Synthesis and Conformational Analysis of Jasplakinolide Analogues and Approach towards the Synthesis of the Stereotetrad of Cruentaren A

Synthese und Konformations Analyse von Jasplakinolidanaloga sowie ein Vorschlag zur Synthese der Stereotetrade von Cruentaren A

DISSERTATION

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Publications:

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Abbreviations

abs.	absolute
Ac	Acetyl
arom.	aromatic
BBN (9-)	9-Borabicyclo[3.3.1]nonane
Bn	Benzyl
br	broad (NMR)
Boc	tert. Butoxy carbonyl
Bu	Butyl
BuLi	Butyllithium
c	Concentration
COSY	Correlation Spectroscopy
CSA	Camphor sulfonic acid
δ	Chemical shift in ppm (NMR)
d	Doublet (NMR)
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
de	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridin
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
E	trans
EDC	1-Ethyl-3-(3’-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydro-quinoline
EI	Electron impact
eq	equation
ESI	Electronspray ionization

Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
Fig.	Figure
g	gram (s)
GC	Gas chromatography
h	hour(s)
HOBt	Hydroxybenzotriazole
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IR	Infrared
i-Pr	isopropyl
J	coupling constant
L	liter(s)
LA	Lewis acid
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
m	Multiplet (NMR)
Me	Methyl
MeOH	Methanol
mg	milligram
m/z	Mass to charge ratio (MS)
NMO	N-Methylmorpholin-N-Oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
PE	Petroleum ether
Ph	Phenyl
PLE	Pig liver esterase
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl

PPTS	Pyridinium *para*-toluene sulfonate
Py	Pyridine
PyBoP	Benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
q	Quartet (NMR)
R_f	Retention factor (TLC)
RT	Room temperature (ca. 23 °C)
s	Singlet (NMR)
s	Second
SAA	Sugar aminoacid
t	Triplet (NMR)
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBTU	*N*-[(1*H*-benzotriazolo-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminiumtetrafluoroborate *N*-oxide
THF	Tetrahydrofuran
TfO	Trifluoromethanesulfonate
TPAP	Tetrapropylammonium perruthenate
Triflate	Trifluoromethanesulfonate
UV	Ultraviolet
Z	cis

Chapter I
Synthesis and Conformational Analysis of Jasplakinolide Analogues

1 Introduction

Cells of organisms bacteria, lichens, fungi, plants, animals produce a large variety of organic compounds. Anciently many substances were obtained e.g. food stuff, building materials, dyes, medicines, and other extracts from nature. Plants and animals have provided substances used for their biological activity to heal or to kill and became the foundation of folk medicine. Recent natural product discovery and development of avermectin (anthelminthic), cyclosporin and FK-506 (immunosuppressive), mevinolin and compactin (cholesterol lowering), and taxol and camptothecin (anticancer) have revolutionized therapeutic areas in medicine.[1]

Vastly diversed living organisms of the marine environment are a potential source of new drugs for treatment of antibiotic infections and other deadly diseases. Marine life comprises over half a million species. Due to their unique living environment as compared with the terrestrial organisms, marine organisms produce a wide variety of metabolic substances which often have various unprecedented chemical structures. Enzymes, lipids, poly heterosaccharides as well as secondary metabolites from marine sources can be defined as bioactive marine natural products. In recent years, an increasing number of marine natural products have been reported to exhibit various biological activities such as antimicrobial, physiological and pharmacological ones. Some metabolites have also been noted by their significant toxicities.[2, 3] The effort to find novel antitumor substances from organisms have been increased in recent years and several novel compounds (peptides, polyethers, alkaloids, prostanoids etc.), with antitumor activities, have been isolated from marine sponges, octocorals, algae, tunicates, nudibranchs, bryozoans and so on. Several compounds from marine invertebrates have reached clinical or pre-clinical anticancer trials. They include bryostatin, didemnin B, dolastatin, ecteinascidin, halichondrin B, and elutherobin. Many other compounds with different skeletal structures have also been bioassayed for antitumor activity. Juncusol from an estuarine marsh plant, aplysistatin from a sea hare and aeroplysinin-1 from sponges are only a few of the marine isolates which are undergoing further evaluation for anticancer activity. Table 1 summarizes the reports on antitumor research, involving 14 marine

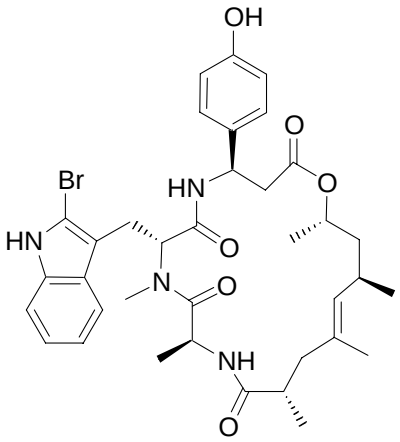
compounds with determined mechanisms of action that included in vitro and/or in vivo studies with human cancer cell lines.[4]

Table 1: Antitumor pharmocology of marine natural products with determined mode of action

Compound	Organism	Chemistry
Agosterol	Sponge	Terpene
Aplidine	Tunicate	Depsipeptide
Auristastatin	Synthetic.	Peptide
Bryostatin	Bryozoa	Macrolide
Curacin D	Alga	Polyketide
Dehydrothyrsiferol	Alga	Terpene
Dolastin 10	Tunicate	Peptide
Ecteinascidin	Tunicate	Quinoline
Eleutherobin	Coral	Terpene
Jasplakinolide	Sponge	Peptide
Naamidine A	Sponge	Imidazole
Octalactin	Bacteria	Polyketide
Sarcodictyins	Coral	Terpene
Spirulan	Alga	Polysaccharide

Currently, about half of all described medicines are extracted or derived from terrestrial plants and organisms. Many synthetic drugs were originally inspired by novel compounds in terrestrial organisms. Although few marine natural products are currently in the market or in clinical trails, marine organisms represent the greatest unexploited source of potential pharmaceuticals. Because of the unusual diversity of chemical structures isolated from marine organisms, there is an intense interest in screening marine natural products for their biomedical potential. New drug discoveries indicate that marine organisms have a tremendous potential for new pharmaceuticals and will become a much more prolific source than any other

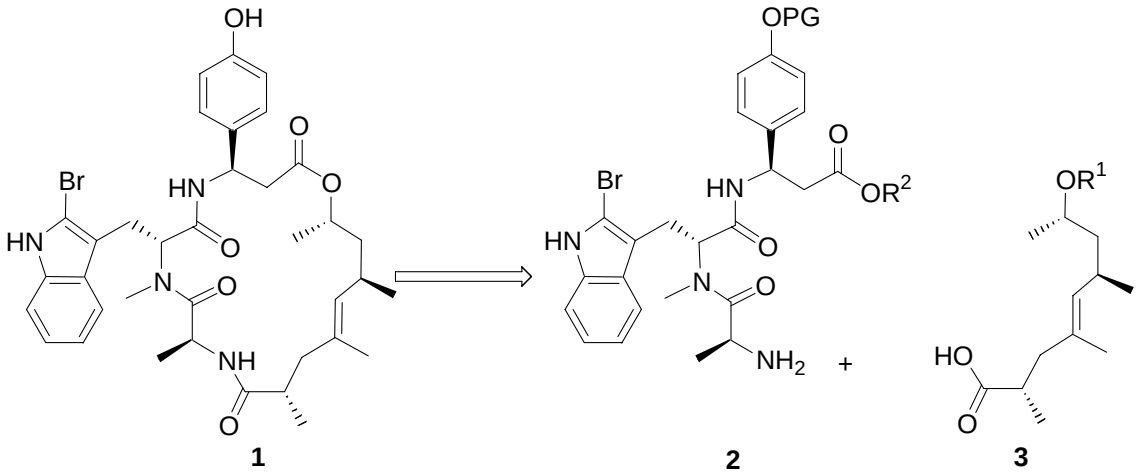
group of terrestrial organisms. The cyclodepsipeptide jasplakinolide (**1**) is a notable example of the marine toxins that shows promising biological activities.



Jasplakinolide (1)

Figure 1.1: Structure of marine natural product jasplakinolide **1**

Jasplakinolide (Figure 1.1) was isolated from the marine sponges *Jaspis splendens*.[5] Jasplakinolide was first described as having anthelminthic, antifungal properties.[6] It represents a new class of bioactive cyclic depsipeptides. The structure of jasplakinolide contains both peptide and polypropionate units as shown in Scheme 1. It is a part of a growing family of structurally related other natural products like geodiamolides A-F, neosiphoniamolide, chondramides, doliculide, with the first two having the same polypropionate structure as jasplakinokide, the 8-hydroxy acid **3** (Scheme 1). This hydroxy acid contains four methyl groups in 1,3-distance giving rise to two *syn*-pentane interactions and one 1,3-allylic interaction. Jasplakinolide and the other mentioned cyclodepsipeptides possess very high activity against a number of tumor-derived cell lines, and therefore appeared to be very promising candidates for cancer therapy. This has made them very attractive for further biological investigation and structure activity relationship (SAR) studies.



Scheme 1: Tripeptide and polypropionate parts of jasplakinolide

Restricting the conformational flexibility of medium-sized polypeptides has proven a valuable approach towards understanding the structural and conformational features of bioactivity. Thus, in the case of peptide hormones, a number of studies in the past 20 years have shown that this approach can lead to the discovery of analogues with potential agonistic or antagonistic properties. The rationally designed conformationally constrained analogues are in both cases tools for understanding the structure activity relationships of the natively occurring polypeptides and lead structures for the development of novel compounds with therapeutic and diagnostic applications.

In this direction, our target was focused on the design and synthesis of novel ω-amino- and hydroxy acids which have the similarity to the jasplakinolide polypropionate part **3** and to synthesize novel analogues of jasplakinolide using these amino- and hydroxy acids. Furthermore it was planned to study their solution conformations as well as biological activities to gain some information concerning their structure-activity relationships. The ω-amino- and hydroxy acids were designed on the basis of non bonded interactions such as 1,3-allylic strain and *syn*-pentane interactions to get the restricted conformations for the analogues.

2 Literature Review

2.1 Summary of biological activity of Jasplakinolide and other related compounds

Jasplakinolide (jaspamide), was first reported in 1986 as a novel biological active cyclodepsipeptide.[5, 7] It was isolated from the Indo-Pacific marine sponge *Jaspis johnstoni* (order Astrophorida), now known as *Jaspis splendens* or *Jaspis sp*. Quite unexpectedly, it was reencountered during bioassay-guided isolations with extract fractions from Auletta cf. constricta (order Halichondrida) possessing in vitro cytotoxicity to HT-29 cells. Jasplakinolide was also shown to possess potent antiproliferative activity[8] in the NCI-60 cell line screen, which prompted extensive further investigation of its properties and mechanism of action. Additional studies demonstrated jasplakinolide to be especially active against a number of tumor derived cell lines, human prostate carcinoma, and myeloid leukemia.[9] This drug was observed to be active in vivo against Lewis lung carcinoma and human prostate carcinoma xenografts.[10] A number of investigators have found jasplakinolide to be an invaluable tool to probe cytoskeletal proteins and to observe the role of actin microfilaments. For example, Bubb et al. found that jasplakinolide induces actin polymerization in a similar fashion to phalloidin. The results imply that jasplakinolide exerts its cytotoxic effect by inducing actin polymerization and/or inhibiting the depolymerization of muscle actin filaments.[11, 12] Actin is an extremely conserved protein which forms the cytoskeleton in all eukaryotic cells. The cytoskeleton is a dynamic three-dimensional structure that fills the cytoplasm. This structure involved in movement and stability of the cell. The long fibers of the cytoskeleton are polymers of subunits. The primary types of fibers comprising the cytoskeleton are microfilaments, microtubules, and intermediate filaments (Figure 2.1.1).

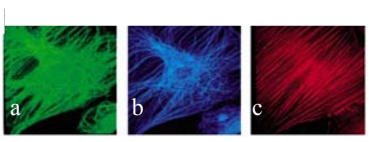


Figure 2.1.1 a) Intermediate filaments
b) Microtubules
c) Microfilaments (actin)

Microtubules are cylindrical tubes, 20-25 nm in diameter. They are composed of subunits of the protein tubulin, these subunits are termed alpha and beta. Microtubules act as a scaffold to determine cell shape, and provide a set of "tracks" for cell organelles and vesicles to move on. Microtubules also form the spindle fibers for separating chromosomes during mitosis. When arranged in geometric patterns inside flagella and cilia, they are used for locomotion. Actin is a globular structural protein that polymerizes in a helical fashion to form an actin filament (or microfilament). Actin filaments provide mechanical support for the cell, determine the cell shape, enable cell movements and participate in certain cell junctions, in cytoplasmic streaming and in contraction of the cell during cytokinesis. In muscle cells they play an essential role, along with myosin, in muscle contraction. Cellular actin exists in two forms: as monomeric actin (G-actin) and as filamentous actin (F-actin). Linking monomers (G-actin) to each other, forming long thread like structures, creates filamentous actin called F-actin. F-actin has a polar structure with a fast growing barbed (+) end and slow growing pointed (-) end. The barbed end favored for polymerization and monomers (G-actin) preferentially are added to this end in their ATP-form.[13] After incorporation in F-actin, ATP hydrolyses to ADP and as such the monomer (G-actin) becomes less stable at the pointed end, leading in turn to depolymerization at the pointed end. This process is called tread milling (Figure 2.1.2). Like phalloidin, jasplakinolide seems to be bind in a cleft between two monomers of F-actin at the pointed end and thus prevents the depolymerization by disturbing the dynamic nature (steady state) of F-actin. In fact, it was demonstrated that exposure of living cells to jasplakinolide results in the formation of multinucleated cells and disruption of actin in these cells.[14-16]

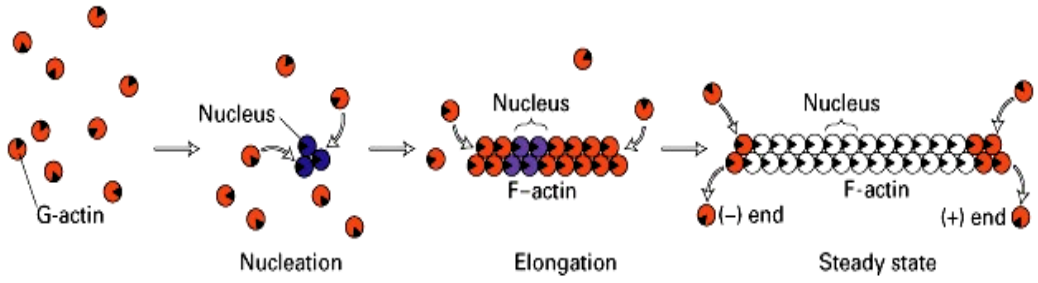


Figure 2.1.2: Formation of F-actin and process of tread milling

2.2 Modeling the jasplakinolide binding site on actin filaments

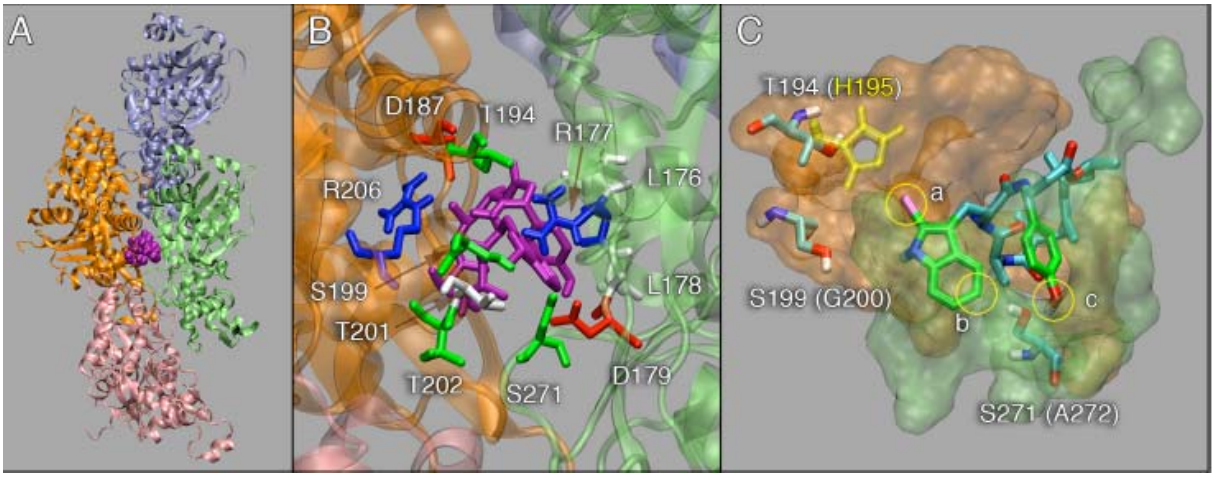


Figure 2.2: Molecular docking studies of jasplakinolide bound to F-actin A) jasplakinolide (purple) binds between adjacent monomers and stabilizes lateral interactions in the filament B) Closeup of the same view as in A showing key actin residues that interact with jasplakinolide (purple). C) Expanded view of pocket showing the side groups of residues in host actin that interact with jasplakinolide, differences in parasite actin shown in brackets. His (195) in gold.

Computer simulation studies of protein-protein interactions provided information about molecular interactions that occur during the actin nucleation and polymerization and these are highly relevant to binding of small molecules. Recent modeling studies[17] described the binding site for jasplakinolide in muscle actin filament. Jasplakinolide binds in a cleft between two adjacent monomers bridging lateral interactions between adjacent monomers in the filament (Figure 2.2). Notably, this same site is targeted by the related cyclic peptide phallodin, despite the fact that two structures are not highly similar. Binding of jasplakinolide bridges between long pitch strands of two monomers of F-actin, stabilizes the filament from depolymerization. Small molecule docking studies make very clear predictions about the residues on actin that are important for binding to jasplakinolide. Closer examination of the jasplakinolide molecule docked to the actin filament reveals that the closest residues are D187, T201-T202, R206 on one monomer and L176-R177-L178-D179 on the other (muscle actin numbering). All of these contacts are within ~4 Angstroms and likely are sufficiently close to interaction with the side groups of jasplakinolide (Figure 2.2 B).

2.3 The family of jasplakinolide

Cyclodepsipeptides are characterized by the presence of at least one ester bond because they contain a hydroxy acid. Furthermore they contain unusual amino acids, which may be extended, *N*- methylated, hydroxylated, or halogenated. Occasionally they contain fragments from other biosynthetic pathways, for example polyketides. The substituents on the polyketide fragment might be used as conformational controlling elements. Some illustrative examples of cyclodepsipeptides are jasplakinolide (**1**), geodiamolide (**4**), chondramide C (**5**), doliculide (**6**) (Figure 2.3.1). While jasplakinolide (**1**) has a 19-membered ring system, the chondramides and geodiamolide feature a smaller, 18-membered ring. Nevertheless, the similarity between jasplakinolide and the chondramides is quite high since they share essentially the same tripeptide fragment. Thus, there is a β-amino acid, an *N*-methyl-tryptophan, and an alanine in both depsipeptides. In the chondramides the ω-hydroxy acid is one carbon shorter than in jasplakinolide. On the other hand, the ω-hydroxy acid is the same in jasplakinolide and geodiamolide. A somewhat related biological activity is reported for the geodiamolides which supposedly cause microfilament disruption.[18] These observations highlight the role of the tripeptide fragment as determinant of the mode of action. Even though doliculide (**6**) seems to be similar to geodiamolide (**4**), in its biological activity it is comparable to jasplakinolide and chondramide C.

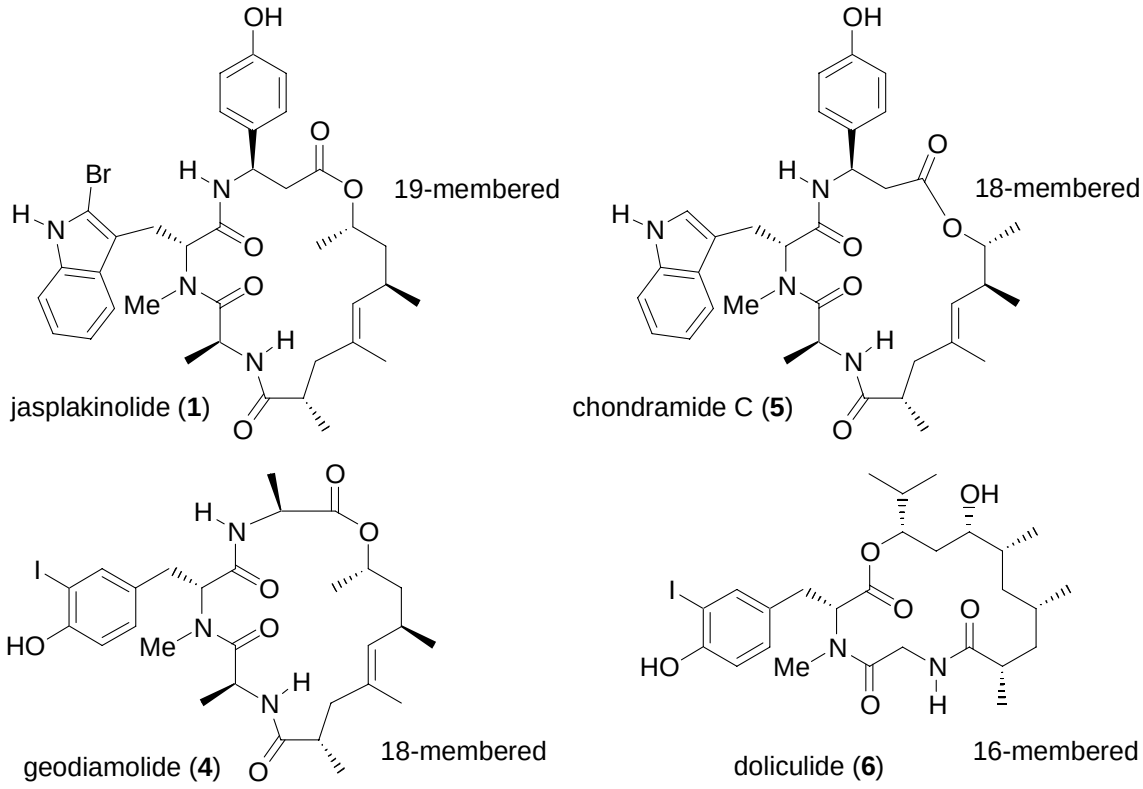


Figure 2.3.1 Structures of jasplakinolide and related depsipeptides.

In a recent study[19] of doliculide (**6**) it was shown that it can potently enhance the assembly of purified actin and inhibit the binding of FITC (fluorescein isothiocyanate) labelled phallodin to actin polymer, like as the jasplakinolide, chondramide C, and phallodin. Treatment of cells with doliculide caused them to arrest at cytokinesis and caused substantial rearrangement of intracellular F-actin.[19] Similarly, Sasse et al.[20] found that chondramide and phallodin differed little in their ability to displace a fluorescent phallodin derivative from actin polymer. These observations suggest nearly identical affinity of the four compounds (doliculide (**6**), jasplakinolide (**1**), chondramide (**5**), phallodin) for actin polymer and encouraged to search for a common pharmacophore among these peptides. From the modelling studies (Figure 2.3.2), it can be noticed that almost every atom of doliculide overlaps with atoms in either jasplakinolide, phallodin or chondramide C. Of particular note is that the benzyl group of doliculide corresponds to the indole group of other peptides and that the iodine atom of doliculide overlaps reasonably well with the bromine atom of

jasplakinolide. In short, the phenyl ring and isopropyl group of doliculide occupy the same region of space as the indole and the phenyl rings of jasplakinolide.

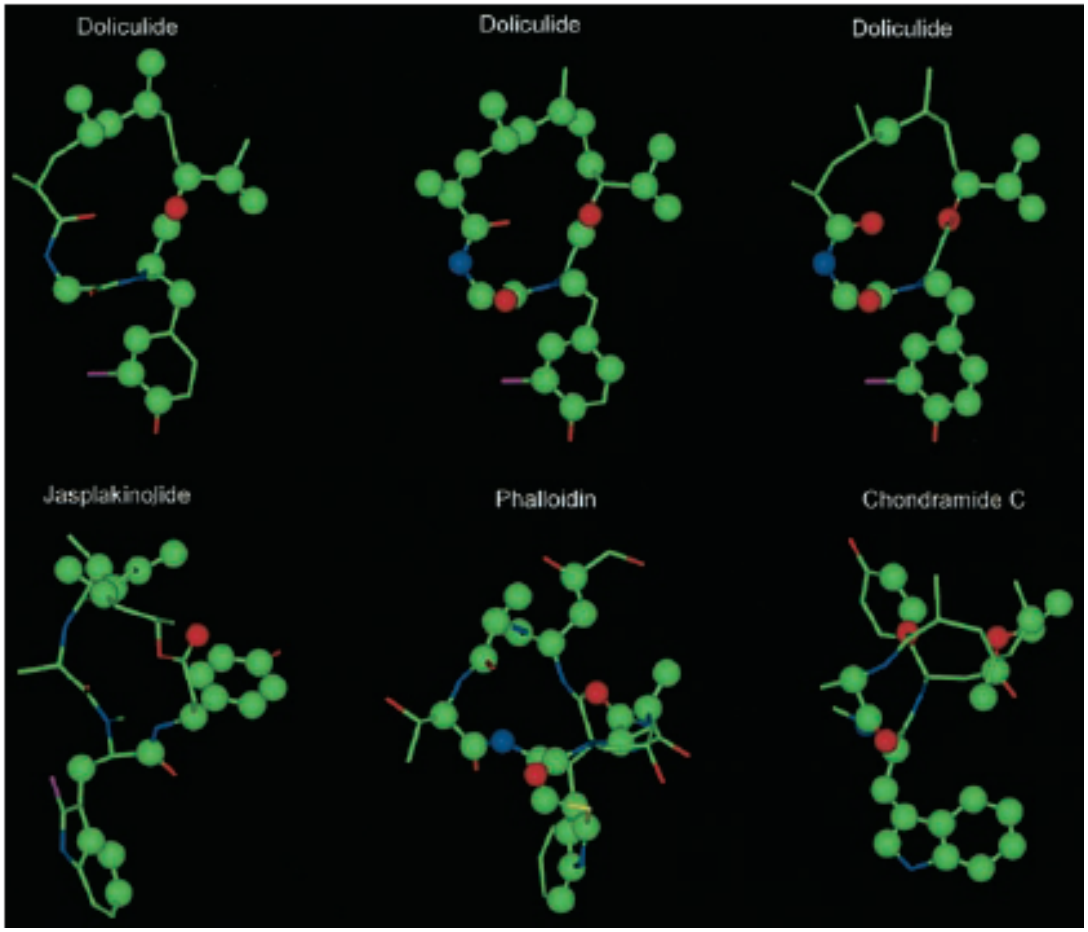


Figure 2.3.2: Comparison of computational volume overlap structures of doliculide with jasplakinolide, phalloidin, and chondramide C. The overlapping structures of doliculide with jasplakinolide (*left*), with phalloidin (*center*), and with chondramide C (*right*) are shown with the molecules separated but in the same orientation in space. For each vertical pair of molecules, matching atoms within their van der Waals radii are shown as *spheres* superimposed on the *stick figure representations* of each molecule. Carbon atoms are shown in *green*, oxygen in *red*, nitrogen in *blue*, sulfur in *yellow*, and halides in *magenta*. Hydrogen atoms are not shown.

2.4 Conformational (peptidomimetical) studies of small peptides

For a number of biologically active peptides the incorporation of conformationally constrained amino acids has given rise to analogues with improved biological activities.[21] Presumably, a constrained analogue that retains biological activity is represented in solution

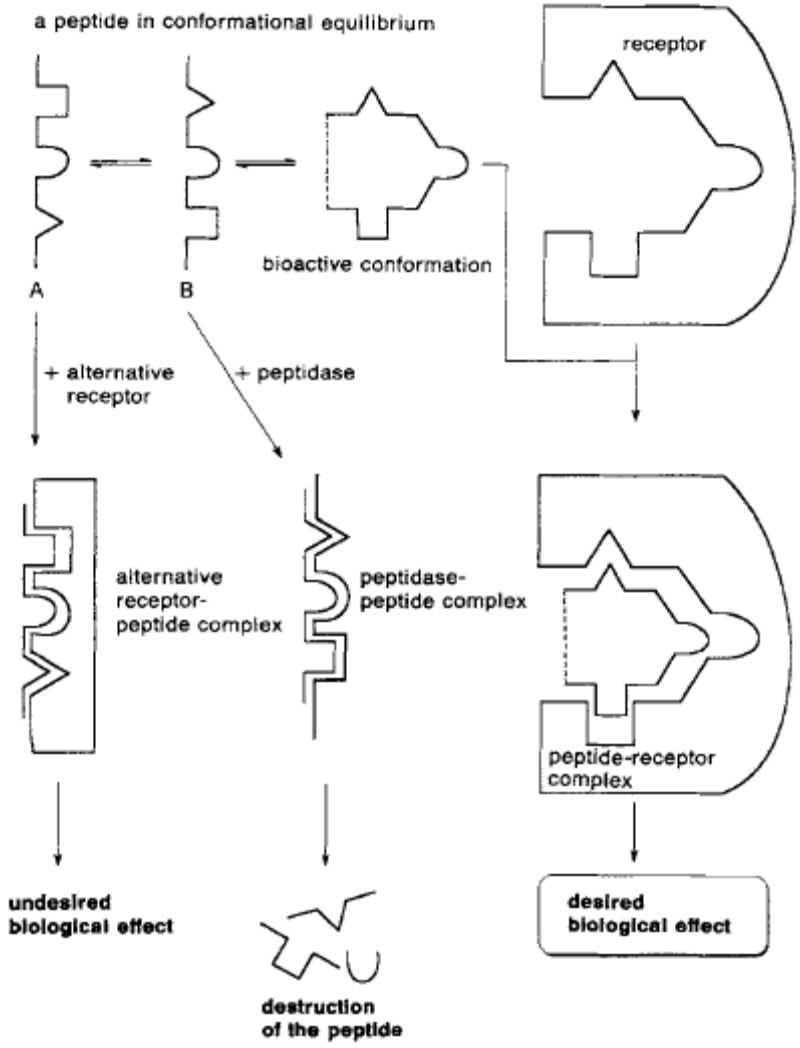


Figure 2.4.1: Relation of conformation vs biological effect.[22]

by a set of conformations that is smaller than that of the native unconstrained peptide, and that set of constrained analogue conformations in solution contains a larger fraction of the receptor bound conformation(s). Indeed, in certain cases multiple substitutions of constrained amino

acids have given potent analogues with sufficient rigidity to display discrete solution conformations that are suggestive of bioactive conformation. Peptides bearing conformational constraints have often displayed superior stability to enzymatic degradation as well.[23] In solution peptides exist as a variety of conformations that are in dynamic equilibrium with each other. If a conformational restriction is introduced to the bioactive conformation of the peptide, forms A and B (Figure 2.4.1) can not arise. Thus the interaction with alternative receptors and peptidases is suppressed or does not occur. In this fashion a desired biological effect can be obtained.[22] Figure 2.4.2 explains the analogue (peptidomimetic) drug design principles.

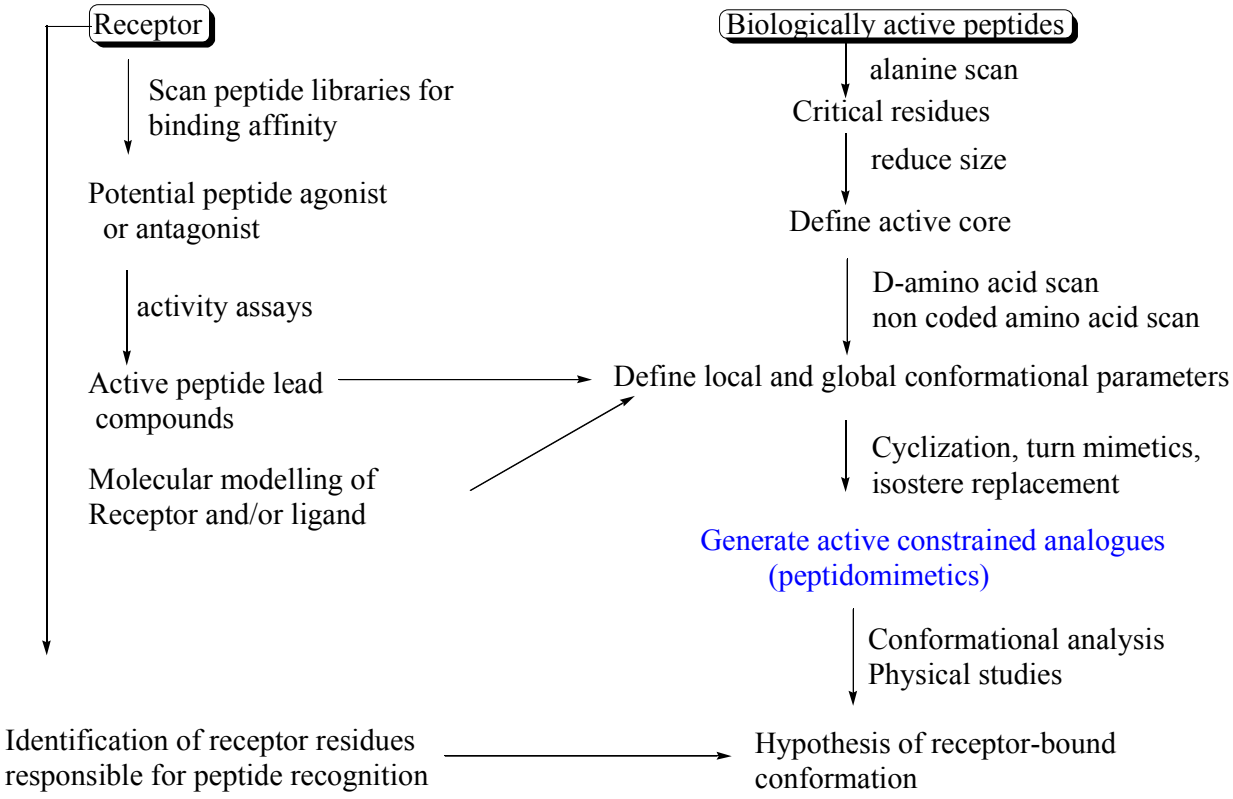
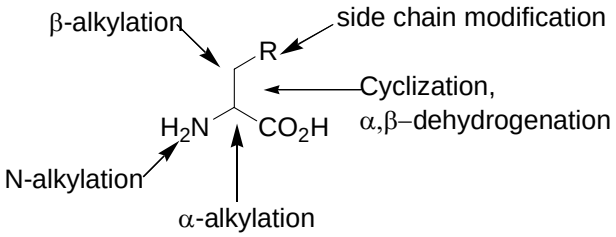
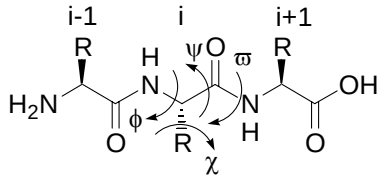


Figure 2.4.2: Analogue (peptidomimetic) drug design principles.

Several possibilities exist for the synthesis of conformationally restricted and/or metabolically stable peptidomimetics at the amino acid level. The systematic exchange of individual amino acids by α-C alkylated, α-*N* alkylated, and D-amino acids is well established. In addition, α,β-

unsaturated, cyclic and β-amino acids as well as amino acids with sterically demanding side chains may also be employed. The Table in the down describes the effect on conformation with the modification on the amino acid.[24]





representative diagram for ϕψϖχ angles

Modification	conformational effect
1. Backbone N-alkylation	φ, ψ, χ are constrained, facilitates cis-trans isomerism.
2. Backbone C-alkylation	φ, ψ are constrained to a helical or extended linear structure.
3. D-amino acid/proline substitution	Favors formation of β-turn structures.
4. Peptide bond isosteres	ω can be fixed at 0 or 180°, or allowed greater freedom of rotation.
5. Cyclic amino acids	ω can be biased to 0 or 180°, φ, ψ are biased towards formation of β-turns or γ-turns, χ can also be affected.
6. Dehydroamino acids	Fix χ at 0 or 180°.
7. β-alkylation	Constrain χ, may also affect backbone conformation.

2.4.1 Secondary Structure Motifs: β turns

So far a crucial disadvantage of modifications (above Table) is, that the resulting conformation can not be predicted. As a result biophysical investigations are necessary to obtain conformational-activity relationships for each and every derivative prepared. For this reason it is desirable to have methods available that induce a specific target conformation. A secondary structure mimetic is a building block that forces a defined secondary structure after

incorporation into a peptide. An ideal mimic will have a rigid scaffold that orients the sidechain residues in the same direction as the natural peptide, while confering better solubility and/or resistance to enzymatic degradation. β-Turns are the most frequently mimicked protein secondary structures. β-Turns are defined as a tetrapeptide sequence where the distance between α-C_i and α-C_{i+3} is less than or equal to 7 Å (Figure 2.4.3). The turn can be stabilized by chelation of a cation, such as Ca^{2+} or intramolecular hydrogen bonds. In linear peptides turn arises mainly due to the tendency to form intra molecular hydrogen bonds. The β-turn is a structural motif common to many biologically active cyclic peptides[25] and has been postulated in many cases for the biologically active form of linear peptides. For this reason it is a frequently imitated secondary structure.[26]

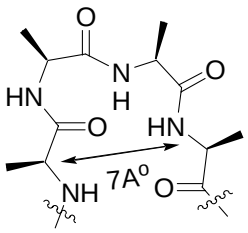


Figure 2.4.3: β-turn.

There are certainly several ways of constructing conformationally locked and well-defined structures of analogues of natural cyclic peptides using different strategies by introducing different amino acids which are having some key features to control the conformations. The following summary describes the utility of different kind of modifications of peptides which are having key features in controlling the conformations to give specific secondary structures such as β-turns.

2.4.2 Sugar Amino acids (SAA)

Since proteins tend to confer their biological activity through small regions of their folded structures, in principle their functions could be reproduced in much smaller designed molecules that retain these crucial surfaces. Introduction of sugar amino acids (SAA) in peptides can adopt secondary turn or helical structures and thus may allow to mimic helices or

sheets. Kessler et al.[27] explored the conformational influence of several SAA (Figure 2.4.5) into different model and biologically active peptides. After studying the NMR, CD and considering molecular modeling calculations, they came to the conclusion that sugar amino acids (SAA) can cause both global as well as local constraints.

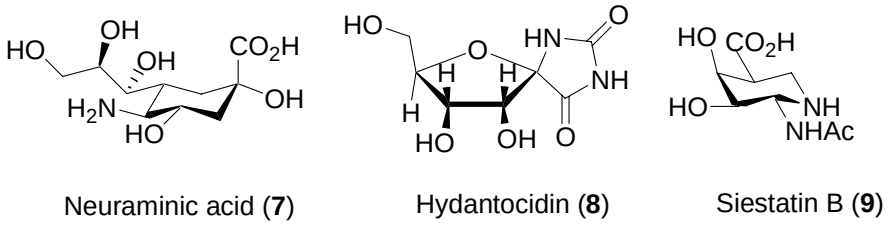


Figure 2.4.4: Naturally occurring sugar amino acids.

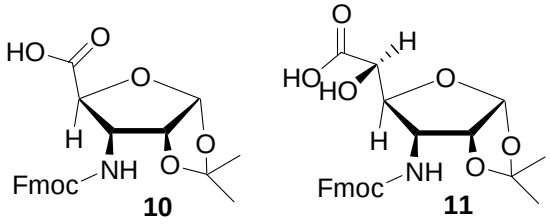


Figure 2.4.5: Kessler's β-sugar amino acids.[28]

Somatostatin, a 14 amino acid peptide containing a 38-membered macrocycle is a hormone formed in the hypothalamus. Structure-conformation-activity studies had suggested that a β-turn composed of Phe-Trp-Lys-Thr is important for biological activity. Much of reminder of the hormone apparently functions as scaffold and can be replaced with simpler structural units. Many simpler analogues were designed[29] and they proved to be very active against tumor cell growth and were able to induce apoptosis.

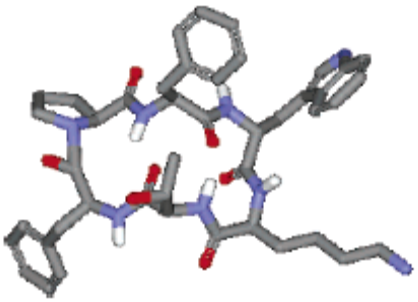


Fig 2.4.6: Model of the bioactive conformation of somatostatin hexapeptide analogues: [cyclo-(Pro-Phe-D-Trp-Lys-Thr-Phe)].

Kessler et al. replaced proline in the bioactive conformation (Figure 2.4.6) of the somatostatin hexapeptide analogue with various sugar amino acids (SAA).[30] NMR and other studies showed that there was a β-turn due to the SAA. Somatostatin analogues **12** and **13** containing SAA **10** exhibit strong antiproliferative and apoptic activity against the multidrug resistant hepatomic carcinoma. Results reveal that by introducing the SAA in a peptide backbone, pharmacokinetic properties can easily be improved as well as bioavailability, and enzymatic stability of the compounds will most likely also be enhanced.

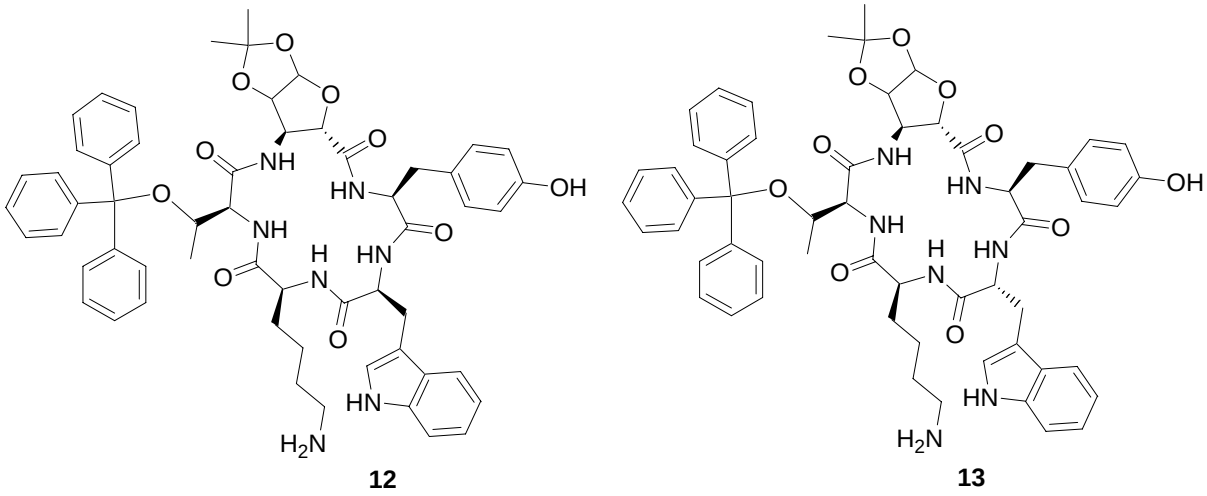


Figure 2.4.7: Sugar amino acid **10** containing compounds **12** and **13** with antiproliferative and apoptotic activity in the low μM range.

2.4.3 β-Amino acids

A peptidomimetic approach that has emerged in recent years with significant potential is the use of β-amino acids. β-Amino acids are similar to α-amino acids in that they contain an amino terminus and carboxyl terminus. β-Amino acids, with a specific side chain, can exist as the R or S isomers at either α (C2) carbon or β (C3) carbon. This results, in a total of four possible isomers for any given side chain. The flexibility to generate a vast range of stereo and regio isomers, together with the possibility of disubstitutions, significantly expands the structural diversity of β-amino acids thereby providing enormous scope for molecular design.

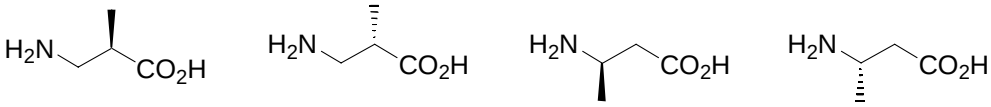
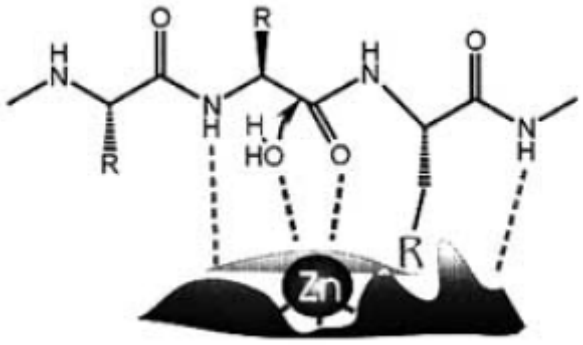


Figure 2.4.8: Structure of β-amino acids and the side chain stereochemistry of the four possible isomers of a mono-substituted β-amino acid.

The incorporation of β-amino acids has been successful in creating peptidomimetics that not only have potent biological activity, but are also resistant to proteolysis. In a recent study of designing enzyme inhibitors of the endo-peptidase, scissile α-amino acid was replaced with a β-amino acid against proteolysis. A likely mechanism for the stabilization of a peptide bond by a β-amino acid involves the displacement of scissile bond from the active site due to the presence of an additional carbon atom in the back bone and preventing proteolysis (Figure 2.4.9).[31]



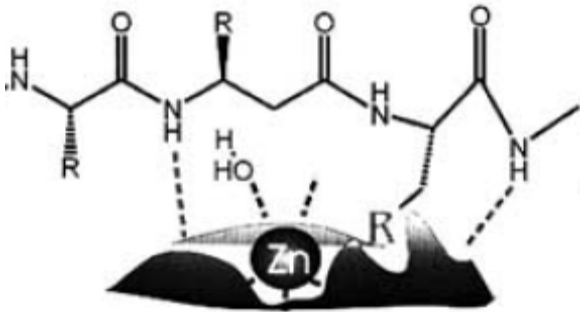


Figure 2.4.9: Schematic diagram of the binding of an α-peptide (upper panel) and a β-amino acid containing peptide (lower panel) to the active site of EP24.15 demonstrating how a β-peptide may bind but is not cleaved by the peptidase.[31]

There are several biologically known active cyclic peptides containing β-amino acids. Jasplakinolide, the chondramides contain the β-phenyl alanine and taxol contains a α-hydroxy β-amino acid derivative. There are plenty of examples where an α-amino acid replaced by β-amino acid resulting in higher biological activity and increased stability to proteolysis.[32, 33]

2.4.4 *N*-Methyl amino acids (NMA)

NMA containing peptide natural products (peptides, depsipeptides) have been isolated from a variety of sources and their secondary metabolites (e.g. vancomycin, cyclosporin, actinomycin D) have found clinical use due in part to physical properties and chemical stability conferred by NMAs present in their structures.[34] Short poly *N*-methylated peptides or peptides containing altering N-methyl amide and normal amide bonds have been especially successful as inhibitors of amyloidosis *ie* the process of protein aggregation thought to be, at least partially responsible for Alzheimer's disease, type II diabetes etc.[35, 36] (Amyloidosis refers to the extracellular deposition of a protein called amyloid. This protein deposition can affect multiple organs. The deposition of amyloid may be a byproduct of normal aging, or may occur with several other conditions). Studies of NMA containing peptides reveal that *N*-methyl amino acid residues increase the proteolytic stability, increase membrane permeability (lipophilicity), and alter the conformational characteristics or properties of amide bonds.[37]

In 1967, Goodmann et al. proposed that poly *N*-methyl alanine adopts a helical conformation by using low resolutions methods like circular dichroism (CD) spectroscopy, one dimensional ^{1}H NMR spectroscopy and some theoretical calculations. In contrast to this work more recent literature, especially in biological journals, assumes that peptides containing *N*-methyl amino acids prefer an extended conformation. The rationale for this is a report by Viteroux et al. in which they studied the effect of *N*-methylation on the conformation of amide bonds through the use of homo- and hetero-chiral dipeptides, in which one amide bond was *N*-methylated. In this paper it was suggested that homo-chiral dipeptides with an internal *N*-methylated bond prefer a cis-amide form, giving the peptide **β-turn** characteristics while hetero-chiral dipeptides exist in the trans-amide form. Comparison of these effects with dipeptides containing a proline residue concluded that the effect of *N*-methylation giving a tertiary amide was less than the geometrical constraints conferred by proline residues.[38] More recently Arvidsson et al.[39] studied the synthesis and crystal structures of poly N-methyl alanine (penta and hexa) and hetero poly *N*-methyl peptide containing various α-amino acids. In this paper they found that both homo poly *N*-methyl alanine and hetero poly *N*-methyl peptide adopt an extended conformation (β-strand) and all amide bonds populated the trans amide form which allows the formation of hydrogen bond between natural α-peptides. The dihedral angle values revealed that, only every second residue can interact with the sheet conformation of α-peptide. These results exposed that the peptides with alternating *N*-methyl groups can inhibit the growth of β-sheet conformation of the natural α-peptide and thus can inhibit amyloidosis.

2.4.5 Non bonded interactions

Most of the polyketides isolated from nature have very complex structures containing methyl groups in different configurations. One can wonder why nature makes such complicated molecules which are having many methyl groups in a symmetric or complex way. Such considerations strengthen the notion that the presence of the numerous methyl side groups is somehow connected with the backbone conformation of these molecules. The methyl groups do not affect the flexibility of the backbone, yet they reduce the number of low energy local conformers with the result that such molecules preferentially populate certain

conformations. In short, these polyketides may be called as 'flexible molecules with defined shape'.[40]

Two principles become evident, that nature uses to destabilize undesired conformations: one is to avoid the 1,3-allylic interaction and the other is to avoid *syn*-pentane interactions. In a substance as depicted in Figure 2.4.10, a single conformation of the vinylic bond is almost completely populated in which the H-C-C=C dihedral angle lies within 0±30°. The eclipsed interaction is consequently more costly (16.3 kJ mol^{-1}) and the bond rotates in a way to release the repulsive interaction as shown in Figure 2.4.10.

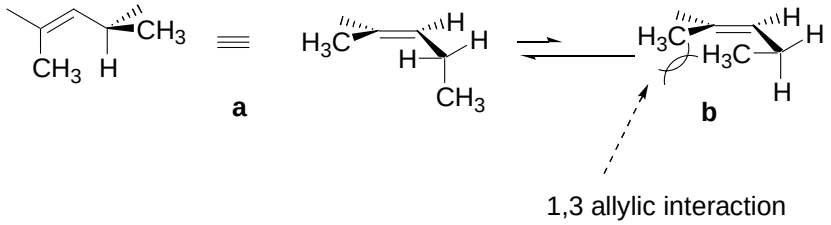


Figure 2.4.10 Preferred local conformation of a 1,1-disubstituted allylic system

A destabilizing *syn*-pentane interaction is created when a hydrocarbon chain is folded such a way that a gauche+ (60°) dihedral angle is followed by gauche- (300°) along the backbone as illustrated in Figure 2.4.11. This places in the case of Figure 2.4.11, two methyl groups into a similar spatial proximity, as formed in a 1,3-diaxial arrangement on a cyclohexane ring. The conformation shown in Figure 2.4.11 is no minimum on the energy hyper surface; rather the molecule relaxes by increasing the backbone dihedral angle. The resulting conformers are still higher in energy (about 14 kJ mol^{-1}) than unstrained conformers. For this reason, linear hydrocarbon chains in alkanes adopt conformations that are free of such *syn*-pentane interactions. The methyl side groups in the polyketide natural products cause the substructures of the kind in Figure 2.4.11 to have only two conformations that are free from such destabilizing interactions.[41, 42]

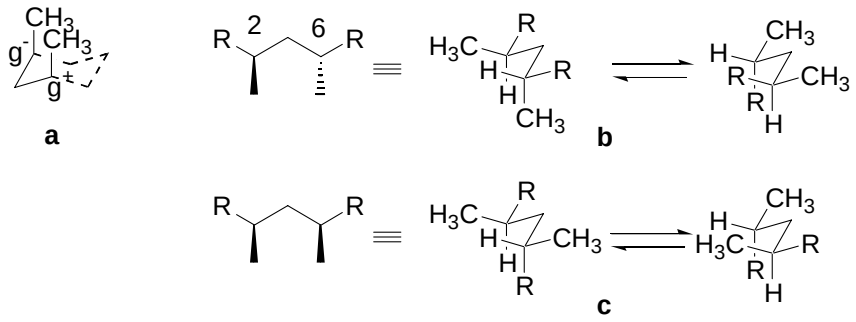


Figure 2.4.11 a) Destabilized by *syn*-pentane interaction; b, c) diconformational segments of 2,4,6… *n*-polymethylated alkane chains.

The 8-hydroxy acid (**3**) of jasplakinolide (**1**) is a good example, which fits in the definition 'flexible molecule with defined shape'. The hydroxy acid **3** contains four methyl groups in a 1,3-distance. One can identify two *syn*-pentane interactions and one 1,3-allylic interactions. Due to these interactions (because of methyl groups) both functional groups at both ends of the chain point in one direction and allow bridging with a peptide fragment. Based on the work of Hoffman et al. one can assume that the conformation of the chain is largely determined by the central double bond and the three other methyl groups. While definitely several low energy conformations are possible, an arrangement such as one depicted in Figure 2.4.12 should be accessible. Conformational search runs (Macromodel 7.0, MM2* force field, 1000 starting structures) for the hydroxy acid **3** found four conformers within 4.184 kJ mol^{-1} of the minimum in which the third lowest conformer (ΔE = 2.00 kJ mol^{-1}) matches the expected conformation for hydroxy acid **3** depicted in Figure 2.4.12. This would allow an easy bridging. The conformation of the central part is governed by 1,3-allylic strain. The dihedral angles of the single bonds next to the allylic system are gauche+ (60^o) and gauche- (300^o), respectively.[43]

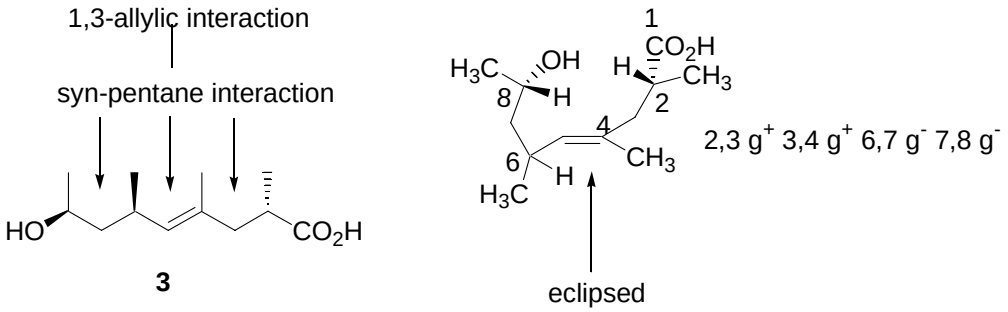


Figure 2.4.12: Possible conformation of the 8-hydroxy acid **3** due to the avoidance of CH_3-CH_3 steric interactions.

In recent sequel publications, Terracciano et al.,[44, 45] described the synthesis and conformational analysis of simplified analogues of jasplakinolide (Figure 2.4.13). In the first publication,[44] the polyketide part was modified by replacing the 8-hydroxy acid **3** with commercially available 5-aminopentanoic acid, 6-aminohexanoic acid, 8-aminooctanoic acid. In the peptide part D-*N*-methyl-2-bromotryptophane and D-β-tyrosine were replaced with D-tryptophane and L-valine basing on the theory discussed earlier in section 2.3, in order to gain information about the pharmocophoric part of jasplakinolide. But there is no rational conformational constraint within the analogues **14**, **15** and **16**. Moreover, there was no significant biological activity. This may be due to the lack of conformational elements in the polyketide part of these analogues. In the second publication,[45] hydroxy acid **3** was replaced with substrate **17**. Hydroxy acid **17** was designed by substituting the allylic part with a *meta* substituted aromatic part in the place of allylic part and replacing one of the methylene group in the chain with its isosteric oxygen. In addition, the methyl groups were removed in the design process. Therefore, while showing some constraint, hydroxy acid **17** is lacking the crucial *syn*-pentane interactions. The results revealed that there was neither good correlation in the conformations of the analogues with the natural product and nor specific biological activity towards the F-actin. There was no specific β-turn type II secondary structure for the analogues in which the hydroxy acid was specifically designed to get secondary structure motifs. It seems that in this publication, there was given more importance to the tripeptide part than the polyketide fragment as it was thought that the tripeptide fragment is the key determinant for exerting the biological activity.

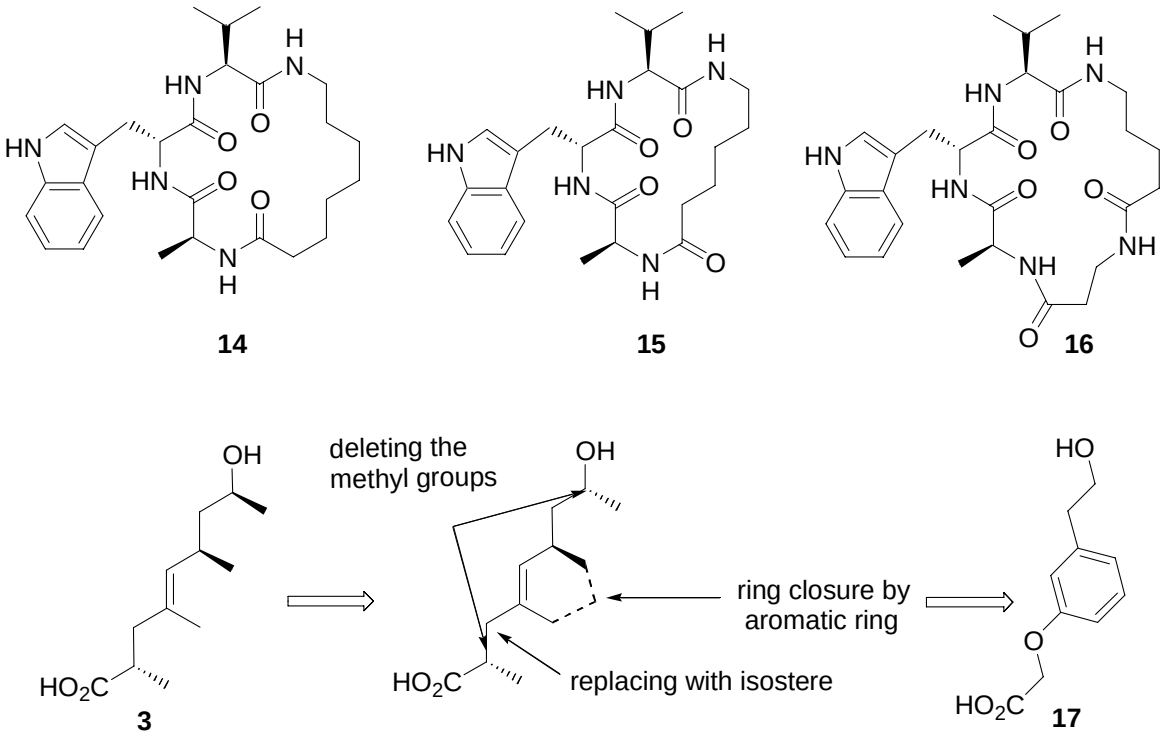


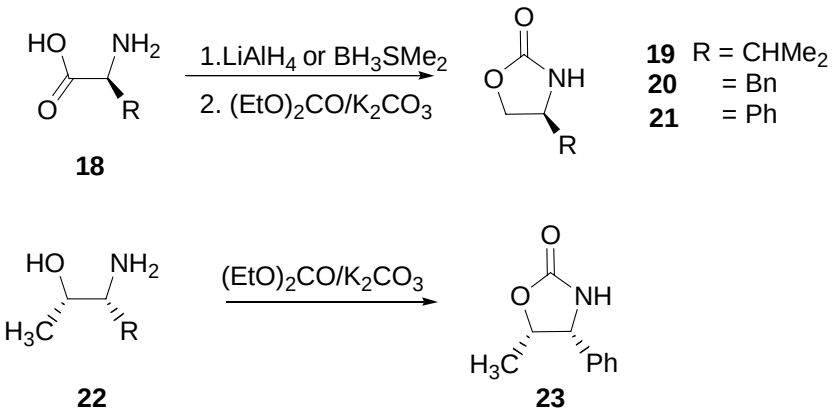
Figure 2.4.13: Jasplakinolide analogues (above); replacement of the allylic part with an aromatic ring in the polyketide part of jasplakinolide.[45]

2.5 Key reactions and mechanisms

2.5.1 Stereo selective alkylation's using chiral auxiliaries

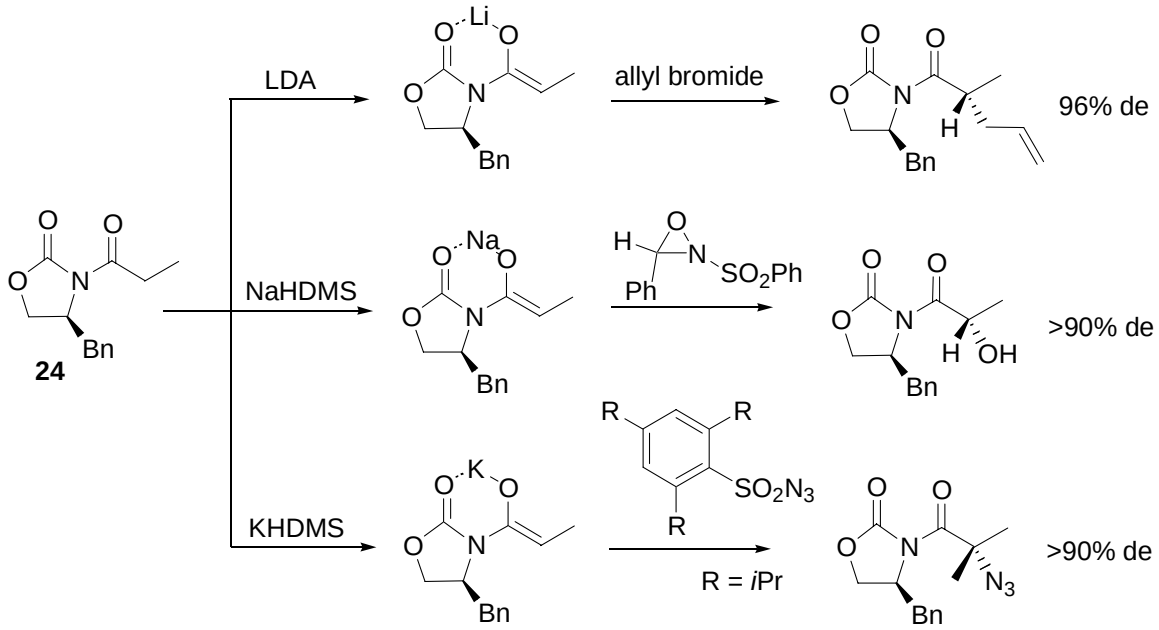
A classical strategy to obtain enantiomerically pure compounds is based on the use of chiral auxiliaries. Thus, a chiral, enantiomerically pure compound is attched to an achiral starting material. This way enantiotopic groups or faces become diastereotopic. After the diastereoselective reaction on the conjugate, removal of the auxiliary provides only the derived enantiomer of the product. The versatile oxazolidine-2-one based chiral auxiliary was first developed by Evans et al. in 1981.[46] The auxiliaries are easy to prepare from α-amino acids. Reduction of the amino acid to the amino alcohol and subsequent cyclization using diethyl

carbonate gives the chiral auxiliary. For instance chiral oxazolodin-2-ones **19-21** and **23** are available from valine, phenyl alanine, phenyl glycine, and norephedrine, respectively.[47, 48]



Scheme 3: Synthesis of chiral auxiliaries from the corresponding α-amino acids or amino alcohols.

Evans chiral auxiliaries have been utilized in a wide variety of synthetic transformations[49] such as asymmetric *syn*-aldol reactions, stereoselective alkylations, stereoselective differentiation of enantiotopic groups in molecules bearing prochiral centers, asymmetric Diels-Alder reactions, and the synthesis of β-amino acids etc.[50] Scheme 4 describes some important reactions of propionyloxazolidinone **24** with various electrophiles.



Scheme 4: Different reactions using different bases and electrophiles on propionyl oxazolidinone **24**.

The high selectivity of alkylations using propionyl derivative **24** can be explained on the basis of a selective enolate formation and approach of the electrophile from the less hindered side of the enolate. Amides invariably give only *Z*-enolate upon treatment with bulky bases like LDA (Figure 2.5.1) because the A(1,2) torsional strain dominates over the 1,3-diaxial interaction in the chair like transition states of the deprotonation step.

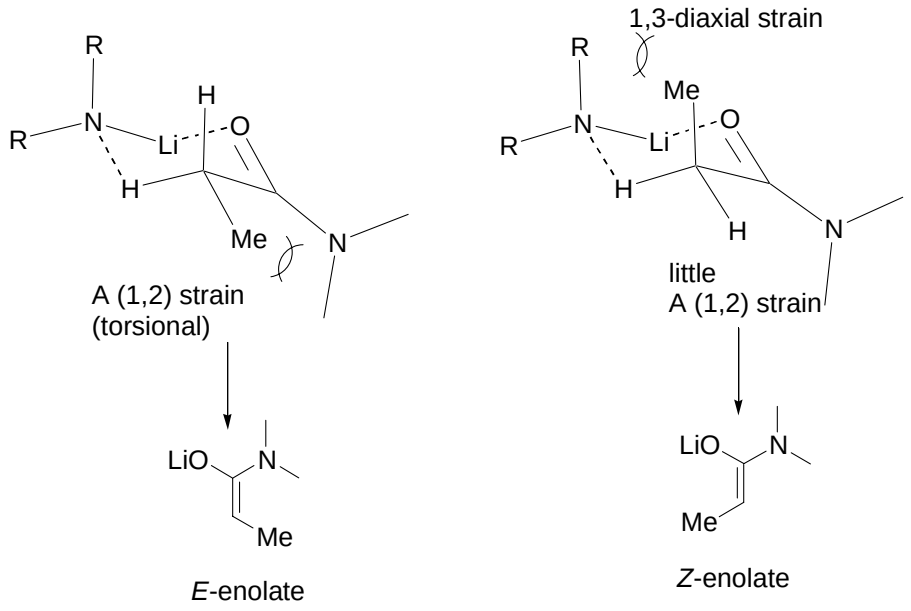


Figure 2.5.1: Possible explanation for the formation of *Z*-enolate.

There are two conformations possible for the propionyl derivative **24** and for the enolate **25**. But because of the chelation of oxygens with lithium, one conformation (Figure 2.5.2) is highly favored due to the chelation. This way efficient differentiation of the two enolate faces is guaranteed. Now the enolate attacks the electrophile from the less hindered side (Figure 2.5.3) forming the product with excellent diastereoselectivity for the compound **26**.[50]

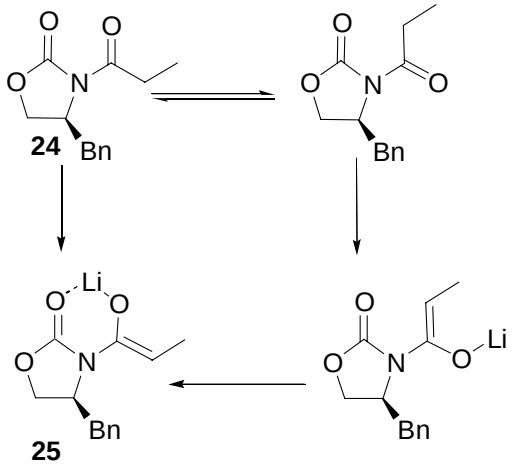


Figure 2.5.2: Possible conformations of chiral auxiliary and enolate.

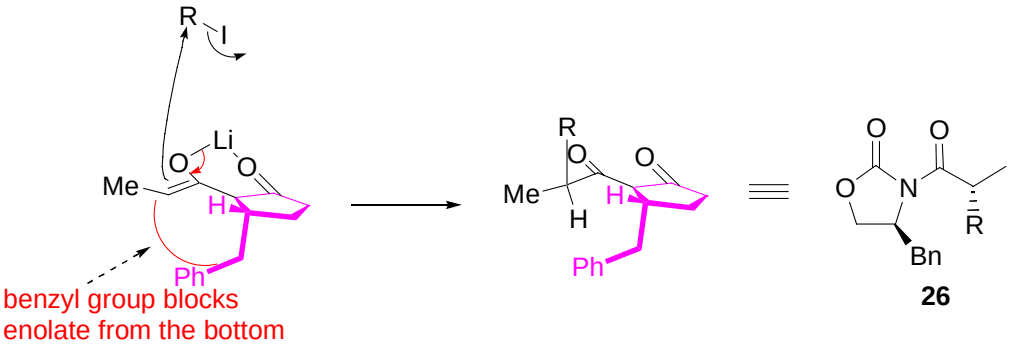
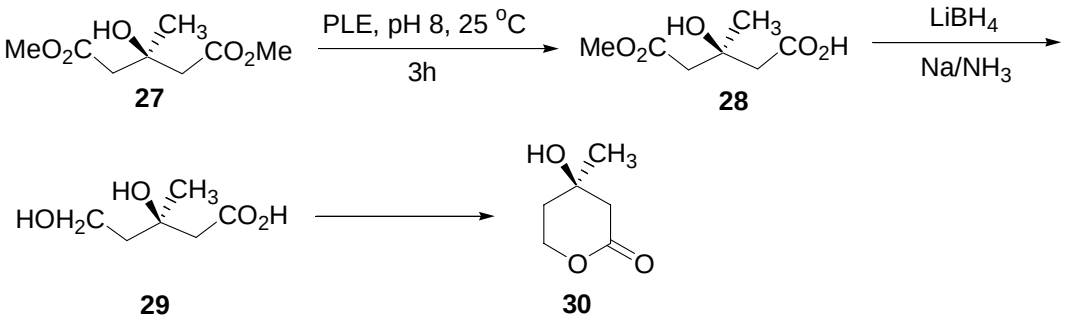


Figure 2.5.3: Attack of enolate from less hindered side.

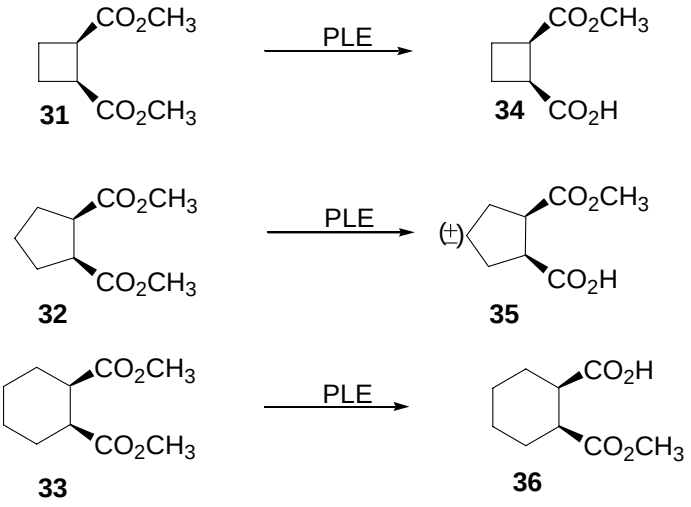
2.5.2 Enzymatic hydrolysis using Pig liver esterase (PLE, EC 3.1.1.1)

Enzymes are now accepted as useful catalysts for a broad range of organic transformations due to their capacities for inducing efficient asymmetric transformations. Hydrolases are currently the enzyme group that receives the most attention. Among the hydrolases, the esterase that has seen most extensive utilization is pig liver esterase (PLE, EC 3.1.1.1). PLE is a serine protease that catalyzes the hydrolysis of a broad range of carboxylic acid esters. The potential of PLE in organic synthesis first emerged when Sih and coworkers reported the PLE catalyzed enantioselective hydrolysis of diester **27** (Scheme 5). PLE is capable of enantiomeric and enantiotopic group specificity and widely employed for providing chiral acid ester synthons from prochiral diester substrates. In addition PLE can also be used to resolve racemic mono esters.[51]



Scheme 5: Asymmetric hydrolysis of symmetric diester.

Complications arose when PLE showed uncertainty about the stereochemistry towards certain substrate groups. For example within the homologous series of monocyclic meso diesters **31-33**, the stereoselectivity of PLE hydrolysis reverses itself. For the cyclobutane diester **31**, the S-ester is hydrolyzed to give **34**, while for the cyclohexane substrate **33**, the acid-ester **36** from R-ester cleavage is formed. Both **34** and **36** are enantiomerically pure. The cyclopentane substrate **32** represents the changeover point, with the acid-ester **35** being virtually racemic. Initially it was thought that the variability in stereoselectivity is due to the commercially available PLE that contain the similar proteins with some having R- and other S- preference (isoenzymes). The separated PLE components did not change the stereospecificity of **31-33**, thereby demonstrating that, although commercial PLE is a mixture, it behaves as if it is single species.



2.5.2.1 Modeling the active site of PLE

Due to the uncertainty in the stereochemistry of PLE towards certain substrates and the lack of an X-ray structure, an empirical approach was put forward, the active site model (Figure 2.5.4) for PLE, as proposed by Toone et al.[51] in 1990. This model is a theoretical approach using computer modeling studies and based on the analysis of experimental results of PLE catalyzed hydrolysis of literature known substrates. First, the active-site location of the catalytically vital serine residue involved in the ester hydrolysis was arbitrarily fixed in a unique location in the space. Then using computer graphics, for each substrate the ester group that becomes hydrolyzed was placed in the nucleophile region and the remaining parts of the

substrates were overlaid in order to identify the components that could occupy common volumes. The analysis resulted in an illustrative active-site model (Figure 2.5.4) for PLE.

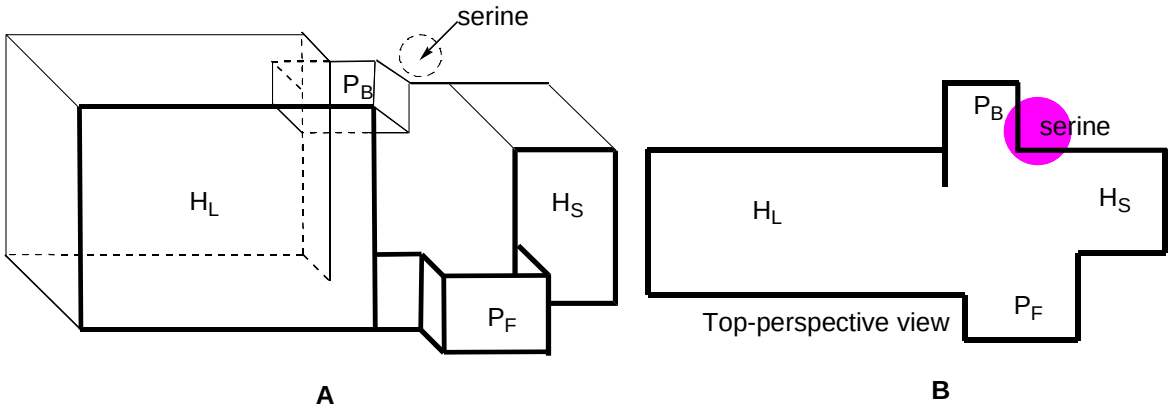


Figure 2.5.4 Active-site model for PLE.

The catalytically essential region is that of the serine residue, which initiates hydrolysis by its attack on the carbonyl group of the susceptible ester function. The binding regions controlling the specificity are composed of four pockets of which two are hydrophobic ($H_{L(large)}$ and $H_{S(small)}$) which interact with the aliphatic or aromatic hydrocarbon portions of a substrate and two others that are more polar in character ($P_{F(front)}$ and $P_{B(back)}$). The larger of two hydrophobic zones, H_L, has a volume of approximately 33 $Å^3$, while the smaller H_S pocket has a roughly 5.5 $Å^3$. Polar groups such as hydroxyl, amino, carbonyl, nitro, etc. are excluded from these areas. However, the hydrophobic pockets can accommodate less polar hetero atom functions such as halogen, and ether, or ketal oxygen atoms, if necessary. The remaining two groups accept more polar or hydrophilic groups. They are located at the front (P_F) and back (P_B) of the active site, respectively. Unlike the other binding regions, the rear boundary is open, and hydrogen bonding or similar groups may extend out beyond the back of this region. The area above the model is also open, and is completely accessible to any substrate moiety that needs to locate there. Such groups may extend in this direction without restriction. This model reveals the differences in the stereochemistry of the homologous series **31-33** towards the hydrolysis with PLE. Small hydrophobic groups bind in H_S until they become too large to do so, at which point the substrate orientation must turn around to place the large hydrophobic groups in H_L pocket, where there is room to accommodate it. It is this 'turning over'

requirement that is responsible for the S-to-R (and vice versa) switches observed experimentally. Figure 2.5.5 explains the reversal of stereochemistry for the series **31-33**.

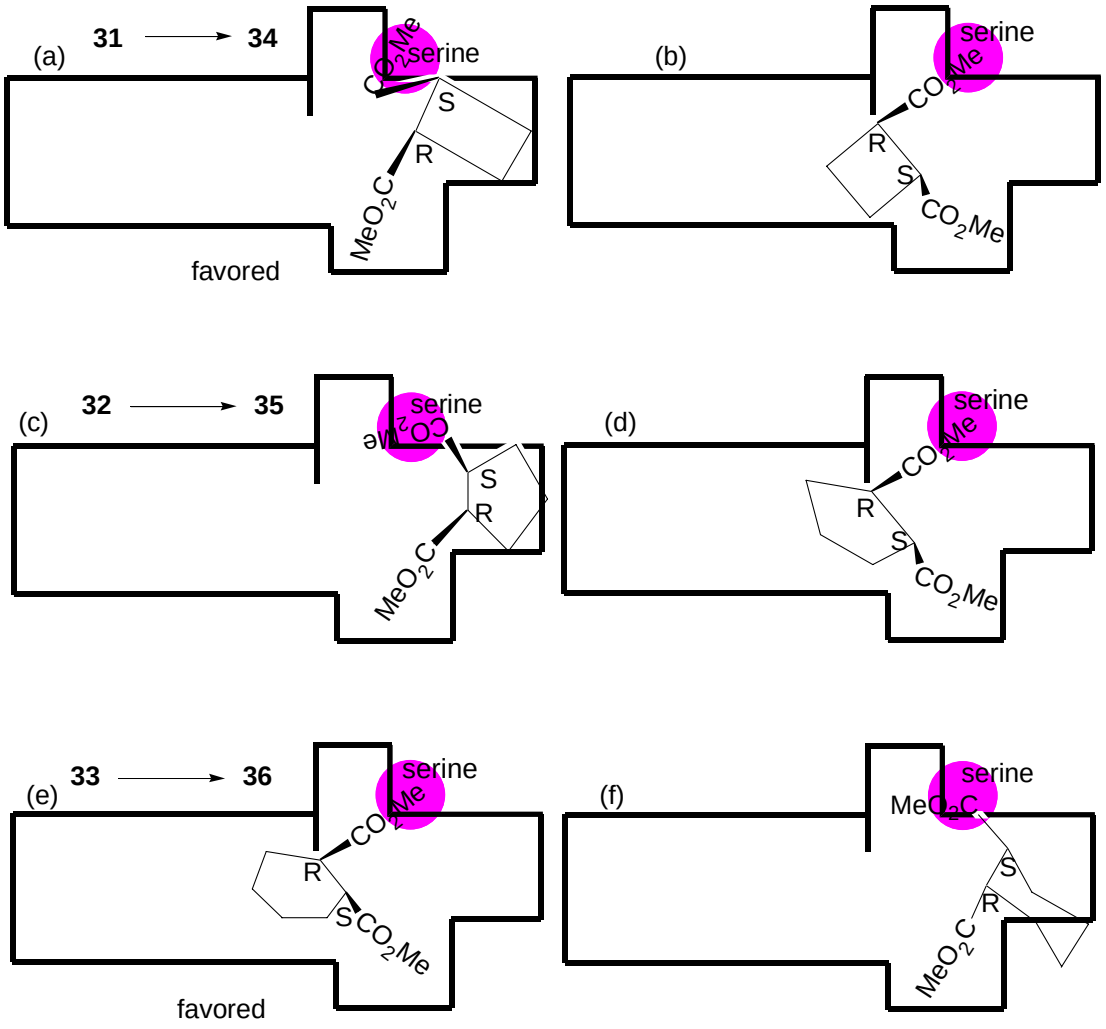


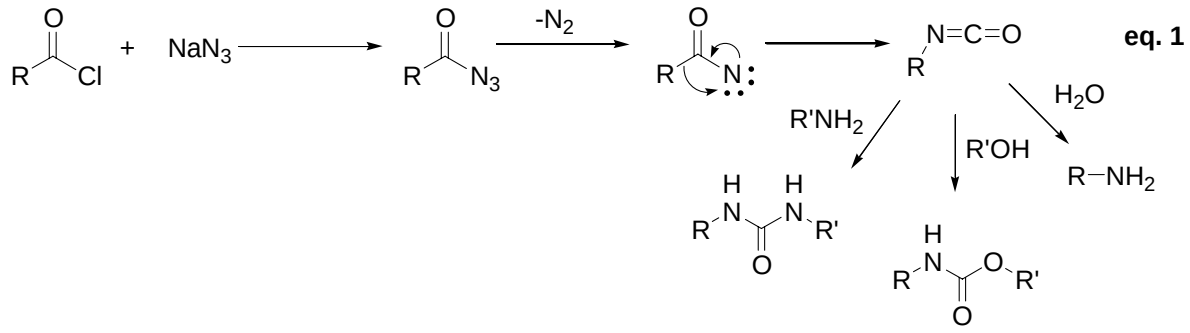
Figure 2.5.5: A top perspective view of the active-site model for the hydrolysis of the homologous diester series **31-33**.[52]

The top perspective view of the active site model is used to illustrate the binding-mode selections for the diesters **31-33.** Dimethyl cyclobutane-1,2-dicaroboxylate **31** bound into the active site with its 'S' centre ester in the serine sphere and thus being hydrolyzed (Figure 2.5.5a). In this orientation the 'R' centre can locate acceptably within the P_F pocket and the cyclobutyl group is directed in to the H_S site, where it fits well. This is clearly a favorable 'ES' complex. The alternative binding mode required for hydrolysis of the R-centre ester would

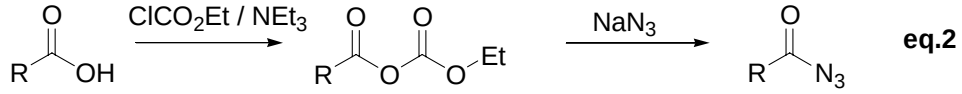
place a portion of the cyclobutane ring in the H_L pocket. Since binding of hydrophobic groups must occur in the H_S rather than the H_L site if sterically possible. It seems to be the hydrophobic part that is cyclobutane ring sterically fits well in H_S leading to the formation of S-acid product **34**. In the case of dimethyl cyclohexane-1,2-dicarboxylate **33** the binding depicted in Figure 2.5.5e shows the preferred ES-complex for hydrolysis of the R-center ester 2R-acid **36**, with the cyclohexane ring bound in the large hydrophobic pocket H_L. Hydrolysis of the 'S' centre would require an orientation as shown in Figure 2.5.5f. This is precluded since the H_S pocket is clearly too small to accept the six-membered ring. According to the active-site model (Figure 2.5.5c and d), hydrolysis of dimethyl cyclopentane-1,2-dicarboxylate **32** is the intermediate between the two cases **31** and **33** since it can fit into both H_S and H_L but the cyclopentane group is marginally too large for an optimum fit into H_S, resulting in a slight preference for hydrolysis on the R side (experimental result showed 17% *ee*) which satisfies the experimental result.

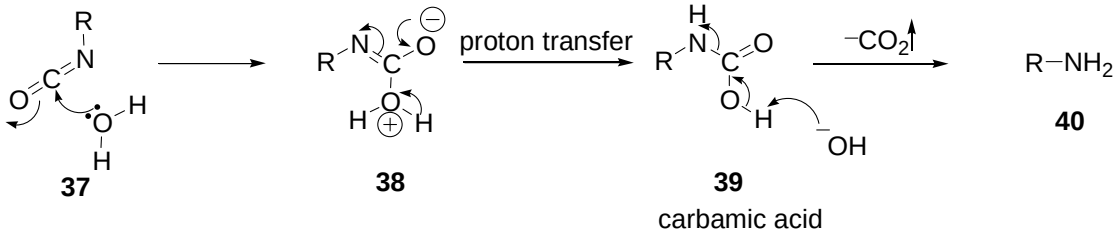
2.5.3 Formation of protected amines (carbamates) via Curtius Rearrangement

The Curtius rearrangement (eq.1) involves the thermal decomposition of acyl azides into amines via an isocyanate intermediate. The reaction might be explained with the loss of nitrogen from the acyl azide forming an acyl nitrene species. Migration of the 'R' group to the electron deficient nitrene would then form the isocyanate. The isocyanate can be trapped by a variety of nucleophiles such as H_2O, amines, or alcohols to get amines, acylureas, or carbamates, respectively (eq. 1). Curtius rearrangement is one of the most widely used methods to synthesize amine derivatives and over 1000 references can be found in the literature related to the rearrangement which points to the potential of the reaction.[53] This is a very general reaction and can be applied to any carboxylic acid: aliphatic, aromatic, acyclic, heterocyclic, unsaturated, and other polyfunctionalized carboxylic acids.



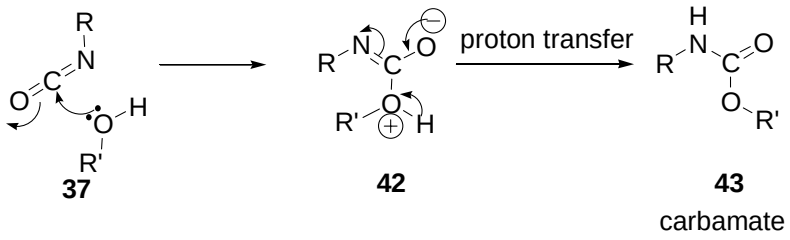
A number of methods have been developed to obtain acyl azides from carboxylic acid derivatives, such as acyl chlorides, mixed anhydrides, and hydrazides. Normally, obtaining the acyl chloride from carboxylic acid sometimes might cause racemization (if the compound has a chiral centre next to carbonyl group) or decomposition. In 1961, Weinstock reported the formation of acyl azides from the mixed anhydride which in turn can be obtained by treatment of carboxylic acid with ethyl chloroformate (eq. 2).[54]





Scheme 6: Formation of amines from isocyanate.

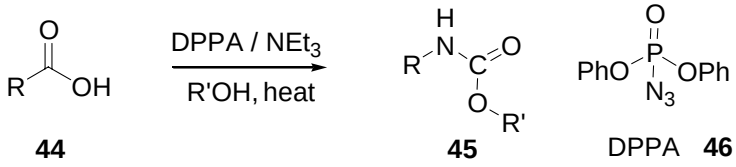
Isocyanate **37** upon hydrolysis with H_2O forms the amine via unstable carbamic acid intermediate **39** as shown in Scheme 6. The carbamic acid **39** decomposes in presence of base and gives amine **40**.



Scheme 7: Formation of carbamate from isocyanate.

Isocyanate **37** upon treatment with alcohols produces the protected amines which are called carbamates (Scheme 7). The mechanism is similar to that of Scheme 6, but here the carbamates are stable as opposed to the carbamic acid. A variety of alcohols can be used to produce the corresponding carbamates. For example *t*-BuOH produces the Boc-protected amine, fluorenyl alcohol gives the Fmoc-protected amine and benzyl alcohol produces the Cbz-protected amine.

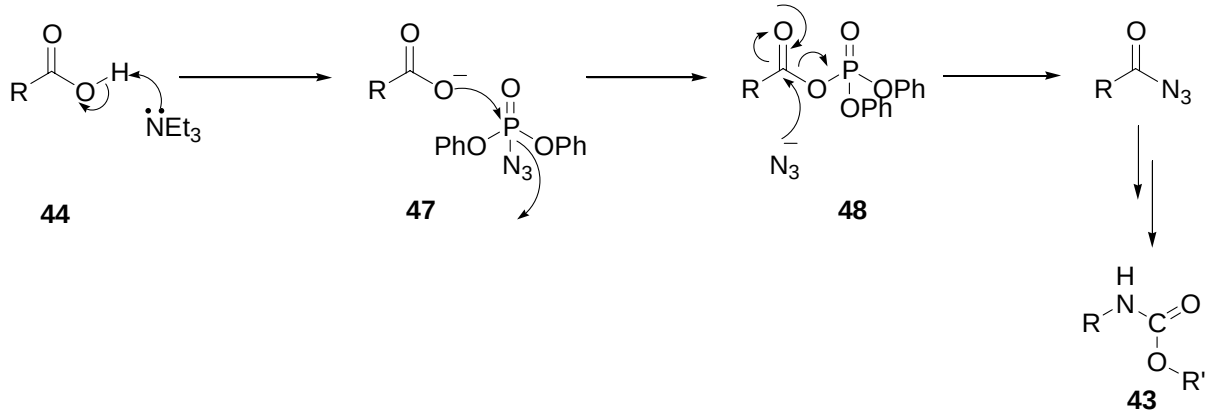
In 1974, Yamada et al.[55, 56] reported a modification of the Curtius rearrangement using diphenyl phosphoryl azide (DPPA) (**Scheme 8**). Using this reagent carboxylic acids yield amine derivatives (especially carbamates) in a single operation (does not require the acyl chlorides or mixed anhydrides). Diphenyl phosphorizidate serves as azide source as well as the coupling reagent, producing the mixed carboxylic phosphoric anhydride in the presence of triethyl amine.



Scheme 8: Modified Curtius rearrangement.[57, 58]

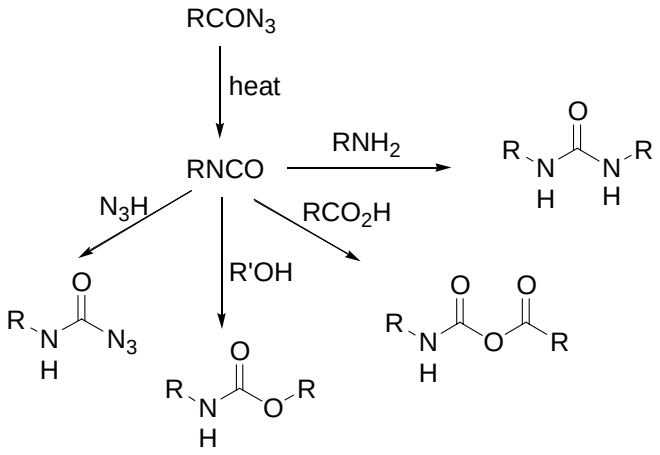
The initial stage of the reaction involves the interaction of the carboxylate anion **47** with the phosphorous atom of DPPA **46** by releasing the azide anion to form the activated carboxylic phosphorus ester **48** (a mixed anhydride of carboxylic acid and phosphoric acid diester) as shown in Scheme 9. Now the azide attacks back on the carbonyl carbon of **48** to form the

carboxylic azide which on heating rearranges to the isocyanate according to same mechanism as that of ordinary Curtius rearrangement (eq 1). DPPA became the most widely used reagent for the one-pot synthesis of urethanes from carboxylic acids such as aliphatic, aromatic, heterocyclic ones etc. because the reaction needs neither a strong acid nor a strong base and it produces the acyl azide directly from the carboxylic acid without requirement of acid chlorides or mixed anhydrides.



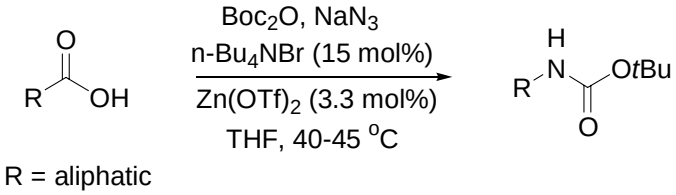
Scheme 9: Possible mechanism for the formation of acyl azide using DPPA.

There is the possibility that side products are formed when DPPA is being used in the Curtius rearrangement. In some cases, hydrazoic acid formed in the reaction mixture can react with the isocyanate to give a carbamoyl azide. Urea and ester derivatives can be formed, though in rare cases, by addition of the starting carboxylic acid to the isocyanate (Scheme 10).



Scheme 10: Possible side products in modified curtius rearrangement.[56]

Recently, Lebel et al.[53] reported a one-pot synthesis of Boc-protected amines via Curtius rearrangement using di-*tert*-butyl dicarbonate, sodium azide, tetrabutylammonium bromide and zinc(II) triflate (Scheme 11).



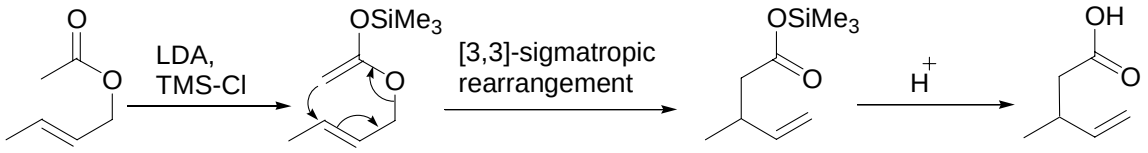
Scheme 11: One-pot synthesis of Boc-protected amines.

In the above reaction, an excess of NaN_3 is used to produce in situ $BocN_3$ in the presence of phase transfer catalyst n-Bu_4NBr. Upon the addition of 1-adamantancarboxylic acid to this mixture the formation of corresponding azide was observed. When the reaction mixture was heated to 80 ^oC, the Curtius rearrangement occurred and gave the desired carbamate. The acyl azide was converted to the corresponding isocyanate at 40 ^oC, but the carbamate was obtained in low yield. This observation suggested that the addition of *tert*-butoxy moiety to the isocyanate intermediate was slow at 40 ^oC. It was thought that the addition of Lewis acid in catalytic amounts can accelerate the formation of the carbamate. After examining several Lewis acids it was found that $Zn(OTf)_2$ can act as very good Lewis acid catalyst for the above transformation at 40 ^oC which gave more than 90% yield. This study reveals that the Zn catalyst is not involved in the formation of the isocyanate, but rather accelerates the formation of the carbamate through the formation of a zinc carbamoyl bromide species. The exact kinetics and mechanism of this reaction are still unknown.

2.5.4 Ireland-Claisen Rearrangement

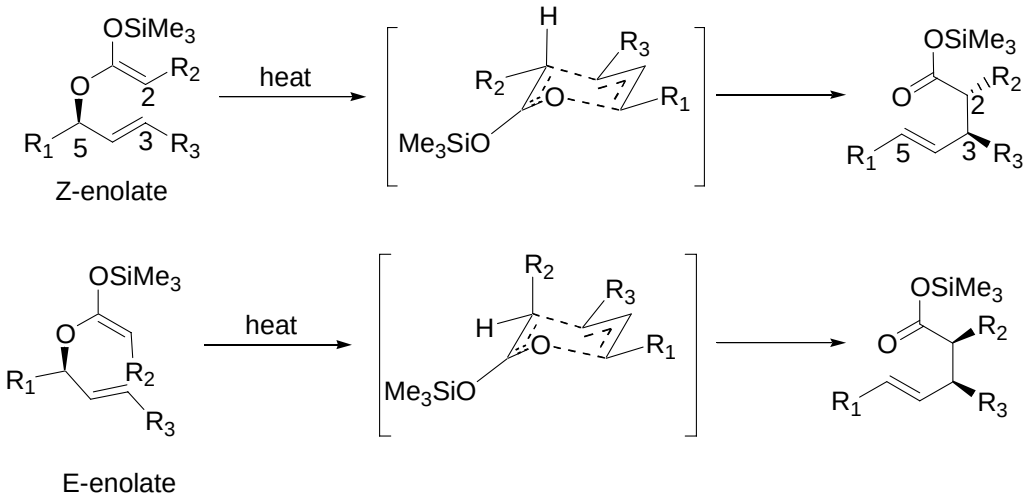
The Ireland-Claisen rearrangement is a mild variant of the Claisen rearrangement, employing the allyl ester of a carboxylic acid ester instead of an allyl vinyl ether (Scheme 12). The ester is converted to its silyl ketene acetal which rearranges at temperatures below 100 ^oC. The intermediate product of the rearrangement, a carboxylic acid silyl ester can not be isolated

and is hydrolyzed during the workup. Thus, Ireland-Claisen rearrangement offers a simple access to chain extended carboxylic acids (1,4-unsaturated carboxylic acids).



Scheme 12: Ireland-Claisen rearrangement.

Since its introduction in 1972, the Ireland-Claisen rearrangement[59] has became widely used in the synthesis of a diverse range of natural products and other targets.[60] The popularity of the reaction is due to several factors: (i) the ease of preparation of the allylic ester reactants; (ii) the ability to control the E/Z geometry of the ester enolate and hence the relative stereochemistry between C-2 and C-3 of the pentenoic acid product; (iii) the frequently high transfer between the allylic stereo center C-5 of the allyl ketene acetal and newly formed stereocenters at C-2 and/or C-3 of the pentenoic acid (Scheme 13); (iv) the generally high level of alkene stereocontrol.[61]



Scheme 13: Chair-like transition states in Ireland-Claisen rearrangement.

2.5.4.1 Effect of reaction conditions on the stereoselectivity of silyl ketene acetal formation

Silyl ketene acetal geometry is controlled by the selective formation of the *E*- and *Z*-ester enolates. Normally esters tend to form *E*-enolates with bases like LDA in THF at -78 ^{o}C by avoiding the severe 1,3 diaxial interactions between the *N*-isopropyl group of LDA and the substituent in the ester as shown in the six-membered transition state (Figure 2.5.6).

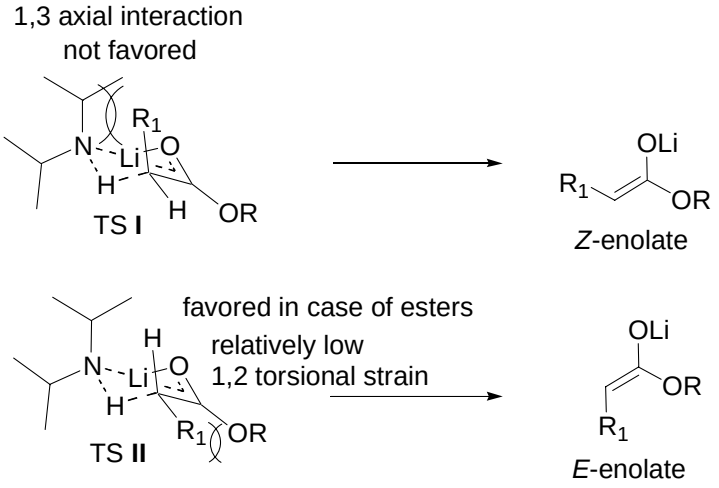


Figure 2.5.6: Transition state diagram for the enolate formation of esters with LDA.

According to the transition state diagram (Figure 2.5.6), in THF solution the metal cation Li^+ coordinates with the carbonyl carbon and the base. The kinetic enolization of esters in THF is postulated to operate through a cyclic transition state TS **I** (Figure 2.5.6). In 1991 Ireland et al.[62] reported that the addition of dipolar solvents (additives) such as HMPA, DMPU, or TMEDA can switch the enolate geometry to Z, favoring the thermodynamic product of the reaction. A switch from a preference of TS **I** in THF to TS **II** for the deprotonation in the presence of dipolar solvents appears questionable at first, due to a severe 1,3-diaxial interaction between the *N*-isopropyl group and R_1 substituent in TS **II**. However, the presence of additives such as HMPA or DMPU results in greater degree of solvation of the lithium cation and weakened Li^+-carbonyl oxygen interaction. A decrease in polarization of the carbonyl oxygen bond also results in a significantly less reactant like transition states, as the α-C-H bond becomes more difficult to extend and break. It is important to note that a strong

solvation of Li^+ ions may lead to a relative stabilization TS **II** over TS **I** through the occurrence of a late transition state. In a very strongly complexing solvent system, a continual change from an expanded to cyclic to an acyclic transition state is expected. In fact, an acyclic transition state can be considered as an extreme situation of an expanded cyclic transition state with a strongly solvated base counter ion (Figure 2.5.7).[62, 63]

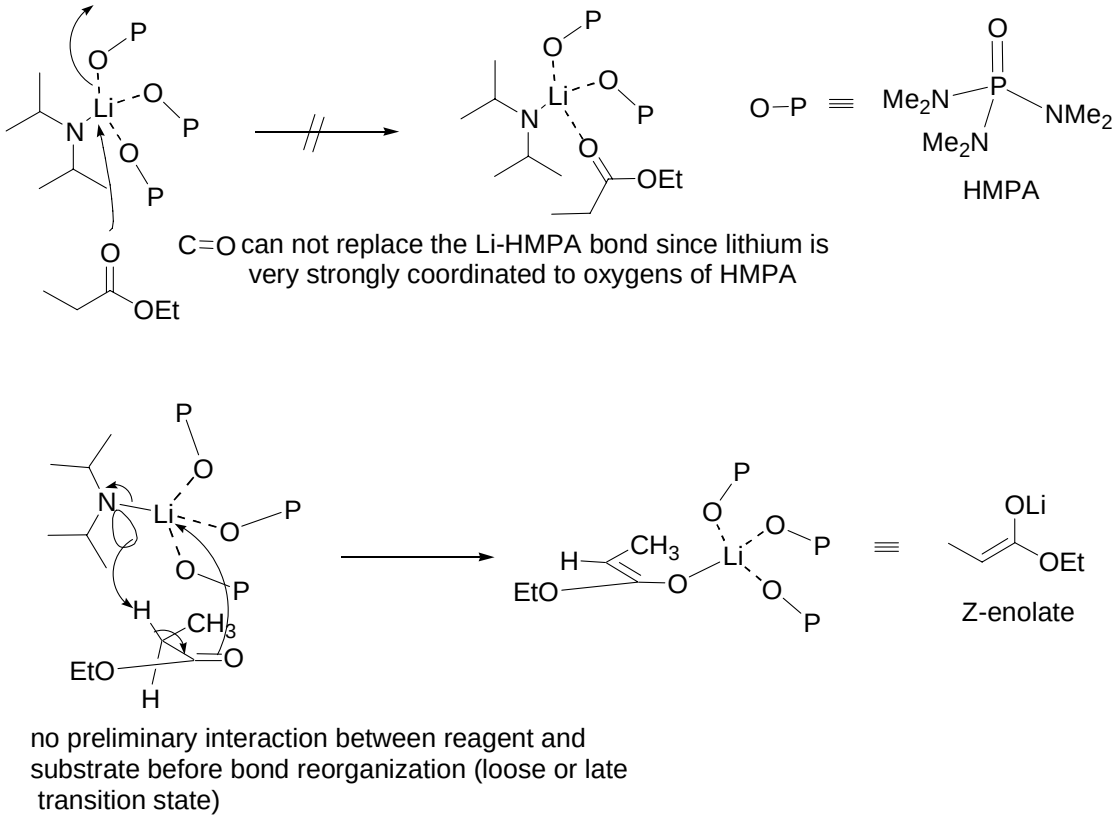


Figure 2.5.7: Model for solvation of lithium with HMPA and deprotonation of an ester.

Table 2 summarizes the effect of polar solvents on the formation of *E*/*Z* enolates of ethyl propionate. After examining different combinations of solvent systems, Ireland et al. reported that THF/45% DMPU or THF/23% HMPA are suitable solvent system for the formation of thermodynamic *Z*-enolate. This proves that enolate formation can proceed in both ways either under kinetic or thermodynamic control by changing the solvent system and thus controls the relative stereochemistry of newly forming chiral centers. But there is no comprehensive explanation for the formation of *Z*-enolate caused by the addition of dipolar solvents such as DMPU or HMPA until today.

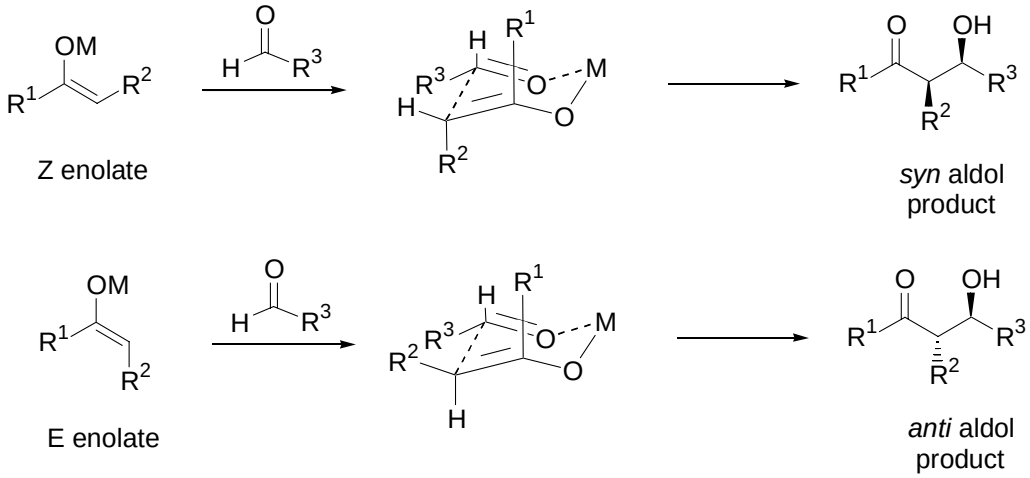
Table 2. Effect of solvent on stereoselectvity of silyl ketene acetal formation of ethyl propionate with LDA

Entry	Solvent	Ester:base	Z:E	Yield%
1	**THF**	**1:1**	**6:94**	**90**
2	THF/25%TMEDA	1:1	60:40	50
3	THF/50%TMEDA	1:1	----	0
4	THF/15% DMPU	1:1	37:63	90
5	THF/30% DMPU	1:1	67:30	85
6	**THF/45% DMPU**	**1:1**	**93:7**	**90**
7	THF/23% HMPA	1:1	85:15	90

2.5.5 *Syn* selective Evans Aldol reaction

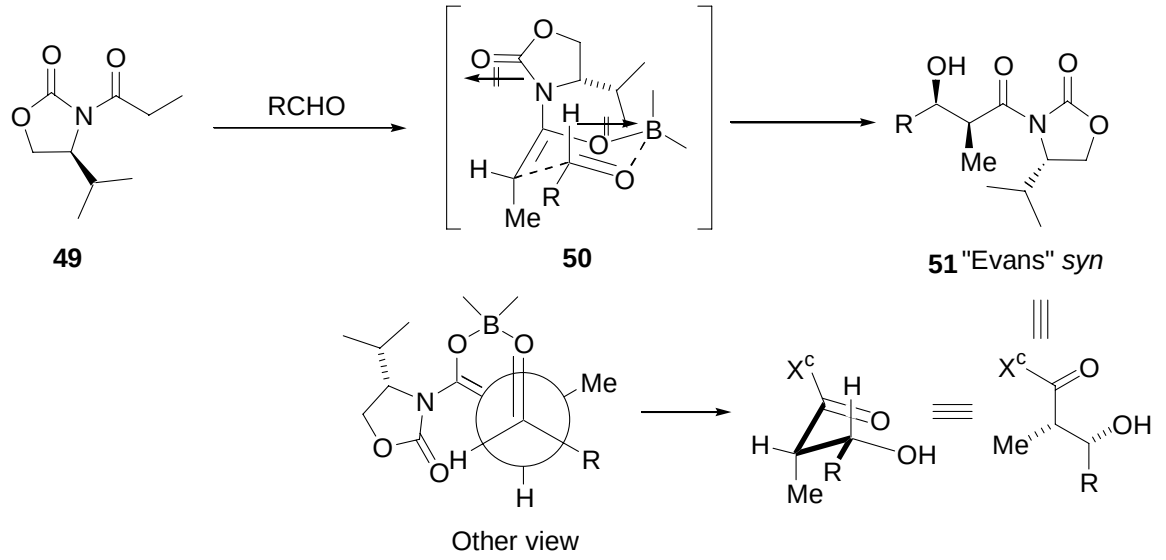
The aldol reaction is one of the most important methods of forming carbon-carbon bonds. The addition of an enolate to an aldehyde leads to the formation of at least one chiral center. This reaction, a classical method for the construction of carbon chains with oxygen functionality in 1,3-positions, has undergone remarkable changes in the last twenty years. The impulse for this development was given by the increasingly ambitious synthetic goals, which were provided in particular by the macrolide and polyether antibiotics with their many functional groups. New and particularly stereoselective variants of the aldol reaction have proved to provide the key to success. Chiral auxiliary chemistry has been exploited in asymmetric aldol reactions to generate both *syn* and *anti* selective products till to date since it was pioneered by Evans et al. in 1981.[46]

In general, *E*-enolates of ketones or ester derivatives produce *anti* aldol products and *Z*-enolates produce *syn* aldol reactions according to chair-like transition state proposed by Zimmerman, well known as Zimmerman-Traxler model (Scheme 14).[64]



Scheme 14: Zimmerman-Traxler transition states for *E*- and *Z* enolates.

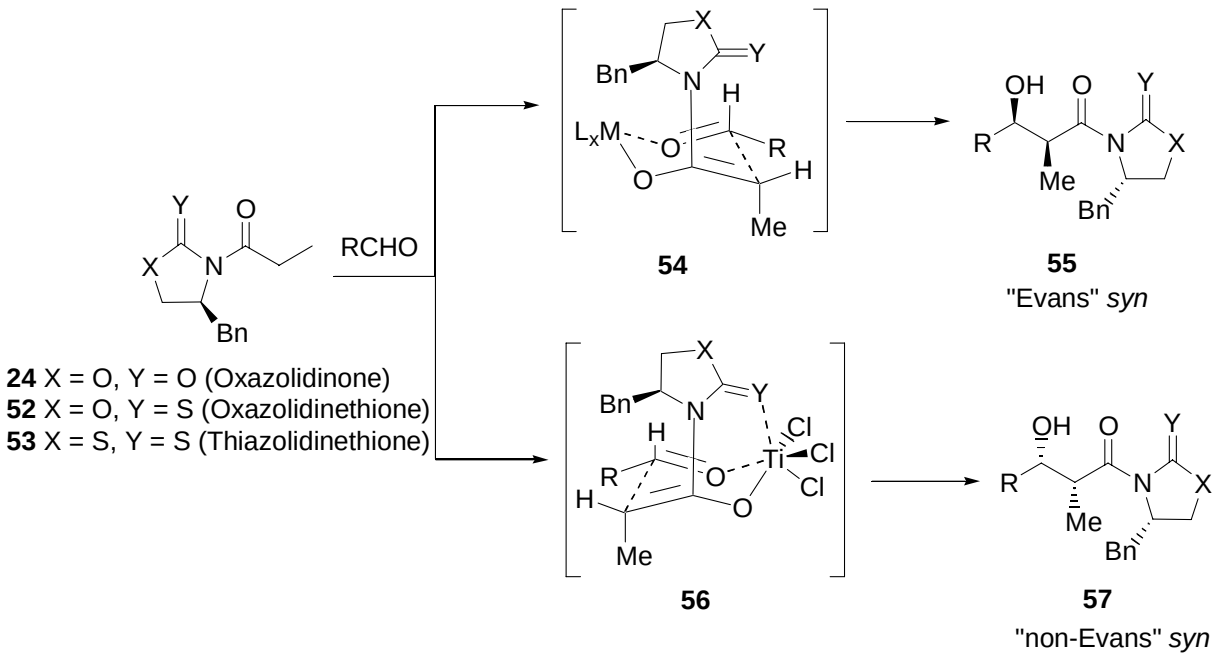
Evans et al. reported the application of chiral *N*-acyl oxazolidinones for diastereoselective syn aldol reactions.[65] After pioneering, this strategy became a very important tool in the synthesis of a broad range of bioactive natural products. Since acylated oxazolidinone is an imide, it forms exclusively *Z*-enolate (Figure 2.5.1) resulting in *syn* aldol product. To generate the *Z*-enolate of *N*-acyl oxazolidinone, the combination of dibutylboron triflate and triethylamine were used since boron forms a strong and short bond with oxygen and thus forms a tight six membered chair like transition state that leads to *syn* aldol adduct with high preference. The observed high diastereoselectivity of one *syn* product over the other is due to the arrangement of the carbonyl group of the oxazolidinone and the C-O bond of enolate arranges in an anti fashion to each other in order to minimize dipole repulsions. In this arrangement the aldehyde approaches the enolate from the less hindered side of the chiral auxiliary (Scheme 15).



Scheme 15: Favored transition states in the asymmetric aldol addition of boron enolates of chiral *N*-acyl oxazolidinones.

More recently, Crimmins and coworkers published a detailed account of their work in asymmetric aldol additions employing titanium(IV) enolates of *N*-acyloxazolidinones, *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones.[66] Crimmins addressed the importance of the dialkylboron enolates of *N*-acyloxazolidinones as the most commonly used enolates for the preparation of the Evans *syn* products.

The reaction with boron enolates proceeds via the non-chelated transition state **54** to deliver the well-known Evans *syn* products **55** (Scheme 16). However, the use of titanium(IV) enolates of *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones allows the reaction to proceed via the chelated transition state **56** to deliver the non-Evans *syn* products **60**. Furthermore, Crimmins reported the potential of titanium(IV) enolates of *N*-acyloxazolidinone **24**, *N*-acyloxazolidinethiones **52** and *N*-acylthiazolidinethiones **53** for the preparation of both Evans and non-Evans *syn* aldol products by variation of the reaction conditions.



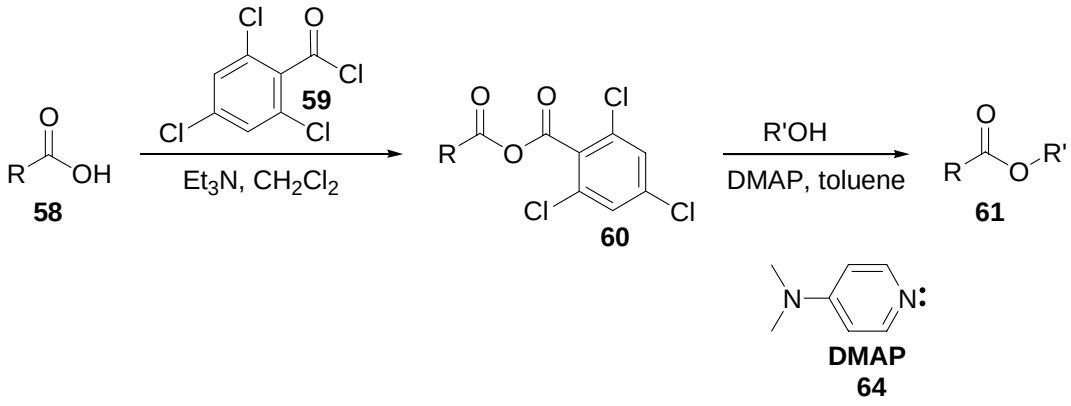
Scheme 17: Non-chelated **(54)** and chelated **(56)** transition states in the asymmetric aldol addition of titanium(IV) enolates of *N*-acyloxazolidinone, *N*-acyloxazolidinethiones and thiazolidinethiones.

Crimmins found that the diastereoselectivity of the titanium(IV) enolates of *N*-acyloxazolidinone, *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones to deliver the Evans *syn* product **55** is dependent on the nature and amount of the base used to generate the enolates. The Evans *syn* products were obtained, via the non-chelated transition state **54**, when titanium enolates were formed in the presence of two equivalents of a base such as (–)-sparteine. It was suggested that the second equivalent of amine coordinates to the metal center preventing further coordination of the imide or thioimide carbonyl to the metal center. Non-Evans *syn* products were obtained when only one equivalent of amine was used to generate the enolates of *N*-acyloxazolidinethiones and *N*-acylthiazolidinethiones. In this case the imide carbonyl or the thiocarbonyl coordinated to the metal center to produce the highly ordered chelated transition state **56**. Coordination of the imide carbonyl or thiocarbonyl to the metal center led to reversal of the π-facial orientation of the enolate in the transition state.[66]

2.5.6 Esterification using the Yamaguchi method and DCC/DMAP conditions

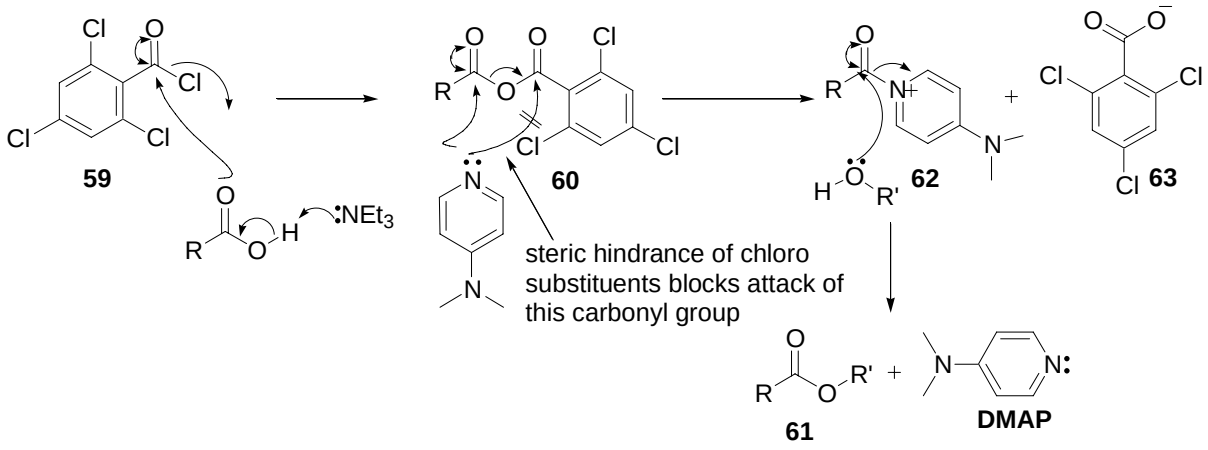
2.5.6.1 Yamaguchi esterification

Yamaguchi esterification[67] is one of the important tools in the total synthesis of many biological active natural and unnatural lactones as they contain at least one ester bond in their core structure. The Yamaguchi esterification allows mild conditions for the synthesis of highly functionalized esters.[68-71] The reaction sequence involves the formation of mixed anhydride **60** using the so-called Yamaguchi reagent i.e 2,4,6-trichlorobenzoyl chloride **59** with the carboxylic acid. The reaction of an alcohol with the mixed anhydride **60** in presence of DMAP generates the desired ester (Scheme 17).



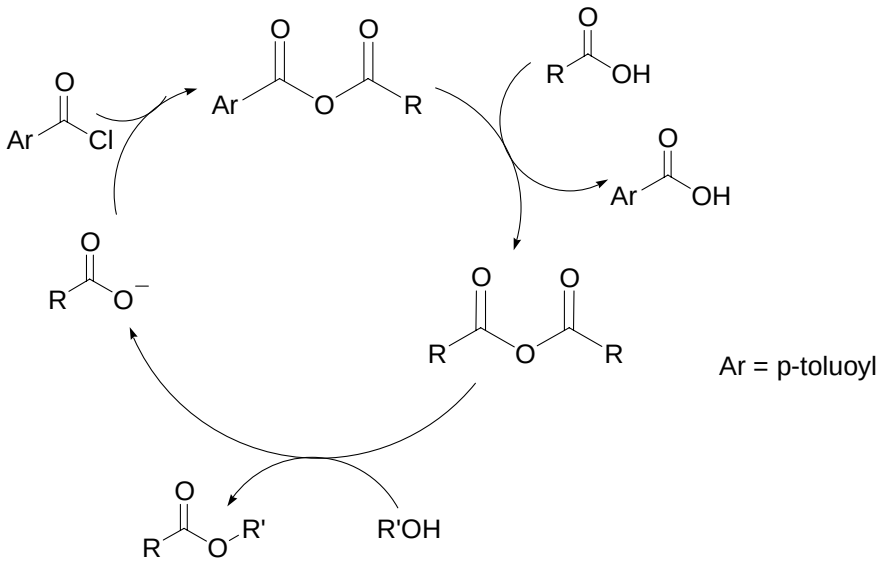
Scheme 17: Yamaguchi esterification.

The mechanism involves the replacement of the chloride in 2,4,6-trichlorobenzoyl chloride by the carboxylate giving rise to mixed anhydride **60**. DMAP (**64**) is a stronger nucleophile than alcohol, therefore it attacks the mixed anhydride **60**. Since the chlorine atoms on the benzene ring create steric crowding around the aromatic carbonyl group in the mixed anhydride **60**, DMAP attacks regioselectively on the carbonyl group of the former carboxylic acid leading to the formation of an acylated pyridinium salt **62** between carboxylic acid and DMAP. As DMAP is a good leaving group, attack of alcohol is quite fast and leads to ester bond formation (Scheme 18).



Scheme 18: Mechanismof the Yamaguchi esterification.

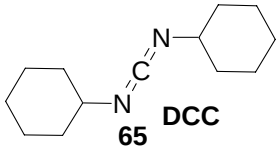
Recently Santalucia Jr. et al.[72] showed that aliphatic carboxylic acids can form ester bonds in a single step procedure by reacting with para-substituted unhindered benzoyl chlorides through the intermediacy of aliphatic symmetrical anhydrides. The byproduct of this step is the aliphatic carboxylate, which reenters the cycle (Scheme 19). Thus, until the regioselective completion of the reaction, there is always aliphatic carboxylate remaining, competing with the aromatic carboxylate, and the alcohol. The mechanism is based on the assumption that aliphatic carboxylates are better nucleophiles than aromatic carboxylates and alcohols. However, the aliphatic anhydride is also more electrophilic towards DMAP (not shown in the Scheme) or the alcohol than is the aromatic carbonyl of the mixed anhydride that is produced in situ. This proposed mechanism suggests that any aromatic acid chloride should be capable of producing preferentially and in situ the symmetric aliphatic anhydrides that then could be used in regioselective synthesis of aliphatic esters. It is important to consider the relationship between steric effects, electronic effects, and reactivity. The aliphatic anhydride produced in situ must be more electrophilic toward the alcohol than the aromatic carbonyl of the mixed aliphatic-aromatic anhydride for this procedure to succeed. *p*-Toluoyl chloride proved to be ideal for this transformation and catalytic amounts of DMAP are sufficient for the efficient transformation.



Scheme 19: Proposed reaction cycle for the esterification using aromatic acid chlorides.

2.5.6.2 Esterification using DCC/DMAP conditions (Steglich esterification)

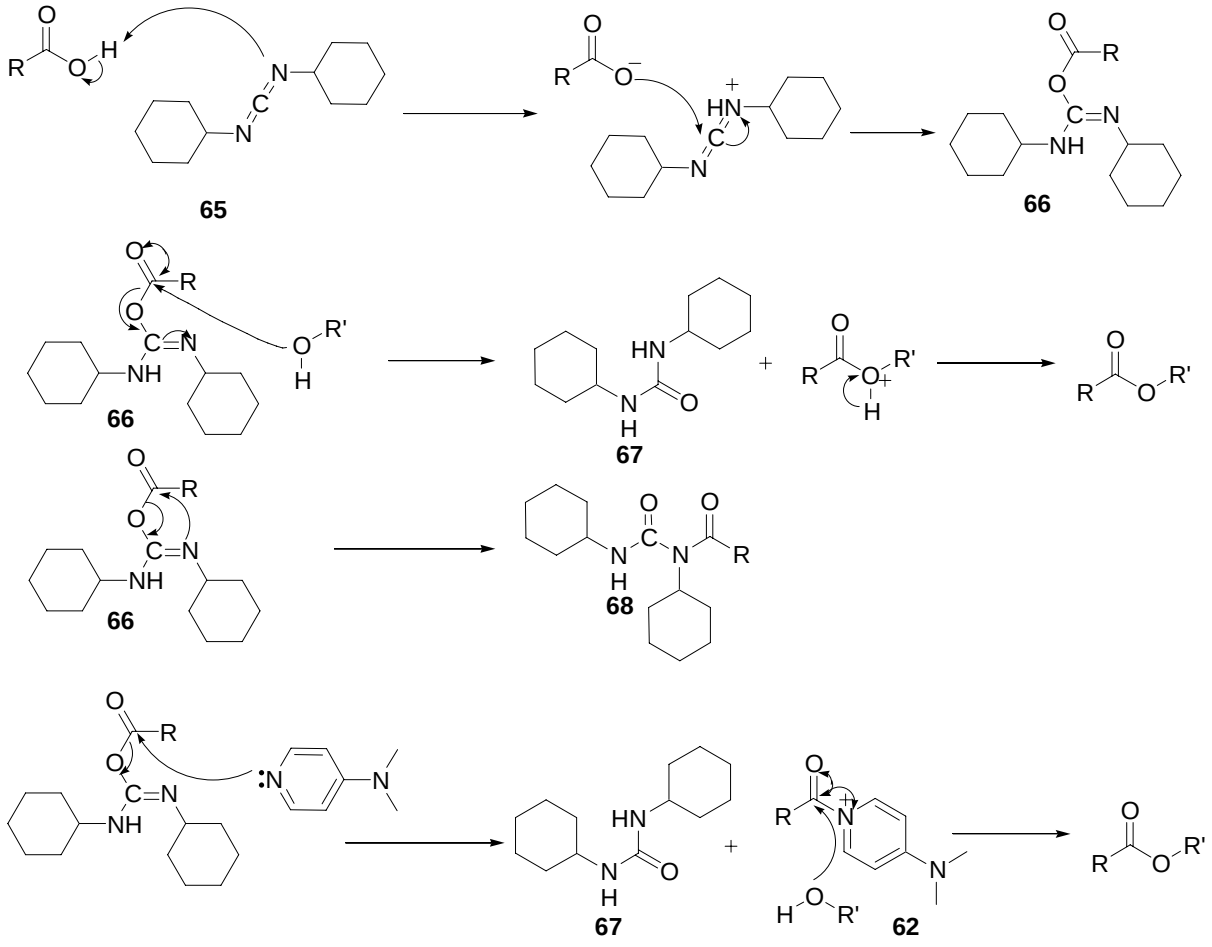
Esterification using dicyclohexylcarbodiimide (DCC) **65** is a mild reaction which allows the conversion of sterically demanding and acid labile substrates.[73, 74] It is one of the convenient methods for the formation of *tert*-butyl esters because *t*-BuOH tends to form carbocations and isobutene in acidic conditions.



65 **DCC**

Carboxylic acid reacts with DCC **65** to form O-acylisourea **66** intermediate, which offers similar reactivity to the corresponding acid anhydride like in the Yamaguchi esterification. Now the alcohol may attack the activated carboxylic acid to form an ester and stable dicyclohexyl urea **67** (DHU). But the attack of the alcohol is slower due to less nucleophilicity of the alcohol towards the O-acyl isourea **66**. Without the presence of catalytic amounts of bi character species (nucleophile as well as leaving group) such as DMAP, the acyl group can migrate to the nitrogen, leading to the formation of *N*-acyl-dicyclohexyl urea **68**. A common explanation of the DMAP acceleration suggests that DMAP, as a stronger nucleophile than

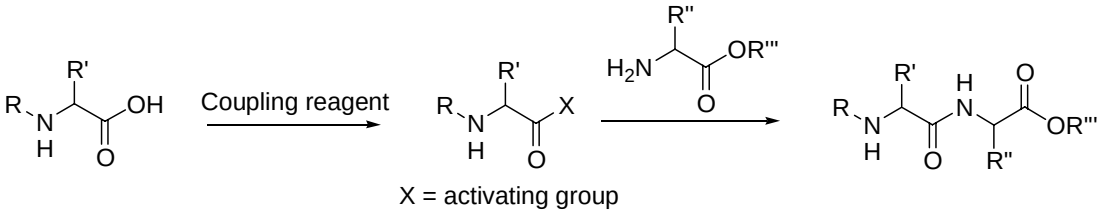
alcohol, reacts with the *O*-acylisourea **66** leading to a reactive acyl pyridinium species **62** ("active ester"). This intermediate cannot form intramolecular side products but reacts rapidly with alcohols. DMAP acts as an acyl transfer reagent in this way, and subsequent reaction with the alcohol gives the ester (Scheme 20).



Scheme 20: Mechanism for the formation of ester using DCC **62**.

2.5.7 Coupling reagents in solution phase peptide synthesis

A large number of natural products are based upon a peptide framework and exhibit a spectrum of biological activity. Over 200 new peptide based drugs are under different stages of development with 50% of them under clinical trials are prior to approval.[75] Due to the importance of peptides, it has become a challenge for synthetic chemists to develop methodologies to construct peptides over the past few decades.[76, 77] A key step in the peptide production process is the formation of an amide bond. This requires activation of carboxylic acids which is usually carried out using so-called the '**Peptide coupling reagents**' (Scheme 21).



Scheme 21: General strategy for peptide bond formation.

The area of coupling reagents began in the early 1950's with the introduction of DCC **65**, which at that time was already known and well studied. The difficulty in the complete removal of dicyclohexyl urea **67**, the byproduct from the reaction mixture, led to the development of several modified carbodiimide reagents (Figure 2.5.9).

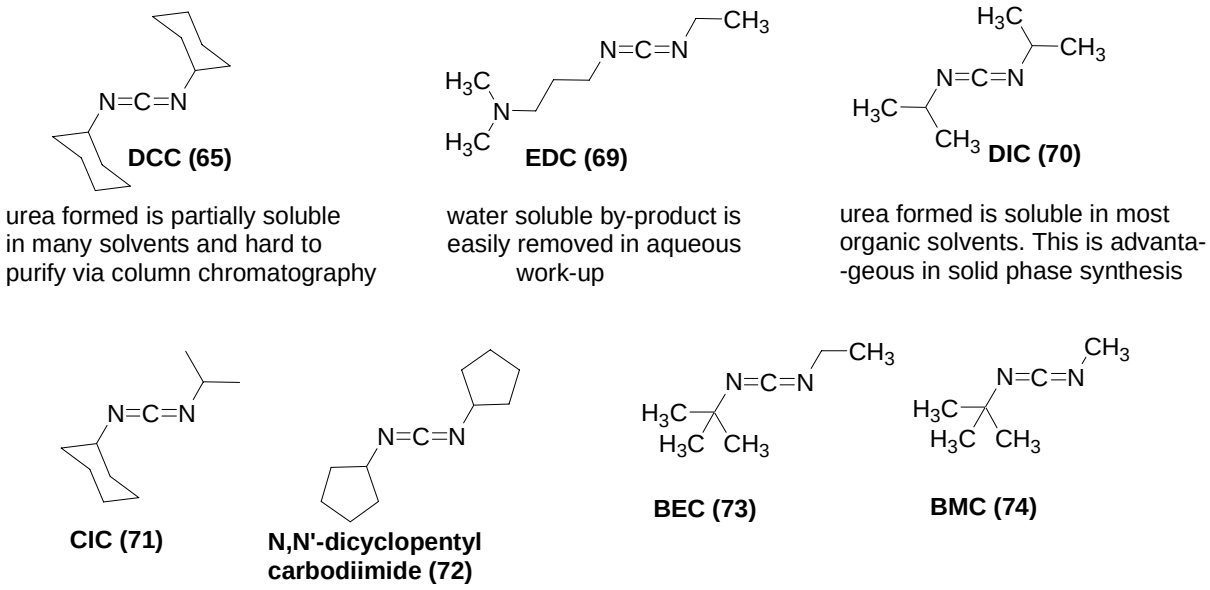
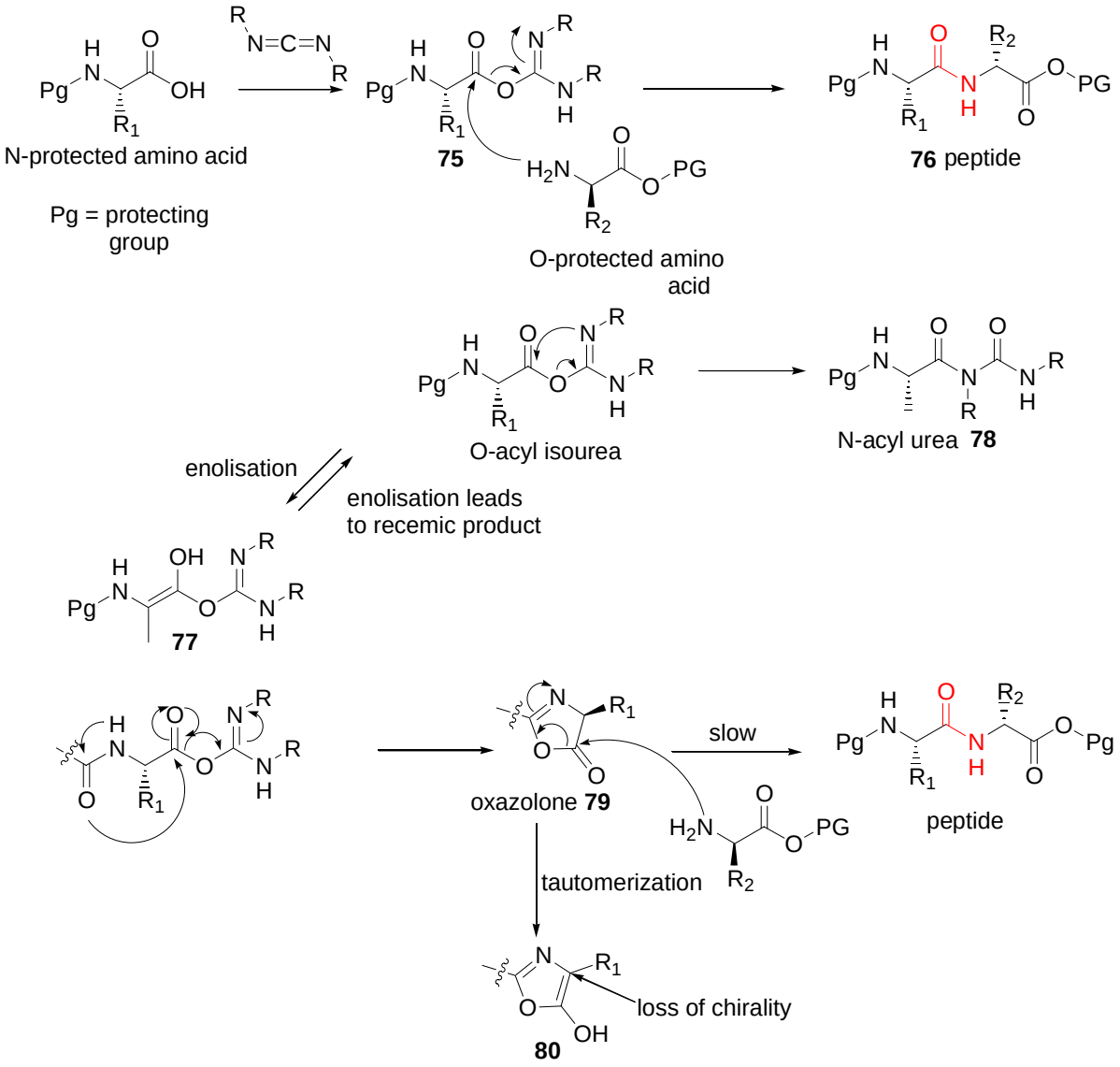


Figure 2.5.9: Various carbodiimide coupling reagents[78]

Unfortunately, carbodiimides did not come close to being 'ultimate' coupling reagents, because their high reactivity provokes racemization and side reactions. As shown in the esterification with DCC (Scheme 20), *N*-protected amino acid reacts with carbodiimide to form O-acyl isourea **75** which is the active species for the amide bond formation (Scheme 22). The O-acyl isourea **75** can react with the free amino group of an amino acid to give the corresponding amide **76**. This is the desired way of the process. The reactive O-acyl isourea **75**, however, can undergo enolization to **77** with a corresponding loss of chirality.

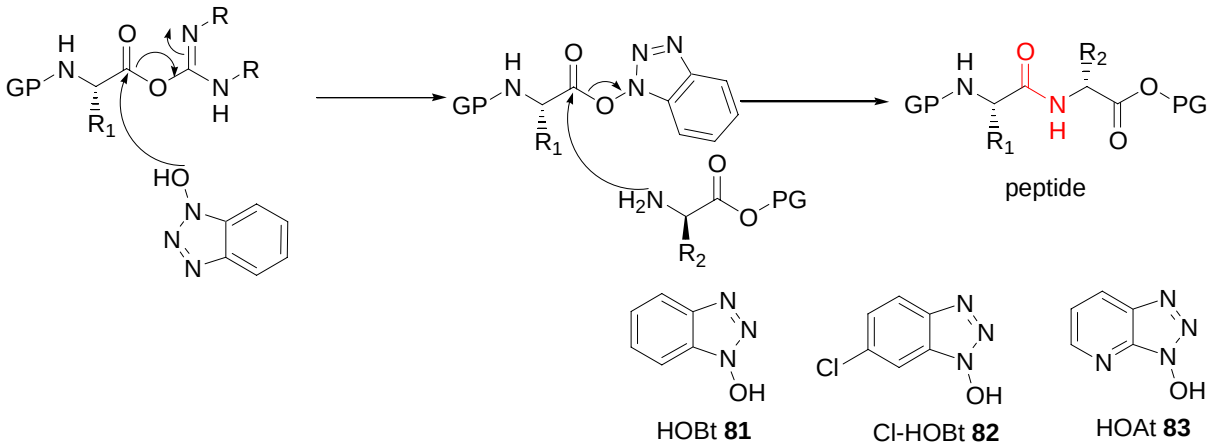


Scheme 22: Activation of *N*-protected amino acids with carbodiimide reagents.

Furthermore, it can also suffer a rearrangement to give the *N*-acyl urea **78**, which is not reactive. Last, but not least, it can sustain an intramolecular cyclization to give 5(4*H*)-oxazolone **79**, which is less reactive than the O-acyl isourea and can tautomerize to **80** with a corresponding loss of chirality as well.

At the beginning of the 1970's 1-hydroxy benzotriazole **81** (HOBt) was proposed as additive to DCC **65** to suppress racemization during the peptide coupling.[79, 80] Since then other benzotriazole derivatives such as 1-hydroxy-5-chloro-benzotriazole **82** (Cl-HOBt) or 1-

hydroxy-7-aza-benzotriazole **83** have also been used. The OBt-active esters of amino acids are less reactive than the O-acyl isourea, but more stable and less prone to racemization. All these factors make the addition of benzotriazole derivatives almost mandatory to maintain high yields and chiral configuration during the peptide bond formation with carbodiimide activation (Scheme 23).



Scheme 23: Formation of peptide bonds via OBt esters.

In the last decade onium (phosphonium and ammonium/uronium) salts of hydroxy-benzotriazole derivatives have been introduced for the formation of peptide bonds.[77]

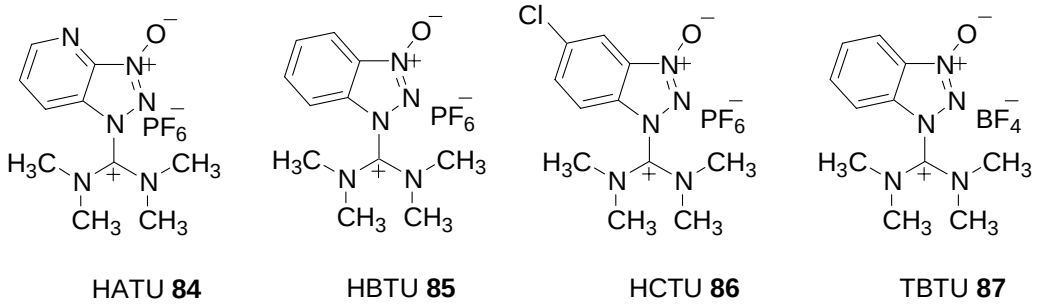
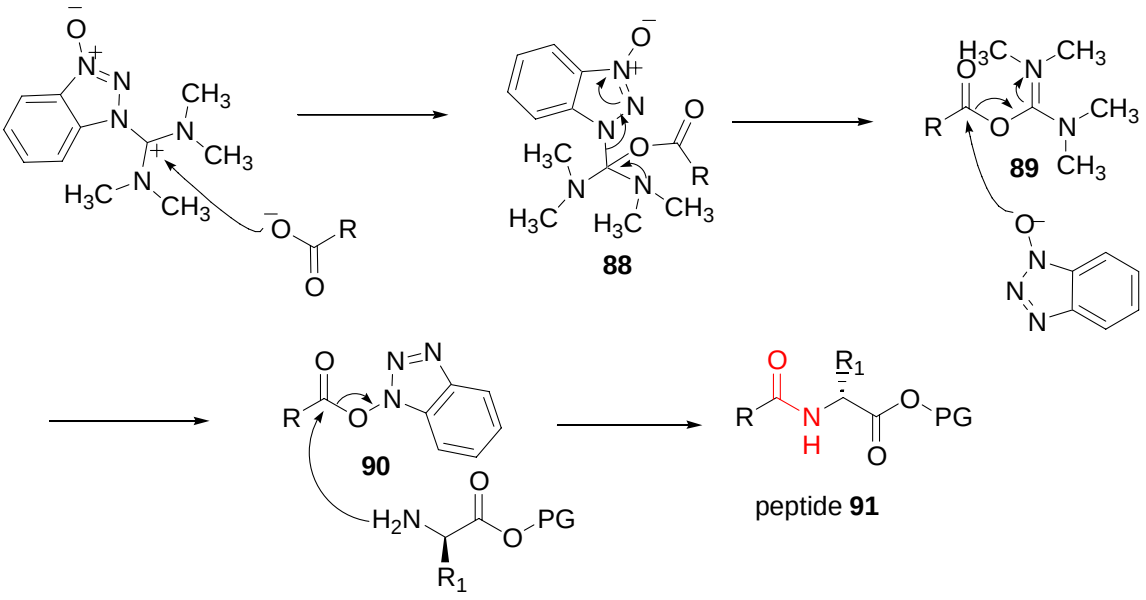


Figure 2.5.10: Common uronium coupling reagents.

HATU = *N*-[Dimethylamino)-1*H*-1,2,3-triazolo[4,5-b]pyridine-1-methylene]-*N*-methaminium hexafluorophosphate; HBTU = *N*-[(1*H*-benzotriazolo-1-yl)(dimethylamino)methylene]-*N*-

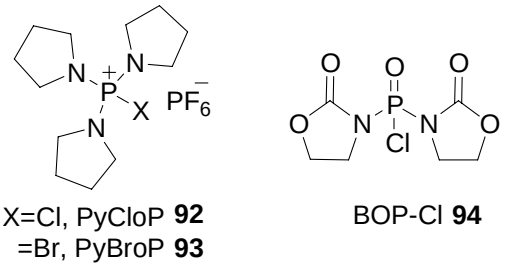
methylmethanaminium hexafluorphosphate *N*-oxide; HCTU = *N*-[(1*H*-6-Chlorobenzotriazolo-1-yl)(dimethylamino)methylene]-*N*-methylmethanaminium hexafluorphosphate *N*-oxide.

The species that reacts with onium salts is the carboxylate and therefore the presence of at least one equivalent of base is essential. The intermediate species, acyloxy-phosponium or amidinium salts have not been detected and react immediately with the benzotriazole derivative to give the corresponding OBt ester, which reacts with the amino component to give the corresponding amide (Scheme 24).



Scheme 24: Mechanism for the formation of peptide using uronium reagents.

It is difficult to form a peptide bond with *N*-alkyl amino acids as the steric bulk of an alkyl group on the amine reduces its nucleophilicity, slowing the reaction rate and thus leading to undesired side products. Furthermore, racemization is more problematic because of the α-proton which is now the most acidic proton whereas in natural amino acids the amide proton would be deprotonated first. It is important to note that in the case of *N*-methyl amino acids, HOBt suppresses the reaction rate and benzotriazole base reagents should be avoided in most cases. But there are some reagents which make the *N*-alkyl amino acid coupling feasible. PyBroP, PyCloP, BOP-Cl are the most general reagents for *N*-alkyl coupling reactions.[81]



X=Cl, PyCloP **92**
=Br, PyBroP **93**

BOP-Cl **94**

Figure 2.5.11: Common reagents for the peptide coupling of *N*-alkyl amino acids derivatives.

PyCloP = Chlorotrispyrrolidinophosphonium hexafluorophosphate;

PyBroP = Bromotrispyrrolidiniphosphonium hexafluorophosphate;

BOP-Cl = Bis(2-oxo-3-oxazolidinyl)phosphonic chloride.

3 Goal of research

The purpose of the present project is to construct conformationally constrained analogues of the depsipeptide jasplakinolide. Constraining the conformation of a peptide fragment by incorporating it in a macrocyclic structure represents an important strategy for enhancing both the binding strength and selectivity. In addition, this maneuver can suppress unwanted proteolysis. Studying the solution conformation of such a macrocyclic structure can provide important information on the peptide surface structure and the area that is presented to a receptor. Jasplakinolide, geodiamolide, chondramide, and doliculide display similar biological properties. Although several syntheses of jasplakinolide had been reported when this project began, there were no reports where variations had been performed. Jasplakinolide is ideally suited for modification due to its modular structure. As we discussed earlier, jasplakinolide is composed of hydrophobic polypropionate and polar peptide chains. The interest for the construction of analogues of jasplakinolide and as well as the others in the family of these novel biologically active macrocycles, lies in the synthesis of the polypropionate fragment as it might function as a conformational constraining element for these macrocycles through non bonded interactions like *syn*-pentane and 1,3-allylic interactions. Even though the synthesis of the polypropionate part, a 8-hydroxy acid is feasible,[43, 82, 83] the preparation of larger amounts is quite costly. Keeping the non bonded interactions as conformational controlling elements in mind, novel ω-amino and hydroxy acids were rationally designed in order to synthesize and study the solution conformations of jasplakinolide like cyclic peptides and depsipeptides.

Two recent publications from Terracciano et al. pointed to the importance of the polypropionate part in the construction of conformationally rigid analogues of jasplakinolide.[44, 45] Due to the lack of non bonded interactions in the polypropionate part of the Terracciano analogues, there were neither good restriction in the conformations nor good biological activity which supports our idea behind the synthesis of jasplakinolide analogues using rationally designed amino and hydroxy acids.

The objective of this study was the design and synthesis of novel amino and hydroxy acids which are bearing conformational controlling elements and to use them for constructing jasplakinolide like molecules in order to understand the structure-activity relationship using conformational and biological studies. These newly synthesized analogues should give some idea about the pharmacophoric part of the natural product.

4 Results and Discussion

4.1 Design of the novel ω-amino and hydroxy acids

The design of the amino acid **95** followed from looking at the conformational control elements in the hydroxy acid **3** (Figure 4.1.1). Thus, the 1,3-allylic interaction around the central trisubstituted double bond should position the allylic C-H in an eclipsed orientation to the double bond.[40] As a consequence, the methyl group at C-6 will point downwards and orient the 2-hydroxypropyl terminus to the other side, out of the plane of the double bond. The conformational situation at the carboxyl terminus seems to be less defined. Nevertheless, avoidance of *syn*-pentane interaction between C2-Me and C4-Me will cause the carboxyl group to point out of the plane of the central double bond as well. Our design plan then called for a rigidification of the vinylic C5-C6 bond. Accordingly, the allylic H was replaced with a two-carbon segment (see dashed lines in Figure 4.1.1), resulting in a *meta*-substituted aryl core. This simplification removes the stereocenter at C-6.

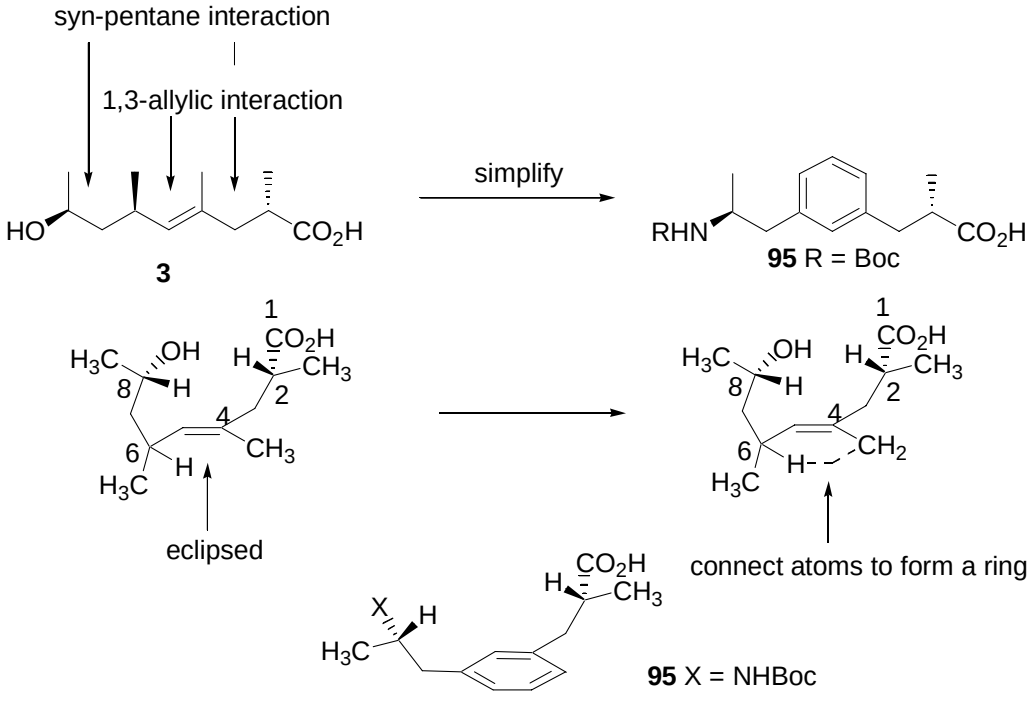


Figure 4.1.1: Design of the novel ω-amino acid **95**.[84]

In order to probe the design process, conformational search runs (Macromodel 7.0, MM2* force field, 1000 starting structures) were carried out on hydroxy acid **3** and the amino acid **95** (without the *N*-Boc protecting group). The search for the hydroxy acid **3** found four conformers within 4.184 kJ mol^{-1} of the minimum. The lowest conformer has the allylic C-H eclipsing the C4-Me, but only the carboxyl group is pointing out of the plane of the double bond (Figure 4.1.2). In the next lowest conformer **3b** (ΔE = 0.93 kJ mol^{-1}) 6-H, surprisingly, is

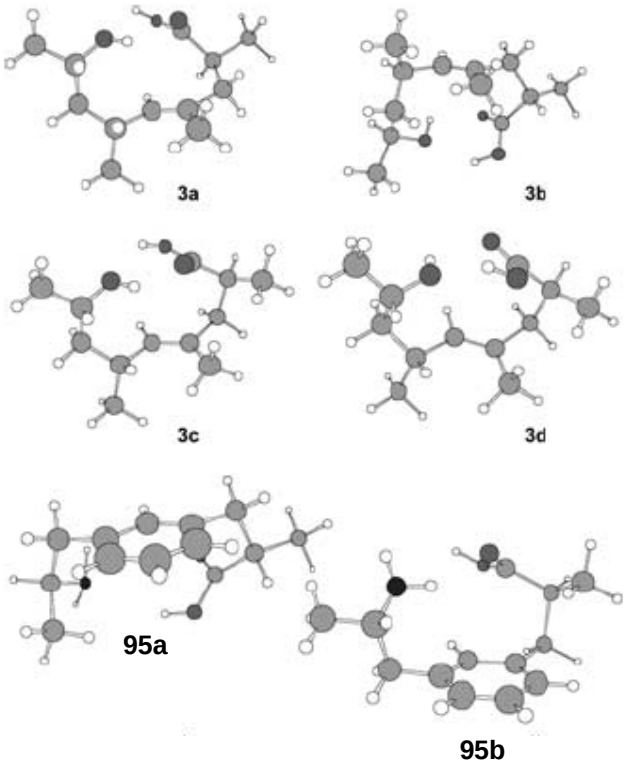


Figure 4.1.2: Calculated low energy conformations of the hydroxyacid **3** and amino acid **95** (Chem3D representations).

anti to the C4-Me. Basically, C4-Me is bisecting the angle C6-Me/C-6/C-7. This orients both termini to the other side of the central л-system. Conformers **3c** (ΔE = 2.00 kJ mol^{-1}) and **3d** (ΔE = 4.10 kJ mol^{-1}) actually match the expected conformation. Thus, 6-H eclipses the vinylic methyl and both termini extend nicely to one side. For the amino acid **95** we found two minimum energy conformers within 4.184 kJ mol^{-1} of the absolute minimum (E = 36.0 kJ mol^{-1}). In all cases the termini are pointed more or less orthogonal to the plane of the aryl ring. In

the second lowest conformer **95b** ($\Delta E = 2.45$ kJ mol^{-1}) the termini point to the opposite side of the aryl ring. Conformer **95b** does have striking similarity to the conformer **3c** of the hydroxy acid. Most likely electrostatic interaction and hydrogen bonding cause a substantial gain in energy if both groups point to the same side. By looking at several of the calculated minima, it seems that the conformation of the aryl analogue is more ordered and less flexible. An overlay of **3c** and **95b** shows a decent overlap validating the original design (Figure 4.1.3).

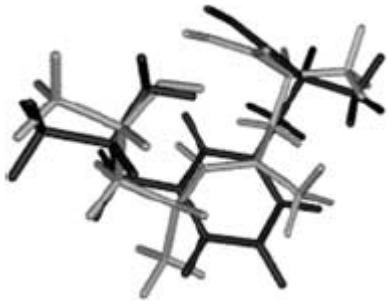
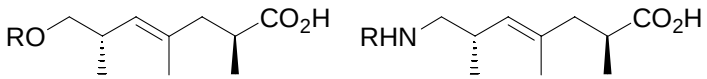


Figure 4.1.3: Overlay of the calculated conformers **3c** and **95b** (grey, hydroxy acid; black, aromatic amino acid).

Based on the non-bonded interactions the hydroxy acid **96** and the corresponding ω-amino acid **97** were designed as well. These are truncated versions of the 8-hydroxy acid **3** of jasplakinolide.



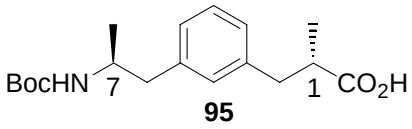
96 R = TBS or TBDPS **97** R = Boc

Figure 4.1.4: Structures of hydroxy- and amino acids **96** and **97**.

It can be seen that the amino and hydroxy acids **96** and **97** have one 1,3–allylic interaction and one *syn* pentane interaction. Due to the non bonded interactions, the methyl groups avoid steric repulsions and make the molecules less flexible. As a result of this, the carboxyl and hydroxy or amino groups at the end of the chain might point in one direction, thereby allowing bridging with a peptide fragment.

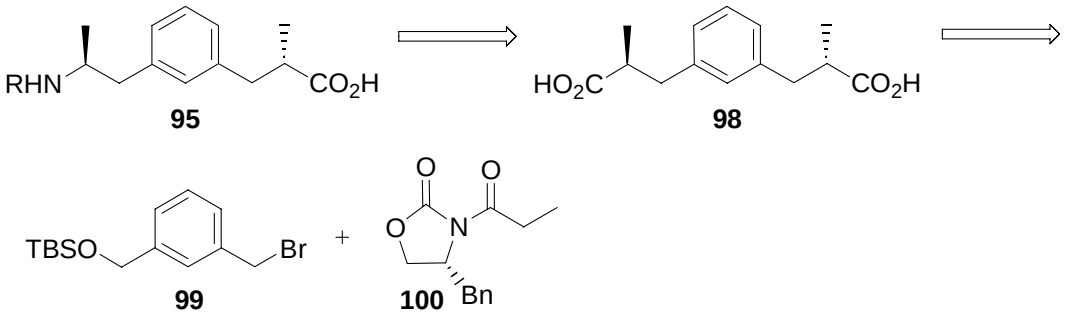
4.2 Retrosynthetic analysis and synthetic pathways for the designed amino and hydroxy acids

4.2.1 Retrosynthetic analysis of amino acid 95



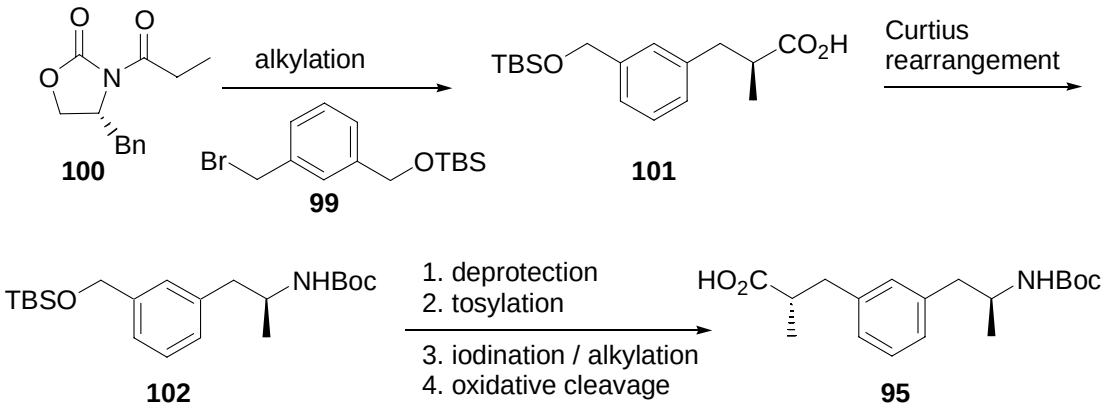
95

The amino acid **95** contains two stereocenters. If the amino function is generated by Curtius rearrangement, a possible precursor could be the C_2 symmetric dicarboxylic acid **98**. This symmetry might be exploited for the synthesis of **95** (Scheme 26).



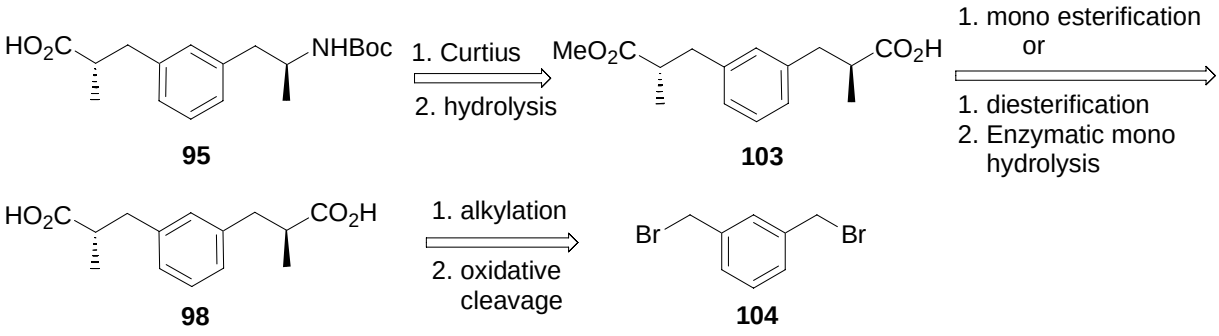
Scheme 26: Retrosynthetic plan for the novel ω-amino acid **95**.

Initially, the synthetic plan was to create both stereocenters individually by using asymmetric Evans alkylation as shown in Scheme 27. The amino group in the amino acid **95** could be obtained from a Curtius rearrangement of the acid **101** which can be synthesized by the hydrolysis of Evans alkylation product, which in turn could be obtained by alkylation of propionyl oxazolidinone **100** with benzyl bromide derivative **99**. As the benzyl bromide derivative **99** is not commercially available, it needs at least 3 steps to synthesize **99**. The total sequence would require around 10 steps to synthesize the amino acid **95** excluding the synthesis of chiral reagent **100**.



Scheme 27: Initial synthetic plan for the novel ω-amino acid **95**.

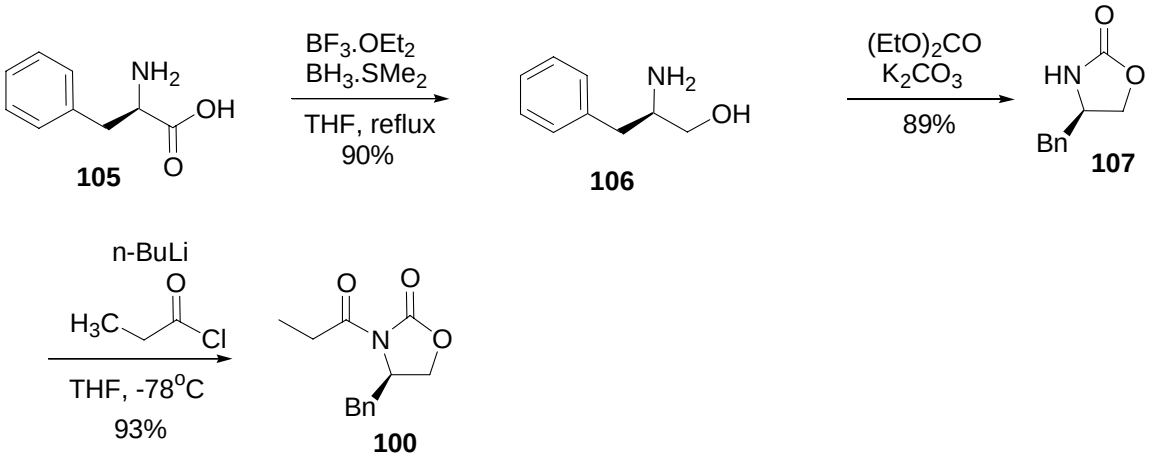
Based on the symmetry considerations discussed before, another route was developed for the sythesis of amino acid **95** from commercially available dibromo benzyl derivative **104** as shown in Scheme 28. In this pathway, amino acid **95** could be obtained by Curtius rearrangement and hydrolysis of the mono acid **103**, which can be obtained from the diacid **98** either by mono esterification in one step or by diesterification followed by selective enzymatic monohydrolysis in two steps. The diacid **98** can be obtained in two steps by double alkylation using propionyl oxazolidinone **100** with dibromo benzyl derivative **104** followed by hydrolytic removal of the chiral auxiliary.[85]



Scheme 28: Alternative pathway for amino acid **95**.

4.2.2 Synthesis of amino acid 95

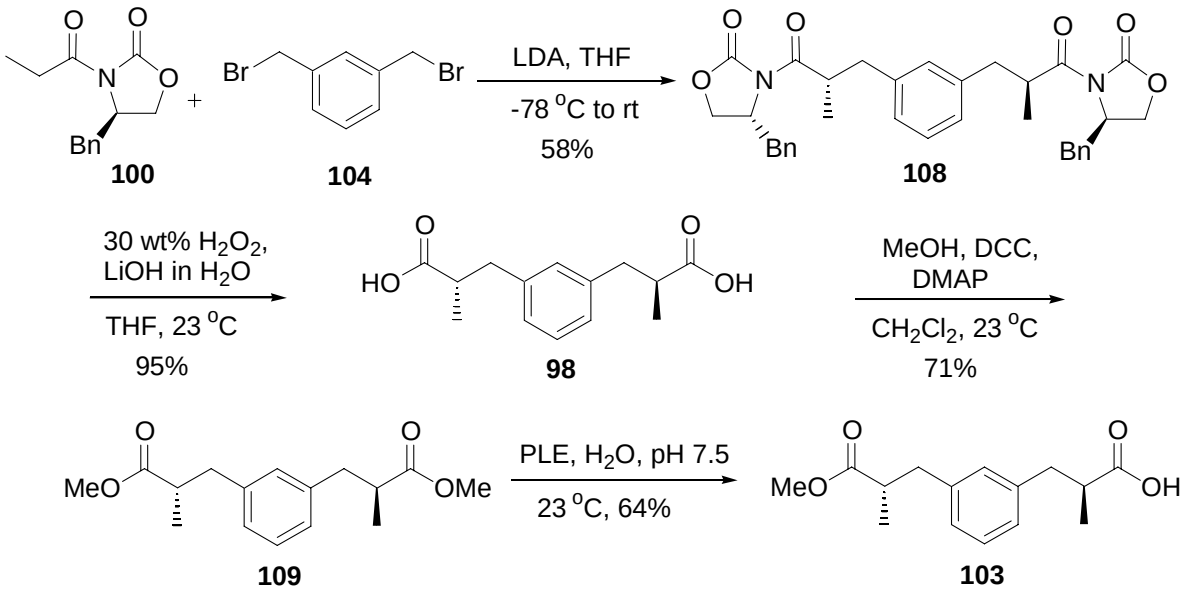
The synthesis of amino acid **95** began with commercially available 1,3-bis(bromomethyl)benzene (**104**), which was subjected to double alkylation with propionyl oxazolidinone **100**. The propionyl oxazolidinone **100** was synthesized from R-phenylalanine **105** according to an Evans procedure[86, 87] as shown in Scheme 29.



Scheme 29: Synthesis of *N*-propionyl-oxazolidinone **100**.

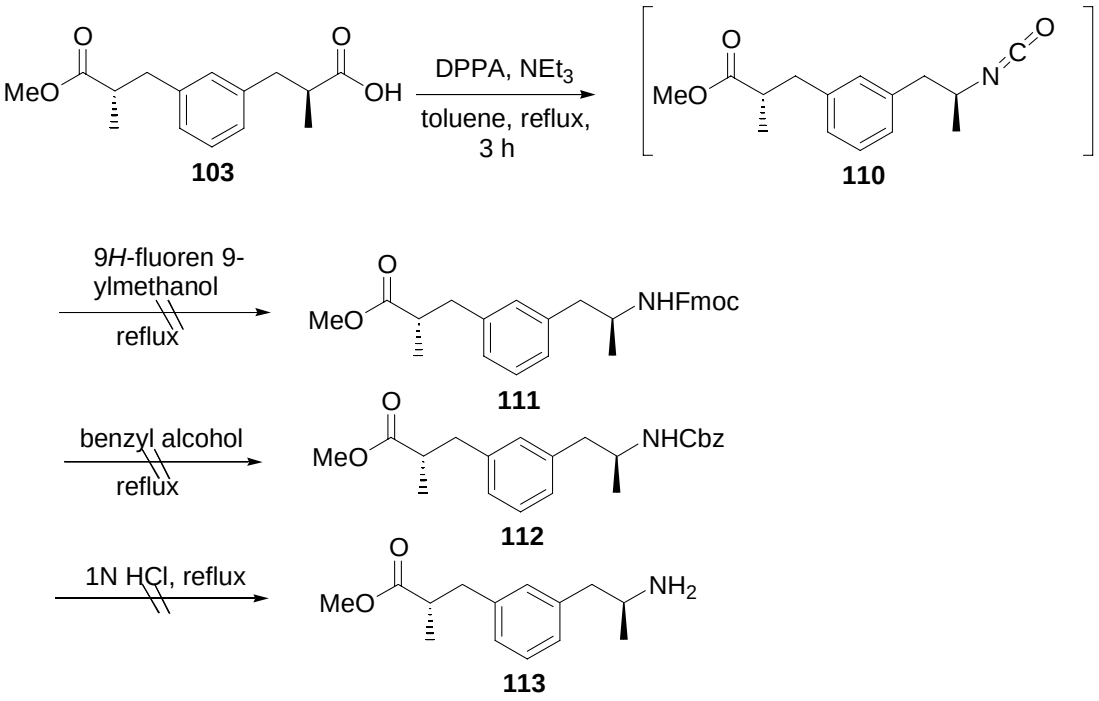
Initially for the alkylation, NaHDMS was used as a base. Even though the dialkylated product was formed, the yield was very low irrespective of the amount of excess chiral reagent **100** used and the mono alkylated product formed predominantly. LDA proved to be good reagent for this dialkylation. In small scale reaction yields were moderate varying from 50-55% and in large scale reaction yields were better producing up to 60% of the desired compound **108**. (Scheme 30). The yield might be increased by using excess of propionyl oxazolidinone. Oxidative hydrolysis of chiral auxiliary led to the diacid **98**, which was in turn converted to the dimethyl ester **109** via DCC-mediated esterification. This maneuver was necessary in order to allow for a monohydrolysis of the homotopic ester groups. This could be achieved by esterase induced hydrolysis. It is necessary to use only catalytic amounts of pig liver esterase for this purpose. Otherwise, over hydrolysis can occur in no time and convert diester **109** back to the diacid **98**. In this case, 100 units (2.5 mg) of pig liver esterase were used for the conversion of

one mmol of dimethyl ester **109** to mono ester **103** in 12 h at room temperature (Scheme 30).[88]

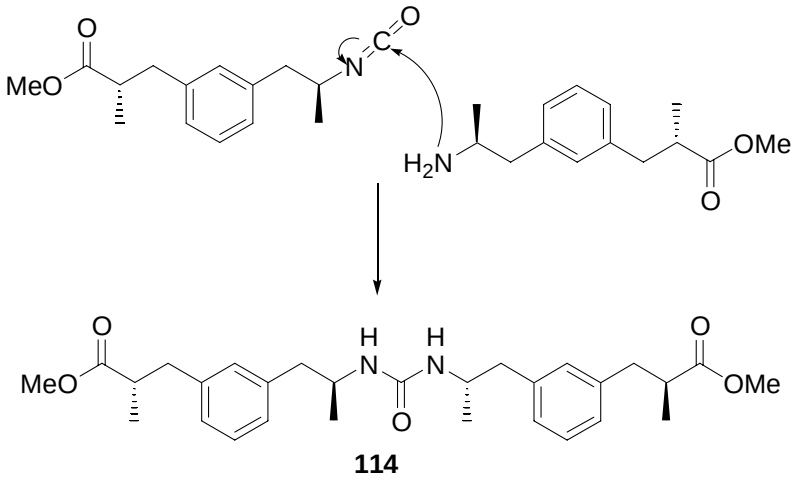


Scheme 30: Synthesis of mono ester **105**.

With the monoester **103** in hand, the Curtius rearrangement was tried to synthesize the Fmoc protected amino acid in presence of DPPA/NEt_3 and 9*H*-fluoren-9-ylmethanol (Scheme 31). However, the reaction did not work and the reactant got decomposed. The same was observed when benzyl alcohol was used in order to obtain the Cbz protected amino acid as reported in literature.[89] Also attempts failed to synthesize the unprotected amine by Curtius rearrangement using 1 N HCl as reported in our lab.[90] Then it was decided to follow the same procedure as reported in the original literature[57, 58] to make the Boc protected amino acid using *t*-BuOH as the nucleophile for attack on the isocyanate **110**. Initially the reaction worked with very low yield and the major product obtained was the urea derivative **114**. The reason for obtaining the urea **114** might be due to water in *t*-BuOH. Then some isocyanate could react with water and form the amine **113**, which in turn would act as nucleophile and attack the isocyanate as shown in Scheme 32. This result was confirmed by using NMR and HRMS methods. As both products were not separable by column chromatography the NMR was not very pure.



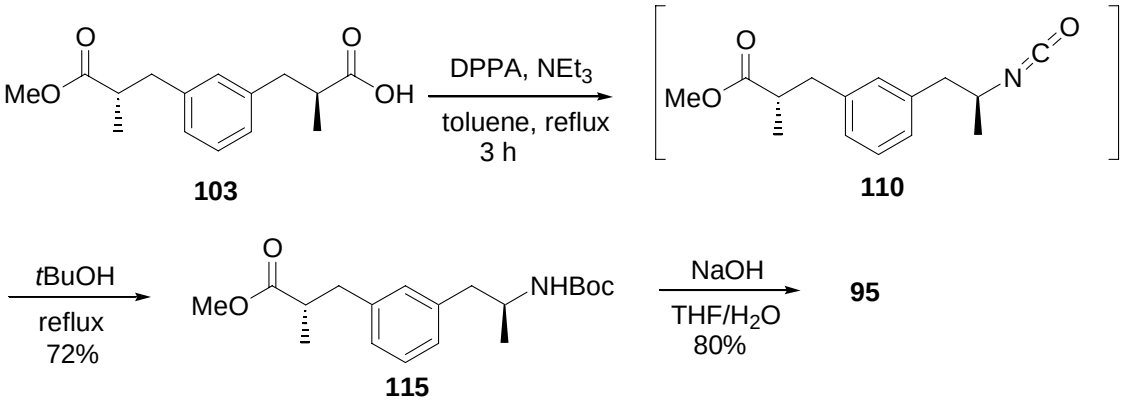
Scheme 31: Attempts to perform the Curtius rearrangement on acid **103**.



Scheme 32: Mechanism for the formation of the urea **114**.

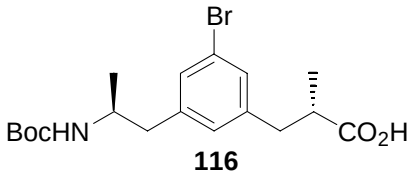
After realizing that *tert*-butanol can act as good nucleophile towards isocyanate **110**, the mono acid **103** was treated with diphenylphosporyl azide followed by heating of the reaction mixture in the presence of distilled *tert*-butanol. This affected a Curtius rearrangement resulting in the

N-Boc protected ω-amino acid ester **115** in good yield. Basic hydrolysis of the ester led to the desired acid **95** (Scheme 33). This route secures the novel amino acid **95** in gram quantities.



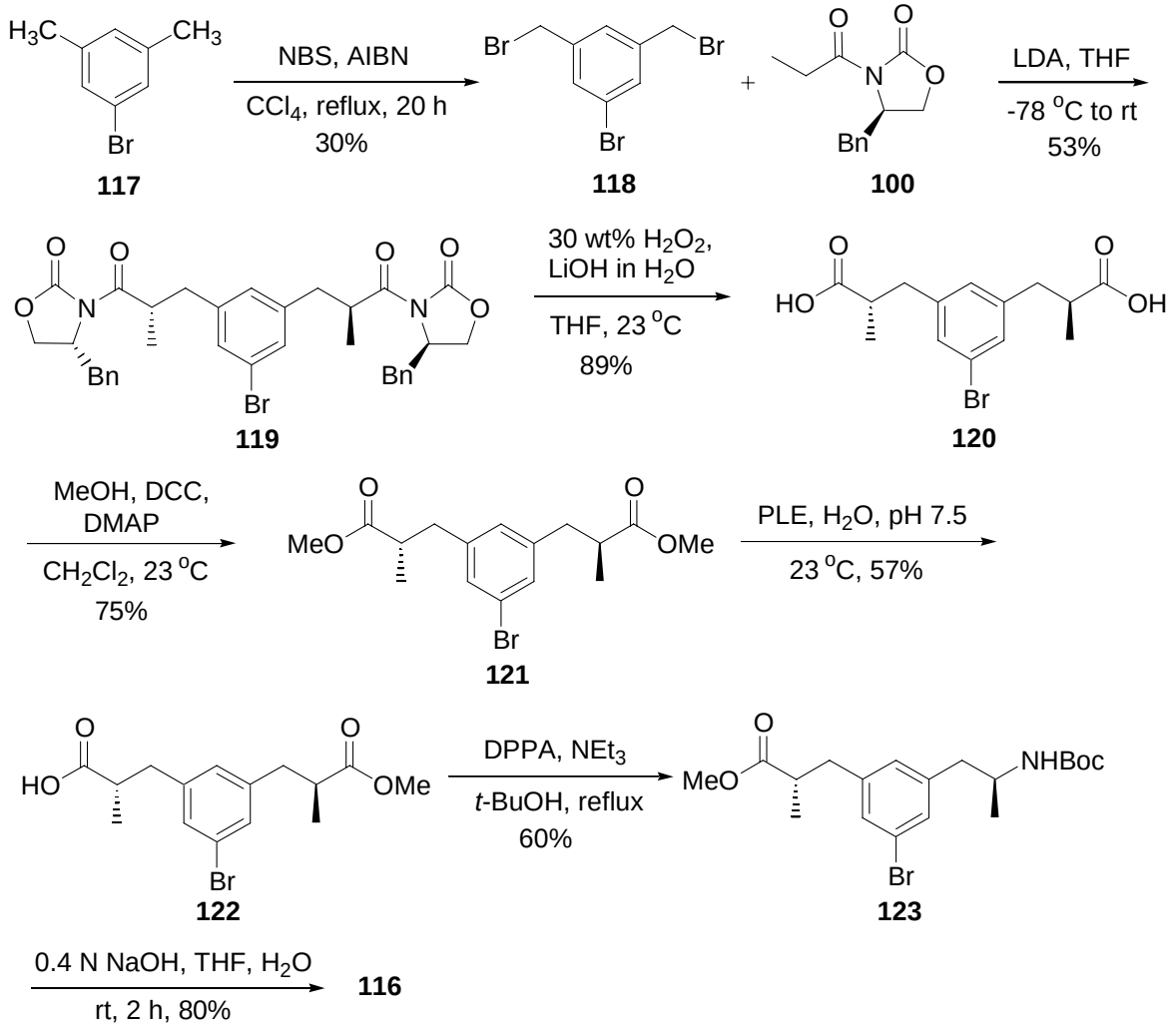
Scheme 33: Synthesis of amino acid **95**

After successfully achieving the synthesis of ω-amino acid **95**, we decided to synthesize the corresponding bromo amino acid **116** which has the bromine in the 3rd position of the aromatic ring of the amino acid **95**. The purpose of the synthesis amino acid **116** is, that it can create conformational constraint in cyclic peptides and at the same time some side chains could be attatched to the resulting peptides through the aromatic region of this amino acid using various coupling reactions.



Almost the same strategy was used in order to synthesize bromo amino acid **116** (cf. Schemes 30 and 33). The synthesis of amino acid **116** started with commericially available 3,5-dimethylbromobenzene **117**. Radical bromination of **117** using *N*-bromosuccinimide in presence of AIBN provided the tribromo benzyl derivarive **118** in 30% yield.[91, 92] Alkylation of propionyl oxazolidinone **100** with bromo benzyl derivative **118** using LDA at -78 ^{o}C produced the double alkylated product **119** in 53% yield (Scheme 34). Subsequent cleavage of the chiral auxiliary using mild oxidative hydrolysis conditions (H_2O_2 / LiOH) gave the diacid

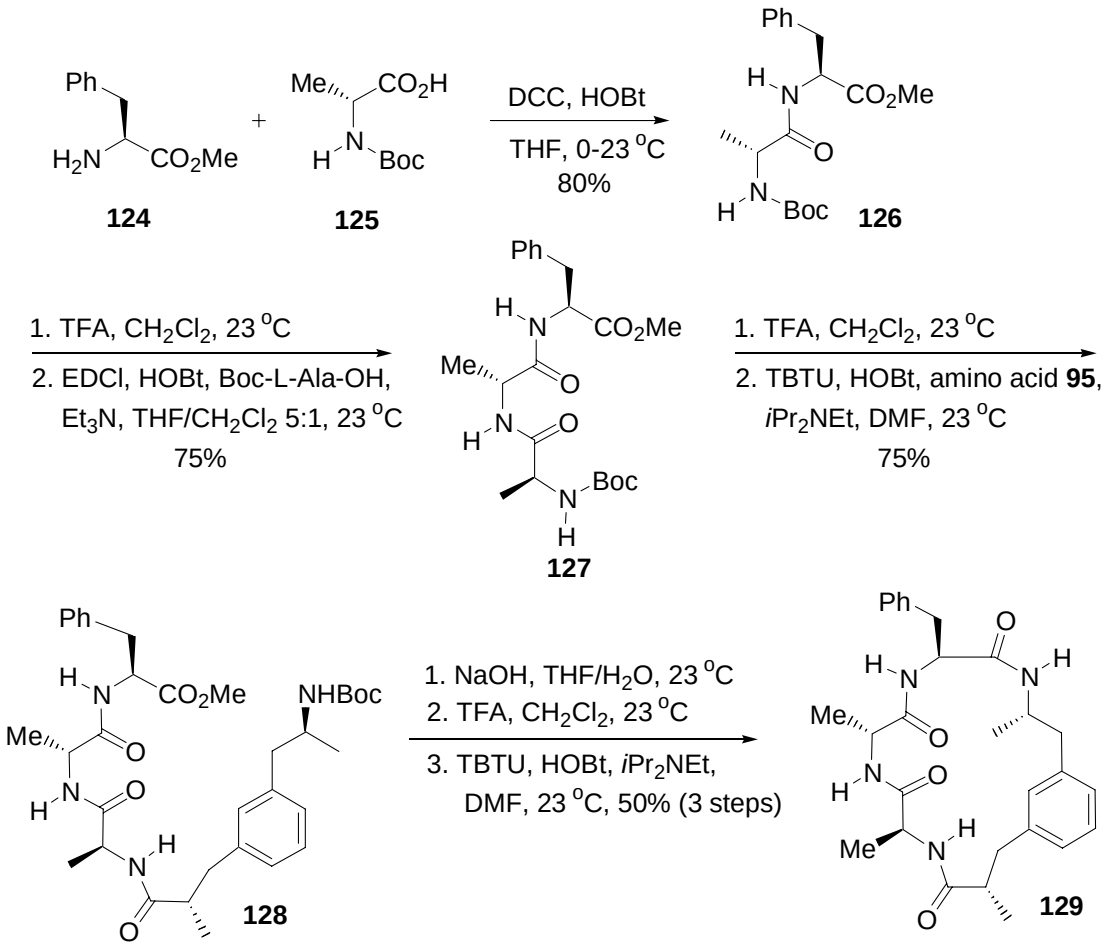
120 in 89% yield. DCC mediated esterification of diacid **120** with methanol in presence of catalytic amounts of DMAP produced the dimethyl ester **121** in 75% yield. Enzymatic monohydrolysis of the diester **121** using Pig liver esterase led to the monoester **122** in 57% yield. Curtius rearrangement of the resulting monoester **122** using DPPA in presence of triethylamine in *t*-BuOH afforded the corresponding Boc protected amino acid methylester **123** in 60% yield. Basic hydrolysis of the methylester **123** using 0.4 N NaOH produced the desired bromo amino acid **116** in 80% yield.



Scheme 34: Synthesis of bromo amino acid **116**.

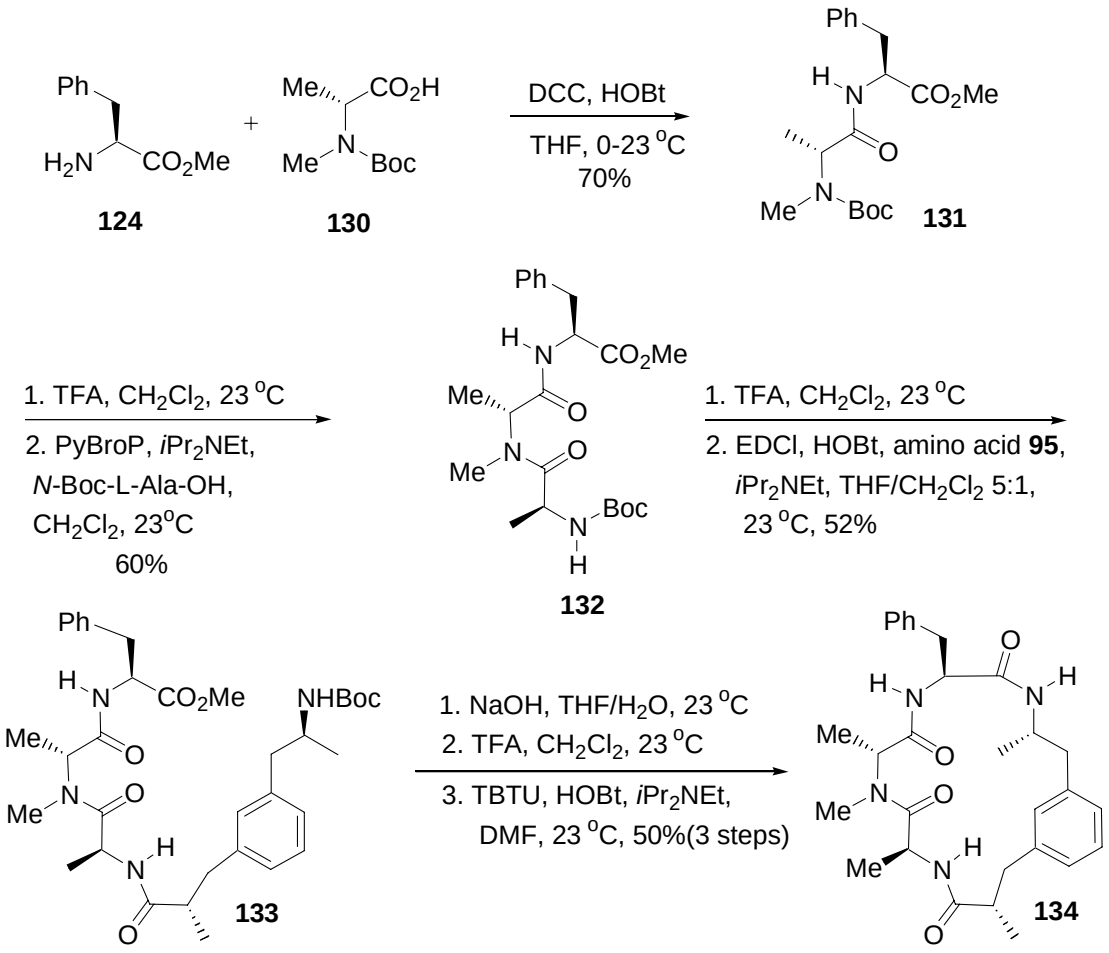
4.2.3 Synthesis of jasplakinolide analogues by incorporating the amino acid 95

With the amino acid **95** in hand, the synthesis of various macrocyles was targeted, in which the two ends of the acid **95** are bridged with some tripeptide fragments. Our goal was to prepare pairs of tripeptide fragments with one of them carrying a *N*-methyl group at the middle amino acid. The conformational analysis of the corresponding macrocycles should provide some hints on the mutual influence of the parts contained in the macrocycle. For this study L-phenylalanine, D-alanine, L-alanine were chosen to form a tripeptide. The tripeptide was assembled by a classical Boc strategy as shown in Scheme 35. That is, DCC-mediated condensation of the phenylalanine derivative **124** with *N*-Boc-D-alanine **125** gave the dipetide **126**. After cleavage of the Boc protecting group with trifluoroacetic acid, coupling of the free amine with *N*-Boc-L-alanine using the coupling reagent 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI) provided the tripeptide **127** in 75% yield. Cleavage of Boc using TFA and TBTU mediated condensation of the resulting amine with the amino acid **95** led to the acyclic tetrapeptide **128**. Hydrolysis of the methyl ester, removal of the Boc group and macrolactam formation with 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) in DMF (0.001 M) gave rise to jasplakinolide (geodiamolide) analogue **129** in 50% yield (Scheme 35).



Scheme 35: Synthesis of jasplakinolide (geodiamolide) analogue **129**.

In a similar manner, tripeptide **132** was assembled (Scheme 36). Here, *N*-Boc-*N*-methyl-D-alanine[93, 94] **130** became the central amino acid fragment. For the formation of the peptide bond to the *N*-methylated amine, the coupling reagent bromotrispyrrolidinophosphonium hexafluorophosphate (PyBroP) came to use. After liberation of the terminal amine using TFA, EDCI-mediated condensation with the amino acid **95** provided the *seco*-compound **133**. Ester hydrolysis, cleavage of the Boc protecting group and macrolactam formation using the same conditions as for **129** delivered the jasplakinolide (geodiamolide) analogue **134** with a *N*-methyl amide group.



Scheme 36: Synthesis of jasplakinolide (geodiamolide) analogue **134** containing a *N*-methyl amide bond.

One more pair of jasplakinolide analogues **135** and **136** were synthesized by incorporating the amino acid **95**. These analogues were prepared using a similar strategy by Shazia Yasmeen. The variation of these analogues from the others **129** and **134** is the presence of a β-amino acid. The compounds **135** and **136** are structurally similar to jasplakinolide as both are 19-membered macrocycles. The four analogues containing the amino acid **95** were synthesized in order to probe the conformational variations between the substrates containing different ring size and effect of *N*-methyl amide bond on the conformations of similar macrocycles.[84] The detailed conformational analysis will be discussed in the conformational analysis section.

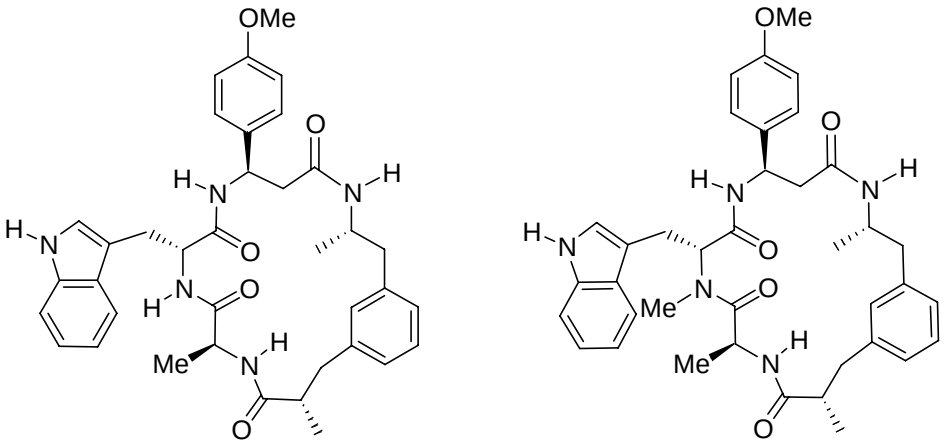
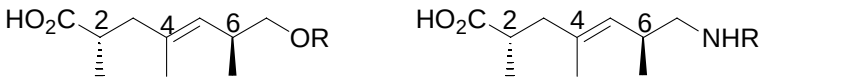


Figure 4.2.1: Jasplakinolide analogues containing a β-amino acid and amino acid **95**.

4.2.4 Retrosynthetic analysis of hydoxy and amino acids 96 and 97

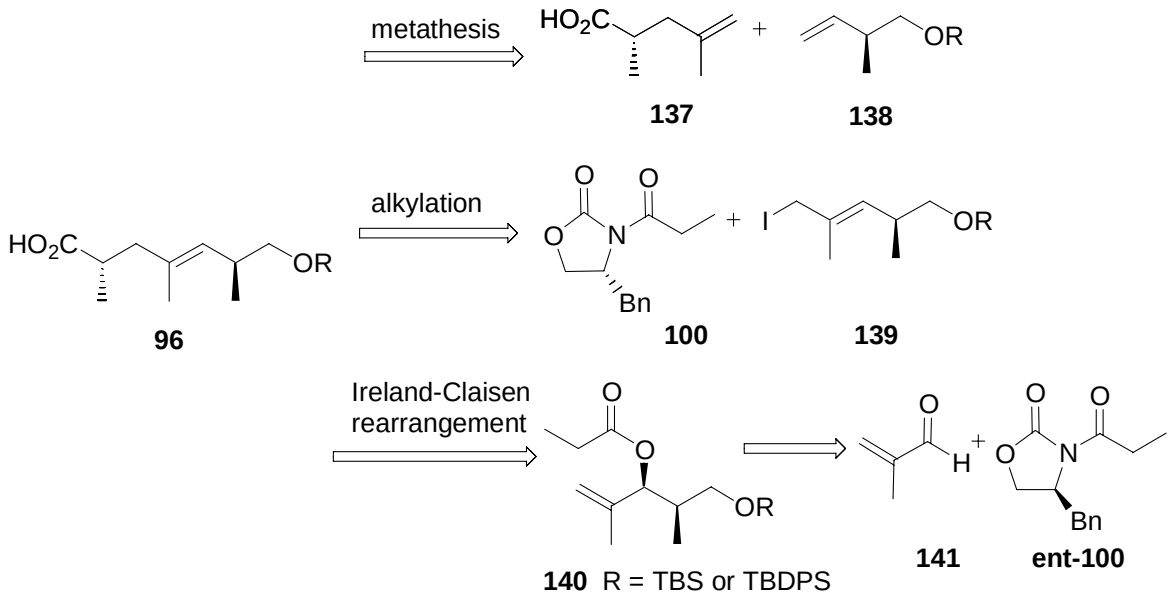
While the amino acid **95** was relatively easy to synthesize, it seemed that the aryl ring imposes too much conformational constraint. Therefore we decided to design and synthesize truncated versions of the hydroxy acid **3** of jasplakinolide. By removing a *syn*-pentane interaction on the alcohol terminus we reached hydroxy acid **96** and amino acid **97**. They should be easily accessible. One further advantage would be that the pair **96**/**97** should allow to probe the effect of an ester versus amide bond on the conformation of a derived macrocycle.



96 R = TBS or TBDPS **97**

From a retrosynthetic point of view, one has to address the two chiral centers at C-2 and C-6 and the double bond configuration. As both acids contain the same core structure and the amino acid **97** might be fashioned from the hydroxy acid **96**, a divergent synthesis could be possible. The cleavage of the C4-C5 olefin bond results in two allylic fragments **137** and **138**. The union of these two moieties may be envisaged via a metathesis coupling as shown in Scheme 37. As previous experience in our lab showed the cross metathesis leads to side products and does not really work for this alkene combination.[95, 96] An alternative would be

alkylation of propionyl oxazolidinone **100** with alkyl iodide **139**. However, in this strategy synthesis of the alkyl iodide would require too many steps and costly the Roche ester as a starting material. Therefore, it was decided to use the Ireland-Claisen rearrangement as a key step to synthesize the hydroxy acid **96**, as it has been reported in previous syntheses of jasplakinolide hydroxy acid **3**. This way the synthesis of hydroxy acid **96** should require only 5 steps. Evans *syn* aldol reaction[97] between *N*-propionyl oxazolidinone **ent-100** and methacrolein **141** would provide the chiral center at C-6. The ester **140** could be obtained from aldol product **142** by subsequent reduction, monoprotection and acylation. Finally, the Ireland-Claisen rearrangement of ester **140** would provide the chiral centre at C-2 and as well as the *E*-configuration around the double bond.

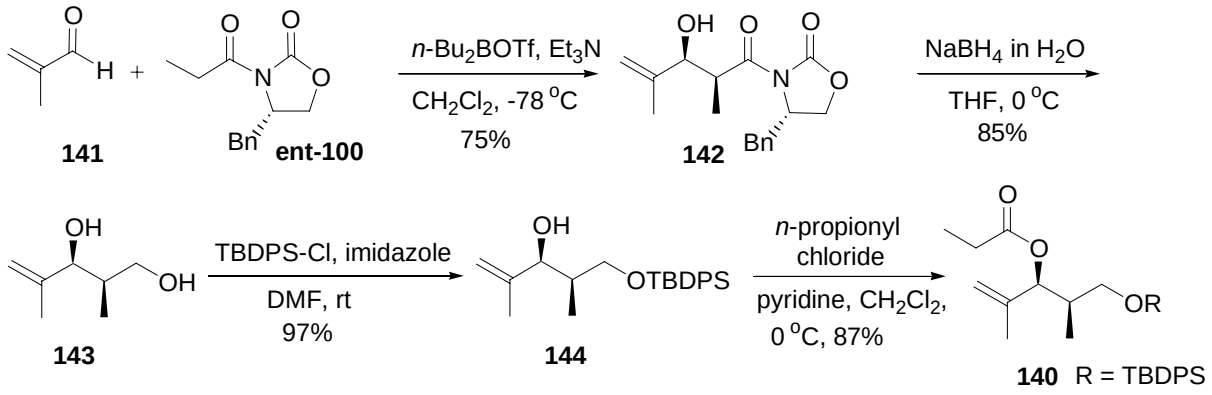


Scheme 37: Possible retrosynthetic cuts for hydroxy acid **96**.

4.2.5 Synthetic pathway for hydroxy acid 96

The synthesis of the hydroxy acid **96** was started with a known *syn* selective aldol reaction between commercially available methacrolein **141** and propionyl oxazolidinone **ent-100**.[97] The propionyl oxazolidinone **ent-100** was synthesized from *S*-phenylalanine using the same procedure as shown in Scheme 29. The asymmetric Evans aldol reaction of methacrolein

141 with *N*-propionyl oxazolidinone **ent-100** in the presence of dibutylboron triflate as Lewis acid and triethylamine as base at -78 °C produced the *syn* aldol product **142** in 75% yield (Scheme 38). A subsequent reductive removal of the chiral auxiliary using sodium borohydride (2.3 M in H_2O) in THF (0.1 M) at 0 °C afforded the 1,3-diol **143** in 86% yield. Monoprotection of the primary alcoholic group with TBDPS-Cl in presence of imidazole at 23 °C provided the mono protected silyl ether **144** in 97% yield. Subsequent acylation of alcohol using *n*-propionyl chloride in presence of pyridine at 0 °C provided the desired ester **140** to perform Ireland-Claisen rearrangement in 87% yield.



Scheme 38: Synthesis of ester **140**.

Ireland-Claisen rearrangement of the ester **140** would provide the required chiral center at C-2. The configuration at C-2 will depend on the geometry of enolate. The speciality of the Ireland-Claisen rearrangement is that the geometry of the enolate can be controlled by using the appropriate reaction conditions. Thus, one can obtain selectively both configurations at the new chiral center by changing the solvents. In our case, *Z*-enolate will provide the required configuration at C-2 through a six-membered chair like transition state (Figure 4.2.2). As reported in the literature,[63] LDA in THF/HMPA was used as base to generate the Z-enolate.

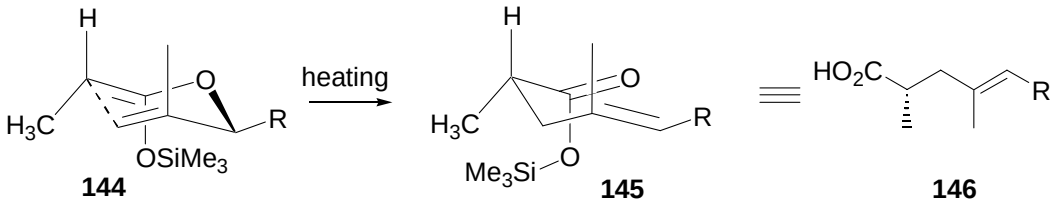
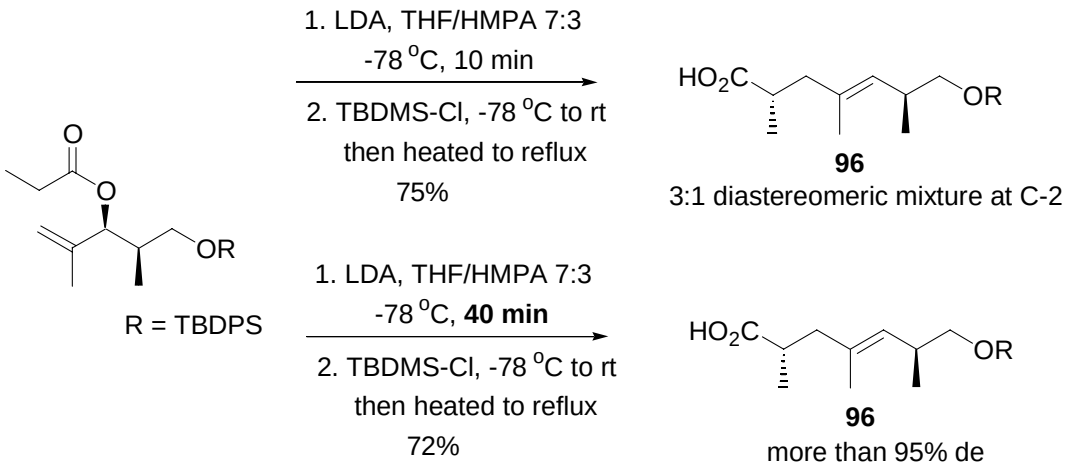


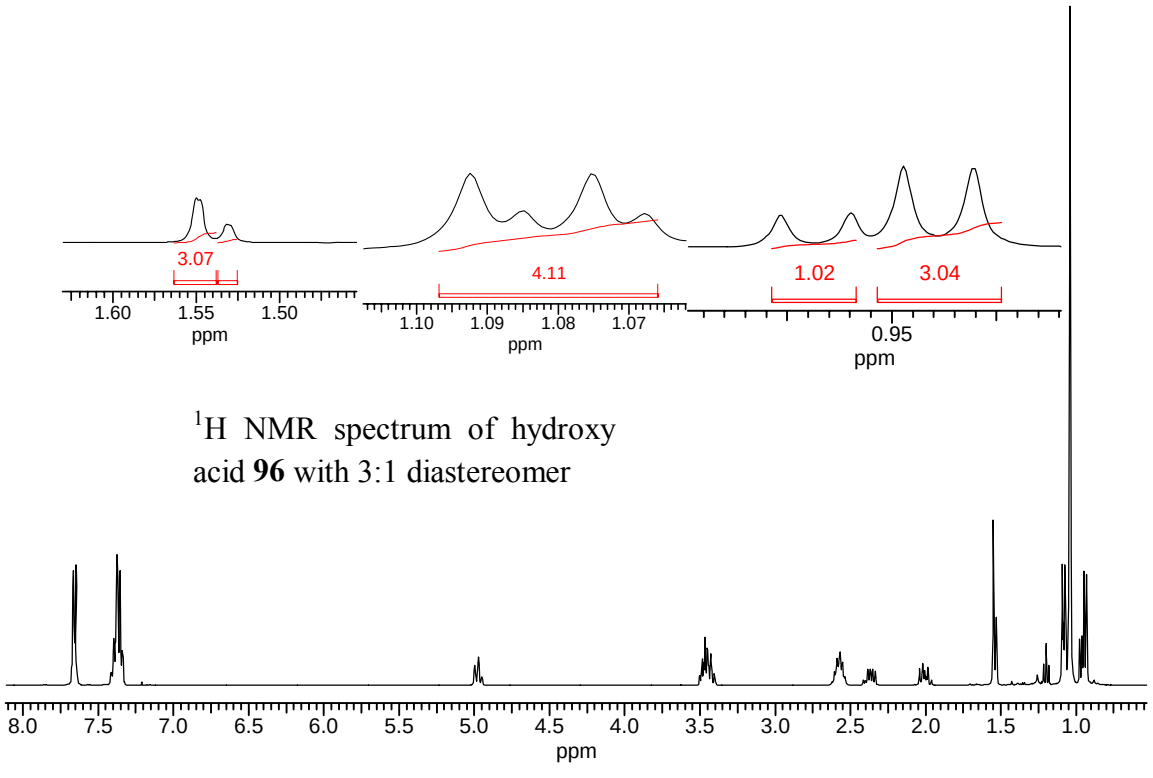
Figure 4.2.2: Possible transition state to from the required configuration from *Z*-enolate.

As we discussed earlier in section 2.5.4, the solution of ester **140** in THF (1.0 M) was added to a solution of LDA in THF/HMPA (7:3) at -78 ^{o}C. After 10 minutes, a solution of TBDMS-Cl in THF (nearly 2.0 M) was added to the reaction mixture at -78 ^{o}C in order to trap the enolate as silylketene actal. The rearrangement followed smoothly and formed the required acid in 75% yield but with very poor diastereomeric ratio (3:1) at C-2 and it was almost impossible to separate the two diastreomers by column chromatography. The formation of *Z*-enolate depends on some important factors such as the solvent and the reaction time as the formation of the *Z*-enolate is a thermodynamically controlled reaction. Therefore, we decided to stir the reaction mixture longer prior to the addition of TBDMS-Cl. This time, the solution of TBDMS-Cl was added after 40 minutes and this logic worked nicely and high diasteroselectivity was observed with more than 95% of the desired product with 72% yield (Scheme 39). The ^{1}H NMR (Figure 4.2.3) of both the diastereomeric mixture and the pure compound **96** illustrate the obtained results.



Scheme 39: Ireland-Claisen rearrangement of ester **140** under different reaction conditions.

The highlighted regions of the spectra (Figure 4.2.3) correspond to the methyl protns of the hydroxy acid **96** at C-2 (0.95 ppm), C-6 (1.09 ppm) and C-4 (1.56 ppm) positons, respectively.



^{1}H NMR spectrum of hydroxy acid **96** with 3:1 diastereomer

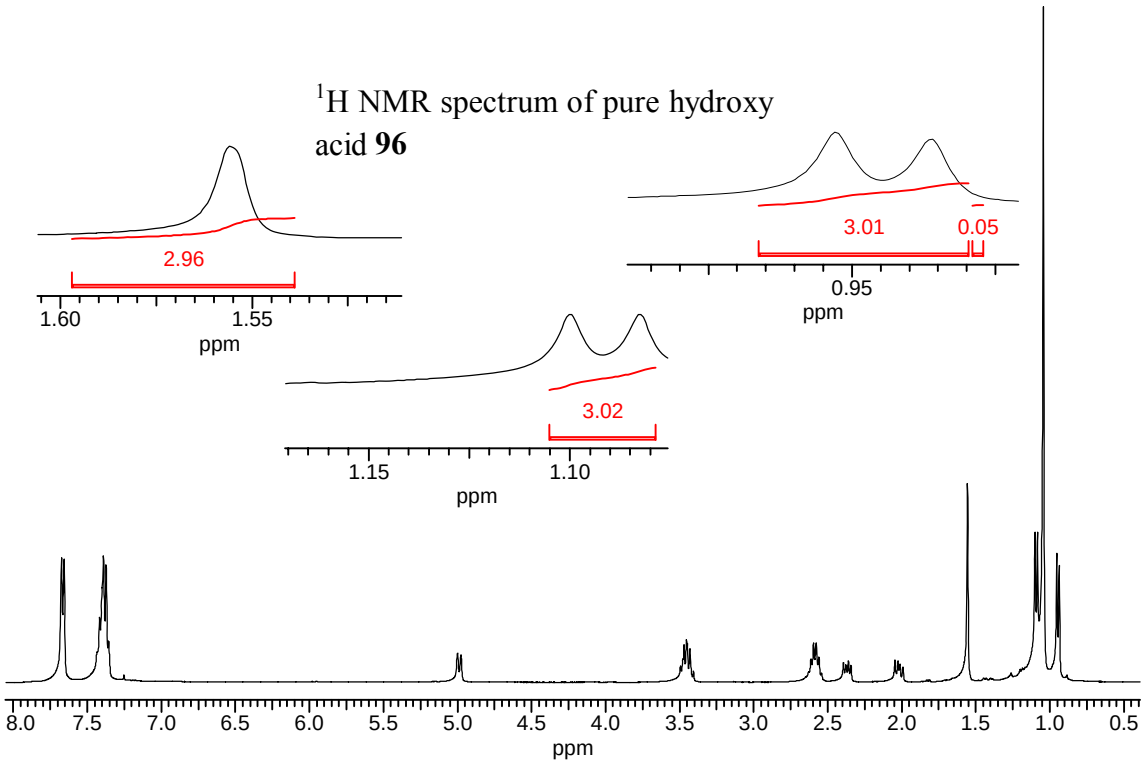
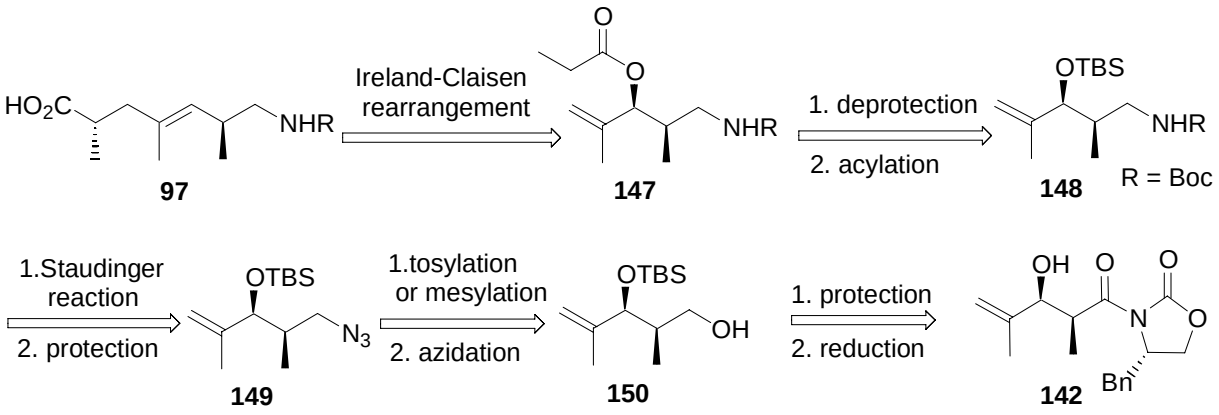


Figure 4.2.3: ^{1}H NMR spectra of hydroxy acid **96** obtained under two reaction conditions.

4.2.6 Retrosynthetic analysis of amino acid 97

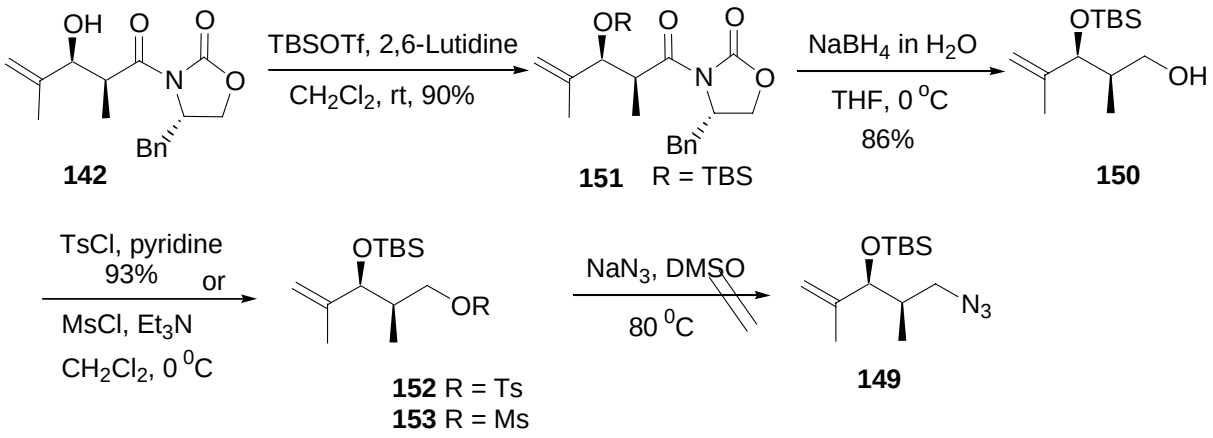
With a good route to hydroxy acid **96** available, we thought it might be the simplest to substitute the hydroxyl function with an amine equivalent (for example azide). However, this strategy would require several protection and deprotection steps. As an alternative, we considered introducing the amino function earlier, for example on primary alcohol **150** (Scheme 40). Ireland-Claisen rearrangement of the ester **147** would provide the amino acid **97**. The ester **147** could be prepared from the protected amino alcohol **148** by deprotection of the alcohol and acylation with *n*-propionyl chloride. The protected amino alcohol **148** might be obtained by Staudinger reaction of azide **149** followed by protection of the resulting amine. In turn, the azide **149** could be traced back to alcohol **150** and the aldol product **142**.



Scheme 40: Retrosynthetic analysis of amino acid **97**.

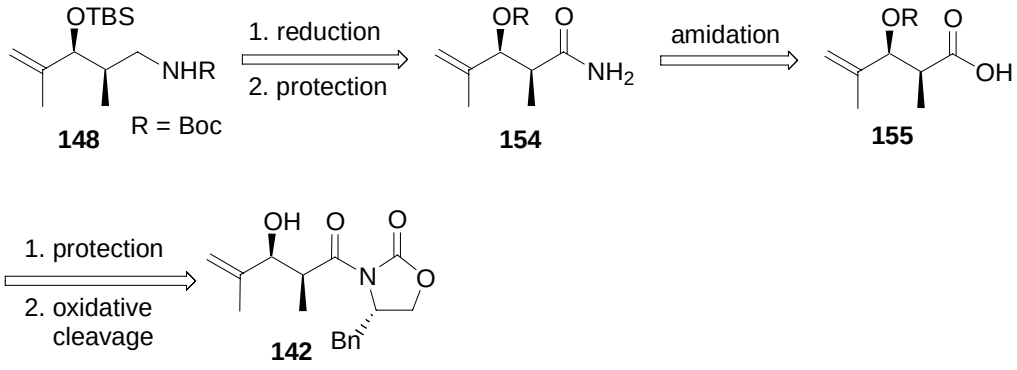
4.2.7 Synthetic pathway for amino acid 97

The synthesis of amino acid **97** started with the *syn* aldol product **142**. Silylation (1.6 equiv TBSOTf, 2.5 equiv of 2,6-lutidine at 23 ^{o}C, 12 h) of the secondary alcohol led to the silyl ether **151** in 90% yield. Reductive removal of the chiral auxiliary using sodium borohydride in THF at 0 ^{o}C afforded the secondary alcohol protected 1,3-diol **150** in 86% yield. Tosylation of **150** using tosyl chloride in presence of pyridine at 0 ^{0}C afforded the primary tosylate **152** in 92% yield. Attempts for the synthesis of azide **149** using sodium azide[98] at 80 ^{o}C in DMSO led to decomposition of the starting material with a very bad smell. The same was observed with mesylate **153**. Using DPPA/DBU conditions to synthesize the azide **149** led to the formation of the corresponding phosphoryl ester along with some side products. The reason for the failure of the reaction might be due to the formation of [1,3]-dipolar cycloadduct.



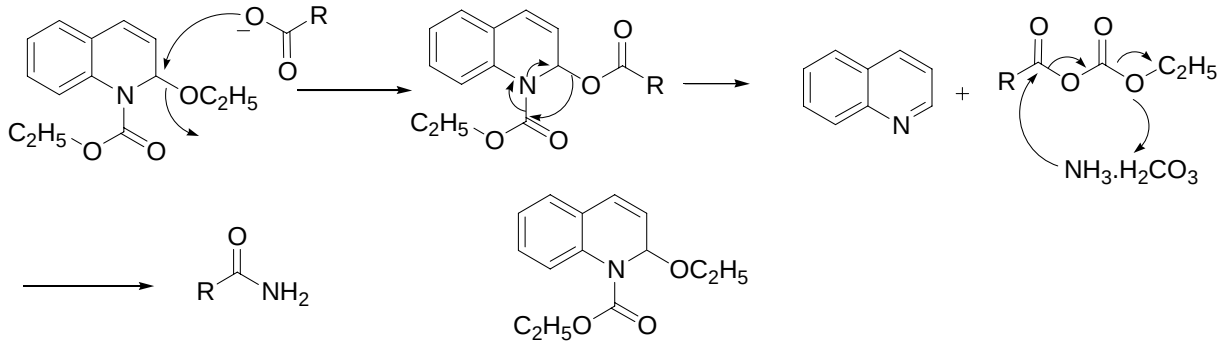
Scheme 41: Attempts for the synthesis of azide **149**.

At this point, it became necessary to consider other synthetic possibilities for the synthesis of amino acid **97** avoiding the azide pathway. The synthesis of amino acid **97** requires mainly introduction of an amine group, because the remainder of the synthesis will build upon the aldol reaction and Ireland-Claisen rearrangement. The amine could be synthesized by reduction of an amide which in turn should be available from the corresponding acid.[99] Keeping this strategy in mind, a second retrosynthetic plan was proposed for amino acid **97** with the amide **154** as key intermediate (Scheme 42). The protected amino alcohol **148** would be synthesized from the amide **154** by reduction and protection of the resulting amine. The amide **154** would be prepared from the carboxylic acid **155** via amidation using a suitable ammonia source.[99]



Scheme 42: Retrosynthetic analysis for amino acid **100** through amide **154**.

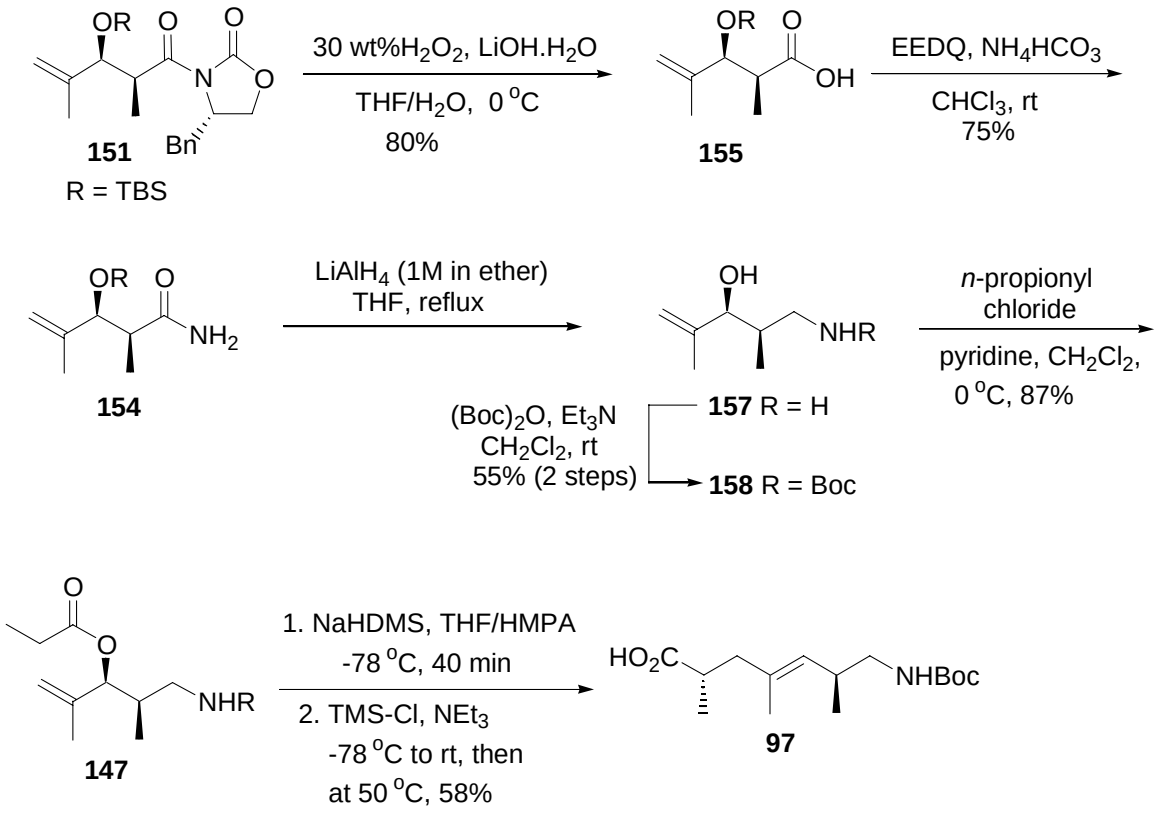
In this way, the synthesis of amino acid **97** started from the silylated *syn* aldol product **151** as shown in Scheme 44. Oxidative cleavage of **151** using H_2O_2/LiOH conditions provided the carboxylic acid **155** in 80% yield. The carboxylic acid **155** was converted to amide **154** using EEDQ **156** and $(NH_4)HCO_3$ at room temperature in 72% yield.[100, 101] The same transformation can be accomplished with ethyl chloroformate and triethylamine followed by NH_3 or one can use coupling reagents like EDC *(N*-Ethyl-*N*'-(3-dimethylaminopropyl)-carbodiimide hydrochloride) followed by NH_3.[99] But, in this case the reaction did not work with the EDC/NH_3 conditions.



Scheme 43: Possible mechanism for the formation of an amide from acid using EEDQ **156**.

Reduction of amide **154** using $LiAlH_4$ (1.0 M solution in ether) under reflux for 1 h produced the desired amine **157** but with concomitant deprotection of the alcohol as shown in Scheme 44. As the alcoholic functional group will not affect the protection of the amine using Boc anhydride, the crude amino alcohol was protected by using Boc-anhydride in presence of triethylamine providing the Boc protected amino alcohol **158** in 55% yield over two steps. Acylation of **158** using *n*-propionyl chloride in the presence of pyridine provided the required ester **147** for Ireland-Claisen rearrangement in 90% yield. LDA in THF/HMPA (7:3) was employed for the Ireland-Claisen rearrangement of the ester **147**. But the reaction did not work and the starting material was recovered. The reason might be that the deprotonation occurred on the amine since only 1.1 eq of base was used for this rearrangement. Thus, the deprotonation of ester **145** requires more than two equivalents of base. Infact, Ireland-Claisen rearrangement using NaHDMS (6.0 eq) in THF/HMPA (7:3) at -78 ^oC, trapping the enolate

with TMS-Cl and acidic work-up produced the desired amino acid **97** in 58% yield with excellent diastereoselectivity (> 96%).

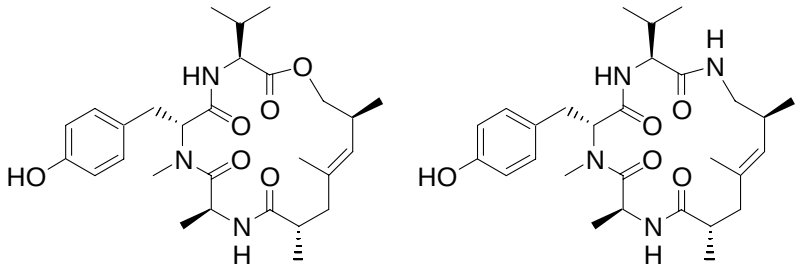


Scheme 44: Synthetic scheme for amino acid **97**.

4.2.8 Synthesis of jasplakinolide (geodiamolide) analogues using 96 and 97

As we discussed earlier in Section 2.3, the comparative modeling studies of doliculide, jasplakinolide, and chondramide C revealed that the isopropyl group occupies the same volume as the phenyl group and the indole ring occupies the same volume as the benzyl group in space. On the basis of these considerations, in the design of analogues **159** and **160** of jasplakinolide we decided to replace the unusual amino acids *N*-methyl-2-bromo D-tryptophan and *β*-D-tyrosine with *N*-methyl-D-tyrosine and L-valine respectively and to substitute the polypropionate portion with the novel hydroxy and amino acids **96** and **97**, respectively to form depsipeptide **159** and macrolactam **160**. The conformational studies of these macrocycles

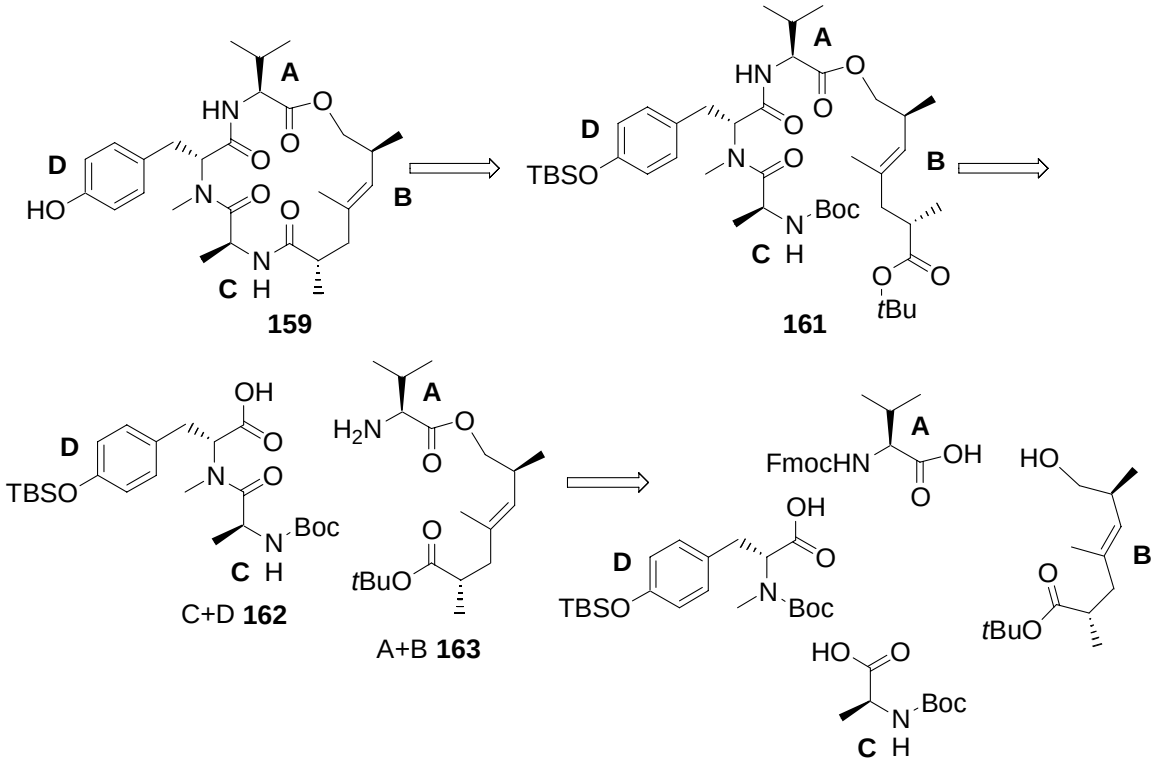
might provide some information regarding the influence of amide and ester bond on the solution structures. This was the idea behind the synthesis of the novel hydroxy- and amino acids **96** and **97**.



159 **160**

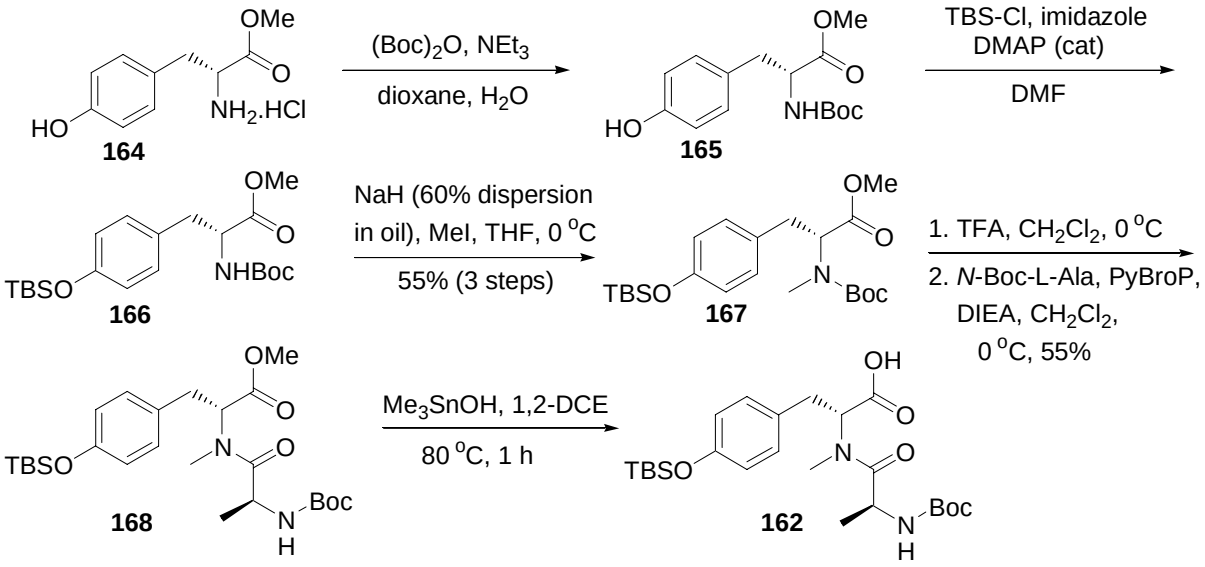
Figure 4.2.4: Analogues of jasplakinolide (geodiamolide) containing hydroxy- and amino acids **96** and **97**.

As both analogues contain the same tripeptide, it was thought to synthesize the tripeptide fragment and couple it with the corresponding acids. Initially it was planned to synthesize analogue **159** using a classical Boc strategy, which would require a macrolactonization in the final steps. As the macrolactonization failed to give good yields in the total syntheses of jasplakinolide and geodiamolide, it was planned to combine a dipeptide fragment with an amino acid (valine)-hydroxy acid fragment which would allow for a more facile macrolactamization (Scheme 45).



Scheme 45: Coupling strategy for the synthesis of the analogue **159**.

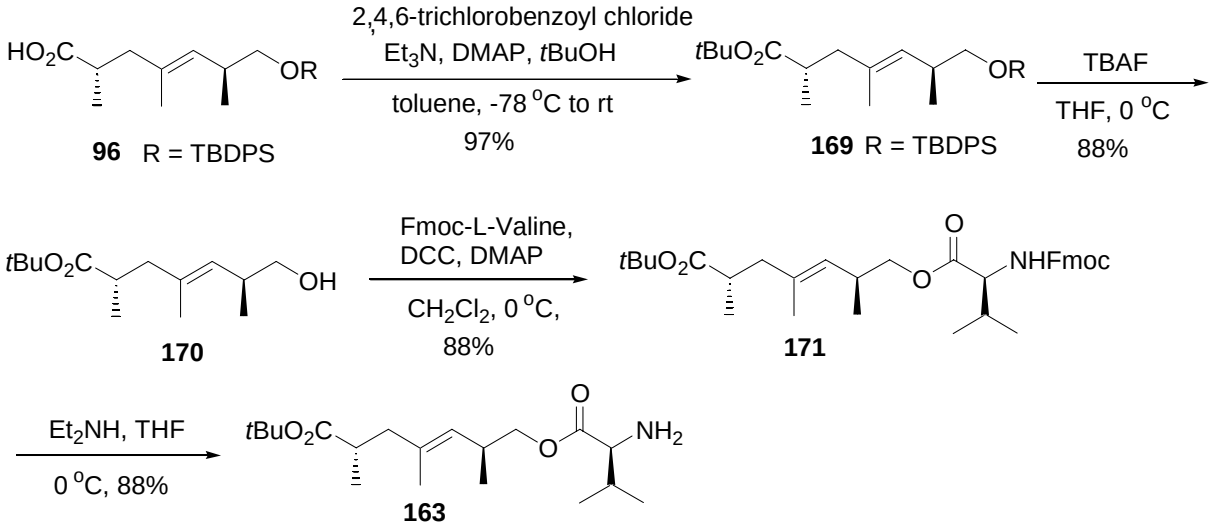
The *N*-methyl D-tyrosine derivative **D** was synthesized from D-tyrosine methyl ester **164** in three steps.[102] First step was the protection of amine group using Boc anhydride, followed by silylation of the hydroxy function as silyl ether yielding fully protected tyrosine **166** as shown in Scheme 46. *N*-methylation of **166** by using NaH (60% dispersion in mineral oil) for deprotonation and MeI conditions at 0 °C afforded the *N*-methyl D-tyrosine derivative **167** in 55% yield over 3 steps. Deprotection of the Boc group of **167** with trifluoroacetic acid (TFA) provided the corresponding free amine. PyBroP mediated coupling of the crude amine with *N*-Boc-L-alanine provided the dipeptide **168** in 55% yield.[81, 103] The subsequent hydrolysis of the methyl ester on dipeptide **168** posed a challenge since conditions would have to be found that leave the phenolic silyl ether intact. Basic hydrolysis of dipeptide **168** using NaOH (0.4 N) led to hydrolysis as well as cleavage of the silyl group on the phenol. Therefore, the mild reagent trimethyl tin hydroxide was used for the hydrolysis.[104, 105] Indeed, the methyl ester cleaved without disturbing the silyl group on the phenol giving the desired acid **162**.



Scheme 46: Synthesis of dipeptide fragment **162**.

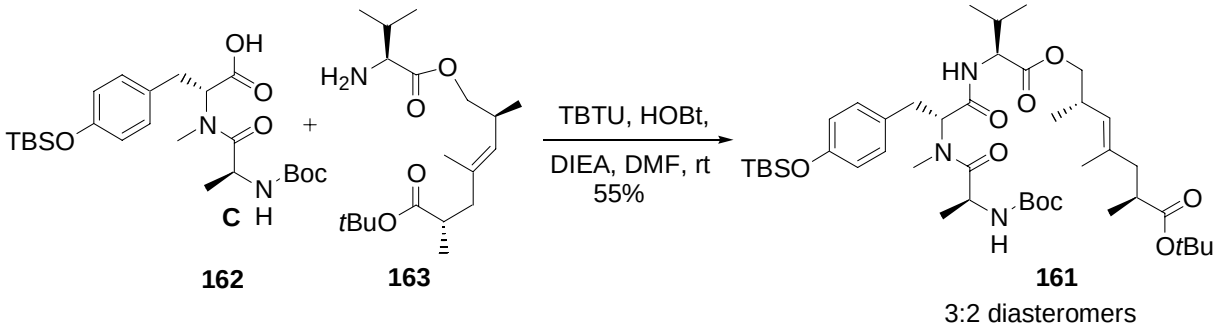
The other fragment A+B **163** could be obtained from the hydroxy acid **96** and Fmoc-L-valine in four steps. As the linear depsipeptide needs the deprotection of both the amine and the carboxylic group prior to cyclization, it would be ideal having similar protecting groups on both sides, which could be cleaved in a single step. As the dipeptide **162** has a Boc-protecting group at the *N*-terminus, it would be ideal to have a *tert*-butyl group on the C-terminus, so that both groups could simultaneously be cleaved by TFA. The synthesis of fragment **163** was started with the protection of hydroxy acid **96** with a *tert*-butyl group as shown in Scheme 47. DCC mediated esterification of hydroxy acid **96** with *tert*-butanol in presence of DMAP as catalyst provided the desired product **169** in very low yield around 25%. Addition of higher amounts of the catalyst did not improve the yield. Then it was decided to employ the Yamaguchi esterification using 2,4,6-trichlorobenzoyl chloride and DMAP. Esterification of hydroxy acid **96** with *tert*-butanol using Yamaguchi conditions with excess of reagents provided the desired protected acid **169** in almost quantitative yield.[70] After obtaining the protected hydroxy acid **169**, the TBDPS group was removed in order to couple the resulting alcohol with Fmoc-L-valine. Deprotection of the silyl group using TBAF provided the hydroxy ester **170** in 90% yield. DCC mediated esterification of Fmoc-L-valine with hydroxy compound **170** furnished the ester **171** in 88% yield. Finally, removal of the Fmoc group using

diethylamine led to the desired amine **163** in 88% yield. This way the fragment A+B was obtained.



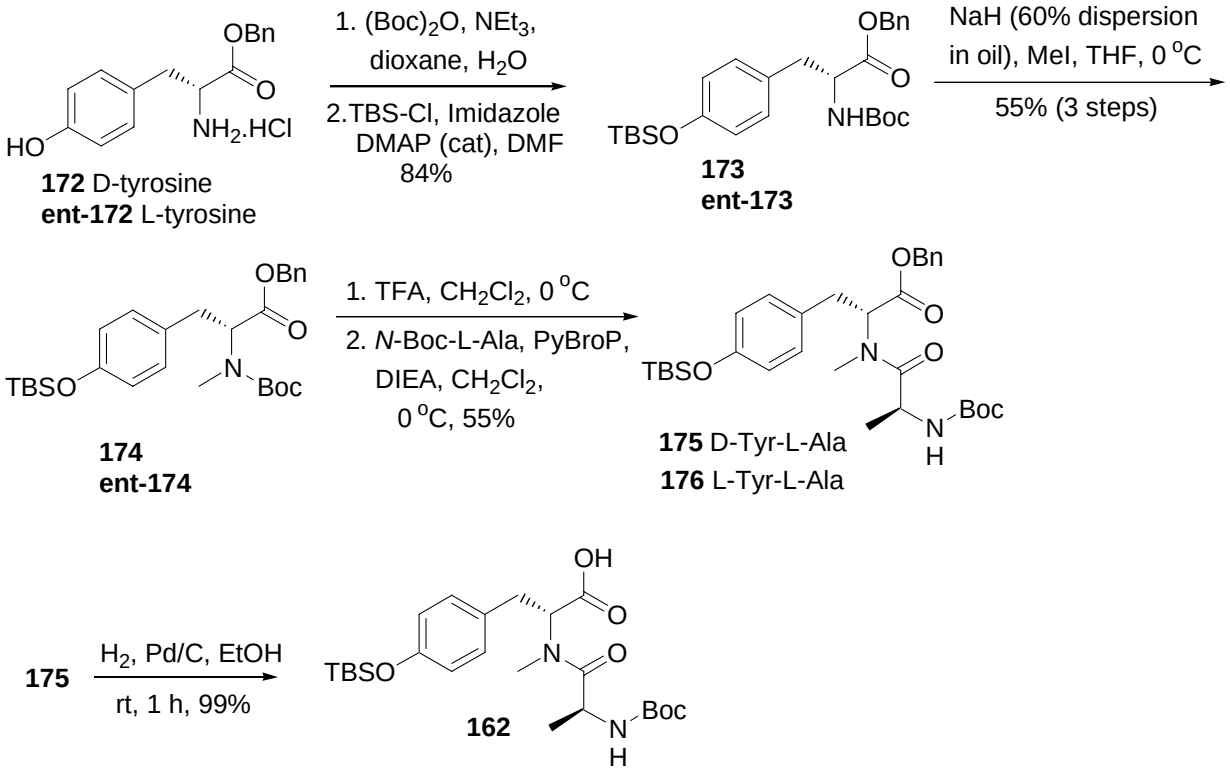
Scheme 47: Synthesis of amine fragment **163**.

TBTU mediated coupling of the fragments **162** and **163** provided the desired linear depsipetide **161** in 55% yield, but as a diastereomeric mixture with 3:2 ratio (Scheme 48). Careful inspection of the ^{1}H- and ^{13}C NMR spectra of **161** showed that several peaks were doubled. Even TLC showed two clear spots of the diastereomeric mixture. Hence, rotamers around the boc-group could be ruled out. This result was very unusual as the amine **163** was diastereomerically pure and TBTU mediated coupling in our experience always provided the coupled product without racemization.



Scheme 48: Synthesis of linear depsipeptide **161**.

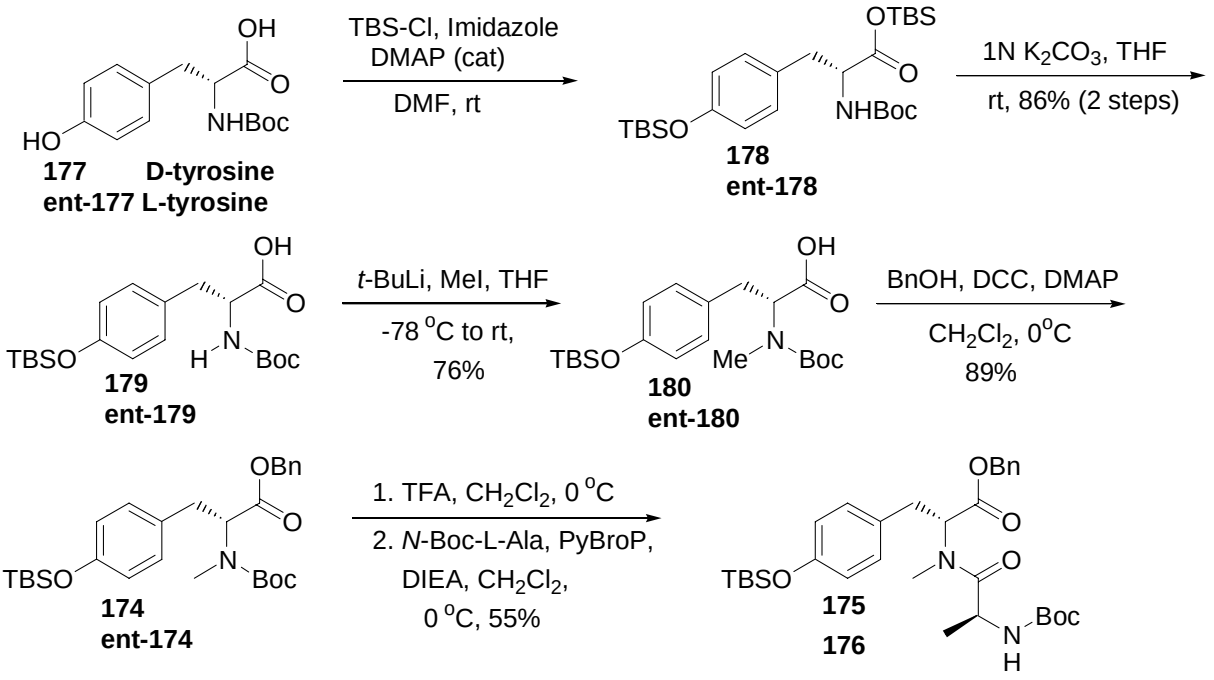
We suspected that the problem might lie within the dipeptide acid part **162**. It was thought that racemization might have occured in the hydrolysis step (Scheme 46). In order to probe this hypothesis, the methyl ester was replaced with the benzyl ester which should allow for a racemization free hydrolysis. As the dipeptide acid **162** was known from literature,[102] we decided to follow the same strategy for the synthesis of dipeptide acid **162** as in the literature. For this purpose, D-tyrosine benzyl ester **172** was chosen and were followed similar steps as in Scheme 46 to the fully protected D-tyrosine derivative **173**. Subsequent *N*-methylation of **173** using NaH (60% dispersion in mineral oil) followed by addition of MeI provided the *N*-methyl–D-tyrosine derivative **174**. Deprotection of the Boc group using TFA and PyBroP mediated coupling of the resulting amine with *N*-Boc-L-alanine provided the dipeptide **175**. Subsequent hydrogenation led to the dipeptide acid **162**. TBTU mediated coupling of the acid **162** with amine **163** provided the same result as in Scheme 48. The optical rotation of the dipeptide **175** was measured in order to compare the optical purity with the known literature value; surprisingly both values had no comparison. So the total problem lied somewhere in the synthesis of dipeptide and not the coupling step to **161**. It might be possible that the racemization had occured during the *N*-methylation of the D-tyrosine derivative. To prove this, a series of experiments were performed (Scheme 49 and 50). The above sequence was repeated with L-tyrosine benzyl ester **ent-172** in order to synthesize the dipeptide consisting of L-tyrosine and *N*-Boc-L-alanine. The synthesis was done in order to compare the NMR spectra of both compounds **175** and **176**.



Scheme 49: Synthesis of dipeptide acid **162** from tyrosine benzylester **172**.

Finally, the L- and D- tyrosine derivatives **174** and **ent-174** were prepared by a differenet method (Scheme 50).[106] The idea here was to see whether the *N*-methylation step caused racemization. In this pathway the syntheses of dipeptides **175** and **176** were started with the commercially available *N*-Boc-D- and L-tyrosine **177** and **ent-177**. Protection of the phenol group using TBDMS-Cl in presence of imidazole produced the disilylated products **178** and **ent-178**. Treatment of silyl esters with 1 N K_2CO_3 cleaved the silyl group on the acid leading to the phenol protected products **179** and **ent-179**. *N*-Methylation of **179** and **ent-179** was achieved by producing the dianion using 2.5 eq of *t*-BuLi. Treatment of **179** and **ent-179** with *t*-BuLi at -78 °C and subsequent addition of MeI produced the *N*-methyl tyrosine **180** and **ent-180** derivatives in good yields. Subsequent protection of the acid function with benzyl alcohol using DCC in presence of DMAP as catalyst gave the esters **174** and **ent-174**. Subsequent removal of the Boc group using TFA in CH_2Cl_2 at 0 °C gave the crude amine, and PyBroP mediated coupling of the crude amine with *N*-Boc-L-alanine in presence of Hünig's base furnished the corresponding dipeptides **175** and **176**, respectively. Surprisingly, the products **174** and **ent-174** that were synthesized according to Scheme 50 have nearly the same optical

rotation values with different signs +71.8 and -69.2. In contrast, optical rotation value of the compounds **174** and **ent-174** (both Land D) synthesized via Scheme 49 showed **zero**. But, the optical rotation of the tyrosine derivative **173** (before *N*-methylation step) correlated with the literature value.[102] So, at this point we can clearly say that the base NaH (60% dispersion in mineral oil) caused the racemization at the α-chiral center in both the benzyl and the methyl esters. The ^{1}H NMR spectra of dipeptides **175** and **176** derived from both Schemes 49 and 50 clearly show the racemization pattern. The expanded regions of the spectra clearly showed the different chemical shift values for the chiral methyl groups (0.85 ppm in **175** and 1.18 ppm in **176**) in the compounds **175** and **176** (Figure 4.2.5).



Scheme 50: Synthesis of dipeptides **175** and **176** using D and L-tyrosine derivatives **177** and **ent-177**.

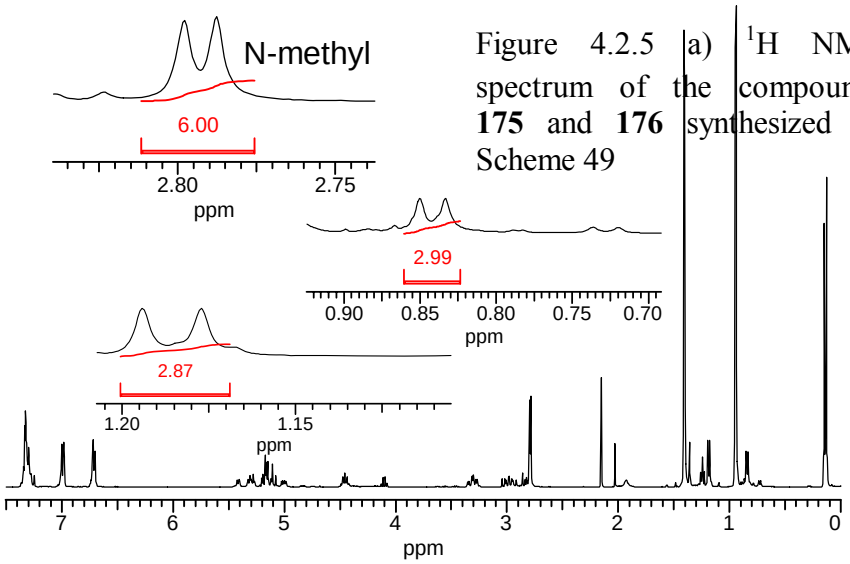
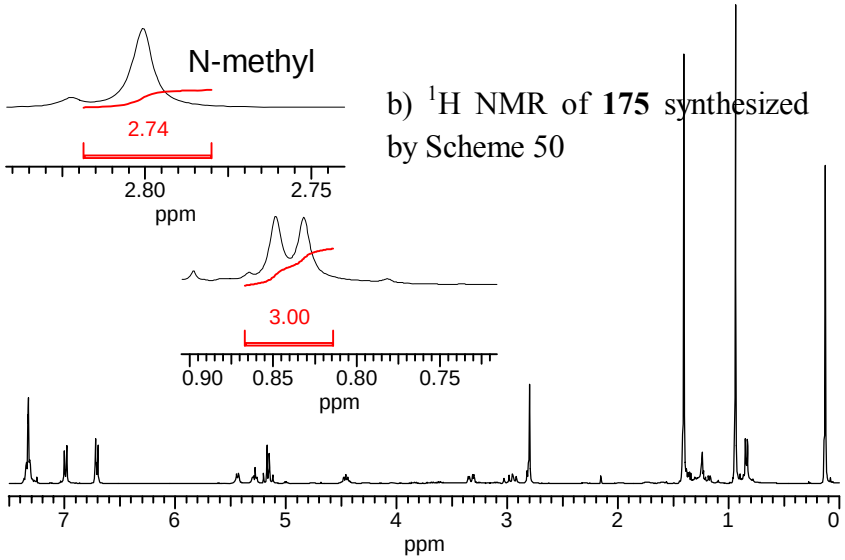
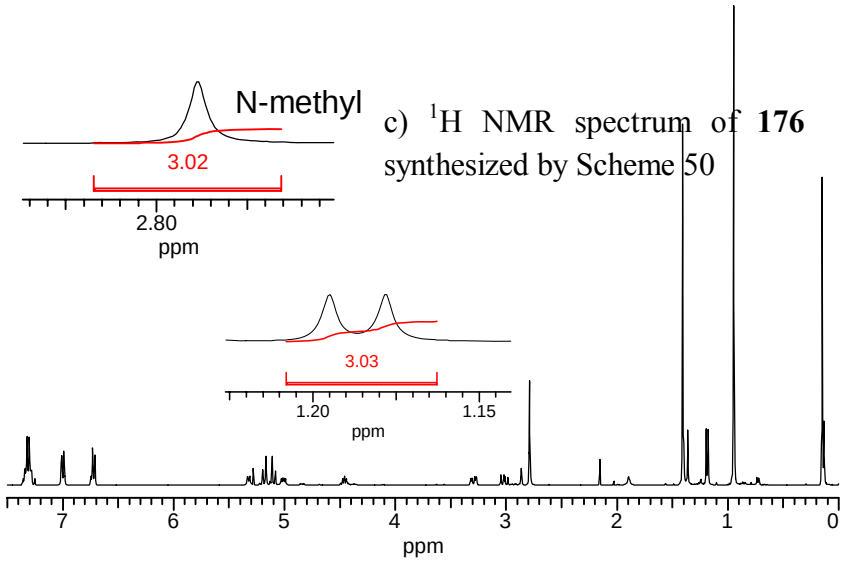


Figure 4.2.5 a) ^{1}H NMR spectrum of the compounds **175** and **176** synthesized by Scheme 49

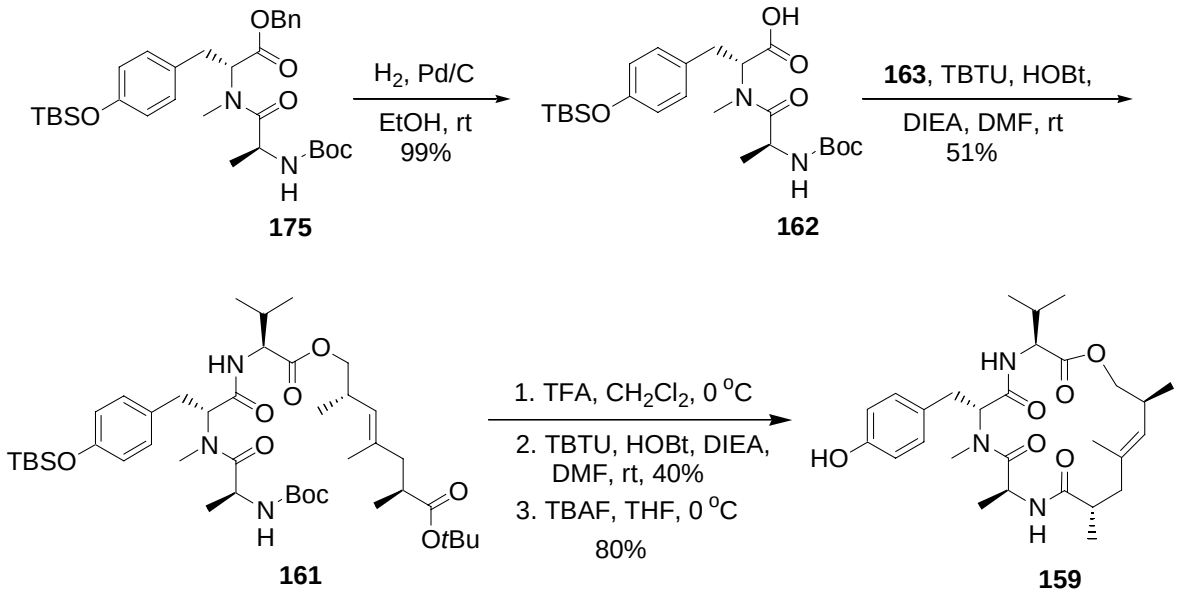


b) ^{1}H NMR of **175** synthesized by Scheme 50



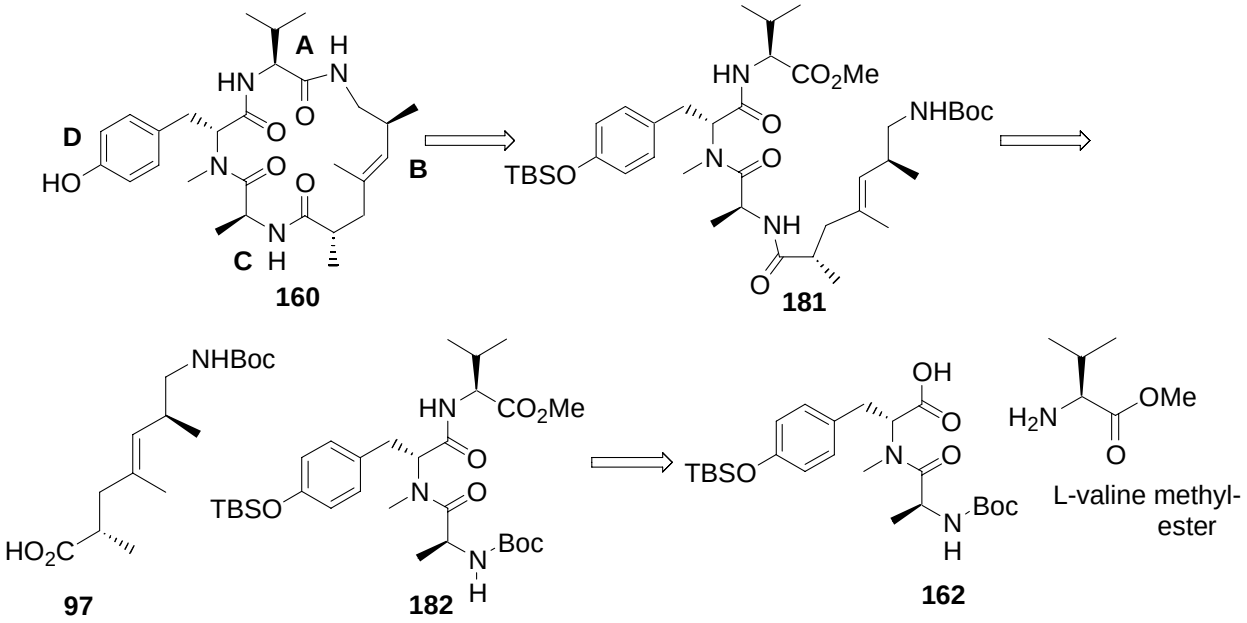
c) ^{1}H NMR spectrum of **176** synthesized by Scheme 50

After proving that the racemization occurred in the *N*-methylation step with the base NaH (60% dispersion in mineral oil), the dipeptide **175** was then synthesized according to the Scheme 50. The dipeptide **175** was subjected to hydrogenation using Pd/C as catalyst in order to remove the benzyl protecting group resulting in the diastereomerically pure free acid compound **162** (Scheme 51). TBTU mediated coupling of **162** with amine **163** provided the linear depsipeptide **161** in 55% yield. Both protecting groups could now be removed in one step by using trifluoroacetic acid. After concentration of reaction mixture, the macrolactam formation was carried out in DMF (0.001 M) using TBTU in presence of HOBt at room temperature which led to the formation of the TBS protected cyclic depsipeptide. A final deprotection using TBAF gave the desired cyclic depsipeptide **159**.



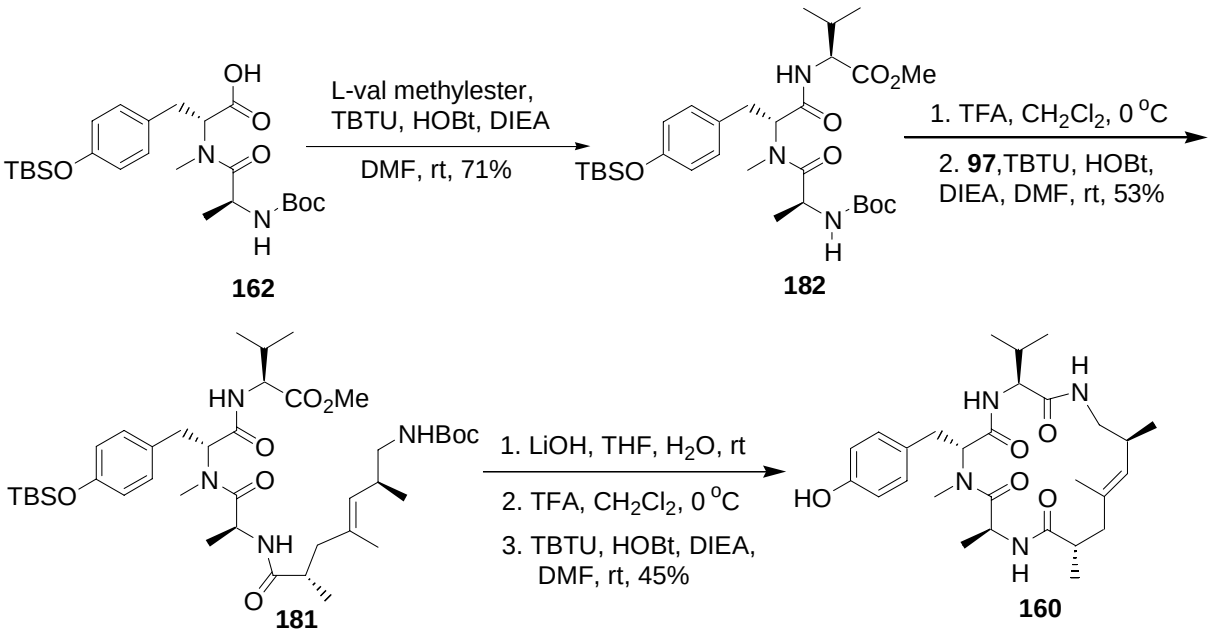
Scheme 51: Synthesis of analogue **159**.

In order to reach the amide analogue **160**, it was decided to assemble tripeptide **182** and to combine it with amino acid **97** to get the *seco*-compound **181**, which on macrolactamization should provide macrolactam **160** (Scheme 52).



Scheme 52: Coupling strategy for the analogue **160**.

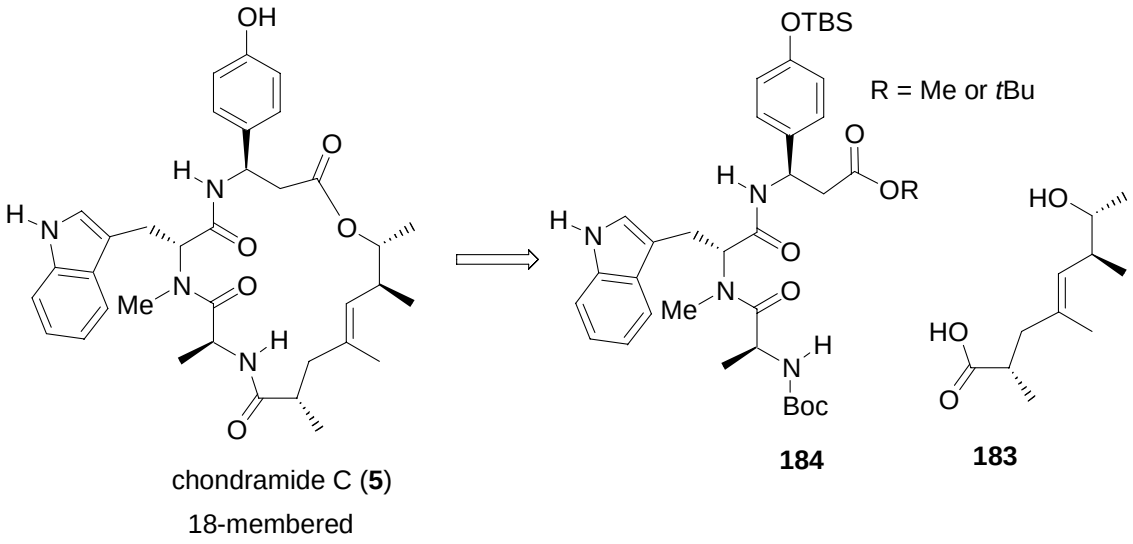
The synthesis of analogue **160** was started with the dipeptide acid **162** which was synthesized according to Scheme 50. TBTU mediated coupling of **162** with L-valine methylester hydrochloride salt in presence of HOBt produced the tripeptide **181** in 71% yield. At this point, the Boc protecting group at the *N*-terminus was removed with trifluoroacetic acid, followed by amide formation of the resulting amine with amino acid **100** using TBTU to produce the linear tetrapeptide **181**. Ester hydrolysis of **181** not only cleaved the ester function but also the silyl phenyl ether. Boc deprotection of the resulting product using TFA produced the *seco*-acid which on macrolactamization with TBTU in presence of HOBt produced the desired macrolactam **160** (Scheme 53). The detailed conformational analysis of the compounds **159** and **160** will be discussed in the conformational analysis section.



Scheme 53: Synthesis of jasplakinolide analogue **160**.

4.2.9 Synthesis of Nor-methyl Chondramide C

The chondramides are cyclodepsipeptides produced by strains of myxobacterium, *Chondramyces crocatus*.[107, 108] The structures of the chondramides published so far are related to jasplakinolide. Besides different substituents, the chondramides have an 18-membered macrocyclic ring instead of the 19-membered ring system of jasplakinolide. Both compounds inhibit the growth of yeasts and show cytostatic activities. Chondramide C, which is quite similar to jasplakinolide, appears to have antiproliferative activity against carcinoma cell lines by targeting the actin cytoskeleton.[20, 109] Structurally and activity wise chondramide C is similar to jasplakinolide. Chondramide C contains a tripeptide similar to jasplakinolide except for the bromine on the indole ring and a hydroxy acid unit which is one carbon shorter than the jasplakinolide hydroxy acid. The hydroxy acid of chondramide C also has non bonded interactions like the jasplakinolide hydroxy acid. As the configuration of chondramide C was not yet fully determined, but based on the similar biological activity and same binding site as the jasplakinolide, the configuration of chondramide C proposed was similar to the one of jasplakinolide.[110]

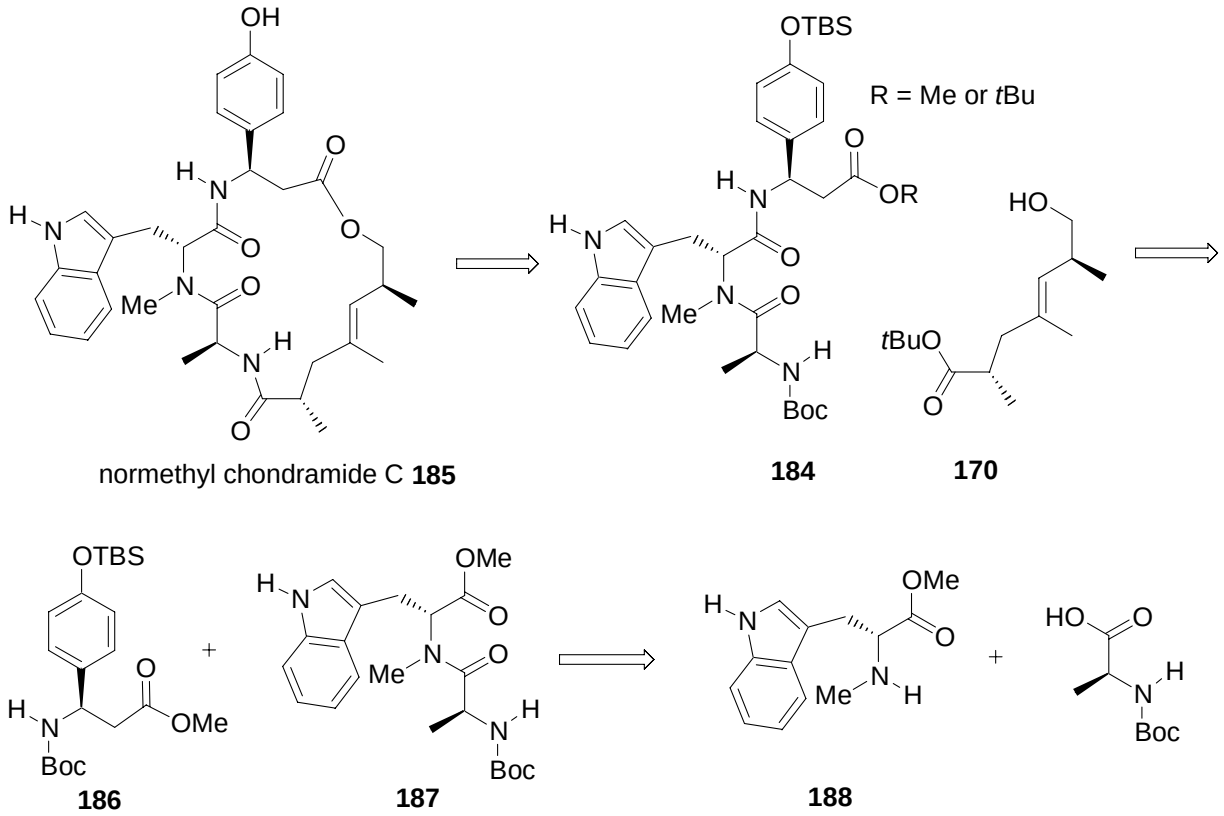


Scheme 54: Retrosynthetic analysis of the **proposed** structure of chondramide C.

The hydroxy acid **183** of chondramide C has four methyl groups and one double bond in which three of the methyl groups are placed in 1,3-distance to each other giving rise to one *syn* pentane interaction and one allylic strain which make the molecule less flexible. Two methyl groups are placed in 1,2-distance so that the rotation of methyl groups around the single bond might be restricted. Thus, the hydroxy acid **183** should have a definite conformation. If one compares the hydroxy acid of chondramide C and hydroxy acid **96**, one can recognize that they have the same chain length and differ only by the methyl group at C-7. Thus, it was interesting to compare the biological activity of the chondramide C analogue containing the same tripeptide and hydroxy acid **96** which we call as nor methyl chondramide C **185**.

As nor methyl-chondramide C contains the tripeptide and hydroxy acid parts, it was decided to assemble the tripeptide **184** and to combine it with the ester **170** to form the linear depsipeptide which on macrolactam formation would provide the desired product **185** (Scheme 56). The tripeptide part contains three different amino acids; β-D-tyrosine derivative, *N*-methyl D-tryptophane and L-alanine. As the tripeptide is similar to the tripeptide part in the analogue **134,** it was decided to follow a similar strategy to construct the tripeptide. The necessary β-D-tyrosine derivative **186** was synthesized according to a known literature

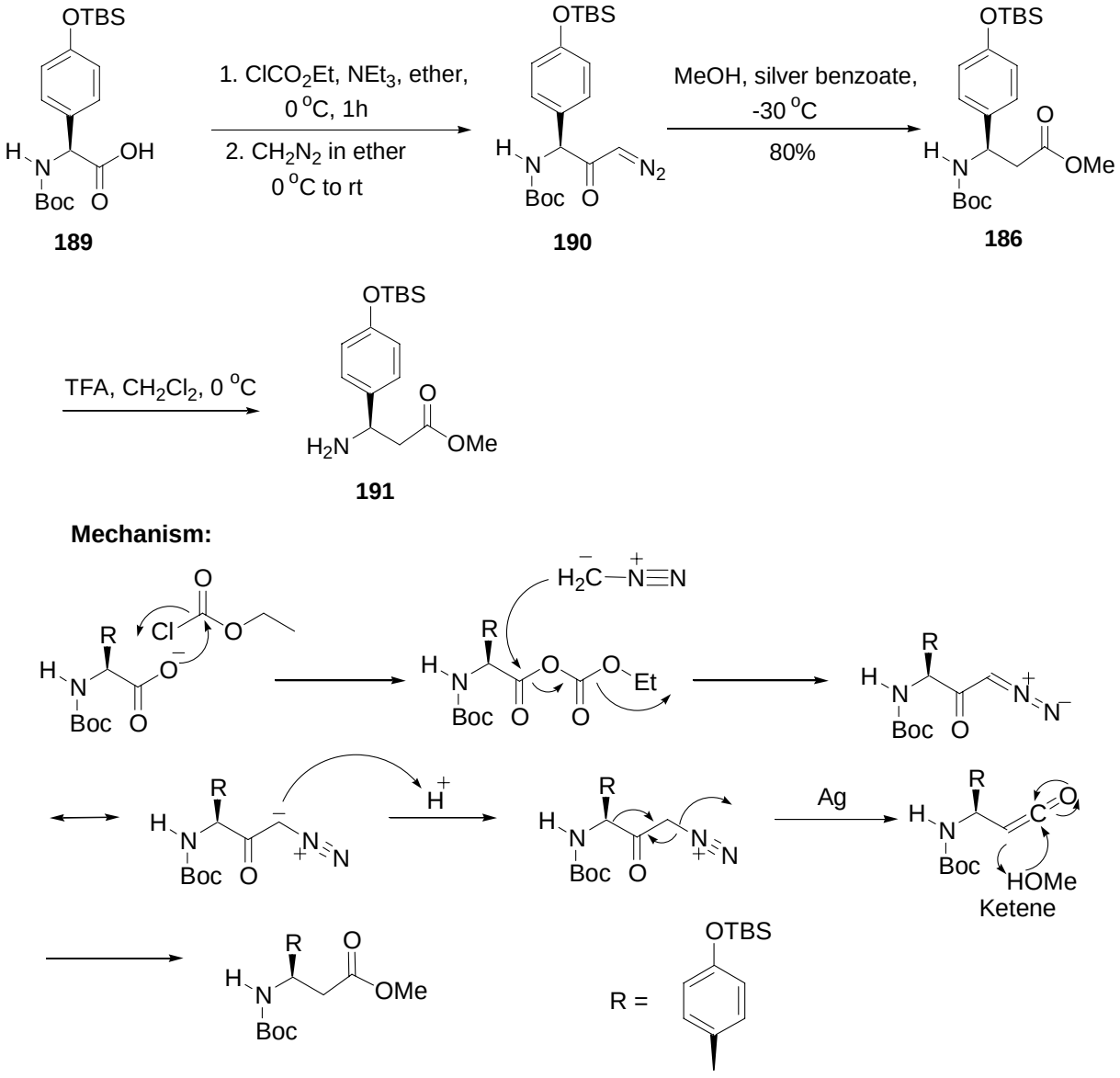
procedure[111] using an Arndt-Eistert reaction as the key step. The dipeptide **187** was synthesized according to a known literature procedure as well.[112]



Scheme 55: Coupling strategy for normethyl chondramide C **185**.

The synthesis of β-D-tyrosine derivative **186** started with the silyl ether of *p*-hydroxy *N*-Boc-L-phenyl glycine **189** as shown in Scheme 56. Accrording to a recent literature procedure, a commercially available solution of trimethylsilyl diazomethane in ether was employed to produce the diazoketone **190** instead of using diazomethane.[113] The acid **189** was treated with ethyl chloroformate in presence of triethylamine to produce the mixed anhydride. To this mixed anhydride a solution of trimethylsilyl diazomethane in ether was added in order to produce the diazoketone **190**. However, all attempts failed to produce the diazoketone with trimethylsilyl diazomethane. There was no other way except using diazomethane to synthesize the compound **190** from acid **189**. Accordingly, a freshly prepared solution of diazomethane solution in ether was added to the crude reaction mixture consisting the mixed anhydride at 0 ^{o}C. The crude product **190** was almost pure on TLC after work up, so it was used for the Wolf-

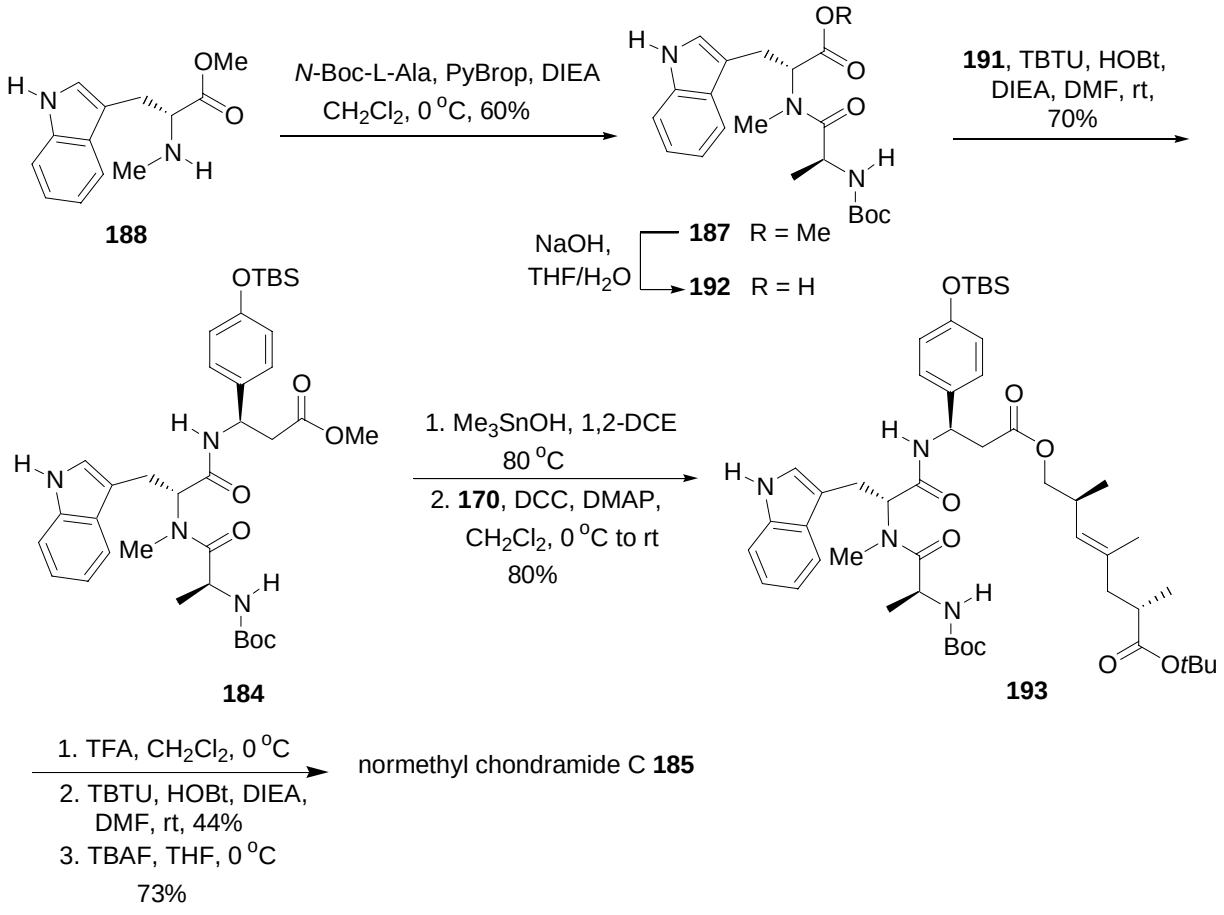
rearrangement without any purification. Rearrangement occurred without any problem with methanol in presence of silver benzoate, producing the desired product **186** in 80% yield (Scheme 56). The β-tyrosine derivative **186** was treated with trifluroacetic acid in order to deliver the crude amine **191**.



Scheme 56: Synthesis and mechanism for the formation of β-tyrosine derivative **186**.

The synthesis of dipeptide **187** started with *N*-methyl D-tryptophane methyl ester **188** (Scheme 57). PyBroP mediated coupling of *N*-Boc-L-alanine with *N*-methyl D-tryptophane methylester

188 in presence of diisopropylethylamine produced the desired dipeptide **187**. At this point, the methyl ester at the C terminus was cleaved to produce the dipeptide acid **192**. TBTU mediated coupling of dipeptide acid **192** and β-amino ester **191** in presence of HOBt produced the desired tripeptide **184** in 70% yield. Trimethyl tinhydroxide[104, 105] mediated hydrolysis of tripeptide **184** furnished the tripeptide acid which on esterification using DCC in presence of catalytic amounts of DMAP with hydroxy acid derivative **170** gave the *seco* compound **193** in 80% yield for two steps. Trifluoroacetic acid mediated cleavage of both protecting groups Boc and *t*Bu and subsequent macrolactam formation using TBTU in presence of HOBt in DMF at room temperature led to the TBS protected nor methyl chondramide C which on treatment with TBAF produced normethyl chondramide C **185** (Scheme 57).



Scheme 57: Total synthesis of normethyl chondramide C **185**.

4.2.10 Design and the synthesis of analogues of hydroxy acid 96

Cyclic peptides provide ideal scaffolds for exploring structure-activity relationships in ligand-receptor interactions. Cyclization serves to increase membrane permeability by elimination the charged termini and facilitating internal hydrogen bonded conformers. Cyclization of peptides introduces an extra element of constraint (e.g. double bond, aromatic ring etc.), which confers conformational restriction to the peptide leading to an entropically advantageous mode of binding to the target protein.[114] As the hydroxy- or amino acid **96** or **97** contain the central allylic system and a methyl group at the allylic position to the double bond, the resulting 1,3-allylic interaction makes the molecule less flexible. As we mentioned in the design of amino acid **95** (Figure 4.2.1), the *m*-xylol ring can provide a similar restriction as an allylic system. With this in mind the amino- and hydroxy acids **194** and **195** were designed in order to construct some cyclic peptides. Recently, some working groups[115-120] synthesized some small cyclic peptides (Figure 2.4.6) containing an aromatic ring as central part to mimic β-turns and they successfully created β-turn mimics .

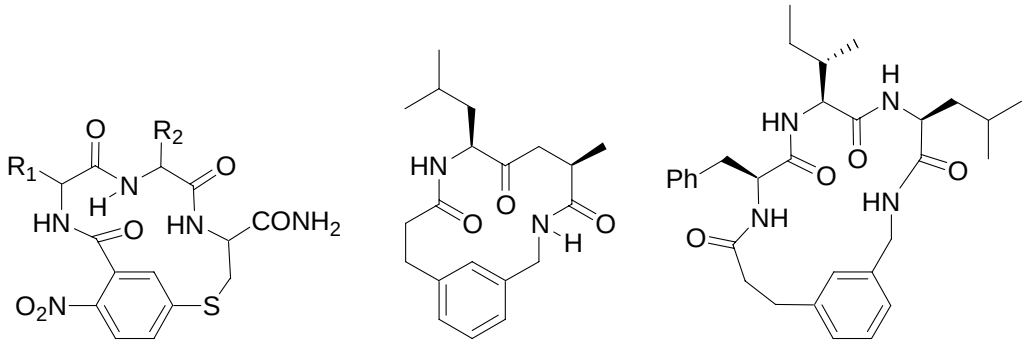
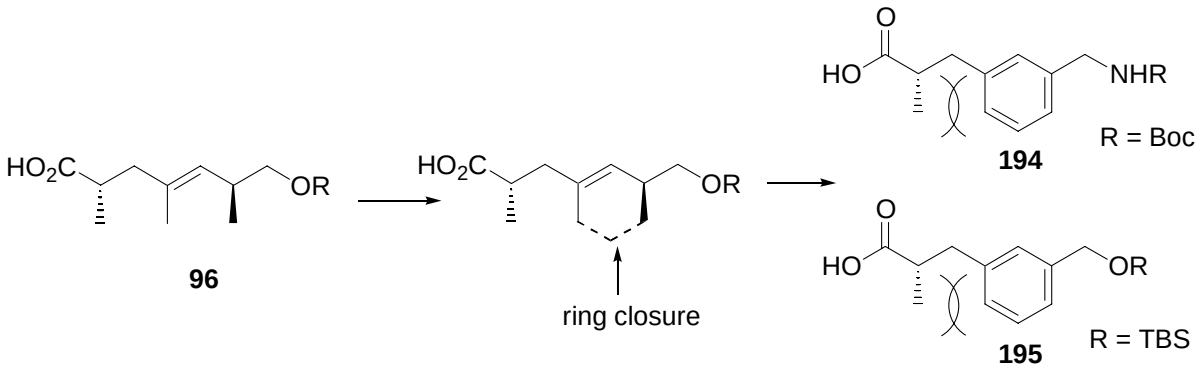


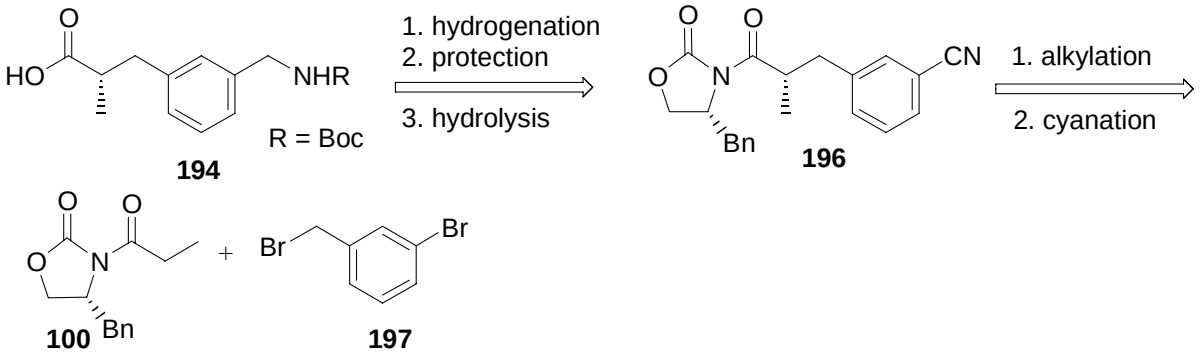
Figure 4.2.6: Some examples of peptidomimetics containing aromatic ring as central part.



Scheme 58: Replacement of the allylic system of hydroxy acid **96** with a *meta*-substituted aromatic portion.

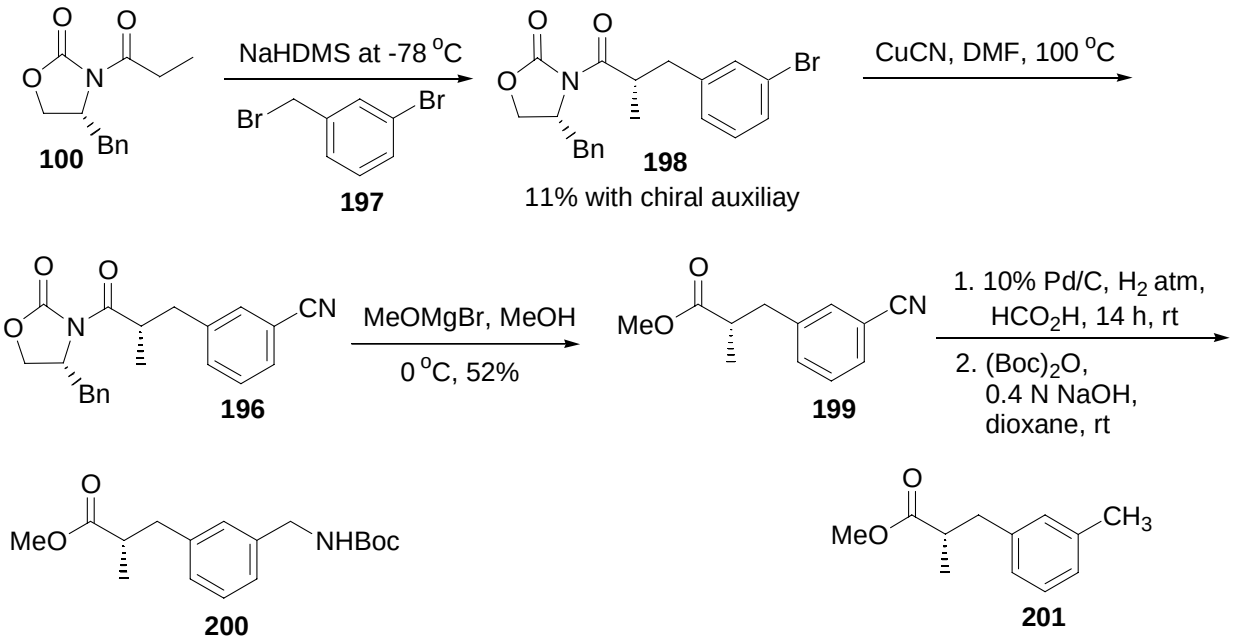
4.2.11 Retrosynthetic analysis and synthesis of amino acid 194

As one can see amino acid **194** contains a α-methyl carboxylic acid on one side and a methylamine group on the other side of the benzene ring. It should be possible to synthesize the α-methyl carboxylic acid by hydrolysis of the Evans alkylation product between propionyl oxazolidinone and a benzyl bromide derivative. The methylamine group could be obtained by reduction of a cyano group either by hydrogenation or by hydride reduction. In turn, the cyano group might be obtained by ipso substitution of the bromide with copper(I) cyanide.[120] Thus, a suitable electrophile for the synthesis of amino acid **194** might be 3-bromobenzyl bromide.



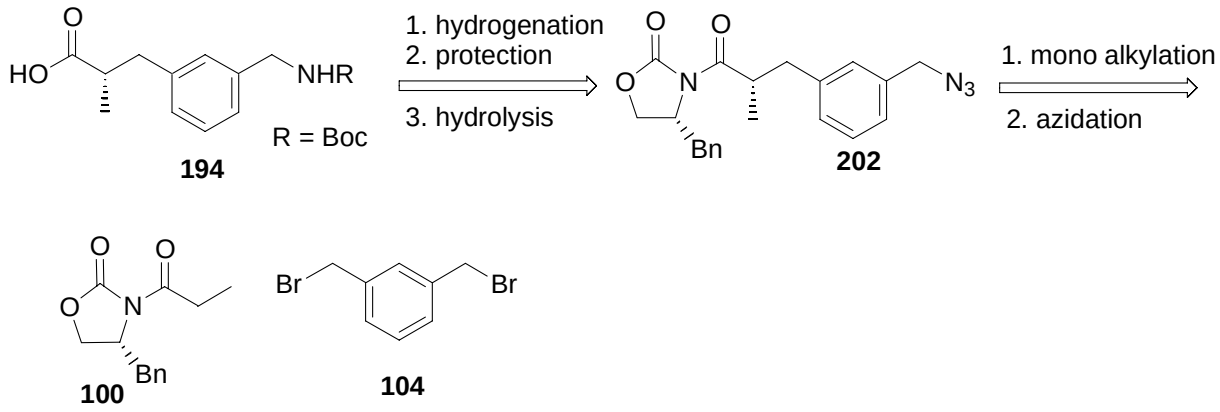
Scheme 59: Retrosynthetic analysis for amino acid **194**.

The synthesis was started with commercially available 3-bromobenzylbromide **197** and propionyl oxazolidinone. Alkylation of propionyloxazolidinone **100** with 3-bromobenzylbromide using a 2 M solution of NaHDMS at -78 ^{o}C produced the corresponding alkylated product **198** in 50% yield, contaminated with propionyl oxazolidinone **100** in about 10%. The cyanation (S_NAr reaction) of the alkylation product **198** using copper(I) cyanide in DMF at 100 ^{o}C produced the corresponding cyanide **196** in 58% yield.[120] Hydrogenation of the cyanide **196** in presence of Pd/C and formic acid did not provide the corresponding amine .[119] Attempts to prepare the amine using hydrogenation in different solvents such as ethanol and ethyl acetate did not provide a good result. It might be possible that due to the steric crowding of the chiral auxiliary, cyanide can not sit on the surface of the catalyst, thus there is no hydrogenation. Therefore, the chiral auxiliary was cleaved by in situ generation of methoxy magnesium bromide using methylmagnesium bromide in methanol to get the corresponding methyl ester **199** in 55% yield. Hydrogenation of the nitrile **199** in presence of 10% Pd/C and formic acid in methanol produced the corresponding amine salt in 14 hours at room temperature. Protection of the amine using Boc-anhydride in presence of 1N NaOH produced the Boc-amino acid ester **200** in 70% yield. However, this hydrogenation was not really reproducable. In some runs we observed formation of the over reduced toluene derivative **201**. This result was confirmed by NMR spectra. Even though the synthesis is short, the yields were quite low in each step and the hydrogenation is not a reliable procedure.



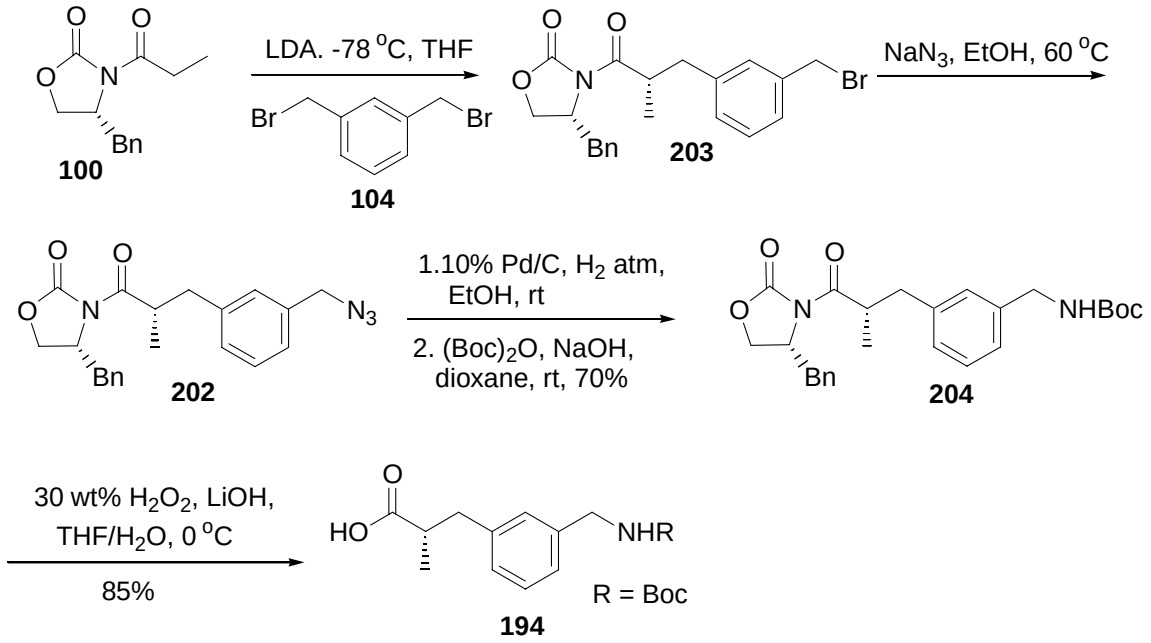
Scheme 60: Attempted route for the synthesis of amino acid **194**.

Since Scheme 60 led to the undesired side product in the hydrogenation, a method was sought that would provide the amino acid **194** in less number of steps. In the present Scheme, we decided to use dibromobenzyl derivative **104** to avoid the reduction of the cyanide group. The key steps involved in the present strategy were an asymmetric Evans alkylation and S_N2 displacement, reduction and hydrolysis.



Scheme 61: Retrosynthetic analysis for amino acid **194** using a mono alkylation strategy.

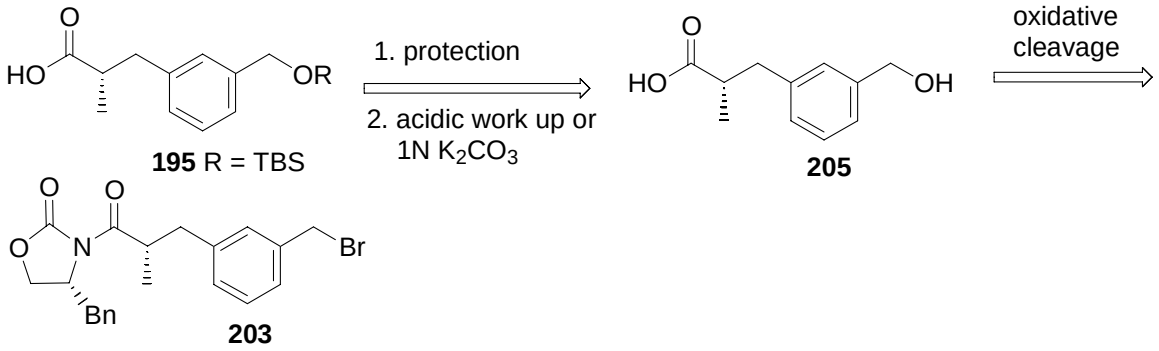
The crucial step in the synthesis using Scheme 61 is to achieve a selective mono alkylation. As we mentioned in the synthesis of the novel ω-amino acid **95**, the dialkylated product can be synthesized using an excess of chiral reagent. It is obvious that using excess alkylating reagent should produce the mono alkalated product as major product due to reduced availability of the enolate. Synthesis of amino acid **194** was started with the commercially available benzyl bromide derivative **104** as shown in Scheme 62. Alkylation of propionyl oxazolidinone **100** with 3 equivalents of benzyl bromide derivative **104** using LDA at -78 ^{o}C produced the mono alkylated product **203** in 60% yield. The excess benzylbromide derivative was recovered by washing the reaction mixture with hexane as it dissolves well in hexane. The S_N2 displacement of bromide with azide using sodium azide in ethanol at 60 ^{o}C afforded the desired azide **202** in 85% yield. The crude azide **202** was almost pure and it was used without further purification. The reduction of azide[121] to amine in presence of 10% Pd/C and hydrogen atmosphere produced the desired amine. Subsequent protection of the amine using Boc-anhydride in presence of 1 N NaOH delivered the Boc protected amino acid derivative **204** in 70% yield. The hydrolytic cleavage of the resulting product using 30 wt% H_2O_2 and lithium hydroxide led to the the desired amino acid **194** in 80% yield. This way the amino acid was secured in less number of steps with good yields (Scheme 62).



Scheme 62: Efficient synthesis of amino acid **194**.

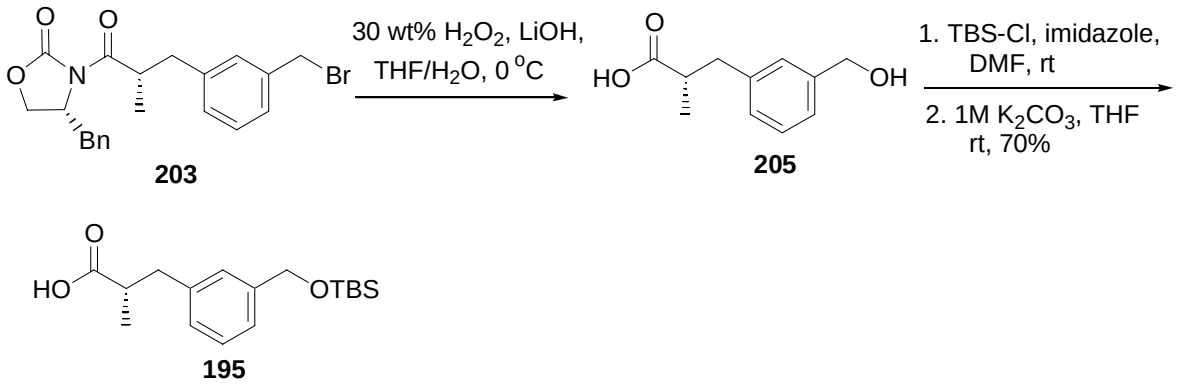
4.2.12 Synthesis of hydroxy acid 195

Hydroxy acid **195** also has one methyl group α to the carboxylic group. Therefore, the synthesis of the hydroxy acid **195** should be possible from the mono alkylated product **203**. Hydrolysis of monoalkylated product **203** would generate the carboxylic acid as well as cause nucleophilic attack of hydroxide at the benzylic position by replacement of the bromide. This way unprotected hydroxy acid **205** might be obtained in a single step. The protection of the hydroxy group as silyl ether and basic hydrolysis of the silyl ester should then provide the desired hydroxy acid **195** in just a few steps.



Scheme 64: Retrosynthetic analysis for hydroxy acid **195**.

The synthesis of hydroxy acid **195** started with the mono alkylation product **203**. The hydrolytic cleavage of the chiral auxiliary indeed produced the desired unprotected hydroxy acid **205** in 70% yield. The protection of hydroxy acid using TBDMS-Cl in presence of imidazole led to the TBS protected hydroxy acid silyl ester which on treatment with 1M K_2CO_3 in THF produced the hydroxy acid **195** in 70% yield (Scheme 65).



Scheme 65: Synthesis of hydroxy acid **195**.

4.3 Conformational studies

4.3.1 Conformational studies of jasplakinolide analogues 129, 134, 135 and 136

Aside from variations in the side chains, the major difference of the four analogs **129**, **134**, **135** and **136** is the replacement of the polypropionate subunit with a *m*-xylyl containing amino acid **95**. The 19-membered systems **135** and **136** are structurally closely related to the natural compound jasplakinolide. Compound **136** possesses a secondary amide in position 16 (Figure 4.3.1). ^{1}H and ^{13}C resonance assignments via DQFCOSY, ROESY/NOESY and HMQC spectra were performed in DMSO-d_6 and gave a single signal set for **135** and a doubled signal set for **136** with the *trans* isomer of the *N*-methylated amide populated for > 99%.

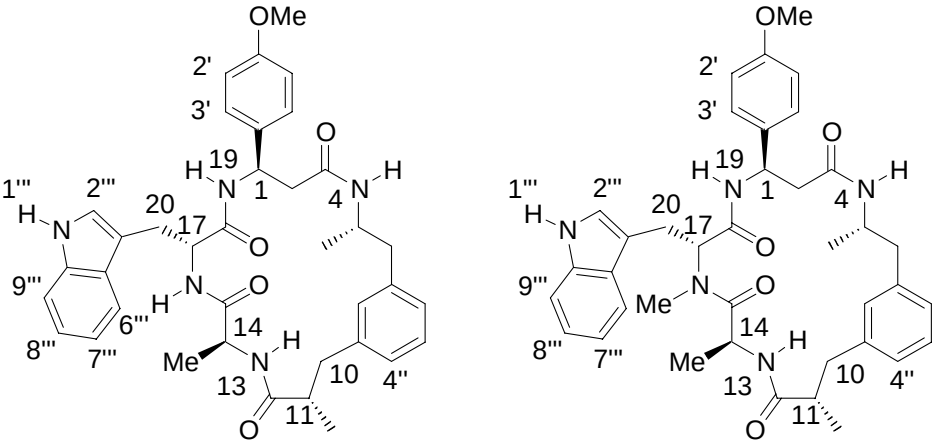


Figure 4.3.1: Structures for the 19-membered ring analogs **135** and **136** with the numbering systems used.

One large and one small $^{3}J_{HH}$ coupling constant (Table 3) for the methylene groups in positions 2, 6 and 10 of **130** and in positions 6 and 10 for **131** are typical for a well defined *gauche-anti* orientation with preference for the major rotamer(s) as distinguished by characteristic ROE signals. This allowed the assignment of the *pro-R* and *pro-S* protons of the

methylene groups. Due to signal overlay a statement on the methylene protons in position 2 of **136** was not possible.

Table 3. $^{3}J_{HH}$ coupling constants in Hz of the methylene protons in **129**, **134**, **135** and **136**. Due to identical chemical shift for $H10^{h}/H10^{t}$ of **129** and $H2^{h}/H2^{t}$ of **136**, resp. the coupling constants could not be determined.

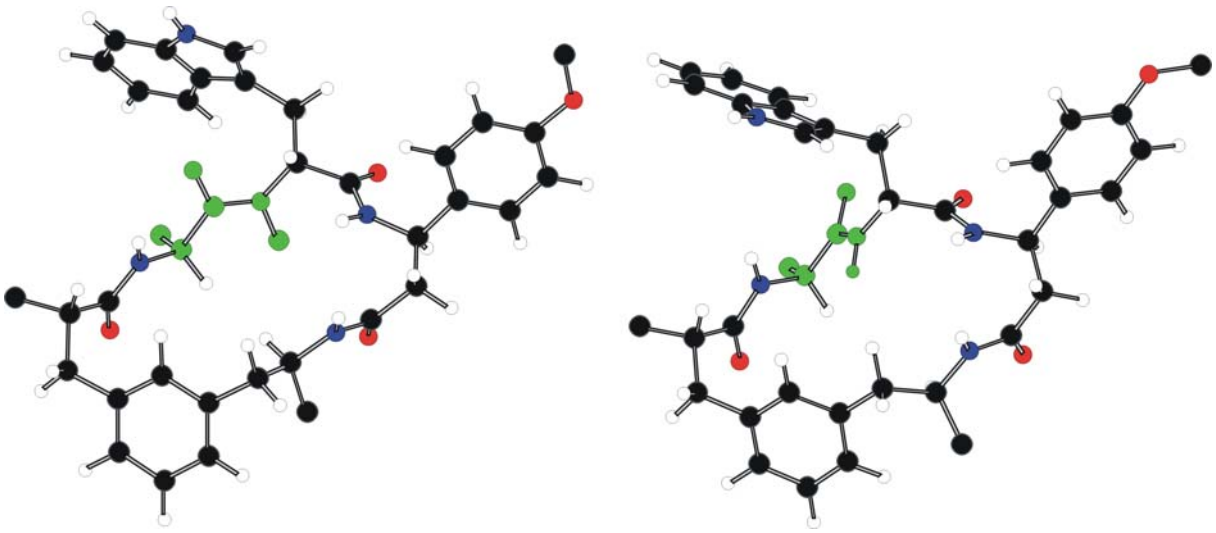
	129	**134**		**135**	**136**
$^{2}J_{H1h,H1t}$	13.5	14.0	$^{2}J_{H2h,H2t}$	13.6	n.d.
$^{3}J_{H1h,H2}$	n.d.	12.7	$^{3}J_{H2h,H1}$	4.3	n.d.
$^{3}J_{H1t,H2}$	3.7	3.6	$^{3}J_{H2t,H1}$	10.4	n.d.
$^{2}J_{H6h,H6t}$	13.1	13.1	$^{2}J_{H6h,H6t}$	13.0	12.9
$^{3}J_{H6h,H5}$	6.1	~ 7 (from COSY)	$^{3}J_{H6h,H5}$	10.6	9.0
$^{3}J_{H6t,H5}$	4.1	~ 5 (from COSY)	$^{3}J_{H6t,H5}$	3.7	4.7
$^{2}J_{H10h,H10t}$	n.d.	12.6	$^{2}J_{H10h,H10t}$	11.0	14.0
$^{3}J_{H10h,H11}$	n.d.	11.3 (via H11)	$^{3}J_{H10h,H11}$	2.7	3.1
$^{3}J_{H10t,H11}$	n.d.	4.0	$^{3}J_{H10t,H11}$	13.7	10.3

With ROESY and NOESY measurements characteristic proton-proton interactions could be determined and transferred into proton-proton distances by integration. They are in very good agreement for compounds **135** and **136** corresponding to a minor influence of the *N*-methylation in position 16 on the overall structure. No intensive cross signals were found between H α-protons of adjacent amino acids, thus proving *trans* conformation for all amide bonds. The methylated amide in **136** leads to an energy barrier which gives rise to a separated signal set for the *cis*-amide. The signal set for the *cis* isomer is populated to less than 1%. The significant preference for the *trans* rotamer, to such an extent unusual for a tertiary amide, was found for the natural compound jasplakinolide as well,[122] thus emphasizing the good analogy of synthetic analog and natural product.

The dynamical properties of the whole macrocycles **135** and **136** are consistent including the side chains having the same dynamical behavior as the macrocyclic ring. The newly inserted *m*-xylyl unit performs an oscillating movement as ROESY data yield only mean proton-proton

distances for several possible orientations of the phenyl ring in relation to the macrocyclic ring. Via temperature measurements, which gave temperature coefficients for the amidic NH protons in the range of –3.7 to –6.0 ppb K^{-1}, transannular hydrogen bonds could be excluded but nevertheless, as coupling constants and ROESY data show, the 19-membered analogs **135** and **136** are rigid macrocyclic structures.

Within a MD simulation, calculated structures of **135** and **136** are very well comparable with each other, the only difference being the orientation of the N*H* proton respectively the *N*-methyl group in position 16 with the proton in **135** pointing into the middle of the macrocyclic ring and the methyl group in **136** oriented towards the lower side of the ring (Figure 4.3.2).



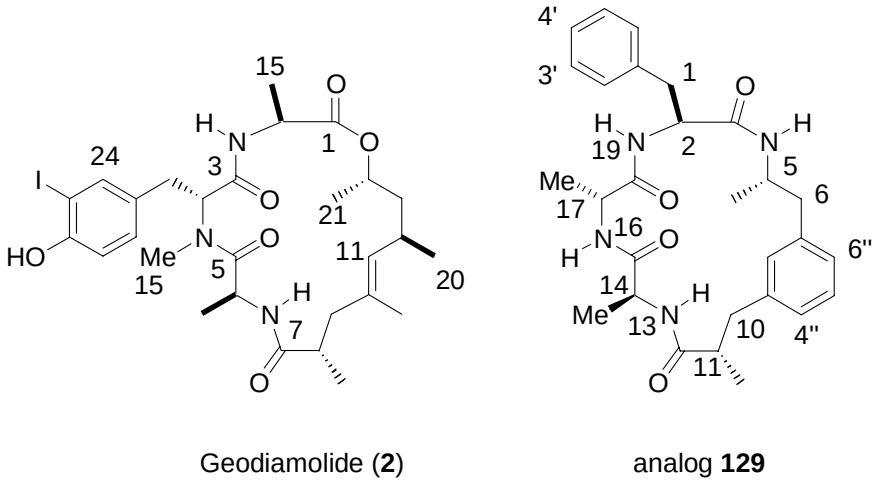
136 **135**

Figure 4.3.2: Energy-minimized structures for **135** and **136** after a 100 ps MD Simulation at 300 K. In green torsion with the largest difference for **135** and **136** with the *N*-methyl group in **136** oriented onto the lower side of the ring and the NH proton in position 16 of **135** pointing into the macrocyclic ring.

The results presented above are in accordance with NMR structural investigations of jasplakinolide.[122] Jasplakinolide does not possess any hydrogen bonds nor a higher fraction of *cis*-amide, either. The ^{3}J coupling constants yield a more flexible structure for the natural analog in comparison to the compounds **135** and **136**, however the difference is small. The

orientation of the two aromatic side chains were not determined in detail in the study presented here. But a possible „tweezer“ structure as stated in literature cannot be supported by NOEs between side chain protons.

The 18-membered rings of compounds **129** and **134** show several structural differences when compared to jasplakinolide. They are rather analogs of geodiamolide with a difference in the position of the aromatic amino acid (Figure 4.3.3).[121]



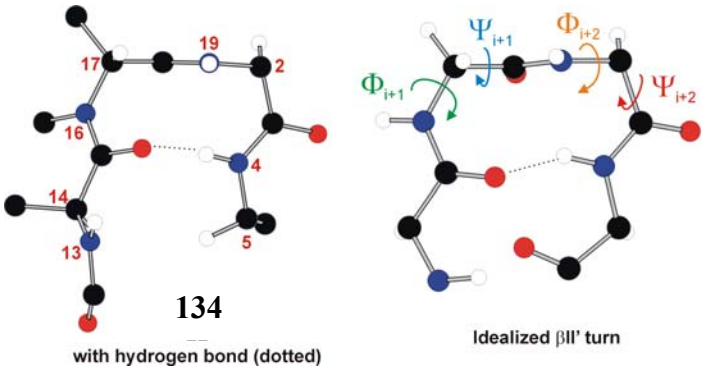
Geodiamolide (**2**) analog **129**

Figure 4.3.3: Structures for the natural compound geodiamolide and the 18-membered ring analog **129** with the numbering systems used.

^{1}H and ^{13}C signal assignment was done by DQF-COSY, ROESY/NOESY, and HMQC spectra in DMSO-d_6 with results comparable to the 19-membered macrocycles: a single signal set for **129**, the non-methylated amide and a doubled signal set for **134** with the *cis* isomer of the *N*-methylated amide populated to less than 1%. Investigation of the NOESY/ROESY data results in mean values of proton-proton distances being significant for the fast exchange of several conformers. Thus the 18-membered rings **129** and **134** are more flexible than the systems described above and a preferred structure can not be calculated on the basis of experimental ROE data. ROESY data confirm a *trans* configuration for all amide bonds in **129**, respectively **134**. Additionally the ROESY data reveal again an oscillatory movement for the *m*-xylyl unit like in **135** and **136**. In case of the geodiamolide analogs **129** and **134** there are consistent dynamics for the whole molecule but rather an independent dynamical behavior of the side

chains, i. e. benzyl- and methyl groups, as seen in ROESY spectra with cross signals of different sign. The methylene groups in position 1 of **129** and in positions 1 and 10 of **134** exhibit one large and one small $^{3}J_{HH}$ coupling constant (Table 3) defining a preferred *gauche-anti* orientation whereas in position 6 the coupling constants possess mediated values upon the presence of several rotamers. Temperature measurements yield low temperature coefficients for N*H*4 and N*H*13 for both structures (N*H*4: -1.0 resp. –1.1 ppb K^{-1}; N*H*13: +0.4 resp. –1.1 ppb K^{-1}) with a high probability for those N*H* protons to take part in an intramolecular hydrogen bond.

When calculating only a partial structure for **134** with NOESY/ROESY data a betaII'-turn-like structure is obtained for the macrocyclic part containing the phenylalanine unit. For this case N*H*4 is part of a transannular hydrogen bond with CO(15) as partner, whereas for N*H*13 there is no geometrically reasonable arrangement for the formation of a hydrogen bond (Figure 4.3.4). At least for this section of the macrocyclic ring the ROESY data obtained are in accordance with the distances typical for betaII ‘turns.

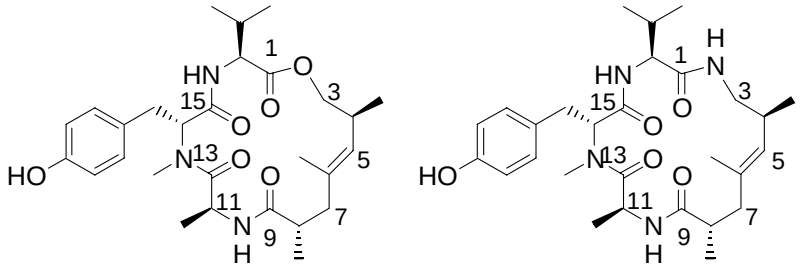


Angle	**134**	ideal βII turn
Φi+1	81°	60°
Ψi+1	-108°	-120°
Φi+2	-81°	-80°
Ψi+2	-1°	0°

Figure 4.3.4: Comparison of the calculated partial structure of **134** with a betaII-turn structure.

Nevertheless, the 18-membered rings **129** and **134** are more flexible compared to **135**, **136** or jasplakinolide and an equilibrium of several fast exchanging conformers is existent.

4.3.2 Conformational studies of geodiamolide analogues 159 and 160



159 **160**

Figure 4.3.5: Structures for the 17-membered ring analogs **159** and **160** with the numbering systems used.

The major variation between the analogues **159** and **160** and the natural product geodiamolide is the ring size, the former ones contain a 17-membered ring while the latter one contains a 18-membered ring. Compound **159** is a depsipeptide while **160** is a macrolactam. Homo- and heteronuclear signal assignments of **159** and **160** are based on DQF-COSY, HSQC and HMBC spectra, respectively. Rotating-frame NOESY (ROESY) and NOESY spectra corroborate the signal assignments. Each exhibits a single ^{1}H and ^{13}C NMR signal set in DMSO-d_6 and the absence of NOE-contacts expected for *cis*-amide bonds approve the *trans* configuration for all amide bonds in both macrocyclic rings **159** and **160**. $^{3}J_{HH}$ and $^{2}J_{HH}$ coupling constants are taken directly from the well-resolved ^{1}H NMR spectra after Lorentz-Gauss transformation. The temperature dependence of the N*H* chemical shifts yields information about the solvent accessibility of the amide protons.[124-127] Values between –5.8 and –7.6 ppb K^{-1} exclude strong intramolecular hydrogen bonds in both molecules.

57 ROEs are observed for the lactone **159** and 45 ROEs for the lactam **160**. The volume integrals translate into average proton-proton distances according to published methods.[128] The common motif Val-D-Tyr-Ala adopts a mainly extended conformation with interresidue $C^{\alpha}Hi$ - NH*i+1* average distances between 2.2 and 2.4 Å and intraresidue $C^{\alpha}Hi$ - NH*i* distances approaching 3 Å. 1,3-allylic strain in the polypropionate moiety is documented by the strong ROE contact 4H – $6H_3$ in both molecules. $^{3}J_{HH}$ coupling constants and ROEs allow the

prochiral assignment of the *pro-R* and *pro-S* protons of the methylene groups' 3-CH_2 and 7-CH_2 which form the flexible joints between both termini of the polypropionate unit and the tripeptide unit. In both molecules, one of the $^3J_{H3,H4}$ and one of the $^3J_{H7,H8}$ coupling constants is small (Table 4), by this proving that a main rotamer is adopted around the 3C-4C and the 7C-8C bond in both molecules. Differences between **159** and **160** are detected only for the 3-CH_2 which neighbours the lactone in **159** and the amide in **160**, respectively. The rotamer with a *gauche-anti* orientation is dominating in **160** and the *gauche-gauche* orientation in **159**. The 18-CH_2 protons are well resolved in the case of the lactone but form a higher-order spin system in the case of the lactam. Chemical shift differences between compounds 1 and 2 are restricted to the *Northern* half of the macrocyclic rings in the region of the Val residue.

Selected NOEs and ^3J coupling constants served as weak distance and torsional restraints in molecular dynamics simulations. The average structures represent minima on the potential energy surface and the energy minimized structures are shown in Figure 4.3.6. Structural differences are confined to the amino acid Val. The more folded structure of the lactone brings 13-NMe and 6-Me in closer contact which is documented by a relatively short long-range NOE of 3.1 Å. The main difference between the ring-constrained analogs investigated here and the parent macrolide geodiamolide[123] is an approximately 180° rotation of the propionate relative to the tripeptide unit. As a consequence, the 6-Me group is oriented to the opposite side of the macrocyclic rings which is documented by the intense transannular 13-NMe – 6-Me NOE. The distance between these two groups is 7.7 Å in geodeamolide where they are positioned on opposite ring sides (Figure 4.3.6). Such a strong effect of a ring contraction from a 18-membered ring in geodiamolide to a 17-membered ring in **159** and **160** is completely unexpected but well documented by the solution NMR data analyzed here.

Table 4: ^{2}J and ^{3}J coupling constants of **159**and **160** in [Hz]

Coupling	**159**	**160**
$^{2}J_{H3h,H3t}$	10.9 Hz	12.9 Hz
$^{3}JH_{3h,H4}$	2.5 Hz	9.1 Hz
$^{3}J_{H3t,H4}$	5.4 Hz	2.6 Hz
$^{2}J_{H7h,H7t}$	15.1 Hz	16.0 Hz
$^{3}J_{H7h,H8}$	<2 Hz	<2 Hz
$^{3}J_{H7t,H8}$	11.1 Hz	≈10 Hz (COSY)

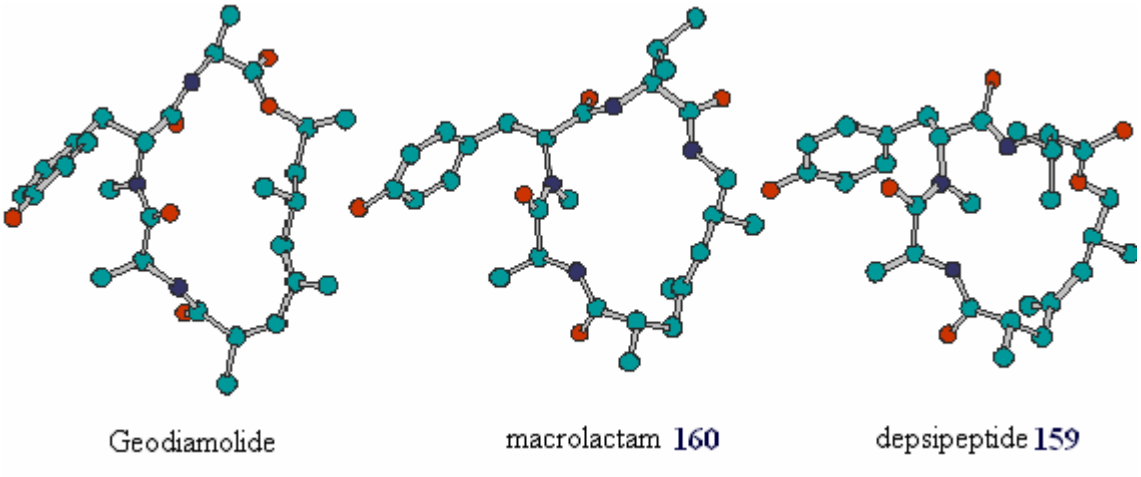


Figure 4.3.6: Energy minimized structures of compounds geodiamolide, **159**, and **160**.

Chapter II

Approach towards the Synthesis of the Stereotetrad of Cruentaren-A

5 Introduction

Benzolactones may be viewed as privileged structures in nature since there are so many of them and they do show a broad range of biological activity. They may be classified according to their ring size, the substituents on the benzoic acid, and the nature of the side chain that extends from the secondary alcohol function that is engaged in the lactone. Salicylihalamide A (**206**) and apicularen A (**207**) are members of the so-called benzolactone enamides (Figure 5.1).[130] These compounds possess an extended side chain with an enamide functionality that is necessary for the biological activity. It is assumed that protonation of the side chain generates an electrophilic acyliminium ion.[131] Many other benzolactones just have a methyl substituent at the lactone. Zearalenone (**208**) is a fungal metabolite that exhibits anabolic and antibacterial activity.[132] Among the benzolactones that shows promising biological activities, cruentaren A (**209**) is a notable example.

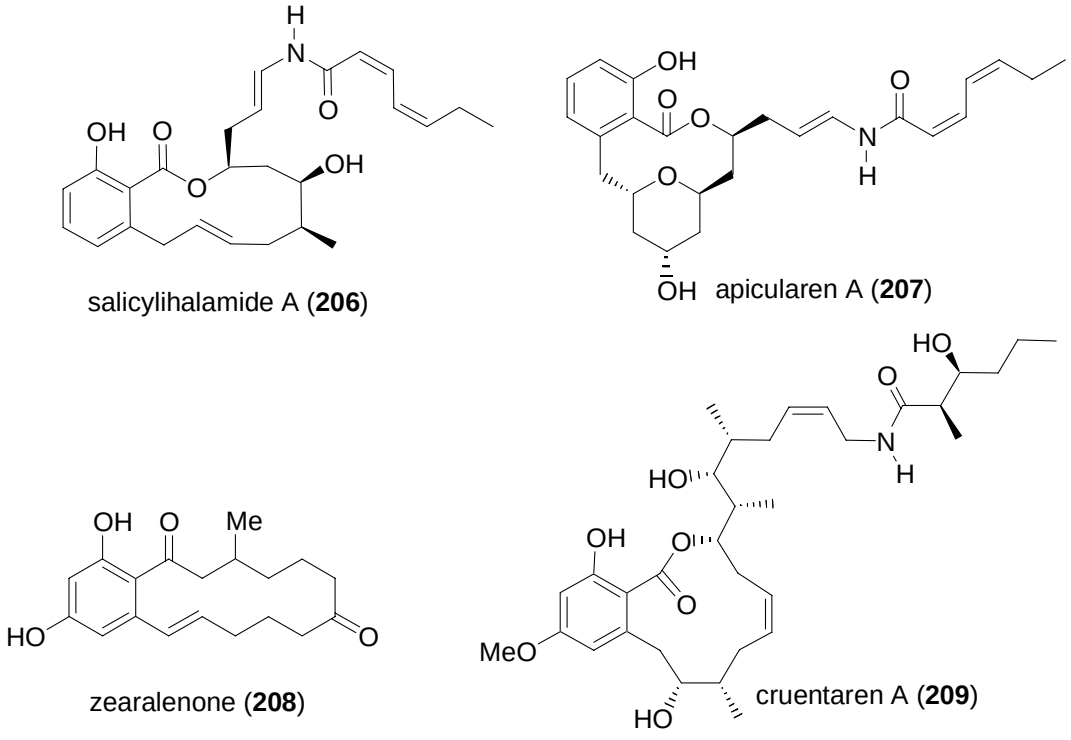
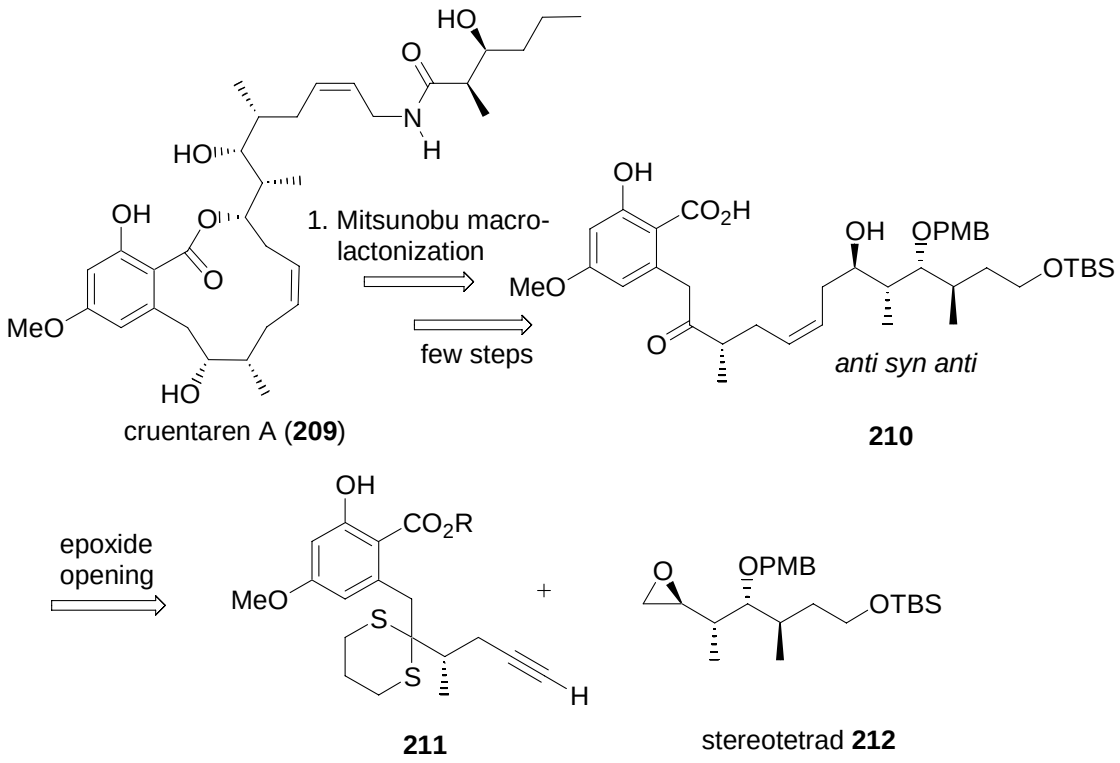


Figure 5.1: Structures of some important benzolactones

The macrolide cruentaren A is a highly cytotoxic and antifungal natural product, isolated from the strain *Byssophaga cruenta* by the Höfle research group in Braunschweig, Germany. Structurally it belongs to the benzolactone family of natural products (Figure 5.1). It features a 12-membered macrolactone ring and an allylamine side chain. Plus, there are some stereocenters, a further typical feature of polyketides. Cruentaren A was originally patented as a pesticide but in the meantime it turned out that it is a selective inhibitor of F-ATPase. But it does not inhibit the V-ATPase which is the target of the benzolactone enamides. This selectivity is quite impressive and synthesis of cruentaren analogues might provide some information about the groups on cruentaren A that are responsible for this difference. One might speculate that the allylamine rearranges to an enamide. It is interesting to note that there are some other allylamine containing natural products, for example leucasandrolide and ajudazol. Thus, synthetic chemistry will be necessary to clarify a range of questions posed by the above benzolactones.

A possible retrosynthetic analysis for cruentaren A is shown in Scheme 66. It is based on a Mitsunobu macrolactonization reaction. The *seco*-acid **210** would then be constructed from alkyne **211** and epoxide **212**. Other equivalents for alkyne **211** are of course conceivable. On the other hand, compound **212** containing a stereotetrad seems to be an indispensable intermediate, even for other strategies such as alkyne ring-closing metathesis.



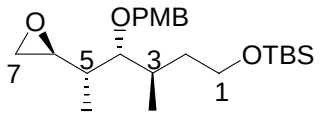
Scheme 66: Retrosynthetic pathway to cruentaren A.

Here, in this work a total synthesis of cruentaren A is not proposed. Instead, our target was an efficient synthesis of the stereotetrad **212**.

6 Synthesis of stereotetrad 212

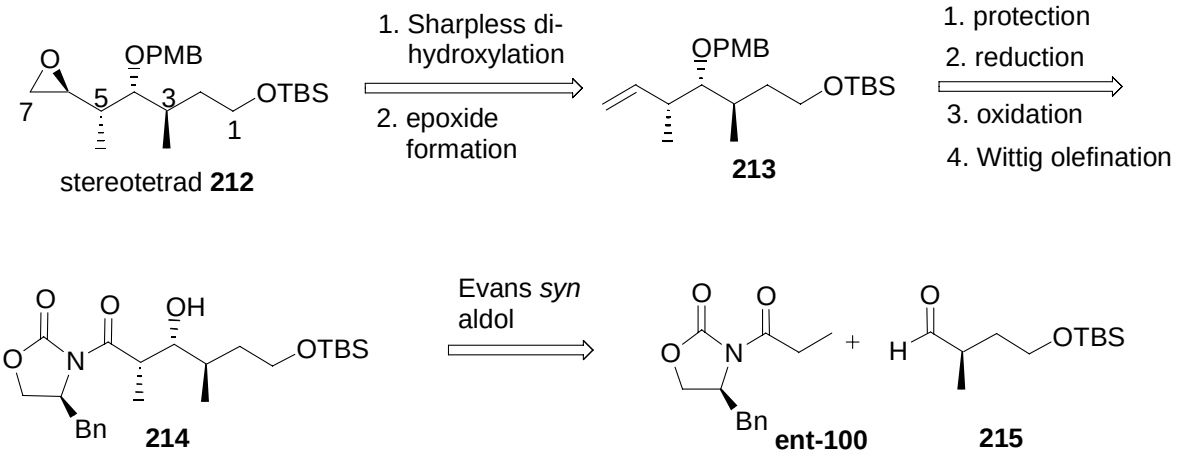
6.1.1 Retrosynthetic analysis of stereotetrad 212

From a retrosynthetic stand point one has to address the four chiral centers which are arranged in *anti-syn-anti* fashion.[133] It would be better to synthesize the epoxide in the final steps to avoid unnecessary side reactions. Thus, it was thought to start the synthesis from the right side of the epoxide **212**.



stereotetrad **212**

Even though there are several accessible retrosynthetic analyses possible for the synthesis of stereotetrad **212**, it was decided to follow Scheme 67 which involves an Evans *syn* aldol reaction[46] and a Sharpless dihydroxylation reaction[134] as key steps to create the stereo centers on positions 4, 5 and 6, respectively.



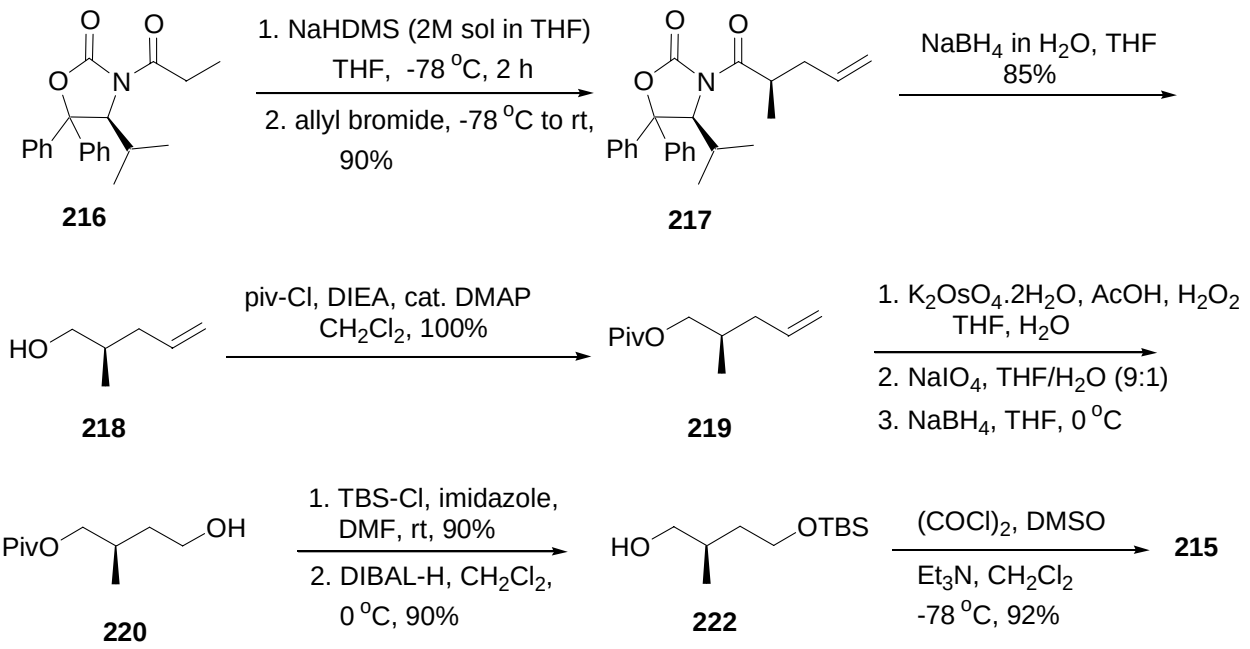
Scheme 67: Retrosynthetic analysis for the compound **212**

Epoxide **212** might be obtained from the corresponding olefin **213** in two steps using an asymmetric Sharpless dihydroxylation followed by closing the epoxide. It should be noted that the configuration of the hydroxyl group formed in the dihydroxylation could be analyzed by forming the six-membered acetal. In turn, the olefin **213** would be obtained from the *syn* aldol product **214** in few steps using protection, reduction, oxidation and Wittig olefination. The aldehyde **215** could be achieved in few steps using asymmetric alkylation as the key step.

6.1.2 Synthesis of aldehyde 215

There are several methods known to prepare aldehyde **215**.[135-138] The synthesis of the aldehyde **215** followed almost the similar pathway as reported by Crimmins et al. [138] (Scheme

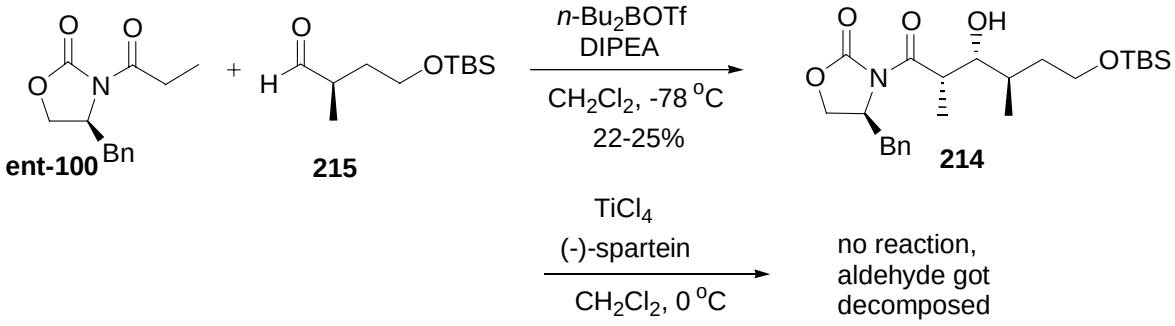
68). The synthesis began with alklylation of the Seebach auxiliary **216** with allyl bromide.[139] After successfully achieving the alkylated product **217**, the chiral auxiliary was removed using $NaBH_4$ in THF/H_2O to get the alcohol **218** in almost quantitative yield. Subsequent protection of the alcohol **218** using pivaloyl chloride in presence of diisopropylethylamine and a catalytic amount of DMAP furnished the corresponding pivalate **219** in almost quantitative yield. Dihydroxylation of pivalate **219** by in situ generated osmium tetroxide using $K_2OsO_4.2H_2O/AcOH/H_2O_2$[140] produced the diol which on oxidative cleavage using sodium periodate gave the aldehyde which on reduction led to the alcohol **220**. It should be noted that compound **220** could be obtained also by ozonolysis of the alkene **219**. Subsequent silylation of the alcohol **220** using TBS-Cl in presence of imidazole produced the silylated alcohol **221** in almost quantitative yields, which was subjected to reductive removal of the pivaloyl group using DIBAL-H at 0 °C leading to alcohol **222**. The latter was subjected to Swern oxidation to give aldehyde **215**.



Scheme 68: Synthesis of aldehyde **215**.

After having successfully synthesized aldehyde **215**, an aldol reaction was performed between Evans reagent **ent-100** and the aldehyde **215**. However, a dibutylboron triflate mediated aldol

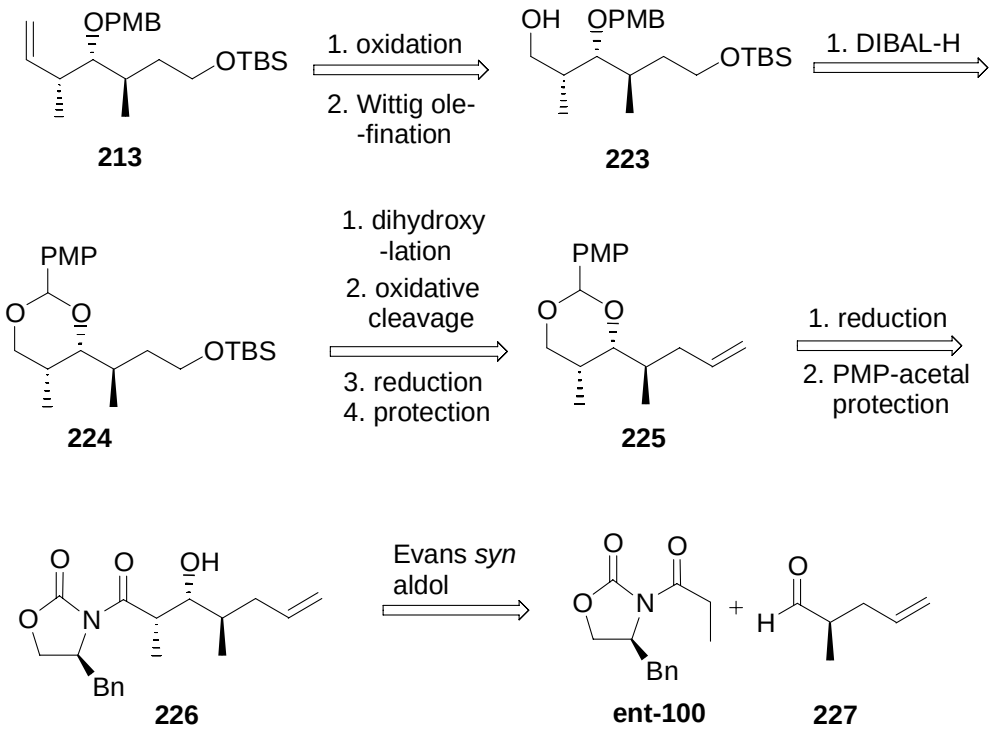
reaction between the Evans reagent **ent-100** and the aldehyde **215** in presence of triethylamine at -78 °C produced the aldol product **214** in very low yields. Attempts to increase the yield did not give better results. The corresponding $TiCl_4$/(-)-sparteine mediated aldol reaction did not produce the product at all. At this point, we decided to follow a new strategy to synthesize the compound **212** by avoiding the aldol reaction with aldehyde **215** as the production of this aldehyde is costly and the aldol reaction might need an excess of aldehyde.



Scheme 69: Attempts to synthesis the compound **214**

6.1.3 Second retrosynthetic pathway for epoxide 212

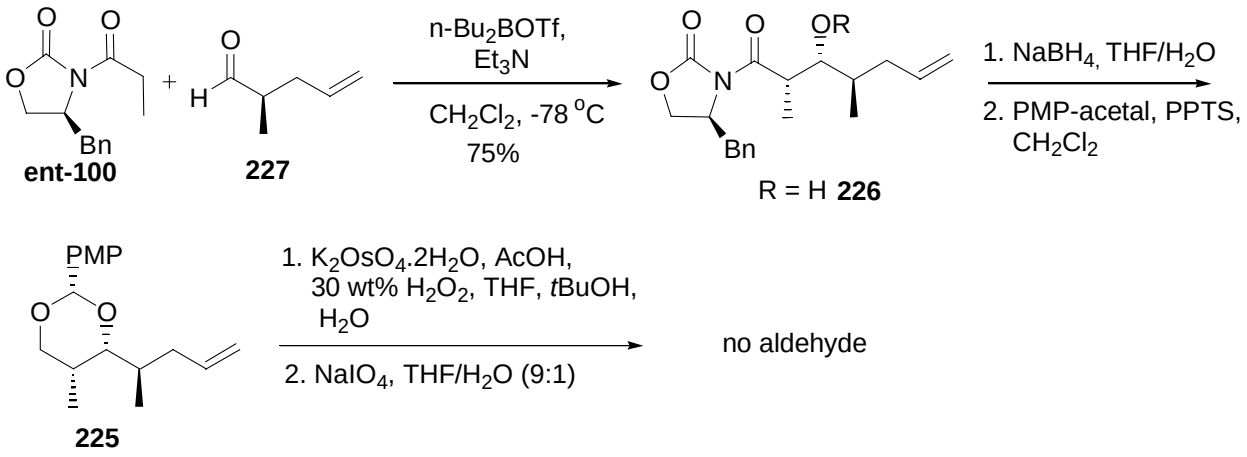
In the second retrosynthetic pathway we decided to synthesize the terminal hydroxyl group after introducing the *syn* methyl and hydroxyl groups in the stereotetrad **212**. In this plan, the olefin **213** would originate from the alcohol **223** like in the last proposal (Scheme 70). The alcohol **223** could be prepared from the reduction of PMP-acetal **224** using DIBAL-H. The PMP-acetal **224** would be prepared from olefin **225** by dihydroxylation, oxidative cleavage, reduction and protection of the resulting alcohol. The olefin **225** could be prepared from the aldol product **226** by reduction and protection of the resulting diol with the *p*-methoxy benzaldehyde acetal.



Scheme 70: Second retrosynthetic pathway for the epoxide **212**.

6.1.4 Synthetic pathway

The synthesis was started with the aldol reaction between the aldehyde **227** and the propionyl oxazolidinone **ent-100**. The aldehyde **227** was prepared by a known procedure.[141] *n*-Butylboron triflate mediated aldol reaction in presence of the base triethylamine between the aldehyde **227** and the chiral reagent **ent-100** furnished the aldol product **226** in 72% yield with good diastereoselectivity (Figure 6.1) as shown in Scheme 71. Subsequent reduction of the aldol product **226** using $NaBH_4$ in H_2O gave the diol which was protected using *p*-methoxy benzaldehyde dimethyl acetal in presence of catalytic amounts PPTS to furnish the PMP-protected olefin **225**. The alkene **224**, was then subjected to dihydroxylation using potassium osmate dihydrate. The resulting diol then cleaved without further purification using sodium periodate. However this process was a very messy reaction. There could be no product observed in LC-MS.



Scheme 71: Attempts for the synthesis of alcohol **223**

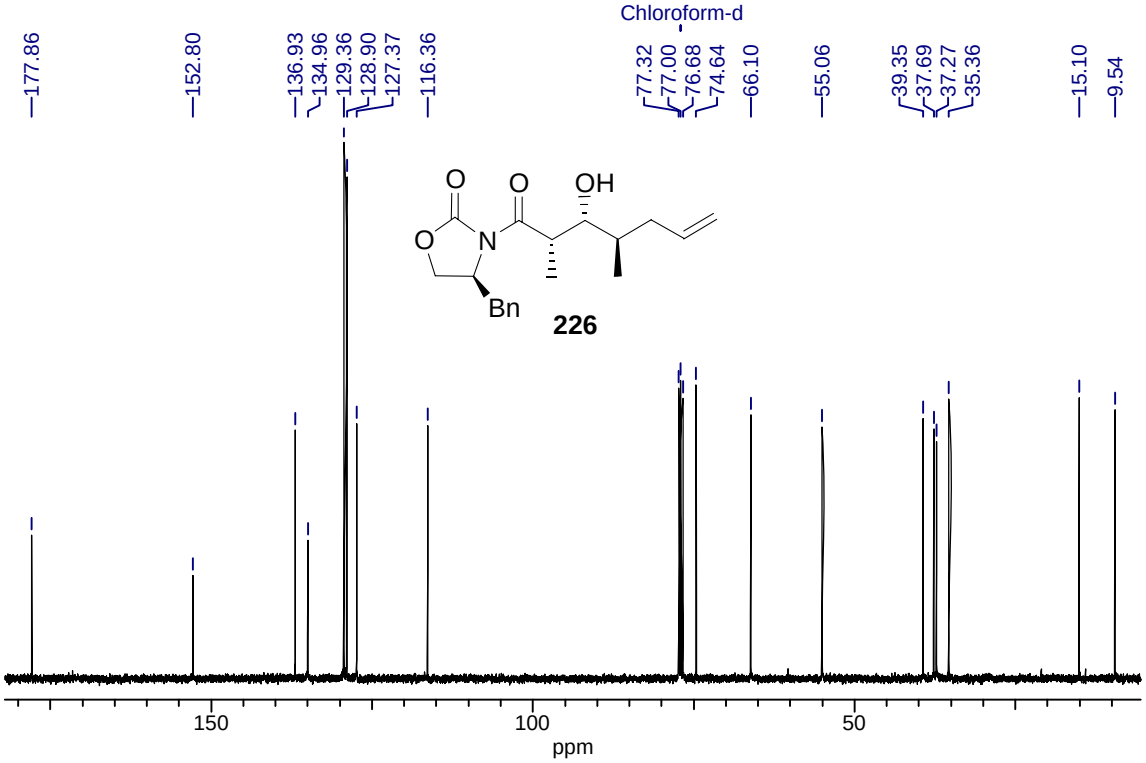
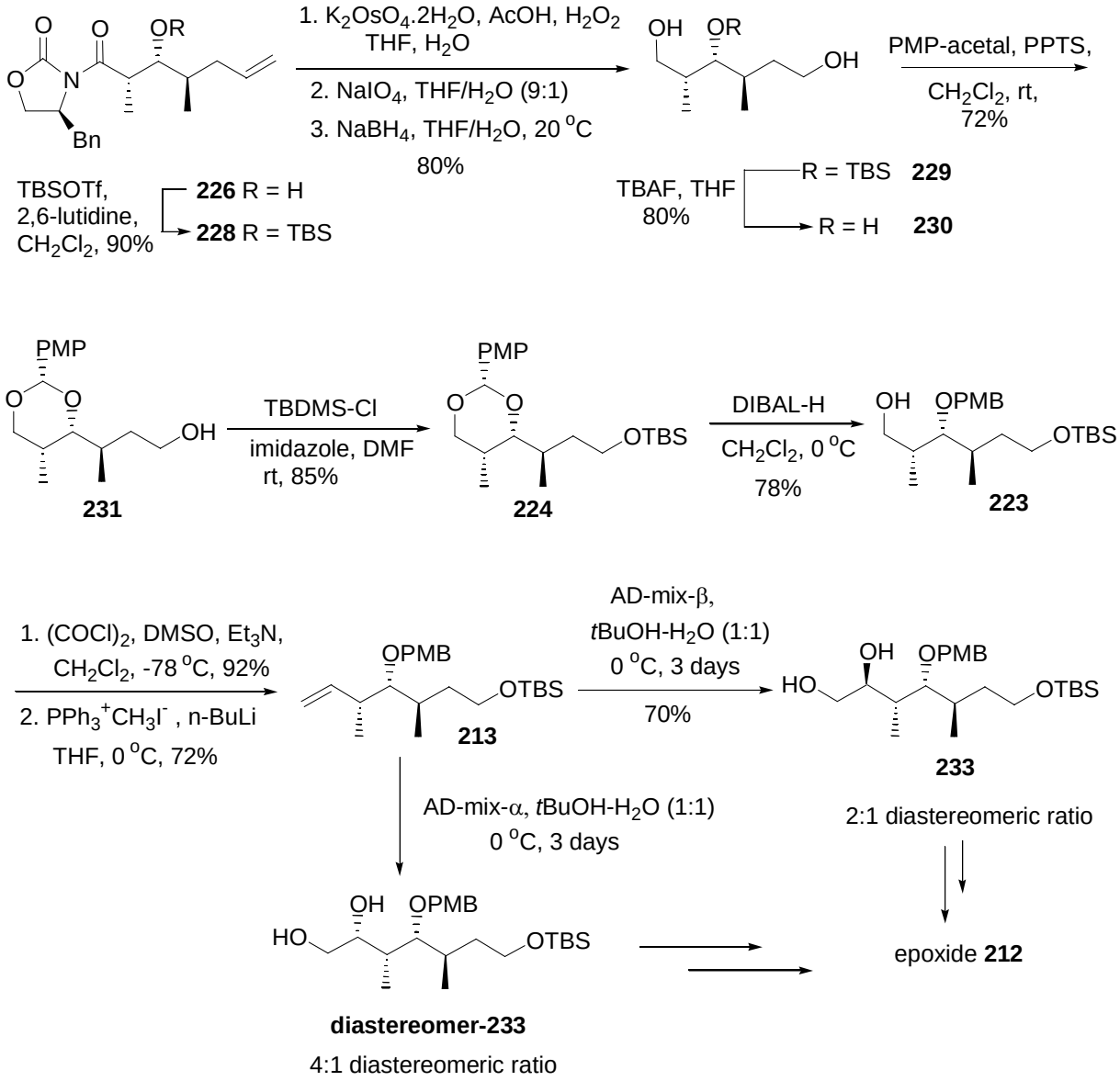


Figure 6.1: ^{13}C NMR spectrum of *syn* aldol product **226**.

At this point, we decided not to introduce the PMP-acetal before oxidative cleavage of the double bond. Thus, the aldol product was silylated using TBDMS-triflate in presence of 2,6-lutidine to get the silylated ether **228**, which was on reductive cleavage of the chiral auxiliary

using sodium borohydride led to the 1,6-diol **229** (Scheme 72). TBAF mediated cleavage of the silyl ether in compound **229** produced the 1,3,6-triol **230** in 80% yield. Subsequent protection of 1,3-diol subunit using *p*-methoxybenzaldehydedimethyl acetal in presence of catalytic amounts of PPTS gave the 1,3 PMP-acetal product **231** in 75% yield. Protection of the terminal alcoholic group in **231** provided the PMP-acetal product **224**. Regioselective reductive opening of the acetal **224** to PMB-alcohol **223** was achieved with DIBAL-H at 0 ^{o}C in 75% yield. The resulting alcohol **223** was oxidized under Swern oxidation conditions leading to the corresponding aldehyde **232** which was subjected to a Wittig olefination using methyltriphenylphosphonium iodide ($Ph_3P^+CH_3I^-$) in presence of *n*-BuLi at 0 ^{o}C giving the required olefin **213** 72% yield. The synthesis of the epoxide **212** completely depends on the selectivity of the Sharpless dihydroxylation step.[129] Even if the selectivity will be low, both isomers might be separable. AD-mix-β mediated dihydroxylation of the olefin **213** produced the dihydroxylated product **233** in 70% yield in 3 days at 0 ^{o}C with an approximate diastereomeric ratio of 2:1 (determined from ^{13}C NMR spectrum, Figure 6.2). Unfortunately, the two diastereomers could not be separated on flash chromatography. AD-mix-α mediated dihydroxylation produced a better selectivity 4:1 with opposite facial selectivity. In this case a few milligrams (around 5 mg) of pure product could be isolated by flash chromatography. The opposite facial selectivity could be explained using ^{13}C NMR spectra of both diastereomeric mixtures as illustrated in Figure 6.2. The expanded region cleary showed the two different chemical shifts for the methyl group at 5th position for both diastereomeric mixtures (8.6 ppm for major diastereomer obtained using AD-mix-β and 11.4 ppm for major diastereomer obtained using AD-mix-α). Due to the small amounts of diols the configurations could not been designed definitely. At this point, one should note that one could in principle use the diol mixture. After epoxide opening separation of the diastereomers might be possible. Using appropriate reaction conditions for macrolactonization (Mitsunobu s. Yamaguchi) the two isomers should converge to one product.



Scheme 72: Synthetic pathway for epoxide **212**.

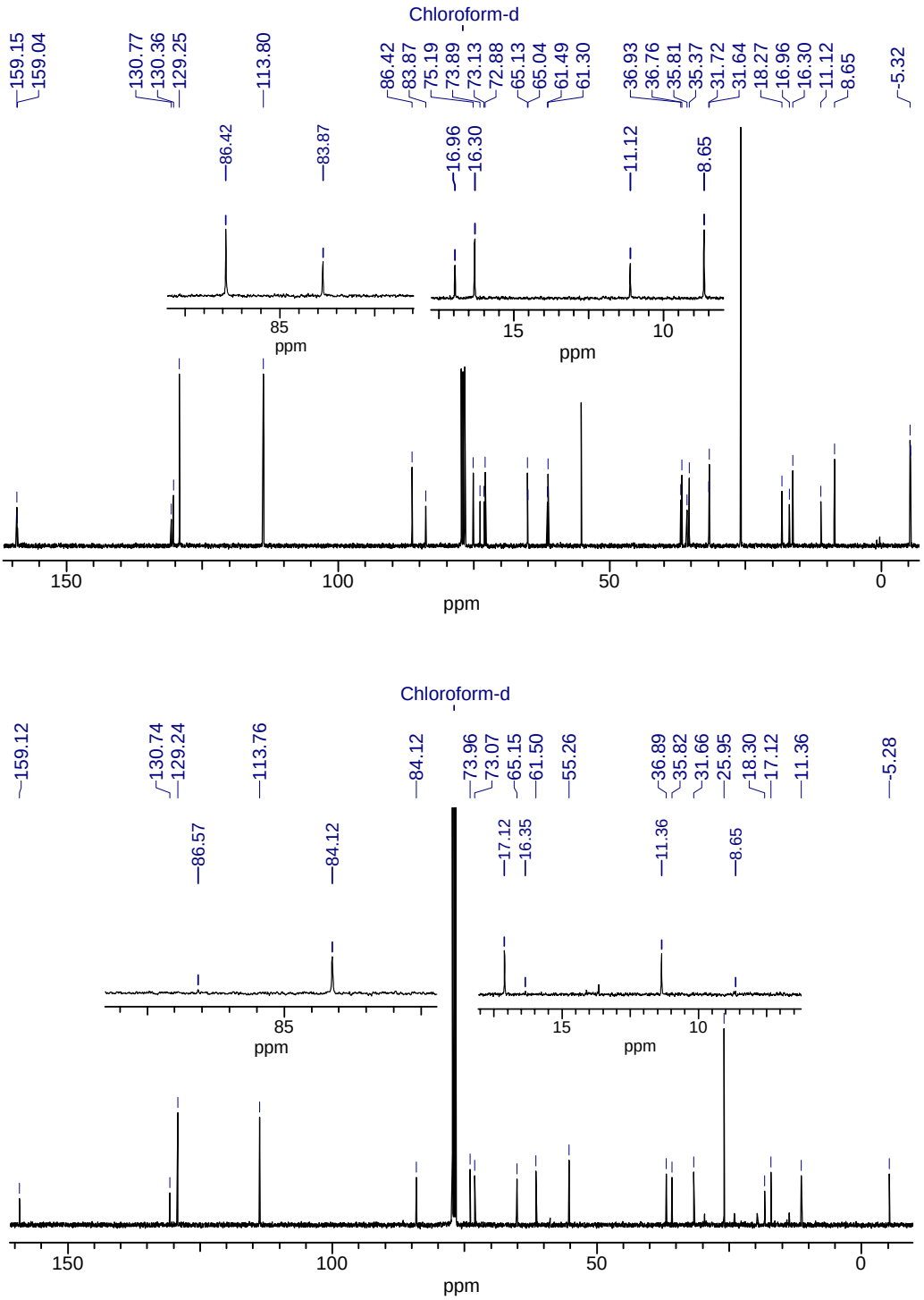


Figure 6.2: ^{13}C NMR spectra of dihydroxylation products **233** and **diastereomer-233** obtained by using AD-mix-β (upper) and AD-mix-α (lower).

The stereochemical outcome in the Sharpless dihydroxylation might be determined using the Rychnovsky ^{13}C method.[142] Protection of the primary alcohol and removal of the PMB protecting group would provide the 1,3-diol which on protection using 2,2-dimethoxypropane in presence of CSA could provide the acetonide. It is known that the carbons of the methyl groups in the acetonide of a 1,3-diol will exhibit different chemical shifts depending on the relative stereochemistry. For example, in the case of a *syn*-1,3-diol acetonide, the two methyl groups adopt different orientations (one is axial and the other is equatorial). So they have different chemical shifts, and also the quarternery carbon typically appears at 98.5 ppm. In case of an *anti* 1,3-diol, however, the acetonide will adopt a twist-boat form and the two methyl groups become more equivalent. Therefore they have similar chemical shifts and the quaternary carbon usually appears at 100.6 ppm.

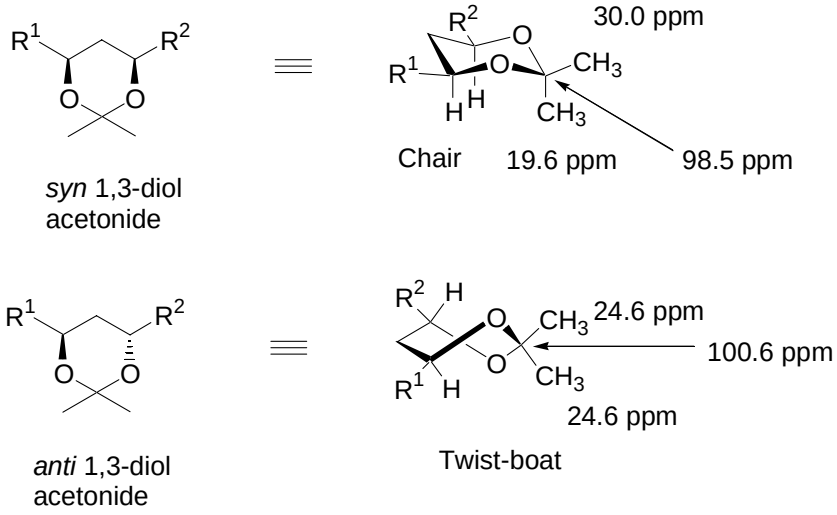


Figure 6.3: Rychnovsky ^{13}C acetonide method for 1,3-diol stereo assignments.

7 Summary and Conclusion

This dissertation contains two chapters. Chater I includes the efficient synthesis of rationally designed amino- and hydroxy acids **95**, **96**, **97, 116**, **194**, **195** which incorporate conformational constraints due to non bonded interactions such as *syn*-pentane and 1,3-allylic strain. The design of the novel amino and hydroxy acids was guided by the polypropionate sector **3** of the depsipeptide jasplakinolide.

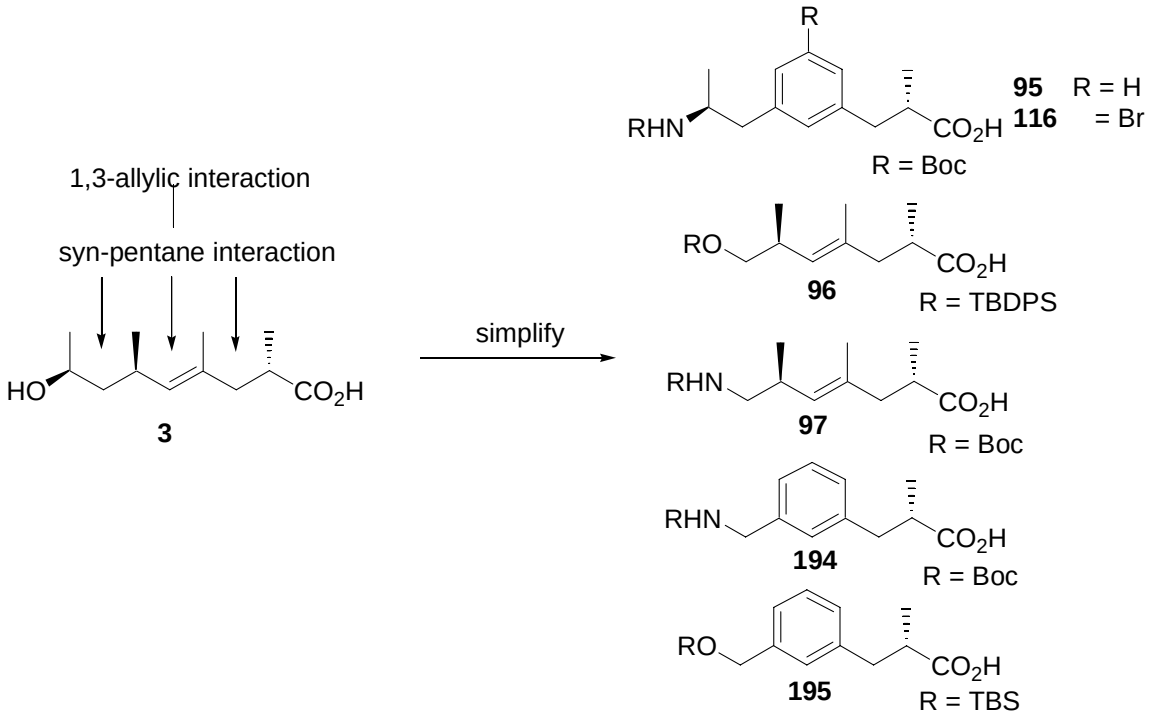
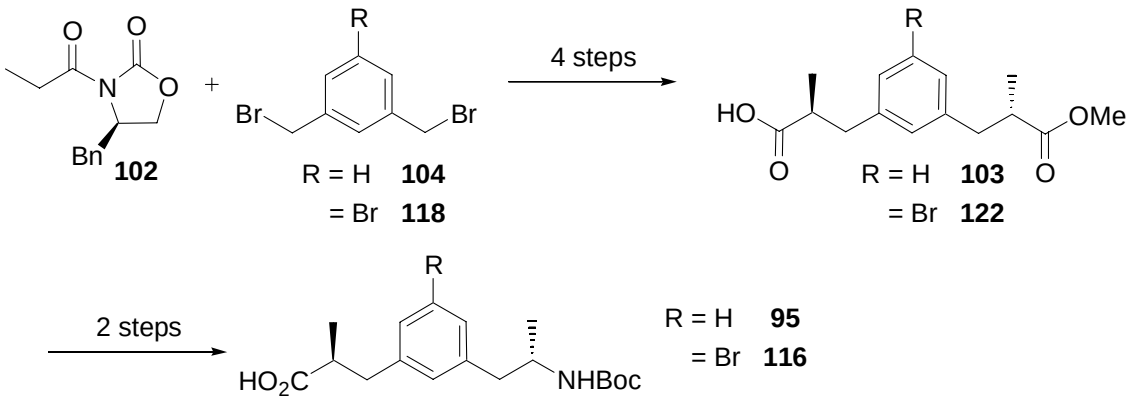


Figure 7.1 Rational design of the novel ω-amino and hydroxy acids based on non bonded interactions

The syntheses of these amino- and hydroxy acids were achieved in a few steps with good yields. The amino acid **95** and **116** were synthesized in a similar pathway in six steps by using a double alkylation, enzyme mediated hydrolysis of a homotopic diester and a Curtius rearrangement as key steps. This way, the novel ω-amino acids **95** and **116** can be prepared in gram quantities.



Scheme 73: Key substrates in the synthesis of novel amino acids **95** and **116**

The amino acid **95** was incorporated into four macrolactams **129**, **134**, **135** and **136**. The former two feature a 18-membered ring whereas the latter two have a 19-membered ring.

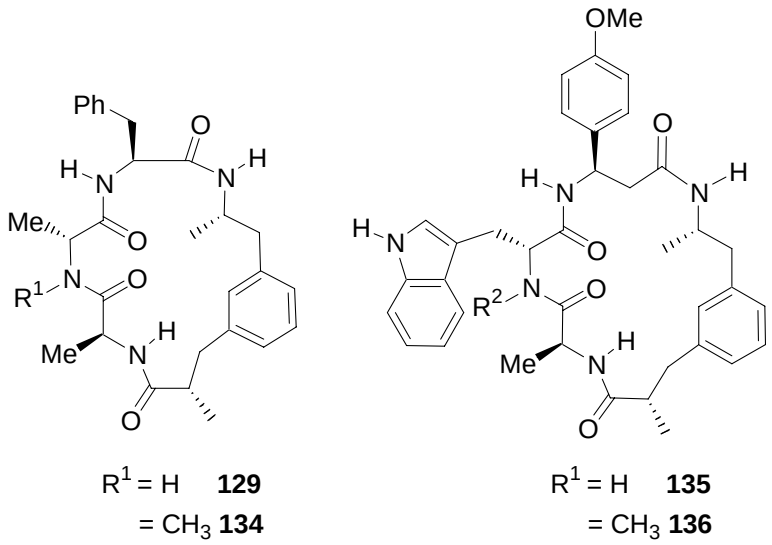
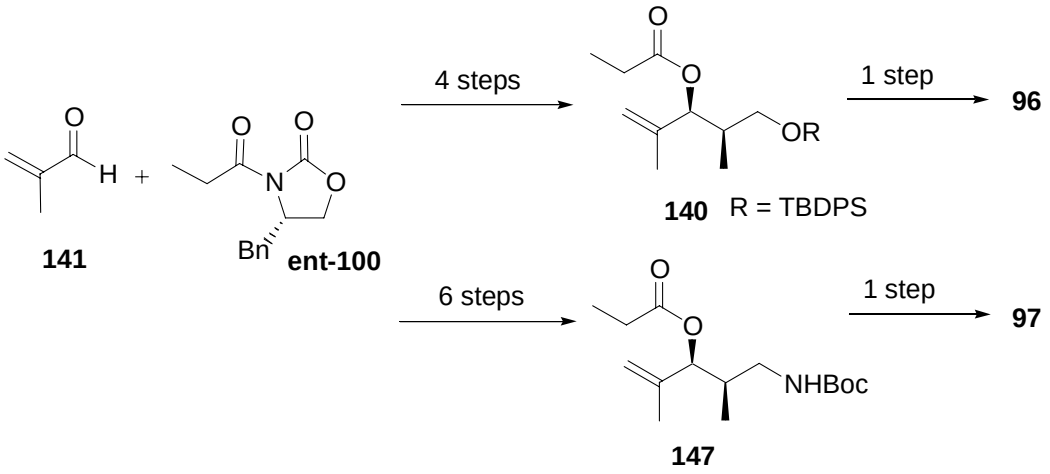


Figure 7.2: The structures of geodiamolide and jasplakinolide analogues.

For the two larger ones, conformational analysis showed that the macrocyclic rings are more rigid than the jasplakinolide ring, but all in all their conformations are very well comparable to the natural product. Like stated for jasplakinolide in the literature, the 19-membered analogs exhibit neither intramolecular hydrogen bonds, nor is the *cis*-rotamer populated in case of *N*-methylation (**136**). The conformational features of the 18-membered (geodiamolide) analogs

are quite different. The macrocyclic ring of compounds **129** and **134** is more flexible than the other investigated systems. Due to the increased flexibility and signal overlap a distinct solution structure for **129** and **134** could not be gained. Whether the ring size or the additional aromatic side chains in **135** and **136** cause a stabilizing effect on the macrocyclic system could not be determined. But both features are differing for **129** and **134** and might thus be an explanation for the higher flexibility of these smaller macrocycles. In addition both *N*-methylated analogs (**134** and **136**) populate the *trans*-amide conformer to more than 99%.

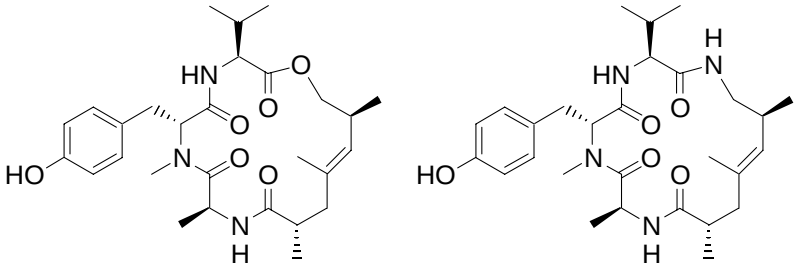
The novel hydroxy and amino acids **96** and **97** were obtained via a divergent synthesis starting from an Evans aldol reaction. Reduction, mono protection, acylation, and an Ireland-Claisen rearrangement provided the hydroxy acid **96** in good yields. Protection, hydrolysis, amidation, reduction, acylation and an Ireland-Claisen rearrangement gave rise to the amino acid **97** with excellent diastereoselectivity and good yields.



Scheme 74: Key components in the synthesis of hydroxy- and amino acids **96** and **97**.

The hydroxy- and amino acids were incorporated into a tripeptide to get a depsipeptide **159** and a macrolactam **160**. The structural differences of **159** and **160** are confined to the amino acid valine. The more folded structure of the lactone **159** brings the *N*-methyl and allylic methyl group in closer contact which is documented by a relatively short range NOE of 3.1 Å. The main difference between the ring-constrained analogues investigated here and the parent macrolide geodiamolide is an approximately 180° rotation of the propionate relative to the

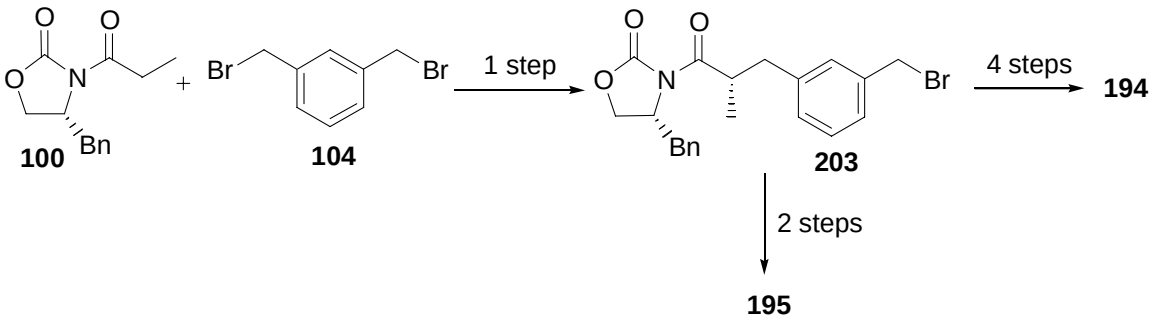
tripeptide unit. As a consequence, the allylic methyl group is oriented to the opposite side of the macrocyclic rings which is documented by the intense transannular NMe and allylic methyl NOE. The distance between these two groups is 7.7 Å in geodiamolide where they are positioned on the opposite ring sides. Such a strong effect of a ring contraction from a 18-membered ring in geodiamolide to a 17-membered ring in **159** and **160** is completely unexpected but well documented by the solution NMR data. It should be noted that both macrocycles populate the *trans*-amide conformer more than 99%.



159 **160**

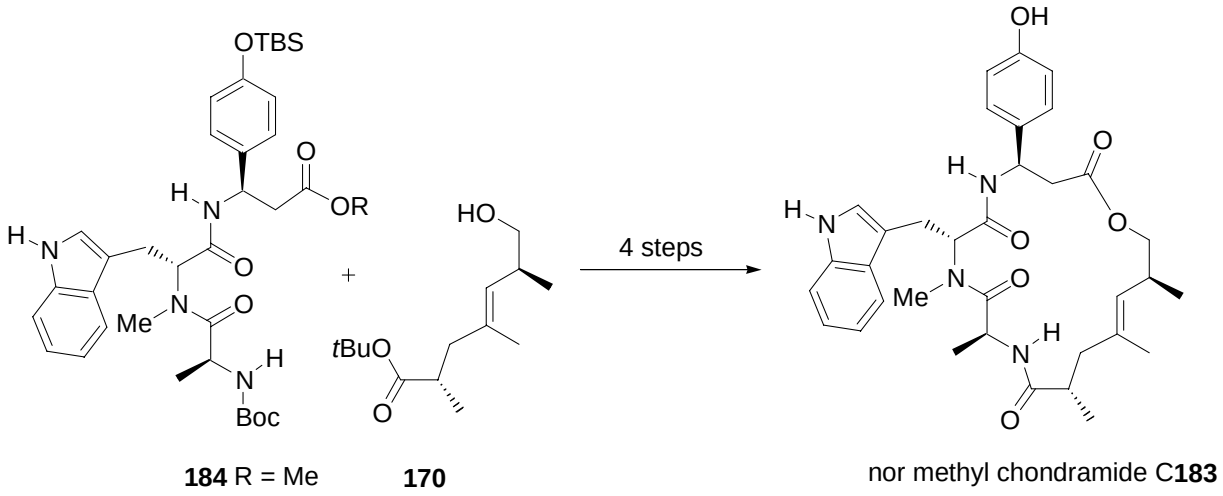
Figure 7.3: Geodiamolide analogues containing the hydroxy- and amino acids **96** and **97**.

The replacement of allylic system with the *meta* substituted aromatic ring in the above amino- and hydroxy acids **96** and **97** led to the design of the novel amino acids **194** and **195**. The amino acid **194** was prepared using the same starting materials as were used for the amino acid **95**. Different reaction conditions allowed for a divergent synthesis and produced the amino acid **195** in five steps with very good yields. The synthesis of hydroxy acid **195** was achieved in only three steps using the same starting materials. The construction of macrocycles using these acids is underway.



Scheme 75: Key intermediates in the synthesis of amino-and hydroxy acids **194** and **195**.

Nor methyl chondramide C **185** was efficiently synthesized by incorporating the hydoxy acid **96** into the tripeptide **183** as shown in Scheme 76. Normethyl chondramide C did show an activity towards the L929-Mausfibroblast cells with an IC_{50} value of 0.25 µM (150 ng/mL). The synthesis of the macrocycles described in this thesis reveals the fact that it is more easy to form the amide bond rather the ester in order to close the ring.



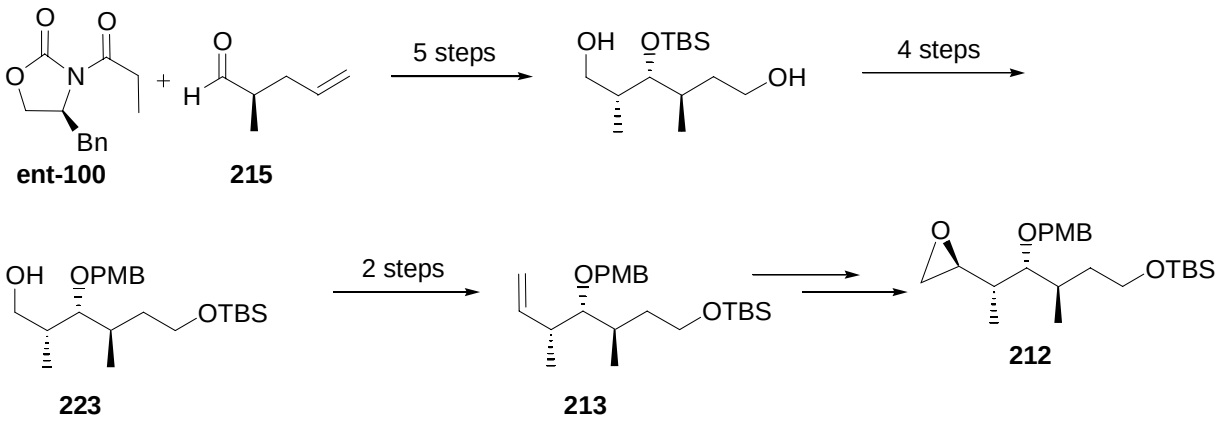
184 R = Me **170** nor methyl chondramide C**183**

Scheme 76: Key components in the synthesis of nor methyl chondramide C.

The syntheses of amino- and hydroxy acids were achieved in a maximum five to six steps using similar starting materials but building upon divergent syntheses. The main reactions involved in the synthesis of these acids were the Evans asymmetric alkylation and aldol reactions with propionyl oxazolidinone to create the chiral centers carrying methyl groups. The novel amino and hydroxy acids could serve as novel workbenches for restricting the

conformation of small peptides. Furthermore, the aryl group might serve as a handle for attachment of derived macrocycles to a solid surface. The incorporation of the *m*-xylene subunit into the amino acid indicates that small structural modifications can have subtle effect on a macrocyclic structure.

Chapter II describes efforts towards the synthesis of the stereotetrad **212** of cruentaren A (**209**). The key steps in this synthesis were an asymmetric Evans *syn* aldol reaction and a Sharpless dihydroxylation reaction. As the Sharpless dihydroxylation did not provide good diastereoselectivity, it is necessary to follow some other pathway to create the diastereomerically pure epoxide **212**. But, it should be noted that this synthesis will become efficient if both isomers could be separated from each other after the Sharpless dihydroxylation step.



Scheme 76: Key intermediates in the synthesis of epoxide **212**

8 Experimental Section

8.1 General Remarks

8.1.1 Chemicals and Working Techniques

The chemicals were purchased from the firms Acros, Aldrich, Fluka, Lancaster, Avocado and Merck. All reagents were obtained from commercial suppliers, and were used without further purification unless otherwise stated. All solvents were distilled and/or dried prior to use by standard methodology except for those, which were reagent grades. The applied petroleum ether fraction had a boiling point of 40-60 ^{o}C. Anhydrous solvents were obtained as follows: THF, diethyl ether and toluene by distillation from sodium and benzophenone; dichloromethane and chloroform by distillation from calcium hydride; acetone by distillation from phosphorous pentoxide. Absolute triethylamine and pyridine and diisopropylethylamine were distilled over calcium hydride prior to use. Unless and otherwise mentioned, all the reactions were carried out under a nitrogen atmosphere and the reaction flasks were pre-dried by heat gun under high vacuum. All the chemicals, which were air or water sensitive, were stored under inert atmosphere. Compounds that are not described in the experimental part were synthesized according to the literature.

8.1.2 NMR-spectroscopy

Except for the final compounds (600 MHz), all the spectra were measured on a Bruker Advance 400 spectrometer, which operated at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei, respectively. ^{1}H and ^{13}C NMR spectra were performed in deuterated solvent and chemical shifts were assigned by comparison with the residual proton and carbon resonance of the solvent and tetramethylsilane (TMS) as an internal reference (δ = 0). Data are reported as follows: chemical shift (multiplicity: s = singlet, d = doublet, t = triplet, ddd = doublet of

doublet of doublet, dt = doublet of triplet, td = triplet of doublet, m = multiplet, br = broadened, *J* = coupling constant (Hz), integration, peak assignment in italic form).

8.1.3 Mass Spectrometry

Mass spectra were recorded on a Finnigan Triple-Stage-Quadrupol Spectrometer (TSQ-70) from Finnigan-Mat. High-resolution mass spectra were measured on a modified AMD Intectra MAT 711 A from the same company. The used mass spectrometric ionization methods were electron-impact (EI), fast-atom bombardment (FAB) or field desorption (FD). FT-ICR-mass spectrometry and HR-FT-ICR mass spectra were measured on an APEX 2 spectrometer from Bruker Daltonic with electrospray ionization method (ESI). Some of the mass spectra were also measured on an Agilent 1100 series LC-MSD. Analytical HPLC-MS: HP 1100 Series connected with an ESI MS detector Agilent G1946C, positive mode with fragmentor voltage of 40 eV, column: Nucleosil 100–5, C-18 HD, 5 µm, 70 × 3 mm Machery Nagel, eluent: NaCl solution (5 mM)/acetonitrile, gradient: 0/10/15/17/20 min with 20/80/80/99/99% acetonitrile, flow: 0.6 mL min^{-1}. High resolution mass (HRMS) are reported as follows: (ESI): calcd mass for the related compound followed by found mass.

8.1.4 Infrared Spectroscopy

The FT-IR spectra were recorded on a Fourier Transform Infrared Spectrometer model Jasco FT/IR-430. Solid samples were pulverized with potassium bromide and percent reflection (R%) was measured. The percent transmittance (T%) of liquid substances were measured in film between potassium bromide plates. Absorption band frequencies are reported in cm^{-1}.

8.1.5 Polarimetry

Optical rotations were measured on a JASCO Polarimeter P-1020. They are reported as follows: $[\alpha]^{temperature}D$ (concentration, solvent). The unit of *c* is g/100 mL. Anhydrous CH_2Cl_2 or $CHCl_3$ was used as a solvent. For the measurement the sodium D line = 589 nm was used.

8.1.6 Melting Points

Melting points were determined with a Büchi Melting point B-540 apparatus and were not corrected.

8.1.7 Chromatographic Methods

Flash column chromatography was performed using flash silica gel (40-63 μm, 230-400 mesh ASTM) from Macherey-Nagel.

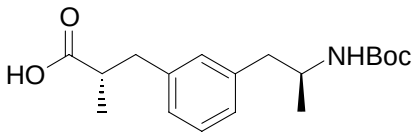
Gas chromatography was performed on a CHROMPACK CP 9000 using a flame ionization detector, and carrier gas H_2. For GC-MS coupled chromatography, a GC-system series 6890 with an injector series 7683 and MS-detector series 5973 from Hewlett Packard was used, with EI method, and carrier gas He. Analytical HPLC was performed on a Hewlett Packard HP 1100 system.

Analytical thin layer chromatography (TLC) was performed on precoated with silica gel 60 F_{254} plates (Merck) or Polygram Sil G/UV_{254} (Macherey Nagel). The compounds were visualized by UV_{254} light and the chromatography plates were developed with an aqueous solution of molybdophosphorous acid or an aqueous solution of potassium permanganate (heating with the hot gun). For preparation of the molybdate solution 20 g ammonium molybdate [$(NH_4)_6Mo_7O_{24}.4H_2O$] and 0.4 g $Ce(SO_4)_2.4H_2O$ were dissolved in 400 mL of 10% H_2SO_4. The potassium permanganate solution was prepared from 2.5 g $KMnO_4$ and 12.5 g Na_2CO_3 in 250 mL H_2O.

8.1.8 Experimental procedures

All the experimental procedures are arranged in the ascending order of number of the compound.

(2*S*)-3-(3-{(2*S*)-2-[(*tert*-Butoxycarbonyl)amino]propyl}phenyl)-2-methylpropanoic acid (95)



NaOH (80 mg) in H_2O (5 mL) was added to a stirred solution of methyl ester **103** (0.55 g, 1.64 mmol) in THF (12 mL). The reaction mixture was stirred for 14 h at room temperature before being poured into water (25 mL) and extracted with diethyl ether (3 × 10 mL). The aqueous layer was acidified to pH 2-3 with 1N HCl and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) resulting in acid **95** as a white solid (0.44 g, 85%).

R_f = 0.45 (1:3 ethyl acetate/petroleum ether);

M.P. = 104-106 ^oC;

$[\alpha]^{23}_D$ = +6.01 (c 0.56, CH_2Cl_2);

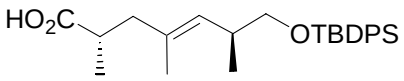
IR (film): ν_{max} = 3326, 2974, 2930, 1706, 1653, 1507, 1248, 1169 cm^{-1};

^{1}H NMR (400 MHz, CD_3OD): δ = 0.94 (d, *J* = 6.1 Hz, 3H, CH_3NHR), 0.99 (d, *J* = 6.6 Hz, 3H, CH_3CO_2H), 1.28 (s, 9H, $C(CH_3)_3$), 2.45-2.66 (m, 4H, benzylic H, CH), 2.86 (dd, *J* = 12.6, 6.1 Hz, 1H, benzylic H), 3.19 (s, 1H, NH), 3.61-3.66 (m, 1H, C*H*NH), 6.91-6.92 (m, 3H, aryl H), 7.06 (t, *J* = 7.5 Hz, 1H, H_m, aryl H);

^{13}C NMR (100 MHz, CD_3OD): δ = 17.2 (CH_3CHNH), 20.5 (CH_3CHCO_2H), 28.8 ($C(CH_3)_3$), 40.7 (CH_2CHCO_2H), 42.7 ($CHCO_2H$), 43.8 (CH_2CHNH), 49.5 (CHNH), 79.8 (Boc C), 127.9, 128.3, 129.2, 131.2, 140.3, 140.7 (aryl), 157.7 (Boc C=O), 179.9 (CO_2H);

HRMS (ESI): calcd for $C_{18}H_{27}NO_4$ $[M+Na]^+$ 344.18323, found 344.18313.

(2*S*,4*E*,6*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-2,4,6-trimethylhept-4-enoic acid (96)



To a solution of diisopropyl amine (0.20 mL, 1.40 mmol) in dry THF (2 mL) was added *n*-BuLi (2.5 M solution in hexane) (0.56 mL, 1.40 mmol) at 0 °C. Stirring was continued for 30 min at 0 °C. HMPA (0.5 mL) was added and the reaction mixture cooled to -78 °C. Ester **140** (500 mg, 1.17 mmol) in dry THF (0.3 mL) was added dropwise to the above reaction mixture and after stirring for an hour at -78 °C, TBDMS-Cl (265 mg, 1.76 mmol) in THF (0.6 mL) was added dropwise. After 30 min stirring at -78 °C, the cooling bath was removed and reaction mixture brought to room temp and heated at 60 °C for 10 h. The reaction mixture was cooled to room temperature and treated with saturated NH_4Cl (5 mL) and then diluted with 1N HCl (5 mL), followed by stirring for 5 min. The mixture was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) resulting in pure hydroxy acid **96** (360 mg, 72%) as a colorless gel.

R_f = 0.45 (1:3 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = +4.3 (c 1.13, CH_2Cl_2);

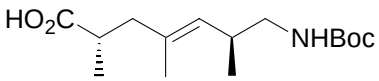
IR (film): υ_{max} = 3448, 2966, 2879, 1718, 1629, 1439, 1377, 1195, 1159, 1103, 1053 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCH$_2$O), 1.04 (s, 9H, C(C*H*$_3$)$_3$), 1.09 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCO), 1.56 (s, 3H, C*H*$_3$), 2.02 (dd, *J* = 13.4, 8.1 Hz, C*H*$_2$CO$_2$), 2.37 (dd, *J* = 13.3, 6.7 Hz, C*H*$_2$CO$_2$), 2.54-2.63 (m, 2H, C*H*, C*H*), 3.41-3.49 (m, 2H, CH_2OH), 4.99 (d, *J* = 9.1 Hz, 1H, olefin *H*), 7.36-7.43 (m, 6H, aromatic), 7.82 (d, *J* = 6.8 Hz, 4H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8 (C*H*$_3$), 16.2 (C*H*$_3$CHCO), 17.3 (C*H*$_3$CHCH$_2$O), 19.2 (quarternery), 26.8 (3C, *t*Bu), 35.4 (*CH*CO$_2$), 37.8 (*CH*CH$_2$O), 43.8 (*CH*$_2$CO), 68.5 (CH_2O), 127.6, 129.5 (aromatic), 130.8 (olefinic), 132.0 (aromatic), 134.0 (olefin quarternary), 135.6 (aromatic), 182.8 (CO_2H);

HRMS (EI): calcd for $C_{26}H_{36}O_3Si$ $[M+Na]^+$: 447.23259, found 447.23264.

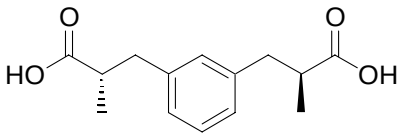
(2*S*,4*E*,6*S*)-7-[(*tert*-Butoxycarbonyl)amino]-2,4,6-trimethylhept-4-enoic acid (97)



To solution of ester **147** (140 mg, 0.49 mmol) in THF / HMPA (1.0/0.3 mL) was added a 2 M solution of NaHDMS in THF (1.5 mL) at -78 °C. After stirring for 45 min at -78 °C, TMS-Cl (0.5 mL, 4.00 mmol) and Et_3N (0.20 mL, 1.50 mmol) were added simultaneously. After 15 min, the cooling bath was removed and the reaction mixture was allowed to come to room temperature in 1 h. The mixture was heated at 60 °C for 5 h. The reaction mixture was treated with saturated aq. NH_4Cl (2 mL) and diluted with 1N HCl (2 mL), then extracted with ethyl acetatae (3 x 5 mL). The combined organic layers washed with brine (4 mL), dried (Na_2SO_4), filtered, and concentrated in *vacuo* to give the crude amino acid which was purified by flash chromatography (1:1 ethyl acetate/petroleum ether). This way the pure amino acid **97** (90 mg, 65%) was obtained as a colorless oil.

R_f = 0.45 (1:1 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -34.6 (c 0.62, CH_2Cl_2);
IR (film): υ_{max} = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.6 Hz, 3H, *CH_3*NHBoc), 1.12 (d, *J* = 6.8 Hz, 3H, *CH_3*CHCO), 1.42 (s, 9H, *t*Bu), 1.62 (s, 3H, CH_3C=C), 2.03-2.10 (m, 1H, *CH_2*CHCO), 2.34-2.39 (m, 1H, *CH_2*CHCO), 2.56-2.67 (m, 2H, *CH*NH, *CH*CO), 2.76-2.78 (m, 1H, *CH_2*NH), 3.11-3.14 (m, 1H, *CH_2*NH), 4.55 (broad s, 1H, NH), 4.91 (d, *J* = 9.4 Hz, 1H, olefinic *CH*);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1 (*CH_3*C=C), 16.3 (*CH_3*CHCO), 18.2 (*CH_3*$CHCH_2$NH), 28.4 (3C, *t*Bu), 33.0 (*CH*CH_2NH), 37.9 (*CH*CO), 45.4 (*CH_2*CHCO), 46.4 (*CH_2*NH), 79.1 (Boc quarternary), 130.8 (CH olefinic), 133.4 (olefin quarternary), 156.00 (Boc C=O), 181.9 (acid C=O);
HRMS (EI): calcd for $C_{15}H_{27}NO_4$ $[M+Na]^+$: 308.18323, found 308.18317.

(2*S*)-3-{3-[(2*S*)-2-Carboxypropyl]phenyl}-2-methylpropanoic acid (98)



To a solution of the bisalkylated compound **108** (7.50 g, 13.2 mmol) in THF (250 mL), H_2O_2 (11.7 mL of a 30 wt% solution, 102.7 mmol) was added at 0 °C through a syringe, followed by the addition of lithium hydroxide monohydrate (2.20 g, 51.4 mmol), dissolved in water (120 mL). The solution was stirred at 0 °C for 5 h. Subsequently, saturated Na_2SO_3 solution (100 mL) and saturated $NaHCO_3$ solution (100 mL) were added at 0 °C. The whole mixture was partially concentrated in *vacuo* and diluted with water (100 mL). The aqueous layer was extracted with dichloromethane (3 × 75 mL) to recover the auxiliary. The aqueous layer was then acidified at 0 °C to pH 1.5 using 6M HCl and then extracted with ethyl acetate (4 × 100 mL). The combined ethyl acetate layers were dried ($MgSO_4$), filtered, and concentrated in *vacuo* yielding a colorless oily residue **98** (2.95 g, 90%).

$[\alpha]^{25}_D$ = +35.5 (c 0.42, CH_2Cl_2);

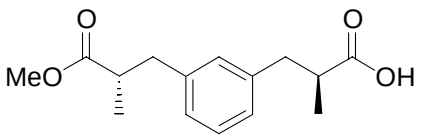
IR (film): ν_{max} = 3500-2500 (broad), 1702, 1589, 1463, 1292, 1199, 1044 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.8 Hz, 6H, CH_3), 2.62-2.72 (m, 2H, benzylic H), 2.75-2.83 (m, 2H, CH), 3.10 (dd, *J* = 13.1, 6.1 Hz, 2H, benzylic H), 7.07 (d, *J* = 7.1 Hz, aryl H), 7.10 (s, 1H, H_o, aryl H), 7.26 (t, *J* = 7.6 Hz, 1H, H_m, aryl H), 11.79 (broad, 2H, CO_2H);

^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.3 (CH_3), 39.1 (benzylic), 41.3 (CH), 127.1, 128.4, 129.7, 139.0 (aryl), 182.7 (CO_2H);

HRMS (EI): calcd for $C_{14}H_{18}O_4$ $[M]^+$: 250.12049, found 250.118291.

(2*S*)-3-{3-[(2*S*)-3-Methoxy-2-methyl-3-oxopropyl]phenyl}-2-methylpropanoic acid (103)



A solution of diester **109** (2.50 g, 9.0 mmol) in MeOH (5 mL) was emulsified under vigorous stirring in NaCl solution (0.1 M, 646.75 mL) to which pH 7 phosphate buffer (3.25 mL) was added, making the solution 3 mM in phosphate. Then a suspension of PLE (25 mg, 1000 units, Sigma Aldrich, E-3019) in 3.2 M $(NH_4)_2SO_4$ solution (1 mL) was added. During the hydrolysis the pH was kept between 7 and 7.5 by the controlled addition of NaOH solution (0.1 N). After observing the formation of diacid in HPLC-MS (maximum 12 h), the reaction mixture was washed with CH_2Cl_2 (2 × 500 mL). The aqueous phase was acidified to pH 2.5 with 25% hydrochloric acid and extracted with ethyl acetate (3 × 500 mL). The combined organic layers (CH_2Cl_2 and EtOAc) were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatography (1:4 ethyl acetate/petroleum ether) to provide the mono acid mono ester **103** (1.52 g, 64%) as a colorless oily compound.

R_f = 0.4 (1:4 ethylacetate/petroleum ether,)

$[\alpha]^{25}_D$ = +46.2 (c 1.07, CH_2Cl_2);

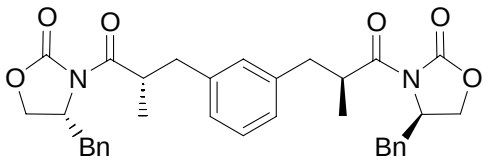
IR (film): ν_{max} = 3024, 2975, 1736, 1707 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 6.8 Hz, 3H, $CH_3CHCO_2CH_3$), 1.08 (d, *J* = 7.1 Hz, 3H, CH_3CHCO_2H), 2.53-2.58 (m, 2H, benzylic H), 2.62-2.68 (m, 2H, CH), 2.94 (ddd, *J* = 19.4, 13.1, 6.4 Hz, 2H, benzylic H), 3.55 (s, 3H, OCH_3), 6.90-6.96 (m, 3H, aryl H), 7.12 (t, *J* = 7.5 Hz, 1H, H_m, aryl H), 10.49(broad, 1H, CO_2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4 ($CH_3CO_2CH_3$), 16.6 (CH_3CO_2H), 39.1 ($CH_2CHCO_2CH_3$), 39.6 (CH_2CHCO_2H), 41.4 ($CHCO_2H$), 51.5 (OCH_3), 126.9, 127.0, 128.4, 129.8, 139.0 (aryl), 176.4 (CO_2Me), 182.3 (CO_2H);

HRMS (EI): calcd for $C_{15}H_{20}O_4$ $[M]^+$: 264.133877, found 264.136141.

(4*R*)-4-Benzyl-3-[(2*S*)-3-(3-{(2*S*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-methyl-3-oxopropyl}phenyl)-2-methylpropanoyl]-1,3-oxazolidin-2-one (108)



To a solution of diisopropylamine (8.0 mL, 56.2 mmol) in THF (190 mL) was added *n*-butyllithium (22.5 mL, 56.2 mmol, 2.5 M in hexane) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, before it was cooled to -78 °C. At this point propionyl oxazolidinone **100** (12.0 g, 51.5 mmol), dissolved in THF (210 mL) was added. After being stirred for 1.5 h at –78 °C, the solid 1,3-bis-(bromomethyl)-benzene (**104**) (6.17 g, 23.4 mmol) was added in one portion. Stirring was continued for 24 h with simultaneous warming of the reaction mixture to room temperature. The reaction was quenched with 60 mL of NH_4Cl, and then most of the organic solvent was removed in *vacuo*. The remainder was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (3:7 ethyl acetate/petroleum ether) to give **108** as a sticky compound (7.72 g, 58%).

R_f = 0.45 (3:7 ethyl acetate/petroleum ether);

$[\alpha]^{25}_D$ = -21.9 (c 1.50, CH_2Cl_2);

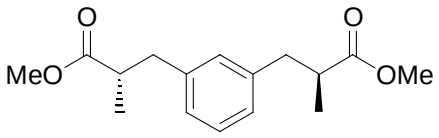
IR (film): ν_{max} = 3028, 2976, 2932, 1770, 1694, 1604, 1588, 1487, 1455, 1393, 1288, 1210, 1103, 1053 cm-1;

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, *J* = 6.6 Hz, 6H, CH_3), 2.54-2.69 (m, 4H, benzylic H), 3.11-3.18 (m, 4H, $PhCH_2$), 4.10-4.20 (m, 6H, C*H*CH_3, OCH_2), 4.64-4.70 (m, 2H, NCH), 7.09-7.32 (m, 14H, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.2 (CH_3), 37.3 ($PhCH_2$), 39.1 (*C*HCH_3), 39.9 (benzylic), 54.7 (NCH), 65.5 (OCH_2), 126.8, 127.9, 128.5, 129.0, 130.1, 134.9, 138.9 (aryl), 152.6 (NCO_2), 176.1 (CO);

HRMS (EI): calcd for $C_{34}H_{36}N_2O_6$ $[M]^+$: 568.257798, found 568.257289.

Methyl (2*S*)-3-{3-[(2*S*)-3-Methoxy-2-methyl-3-oxopropyl]phenyl}-2-methylpropanoate (109)



To a solution of diacid **98** (3.20 g, 12.8 mmol), methanol (1.4 mL, 32.8 mmol) and DMAP (96 mg) in dry CH_2Cl_2 (37 mL) was added at 0 °C a solution of DCC (8.12 g, 39.4 mmol) in CH_2Cl_2 (26 mL). The solution was stirred at 0 °C for 30 min and then at room temperature for 6 h. The white precipitate was filtered off, the solvent was evaporated, and the residue was redissolved in diethyl ether. The ether solution was washed successively with cold 1 N HCl, $NaHCO_3$ solution, and brine. The dried (Na_2SO_4) ether layer was filtered, and concentrated. The crude product was purified by flash chromatography (1:9 ethyl acetate/petroleum ether) to provide the diester **109** as an oily compound (2.52 g, 71%).

R_f = 0.38 (1:9 ethyl acetate/petroleum ether);

$[\alpha]^{25}_D$ = +40.1 (c 0.61, CH_2Cl_2);

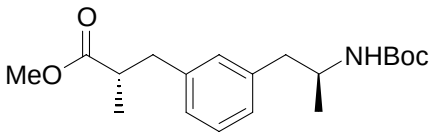
IR (film): ν_{max} = 2974, 2951, 1736, 1459, 1375, 1361, 1164 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.5 Hz, 6H, CH_3), 2.61-2.67 (m, 2H, benzylic H), 2.69-2.77 (m, 2H, CH), 3.00 (dd, *J* = 13.1, 6.7 Hz, 2H, benzylic H), 3.64 (s, 6H, OCH_3), 6.97 (s, 1H, H_o, aryl H), 7.01 (d, *J* = 7.6 Hz, 2H, aryl H), 7.20 (t, *J* = 7.6 Hz, 1H, H_m, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3), 39.6 (benzylic), 41.6 (CH), 51.5 (OCH_3), 126.9, 128.3, 129.6, 139.3 (aryl), 176.4 (CO_2Me);

HRMS (EI): calcd for $C_{16}H_{22}O_4$ $[M]^+$: 278.15179, found: 278.152648

Methyl (2*S*)-3-(3-{(2*S*)-2-[(tert-Butoxycarbonyl)amino]propyl}phenyl)-2-methylpropanoate (115)



A solution of the monoester **103** (0.80 g, 3.03 mmol) in toluene (23 mL) was treated with triethylamine (0.5 mL, 3.33 mmol) and DPPA (0.66 mL, 3.03 mmol). After stirring for 30 min, the mixture was heated to reflux for 3.5 h. The isocyanate formation was monitered by IR for the appearance of a strong signal in the 2300-2200 cm^{-1} region and disappearance of the carboxylic acid carbonyl peak. The reaction mixture was cooled to 50 °C, *tert*-butanol (3 mL, 10 eq) was added via syringe and the solution heated to reflux for 20 h. The reaction was cooled to room temperature and quenched with saturated $NaHCO_3$ solution (25 mL). The mixture was extracted with diethyl ether (3 × 25 mL). The combined ether extracts were dried (Na_2SO_4), filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatogrophy (1:5 ethyl acetate/petroleum ether), to provide compound **115** as an oil (0.73 g, 72%).

R_f = 0.55 (1:5 ethyl acetate/petroleum ether);

$[\alpha]^{23}_D$ = +12.3 (c 0.21, CH_2Cl_2);

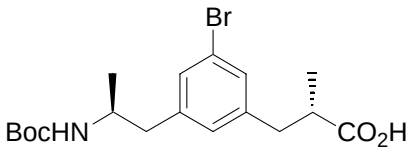
IR (film): ν_{max} = 3361, 2973, 2930, 2359, 1735, 1710, 15516, 1364, 1166 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CHCO$_2$Me), 1.06 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CHNR), 1.36 (s, 9H, C(CH$_3$)$_3$) 2.51-2.58 (m, 2H, benzylic H), 2.63-2.68 (m, 1H, CHCO$_2$Me), 2.75 (dd, *J* = 13.1, 5.3 Hz, 1H, benzylic H), 2.93 (dd, *J* = 13.1, 6.4 Hz, 1H, benzylic H), 3.57 (s, 3H, OCH$_3$), 3.81 (br s, 1H, C*H*NHR), 4.31 (br s, 1H, NH), 6.90-7.32 (m, 4H, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (*C*H$_3$CHCO$_2$Me), 19.7 (C*H*$_3$CHNHR), 28.0 (C(CH$_3$)$_3$)), 39.2 (*C*H$_2$CHCO$_2$Me), 41.0 (CHCO$_2$Me), 42.5 (*C*H$_2$CHNHR), 47.1 (CHNHR), 51.2 (OCH$_3$), 78.8 (Boc quaternary C), 126.6, 127.2, 127.9, 129.9, 137.9, 139.0 (aryl), 154.8 (Boc CO), 176.2 (CO$_2$Me);

HRMS (EI): calcd for $C_{19}H_{29}NO_4$ $[M]^+$: 335.209636, found 335.207186.

(2*S*)-3-(3-Bromo-5-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]propyl}phenyl)-2-methylpropanoic acid (116)



The procedure for amino acid **95** was used with methyl ester **123** (130 mg, 0.31 mmol) in THF (2.5 mL) and NaOH (20 mg) in H_2O (1.0 mL) to yield 100 mg (80%) of the bromo amino acid **116** after prurification by flash chromatography (1:3 ethyl acetate/petroleum ether) as a colorless gel.

R_f = 0.41 (1:3 ethyl acetate/petroleum ether);

$[\alpha]^{23}_D$ = +11.0 (c 1.00, CH_2Cl_2);

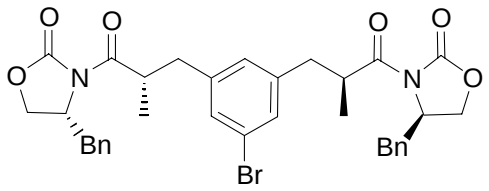
IR (film): ν_{max} = 3326, 2974, 2930, 1706, 1653, 1507, 1248, 1169 cm^{-1};

^{1}H NMR (400 MHz, CD_3OD): δ = 1.06 (d, *J* = 6.3 Hz, 3H, CH_3NHR), 1.11 (d, *J* = 6.8 Hz, 3H, CH_3CO_2H), 1.37 (s, 9H, $C(CH_3)_3$), 2.58-2.70 (m, 4H, benzylic H, CH), 2.93 (dd, *J* = 12.9, 6.8 Hz, 1H, benzylic H), 3.72-3.78 (m, 1H, C*H*NH), 4.96 (br s, 1H, CH*NH*), 7.00 (s, 1H, aryl H), 7.19 (s, 1H, aryl H), 7.20 (s, 1H, aryl H);

^{13}C NMR (100 MHz, CD_3OD): δ = 17.2 (CH_3CHNH), 20.6 (CH_3CHCO_2H), 28.8 ($C(CH_3)_3$), 40.1 (CH_2CHCO_2H), 42.3 ($CHCO_2H$), 43.3 (CH_2CHNH), 48.8 (CHNH), 79.8 (Boc C), 122.9, 130.1, 130.7, 131.3, 142.6, 143.0 (aryl), 157.5 (Boc C=O), 179.4 (CO_2H);

HRMS (ESI): calcd for $C_{18}H_{26}BrNO_4$ $[M+Na]^+$ 422.09374, found 422.09422.

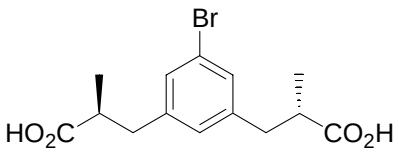
(4*R*)-4-Benzyl-3-[(2*S*)-3-(3-bromo-5-{(2*S*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-methyl-3-oxopropyl}phenyl)-2-methylpropanoyl]-1,3-oxazolidin-2-one (119)



The alkylation procedure (for the compound **108**) was used with propionyl oxazolidinone **100** (4.35 g, 18.30 mmol) in THF (90 mL) and the tribromo derivative **118** (3.00 g, 8.75 mmol), diisopropylamine (3.00 mL, 21.00 mmol), and *n*-BuLi (8.40 mL, 2.5 M in hexane, 21.00 mmol) to yield 3.00 g (53%) of double alkylation product **119** after flash chromatography (1:3 ethyl acetate/petroleum ether) as a light yellow gel.

R_f = 0.38 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -11.4 (c 2.11, CH_2Cl_2);
IR (film): ν_{max} = 3028, 2976, 2932, 1770, 1694, 1604, 1588, 1487, 1455, 1393, 1288, 1210, 1103, 1053 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.09 (d, *J* = 6.8 Hz, 6H, CH_3), 2.49-2.55 (m, 4H, benzylic H), 3.01-3.10 (m, 4H, $PhCH_2$), 3.94-3.99 (m, 2H, C*H*CH_3), 4.01-4.07 (m, 2H, OCH_2), 4.10 (t, *J* = 8.5 Hz, 2H, OCH_2), 4.56-4.62 (m, 2H, NCH), 7.02 (d, *J* = 6.6 Hz, 4H, aryl), 7.09 (s, 1H, aryl), 7.18-7.24 (m, 8H, aryl);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3), 37.7 ($PhCH_2$), 39.2 (*C*HCH_3), 39.5 (benzylic), 55.1 (NCH), 65.9 (OCH_2), 122.2, 127.3, 128.9, 129.3, 130.2, 135.2, 141.5 (aryl), 153.0 (NCO_2), 176.0 (CO);
HRMS (EI): calcd for $C_{34}H_{35}BrN_2O_6$ $[M+Na]^+$: 671.15707, found 671.15644.

(2*S*)-3-{3-Bromo-5-[(2*S*)-2-carboxypropyl]phenyl}-2-methylpropanoic acid (120)



The procedure for diacid **98** was used with the double alkylated product **119** (2.50 g, 3.86 mmol) in THF (80 mL), 30 wt% H_2O_2 (3.15 mL, 30.88 mmol) and lithium hydroxide monohydrate (650 mg, 15.44 mmol) in H_2O (30 mL) to provide 1.13 g of diacid **120** (89%) after workup. The crude product was used without any purification.

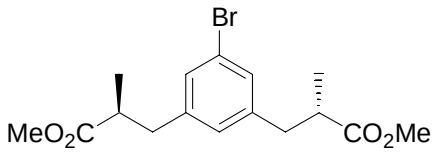
$[\alpha]^{20}_D$ = +40.5 (c 1.00, CH_2Cl_2);
IR (film): ν_{max} = 3500-2500 (br), 1700, 1585, 1465, 1292, 1199, 1044 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.8 Hz, 6H, CH_3), 2.64 (dd, *J* = 12.9, 7.1 Hz, 2H, benzylic H), 2.68-2.75 (m, 2H, CH), 2.92 (dd, *J* = 12.9, 6.6 Hz, 2H, benzylic H), 6.92 (s, 1H, aryl), 7.17 (s, 2H, aryl);

^{13}C NMR (400 MHz, $CDCl_3$): δ = 16.5 (CH_3), 38.9 (benzylic), 41.1 (CH), 122.3, 128.4, 130.2, 141.1 (aryl), 181.4 (CO_2H);

HRMS (EI): calcd for $C_{14}H_{17}BrO_4$ $[M-H]^-$: 327.02375, found 327.02366.

Methyl (2*S*)-3-{3-bromo-5-[(2*S*)-3-methoxy-2-methyl-3-oxopropyl]phenyl}-2-methylpropanoate (121)



The procedure for diester **109** was used with diacid **120** (1.10 g, 3.34 mmol) in dichloromethane (10 mL) and DCC 1.73 g, 8.35 mmol) in dichloromethane (8.0 mL), DMAP (245 mg, 2.00 mmol) to yield the diester **121** (895 mg, 75%) after purification by flash chromatography (1:9 ethyl acetate/petroleum ether) as a colorless oil.

R_f = 0.44 (1:9 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = +52.4 (c 1.05, CH_2Cl_2) ;

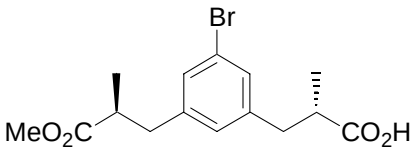
IR (film): ν_{max} = 2974, 2951, 1736, 1459, 1375, 1361, 1164 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.1 Hz, 6H, CH_3), 2.53 (dd, *J* = 13.3, 7.5 Hz, 2H, benzylic H), 2.59-2.7 (m, 2H, CH), 2.88 (dd, *J* = 13.3, 7.0 Hz, 2H, benzylic H), 3.57 (s, 6H, OCH_3), 6.82 (s, 1H, aryl), 7.09 (s, 2H, aryl);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3), 39.0 (benzylic), 41.1 (CH), 51.4 (OCH_3), 122.1, 128.3, 129.8, 141.4 (aryl), 175.8 (CO_2Me);

HRMS (EI): calcd for $C_{16}H_{21}BrO_4$ $[M]^+$: 379.05154, found, 379.05137.

(2*S*)-3-{3-Bromo-5-[(2*S*)-3-methoxy-2-methyl-3-oxopropyl]phenyl}-2-methylpropanoic acid (122)



A solution of diester **121** (820 mg, 2.23 mmol) in MeOH (1.25 mL) was emulsified under vigorous stirring in NaCl solution (0.1 M, 160.0 mL) to which pH 7 phosphate buffer (0.80 mL) was added, making the solution 3 mM in phosphate. Then a suspension of PLE (12 mg, 240 units, Sigma Aldrich, E-3019) in 3.2 M $(NH_4)_2SO_4$ solution (0.25 mL) was added. During the hydrolysis the pH was kept between 7 and 7.5 by the controlled addition of NaOH solution (0.1 N). After observing the formation of diacid in LC-MS (7-8 h), the reaction mixture was washed with CH_2Cl_2 (2 x 200 mL). The aqueous phase was acidified to pH 2.5 with 25% hydrochloric acid and extracted with ethyl acetate (3 x 200 mL). The combined organic layers (CH_2Cl_2 and EtOAc) were dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The crude product was purified by flash chromatography (1:4 ethyl acetate/petroleum ether) to provide the mono acid mono ester **122** (435 mg, 57%) as a colorless oily compound.

R_f = 0.44 (1:4 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = +48.4 (c 0.98, CH_2Cl_2);

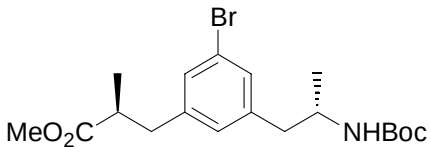
IR (film): ν_{max} = 3020, 2970, 1735, 1707 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCO$_2$CH$_3$), 1.15 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHCO$_2$H), 2.58 (dd, *J* = 13.4, 7.8 Hz, 2H, benzylic H), 2.64-2.75 (m, 2H, CH), 2.93 (dd, *J* = 12.4, 6.1 Hz, 1H, benzylic H), 2.98 (dd, *J* = 12.6, 5.8 Hz, 1H, benzylic H), 3.62 (s, 3H, OCH_3), 6.89 (s, 1H, aryl H), 7.15 (s, 1H, aryl H), 7.17 (s, 1H, aryl H), 9.62 (br, 1H, CO_2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5 (*C*H$_3$CO$_2$CH$_3$), 16.7 (CH$_3$CO$_2$H), 38.7 (*C*H$_2$CHCO$_2$CH$_3$), 39.1 (*C*H$_2$CHCO$_2$H), 41.0 (*CH*CO$_2$CH$_3$), 41.2 (*C*HCO$_2$H), 51.7 (OCH_3), 122.3, 128.5, 130.0, 130.1, 141.2, 141.6 (aryl), 176.2 (CO_2Me), 181.7 (CO_2H);

HRMS (EI): calcd for $C_{15}H_{19}BrO_4$ $[M-H]^-$: 341.03940, found 341.03930.

Methyl (2*S*)-3-(3-bromo-5-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]propyl}phenyl)-2-methylpropanoate (123)



To a stirred solution of monoester mono acid **122** (320 mg, 0.93 mmol) in *t*BuOH (10 mL) were added triethylamine (0.15 mL, 1.02 mmol) and DPPA (0.20 mL, 0.93 mmol) successively at room temperature. After stirring for 0.5 h at room temperature the reaction mixture was heated to reflux for 10 h. The reaction mixture was treated with saturated aq. $NaHCO_3$ (10 mL). The resulting mixture was extracted with diethyl ether (3 x 10 mL). The combined ether layers were dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (1:5 ethyl acetate/petroleum ether) to produce the corresponding Boc carbamate **123** (210 mg, 55%) as a colorless oil.

R_f = 0.52 (1:5 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = +12.3 (c 1.05, CH_2Cl_2);

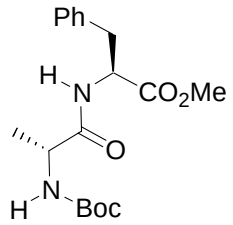
IR (film): ν_{max} = 3361, 2973, 2930, 2359, 1735, 1710, 15516, 1364, 1166 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHCO$_2$Me), 1.07 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHNR), 1.36 (s, 9H, C(CH$_3$)$_3$) 2.48-2.55 (m, 2H, benzylic H), 2.59-2.68 (m, 1H, CHCO$_2$Me), 2.73 (dd, *J* = 13.0, 3.9 Hz, 1H, benzylic H), 2.90 (dd, *J* = 13.4, 6.8 Hz, 1H, benzylic H), 3.58 (s, 3H, OCH$_3$), 3.78 (br s, 1H, C*H*NHR), 4.30 (br s, 1H, NH), 6.83 (s, 1H, aryl), 7.10 (s, 2H, aryl);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (*C*H$_3$CHCO$_2$Me), 20.0 (C*H*$_3$CHNHR), 28.3 (C(CH$_3$)$_3$)), 39.1 (*C*H$_2$CHCO$_2$Me), 41.2 (*C*HCO$_2$Me), 42.4 (*C*H$_2$CHNHR), 47.4 (CHNHR), 51.7 (OCH$_3$), 79.2 (Boc quaternary C), 122.1, 126.1, 128.9, 129.9, 140.5, 141.6 (aryl), 155.1 (Boc CO), 176.1 (CO$_2$Me);

HRMS (EI): calcd for $C_{19}H_{28}BrNO_4$ $[M+Na]^+$: 436.10939, found 436.10826.

Methyl N-(*tert*-butoxycarbonyl)-D-alanyl-L-phenylalaninate (126)



To a stirred solution of *N*-Boc-D-alanine (**125**) (1.10 g, 5.6 mmol), L-phenylalanine methylester (**124**) (1.00 g, 5.6 mmol), hydroxybenzotriazole (0.75 g, 5.6 mmol) in dry THF (45 mL) was added a solution of DCC (1.5 g, 7.25 mmol) in THF (11 mL) at 0 °C. Stirring was continued for 12 h at room temperature. The dicyclohexylurea was filtered off, washed with cold diethyl ether and the filtrate was concentrated. Purification was done by flash chromatography (1:3 ethyl acetate/petroleum ether) yielding a colorless solid **126** (1.55 g, 80%).

R_f = 0.35 (1:3 ethyl acetate/petroleum ether);

M.P. = 98-99 ^oC;

$[\alpha]^{23}_D$ = +59.8 (c 0.40, CH_2Cl_2);

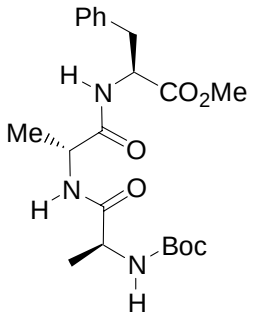
IR (KBr): ν_{max} = 3304, 2987, 2930, 1732, 1664, 1517, 1317 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 7.1 Hz, 3H, CH_3), 1.36 (s, 9H, $C(CH_3)_3$), 3.00 (dd, *J* = 13.8, 6.2 Hz, 1H, benzylic H), 3.05-3.10 (m, 1H, benzylic H), 4.04-4.18 (m, 1H, CHNH), 4.77-4.81 (m, 1H, $CHCO_2Me$), 4.95 (br s, 1H, NHBoc), 6.60 (br s, 1H, $NHCHCO_2Me$), 7.03-7.22 (m, 5H, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4 (CH_3), 28.2 ($C(CH_3)_3$), 37.8 (benzylic), 49.9 (*C*HCO_2Me), 52.3 (OCH_3), 53.0 (CHNHBoc), 80.0 (Boc C), 127.1, 128.5, 129.2, 135.7 (aryl), 155.3 (Boc C=O), 171.7 (CO_2Me), 172.2 (CONH);

HRMS (EI): calcd for $C_{14}H_{18}N_2O_5$ $[M\text{-}C(CH_3)_3]^+$: 294.119319, found 294.121541.

Methyl N-(*tert*-Butoxycarbonyl)-L-alanyl-D-alanyl-L-phenylalaninate (127)



A solution of peptide **126** (1.0 g, 2.8 mmol) in CH_2Cl_2 (22 mL) was treated with CF_3CO_2H (2.2 mL) and the mixture stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification. To a cooled (0 °C) solution of the crude amine salt (240 mg, 0.96 mmol) and *N*-Boc-L-alanine (181 mg, 0.96 mmol) in THF (11 mL) and CH_2Cl_2 (2.5 mL) were added 1-hydroxybenzotriazole (130 mg, 0.96 mmol), Et_3N (0.32 mL, 2.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (239 mg, 1.25 mmol). The mixture was then stirred at room temperature for 16 h. The solvent was removed in *vacuo*, and the residue purified by flash chromatography (2:3 ethyl acetate/petroleum ether) to provide the tripeptide **127** as a colorless solid (0.30 g, 75%).

R_f = 0.33 (2:3 ethyl acetate/petroleum ether);

M.P = 149-151 ^oC;

$[\alpha]^{28}_D$ = +19.1 (c 0.4796, CH_2Cl_2);

IR (KBr): ν_{max} = 3277, 2979, 2748, 1753, 1707, 1645, 1519, 1456, 1370, 1166 cm^{-1};

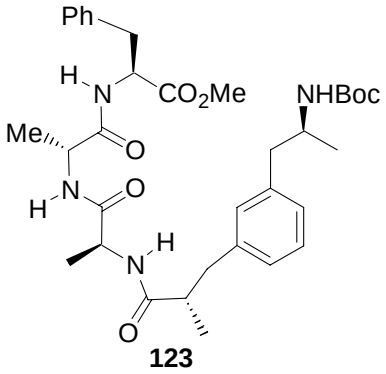
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.1 Hz, 3H, $CH_3CHNHBoc$), 1.24 (d, *J* = 7.0 Hz, 3H, CH_3CONH), 1.36 (s, 9H, $C(CH_3)_3$), 2.96 (dd, *J* = 13.9, 7.1 Hz, 1H, benzylic H), 3.07-3.12 (m, 1H, benzylic H), 3.62 (s, 3H, OCH_3), 4.02-4.17 (m, 1H, CHNHBoc), 4.40-4.47 (m, 1H, CHNHCO), 4.73-4.78 (m, 1H, $CHCO_2Me$), 5.11 (d, *J* = 7.3 Hz, 1H, NHBoc), 6.84 (d, *J* = 7.3 Hz, 1H, $NHCO_2Me$), 6.95 (d, *J* = 6.6 Hz, 1H, NHCO), 7.05-7.22 (m, 5H, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1 ($CH_3CHNHBoc$), 18.4 ($CH_3CHCONH$), 28.3 $C(CH_3)_3$), 37.8 (benzylic), 48.5 (CHCONH), 50.2 (*C*HNHBoc), 53.2 ($CHCO_2Me$), 80.1 (Boc

C), 127.0, 128.5, 129.2, 135.8 (aryl), 155.3 (Boc C=O), 171.7 (CO_2Me), 171.8 (NHCO), 172.6 (CH_2NHCO);

HRMS (EI): calcd for $C_{21}H_{31}N_3O_6$ $[M]^+$: 421.221247, found 421.225247.

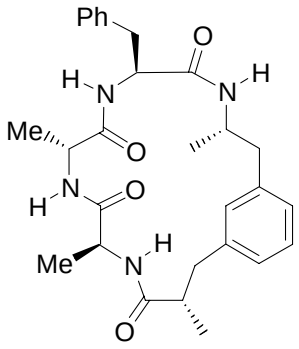
Methyl N-[(2*S*)-3-(3-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]propyl}phenyl)-2-methylpropanoyl]-L-alanyl-D-alanyl-L-phenylalaninate (128)



123

A solution of peptide **127** (100 mg, 0.24 mmol) in CH_2Cl_2 (2 mL) was treated with CF_3CO_2H (0.18 mL), and the mixture stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue was dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification. To a solution of crude amine salt and Boc-protected ω-amino acid **95** (77 mg, 0.24 mmol) in dimethyl formamide (2 mL) were added TBTU (77 mg, 0.24 mmol), HOBt (34 mg, 0.24 mmol), DIEA (0.1mL, 0.576 mmol) and the mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with water (3 mL) and extracted with ethyl acetate (3 × 4 mL). The combined ethyl acetate layers were washed with water resulting in almost pure tetrapeptide **128** (133 mg, 90%) as judged by HPLC-MS. This material was used for the macrolactam formation without any further purification.

(3*S*,6*S*,9*R*,12*S*,15*S*)-6-Benzyl-3,9,12,15-tetramethyl-4,7,10,13-tetraaza bicyclo[15.3.1]henicosa-1(21),17,19-triene-5,8,11,14-tetrone (129)



NaOH (7.7 mg), dissolved in H_2O (0.5 mL) was added to a stirred solution of tetrapeptide **128** (100 mg, 0.160 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h at room temperature before being poured into water (5 mL) and extracted with diethyl ether (3 × 5 mL). The aqueous layer was acidified to pH 2-3 with 1N HCl and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated providing the carboxylic acid in almost quantitative yield. This compound was used directly in the next step. A solution of above Boc-protected tetrapeptide acid (90 mg, 0.145 mmol) in CH_2Cl_2 (1.2 mL) was treated with CF_3CO_2H (0.11 mL, 1.45 mmol), and the mixture stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue was dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the macrolactamization without any further purification. Thus, the residue was dissolved in DMF (140 mL) and the stirred solution treated successively with TBTU (140 mg, 0.435 mmol), HOBt (59 mg, 0.435 mmol), and *i*Pr_2EtN (0.08 mL, 0.44 mmol) at room temperature. The resulting solution was stirred for 14 h at room temperature and then partitioned between ethyl acetate and water. After separation of the layers, the water layer was extracted with ethyl acetate (2 × 75 mL), and the combined organic layers were washed successively with water, 5% aqueous $KHSO_4$, water, half-saturated $NaHCO_3$, and brine. After being dried ($MgSO_4$), filtered, and concentrated in *vacuo*, the resulting residue was purified by flash chromatography (ethyl acetate) to give the macrocycle **129** as a colorless solid (40 mg, 50%, 3 steps).

$\mathbf{R_f}$ = 0.5 (ethyl acetate);

M.P. = 258-260 ^{o}C;

$[\alpha]^{28}_{D}$ = -14.8 (c 0.1911, CH_2Cl_2);

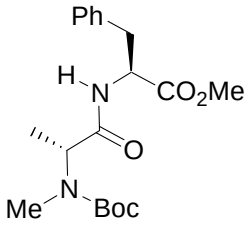
IR (film): ν_{max} = 3297, 2931, 1888, 1640,1526, 1446 cm^{-1};

^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.01 (d, *J* = 7.3 Hz, 5-CH_3), 1.06 (d, *J* = 6.6 Hz, 3H, 11-CH_3), 1.11 (d, *J* = 7.3 Hz, 3H, 5-CH_3), 1.12 (d, *J* = 6.6 Hz, 3H, 14-CH_3), 2.50 (m, 2H, 6-H, 11-H), 2.59-2.67 (m, 2H, 10-H), 2.86-2.95 (m, 2H, 1-H, 6-H), 3.33 (dd, *J* = 13.9, 3.7 Hz, 1H, 1-H), 3.74-3.79 (m, 1H, 17-H), 3.94-4.03 (m, 3H, 2-H, 14-H, 5-H), 6.75-6.79 (m, 2H, 4''-H, 6''-H), 6.83 (d, *J* = 7.3 Hz, 2H, 4-NH, 13-NH), 6.94 (s, 1H, 2''-H), 6.98 (dd, *J* = 7.3, 7.3 Hz, 1H, 5''-H), 7.15-7.19 (m, 3H, 4'-H, aryl H), 7.23-7.27 (m, 2H, aryl H), 8.17 (d, *J* = 8.1 Hz, 1H, 19-NH), 8.34 (br s, 1H, 16-NH);

^{13}C NMR (150 MHz, DMSO-d_6): δ = 15.8 (CH_3-17), 17.9 (CH_3-11), 18.3, 19.1 (CH_3-5, CH_3-14), 34.6 (C-1), 39.1 (C-6), 39.5 (C-10), 42.0 (C-11), 45.0 (C-5), 47.6 (C-14), 49.6 (C-17), 54.4 (C-2);

HRMS (EI): calcd for $C_{28}H_{36}N_4O_4$ $[M]^+$: 492.273621, found 492.271404.

Methyl N-(*tert*-butoxycarbonyl)-N-methyl-D-alanyl-L-phenylalaninate (131)



To a stirred solution of *N*-Boc-*N*-methyl-D-alanine (**130**) (1.5 g, 7.4 mmol), L-phenylalanine methylester (**124**) (1.3 g, 7.4 mmol), and hydroxybenzotriazole (0.99 g, 7.4 mmol) in dry THF (60 mL) was added a solution of DCC (2.3 g, 11.1 mmol), dissolved in THF (11 mL) at 0 °C. Stirring was continued for 7 h at room temperature. The dicyclohexylurea was filtered off, washed with cold diethyl ether and the filtrate concentrated. Purification of the residue by flash chromatography (1:5 ethyl acetate/petroleum ether) gave a colorless gel-like compound **131** (2.10 g, 75%).

R_f = 0.33 (1:5 ethyl acetate/petroleum ether);

$[\alpha]^{25}_D$ = +62.8 (c 0.89, CH_2Cl_2);

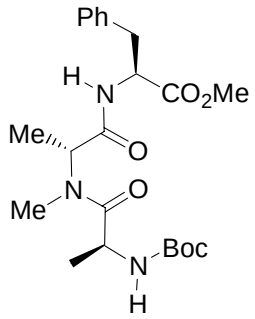
IR (film): ν_{max} = 3327, 2977, 2934, 2118, 1746, 1688, 1515, 1455, 1390, 1154 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.8 Hz, 3H, CH_3), 1.37 (s, 9H, $C(CH_3)_3$), 2.64 (s, 3H, NCH_3), 2.99-3.07 (m, 2H, benzylic H), 3.63 (s, 3H, OCH_3), 4.71-4.77 (m, 2H, $CHCO_2Me$, CHMe), 6.50 (br s, 1H, N*H*$CHCO_2Me$), 7.03 (d, *J* = 7.3 Hz, 2H, H_o, aryl H), 7.15-7.23 (m, 3H, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2 (CH_3), 28.3 ($C(CH_3)_3$), 29.7 (NCH_3), 37.8 (benzylic), 52.2 (OCH_3, *C*HCO_2Me), 52.9 (*C*HNHBoc), 80.5 (Boc C), 127.1, 128.6, 129.1, 135.7, 171.3 (CO_2Me), 171.7 (CONH);

HRMS (EI): calcd for $C_{19}H_{28}N_2O_5$ $[M]^+$: 364.199791, found 364.198514.

Methyl N-(*tert*-Butoxycarbonyl)-L-alanyl-N-methyl-D-alanyl-L-phenylalaninate (132)



A solution of peptide **131** (1.0 g, 2.8 mmol) in CH_2Cl_2 (22 mL) was treated with CF_3CO_2H (2.2 mL), and the mixture was stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification. To a stirred solution of the crude amine salt, N-Boc-alanine (0.53 g, 2.8 mmol), and PyBroP (1.3 g, 2.8 mmol) in CH_2Cl_2 (3 mL) was added DIPEA (1.4 mL, 8.4 mmol) at 0 °C and the mixture stirred at room temperature for 3 h. The solvent was removed in *vacuo* and the residue purified by flash chromatography (1:1 ethyl acetate/petroleum ether) to provide a gel-like compound **132** (0.69 g, 58%).

R_f = 0.45 (1:1 ethyl acetate/petroleum ether);

$[\alpha]^{25}_D$ = +62.4 (c 1.79, CH_2Cl_2);

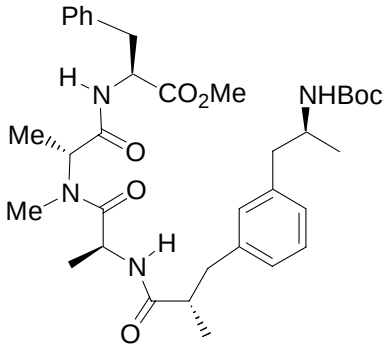
IR (film): ν_{max} = 3327, 2979, 1742, 1682, 1642, 1520, 1455, 1249, 1169 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHNCH$_3$), 1.23 (d, *J* = 7.8 Hz, 3H, C*H*$_3$CHNHBoc), 1.37 (s, 9H, C(CH$_3$)$_3$), 2.85 (s, 3H, NCH$_3$), 2.97 (dd, *J* = 13.9, 7.1 Hz, 1H, benzylic H), 3.04-3.09 (m, 1H, benzylic H), 3.60 (s, 3H, OCH$_3$), 4.44-4.50 (m, 1H, CHNHBoc), 4.65-4.70 (m, 1H, CHCO$_2$Me), 5.11 (q, *J* = 6.3 Hz, 1H, C*H*NCH$_3$), 5.31 (d, *J* = 6.8 Hz, 1H, NHBoc), 6.70 (d, *J* = 7.8 Hz, 1H, N*H*CHCO$_2$Me), 7.05 (d, *J* =7.3 Hz, 2H, H$_o$, aryl H), 7.14-7.24 (m, 3H, aryl H);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (*C*H$_3$CHCO), 17.9 (*C*H$_3$CHNHBoc), 28.2 (C(CH$_3$)$_3$), 30.3 (NCH$_3$), 37.4 (benzylic), 46.6 (CHNHBoc), 52.1 (OCH$_3$, CHNMe), 53.0 (*C*HCO$_2$Me), 79.6 (Boc C), 127.0, 128.4, 129.0, 135.9 (aryl) 155.3 (Boc C=O), 170.4 (CO$_2$Me), 171.7 (CONMe), 173.7 (CONH);

HRMS (EI): calcd for $C_{22}H_{33}N_3O_6$ $[M]^+$: 435.236897, found 435.240391.

Methyl *N*-[(2*S*)-3-(3-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]propyl}phenyl)-2-methylpropanoyl]-L-alanyl N-methyl-D-alanyl-L-phenylalaninate (133)



A solution of tripeptide **132** (180 mg, 0.413 mmol) in CH_2Cl_2 (3.5 mL) was treated with CF_3CO_2H (0.32 mL), and the mixture stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification. To a cooled (0 °C) solution of the crude amine salt and amino acid **95** (133 mg, 0.413 mmol) in THF (7 mL)

and CH_2Cl_2 (1.5 mL) were added 1-hydroxybenzotriazole (56.2 mg, 0.413 mmol), Et_3N (0.15 mL, 1.03 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (103 mg, 0.54 mmol), followed by stirring of the mixture at room temperature for 16 h. The solvent was removed in *vacuo*, and the residue purified by flash chromatography (ethyl acetate/petroleum ether, 1:1) to provide a colorless gel-like compound **133** (0.14 g, 55%).

R_f = 0.33 (1:1 ethylacetate/petroleum ether);

$[\alpha]^{25}_D$ = +61.5 (c 0.52, CH_2Cl_2);

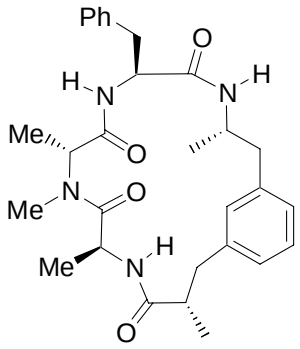
IR (film): ν_{max} = 3315, 2975, 2932, 1742, 1644, 1526, 1455, 1391, 1247, 1172 cm^{-1};

^{1}H NMR (400 MHz, CD_3OD): δ = 1.04 (d, *J* = 6.6 Hz, 6H, C*H*$_3$CHNH, $CH_2CH(CH_3)$), 1.23 (d, *J* = 7.3 Hz, 3H, C*H*$_3$CHN(CH_3)), 1.30 (d, *J* = 7.1 Hz, 3H, C*H*$_3$CHNHBoc), 1.36 (s, 9H, $C(CH_3)_3$), 2.40-2.72 (m, 4H, benzylic H), 2.86 (s, 3H, NCH_3), 3.09-3.16 (m, 2H, $PhCH_2$), 3.58 (s, 3H, OCH_3), 3.68 (m, 1H, NHBoc), 4.50-4.60 (m, 2H, C*H*(CH_3)NH, C*H*(CH_3)NHBoc), 5.03 (q, *J* = 7.1 Hz, 1H, C*H*(CH_3)NCH_3), 6.89-7.20 (m, 11H, aryl H, $PhCH_2$C*H*N*H*), 7.90 (br s, 1H, COCHN*H*);

^{13}C NMR (100 MHz, CD_3OD): δ = 14.0 (*C*H_3CHN(CH_3)), 16.7 (CH_2CH(*C*H_3)), 17.4 (*C*H_3CHNH), 20.6 (*C*H_3CHNHBoc), 28.8 ($C(CH_3)_3$), 31.4 (NCH_3), 38.1 ($PhCH_2$), 38.9 (*C*H(CH_3)CO), 40.7 (*C*H_2CH(CH_3)CO), 43.0 (*C*H_2CH(CH_3)NH), 47.3 (*C*H(CH_3)NH), 52.7 (*C*H(CH_3)NCH_3), 53.8 (OCH_3), 55.5 ($CHCO_2Me$), 79.8 (Boc C), 127.8, 128.0, 128.3, 129.2, 129.4, 130.2, 138.4, 140.4, 140.8 (aryl), 157.7 (Boc C=O), 173.1 (N(CH_3)CO), 173.4 (CO_2Me), 175.2 (*C*OCHN(CH_3)), 178.7 (NHCOCH);

HRMS (EI): calcd for $C_{35}H_{50}N_4O_7$ $[M+Na]^+$: 661.35717, found 661.34712.

(3*S*,6*S*,9*R*,12*S*,15*S*)–6–Benzyl-3,9,10,12,1–pentamethyl-4,7,10,13-tetraazabicyclo[15.3.1]henicosa-1,17,19–trien-5,8,11,14–tetrone (134)



NaOH (7.5 mg) in H_2O (0.5 mL) was added to a stirred solution of tetrapeptide **133** (100 mg, 0.156 mmol) in THF (3 mL). The reaction mixture was stirred for 1 h at room temperature before being poured into saturated $NaHCO_3$ solution (5 mL) and extracted with diethyl ether (3 × 5 mL). The aqueous layer was acidified to pH 2-3 with 1N HCl and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in *vacuo* to give the free acid in almost quantitative yield. This acid was used for the next step without further purification. To a solution of above N-Boc protected tetrapeptide acid (90 mg, 0.144 mmol) in CH_2Cl_2 (1.2 mL) was added CF_3CO_2H (0.11 mL, 1.45 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue was dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the macrolactamization without any further purification. The residue was dissolved in DMF (140 mL) and the stirred solution was treated successively with TBTU (140 mg, 0.435 mmol), HOBt (59 mg, 0.435 mmol), and *i*Pr_2NEt(0.08 mL, 0.435 mmol) at room temperature. The solution was stirred at room temperature for 14 h and then partitioned between ethyl acetate and water. After separation of the layers, the water was layer extracted with ethyl acetate (2 × 75 mL). The combined organic layers were washed successively with water, 5% aqueous $KHSO_4$, water, half-saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate) to provide a colorless sticky solid **134** (50 mg, 62%, 3 steps).

R_f = 0.55 (ethyl acetate);

$[\alpha]^{28}_{D}$ = +18.0 (c 0.30, CH_2Cl_2);

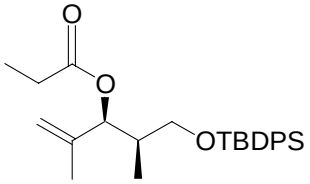
IR (film): ν_{max} = 3302, 2933, 1633, 1520, 1455 cm^{-1};

^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.97 (d, *J* = 7.3 Hz, 17-CH_3), 1.07 (d, *J* = 7.3 Hz, 3H, CH_3), 1.09 (d, *J* = 5.9 Hz, 3H, 11-CH_3), 1.10 (d, *J* = 5.9 Hz, 3H, CH_3), 2.36-2.43 (m, 1H, 11-H), 2.48 (m, 1H, 10-H), 2.49 (m, 1H, 6-H), 2.60-2.70 (m, 2H, 10-H, 1-H), 2.84 (s, 3H, NCH_3), 2.95 (dd, *J* = 13.2, 3.7 Hz, 1H, 6-H), 3.35 (dd, *J* = 13.6, 3.3 Hz, 1H, 1-H), 4.04-4.08 (m, 1H, 5-H), 4.22-4.29 (m, 2H, 17-H, 2-H), 4.39-4.44 (m, 1H, 14-H), 6.46 (br s, 3H, 13-NH), 6.50 (d, *J* = 8.1 Hz, 4-NH), 6.65, 6.70 (2 d, *J* = 7.3 Hz, 2H, 4''-H, 6''-H), 6.90 (dd, *J* = 7.3, 7.3 Hz, 1H, 5''-H), 6.93 (s, 1H, 2''-H), 7.15-7.19 (m, 1H, 4'-H), 7.21-7.27 (m, 4H, 2'-H, 4'-H), 8.31 (d, *J* = 8.8 Hz, 1H, 19-NH);

^{13}C NMR (150 MHz, DMSO-d_6): δ = 14.3 (CH_3-17), 17.5 (CH_3-11), 18.4 (CH_3-5, CH_3-14), 30.5 (NCH_3), 35.4 (C-1), 38.6 (C-6), 40.5 (C-10), 43.6 (C-11), 44.3 (C-5), 44.7 (C-14), 53.3 (C-17), 53.4 (C-2);

HRMS (ESI): calcd for $C_{29}H_{38}N_4O_4$ $[M+Na]^+$: 529.27853, found 529.27827.

(1*S*)-1-((1*R*)-2-{[*tert*-Butyl(diphenyl)silyl]oxy}-1-methylethyl)-2-methylprop-2-enyl propionate (140)



To a solution of alcohol **144** (500 mg, 1.36 mmol) in dry CH_2Cl_2 (5 mL) were added pyridine (0.22 mL, 2.68 mmol) and *n*-propionyl chloride (0.18 mL, 2.00 mmol) at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (4 mL) and washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (5:95 ethyl acetate/petroleum ether) resulting in the acylated product **140** (500 mg, 87%) as a colorless gel.

R_f = 0.55 (5:95 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = -11.0 (c 1.02 CH_2Cl_2);

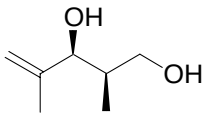
IR (film): υ_{max} = 3066, 2938, 2865, 1739, 1519, 1461, 1095 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3H, *CH_3*CH), 1.05 (s, 9H, *t*Bu), 1.12 (t, *J* = 7.6 Hz, 3H, CH_2*CH_3*), 1.67 (s, 3H, *CH_3*C=CH), 1.96-2.02 (m, 1H, *CH*CH_2O), 2.31 (q, *J* = 7.6 Hz, 3H, *CH_2*CH_3), 3.48-3.51 (m, 2H, *CH_2O*), 4.84 (s, 1H, olefinic), 4.87 (s, 1H, olefinic), 5.34 (d, *J* = 5.1 Hz, 1H, *CH*O), 7.35-7.42 (m, 6H, aromatic), 7.64 (t, *J* = 5.1 Hz, 4H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.2 (CH_2*CH_3*), 11.2 (*CH_3*CH), 19.0 (*CH_3*C=C), 19.2 (quarternary TBDPS), 26.8 (3C, *t*Bu), 27.7 (*CH_2*CH_3), 37.7 (*CH*CH_3), 65.4 (*CH_2*OH), 76.5 (*CH*OH), 112.0 (olefinic CH_2), 127.6, 129.6, 133.6, 133.7, 135.6, 135.6 (aromatic), 142.3 (olefinic quarternary);

HRMS (EI): calcd for $C_{26}H_{36}O_3Si$ $[M+Na]^+$: 447.23259, found 447.23264.

(2*R*,3*S*)-2,4-Dimethylpent-4-ene-1,3-diol (143)



To a solution of aldol product **142** (1.00 g, 3.30 mmol) in THF (90 mL) was added $NaBH_4$ (620 mg, 16.50 mmol) in H_2O (20 mL) at 0 ^oC. The mixture was stirred for 7 h at room temperature. The reaction mixture was treated with saturated aq. NH_4Cl (20 mL) and stirred for 1 h at room temperature. After separation of the layers, the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatoghaphy (5:95 ethylacetate/dichloromethane) to obtain the pure diol **143** (365 mg, 85%) as colorless oil.

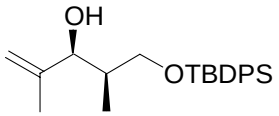
R_f = 0.23 (5:95 ethyl acetate/dichloromethane);

$[\alpha]^{20}_D$ = -14.2 (c 1.02, CH_2Cl_2);

IR (film): υ_{max} = 3370, 2965, 2931, 1446, 1095 cm^{-1};

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.8 Hz, 3H, *CH*$_3$CH), 1.69 (s, 3H, *CH*$_3$C=C), 1.84-1.89 (m, 1H, *CH*CH_2O), 2.51 (br s, 1H, *OH*), 2.60 (br s, 1H, OH), 3.63-3.71 (m, 2H, CH_2O), 4.22 (br s, 1H, *CH*O), 4.91 (s, 1H, olefinic), 4.93 (s, 1H, olefinic);
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 9.8 (*CH*$_3$CH), 19.4 (*CH*$_3$C=C), 37.2 (*CH*CH_3), 66.8 (*CH*$_2$OH), 77.4 (*CH*OH), 110.6 (olefinic CH_2), 146.3 (olefinic quarternary);

(3*S*,4*R*)-5-{[*tert*-Butyl(diphenyl)silyl]oxy}-2,4-dimethylpent-1-en-3-ol (144)

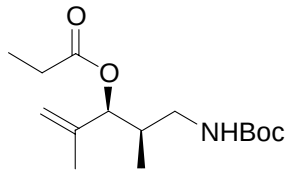


To a stirred solution of alcohol **143** (300 mg, 2.30 mmol) in dry DMF (10 mL), were added imidazole (392 mg, 5.75 mmol) and TBDPS-Cl (380 mg (0.65 mL), 2.53 mmol) successively at room temperature. Stirring was continued for 12 h. Then the reaction mixture was diluted with water (10 mL) and stirred for 0.5 h before the mixture was extracted with diethyl ether (3 x 15 mL). The combined ether layers were washed with 1 N HCl (10 mL), saturated aq. $NaHCO_3$ (10 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated in *vacuo* to furnish the crude product which was purified by flash chromatography (5:95 ethyl acetate/petroleum ether) giving the mono protected alcohol **144** (870 mg, 97%) as a colorless gel compound.

R_f = 0.24 (5:95 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -6.5 (c 1.00, CH_2Cl_2);
IR (film): υ_{max} = 3370, 2965, 2931, 1446, 1095 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3H, *CH*$_3$CH), 1.06 (s, 9H, *t*Bu), 1.66 (s, 3H, *CH*$_3$C=CH), 1.83-1.90 (m, 1H, *CH*CH_2O), 3.68 (dd, *J* = 10.1, 5.6 Hz, 1H, *CH*$_2$O), 3.71-3.75 (m, 1H, *CH*$_2$*O*), 4.33 (br s, 1H, *CH*O), 4.90 (s, 1H, olefinic), 5.03 (s, 1H, olefinic), 7.37-7.43 (m, 6H, aromatic), 7.66-7.72 (m, 4H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.7 (*CH*$_3$CH), 19.2 (quarternary TBDPS), 19.4 (*CH*$_3$C=C), 26.9 (3C, *t*Bu), 37.3 (*CH*CH_3), 68.0 (*CH*$_2$OH), 76.3 (*CH*OH), 110.5 (olefinic CH_2), 127.7, 129.7, 134.8, 135.6, 135.7 (aromatic), 145.7 (olefinic quarternary);

HRMS (EI): calcd for $C_{23}H_{22}O_2Si$ $[M+Na]^+$: 391.20631, found 391.20627.

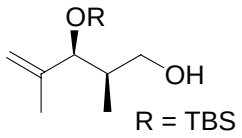
(1*S*)-1-{(1*R*)-2[(*tert*-Butoxycarbonyl)amino]-1-methylethyl}-2-methylprop-2-enyl propionate (147)



To a solution of alcohol **158** (130 mg, 0.57 mmol) in dry CH_2Cl_2 (5 mL) were added pyridine (0.09 mL, 1.14 mmol) and *n*-propionyl chloride (0.07 mL, 0.79 mmol) at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 12 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (4 mL) and washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (1:9 ethylacetate/petroleum ether) providing the acylated product **147** (145 mg, 91%) as a colorless oil.

R_f = 0.40 (1:9 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -15.6 (c 0.95, CH_2Cl_2);
IR (film): υ_{max} = 3374, 2974, 2935, 1712, 1511, 1172 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (d, *J* = 6.8 Hz, 3H, CH_3CH), 1.15 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 1.42 (s, 9H, *t*Bu), 1.69 (s, 3H, CH_3C=C), 2.01-2.04 (m, 1H, $CH$$CH_3$), 2.37 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 2.78-2.85 (m, 1H, CH_2NH), 3.08-3.15 (m, 1H, CH_2NH), 4.90 (br s, 3H, *NH*, olefinic *CH*), 5.19 (br s, 1H, *CH*O);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.2 (CH_2CH_3), 11.8 (CH_3CH), 19.3 (CH_3C=C), 27.7 (CH_2CH_3), 28.4 (3C, *t*Bu), 35.1 ($CH$$CH_3$), 43.2 ($CH_2$NH), 76.4 (*CH*OH), 79.2 (Boc quarternary), 112.1 (CH_2 olefinic), 141.9 (olefinic quarternary), 156.0 (Boc C=O), 174.0 (ester C=O);
HRMS (EI): calcd for $C_{15}H_{27}NO_4$ $[M+Na]^+$: 308.18323, found 308.18339.

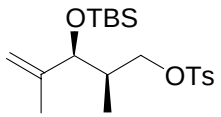
(2*R*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-en-1-ol (150)



To a solution of protected aldol product **151** (500 mg, 1.20 mmol) in THF (32 mL) was added $NaBH_4$ (225 mg, 6.00 mmol) in H_2O (12 mL) at 0 ^oC. The reaction stirred for 7 h at room temperature. The reaction mixture was treated with saturated aq. NH_4Cl (10 mL) and stirred for 1 h at room temperature. After separation of the layers, the aqueous layer extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product. The crude product was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) to afford the pure diol **150** (220 mg, 76%) as colorless oil.

R_f = 0.23 (1:3 ethyl acetate/petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05, 0.01 (two s, 6H, $Si(CH_3)_2$), 0.85 (d, *J* = 7.1 Hz, 3H, CH_3CH), 0.89 (s, 9H, *t*Bu), 1.70 (s, 3H, CH_3C=C), 1.81-1.87 (m, 1H, $CHCH_2O$), 3.47 (dd, *J* = 10.9, 5.3 Hz ,1H, CH_2O), 3.56 (dd, *J* = 10.7, 7.0 Hz,1H, CH_2O), 4.22 (d, *J* = 5.1 Hz, 1H, *CH*OTBS), 4.87 (s, 1H, olefinic), 4.91 (s, 1H, olefinic);
^{13}C-NMR (100 MHz, $CDCl_3$): δ = -4.7, -5.3 ($Si(CH_3)_2$), 11.9 (CH_3CH), 18.2 (quarternary TBS), 18.6 (CH_3C=C), 25.8 (3C, *t*Bu), 39.4 ($CHCH_3$), 65.9 (CH_2OH), 78.1 (*CH*OTBS), 112.0 (olefinic CH_2), 146.4 (olefinic quarternary).

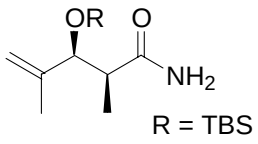
(2*R*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-enyl 4-methoxybenzene sulfonate (152)



To a solution of alcohol **150** (100 mg, 0.41 mmol) in pyridine (1 mL) was added tosyl chloride (260 mg, 1.34 mmol) at 0 ^{o}C and the solution stirred for 4 h at 0 ^{o}C. Pre cooled water (1 mL) was added and the reaction mixture stirred for 30 min at 0 ^{o}C. The reaction mixture was diluted with diethyl ether (5 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 3 mL) and the combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), filtered and evaporated to give the crude product which was purified by flash chromatography (1:9 ethyl acetate/petroleum ether) providing the pure tosylated product **152** (150 mg, 92%) as a colorless gel.

R_f = 0.40 (1:9 ethyl acetate/petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.06, -0.03 (two s, 6H, $Si(CH_3)_2$), 0.82 (d, *J* = 6.8 Hz, 3H, *CH_3*CH), 0.84 (s, 9H, *t*Bu), 1.91 (s, 3H, *CH_3*C=C), 1.85-1.94 (m, 1H, *CH*CH_2O), 2.44 (3H, methyl(toluene)), 3.78 (dd, *J* = 9.5, 6.4 Hz, 1H, CH_2O), 3.91-3.95 (m, 2H, C*H_2*O,*CH*OTBS), 4.87 (s, 1H, olefinic), 4.91 (s, 1H, olefinic), 7.33 (d, *J* = 8.1 Hz, 2H, aromatic), 7.77 (d, *J* = 8.3 Hz, 2H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.3, -4.6 ($Si(CH_3)_2$), 11.2 (*CH_3*CH), 18.1 (*CH_3*C=C), 21.6 (methyl(toluene)), 25.8 (3C, *t*Bu), 36.7 (*CH*CH_3), 72.3 (*CH_2*OH), 75.7 (*CH*OTBS), 112.5 (olefinic CH_2), 127.9, 129.8, 133.1, 144.7 (aromatic), 146.4 (olefinic quarternary);

(2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-enamide (154)

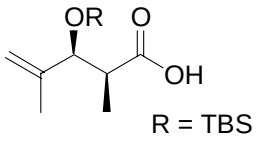


To a solution of acid **155** (400 mg, 1.54 mmol) in dry $CHCl_3$ (10 mL) were added NH_4HCO_3 (360 mg, 4.50 mmol) and EEDQ (410 mg, 1.66 mg) at room temperature. The mixture was stirred for 48 h at room temperature, then diluted with dichoromethane (15 mL). The reaction mixture was washed with water (10 mL) and then with brine (10 mL). The dried (Na_2SO_4) organic layer was filtered and concentrated in *vacuo* to give the crude product which was

purified by flash chromatography (1:1 ethylacetate/petroleum ether) providing the pure amide **154** (300 mg, 75%) as a colorless oil.

R_f = 0.40 (1:1 ethylacetate/petroleum ether);
$[\alpha]^{20}_D$ = -4.5 (c 1.18 CH_2Cl_2);
IR (film): υ_{max} = 3340, 3193, 2935, 2892, 1662, 1461, 1072 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.03 (s, 3H, *CH*$_3$TBS), 0.02 (s, 3H, *CH*$_3$TBS), 0.86 (s, 9H, *t*Bu), 1.07 (d, *J* = 7.1 Hz, 3H, *CH*$_3$CH), 1.66 (s, 3H, CH_3C=C), 2.40-2.46 (m, 1H, *CH*CO), 4.21 (d, *J* = 5.8 Hz, 1H, *CH*O), 4.84 (s, 1H, olefinic), 4.91 (s, 1H, olefinic), 5.91, 6.13 (br s, 2H, amide);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.4, -4.8 (CH_3TBS), 12.5 (*CH*$_3$CH), 18.0 (*CH*$_3$C=C), 18.1 (quarternary TBS), 25.8 (3C, *t*Bu), 45.4 (*CH*CO), 77.8 (*CH*OTBS), 113.2 (CH_2 olefinic), 144.7 (olefinic quarternary), 177.2 ($CONH_2$);
HRMS (EI): calcd for $C_{13}H_{27}NO_2Si$ $[M+Na]^+$: 280.17033, found 280.17021.

(2*S*,3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpent-4-enoic acid (155)

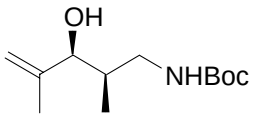


To a solution of the protected aldol product **151** (1.00 g, 2.4 mmol) in THF (25 mL) was added H_2O_2 (1.2 mL of a 30 wt% solution, 9.6 mmol) at 0 ^oC through a syringe, followed by the addition of $LiOH{\cdot}H_2O$ (200 mg, 4.80 mmol) in water (12 mL). The solution was stirred at 0 ^oC for 5 h. Subsequently, saturated Na_2SO_3 solution (10 mL) and saturated $NaHCO_3$ solution (10 mL) were added at 0 ^oC. The whole mixture was partially concentrated in *vacuo* and diluted with water (10 mL). The aqueous layer was extracted with dichloromethane (3 x 25 mL) to recover the auxiliary. The aqueous layer was then acidified at 0 ^oC to pH 3 by using 1N HCl and then extracted with ethyl acetate (4 x 25 mL). The combined ethyl acetate layers were dried ($MgSO_4$), filtered, and concentrated to furnish an oily residue. Due to presence of some of the desired acid in the dichloromethane layer along with the chiral auxiliary, this mixture

was purified by using flash chromatography (1:3 ethyl acetate/petroleum ether) giving the pure acid **155** (480 mg, 77% from both dichloromethane and ethyl acetate layers) as a colorless oily residue.

R_f = 0.35 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -11.4 (c 1.10 CH_2Cl_2);
IR (film): υ_{max} = 3100, 2938, 2892, 2618, 1708, 1461, 1079 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.01(s, 3H, *CH*$_3$TBS), 0.02 (s, 3H, *CH*$_3$TBS), 0.87 (s, 9H, *t*Bu), 1.11 (d, *J* = 7.1 Hz, 3H, *CH*$_3$CH), 1.69 (s, 3H, CH_3C=C), 2.59-2.65 (m, 1H, *CH*CO), 4.32 (d, *J* = 5.8 Hz, 1H, *CH*O), 4.86 (s, 1H, olefinic), 4.95 (s, 1H, olefinic), 11.42 (br s, CO_2H);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.4, -4.7 (CH_3TBS), 11.3 (*CH*$_3$CH), 17.7 (*CH*$_3$C=C), 18.1 (quarternary TBS), 25.7 (3C, tBu), 44.3 (*CH*CO), 77.3 (*CH*OTBS), 113.2 (CH_2 olefinic), 144.7 (olefinic quarternary), 180.8 (CO_2H);
HRMS (EI): calcd for $C_{13}H_{26}O_3Si$ $[M+Na]^+$: 281.15434, found 281.15424.

tert-butyl (2*R*,3*S*)-3-hydroxy-2,4-dimethylpent-4-enylcarbamate (158)

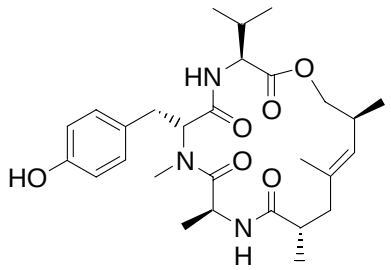


To a solution of amide **154** (275 mg, 1.07 mmol) in dry THF (5 mL) was added $LiAlH_4$ (1 M solution in ether, 4.0 mL, 4.00 mmol) at 0 ^oC. The mixture was stirred for 0.5 h at 0 ^oC, then gradually brought to room temperature by removing the ice bath. Thereafter, the mixture was heated to reflux for 2 h. The mixture was cooled to room temperature and carefully worked up by the dropwise and sequential addition of 0.2 mL of water, 0.2 mL of 15% aqueous NaOH and an additional 0.5 mL of water. The reaction mixture was filtered through a bed of celite and the celite bed washed thoroughly with ether (6 x 10 mL). The combined filtrates were dried ($MgSO_4$), and concentrated in *vacuo* to produce the crude amino alcohol which was used for next step (Boc protection) without any further purification.

To the crude aminol in dry CH_2Cl_2 (5 mL) were added NEt_3 (0.27 mL, 2.00 mmol) and Boc anhydride (270 mg, 1.25 mmol) at room temperature. After stirring for 12 h, the reaction mixture was acidified up to pH 3 by using 5% aqueous $KHSO_4$. The reaction mixture was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (5 mL), brine (5 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude protected aminol which was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) to provide the product **158** (145 mg, 59% two steps) as a colorless oil.

R_f = 0.35 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -4.9 (c 1.00, CH_2Cl_2);
IR (film): υ_{max} = 3363, 2973, 2931, 1689, 1523, 1072 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.8 Hz, 3H, *CH_3*CH), 1.42 (s, 9H, *t*Bu), 1.67 (s, 3H, CH_3C=C), 1.75-1.80 (m, 1H, *CH*CH_3), 2.91-2.98 (m, 2H, *CH_2*NH, *OH*), 3.24-3.31 (m, 1H, *CH_2*NH), 4.02 (br s, 1H, *CH*OH), 4.90 (br s, 2H, *NH*, olefinic *CH*), 5.03 (s, 1H, olefinic CH);
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.6 (CH*CH_3*), 19.5 (*CH_3*C=C), 28.4 (3C, tBu), 36.3 (*CH*CH_3) 43.8 (*CH_2*NH), 74.1 (*CH*OH), 79.1 (Boc quarternary), 110.5 (CH_2 olefinic), 145.7 (olefinic quarternary), 157.1 (Boc C=O);
HRMS (EI): calcd for $C_{12}H_{23}NO_3$ $[M+Na]^+$: 252.15701, found 252.15697.

(3*S*,6*R*,9*S*,12*R*,16*R*)-6-(4-Hydroxybenzyl)-3-isopropyl-7,9,12,14,16-pentamethyl-1-oxa-4,7,10-triazacycloheptadec-14-ene-2,5,8,11-tetrone (159)



To a solution of linear depsipeptide **161** (40 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.08 mL, 0.99 mmol) at 0 ^oC. Stirring was continued for 2 h, at this time TLC showed the complete consumption of reactant **161**. The solvent was removed in *vacuo* and the residue dried by azeotropic removal of H_2O with toluene. The crude material was used for the next step without further purification. To a solution of crude amine salt in dry DMF (50 mL) were added DIEA (0.04 mL, 0.20 mmol), HOBt (20 mg, 0.15 mmol) and TBTU (48 mg, 0.15 mmol) successively at room temperature. The solution was stirred at room temperature for 18 h and then partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate layers were washed successively with 5% aqueous $KHSO_4$, water, half saturated aq. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatogaphy (1:1 ethyl acetate/petroleum ether) providing the pure cyclic depsipeptide (12 mg, 39%) as a colorless oil.

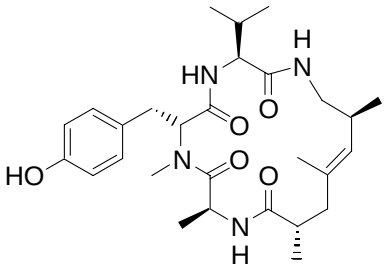
To the above TBS protected cyclic depsipeptide (12 mg, 0.02 mmol) in THF (0.2 mL) was added TBAF containing 5% water (1 M solution in THF, 0.04 ml, 0.04 mmol) at 0 ^oC. The solution was stirred for 3 h at 0 ^oC. The mixture was concentrated in *vacuo* and the crude macrocycle purified by flash chromatography (7:3 ethyl acetate/petroleum ether) yielding the pure cyclic depsipeptide **159** (8 mg, 80%) as a colorless oil.

R_f = 0.22 (7:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +11.6 (c 0.70, CH_2Cl_2);
IR (film): υ_{max} = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1};
^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.86 (*CH_3*CHCH_2O), 0.87 (Val Me), 0.93 (d, *J* = 6.7 Hz, 3H, Val Me), 0.95 (d, *J* = 6.6 Hz, 3H, Ala Me), 1.01 (d, *J* = 6.9 Hz, 3H, *CH_3*CHCO), 1.56 (s, 3H, *CH_3*C=C), 1.83 (d, *J* = 14.9 Hz, 1H, *CH_2^h*CHCO), 2.02 (*p*-sextett. *J* = 6.7 Hz, 1H, Val *CH*), 2.25 (dd, *J* = 15.1, 11.1 Hz, 1H, *CH_2^t*CHCO), 2.36-2.43 (m, 1H, *CH*CO), 2.56-2.63 (m, 1H, *CH*CH_2O), 2.66 (dd, *J* = 14.3, 8.1 Hz, 1H, Tyr CH_2^h), 2.79 (s, 3H, NMe), 3.00 (dd, *J* = 14.3, 6.4 Hz, 1H, Tyr *CH_2^t*), 3.70 (dd, *J* = 10.8, 2.5 Hz *CH_2^h*O), 4.04 (pt, *J* = 7.7 Hz, Val *CH*), 4.18 (dd *J* = 10.9, 5.4 Hz, 1H, *CH_2^t*O), 4.52 (qn, *J* = 6.9 Hz, 1H, Ala *CH*), 5.05 (d, *J* = 8.0 Hz, olefinic), 5.24 (dd, *J* = 8.7, 6.5 Hz, 1H, Tyr *CH*), 6.61 (d, *J* = 8.5 Hz, 2H, TyrArH_{meta}), 6.98 (d,

J = 8.5 Hz, 2H, TyrArH_{ortho}), 7.43 (d, *J* = 7.7 Hz, 1H, Val NH), 8.05 (d, *J* = 7.8 Hz, 1H, Ala NH), 9.05 (s, Tyr-OH);

^{13}C NMR (600 MHz, DMSO-d_6): δ = 16.9 (Ala CH_3), 17.8 (*CH_3*C=C), 18.8 (Val CH_3), 19.5 (*CH_3*CHCO), 29.1 (Val CH), 29.8 (NCH_3), 31.3 (*CH*CH_2O), 32.4 (Tyr CH_2), 38.5 (*CH*CO), 40.6 (*CH_2*CHCO), 44.0 (Ala CH), 56.3 (Tyr CH), 58.8 (Val CH), 68.1 (*CH_2*O), 114.4 (TyrAr meta), 125.2 (CH olefinic), 127.7 (C_{ipso}Ar), 129.5 (TyrAr_{ortho}), 133.8 (olefinic quarternary), 155.3 (C-OH Ar), 169.8 (Tyr CO), 170.2 (Val CO), 171.5 (Ala CO), 174.1 (CH_2CH*CO*); **HRMS (EI)**: calcd for $C_{28}H_{41}N_3O_6Si$ $[M+Na]^+$: 538.28876, found 538.28906.

(3*S*,6*R*,9*S*,12*R*,16*R*)-6-(4-Hydroxybenzyl)-3-isopropyl-7,9,12,14,16-pentamethyl-1,4,7,10-tetraazacycloheptadec-14-ene-2,5,8,11-tetrone (160)



0.4 N LiOH.H_2O (0.08 mL, 0.03 mmol) was added dropwise to a stirring solution of linear tetrapeptide **181** (20 mg, 0027 mmol) in THF (0.5 mL). The reaction mixture was stirred for 2 h at room temperature before it was acidified up to pH 3 using 1 N HCl and extracted using ethyl acetate (3 x 2 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in *vacuo* to furnish the TBS deprotected free acid in quantitative yield. This acid was used for the next step without further purification. To a solution of the above *N*-Boc protected free acid (17 mg, 0.027 mmol) in CH_2Cl_2 (0.3 mL) was added TFA (0.02 mL, 0.99 mmol) at 0 ^oC. Stirring was continued for 2 h. The solvent was concentrated in *vacuo* and the residue dried by azeotropic removal of H_2O with toluene. The crude material was used for the next reaction without any further purification. To a solution of crude amine salt in dry DMF (20 mL) were added DIEA (0.01 mL, 0.08 mmol), HOBt (8 mg, 0.06 mmol) and TBTU (19 mg, 0.06 mmol) successively at room temperature. The solution was stirred at room temperature for 18 h and then partitioned between ethyl acetate and water. The aqueous layer

was extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate layers were washed successively with 5% aqueous $KHSO_4$, water, half saturated aq. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (ethyl acetate) to deliver the macrolactam **160** (6 mg, 45%) as a colorless oil.

R_f = 0.55 (ethyl acetate);

$[\alpha]^{20}_D$ = -72.0 (c 0.40, CH_2Cl_2);

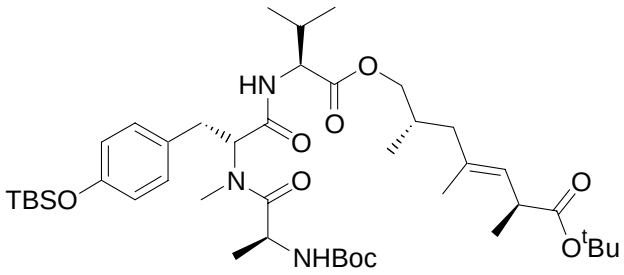
IR (film): υ_{max} = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1};

^{1}H NMR (600 MHz, DMSO-d_6): δ = 0.66 (dd, *J* = 3.7, 3.6 Hz, 6H, Val CH_3), 0.84 (d, *J* = 7.0 Hz, 3H, *CH_3*CHCH$_2$NH), 0.98 (d, *J* = 6.9 Hz, 3H, *CH_3*CHCO), 1.04 (d, *J* = 7.0 Hz, 3H, Ala Me), 1.46 (s, 3H, *CH_3*C=C), 1.76 (d, *J* = 15.9 Hz, 1H, *CH_2^h*CHCO), 2.20 (m, 2H, Val *CH, CH_2^t*CHCO), 2.53 (m, 1H, *CH*CO), 2.54 (m, 1H, *CH*CH$_2$NH), 2.83 (ddd, *J* = 12.9, 5.6, 2.6 Hz, 1H, *CH_2^t*NH), 2.91 (d, *J* = 8.2 Hz, 2H, Tyr CH_2), 3.06 (s, 3H, NMe), 3.14 (ddd, *J* = 13.1, 9.1, 6.0 Hz, 1H, *CH_2^h*NH), 4.06 (dd, *J* = 9.6, 4.9 Hz, Val *CH*), 4.59 (qn, *J* = 6.9 Hz, 1H, Ala *CH*), 4.96 (d, *J* = 8.0 Hz, olefinic), 5.01 (t, *J* = 8.2 Hz, 1H, Tyr *CH*), 6.64 (d, *J* = 8.5 Hz, 2H, TyrArH_{meta}), 7.03 (d, *J* = 8.5 Hz, 2H, TyrArH_{ortho}), 7.43 (t, *J* = 5.8 Hz, 1H, CH$_2$*NH*), 7.87 (d, *J* = 9.7 Hz, 1H, Val NH), 8.00 (d, *J* = 7.0 Hz, 1H, Ala NH), 9.10 (s, Tyr-OH);

^{13}C NMR (600 MHz, DMSO-d_6): δ = 16.7 (Val CH_3), 16.9 (Ala CH_3), 17.8 (*CH_3*C=C), 18.8 (*CH_3*CHCH$_2$NH), 18.9 (Val CH_3), 19.5 (*CH_3*CHCO), 28.1 (Val CH), 30.7 (NCH_3), 31.6 (*CH*CH$_2$NH), 32.9 (Tyr CH_2), 36.7 (*CH*CO), 41.1 (*CH_2*CHCO), 44.3 (Ala CH), 45.7 (*CH_2*NH), 56.7 (Val CH), 57.6 (Tyr CH), 114.6 (TyrAr$_{meta}$), 126.7 (CH olefinic), 126.8 (C $_{ipso}$Ar), 129.2 (TyrAr$_{ortho}$), 133.6 (olefinic quarternary), 155.5 (C-OH Ar), 170.4 (Val CO), 170.9 (Tyr CO), 174.4 (CH$_2$CH*CO*), 174.8 (Ala CO);

HRMS (EI): calcd for $C_{28}H_{42}N_4O_5Si$ $[M+Na]^+$: 537.30474, found 537.30438.

(2*S*,3*E*,6*S*)-7-*tert*-Butoxy-2,4,6-trimethyl-7-oxohept-3-enyl *N*-(*tert*-butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosyl-L-valinate (161)

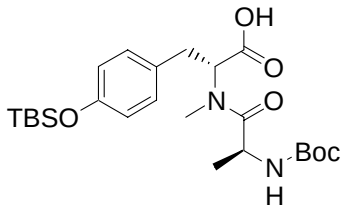


To a solution of acid **162** (70 mg, 0.15 mmol), amine **163** (50 mg, 0.15 mmol) in dry DMF (1.5 mL) were added DIEA (0.07 mL, 0.44 mmol), HOBt (20 mg, 0.15 mmol) and TBTU (47 mg, 0.15 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature, before it was treated with water (2 mL) and stirred for further 5 min and extracted with ethyl acetate (3 x 4 mL). The combined ethyl acetate layers were washed with 1 N HCl (3 mL), saturated aq. $NaHCO_3$ (3 mL), brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (15:85 ethyl acetate/petroleum ether) providing the pure linear depsipeptide **161** (60 mg, 51%) as a colorles oil.

R_f = 0.37 (15:85 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +28.0 (c 0.50, CH_2Cl_2);
IR (film): υ_{max} = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.12 (s, 6H, CH_3TBS), 0.85 (d, *J* = 6.1 Hz, 3H, Val *CH_3*), 0.87 (d, *J* = 6.1 Hz, 3H, Val *CH_3*), 0.89 (d, *J* = 6.8 Hz, 3H, *CH_3*CHCH_2O), 0.93-0.95 (m, 12H, *t*Bu(TBS), *CH_3*CHCO), 1.02 (d, *J* = 6.8 Hz, 3H, Ala *CH_3*), 1.38,1.40 (two s, 18H, *t*Bu, Boc *t*Bu), 1.60 (s, 3H, CH_3C=C), 1.91-1.97 (m, 1H, Val *CH*), 2.10-2.18 (m, 1H, *CH_2*CHCO), 2.28-2.34 (m, 1H, *CH_2*CHCO), 2.42-2.48 (m, 1H, *CH*CO), 2.70-2.75 (m, 1H, *CH*CH_2O), 2.84-2.88 (m, 1H, Tyr *CH_2*), 2.91 (s, 3H, N*CH_3*), 3.29 (dd, *J* = 14.9, 5.8 Hz, 1H, Tyr *CH_2*), 3.84-3.92 (m, 1H, *CH_2*O), 4.39-4.45 (m, 1H, Ala CH), 4.92 (d, *J* = 8.8 Hz, CH olefinic), 5.25 (d, *J* = 7.1 Hz, Val CH), 5.28 (br s, 1H, Ala NH), 5.49 (dd, *J* = 10.4, 5.8 Hz, 1H, Tyr CH), 6.59 (d, *J* = 8.8 Hz, 1H, Val NH), 6.69 (d, *J* = 8.1 Hz, 2H, aromatic), 7.01 (d, *J* = 8.3 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.5 (2C, CH_3TBS), 16.0 (*CH_3*C=C), 16.8 (*CH_3*CHCO), 17.6 (Val *CH_3*), 17.7 (Val CH_3, *CH_3*CH_2CHO), 18.2 (quarternary C, *t*Bu (TBS)), 19.1 (Ala *CH_3*), 25.6 (3C, *t*Bu (TBS)), 28.1, 28.3 (6C, *t*Bu, Boc *t*Bu), 30.6 (*CH*CH_2O), 30.8 (Val CH), 31.8 (NCH_3), 34.3 (Tyr CH_2), 38.6 (*CH*CO), 43.9 (*CH_2*CHO), 46.6 (Ala CH), 57.2 (Val CH), 57.4 (Tyr CH), 69.5 (CH_2O), 79.6, 79.9 (2C, quarternary C (Boc, *t*Bu)), 120.0, 128.2, 129.4 (aromatic), 129.7 (CH olefinic), 134.4 (olefinic quarternary), 154.4 (Boc C=O), 155.3 (phenolic), 170.1 (Tyr CO), 171.7 (Val CO), 174.5 (Ala CO), 176.4 (CO_2*t*Bu);
HRMS (EI): calcd for $C_{43}H_{73}N_3O_9Si$ $[M+Na]^+$: 826.50083, found 826.50078.

***N*-(*tert*-Butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosine (162)**



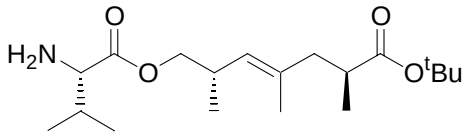
160

To a solution of dipeptide **175** (400 mg, 0.70 mmol) in ethanol (5 mL) was added 10% Pd/C (80 mg). The reaction mixture was connected to a hydrogenation machine (Parr apparatus) and shaked for 16 h in a hydrogen atmosphere at around 2 atm (30 psi) pressure at room temperature. The reaction mixture was filtered through a bed of celite and the celite bed was washed with ethyl acetate (2 x 5 mL). The filtrate was concentrated in *vacuo* to afford the crude acid **162** which was used for the further reaction without purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (s, 6H, CH_3TBS), 0.86 (d, *J* = 7.6 Hz, 3H, Ala *CH_3*), 0.94 (s, 9H, *t*Bu(TBS)), 1.40, (s, 9H, Boc *t*Bu), 2.85 (s, 3H, NCH_3), 2.93-3.03 (m, 1H, Tyr *CH_2*), 3.34 (dd, *J* = 14.7, 4.3 Hz, 1H, Tyr*CH_2*), 4.47- 4.53 (m, 1H, Ala CH), 5.28 (dd, *J* = 11.2, 3.9 Hz, 1H, TyrCH), 5.56 (d, *J* = 8.1 Hz, 1H, Ala NH), 6.72 (d, *J* = 8.3 Hz, 2H, aromatic) 7.00 (d, *J* = 8.3, 2H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.6 (2C, CH_3TBS), 18.2 (Ala *CH_3*), 18.2 (quarternary C, *t*Bu (TBS)), 25.6 (3C, *t*Bu (TBS)), 28.3 (Boc *t*Bu), 32.6 (NCH_3), 33.7 (Tyr CH_2), 46.5 (Ala

CH), 52.0 (OCH_3), 58.4 (Tyr CH), 79.8 (quarternary C Boc), 120.2, 129.1, 129.7 (aromatic), 154.5 (Boc C=O), 155.3 (phenolic), 173.6 (Ala CO), 174.2 (Tyr CO).

***tert*-Butyl (2*S*,4*E*,6*S*)-2,4,6-trimethyl-7-(L-valyloxy)hept-4-enoate (163)**



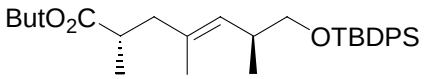
Et_2NH (7 mL) was added to a pre-cooled solution (0 °C) of F-moc protected valine ester **171** (150 mg, 0.27 mmol) in dry THF (7 mL). The reaction mixture was stirred for 15 min at 0 °C and then at room temperature for 3 h. The solution was concentrated in *vacuo* and the resulting oil was purified by flash chromatography (5:95 methanol/dichloromethane) to deliver the pure amine **163** (80 mg, 88%) as a pale yellow oil.

R_f = 0.25 (5:95 methanol/dichloromethane);
IR (film): υ_{max} = 3351, 2969, 2904, 1724, 1677, 1454, 1369, 1153 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3H, Val *CH_3*), 0.96 (d, *J* = 6.8 Hz, 6H, Val CH_3, *CH_3*CH_2O), 1.03 (d, *J* = 7.1 Hz, 3H, *CH_3*CHCO), 1.41 (s, 9H, *t*Bu), 1.62 (s, 3H, *CH_3*C=CH), 1.93-2.03 (m, 2H, *CH_2*CHCO, Val *CH*), 2.13-2.20 (m, 1H, *CH*NH), 2.32 (dd, *J* = 13.3, 8.2 Hz, 1H, *CH_2*CHCO), 2.43-2.51 (m, 1H, *CH*CH_2O), 2.71-2.79 (m, 1H, *CH*CO), 3.88-3.98 (m, 2H, Val*CH*, *CH_2*O), 4.11 (dd, *J* = 10.2, 8.2 Hz, 1H, *CH_2*O), 4.22 (t, *J* = 7.0 Hz, 1H, *CH*Fmoc), 4.30 (dd, *J* = 9.0, 4.7 Hz, 1H, *CH_2*Fmoc), 4.34-4.43 (m, 1H, *CH_2*Fmoc), 4.94 (d, *J* = 9.1 Hz, 1H, olefinic), 5.34 (d, *J* = 9.1 Hz, 1H, NH), 7.30 (t, *J* = 7.3 Hz, 2H, aromatic Fmoc), 7.39 (t, *J* = 7.3 Hz, 2H, aromatic Fmoc), 7.60 (d, *J* = 5.6 Hz, 2H, aromatic Fmoc), 7.75 (d, *J* = 7.7 Hz, 2H, aromatic Fmoc);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (*CH_3*C=CH), 16.8 (*CH_3*CH_2O), 17.5 (2C, Val CH_3), 18.9 (*CH_3*CHCO), 28.0 (3C, *t*Bu), 31.4 (*CH*CH_2O), 32.0 (Val CH), 38.6 (*CH*CO), 43.8 (*CH_2*C=CH), 47.1 (Fmoc CH), 59.0 (*CH*NH), 67.0 (Fmoc CH_2), 67.5 (CH_2O), 79.8 (Boc quarternary), 119.9, 125.1, 127.0, 127.7 (Fmoc aromatic), 128.1 (CH olefinic), 134.5 (C

olefinic), 141.3, 143.7, 143.9 (Fmoc aromatic), 156.2 (NHCO), 172.1 (Val CO), 175.7 (CO_2*t*Bu);

HRMS (EI): calcd for $C_{19}H_{35}NO_4$ $[M+H]^+$: 342.26389, found 342.26393.

***tert*-Butyl (2*S*,4*E*,6*S*)-7-{[*tert*-Butyl(diphenyl)silyl]oxy}-2,4,6-trimethylhept-4-enoate (169)**



To a stirring solution of hydroxy acid **96** (300 mg, 0.71 mmol), DMAP (1.23 g, 10.61 mmol), Et_3N (1.00 mL, 7.10 mmol), and *t*BuOH (0.40 mL, 0.36 mmol) in dry toluene (70 mL) was added 2,4,6-trichlorobenzoyl chloride (1.1 mL, 7.10 mmol) at -78 ^oC. After stirring for 30 min at -78 ^oC, the reaction mixture was brought to room temperature by removing the cooling bath, and then stirred additionally for 12 h at room temperature. The reaction mixture was treated with saturated aqueous $NaHCO_3$ (25 mL). After separation of the layers, the aqueous layer was extracted with ethy lacetate (3 x 15 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated in *vacuo* to afford the crude product which was purified by flash chromatography (5:95 ethyl acetate/petroleum ether) giving the pure product **169** (330 mg, 96%) as a colorless oil.

R_f = 0.22 (5:95 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = + 7.7 (c 0.71, CH_2Cl_2);

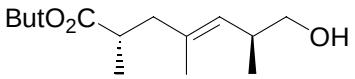
IR (film): υ_{max} =3066, 2962, 2931, 2861, 1727, 1461, 1369, 1153, 1110 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.8 Hz, 3H, *CH*$_3$$CH_2O$), 1.03 (d, *J* = 8.1 Hz, 3H, *CH*$_3$CO), 1.04 (s, 9H, *t*BuSi), 1.41 (s, 9H, *t*Bu), 1.54 (s, 3H, *CH*$_3$C=C), 1.95 (dd, *J* = 13.6, 7.3 Hz, 1H, *CH*$_2$CO), 2.30 (dd, *J* = 13.4, 7.3 Hz, 1H, *CH*$_2$CO), 2.41-2.50 (m, 1H, *CH*CO), 2.54-2.61 (m, 1H, *CH*CH_2O), 3.39 (dd, *J* = 16.2, 6.8 Hz, 1H, *CH*$_2$O), 3.45-3.49 (m, 1H, CH_2O), 4.95 (d, *J* = 9.1 Hz, 1H, olefinic), 7.35-7.41 (m, 6H, aromatic), 7.66 (d, *J* = 6.8, 4H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9 (*CH*$_3$C=CH), 16.9 (*CH*$_3$$CH_2O$), 17.4 (*CH*$_3$ CHCO), 19.2 (Si*C*$(CH_3)_3$), 26.8 (3C, SiC(*CH*$_3$)$_3$), 28.1 (3C, *t*Bu), 35.4 (*CH*CH_2O), 38.7 (*CH*CO), 44.1

(*CH*$_2$C=CH), 68.6 (CH_2O), 79.7 (Boc quarternary), 127.5, 129.5 (aromatic), 129.8 (CH olefinic), 132.8 (aromatic), 133.9 (olefinic), 135.6 (aromatic), 175.9 (CO_2*t*Bu);
HRMS (EI): calcd for $C_{30}H_{44}O_3Si$ $[M+Na]^+$: 503.29519, found 503.29502.

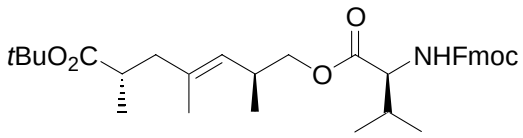
tert-Butyl (2*S*,4*E*,6*S*)-7-hydroxy-2,4,6-trimethylhept-4-enoate (170)



To a solution of protected hydroxy acid **169** (300 mg, 0.63 mmol) in THF (5 mL) was added TBAF (1 M solution in THF containing 5% H_2O, 0.75 mL, 0.75 mmol) at 0 ^oC. The reaction mixture was stirred until the TLC showed the complete consumption of reactant (4-5 h). The reaction mixture was concentrated in *vacuo* and purified by flash chromatography (1:3 ethyl acetate/petroleum ether) to give the pure alcohol **170** (135 mg, 90%) as a colorless oil.

R_f = 0.35 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -15.7 (c 0.77, CH_2Cl_2);
IR (film) υ_{max} = 3384, 2973, 2930, 2872, 1729, 1457, 1367, 1151 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3H, *CH*$_3$$CH_2O$), 1.06 (d, *J* = 7.1 Hz, 3H, *CH*$_3$CHCO), 1.41 (s, 9H, *t*Bu), 1.65 (s, 3H, *CH*$_3$C=CH), 2.05-2.07 (m, 1H, *CH*$_2$CHCO), 2.32 (dd, *J* = 13.3, 8.2 Hz, 1H, *CH*$_2$CHCO), 2.46-2.55 (m, 1H, *CH*CO), 2.56-2.65 (m, 1H, *CH*CH_2O), 3.29 (dd, *J* = 10.2, 8.2 Hz, 1H, *CH*$_2$O), 3.44 (dd, *J* = 10.4, 5.8 Hz, 1H, *CH*$_2$O), 4.90 (d, *J* = 9.4, 1H, olefinic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (*CH*$_3$C=CH), 16.9 (*CH*$_3$$CH_2O$), 17.1 (*CH*$_3$CHCO), 28.1 (3C, *t*Bu), 35.5 (*CH*CH_2O), 39.0 (*CH*CO), 43.8 (*CH*$_2$C=CH), 67.8 (CH_2O), 80.0 (Boc quarternary), 129.1 (CH olefinic), 135.3 (C olefinic), 175.8 (CO_2*t*Bu);
HRMS (EI): calcd for $C_{34}H_{45}NO_6$ $[M+Na]^+$: 265.17742, found 265.17750.

tert-Butyl (2_S_,4_E_,6_S_)-7-({_N_-[(9_H_-fluoren-9-ylmethoxy) carbonyl]–L-valyl}oxy)-2,4,6-trimethylhept-4-enoate (171)



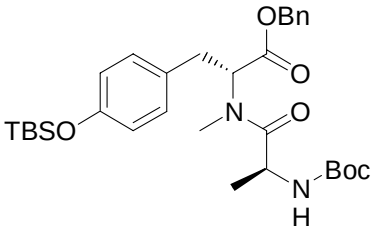
To a solution of hydroxy acid derivative **170** (100 mg, 0.41 mmol), Fmoc-L-Valine (140 mg, 0.41 mmol) and DMAP (25 mg, 0.20 mmol), in dry CH_2Cl_2 (4 mL) was added a solution of DCC (110 mg, 0.53 mmol) in dry CH_2Cl_2 (0.6 mL) dropwise at 0 ^oC. The reaction mixture was stirred for 0.5 h at 0 ^oC, then stirred for 10 h at room temperature. The reaction mixture was diluted with diethyl ether (10 mL) and filtered to remove the cyclohexyl urea and the precipitate washed twice with diethyl ether (5 mL). The filtrate was concentrated to give the crude product which was purified by flash chromatography (1:4 ethyl acetate/petroleum ether) providing the pure product **171** (205 mg, 88%) as a colorless gel.

R_f = 0.30 (1:4 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -5.9 (c 0.87, CH_2Cl_2);
IR (film): υ_{max} = 3351, 2969, 2904, 1724, 1677, 1454, 1369, 1153 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 3H, *CH_3*CH_2O), 0.97 (d, *J* = 6.3 Hz, 6H, Val CH_3), 1.03 (d, *J* = 6.8 Hz, 3H, *CH_3*CHCO),1.41 (s, 9H, *t*Bu), 1.62 (s, 3H, *CH_3*C=CH), 1.96 (dd, *J* = 13.6, 7.3 Hz, 1H, *CH_2*CHCO), 2.13-2.20 (m, 1H, *CH*NH), 2.32 (dd, *J* = 13.3, 8.2 Hz, 1H, *CH_2*CHCO), 2.43-2.51 (m, 1H, *CH*CH_2O), 2.71-2.79 (m, 1H, *CH*CO), 3.88-3.98 (m, 2H, Val*CH*, *CH_2*O), 4.11 (dd, *J* = 10.2, 8.2 Hz, 1H, *CH_2*O), 4.22 (t, *J* = 7.0 Hz, 1H, *CH*Fmoc), 4.30 (dd, *J* = 9.0, 4.7 Hz, 1H, *CH_2*Fmoc), 4.34-4.43 (m, 1H, *CH_2*Fmoc), 4.94 (d, *J* = 9.1 Hz, 1H, olefinic), 5.34 (d, *J* = 9.1 Hz, 1H, NH), 7.30 (t, *J* = 7.3 Hz, 2H, aromatic Fmoc), 7.39 (t, *J* = 7.3 Hz, 2H, aromatic Fmoc), 7.60 (d, *J* = 5.6 Hz, 2H, aromatic Fmoc), 7.75 (d, *J* = 7.7 Hz, 2H, aromatic Fmoc);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0 (*CH_3*C=CH), 16.8 (*CH_3*CH_2O), 17.5 (2C, Val CH_3), 18.9 (*CH_3*CHCO), 28.0 (3C, *t*Bu), 31.4 (*CH*CH_2O), 32.0 (Val CH), 38.6 (*CH*CO), 43.8 (*CH_2*C=CH), 47.1 (Fmoc CH), 59.0 (*CH*NH), 67.0 (Fmoc CH_2), 67.5 (CH_2O), 79.8 (Boc quarternary), 119.9, 125.1, 127.0, 127.7 (Fmoc aromatic), 128.1 (CH olefinic), 134.5 (C

olefinic), 141.3, 143.7, 143.9 (Fmoc aromatic), 156.2 (NHCO), 172.1 (Val CO), 175.7 (CO_2tBu);

HRMS (EI): calcd for $C_{34}H_{45}NO_6$ $[M+Na]^+$: 586.31391, found 586.31401;

Benzyl *N*-(*tert*-butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosinate (175)



To a solution of D-tyrosine benzylester derivative **174** (650 mg, 1.30 mmol) in CH_2Cl_2 (10 mL) was added CF_3COOH (1.0 mL, 13.0 mmol), and the mixture was stirred at room temperature for 1 h. The solvent was removed in *vacuo*, and the residue was dried by azeotropic removal of H_2O with toluene. The crude material was subjected to the next reaction without further purification. To a stirred solution of crude amine, *N*-Boc-L-alanine (240 mg, 1.30 mmol), and PyBroP (635 mg, 1.30 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC was added iPr_2NEt (0.8 mL, 4.70 mmol) and then the mixture was allowed to stir for 3 h at room temperature. The solvent was removed in *vacuo* and the residue purified by flash chromatography (1:3 ethyl acetate/petroleum ether) to give the dipeptide **175** (403 mg, 55%) as a colorless gel.

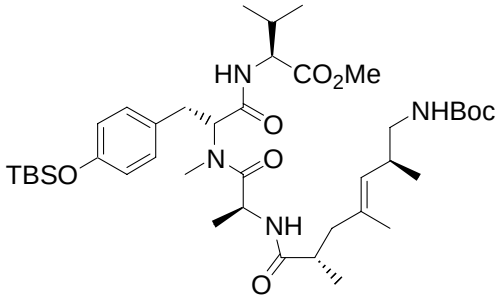
R_f = 0.45 (1:3 ethyl acetate/petroleum ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (s, 6H, CH_3TBS), 0.84 (d, *J* = 6.8 Hz, 3H, Ala *CH_3*), 0.94 (s, 9H, *t*Bu(TBS)), 1.41 (s, 9H, Boc *t*Bu), 2.80 (s, 3H, NCH_3), 2.95 (dd, *J* = 14.5, 11.8 Hz, 1H, Tyr*CH_2*), 3.33 (dd, *J* = 14.8, 4.9 Hz, 1H, Tyr*CH_2*), 4.43- 4.50 (m, 1H, Ala CH), 5.12-5.20 (m, 2H, *CH_2*Ph), 5.26-5.30 (m, 1H, TyrCH), 5.44 (d, *J* = 7.8 Hz, 1H, Ala NH), 6.71 (d, *J* = 8.6 Hz, 2H, aromatic), 6.99 (d, *J* = 8.6 Hz, 2H, aromatic), 7.31-7.34 (5H, aromatic CO_2Bn);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.6 (2C, CH_3TBS), 18.2 (Ala *CH_3*), 18.2 (quarternary C, *t*Bu (TBS)), 25.6 (3C, *t*Bu (TBS)), 28.3 (Boc *t*Bu), 32.6 (NCH_3), 33.7 (Tyr CH_2), 46.5 (Ala

CH), 52.0 (OCH_3), 58.4 (Tyr CH), 79.8 (quarternary C Boc), 120.2, 129.1, 129.7 (aromatic), 154.5 (Boc C=O), 155.3 (phenolic), 173.6 (Ala CO), 174.2 (Tyr CO).

Methyl *N*-{(2*S*,4*E*,6*S*)-7-[(*tert*-butoxycarbonyl)amino]-2,4,6-trimethylhept-4-enoyl}-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosyl-L-valinate (181)



To solution of tripeptide **182** (30 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.03 mL, 0.5 mmol) at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. The solvent was removed in *vacuo* and the residue was dried by azeotropic removal of H_2O with toluene. The crude material was used for the next reaction without further purification. To a solution of crude amine salt and amino acid **97** (15 mg, 0.05 mmol) in dry DMF (1 mL) were added DIEA (0.02 mL, 0.25 mmol), HOBt (7 mg, 0.05 mmol) and TBTU (16 mg, 0.05 mmol) successively. The reaction mixture was stirred for 2 h before it was diluted with water (2 mL), stirred for 5 min, and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were washed with 1 N HCl (2 mL), saturated aq. $NaHCO_3$ (2 mL), brine (2 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (1:1 ethyl acetate/petroleum ether) producing the pure tetrapeptide (20 mg, 53%) as a colorless gel.

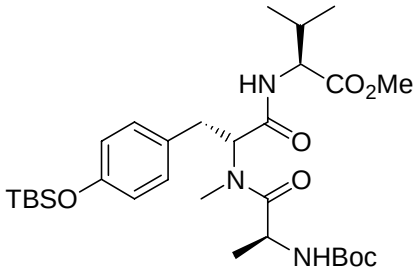
R_f = 0.52 (1:1 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +16.6 (c 0.84, CH_2Cl_2);
IR (film): υ_{max} = 3361, 2974, 2930, 1735, 1712, 1511, 1172 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13 (s, 6H, CH_3TBS), 0.87 (d, *J* = 6.8 Hz, 3H, Val *CH_3*), 0.88 (d, *J* = 6.8 Hz, 3H, Val *CH_3*), 0.89 (d, *J* = 7.6 Hz, 3H, *CH_3*CHCH_2O), 0.91-0.94 (m, 12H,

*t*Bu (TBS), *CH*$_3$CHCO), 1.04 (d, *J* = 6.8 Hz, 3H, Ala *CH*$_3$), 1.41 (s, 9H, Boc *t*Bu), 1.56 (s, 3H, CH_3C=C), 1.97-2.03 (m, 1H, Val *CH*), 2.13-2.21 (m, 1H, *CH*CH_2NH), 2.27 (dd, *J* = 13.8, 6.7 Hz, 1H, *CH*$_2$CHCO), 2.33-2.40 (m, 1H, *CH*$_2$CHCO), 2.53-2.56 (m, 1H, *CH*CO), 2.75-2.81 (m, 1H, *CH*$_2$NH), 2.85-2.89 (m, 1H, *CH*$_2$NH), 2.93 (s, 3H, N*CH*$_3$), 3.08-3.12 (m, 1H, Tyr *CH*$_2$), 3.29 (dd, *J* = 14.9, 6.1 Hz, 1H, Tyr *CH*$_2$), 3.69 (s, 3H, O*CH*$_3$), 4.41 (dd, *J* = 8.5, 5.8 Hz, 1H, Val CH), 4.61-4.68 (m, 1H, Ala *CH*), 4.75 (br s, 1H, *NH*Boc), 4.89 (d, *J* = 9.1 Hz, *CH* olefinic), 5.48 (dd, *J* = 10.6, 6.1 Hz, 1H, Tyr *CH*), 6.37 (d, *J* = 5.8 Hz, 1H, Val NH), 6.70 (d, *J* = 8.3 Hz, 2H, aromatic), 7.02 (d, *J* = 8.3 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.5 (2C, CH_3TBS), 16.4 (*CH*$_3$C=C), 16.9 (*CH*$_3$CHCO), 17.4 (Ala *CH*$_3$), 17.9 (Val CH_3), 18.2 (quarternary C, *t*Bu (TBS)), 18.2 (Val *CH*$_3$), 19.0 (*CH*$_3$CHCH_2NH), 25.6 (3C, *t*Bu (TBS), 28.4 (3C, Boc *t*Bu), 30.4 (NCH_3), 30.8 (*CH*CH_2NH), 32.8 (Val CH), 33.0 (Tyr CH_2), 39.2 (*CH*CO) 43.8 (*CH*$_2$CHCO), 45.5 (*CH*$_2$NH), 46.5 (Ala CH), 52.1 (OCH_3), 57.1 (Tyr CH)), 57.7 (Val CH), 77.9 (quarternary C Boc), 120.1, 128.2, 129.3 (aromatic), 129.7 (CH olefinic), 130.5 (olefinic quarternary), 154.1 (phenolic), 156.1 (Boc C=O), 170.1 (Ala CO), 172.3 (Tyr CO), 174.3 (Val CO), 175.7 (CO_2Me);

HRMS (EI): calcd for $C_{40}H_{68}N_4O_8Si$ $[M+Na]^+$: 783.46986, found 783.47035.

Methyl *N*-(*tert*-butoxycarbonyl)-L-alanyl-*O*-[*tert*-butyl(dimethyl)silyl]-*N*-methyl-D-tyrosyl-L-valinate (182)

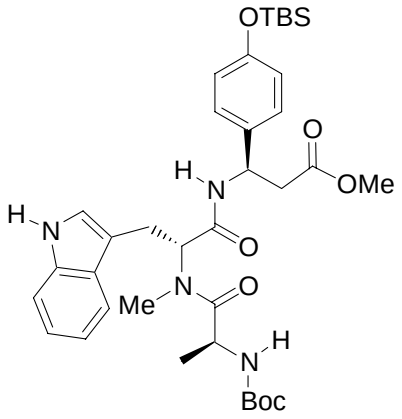


To a solution of dipeptide acid **162** (200 mg, 0.42 mmol), and L-valine methyl ester hydrochloride (70 mg, 0.42 mmol) in dry DMF (4 mL) were added DIEA (0.18 mL, 1.05 mmol), HOBt (58 mg, 0.42 mmol) and TBTU (135 mg, 0.42 mmol) at room temperature. The resulting reaction mixture was stirred for 3 h at room temperature. The reaction mixture was treated with water (5 mL), stirred for further 5 min, and extracted with ethyl acetate (3 x 10

mL). The combined ethyl acetate layers were washed with 1 N HCl (5 mL), saturated aq. $NaHCO_3$ (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in *vacuo* to furnish the crude product which was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) yielding the pure tripeptide **182** (177 mg, 71%) as a colorless gel.

R_f = 0.44 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +45.4 (c 1.01, CH_2Cl_2);
IR (film): υ_{max} = 3336, 2962, 2930, 1739, 1685, 1511, 1172, 1052 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 6H, CH_3TBS), 0.85 (d, *J* = 6.1 Hz, 3H, Val *CH_3*), 0.87 (d, *J* = 6.1 Hz, 3H, Val *CH_3*), 0.89 (d, *J* = 7.6 Hz, 3H, Ala *CH_3*), 0.92 (s, 9H, *t*Bu(TBS)), 1.37 (s, 9H, Boc *t*Bu), 2.10-2.18 (m, 1H, Val *CH*), 2.84-2.87 (m, 1H, Tyr *CH_2*), 2.91 (s, 3H, NCH_3), 3.28 (dd, *J* = 14.8, 5.4 Hz, 1H, Tyr CH_2), 3.68 (s, 3H, OCH_3), 4.39-4.42 (m, 2H, Ala CH, Val CH), 5.26 (d, *J* = 6.3 Hz, 1H, Ala NH), 5.49 (dd, *J* = 9.9, 5.9 Hz, 1H, Tyr CH), 6.61 (d, *J* = 8.3 Hz, 1H, Val NH), 6.69 (d, *J* = 7.8 Hz, 2H, aromatic), 7.00 (d, *J* = 7.6 Hz, 2H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.6 (2C, CH_3TBS), 17.5 (Val *CH_3*), 17.8 (Val CH_3), 18.1 (quarternary C, tBu (TBS)), 19.0 (Ala *CH_3*), 25.6 (3C, *t*Bu (TBS)), 28.2 (Boc *t*Bu), 30.4 (NCH_3), 30.8 (Val CH), 32.7 (Tyr CH_2), 46.6 (Ala CH), 52.0 (OCH_3), 57.1 (Val CH), 57.5 (Tyr CH), 79.6 (quarternary C Boc), 120.0, 129.3, 129.7 (aromatic), 154.4 (Boc C=O), 155.3 (phenolic), 170.2 (Tyr CO), 172.0 (Ala CO), 174.8 (Val CO);
HRMS (EI): calcd for $C_{30}H_{51}N_3O_7Si$ $[M+Na]^+$: 616.33885, found 616.33956.

N-(*tert*-Butoxycarbonyl)-L-alanyl-*N*-{(1*R*)-3-methoxy-3-oxo-1-[4-(1,1,2,2-tetramethylpropoxy)phenyl]propyl}-*N*-methyl-D-tryptophanamide (184)



To solution of β-D tyrosine derivative **186** (90 mg, 0.23 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (0.18 mL, 2.3 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The solvent was removed in *vacuo* and residue dried by azeotropic removal of H_2O with toluene. The crude material was used for the next reaction without further purification. To a solution of the crude amine salt, and dipeptide acid **192** (90 mg, 0.23 mmol) in dry DMF (2 mL) were added *i*Pr_2NEt (0.09 mL, 0.56 mmol), HOBt (32 mg, 0.23 mmol), and TBTU (74 mg, 0.23 mmol) successively. The resulting mixture was stirred for 2 h. The reaction mixture was diluted with water (2 mL), stirred for 5 min and extracted with ethyl acetate (3 x 4 mL). The combined organic layers were washed with 1 N HCl (2 mL), saturated aq. $NaHCO_3$ (2 mL), brine (2 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (1:1 ethyl acetate/petroleum ether) to furnish the pure tripeptide **184** (100 mg, 70%) as a colorless gel.

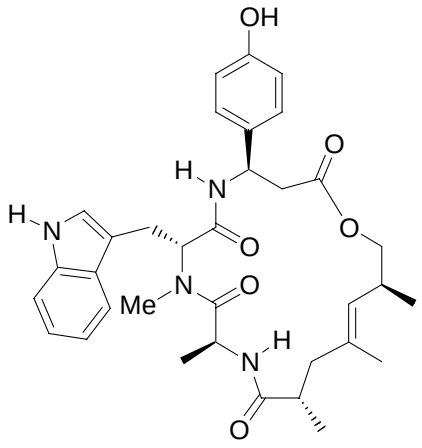
R_f = 0.44 (1:1 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +22.0 (c 0.423, CH_2Cl_2);
IR (film): υ_{max} = 3335, 2935, 2850, 1730, 1680, 1515, 1260, 1170 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.16 (s, 6H, CH_3TBS), 0.90 (d, *J* = 6.8 Hz, 3H, Ala CH_3), 0.95 (s, 9H, *t*Bu(TBS)), 1.39 (s, 9H, Boc *t*Bu), 2.75 (dd, *J* = 15.5, 5.4 Hz, 1H, β-Tyr CH_2), 2.82-2.88 (m, 1H, β-Tyr CH_2), 2.91 (s, 3H, NCH_3), 3.21 (dd, *J* = 15.6, 10.5 Hz, 1H, Trp CH_2), 3.42 (dd, *J* = 15.9, 5.3 Hz, 1H, Trp CH_2), 3.59 (s, 3H, OCH_3), 4.39 (qn, *J* = 6.8 Hz, 1H, Ala CH), 5.34-5.40 (m, 1H, β-Tyr CH), 5.61 (dd, *J* = 10.1, 5.6 Hz, Trp CH), 6.72 (d, *J* = 8.3 Hz, 2H, β-Tyr aromatic), 6.93 (s, 1H, Trp aromatic), 7.00 (d, *J* = 8.3 Hz, 1H, β-Tyr NH), 7.07 (d, *J* = 7.8 Hz, 2H, Tyr aromatic), 7.10 (s, 1H, Trp aromatic), 7.15 (t, *J* = 7.2 Hz, 1H, Trp aromatic),

7.31 (d, *J* = 8.1 Hz, 1H, Trp aromatic), 7.58 (d, *J* = 7.8 Hz, 1H, Trp aromatic), 8.31 (s, 1H, Indole NH);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.5 (2C, CH_3TBS), 17.1 (Ala *CH*$_3$), 18.1 (quarternary C, *t*Bu (TBS)), 23.1 (Trp CH_2), 25.6 (3C, *t*Bu (TBS)), 28.3 (Boc *t*Bu), 30.7 (NCH_3), 40.3 (β-Tyr CH_2), 46.3 (Ala CH), 49.3 (β-Tyr CH), 51.7 (OCH_3), 56.5 (Trp CH), 79.7 (quarternary C Boc), 110.9, 111.0, 118.5, 119.3 (Trp aromatic), 120.1 (β-Tyr aromatic), 121.9, 122.0 (Trp aromatic), 127.3 (β-Tyr aromatic), 133.3 (Tyr aromatic), 136.1 (aromatic), 154.9 (Boc CO), 155.5 (phenolic), 169.2 (Trp CO), 171.1 (β-Tyr CO), 174.3 (Ala CO);

HRMS (EI): calcd for $C_{36}H_{53}N_4O_7Si$ $[M+Na]^+$: 681.36780, found 681.36692.

Normethyl chondramide C (185)



To a solution of linear depsipeptide **193** (45 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.08 mL, 0.99 mmol) at 0 °C. The resulting mixture was stirred for 2 h at 0 °C; at this point TLC showed the complete consumption of reactant. The solvent was removed in *vacuo* and the residue dried by azeotropic removal of H_2O with toluene. The crude material was used for the next reaction without further purification. To a solution of crude amine salt in dry DMF (50 mL) were added DIEA (0.04 mL, 0.20 mmol), HOBt (20 mg, 0.15 mmol) and TBTU (48 mg, 0.15 mmol) successively at room temperature. The solution was stirred at room temperature for 18 h and then partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate layers were washed successively with 5% aqueous $KHSO_4$ solution, water, half saturated aqueous $NaHCO_3$ solution, brine, dried ($MgSO_4$), filtered and concentrated in *vacuo* to furnish the crude product. The crude product was purified by flash chromatogaphy (1:1 ethyl

acetate/petroleum ether) to yield the pure cyclic depsipeptide (16 mg, 44%) as a colorless solid.

To the above TBS protected cyclic depsipeptide (16 mg, 0.02 mmol) in THF (0.2 mL) was added TBAF containing 5% water (1 M solution in THF, 0.04 mL, 0.04 mmol) at 0 ^{o}C. The solution was stirred for 3 h at 0 ^{o}C. The mixture was concentrated in *vacuo* and the crude material was purified by flash chromatography (7:3 ethyl acetate/petroleum ether) to provide pure normethyl chondramide C (10 mg, 73%) as a colorless powder.

R_f = 0.35 (ethyl acetate);

$[\alpha]^{20}_D$ = +32.1 (c 0.137, CH_2Cl_2);

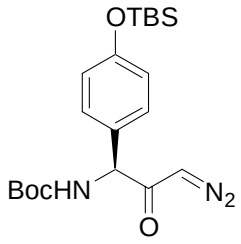
IR (film): υ_{max} = 3360, 2950, 2850, 1710, 1510, 1170 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 3H, *CH_3*CHCH_2O), 1.01 (d, *J* = 6.8 Hz, 3H, Ala Me), 1.16 (d, *J* = 6.5 Hz, 3H, *CH_3*CHCO), 1.63 (s, 3H, *CH_3*C=C), 2.04-2.07 (m, 1H, *CH_2*CHCO), 2.17-2.24 (m, 1H, *CH_2*CHCO), 2.44-2.50 (m, 1H, *CH*CO), 2.58-2.62 (m, 1H, *CH*CH_2O), 2.66-2.88 (m, 2H, β-Tyr CH_2), 3.02 (s, 3H, NMe), 3.12 (dd, *J* = 15.0, 8.5 Hz, 1H, Trp *CH_2*), 3.30 (dd, *J* = 15.0, 7.5 Hz Trp *CH_2*), 3.83 (dd *J* = 10.1, 5.6 Hz, 1H, *CH_2*O), 3.91 (dd *J* = 10.2, 4.7 Hz, 1H, *CH_2*O), 4.65-4.70 (m, 1H, Ala *CH*), 4.93 (d, *J* = 8.0 Hz, olefinic), 5.20-5.26 (m, 1H, β-Tyr *CH*), 5.46 (t, *J* = 8.0 Hz, 1H, Trp CH), 6.43 (d, *J* = 5.8 Hz, 1H, Ala NH), 6.67 (d, *J* = 8.3 Hz, 2H, β-Tyr aromatic), 6.89 (d, *J* = 8.3 Hz, 2H, β-Tyr aromatic), 6.71 (s, 1H, Trp aromatic), 6.92 (s, 1H, β-Tyr NH), 7.08 (t, *J* = 7.3 Hz, 1H, Trp aromatic), 7.15 (t, *J* = 7.5 Hz, 1H, Trp aromatic), 7.30 (d, *J* = 8.1 Hz, 1H, Trp aromatic), 7.54 (d, *J* = 7.8 Hz, 1H, Trp aromatic), 8.26 (s, IndoleNH);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (*CH_3*CHCO), 18.0 (*CH_3*C=C), 18.1 (*CH_3*CHCH_2O), 18.9 (Ala CH_3), 23.9 (Trp CH_2), 30.7 (NCH_3), 31.8 (*CH*CH_2O), 40.4 (*CH*CO), 41.1 (*CH_2*CHCO), 42.5 (CH_2β-Tyr), 45.7 (Ala CH), 49.7 (CH β-Tyr), 56.3 (Trp CH), 69.6 (*CH_2*O), 110.2, 111.2 (Trp aromatic), 115.6 (β-TyrAr_{meta}), 118.4, 119.5, 122.1, 122.5 (Trp aromatic), 125.7 (CH olefinic), 127.0 (β-Tyr C_{ipso}), 127.2 (β-TyrAr_{ortho}), 132.2 (Trp aromatic), 136.2 (olefinic quarternary), 155.6 (C-OH Ar), 169.5 (Trp CO), 170.9 (β-Tyr CO), 174.3 (Ala CO), 175.3 (CH_2CH*CO*);

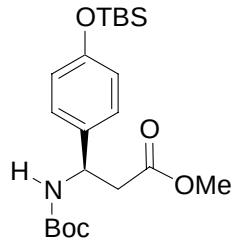
HRMS (EI): calcd for $C_{34}H_{42}N_4O_6$ $[M+Na]^+$: 625.29966, found 625.29888.

(2S–[(*tert*–Butoxycarbonyl)amino](4–{[*tert*-butyl(dimethyl)silyl]oxy}-α-diazoacetylbenzylamine (190)



To a solution of acid **189** (1.00 g, 2.62 mmol) in ether (20 mL) were added triethylamine (0.41 mL, 2.91 mmol), and ethyl chlorocarbonate (0.28 mL, 2.62 mmol) successively at 0 ^{o}C. The resulting reaction mixture was stirred at the same temperature for 1 h. Thereafter, a solution of diazomethane in ether (20 mL, 0.127 M) was added and the mixture was stirred for 12 h at room temperature. The reaction mixture was washed with water and the layers were separated. The organic layer was then dried over anhydrous $MgSO_4$, filtered, and concentrated in *vacuo* to give a yellow colored solid. The crude product was almost pure on TLC, so the crude diazoketone was used for next reaction without any purification.

Methyl (3*R*)-3-[(*tert*-Butoxycarbonyl)amino]-3-(4-{[*tert*-butyl(dimethyl)silyl]oxy}phenyl) propanoate (186)

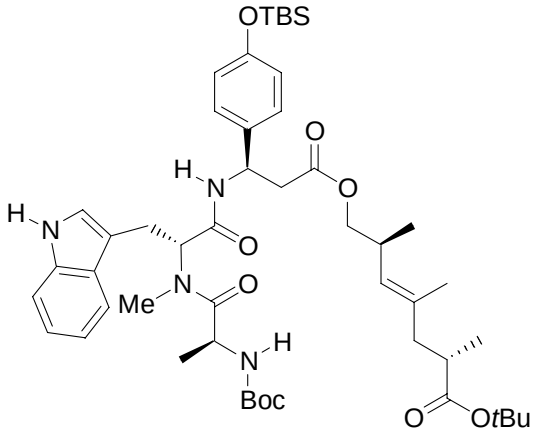


To a solution of diazoketone **190** (400 mg, 0.98 mmol) in absolute methanol (10 mL) was added dropwise a solution of of silver benzoate (23 mg, 0.1 mmol) in triethylamine (0.3 mL, 2.0 mmol) at -30 ^{o}C. The reaction mixture was slowly brought to room temperature in 3 h. The reaction mixture was stirred additionally 1 h at room temperature. The mixture was filtered

through a bed of celite and the filtrate concentrated in *vacuo* to get the crude product. The crude product was purified by flash chromatography (1:4 ethyl acetate/petroleum ether) to provide the pure ester **186** (340 mg, 80%) as a light yellow colored gel.

R_f = 0.40 (1:4 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +36.1 (c 0.21, CH_2Cl_2);
IR (film): υ_{max} = 3360, 2950, 2850, 1710, 1510, 1170 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 6H, CH_3TBS), 0.95 (s, 9H, *t*Bu(TBS)), 1.41 (s, 9H, Boc *t*Bu), 2.76 (dd, *J* = 15.0, 5.9 Hz, 1H, CH_2), 2.83-2.87 (m, 1H, CH_2), 3.59 (s,3H, OCH_3), 5.03 (br s, 1H, CH), 5.34 (br s, 1H, NH), 6.77 (d, *J* = 8.3 Hz, 2H, aromatic), 6.77 (d, *J* = 8.3 Hz, 2H, aromatic), 7.00 (d, *J* = 8.34 Hz, 2H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.5 (2C, CH_3TBS), 18.2 (quarternary C, *t*Bu (TBS)), 25.6 (3C, *t*Bu (TBS)), 28.3 (Boc *t*Bu), 40.9 (CH_2), 51.7 (OCH_3), 120.1, 127.2, 138.1 (aromatic), 155.0 (Boc CO), 155.1 (phenolic);
HRMS (EI): calcd for $C_{21}H_{35}NO_5Si$ $[M+Na]^+$: 432.21767, found 432.21796.

_N_-(*tert*-Butoxycarbonyl)-L-alanyl-_N_-{(1_R_)-3-{[(2_S_,6_S_)-7-*tert*-butoxy-2,4,6-trimethyl-7-oxohept-3-enyl]oxy}-3-oxo-1-[4-(1,1,2,2-tetramethylpropoxy)phenyl]propyl}-_N_-methyl-D-tryptophanamide (193)



To a solution of tripeptide **184** (50 mg, 0.08 mmol) in 1,2-dichloroethane (1 mL) was added trimethyltin hydroxide (68 mg, 0.38 mmol) at room temperature. The mixture was heated at 80

^{o}C for 5 h. After cooling to room temperature, the reaction mixture was treated with 5% aqueous $KHSO_4$ until pH ~3 and extracted with ethyl acetate (3 x 4 mL). The combined ethyl acetate layers were washed with brine (5 mL), dried (Na_2SO_4), filtered, and concentrated in *vacuo* to give the crude acid which was used without further purification.

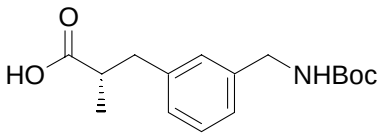
To a solution of crude acid, alcohol component **170** (20 mg, 0.08 mmol), and DMAP (5 mg) in dry CH_2Cl_2 (1 mL) was added a solution of DCC (21 mg, 0.1 mmol) in CH_2Cl_2 (0.2 mL) at 0 ^{o}C. The resulting reaction mixture was stirred for 0.5 hour at 0 ^{o}C and then 12 h at room temperature. The dicyclohexyl urea was filtered off and the precipitate was washed with ether (3 x 4 mL). The filtrate was concentrated in *vacuo* to provide the crude product. The crude product was purified by flash chromatography (1:1 ethyl acetate/petroleum ether) to furnish the pure product **193** (50 mg, 72% over two steps) as a colorless gel.

R_f = 0.44 (1:1 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +10.2 (c 0.50, CH_2Cl_2);
IR (film): υ_{max} = 3336, 2930, 2850, 2300, 1730, 1685, 1515, 1260, 1160 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15 (s, 6H, CH_3TBS), 0.86 (d, *J* = 7.6 Hz, *CH_3*$CHCH_2O$), 0.88 (d, *J* = 7.6 Hz, 3H, Ala CH_3), 0.95 (s, 9H, *t*Bu(TBS)), 1.02 (d, *J* = 6.8 Hz, *CH_3*$CHCO_2t$Bu), 1.39, 1.41 (2s, 18H, Boc *t*Bu, *t*Bu), 1.57 (s, 3H, olefinic CH_3), 1.94 (dd, *J* = 13.6, 7.6 Hz, 1H, *CH_2*$CHCO_2t$Bu), 2.28 (dd, *J* = 13.6, 7.6 Hz, 1H, *CH_2*$CHCO_2t$Bu), 2.41-2.48 (m, 1H, $CHCO_2t$Bu), 2.58-2.64 (m, 1H, *CH*CH_2O), 2.74 (dd, *J* = 15.5, 5.9 Hz, 1H, β-Tyr CH_2), 2.86 (dd, *J* = 16.6, 8.2 Hz, 1H, β-Tyr CH_2), 2.90 (s, 3H, NCH_3), 3.20 (dd, *J* = 15.7, 10.6 Hz, 1H, Trp CH_2), 3.43 (dd, *J* = 15.8, 5.2 Hz, 1H, Trp CH_2), 3.69-3.74 (m, 1H, CH_2O), 3.83 (dd, *J* = 10.1, 6.6 Hz, 1H, CH_2O), 4.36 (qn, *J* = 6.7 Hz, 1H, Ala CH), 4.88 (d, *J* = 9.4 Hz, 1H, CH olefinic), 5.35 (q, *J* = 6.9 Hz, 1H, β-Tyr CH), 5.59 (dd, *J* = 9.9, 5.6 Hz, Trp CH), 6.71 (d, *J* = 8.3 Hz, 2H, β-Tyr aromatic), 6.93 (s, 1H, Trp aromatic), 7.01 (d, *J* = 8.1 Hz, 1H, β-Tyr NH), 7.07-7.09 (m, 2H, β-Tyr aromatic), 7.14 (t, *J* = 7.3 Hz, 1H, Trp aromatic), 7.30 (d, *J* = 8.1 Hz, 1H, Trp aromatic), 7.36 (t, *J* = 8.1 Hz, 1H, Trp aromatic), 7.57 (d, *J* = 7.8 Hz, 1H, Trp aromatic), 8.29 (s, 1H, Indole NH);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.5 (2C, CH_3TBS), 16.7 (*CH_3*$CHCO_2t$Bu), 17.0 (quarternary C, *t*Bu (TBS)), 17.4 (*CH_3*$CHCH_2O$), 18.1 (Ala *CH_3*), 23.2 (Trp CH_2), 25.6 (3C, *t*Bu (TBS)), 28.0, 28.3 (6C, *t*Bu, Boc *t*Bu), 30.8 (NCH_3), 31.9 (*CH*CH_2O), 38.6 (*CH*CO_2tBu), 40.5 (β-Tyr CH_2), 43.8 (*CH_2*$CHCO_2t$Bu), 46.6 (Ala CH), 49.4 (β-Tyr CH), 56.6 (Trp CH),

68.8 (CH_2O), 79.7, 79.8 (quarternary C Boc, *t*Bu), 111.0, 118.5, 119.3 (Trp aromatic), 120.0 (β-Tyr aromatic), 121.9, 122.0 (Trp aromatic), 127.4 (β-Tyr aromatic), 128.2 (aromatic), 129.5 (aromatic), 133.3 (Tyr aromatic), 134.2, 134.8, 136.1 (aromatic), 154.9 (Boc CO), 155.6 (phenolic), 169.2 (Trp CO), 170.7 (β-Tyr CO), 174.3 (Ala CO), 175.7 (CO_2*t*Bu);

HRMS (EI): calcd for $C_{49}H_{74}N_4O_9Si$ $[M+H]^+$: 891.52978, found 891.53001.

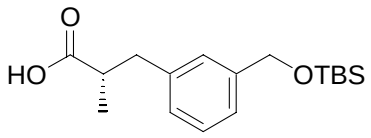
(2*S*)-3-(3-{[(*tert*-Butoxycarbonyl)amino]methyl}phenyl)-2-methylpropanoic acid (194)



To a solution of oxazolidinone **204** (300 mg, 0.66 mmol) in THF (10 mL) were added 30 wt% H_2O_2 (0.28 mL, 2.64 mmol) and 0.4 N lithium hydroxide monohydrate solution (3.3 mL, 1.32 mmol) successively at 0 ^oC. The resulting reaction mixture was stirred for 3 h at 0 ^oC before it was treated with saturated aqueous Na_2SO_3 solution (6 mL) and saturated aqueous $NaHCO_3$ solution (6 mL) at 0 ^oC. The mixture was extracted with dichloromethane (2 x 10 mL) to remove the chiral auxiliary. The aqueous layer was acidified to pH~3 by the addition of 1 N HCl and extracted with ethyl acetate (3 x 15 mL). The combined ethyl acetate layers were dried over Na_2SO_4, filtered and concentrated in *vacuo* to furnish the almost pure amino acid **194**. But due to the presence of amino acid in the dichloromethane layer, both the products from the ethyl acetate and dichloromethane layers were combined and purified using flash chromatography (2:3 ethyl acetate/petroleum ether) to afford the pure acid **194** (155 mg, 80%) as a colorless gel.

R_f = 0.44 (2:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +18.3 (c 0.96, CH_2Cl_2);
IR (film): υ_{max} = 3410, 2965, 2935, 1780, 1700, 1515, 1380 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.1 Hz, 3H, CH_3), 1.48 (s, 9H, *t*Bu), 2.68 (dd, 13.3, 8.0 Hz, 1H, CH_2CH), 2.77 (td, *J* = 14.0, 6.8 Hz, 1H, $CHCH_3$), 3.08 (dd, *J* = 13.4, 6.3 Hz, 1H, CH_2CH), 4.31 (d, *J* = 5.1 Hz, 2H, CH_2N), 4.89 (br s, 1H, NH), 7.10-7.16 (m, 3H, aromatic), 7.28 (d, *J* = 6.8 Hz, 1H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5 (CH_3), 28.4 (3C, *t*Bu), 39.2 (CH_2CH), 41.1 ($CHCH_3$), 44.6 (CH_2NH), 79.8 (Boc quarternary), 125.6, 128.0, 128.7, 139.0, 139.5 (aromatic), 155.3 (Boc C=O), 181.3 (CO_2H);
HRMS (EI): calcd for $C_{16}H_{23}NO_4$ $[M+Na]^+$: 316.15193, found 316.15113.

(2*S*)-3-[3-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)phenyl]-2-methylpropanoic acid (195)



To a solution of crude unprotected hydroxy acid **205** (50 mg, 0.26 mmol) in DMF (3 mL) imidazole (50 mg, 0.78 mmol) and TBDMS-Cl (90 mg, 0.57 mmol) were added successively at room temperature. The reaction mixture was stirred for 12 h at room temperature. H_2O (5 mL) was added to reaction mixture and stirring was continued for 30 min. The resulting mixture was extracted with diethyl ether (3 x 5 mL). The combined ether layers were successively washed with 1 N HCl (5 mL), saturated aq. $NaHCO_3$ solution (5 mL) and then with brine (5 mL). The dried (Na_2SO_4) layer was filtered and concentrated in vacuo to give the crude product. This adduct was dissolved in THF (1 mL) and 1 M K_2CO_3 (1 mL) was added to the solution at room temperarure and the mixture stirred for 45 min at room temperature. The resulting mixture was acidified to pH~3 by adding 1 N HCl. The mixture was extracted with ethyl acetate (3 x 3 mL). The combined ethyl acetate layers were dried on Na_2SO_4, filtered and evaporated to get the crude TBS protected hydroxy acid which was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) providing the pure hydroxy acid **195** (55 mg, 70%) as a colorless gel.

R_f = 0.50 (1:3 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = +22.9 (c 1.18, CH_2Cl_2);

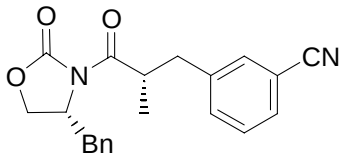
IR (film): υ_{max} = 3740, 3180, 2930, 2850, 1700, 1520, 1170, 840 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 6H, CH_3TBS), 0.95 (s, 9H, *t*Bu(TBS)), 1.17 (d, *J* = 7.1 Hz, 3H, CH*CH*$_3$), 2.66 (dd, *J* = 13.3, 8.2 Hz, 1H, *CH*$_2$CH), 2.71-2.81 (m, 1H, *CH*CO_2H), 3.10 (dd, *J* = 13.4, 6.3 Hz, 1H, *CH*$_2$CH), 4.73 (s, 2H, CH_2OTBS), 7.07 (d, *J* = 7.3 Hz, 1H, aromatic), 7.15 (s, 1H, aromatic), 7.19 (d, *J* = 7.8 Hz, 1H, aromatic), 7.26 (t, *J* = 7.5 Hz, 1H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.3 (2C, CH_3TBS), 16.4 (CH*CH*$_3$), 18.4 (quarternary C, *t*Bu (TBS)), 25.9 (3C, *t*Bu (TBS)), 39.2 (*CH*$_2$CHCO_2), 64.9 (CH_2OTBS), 124.20, 126.7, 127.6, 128.3, 138.9, 141.5 (aromatic), 182.5 (CO_2H);

HRMS (EI): calcd for $C_{17}H_{28}O_3Si$ [M-H]$^-$: 307.17349, found 307.17354.

3-{(2*S*)-3-[(4*R*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-2-methyl-3-oxopropyl}benzonitrile (196)



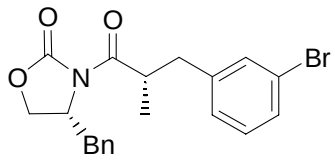
To a solution of crude alkylation product **198** (400 mg, 0.99 mmol) in DMF (4 mL) was added copper(I) cyanide (100 mg, 1.10 mmol) at room temperature. The reaction mixture was heated at 100 ^oC for 12 h. The hot reaction mixture was poured in a solution of $FeCl_3$ (100 mg) in 4 mL of water. The resulting mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and evaporated. The crude product was purified by flash chromatography (1:4 ethylacetate/petroleum ether) to furnish the pure nitrile **196** (200 mg, 57%) as a colorless gel.

R_f = 0.38 (1:4 ethyl acetate/petroleum ether);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3H, CH_3), 2.55-2.58 (m, 1H, benzylic H), 2.60-2.63 (m, 1H, benzylic H), 3.04 (dd, *J* = 13.4, 3.3 Hz, 1H, CH_2Ph), 3.14 (dd, *J* = 13.4, 6.8 Hz, 1H, CH_2Ph), 3.95-4.04 (m, 1H, C*H*CH_3), 4.09 (dd, *J* = 9.1, 2.8 Hz, 1H, CH_2O), 4.15 (t, *J* = 8.5 Hz, 1H, CH_2O), 4.59-4.65 (m, 1H, NCH), 7.00-7.01 (m, 2H, aromatic), 7.17-7.25 (m, 3H, aromatic), 7.34 (t, *J* = 7.7 Hz, 1H, aromatic), 7.45 (d, *J* = 7.6 Hz, 1H, aromatic), 7.50 (d, *J* = 7.6 Hz, 1H, aromatic), 7.53 (s, 1H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5 (CH_3), 37.7 ($PhCH_2$), 39.1 (*C*HCH_3), 39.5 (benzylic), 55.1 (NCH), 66.0 (OCH_2), 112.4 (aromatic), 118.8 (CN), 127.4, 128.9, 129.2, 129.3, 130.3, 132.8, 140.7 (aromatic), 153.0 (NCO_2), 175.6 (CO).

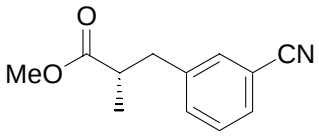
(4*R*)-4-Benzyl-3-{(2*S*)-3-[3-(bromomethyl)phenyl]-2-methylpropanoyl}-1,3-oxazolidin-2-one (198)



To a solution of propionyl oxazolidinone **100** (500 mg, 2.15 mmol) in dry THF (10 mL) was added a 2.0 M solution of NaHDMS in THF (1.60 mL, 3.21 mmol) at -78 ^{o}C. The reaction mixture was stirred for 2 h at -78 ^{o}C. A solution of 3-brombenzyl bromide (1.34 g, 5.36 mmol) in THF (4 mL) was added dropwise at -78 ^{o}C. The reaction mixture was stirred for 6 h at -78 ^{o}C and brought to room temperature by removing the cooling bath. The reaction mixture was treated with saturated aqueous NH_4Cl solution (10 mL) and partially concentrated in *vacuo*. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layers were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography (1:4 ethyl acetate/petroleum ether) to afford the desired alkylated product **198**, which conatained about 15% of the chiral auxiliary **100** (determined by NMR).

R_f = 0.56 (1:3 ethyl acetate/petroleum ether);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8 (CH_3), 37.6 ($PhCH_2$), 39.3 (*C*HCH_3), 39.5 (benzylic), 55.0 (NCH), 65.9 (OCH_2), 122.3, 127.3, 128.0, 128.8, 129.3, 129.9, 132.2, 135.0, 141.5 (aromatic), 152.9 (NCO_2), 176.0 (CO).

Methyl (2*S*)-3-(3-cyanophenyl)-2-methylpropanoate 199

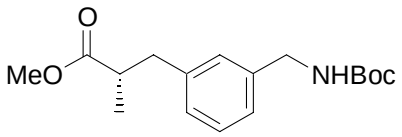


Methylmagnesium bromide (3 M solution in THF, 0.20 mL, 0.55 mmol) was added to pre-cooled (0 ^{o}C) absolute methanol (4.5 mL). After stirring for 20 minutes, this solution was added via cannula to a solution of oxazolidinone **196** in absolute methanol (4.5 mL) at 0 ^{o}C. The resulting reaction mixture was stirred for 6 h at 0 ^{o}C. The reaction mixture was acidified

with 1 N HCl until pH~3 and concentrated in *vacuo* to remove the methanol. The resulting aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to obtain the crude product which was purified using flash chromatography (1:3 ethyl acetate/petroleum ether) to give the pure methylester **199** (30 mg, 52%) as a colorless gel.

R_f = 0.53 (1:3 ethyl acetate/petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.8 Hz, 3H, CH_3), 2.68-2.75 (m, 2H, benzylic H), 2.99-3.06 (m, 1H, C*H*CH_3), 3.62 (s, 3H, OCH_3), 7.35-7.41 (m, 2H, aromatic), 7.45 (s, 1H, aromatic), 7.48-7.51 (m, 1H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9 (CH_3), 39.1 (benzylic), 41.1 (*CH*CH_3), 55.7 (OCH_3), 112.4 (aromaric), 118.8 (CN), 129.2, 130.2, 132.4, 133.5, 140.8 (aromatic), 175.6 (CO_2Me).

Methyl(2*S*)-3-(3-{[(*tert*-butoxycarbonyl)amino]methyl}phenyl)-2-methylpropanoate (200)



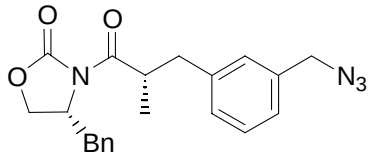
A solution of cyano compound **199** (25 mg, 0.11 mmol) in methanol (0.5 mL) was added to a suspension of 10% Pd/C (10 mg) and formic acid (0.06 mL) in ethanol (0.5 mL). The resulting mixture was shaken under hydrogen atmosphere at around 2 bar pressure for 14 h. The reaction mixture was filtered through a celite bed and the bed washed with ethyl acetate (3 x 1 mL). The combined organic layers were evaporated to give the crude amine formate salt (28 mg). The compound was used for the protection without further purification.

To the crude amine salt in dioxane/H_2O (2:1) (0.6 mL) was added 1 N NaOH (0.16 mL, 0.16 mmol) followed by Boc anhydride (27 mg, 0.121 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature. The reaction mixture was acidified with 5% aq. $KHSO_4$ to pH~3. The resulting mixture was extracted with ethyl acetate (3 x 4 mL). The combined ethyl acetate layers were washed with brine (4 mL), dried (Na_2SO_4),

filtered and concentrated in *vacuo* to give the crude product which was purified using flash chromatography (15:85 ethyl acetate/petroleum ether) to afford the pure amino acid methylester **200** (20 mg, 59% over two steps) as a colorless gel.

R_f = 0.44 (15:85 ethyl acetate/petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 6.8 Hz, 3H, CH_3), 1.45 (s, 9H, *t*Bu), 2.63 (dd, *J* = 13.1, 7.8 Hz, 1H, benzylic H), 2.71 (td, *J* = 14.0, 6.7 Hz, 1H, *CH*CH_3), 3.00 (dd, *J* = 13.1, 6.6 Hz, 1H, benzylic H), 3.63 (s, 3H, OCH_3), 4.27 (d, *J* = 5.6 Hz, 2H, *CH_2*NH), 4.81 (br s, 1H, NH), 7.04 (d, *J* = 7.8 Hz, 1H, aromatic), 7.05 (s, 1H, aromatic), 7.23 (t, *J* = 7.7 Hz, 1H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.7 (CH_3), 28.4 (3C, *t*Bu), 39.6 (benzylic), 41.3 (*CH*CH_3), 44.6 (CH_2NH), 51.6 (OCH_3), 125.5, 127.9, 128.0, 128.6, 139.0, 139.8 (aromatic), 155.8 (Boc CO), 176.5 (CO_2Me).

(4*R*)-3-{(2*S*)-3-[3-(azidomethyl)phenyl]-2-methylpropanoyl}-4-benzyl-1,3-oxazolidin-2-one (202)



To a solution of the mono alkylation product **202** (2.00 g, 4.80 mmol) in ethanol (30 mL) was added sodium azide (650 mg, 10.10 mmol) at room temperature. The reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to room temperature, treated slowly with water and concentrated in *vacuo*. The resulting mixture was dissolved in ethyl acetate (30 mL) and washed with water (2 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in *vacuo* to obtain almost pure azide (1.55 g, 85%) as a pale yellow gel.

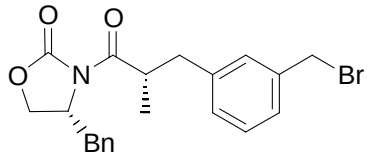
R_f = 0.44 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -19.0 (c 1.07, CH_2Cl_2);
IR (film): υ_{max} = 2975, 2930, 2850, 2098, 1780, 1697, 1100 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.6 Hz, 3H, CH_3), 2.48 (dd, *J* = 13.4, 9.4 Hz, 1H, benzylic H), 2.60 (dd, *J* = 13.1, 7.6 Hz, 1H, CH*CH_2*Ph), 3.01 (dd, *J* = 13.4, 9.4 Hz, 1H, benzylic H), 3.09 (dd, *J* = 13.3, 7.2 Hz, 1H, CH*CH_2*Ph), 4.01-4.10 (m, 3H, C*H*CH_3, CH_2O), 4.22 (s, 2H, CH_2N_3), 4.55-4.61 (m, 1H, NCH), 6.99 (d, *J* = 7.6 Hz, 1H, aromatic), 7.00 (s, 1H, aromatic), 7.09 (d, *J* = 7.1 Hz, 1H, aromatic), 7.17-7.23 (m, 6H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3), 37.6 ($PhCH_2$), 39.5 (*CH*CH_3), 39.6 (benzylic), 54.6 (CH_2N_3), 55.1 (NCH), 65.9 (OCH_2), 126.3, 127.2, 128.8, 129.2, 129.3, 135.1, 135.3, 139.9 (aromatic), 153.0 (NCO_2), 176.2 (CO);

HRMS (EI): calcd for $C_{21}H_{22}N_4O_3Si$ $[M+Na]^+$: 401.15841, found 401.15804.

(4*R*)-4-Benzyl-3-{(2*S*)-3-[3-(bromomethyl)phenyl]-2-methylpropanoyl}-1,3-oxazolidin-2-one (203)



To a solution of diisopropylamine (4.80 mL, 33.5 mmol) in absolute THF (60 mL) was added *n*-BuLi (2.5 M solution in hexane, 13.40 mL, 33.5 mmol) at 0 ^oC. The resulting mixture was stirred for 20 min at 0 ^oC and cooled to -78 ^oC. A solution of propionyl oxazolidinone **100** (6.00 g, 25.75 mmol) in absolute THF (12 mL) was added dropwise to the above solution of LDA. The reaction mixture was stirred for 2 h at -78 ^oC. A solution of α,α'-dibromo m-xylene **104** (17.0 g, 64.4 mmol) in absolute THF (20 mL) was added dropwise to the reaction mixture at -78 ^oC. The resulting reaction mixture was stirred for 4 h at -78 ^oC and slowly warmed to room temperature in 4 h. The reaction mixture was treated with saturated aqueous NH_4Cl solution (30 mL) and then the mixture was partially concentrated in *vacuo*. The resulting aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined ethyl acetate layers were washed with saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in *vacuo* to give the crude product. Most of the excess α,α'-dibromo m-xylene was removed by dissolving the crude product in hexane (50 mL). The remaining

crude product was purified using flash chromatography (1:3 ethyl acetate/petroleum ether) to give the pure mono alkylation product **203** (6.20 g, 58%) as a colorless gel.

R_f = 0.50 (1:3 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = -16.8 (c 1.23, CH_2Cl_2);

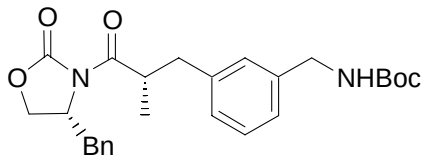
IR (film): υ_{max} = 2975, 2905, 2850, 1780, 1697, 1385, 1200 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3H, CH_3), 2.48 (dd, *J* = 13.7, 9.6 Hz, 1H, benzylic H), 2.60 (dd, *J* = 13.3, 7.5 Hz, 1H, CH_2Ph), 2.99 (dd, *J* = 13.4, 3.3 Hz, 1H, benzylic H), 3.06 (dd, *J* = 13.3, 7.5 Hz, 1H, CH_2Ph), 4.02 (dd, *J* = 9.1, 3.0 Hz, 1H, CH_2O), 4.05-4.11 (m, 2H, C*H*CH_3, CH_2O), 4.39 (s, 2H, CH_2Br), 4.55-4.61 (m, 1H, NCH), 6.99 (d, *J* = 7.6 Hz, 1H, aromatic), 7.00 (s, 1H, aromatic), 7.14-7.20 (m, 6H, aromatic), 7.24 (s, 1H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.8 (CH_3), 33.5 (CH_2Br), 37.7 ($PhCH_2$), 39.4 (*CH*CH_3), 39.6 (benzylic), 55.1 (NCH), 65.9 (OCH_2), 127.2, 127.3, 128.6, 129.3, 129.5, 129.8, 129.9, 135.1, 137.8, 139.8 (aromatic), 153.0 (NCO_2), 176.3 (CO);

HRMS (EI): calcd for $C_{21}H_{22}BrNOSi$ $[M+Na]^+$: 438.06753, found 438.06839.

tert-Butyl 3-{(2*S*)-3-[(4*R*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]-2–methyl–3-oxopropyl} benzylcarbamate (204)

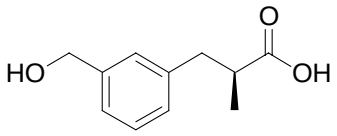


A solution of azide **202** (400 mg, 1.06 mmol) in ethanol (5 mL) was added to 10% Pd/C (40 mg) in a hydrogenation vessel. The reaction mixture was shaken under hydrogen atmosphere at around 2 bar pressure for 20 h. The reaction mixture was filtered through a bed of celite and the celite bed was washed with ethyl acetate (5 mL). The filtrate was concentrated in *vacuo* to get the crude amine which was used for the protection reaction without further purification. To a solution of crude amine in dioxane/H_2O (2:1) (6 mL) was added 1 N NaOH (2.2 mL, 2.2 mmol) followed by the addition of Boc-anhydride (272 mg, 1.25 mmol) at room temperature.

The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was acidified to pH~3 using 5% aq. $KHSO_4$ and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined ethyl acetate layers were washed with brine (15 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude product which was purified by flash chromatography (1:3 ethyl acetate/petroleum ether) providing the pure product **204** (330 mg, 65%) as a colorless gel.

R_f = 0.53 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = -15.9 (c 0.97, CH_2Cl_2);
IR (film): υ_{max} = 3410, 2965, 2935, 2850, 1780, 1700, 1515, 1380, 1240 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 6.8 Hz, 3H, CH_3), 1.42 (s, 9H, *t*Bu), 2.55 (dd, *J* = 13.5, 9.5 Hz, 1H, benzylic H), 2.62 (dd, *J* = 13.3, 8.0 Hz, 1H, CH_2Ph), 3.04-3.08 (m, 1H, benzylic H), 3.08-3.14 (m, 1H, CH_2Ph), 4.03-4.10 (m, 2H, C*H*CH_3, CH_2O), 4.15 (t, *J* = 8.5 Hz, 1H, CH_2O), 4.24 (d, *J* = 5.3 Hz, 2H, *CH_2*NH), 4.61-4.67 (m, 1H, NCH), 4.76 (br s, 1H, NH), 7.03 (d, *J* = 6.3 Hz, 1H, aromatic), 7.04 (s, 1H, aromatic), 7.11 (d, *J* = 7.3 Hz, 1H, aromatic), 7.15-7.17 (m, 2H, aromatic), 7.21-7.29 (m, 4H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6 (CH_3), 28.4 (3C, *t*Bu), 37.7 ($PhCH_2$), 39.5 (benzylic), 39.7 (*CH*CH_3), 44.6 (CH_2NH), 55.1 (NCH), 65.9 (OCH_2), 79.4 (Boc quarternary), 125.6, 127.3, 128.3, 128.5, 128.6, 128.9, 129.4, 135.1, 138.9, 139.6 (aromatic), 153.0 (NCO_2), 155.8 (Boc CO), 176.5 (CO);
HRMS (EI): calcd for $C_{26}H_{32}N_2O_5Si$ $[M+Na]^+$: 475.22034, found 475.22056.

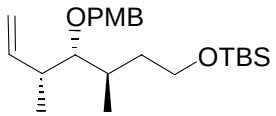
(2*S*)-3-[3-(Hydroxymethyl)phenyl]-2-methylpropanoic acid (205)



To a solution of monoalkylation product **203** (200mg, 0.48 mmol) in THF (10 mL) were added 30 wt% H_2O_2 (0.33 mL, 2.88 mmol) and 0.4 N lithium hydroxide monohydrate solution (3.60 mL, 1.44 mmol) successively at 0 ^oC. The resulting reaction mixture was stirred for 7 h at 0

^{o}C. The reaction mixture was then treated with saturated aqueous Na_2SO_3 solution (8 mL) and saturated aqueous $NaHCO_3$ solution (8 mL) at 0 ^{o}C. The mixture was extracted with dichloromethane (2 x 10 mL) to remove the chiral auxiliary. The aqueous layer acidified to pH~2 by the addition of 6 N HCl. The aqueous layer was carefully extracted with ethyl acetate (4 x 15 mL). The combined ethyl acetate layers were dried over Na_2SO_4, filtered and concentrated in *vacuo* to afford the crude hydroxy acid **205** (65 mg, 70%) as a colorless oil. The crude mixture was used further without any purification.

tert-Butyl({(3*R*,4*R*,5*R*)-4-[(4-methoxybenzyl)oxy]-3,5-dimethylhept-6-enyl}oxy)dimethylsilane (213)



To a solution of methyltriphenylphosphonium iodide (1.23 g, 3.05 mmol) in THF (60 mL) was added a 2.5 M solution of *n*-BuLi (1.50 mL, 3.56 mmol) in hexane at 0 ^{o}C. The resulting mixture was stirred for 30 min at 0 ^{o}C and a solution of aldehyde **232** (800 mg, 2.03 mmol) in THF (6 mL) was added at 0 ^{o}C. The mixture was stirred for further 2 h at 0 ^{o}C. The reaction mixture was treated with pH 7 phosphate buffer (30 mL). The resulting aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash chromatography (5:95 ethyl acetate/petroleumether) to obtain the pure alkene **213** (590 mg, 74%) as a colorless gel.

R_f = 0.55 (5:95 ethyl acetate/petroleum ether);

$[\alpha]^{25}_D$ = +5.24 (c 1.01, CH_2Cl_2);

IR (film): ν_{max} = 3070, 2950, 2860, 1620, 1515, 1460, 1250, 1170 cm^{-1};

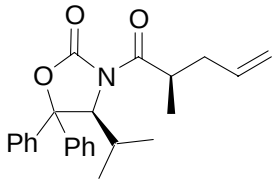
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $Si(CH_3)_3$), 0.88 (s, 9H; *t*Bu), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3), 1.07 (d, *J* = 6.8 Hz, 3H, $CH_3CHCH{=}CH_2$), 1.32-1.41 (m, 1H, $CHCH_2CH_2OTBS$), 1.79-1.92 (m, 2H, CH_2CH_2OTBS), 2.43-2.51 (m, 1H, $CHCH{=}CH_2$), 3.06

(dd, *J* = 6.6, 4.6 Hz, 1H, CHOPMB), 3.56-3.62 (m, 1H, CH_2OTBS), 3.65-3.71 (m, 1H, *CH*$_2$OTBS), 3.79 (s, 3H, OCH_3), 4.49 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 4.52 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 4.96 (d, *J* = 10.4 Hz, 1H, olefinic CH_2 cis), 5.04 (d, *J* = 17.2 Hz, 1H, olefinic CH_2 trans), 5.81 (ddd, *J* = 17.3, 10.2, 8.1 Hz, 1H, CH olefinic), 6.86 (d, *J* = 8.6 Hz, 2H, aromatic), 7.27 (d, *J* = 8.8 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.31, -5.28 (2C, $Si(CH_3)_3$), 15.9 (*CH*$_3$CHCH$_2$), 17.2 (*CH*$_3$CHCH=CH$_2$), 18.3 (TBS quarternary), 26.0 (3C, *t*Bu), 32.5 (*CH*CH_2OH), 34.5 (*CH*$_2$CH$_2$OTBS), 40.9 (*CH*CH_2CH_2OTBS), 55.3 (OCH_3), 61.6 (CH_2*CH*$_2$OTBS), 74.5 (CH_2Ph), 88.0 (CHOPMB), 113.6 (aromatic), 113.8 (olefin CH_2), 129.1 (aromatic) 131.3 (C_{ipso} aromatic), 142.5 (olefin CH), 159.0 ppm (phenolic);

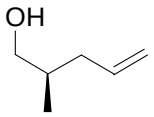
HRMS (EI): calcd for $C_{23}H_{40}O_3Si$ $[M+Na]^+$: 415.26389, found 415.26386.

(4*S*)-4-Isopropyl-3-[(2*R*)-2-methylpent-4-enoyl]-5,5-diphenyl-1,3-oxazolidin-2-one (217)



To a solution of auxiliary **216** (14.0 g, 41.54 mmol) in dry THF (90 mL) was added a 2.0 M solution of NaHDMS (25 mL, 50.0 mmol) at -78 ^oC. The reaction mixture was stirred for 2 h at -78 ^oC. Allylbromide (20.0 mL, 207.7 mmol) was added dropwise to the above mixture over 20 min at -78 ^oC. The resulting reaction mixture was stirred for 2 h at -78 ^oC and slowly brought to room temperature by switching off the cooling machine and stirred overnight. The reaction mixture was treated with saturated aqueous NH_4Cl solution (50 mL) and diluted with diethyl ether (100 mL). The layers were separated and the aqueous layer extracted with ether (3 x 50 mL). The combined ether layers were washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried (Na_2SO_4), filtered and evaporated to obtain the almost pure alkylated product as a pale yellow solid which was used for the next step without purification.

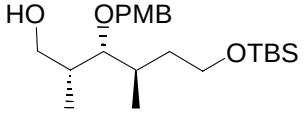
(2*R*)-2-Methylpent-4-en-1-ol (218)



To a solution of the alkylation product **217** (41.54 mmol) in THF (800 mL) was added a solution of $NaBH_4$ (9.40 g, 249.3 mmol) in H_2O (200 mL) at 0 °C. The resulting reaction mixture was stirred for 12 h at room temperature. The reaction mixture was treated with saturated aqueous NH_4Cl solution (100 mL) at 0 °C and stirred for 1 h at 0 °C. The layers were separated and the aqueous layer was extracted with ether (2 x 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (200 mL), brine (200 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo* to give the crude alcohol. As the chiral auxiliary is insoluble in ether, the chiral auxiliary was removed by filtration and the remaining crude product purified by flash chromatography (1:1 ether/petroleum ether) to deliver the pure alcohol **218** (3.5 g, 90% two steps) as a light yellow colored oil.

R_f = 0.45 (1:1 ether/petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3H, CH_3), 1.65-1.77 (m, 1H, *CH*CH_3), 1.91 (ddd, *J* = 14.1, 7.3, 7.1 Hz, 1H, CH*CH_2*), 2.12-2.19 (m, 1H, CH*CH_2*), 3.42 (dd, *J* = 10.5, 5.4 Hz, 1H, CH_2O), 3.49 (dd, *J* = 10.8, 5.4 Hz, 1H, CH_2O), 4.99 (d, *J* = 9.1 Hz, 1H, cis H), 5.02 (d, *J* = 15.4 Hz, 1H, trans H), 5.73 (CH olefinic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3 (CH_3), 35.5 (CH*CH_2*), 37.8 (*C*HCH_3), 67.8 (OCH_2), 116.0 (olefinic CH_2), 136.9 (olefinic CH).

(2*S*,3*S*,4*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-[(4-methoxybenzyl)oxy]-2,4-dimethylhexan-1-ol (223)



To a solution of acetal **224** (1.20 g, 3.04 mmol) in CH_2Cl_2 (30 mL) was added a 1 M solution of DIBAL-H in hexane (9.10 mL, 9.10 mmol) at 0 ^oC. The reaction mixture was stirred for 4 h at 0 ^oC and then treated with saturated sodium potassium tartarate solution (20 mL) at 0 ^oC. The solution was stirred vigorously for 1 h at room temperature and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with water (20 mL) and then with brine. The organic layer was dried on Na_2SO_4, filtered and concentrated in *vacuo* to give the crude product which on purification by flash chromatography (1:3 ethyl acetate/petroleum ether) led the pure alcohol **223** (940 mg, 78%) as a colorless oil.

R_f = 0.40 (1:3 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = -4.7 (c 1.08, CH_2Cl_2);

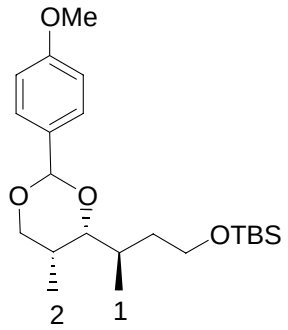
IR (film): ν_{max} = 3430, 2935, 2850, 1620, 1515, 1460, 1250, 1090 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = -0.03 (s, 6H, $Si(CH_3)_3$), 0.82 (s, 9H; *t*Bu), 0.86 (d, *J* = 6.8 Hz, 6H, $2CH_3$), 1.22-1.33 (m, 1H, *CH*CH_2CH_2), 1.78-1.89 (m, 2H, *CH*$_2$$CH_2$OTBS), 2.13 (br s, 1H, *CH*CH_2OH), 3.25 (dd, *J* = 6.4, 3.7 Hz, 1H, CHOPMB), 3.45-3.51 (m, 2H, CH_2OTBS), 3.55-3.59 (m, 1H, *CH*$_2$OH), 3.62-3.66 (m, 1H, *CH*$_2$OH), 3.70 (s, 3H, OCH_3), 4.40 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 4.48 (d, *J* = 10.9 Hz, 1H, CH_2Ph), 6.78 (d, *J* = 8.6 Hz, 2H, aromatic), 7.19 (d, *J* = 8.6 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.39, -5.34 (2C, $Si(CH_3)_3$), 11.5 (CH_3(1)), 16.6 (CH_3(2)), 18.2 (TBS quarternary), 25.9 (3C, *t*Bu), 32.1 (*CH*CH_2OH), 35.5 (*CH*$_2$$CH_2$OTBS), 37.5 (*CH*$CH_2CH_2$OTBS), 55.1 ($OCH_3$), 61.5 ($CH_2$*CH*$_2$OTBS), 66.3 ($CH_2$OH), 73.4 ($CH_2$Ph), 84.2 (CHOPMB), 113.6, 129.1 (aromatic) 131.0 (C_{ipso} aromatic), 159.0 (phenolic);

HRMS (EI): calcd for $C_{22}H_{40}O_4Si$ $[M+Na]^+$: 419.25881, found 419.25891.

tert-Butyl({(3*R*)-3-[(4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]butyl}oxy) dimethylsilane (224)



To a solution of compound **231** (1.10 g, 3.92 mmol) in DMF (40 mL) was added imidazole (670 mg, 9.80 mmol) at room temperature followed by the addition of TBDMS-Cl (770 mg, 5.10 mmol). After being stirred overnight, the mixture was diluted with water (40 mL). The resultant mixture was stirred for 5 min. The mixture was extracted with diethylether (3 x 50 mL). The combined ether layers washed with 1 N HCl (40 mL), sat.$NaHCO_3$ (40 mL) and then with brine (40 mL). The organic layer dried over Na_2SO_4, filtered and concentrated in vacuo to get the crude product. The crude product was purified by flash chromatography (5:95 ethyl acetate/petroleum ether) to furnish the pure product **224** (1.30 g, 84%) as colorless oil.

R_f = 0.45 (5:95 ethyl acetate/petroleum ether);

$[\alpha]^{20}_D$ = +20.5 (c 1.00, CH_2Cl_2);

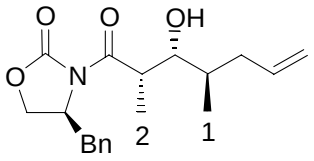
IR (film): ν_{max} = 2950, 2850, 1620, 1515, 1250, 1100 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 6H, $Si(CH_3)_3$), 0.86 (d, *J* = 6.6 Hz, 3H, CH_3(1)), 0.87 (s, 9H, *t*Bu), 1.13 (d, *J* = 7.1 Hz, 3H, CH_3(2)), 1.32 (td, *J* = 14.0, 6.7 Hz,1H, CH_2CH_2OTBS), 1.66 (qd, *J* = 6.8, 1.8 Hz, 1H, $CHCH_2O$), 1.71-1.80 (m, 1H, $CHCH_2CH_2$), 1.97-2.05 (m, 1H, CH_2CH_2OTBS), 3.48 (dd, *J* = 10.0, 1.9 Hz, 1H, CHO), 3.68 (t, *J* = 7.2 Hz, 2H, CH_2OTBS), 3.79 (s, 3H, OCH_3), 3.99-4.05 (m, 2H, CH_2O), 5.41 (s, 1H, CHO_2), 6.87 (d, *J* = 8.8 Hz, 2H, aromatic), 7.41 (d, *J* = 8.6 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = -5.28 (2C, $Si(CH_3)_3$), 10.6 (CH_3(2)), 14.7 (CH_3(1)), 18.3 (TBS quaternary), 26.0 (3C, *t*Bu), 30.0 ($CHCH_2O$), 31.6 ($CHCH_2CH_2OH$), 36.2

(*CH*$_2$CH$_2$OTBS), 55.3 (OCH$_3$), 61.8 (CH$_2$*CH*$_2$OTBS), 74.0 (CH$_2$O), 84.2 (CHO), 101.4 (CHPh), 113.5, 127.3 (aromatic) 131.6 (C_{ipso} aromatic), 159.7 (phenolic);
HRMS (EI): calcd for $C_{22}H_{38}O_4Si$ $[M+H]^+$: 395.26121, found 395.24154.

(4*S*)-4-Benzyl-3-[(2*S*,3*R*,4*R*)-3-hydroxy-2,4-dimethylhept-6-enoyl]-1,3-oxazolidin-2-one (226)



A solution of oxalyl chloride (2.50 mL, 28.75 mmol) in dry CH_2Cl_2 (55 mL) was cooled to -78 ^oC and a solution of DMSO (4.10 mL, 57.5 mmol) in dry CH_2Cl_2 (8 mL) was added dropwise to the above cooled solution. After 5 min, a solution of alcohol **218** (2.60 g, 26.00 mmol) in dry CH_2Cl_2 was added dropwise to the above solution at -78 ^oC. Stirring was continued for 30 min at -78 ^oC and Et_3N (13.8 mL, 130 mmol) was added over 5 min, during which the solution became a colorless heterogeneous mixture. At this point the cooling machine was switched off and the reaction mixture slowly allowed to reach room temperature over 2.5 h. Water (50 mL) was added to the reaction mixture and the layers were separated. The dichloromethane layer was washed with 1 N HCl (4 x 20 mL), saturated $NaHCO_3$ solution (20 mL), then with brine (30 mL), and finally dried (Na_2SO_4). After filtration, the solution was partially concentrated by keeping the water bath at 50 ^oC and pressure at 750 mbar until it became about 10 mL. This solution was used for the aldol reaction without purification by taking the yield as 100%.

To a solution of chiral reagent **ent-100** (3.60 g, 15.5 mmol) in CH_2Cl_2 (40 mL) was added dropwise 1 M solution of *n*-butylboron triflate (18.6 mL, 18.6 mmol) at 0 ^oC, followed by NEt_3 (2.8 mL, 28.1 mmol). The resulting solution was cooled to -78 ^oC in 20-25 min. After being stirred for 5 min at -78 ^oC, the crude solution of aldehyde was added to the reaction mixture. The resulting reaction mixture was stirred for 3 h at -78 ^oC and then gradually warmed to room temperature over a period of 2 h, and stirred at room temperature for 1.5 h. The reaction mixture was treated with pH 7 aqueous phosphate buffer (30 mL) followed by a 2:1 mixture of MeOH and 30 wt% aqueous H_2O_2 (60 mL). The reaction mixture was stirred

for 1 h. The reaction mixture was partially concentrated in vacuo and the resultant was extracted with diethyl ether (3 x 50 mL). The combined ether layers were washed with saturated $NaHCO_3$ solution (40 mL), brine, dried (Na_2SO_4), filtered and concentrated in *vacuo* to get the crude aldol product. The crude product was purified by flash chromatography (5:95 ethyl acetate/dichloromethane) to afford the pure aldol product **226** (4.0 g, 78%) as a colorless gel.

R_f = 0.33 (5:95 ethyl acetate/dichloromethane);

$[\alpha]^{20}_D$ = +50.3 (c 1.10, CH_2Cl_2);

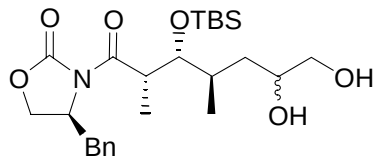
IR (film): ν_{max} = 3510, 2970, 2850, 1780, 1690, 1385, 1210 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.8 Hz, 3H, CH_3(1)), 1.26 (d, *J* = 7.1 Hz, 3H, CH_3(2)), 1.65-1.75 (m, 1H, *CH*CH_2CH_2), 1.93-2.01 (m, 1H, *CH_2*$CH{=}CH_2$), 2.52-2.56 (m, 1H, *CH_2*$CH{=}CH_2$), 2.81 (dd, *J* = 13.4, 9.4 Hz, 1H, $PhCH_2$), 3.09 (d, *J* = 3.0 Hz, 1H, OH), 3.27 (dd, *J* = 13.4, 3.0 Hz, 1H, $PhCH_2$), 3.65 (d, *J* = 9.1 Hz, 1H, *CH*OH), 3.96 (qd, *J* = 7.0, 1.9 Hz, COCH), 4.20 (dd, *J* = 9.2, 2.9 Hz, 1H, CH_2O), 4.24 (m, 1H, CH_2O), 4.69 (m, 1H, CHN), 5.04 (d, *J* = 9.9 Hz, CH_2 olefinic cis), 5.07 (d, *J* = 16.9 Hz, CH_2 olefinic trans), 5.78-5.88 (m, 1H, CH olefinic), 7.22 (d, *J* = 7.1 Hz, 2H, aromatic), 7.30 (d, *J* = 7.1 Hz, 1H, aromatic), 7.35 (t, *J* = 7.2 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.5 (CH_3(2)), 15.1 (CH_3(1)), 35.4 (*CH*CH_2), 37.3 ($CH_2CH{=}CH_2$), 37.7 ($PhCH_2$), 39.4 (CO*CH*), 55.1 (CHN), 66.1 (CH_2O), 74.6 (CHOH), 116.4 (CH_2 olefin), 127.4, 128.9, 129.4, 135.0 (aromatic), 136.9 (CH olefin), 152.8 (NCO_2), 177.9 (CO);

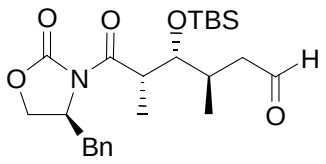
HRMS (EI): calcd for $C_{19}H_{25}NO_4$ $[M+Na]^+$: 354.16758, found 354.16775.

(4*S*)-4-Benzyl-3-((2*S*,3*R*,4*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-6,7-dihydroxy-2,4-dimethylheptanoyl)-1,3-oxazolidin-2-one



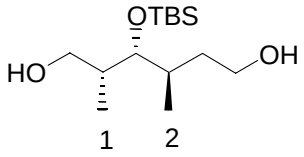
To a solution of protected aldol product **228** (4.50 g, 10.00 mmol), NMO (2.70 g, 20.00 mmol) in a 8:1 mixture of THF and *tert*-BuOH (90 mL) was added a pre prepared catalytic solution of osmium tetroxide in water (20 mL, 0.8 mmol) (prepared by dissolving $K_2OsO_4.2H_2O$ (240 mg, 0.8 mmol) in water (20 mL) to make the whole solution to 0.04 M). After being stirred for 12 h, the reaction mixture was treated with 10% aqueous $Na_2S_2O_3$ solution (20 mL). The resultant mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo* to give the crude diol which was used for the next step without further purification.

(3*R*,4*R*,5*S*)-6-[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]-4-{[*tert*-butyl(dimethyl)silyl]oxy}-3,5-dimethyl-6-oxohexanal



To a solution of the above dihydroxylated product in a 9:1 mixture of THF and H_2O (40 mL) was added $NaIO_4$ (6.40 g, 30.00 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with water (30 mL) and extracted with ether (3 x 40 mL). The combined ether layers were washed with water (40 mL) and then with brine (40 mL). The ether layer was dried over Na_2SO_4, filtered and concentrated in *vacuo* to furnish the crude aldehyde which was used for the reduction step without further purification.

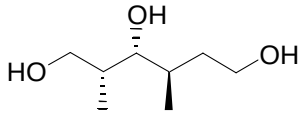
(2*R*,3*R*,4*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,4-dimethylhexane-1,6-diol (229)



To a solution of the crude aldehyde in THF (200 mL) was added a solution of $NaBH_4$ (2.62 g, 70.0 mmol) in H_2O (50 mL) at 0 ^oC. After being stirred over night at room temperature, the reaction was quenched by the addition of saturated NH_4Cl solution (50 mL). The resulting layers were separated and the aqueous layer extracted with ethyl acetate (3 x 75 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in *vacuo* to obtain the crude diol which was purified using flash chromatography (1:4 ethyl acetate/dicloromethane) leading to the pure diol **229** (2.20 g, 80% yield) as colorless oil.

R_f = 0.33 (1:4 ethyl acetate/dichloromethane);
$[\alpha]^{20}_D$ = -7.10 (c 1.06, CH_2Cl_2);
IR (film): ν_{max} = 3340, 2925, 2850, 1770, 1460, 835 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H, $Si(CH_3)_2$), 0.88 (d, *J* = 7.1 Hz, 3H, CH_3(1)), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3(2)), 1.35-1.43 (m, 1H, *CH*CH_2CH_2), 1.73-1.92 (m, 3H, CH*CH_2*CH_2, *CH*CH_2OH), 2.06 (br s, 1H, OH), 3.47-3.66 (m, 4H, CH_2OH, CH_2*CH_2*OH), 3.71-3.77 (m, 1H, CHOTBS);
^{13}C NMR (100 MHz, $CDCl_3$): δ = -4.24, -3.95 (2C, $Si(CH_3)_3$), 12.6 (CH_3(1)), 17.4 (CH_3(2)), 18.4 (TBS quaternary), 26.0 (3C, *t*Bu), 34.1 (*CH*CH_2CH_2), 35.5 (*CH_2*CH_2OH), 38.9 (*CH*CH_2OH), 61.1 (CH_2*CH_2*OH), 66.2 (CH_2OH), 78.1 (CHOTBS);
HRMS (EI): calcd for $C_{14}H_{32}O_3Si$ $[M+Na]^+$: 299.20129, found 299.20110.

(2*R*,3*R*,4*R*)-2,4-Dimethylhexane-1,3,6-triol (230)

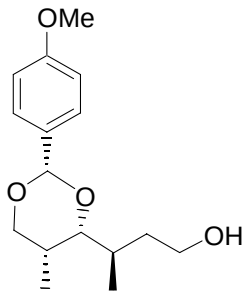


To a solution of diol **229** (2.10 g, 7.60 mmol) in THF (35 mL) was added a 1 M solution of TBAF in THF (19.0 mL, 19.0 mmol) at room temperature. The resulting reaction mixture was stirred for 7 h at room temperature. The reaction mixture was evaporated to give the crude

product. The crude product was purified by flash chromatography (7:93 methanol/dichloromethane) to afford the pure triol **230** (1.01 g, 82%) as colorless oil.

R_f = 0.23 (7:93 methanol/dichloromethane);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, *J* = 6.6 Hz, 3H, CH_3(1)), 0.93 (d, *J* = 6.8 Hz, 3H, CH_3(2)), 1.40-1.45 (m, 1H, *C*$H_2$$CH_2$OTBS), 1.57-1.65 (m, 1H, *C*$H_2$$CH_2$OTBS), 1.70-1.80 (m, 2H, *C*H$CH_2$$CH_2$OH, *C*H$CH_2$OH), 3.42-3.46 (m, 1H, *C*HOH), 3.54-3.76 (m, 4H, CH_2OH, CH_2*C*H_2OH), 4.41 (br s, 1H, OH);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.7 (CH_3(2)), 17.5 (CH_3(1)), 35.0 (*C*H$CH_2$$CH_2$), 35.9 (*C*H$CH_2$OH), 37.6 (*C*$H_2$$CH_2$OH), 61.0 ($CH_2$*C*$H_2$OH), 67.8 ($CH_2$OH), 78.3 (CHOH);

(3*R*)-3-[(4*S*,5*S*)-2-(4-Methoxyphenyl)-5-methyl-1,3-dioxan-4-yl]butan-1-ol (231)

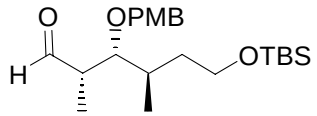


To a solution of triol **230** (1.00 g, 6.16 mmol) in CH_2Cl_2 (60 mL) was added *p*-methoxybenzaldehyde dimethyl acetal (1.26 mL, 6.78 mmol) at room temperature followed by the addition of PPTS (154 mg, 0.62 mmol). The resulting mixture was stirred for 2 h at room temperature. The reaction mixture was concentrated in *vacuo* and purified by flash chromatography (1:3 ethyl acetate/petroleum ether) to get the pure product **231** (1.20 g, 72%) as a colorless oil.

R_f = 0.45 (1:3 ethyl acetate/petroleum ether);
$[\alpha]^{20}_D$ = +21.6 (c 1.09, CH_2Cl_2);
IR (film): ν_{max} = 3420, 2960, 2850, 1620, 1515, 1450, 1030 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3H, CH_3(1)), 1.16 (d, *J* = 7.1 Hz, 3H, CH_3(2)), 1.46 (dt, *J* = 19.1, 6.1 Hz, 1H, *CH*$_2$$CH_2OH$), 1.64-1.70 (m, 1H, *CH*CH_2CH_2OH), 1.75-1.80 (m, 1H, *CH*CH_2O), 2.09 (br s, 1H, OH), 3.51 (dd, *J* = 10.0, 2.2 Hz, 1H, CHO), 3.55-3.61 (m, 1H, *CH*$_2$OH), 3.64-3.70 (m, 1H, *CH*$_2$OH), 3.78 (s, 3H, OCH_3), 4.02 (s, 2H, CH_2O), 5.43 (s, 1H, CHPh), 6.87 (d, *J* = 8.8 Hz, 2H, aromatic), 7.40 (d, *J* = 8.8 Hz, 2H, aromatic);
^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8 (CH_3(1)), 15.5 (CH_3(2)), 30.1 (*CH*CH_2O), 32.3 (*CH*CH_2CH_2OH), 37.4 (*CH*$_2$$CH_2OH$), 55.2 ($OCH_3$), 61.4 ($CH_2$*CH*$_2$OH), 73.9 ($CH_2OH$), 84.2 (CHO), 101.9 (CHPh), 113.6, 127.3 (aromatic) 131.1 (C_{ipso} aromatic), 159.9 (phenolic);
HRMS (EI): calcd for $C_{16}H_{24}O_4$ $[M+Na]^+$: 303.15668, found 303.15653.

(2*R*,3*S*,4*R*)-6-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-[(4-methoxybenzyl)oxy]-2,4-dimethylhexanal (232)



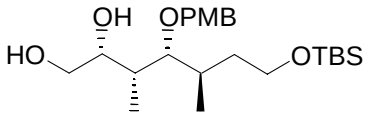
A solution of oxalyl chloride (0.23 mL, 2.52 mmol) in CH_2Cl_2 (5 mL) was cooled to -78 °C. To this solution, a solution of DMSO (0.37 mL, 5.04 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise. After stirring for 15 min, a solution of alcohol **222** (900 mg, 2.27 mmol) was added drop wise to the above mixture at -78 °C. After the reaction mixture was stirred for 1 h, triethylamine (1.3 mL, 9.43 mmol) was added dropwise at -78 °C and the mixture allowed to reach room temperature over the course of 4 h. Then the mixture was diluted with water (4 mL) and CH_2Cl_2 (4 mL). The organic layer was washed with 1 N HCl (5 mL), saturated aqueous $NaHCO_3$ solution (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The crude product was filtered through a short pad of silica gel (1:3 ethyl acetate/petroleum ether) to afford aldehyde (800 mg, 89%) as colorless oil.

R_f = 0.40 (1:3 ethyl acetate/petroleum ether);
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H, $Si(CH_3)_3$), 0.86 (s, 9H, *t*Bu), 0.88 (d, *J* = 6.8 Hz, 3H, CH_3), 1.16 (d, *J* = 6.8 Hz, *CH*$_3$CHCHO), 1.78-1.97 (m, 3H, *CH*CH_2CH_2,

CH$_2$CH$_2$OTBS), 2.56-2.62 (m, 1H, *CH*CHO), 3.59-3.72 (m, 3H, CHOPMB, *CH*$_2$OTBS), 3.79 (s, 3H, OCH$_3$), 4.37 (d, *J* = 10.9 Hz, 1H, CH$_2$Ph), 4.41 (d, *J* = 10.9 Hz, 1H, CH$_2$Ph), 6.85 (d, *J* = 8.6 Hz, 2H, aromatic), 7.20 (d, *J* = 8.6 Hz, 2H, aromatic), 9.76 (s, 1H, CHO);

^{13}C NMR (100 MHz, CDCl$_3$): δ = -5.35, -5.30 (2C, Si(CH$_3$)$_3$), 8.4 (*CH*$_3$CHCHO), 16.3 (CH$_3$), 18.3 (TBS quarternary), 25.9 (3C, *t*Bu), 32.8 (*CH*CH$_2$CH$_2$), 35.5 (*CH*$_2$CH$_2$OTBS), 49.0 (*CH*CHO), 55.3 (OCH$_3$), 61.3 (CH$_2$*CH*$_2$OTBS), 73.1 (CH$_2$Ph), 84.2 (CHOPMB), 113.7, 129.2 (aromatic) 131.4 (C$_{ipso}$ aromatic), 159.2 (phenolic), 204.8 (CHO).

7-*O*-[*tert*-Butyl(dimethyl)silyl]-3,5,6-trideoxy-4-*O*-(4-methoxybenzyl)-3,5-dimethyl-D-*gluco*-heptitol (diastereomer-233)



To a solution of olefin **212** (25 mg, 0.064 mmol) in a mixture of 1:1 H$_2$O and *tert*-butanol (1.0 mL) was added AD-mix-α (90 mg) at 0 °C. Stirring was continued for 3 d at 0 °C. The reaction was quenched with 10% Na$_2$S$_2$O$_3$ solution (1 mL) at 0 °C. The mixture was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and concentrated to give the crude diol in 4:1 diastereomeric mixture which was purified by flash chromatography (1:1 ethylacetate/petroleum ether) to get the pure diol **diastreomer-233** (5 mg, yield was not determined because of very small amounts) as an oil.

R$_f$ = 0.50 (1:1 ethyl acetate/petroleum ether);

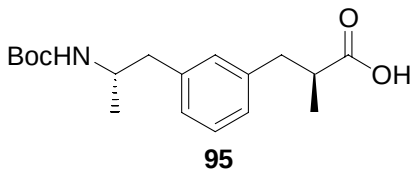
^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.03 (s, 6H, Si(CH$_3$)$_3$), 0.88 (s, 12H, *t*Bu, *CH*$_3$CHCH$_2$), 0.91 (d, *J* = 7.1 Hz, 3H, *CH*$_3$CHCH), 1.30-1.44 (m, 2H, *CH*$_2$CH$_2$OTBS), 1.90-1.77 (m, 2H, *CH*CHOH, *CH*CH$_2$CH$_2$), 2.56-2.62 (m, 1H, *CH*CH$_2$O), 3.47-3.51 (m, 2H, CHOPMB, *CH*OH), 3.60-3.73 (m, 4H, *CH*$_2$OH, *CH*$_2$OTBS), 3.79 (s, 3H, OCH$_3$), 4.55 (s, 2H, CH$_2$Ph), 6.86 (d, *J* = 8.6 Hz, 2H, aromatic), 7.26 (d, *J* = 7.3 Hz, 2H, aromatic);

^{13}C NMR (100 MHz, CDCl$_3$): δ = -5.34, -5.28 (2C, Si(CH$_3$)$_3$), 11.4 (*CH*$_3$CHCH), 16.3 (*CH*$_3$CHCH$_2$), 18.3 (TBS quarternary), 26.0 (3C, *t*Bu), 31.6 (*CH*CH$_2$CH$_2$), 35.8

(*CH*$_2$CH$_2$OTBS), 36.9 (*CH*CHOH), 55.3 (OCH_3), 61.5 (CH$_2$*CH*$_2$OTBS), 73.1 (CH_2Ph), 84.1 (CHOPMB), 113.8, 129.2 (aromatic) 131.4 (C_{ipso} aromatic), 159.1 (phenolic).

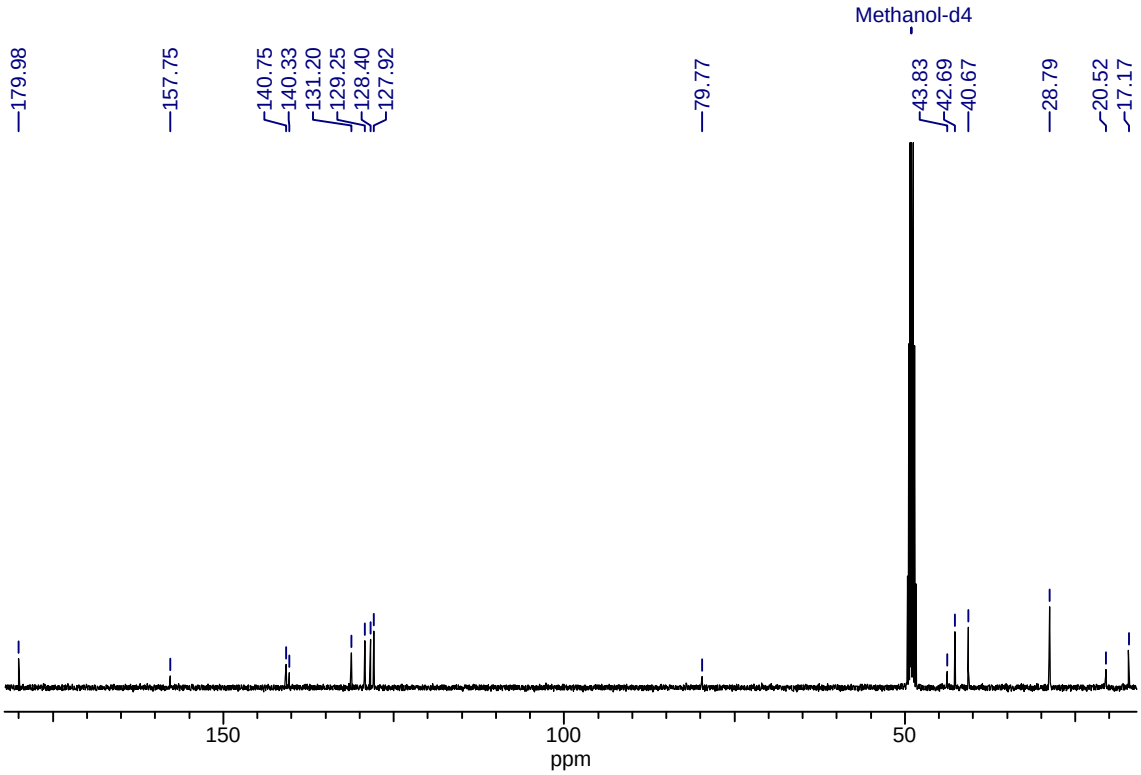
9 Appendix

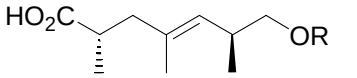
9.1 NMR-Spectra for important compounds


BocHN
O
OH

95

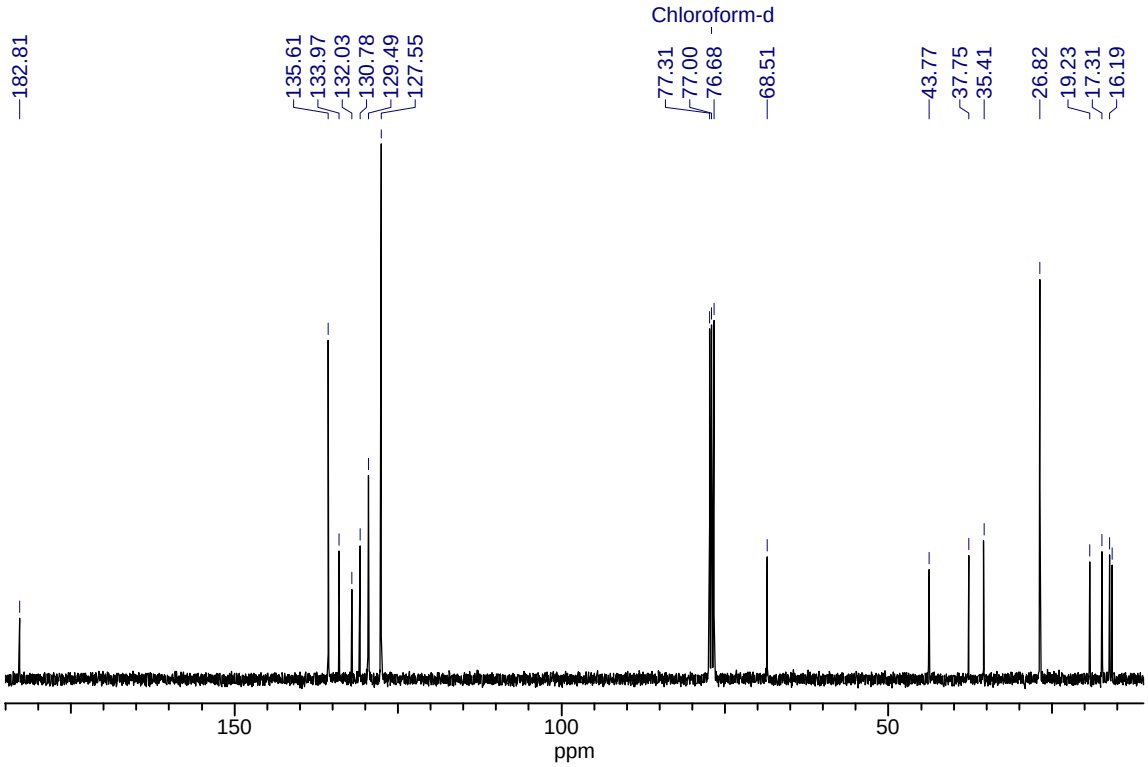
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

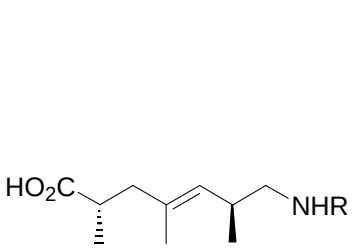

Methanol-d4
179.98
157.75
140.75
140.33
131.20
129.25
128.40
127.92
79.77
43.83
42.69
40.67
28.79
20.52
17.17
150
100
50
ppm


HO2C
OR

96 R = TBDPS

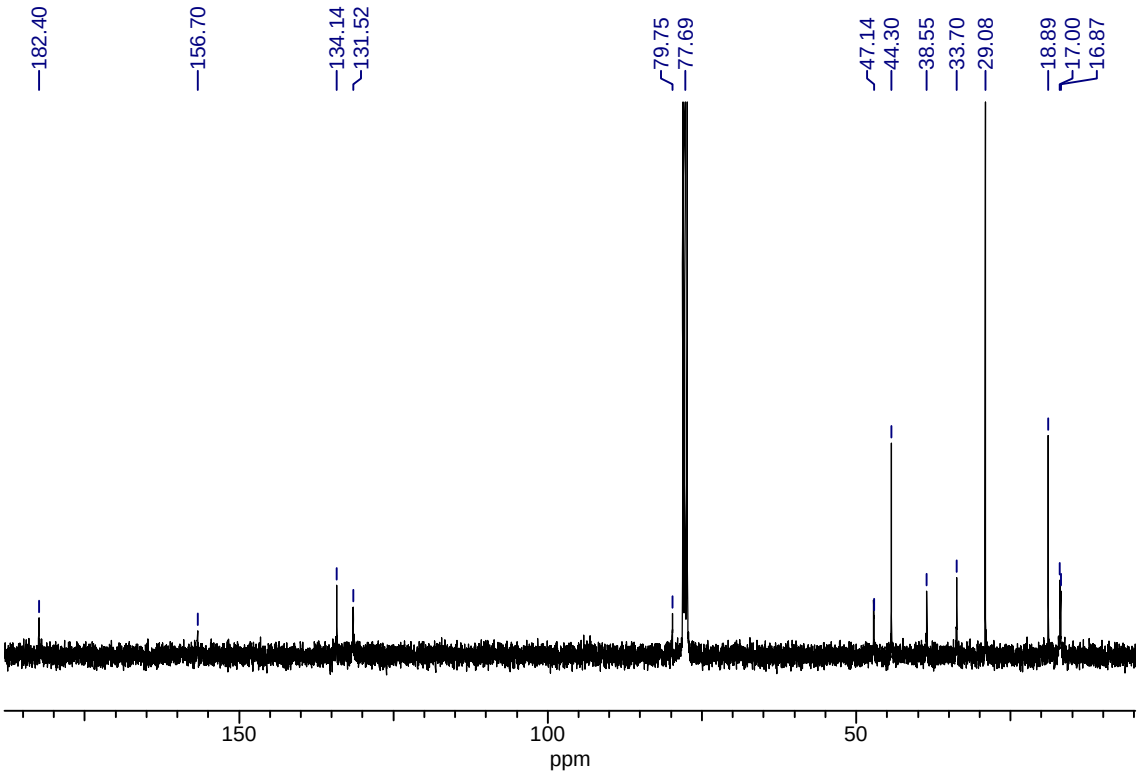
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
182.81
135.61
133.97
132.03
130.78
129.49
127.55
77.31
77.00
76.68
68.51
43.77
37.75
35.41
26.82
19.23
17.31
16.19
150
100
50
ppm


HO2C
NHR

97

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm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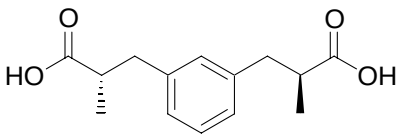
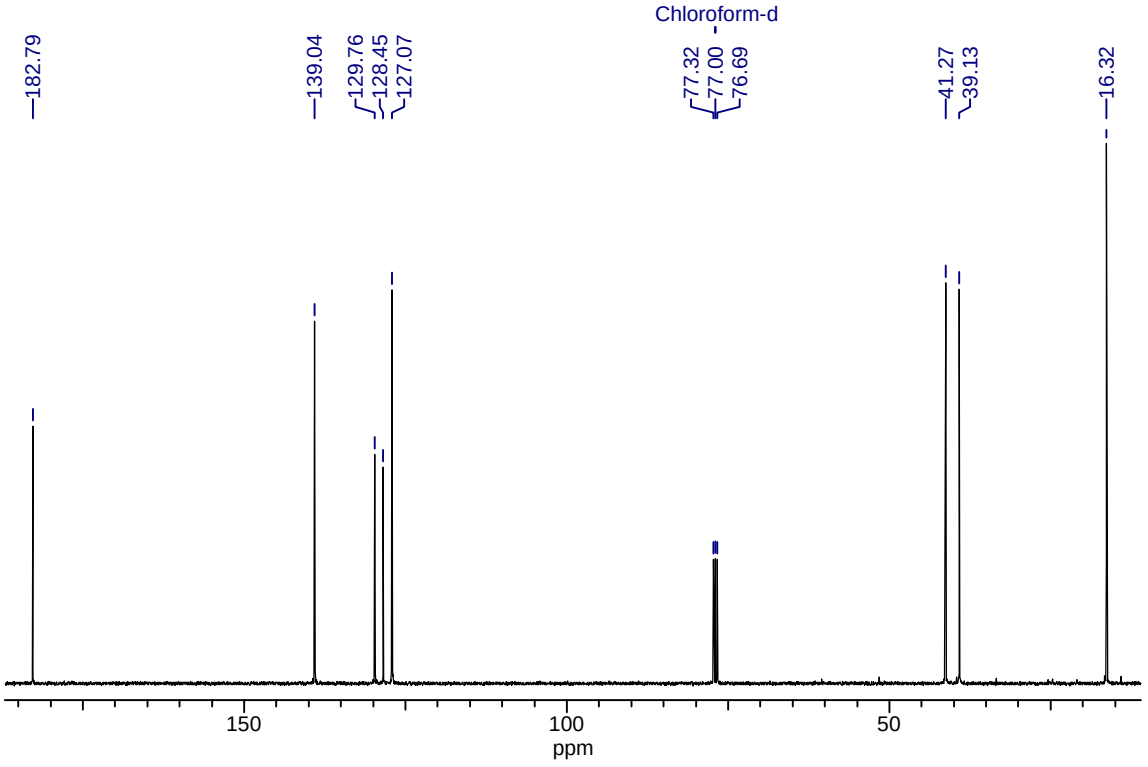
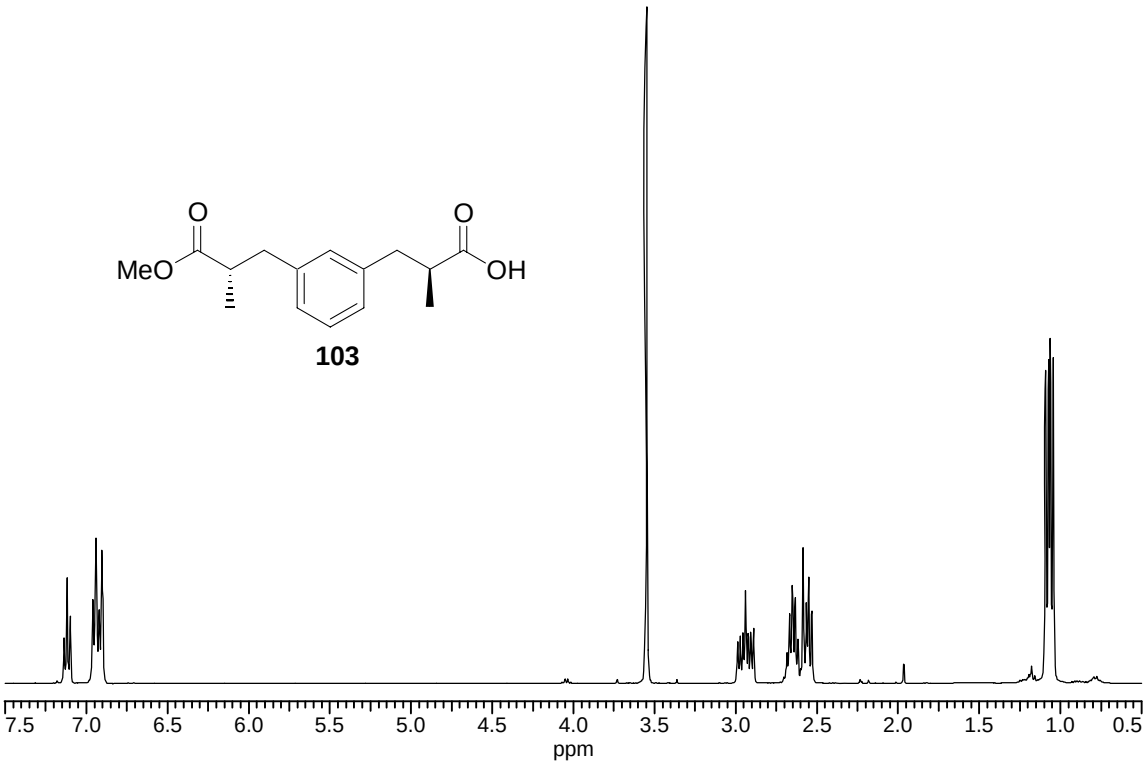
156.70
134.14
131.52
79.75
77.69
47.14
44.30
38.55
33.70
29.08
18.89
17.00
16.87
150
100
50
ppm


O
HO
O
OH

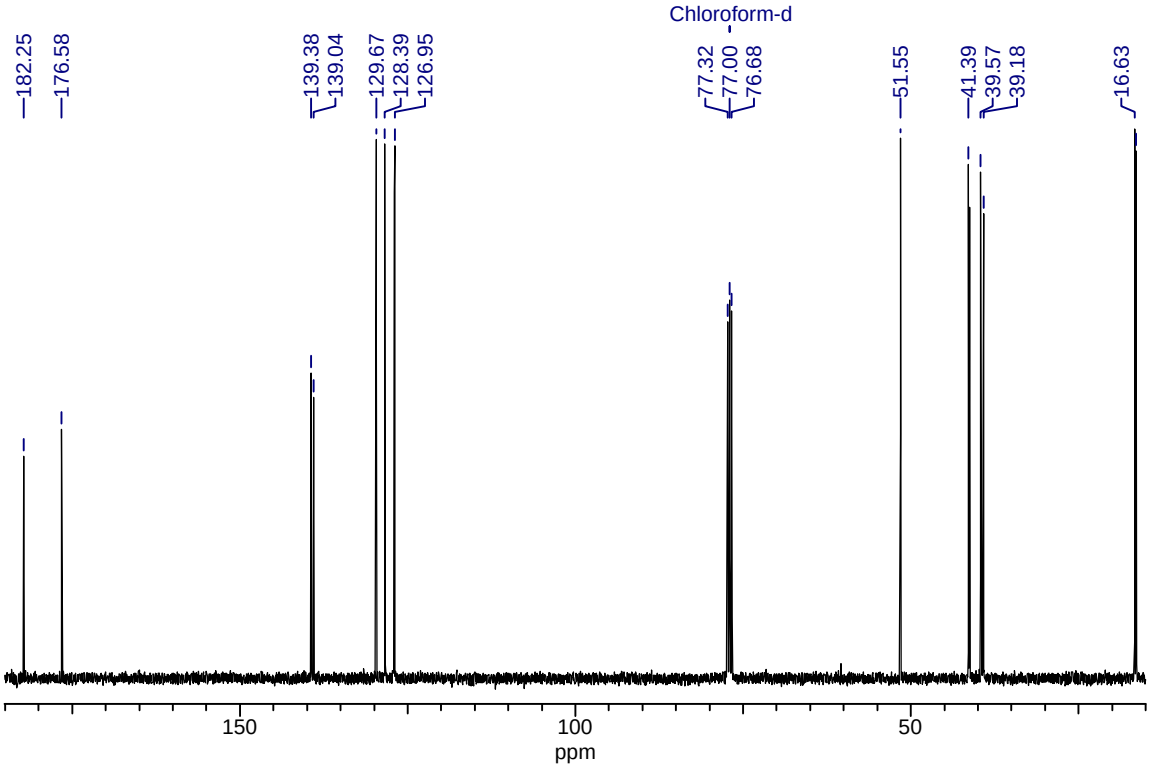
98

12
11
10
9
8
7
6
5
4
3
2
1
ppm


182.79
139.04
129.76
128.45
127.07
Chloroform-d
77.32
77.00
76.69
41.27
39.13
16.32
150
100
50
ppm


O
MeO
O
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

103


Chloroform-d
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176.58
139.38
139.04
129.67
128.39
126.95
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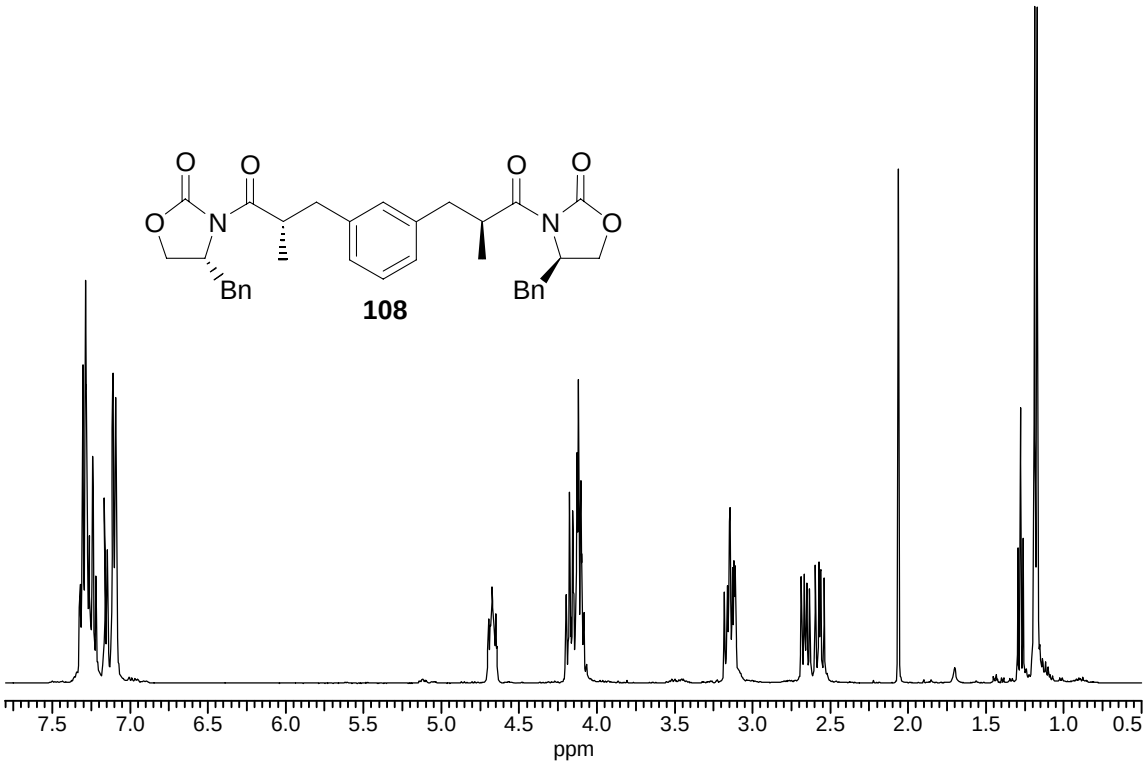
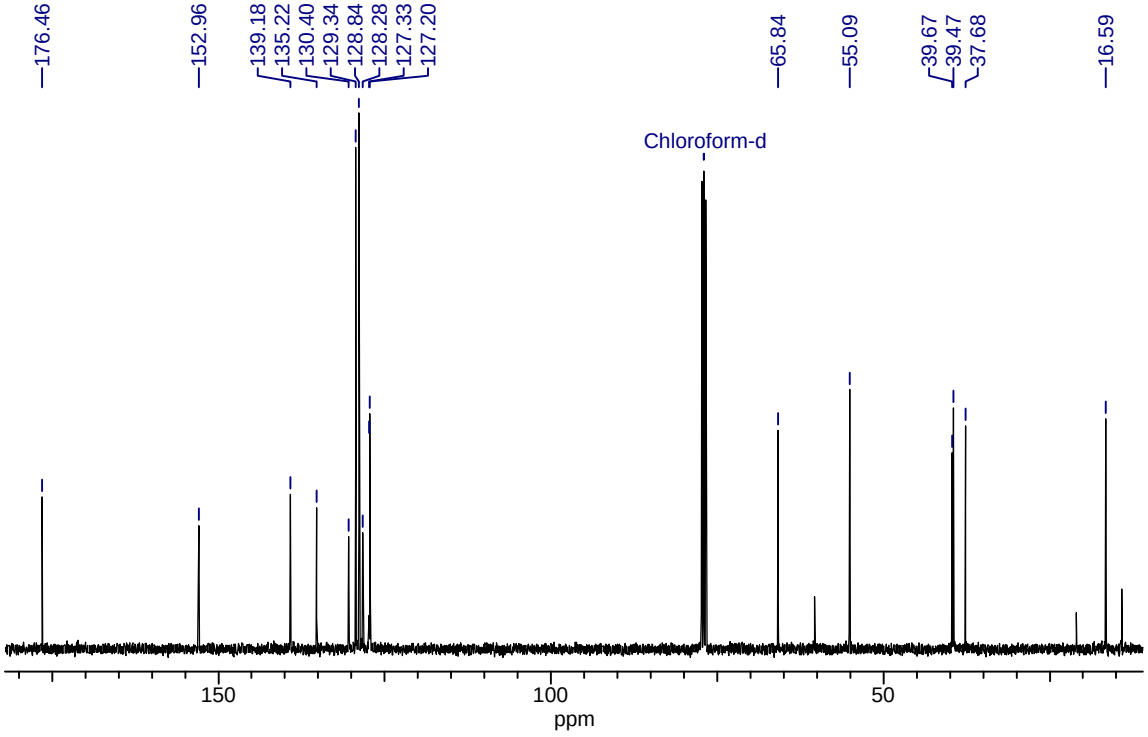
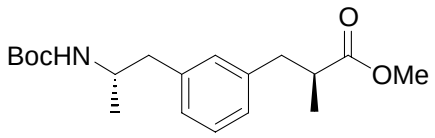
77.00
76.68
51.55
41.39
39.57
39.18
16.63
150
100
50
ppm


O
O
O
O
N
N
O
O
Bn
Bn
108
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


176.46
152.96
139.18
135.22
130.40
129.34
128.84
128.28
127.33
127.20
65.84
55.09
39.67
39.47
37.68
16.59
Chloroform-d
150
100
50
ppm


BocHN
O
OMe

115

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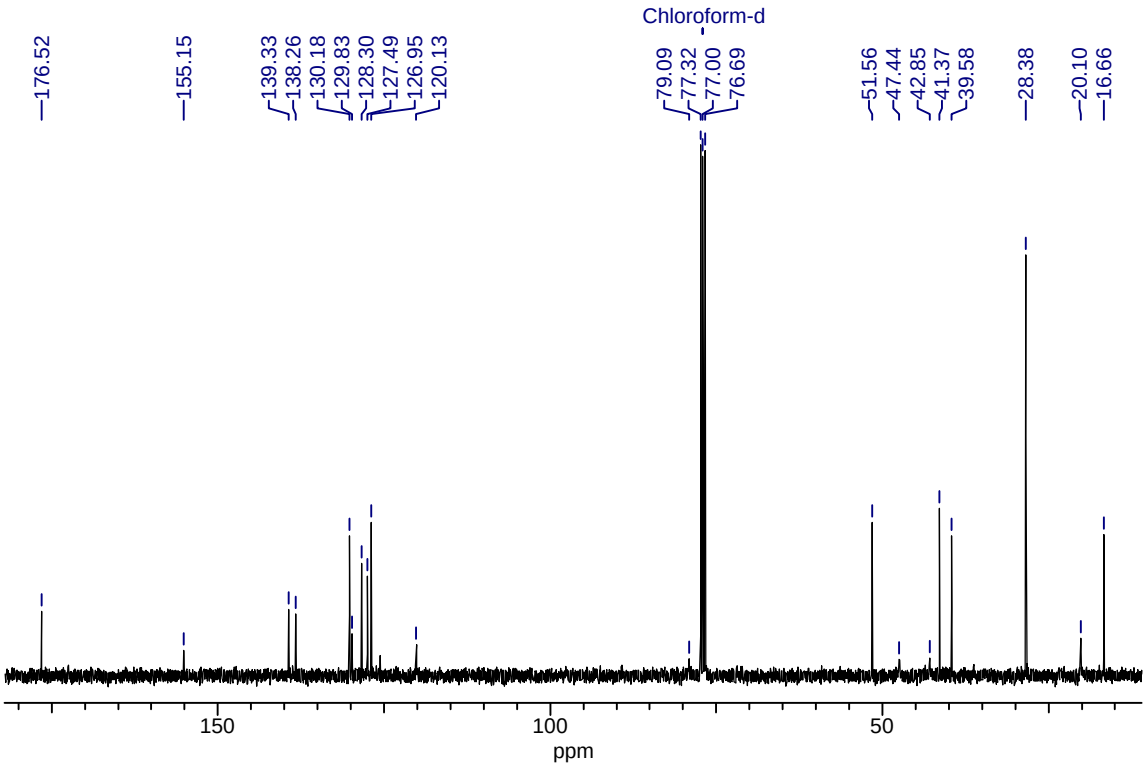
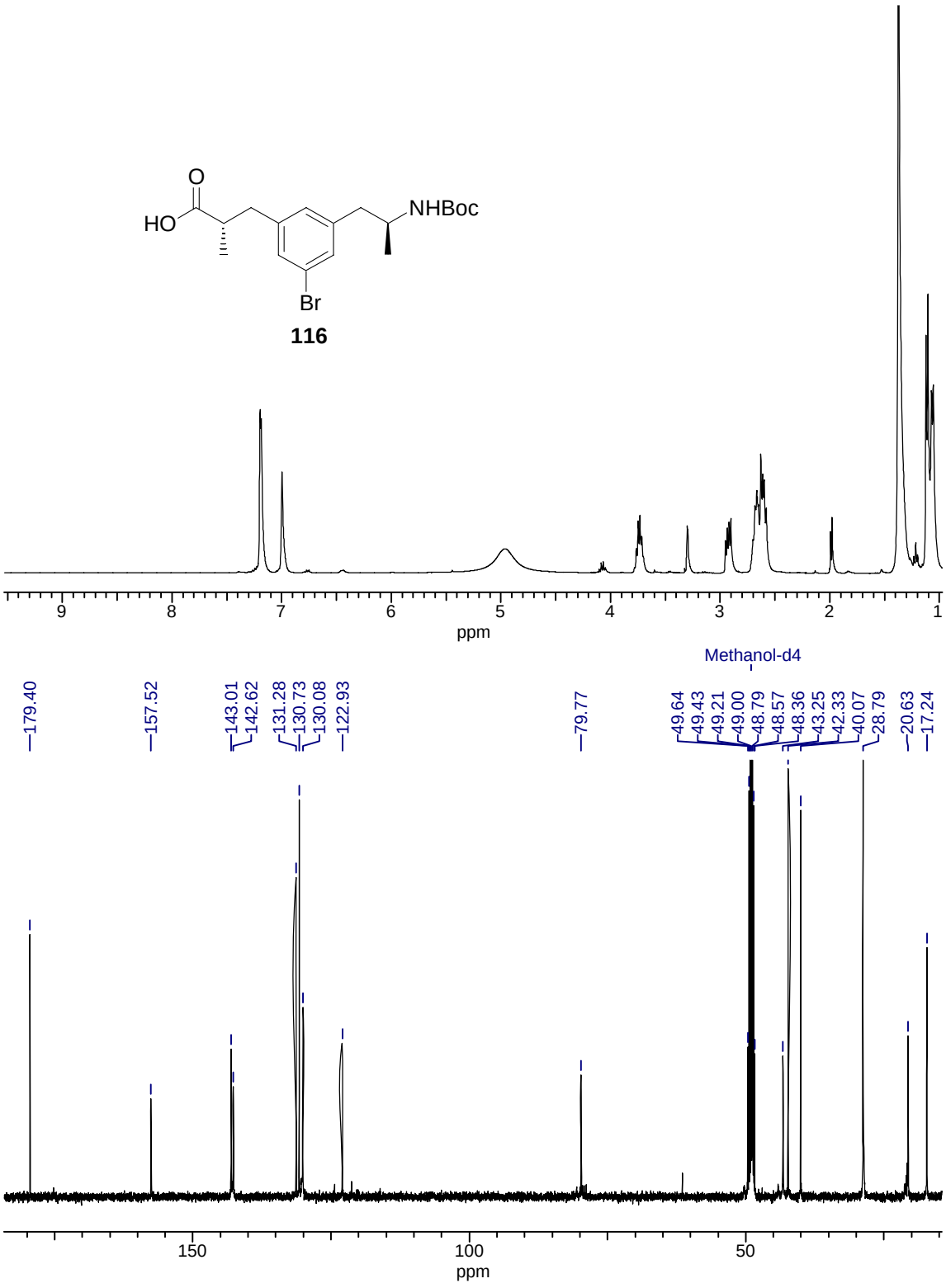
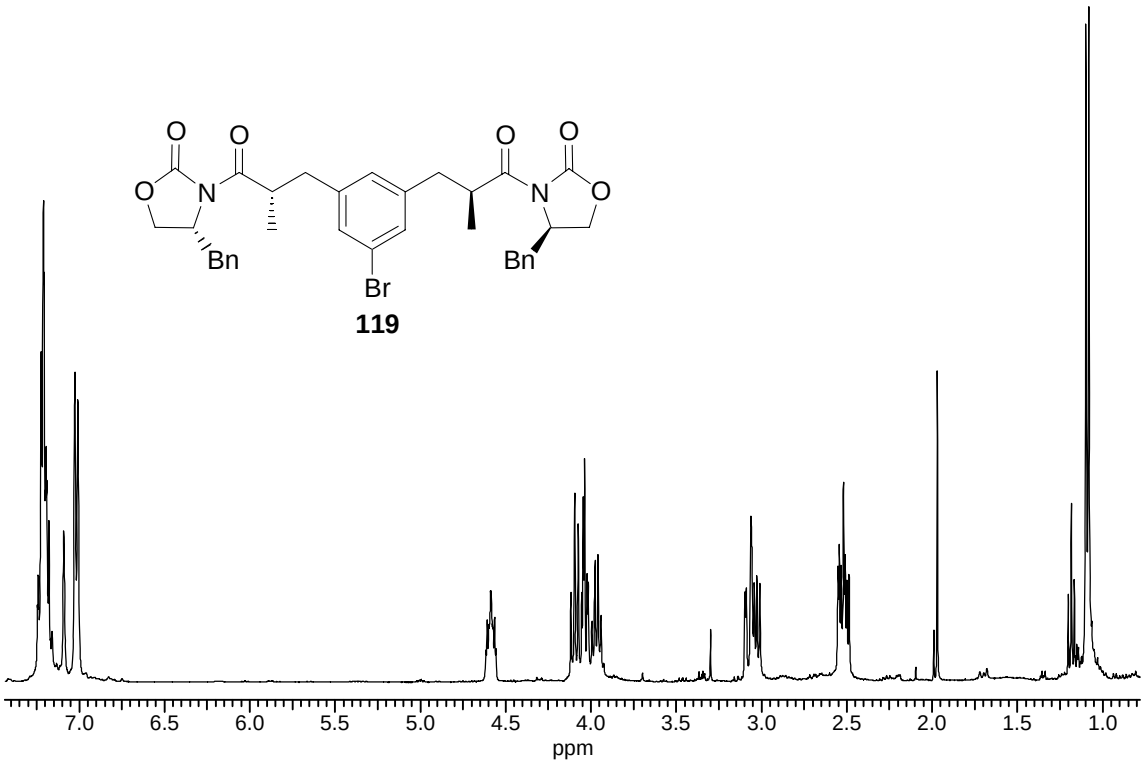
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

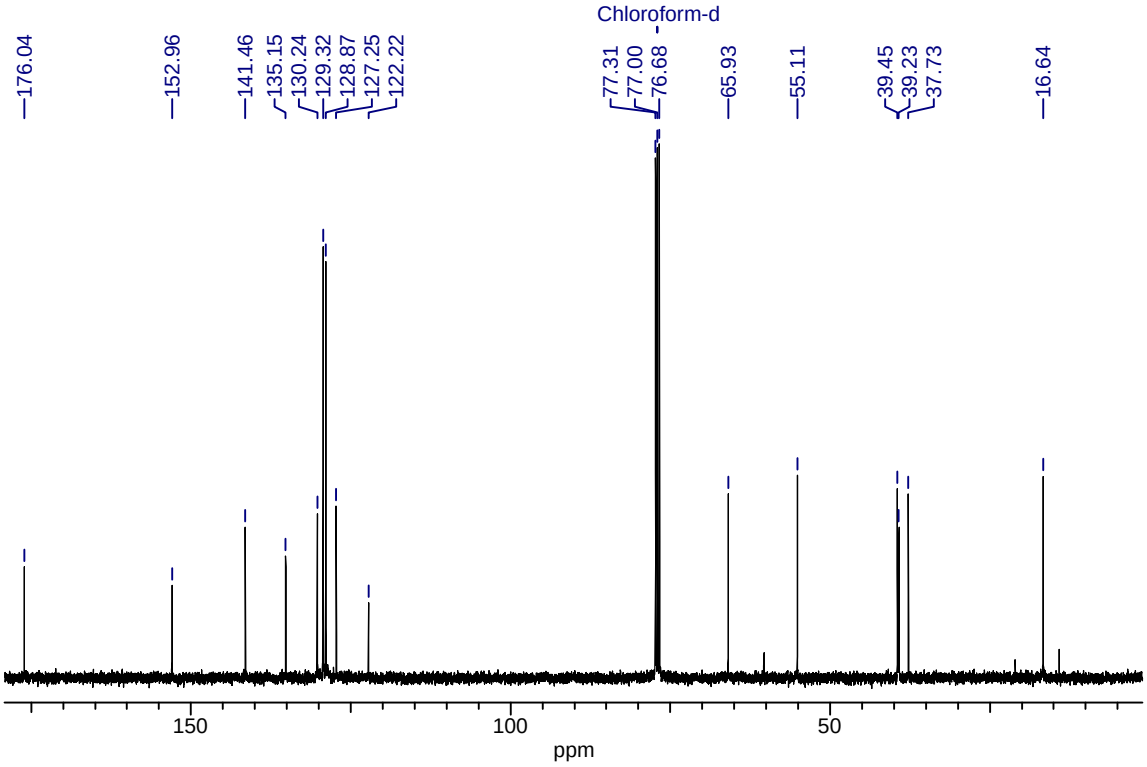

176.52
155.15
139.33
138.26
130.18
129.83
128.30
127.49
126.95
120.13
Chloroform-d
79.09
77.32
77.00
76.69
51.56
47.44
42.85
41.37
39.58
28.38
20.10
16.66
150
100
50
ppm

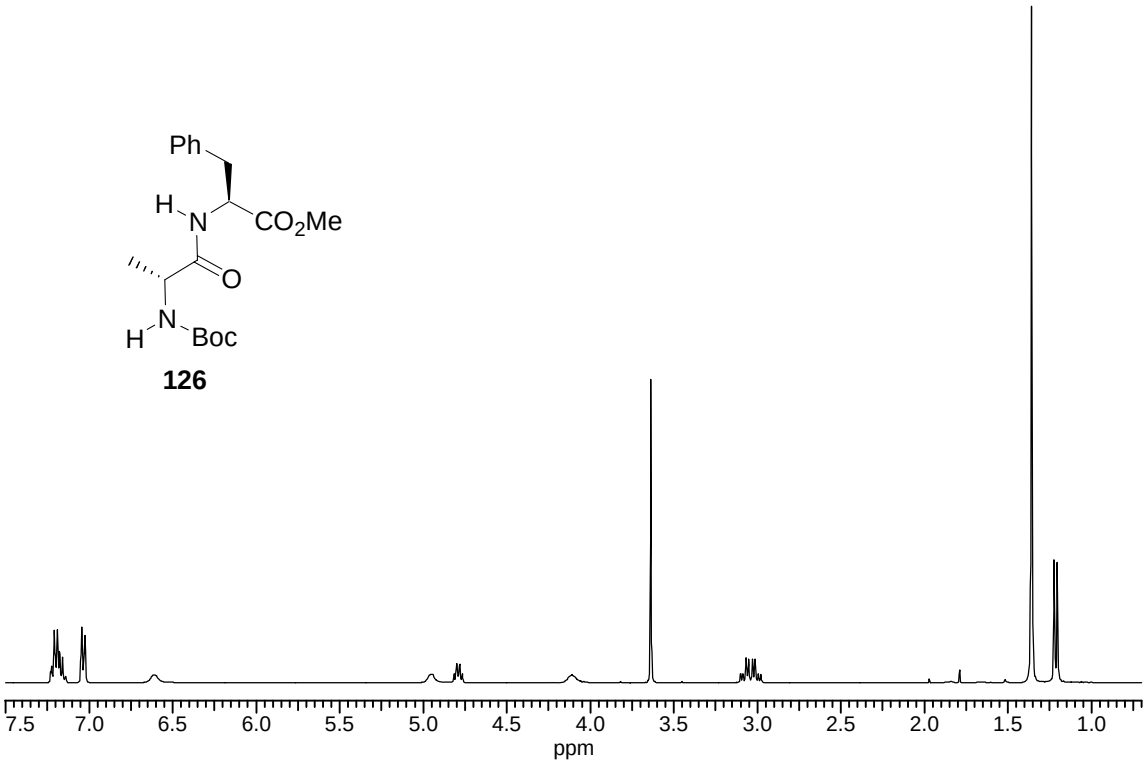

O
HO
NHBoc
Br
9
8
7
6
5
4
3
2
1
ppm
Methanol-d4
179.40
157.52
143.01
142.62
131.28
130.73
130.08
122.93
79.77
49.64
49.43
49.21
49.00
48.79
48.57
48.36
43.25
42.33
40.07
28.79
20.63
17.24
150
100
50
ppm

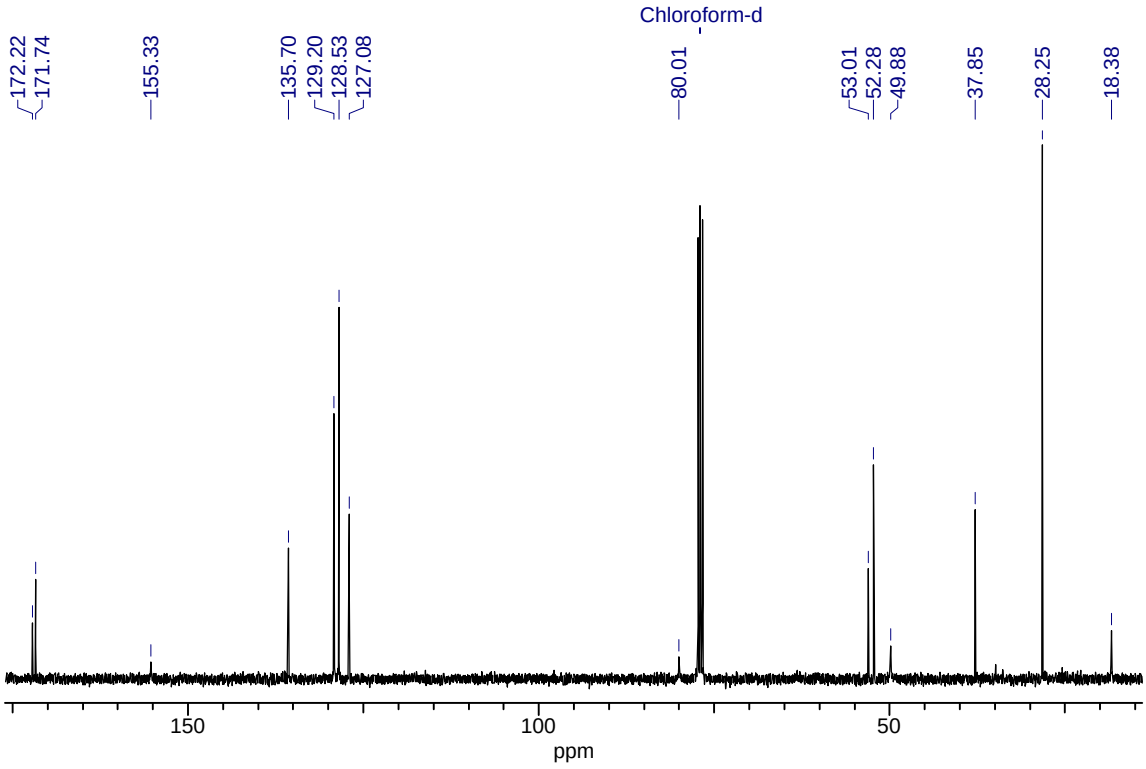
116

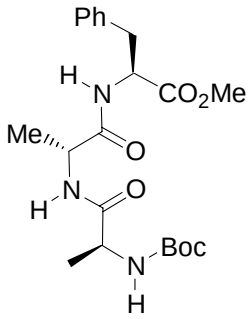

O
O
O
O
N
N
O
O
Bn
Bn
Br
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

119


Chloroform-d
176.04
152.96
141.46
135.15
130.24
129.32
128.87
127.25
122.22
77.31
77.00
76.68
65.93
55.11
39.45
39.23
37.73
16.64
150
100
50
ppm

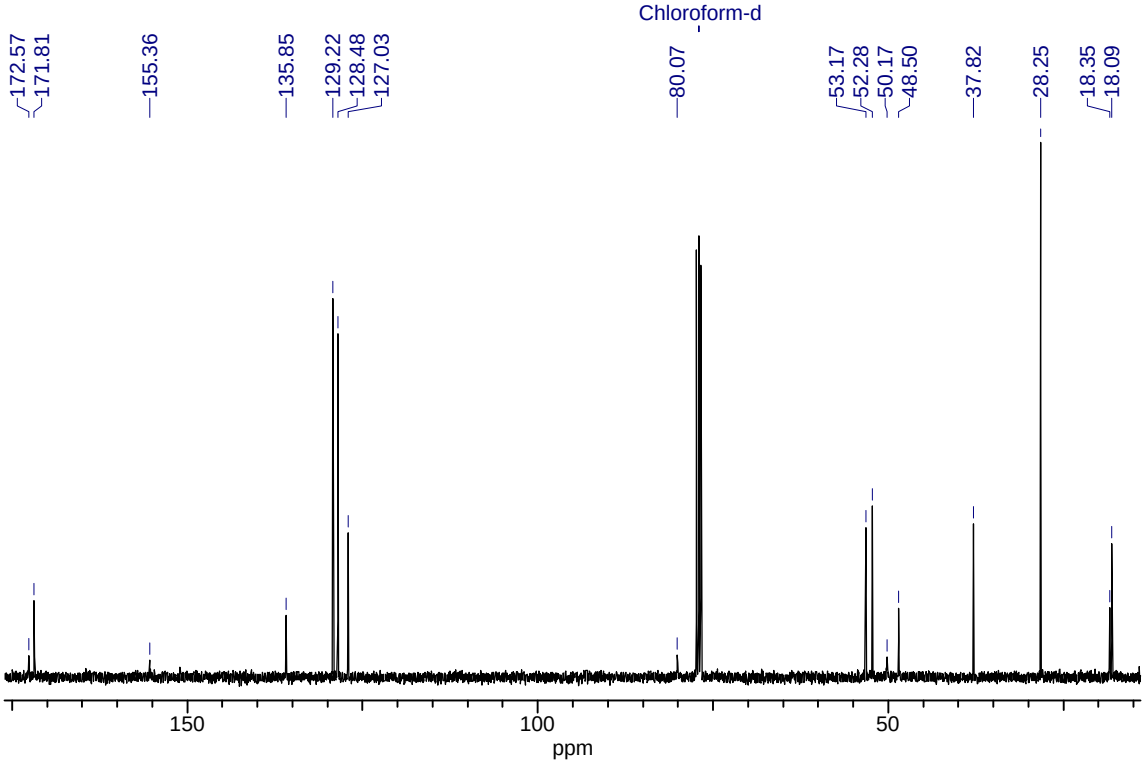

Ph
H
N
CO2Me
O
N
H
Boc
126
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

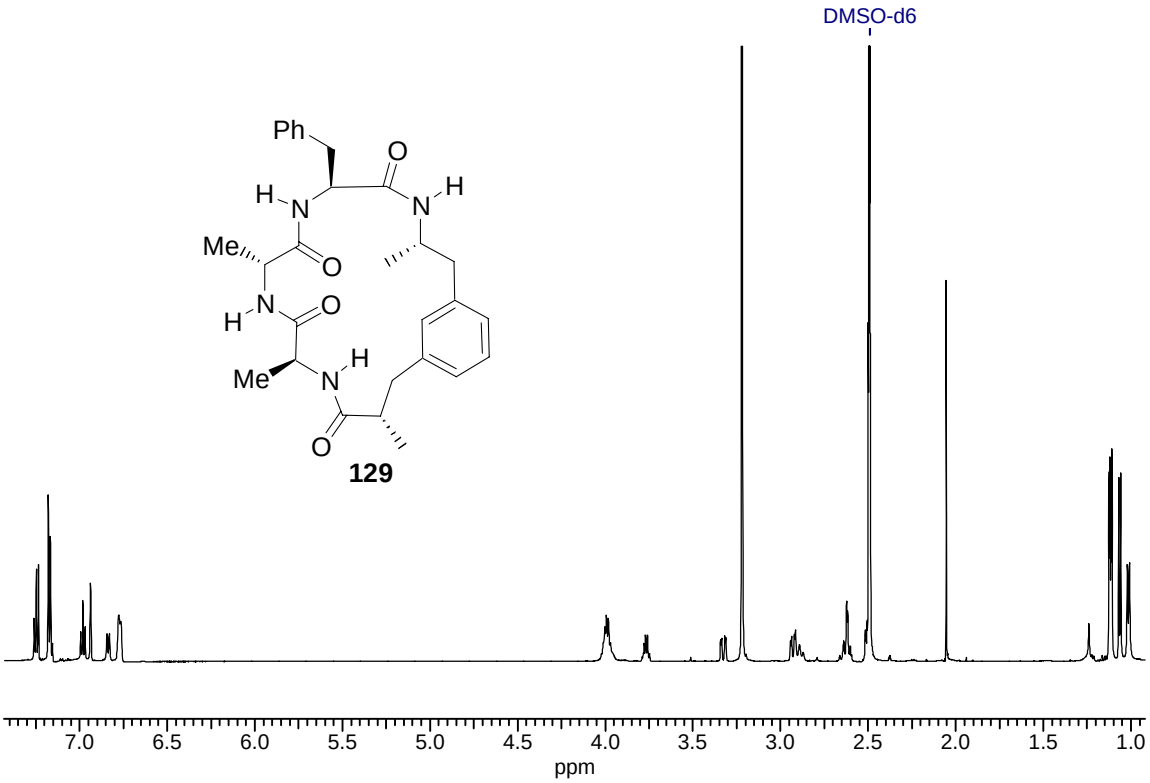

Chloroform-d
172.22
171.74
155.33
135.70
129.20
128.53
127.08
80.01
53.01
52.28
49.88
37.85
28.25
18.38
150
100
50
ppm

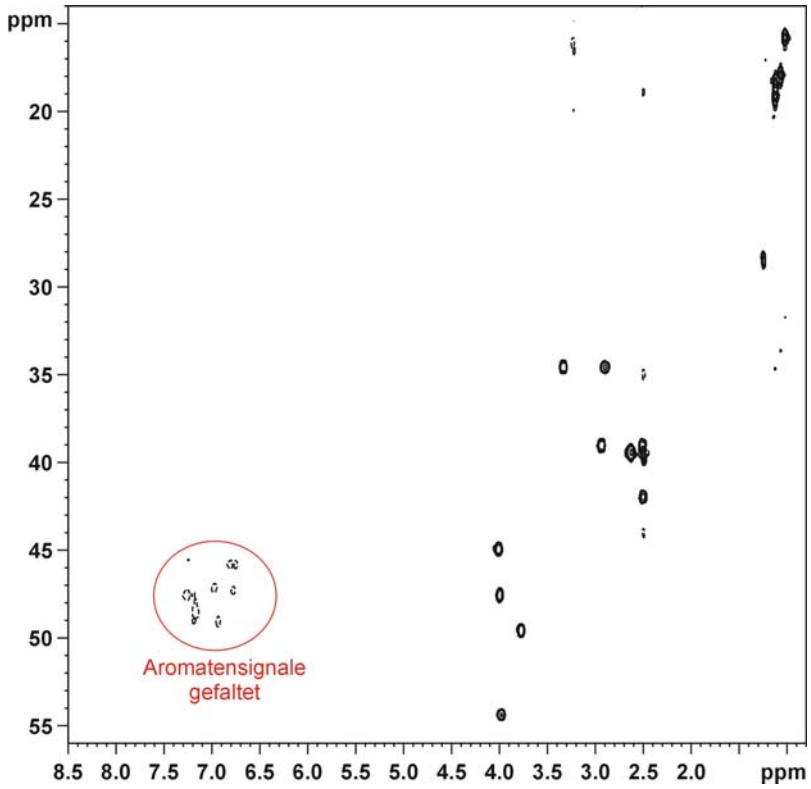

Ph
H
N
CO2Me
Me
O
N
O
H
Boc
N
H

127

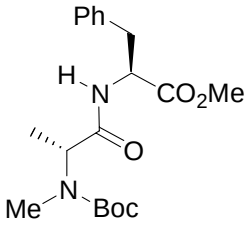
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
172.57
171.81
155.36
135.85
129.22
128.48
127.03
80.07
53.17
52.28
50.17
48.50
37.82
28.25
18.35
18.09
150
100
50
ppm



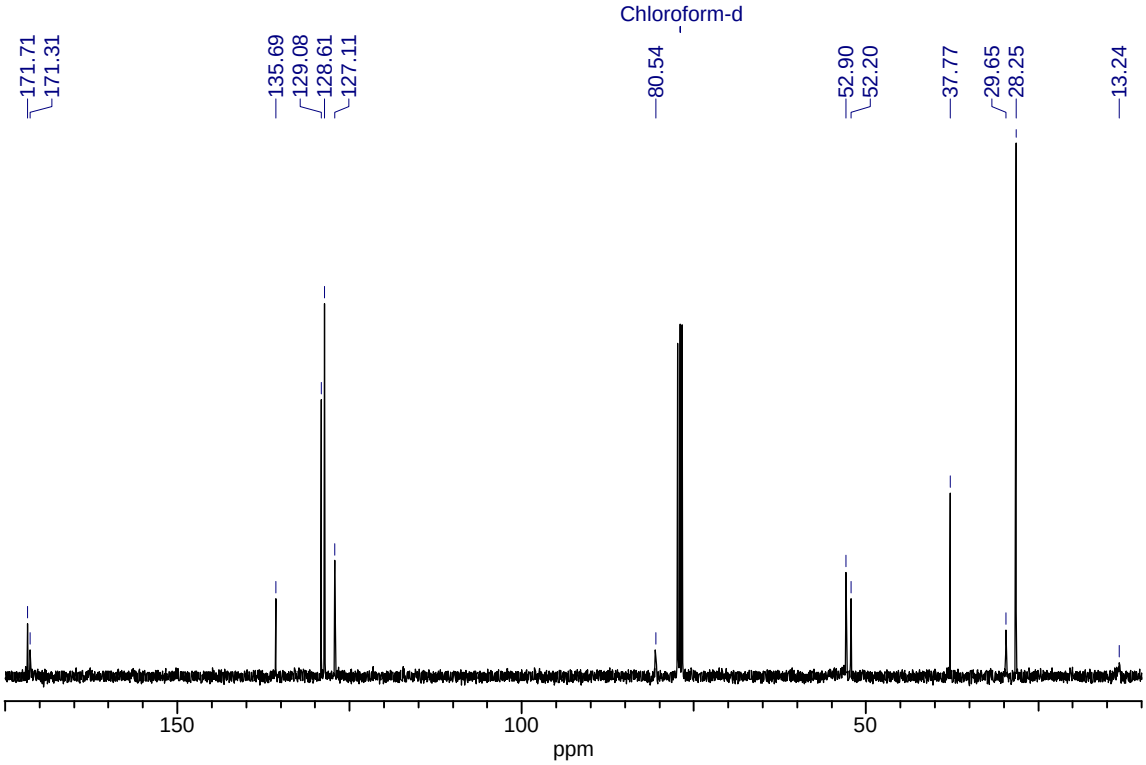


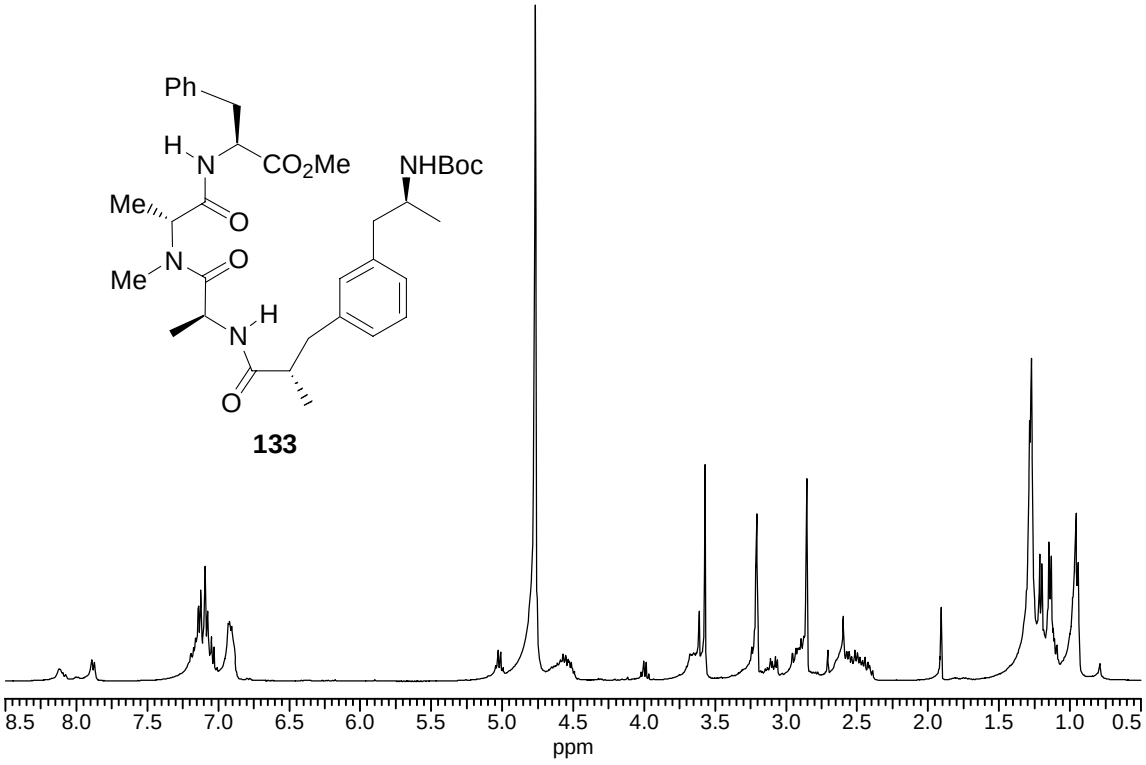
HMQC spectrum of macrocycle **129** (320 K, 600 MHz, DMSO-d_6).


Ph
H
N
CO2Me
O
N
Me
Boc

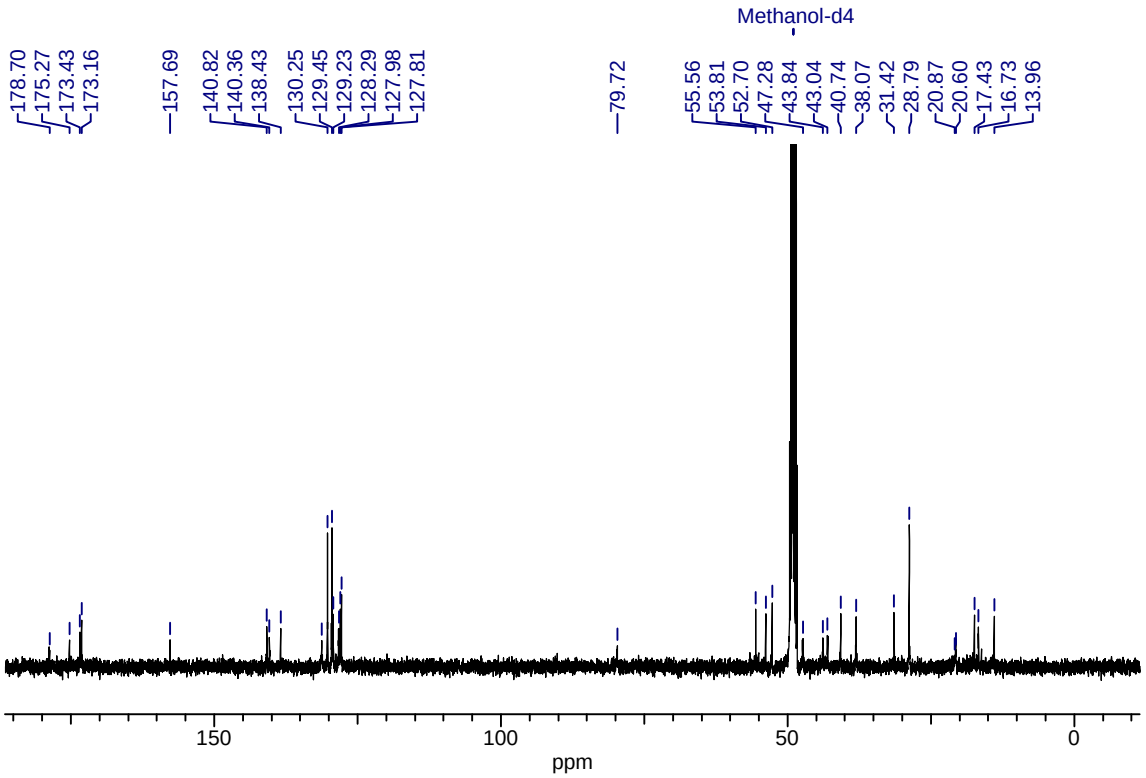
131

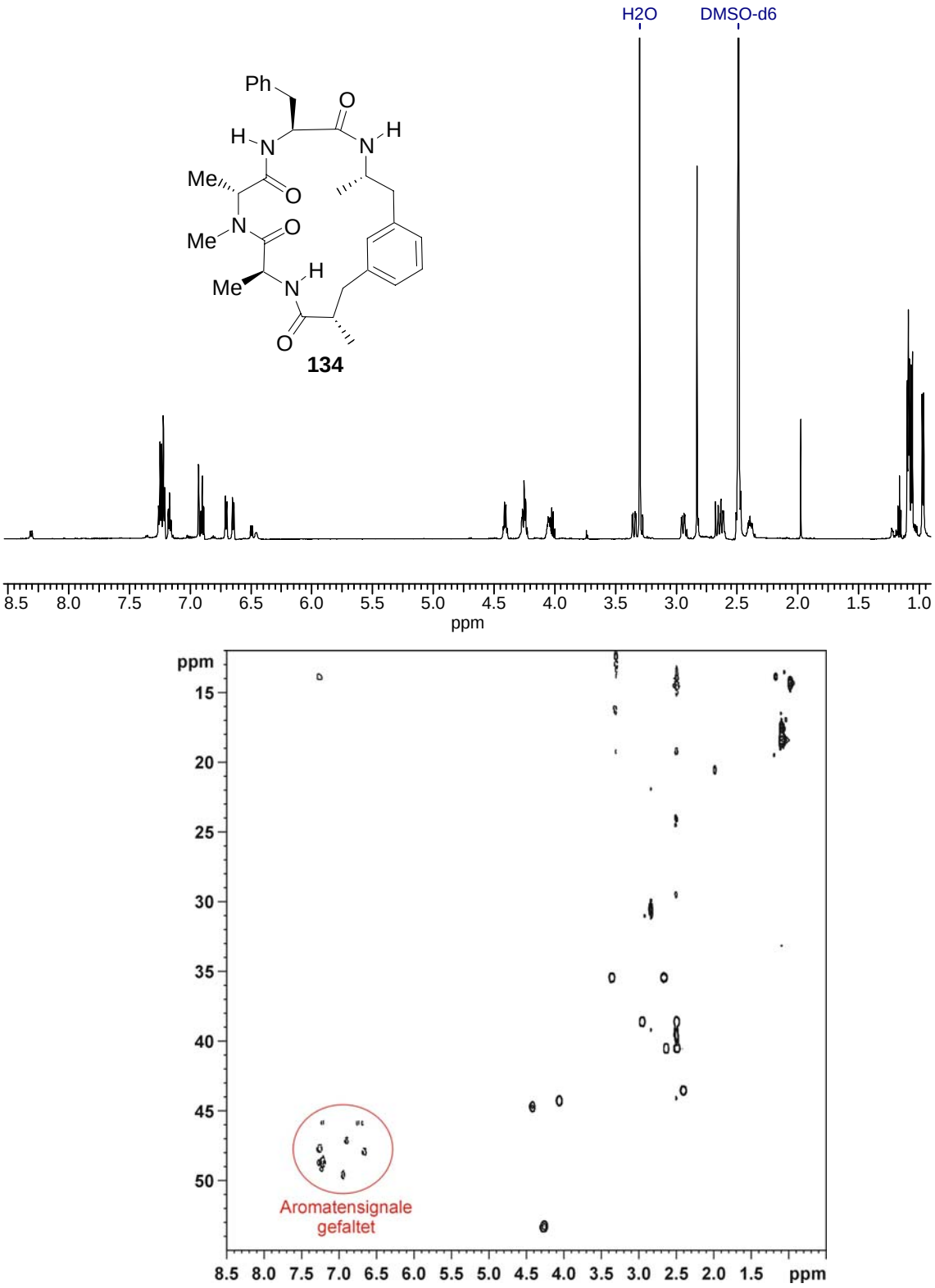
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
171.71
171.31
135.69
129.08
128.61
127.11
80.54
52.90
52.20
37.77
29.65
28.25
13.24
150
100
50
ppm

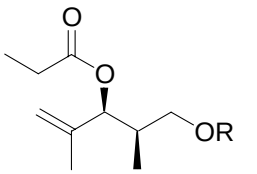

Ph
H
N
CO2Me
NHBoc
Me
O
N
O
Me
H
N
O
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

133


Methanol-d4
178.70
175.27
173.43
173.16
157.69
140.82
140.36
138.43
130.25
129.45
129.23
128.29
127.98
127.81
79.72
55.56
53.81
52.70
47.28
43.84
43.04
40.74
38.07
31.42
28.79
20.87
20.60
17.43
16.73
13.96
150 100 50 0
ppm

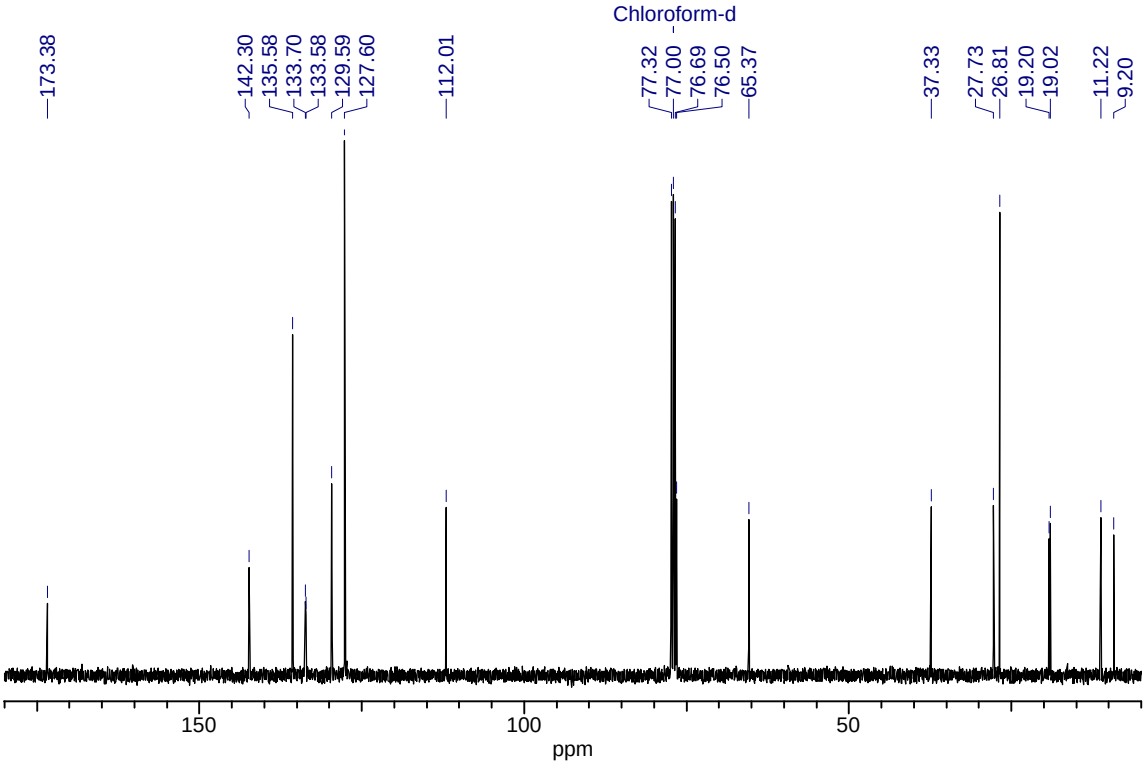


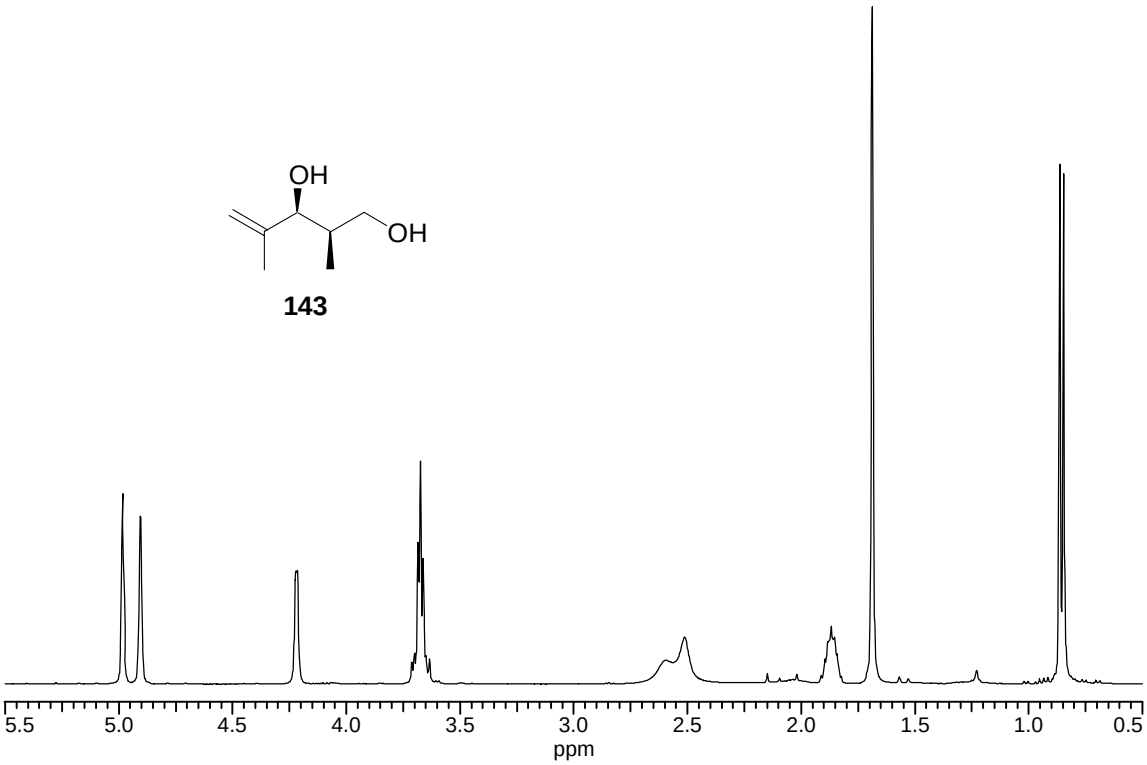
HMQC spectrum of macrocycle **134** (300 K, 600 MHz, DMSO-d_6).

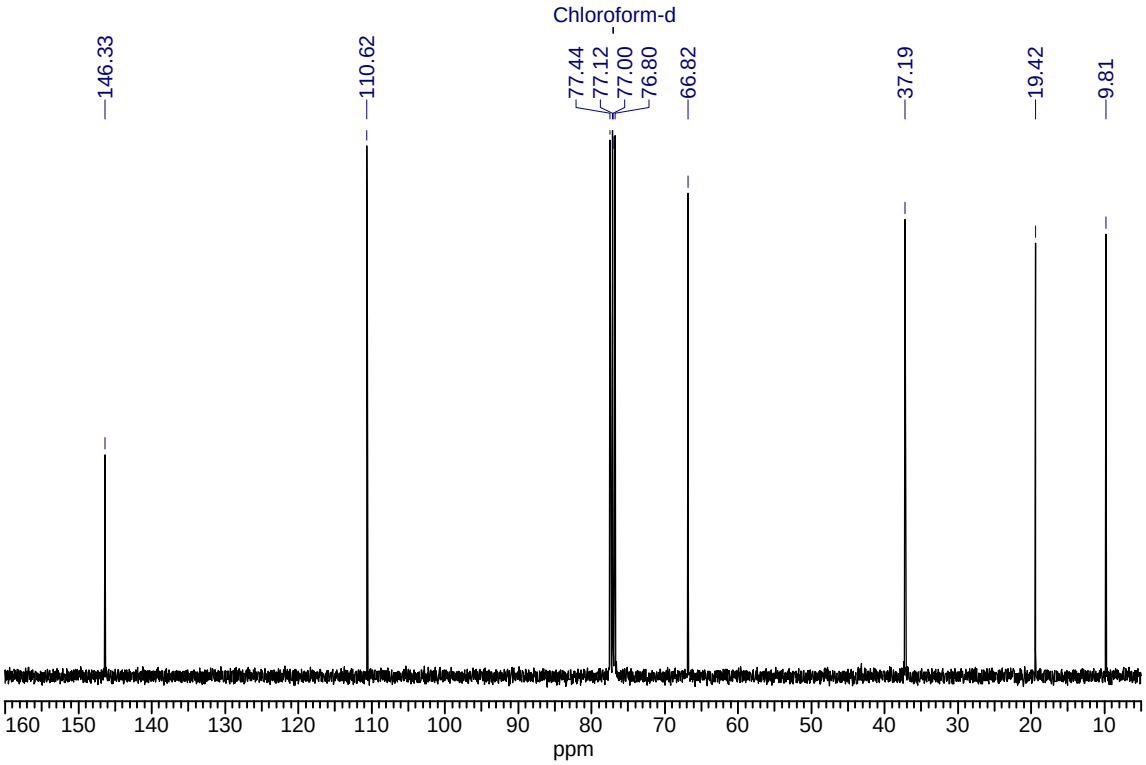

O
O
OR

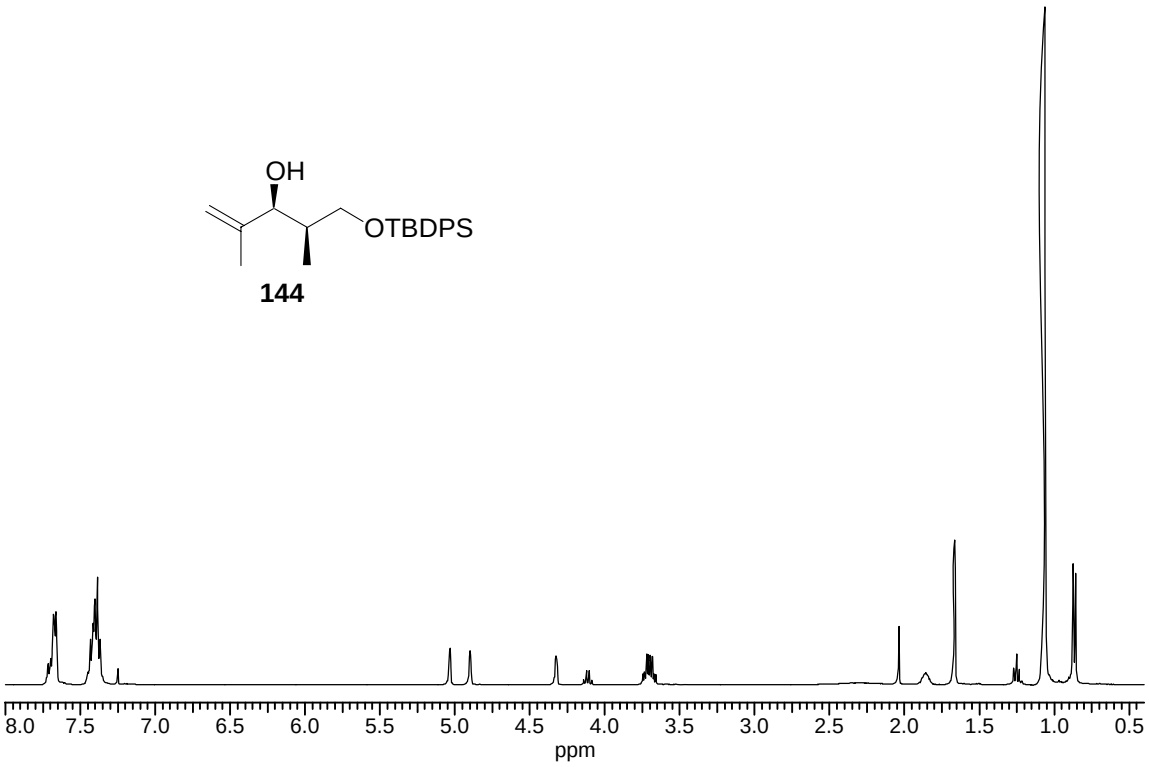
R = TBDPS **140**

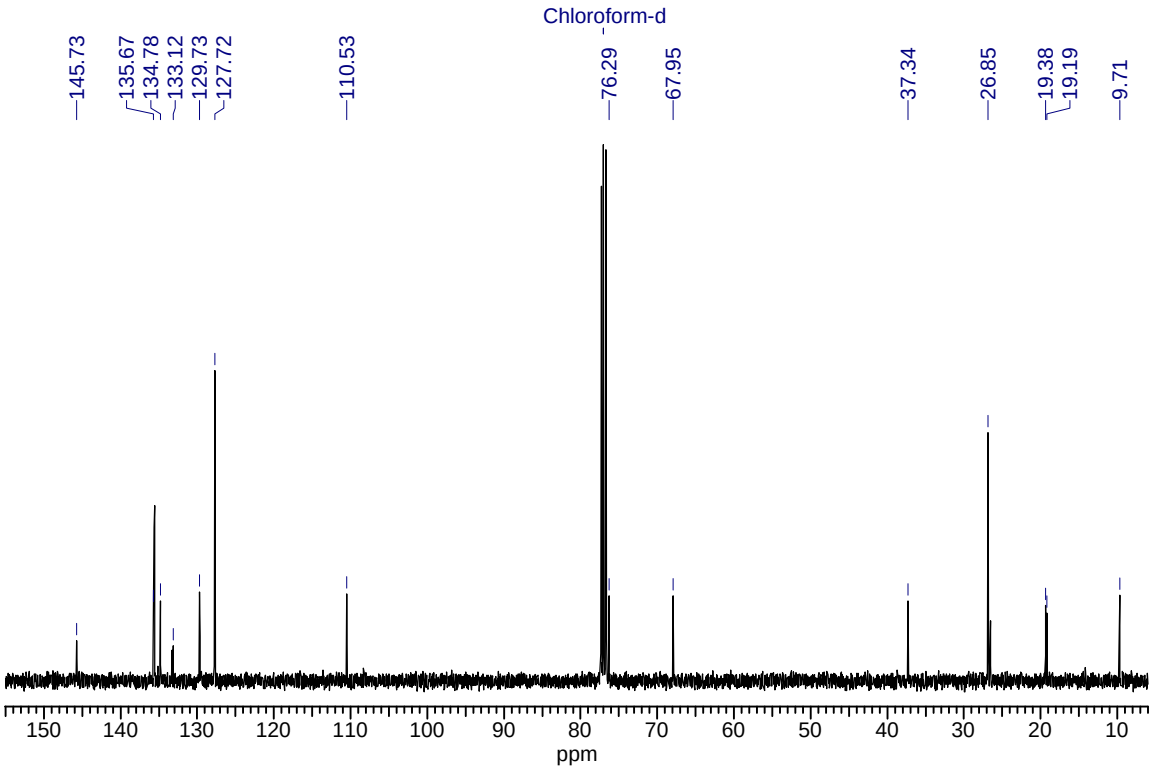
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

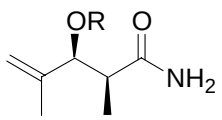

Chloroform-d
173.38
142.30
135.58
133.70
133.58
129.59
127.60
112.01
77.32
77.00
76.69
76.50
65.37
37.33
27.73
26.81
19.20
19.02
11.22
9.20
150
100
50
ppm


OH
OH
143
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Chloroform-d
146.33
110.62
77.44
77.12
77.00
76.80
66.82
37.19
19.42
9.81
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

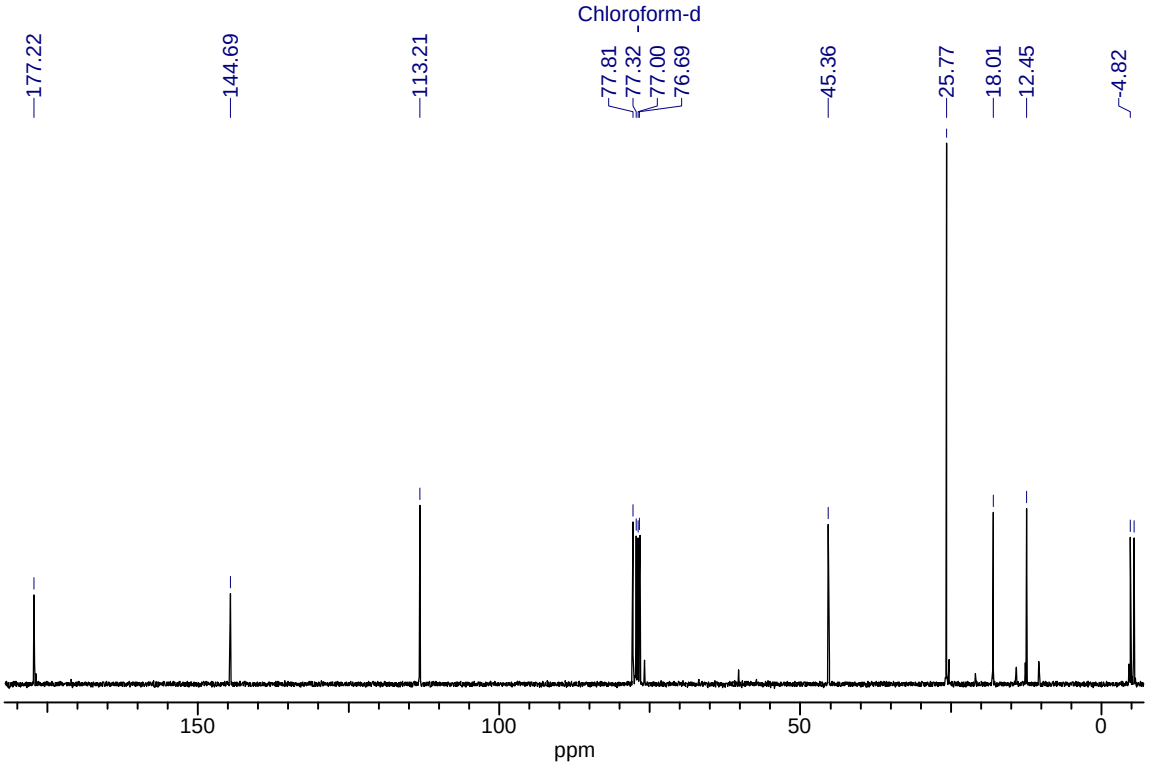

OH
OTBDPS
144
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

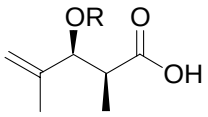

Chloroform-d
145.73
135.67
134.78
133.12
129.73
127.72
110.53
76.29
67.95
37.34
26.85
19.38
19.19
9.71
150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


OR
O
NH2

154 R = TBS

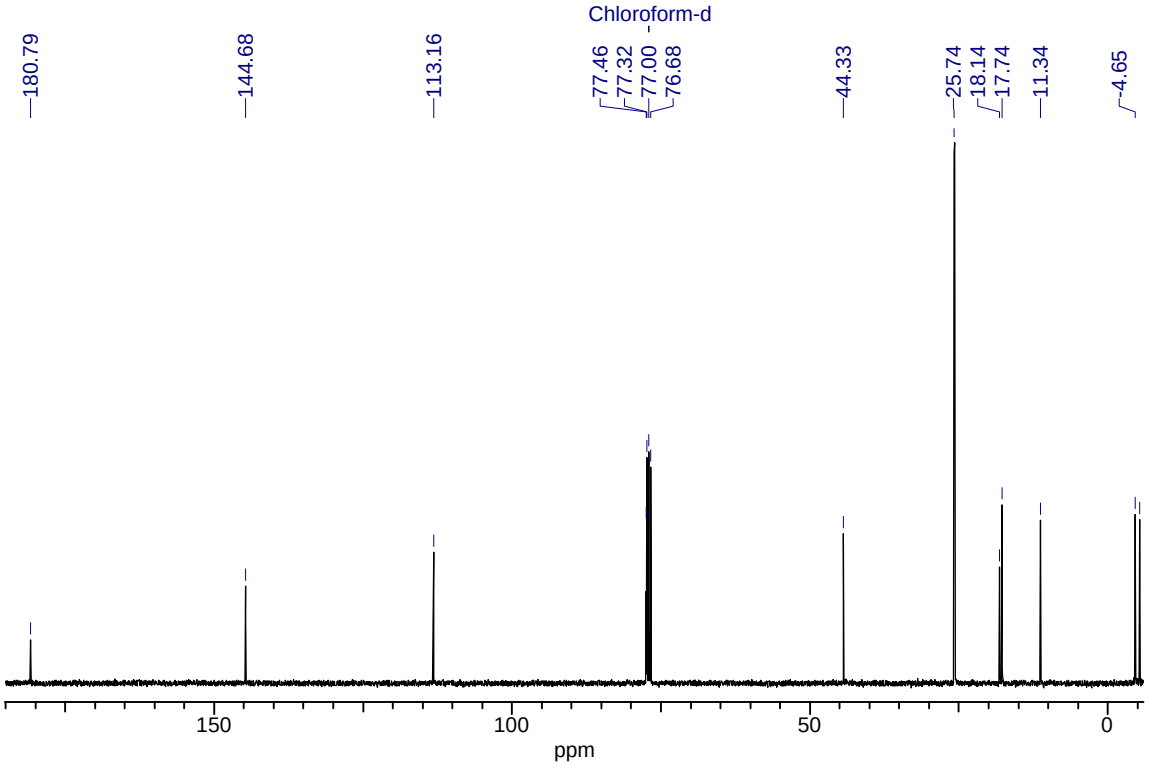
7
6
5
4
3
2
1
0
ppm

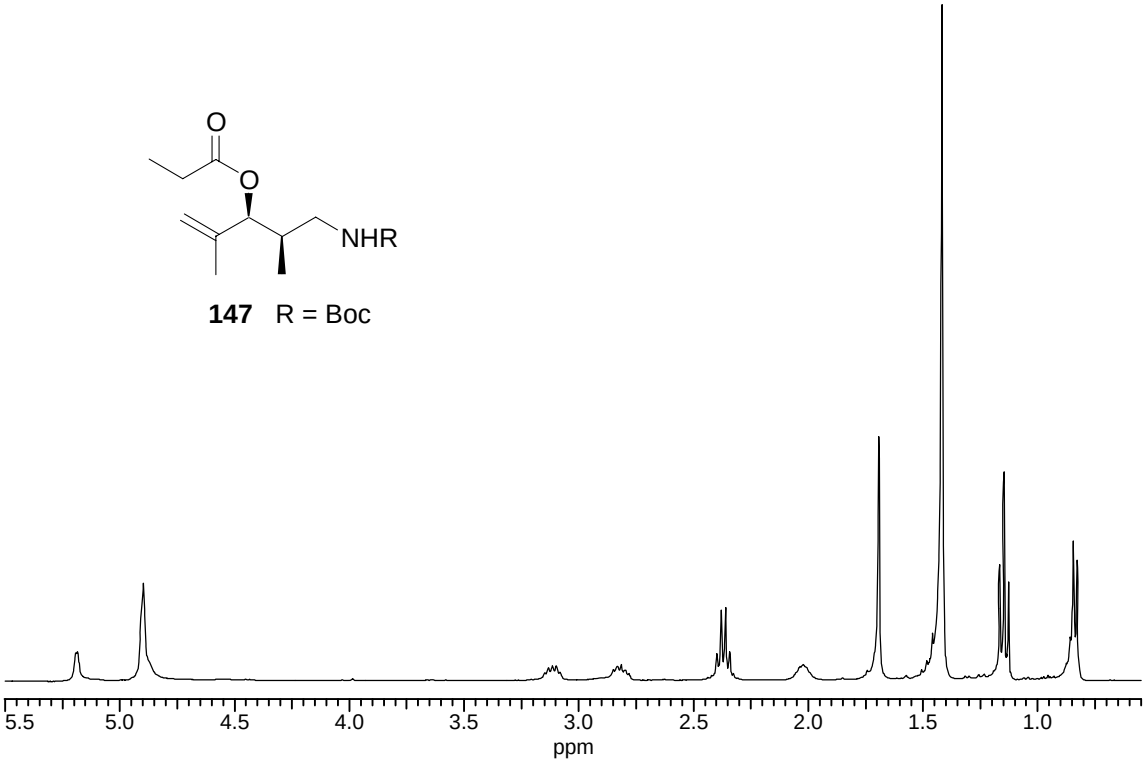

Chloroform-d
177.22
144.69
113.21
77.81
77.32
77.00
76.69
45.36
25.77
18.01
12.45
4.82
150
100
50
0
ppm


OR
O
OH

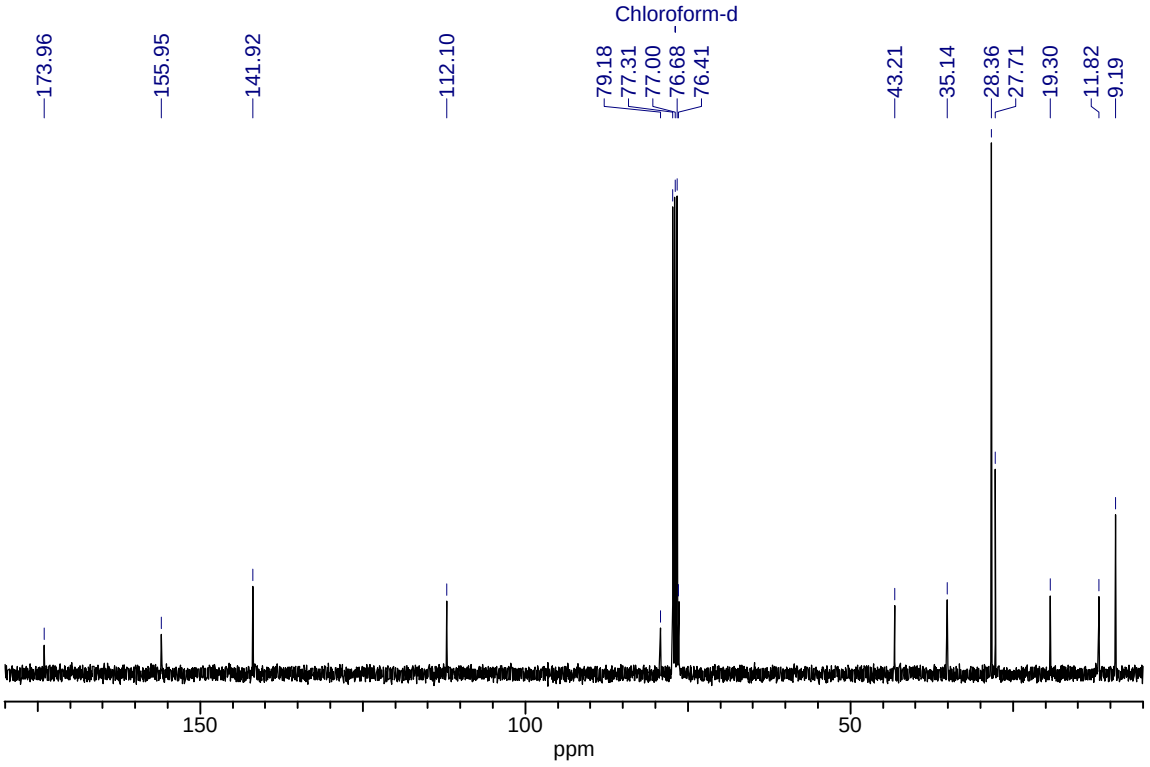
155 R = TBS

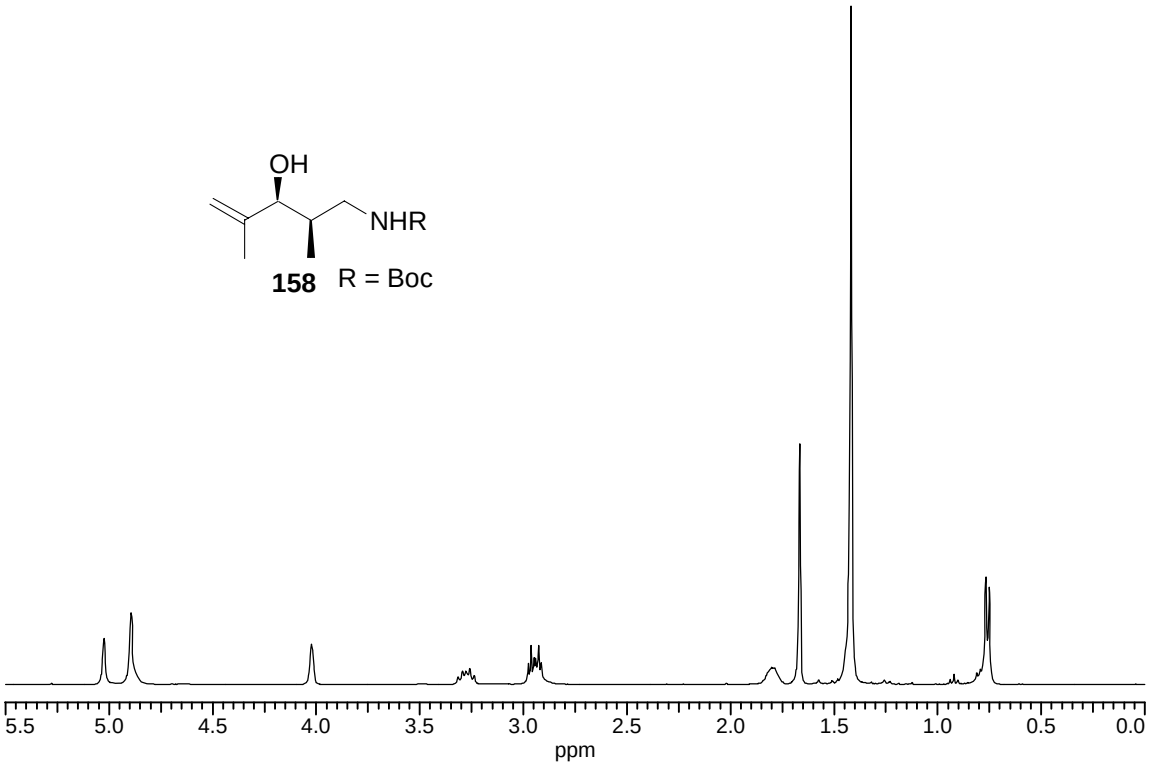
11
10
9
8
7
6
5
4
3
2
1
0
ppm

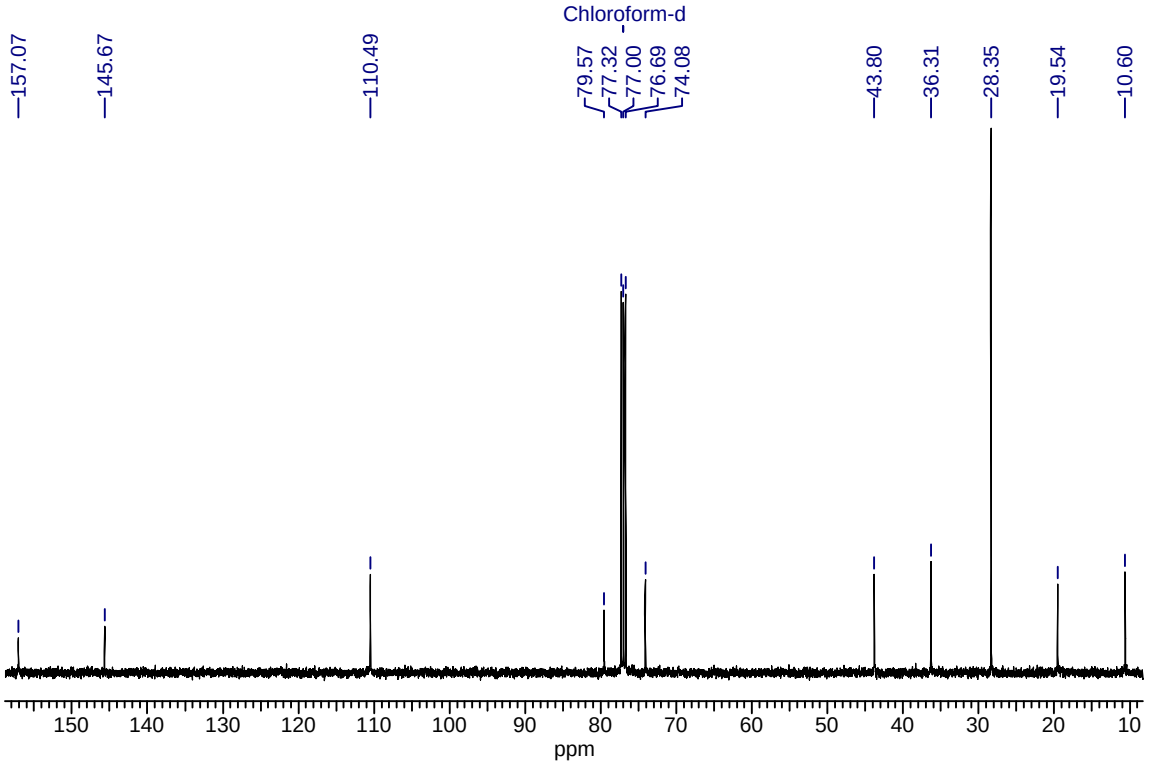

Chloroform-d
180.79
144.68
113.16
77.46
77.32
77.00
76.68
44.33
25.74
18.14
17.74
11.34
-4.65
150
100
50
0
ppm

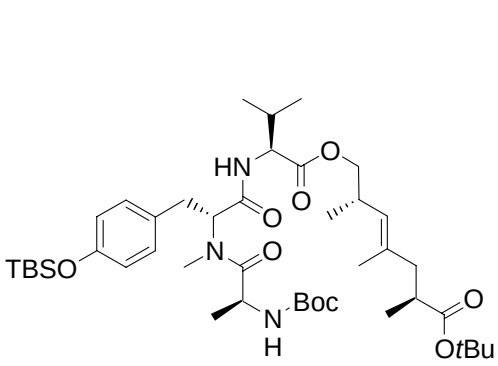

O
O
NHR
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

147 R = Boc


Chloroform-d
173.96
155.95
141.92
112.10
79.18
77.31
77.00
76.68
76.41
43.21
35.14
28.36
27.71
19.30
11.82
9.19
150
100
50
ppm

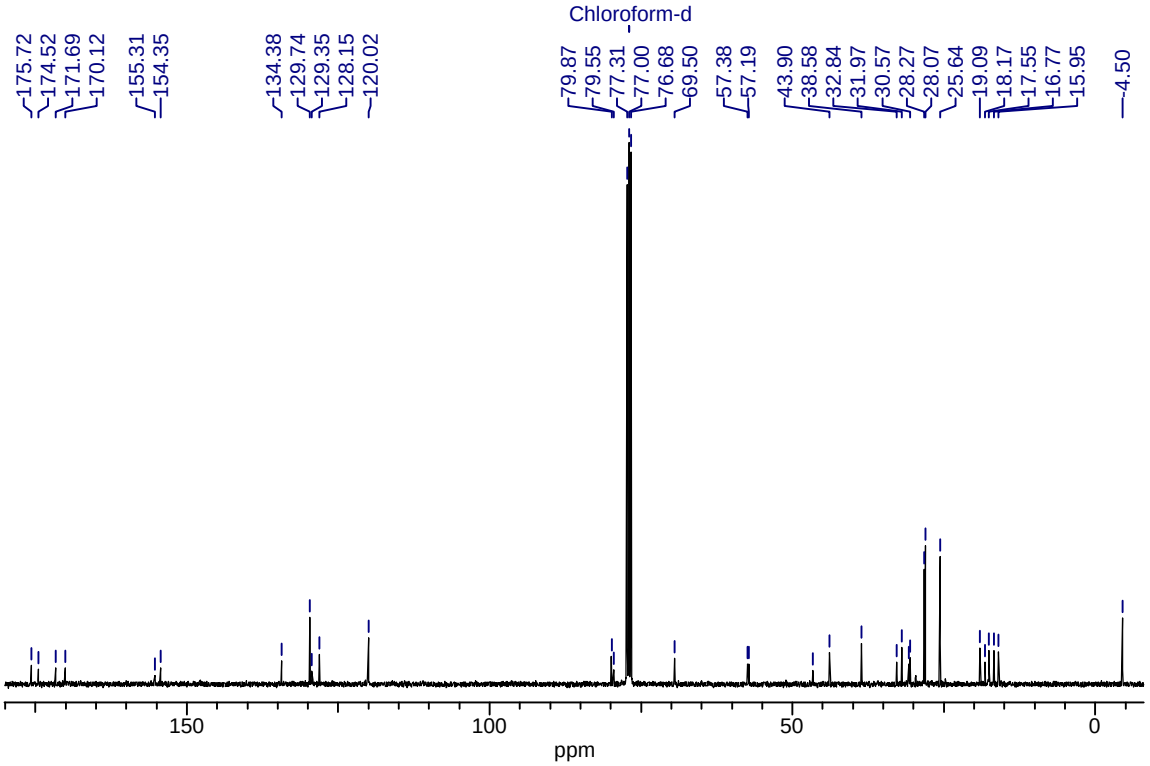

OH
NHR
158 R = Boc
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

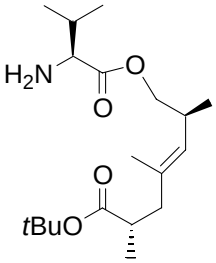

Chloroform-d
157.07
145.67
110.49
79.57
77.32
77.00
76.69
74.08
43.80
36.31
28.35
19.54
10.60
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


HN
O
O
TBSO
N
O
Boc
N
H
O
O*t*Bu

161

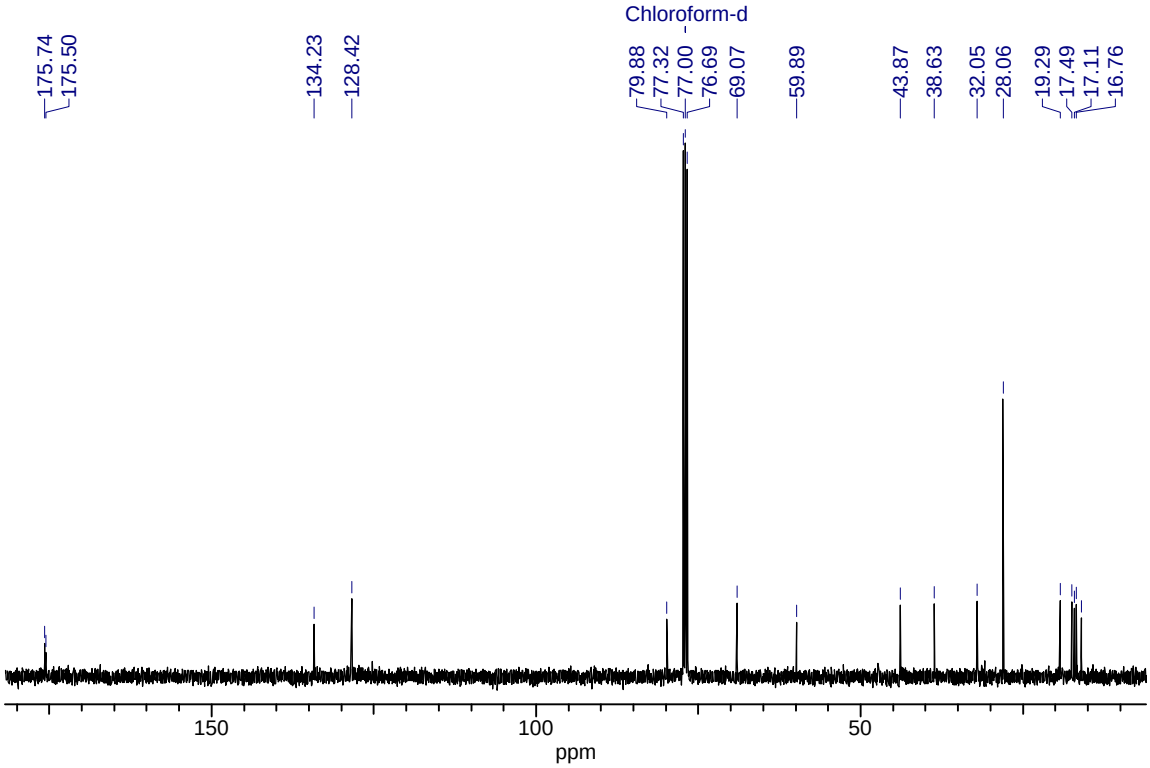
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

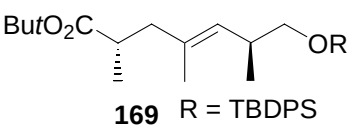

Chloroform-d
175.72
174.52
171.69
170.12
155.31
154.35
134.38
129.74
129.35
128.15
120.02
79.87
79.55
77.31
77.00
76.68
69.50
57.38
57.19
43.90
38.58
32.84
31.97
30.57
28.27
28.07
25.64
19.09
18.17
17.55
16.77
15.95
4.50
150
100
50
0
ppm


H2N
O
O
O
tBuO

163

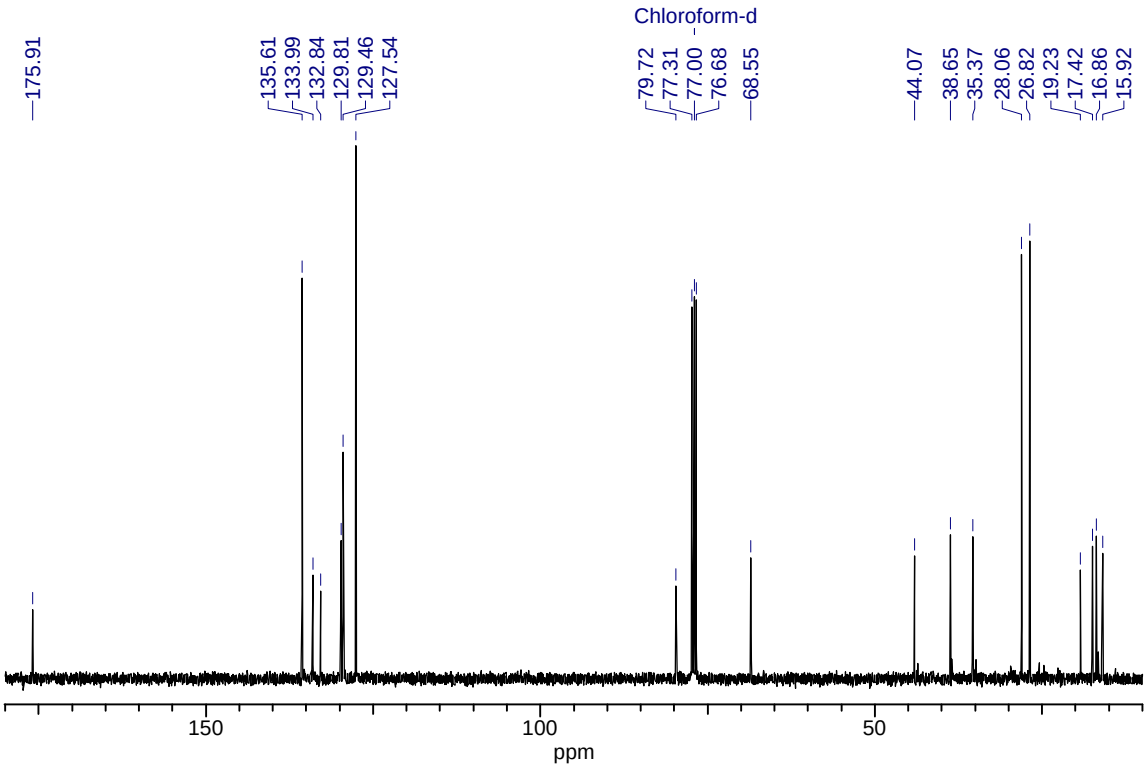
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

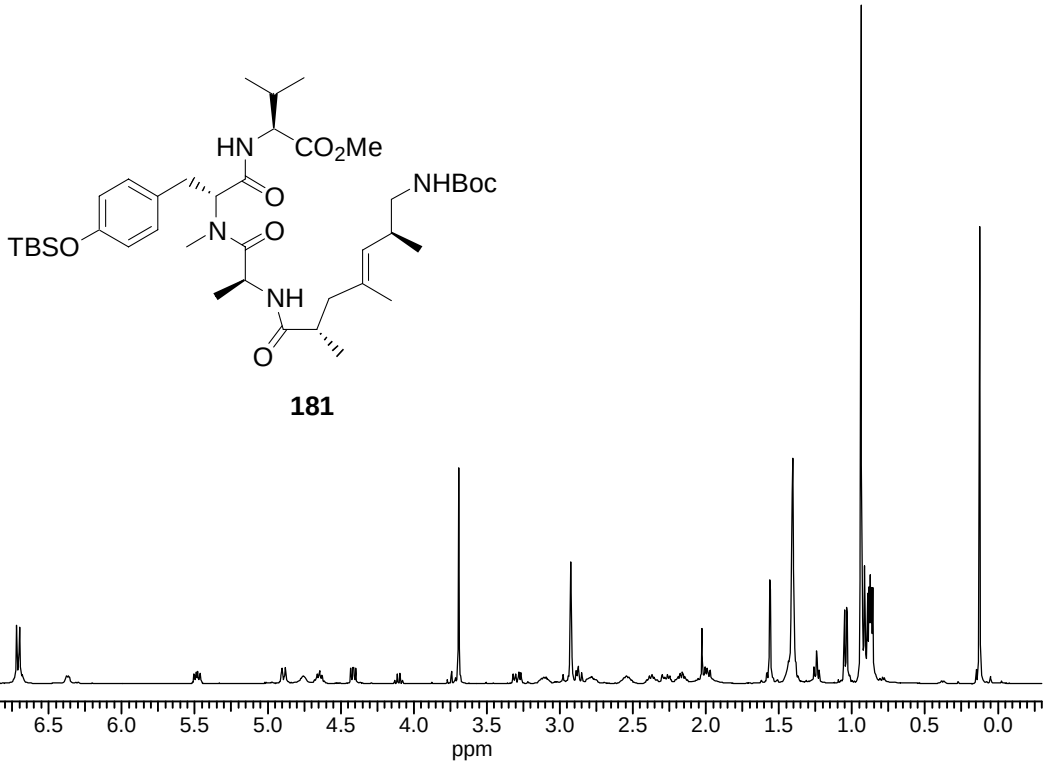

Chloroform-d
175.74
175.50
134.23
128.42
79.88
77.32
77.00
76.69
69.07
59.89
43.87
38.63
32.05
28.06
19.29
17.49
17.11
16.76
150
100
50
ppm


ButO2C
OR

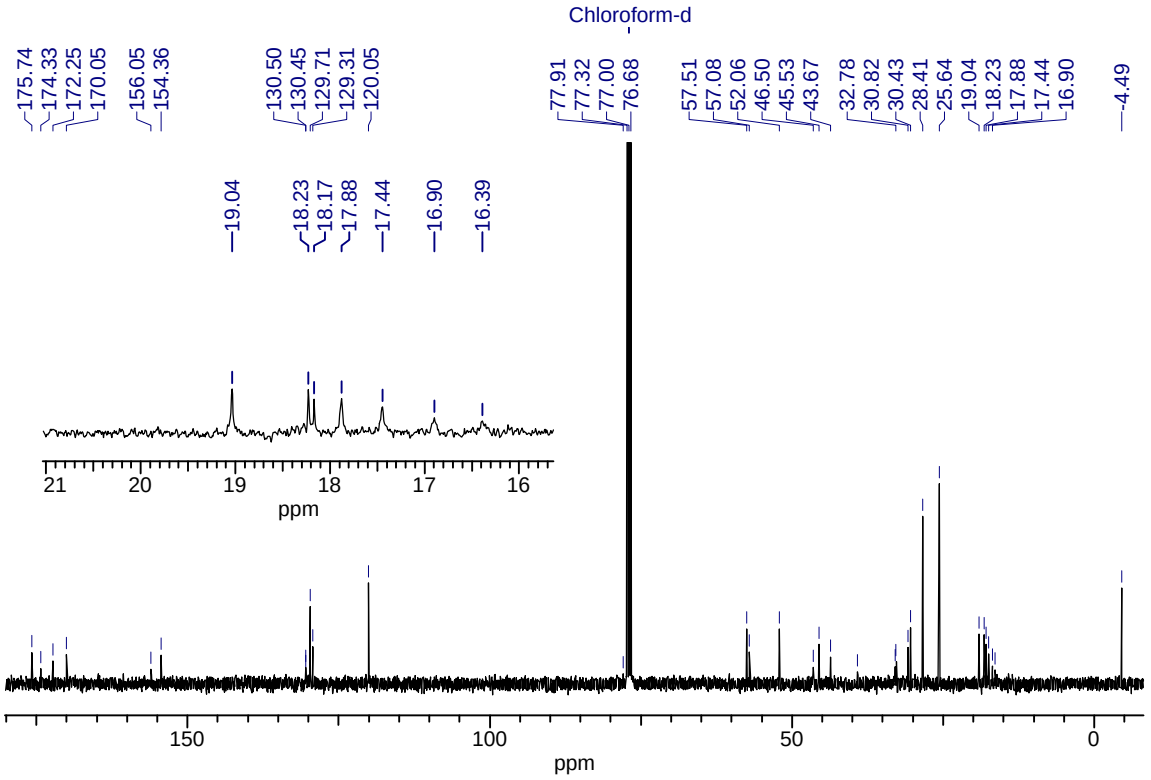
169 R = TBDPS

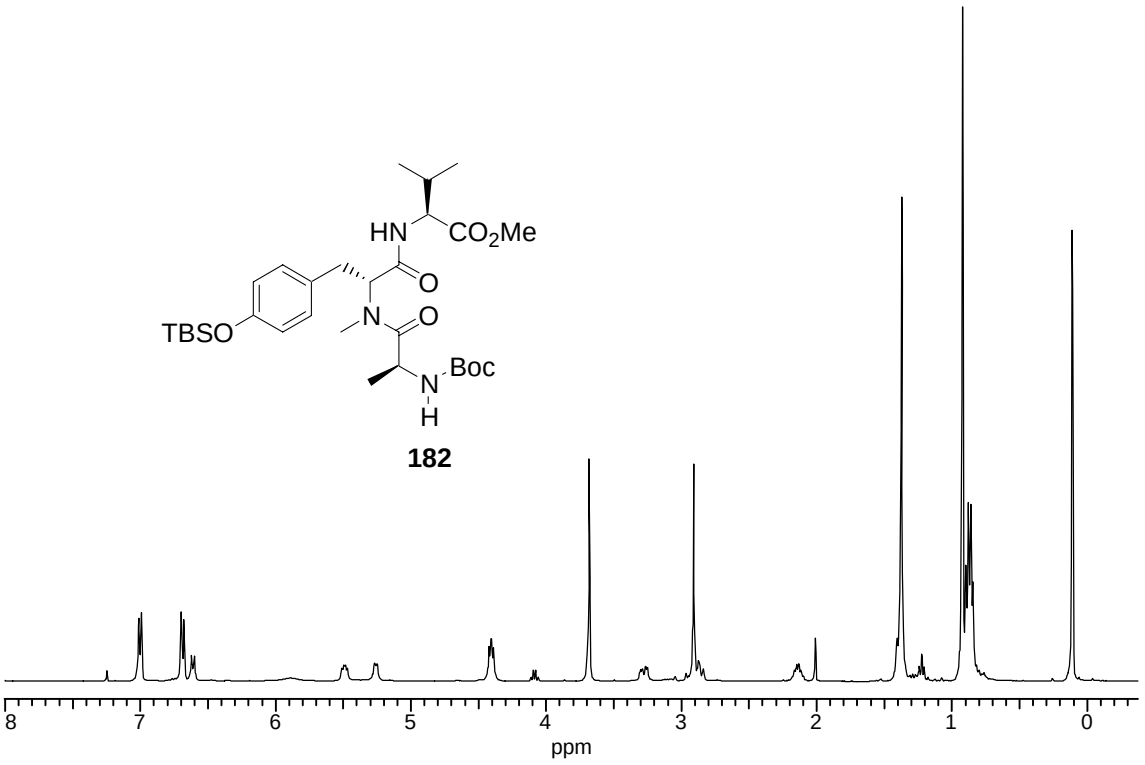
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

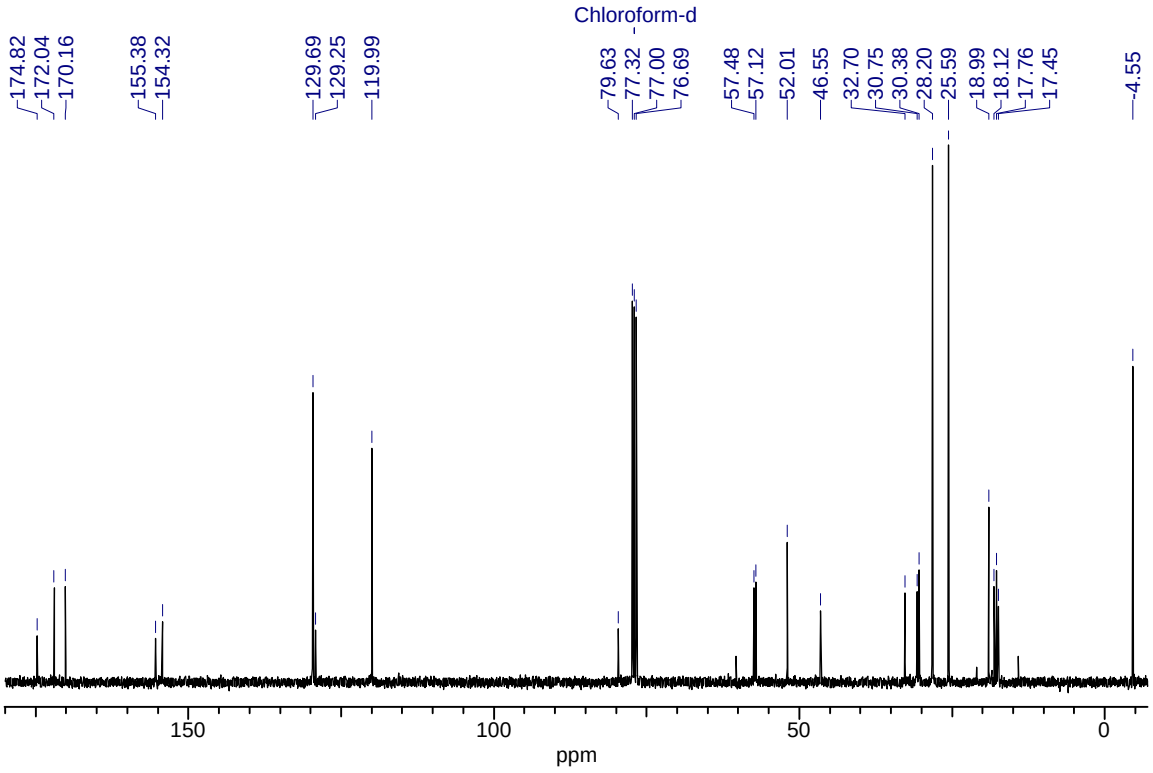

Chloroform-d
175.91
135.61
133.99
132.84
129.81
129.46
127.54
79.72
77.31
77.00
76.68
68.55
44.07
38.65
35.37
28.06
26.82
19.23
17.42
16.86
15.92
150
100
50
ppm

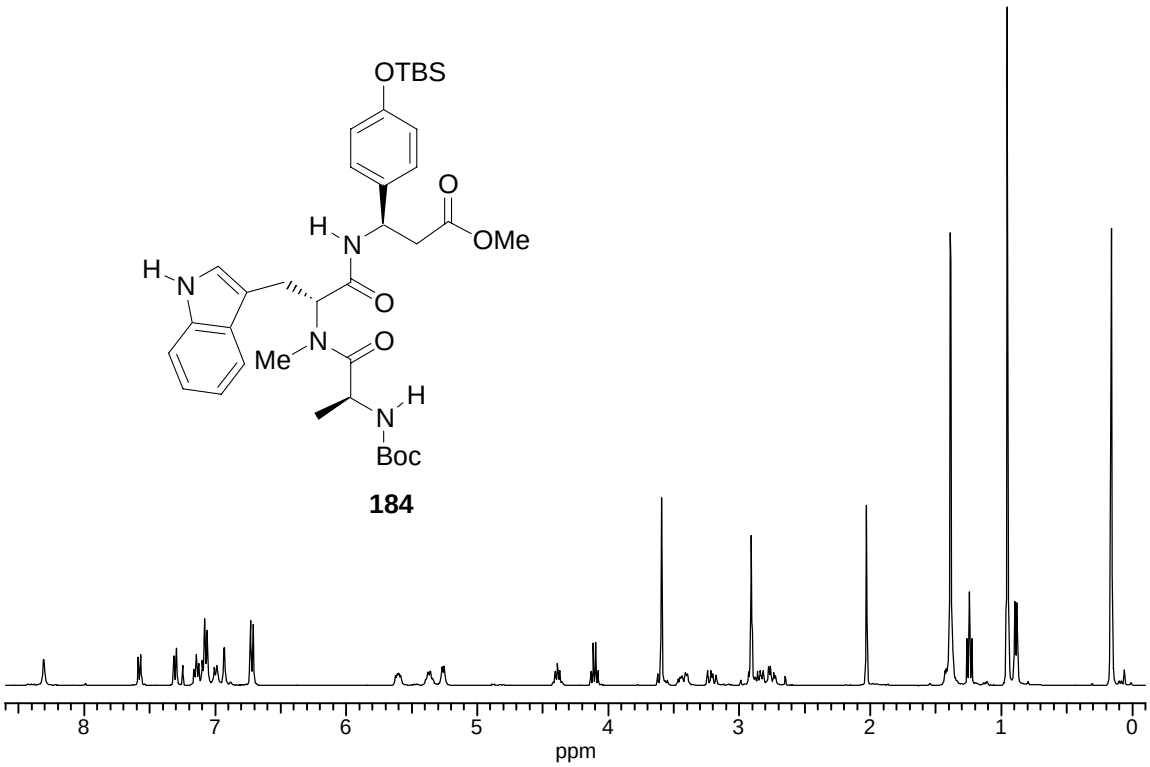

HN
CO2Me
NHBoc
O
N
O
TBSO
NH
O
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm

181

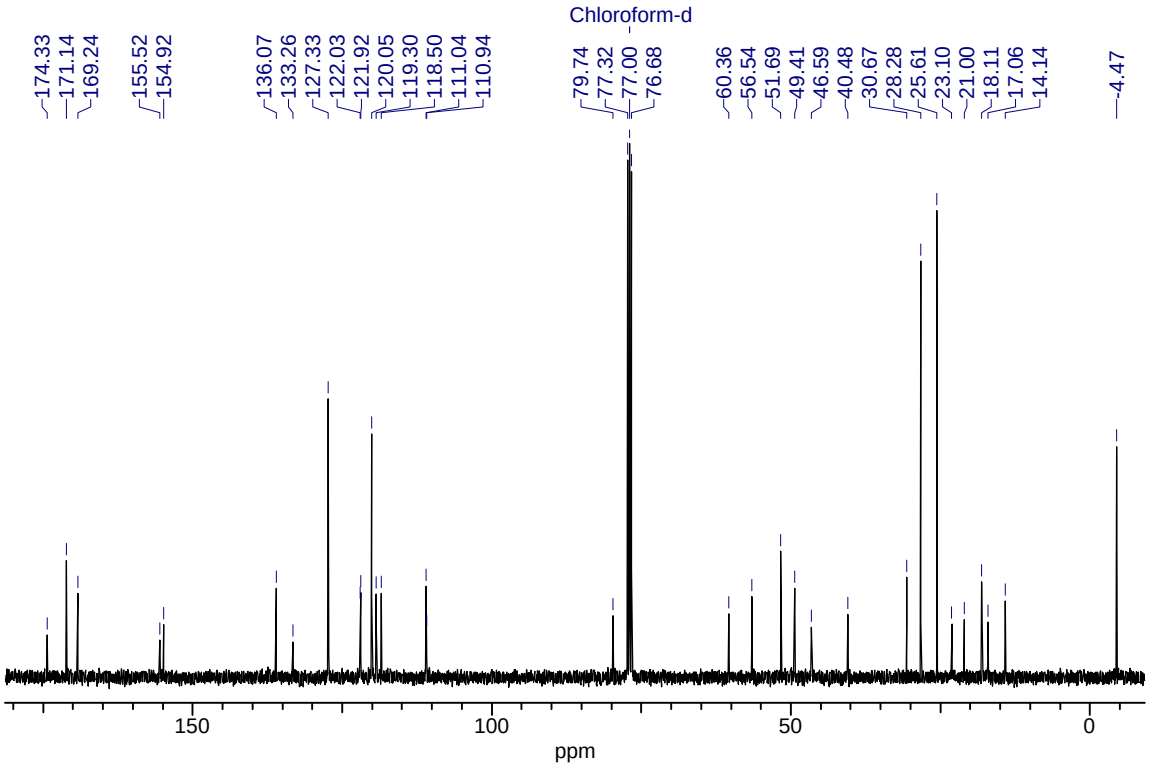

Chloroform-d
175.74
174.33
172.25
170.05
156.05
154.36
130.50
130.45
129.71
129.31
120.05
77.91
77.32
77.00
76.68
57.51
57.08
52.06
46.50
45.53
43.67
32.78
30.82
30.43
28.41
25.64
19.04
18.23
17.88
17.44
16.90
-4.49
19.04
18.23
18.17
17.88
17.44
16.90
16.39
21 20 19 18 17 16
ppm
150 100 50 0
ppm

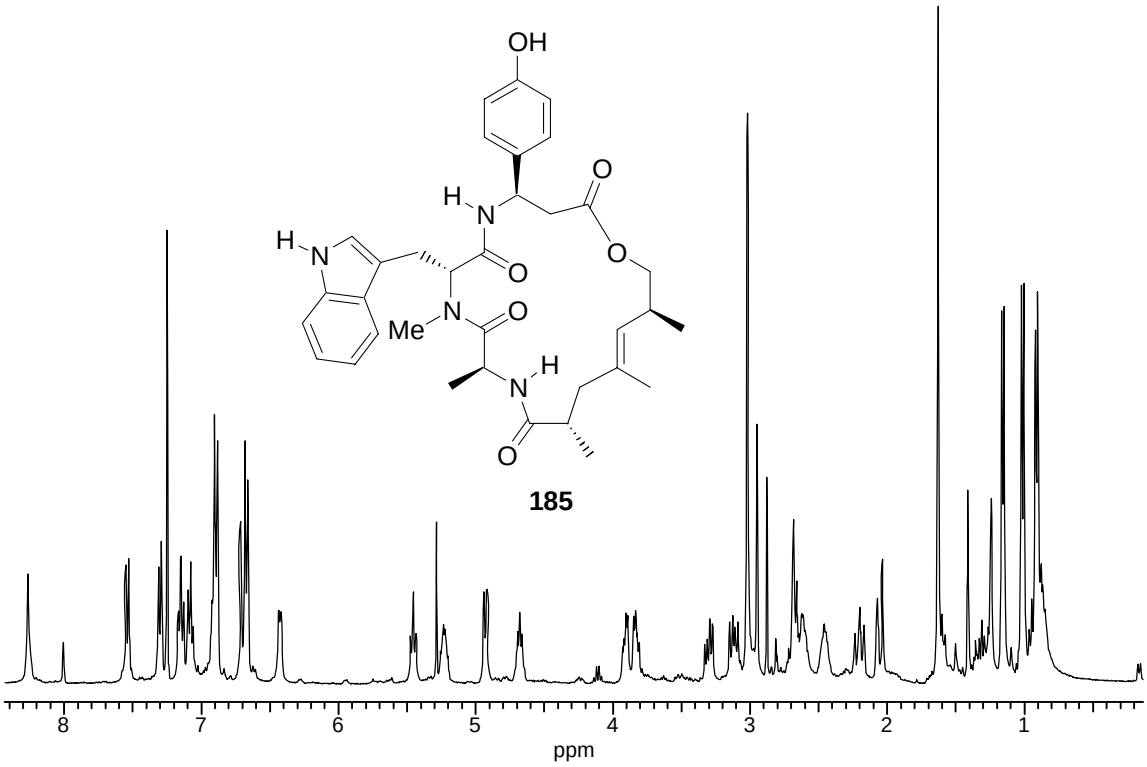

HN
CO2Me
O
N
O
TBSO
Boc
N
H
182
8
7
6
5
4
3
2
1
0
ppm


Chloroform-d
174.82
172.04
170.16
155.38
154.32
129.69
129.25
119.99
79.63
77.32
77.00
76.69
57.48
57.12
52.01
46.55
32.70
30.75
30.38
28.20
25.59
18.99
18.12
17.76
17.45
-4.55
150
100
50
0
ppm


OTBS
O
H
N
OMe
H
N
O
Me
N
O
H
N
Boc
8
7
6
5
4
3
2
1
0
ppm

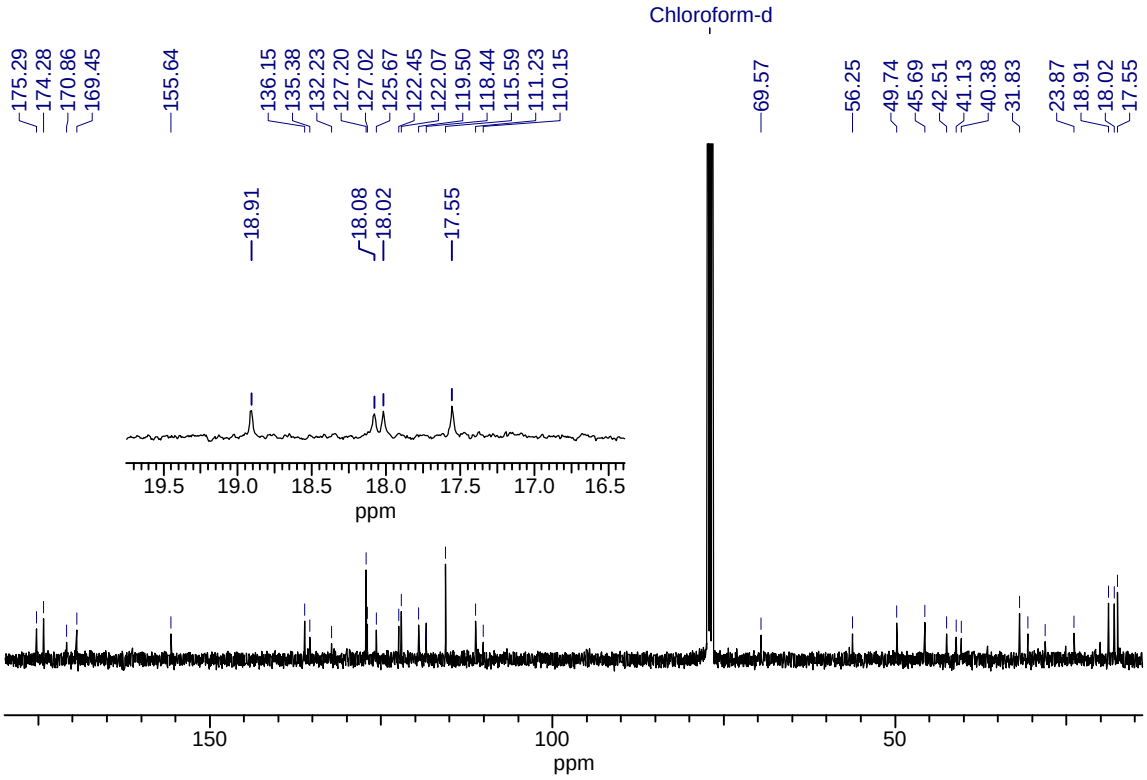
184

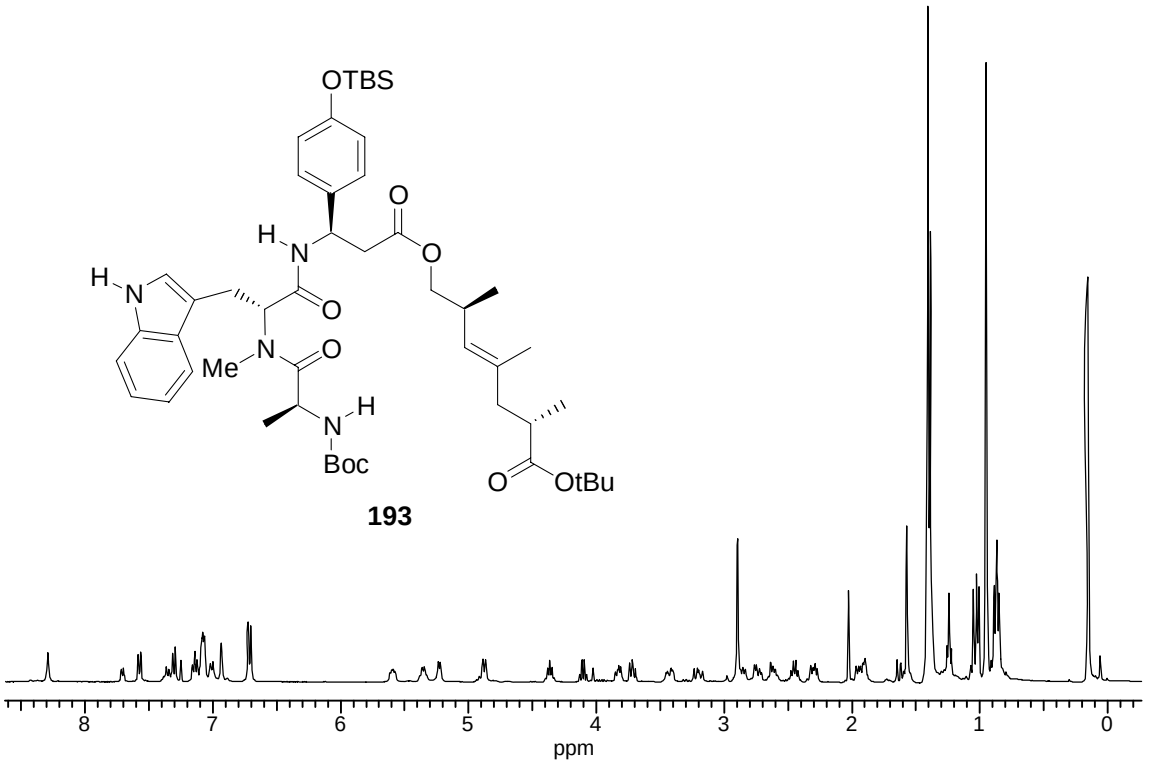

Chloroform-d
174.33
171.14
169.24
155.52
154.92
136.07
133.26
127.33
122.03
121.92
120.05
119.30
118.50
111.04
110.94
79.74
77.32
77.00
76.68
60.36
56.54
51.69
49.41
46.59
40.48
30.67
28.28
25.61
23.10
21.00
18.11
17.06
14.14
-4.47
150
100
50
0
ppm

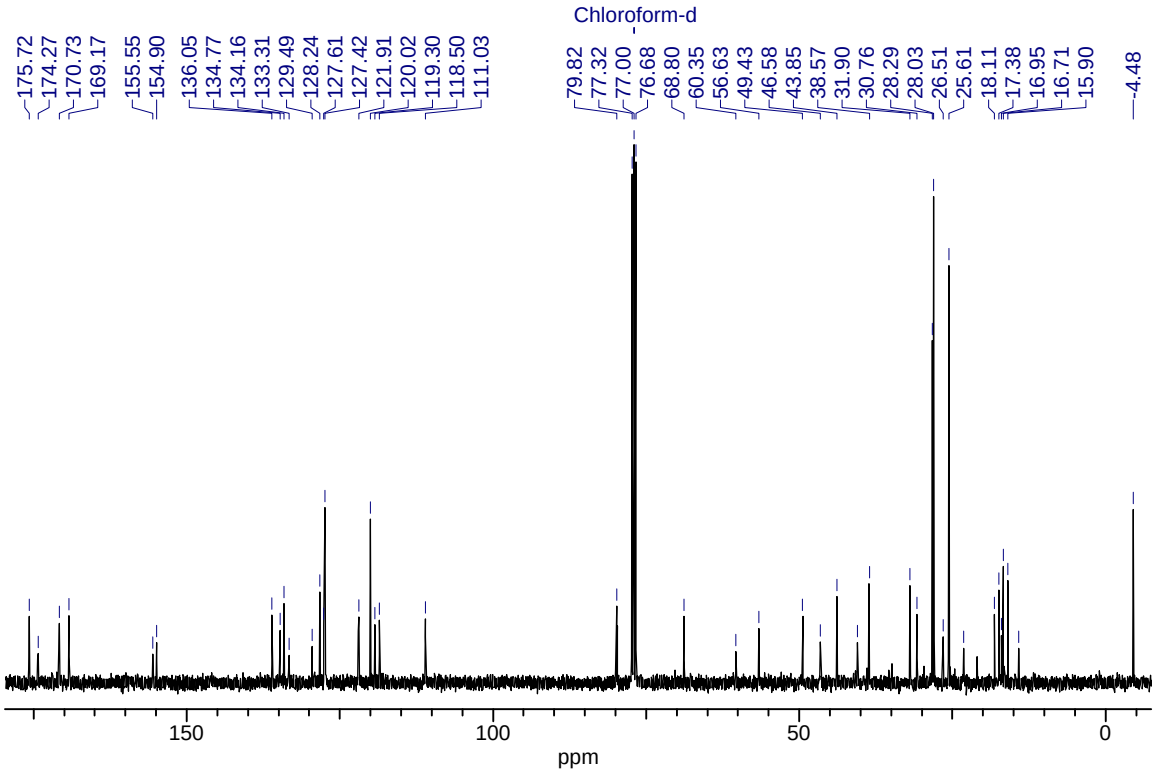

OH
H
N
O
O
H
N
O
N
Me
O
H
N
O
O

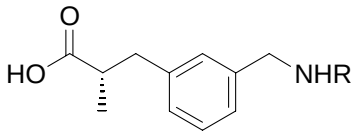
185

8
7
6
5
4
3
2
1
ppm


Chloroform-d
175.29
174.28
170.86
169.45
155.64
136.15
135.38
132.23
127.20
127.02
125.67
122.45
122.07
119.50
118.44
115.59
111.23
110.15
69.57
56.25
49.74
45.69
42.51
41.13
40.38
31.83
23.87
18.91
18.02
17.55
18.91
18.08
18.02
17.55
19.5
19.0
18.5
18.0
17.5
17.0
16.5
ppm
150
100
50
ppm

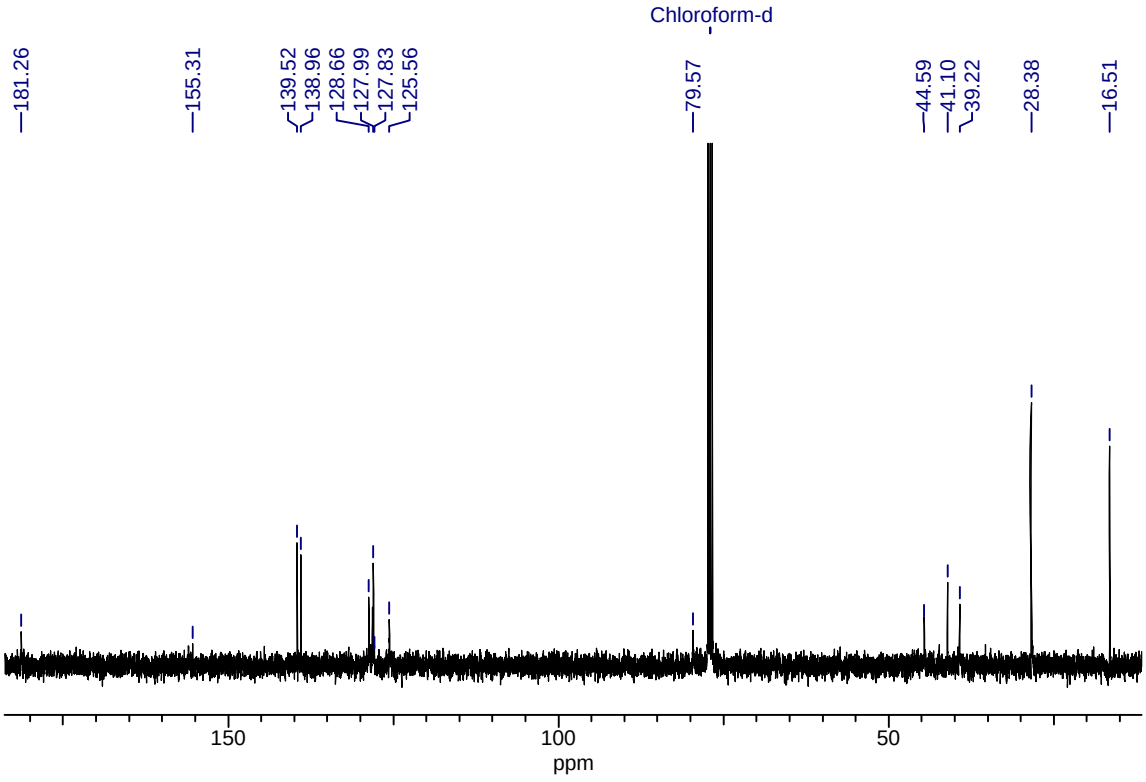

OTBS
O
H
N
O
H
N
O
Me
N
O
H
N
Boc
O
OtBu
193
8
7
6
5
4
3
2
1
0
ppm

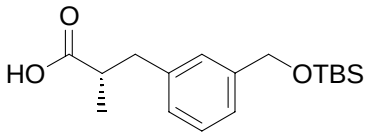

Chloroform-d
175.72
174.27
170.73
169.17
155.55
154.90
136.05
134.77
134.16
133.31
129.49
128.24
127.61
127.42
121.91
120.02
119.30
118.50
111.03
79.82
77.32
77.00
76.68
68.80
60.35
56.63
49.43
46.58
43.85
38.57
31.90
30.76
28.29
28.03
26.51
25.61
18.11
17.38
16.95
16.71
15.90
4.48
150
100
50
0
ppm


O
HO
NHR

194 R = Boc

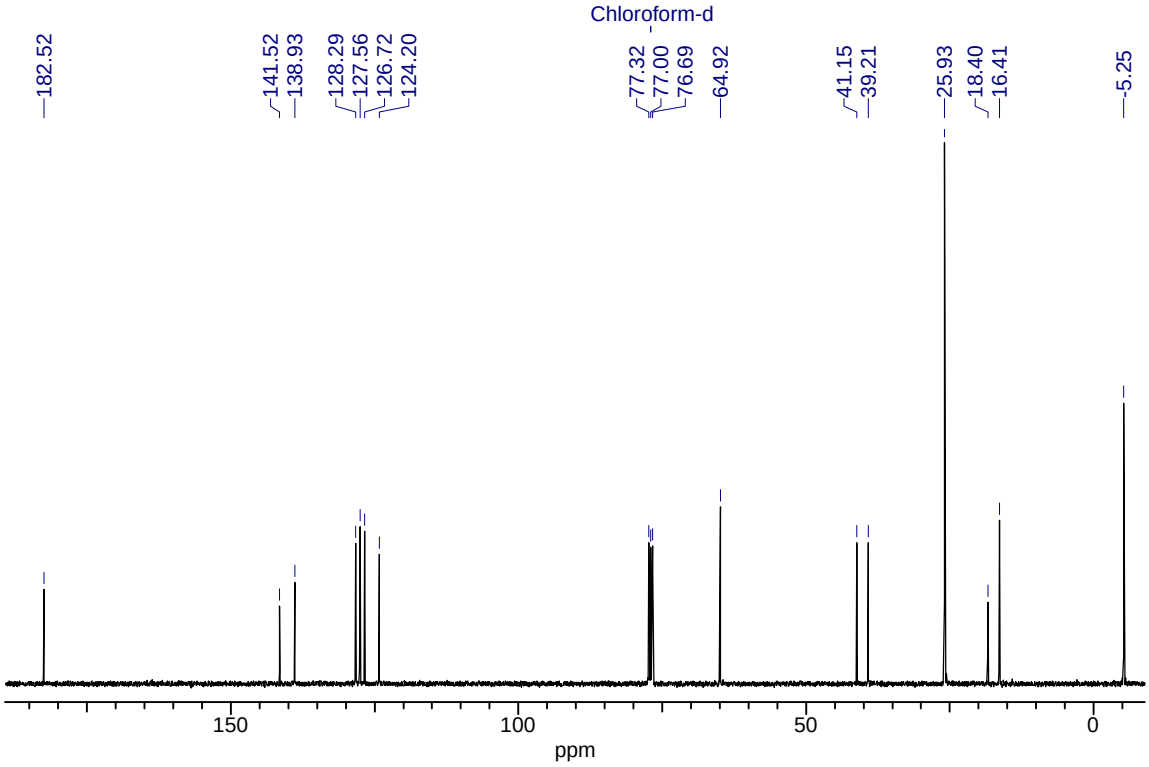
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

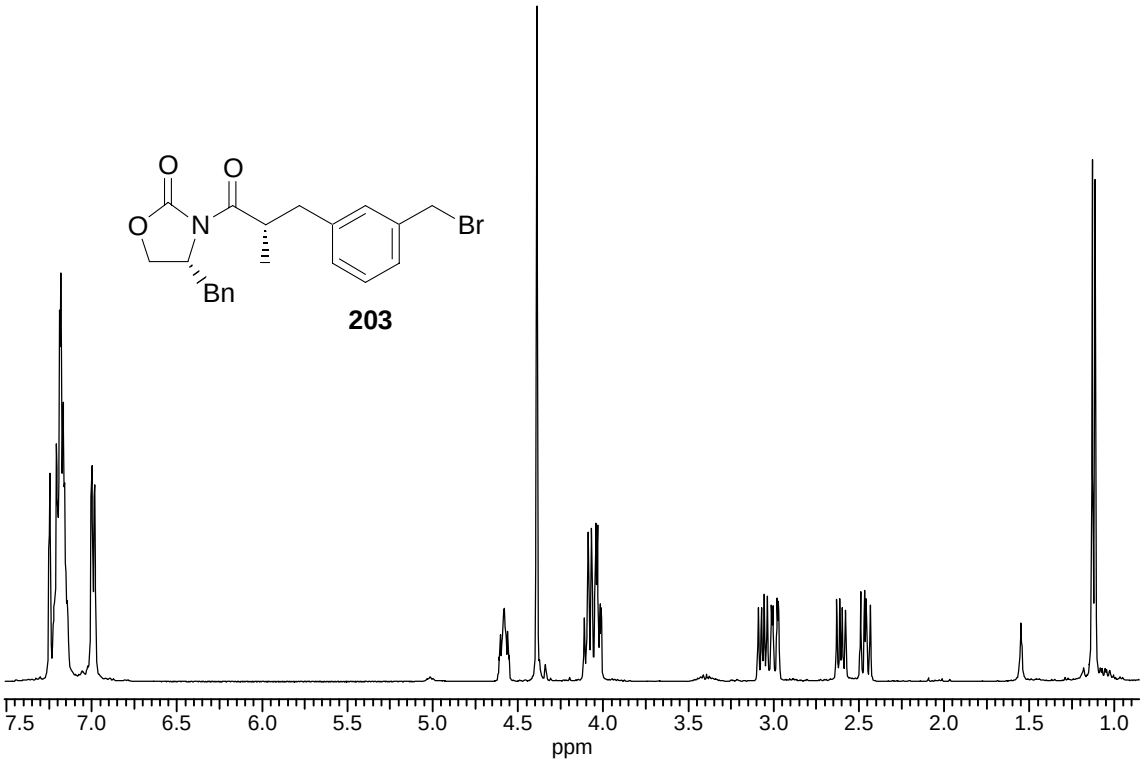

Chloroform-d
181.26
155.31
139.52
138.96
128.66
127.99
127.83
125.56
79.57
44.59
41.10
39.22
28.38
16.51
150
100
50
ppm


O
HO
OTBS

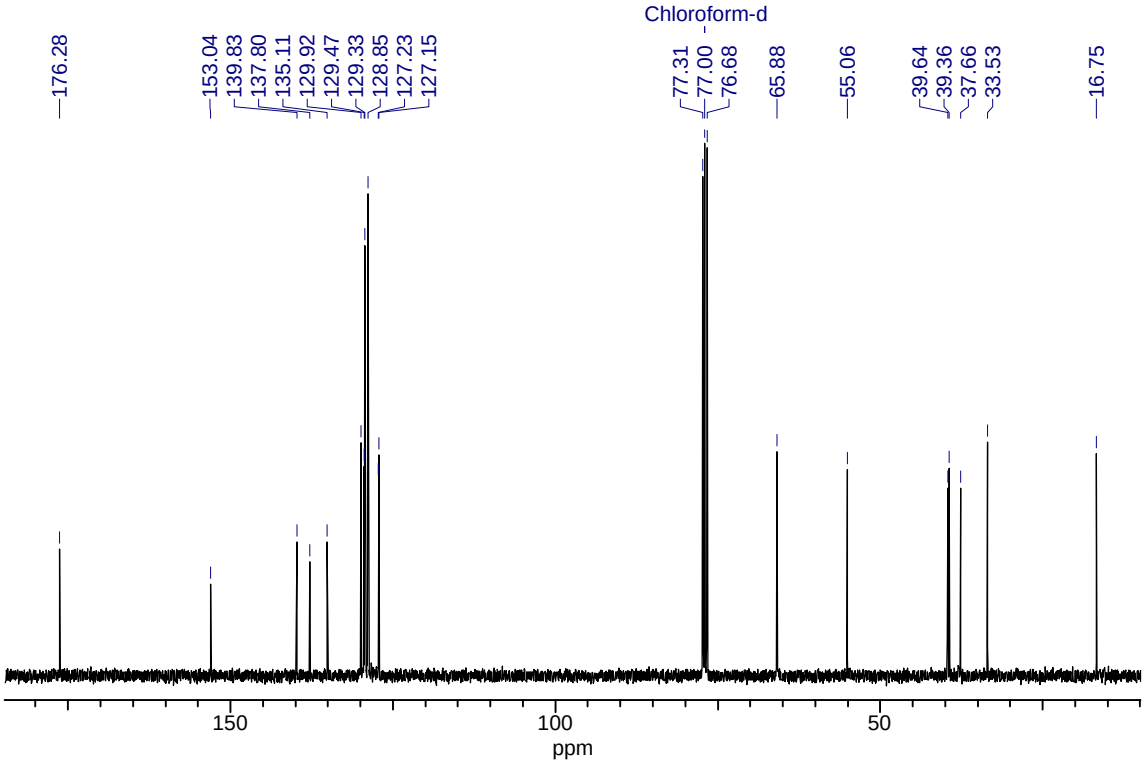
195

10
9
8
7
6
5
4
3
2
1
0
ppm


Chloroform-d
182.52
141.52
138.93
128.29
127.56
126.72
124.20
77.32
77.00
76.69
64.92
41.15
39.21
25.93
18.40
16.41
-5.25
150
100
50
0
ppm


O
O
O
N
Br
Bn
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

203


Chloroform-d
176.28
153.04
139.83
137.80
135.11
129.92
129.47
129.33
128.85
127.23
127.15
77.31
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65.88
55.06
39.64
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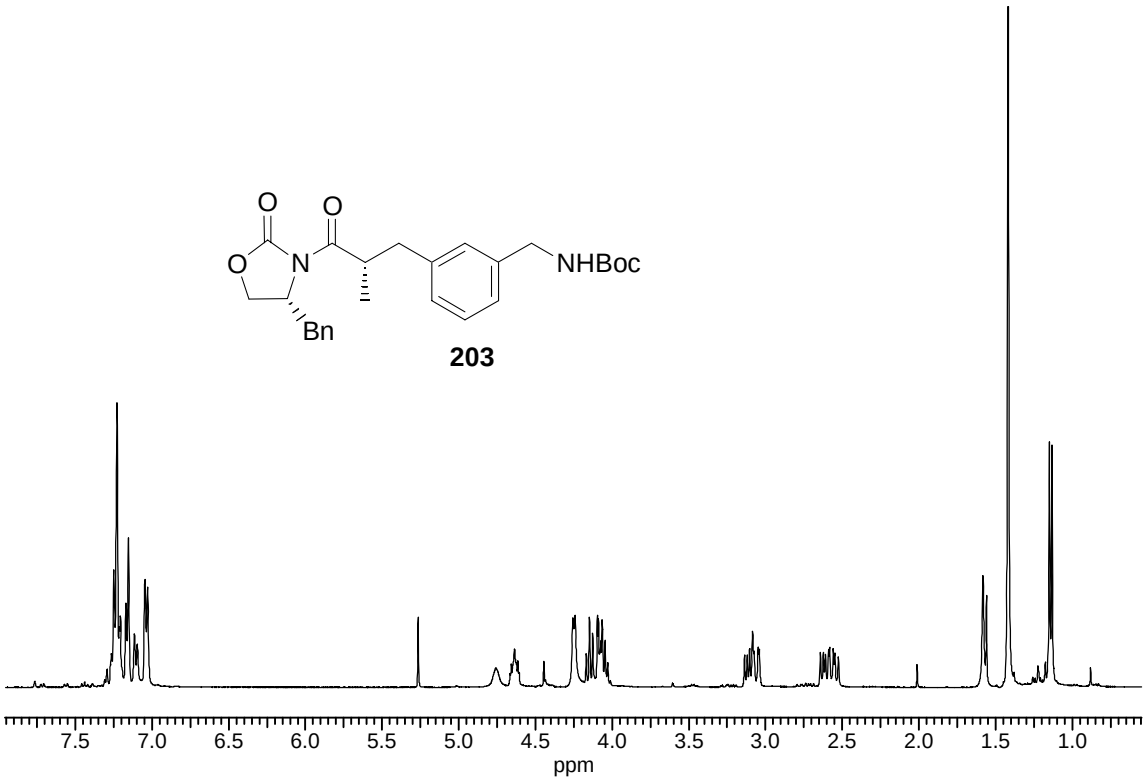
37.66
33.53
16.75
150
100
50
ppm


O
O
O
N
NHBoc
Bn
7.5
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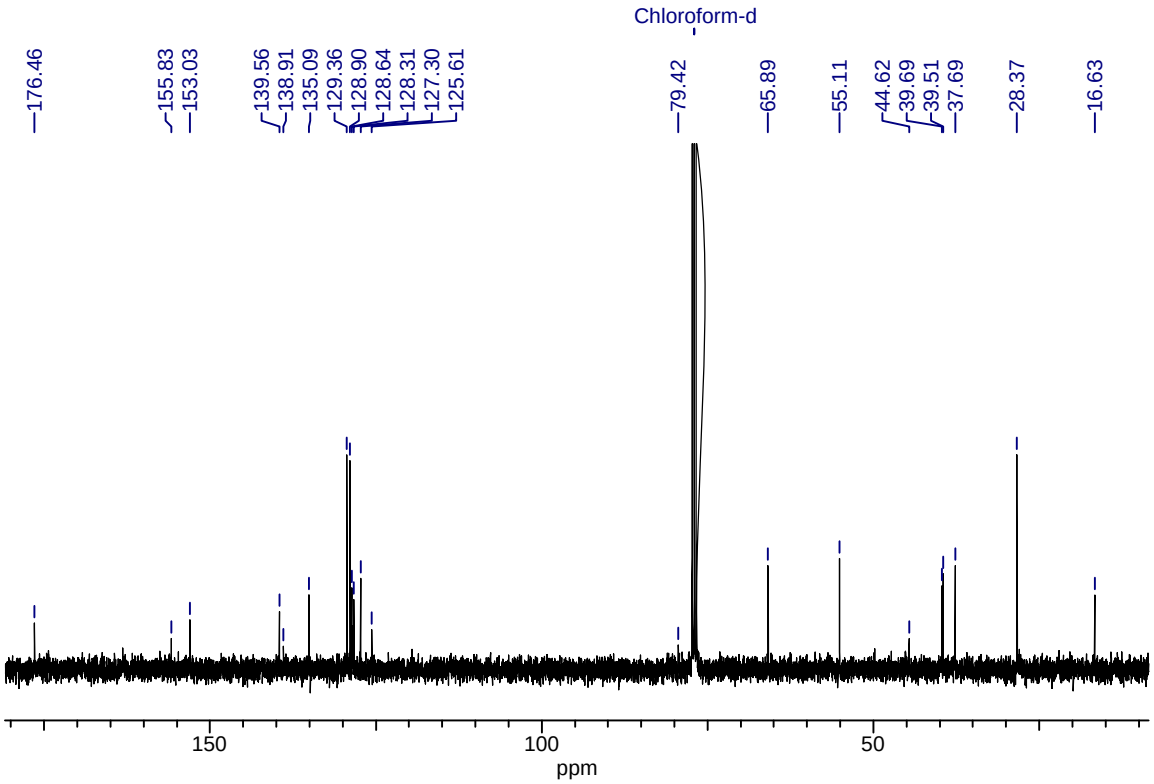
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

203


Chloroform-d
176.46
155.83
153.03
139.56
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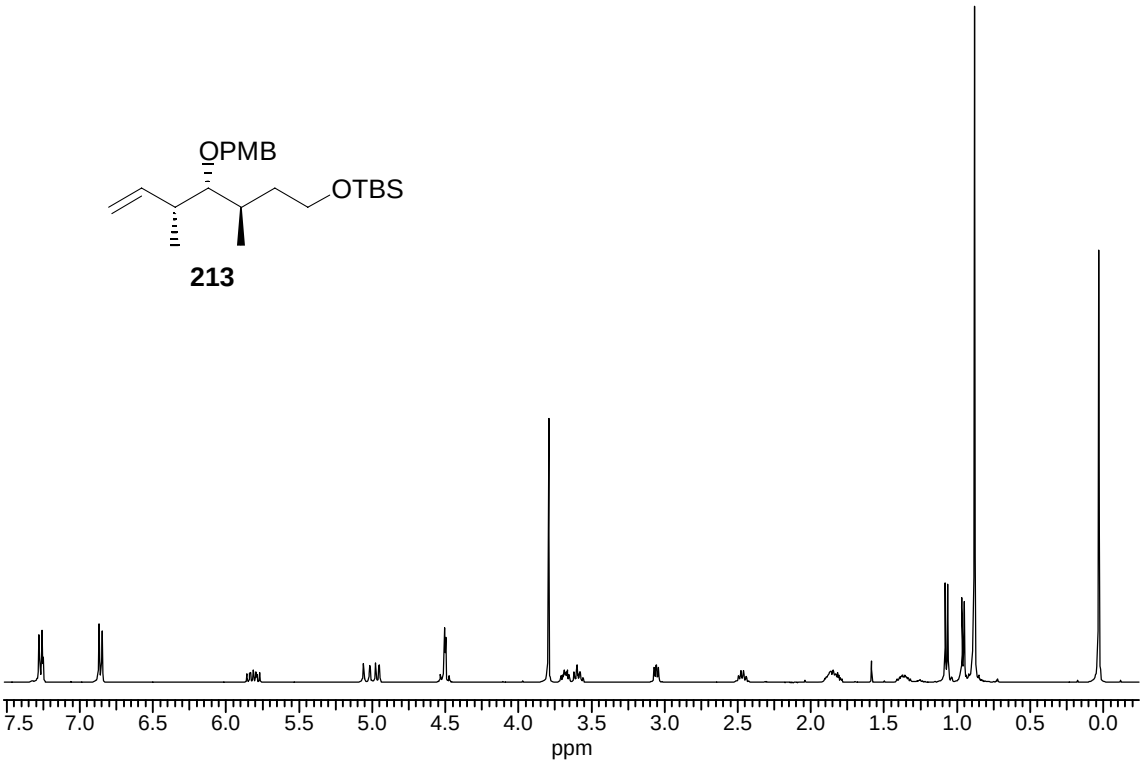
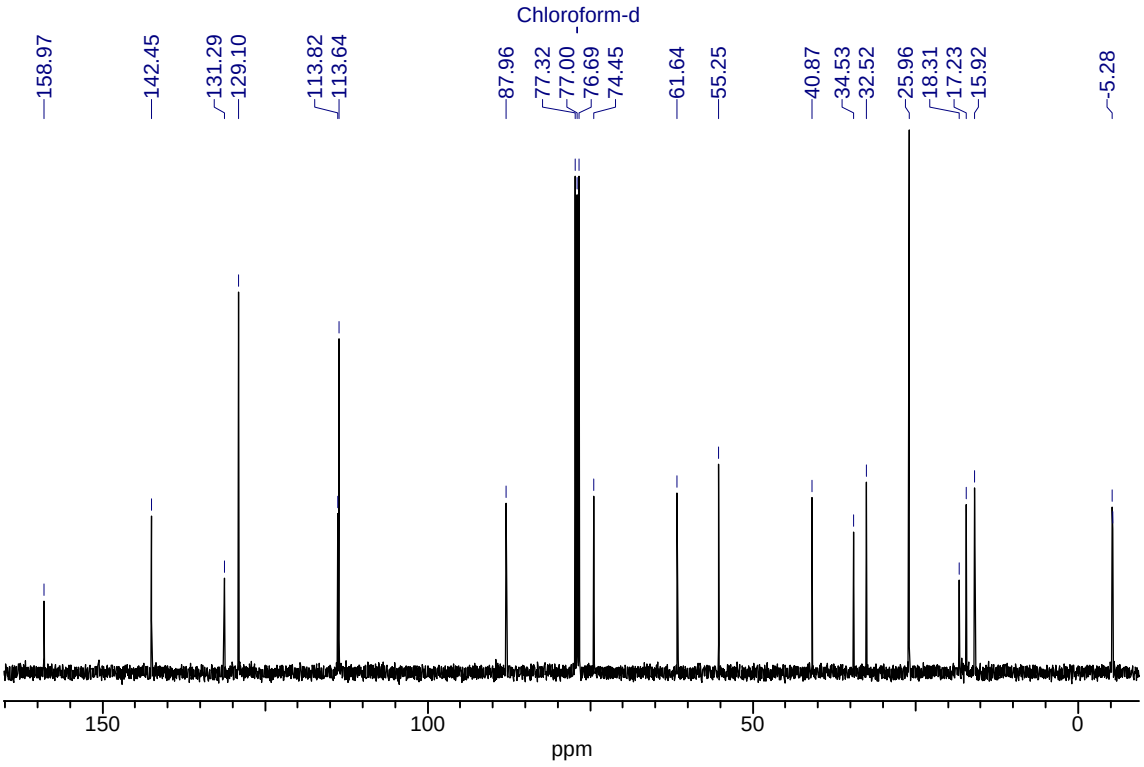
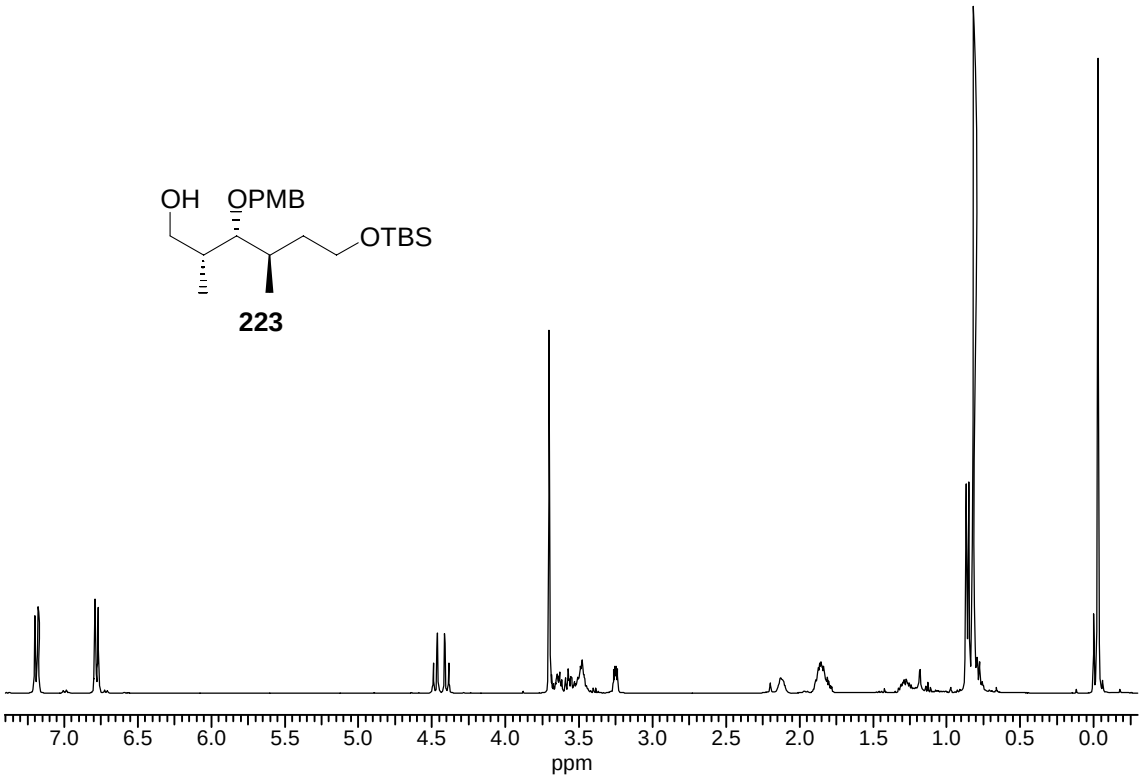
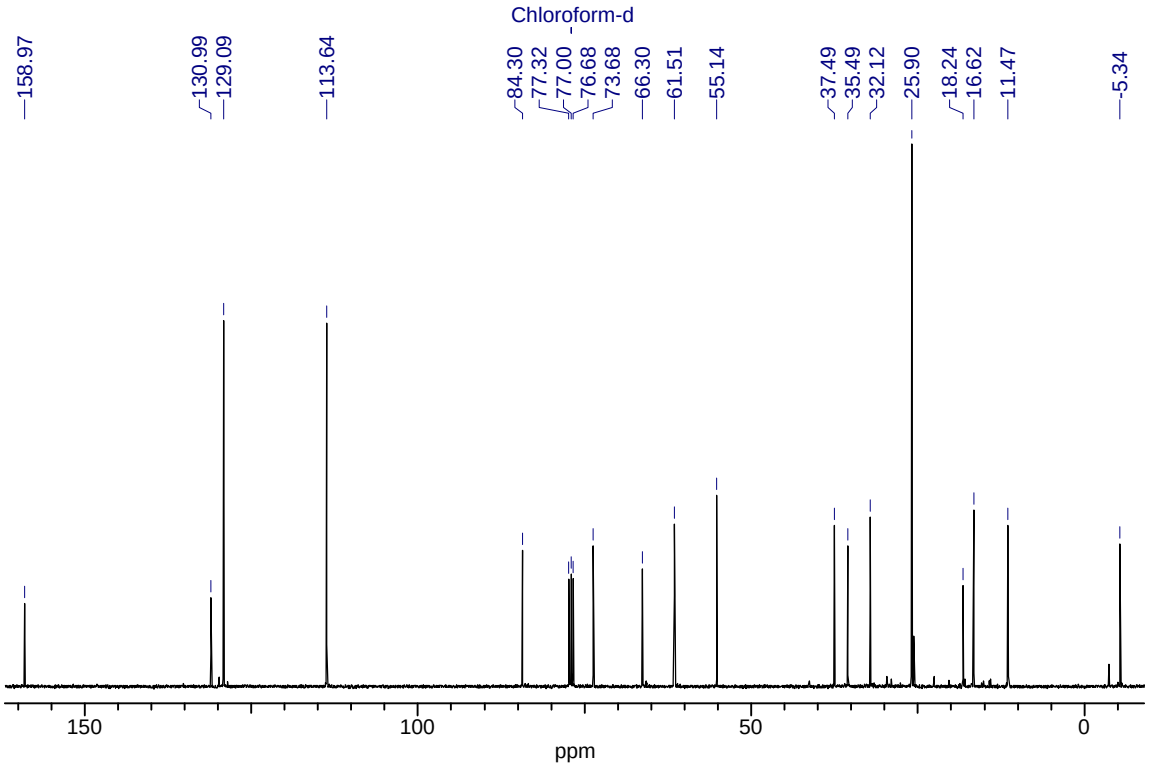
135.09
129.36
128.90
128.64
128.31
127.30
125.61
79.42
65.89
55.11
44.62
39.69
39.51
37.69
28.37
16.63
150
100
50
ppm


OPMB
OTBS
213
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


Chloroform-d
158.97
142.45
131.29
129.10
113.82
113.64
87.96
77.32
77.00
76.69
74.45
61.64
55.25
40.87
34.53
32.52
25.96
18.31
17.23
15.92
5.28
150 100 50 0
ppm


OH
OPMB
OTBS
223
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm


Chloroform-d
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130.99
129.09
113.64
84.30
77.32
77.00
76.68
73.68
66.30
61.51
55.14
37.49
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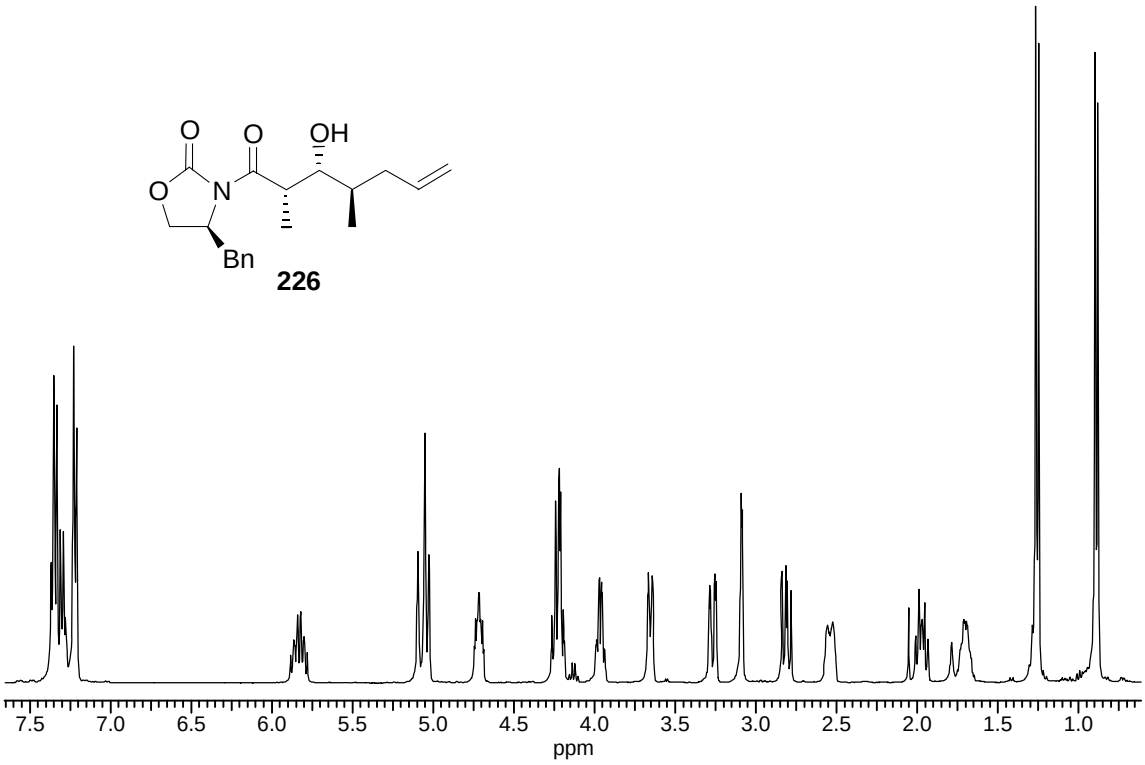
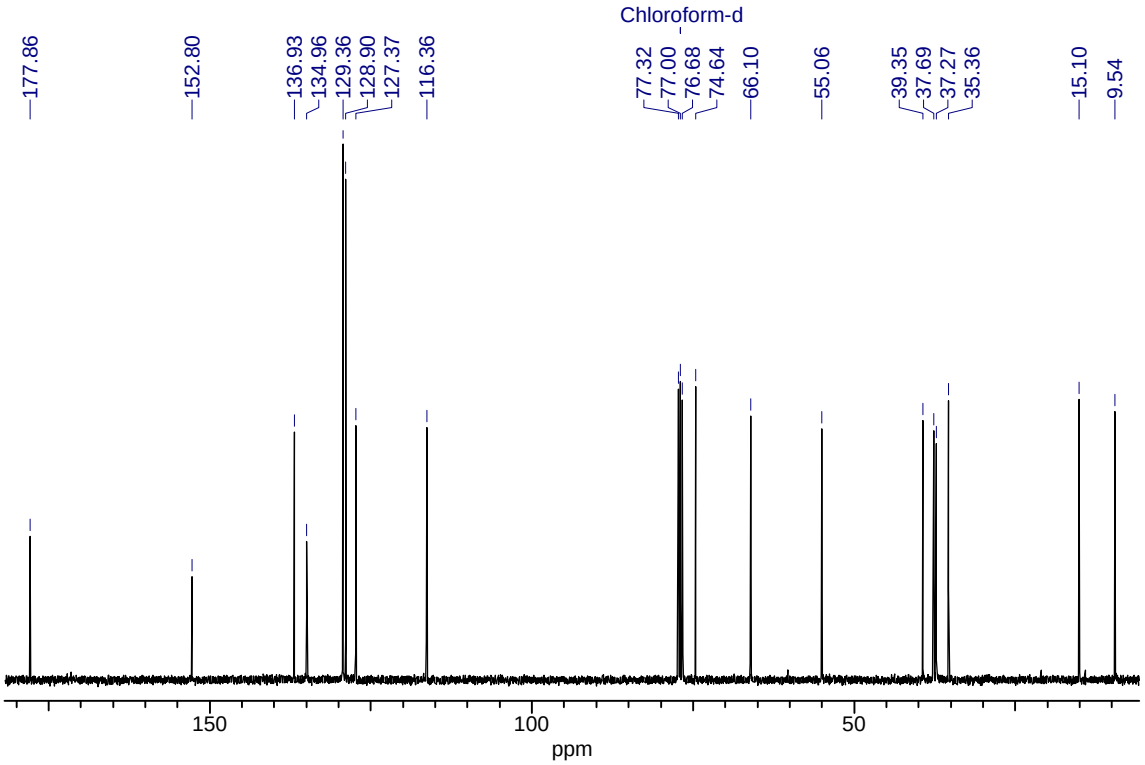
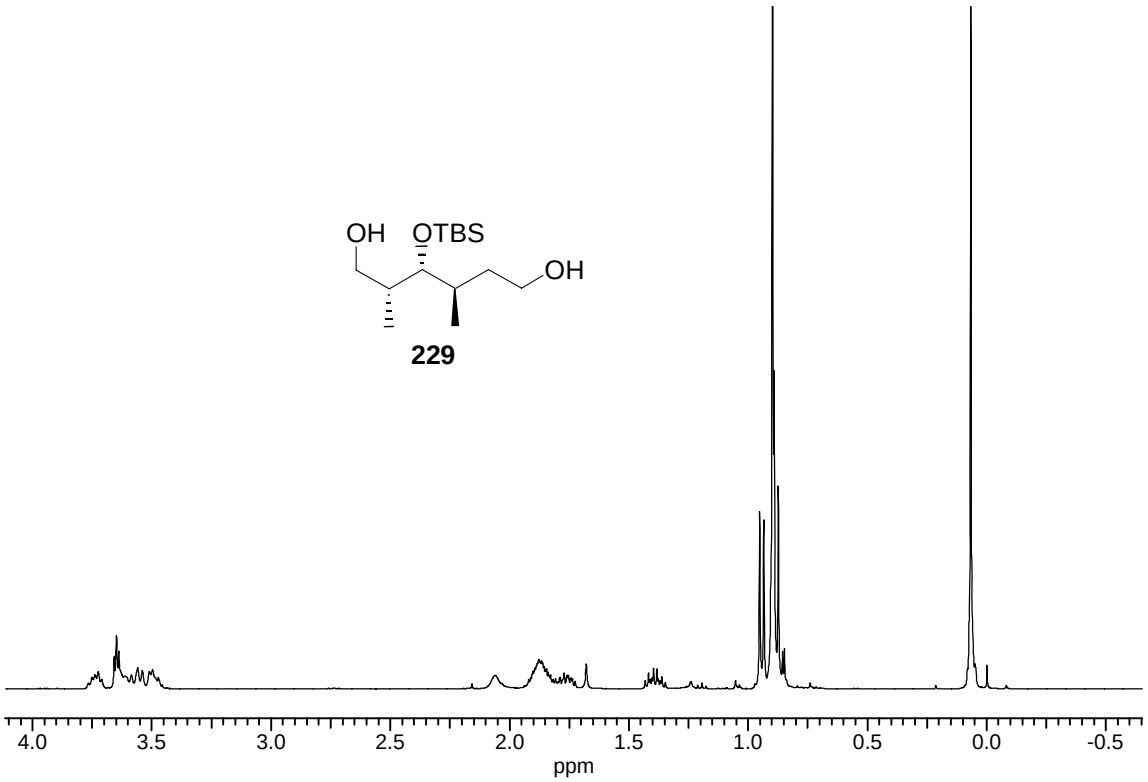
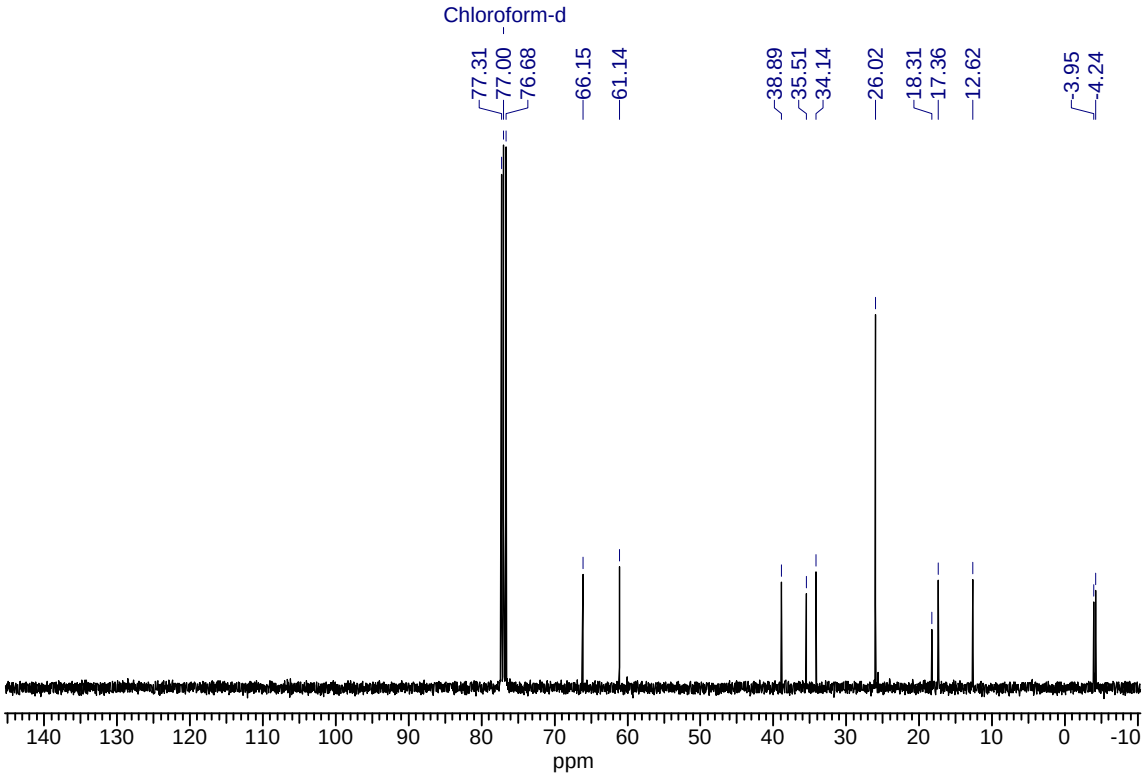
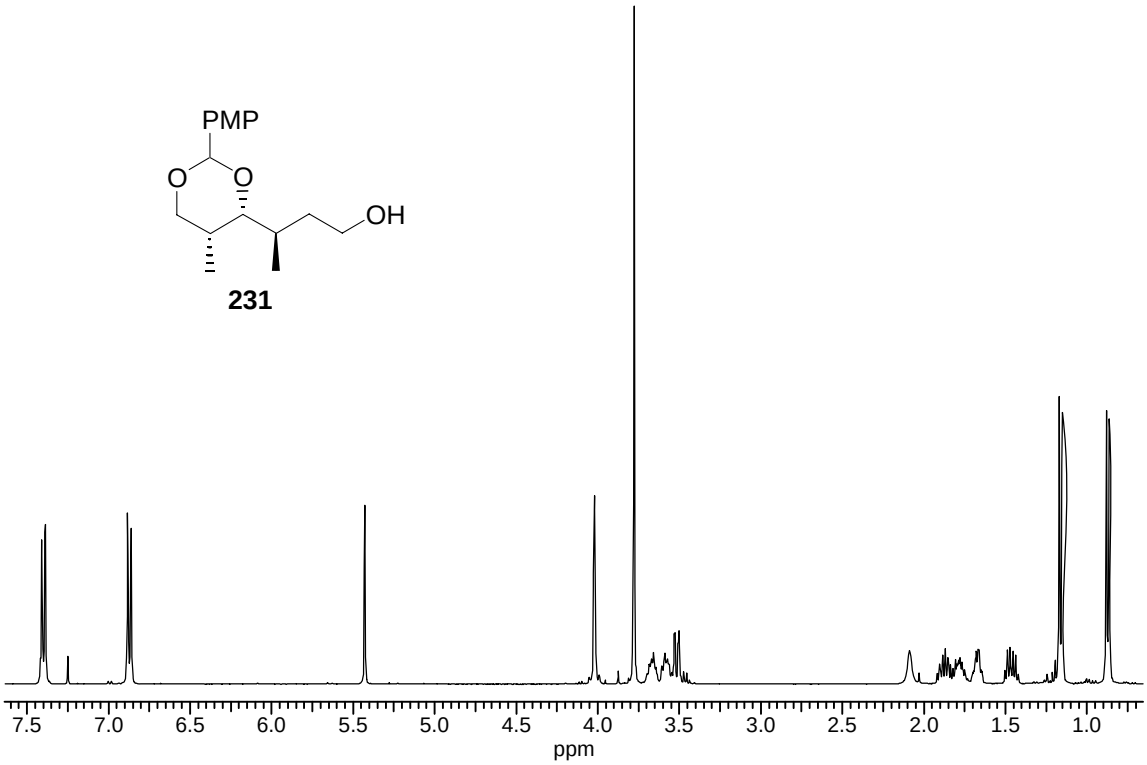
32.12
25.90
18.24
16.62
11.47
-5.34
150
100
50
0
ppm

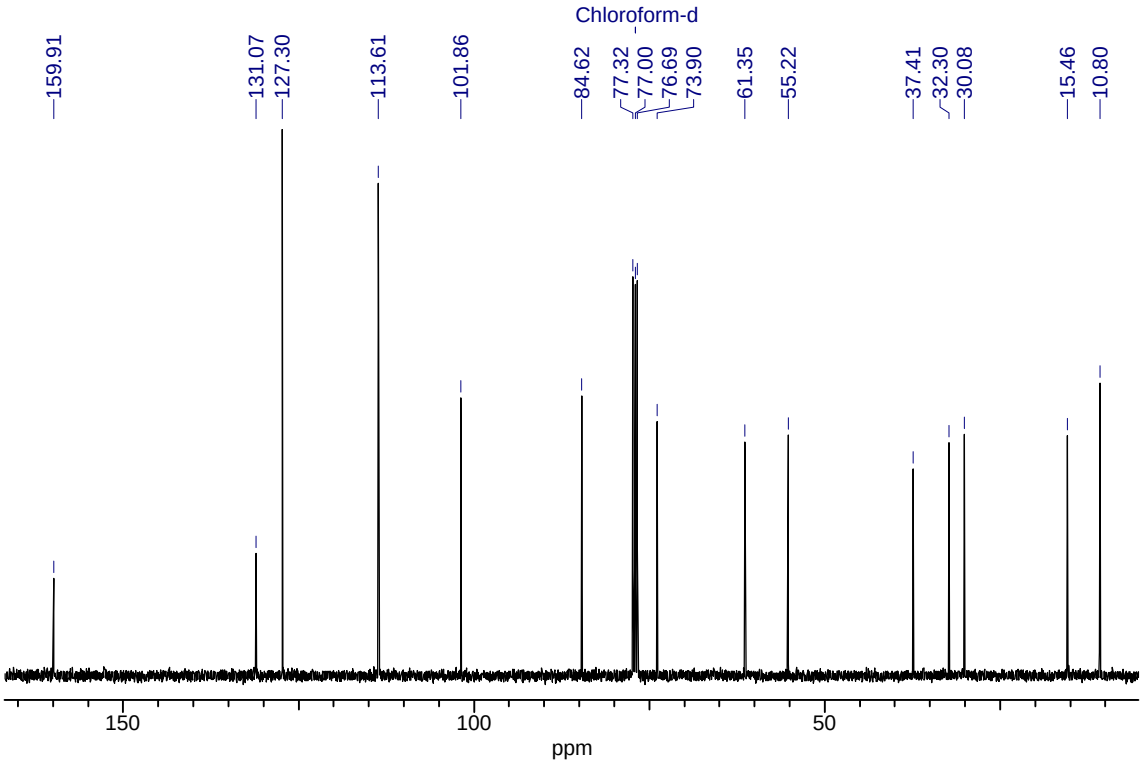

O
O
OH
O
N
Bn
226
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
177.86
152.80
136.93
134.96
129.36
128.90
127.37
116.36
77.32
77.00
76.68
74.64
66.10
55.06
39.35
37.69
37.27
35.36
15.10
9.54
150
100
50
ppm


OH
OTBS
OH
229
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm


Chloroform-d
77.31
77.00
76.68
66.15
61.14
38.89
35.51
34.14
26.02
18.31
17.36
12.62
-3.95
-4.24
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm


PMP
O
O
OH
231
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


Chloroform-d
159.91
131.07
127.30
113.61
101.86
84.62
77.32
77.00
76.69
73.90
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55.22
37.41
32.30
30.08
15.46
10.80
150
100
50
ppm

9.2 Bibiliography

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