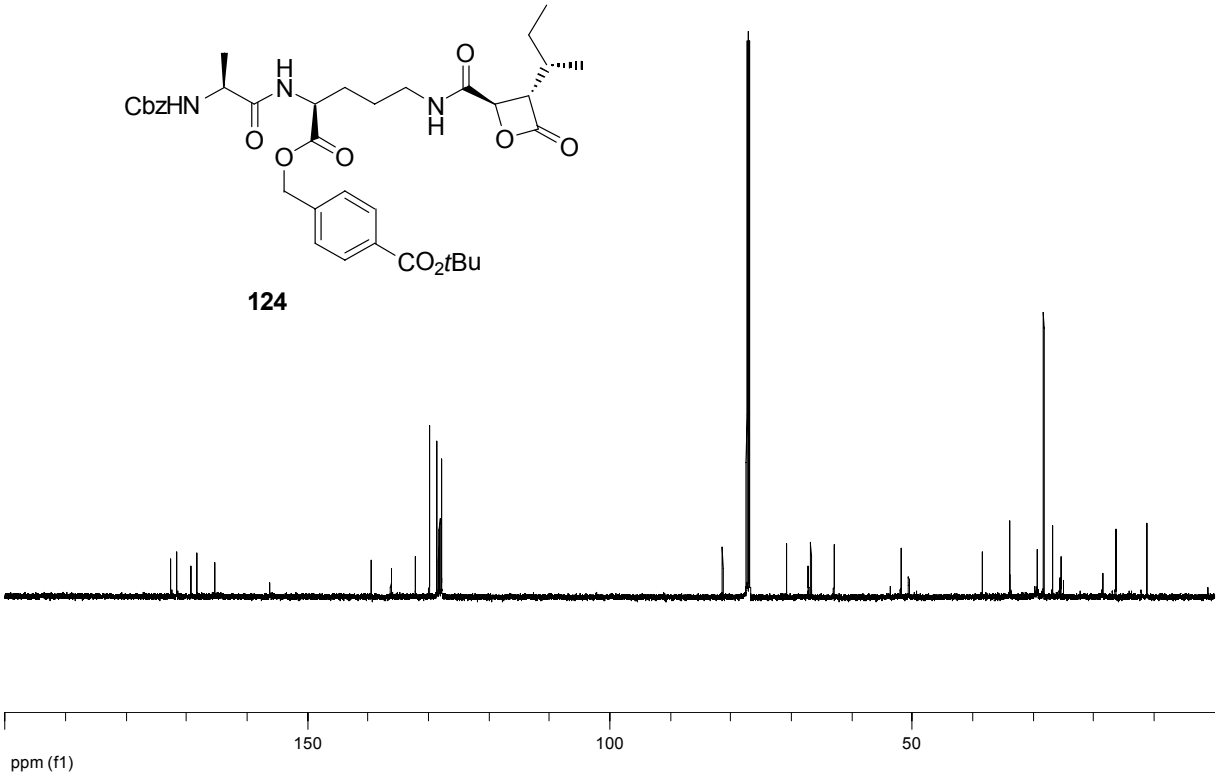
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)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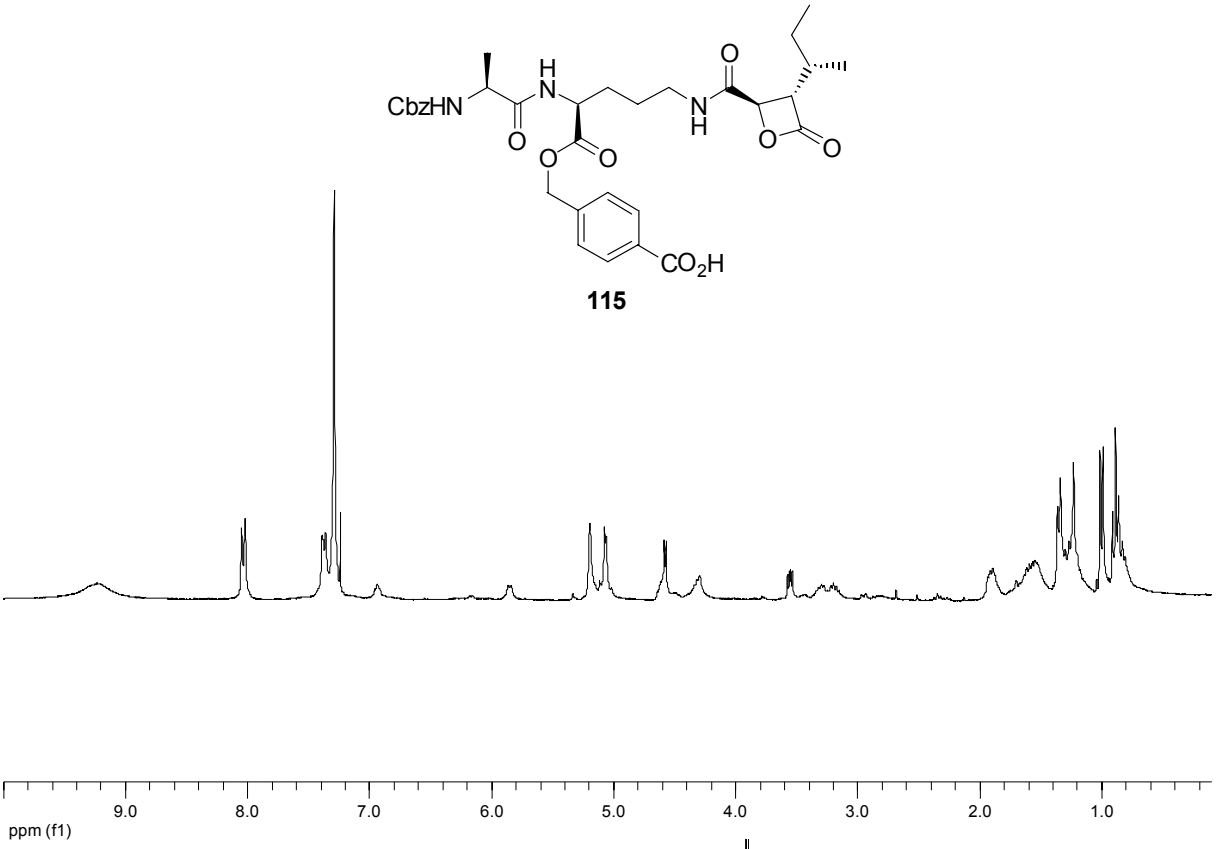
N
O
O
O
O
N
H
O
O
O
CO2tBu
124
150
100
50
ppm (f1)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H
N
O
O
O
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N
H
O
O
O
CO2H
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6.0
5.0
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3.0
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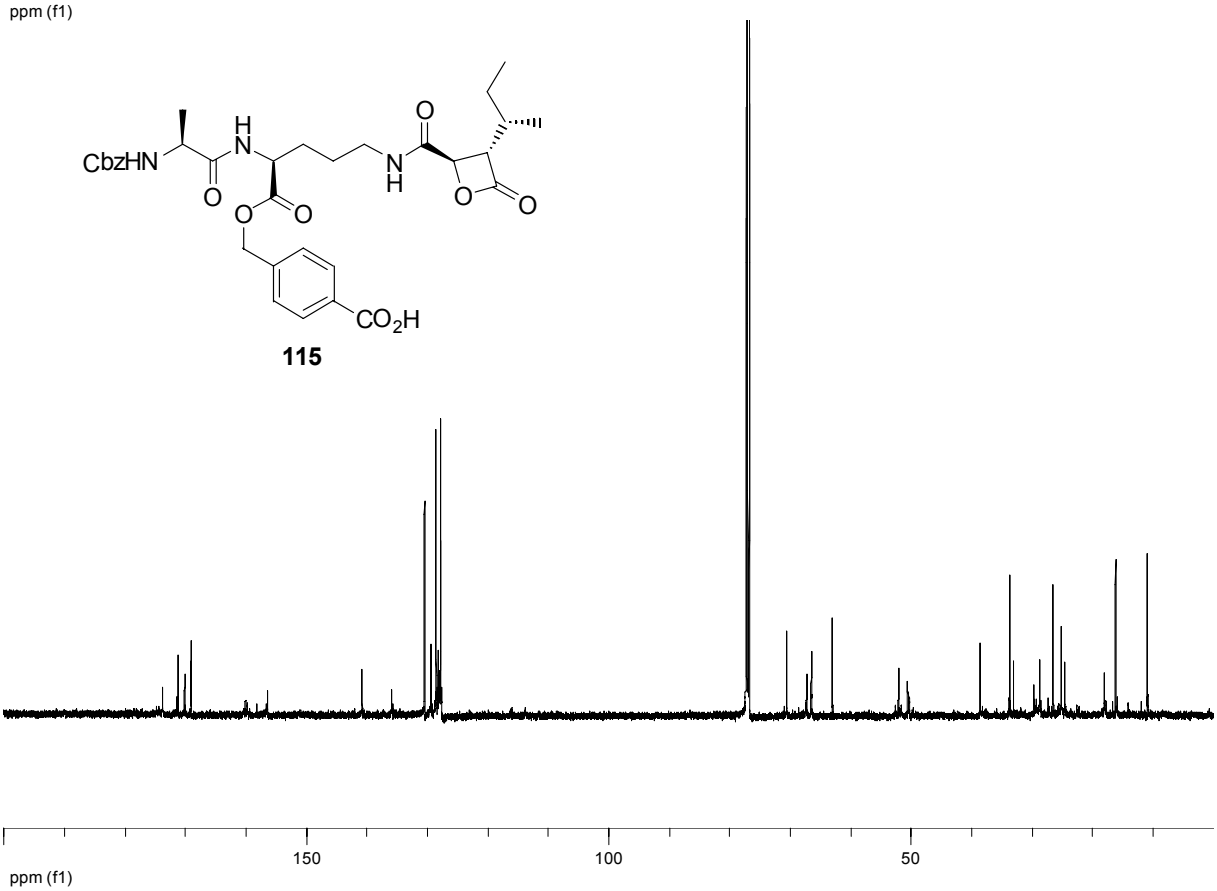
1.0
ppm (f1)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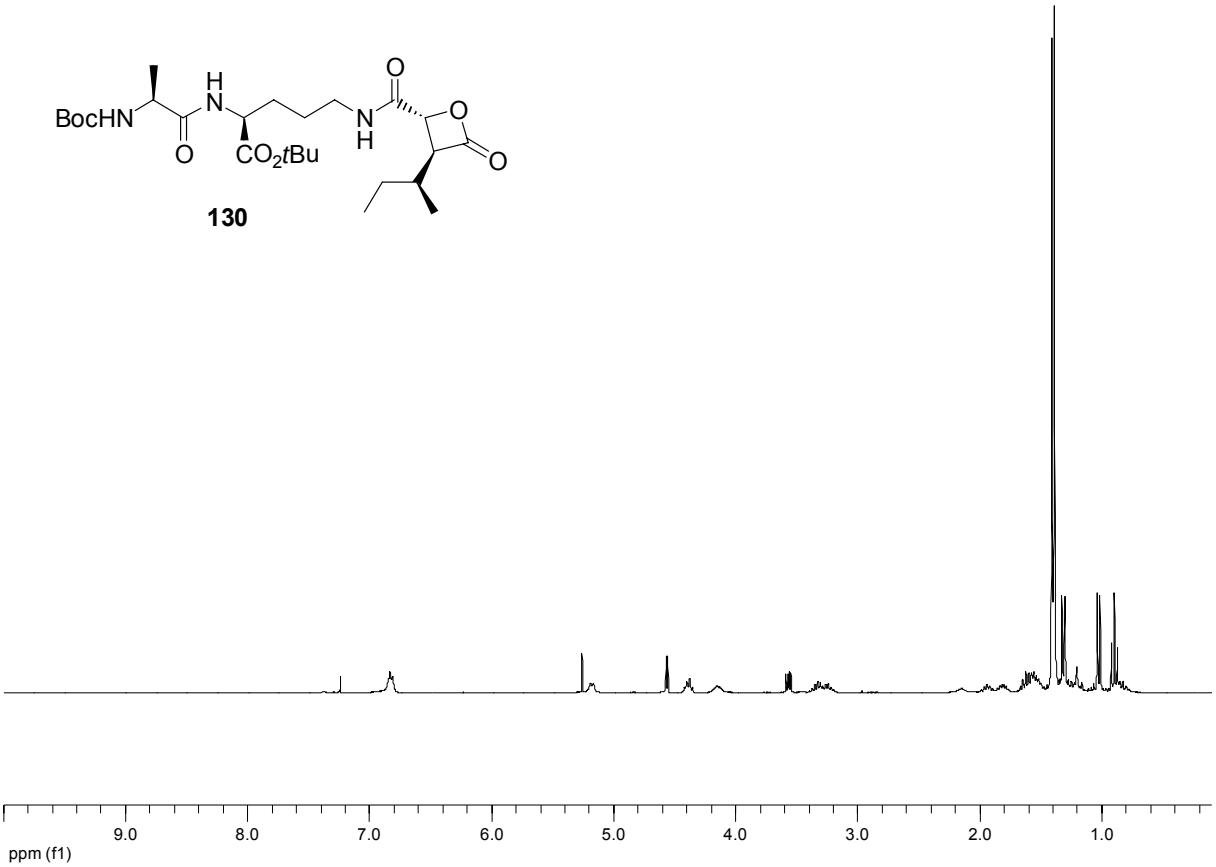
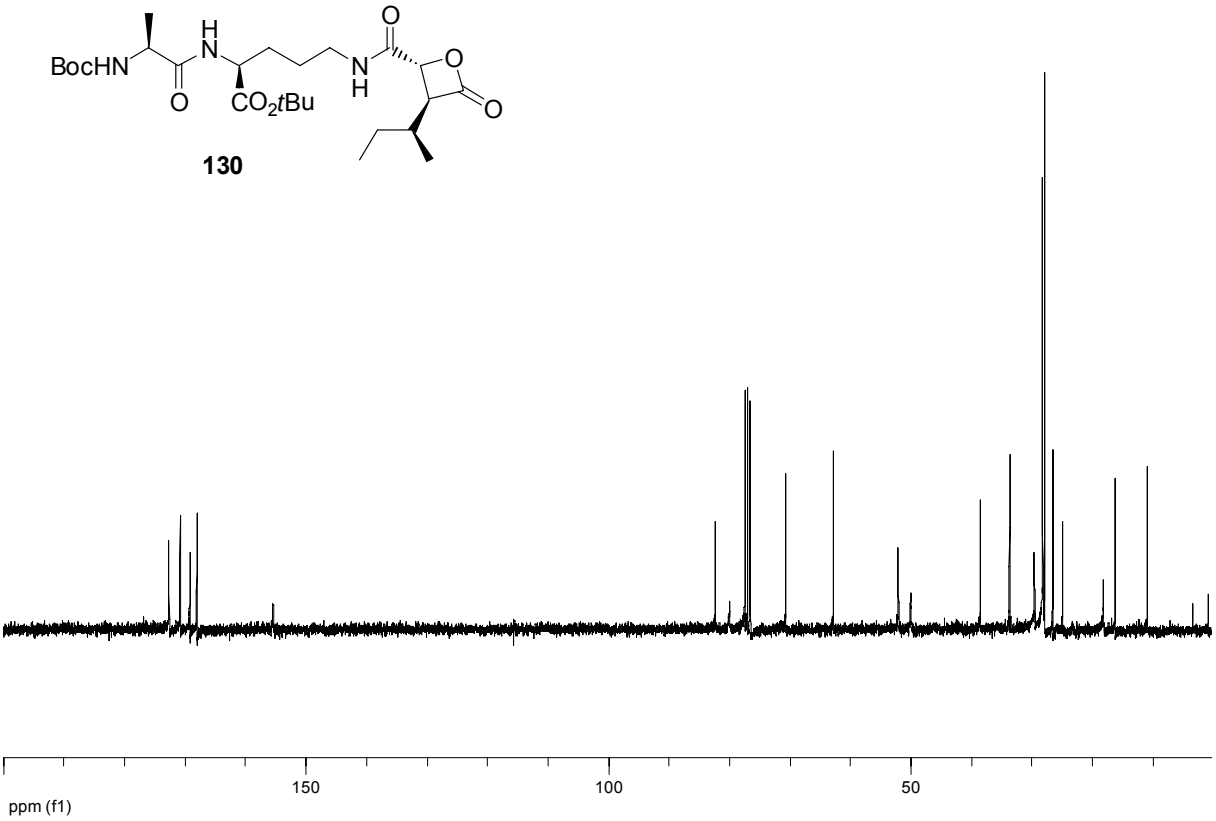
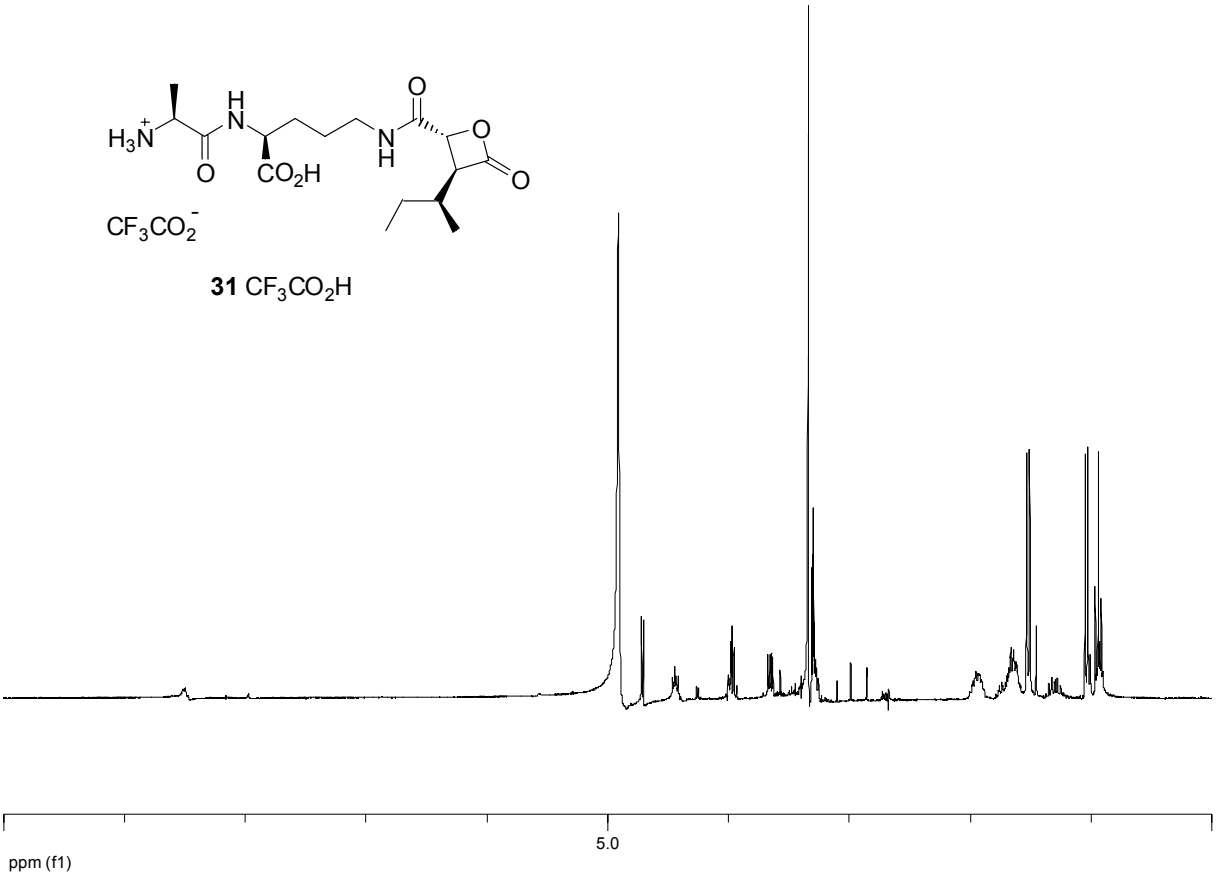
N
O
O
O
O
N
H
O
O
O
CO2H
115
150
100
50
ppm (f1)


BocHN
H
N
O
CO2tBu
N
H
O
O
O
130
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


BocHN
H
N
O
CO2tBu
N
H
O
O
O
130
150
100
50
ppm (f1)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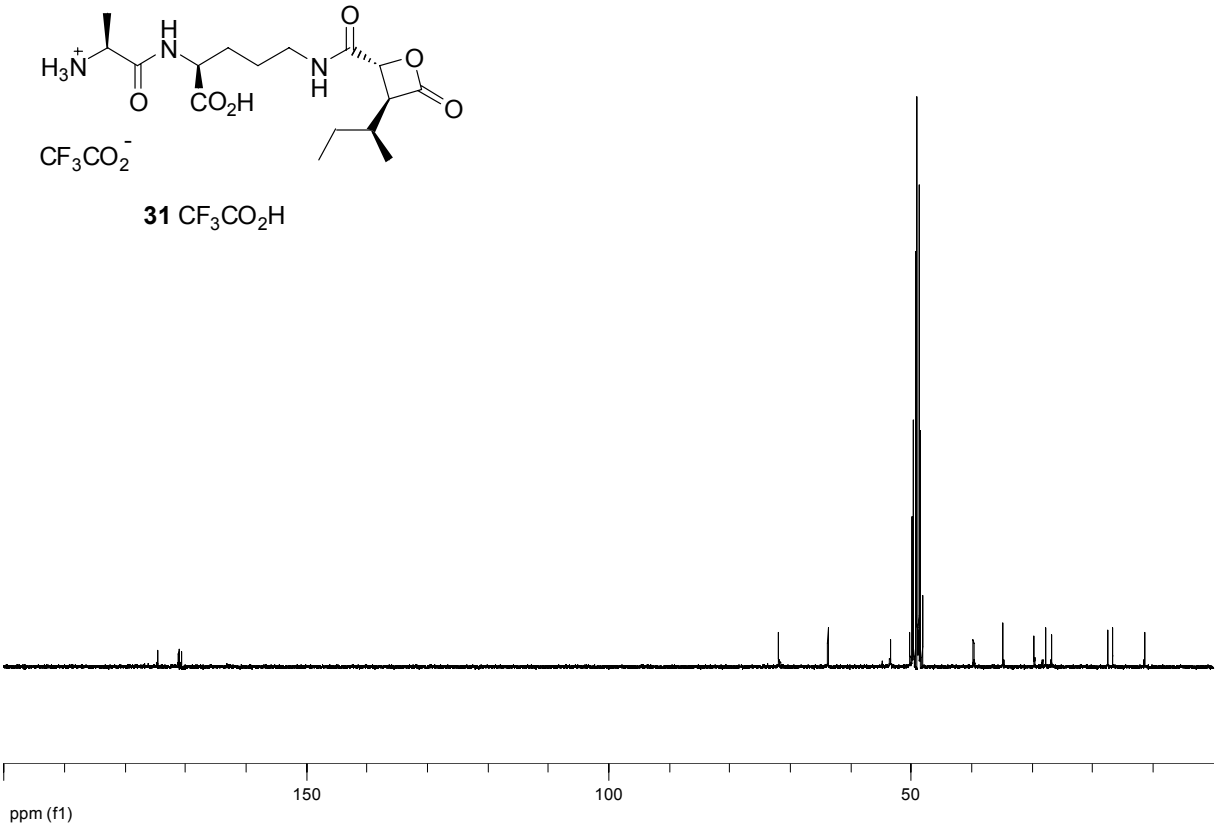
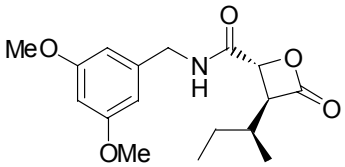
H
N
O
CO2H
N
H
O
O
O
CF3CO2-
31 CF3CO2H
5.0
ppm (f1)


H3N+
H
N
O
CO2H
N
H
O
O
O
CF3CO2-
31 CF3CO2H
150
100
50
ppm (f1)



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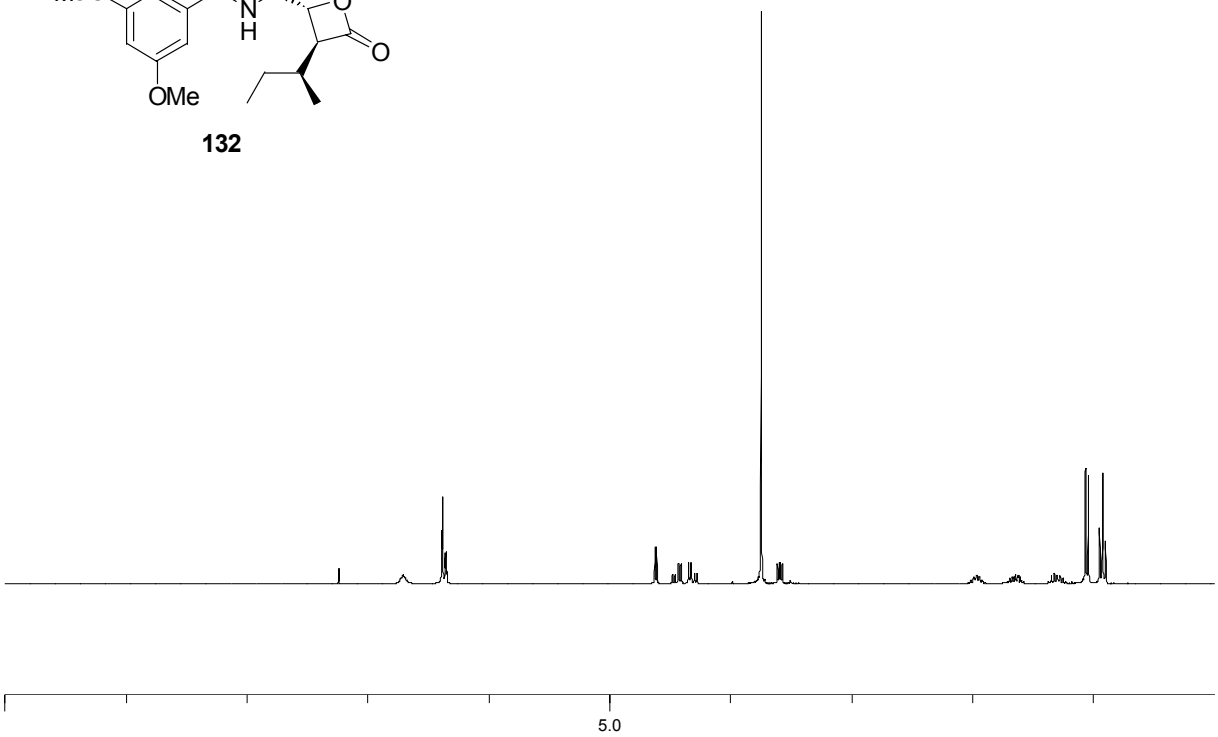

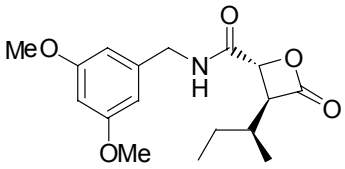

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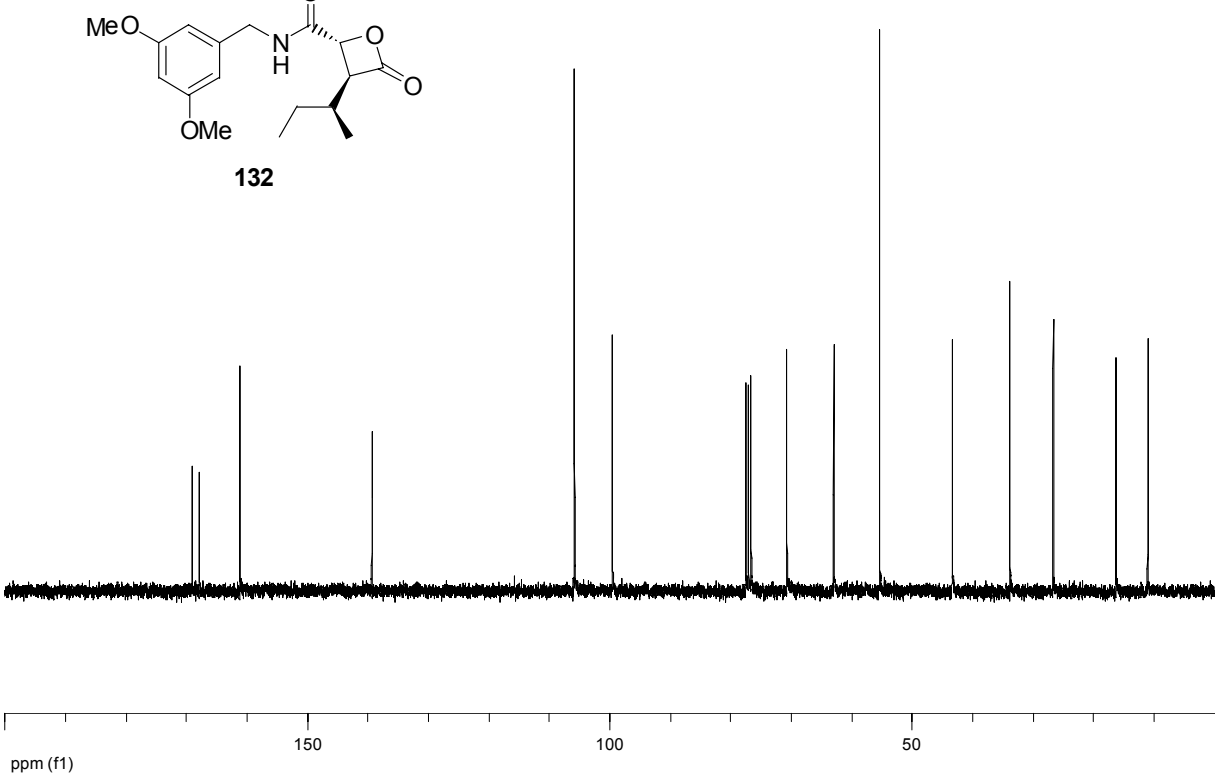

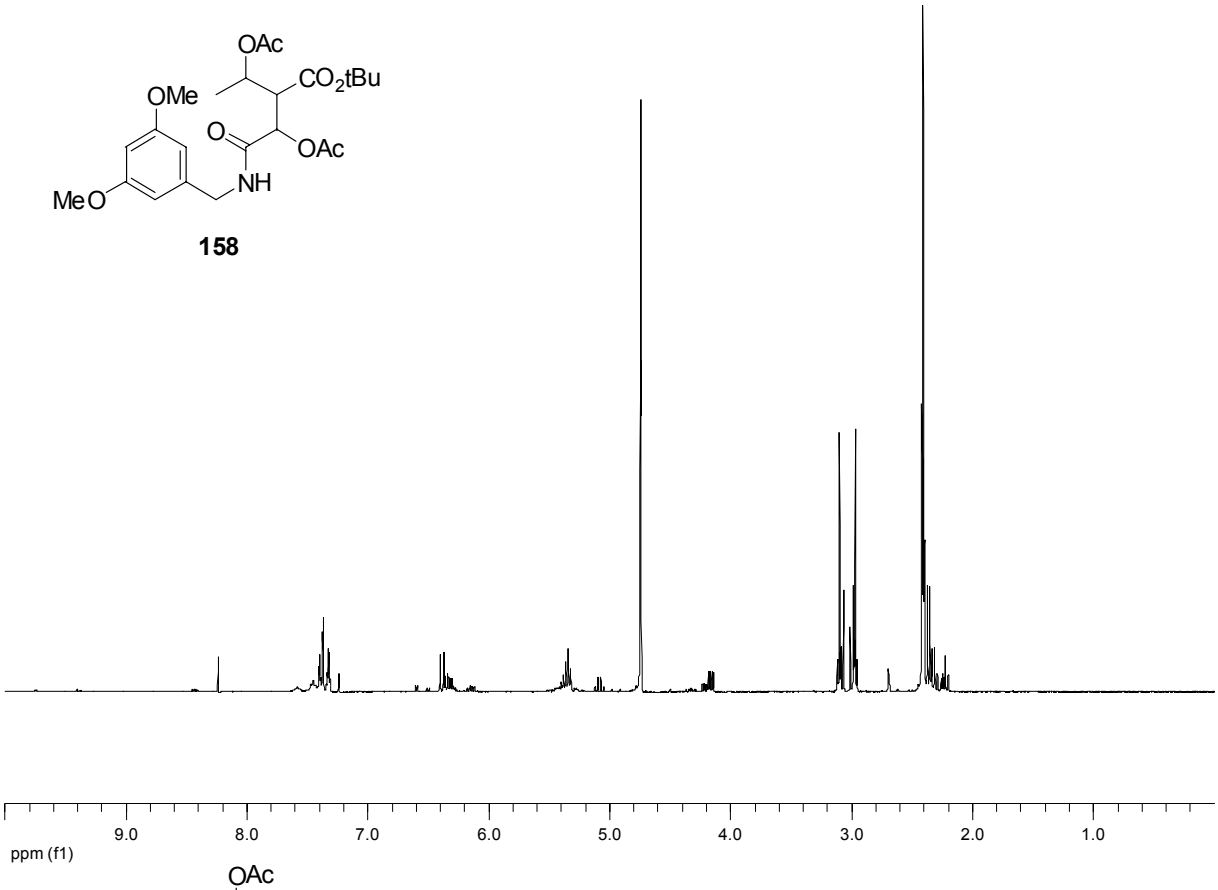
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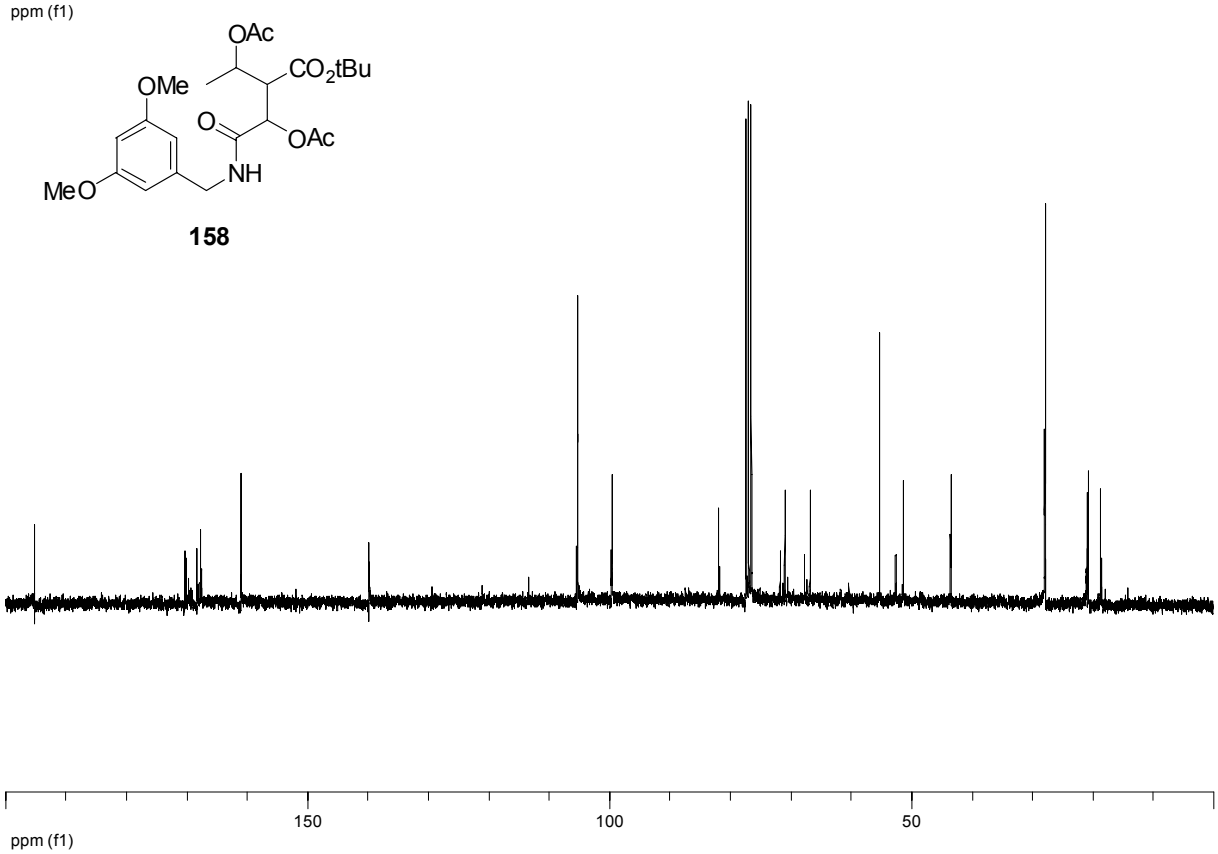
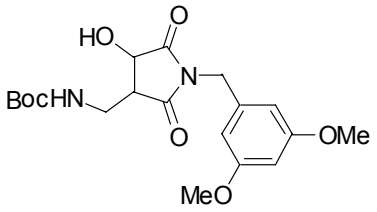
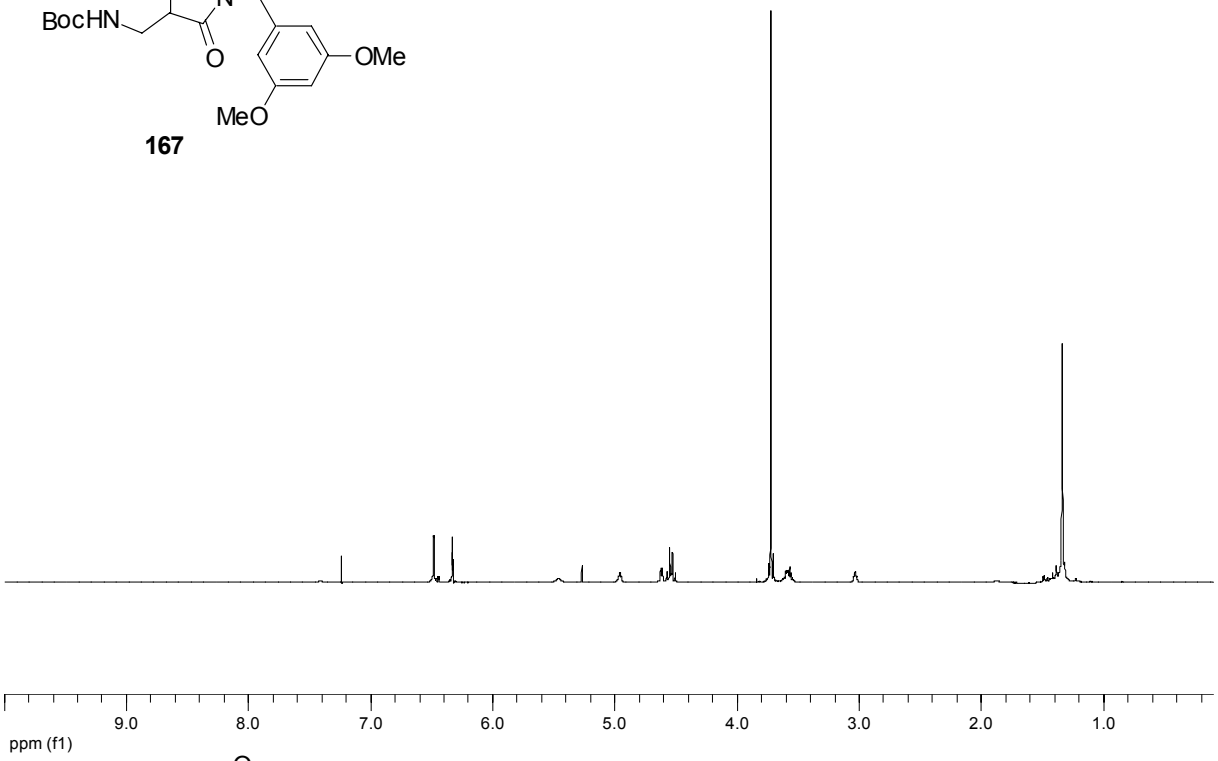
CO2tBu
OMe
O
OAc
NH
MeO
158
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (f1)


OAc
CO2tBu
OMe
O
OAc
NH
MeO
158
150
100
50
ppm (f1)


HO
O
N
BocHN
O
OMe
MeO

167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5.0
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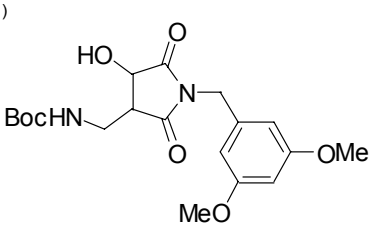
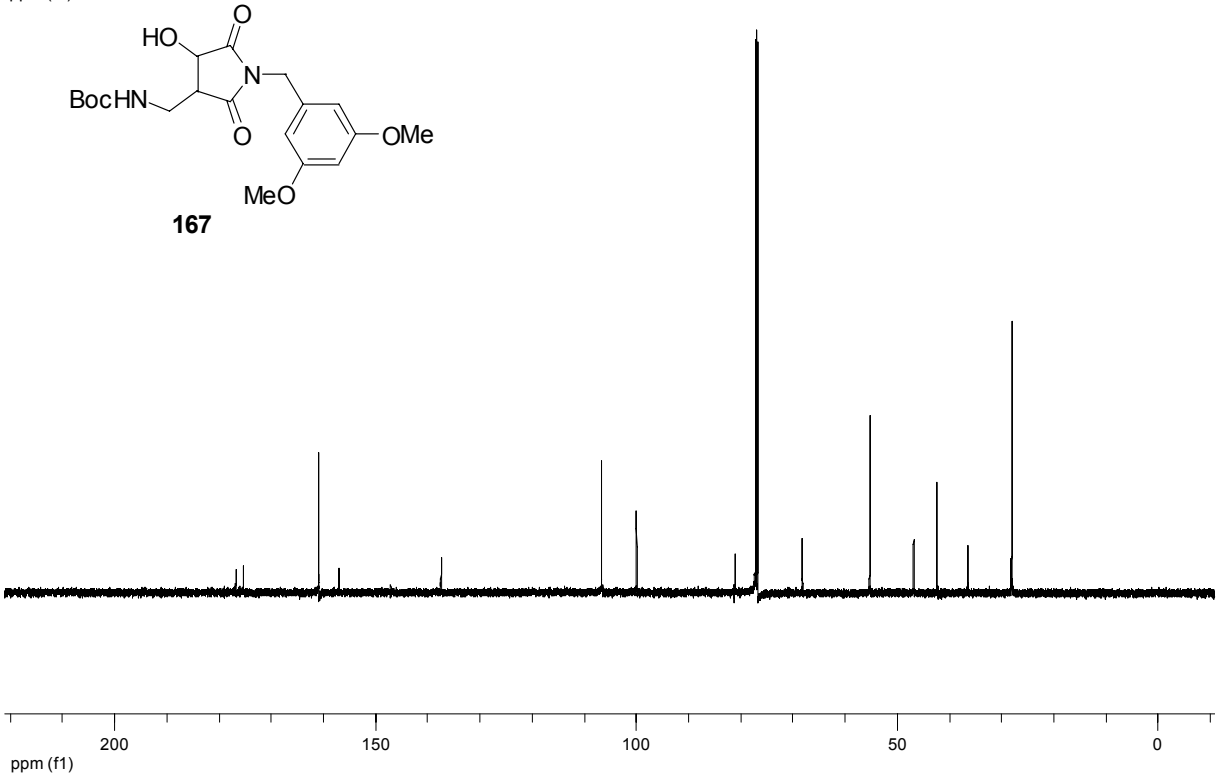
3.0
2.0
1.0
ppm (f1)

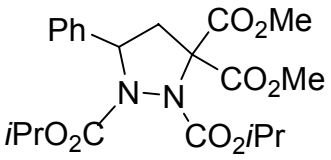

HO
O
N
BocHN
O
OMe
MeO

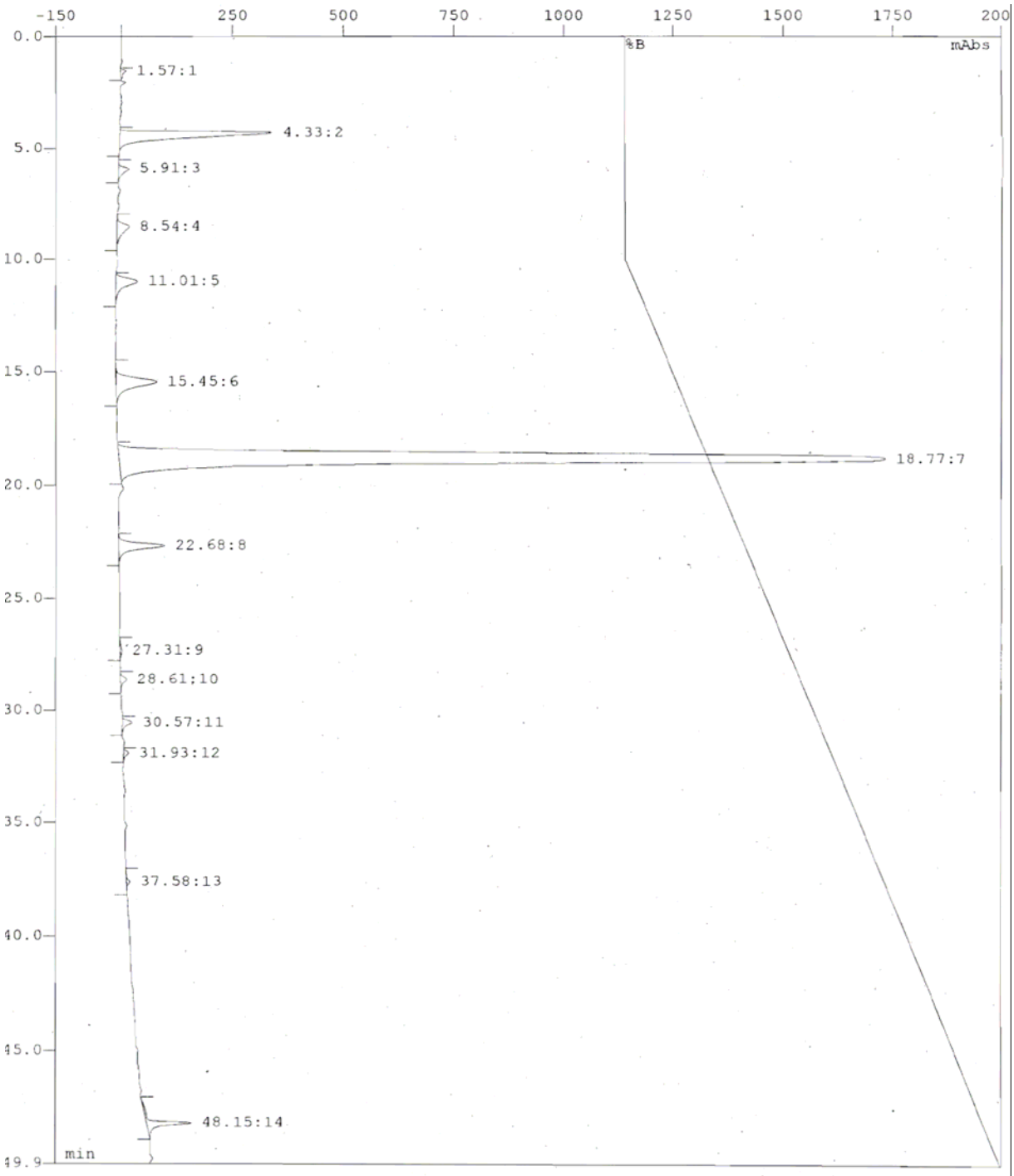
167


200
150
100
50
0
ppm (f1)

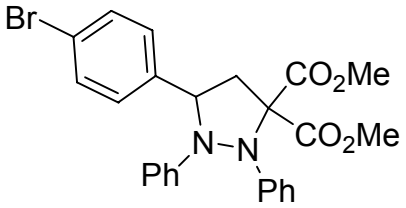
Copies of the HPLC Chtomatograms

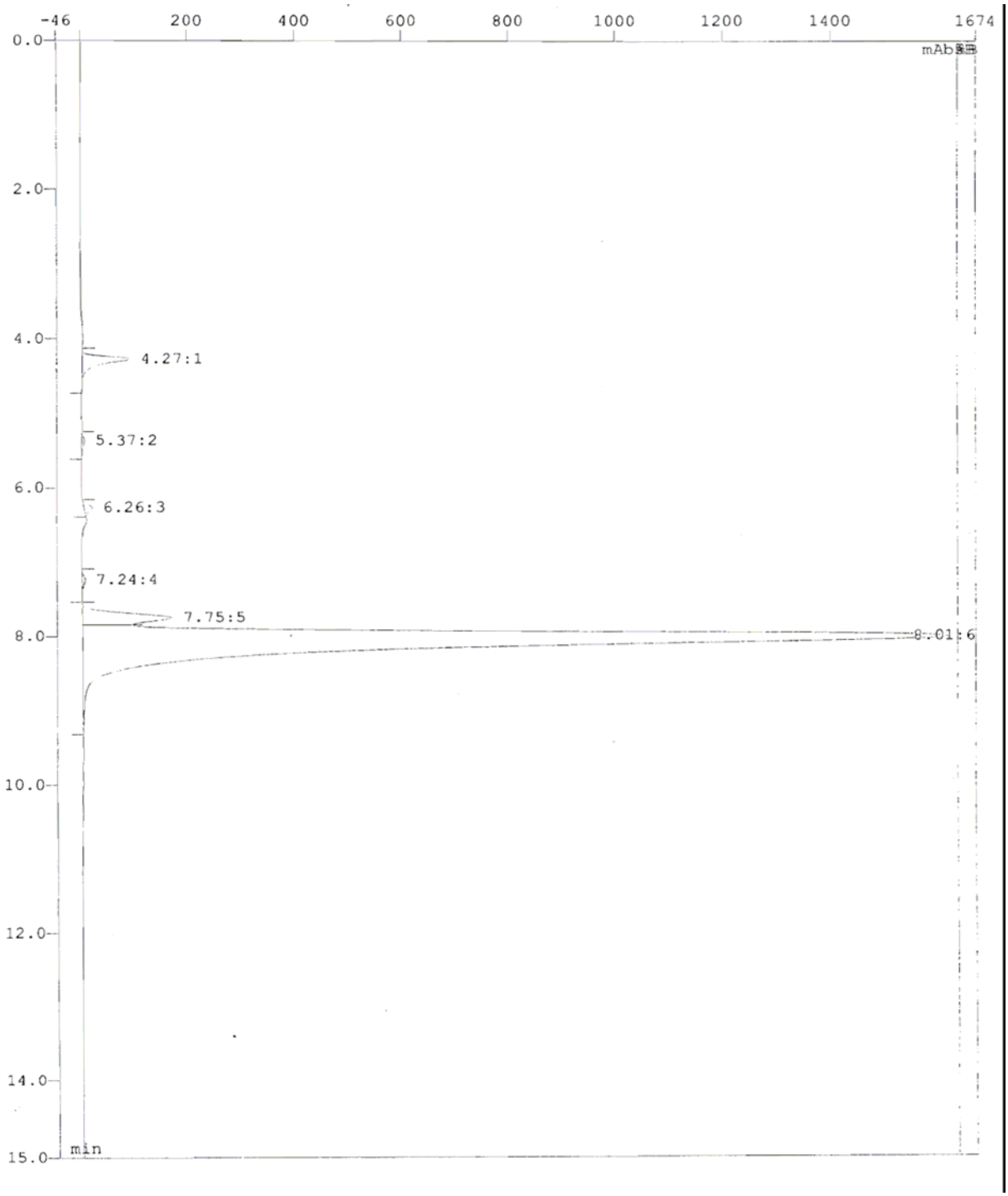
Copy of HPLC chromatogram for compound ***101aa***



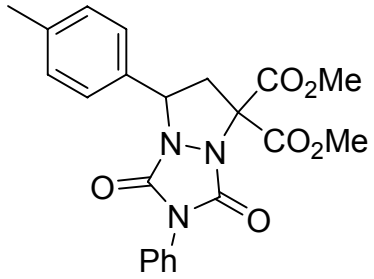


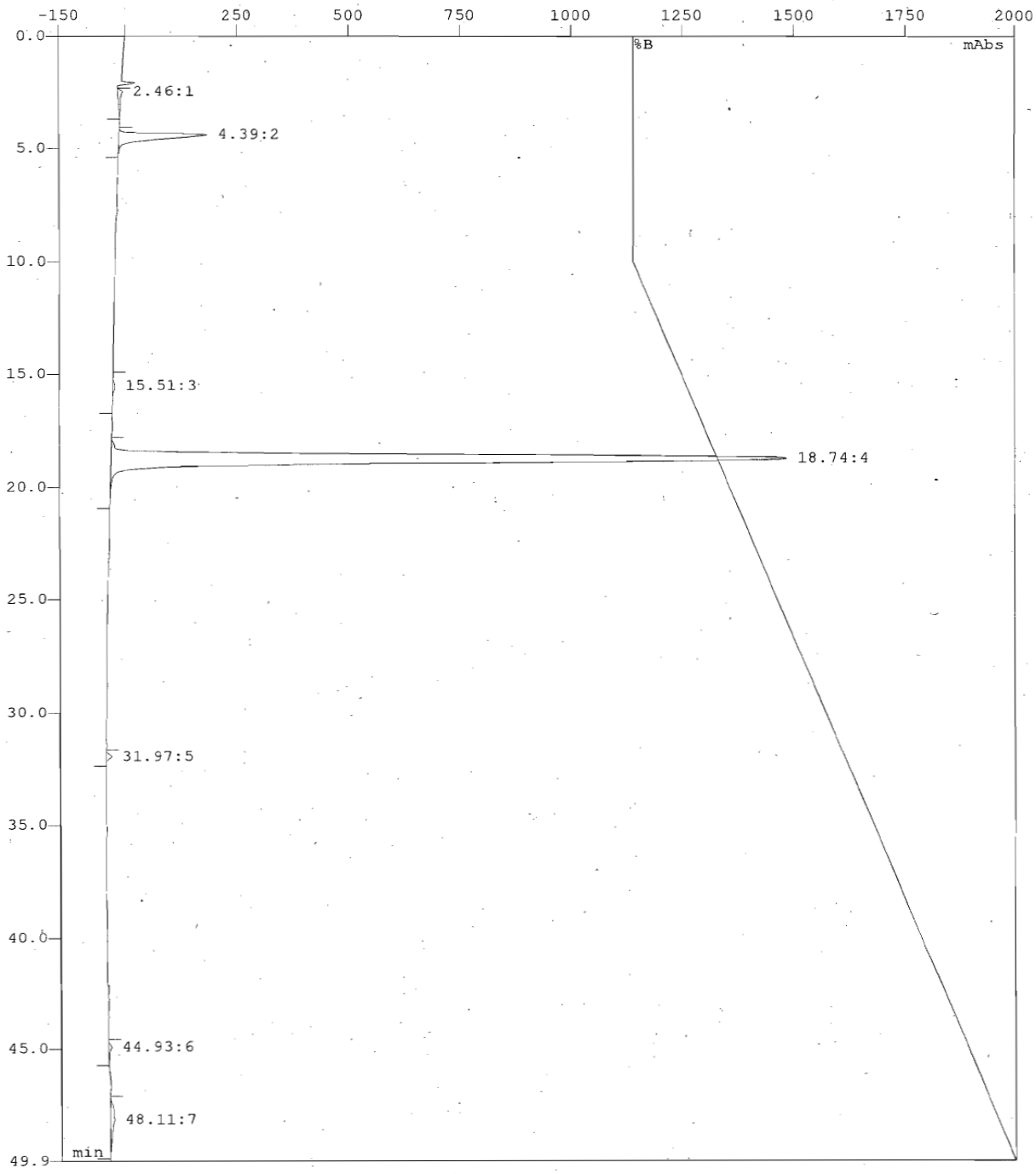
Copy of HPLC chromatogram for compound ***101cc***



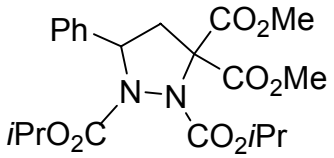


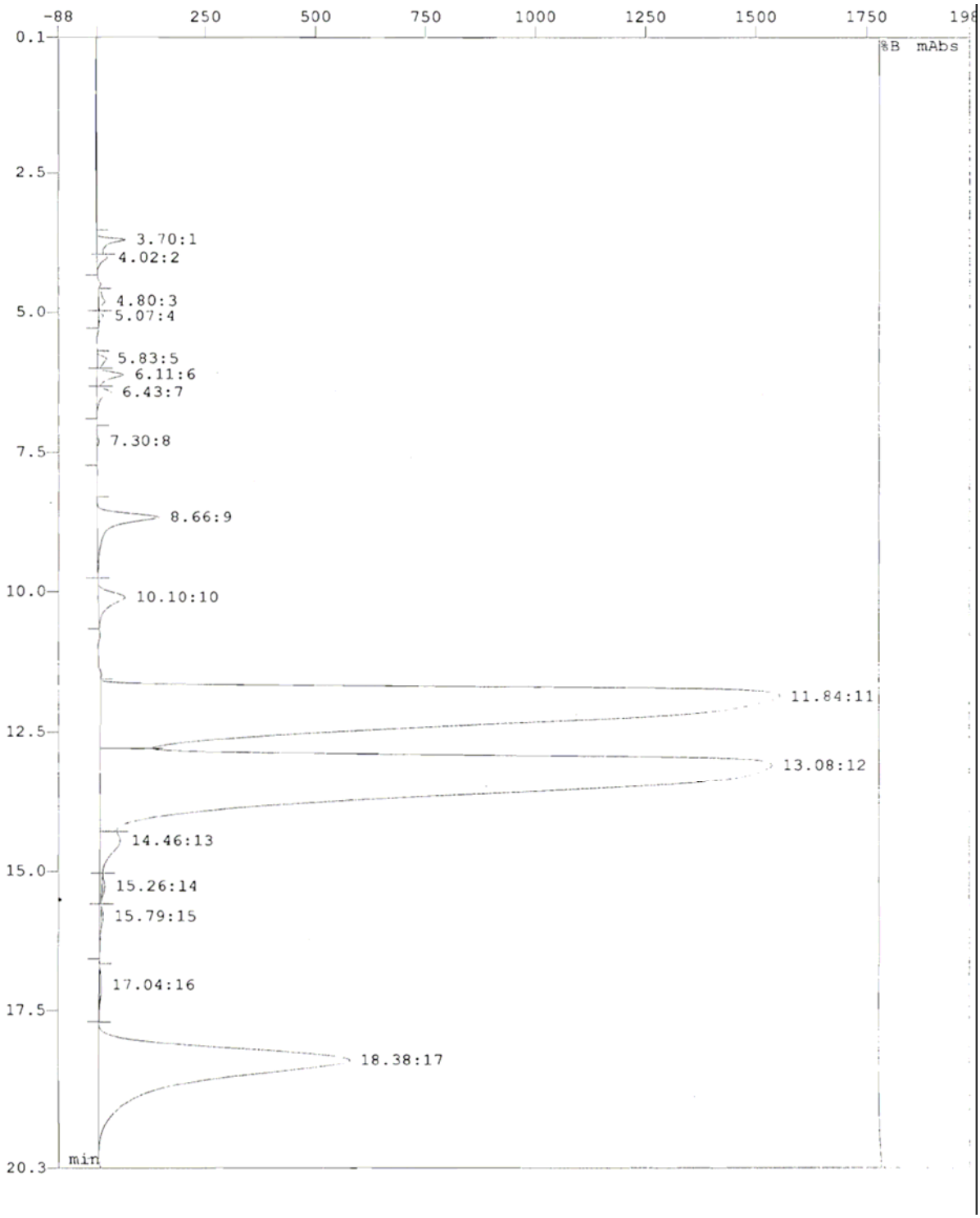
Copy of HPLC chromatogram for compound ***101bd***



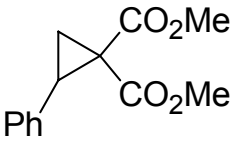


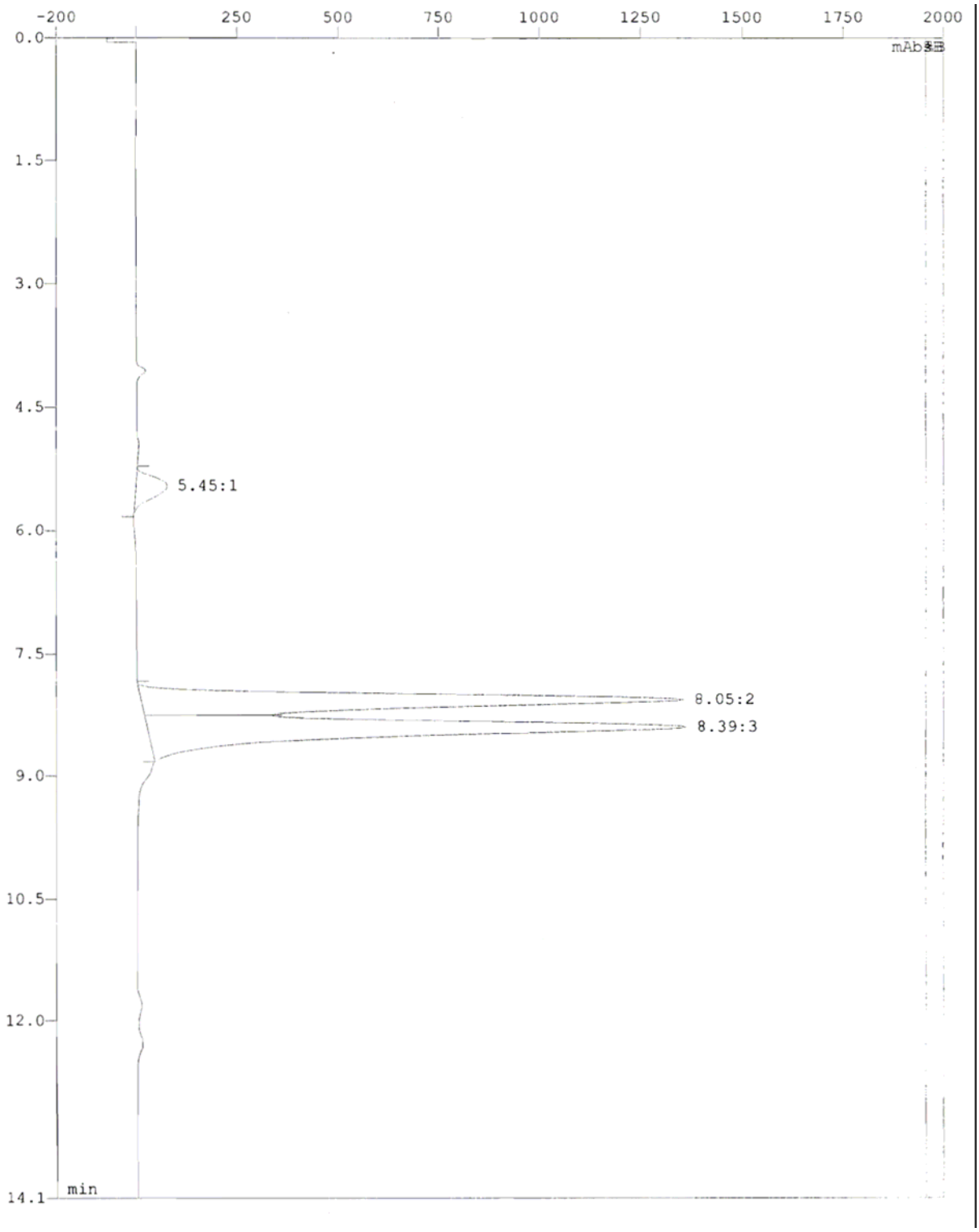
*Copy of HPLC chromatogram for compound rac-**101aa** on the chiral-phase column*



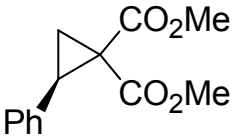


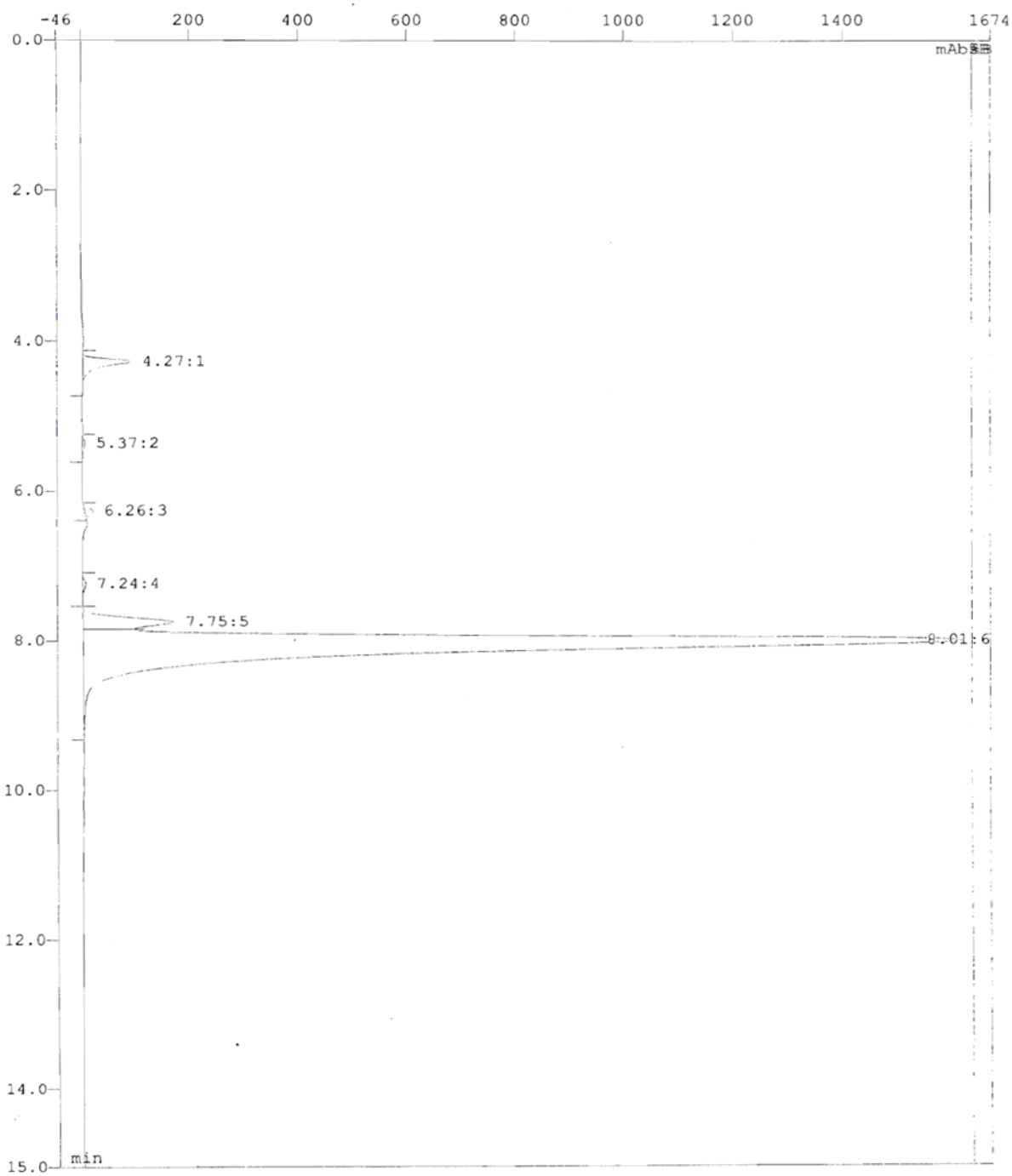
*Copy of HPLC chromatogram for compound rac-**17a** on the chiral-phase column*





*Copy of HPLC chromatogram for compound (R)-**17a** on the chiral-phase column*





Crystallographic Data

The X-Ray CIF files for the structures **101bd** and **102bd** have been deposited at the Cambridge Crystallographic Data Center (CCDC): deposition numbers CCDC 637274 and 637275. Copies of the data can be obtained, free of charge, from CCDC, 12 Union Road , Cambridge, CB2 1EZ UK (e-mail: deposit@ccdc.cam.ac.uk; Internet: //www.ccdc.cam.ac.uk).

Acknowledgement

I would like to thank Professor Dr. A. de Meijere for giving me an opportunity to work in his brilliant group, for his help and support during this difficult period of the work on my PhD thesis. I am grateful also for opening me new perspectives in my life and career.

My thanks are also due to Dr. V. Belov for his help in and outside the laboratory. I would like to thank Dr. S. Kozhushkov for his support.

My thanks go to Prof. Dr. M. Groll for the cooperation, interesting discussions and introduction into the biochemical and medicinal applications of organic chemistry.

I am also very grateful to my nice colleagues for the wonderful working atmosphere: Michael, Oleg, Sergey, Karsten, Marco, Irina, Ligang, Tine, Vitaly, Shamil, Hans, Alexander, André, Mario, Daniel, Andrey, Aydin, Stefan, Heiko and Alessandra.

I am indebted to Prof. Dr. A. de Meijere and Degussa Foundation (Prof. Dr. W. Leuchtenberger, Mrs. K. Schipporeit and Mrs. I. Gudelj) for the financial support of my studies.

I also thank Dr. M. Es-Sayed for the fruitful and interesting discussions.

I am very thankful to Prof. Dr. L. F. Tietze for co-refereeing this thesis.

I am very grateful to Mr. Machinek and his entire group for the fast and precise NMR measurements and discussions of complicated NMR problems, to Dr. H. Frauendorf and Mrs. G. Udvarnoki, to Mr. F. Hambloch for the elemental analysis, to Mrs. E. Pfeil for the measurements of optical rotations, to Stefan and Heiko for their help with the computers.

I am very thankful to Anja Hofmeister for the X-ray analysis of my compounds.

I appreciate the assistance and help of Mrs. G. Keil-Knepel in many organization issues.

I thank Oleg for his advises, discussions and co-working on the publications.

My thanks also go to Michael and his family for inviting me to Zürich.

I am very thankful to Dr. A. P. Molchanov for his support and patience.

I am very grateful to Alexander and Vitaly for the careful proofreading of this manuscript.

I thank the whole team of the 'BASF Summercourse 2006' for their organization of my stay in Mannheim, interesting lectures and for the introduction into the world of chemical industry.

I am very grateful to Hans, Tine, Nadja and Sonja for the corrections of my German in the documents.
My thanks go to Karsten for his supporting of my interest in correct German language and for the common interest in classical and rock music.
I am grateful to Dr. V. Sokolov for the brilliant chess games he played here.
I thank Oleg and Sergey for our common car trips.
I am also very grateful to Oleg, Sergey, Tine, Michael, Mario, Ligang, Tanja, Sonja, Nadja, Sveta, Denis, Vitaly, Lena, Dina, Olya, Irina, Sergey, and Katja for the support, friendship and making my life in Göttingen better.

Thank you all!

Lebenslauf

Ich wurde am 07. September 1982 als Sohn des Chemikers Sergey Korotkov und seiner Ehefrau, der Ingenieurin Tatiana Korotkova geb. Vinogradova, in Leningrad (USSR) geboren.

Von September 1989 bis Juli 1995 besuchte ich die Grund- und Mittelschule N 138, und von September 1995 bis Juli 1999 besuchte ich das Physiko-Mathematische Lyzeum N 239 in Sankt-Petersburg, an dem ich im Juni 1999 das Abitur mit der Silbermedaille ablegte. Während der Schulzeit nahm ich in den Jahren 1998 und 1999 an den Chemischen Allunions-Schülerolympiaden teil.

Im Herbstsemester 1999 begann ich das Studium der Chemie an der Staatlichen Universität Sankt-Petersburg, Russland. Meine Freizeit verbrachte ich als freiwilliger wissenschaftlicher Mitarbeiter in der Gruppe von Prof. Dr. R. R. Kostikov. Im Herbstsemester 2003 erhielt ich ein Stipendium von Prof. Dr. Armin de Meijere.

Zum Juni 2004 fertigte ich unter der wissenschaftlichen Anleitung von Dr. A. P. Molchanov meine Diplomarbeit zu dem Thema "Reaktionen von spirocyclischen 1-Pyrazolinen und 2-Pyrazolin-3-carbonsäureestern mit halogenierenden Reagenzien" an.

Am 22. Juni 2004 bestand ich meine Diplomprüfung vor der Staatlichen Prüfungskommission, wobei mir die Qualifizierung des Diplom-Chemikers "mit Auszeichnung" zuerkannt wurde.

Seit Oktober 2004 arbeite ich an meine Dissertation unter wissenschaftlicher Anleitung von Prof. Dr. Armin de Meijere. Von April 2005 bis März 2006 wurde ich mit der Betreuung von Studenten im Organisch-chemischen Grundpraktikum und der Betreuung der Übungen und Klausuren zur Vorlesung „Experimentalchemie II: Organische Chemie" betraut.

Im Winter 2006 erhielt ich ein Stipendium der Degussa-Stiftung.

Von 28. August bis 09. September 2006 nahm ich im BASF-Sommerkurs teil.

Meine Sprachkenntnisse sind: Englisch – gut, Deutsch – gut.

List of Publications

Publications

9. M. Limbach, A. Janssen, V. S. Korotkov, C. Funke, A. de Meijere, *Eur. J. Org. Chem*, **2008**, "An Easy Access to β-Aminocyclobutenecarboxylates and Their Incoperation into Small Peptides"; in preparation

8. M. Groll, V. S. Korotkov, O. V. Larionov, A. V. Lygin, A. de Meijere, *J. Am. Chem. Soc.*, **2008**, in preparation. "Structural Characterization of the 20 S Proteasome from Saccharomyces Cerevisiae Cocrystallized with Some New Belactosin C Congeners".

7. V. Chaplinski, H. Winsel, M. Kordes, B. Stecker, Oleg V. Larionov, Vadim S. Korotkov, Sergei I. Kozhushkov, Andrey I. Savchenko, A. de Meijere, *Chem. Eur. J.* **2008***,* in preparation. "Versatile Preparation of Cyclopropylamines from Carboxamides – A Replete Experimental Account".

6. M. Limbach, V. S. Korotkov, M. Es-Sayed, A. de Meijere, *Org. Biomol. Chem.* **2008**, in press. "High Yielding Selective Accesses to Spirocyclopropanated 4-Oxopiperazinecarboxylates and 1,4-Diazepane-2,5-diones from Methyl 2-Chloro-2-cyclopropylideneacetate".

5. V. S. Korotkov, O. V. Larionov, A. Hofmeister, J. Magull, A. de Meijere, *J. Org. Chem.* **2007**, *72*, 7504–7510. "$GaCl_3$-Catalyzed Insertion of Diazene Derivatives into the Cyclopropane Ring"

4. V. S. Korotkov, O. V. Larionov, A. de Meijere, *Synthesis,* **2006**, *21,* 3542–3546. „The $Ln(OTf)_3$ – Catalyzed Insertion of Aryl Isocyanides into the Cyclopropane Ring"

3. A. P. Molchanov, V. S. Korotkov, R. R. Kostikov, *Russ. J. Org. Chem.* **2006**,

42, 1146–1150. “Reactions of Substituted Spiro[1,2,3,4-tetrahydronaphthalene-2,3’-(1’-pyrazolines)] with Chlorinating Agents”

2. A. P. Molchanov, V. S. Korotkov, J. Kopf, R. R. Kostikov, *Russ. J. Org. Chem.* **2005**, *41,* 1036–1042. “Reactions of Substituted Ethyl 1,2,3,4,4’,5’-Hexahydrospiro-[naphthalene-2,5’-pyrazole]-3’-carboxylates with Halogens”

1. A. P. Molchanov, V. S. Korotkov, R. R. Kostikov, *Russ. J. Org. Chem.* **2004**, *40,* 470–473. “Reactions of Aliphatic Diazo Compounds: VI. Reactions of Diazomethane and Ethyl Diazoacetate with *(E)*-2-Arylmethylene-1,2,3,4-tetrahydronaphthalen-1-ones”

Posters:

3. “*$GaCl_3$-Catalyzed Insertion of Azodicarboxylates and Related Compounds into Cyclopropane Rings*” V. S. Korotkov, A. de Meijere, “5th Asian-European Symposium”, Obernai, France, 25–28 Mai, 2008

2. *“On the Reactions of Spyrocyclic Pyrazolines with Halogenation Agents”*
   V. S. Korotkov, A. P. Molchanov, “Modern Trends in Organic Chemistry“, Saint-Petersburg, Russia, 15–17 Juni, 2004

1. *“On the Regioselectivity Reactions of Diazoacetate and Diazomethane with Benzylidenetetralones”*
   V. S. Korotkov, A. P. Molchanov, „Organic Synthesis in the New Century“, Saint-Petersburg, Russia, 24–26 Juni, 2002.