Helsinki University of Technology

Department of Chemical Technology

Laboratory of Organic Chemistry

TOTAL SYNTHESIS OF AMAMINOL A

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Abstract

This thesis includes an extensive review of preparation of bicyclo[4.3.0]nonane derivatives. Bicyclo[4.3.0]nonanes can be prepared by several methods. The most important preparation method of bicyclo[4.3.0]nonanes is intramolecular Diels-Alder cycloaddition (IMDA). Several biologically active natural and unnatural compounds contain bicyclo[4.3.0]nonanes in their molecular framework. The synthetic efforts toward natural compounds such as pulo'upone, isopulo'upone, indanomycin, stawamycin, cochleamycin A, ikarugamycin and lepicidin A are surveyed in this thesis. The second part of the review includes preparation methods for bicyclo[4.3.0]nonane derivatives.

The synthesis part of this thesis presents my own results of synthetic efforts on amaminol A. Amaminol A was obtained as the side product from the synthesis of amaminol A diastereomer. Although amaminol A was obtained as the side product, the developed route allows the preparation of amaminol A as the major product by changing the stereochemistry of the employed organocatalyst. The bicyclo[4.3.0]nonane part of amaminol A was obtained utilizing two different types of IMDA's. These were chiral auxiliary induced and organocatalytic IMDA cycloadditions. Many active organic molecules include vicinal amino alcohol moieties in their molecular framework. The preparation of vicinal amino alcohols from α-amino ketones was also studied in this thesis. Chelation type reduction was found to give the highest diastereoselectivities with *N*-*tert*-butylcarbamate protected α-amino ketone.

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I thank my mother and brothers for their support during my studies. However, the warmest thanks goes to my wife Mervi for her love and understanding during my long working hours in the research laboratory. You also encouraged me during my difficult moments. Mervi, you made this possible, I will always thank you for that.

Finally, I would like to dedicate this thesis for two special persons. The first special person is my deceased father, who died in cancer in the summer 1988. I believe that he might has been proud of me for my effort in trying to develop compounds which might be usefull for cancer drug research. The second special person is my lovely daughter Emilia who born during the preparation of the manuscript for this thesis. Your birth started the final spurt and your birth also confirmed what is important in life to me; to create and cherish life.

Kokkola, July 2003 Sami Selkälä

Abbreviations and definitions

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
BBEDA	*N,N*-bis(benzylidene)-ethylenediamine
9-BBN	9-boranbicyclo[3.3.1]nonane
BHT	2,6-di-*tert*-butyl-4-methylphenol
BINAL	2,2'-dihydroxy-1,1'-binaphthyl aluminium hydride
BMS	borane dimethyl sulfide
BOC	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
t-Bu	*tert*-butyl
Bn	benzyl
Bzl, Bz	benzoyl
Bu	*n*-butyl
Burgess reagent	$CH_3OC(O)NSO_2N(CH_2CH_3)_3$
CAN	ceric ammonium nitrate
CBS	Corey-Bakshi-Shibata oxazaborolidine
Cbz	carbobenzyloxy
CDI	1,1-carbonyldiimidazole
m-CPBA	*m*-chloroperbenzoic acid
CSA	camphorsulfonic acid

dba	dibenzylideneacetone
DBB	di-*tert*-butylbisphenyl
DBNE	(+)-*N,N*-dibutylnorephedrine
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Dess-Martin oxidation	oxidation employing Dess-Martin periodinane {C6H4-C(O)OI[OC(O)CH_3]$_3$-}
DEAD	diethyl azodicarboxylate
DHP	dihydropyran
DHQ	dihydroquininyl
DHQD	dihydroquinidinyl
DIBAL-H	diisobutyl aluminum hydride
DIC	diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
E	entgegen (trans)
ee	enantiomeric excess
Et	ethyl

Fmoc	9-fluorenylmethoxycarbonyl
(M)HMDS	(M = Li, Na, K) hexamethyldisilazide
HMPA	hexamethylphosphorictriamide
HOBT	hydroxybenzotriazole
HWE	Horner-Wadsworth-Emmons
IBX	*o*-iodoxybenzoic acid
IMDA	Intramolecular Diels-Alder cycloaddition
LDA	lithium diisopropylamide
MCPBA, *m*-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
Mes	mesityl (2,4,6-trimethylphenyl)
Ms	methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butylether
NACAA	nicotinic-chromic anhydride betaine reagent
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NPSS	*N*-(phenylsulfenyl)succinimide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl

PHAL	phthalazine
PhH	benzene
PhMe	toluene
Piv	pivaloyl
PMB	*para*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
PTSA, *p*-TsOH	*p*-toluenesulfonic acid
i-Pr	isopropyl
Pyr	pyridine
rfx	refluxing conditions
r.t.	room temperature
L-Selectride®	lithium tri-*sec*-butylborohydride
SEM	[(trimethylsilyl)ethoxy]methyl
Sia	siamyl
TBAF	tetrabutylammonium fluoride
TBDMS, TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic(yl) acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl

Ts	*para*-toluenesulfonyl
Z	zusammen (cis)

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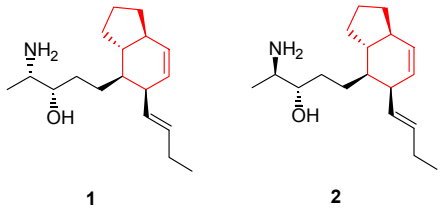
1 Introduction

This work was initiated in 2000 at the Helsinki University of Technology. The work was financially supported by a grant from Neste Foundation. The inspiration for this work was born from the fact that there are not that many synthetically prepared, nature like, cytotoxic compounds against murine leukemia cells. Amaminols A and B were recently isolated from an unidentified tunicate of the family Polyclinidae (1) and found to be cytotoxic against murine leukemia cells.

2 Amaminol A and B

Isolation and identification of amaminols A **1** and B **2** was reported in 2000 by Sata and Fusetani (1). Amaminols A **1** and B **2** were found to be cytotoxic against P388 murine leukemia cells with an IC_{50} value of 2.1 μg/mL. Amaminols A **1** and B **2** contain an interesting *trans*-fused hexahydroindene substructure (colored with red in Figure 1), which has most likely been formed by an intramolecular Diels-Alder reaction from a triene in nature.



1 **2**

Figure 1. Structure of amaminols A **1** and B **2**.

Amaminol A **1** and B **2** contain six chiral centers and four of them can be created by stereoselective intramolecular Diels-Alder reaction. The remaining two chiral centers can be derived from an amino acid. Amaminol A **1** and B **2** are closely related to aliphatic amino alcohols, which are isolated from marine sponges, *Xestospongia* sp. and *Leucetta microraphis*. Other related aliphatic compounds are isolated from tunicates, *Didemnum* sp. and *Pseudodistoma crucigaster.*

2.1 Aliphatic amino alcohol relatives of amaminol A and B

Amaminol A **1** and the related amino alcohols are biogenetically derivable from (*S*)-alanine **3** and amaminol B **2** related amino alcohols are derivable from (*R*)-alanine **4** (Figure 2).

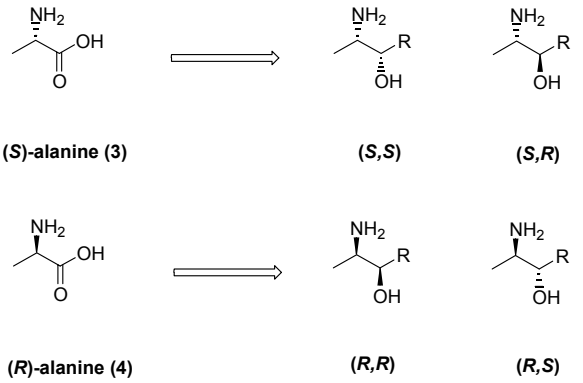
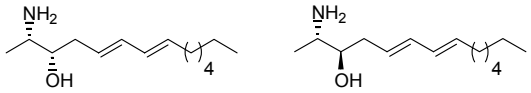


Figure 2. Biogenetic formation of amaminol A **1** and B **2** related amino alcohols from (*S*)-alanine **3** and (*R*)-alanine **4**.

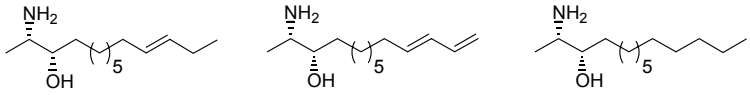
Gulavita *et al.* (2) has isolated two diastereomeric aliphatic 2-aminotetradeca-5,7-dien-3-ols **5** and **6** from a sponge, *Xestospongia* sp. (Figure 3). These are formed biogenetically from (*S*)-alanine **3**.



5 **6**

Figure 3. (2*S*)-Aminotetradeca-5,7-dien-3(*S/R*)-ol (**5**/**6**).

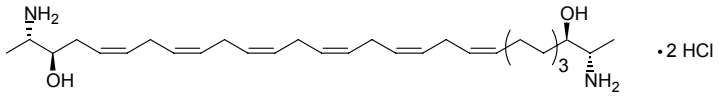
Jiménez *et al.* (3) have isolated (*S,S*)-amino alcohols **7-9** from *Xestospongia* sp. (Figure 4). Their structures differ only in the degree of saturation of the chain. (*S,S*)-amino alcohols **7-9** are biogenetically derived from (*S*)-alanine **3**.



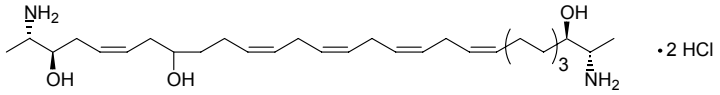
7 **8** **9**

Figure 4. (*S,S*)-Amino alcohols **7-9** isolated from sponge *Xestospongia* sp.

A few years later Kong *et al.* (4) isolated two polyunsaturated (*S,R*)-amino alcohols leucettamol A **10** and B **11** from *Leucetta microraphis* (Figure 5). These are also biogenetic products of (*S*)-alanine **3**.



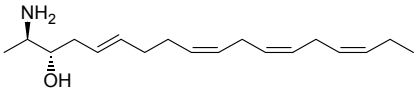
Leucettamol A (10)



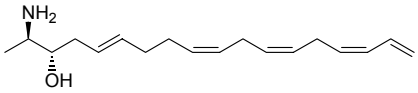
Leucettamol B (11)

Figure 5. Structures of leucettamol A **10** and B **11**.

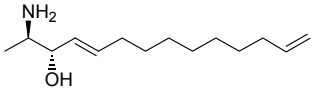
(*R*)-Alanine **4** derived amino alcohols have been isolated from tunicates. Jares-Erijman *et al.* found polyunsaturated (*R,S*)-amino alcohols **12-14** from *Pseudodistoma crucigaster* tunicate (5). These amino alcohols were named as crucigasterins (Figure 6).



Crucigasterin 277 (12)



Crucigasterin 275 (13)

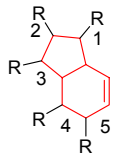


Crucigasterin 225 (14)

Figure 6. Structure of crucigasterins **12-14**.

2.2 Cyclic relatives of amaminol A and B

In this chapter, cyclic relatives of amaminol A **1** and B **2** are presented. The compounds are restricted so that only bicyclo[4.3.0]nonane derivatives are presented (see Figure 7 red colored part). Furthermore, natural compounds having substituents at positions 1, 2, 3, 4 and 5 are presented. The reason for the predefinition is that there are over a thousand compounds, which hold substituted bicyclo[4.3.0]nonane as substructure and it would be enormous if not possible to present all of them in this thesis. The biological activity of the presented compounds are also presented if available. If the partial or total synthesis of the presented natural compound is published, it is also covered in the following chapters.



R = H, alkoxy or alkyl group

Figure 7. Structure of substituted bicyclo[4.3.0]nonane.

2.2.1 Pulo'upone and isopulo'upones

(-)-Pulo'upone **15** (Figure 8) was isolated by Scheuer and Coval in 1985 from cold dried animals in Hawaii (6). Despite the enormous work that has been done in synthesizing pulo'upone it's biological activity has not been fully determined and justified. Pulo'upones include substituted *trans*-fused *endo*-bicyclo[4.3.0]nonane structure.

(-)-Isopulo'upone **17** was found later in 1993 by Spinella *et al.* from *Navax inermis* and its prey *Bulla gouldiana* (7). (-)-Isopulo'upone **17** has been found to be very toxic below

10 ppm to mosquito fish *Gambusia affinis* and it is toxic against brine shrimp *Artemia salina* with LD_{50} = 2.2 ppm (7). Isopulo'upones **17/18** are a isomers of pulo'upones **15/16**.

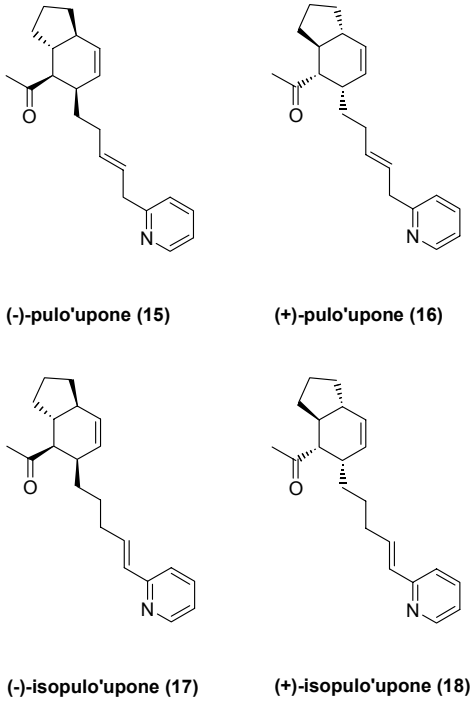
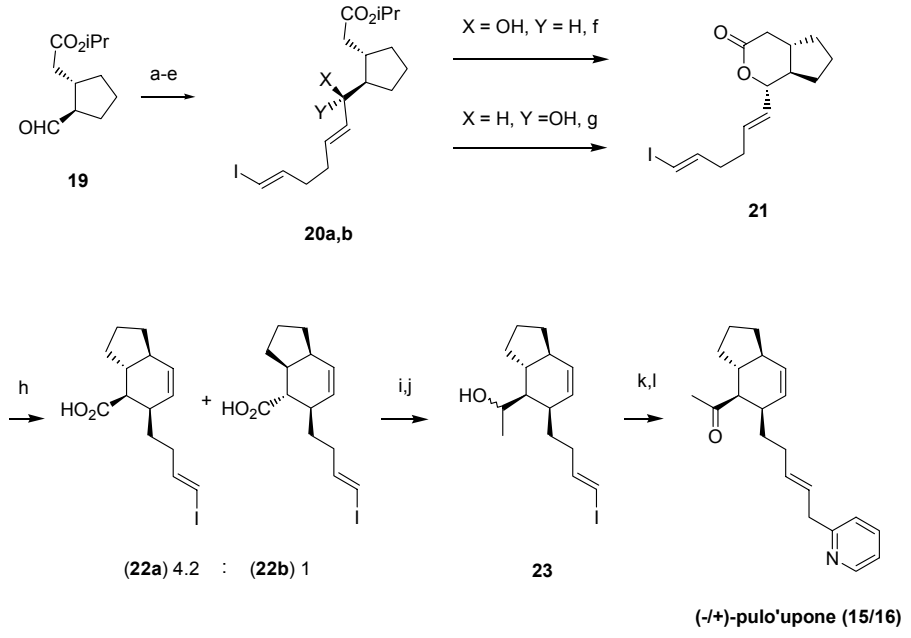


Figure 8. Structures of pulo'upones **15**/**16** and isopulo'upones **17**/**18**.

In the following chapters, the total syntheses of pulo'upones **15/16** and isopulo'upone **17/18** are presented in a chronological order. The chapters are divided according to the research groups.

2.2.1.1 Burke

Burke *et al.* published the first total synthesis of pulo'upone **15/16** in 1988 (8). However, this synthesis route lead to racemic product. Burke *et al.* used retrohetero Diels-Alder reaction (RHDA) to construct substrate *in situ* for intramolecular Diels-Alder reaction of pulo'upones **15/16** (Scheme 1). Burke *et al*. used cyclic chiral aldehyde **19** as the starting material for oxidation. The formed acid was transformed to acid chloride, which allowed the formation of phosphonate for HWE (Horner-Wadsworth-Emmons) reaction (11). HWE olefination proceeded in high yield (91%) to afford an iodo diene derivative. Reduction of the enone gave a mixture of diastereomers allyl alcohols **20a/b**, which were both transformed to lactone **21** by two separate methods. After conversion of the lactone to trimethylsilyl ketene acetal, thermal RHDA and hydrolysis afforded a separable mixture of *endo/exo*-cycloadducts **22a/b**. The *endo*-adduct **22a** was reduced, oxidized and methylated to give a diastereomeric mixture of carbinols **23**. Treatment with picolyl cuprate and Swern oxidation finalized the synthesis of racemic pulo'upone (**15/16**).

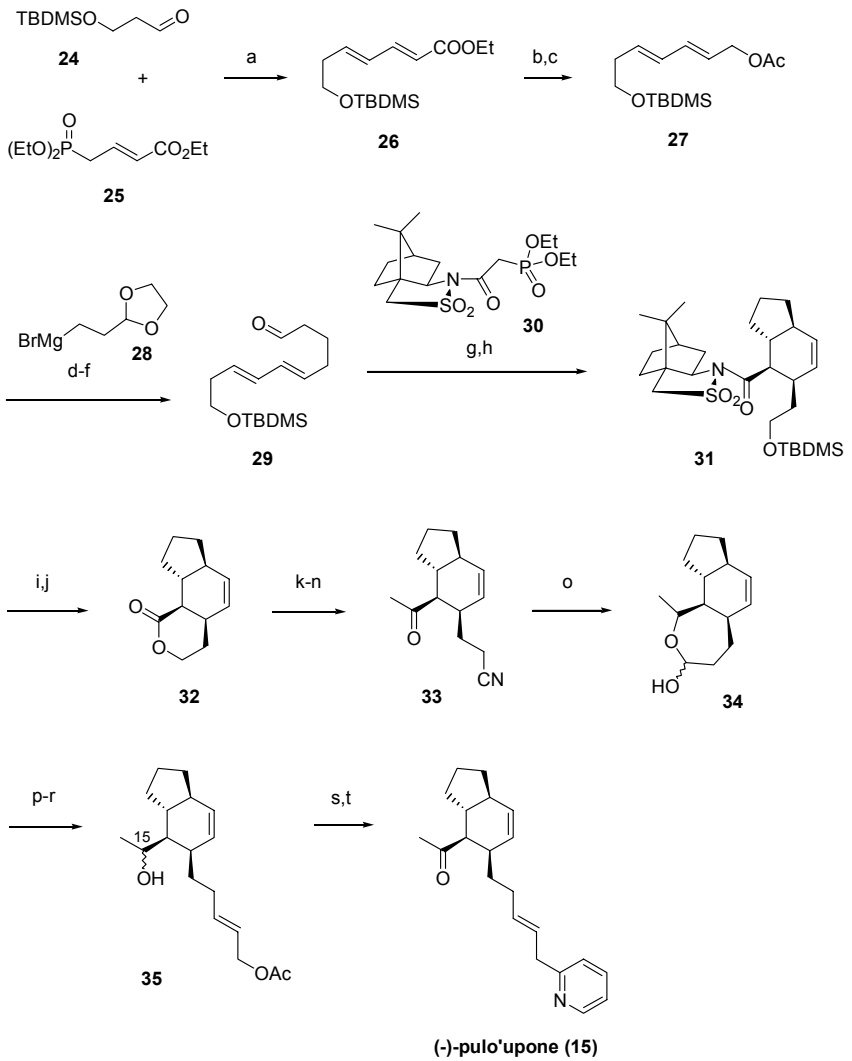


Scheme 1. Reagents and conditions: a) $H_2Cr_2O_7$, H_2O/acetone, 25 °C, 30 min; b) $(COCl)_2$, PhH, 25 °C, 12 h; c) $MeP(O)(OMe)_2$, *n*-BuLi, $MgBr_2 \cdot OEt_2$, -78 °C -> -30 °C (62 % for 3 steps); d) *E*-5-iodo-4-pentenal, NaH, THF, 0 -> 25 °C (91 %); e) $NaBH_4$, $CeCl_3$, MeOH, 25 °C (98 %); f) NaOH, H_2O/THF; H^+; Ph_3P, DEAD, PhMe, -30 °C (63 %); g) NaOH, H_2O/THF/MeOH; H^+; morpho CDI, DMAP, CH_2Cl_2, 0 -> 25 °C (88 %); h) LiHMDS, Me_3SiCl, Et_3N, -100 -> 25 °C, remove THF *in vacuo*, add xylenes; 140 °C, 12 h, aq. HCl (71 %); i) DIBAL-H, PhMe, 25 °C; j) $(COCl)_2$, DMSO, Et_3N, THF, -78 °C -> -35 °C; MeMgBr, Et_2O, -78 °C (72 %); k) picoline, *n*-BuLi, THF, 0 °C; CuCN, THF, -78 °C; l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C (71 %).

2.2.1.2 Oppolzer

Oppolzer *et al.* used asymmetric intramolecular Diels-Alder (IMDA) reaction to synthesize (-)-pulo'upone (9). Chiral camphor sultam derivative was used for the chiral induction. HWE reaction of silylated aldehyde **24** with ethyl crotonic phosphonate **25** afforded the conjugated *E,E*-diene **26** in low yield (47 %). (Scheme 2). Further reduction and acetylation afforded the silylated diene acetate **27**. S_N2 reaction of dienylacetate **27** with magnesiumbromo dioxolane derivative **28**, followed by hydrolysis and silylation sequence, afforded the diene aldehyde **29**. The sultam auxiliary was connected to the main skeleton by a HWE olefination of the chiral phosphonate **30** with diene aldehyde **29**. The produced (*E,E,E*)-trienylsultam was subjected to Lewis acid (dimethylaluminium chloride) promoted IMDA. The IMDA reaction was very slow and two portions of Me_2AlCl was required to obtain full conversion. *Endo*-adduct **31** was obtained from IMDA with good yield and high enantioselectivity (71 %, 93 %ee). The sultam auxiliary was cleaved by desilylation and lactonization gave tricyclic lactone **32**. Lactone **32** was opened by methylation and further derivatized by tosylation, iodination and cyanation. Nitrile **33** was reduced with DIBAL-H to produce lactol **34**, which was subjected to Wittig olefination. Reduction of the resulting methyl enoate and selective acetylation of the allylic alcohol gave allylacetate **35** as a mixture of *E*:*Z*-isomers (94:6) and C15-

epimers (3:1). Coupling of allylacetate **35** with di-(2-pyridyl)copperlithium and Swern oxidation of the alcohol group gave pure (-)-pulo'upone **15**.



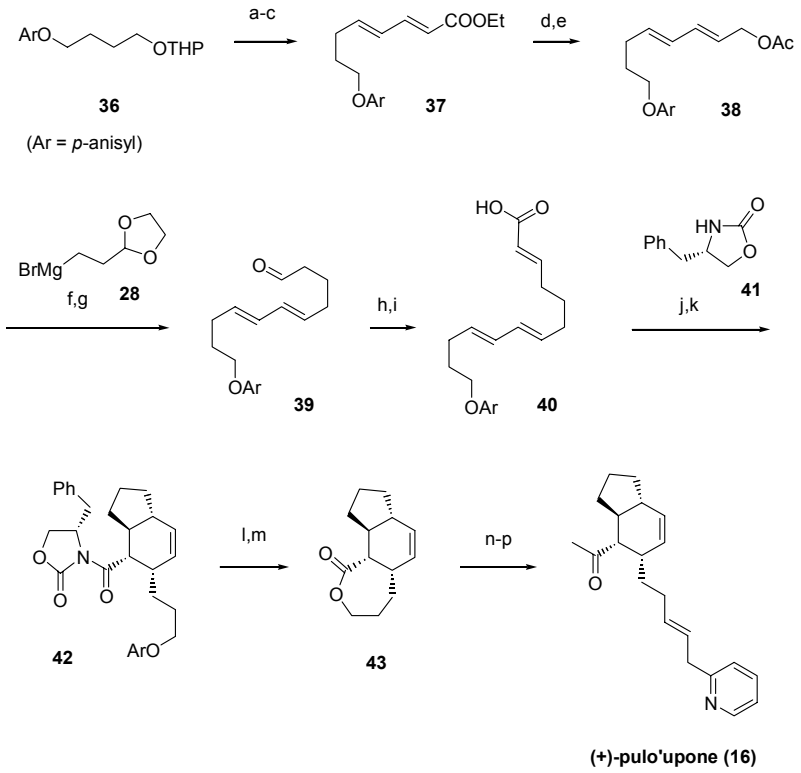
Scheme 2. Reagents and conditions: a) aldehyde **24**, LDA, THF, -78 °C -> r.t.; then phosphonate **25**, -40 °C, 10 min, -> r.t. (47 %); b) DIBAL-H, hexane/Et_2O (1:1), 0 °C, 2 h; r.t., 1 h; c) Ac_2O, pyr, r.t., 2 h (94 % over 2 steps); d) Li_2CuCl_4, Grignard reagent **28**, 2 h, -10 °C, 30 min (62 %); e) 0.4 M HCl, acetone/H_2O (2:1), r.t., 5 h; f) TBDMSCl, NEt_3,

DMAP, r.t., 2 h (63 %); g) phosphonate **30**, DBU, aldehyde **29**, LiCl, CH_3CN, r.t., 2 h (89 %); h) Me_2AlCl, CH_2Cl_2, -20 °C, 80 h, Me_2AlCl, -10 °C, 50 h (63 %); i) $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t., 1 h, j) LiH, DMF, r.t., 16 h (89 % over 2 steps); k) MeLi, lactone **32**, Et_2O, -78 °C, 30 min; l) TsCl, pyr, 0 °C, 10 h, +10 °C, 5 h (80 % over 2 steps); m) NaI, acetone, 35 °C, 3 h; n) *n*-Bu_4NCN, CH_2Cl_2, 40 °C, 2 h (86 % over 2 steps); o) DIBAL-H, Et_2O, 0 °C, then r.t., 1 h (75 %); p) Ph_3P=CHCOOMe, 60 °C, 6 h; q) DIBAL-H, -70 °C, CH_2Cl_2; r) Ac_2O, pyr, DMAP, 0 °C, 2 h, r.t., 1 h (79 % over 3 steps); s) 2-bromopyridine, *n*-BuLi, Et_2O, -60 °C, CuI, n-Bu_3P; t) $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C, 2 min, then alcohol **35**, -50 °C, 25 min, NEt_3, -60 °C, 10 min, r.t., 15 min (81 % over 2 steps).

2.2.1.3 Takano

The second synthesis of pulo'upones **15/16** using asymmetric IMDA reaction was reported by the Takano group (10). They used the chiral oxazolidinone **41** developed by Evans group (79) to induce the asymmetric IMDA cycloaddition. The synthesis of the main skeleton started from *para*-anisyl ether **36** by removing the tetrahydropyranyl protecting group with *para*-toluene sulphonic acid (Scheme 3). Oxidation with pyridinium chlorochromate followed by HWE olefination (11) afforded the dienyl ester **37** in moderate yield (45 %). Reduction and acetylation gave dienylacetate **38**. An S_N2 reaction with the Grignard reagent **28** gave a diene ketal. This was subjected to hydrolysis to aldehyde **39** and HWE reaction to produce triene ester. Ester was hydrolyzed in basic conditions to trienyl acid **40**. Chiral oxazolidinone **41** was attached *via* a lithium salt to the trienyl acid chloride, which was prepared previously from the acid **40** with oxalyl chloride. The amide formation was surprisingly low yielding (59 %). Dimethylaluminium chloride was used as the Lewis acid to promote IMDA cycloaddition. The cycloadduct **42** was obtained in moderate yield (52 %) after chromatographic purification. Removal of the chiral auxiliary was not obtained by hydrolysis with inorganic bases. However, the chiral oxazolidinone **41** was removed by deprotecting the *p*-anisyl group with cerium ammonium nitrate followed by generation of

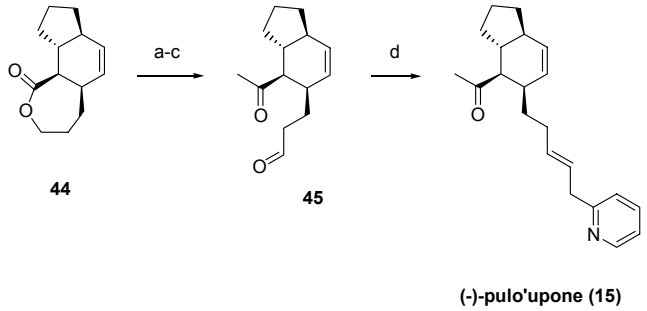
the lithium alcoholate with *n*-butyl lithium, which enabled lactonization. Methylation of the carbonyl group was obtained in low yield (12 %). However, the synthesis of (+)-pulo'upone **16** was continued by PCC oxidation and Wittig reaction of the resulting aldehyde with the lithium salt of 2-(2-pyridyl)ethyltriphenylphosphonium iodide. The *E*:*Z*-selectivity of the Wittig reaction was 1:3.



Scheme 3. Reagents and conditions: a) *p*-TsOH, MeOH, r.t. (95 %) b) PCC, MS 3Å, CH_2Cl_2, r.t., 15 min; c) triethyl 4-phosphonocrotonate, LHMDS, THF, -40 -> r.t., 12 h (45 % over 2 steps); d) DIBAL-H, Et_2O, -78 °C, 1 h; e) Ac_2O, pyr, r.t., 14 h (97 % over 2 steps); f) Grignard reagent **28**, cat. Li_2CuCl_4, -30 °C, 2 h (74 %); g) AcOH-H_2O-THF, 80 °C, 4 h; h) methyl diisopropylphosphonoacetate, *t*-BuOK, THF, -20 °C, 5 h (74 % over 2 steps); i) 10% NaOH, MeOH, THF, r.t., 10 h (57 %); j) $(COCl)_2$, PhMe, r.t., 20 h; then oxazolidinone **41**, *n*-BuLi, THF, -78 °C, 1.5 h (59 %); k) Me_2AlCl, CH_2Cl_2, -30 °C, 5 h

(52 %); l) CAN, CH_3CN-H_2O, 0 °C, 15 min; m) *n*-BuLi, THF, 0 °C, 1 h (76 %); n) MeLi, THF, -78 °C, 1 h (12 %); o) PCC, MS 3Å, CH_2Cl_2, r.t., 15 min (95 %); p) 2-(2-pyridyl)ethyltriphenylphosphonium iodide, *n*-BuLi, THF, 0 °C, 5 h (11 %).

Takano *et al.* synthesized (-)-pulo'upone **15** by an improved method, in which they used DIBAL-H for reducing lactone **44**. This was followed by methylation and oxidation to afford ketoaldehyde **45** in 42 % overall yield (Scheme 4) (10). (-)-Pulo'upone **15** was synthesized with this method and using otherwise same reactions as in the synthesis of (+)-pulo'upone **16**.

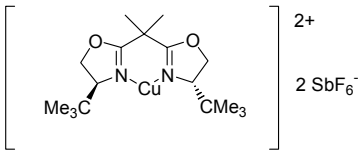


Scheme 4. Reagents and conditions: a) DIBAL-H, THF, -78 °C; b) MeLi, THF-Et_2O, -78 °C -> r.t. (70 % over 2 steps); c) PCC, MS 3Å, CH_2Cl_2, r.t., 30 min (60 %); d) 2-(2-pyridyl)ethyltriphenylphosphonium iodide, *n*-BuLi, THF, 0 °C, 5 h (11 %).

2.2.1.4 Evans

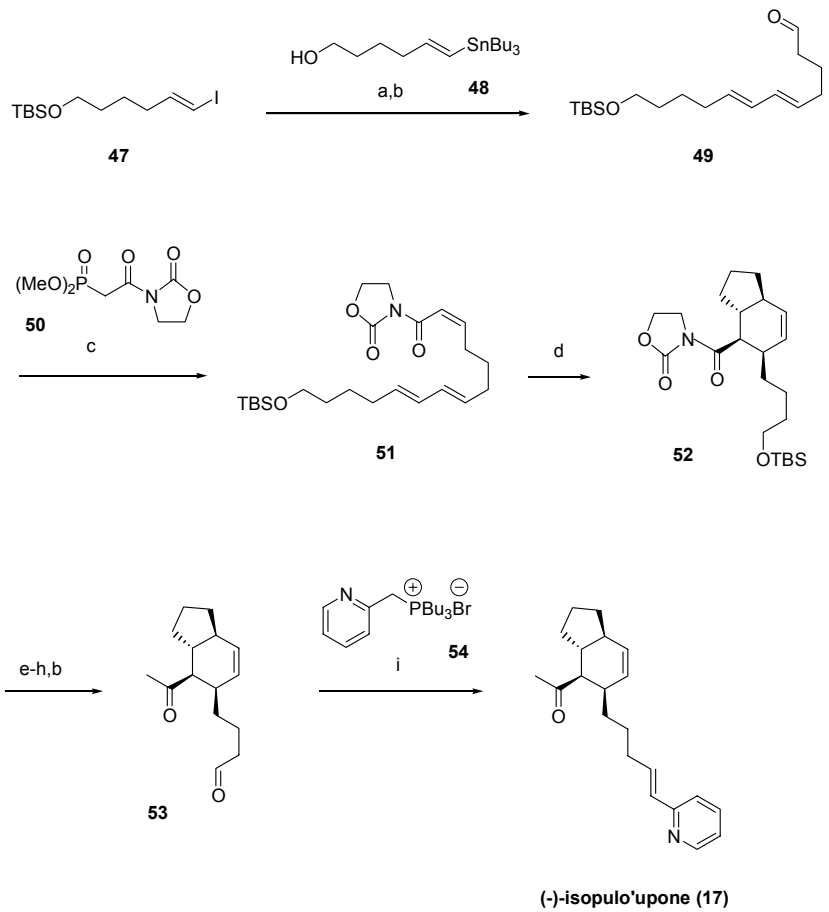
Total synthesis of (-)-isopulo'upone **17** was reported in 1997 by the Evans group (12). A novel catalytic IMDA reaction was utilized to prepare the bicyclo[4.3.0]nonane part of (-)-isopulo'upone **17**. Evans *et al.* prepared the precursor for the IMDA cycloaddition starting from vinyl iodide **47** and vinyl stannane **48** (Scheme 5). The terminal alcohol

group was oxidized by Swern oxidation. The resulting aldehyde was subjected to HWE reaction to afford the trienimide **51** intermediate with an *E*:*Z*-selectivity of 27:1. Chiral C_2-symmetric Cu(II) complex **46** derived from (*S,S*)-*tert*-butylbis(oxazoline), copper chloride and hexafluoroantimonate (Figure 9) catalyzed IMDA of trienimide **51** to give the *endo*-cycloadduct **52** in high yield (81 %). The cycloaddition catalyzed by **46** gave cycloadduct **52** with excellent diastereo- and enantioselectivity (>99:1 *endo/exo*; 96 %ee). The hindered imide **52** was opened by thioesterification in high yield (90 %). Lindlar's catalyst accompanied with triethylsilane and 1-decene allowed reduction of the thioester without concomitant reduction of the endocyclic double bond. Methylation gave an 8:1 mixture of diastereomers and further desilylation and oxidation afforded aldehyde **53**. Wittig reaction using tributylphosphonium bromide and *n*-butyllithium was used to prepare (-)-isopulo'upone **17** in 90 % yield as an isomeric mixture (*E*:*Z*, 12:1). The synthetic route developed by Evans group is clearly the shortest and highest yielding synthetic path to prepare iso- and pulo'upone type compounds.



46

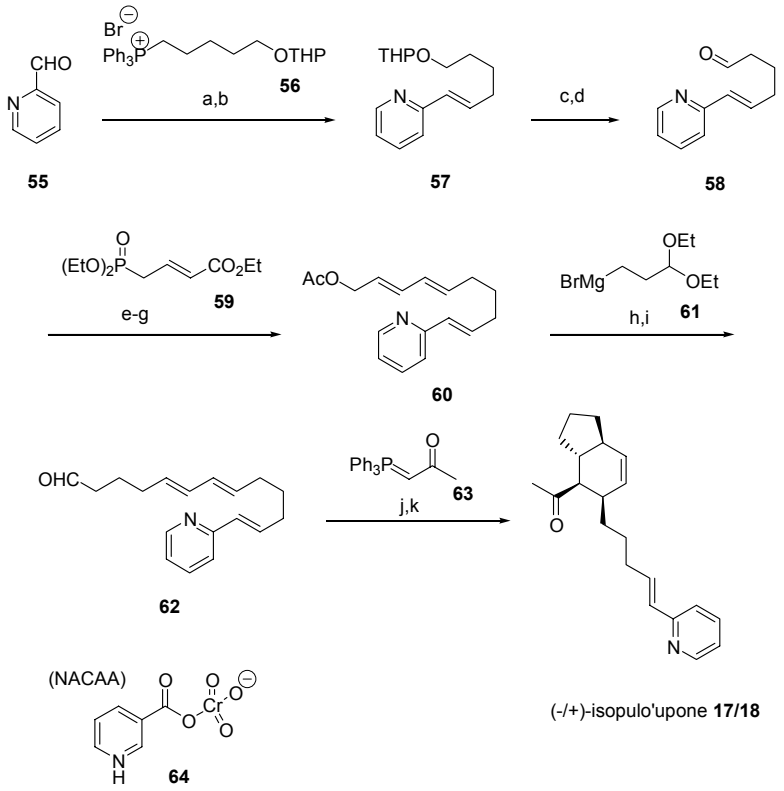
Figure 9. Evans C_2-symmetric copper(II) catalyst **46**.



Scheme 5. Reagents and conditions: a) $Pd_2(dba)_3 \cdot CHCl_3$, DMF, r.t., 16 h (72 %); b) $(COCl)_2$, DMSO, Et_3N, -78 -> -40 °C; c) NaHMDS, THF, r.t., 26 h (77 % over 2 steps); d) 5 mol-% Cu(II)catalyst **46**, CH_2Cl_2, r.t., 24 h (81 %); e) LiSEt, THF, 0 °C, 15 min (90 %); f) Et_3SiH, 5% $Pd/CaCO_3$/quinoline, 1-decene, acetone, r.t., 2 h; g) MeMgCl, THF, -78 °C; h) 1% HCl/EtOH, r.t., 10 min (90 % over 3 steps); i) tributylphosphonium bromide, *n*-BuLi, THF, -20 °C, then aldehyde **53**, r.t., 45 min (90 %).

2.2.1.5 Hase

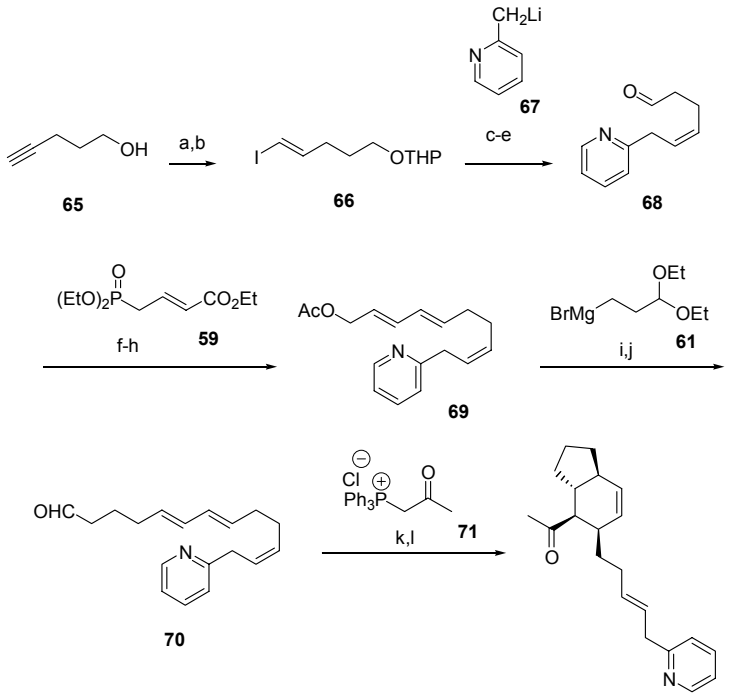
Hase *et al.* have prepared racemic isopulo'upone **17/18** using a thermal IMDA cycloaddition of a tetraene ketone (13). Preparation of the precursor for IMDA reaction started from 2-picolinaldehyde **55** (Scheme 6). Wittig reaction of **55** with 5-(2-tetrahydropyranyloxy)-pentylphosphonium potassium salt **56** produced an *E*:*Z*-mixture (3:7) of stereoisomers. The undesired *Z*-isomer was transformed to the *E*-isomer **57** by daylight lamp irradiation of the stereoisomer mixture in the presence of diphenyldisulfide. After removing the protecting group (THP), the alcohol was oxidized with NACAA **64** to aldehyde **58**. HWE reaction of the aldehyde **58** with crotyl phosphonate **59** gave trienyl ester. Reduction and acetylation of the ester derivative afforded trienyl acetate **60** for chain elongation. Copper catalyzed (Li_2CuCl_4) reaction of the acetate **60** with the Grignard reagent **61** and hydrolysis of the resulting acetal afforded the triene aldehyde **62** in 55 % yield. The relatively low yield was probably due to isomerization and hydrolysis of the diene acetate **60** during the Grignard reaction. Wittig olefination of aldehyde **62** produced a triene ketone ready for the thermal IMDA. A long reaction time was required for complete conversion to afford *endo*-cycloadduct **17/18** in 86 % yield.



Scheme 6. Reagents and conditions: a) K_2CO_3, H_2O, dioxane (90 %); b) hν, PhSSPh (99 %); c) 1 M HCl, 10 h (85%); d) NACAA, CH_2Cl_2, pyr, 20 min, r.t. (70 %); e) phosphonate **59**, LiHMDS, THF, -78 °C, then aldehyde **58**, THF, -60 → r.t. (68 %); f) $LiAlH_4$, Et_2O, -30 °C, 1 h (90 %); g) Ac_2O, pyr, r.t. (98 %), h) Grignard reagent **61**, Li_2CuCl_4, THF, -30 °C, 3 h; i) 10 % H_2SO_4, acetone, r.t., 1 h (55 % over 2 steps); j) phosphorane ylide **63**, CH_2Cl_2, 40 °C, 48 h (76 %); k) PhMe, 48 h, 110 °C (86 %).

Hase *et al.* have also prepared racemic pulo'upone **15/16** using the thermal IMDA cycloaddition for tetraenyl ketone (14). Preparation of the precursor for IMDA reaction started from 4-pentyn-1-ol **65** (Scheme 7). 4-Pentyn-1-ol **65** was reacted with DIBAL-H and iodine to afford 5-iodo-*4E*-penten-1-ol. After tetrahydropyran protection of the

alcohol, vinyl iodide **66** was reacted with 2-picolinylcuprate **67** to afford a pyridylhexenol derivative. After removing the protecting group (THP), the resulting alcohol was oxidized to aldehyde **68**. HWE reaction of aldehyde **68** with crotyl phosphonate **59** gave trienyl ester. Reduction and acetylation of ester derivative afforded trienyl acetate **69** ready for chain elongation. Reaction of acetate **69** with Grignard reagent **61** catalyzed by copper salt (Li_2CuCl_4) and hydrolysis of the resulting acetal afforded trienyl aldehyde **70** geared up for Wittig reaction. After Wittig reaction of **70** with **71**, the synthesis was completed by heating the resulting tetraene ketone at 110 °C for 2 days. Thermal IMDA afforded a racemic mixture of pulo'upones **15/16** in high yield (86 %).

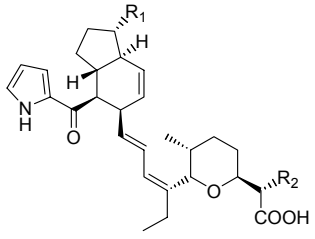


(-/+)-pulo'upone **15/16**

Scheme 7. Reagents and conditions: a) DIBAL-H, PhMe, alcohol 65, hexane, -30 °C, then 2 h, 50 °C, THF, I_2, -50 °C → r.t., 1 h (54 %); b) DHP, HCl, 0 °C → r.t., 3 h; c) *n*-BuLi, 2-picoline, THF, -60 → -50 °C, 30 min, CuCN, -60 → -15 °C, 10 min, vinyliodide 66, THF, -70 → -30 °C, 3 h; d) HOAc-THF-H_2O, 45-50 °C, 12 h (64 %); e) NACAA, CH_2Cl_2, pyr, r.t., 20 min (70 %); f) crotylphosphonate **59**, THF, LiHMDS, -78 → -50 °C, then aldehyde **68**, THF, -50 → r.t. (50 %); g) $LiAlH_4$, Et_2O, -30 °C, 1 h (88 %); h) Ac_2O, pyr, r.t. (95 %); i) Grignard reagent **61**, Li_2CuCl_4, THF, -30 °C, 3 h (55 %); j) 10 % H_2SO_4, acetone (95 %); k) phosphorane salt **71**, K_2CO_3, dioxane, H_2O, 95 °C, 12 h (70 %) ; l) PhMe, 48 h, 110 °C (86 %).

2.2.2 *Pyrroloketoindanes*

Pyrroloketoindane compounds have been isolated from *Streptomyces* species (Figure 10). This family of natural products include indanomycin (X-14547A) **72**, (15) 16-deethylindanomycin (A83094A) **73** (16), homoindanomycin **74** (17) and cafamycin **75** (18). Indanomycin **72** is a carboxylic acid ionophore produced by *Streptomyces antibioticus*, NRRL 8167 (15). Pyrroloketoindanes **72-75** have a trisubstituted *trans*-fused *endo*-bicyclo[4.3.0]nonane substructure. Pyrroloketoindanes are named according to their pyrrole part.



72 R_1 = Et, R_2 = Me
73 R_1 = H, R_2 = Me
74 R_1 = Et, R_2 = Et
75 R_1 = H, R_2 = Et

Figure 10. Pyrroloketoindanes **72-75** isolated from *Streptomyces*.

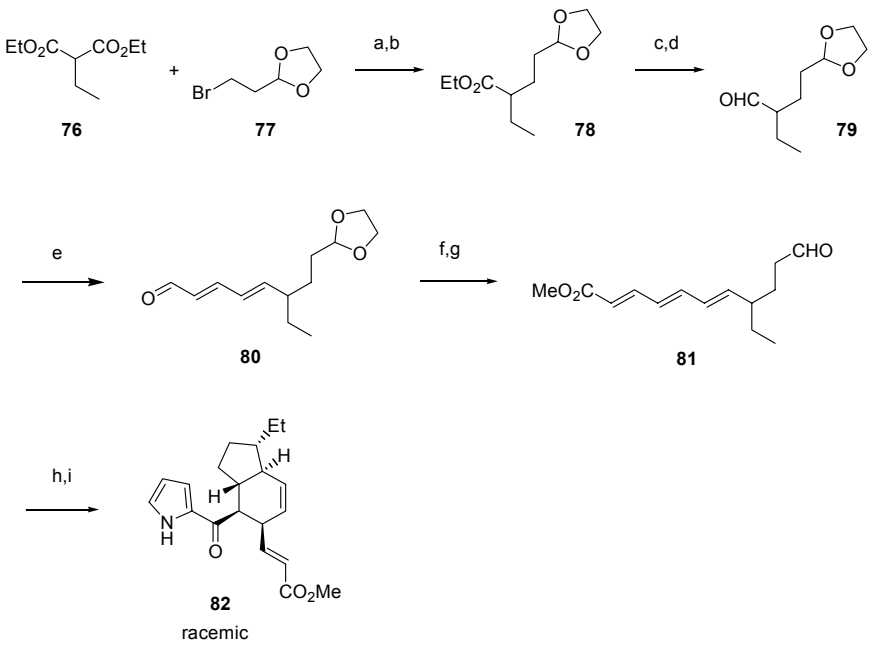
Synthetic efforts towards homoindanomycin **74**, cafamycin **75** or A83094A **73** have not been reported. The synthesis efforts towards pyrroloketoindanes have mainly focused to indanomycin **72**. Indanomycin **72** has potent *in vitro* activity against Gram-positive bacteria, exhibits both antineoplastic and antihypertensive properties, and is an effective ruminant growth promotant by improving feed utilization (19). Indanomycin **72** is also capable to bind mono-, di- and trivalent metal cations, making them miscible in organic solvents.

2.2.2.1 Indanomycin **72**

Indanomycin **72** has been synthesized by several research groups. The synthetic efforts are presented in the following chapters. The chapters are divided according to research groups.

2.2.2.1.1 Roush

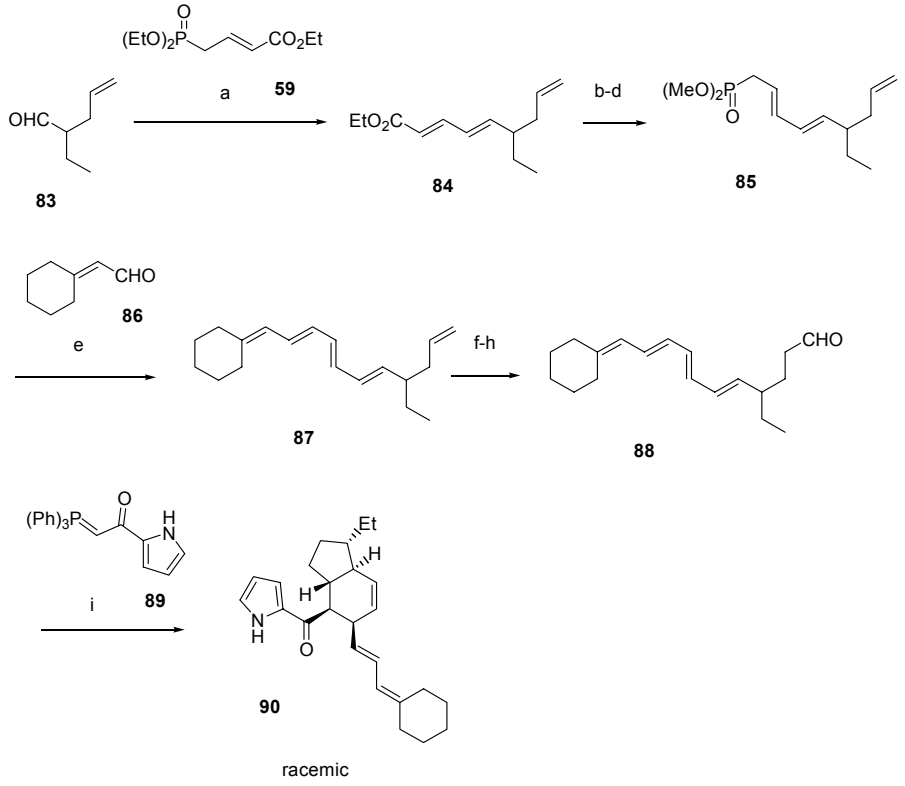
Roush *et al.* (20) have reported the first synthesis of *trans*-fused hexahydroindene structure of indanomycin **72**. Their idea was to prepare the hexahydroindene structure by *endo*-selective Lewis acid promoted IMDA. The synthetic sequence for the precursor of IMDA cycloaddition is presented in Scheme 8. Alkylation of **76**, followed by decarboxylation afforded ester dioxolane **78**. Aldehyde **79** was obtained by reduction - oxidation sequence. Alkylation of aldehyde **79** was followed by mild hydrolysis to afford diene aldehyde **80** in moderate yield (70 %). Wittig reaction and hydrolysis of the dioxolane gave triene ester aldehyde **81**. The pyrrole part was obtained by Wittig reaction of aldehyde **81** with phosphorane pyrrole. IMDA was promoted by ethylaluminum chloride to afford a racemic mixture of cycloadducts **82** in moderate yield (71 %). The overall process was not very high yielding due to moderate yielding intermediate steps.



Scheme 8. Reagents and conditions: a) NaOEt, EtOH, rfx, 13 h (53-55 %); b) LiCl, H_2O, DMSO, rfx (83 %); c) $LiAlH_4$ (93-100 %); d) PDC, CH_2Cl_2 (67-70 %); e) $CH_3OCH{=}CHC{\equiv}CH$, *n*-BuLi, THF, -78 °C to r.t., 3 h; then EtOH, $LiAlH_4$, 3 h, 23 °C; then 1M HCl, 2-3 h, 23 °C (70 %); f) $(Ph)_3PCHCOOMe$, C_6H_6, rfx (81 %) ; g) H_3O^+ (79 %); h) $(Ph)_3PCHCO$-pyrrole, CH_2Cl_2, r.t., 3 days (57 %); i) $EtAlCl_2$, CH_2Cl_2, 0 °C to r.t. in 1.5 hours (71 %).

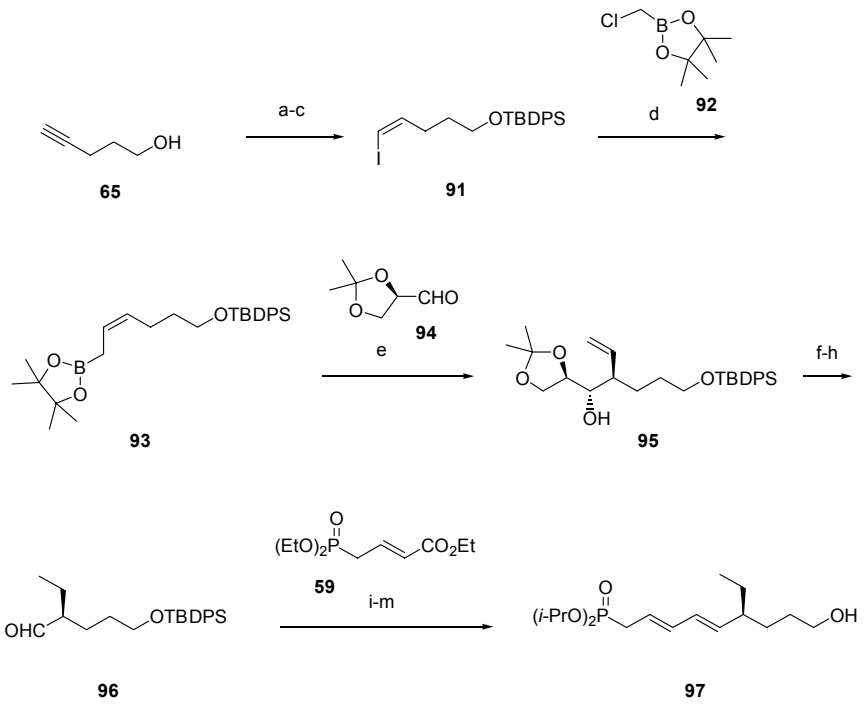
Roush *et al.* have also reported a different approach to synthesize indanomycin **72**. The synthesis was based on the idea that the coupling of the two halves is made before the IMDA reaction. The pentaene model compound was prepared and successfully cyclized to *trans*-fused hexahydroindene cycloadduct **90** in moderate yield (53 %). The pentaene intermediate was prepared as presented in the Scheme 9 (21). Aldehyde **83** was subjected for HWE reaction and the formed ester **84** was reduced. Substitution of the hydroxyl group with bromine was followed by phosphonate **85** formation. Further HWE reaction afforded tetraene **87**, which was hydroborated with 9-BBN. Alkaline hydrogen peroxide treatment hydrolyzed the borane to afford a primary alcohol intermediate. Swern

oxidation of the terminal alcohol was followed by Wittig reaction with pyrrole phosphorane under thermal conditions, which leads simultaneously to IMDA cycloaddition. The ratio of *endo*-**90** to *exo*-cycloadducts were 53:17. The *endo*-cycloadduct was isolated by chromatography in 53 % yield.



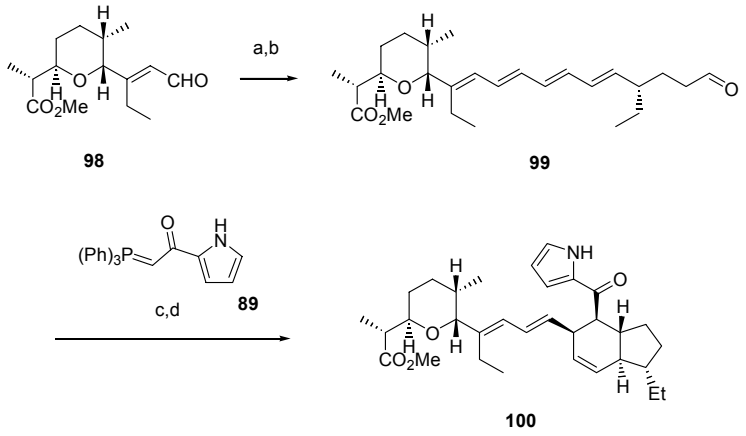
Scheme 9. Reagents and conditions: a) LDA, THF, - 40 °C (95 %); b) $LiAlH_4$, Et_2O, 0 °C (92 %); c) Ph_3PBr_2, CH_3CN, 0 °C; d) $(MeO)_3P$, PhMe, 110 °C (78 % over 2 steps); e) phosphonate **85**, aldehyde **86**, DME, KO*t*-Bu, DME, 0 °C, 1.5 h (95 %); f) 9-BBN, THF, 0 °C; g) NaOH, H_2O_2 (84 %); h) TFAA, DMSO, DIPEA, CH_2Cl_2, - 78 °C -> 23 °C (80 %); i) ylide **89**, CH_2Cl_2-MeOH (2:1), 40 °C, 39 h (53 %).

Roush *et al.* synthesized optically pure indanomycin **72** by creating the chiral center (C8) in the five membered ring of bicyclo[4.3.0]nonane system by a reaction between chiral aldehyde **94** and boronate **93** (22). Boronate **93** was prepared from commercially available 4-pentynol **65** according to Scheme 10. Silylation of 4-pentynol **65** was followed by lithiation of the triple bond and iodination to afford iodo alkyne. Reduction by hydroboration-protonolysis gave *Z*-alkenyl iodide **91**. Second lithiation and reaction with pinacol (chloromethyl)boronate **92** afforded intermediate boronate **93**, which was reacted without purification with *D*-glyceraldehyde acetonide **94**. The double bond of **95** was reduced with diimide and the acetonide was hydrolyzed. The resulting triol was oxidized to afford aldehyde **96**. Diene ester was obtained by reaction between aldehyde **96** and the lithium anion of triethyl 4-phosphonocrotonate **59**. Subsequent reduction with lithium aluminium hydride, bromination and reaction with sodium diisopropyl phosphite afforded phosphonate. Finally, desilylation by fluoride ion afforded hydroxyl phosphonate **97** in moderate yield (39 % over 3 steps).



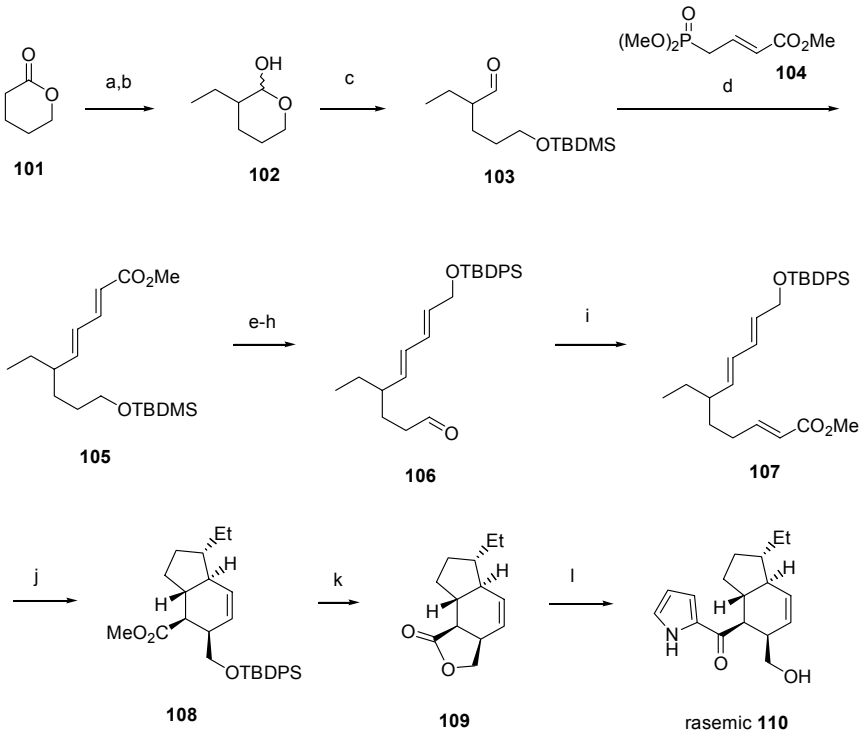
Scheme 10. Reagents and conditions: a) TBDPSCl, imidazole, DMF, 23 °C (95 %); b) *n*-BuLi, THF, -78 °C, then I_2, -78 -> -30 °C, 2 h (95 %); c) 9-BBN, THF, 23 -> 70 °C, 4 h, then AcOH, 25 °C, 30 min (65-70 %); d) *t*-BuLi, Et_2O, -78 °C, 1 h, then boronate **92**, -78 °, then 23 °C; e) aldehyde **94**, CH_2Cl_2, 23 °C, 12-24 h (55 %); f) NH_2NH_2, $NaIO_4$, CH_3OH, 23 °C; g) AcOH-CH_3OH-H_2O (4:1:1), 60 °C, 1 h; h) $NaIO_4$, THF (78 % over 3 steps); i) phosphonate **59**, LDA, THF, -78 -> 23 °C; j) $LiAlH_4$, Et_2O (82 % over 2 steps); k) Ph_3PBr_2, CH_3CN, 0 °C; l) NaP(O)(O-*i*Pr)$_2$, C_6H_6; m) HF, CH_3CN (39 % over 3 steps).

Reaction of phosphonate **97** with the unsaturated aldehyde **98** afforded tetraene. (Scheme 11) Swern oxidation of the resulting terminal alcohol and reaction with pyrrole phosphorane **89** gave optically pure indanomycin as the methyl ester derivative **100** in moderate yield (51 %) (22).



Scheme 11. Reagents and conditions: a) phosphonate **97**, DME, KO-*t*-Bu, 0 °C, *E:Z* (11:1) (83 %); b) DMSO, TFAA, -78 °C, DIPEA (80 %); c) ylide **89**, $ClCH_2CH_2Cl$, 40 °C, 3 days, then 60 °C, 1 day (51 %).

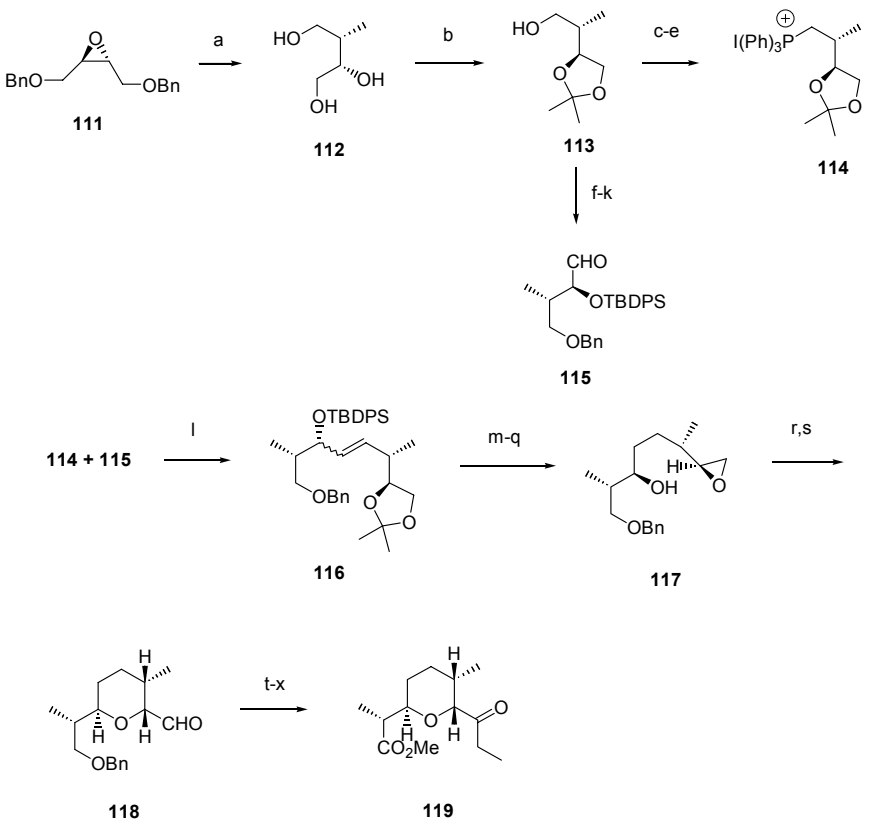
Nicolaou *et al.* (23) have also prepared *trans*-fused hexahydroindene part of indanomycin **72** by an IMDA reaction. However, this method afforded a racemic mixture of cycloadducts **110**. They prepared the precursor for cycloaddition in the following manner (Scheme 12). Ethylation of δ-valerolactone **101** was followed by reduction to elaborate lactol **102**. Lactol **102** was opened by silylation to afford siloxy aldehyde **103**. HWE reaction of **103** with **104** furnished dienoate **105** in very high yield (95 %). Further transformations afforded diene aldehyde **106**. Wittig reaction of aldehyde **106** produced triene ester **107**, which was heated in toluene to afford the cycloadduct **108**. Deprotection with fluoride gave cyclic lactone **109**. The pyrrolyl carbonyl moiety was obtained by alkylation with the Grignard reagent derived from MeMgCl and pyrrole in toluene.



Scheme 12. Reagents and conditions: a) LDA, EtI, THF-HMPA, -78 °C (80 %); b) DIBAL-H, CH_2Cl_2, - 78 °C (100 %); c) *t*-$BuMe_2SiCl$, imidazole, DMF, 25 °C (70%); d)

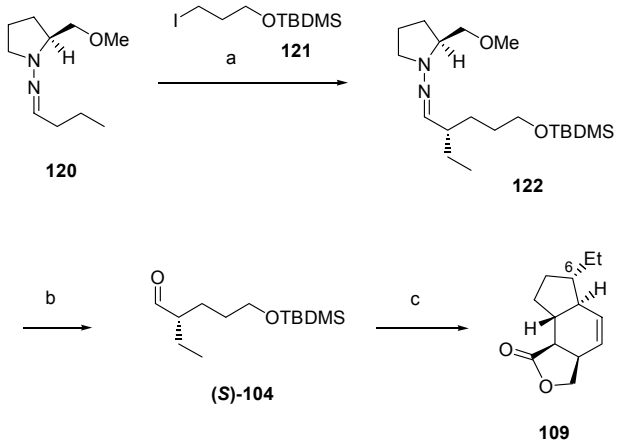
LDA, THF, - 78 °C (95 %); e) DIBAL- H, CH_2Cl_2, - 78 °C (99 %); f) *t*-$BuPh_2SiCl$, imidazole, DMF, 25 °C; g) AcOH-THF-H_2O, 25 °C, 1 h (70 % over 2 steps); h) CrO_3·pyr·HCl, CH_2Cl_2, 25 °C; i) $(Ph)_3P=CHCO_2Me$, PhMe, 25 °C (90 % over 2 steps); j) PhMe, 130 °C, 48 h (70 %); k) *n*-Bu_4NF, THF, 25 °C (100 %); l) pyrrole, MeMgCl, PhMe, 110 °C (80-90 %).

Nicolaou *et al.* (24) have also prepared the optically active tetrahydropyran ring part of indanomycin **72** by starting from benzyl protected epoxide **111** (Scheme 13). Epoxide **111** was opened by alkylation and debenzylated with hydrogenolysis. Selective formation of the acetonide afforded hydroxyl acetonide **113** in high yield (98 %). The right side of tetrahydropyran ring was obtained by tosylation, substitution by iodine and reaction with triphenylphosphine to produce ylide **114** for Wittig reaction. The left side of tetrahydropyran ring **115** was obtained from the same hydroxyl acetonide **113** by benzyl protection, hydrolysis of the acetonide, *t*-butyl acetal formation, *tert*-butyldiphenyl silyl protection, DIBAL-H reduction and oxidation. Acetonide fragment **114** and aldehyde **115** were connected by Wittig reaction. Hydrolysis of the acetonide, selective tosylation, epoxide formation under basic conditions, desilylation and hydrogenation of the double bond afforded epoxy alcohol **117** set for ring formation. Ring closure was achieved effectively (95 %) by using camphorsulphonic acid. The final ester product **119** was prepared by oxidation of the alcohol, alkylation with ethylmagnesium bromide, debenzylation, Jones oxidation and esterification. Nicolaou *et al.* have prepared optically pure *trans*-fused hexahydroindene part of indanomycin **72** by using the SAMP hydrazone **120** to create the correct enantiomer at the C6-position (Scheme 14).(24) The lactone **109** was obtained using the same synthetic route as in the Scheme 12.



Scheme 13. Reagents and conditions: a) $LiCuMe_2$, Et_2O, - 78 °C -> - 40 °C, 10 % Pd/C, EtOH, 25 °C (100 % over 2 steps); b) $(MeO)_2CMe_2$-C_6H_6 (5:1), CSA, 25 °C, 15 h, then CSA, MeOH, 25 °C (98 %); c) TsCl, pyr, 0-25 °C (100 %); d) NaI, acetone, 25 °C, 48 h (85 %); e) PPh_3, CH_3CN-$(EtO)_3CH$ (4:1), 75 °C, 48 h (80 %); f) NaH, BnBr, DME, 0-65 °C (90 %); g) amberlite IR-120, ethylene glycol-DME (2:1), 45 °C (80 %); h) $(Me)_3CCOCl$-pyr, 0-25 °C; i) imidazole, *t*-$BuPh_2SiCl$, DMF, 0-25 °C; j) DIBAL-H, CH_2Cl_2, - 78 °C (85 % over 3 steps); k) CrO_3·pyr·HCl, 4 Å MS, CH_2Cl_2, 25 °C (85 %); l) DMSO, dimsylsodium, PhH, 25 °C (77 %, *E*/*Z* (2:1)); m) amberlite IR-120, ethylene glycol-DME (2:1), 45 °C (80 %); n) TsCl-pyr, - 20 -> 25 °C (75%); o) NaOMe, MeOH, 25 °C (100 %); p) *n*-BuN_4F, THF, 25 °C (100 %); q) 5% Pd/C, H_2, EtOAc (70 %); r) CSA, 25 °C (95 %); s) CrO_3·pyr·HCl, NaOAc, CH_2Cl_2, 25 °C (80 %); t) EtMgBr, PhMe,

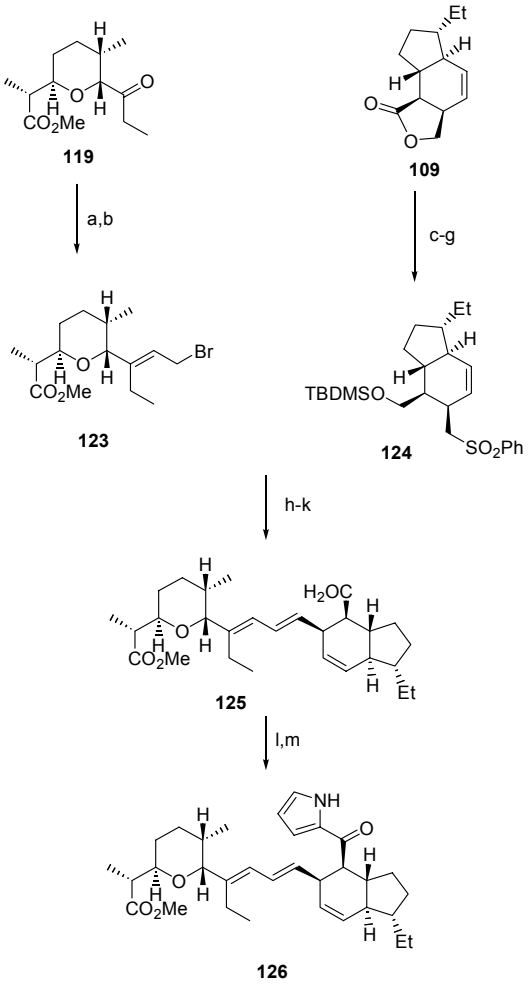
- 78 °C (80 %); u) 10 % Pd/C, H_2, EtOH (100 %); v) Jones reagent, acetone, - 40 -> - 20 °C (90 %); x) CH_2N_2, Et_2O, 0 °C.



Scheme 14. Reagents and conditions: a) LDA, Et_2O, 0 °C, 17 h (85 %); b) O_3, CH_2Cl_2, - 78 °C, 15 min (100 %); c) as in the Scheme 12 (steps d-k).

Nicolaou *et al.* achieved the first total synthesis of indanomycin **72** in 1981 by coupling allylic bromide tetrahydropyran **123** and phenyl sulfone **124** in high yield (97 %) (Scheme 15).(25) Allylic bromide **123** was prepared from the previously synthesized ketone **119** via sequence: alkylation with vinyl magnesiumbromide, bromination and simultaneous rearrangement with phosphorous tribromide. Phenyl sulfone derivative **124** was prepared by using the following sequence of reactions: opening of the lactone **109** with a thiol nucleophile, esterification, reduction and selective oxidation with diphenyl diselenide and hydrogen peroxide. After Julia coupling (29) of allylic bromide **123** with phenyl sulfone **124**, the resulting adduct was desulfurized with Triton B® to give the diene intermediate. Esterification and oxidation of the hydroxyl end to acid provided

ester acid **125**. The acid **125** was activated as pyridyl sulfide for the formation of the acyl pyrrole **126**.

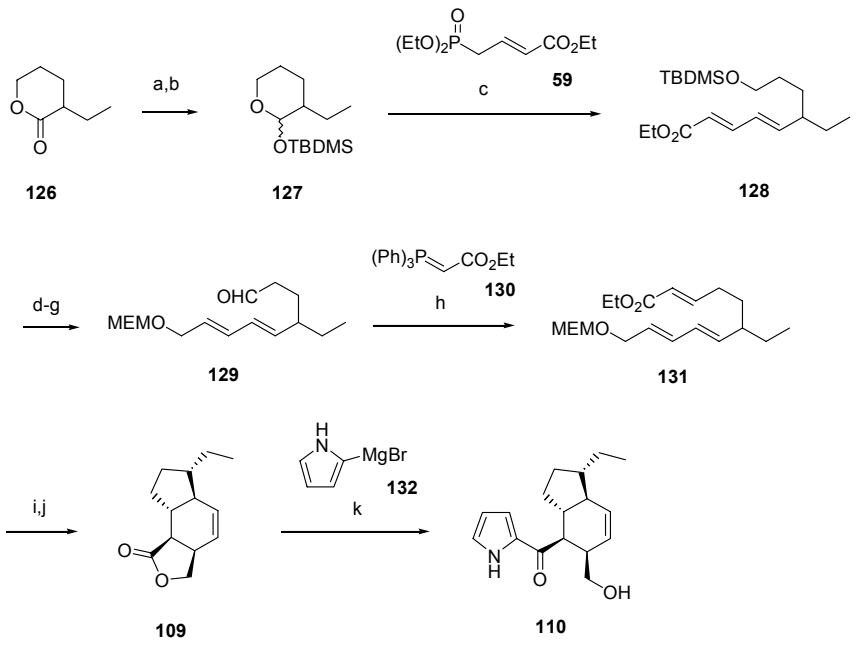


Scheme 15. Reagents and conditions: a) CH_2=CHMgBr, THF, - 78 °C (95 %); b) PBr_3, Et_2O, - 10 °C (*E*/*Z*, 13:5) (90 %); c) LiH, PhSH, DMF, 110 °C, 3 h; d) CH_2N_2, Et_2O, 0

°C; e) $LiAlH_4$, Et_2O, 0 °C (95 % 3 steps); f) Ph_2Se_2, H_2O_2, Et_2O-CH_2Cl_2 (5:1), 0-15 °C, 8 h (82 %); g) TBDMSCl, Et_3N, DMAP, CH_2Cl_2 (95 %); h) sulfone **124**, LDA, THF, - 78 °C, 10 min, HMPA, - 78 °C, 5 min, bromide **123**, THF, - 78 °C, 30 min (97 %); i) 40 % Triton B, MeOH, 45 °C, 24 h; j) CH_2N_2, Et_2O, 0 °C (80 % over 2 steps); k) Jones reagent, acetone, - 10 °C, 2 h (85 %); l) 2,2'-dipyridyl disulfide, Ph_3P, PhMe, 25 °C, 24 h; m) pyrrole, MeMgCl, PhMe-THF, - 20 °C, PhMe, - 78 °C (90 % over 2 steps).

2.2.2.1.3 Ley

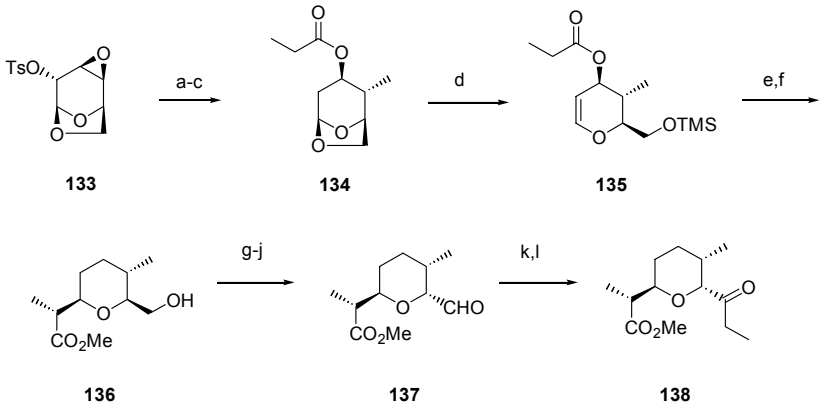
Ley *et al.* (26) prepared the bicyclo[4,3,0]nonene part of indanomycin **72** starting from 2-ethyl-δ-valerolactone **126** (Scheme 16). Lactone **126** was reduced to lactol with DIBAL-H. Resulting lactol was protected by TBDMS-group and reacted with the lithium anion of ethyl-4-diethylphosphonocrotonate **59** to give diene ester **128** in good yield (72 % over 3 steps). The ester group was reduced with DIBAL-H and the formed alcohol was protected as a MEM ether. Selective removal of silyl protection and PCC oxidation gave aldehyde **129** in high yield (96 %). Further reaction of **129** with phosphorane **130** gave the triene ester **131**. IMDA cycloaddition afforded the desired *endo*-cycloadduct in nearly quantitative yield (>90 %). Removal of MEM-protection resulted in the formation of lactone **109**. Relatively stable lactone **109** was converted to hydroxypyrrole **110** with pyrryl magnesium bromide at 100-105 °C.



Scheme 16. Reagents and conditions: a) DIBAL-H, PhMe, -78 °C; b) TBDMSCl, imidazole; c) LDA, phosphonate **59** (72 % over 3 steps); d) DIBAL-H, PhMe, 0 °C; e) MEMCl, DIPEA, CH_2Cl_2 (96 % over 2 steps); f) TBAF, THF; g) CrO_3, pyr, CH_2Cl_2, 25 °C (96 % over 2 steps); h) ylide **130**, CH_2Cl_2, 25 °C (95 %); i) PhMe, rfx, 36-70 h; j) $ZnBr_2$, CH_2Cl_2 (60 % over 2 steps); k) pyrrole **132**, PhMe, 100-105 °C (73 %).

Ley *et al.* (27) were the second group to complete the total synthesis of indanomycin **72**. They prepared the tetrahydropyran ring of indanomycin by a laborious route from 1,6-anhydro-*β-D*-glucose. Methylation, detosylation and acylation sequence gave the bridged intermediate **134** from tosylate **133**, which had previously been prepared from 1,6-anhydro-*β-D*-glucose (Scheme 17). Ring opening with iodotrimethylsilane, followed by DBU treatment gave the unsaturated pyran derivative **135**. Chirality transfer was accomplished using the Claisen ester-enolate rearrangement developed by Ireland *et al.* (28). In this step, enolization, silylation, warming, desilylation and methylation sequence afforded the unsaturated pyran ester alcohol derivative in good overall yield (67 %).

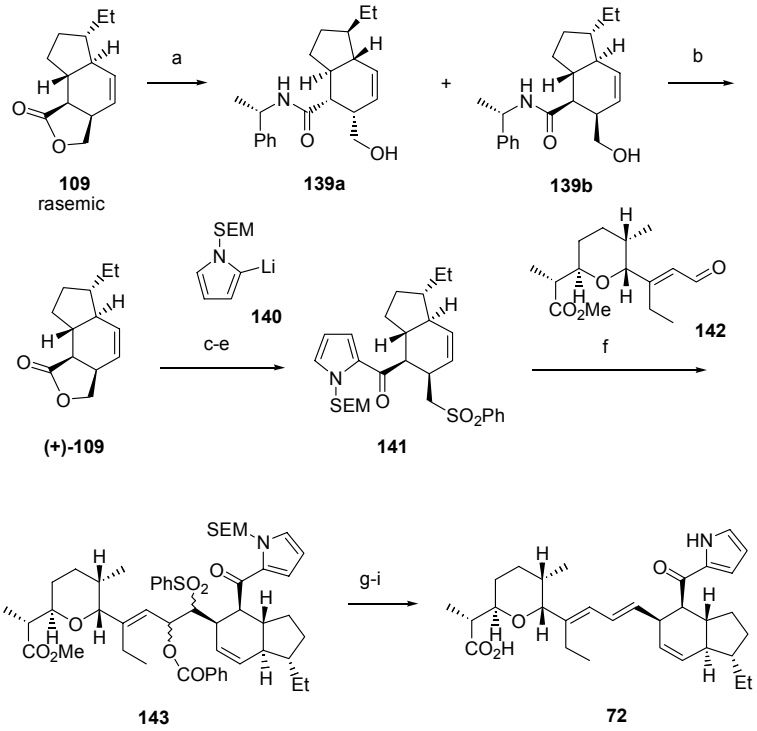
Hydrogenation gave the saturated pyran ring derivative **136**. The diastereomeric aldehyde **137** was elaborated from alcohol **136** by substitution of the hydroxyl group by iodine, elimination to obtain a double bond, hydroboration of the resulting double of bond, oxidative hydrolysis of borane and oxidation of the resulting alcohol. Finally, alkylation of the aldehyde **137** and oxidation of the resulting alcohol gave ethyl ketone **138**.



Scheme 17. Reagents and conditions: a) MeMgCl, CuBr·SMe_2, THF, -10 °C, 4 days (86 %); b) $LiBHEt_3$, THF, 20 °C, 24 h (95 %); c) *n*-BuLi, THF, -78 °C, then EtCOCl, 20 °C, 2 h (97 %); d) Me_3SiI, PhMe, -35 °C, 4 h, then DBU, -> r.t. (75 %); e) LDA, THF, -50 °C, 1 h, then Me_3SiCl, Et_3N, 20 °C, 15 min, 50 °C, 4 h, *n*-BuNF, CH_2N_2 (67 %); f) PtO_2, H_2, EtOAc, 20 °C, 2 h (60 %); g) Ph_3P, imidazole, I_2, PhH, 80 °C, 1.5 h (85 %); h) AgF, pyr, 20 °C, 24 h (96 %); i) BH_3·THF, THF, 20 °C, 48 h, then NaOH, H_2O_2 (55 % over 2 steps); j) PCC, CH_2Cl_2, 20 °C, 48 h (62 %); k) EtMgBr, THF, -30 °C, 15 min; l) H_2CrO_4, acetone, 20 °C, 15 min (96 % over 2 steps).

The previously prepared lactone **109** (26) was resolved to obtain the bicyclo[4.3.0]nonene part of indanomycin **72** (27). Reaction of racemic **109** with *S*-phenylethylamine in the presence of 2-hydroxypyridine gave a separable diastereomeric mixture of lactams **139a,b** (Scheme 18). Hydrolysis of lactam **139b** returned optically pure lactone **109**. The unreactive lactone **109** was opened by a reaction with lithiated

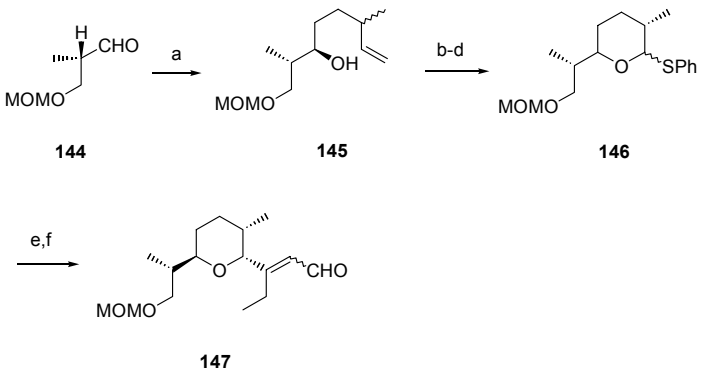
SEM-pyrrole **140** at 100 °C. The unsaturated aldehyde pyran derivative **142** was elaborated from **138** by using the method developed by Nicolaou *et al.* (24). The connection of the pyran derivative **142** and bicyclo[4,3,0]nonane fragment **141** was accomplished using Lythgoe-Kocienski modification of the Julia reaction (29). Highly stereoselective sodium amalgam reduction of the intermediate **143** afforded the diene intermediate. Cleavage of *N*-SEM protection and hydrolysis of ester group completed the synthesis of indanomycin **72**.



Scheme 18. Reagents and conditions: a) $PhCHMeNH_2$, 2-hydroxypyridine, PhMe, 110 °C, 6 h (49 %); b) 0.5 M H_2SO_4, dioxane-H_2O, 80 °C, 1 h (98 %); c) pyrrole **140**, DME, 0-20 °C, 5 min (62 %); d) NPSS, *n*-Bu_3P, C_6H_6, 20 °C, 3 h; e) H_2O_2, $(PhSe)_2$, CH_2Cl_2-Et_2O, 20 °C, 7 h (56 % over 2 steps); f) *n*-BuLi, THF-HMPA, -78 °C, 45 min, then PHCOCl, 20 °C, 2 h; g) Na-Hg, THF-MeOH, -20 °C, 3 h (53 % over 2 steps); h) *n*-BuNF, THF, 0-20 °C, 45 min (72 %); i) NaOH, MeOH-H_2O, 60 °C, 3 h (90 %).

2.2.2.1.4 Boeckman

Boeckman *et al.* (30) have also reported an enantioselective synthesis of indanomycin **72**. The pyran subunit was prepared starting from chiral aldehyde **144** (Scheme 19). Alkylation of chiral aldehyde **144** gave a diastereomeric mixture of alcohols **145**. Ozonolysis of the terminal olefin and base catalyzed epimerization of the secondary methyl group produced a mixture of anomeric lactols (α:β) with a ratio of (1:3). Substitution with thiophenol in the presence of boron trifluoroetherate gave the α-(phenylthio)pyran **146**. Reductive lithiation generated an axial α-lithiopyran, which was condensed with 1-methoxy-1*E*-penten-3-one to afford a 1,2-adduct. Unsaturated pyran aldehyde **147** was generated as a 3:1 mixture of *E*:*Z*-isomers by pyridium *p*-toluenesulfonate catalyzed hydrolysis.

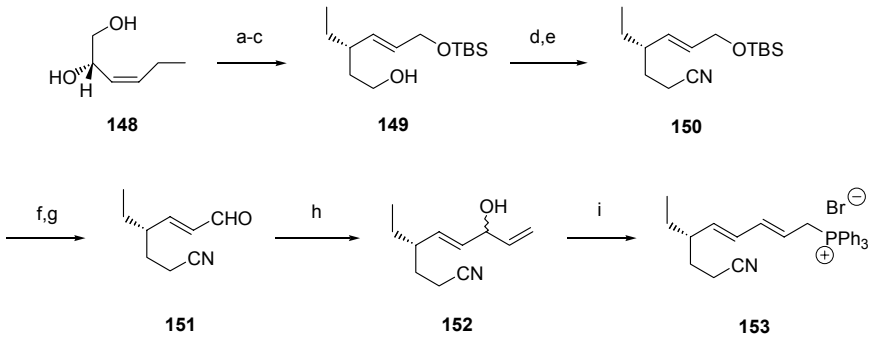


144 **145** **146**

147

Scheme 19. Reagents and conditions: a) $LiCu((CH_2)_2CHCH_3CH{=}CH_2)_2$, Et_2O, -48 °C -> -40 °C, 20 min (93 %); b) O_3, CH_2Cl_2, -78 °C, 15 min, Me_2S, -78 -> 25 °C, 20 min; c) K_2CO_3, MeOH, 23 °C, 3 h; d) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 °C, 10 min (47 %); e) LiDBB, -78 °C, 10 min; then $CH_3CH_2COCH{=}CHOCH_3$, THF, -78 °C, 10 min; f) *p*-TsOH·pyr, CH_2Cl_2, -40 °C, 1 h (42 % over 2 steps).

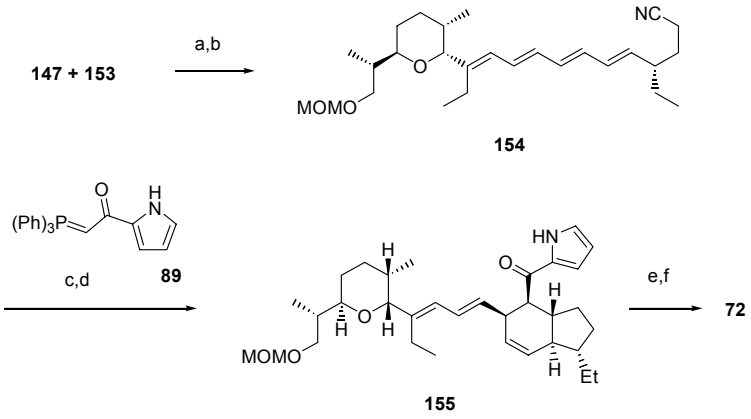
The bicyclo[4.3.0]nonane fragment of indanomycin **72** was prepared from the chiral diol **148** (Scheme 20).(30) Selective silylation of the primary hydroxyl group (31) followed by Claisen ortho ester rearrangement provided the unsaturated ester upon treatment of the monoprotected diol with trimethyl orthoacetate in hot xylenes in the presence of propionic acid. The crude ester was reduced with DIBAL-H to *E*-alcohol **149** in high overall yield (87 %). Tosylation of alcohol **149** and substitution of the tosyl group by cyanide group afforded nitrile intermediate **150**. Unsaturated aldehyde **151** was obtained by desilylation and oxidation. *E,E*-Diene phosphorane intermediate **153** was elaborated by alkylation and phosphorylation with concomitant rearrangement in high yield (87 %).



Scheme 20. Reagents and conditions: a) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 23 °C, 10 h; b) $CH_3C(OCH_3)_3$, $CH_3CH_2CO_2H$, xylenes, rfx, 19 h; c) DIBAL-H, THF, -70 -> 23 °C, 1.5 h (87 % over 3 steps); d) *p*-TsCl, pyr, CH_2Cl_2, 23 °C, 10 h; e) KCN, Me_2SO, 55 °C, 5 h (88 % over 2 steps); f) *n*-BuNF, THF, 0 °C, 20 min; g) PDC, CH_2Cl_2, 23 °C, 12 h (67 % over 2 steps); h) CH_2=CHMgBr, THF, -78 -> 23 °C, 30 min; i) Ph_3P-HBr, CH_2Cl_2, 23 °C, 10 min (87 % over 2 steps).

Boeckman (30) continued the synthesis of indanomycin **72** by a Wittig coupling of the *E*:*Z*-mixture (3:1) of aldehyde **147** and phosphonium salt **153** (Scheme 21). The prepared tetraene mixture was isomerized to *E,E,E,E*-tetraene **154** by treatment with a catalytic amount of I_2 in the presence of potassium carbonate and cesium carbonate. DIBAL-H reduction of the nitrile to aldehyde and Wittig coupling of the resulting aldehyde with

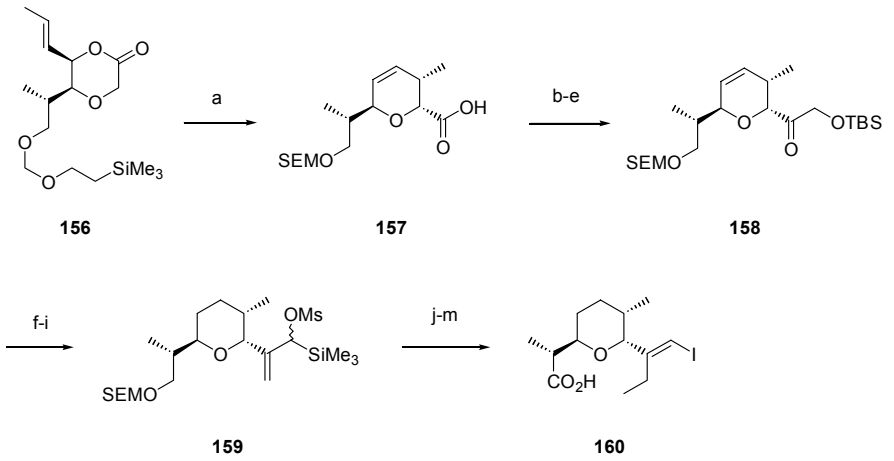
pyrryl phosphorane ylide **89** gave a pentaene intermediate, which was immediately subjected directly to thermal IMDA conditions to afford the cycloadduct **155** in moderate yield (53 %). Indanomycin **72** was finally elaborated by removing the MOM protecting group and oxidizing the resulting alcohol under Jones conditions.



Scheme 21. Reagents and conditions: a) *t*-BuOK, DMF, -23, 1 h, 0 °C, 35 min; b) I_2, hexanes, Cs_2CO_3, K_2CO_3, 23 °C, 20 min (79 %); c) DIBAL-H, -78 °C, 6 min, -> 0 °C, 25 min (83 %); d) phosphorane **89**, $ClCH_2CH_2Cl$, BHT, $SrCO_3$, Cs_2CO_3, 45 °C, 96 h, then 65 °C, 48 h (53 %); e) Me_3SiI, $CHCl_3$, -78 -> -60 °C, 10 min; f) CrO_3, acetone, -23 °C, 1 h (79 %).

2.2.2.1.5 Burke

Burke *et al.* (32) based their synthesis of indanomycin **72** on RHDA cycloaddition, Ireland-Claisen rearrangement and Stille coupling. Ireland-Claisen [3,3] rearrangement of the silyl enolate of lactone **156** afforded the unsaturated pyran derivative **157** (Scheme 22). Vinylsilane methodology was utilized to prepare vinyliodide **160** for Stille coupling (33).

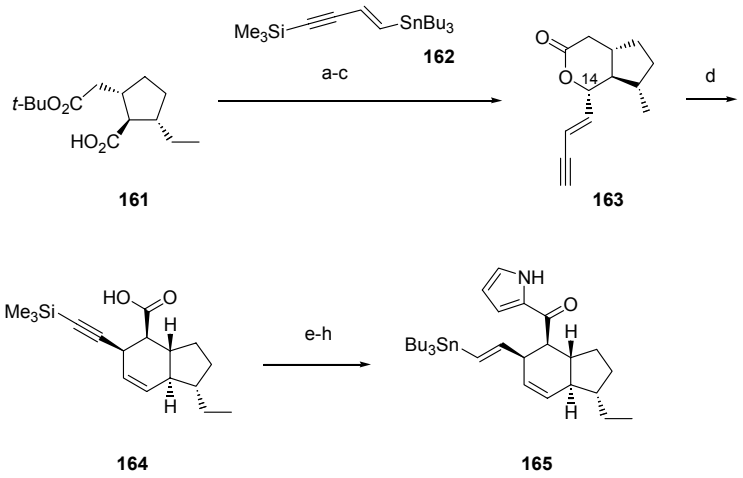


156 **157** **158** **159** **160**

Scheme 22. Reagents and conditions: a) LiHMDS, Me_3SiCl, Et_3N, THF, -78 –> 23 °C, 40 min, PhMe, rfx, 4 h, 5 % HCl, Et_2O; b) NHMe(OMe)·HCl, DCC, DMAP, CH_2Cl_2, (70 % over 2 steps); c) Bu_3SnCH_2OBOM, *n*-BuLi, THF, -78 -> 0 °C (89 %); d) $Pd(OH)_2$, H_2, EtOH, 23 °C, 1.5 h; e) TBDMSCl, imidazole, DMAP, CH_2Cl_2, 23 °C (83 % over 2 steps); f) $Ph_3P{=}CH_2$, THF, -78 -> 0 °C, TBAF·$3H_2O$, 0 -> 23 °C (95 %); g) $BaMnO_4$, CH_2Cl_2, 23 °C; h) $(Me_3Si)_3Al{\cdot}OEt_2$, PhMe, -90 °C; i) Ms_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C; j) MeMgBr, CuCN, THF, -78 -> -40 °C (63 % *E/Z* (3.8:1) over 4 steps); k) NIS, THF, -15 -> 23 °C; SiO_2 (dark) (79 %); l) $LiBF_4$, CH_3CN, 80 °C, 1 h (88 %); m) Jones oxidation (92 %).

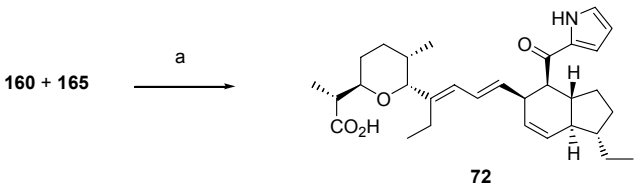
The chiral lactone **163** was prepared from *trans,anti*-trisubstituted cyclopentane **161** (Scheme 23). Palladium catalyzed acylation of vinylstannane **162** with the acid chloride of trisubstituted cyclopentane **161** afforded a ketene intermediate. Luche reduction of the ketene and ester hydrolysis gave the starting material for a DMAP catalyzed lactonization to afford lactone **163** as a mixture of C14 epimers (1.2:1). The lactone was converted to its silyl ketene acetal for RHDA cycloaddition. The cyclic acid **164** was activated as the thiopyridyl ester for pyrrole connection with pyrrolyl magnesium bromide. Finally

reductive alkyne desilylation gave the vinylstannane derivative **165** ready for Stille coupling.



Scheme 23. Reagents and conditions: a) $(COCl)_2$, C_6H_6, DMF; b) $PhCH_2PdCl(PPh_3)_2$, vinylstannane **162**, THF, 50 °C (76 %); c) $NaBH_4$, $CeCl_3$, MeOH, 23 °C, 10 min; aq. NaOH, MeOH, THF, 24 h, aq. HCl; DIC, DMAP, CH_2Cl_2, 23 °C (71 %, 1.2:1 *epimer*); d) LiHMDS, Me_3SiCl, Et_3N, -100 -> 23 °C, 40 min; remove THF, PhMe, rfx, 36 h; 5 % HCl, Et_2O; e) Aldrithiol-2(2,2'-dipyridyl sulfide), PhMe, 23 °C (66 % over 2 steps); f) EtMgBr, pyrrole, PhMe, THF, 0 °C, then thioester, THF, 0 °C (93 %); g) TBAF·$3H_2O$, THF, 0 °C (98 %); h) Bu_3SnH, $Pd(PPh_3)_4$, C_6H_6, 23 °C (71 %).

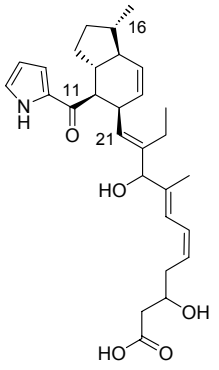
The synthesis of indanomycin **72** was completed by Stille coupling of vinyliodide **160** and vinylstannane **165** in moderate yield (61 %) (Scheme 24). The reaction required the use of freshly prepared $(Ph_3P)_4Pd$ in DMF to avoid reductive dimerization of vinylstannane **165**.



Scheme 24. Reagents and conditions: a) $(Ph_3P)_4Pd$, DMF, 23 °C (61 %).

2.2.2.2 Stawamycin **166**

Stawamycin **166** was isolated from *Streptomyces* in 1995 by Miao *et al.* (34). (Figure 11). Stawamycin **166** is an inhibitor against the Epstein-Barr virus (human herpes virus) BZLF1 transcription factor to DNA with an IC_{50} = 50 μM in a DNA binding assay (34). Stawamycin **166** has a trisubstituted *trans*-fused *endo*- bicyclo[4.3.0]nonane substructure. The only reported efforts towards the synthesis of stawamycin are concentrated on the preparation of bicyclo[4.3.0]nonane fragment.

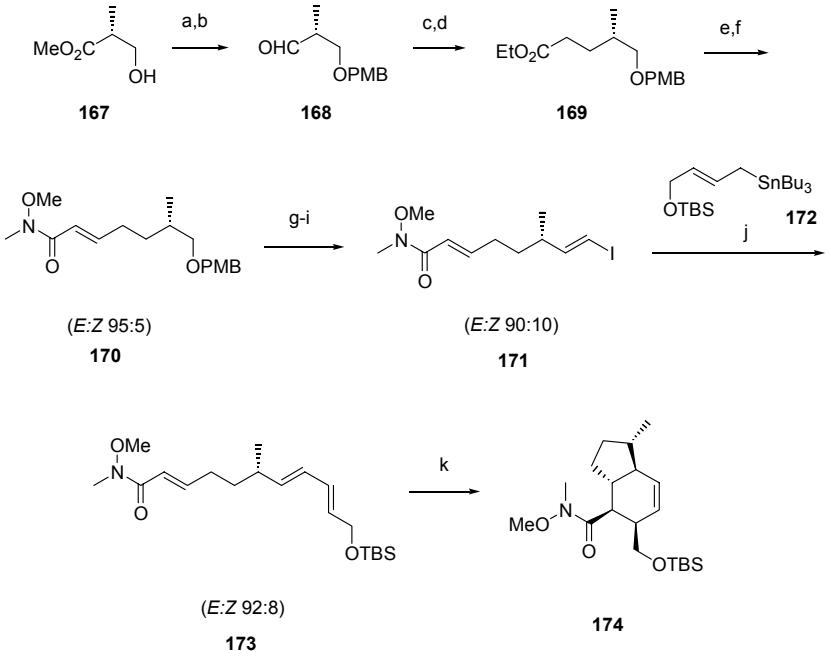


stawamycin (166)

Figure 11. Structure of stawamycin **166**.

Dias *et al.* (35) have recently reported a synthesis of the C11-C21 fragment of stawamycin **166** by a thermal IMDA cycloaddition (Scheme 25). They used the chirality of (*R*)-3-hydroxy-2-methylpropionate **167** for creating the chiral center C16. Stille coupling was utilized for elaborating the triene precursor **173** for IMDA cycloaddition. Stannane **172** was obtained from propargyl alcohol by TBS-protection and tributylstannylation. Unfortunately, thermal IMDA cycloaddition of the Weinreb amide

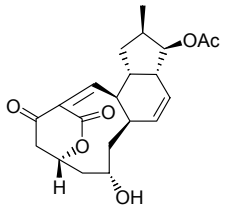
derivatized triene **173** resulted in low diastereoselectivity (48:52, *endo*-**174***:exo*). The desired *endo*-cycloadduct **174** was obtained as a mixture with *exo*-cycloadduct after flash chromatographic purification (*endo:exo,* 48:14) in moderate yield (60 %).



Scheme 25. Reagents and conditions: a) PMB, acetimidate, CSA, CH_2Cl_2, r.t. (94 %); b) DIBAL-H, PhMe, -78 °C; c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rfx (86 % over 2 steps); d) H_2, Pd/C, MeOH, r.t. (91 %): e) DIBAL-H, PhMe, -78 °C; f) $Ph_3P{=}CHCONMeOMe$, CH_2Cl_2, rfx (78 % over 2 steps); g) DDQ, CH_2Cl_2, H_2O (91 %); h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C; i) CHI_3, $CrCl_2$, THF, 0 °C (65 % over 2 steps); j) $(MeCN)_2PdCl_2$, DMF (77 %); k) PhMe, BHT, 150 °C (78 %).

*2.2.3 Cochleamycin A **175***

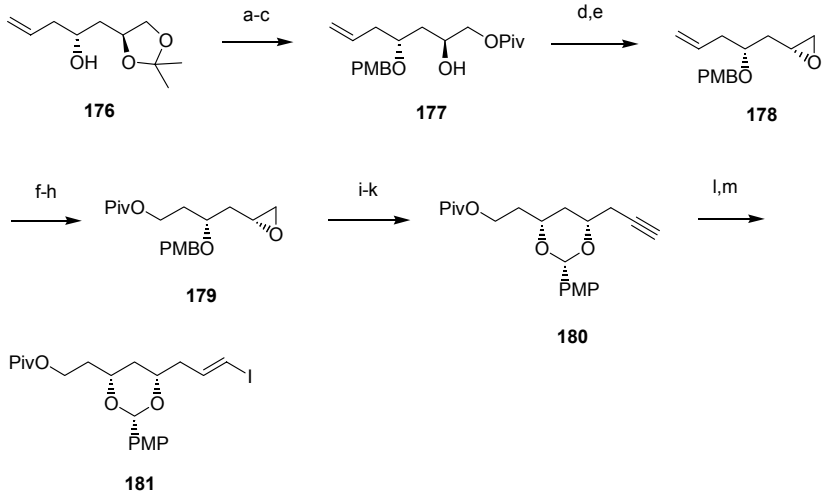
In 1992-1996 the team of Shindo and Kawai (36) isolated and characterized antitumor antibiotics which they named cochleamycins. The structure of cochleamycin A **175** is shown in Figure 12. Cochleamycin A **175** incorporates a tetrasubstituted *cis*-fused bicyclo[4.3.0]nonane fragment.



Cochleamycin A (175)

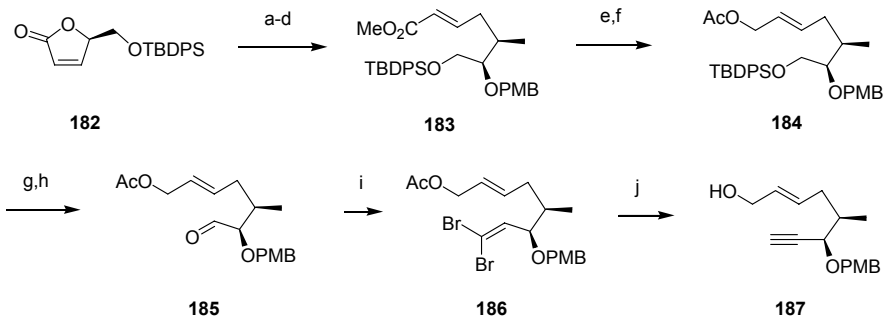
Figure 12. Structure of cochleamycin A **175**.

Paquette and Chang (37) have recently reported synthetic studies towards total synthesis of cochleamycin A **175**. The chirality of *L*-(-)-malic acid was employed to elaborate the vinyl iodide fragment **181** for Sonagashira coupling (38) (Scheme 26). After conversion of *L*-(-)-malic acid to hydroxy acetal **176**, the alcohol group was protected with PMB-group. Deacetalization, pivaloylation, mesylation and cyclization afforded epoxide **178** in high yield (72 % over 4 steps). The left hand side of the vinyl iodide fragment **181** was elaborated by ozonolysis of the terminal double bond, reducing the resulting aldehyde and pivaloyl protection. Chemoselective opening of the oxirane **179** with lithium trimethylsilyl acetylide and desilylation was followed by oxidative cyclization with DDQ to afford the desired protected propargylic alcohol intermediate **180**. Finally, the vinyl iodide fragment **181** was obtained by stannylation and iodine substitution.



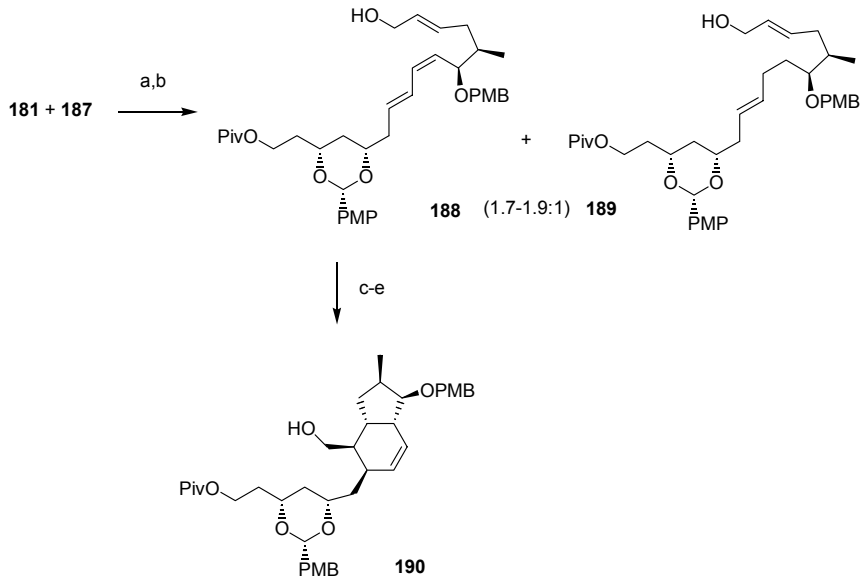
Scheme 26. Reagents and conditions: a) PMBBr, NaH, DMF (100 %); b) CH_3COOH, H_2O, THF (1:1), 50-60 °C (92 %); c) PivCl, pyr, CH_2Cl_2 (91 %); d) CH_3SO_2Cl, DMAP, pyr, CH_2Cl_2 (97 %); e) K_2CO_3, MeOH (89 %); f) O_3, EtOAc, -78 °C, then Ph_3P; g) $NaBH_4$, MeOH, 0 °C; h) PivCl, pyr, CH_2Cl_2 (77 % for 3 steps); i) HC≡CSiMe_3, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, -78 °C; j) (*n*-Bu)$_4$NF, THF, 0 °C (95 % for 2 steps); k) DDQ, 4 Å MS, CH_2Cl_2 (85 %); l) (*n*-Bu)$_3$SnH, AIBN, PhH, rfx (99 %); m) I_2, CH_2Cl_2 (96 %).

The chirality of alkyne **187** was induced from *L-(-)*-ascorbic acid. Butenolide **182** was first prepared from *L*-(-)-ascorbic acid using known methods. With butenolide **182** in hand, this was allowed to react with lithium dimethylcuprate to provide the *trans*-adduct (Scheme 27). After reduction to lactol, HWE reaction of the lactol and PMB-protection of the resulting hydroxyl group the α,β-unsaturated ester **183** was obtained. Further standard operations were employed to elaborate the terminal alkyne fragment **187**.



Scheme 27. Reagents and conditions: a) $(CH_3)_2CuLi$, ether, THF, -30 °C (89 %); b) DIBAL-H, CH_2Cl_2, -78 °C; c) $Ph_3P{=}CHCO_2Me$, C_6H_6, rfx (100 % for 2 steps); d) $PMBC(=NH)CCl_3$, CSA, CH_2Cl_2; e) DIBAL-H, CH_2Cl_2, -78 °C (60 % for 2 steps); f) Ac_2O, DMAP, pyr, CH_2Cl_2 (97 %); g) $(n\text{-Bu})_4NF$, THF, 0 °C (100 %); h) IBX, THF/DMSO (9:1) (90 %); i) CBr_4, Ph_3P, CH_2Cl_2, -78 °C (98 %); j) *n*-BuLi, THF, -78 °C (90 %).

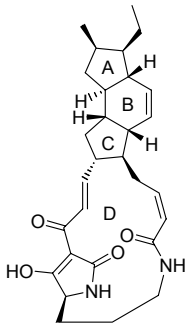
Sonagashira coupling of vinyl iodide **181** and the alkyne fragment **187** afforded the corresponding triene in high yield (82 %) (Scheme 28). Reduction of the alkyne to *E,Z,E*-triene **188** and IBX-oxidation afforded the substrate for the thermal IMDA reaction. The IMDA reaction was immediately followed by reduction of the bicyclic aldehyde to give the cycloadduct **190** via *endo*-transition state. Only one of the two possible *endo*-cycloadducts were obtained. Up to today, Chang and Paquette have not published the final steps, which would complete the synthesis of cochleamycin A **175**.



Scheme 28. Reagents and conditions: a) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N (82 %); b) H_2, Lindlar catalyst, EtOAc/pyr/1-octene (10:1:1) (95 %); c) IBX, THF/DMSO (9:1) (85 %); d) 20 % BHT, PhMe, sealed tube, 195 °C, 26 h; e) $NaBH_4$, MeOH, 0 °C (66 % for 2 steps).

2.2.4 Ikarugamycin **191**

Ikarugamycin **191** (Figure 13) was isolated in 1972 from the culture broth of *Streptomyces phaeochromognes var. ikaruganensis* by Jomon *et al.* (39) and fully characterized by Ito and Hirata (40) in 1972. It has a strong specific antiprotozoal activity, in vitro antiamoebic activity, and activity against some Gram-positive bacteria (39). Ikarugamycin **191** has a macrocyclic structure including *cis*-fused bicyclo[4.3.0]nonane substructure (AB ring junction) and two amide groups.



ikarugamycin (191)

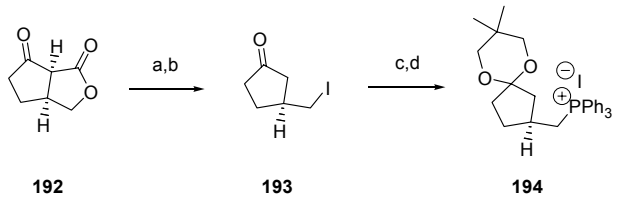
Figure 13. Structure of ikarugamycin **191**.

Several research groups have reported total syntheses of ikarugamycin **191**. Synthesis strategies of research groups of Boeckman, Kurth, Jones and Roush are based on thermodynamic IMDA-reaction. Whitesell *et al.* have used a photocyclization strategy to prepare the tricyclic ABC system of ikarugamycin **191**. The shortest route to the ABC structure of ikarugamycin **191** has been developed by Paquette *et al.* They discovered that an oxy-Cope rearrangement of chiral bicyclo[2.2.1]heptene pentene alcohol affords the tricyclic fragment of ikarugamycin **191**. The synthetic studies of ikarugamycin **191** are presented in the following chapters, which are divided according to research groups.

2.2.4.1 Boeckman

Boeckman *et al.* (41) began the synthesis of the A-ring of ikarugamycin **191** from the bicyclic lactone **192** (Scheme 29). Acid promoted ring opening of the lactone ring with concomitant decarboxylation afforded a bromomethyl cyclopentanone, which was

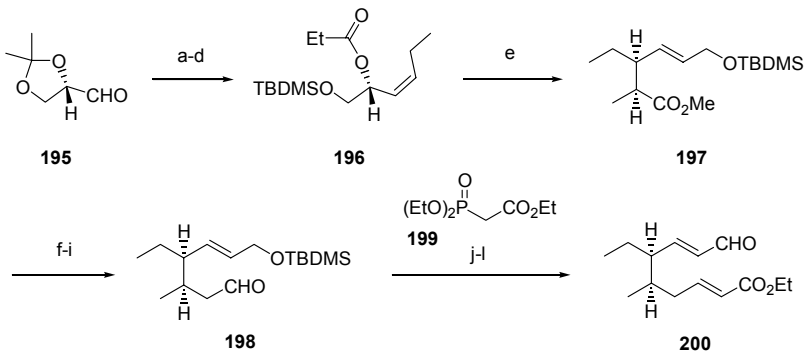
subjected to iodine substitution to give **193**. Phosphoryl ylide **194** was prepared from **193** by ketalization and phosphorylation.



192 **193** **194**

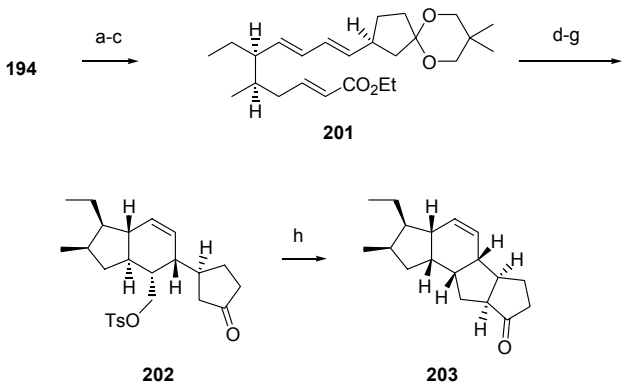
Scheme 29. Reagents and conditions: a) HBr, CH_2Cl_2, -78 °C → r.t., 12 h, then HOAc, 1 h (83 %); b) NaI, acetone, r.t., 40 h (91 %); c) $HOH_2CC(CH_3)_2CH_2OH$, MeOH, *p*-TsOH, PhH, rfx, 9 h (88 %); d) PPh_3, $NaHCO_3$, MeCN, rfx, 96 h (84 %).

The B- and C-rings were synthesized from chiral (*S*)-(-)-glyceraldehyde acetonide **195** (Scheme 30) (41). Wittig reaction of aldehyde **195** with propenyl phosphorane lithium salt afforded the alkene with high *Z*-stereoselectivity. Hydrolysis of the acetonide, silylation of the primary alcohol and acylation gave the allylic ester **196** in good yield (63 %). Ester enolate Claisen rearrangement and esterification with diazomethane afforded a mixture of diastereomeric esters **197** in a ratio (86:14). The ester **197** was reduced with DIBAL-H and the resulting alcohol was activated as a tosylate for nitrile substitution. Reduction of the nitrile to aldehyde **198** with DIBAL-H and subsequent HWE reaction with phosphonate **199** followed by desilylation and oxidation afforded ester aldehyde **200** ready for Wittig coupling.



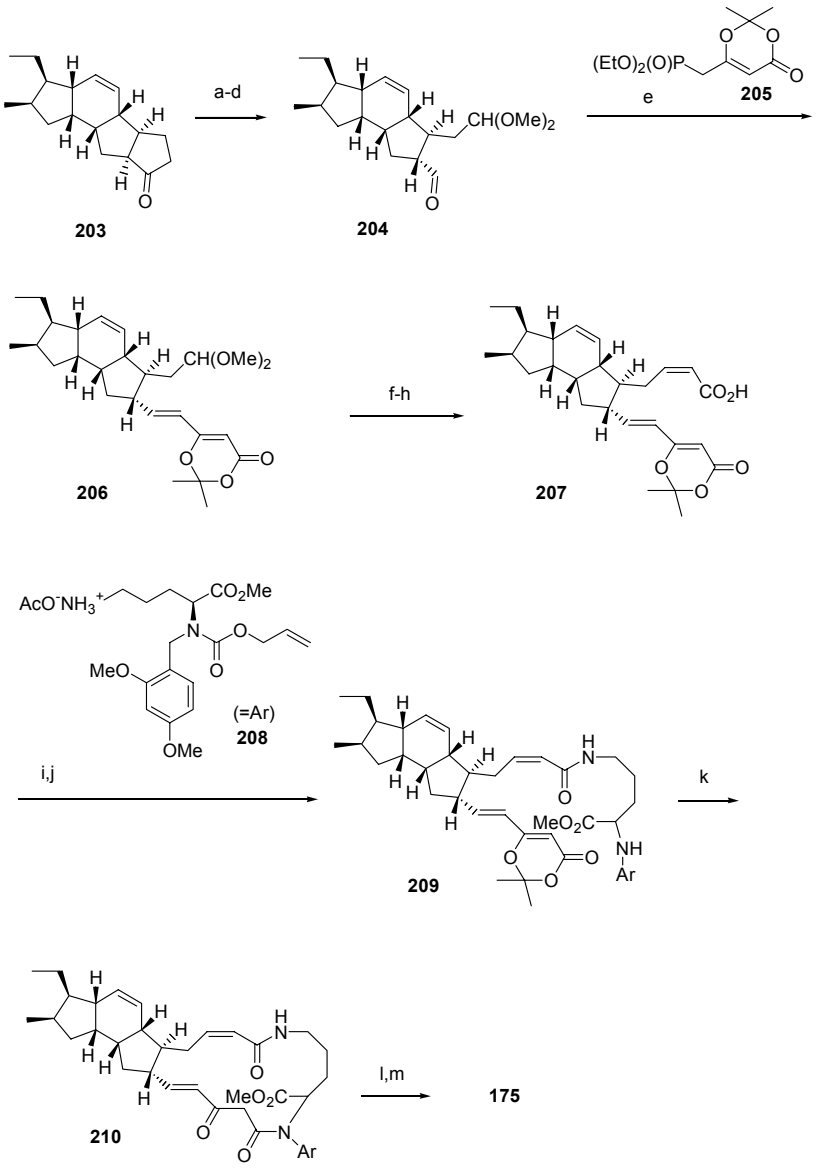
Scheme 30. Reagents and conditions: a) *n*-BuLi, *n*-$PrPh_3Br$, THF, 0 °C, 1 h (67 %); b) EtOH, HCl, r.t., 12 h (83 %); c) TBDMSCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → r.t., 7 h; d) EtCOCl, pyr, CH_2Cl_2, 0 °C → r.t., 15 h (63 % over 2 steps); e) LDA, 23 % HMPA-THF, -78 °C, Me_3SiCl, -78 °C → r.t., 20 h; H_3O^+; CH_3N_2 (74 %); f) DIBAL-H, THF, 0 °C, 1 h (92 %); g) TsCl, pyr, CH_2Cl_2, 0 °C → r.t., 40 h; h) KCN, DMSO, 80 °C, 5 h (61 % over 2 steps); i) DIBAL-H, Et_2O, -20 °C, 30 min; 5 % AcOH/NaOAc (aq. Buffer)-THF-MeOH (1:1:1), r.t., 3 h; j) NaH, phosphonate **199**, -50 → 0 °C, 2 h (77 % over 2 steps); k) THF-H_2O-HOAc (1:1:1), r.t., 16 h, l) PDC, CH_2Cl_2, r.t., 12 h (84 % over 2 steps).

Wittig reaction between the phosphorane ylide **194** and aldehyde **200** afforded the diene **201** as a *E,Z/E,E*-mixture (2:1) (Scheme 31) (40). The *E,Z*-diene was isomerized to the *E,E*-isomer **201** with a catalytic amount of iodine. The resulting *E,E,E*-trienyl ester **201** was subjected to thermal IMDA cycloaddition (140 °C, 70 h) to obtain the A- and B-rings of ikarugamycin **191**. The major *endo*-cycloadduct was obtained in (>5:1) ratio. The C-ring was elaborated by reducing the ester with DIBAL-H and hydrolyzing the ketal protection. Further conversion of the hydroxyl ketone to a crystalline tosylate afforded precursor **202** for cyclization. Tetracyclic ketone **203** was elaborated by intramolecular cyclization using potassium *tert*-butyl alcoholate.



Scheme 31. a) *n*-BuLi, THF-HMPA (10:1), -50 °C → r.t., 1 h; b) aldehyde **200**, -50 → 0 °C, 2 h; c) I_2, hexane, r.t., 6 h (87 % over 3 steps); d) BHT, PhMe, 140 °C, 70 h (87 %); e) DIBAL-H, THF, 0 °C, 1.5 h (87 %); f) 0.5 M HCl-THF (1:1), r.t., 16 h (82 %); g) TsCl, pyr, CH_2Cl_2, 4 °C, 40 h (72 %); h) *t*-BuOK, *t*-BuOH-PhH (1:2), r.t., 20 h (92 %).

Boeckman *et al.* (41) used a ketene-mediated cyclization to construct the 16-membered macrocyclic lactam ring **210**. Preparation of ketene **209** for ring closure started with oxidation of the tetracyclic ketone **203** to tetracyclic acyloins (4:1, α:β) (Scheme 32). Oxidative cleavage and protection of the ensuing ester aldehyde afforded an ester acetal in high yield (90 %). Reduction of the ester and PCC oxidation of the resulting acetal alcohol provided acetal aldehyde, which epimerized to the more stable conformer **204** in the presence of DBU. Next, acetal aldehyde **204** was subjected to a HWE reaction with potassium salt of phosphonate **205** to produce the *E*-dioxinone **206** in moderate yield (65 %). After hydrolysis of the acetal, Boeckman *et al.* used highly *Z*-selective (*Z*:*E* 19:1) Still and Gennari modification (42) of HWE reaction to prepare the *Z*-olefinic side chain of ikarugamycin **191**. After deprotection of the allyl ester, the resulting acid **207** was activated as mesitylene sulphonic anhydride for amide formation with primary amine acetate **208**. The resulting secondary amine **209** was deprotected for ketene intermediated macrocyclization. Boeckman completed the synthesis of ikarugamycin **191** by using a transannular Dieckmann cyclization and deprotection of the *N*-aryl protection.

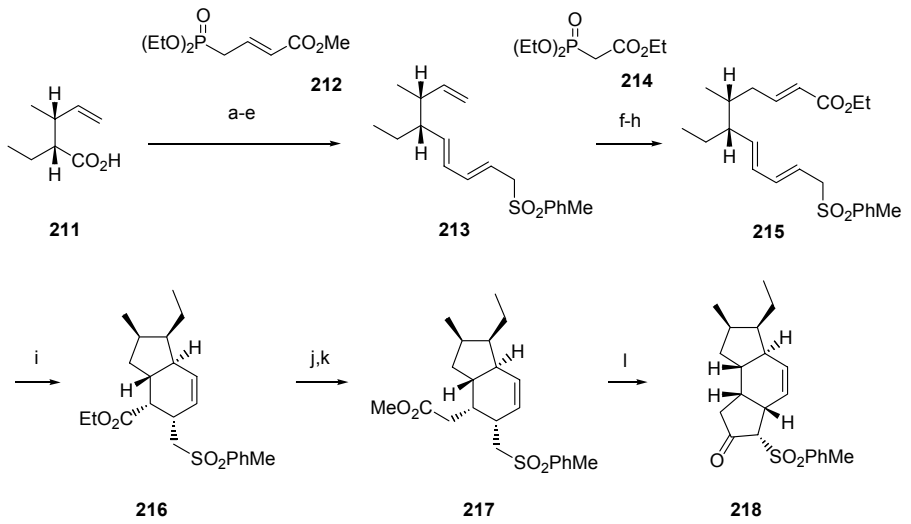


Scheme 32. Reagents and conditions: a) $PhI(OAc)_2$, KOH, MeOH, 25 °C, 8 h; then Amberlyst-15, THF-H_2O (95:5), 25 °C, 24 h (68 %); b) $Pb(OAc)_4$, MeOH-THF (1:1), 0

°C, 0.5 h; then Amberlyst-15, 3Å MS, MeOH, 25 °C, 16 h; c) DIBAL-H, THF, 0 °C, 2 h; d) PDC, 3Å MS, CH_2Cl_2, 25 °C, 0.5 h; then DBU, CH_2Cl_2, 0 °C, 72-150 h (62 % over 3 steps); e) phosphonate **205**, KHMDS, THF, 0 → 25 °C, 4 h (65 %); f) Amberlyst-15, MeCN-H_2O (9:1), 25 °C, 12 h; g) $(CF_3CH_2O)_2(O)PCH_2CO_2CH_2CH{=}CH_2$, K_2CO_3, 18-crown-6, PhMe, -20 → 0 °C, 4 h; h) NH_4OAc, $Pd(PPh_3)_4$, dioxane, 25 °C, 24 h (78 %); i) $MesSO_2Cl$, Et_3N, THF, 25 °C, 10 min; then ammonium salt **208**, DMAP, THF, 25 °C, 4 h (60-80 %); j) HOAc, $Pd(PPh_3)_4$, THF, 25 °C, 12 h (96 %); k) PhMe, 105 °C, 8-10 h (77 %); l) *t*-BuOK, *t*-BuOH, 0 °C, 15 min (75 %); m) TFA, 72 °C, 5 min (55 %).

2.2.4.2 Kurth

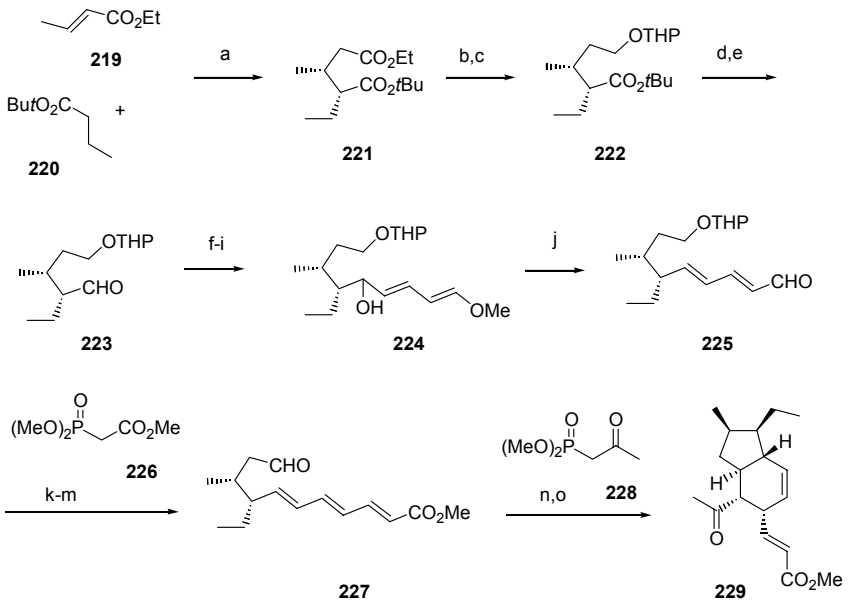
Kurth *et al.* (43) synthesized ABC-ring system of ikarugamycin **191** by a thermal IMDA cycloaddition and sulfone ester cyclization. They used the chiral unsaturated pentenoic acid **211** as the starting material (Scheme 33). Pentenoic acid **211** was reduced with $LiAlH_4$ to the corresponding alcohol and the alcohol was oxidized under Parikh-modified (44) Moffatt oxidation conditions. HWE olefination of the resulting aldehyde with phosphonocrotonate **212** afforded the (*E,E*)-diene ester. Second reduction with DIBAL-H furnished a trienol, which was converted to sulfone **213** by a one-pot tosylation - sulfinate displacement method. Regioselective hydroboration-oxidation with 9-BBN afforded the terminal sulfone alcohol. PCC oxidation and HWE reaction furnished the (*E,E,E*)-triene sulfone **215** precursor for the thermal IMDA cycloaddition. Diastereoselective IMDA cycloaddition resulted in the formation of the crystalline bicycloadduct **216** in moderate yield (70 %). The C-ring was elaborated by homologating the ester **216** with Arndt-Eistert procedure.(45) In this procedure, ester **216** was saponified and the crude acid was converted to the acid chloride. The additional methyl-group was obtained from diazomethane. Finally, sulfone ester cyclization using NaH as the base furnished octahydro-*as*-indacenone **218**.



Scheme 33. Reagents and conditions: a) $LiAlH_4$, Et_2O, 25 °C, 16 h (93 %); b) $PyrSO_3$, Et_3N, DMSO, 25 °C, 1.5 h (83 %); c) phosphonate **212**, LDA, THF, -78 °C, 30 min; then aldehyde, THF, -40 → 0 °C, 1.5 h (67 %); d) DIBAL-H, CH_2Cl_2, -78 °C, 3 h (94 %); e) MeLi, Et_2O-HMPA (3:1), 0 °C, 30 min; then TsCl, HMPA, 0 °C, 2.5 h; then $MePhSO_2Na{\cdot}2H_2O$, DMF, 25 °C, 16 h (88 %); f) 9-BBN, THF, 25 °C, 2.5 h; then NaOH, H_2O, H_2O_2, 25 °C, 2.5 h (81 %); g) PCC, CH_2Cl_2, 25 °C, 2.5 h (89 %); h) phosphonate **214**, KOH, THF, 25 °C, 15 min (71 %); i) *m*-xylene, 139 °C, 32 h (70 %); j) 6 M KOH-EtOH (1:8), rfx, 2 h (95 %); k) SO_2Cl, pyr, CH_2Cl_2, 25 °C, 4 h; then CH_2N_2, Et_2O-THF (2:1), 0 °C, 30 min, 25 °C, 30 min; then Ag_2O, MeOH, 64 °C, 2 h (75 %); l) NaH, THF, 25 °C, 1 h (90 %).

2.2.4.3 Jones

Jones *et al.* (46) chose a tetraene as the precursor for IMDA cycloaddition, which was used to form the AB-ring system of ikarugamycin **191**. They compared the outcome of thermal and Lewis acid promoted IMDA cycloadditions for the tetraene substrate. Lewis acid promoted IMDA was observed to give slightly lower yield due to increased polymerization compared to thermal IMDA. The formation of the ring A fragment was initiated by a Michael addition of *tert*-butyl butyrate enolate **220** to but-2-enoate ester **219** (Scheme 34). This resulted in the formation of a mixture of 2-ethyl-3-methylglutarates **221** (*erythro:threo* (5:1)) in high yield (97 %). Chemoselective reduction of the ethyl ester **221** with $LiBH_4$ was followed by THP-protection of the resulting alcohol. Reduction of the *tert*-butyl ester group with $LiAlH_4$ and PCC oxidation afforded the THP-aldehyde **223** for suitable chain elongation. Reaction of aldehyde **223** with *Z*-1-methoxy-but-1-en-3-yne furnished the corresponding hydroxydienal. HWE reaction of aldehyde **225** with trimethyl phosphonoacetate **226** afforded the triene ester. THP-removal and oxidation with PCC gave the *E,E,E*-triene aldehyde **227**. Finally, the tetraene ketone precursor for IMDA-cycloaddition was obtained from the HWE reaction of the triene aldehyde **227** with *β*-ketophosphonate **228**. Thermal IMDA-cycloaddition of triene ketone gave hexahydroindane cycloadduct in 51 % yield after one crystallization. The same IMDA cycloaddition catalyzed by Et_2AlCl gave 43 % yield for hexahydroindane cycloadduct. The yields of IMDA cycloadditions were low, because the triene ketone was a 5:1 mixture of *erythro*- and *threo*-stereoisomers as obtained from the initial Michael addition.

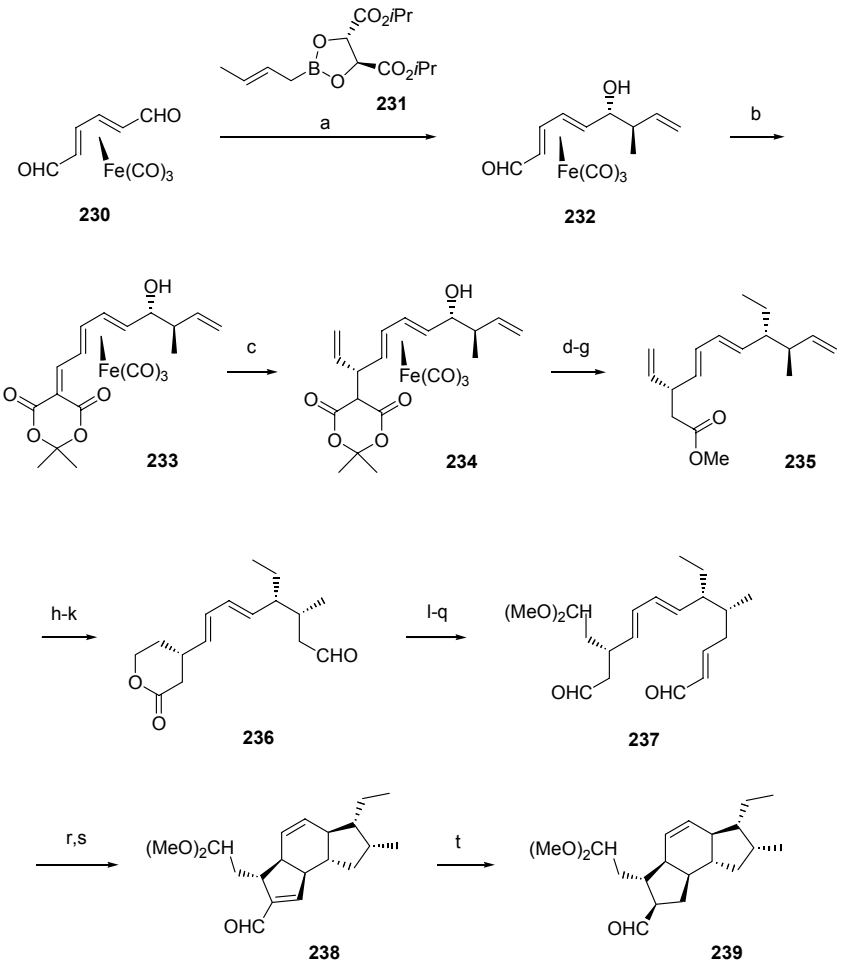


Scheme 34. Reagents and conditions: a) LDA, THF-HMPA, -78 °C (97 %); b) $LiBH_4$, MeOH-Et_2O (83 %); c) DHP, PPTS (93 %); d) $LiAlH_4$, Et_2O, rfx (93 %); e) PCC, NaOAc (89 %); f) (*Z*)-MeOCH=CHC≡CLi, THF, -78 °C; g) EtOH; h) $LiAlH_4$; i) 1 M HCl; j) *p*-TsOH, THF (58 % over 5 steps); k) phosphonate **226**, K_2CO_3, H_2O, 20 °C (82 %); l) Amberlite 15, MeOH (98 %); m) PCC, NaOAc (93 %); n) phosphonate **228**, K_2CO_3, H_2O, 20 °C (82 %); o) PhMe, rfx, 24 h (51 %).

2.2.4.4 Roush

Roush *et al.* (47) synthesized the ABC-ring system of ikarugamycin **191** by a long route (19 steps), starting from *meso*-(η^4-2,4-hexadien-1,6-dial)iron tricarbonyl **230**. The synthesis route is reviewed in a short manner in this chapter. The first key step is the highly enantioselective (≥98 %ee) allylboration of *meso*-(η^4-2,4-hexadien-1,6-dial)iron

tricarbonyl **230** with the chiral borane reagent **231** (Scheme 35). Condensation of the resulting dienyl aldehyde **232** with Meldrum's acid gave the malonate derivative **232**. The second key step was very face-selective (≥97:3) 1,4-addition of vinylmagnesiumbromide to malonate iron tricarbonyl derivative **233**. Acylation of the alcohol, alkylation of allyl acetate, -$Fe(CO)_3$ elimination, hydrolysis of malonate and esterification afforded tetraene ester **235**. Hydroboration of the terminal double bonds was followed by lactonization and Swern oxidation to afford dienyl aldehyde **236**. Furthermore, aldehyde end was subjected to HWE-reaction to obtain the trienyl ester. The lactone was opened and the resulting acid was esterified. After this, trienyl dialdehyde **237** was elaborated via oxidation, acetonide protection, reduction and oxidation sequence. The third key step was the thermal IMDA cycloaddition of trienyl aldehyde, which provided rings A and B of ikarugamycin **191** as a 12:1 mixture of cycloadducts. Diastereomerically pure ABC-ring adduct **238** was obtained by direct cyclization with the trifluoroacetic acid salt of dibenzylamine in high yield (88 %). Reduction of cyclic α,β-unsaturated aldehyde **238** with a copperhydride reagent in wet benzene provided *as*-indacene part of ikarugamycin **191**.

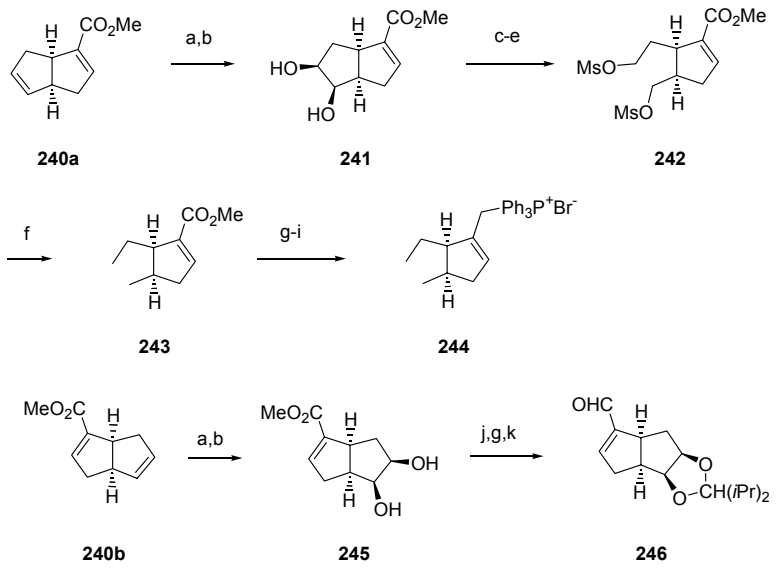


Scheme 35. Reagents and conditions: a) (*S,S*)-borane **231**, 4Å MS, PhMe, -78 °C (90 %); b) Meldrum's acid, pyr (92 %); c) H_2C=CHMgBr, THF, -78 → 0 °C (83-88 %); d) Ac_2O, DMAP, pyr, CH_2Cl_2; e) Et_3Al, CH_2Cl_2, -20 → 0 °C (69-75 % over 2 steps); f) $FeCl_3$, CH_3CN, -15 °C; g) H_2O, 3-pentanone, rfx; then CH_2N_2 (70 % over 2 steps); h) 9-BBN, THF; i) H_2O_2, NaOAc; j) *p*-TsOH, PhMe, 80 °C; k) $(COCl)_2$, DMSO, Et_3N, -78 → 0 °C (57 % over 4 steps); l) phosphonate **226**, LiCl, DBU; m) LiOH, then CH_2N_2; n) $(COCl)_2$, DMSO, Et_3N, -78 → 0 °C; o) $(MeO)_3CH$, *p*-TsOH; p) DIBAL-H, -78 °C; q) Dess-Martin

oxidation (56 % over 6 steps); r) PhH, 85 °C; s) $Bn_2NH_2OCOCF_3$, PhH, 50 °C (88 % over 2 steps); t) $[(Ph_3P)CuH]_6$, PhH, H_2O (85 %).

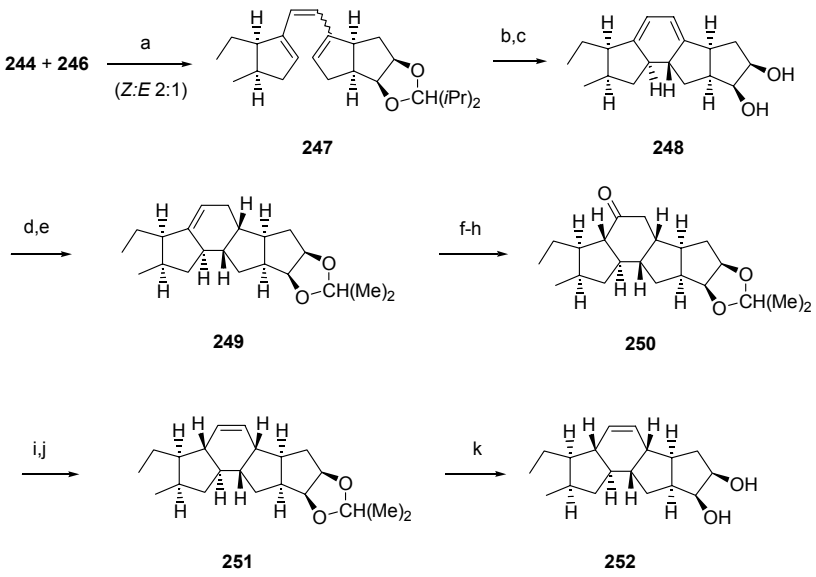
2.2.4.5 Whitesell

Whitesell and Minton (48) have developed an alternative method for preparing the carbocyclic portion of ikarugamycin **191**. Resolution of bicyclic enantiomeric esters **240a,b** and their separate elaboration and combination afforded precursor **247** for photocyclization (Scheme 36). A slightly diastereoselective (1.2:1) dihydroxylation of the *R*-enantiomer of bicyclo[3.3.0]octane **240a** using Woodward oxidation was followed by oxidative cleavage, reduction and mesylation to provide the dimesylate ester **242**. Zinc mediated reduction of dimesylate ester **242** proceeded in good yield (75 %). Finally, the phosphonium salt **244** was obtained via reduction, substitution with bromine and phosphorylation. The aldehyde fragment **246** was constructed from the (*S*)-enantiomer of the bicyclic ester **240b** via Woodward oxidation, deprotection, ketalization, reduction and oxidation.



Scheme 36. Reagents and conditions: a) AgOAc, HOAc, H_2O, r.t., 15 h, 70 °C, 2 h (95 %); b) *p*-TsOH, MeOH, rfx, overnight (95 %); c) $NaIO_4$ (95%); d) $NaBH_4$ (95 %); e) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h (100 %); f) NaI, Zn, DME, rfx, overnight (75 %); g) DIBAL-H (100 %); h) PBr_3, pyr (75 %); i) Ph_3P (90 %); j) $(i\text{-Pr})_2CO$, *p*-TsOH, PhH, 4Å MS, rfx, 28 h (75 %); k) PDC (90 %).

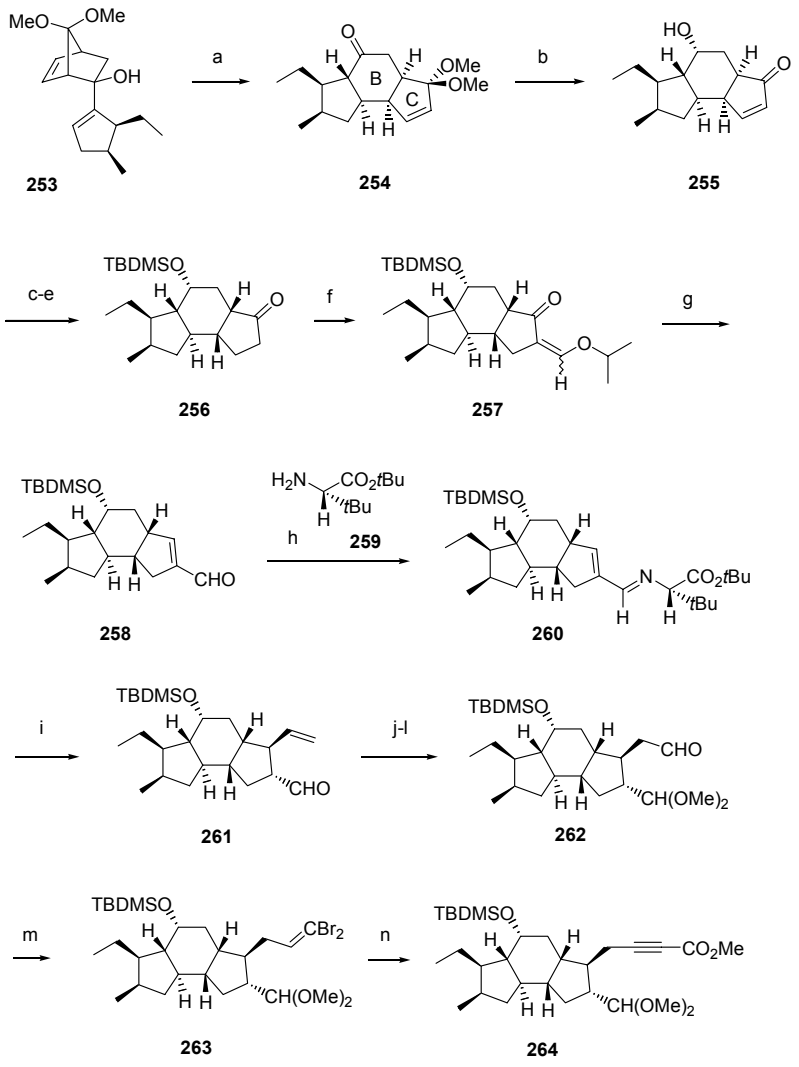
Wittig reaction of unsaturated aldehyde **246** with phosphorane **244** provided the tetracyclic triene **247** precursor for photocyclization (Scheme 37). Photocyclization of triene **247** gave a 4:1 mixture of pentacyclic cycloadducts **248**. The desired cycloadduct was chemoselectively reduced by dissolved metal reduction in moderate yield (45 %). Transacetalization, hydroboration, oxidation and epimerization gave the correct diastereomer of the pentacyclic intermediate **250**. The endocyclic double bond was obtained from ketone phosphorylation and Birch reduction in high overall yield (88 %). Ketal hydrolysis furnished tetracyclic diol intermediate **252** for ikarugamycin **191** synthesis.



Scheme 37. Reagents and conditions: a) phosphorane **244**, Et_2O, *n*-BuLi, 0 °C, aldehyde **246**, 0 → rfx, 1.5 h (79 %); b) hexane, hν, -75 °C, 24 h; c) MeOH-THF (4:1), 2 M HCl, r.t., overnight (50 % over 2 steps); d) Li, NH_3, *t*-BuOH, Et_2O, -78 °C, 4 h, → r.t., overnight; e) acetone, *p*-TsOH, THF (50 % over 2 steps); f) BH_3·THF; H_2O_2, NaOH (77%); g) PDC (90 %); h) NaOMe, MeOH (95 %); i) LDA, HMPA, $((Me)_2N)_2P(O)Cl$; j) Li, NH_3, *t*-BuOH, THF (88 % over 2 steps); k) MeOH-THF (2:1), H_2O, HCl, rfx, 1.5 h (83 %).

2.2.4.6 Paquette

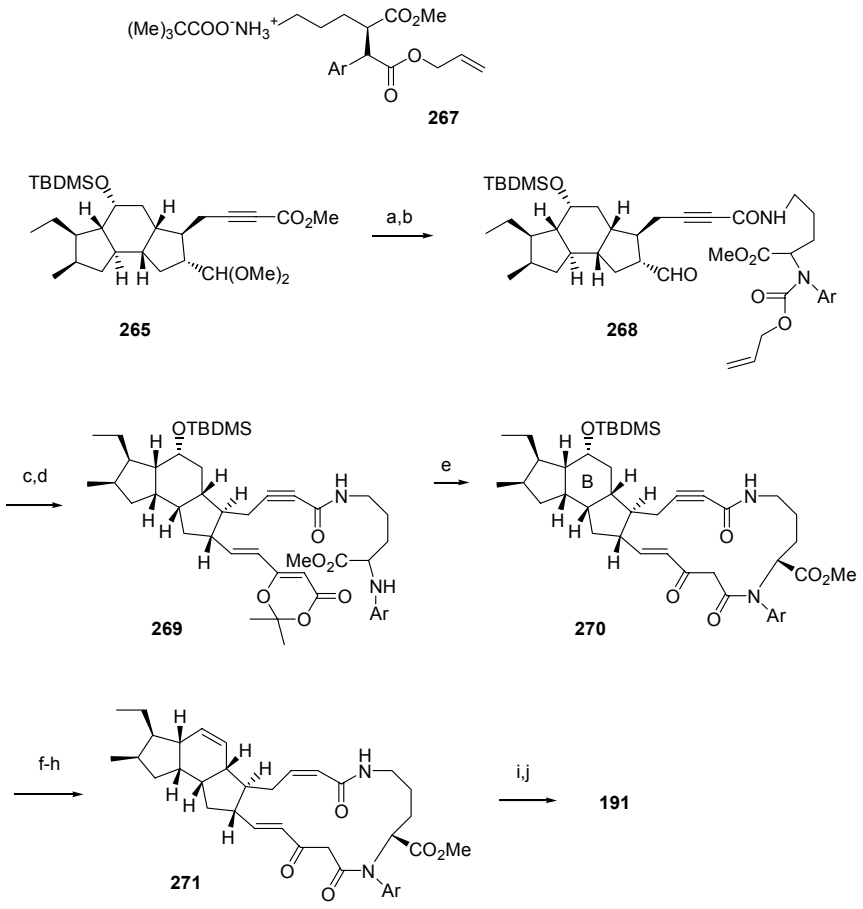
Paquette *et al.* (49) have developed a very short synthesis to the carbotricyclic part of ikarugamycin **191**. They discovered that anionic oxy-Cope rearrangement of tricyclic diene **253** produces tricyclic ketone **254** as a kinetic mixture of epimers (Scheme 38). The undesired epimer was easily epimerized to the correct isomer under basic conditions. Although the oxy-Cope rearrangement produced the wrong stereochemistry at carbon atoms that unite rings B and C at **254**, the correct stereochemistry was achieved by isomerization of tricyclic ketone **255** and reduction of the resulting isomeric ketone. Formylation of ketone **256** provided the basis for the construction of the second side chain. The correct stereochemistry of the side chains in **261** was achieved using Koga's asymmetric 1,4-conjugate addition (50) to aldimine **260**. However, the 1,4-addition of vinylmagnesium bromide to aldimine **260** produced **261** in low yield (22 %). The ratio of diastereomers was 5:1 and the major side product was enal **258**. Ketalization, hydroboration and oxidation furnished ketal aldehyde **262**. Paquette *et al.* prepared the dibromo olefin **263** from the resulting ketal aldehyde **262** for carbonyl homologation and triple bond formation to obtain **264**.



Scheme 38. Reagents and conditions: a) KH, THF, 0 °C, r.t., 2.5 h (64 %); b) DIBAL-H, CH_2Cl_2, -78 °C, 3 h; then 3 M HCl, Et_2O, r.t., 12 h (95 %); c) K_2CO_3, MeOH, 60 °C, 2.5 h (98 %); d) Li, NH_3, THF, -78 °C, 45 min (83 %); e) imidazole, DMF, TBDMSOTf, 25 °C, 1 h (95 %); f) KHMDS, THF, -78 °C, 1 h; then ethyl formate, 25 min, → r.t., 3 h;

then HMPA, 2-iodopropane, 0 °C → r.t., 11 h; g) DIBAL-H, CH_2Cl_2, -78 °C, 2 h; then 30 % HCl, 0 °C → r.t., 3 h (48 % over 2 steps); h) amine **259**, Et_2O, $MgSO_4$, HOAc, 25 °C, 20 h; i) THF, -36 °C, CH_2=CH_2MgBr, 25 min; then 10 % citric acid, 0 °C → r.t., 3 h (22 % over 2 steps); j) $(MeO)_3CH$, *p*-TsOH, 25 °C, 30 min (99 %); k) Sia_2BH, THF, 0 °C, 40 min; NaOH, H_2O_2 → r.t., 10 h (74 %); l) PCC, NaOAc, CH_2Cl_2, 0 °C, 2 h, → r.t., 2 h (89 %); m) CBr_4, CH_2Cl_2, Ph_3P, 0 °C, 15 min (100 %); n) *n*-BuLi, THF, -78 °C, 35 min, → 25 °C, 20 min; $ClCO_2Me$, -78 °C, 40 min, → 10 °C, 1 h (94 %).

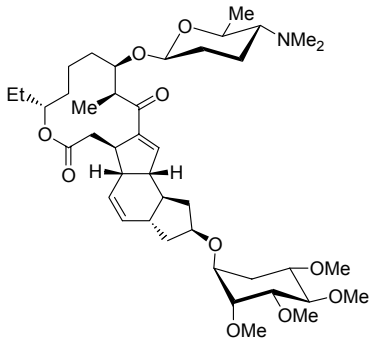
Paquette *et al.* (49) used an approach developed by Boeckmann *et al.* (41) to elaborate the tetramic acid system of ikarugamycin **191**. The only actual difference compared to Boeckmann's approach was the selective hydrogenation of the triple bond of derivative **270** to *Z*-olefin by Lindlar catalyst employing 5 % palladium on barium sulfate (Scheme 39). Desilylation with hydrogen fluoride was followed by dehydration of the hydroxyl group from the ring B using Burgess reagent (51). However, the yield of dehydration was low (36 %). Finally, ikarugamycin was obtained through cyclization and *N*-deprotection.



Scheme 39. Reagents and conditions: a) K_2CO_3, MeOH, 43 °C, 4 h; 2,4,6-$(Me)_3PhSO_2Cl$, THF, 25 °C, 50 min; DMAP, ammonium salt **267**, 16 h (46 %); b) *p*-TsOH, acetone, 25 °C, 3 h (92 %); c) phosphonate **205**, THF, KHMDS, -78 → 0 °C, 25 min, aldehyde **268**, 37 min, → 25 °C, 8 h (88 %); d) HOAc, THF, $(Ph_3P)_4Pd$, Ph_3P, 25 °C, 4 h (71 %); e) PhMe, rfx, 4 h (94 %); f) H_2, Pd-$BaSO_4$, 25 °C, 5 h (79 %); g) MeCN, HF, 25 °C, 13 min (85 %); h) $MeOC(O)NSO_2NEt_3$, PhH, r.t. → 50 °C, 18.5 h (36 %); i) *t*-BuOK, *t*-BuOH, 25 °C, 10 min (66 %); j) TFA, 62 °C, 10 min (20 %).

2.2.5 Lepicidin A **272**

Lepicidin A **272** is a member of tetracyclic macrolides. To date, nine analogues, differing in the degree of N, O, C methylation on the aglygon and sugar constituents, have been isolated. Lepicidin A **272** was isolated in 1990 from the fermentation broth of the soil microbe *Saccharopolyspora spinosa* by Eli Lilly and Company researchers (52) (Figure 14). Lepicidin A **272** exhibits insecticidal activity, particularly against lepidoptera larvae. Lepicidin A **272** consist of a *trans*-fused trisubstituted *endo*- bicyclo[4.3.0]nonane skeleton. Interestingly, it also includes two sugar units. 2,3,4-Tri-*O*-methylrhamnose is α-linked to bicyclo[4.3.0]nonane part and the acid-labile aminosugar *L*-forosamine is β-linked to macrocycle part.



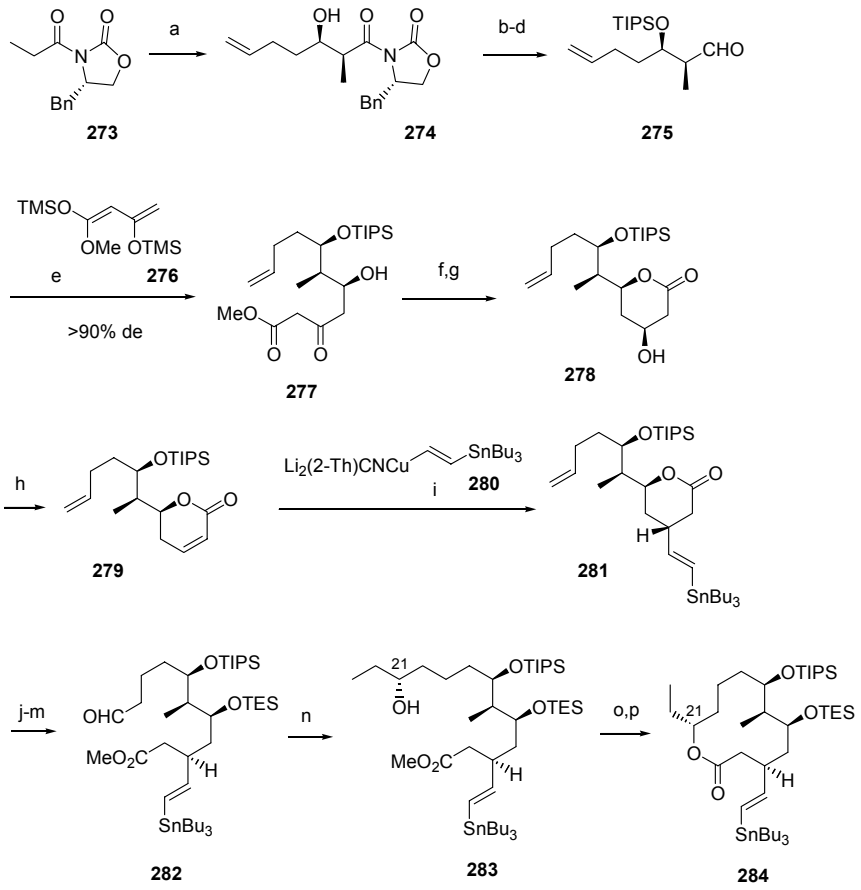
(+)-Lepicidin A (272)

Figure 14. Structure of antibiotic (+)-lepicidin A **272**.

Total synthesis of (+)-lepicidin **272** has only been accomplished by the Evans group and their synthesis is reviewed in the next chapter.

2.2.5.1 Evans

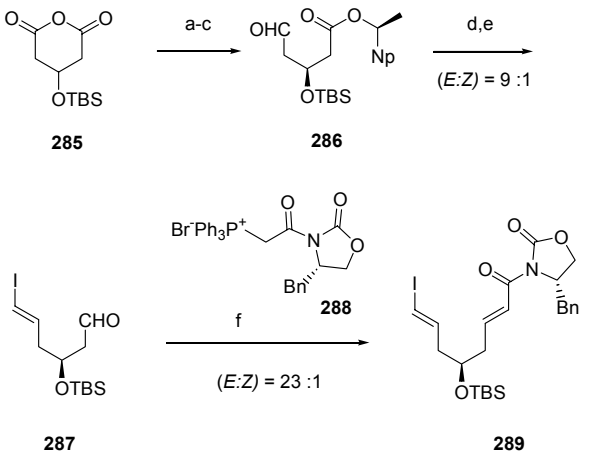
Evans *et al.* (53) has made an enormous work on synthesizing macrolide (+)-A83543A ((+)-lepicidin A **272**) by asymmetric methods. The macrocyclic fragment of (+)-lepicidin **272** was prepared beginning with an asymmetric aldol reaction of chiral oxazolidinone **273** (Scheme 40). Silylation, transamidation and reduction provided the chiral *β*-siloxy aldehyde **275**. Lewis acid promoted aldol reaction of **275** with silylenolate **276** afforded the Felkin adduct **277** with high diastereoselectivity (>20:1). Lactonization was used to protect the hydroxyl and carboxyl groups and it was anticipated that the lactone ring of **279** allowed better stereocontrol in the conjugate addition of vinylstannane **280**. After addition, the lactone ring was opened and the resulting acid esterified. The liberated hydroxyl group was protected as triethylsilyl ether. Selective hydroboration was followed by oxidation to provide aldehyde **282**. Asymmetric (+)-*N,N*-dibutylnorephedrine-catalyzed diethylzinc addition furnished aldehyde **282** to inducing chirality at C21 in **283**. Addition was followed by ester hydrolysis to enable macrolactonization. The macrolactonization was performed under modified Yamaguchi conditions (54) to afford stannane **284**.



Scheme 40. Reagents and conditions: a) Bu_2BOTf, Et_3N, 4-pentenal, CH_2Cl_2, -70 °C, 1 h → 0 °C, 1.5 h; H_2O_2 (90 %); b) MeONHMe·HCl, Me_3Al, CH_2Cl_2, -20 °C → r.t.; c) *i*-Pr_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; d) DIBAL-H, THF, -78 °C (98 % over 3 steps); e) $TiCl_2(O$*i*$-Pr)_2$, CH_2Cl_2, -78 °C (95 %); f) $Me_4NBH(OAc)_3$, MeCN, HOAc, -40 °C; g) PPTS, PhH, rfx (97 % over 2 steps); h) MsCl, Et_3N, CH_2Cl_2, r.t. (93 %); i) stannane **280**, BF_3, THF, -78 °C (97 %); j) LiOH, THF; CH_2N_2; k) Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, -78 °C (90 % over 2 steps); l) Sia_2BH, THF, 0 °C; H_2O_2, $NaHCO_3$, THF, 0 °C; m) pyr·SO_3, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 0 °C (80 % over 2 steps); n) Et_2Zn, DBNE, hexane, 0 °C

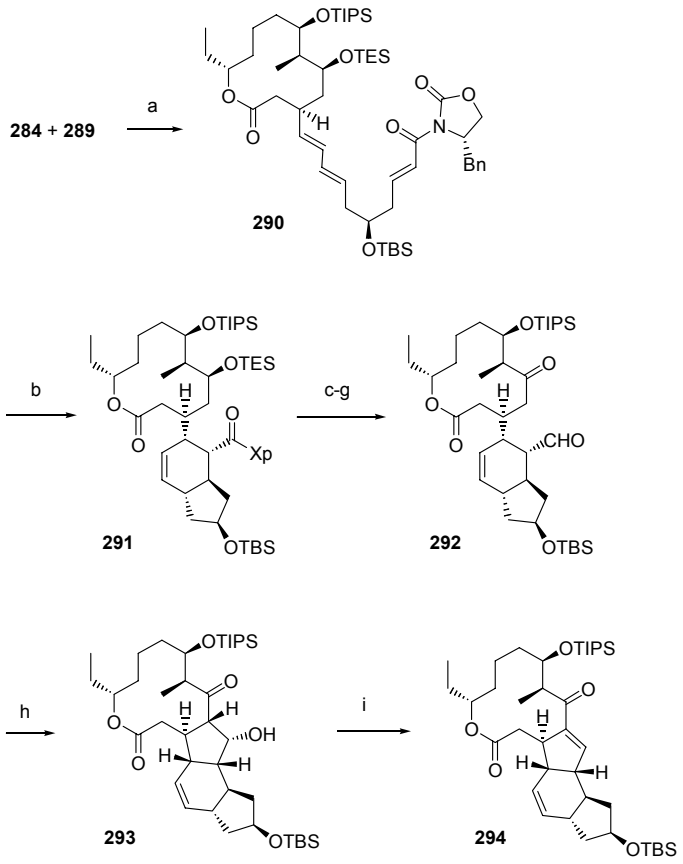
(98%, 82 % de); o) LiOH, *t*-BuOH, 35 °C; p) 2,4,6-trichlorobenzoyl chloride, DIPEA, THF, r.t.; DMAP, PhMe, 110 °C (78 % over 2 steps).

The diene fragment **289** of IMDA precursor was prepared from TBS-protected 3-hydroxy 1,5-dicarboxylate anhydride **285** (Scheme 41) (53). Unsymmetrical enantioselective transesterification with chiral (*S*)-1-hydroxy-ethylnaphthalene differentiated the carboxylate groups of **285** with high enantioselectivity (94 %de). Borane reduction followed by Swern oxidation afforded aldehyde **286**. Aldehyde **286** was reacted with iodoform and chromous chloride to elaborate vinyl iodide as a stereoisomeric mixture (*E*:*Z*, 9:1). Wittig reaction completed the preparation of dienyl vinyliodide fragment **289**.



Scheme 41. Reagents and conditions: a) DMAP, (*S*)-1-hydroxy-ethyl-naphthalene, CH_2Cl_2, -60 °C (89 %, 94 %de); b) $BH_3 \cdot Me_2S$, THF, r.t.; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -70 °C (84 % over 2 steps); d) CHI_3, $CrCl_2$, dioxane/THF, r.t. (80 %); e) DIBAL-H, PhMe, -78 °C (78 %); f) DMAP, $CHCl_3$, 25 → 60 °C (84 %).

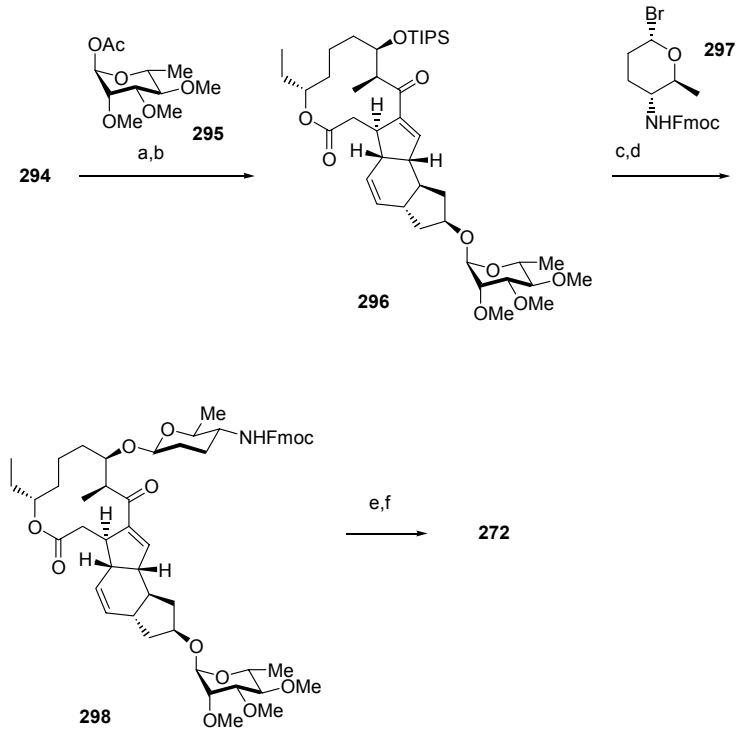
Modified Stille coupling (33) was employed to combine vinyliodide oxazolidinone **289** and macrolactonic stannane **284** to give triene **290** suitable for Lewis acid promoted IMDA cycloaddition (Scheme 42) (53). IMDA-cycloaddition with Me_2AlCl gave the cycloadduct **291** with good diastereoselectivity (10:1). Interestingly, achiral oxazolidinone derivative gave intrinsic asymmetric induction favoring the opposite *endo*-cycloadduct. Although the removal of hindered oxazolidinones is difficult by normal hydrolytic methods, Evans *et al.* overcame this problem using the method developed by Damon and Coppola (LiSEt, THF, room temperature) (55) to afford an easily modifiable thioester. Reduction of the thioester afforded aldehyde **292** ready for intramolecular aldol reaction in high yield. Intramolecular aldol reaction of **292** furnished the tricyclic fragment **293** of lepicidin A **272** with high diastereoselectivity (12:1). Finally, dehydration with Martin sulfurane (56) afforded differentially protected (+)-lepicidin A aglycon **294**.



Scheme 42. Reagents and conditions: a) $Pd_2(dba)_3 \cdot CHCl_3$, $CdCl_2$, DIPEA, 1-methyl-2-pyrrolidinone, 45 °C (69 %); b) Me_2AlCl, CH_2Cl_2, 0 °C → r.t. (71 %); c) LiSEt, THF, r.t. (97 %); d) HOAc, THF-H_2O, r.t.; e) TBSCl, imidazole, CH_2Cl_2, r.t.; f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C (90 % over 3 steps); g) Et_3SiH, 5 % Pd/$CaCO_3$/PbO, acetone, r.t.; h) NaHMDS, THF, -78 °C; i) $Ph_2S(OC(CF_3)_2Ph)_2$, CH_2Cl_2, 0 °C (81 % over 3 steps).

2,3,4-tri-*O*-methyl-*D*-rhamnose was connected to (+)-lepicidin A aglycon **294** after chemoselective desilylation of the TIPS-group.(53) This was followed by deprotection of the TBS-group and glycosidation with *L*-forosamine (Scheme 43). Finally, the synthesis

of (+)-lepicidin A **272** was completed by deprotection of **298** and dimethylation of the resulting free amine.



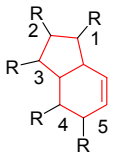
Scheme 43. a) HOAc-THF-H_2O, r.t., 21 h (87 %); b) glycosyl acetate, Ph_3CClO_4, toluene, 0 °C → r.t., 1.5 h (87 %); c) HF, MeCN, r.t., 2.5 h (97 %); d) Fmoc-amine **297**, Ag-zeolite, 4Å MS, CH_2Cl_2, r.t., 2 h (10 %); e) Et_2NH, r.t., 9 h; f) NaOAc, HOAc, H_2O, CH_2O; MeOH, r.t., 10 min, $NaCNBH_3$, 30 min.

2.2.6 Summary

IMDA cycloaddition is undoubtedly the most universal approach to prepare bicyclo[4.3.0]nonane containing natural compounds. The research groups of Roush, Nicolaou, Boeckman, Ley, Kurth, Jones, Paquette, Hase and Dias have used thermal IMDA for the preparation of their target molecules. However, the triene precursor for IMDA has to be chiral itself, if racemic mixture is to be avoided without using chiral catalysts. In some syntheses Lewis acid and covalently bound chiral auxiliary is used to improve diastereo- and enantioselectivity of the IMDA cycloaddition. For example, Oppolzer, Takano, Roush and Evans have used different covalently bound auxiliaries in their natural product synthesis. Furthermore, Evans has used asymmetric copper catalysis in IMDA during the preparation of isopulo'upone. Burke has concentrated on using RHDA cycloreversion in the synthesis of natural compounds. Photocyclization affords also an elegant route to bicyclo[4.3.0]nonanes, however the preparation of the precursor can be laborious as in the synthesis of ikarugamycin (15 steps). The oxy-Cope rearrangement approach also provides a short route to bicyclo[4.3.0]nonanes, which has been demonstrated by Paquette group.

3 Preparation of bicyclo[4.3.0]nonane derivatives

In the previous chapter, natural compounds containing the bicyclo[4.3.0]nonane fragment were presented. In this chapter, the methods to create bicyclo[4.3.0]nonane substructure are surveyed. The compounds are defined so that only bicyclo[4.3.0]nonane derivatives having substituents at positions 1, 2, 3, 4 and 5 are presented.



R = H, alkyl, alkoxy, amino or siloxy group

Figure 15. Substituted bicyclo[4.3.0]nonane structure.

The preparation methods of bicyclo[4.3.0]nonane structures can be divided roughly into thermal IMDA, Lewis acid promoted IMDA, chiral auxiliary induced IMDA and other cycloadditions. A selectivity issue that influences the applicability of all IMDA reactions in the synthesis is diastereoselectivity, if the substrate is chiral or the reaction is catalytic. IMDA reaction is inherently diastereoselective, if the chain linking the diene and dienophile or the other structure include one or more stereocenters. Chiral auxiliary based cycloadditions involve a removable asymmetric subunit. Asymmetric induction in catalytic IMDA are based on the chirality of catalyst ligand(s).

Diels-Alder reaction is assumed to follow a concerted mechanism, however other mechanisms like a stepwise diradical or dipolar mechanism are reported (57). Houk and Brown (58) claimed that IMDA cycloaddition proceed via “twist asynchronity” model. This model assumes that the selectivity of the reaction is controlled by the timing of the bond formation in the transition state. Furthermore, the model assumes that the diene and the dienophile parts have to be on top each other, before the bond formation may occur (Figure 16).

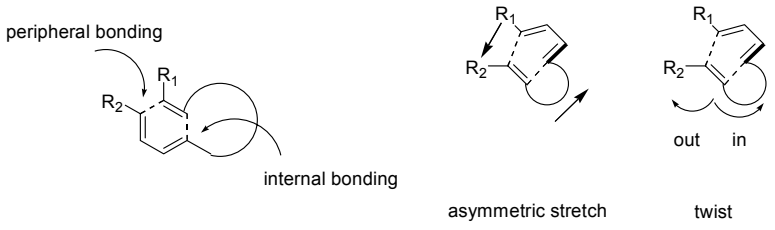


Figure 16. Bonding types and asynchronicity modes.

IMDA reactions may be divided into two categories based on the point of connection of the diene to the dienophile. In the type I reactions, the connecting chain is in the terminus of the diene (Figure 17). The IMDA of *E*-dienes may produce *trans*- and *cis*-fused cycloadducts. If the chain connecting the diene and dienophile is short (less than four carbons), a bridged product is not possible. The formation of bridged type I cycloadducts is possible with the connecting chains of 10 or more atoms (59). *Z*-Dienes with three or four atoms in the connecting chain produce only *cis*-fused products. Type II IMDA includes a tethered dienophile connected to one of the internal diene positions (Figure 18). Type II reaction may produce both *syn*- or *anti*-products.

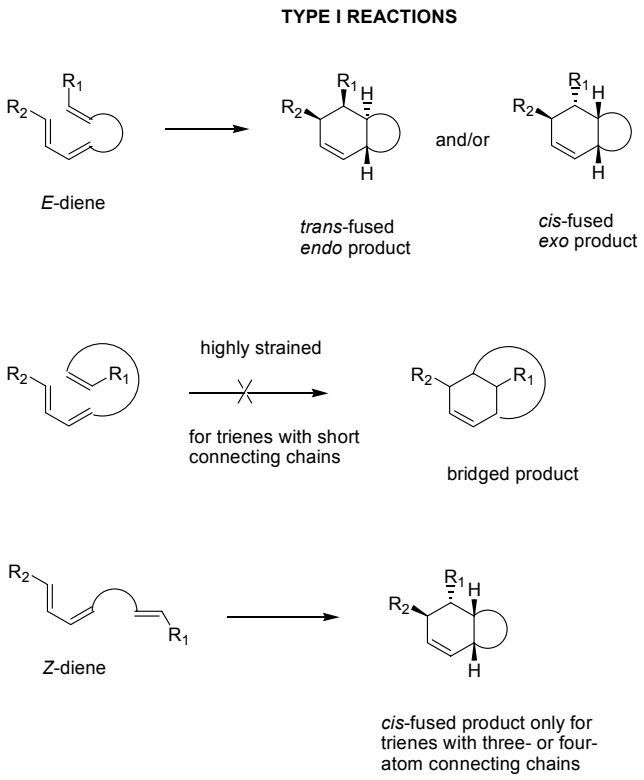


Figure 17. Type I IMDA cycloadditions.

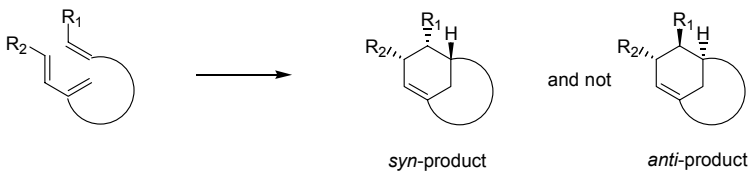


Figure 18. Type II IMDA cycloadditions.

The molecular orbitals of IMDA reaction of type I are shown in Figure 19. The cycloaddition can be activated by lowering the energy of dienophile LUMO (60) by electron withdrawing groups (EWG) and/or by Lewis acids. The diene HOMO can be activated by raising the energy by electron releasing groups (ERG). Both of these activation methods lowers the reaction enthalpy of the reaction by lowering the energy difference (ΔH) of LUMO and HOMO.

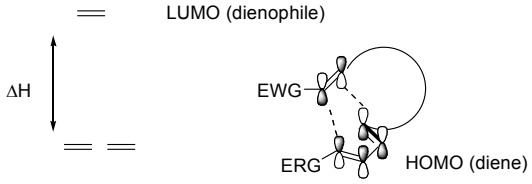


Figure 19. Molecular orbitals of IMDA cycloaddition.

Houk and Lin (61) have calculated that the *cis*-fused transition state of nonatriene is favored enthalpically by *ca.* 1 kcal/mol. Furthermore, the parent nonatriene transition states are assumed to be nearly symmetrical (58). The addition of an electron withdrawing group (CO_2Me) to the terminus of dienophiles results in favoring (0.3-0.5 kcal/mol) the *trans*-fused product. This is due to polarization of the dienophilic double bond that causes the LUMO coefficient at the β-carbon to the carbonyl group to be larger than at the α-carbon. The internal bond formation is more advanced than peripheral bond formation in the transition state. Furthermore, steric or other nonbonding interactions are

developed at an early stage of the cycloaddition, and the transition state that has more *trans*-disubstituted cyclopentanoid character becomes the more stable one. This is resulting from 'twist asynchronicity', which is caused by the torque applied to the internal bond formation. In a similar fashion, if the diene terminus is substituted so that the HOMO coefficient increases, the *trans*-selectivity should increase in the cycloaddition.

In the case of internally activated trienes (for example such as **323** and **324**), stereoselectivity is somewhat different. The LUMO coefficient at the α-carbon of the carbonyl group is greater that at β-carbon. The formation of the peripheral bond is likely to be more advanced in the transition state. However, this form of 'twist asynchronicity' is assumed to be less significant than with the terminally substituted nonatrienes (for example such as **299**).

Stereoselectivity for the *trans*-cycloadducts increases with *trans*-dienophile trienes as the dienophile activating group is changed along the series $CONR_2$<CO_2Me<COMe<CHO. (62). Furthermore, the stereoselectivity increases, if the triene is activated with Lewis acids (62).

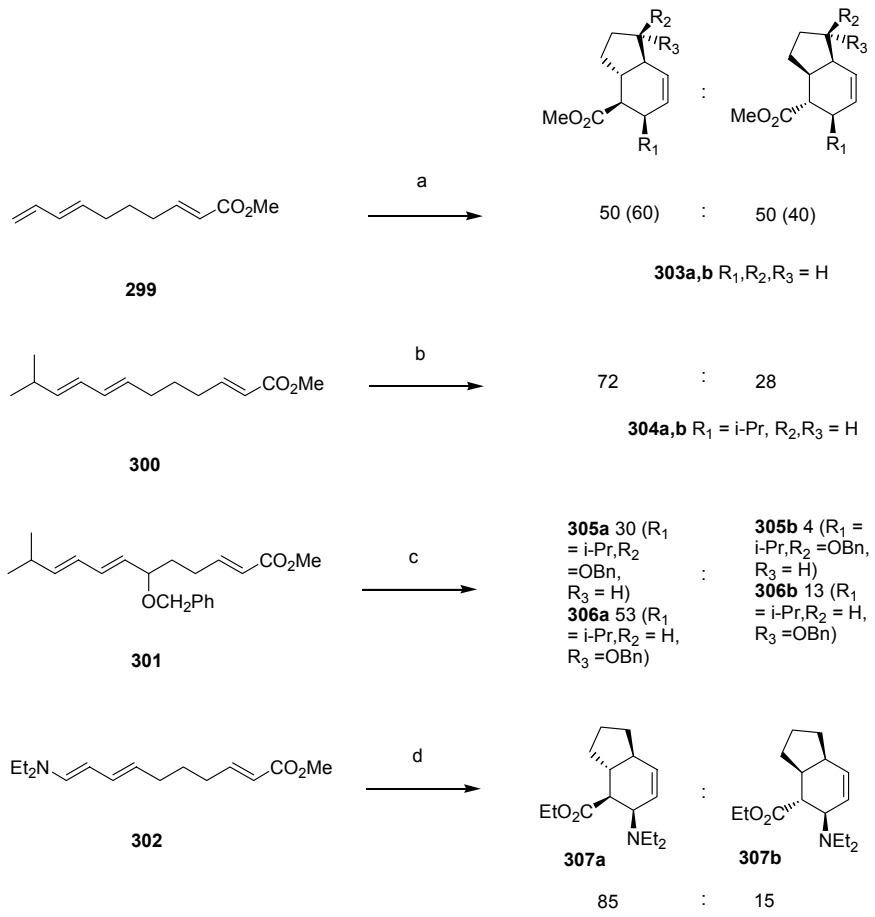
Stereoselectivity of *Z,E,E*-nonatrienes are not greatly affected by changes of the dienophile activating group. However, increased dienophile activation steers the selectivity towards *cis*-fused cycloadduct.

3.1 Thermal cycloadditions

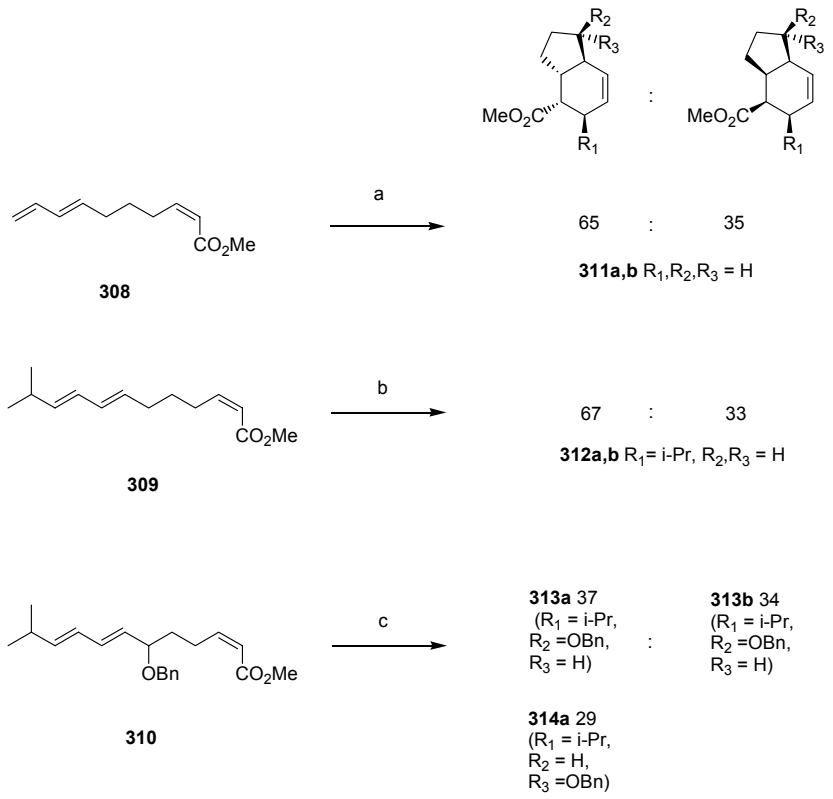
First thermal IMDA cycloaddition examples were reported as early as in 1953 by Alder and Schumaker (63). A few other examples were reported in 1960's, until in mid-1970's a rapid growth of interest occurred (64). Thermal IMDA cycloadditions are normally

performed in a sealed vial. The substrate is usually dissolved in a degassed solution of toluene, mesitylene or benzene and the resulting mixture is boiled in the presence radical inhibitor, usually BHT. House and Cronin (65) reported in 1965 that IMDA reaction of *E,E,E*-triene **299** produces an equal mixture of *trans*- **303a** and *cis*-fused **303b** cycloadducts (Scheme 44). In 1980 Roush *et al.* (66) repeated the same cyclization at 150 ^{o}C. Lower temperature raised the yield to 65 % and the ratio *trans*- **303a** to *cis*-fused **303b** product was found to be 60:40. A larger group (*i*-propyl) at the terminus of the diene in *E,E,E*-triene **300** slightly changed the selectivity of the thermal IMDA. If the diene terminus is substituted by diethylamino-group as in **302**, the *trans*-selectivity is increased considerably (67). The resulting selectivity (85:15) corresponds to an energy difference of 1.1 kcal/mol between the *trans*- and *cis*-transition states.

Z,E,E-Isomer **308** produced a comparable mixture of *trans*- **311a** and *cis*-fused **311b** products (Scheme 45). However, the terminally substituted *Z,E,E*-triene **309** gave comparable results as the unsubstituted **308**. If the α-carbon of the diene in the connecting chain is substituted as in the substrates **301** and **310**, the thermal cycloaddition produces mixture of *endo*- and *exo*-isomers by favoring the *endo*-cycloadducts with *E,E,E*-trienes and *exo*-adducts with *Z,E,E*-trienes. Furthermore, the steric demand of the substituent in this position does not change the *endo*/*exo*-selectivity markedly (68). Roush *et al.* have also found that the *trans*-selectivity for cycloadducts is increased in thermal conditions, if the dienophile group is changed along the series $CONR_2$<CO_2Me<COMe<CHO. However, the aldehyde triene affords only a moderate yield in thermal IMDA presumably due to polymerization (62a).

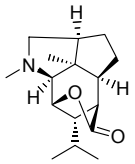


Scheme 44. Reagents and conditions: a) 245 °C, 47 % (150 °C, 65 %); b) 150 °C, 40 h (72 %); c) 115 °C, 110 h; d) 60 °C (62 %).



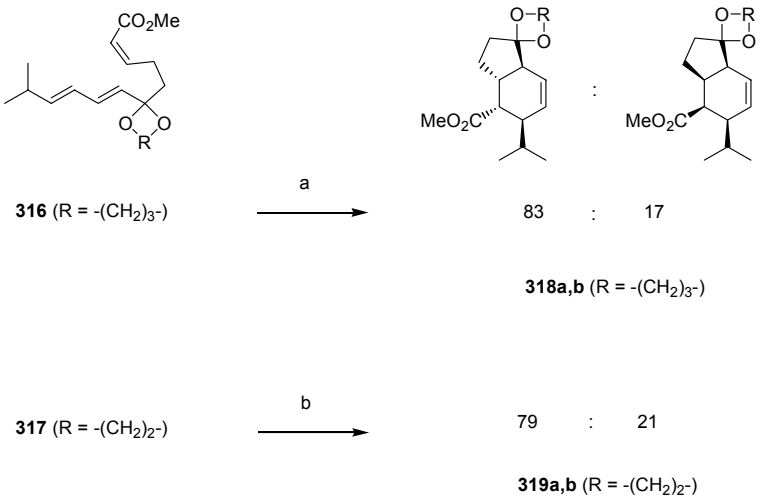
Scheme 45. Reagents and conditions: a) 180 °C, 5 h (75 %); b) 180 °C, 5 h (75 %); c) 115 °C, 44 h (92 %).

In the total synthesis of dendrobine **315** (Figure 20), Roush and Gillis (69) examined the selectivity and yield of the *Z,E,*E-trienes **316** and **317**, which were activated by electron releasing group in the chain connecting the diene and dienophile (Scheme 46). The ring size of the ketone protecting group in IMDA of substrates **316** and **317** had only a minor effect on *endo*/*exo*-selectivity, but the yield of IMDA cycloaddition for substrate **317** was lower.



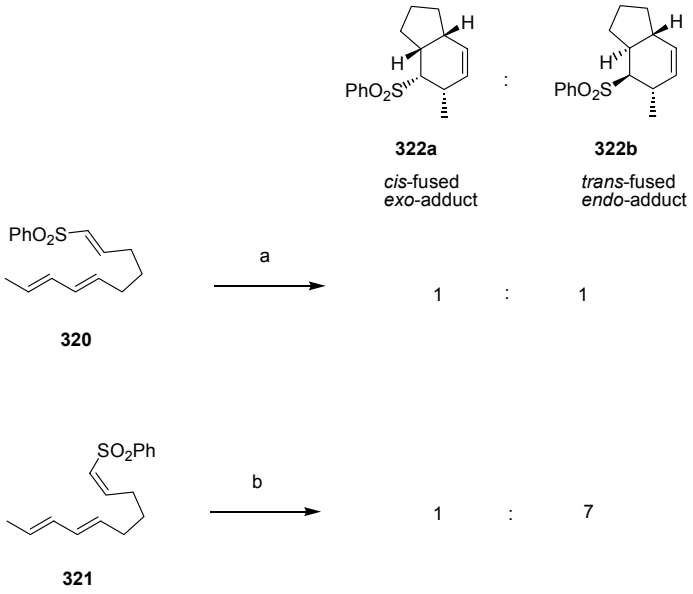
315

Figure 20. Structure of dendrobine **315**.



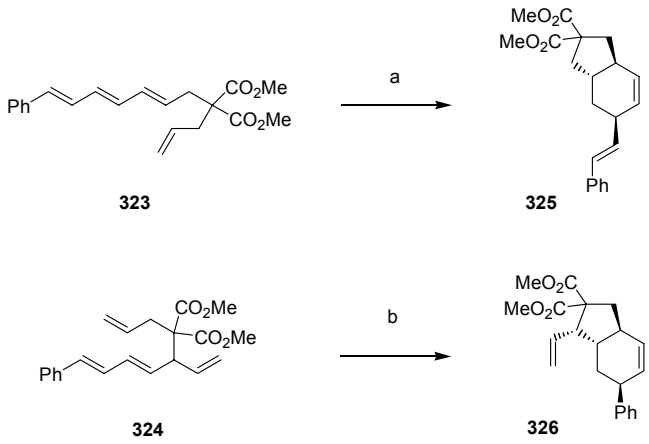
Scheme 46. Reagents and conditions: a) 180 °C, 0.5 h (87-93 %); b) 180 °C, 4 h (73 %).

Craig *et al.* (70) have studied IMDA reactions of sulphonyl-substitued trienes **320,321** (Scheme 47). IMDA reaction of *E,E,E*-triene **320** gave a 1:1 mixture of isomers **322a,b** and *Z,E,E*-triene **321** produced more *trans*-fused cycloadduct **322b** than *cis*-fused **322a**.



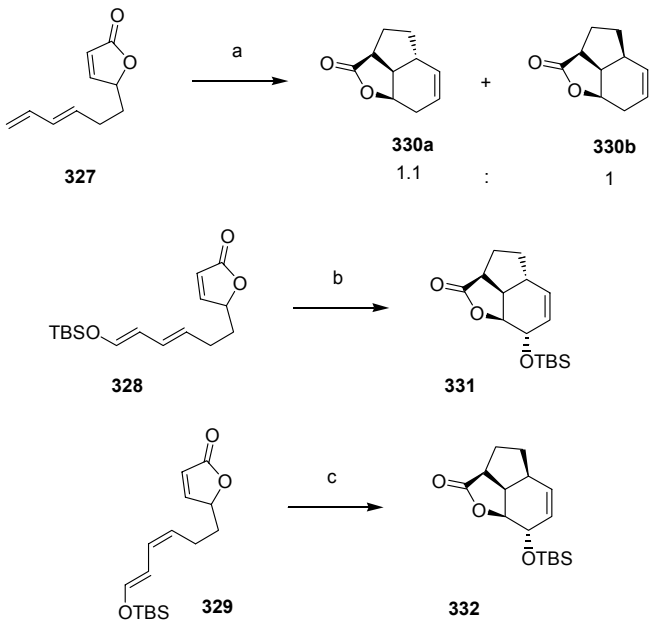
Scheme 47. Reagents and conditions: a) PhMe, 145 °C, 48 h (93 %); b) PhMe, 165 °C, 60 h (63 %).

Trost *et al.* (71) have studied IMDA reactions of tetraenes. They found out that thermal IMDA reaction of terminally activated diacetate dienophiles **323,324** produced *trans*-fused tetrahydroindanes **325, 326** in moderate yields (Scheme 48).



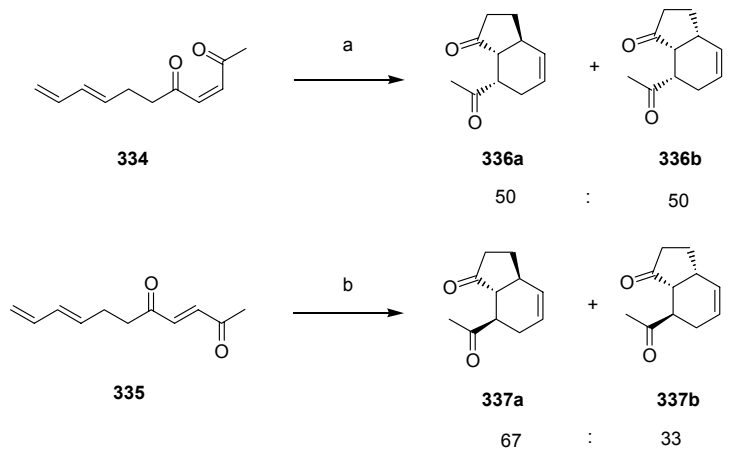
Scheme 48. Reagents and conditions: a) mesitylene, rfx (70 %); b) mesitylene, rfx (73 %).

Burke *et al.* (72) observed out that a rigid butenolide ring is an excellent dienophile for stereospecific IMDA reactions if the diene is substituted by silyloxy-group as in substrates **328, 329.** (Scheme 49). Butenolide *E,E*-diene **328** gave only *trans*-fused cycloadduct **331** and butenolide *Z,E*-diene **329** gave the corresponding *cis*-fused product **332**.



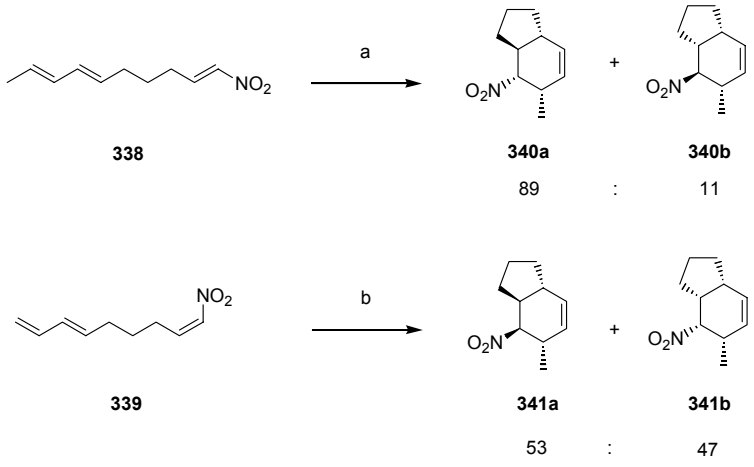
Scheme 49. Reagents and conditions: a) 180 °C (79 %); b) 230 °C (81 %); c) 230 °C (86 %).

LeGoff and Williams (73) have reported that the reaction enthalpy of trienediones **334, 335** is low. The reaction of both isomers **334, 335** are completed in 4 hours at 61 °C. However, the low energy reactions of unsubstituted trienediones are unselective and they provide a nearly 1:1 mixture of *endo/exo*-mixtures. (Scheme 50).



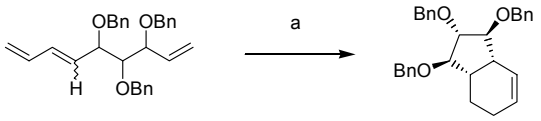
Scheme 50. Reagents and conditions: a) $CDCl_3$, rfx (92 %); b) $CDCl_3$, rfx (82 %).

Kurth *et al.* (74) have studied the IMDA reactions of terminally substituted nitrotrienes **338, 339** (Scheme 51). The nitro-group activated *E,E,E*-triene **338** gave predominantly the *endo*-adduct **340a**. In contrast, *E,E,Z*-nitrotriene **339** gave nearly an equal mixture of *trans*- **341a** and *cis*-fused **341b** products.



Scheme 51. Reagents and conditions: a) PhH, rfx, 30 h (64 %); b) $CDCl_3$, r.t., 3.5 d (73 %).

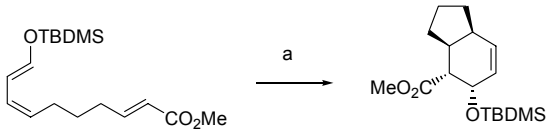
A mixture of *E,Z*-isomers of the tribenzyloxy triene **342** derived from *D*-xylose can be cyclized to a single *cis*-fused adduct **343** (Scheme 52) (75). Thermal isomerization of the internal double bond must occur before the cycloadduct formation or the IMDA cycloaddition of these type of substrates have a common transition state.



342 **343**

Scheme 52. Reagents and conditions: a) PhMe, 160 °C, 2 h (83 %).

IMDA reaction of methyl ester silyloxy *E,Z,E*-triene **344** give *endo*-adduct **345** as the sole product (Scheme 53) (76). The sterically demanding *tert*-butyldimethylsiloxy-group is effectively steering the transition state of the reaction to give the *endo*-adduct. However, the reaction for this type of substrate is very slow (4 days).



344 **345**

Scheme 53. Reagents and conditions: a) PhMe, 170 °C, 4 d (79 %).

3.2 Lewis acid promoted cycloadditions

Lewis acids activate dienophiles in IMDA reactions (Figure 21). Lewis acid withdraws the electrons from the dienophile causing a polarization of the dienophile. The increased reactivity of the dienophile gives a higher reaction rate. This allows lower reaction temperatures, better diastereoselectivities and sometimes better yields.

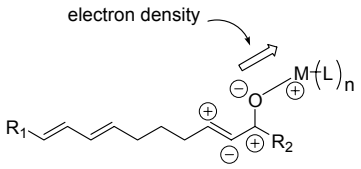
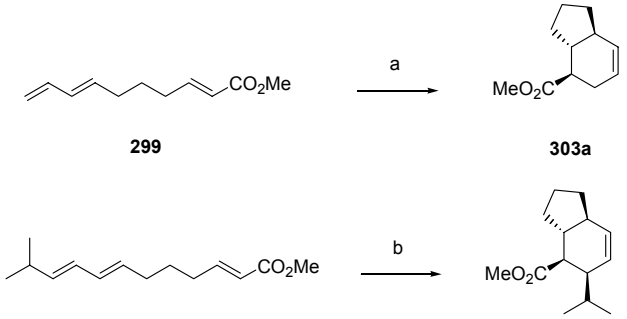


Figure 21. Dienophile polarization by Lewis acid. (n= typically 2-4 ligands)

Polymerization of the triene substrate and alkylation of the dienophile carbonyl are the frequently encountered problems in Lewis acid promoted IMDA cycloadditions. Consequently relatively mild Lewis acids such as the alkylaluminum chlorides are used (77). Furthermore, if the diene is functionalized by an alkoxy substituent, it may lead to the formation of a pentadienyl carbonium ion in presence of Lewis acids (61b). In cases like this, it is recommended to use highly activated dienophile to favor IMDA reaction instead of the pentadienyl carbonium ion decomposition (78).

In the presence of achiral Lewis acids *E,E,E*-trienes **299, 300** give only *trans*-fused cycloadducts **303a, 304a** (Scheme 54) (77,62b). However, other triene isomers give similar *endo/exo*-product ratios as in the thermal conditions. In most cases, stoichiometric

quantities of Lewis acid were required for full conversion. Alkoxy- and alkylaluminum chlorides including menthyl-$OAlCl_2$, $EtAlCl_2$ and Et_2AlCl are found to be highest yielding Lewis acids for triene esters compared to $AlCl_3$, $BF_3{\cdot}Et_2O$, $TiCl_4$ and $SnCl_4$.



Scheme 54. Reagents and conditions: a) menthyl-$OAlCl_2$, 23 °C, 48-60 h (72-79 %); b) menthyl-$OAlCl_2$, 23 °C, 48 h (79-83 %).

Stereoselectivity is not greatly effected by the dienophile substituent in Lewis-acid catalyzed IMDA reactions of nona-trienes (69b). Roush *et al.* have observed that epimerization occurs using triene aldehydes as the substrates, if the cycloaddition is performed at room temperature. However, this problem can be avoided by using low temperatures (69b).

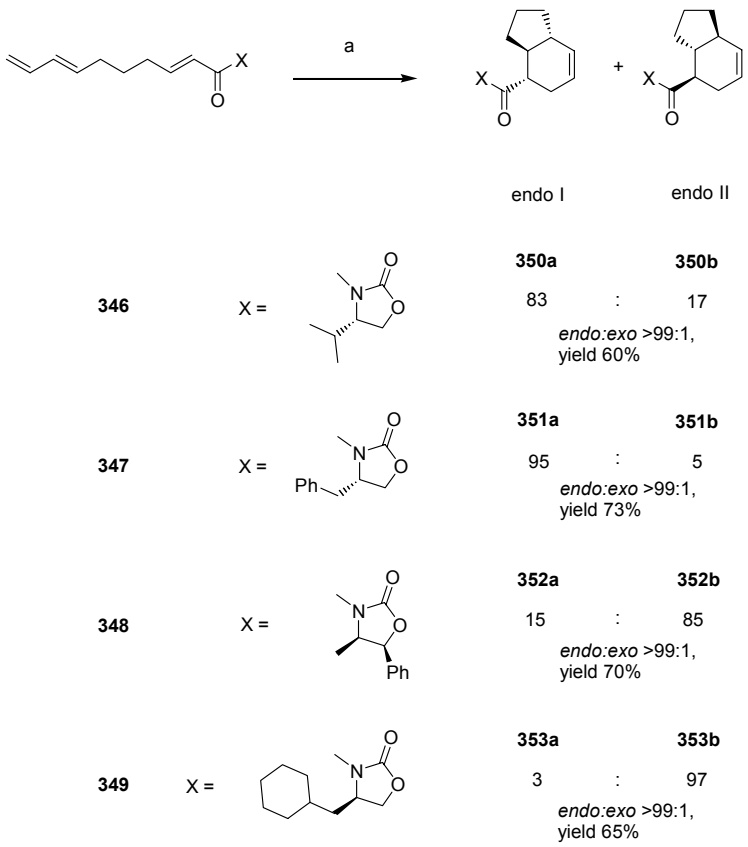
Intramolecularly substituted trienes, which are susceptible to pentadienyl carbonium ion formation (for example such as compounds **301**, **310** or **316**), cannot be cyclized by Lewis acids (62b). This is presumably due to decomposition of the substrates.

3.3 Asymmetric IMDA cycloadditions

Chiral auxiliaries are employed in IMDA cycloadditions to maximize ΔΔG in the transition state of the cycloaddition. The chiral induction can be brought into the reaction either through a covalently bonded ligand or through a chiral catalyst. At first, the methods employing a covalently bound chiral auxiliary are presented. After these, the catalytic versions of producing bicyclo[4.3.0]nonanes by IMDA are presented.

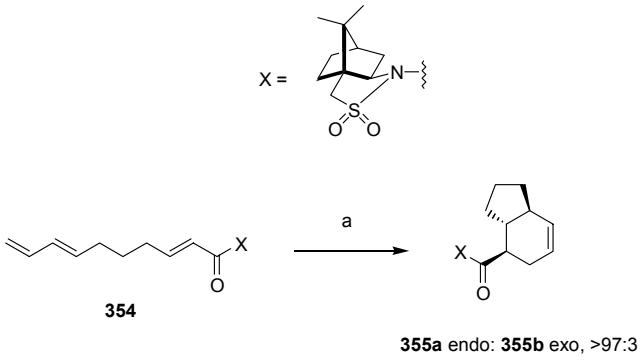
3.3.1 Chiral auxiliary induced IMDA

Evans *et al.* (79) have reported several examples of IMDA reactions of chiral oxazolidinone derived trienes **346-349** (Scheme 55). (*S*)-Phenylalaninol derived oxazolidinone **347** provides higher diastereoselectivities compared to other oxazolidinone analogues **346-349**.



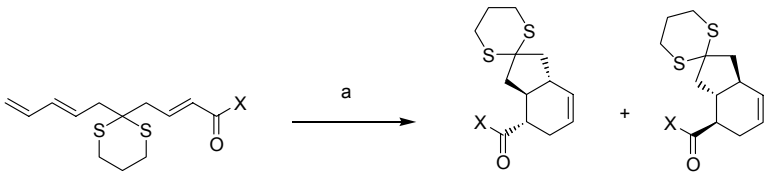
Scheme 55. Reagents and conditions: a) Me_2AlCl, -30 °C, 5 h.

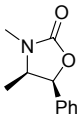
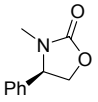
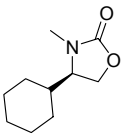
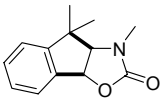
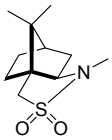
Oppolzer *et al*. (80) have developed chiral auxiliaries from camphor sultam and they have reported that camphor sultam triene **354**, in the presence of $EtAlCl_2$ as a Lewis acid, affords *endo* **355a** :*exo* **355b** cycloadducts with ratio >97:3. The yield of recrystallized product is 75 % (>99 %de) from this reaction (Scheme 56).



Scheme 56. Reagents and conditions: a) $EtAlCl_2$, -20 °C (82 %).

Hoshino *et al.* (81) have studied IMDA reactions of dithiane substituted chiral trienes **356-360** in the presence of Lewis acids (Scheme 57). Saigo's chiral oxazolidinone auxiliary derived triene **359** (82) gave the best enantioselectivity (96 %ee) compared to other chiral trienes **356-360** investigated. In some cases, the reactions were not complete even after 4 days of stirring at –25 °C.

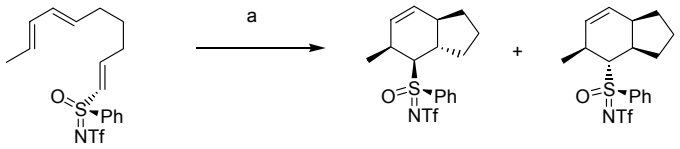


			endo I		*endo II*
			361a		**361b**
356	X =		4.4	:	1
				yield 54%	
			362a		**362b**
357	X =		1	:	1.6
				yield 57%	
			363a		**363b**
358	X =		1.6	:	1
				yield 65%	
			364a		**364b**
359	X =		47	:	1
				yield 55%	
			365a		**365b**
360	X =		14	:	1
				yield 26%	

Scheme 57. Reagents and conditions: a) Me_2AlCl, -25 °C, 4 d.

Craig *et al.* (83) have studied asymmetric thermal IMDA reactions of sulfoximine substituted trienes (Scheme 58). Triflyl sulfoximine triene **366** derivatives were found to give slightly better *endo/exo* selectivities and diastereoselectivities compared to 4-tolylsulfonyl and 2,4,6-triisopropylphenylsulfonyl sulfoximines when the diene terminus

was substituted with a methyl group. Without the terminal methyl group in the diene, the selectivities were similar with all above mentioned sulfoximine triene derivatives.



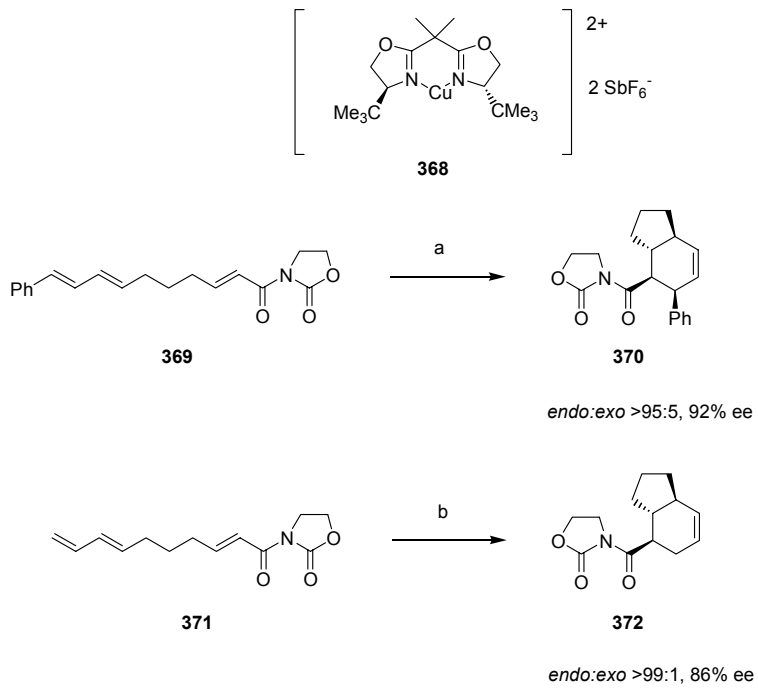
366 **367a** **367b**

90 : 10

Scheme 58. Reagents and conditions: a) PhMe, 125 °C, 45 h (53 %).

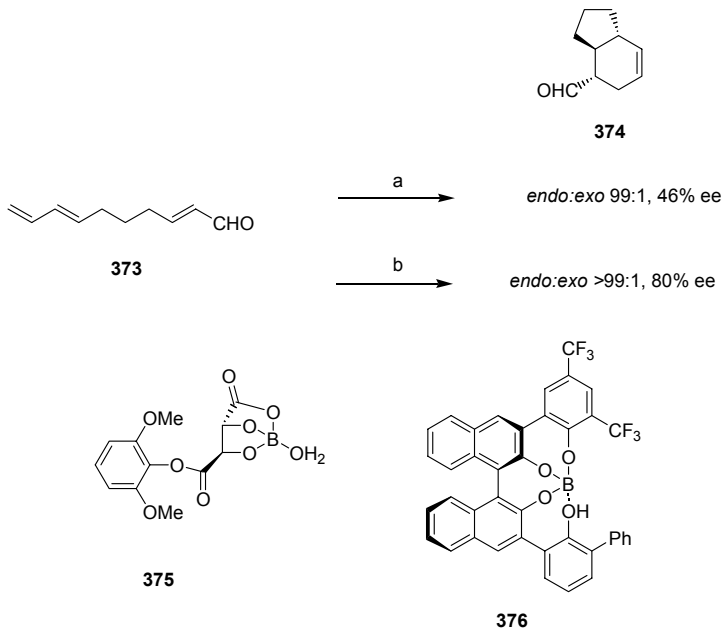
3.3.2 Catalytic asymmetric IMDA cycloadditions

Evans *et al.* (84) have reported that chiral bis(oxazoline) copper complexes catalyze the IMDA-reaction of triene oxazolidinone in a highly selective manner (Scheme 59). This catalyst requires two carbonyl groups in the substrate for effective coordination.



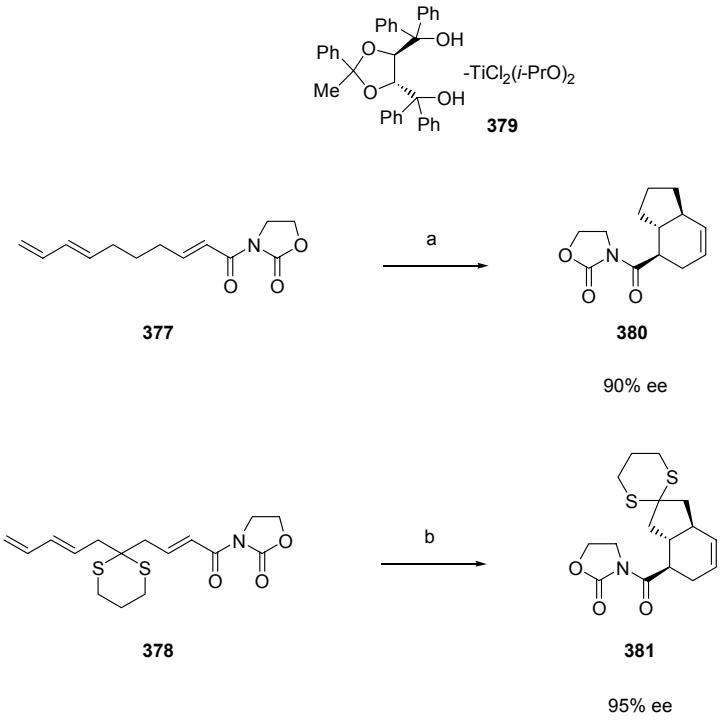
Scheme 59. Reagents and conditions: a) 5 mol-% **368**, CH_2Cl_2, 25 °C, 5 h (86 %); b) 10 mol-% **368**, CH_2Cl_2, 25 °C, 24 h (89 %).

Yamamoto *et al.* (85) have reported that the boron catalyst **375** prepared from (*S*)-mono(2,6-dimethoxybenzoyl)tartaric acid and borane facilitates IMDA cycloaddition of triene aldehyde **373** (Scheme 60). The yield of cycloaddition is good (74 %) at –20 °C with an *endo*:*exo* ratio 99:1. The enantiomeric excess in this reaction was only 46 %ee. Yamamoto *et* al. (86) have developed Brønsted acid-assisted chiral boron catalysts and the binaphthyl derivative **376** catalyses the IMDA reaction of triene aldehyde **373** in high yield (95 %). The cyclization afforded only the *endo*-adduct with 80 %ee (Scheme 60).



Scheme 60. Reagents and conditions: a) 10 mol-% **375**, CH_2Cl_2, -20 °C (74 %); b) 30 mol-% **376**, CH_2Cl_2, -40 °C (95 %).

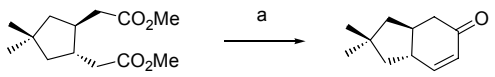
Narasaka *et al.* (87) have developed titanium based catalysts for asymmetric IMDA cycloadditions. High levels of asymmetric induction were achieved with the titanium catalyst **379** prepared *in situ* from $TiCl_2(i\text{-}PrO)_2$ and chiral diol derived from (*R*)-tartaric acid. Molecular sieves (4Å MS) were required to keep the reaction catalytic in titanium reagent. IMDA cycloaddition of trienyl oxazolidinone **377** and corresponding 1,3-dithiane derivative **378** catalyzed by **379** provided cycloadducts **380, 381** with high enantioselectivities (Scheme 61).



Scheme 61. Reagents and conditions: a) 30 mol-% **379**, mesitylene, 4Å MS, 161 h, r.t. (87 %); b) 10 mol-% **379**, mesitylene, 4Å MS, 68 h, r.t. (62 %).

3.4 Other methods

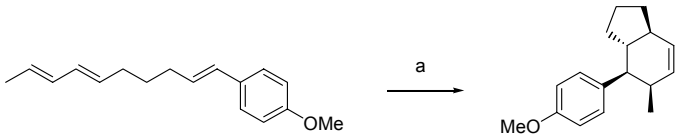
Little *et al.* (88) have reported that the *trans*-diester **382** can be cyclized predominantly to the *trans*-fused enone **383** (Scheme 62).



382 383

Scheme 62. Reagents and conditions: a) Na, Me_3SiCl, PhMe, rfx; then THF-CH_3COOH-H_2O (58 %).

Bauld and Harirchian (89) have prepared bicyclo[4,3,0]nonane derivatives by IMDA reaction induced by cation radicals (Scheme 63). They used tris(4-bromophenyl)aminium hexachlorostibnate as the catalyst and 2,6-di-*tert*-butyl-pyridine as a base to prevent Brønsted acid-catalyzed reactions (90). The cycloaddition of anisyl triene **384** gave high stereoselectivity favoring the *trans*-fused product **385**. The product distribution was similar for *E,E,E*- and *E,E,Z*-trienes. This was proposed to be due to rapid isomerization of the *E,E,Z*-triene to the corresponding *E,E,E*-triene. The product **385** was a racemic mixture of cycloadducts.

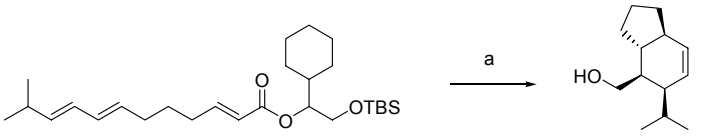


384 385

trans:*cis*-fused (98:2)

Scheme 63. Reagents and conditions: a) 2,6-di-*tert*-butylpyridine, $(p\text{-BrPh})_3^+SbCl_6^-$, 0 °C, 10 min (83 %).

Roush *et al.* (91) have investigated hydrofluoric acid catalyzed IMDA reactions of substituted 2-hydroxyethyl ester trienes (Scheme 64). Although the reaction of triene **386** took 72 hours to complete at room temperature, the reaction afforded the cycloadduct in good yield (78 %) and the *endo:exo* ratio was high ≤98:2. The cycloadduct was reduced to the corresponding alcohol **387** with lithium aluminum hydride for analytical purposes.

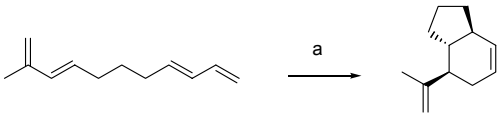


386 **387**

endo:*exo* <98:2

Scheme 64. Reagents and conditions: a) HF, CH_3CN-CH_2Cl_2, 72 h, r.t.; then $LiAlH_4$ (78 %).

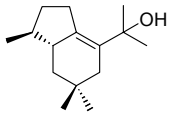
Gorman *et al.* (92) reported in 1995 that tetraene **388** produces bicyclo[4.3.0]nonane **389** in an IMDA catalyzed by triflic acid (Scheme 65).



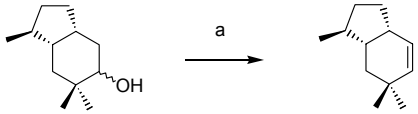
388 **389**

Scheme 65. Reagents and conditions: a) 5 mol-% CF_3SO_3H, CH_2Cl_2, 23 °C, 2 min (86 %).

Tori *et al.* (93) formed hydrindene **392** in the synthesis of conocephalenol **390** by dehydration of the bicyclic alcohol **391** (Scheme 66).



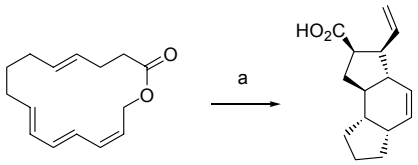
390



391 392

Scheme 66. Reagents and conditions: a) pyr, $POCl_3$ (91 %).

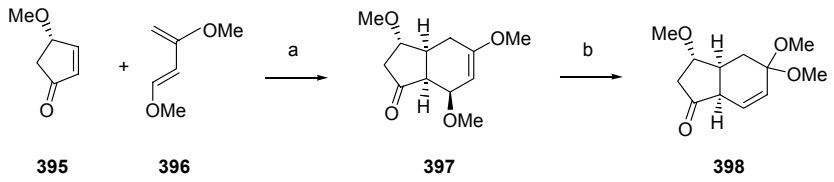
Roush *et al.* (94) have developed a method to produce *trans-anti-cis*-decahydro-*as*-indacene ring system **394** via a transannular IMDA reaction of a functionalized *E,E,E*-cyclododeca-1,6,8-triene **393** (Scheme 67).



393 394

Scheme 67. Reagents and conditions: a) KHMDS, TBSOTf, THF-HMPA, 4 Å MS, -78 → 65 °C; then aq. HCl (35 %).

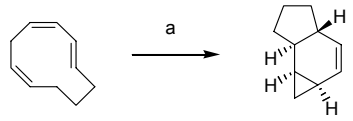
Rokach *et al.* (95) have synthesized the hydrindene derivative **398** by a thermal Diels-Alder reaction of chiral cyclopentenone **395** and 1,3-dimethoxy-1,3-butadiene **396** (Scheme 68). After the formation of the bicyclo[4,3,0]nonane ring **397**, allylic rearrangement afforded the dimethoxy derivative **398**.



395 **396** **397** **398**

Scheme 68. Reagents and conditions: a) xylene, 140 °C, BHT (63 %); b) $(MeO)_3C$, MeOH, PPTS (98 %).

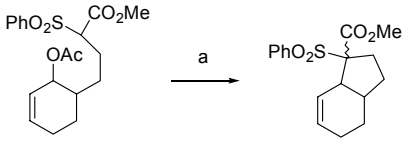
Dauben *et al*. (96) have prepared the hydrindene derivative **400** by a thermal rearrangement of cyclic *cis,cis,trans*-triene **399** (Scheme 69).



399 **400**

Scheme 69. Reagents and conditions: a) PhH-d_6, 125 °C, 1 h (100 %).

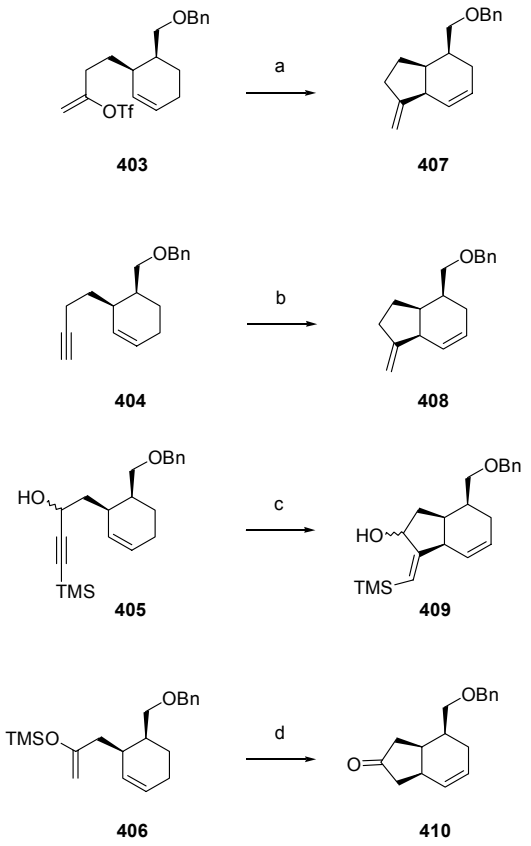
Trost *et al.* (97) have synthesized bicyclo[4.3.0]nonane phenylsulfone esters by an intramolecular cyclization of phenylsulfonyl anion catalyzed by palladium(0) catalyst (Scheme 70). The cyclization of **401** provided a diastereomeric mixture of phenylsulfone esters **402.**



401 **402**

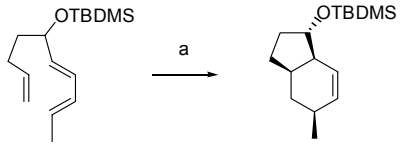
Scheme 70. Reagents and conditions: a) NaH, $(Ph_3P)_4Pd$, THF, rfx (75 %).

Fukumoto *et al.* (98) have investigated the stereoselective asymmetric preparation of *cis*-hydrindene derivatives (Scheme 71). Cycloadduct **407** was obtained by a palladium(II) catalyzed Heck reaction of the triflate derivative **403** in high yield (85 %). Cycloisomerization of **404** and **405** provided the cycloadducts **408** and **409** in high yields (81 and 98 %, respectively). Cycloalkenylation of **406** catalyzed by palladium acetate afforded **410** in good yield (78 %).



Scheme 71. Reagents and conditions: a) $Pd(OAc)_2$, PPh_3, Ag_3PO_4, $CaCO_3$, MeCN, 60 °C (85 %); b) $(Ph_3P)_2Pd(OAc)_2$, Ph_3P, C_6H_6, 60 °C (81 %); c) $Pd(OAc)_2$, BBEDA, CH_2ClCH_2Cl, 60 °C (98 %); d) $Pd(OAc)_2$, MeCN, CH_2Cl_2, 45 °C (78 %).

Livinghouse *et al.* (99) have reported that low valent rhodium complexes catalyse IMDA cycloaddition between an unactivated dienophile and a diene (Scheme 72). The IMDA cycloaddition of *E*,*E*,*E*-triene **411** give exclusively the *cis*-fused product **412**.



411 **412**

Scheme 72. Reagents and conditions: a) THF, $[(i\text{-}C_3HF_4O)_3P]_2RhCl$, 55 °C, 18 h (61 %).

3.5 Summary of preparation of bicyclo[4.3.0]nonane derivatives

It is not surprising that several methods for preparing bicyclo[4.3.0]nonane derivatives have been developed. This is thanks to the wide variety of interesting compounds, which include the bicyclo[4.3.0]nonane substructure or can be derived from a bicyclo[4.3.0]nonane derivative. The major difference between the preparation methods is the product distribution. Some methods favor *endo*-adducts instead of *exo*-adduct and *vice versa*. In some cases, asymmetric induction has also been achieved. Although achiral methods sometimes facilitate short routes to bicyclo[4.3.0]nonanes, the separation of stereoisomers may be difficult and laborious. In the asymmetric methods, the isolation of the desired stereoisomer is usually easier and can usually be done by a single recrystallization step. The chiral auxiliary mediated IMDA cycloadditions (relayed asymmetric induction) usually demand more reaction steps for introducing and removing the auxiliary. This can be avoided using asymmetric catalytic processes (external asymmetric induction) developed especially in the laboratories of Evans, Narasaka or Yamamoto. The catalytic IMDA cycloadditions provide high asymmetric induction and allow flexibility for the substrates. However, the catalysts developed by Evans and Yamamoto require oxazolidinone derived dienophiles to provide high levels of asymmetric induction. Other methods using intermolecular Diels-Alder, Heck,

cycloisomerization or cycloalkenylation reactions are also asymmetric methods and provide useful synthons for organic chemists.

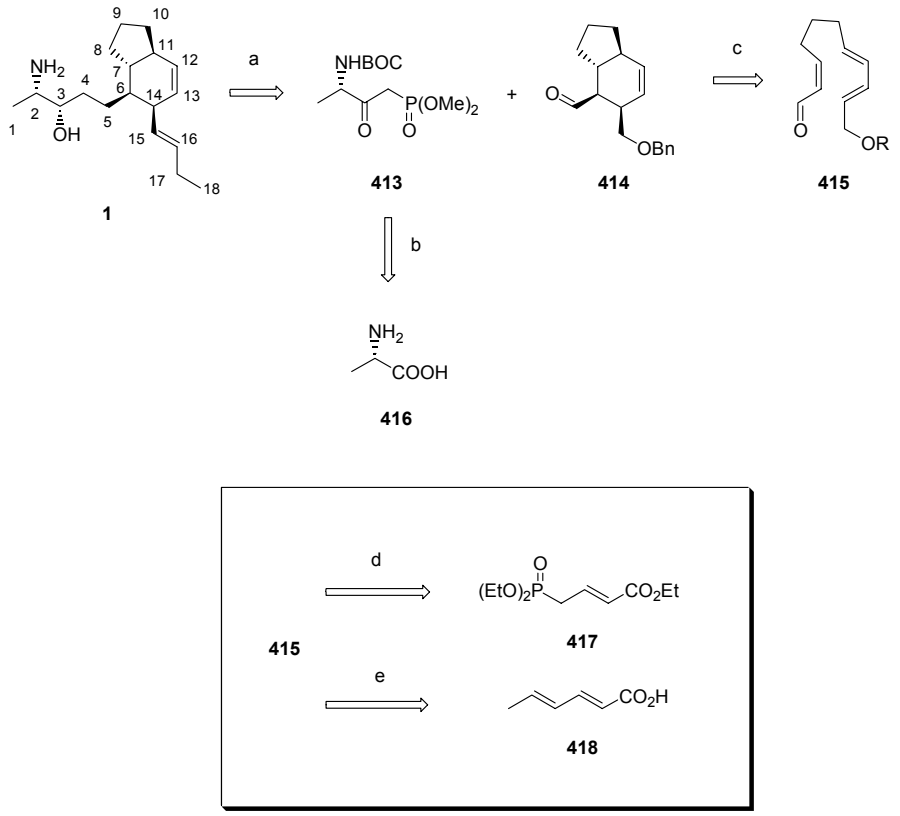
4 Total synthesis of amaminol A (1)

4.1 Introduction

I chose Amaminol A **1** as the target compound since it is a recently isolated compound which is cytotoxic against P388 murine leukemia cells (1). However, the biological activity was not the only reason to synthesize amaminol A **1**. I was introduced to the preparation of vicinal amino alcohol during my master's thesis (100) and indeed amaminol A **1** includes an amino alcohol fragment in it's structure. Furthermore, the group of professor Koskinen (101) has been studying nitrogen containing compounds derivable from amino acids. Although amaminol A **1** has only eighteen carbon atoms, it provides a challenging target for synthesis. The challenges arise from the facts that the carbons C2, C3, C6, C7, C11 and C14 are chiral and they had to be synthesized by asymmetric means. Previous synthetic efforts toward amaminol A **1** had not been reported and I have accomplished the first total synthesis of amaminol A **1**. Although I obtained amaminol A **1** as a side product due to wrong stereochemistry of the IMDA cycloaddition catalyst, amaminol A **1** can probably be synthesized as the major product by changing the stereochemistry of the organocatalyst to the opposite one for the IMDA cycloaddition step.

4.2 Retrosynthetic analysis of amaminol A (1)

Retrosynthetic analysis of amaminol A **1** reveals that the vicinal amino alcohol moiety C1-C3 is derivable from (*S*)-alanine **416** via steps a and b (Scheme 72). Furthermore, the bicyclo[4.3.0]nonane fragment **414** C5-C15 is derivable by a retro-IMDA step (step c). Precursor **415** for the retro-IMDA is derivable from crotylphosphonate **417** (route d) or sorbic acid **418** (route e).



Scheme 72. Retrosynthetic analysis of amaminol A **1**.

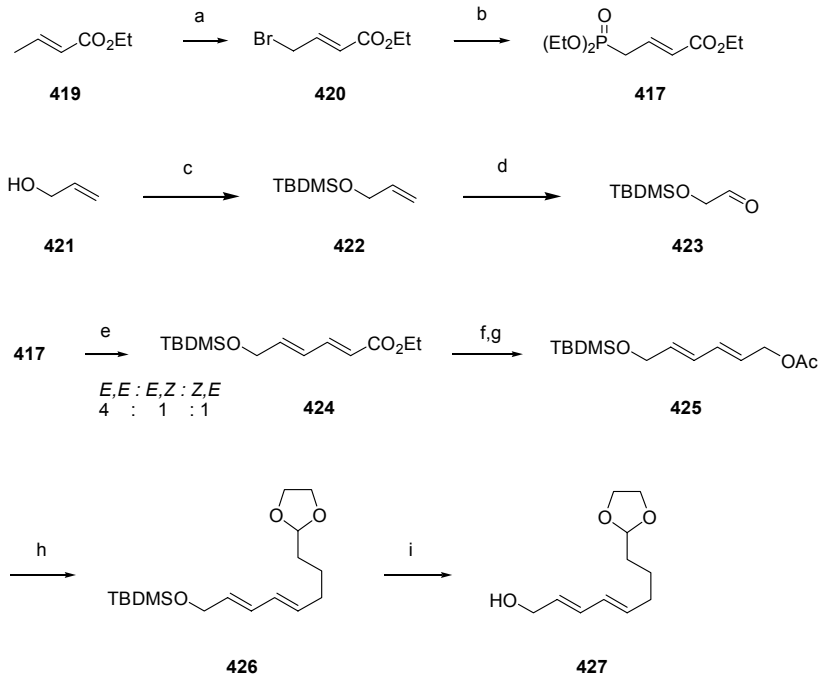
4.3 Synthesis of *E,E,E*-trienes for IMDA cycloadditions

The bicyclo[4.3.0]nonane skeleton of amaminol A **1** was formed by two different methods. At first, the Evans oxazolidinone auxiliary (79) was used to give the asymmetric induction for IMDA cycloaddition. In the second approach, a novel organocatalytic (102) IMDA cycloaddition was used to form the desired bicyclo[4.3.0]nonane derivative.

After analyzing the review chapters of this thesis, it can be summarized that *E*,*E*,*E*-trienes are usually formed via the following sequence: oxidation -> Wittig, HWE reaction or Stille coupling -> oxidation -> Wittig, HWE reaction or Stille coupling sequence. However, the resulting mixtures of *E,Z*-isomers are rather difficult to separate, and usually require liquid chromatography. If large scale preparation is desired, flash chromatographic purification is a laborious and rather expensive method.

My first approach to elaborate the triene precursor for the IMDA cycloaddition was based on a HWE reaction between crotyl phosphonate **417** and protected aldehyde **423** (Scheme 73). At first, allyl alcohol **421** was protected with *tert*-butyldimethylsilyl group. Then the prepared siloxy alkene **422** was ozonolyzed to elaborate the aldehyde **423**. The ozonolysis of siloxy alkene alcohol **422** appeared to be low yielding (56 %), although several work up procedures (Ph_3P, thiourea or DMS) were examined. Phosphonate **417** was prepared by initial bromination of ethyl crotonate **419**. The resulting bromoester **420** was reacted with triethylphoshite in Arbusov reaction (103) to give **417**. After this, the diene **424** was prepared by coupling the aldehyde **423** and the phosphonate **417**. Unfortunately, it was found out that the formation of the *E,E*-diene **424** was difficult with this method. In other words, it gave low yield (40 %) for the *E,E*-product **424** which was also difficult to separate from the other isomers. The low yield was also probably due decomposition of the α-siloxy substituted aldehyde **423**. The diene ester **424** was reduced with DIBAL-H to the corresponding alcohol. The alcohol was then acetylated and the

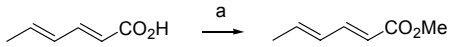
acetylated diene **425** was allowed to react with the Grignard reagent **28** in the presence of a catalytic amount of lithium tetrachlorocuprate (104). Attempts to remove the dioxolane protection of aldehyde **426** group by mild hydrolysis conditions using *para*-toluene sulphonic acid in acetone/water solvent mixture proved more difficult than anticipated. Surprisingly, even the mild hydrolytic conditions deprotected the silyl protecting group to yield diene dioxolane alcohol **427**.



Scheme 73. Reagents and conditions: a) NBS, CCl_4, Bz_2O_2 (70 %); b) $(EtO)_3P$ (55 %); c) TBDMSCl, imidazole, CH_2Cl_2 (92 %); d) O_3, CH_2Cl_2, Ph_3P (56 %); e) LDA, THF, aldehyde **423**, -40 °C (40 % for *E,E*-**424**); f) DIBAL-H, CH_2Cl_2, -78 °C; g) Ac_2O, pyr, r.t. (81 % over 2 steps); h) **28**, Li_2CuCl_4, -20 °C (70 %); i) *p*-TsOH, acetone, H_2O (74 %).

After unsuccessful hydrolysis of acetal protection and sluggish diene formation, I decided to develop a new method for the preparation of *E,E,E*-trienes. The method developed herein avoids chromatographic separations during the first steps of the synthesis. The method starts from esterification of the inexpensive sorbic acid **418** by an acid catalysis

to methyl sorbate **428** with a best yield of 94 % (Scheme 74) (105). The product **428** was easily purified by distillation under reduced pressure.

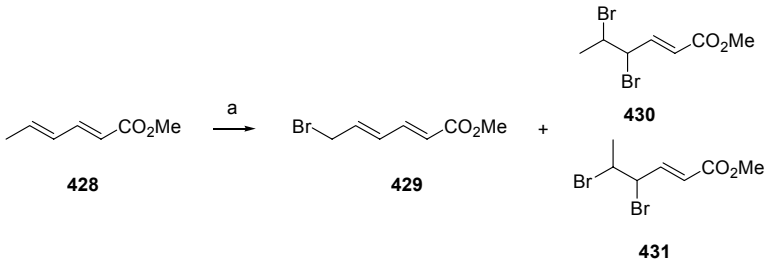


418 **428**

Scheme 74. Reagents and conditions: a) cat. H_2SO_4, MeOH, rfx (94 %).

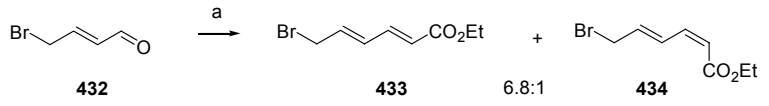
The bromination of methyl sorbate **428** with *N*-bromosuccinimide appeared to be problematic. First of all, the yield (70 %) in the reference article (106) was calculated wrong and the true yield calculated from a mass weight was 55 %. However, this must be the crude yield, because the reported reaction procedure was followed carefully and the best yield obtained by this method was 33 % of pure methyl 6-bromosorbate **429** (Table 1, Entry 2). Furthermore, the reported boiling range of methyl 6-bromosorbate **429** was quite wide (89-94 °C at 0.1 mmHg). I found out that the wide boiling range (74-79 °C at 0.2 mmHg) corresponded a product mixture, which contained only 54 % of the desired methyl 6-bromosorbate **429**. The purity was justified by purifying the distillation fraction of the product by flash chromatography. The main byproducts of bromination reaction was *anti*- **430** and *syn*-4,5-dibromination products **431**. It was also noticed, that the reaction did not go to completion with equimolar halogenating agent (NBS). An excess NBS, a longer reaction time and a lower temperature resulted in better conversion, but slightly worse selectivity to methyl 6-bromosorbate **429** (Entry 3). It was decided that the best reaction conditions for producing methyl 6-bromosorbate **429** were a short reaction time, a slight excess of NBS and a low concentration. It was also observed that a high reaction temperature >130 °C leads to increased formation of polymeric compounds, which lowered the total yield. The reaction was also tested in two different solvents, carbon tetrachloride (Entry 4) and chlorobenzene. It was observed that reaction produced more dibrominated products **430**, **431** when carbon tetrachloride was used as the solvent. The ratio of **430** to **431** was constant regardless which solvent was employed (compare entries 2 and 4). In larger scales (Entries 6 and 7), the reactions were performed in more concentrated solutions to avoid high volumes of chlorobenzene due to it's carcinogenicity. Increased amount of side products **430**, **431** were obtained in more

concentrated solutions. The mixture of brominated products **429-431** were separated from the crude product mixture by distillation under reduced pressure.



Scheme 75. Reagents and conditions: a) PhCl or CCl_4, NBS, 100-150 °C, init. Bz_2O_2.

Wei and Taylor (107) have prepared bromo diene ester **433** via a Wittig reaction of 3-bromo-2*E*-propenal **432** and phosphorane (Scheme 76). Wittig reaction of **432** produced a mixture (6.8:1) of *E,E*- and *E,Z*-diene isomers with an overall yield of 78 %. However, the separation of the isomers are laborious.



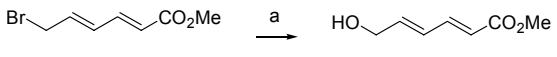
Scheme 76. Reagents and conditions: a) CH_2Cl_2, $Ph_3P{=}CHCO_2Et$, r.t. (78 %).

Table 1. Results of bromination of methyl sorbate **428**.

Entry	**428** [a]	NBS [mol-%]	C mol/l	Solv.	T [° C]	Rxn Time [h]	**428**[b]	**429**	**430**	**431**
1	0.03	104	1.19	PhCl	110-150	2.0	2.9	5.2	1.6	1
2	0.35	104	1.17	PhCl	100-130	1.5	5.6	6.9	1.8	1
3	0.35	120	1.17	PhCl	100-103	16	2.7	5.1	2.0	1
4	0.3	100	3.0	CCl_4	100-110	25	2.6	2.0	1.9	1
5	0.04	105	2.5	PhCl	100-150	1.0	3.2	4.5	2.0	1
6	1.7	103	2.5	PhCl	105-138	0.33	3.4	4.2	1.8	1
7	1.7	104	2.6	PhCl	100-120	0.75	3.4	4.9	1.8	1

[a] Mol of **428**. [b]The product ratios were determined by ^{1}H NMR from the crude product mixture.

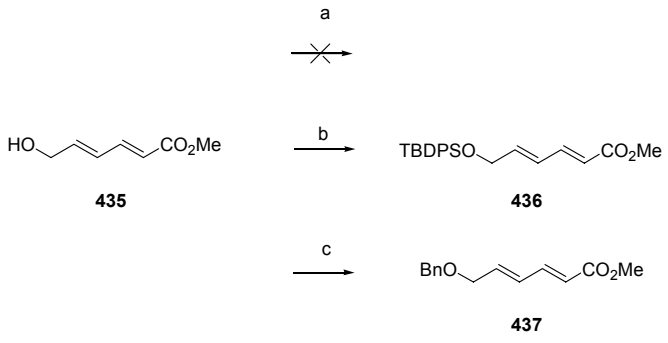
Methyl 6-bromosorbate **429** was the converted to methyl 6-hydroxysorbate **435** by a mild hydrolysis with an yield of 85 % (Scheme 76) (108). The hydrolysis succeeded nicely also with an impure starting material, which was obtained from the brominated product **429** by distillation. The hydrolysis product **435** was easily purified by solvent washing and crystallization.



429 **435**

Scheme 76. Reagents and conditions: a) acetone, $NaHCO_3$, rfx, 2 h (85 %).

The next step was to protect the alcohol of **435**. At first, I chose TBDPS-group as the protecting group due to its relative stability under acidic conditions and due to its easy cleavage with fluoride ion (109). Also, I though that the size of TBDPS-group might be beneficial during the asymmetric IMDA reaction. However, the yield of the silylation was low when TBDPS-Cl was used (Scheme 77), although DMAP (39) was used to catalyze the reaction. Although TBDPS-triflate is more reactive than the corresponding chloride, because triflic acid is a far more better leaving group than hydrogen chloride, the silylates were not employed because they are expensive to use in large scale. Finally, I decided to use benzyl protection due to its moderate steric size and compatibility with different conditions and reagents (109). Closa *et al.* (108) have reported that the reaction of diene alcohol **435** with benzyl trichloroacetimidate give a poor yield (24 %) for the benzylated product **437**. I initially attempted benzyl protection using sodium hydride as the base and benzyl bromide as the alkylating reagent. However, the desired reaction was not observed. Benzyl protection of methyl 6-hydroxysorbate **435** was achieved successfully with benzyl triflate as the alkylating reagent and using an organic base. The first benzylation of hydroxyl group using benzyl triflate and organic base has been reported by Lemieux and Kondo (110). Berry and Hall (111) have reported that *N*-benzylation of the organic base employed can be reduced by using sterically demanding bases such as 2,6-di-*tert*-butylpyridine as the proton scavenger.



Scheme 77. Reagents and conditions: a) NaH, BnBr, $(Bu)_4NI$, THF; b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, r.t., 39 h (<16 %); c) BnOTf, base, -78 → -15 °C (41-93 %).

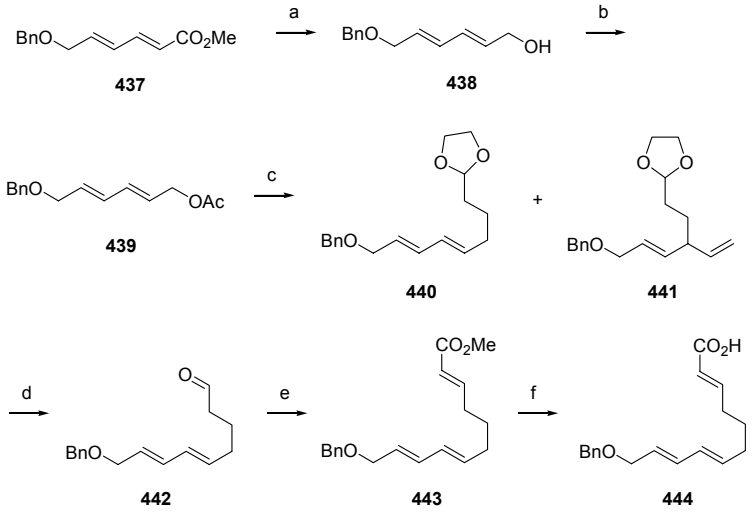
I chose to evaluate 2,6-di-*tert*-butylpyridine, 2,6-dimethylpyridine and 2,4,6-trimethylpyridine as the proton scavengers for the benzylation reaction of methyl 6-hydroxysorbate **435** (Table 2). The highest yields were obtained with 2,6-dimethylpyridine (Entries 3-5). It was surprising that efficient proton scavenger like 2,6-di-*tert*-butylpyridine gave a lower yield (Entry 1) than sterically less demanding 2,6-dimethylpyridine. Several molar ratios for the substrates were screened and the best yield was obtained when 536 mol-% of benzyl triflate and 2,6-dimethylpyridine were used (Entry 4). It was assumed that using excess benzyl triflate there was enough benzylating reagent available during the reaction. The major byproducts were identified to be dibenzylether and *N*-alkylated 2,6-dimethylpyridine, explaining the high benzyl triflate consumption.

Table 2. Benzyl protection of methyl 6-hydroxysorbate **435**.

Entry	Benzyl alcohol[a] [mol-%]	Base for triflic acid[a]	Triflic anhydride[a]	Base for deprotonation[a]	Base[b]	Reaction time[c]	Yield **435**
1	159	161	159	260	DTB	3 h	55 %
2	159	161	159	260	TM	20 h	41 %
3	159	161	159	260	DM	20 h	59 %
4	536	536	536	404	DM	2 h 15 min	93 %
5	300	300	300	200	DM	1 h 45 min	80 %

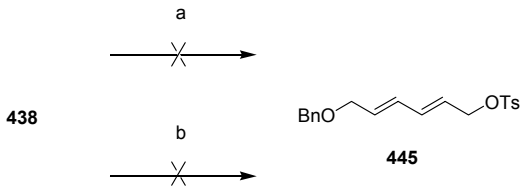
[a] Mol-% compared to **435**. [b] DTB = 2,6-di-*tert*-butylpyridine, TM = 2,4,6-trimethylpyridine, DM = 2,6-dimethylpyridine. [c] The reactions were conducted at equal temperatures and concentrations.

In the next step, the protected diene ester **437** was reduced to alcohol **438** with diisobutylaluminum hydride in high yields (80-90 %). The alcohol **438** was then acetylated with acetic anhydride in pyridine. The acetylation also worked satisfactorily also with crude **438** directly from ester **437** reduction (Scheme 78). The chain elongation was done with Grignard reagent **28**. Lithium tetrachlorocuprate was used in this reaction. An inseparable mixture of isomers **440**, **441** were obtained. The ratio of products varied from 65-85:35-15 depending on the reaction temperature. At lower temperature, more open chain product **440** was obtained . However, the conversion of the reaction was low. The dioxolane protection of **440** was removed by hydrolysis with dilute aqueous HCl in acetone. This method afforded a better yield than hydrolysis in THF and acetic acid. The aldehyde **442** was then subjected to Wittig reaction affording an *E,E,E:E,E,Z*-mixture of trienes **443**. The ratio of *E,E,E*-product to *E,E,Z*-product was 13:1. Ester **443** was hydrolyzed with NaOH in THF to give triene acid **444**.



Scheme 78. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, -78 °C (80 %); b) Ac_2O, pyr, r.t. (91 %); c) **28**, Li_2CuCl_4, -20 – 0 °C (80 %); d) 0.5 M HCl, acetone, r.t. (87 %); e) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rfx (80 %); f) NaOH, THF, 0 °C (99 %).

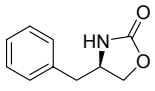
It was initially anticipated that a toluenesulfonyl group would be a better leaving group in the ensuing allylic substitution reaction. Replacement of the acetyl group of acetyl diene **439** was next attempted (Scheme 79). I tried tosylation of **438** using phase transfer conditions (112) and by DMAP catalyzed method. Unfortunately, diene tosylate **445** was very sensitive to dimerization and polymerization, which resulted in no observed product in the crude product mixtures.



Scheme 79. Reagents and conditions: a) TsCl, KOH, $(Bu)_4NHSO_4$, PhH, r.t.; b) TsCl, Et_3N, DMAP, CH_2Cl_2, r.t.

4.3.1 Chiral auxiliary promoted asymmetric IMDA

The chiral auxiliary promoted IMDA approach was chosen based on the fact that oxazolidinone derived chiral auxiliaries developed by Evans usually provide asymmetric induction (Figure 22). The phenylalanine derived oxazolidinone **41** often offers high asymmetric induction in many different types of asymmetric reactions. These chiral oxazolidinones have also been used in Diels-Alder reactions and IMDA reactions for a wide variety of substrates (79).

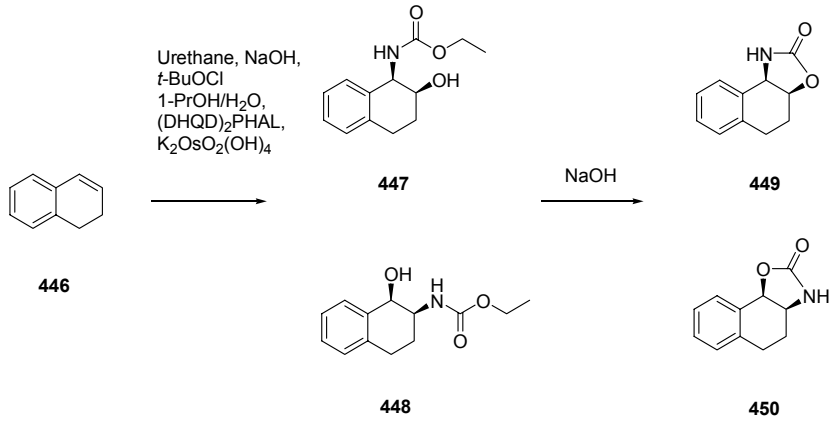


41

Figure 22. Phenylalanine derived oxazolidinone auxiliary **41** developed by Evans group.

I wanted to prepare a new chiral auxiliary, which can be synthesized easily from an inexpensive and readily available starting material. Molecular modeling (Cerius 2, Macromodel 7.0) and previous studies (100) suggested the oxazolidinone **449** derived from 1,2-dihydronaphthalene **446**.

Optically pure oxazolidinone **449** was prepared from 1,2-dihydronaphthalene **446** via a one pot synthesis (113) (Scheme 80). The first step was oxyamination of 1,2-dihydronaphthalene **446**. The second step was the formation of oxazolidinone **449** *in situ* from the *cis*-1-amino-2-alcohol **447**. The reaction was attempted with several catalyst and ligand loadings (Table 3). Urethane gave better yield, enantioselectivity and stereoselectivity compared to benzyl carbamate in this reaction (Table 3, entries 1 and 2).



Scheme 80. Reagents and conditions: a) Urethane, NaOH, *t*-BuOCl, 1-PrOH-H_2O, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$; b) NaOH.

Table 3. Optimization of catalyst and ligand loadings in oxyamination reaction of 1,2-dihydronaphthalene **446**.

Test	Carba-mate	Ligand [mol%]	Catalyst [mol%]	Rxn time 1 step	Rxn time 2 step	NaOH [mol%] 1 step	Yield % **449** / **450**		% e.e. **449** / **450**	
1	Ethyl-	5	4	2 h	4.5 h	305	54	37	79	79
2	Benzyl-	5	4	3 h	18 h	305	39	31	25	63
3	Ethyl-	1.25	1	8.5 h	12 h	305	38	26	50	50
4	Ethyl-	2.5	1	4 h	18 h	155	45	29	61	76
5	Ethyl-	2.5	1.25	21.5 h	3 h	305	46	33	60	69

[a] Yields for the flash chromatographically purified products.

It was interesting to note that sodium hydroxide loading did not dramatically change the yields or enantioselectivities (compare Entries 4 and 5). However, increased sodium hydroxide accelerated the formation of oxazolidinones **449/450** (compare Entries 4 and 5). Furthermore, it was observed that the yield and the enantioselectivity are influenced by the ligand and catalyst loads (compare Entry 1 to 3,4 and 5).

1,2-Dihydronaphthalene **446** derived oxazolidinone **449** forms a rigid pocket like structure (Figure 23), where the angle between the oxazolidinone and the naphthalene moiety is near 90 degrees. The stereopresentation of **449** is obtained from CS Chem3D Pro™. I considered these characters to make oxazolidinone **449** an excellent auxiliary for asymmetric IMDA cycloaddition.

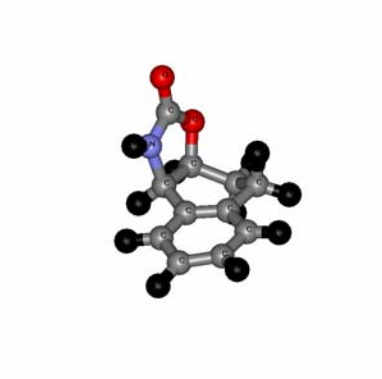
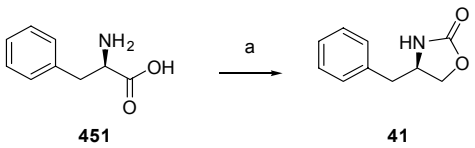


Figure 23. 3D molecular stereorepresentation of oxazolidinone **449**.

The Evans ligand **41** was easily prepared by a one step method developed by Greene *et al.* (114) (Scheme 81). The oxazolidinone **41** was purified by crystallization and the yield was 61 % (>99 %ee). The yield of oxazolidinone **41** can be certainly higher if the reaction parameters and the purification procedure is more studied and developed. However, only minor rasemization of the product was noticed during the reaction as performed according to the procedure developed by Greene *et al.*

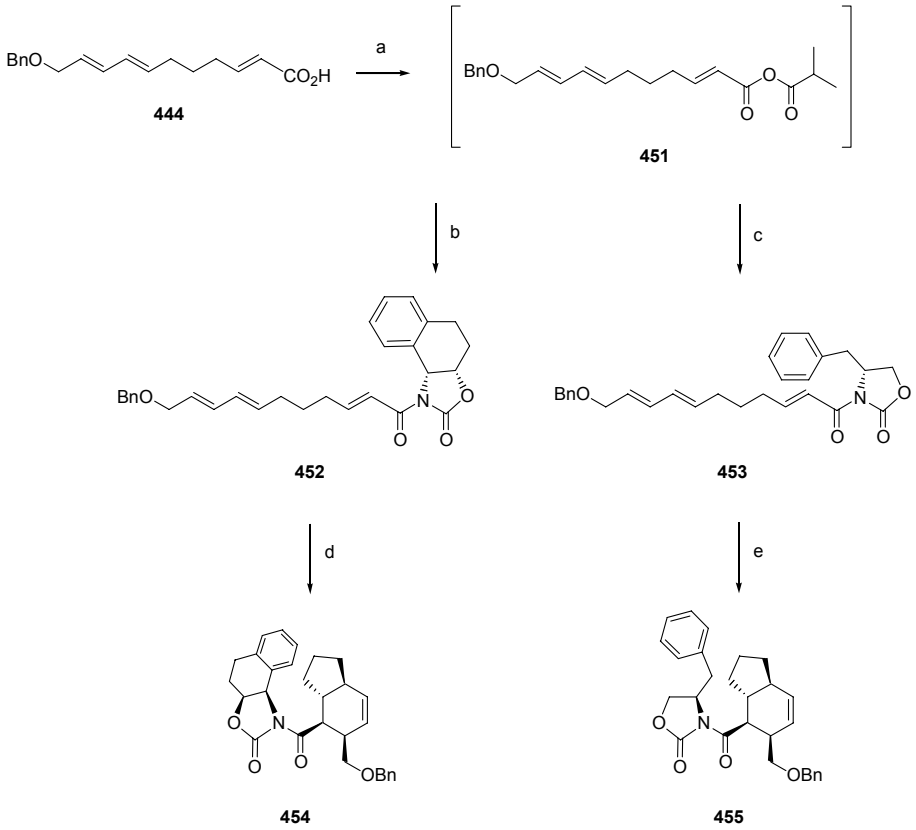


451 **41**

Scheme 81. Reagents and conditions: a) $LiAlH_4$, THF; 10% NaOH; triphosgene; recrystallization (61 %).

The lithiated auxiliaries **449** and **41** were attached to the triene acid **444**, which was activated *in situ* as the mixed anhydride **451** with pivaloyl chloride (Scheme 82). Anhydride activation has been widely used for introducing oxazolidinone ligands to carbonyl groups. For example, Martinelli (115) has used pivaloyl chloride for preparing an anhydride, which was reacted *in situ* with lithium salt of 4-(phenylmethyl)-2-

oxazolidinone. The solubility of the lithium salt of oxazolidinone **449** in THF was lower than that of the oxazolidinone **41**, which probably caused the lower yield for the amide **452** formation. The cycloadducts **454** and **455** were prepared by IMDA reaction by using a mild Lewis acid (Et_2AlCl) to catalyze the reaction. The naphthalene derivative **454** gave lower yield, but very high diastereoselectivity. Actually, the wrong diastereomer was not even observed. The low yield was obtained because the temperature was allowed to rise to r.t. This resulted in the formation of alkylated product, which formed from the reaction with the diethylaluminium chloride. Polymerization of the starting material was also observed. The Evans auxiliary derived triene **453** gave good yield for the cycloadduct **455**. High diastereoselectivity was also noticed in this reaction. The product **455** was crystallized from methanol and the crystal structure of the cycloadduct **455** is presented in Figure 24.



Scheme 82. Reagents and conditions: a) Et_3N, PivCl, Et_2O; b) LDA, **449**, Et_2O (71 %); c) LDA, **41**, Et_2O (85 %); d) Et_2AlCl, 6 h, <-10 °C (23 %); e) Et_2AlCl, 53 h, <-10 °C (72 %).

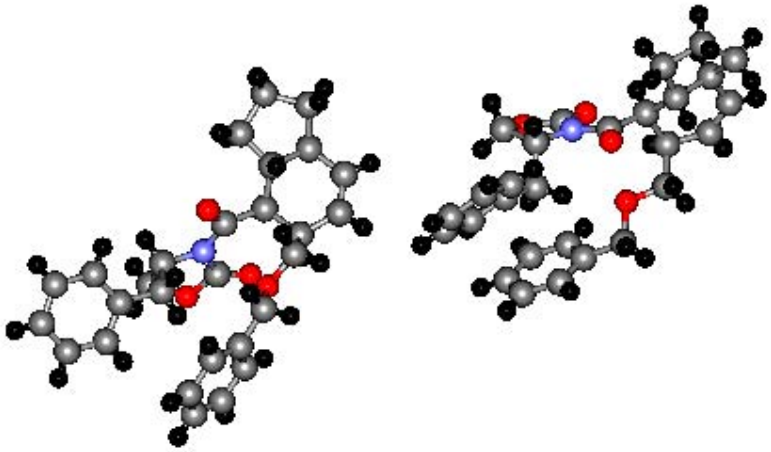


Figure 24. The crystal structure of IMDA cycloadduct **455**.

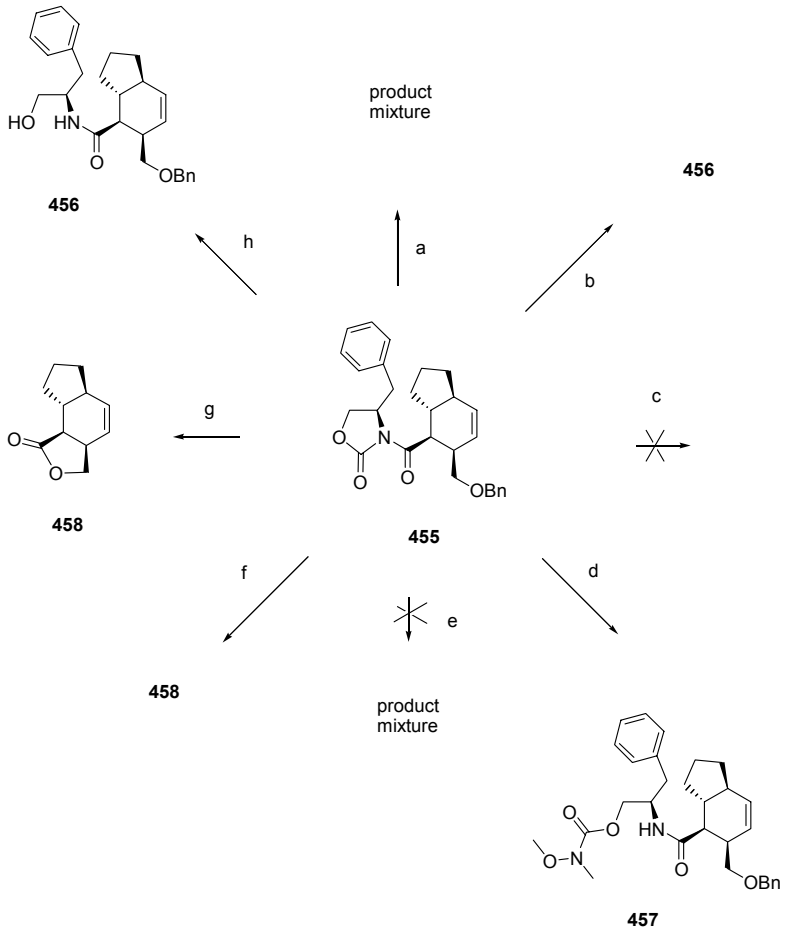
The X-ray crystal structure proved the product to be the (*S*)-*endo*-adduct. Two different forms of *endo*-adducts were found in the crystal structure of **455**. The structures differed mainly in the conformation of the side chains containing the benzyloxy and oxazolidinone moiety.

4.3.1.1 Removal of the chiral auxiliary

After forming the cycloadduct **455** , I attempted to remove the chiral auxiliary by several methods (Scheme 83). The purpose of the auxiliary removal was to enable the formation of the aldehyde, which is required for olefination to connect the amine containing side chain. Although DIBAL-H reduction of α-methyl substituted 3-acyl 4-isopropyl-2-oxazolidinone derivatives were reported to give the corresponding aldehydes (116), I obtained a product mixture containing oxazolidinone ring opened products, oxazolidinone cleavage products and other reduced products. Penning *et al.* (117) have reported that partially hydrolyzed lithium borohydride affords aldehyde products when reacted with α-*tert*-butyldiphenylsiloxy substituted acyloxazolidinone derivatives. However, the reaction of oxazolidinone derivative **455** with inactivated lithium borohydride gave the hydrolysis product **456** as the major product. Aluminum trichloride mixed with *N,N*-dimethylaniline provides debenzylated products with alkylbenzyloxy derivatives (118). When cycloadduct **455** was treated with this reagent mixture, no reaction occurred. The inactivity of this reagent mixture was probably due to decreased reactivity of the aluminum by coordination to the carbonyl oxygen. The cycloadduct **455** was then subjected to transamidation conditions to remove the oxazolidinone (119), but surprisingly the Weinreb amide was formed in a reverse manner to afford **457**.

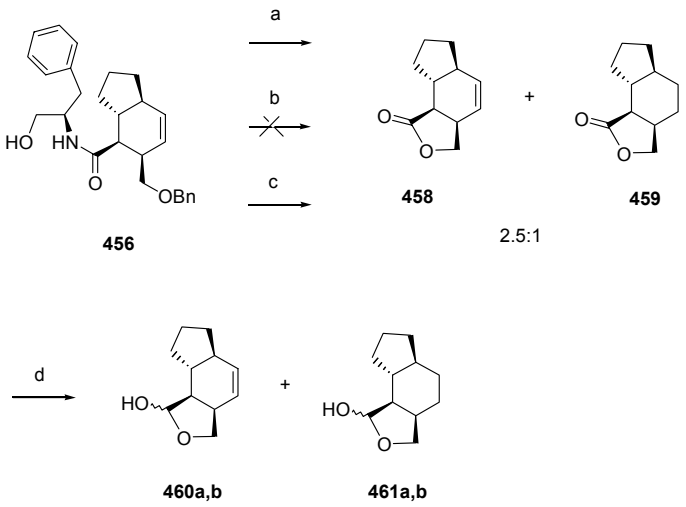
Since the cleavage of the oxazolidine moiety proved difficult, the next attempts were based on the intramolecular assistance of the neighboring hydroxy functionality. Benzyl ether cleavage can be obtained with methanesulphonic acid in chloroform with alkylbenzyloxy derivatives (120). When applied to **455**, a mixture of ring opened products was obtained. Dimethylsulfide complex of borontrichloride in dichloromethane (121) cleaved the benzyl group of **455**. Debenzylation resulted in the unavoidable formation of the lactone **458**. It was possible to recycle the oxazolidinone auxiliary **41**. It has also been reported that DDQ cleaves benzyl groups (122). Treatment of cycloadduct **455** with DDQ in dichloromethane-water (20:1) mixture resulted in the cleavage of the benzyl group and instant formation of the lactone **458**. The yield was low probably due to the small scale. Finally, basic hydrolysis of cycloadduct **455** with KOH in methanol

resulted hydrolytic opening of the oxazolidinone ring to afford an amide alcohol **456** in near quantitative yield.



Scheme 83. Reagents and conditions: a) DIBAL-H, PhMe, -78 °C; b) $LiBH_4$, H_2O, THF (62 %); c) $AlCl_3$-*N,N*-dimethylaniline, CH_2Cl_2; d) MeONHMe·HCl, $AlMe_3$, CH_2Cl_2, -10 → +50 °C (78 %); e) $MeSO_3H$, $CHCl_3$; f) $BCl_3{\cdot}SMe_2$, CH_2Cl_2 (84 %) ligand recovery (74 %); g) DDQ, H_2O, CH_2Cl_2 (40 %); h) KOH, MeOH (>99 %).

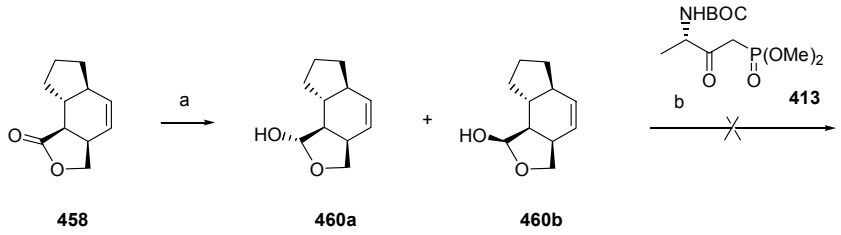
After amide alcohol **456** in hand, debenzylation was attempted with different methods (Scheme 84). Diphosphorous pentasulfide gives debenzylation and lactonization when the carboxylic group is in δ-position to benzyloxy group (123). I assumed that the amide **456** would behave similarly and form lactone **458** after debenzylation with diphosphorous pentasulfide, but only traces of the lactone **458** was found from the product mixture after 1.5 hours reaction time. The reaction was not further studied, because diphosphorous pentasulfide appeared to be rather nasty smelling reagent and more convenient methods were decided to study. Furthermore, acidic hydrolysis with dilute sulphuric acid in dioxane did not result lactonization. However, concentrated solution of hydrochloric acid (6 M HCl) in dioxane resulted in lactonization of the amide **456**. Surprisingly, double bond of amide **456** was also saturated probably through cationic rearrangement under highly acidic conditions. The inseparable mixture of lactones **458, 459** were reduced with DIBAL-H to the corresponding lactols **460, 461** as a mixture of diastereomers. It was clear according to results obtained that the acid protomed lactonization of the amide **456** was pH dependent reaction.



Scheme 84. Reagents and conditions: a) P_4S_{10}, CH_2Cl_2, r.t., 90 min (traces of **458**); b) 0.75 M H_2SO_4, 1,4-dioxane, 100-105°C, 2.5 h; c) 6 M HCl, 1,4-dioxane, 100-105°C, 18.5 h (82 %); d) DIBAL-H, PhMe, -78 °C (62 %).

4.3.1.2 Reactions of the five membered lactol

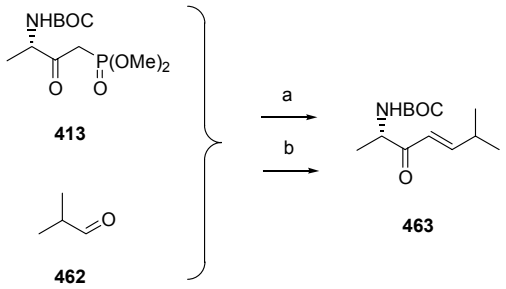
After learning that debenzylation of cycloadduct **455** was followed by unavoidable lactonization, I decided to reduce lactone **458** to lactol **460** and considered that lactol **460** would react with phosphonates or phosphoranes to allow the amino fragment connection. It is known that five membered lactols are commonly used as substrates in Wittig reactions (124). Although acyclic lactols are used as a substrates in HWE reactions (125), a condensation reaction of phosphonates with cyclic lactols are not reported. Lactone **458** produced from the cycloadduct **455** with borontrichloride dimethylsulfide was reduced with DIBAL-H to afford lactols **460a,b** as a 20:1 mixture of diastereomers. The mixture of lactols **460a,b** was subjected to HWE reaction using conditions developed by Mikolajczyk and Balczewski (126). In this method potassium carbonate is partially dissolved in ethanol to avoid racemization of the amino group. *β*-Ketophosphonate **413** was prepared from *N*-BOC-protected *L*-alanine using the procedure developed by Corey and Kwiatkowski (127). However, the lactols **460a,b** appeared to be unreactive toward nucleophilic attack of the phosphonate anion generated from *β*-ketophosphonate **413**.



Scheme 85. Reagents and conditions: a) DIBAL-H, PhMe, -78 °C (72-81 %); b) phosphonate **413**, K_2CO_3, 94 w-% EtOH, r.t.

I decided to study Mikolajczyk and Balczewski modified HWE reaction more closely. The condensation reaction of isobutyraldehyde **462** and phosphonate **413** was chosen as the model reaction (Scheme 86). I found out that the reaction did not proceed in dry ethanol, which was previously distilled from magnesium ethoxide to crushed 3Å

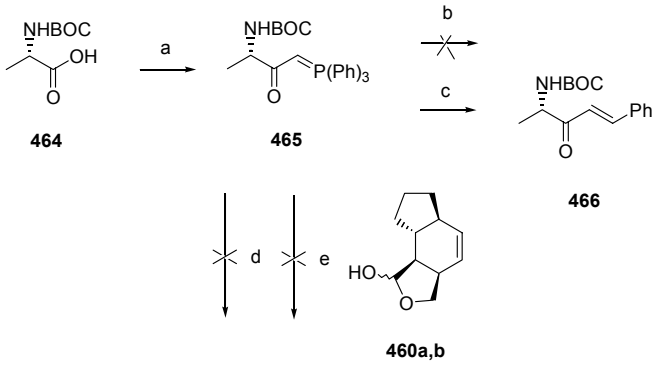
molecular sieves. Interestingly, the reaction did proceed when a few drops of water was added into the slurry reaction mixture. The addition of water improved the solubility of potassium carbonate, which was required for the anion formation. Furthermore, racemization was avoided when just a few percent of water was added. This was probably due to the low concentration of potassium carbonate in the reaction mixture. After observing that water was essential the reaction, I used systematically 94 weight percent ethanol for the reactions and the results did not change noticeably. In comparison, I employed the conditions developed earlier in our group (128) for the same reaction between isobutyraldehyde **462** and phosphonate **413**. I noticed that by using potassium carbonate in dry acetonitrile the reaction was not completed even after 5 days of stirring, which was probably reason for the lower yield (61 %). The slow reaction was also accompanied with racemization of the amino group, which was not observed in the reaction in ethanol. The racemization was determined from the crude product mixture by gas chromatography using chiral column (γ-dextrine).



Scheme 86. Reagents and conditions: a) K_2CO_3, 94 w-% EtOH (69-73 %, >99 % ee); b) K_2CO_3, CH_3CN (61 %, 97 % ee).

An amino acid derived phosphorane ylide **465** was prepared for Wittig reactions from *N*-BOC-protected *L*-alanine **464** by using a modified method developed by Jarosz and Skóra (129) (Scheme 87). The procedure of Jarosz and Skóra were modified so that phenyllithium instead of *n*-butyllithium was employed as the base to avoid alkyl-aryl

exchange of the phosphorane **465**. Miyano and Stealey (130) have reported that the use of phenyllithium instead of butyllithium is essential if higher yields of alkyltriphenylphosphoranes are desired. Acid **464** was activated as an acylimidazoline and reacted with methylenetriphenylphosphorane prepared *in situ* to afford the phosphorane ylide **465**. The ylide **465** was reacted with isobutyraldehyde **462** and benzaldehyde to test the reactivity the phosphorane **465**. Isobutyraldehyde **462** did not react with phosphorane ylide **465** at refluxing dichloromethane. However, benzaldehyde reacted nicely in refluxing benzene with phosphorane **465** to afford the condensation product **466** in good yield (76 %). Racemization of the product **466** was not observed. Unfortunately, phosphorane ylide **465** did not react with lactol **460a,b** in refluxing dichloromethane or benzene.

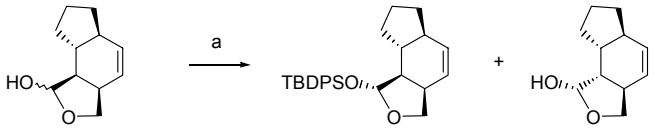


464 **465** **466** **460a,b**

Scheme 87. Reagents and conditions: a) CDI, PhH, r.t.; Ph_3PCH_2Br, PhLi, r.t.; 6 °C → r.t., 1 h (54 %); b) 462, CH_2Cl_2, rfx, 18 h; c) benzaldehyde, PhH, rfx, 45 h (76 %); d) lactol **460a,b**, CH_2Cl_2, + 40 °C, 25 h; e) lactol **460a,b**, PhH, rfx, 24 h.

After these rather discouraging results, I started to look for other ways to open the lactol ring of **460**. Yau and Coward have reported that five membered cyclic lactols can be opened using silylating conditions (TBDPSCl, imidazole, DMF, + 50 °C) to afford an *O*-silylated aldehyde (131). I employed these conditions for the mixture of lactols **460a,b** (Scheme 88). The reaction appeared to be sluggish and several portions of imidazole and TBDPSCl-reagent were required to drive the reaction to completion. The main product was the *O*-silylated lactol **467**. The major side product was the diastereomer **468** of the

lactol **460**. The five membered lactol ring appeared to be more favorable than the aldehyde formation under O-silylating conditions.



460a/b **467** 1.5:1 **468**

Scheme 88. Reagents and conditions: a) TBDPSCl, imidazole, DMF, +50 °C, 22 h (65 %).

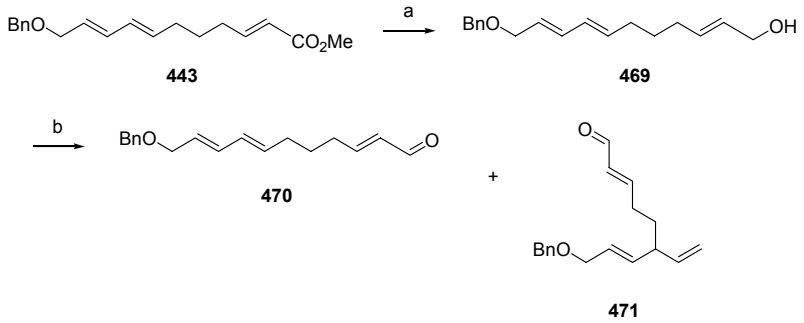
The chiral auxiliary **41** can be removed to yield hydroxyl sulfones by using sulfur anions (55). However, such a cleavage of auxiliaries leads to a longer synthesis route due to extra steps for the introduction and removal of the sulfur containing moiety. At this point, I decided to consider other methods to prepare bicyclo[4.3.0]nonane aldehydes and the results of these experiments are presented in the following chapter.

4.3.2 Organocatalytic asymmetric IMDA

Faced with the problems described above, we turned our attention to the possibility of utilizing the recently described organocatalysis in our problem (132). No solid phase bound IMDA organocatalysts had been previously described, and achievement of solid supported organocatalytic IMDA became our next goal (133).

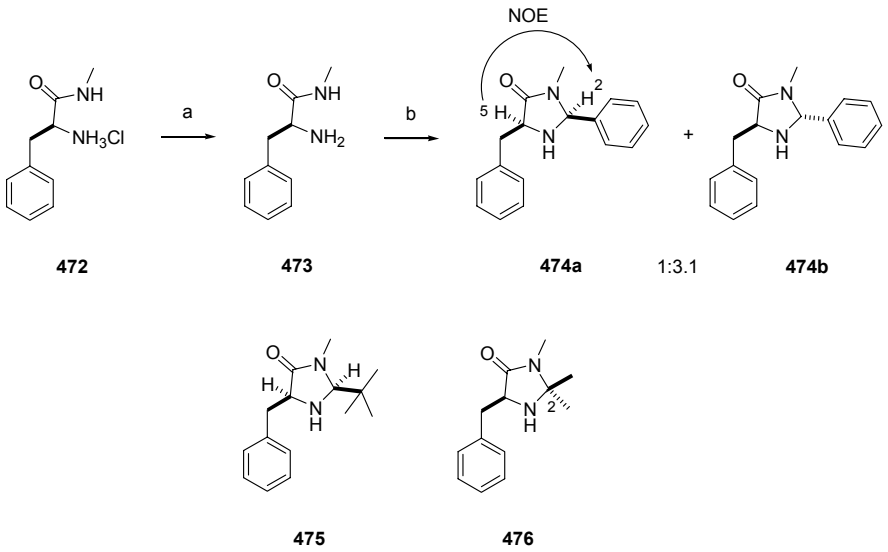
To my surprise, results of organocatalytic IMDA has not been reported prior to my work. However, MacMillan *et al.* mentioned in their patent text (134) that their catalysts can be used in IMDA cycloadditions, but no experimental details were reported. Therefore, different imidazolidinone catalysts were investigated for IMDA cycloaddition. At first, I prepared triene aldehyde **470** as a starting material for the IMDA cycloadditions (Scheme

89). In order to achieve this, triene ester **443** was reduced with DIBAL-H to triene alcohol **469**, which was oxidized preferably without isolation to the corresponding aldehyde **470** with MnO_2. Oxidation required excess of MnO_2 to be completed. The triene aldehyde **470** was susceptible for polymerization and it was preferably stored in a freezer. The linear triene aldehyde **470** was accompanied with inseparable branched aldehyde **471**, which formed in the chain elongation step (see **439→440**+**441**). The ratio of **470** to **471** depended on the chain elongation step as stated before.



Scheme 89. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, -78 °C; b) MnO_2, CH_2Cl_2, r.t., 24 h (89 % over 2 steps).

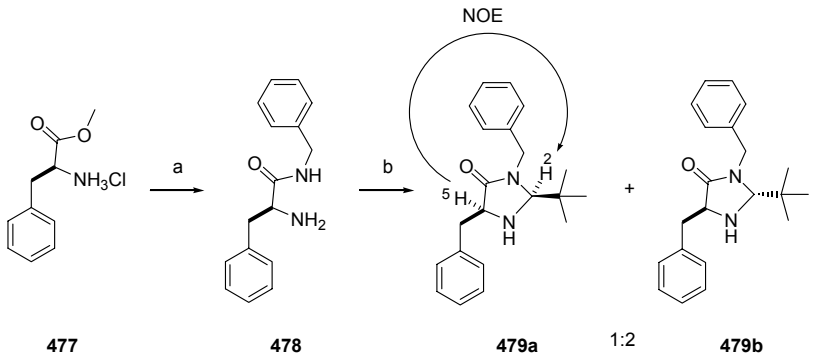
Imidazolidinone catalysts **474-476** (Scheme 90) were prepared according to published procedures (135). The stereochemistries of the catalysts **474-476** were confirmed by NOE-NMR measurements. The cyclization of the amide **473** produced a diastereomeric mixture of imidazolidinones **474a/b** (1:3.1). Unfortunately, the cyclization favored the *trans*-cycloadduct, which was lower in energy. The NOE-NMR showed coupling between the protons H2 and H5 in imidazolidinone ring of **474a**. It was interesting to note that the *cis*-product **474a** did not racemize notably during the long reaction time. However, the *trans*-product **474b** was prone to racemization and cycloadduct **474b** was found to be entirely racemic by chiral HPLC analysis.



Scheme 90. Reagents and conditions: a) $NaHCO_3$, $CHCl_3$; b) BnCHO, PTSA, MeOH, + 75 °C, 4 days (44 %).

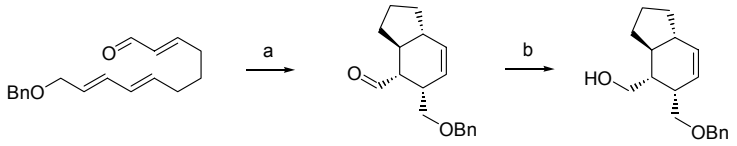
I decided to replace the *N*-methyl group of the organocatalyst **475** with an *N*-benzyl group, because I though that it would make the catalyst more rigid. By rigidifying the catalyst structure, the catalyst should give better enantioselectivity by favoring the desired reaction path to the cycloadduct.

2-Amino-3-phenyl-propionic acid methyl ester hydrochloride salt **477** was directly amidated with benzylamine in high yield (88 %). The cyclization of **478** produced 18 % of the correct diastereomer **479a**. The stereochemistry of the catalyst **479a** was confirmed by NOE-NMR measurement. Consequently, H2 and H5 protons of the imidazolidinone ring showed NOE between them. Notable racemization was not observed for the *cis*-cycloadduct **479a**, however, the *trans*-cycloadduct **479b** was accompanied with racemization.



Scheme 91. Reagents and conditions: a) $BnNH_2$, EtOH, r.t., 23 h (88 %); b) $(Me)_3CCHO$, PTSA, MeOH, rfx, 46 h (56 %).

The starting materials of IMDA cycloadditions were mixtures of linear triene aldehyde **470** and the inseparable branched triene aldehyde **471** (Scheme 92). The linear triene aldehyde **470** was more inclined for polymerization and thus some of the experiments were performed with starting materials containing more of the branched triene aldehyde **471**. However, both aldehydes **470** and **471** are capable of forming the iminium ion with the amine catalyst. The catalyst loadings were calculated according to the total aldehyde amount. The cycloadduct aldehyde **480** was reduced to the corresponding alcohol **481** for analytical purposes. The branched triene aldehyde **471** was unable to cycloaddition and was thus easily separated from the cycloadduct **480** by flash chromatography. The *endo/exo* selectivities were determined by ^1H NMR from the crude product mixtures. The chemical shifts of the carbonyl protons of the *endo*-and *exo*-cycloadduct aldehydes **480** differed by about 0.08 ppm's.



470 + **471** **480** + **471** **481**

Scheme 92. Reagents and conditions: a) organocatalyst, solvent mixture, acid; b) $NaBH_4$, EtOH, r.t.

The results of the organocatalytic IMDA cycloadditions are presented in the Table 4. Catalyst **475** gave highest enantioselectivities (Entry 2, 74 %ee), yields (entry 3, 99 %) and *endo*-selectivities (entries 2, 3, 4 and 7, >99:1) compared to other organocatalysts **474a**, **476** and **474a**. Trimethyl oxazolidinone **476**, which was chiral only at the C5-position was found to give low stereoselectivities (Entry 1), although oxazolidinone **476** is an excellent catalyst for Diels-Alder cycloaddition (135a). The IMDA cycloaddition of triene aldehyde **470** was noticed to be solvent dependent. Acetonitrile appeared to be the best of the examined solvents for this cycloaddition. However, MeOH afforded somewhat higher enantioselectivity (Entries 2 and 3), but an extra step was required for acetal cleavage, which was formed from the aldehyde **480** during the reaction. Also, the yield of the cycloadduct **480** was lower in MeOH than in acetonitrile. The enantioselectivities did not improve significantly using lower temperature (Entries 9 and 10). Furthermore, the low temperature (-20 °C) retarded the reaction significantly, so that the reaction was not complete even after several days of standing. Surprisingly, the enantioselectivity was decreased at lower temperature in the reaction catalyzed by **475** (Entry 3 and 4). In comparison, the enantioselectivity increased slightly, but the *endo*:*exo* ratio became worse when the reaction was catalyzed by **479a** at low temperature (-20 °C). Although a direct comparison between the co-acids can not be made, because the solvent system was also changed, it can be inferred that *p*-toluene sulphonic acid in dichloromethane/*iso*-propanol afforded worse *endo*:*exo* selectivities and enantioselectivities than other solvent/acid systems examined (Entries 5 and 11).

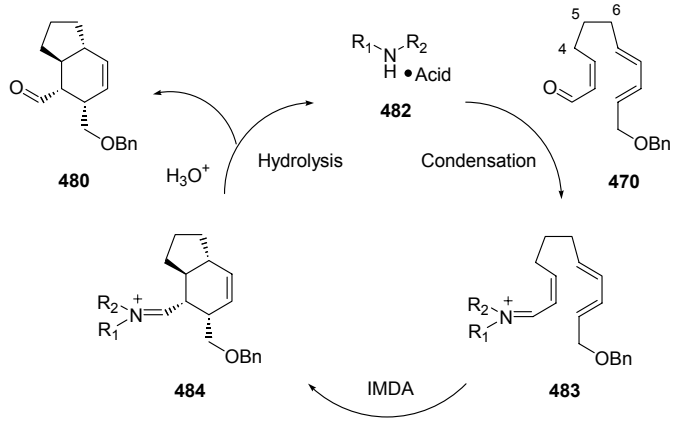
Table 4. The conditions and results of IMDA reaction of the triene aldehyde **470** catalyzed by the organocatalysts **474a**, **475**, **476** and **479a**.

Entry	Catalyst[a]	Temperature	Solvent	Acid	Endo:Exo[b]	Yield[c] (%)	%e.e[d]
1	**474a**	r.t.	H_2O/CH_3CN	0.1 M HCl	>99:1	59	10
2	**475**	r.t.	H_2O/MeOH	0.4 M HCl	>99:1	54	74
3	**475**	r.t.	H_2O/CH_3CN	0.1 M HCl	>99:1	99[e]	72
4	**475**	-20 → +6 °C	H_2O/CH_3CN	0.1 M HCl	>99:1	54	66
5	**475**	-20 → +6 °C	CH_2Cl_2/*i*-PrOH	PTSA	25:1	45	41
6	**475**	-20 → +6 °C	H_2O/THF	TFA	-	-	-
7	**475**[f]	r.t.	H_2O/CH_3CN	0.1 M HCl	>99:1	79	72
8	**476**	0 °C → r.t.	H_2O/MeOH	0.4 M HCl	3.3:1	28	-
9	**479a**	-20 → +6 °C	H_2O/CH_3CN	0.1 M HCl	17:1	40	56
10	**479a**	r.t.	H_2O/CH_3CN	0.1 M HCl	>99:1	54	47
11	**479a**	-20 → +6 °C	CH_2Cl_2/*i*-PrOH	PTSA	14:1	38	12
12	**479a**	-20 → +6 °C	H_2O/THF	TFA	-	-	-

[a] 20 mol-% of the catalyst was used compared to the calculated sum of total moles of aldehydes **470** and **471**. [b] *endo*:*exo* ratios were determined by ^{1}H NMR from the aldehyde

product mixture. [c] Yields of isolated pure aldehydes. The yields were correlated to the amount of linear aldehyde **470** in the beginning of the reaction. [d] For determination of the *ee* values, the aldehyde products were first reduced to alcohols with excess $NaBH_4$ in EtOH, and the resulting alcohols were analyzed by HPLC using chiral Daicel OD column. Absolute and relative configurations were assigned by chemical correlation to compounds obtained by known methods for Diels-Alder reactions or by analogy. [e] The ratio of the linear triene aldehyde **470** to the branched triene aldehyde **471** was 1:3.76 in this reaction. [f] A 5.6 mol-% of the catalyst was used in this reaction.

The proposed mechanism of the organocatalytic IMDA cycloaddition is shown in the Scheme 93. Condensation of triene aldehyde **470** with enantiopure amine **482** leads to the formation of an iminium ion **483**. The iminium ion **483** is active enough to enable asymmetric IMDA cycloaddition with the diene part of the molecule. After the cycloadduct **484** has formed, the amine catalyst **482** is recovered by hydrolysis and the aldehyde cycloadduct **480** is produced. After this, a new catalytic cycle can begin.



Scheme 93. Mechanism of organocatalytic IMDA cycloaddition. The represented stereochemistry of the cycloadduct **480** is obtained with organocatalyst with (*S,S*)-stereochemistry.

The different catalytic activity of the catalyst **476** in Diels-Alder reactions compared to intramolecular Diels-Alder reactions are propably due to steric hindrance between *trans*-methyl group at position 2 of the imidazolidinone ring (see Scheme 90, methyl group at position 2 of **476**) of the catalyst **476** and the aldehyde **470 -**CH_2- groups (see Scheme 93, carbons (4-6) of **470**).

4.4 Preparation of amino alcohol side chain

The following chapters present the results and discussion of preparation of the amino alcohol side chain of amaminol A **1** which was prepared using two different origins of chirality. The first strategy was based on internal asymmetric induction from the existing chiral center of *L*-alanine **3**. Second strategy was based on asymmetric oxyamination reaction.

4.4.1 *Chirality derived from L-alanine*

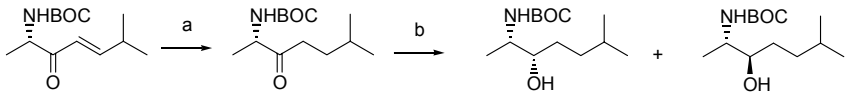
L-Alanine **3** was used as the starting material for two different coupling reagents. These reagents were phosphonate **413** and phosphorane ylide **465**, which were prepared from *L*-alanine in just a few steps. The general idea was to bring the chiral amino functionality as an α-amino ketone and then chemoselectively reduce the formed double enone to obtain the saturated side chain. The final amino alcohol moiety was considered to be formed by diastereoselective reduction using internal asymmetric induction of the amino group.

4.4.1.1 HWE based approach

The amino alcohol side chain of amaminol A **1** was connected using a HWE reaction between aldehyde **480** and *β*-keto phosphonate **413**. At first, stereoselective reduction of **485** to amino alcohols **486a,b** was studied. Previously prepared α-amino ketone **463** was reduced by a method developed by Barrero *et al.* (136). They have reported that enones can be selectively 1,4-reduced with Raney nickel in THF. Raney nickel (type W2) reduction of **463** afforded the saturated α-amino ketone **485** in high yield (89 %) (Scheme 94). Significant racemization (>96 %ee) of the reduction product was not observed by chiral GLC or HPLC analyses.

Reduction of α-amino ketone **485** to α-amino alcohol **486a,b** was studied and several reduction systems were employed (Table 5). *L*-Selectride® in THF gave low 1,2-induction (*syn*:*anti,* 3.5:1) in the hydride addition to α-amino ketone **485** (Entry 1), although *L*-Selectride® is reported to give high asymmetric induction favoring the formation of *syn*-product for *N*-(9-phenylfluoren-9-yl) protected 2-amino-1-phenyl-propan-1-one.(137) The reason for the lower selectivity is probably the greater steric size of *N*-(9-phenylfluoren-9-yl) protection group compared to *N*-BOC group. The stereochemistry of amino alcohols **486a** ($J_{1,2}$ = 5.6-6.6 Hz) and **486b** ($J_{1,2}$ = 2.9-3.5 Hz) were established by ^{1}H NMR analysis. The coupling constant $J_{1,2}$ of **486a** was similar to the coupling constant $J_{1,2}$ obtained for *syn*-amino alcohol **487a**. Deuterated methanol was found to be the best solvent for ^{1}H NMR analysis of amino alcohols **486a,b** and it allowed the calculation of the coupling constants. All tested methods favored formation of *syn*-amino alcohol **486a**. The reductant prepared from $LiAlH_4$ and axially dissymmetric (*S*)-bi-naphthol ((*S*)-BINAL-H) (138) was not active reductant for **485** (Entry 2). Chiral proline based catalyst (139) (*D*-*B*-methyl-CBS) was only slightly *syn*-selective (Entry 3). The chirality of the α-amino ketone **485** probably overcame the chirality of the *D*-*B*-methyl-CBS catalyst or the boron of CBS catalyst did not coordinate effectively to the carbonyl oxygen. Although titanium tetrachloride is an effective chelating agent in the reduction of chiral acyclic γ-amino β-keto ester (140) with borane-pyridine complex, reduction of α-amino ketone **485** was not observed (Entry 4). Zinc bromide is reported to be a good chelating agent in reduction of γ-amino β-keto

sulfoxide.(141) Although it has been reported that the stereoselectivity in DIBAL-H reduction of γ-amino β-keto sulfoxide can be reversed by adding $ZnBr_2$ as a chelating agent, in this case the addition of $ZnBr_2$ to the reduction mixture improved *syn*-selectivity from 3.3:1 to 7.1:1 favoring the formation of amino alcohol **486a** (Entries 5,6 and 8). Zinc bromide is not very soluble in organic solvents. Fortunately, $ZnBr_2$ dissolves in dilute solutions of diethyl ether and THF. Diethyl ether was found to be better solvent than THF in the *syn*-selective reductions including $ZnBr_2$ (Entries 5 and 6). This was probably due to lower coordinating ability of diethyl ether to $ZnBr_2$ compared to THF. Thus, $ZnBr_2$ was chelating more easily to the substrate. *L*-Selectride® was also employed with $ZnBr_2$ and it was noticed that the *syn*-selectivity was slightly improved even at a higher temperature (Entries 1 and 7). Luche conditions (142) afforded also *syn*-selective reduction (*syn*:*anti*, 5.3:1) of the α-amino ketone **485** (Entry 9). It was assumed that lanthanide salt ($CeCl_3$) coordinated effectively to the substrate affording *syn*-selective reduction. All reaction products were not purified and only conversion of the substrate and diastereoselectivity were measured by gas chromatography. The products were solids, which enables purification of the *syn*-product by recrystallization. However, recrystallization of the products were not done, because the reactions were run in small scale (<0.1 mmol).



463 **485** (*S,S*)-**486a** (*S,R*)-**486b**

Scheme 94. Reagents and conditions: a) Raney Ni W2, THF, r.t. (89 %, >96 %ee); b) see table 5.

Table 5. Diastereoselective reduction of α-amino ketone **485**.

Entry	Conditions	**486a**:**486b**[a]	Yield (%)[b]
1	*L*-Selectride®, THF, -95 °C	3.5 : 1	99
2	(*S*)-BINAL-H, THF, -78 °C -> r.t.	-	-
3	(*D*)-*B*-Me-CBS, THF, -24 °C	1.4 : 1	100[c]
4	$TiCl_4$,BH_3·pyr., THF, -78 °C	-	-
5	$ZnBr_2$, DIBAL-H, Et_2O, -78 °C	7.1 : 1	77
6	$ZnBr_2$, DIBAL-H, THF, -78 °C	4.1:1	100[c]
7	$ZnBr_2$, THF, *L*-Selectride®, -78 °C	3.8 : 1	95
8	DIBAL-H, PhMe, -78 °C	3.3:1	99
9	$NaBH_4$, $CeCl_3$·$7H_2O$, MeOH, r.t.	5.3:1	100[c]

[a] The *syn*:*anti* ratios were determined by GLC using Supelco γ-DEX™ 120 column. [b] Yields of isolated, purified amino alcohols **486a,b**. [c] The products were not purified and the conversion of the substrate **485** was determined by GLC using Supelco γ-DEX™ 120 column.

It was clear from the results that if high *syn*-selectivity is desired in the reduction of α-(*N*-BOC)-amino ketone **485**, the reduction is preferably performed with $ZnBr_2$/DIBAL-H/diethyl ether combination. However, Luche conditions would probably afford even higher selectivities, if the reaction is conducted at lower temperature.

The assumed Cram's chelation model (143) of Lewis acid ($ZnBr_2$ or $CeCl_3$) is shown in Figure 25. In this model the metal of the Lewis acid (M) is chelated to two carbonyl oxygens. One of the chelating oxygens belongs to the target carbonyl and other one to the *N*-BOC carbonyl oxygen. After chelation, the reduction occurs from *si*-face of the ketone **485** leading preferably to the formation of the *syn*-amino alcohol **486a**. However, the

reduction was slightly *syn*-selective also without a chelating reagent due to the steric size of *N*-BOC, which blocks the *re*-face of the ketone **485**.

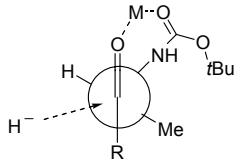
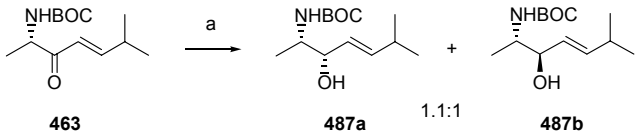


Figure 25. Chelation model of the reduction of α-amino ketone **485**. Ligands of the Lewis acid are omitted for clarity.

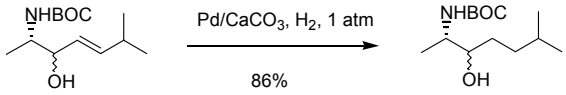
Corey *et al.* (144) has reported that enones can be reducted diastereoselectively with trialkylborohydrides if one of face of carbonyl group is blocked with sufficient steric bulk. By doing this, it is also possible to control the enone conformation as s-cis in order to direct the formation of the desired product. Furthermore, Koskinen group (101g,h) has reported that reductions of chiral *N*-BOC α-amino enones are very dependent on reductant and reaction conditions. Although, *L*-Selectride® in THF is found to reduce *N*-BOC α-amino enones by favoring the formation of *syn* product, reduction of unsaturated α-amino enone **463** with this system resulted very low diastereoselectivity (Scheme 95). The ratio of *syn*-**487a** to *anti*-product **487b** was only 1.1:1.



Scheme 95. Reagents and conditions: a) *L*-Selectride®, Et_2O, -78°C (92 %).

Model reductions of the double bond of the amino alcohols **487a,b** was performed to ensure that the allylic double bond can be selectively reduced in the presence of the other double bond. Palladium on calcium carbonate was chosen as the catalyst, because it has been reported that chemoselectivity is obtained in similar scenarios in synthesis of prostanoids (145). Cyclohexene was added to the reaction mixture to study if the reaction

was chemoselective towards the allylic double bond of **487a,b**. Unfortunately, cyclohexene was reduced to cyclohexane and double bond of **487a,b** (1.1:1) was reduced in high yield (86 %) (Scheme 96).



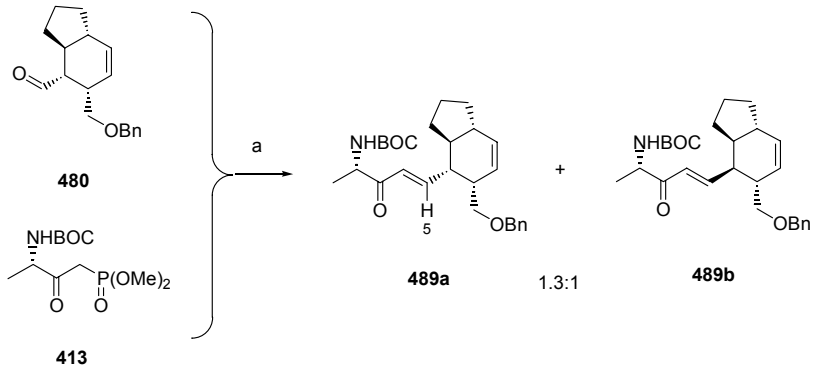
487a/b **488a/b**

Scheme 96. Reagents and conditions: a) cyclohexene, $Pd/CaCO_3$, H_2, 1 amt, r.t. (86 %).

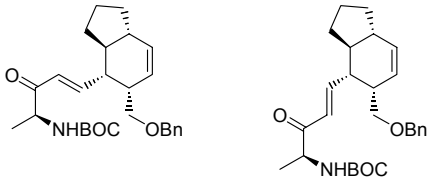
HWE reaction of phosphonate **413** with **480** was attempted with three different reaction systems. At first, the same reaction system (K_2CO_3, 94 w-% EtOH) was used as in the model reactions with isobutyraldehyde **462** (see Scheme 86). Unfortunately, aldehyde **480** epimerized during the long reaction period (Scheme 97). Thus the product was a mixture of diastereomers **489a,b** (1.3:1). Similar epimerization of α-chiral aldehyde is also reported by Edmonds and Abell (146). To suppress the epimerization, the Masamune-Roush (*i*-Pr_2NEt, LiCl, CH_3CN) conditions (147) were examined. However, the reaction became so slow that very low conversion was obtained even after 5 days of stirring. The conversion of the substrate **480** was about 20 % by ^1H NMR. However, the epimeric product was not observed in the crude product. HWE coupling between aldehyde **480** and phosphonate **413** was also tried by using sodium salt of hexamethyldisilazane at –78°C for deprotonation of the phosphonate **413**. However, the no reaction was observed at –78 °C and the reaction temperature was gradually raised to +13 °C. The yield for the product mixture **489a,b** was low very low (21 %). At this case, the ratio of **489a** to **489b** was not determined.

Fortunately, it was possible to separate the diastereomers **489a** and **489b** by flash chromatography. Surprisingly, the product **489a** showed double carbon peaks in ^{13}C NMR. The reason for this was investigated by analyzing the adduct **489a** by 2D NMR measurements including COSY, NOESY, HMBC and HSQC. However, a diastereomer of the product **489a** was not found by these NMR methods. Careful examination of the ^1H NMR spectra of **489a** showed two doublet of doublets peak patterns between 7.03-

6.97 ppm. This corresponds to the proton H(5) as marked in the Scheme 97. The two dd patterns were assumed to be due to two different conformations of the acyclic double bond (Figure 26). Furthermore, the other product was not separable from **489a** by chiral HPLC. It was assumed that the extra signals in the ^{13}C NMR spectrum came from a conformer of the product **489a**. The compound **489a** was also analyzed by molecular modeling. (MM3 force field, Monte Carlo method, Macromodel 7.0) The energy difference between conformers **489a-1** and **489a-2** (Figure 26) was calculated to be 5.8 kJ/mol, which theoretically means that the conformer **489a-2** should not be observed at room temperature, because the energy difference is so large. However, if both conformers formed during the HWE coupling reaction and if the energy barrier between conformer **489a-1** and **489a-2** is so large that conformer **489a-2** does not convert to **489a-2** at room temperature, it is possible that the two conformers **489a-1** and **489a-2** exists as a mixture at room temperature. The product **489a** was analyzed by ^{1}H NMR at higher temperature (+50 °C) to see if the other conformer would disappear, but surprisingly this did not happen. The product **489a** was not crystalline and thus crystal structure analysis was not achieved. The ketone **489a** was derivatized with *p*-nitrophenylhydrazine, but no crystalline product was not obtained.



Scheme 97. Reagents and conditions: a) K_2CO_3, 94 w-% EtOH, r.t., 47 h (79%).



489a-1

Global energy minimum = 84.27 kJ/mol

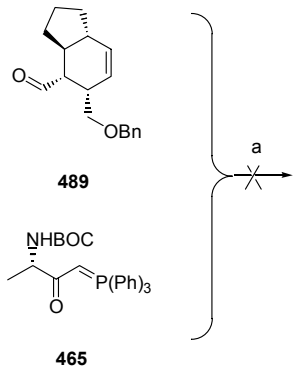
489a-2

Global energy minimum = 90.08 kJ/mol

Figure 26. Two different conformers obtained by computer-assisted molecular modeling.

4.4.2 Wittig approach

The amino alcohol fragment of amaminol A **1** was also attempted to be connected by Wittig reaction. The previously prepared phosphorane ylide **465** was reacted with cyclic aldehyde **480** in refluxing benzene. However, no reaction was observed even after 24 hours of refluxing (Scheme 98).



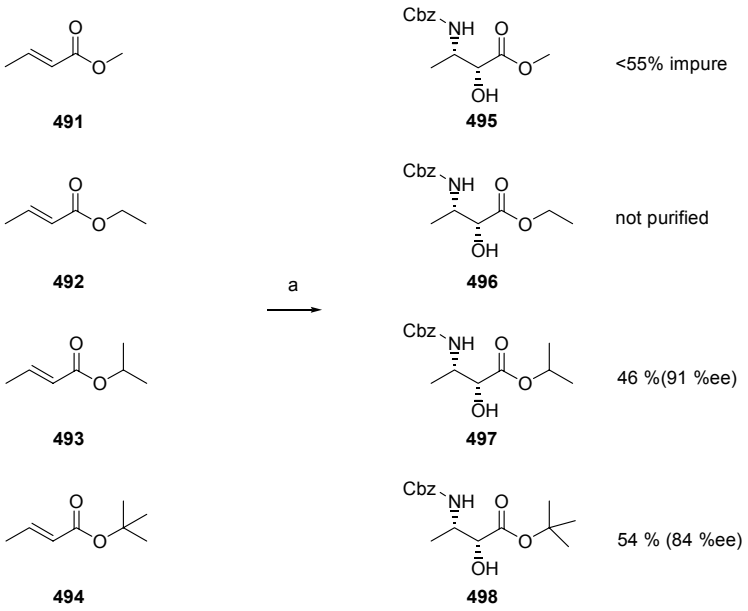
489

465

Scheme 98. Reagents and conditions: a) PhH, +90 °C, 24 h.

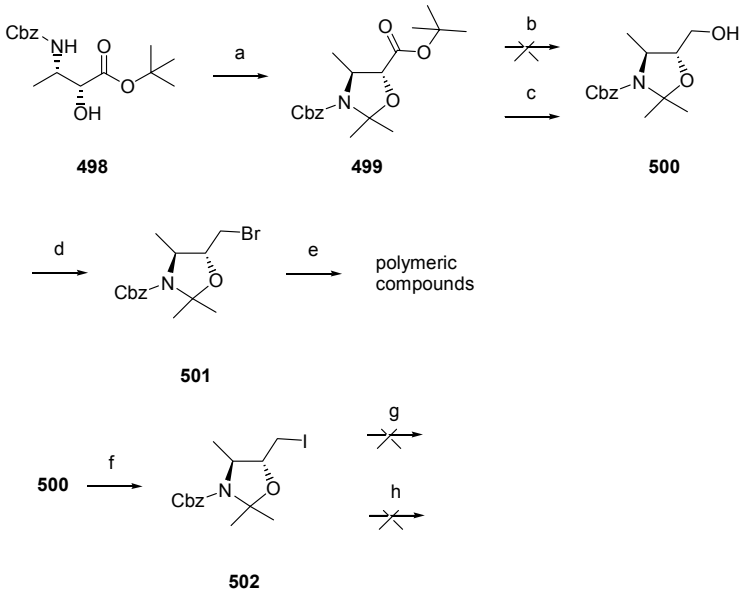
4.4.2.1 Crotonate oxyamination based approach

Another approach to the side chain of amaminol A **1** was designed based on asymmetric oxyamination of crotonic acid ester derivatives (Scheme 99). Four different crotyl esters **491-494** were subjected to Sharpless oxyamination (148). Janda *et al.* (149) have reported that *tert*-butyl crotonic ester **494** can be oxyaminated with high enantioselectivity in acetonitrile. I tried comparable reactions for **491-494** in 1-propanol/water solvent mixture, but lower yields for the products were obtained. This was assumed to be due to hydrolysis of the substrate and the product. Acetonitrile prevented these side reactions effectively and moderate yields for amino alcohol esters **495-498** were obtained. The methyl and ethyl ester products **495** and **496** were difficult to separate from the unreacted benzylcarbamate and thus yields for pure products are not reported. Isopropyl crotonate **493** afforded amino alcohol **497** with higher enantioselectivity (91 %ee), but lower yield (46 %) compared to the corresponding reaction with *t*-butyl crotonate **494**. Enantiopure amino alcohol **498** was obtained by single crystallization from ethyl acetate/hexane (1:4) with an overall yield of 39 %.



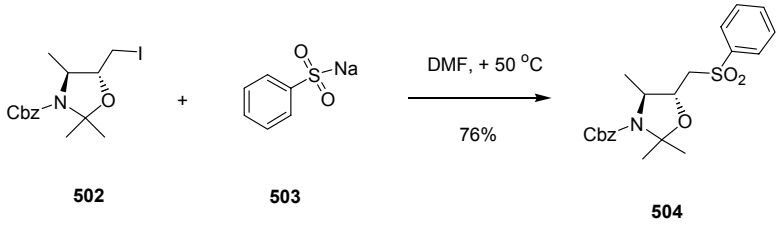
Scheme 99. Reagents and conditions: a) benzyl carbamate, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, CH_3CN-H_2O, 1,3-dichloromethylhydantoin, r.t., 30 – 60 min.

The enantiopure amino alcohol **498** was converted to oxazolidine **499** with 2,2-dimethoxypropane using *p*-toluenesulfonic acid as the catalyst (Scheme 100).(101f) The ester group was selectively reduced with lithium aluminum hydride to oxazolidine alcohol **500**. The same reaction was also attempted with diisobutylaluminum hydride, but a mixture of several products were obtained. Next, the hydroxyl group of **500** was converted to a bromine **501** by using carbontetrabromide and triphenylphosphine. The bromo derivative **501** was subjected to Arbusov reaction (103) to prepare phosphonate reagent for HWE reaction, but unfortunately the bromo derivative **501** was not electrophilic enough for the phosphonate formation. Only polymeric compounds were obtained because of the high temperature required for the reaction. The alcohol **500** was also converted to the iodo derivative **502**. The formation of the phosphorane ylide was unsuccessful from iodo oxazolidine **502**. It was assumed that more a reactive phosphine such as tributylphosphine would form a phosphine coupling reagent. However, tributyl phosphine did not react with iodo oxazolidine **502**.



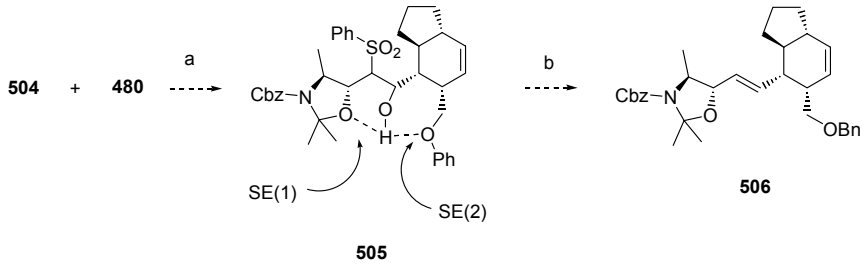
Scheme 100. Reagents and conditions: a) $(MeO)_2CMe_2$, PTSA, rfx (83 %); b) DIBAL-H, PhMe, -78 °C; c) $LiAlH_4$, THF, 0 °C; d) CBr_4, DIPEA, Ph_3P, THF, r.t. (75 % over 2 steps); e) I_2, imidazole, Ph_3P, CH_2Cl_2, r.t. (76 %); f) $(EtO)_3P$, 130-140 °C, 46 h; g) Ph_3P, PhMe, 90 °C, 36 h; h) Bu_3P, CH_3CN, 0 → 65 °C, 24 h.

A phenylsulfoxide derivative **504** was prepared by reacting the iodo oxazolidine **502** with an excess of sodium salt of phenylsulfoxide **503** in DMF. The phenylsulfoxide derivative **504** was prepared for a Julia type coupling of the amino alcohol fragment to cyclic aldehyde **480**.



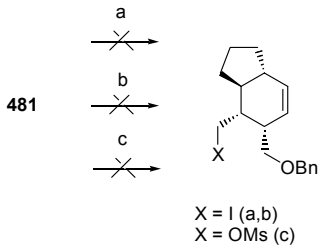
Scheme 101. Reagents and conditions: a) DMF, 50 °C (76 %).

However, the Julia coupling of **480** and **504** was not attempted, because it was assumed that the hydroxyl group of the coupling product **505** would be too hindered to be reduced to the corresponding *E*-olefin **506** with sodium amalgam (Scheme 102). The hydroxyl group of **505** was assumed to be stabilized by the free electron pairs of oxygens of the oxazolidine ring (SE(1)) and benzyloxy chain (SE(2)). Also, a chemoselective reduction of allyl alcohol in the presence of disubstituted *cis*-double bond is not reported or it is difficult to achieve according the experiment that I had performed (see Scheme 96).



Scheme 102. Reagents and conditions: a) base; b) Na/Hg.

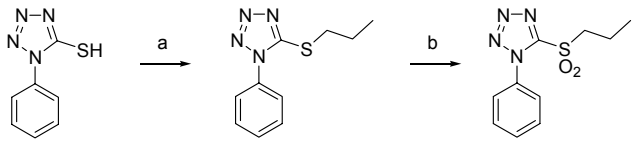
In order to prevent the interference of an intramolecularly hydrogen bonded hydroxyl group, an iodo derivative of alcohol **481** became my next goal (Scheme 103). However, substitution of hydroxyl group of **481** by iodine appeared to be difficult and the reaction was not observed even at 85-90 °C. After this, I tried to prepare the mesylate from the alcohol **481** to activate the alcohol **481** for iodine substitution, but unfortunately mesylation of the alcohol **481** was not observed at room temperature. The alcohol **481** was analyzed by IR in dry benzene and a weak peak was noticed in the region of intramolecular hydrogen-bonding. This provided evidence that the hydroxyl proton was indeed hydrogen bonded to the benzylic oxygen, which was assumed to be the reason for low reactivity of alcohol **481**. The chelated hydroxyl proton was also observed in ^{1}H NMR analysis and it appeared at δ 3.35 as an ABX pattern with coupling constants of 9.6 and 1.7 Hz. These values were obtained in deuterated chloroform solution.



Scheme 103. Reagents and conditions: a) I_2, imidazole, Ph_3P, THF, r.t.; b) I_2, imidazole, PhMe, 85-90 °C; c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, r.t.

4.5 Preparation of the olefinic side chain

I decided to prepare the olefinic side chain of amaminol A **1** by the Julia-Kocienski olefination (150). At first, propyl phenyl tetrazolyl sulfone **509** was prepared from 1-phenyl-*1H*-tetrazole-5-thiol **507** (Scheme 104). Sulfonation of propanol using the Mitsunobu protocol (151) afforded propylsulfine phenyltetrazole **508** in high yield (87 %). Finally, the coupling reagent **509** was obtained by *m*-CPBA oxidation of sulfide **508** with a good yield (83 %).

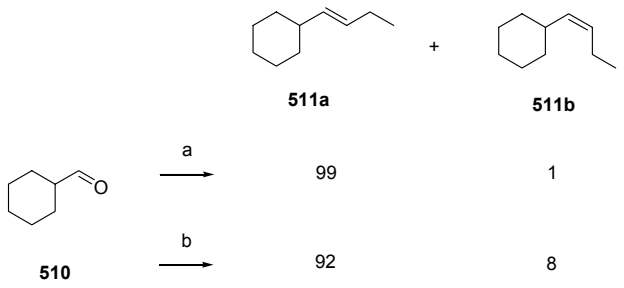


507 **508** **509**

Scheme 104. Reagents and conditions: a) 1-PrOH, Ph_3P, DEAD, 0 → r.t. (87 %); b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, r.t. (83 %).

Model reactions were conducted by reacting phenyltetrazolyl sulfone **509** with cyclohexane carboxaldehyde **510** using two different bases. The reported procedure (150b) was followed precisely. Potassium hexamethyldisilazane gave a highly *E*-selective

olefination (*E*:*Z*, >99:1, measured by ^{1}H NMR from the crude products). Sodium hexamethyldisilazane afforded also a very *E*-selective olefination (*E*:*Z*, >92:8) of carboxaldehyde **510**. The outcome of the reactions differed widely, because the products **511a,b** were highly volatile and they were easily lost during concentration of the product.

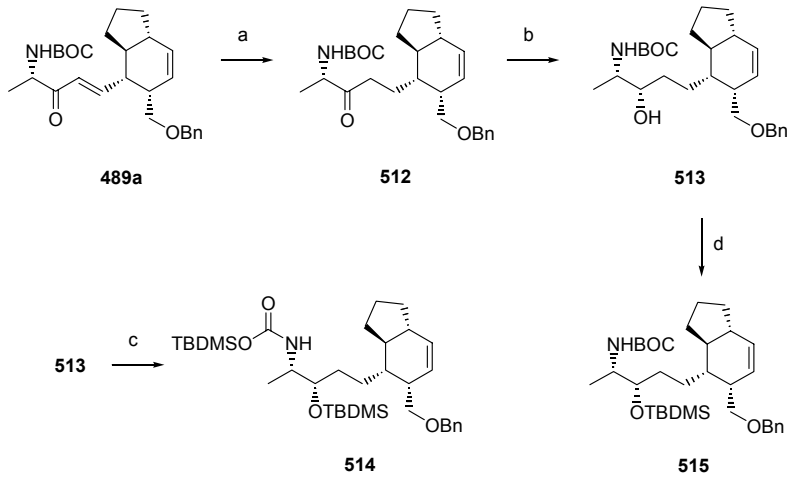


Scheme 104. Reagents and conditions: a) **509**, KHMDS, DME, -60 °C (48 %); b) 509, NaHMDS, DME, -60 °C (81 %).

4.6 Elaboration of amaminol A (1) analog

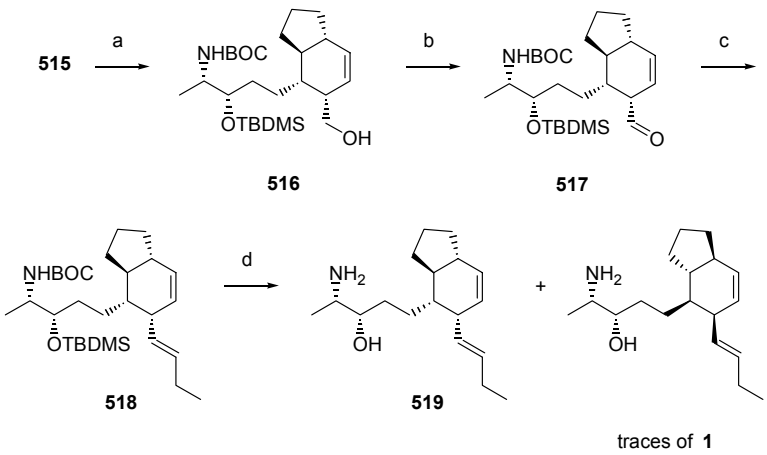
Synthesis towards amaminol A **1** and its analogues was continued by chemoselective reduction of the α-amino enone **489a** with an excess of Raney nickel W2 (152) (Scheme 105). The reaction was accompanied by isomerization of the cyclic double bond above temperatures of 0 °C. Consequently, the length of the reaction time was essential. After the reaction was complete according to TLC analysis, the reaction mixture was rapidly filtered through a pad of silica gel to avoid isomerization. Doubling of carbon signals were also noticed in the ^{13}C NMR spectra of **512** as with **489a** and this phenomenon was observed with the rest of the products after the amino fragment was connected to **480**. The ^{1}H NMR and ^{13}C NMR determinations of **512** and **513** were also performed at higher temperatures (50 °C), but no significant change was observed. After the enone **489a** was reduced to the α-amino ketone **512**, the carbonyl group was reduced with the previously

developed method including diisobutyl aluminum hydride, zinc bromide and diethyl ether. The diastereoselectivity of the reduction was high, and the (*S,R*)-diastereomer was not observed by ^{1}H NMR measurement from the crude product **513**. The same reaction was also repeated with *L*-Selectride® in ether and a mixture of diastereomers were obtained. The crude product was analyzed by ^{1}H NMR and it contained diastereomers *S,S*-**513** and *S,R* in ratio of 2:1. Attempted protection of the hydroxyl group of **513** with *tert*-butyldiphenylsilylchloride and imidazole in DMF (153) solution at 0 → 50 °C proved unsuccessful. Silyltriflates (TIPSOTf and TBDMSOTf) reacted well with amino alcohol **513** in presence of 2,6-lutidine. However, an excess of silyltriflates also lead to reaction of the BOC-group. Sakaitani and Ohfune (154) have also reported that an *N*-BOC group reacts to form *N*-silylcarbamates with 250 mol-% of TBDMSOTf and 100 mol-% of 2,6-lutidine at room temperature. Thus, formation of the *N*-silylcarbamate **514** occurred also at 0 °C, if 300 mol-% of TBDMSOTf and 350 mol-% of 2,6-lutidine were used.



Scheme 105. Reagents and conditions: a) Raney Ni W2, THF, 0 °C, 2 h, 0 °C → r.t., 15 min (89 %); b) $ZnBr_2$, Et_2O, 550 mol-% DIBAL-H, -78 °C, 1 h (85 %); c) 300 mol-% TBDMSOTf, 350 mol-% 2,6-lutidine, CH_2Cl_2, 0 °C (97 %); d) 200 mol-% TBDMSOTf, 250 mol-% 2,6-lutidine, CH_2Cl_2, 0 °C (80 %).

Cleavage of the benzyl group from **515** was attempted with borontrichloride dimethylsulfide ($BCl_3 \cdot SMe_2$) (121), but simultaneous deprotection of the silyl group was observed. Deprotection was also attempted with lithium 4,4'-di-*tert*-butylbiphenyl (LiDBBP) (155), but no reaction was observed. The unreactivity of LiDBBP may be also due to the small scale, because it was difficult to avoid moisture in the reaction mixture. Fortunately, the benzyl group of **515** was selectively removed using Birch reduction (156) (Na/NH_3) (Scheme 106). The hydroxyl group of **516** was transformed to the corresponding aldehyde **517** by Swern oxidation (157). The aldehyde **517** was subjected to the Julia-Kocienski olefination (149) with **509** to form the protected olefinic amino alcohol **518**. Simultaneous cleavage of *N*-BOC and *O*-TBDMS groups were obtained by hydrolysis with concentrated HCl in dioxane. Traces of amaminol A **1** was found from the crude product mixture **519**. This observation was due to the formation of enantiomeric product of **480** in the organocatalytic IMDA cycloaddition.



Scheme 106. Reagents and conditions: a) Na/NH_3, THF, -78 °C (56 %); b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, -78 °C, 30 min (97 %); c) **509**, KHMDS, DME, -55 → -35 → 0 °C, 5 h (70 %); d) dioxane, 32 w-% HCl, r.t., 3.5 h (58 %).

5 Summary

A new method was developed for the preparation of substituted trienes such as benzyloxy triene acid methyl ester **443**. The new method developed employs inexpensive reagents and avoids chromatographic purifications during the first steps of the synthesis.

The chiral auxiliary induced IMDA cycloaddition gave the correct diastereomer for amaminol A **1** synthesis. Difficulties were encountered in removal of the chiral oxazolidinone auxiliary from the cycloadduct **455**. Debenzylation of **455** lead to unavoidable formation of the tricyclic lactone **458**. It appeared to be difficult to activate the lactone **455** for the introduction of the side chains. The alcohol **481** was surprisingly unreactive, because of hydrogen bonding of the hydroxyl group to other side chain oxygens.

A diastereomer **519** of amaminol A **1** can be synthesized using the novel organocatalytic IMDA cycloaddition to prepare the easily modifiable intermediate aldehyde **480**. Unfortunately, the diastereomer **519** of amaminol A **1** was obtained as the final product, because the wrong enantiomer of the organocatalyst was used to prepare the aldehyde **480**. However, it may be possible to synthesize amaminol A **1** as the major product, if the IMDA cycloaddition step is catalyzed with the (*R*,*R*)-organocatalyst.

Diastereoselective reduction of α-amino ketone **485** to *syn*-amino alcohols **486a,b** by chiral reductants were found to be ineffective. However, α-amino ketone **485** can be reduced to α-amino alcohol **486a** with good diastereoselectivity using the novel reduction method employing achiral reductant (diisobutylaluminum hydride) in the presence of zinc dibromide as the coordinating agent in diethyl ether.

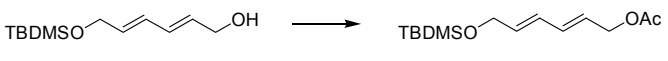
Finally, the diastereomer **519** of amaminol A **1** was synthesized in total 17 steps starting from sorbic acid **418**.

6 Experimental

General: The solvents and starting materials were used as purchased from the suppliers unless otherwise noted. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. Toluene was distilled from metallic sodium. Dichloromethane, benzene and chlorobenzene were distilled from calcium hydride. Methanol was distilled from $Mg(OMe)_2$. Ethanol was distilled from $Mg(OEt)_2$. Distilled water was filtered through Millipore filtration system. The glassware was oven-dried (>120 °C) or flame dried in an oil pump vacuum, when dry conditions were required. The reactions were performed under a positive atmosphere of argon when necessary. The NMR spectra were recorded with a Varian 400-spectrometer (^{1}H NMR, 399.99 MHz, ^{13}C NMR 100.58 MHz) and a Bruker Avance DPX400 spectrometer (^{1}H NMR, 400.13 MHz, ^{13}C NMR 100.62 MHz). Thin layer chromatography was performed on silica mesh 60 coated aluminium plates. For visualization UV light (254 nm) and ninhydrin, phosphomolybdenic acid, anisaldehyde and permanganate solutions was used. The mass spectra were determined on a JEOL JMS-DX303 apparatus (Helsinki University of Technology) and LCT, Micromass (ES+) (University of Oulu, Department of Chemistry). Flash chromatography was performed with 60 mesh silica. FTIR spectra were measured with a Perkin Elmer Spectrum One instrument. The melting points were measured with Gallenkamp MFB-595 apparatus and are not corrected. GC was performed with a Hewlett-Packard 6810 instrument using Supelco gamma-dex 120 column, 30 m, 0.25 mm, 0.25 μm film with He as the carrier gas. Gas velocity was 28 cm/sec. FID detector was used. For chiral HPLC, Daicel OD column was used (5 x 0.46 cm, 25 x 0.46 cm) with UV detection at l = 254 nm, and a flow rate 0.8 mL/min, unless otherwise noted. The eluent was a mixture of isopropanol and hexane.

6.1 Preparation of triene derivatives

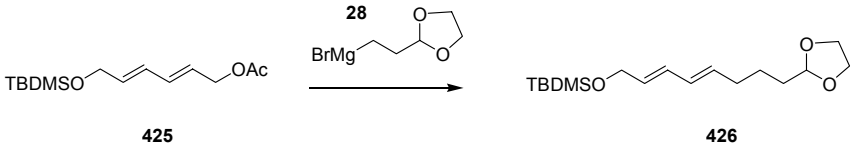
6.1.1 Acetic acid 6-(*tert*-butyl-dimethyl-silanyloxy)-hexa-2*E*,4*E*-dienyl ester (425)



520 **425**

Dry pyridine (8.70 g, 111 mmol, 1000 mol-%) was added into the reaction flask which contained 6-(*tert*-Butyldimethylsilanyloxy)-hexa-2,4-dien-1-ol **520** (2.53 g, 11.1 mmol, 100 mol-%). Acetic anhydride (11.23 g, 111 mmol, 1000 mol-%) was added, which resulted in the formation of an orange solution. After stirring for 3 hours, excess pyridine and acetic anhydride (9.6 mL) were evaporated (15-17 mmHg/40-45 °C). The mixture was cooled and diluted with ether (100 mL) and washed twice with an ice cold solution of 0.5 M H_3PO_4 (50 mL). The water layer was back extracted with ether (20 mL). The combined organic layers were washed again with an ice cold solution of 0.5 M H_3PO_4 (50 mL), twice with a 5 w-% solution of $NaHCO_3$ (50 mL) and brine (20 mL). The combined water layers from $NaHCO_3$ washes were extracted with ether (50 mL). The layers were separated and the organic layer was washed with brine (20 mL). The combined organic layers were dried with Na_2SO_4 and filtered. The solvents were evaporated to give 3.84 g of crude product. The crude product was purified by flash chromatography (5% EtOAc/C_6) to give **425** (2.65 g, 88 %). R_f (15 % EtOAc/C_6, *E,E*-**2**) = 0.49. ^{1}H NMR ($CDCl_3$, 399.99 MHz) δ 6.27 (m, 2H), 5.81 (dt, 1H, *J* = 14.4, 4.4 Hz), 5.73 (m, 1H), 4.59 (d, 2H, *J* = 6.8 Hz), 4.23 (d, 2H, *J* = 4.2 Hz), 2.07 (s, 3H), 0.91 (m, 9H), 0.07 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.59 MHz) δ 171.4, 135.0, 134.6, 129.0, 126.5, 65.4, 63.9, 26.6, 21.6, 19.1, -4.6. FT-IR (thin film) 2956, 2931, 2858, 1744, 1381, 1362, 1232, 1127, 1093, 960, 837, 777 cm^{-1}. HRMS (EI) calculated for [M-CH_3COO] $C_{12}H_{23}OSi$: 211.1518, found 211.1535.

6.1.2 2-(8-(*tert*-Butyldimethylsilanyloxy)-octa-4*E*,6*E*-diene))-1,3-dioxolane (426)

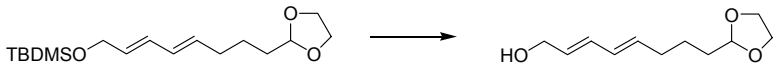


425 426

2-(2-Bromoethyl)-1,3-dioxolane (1.19 g, 6.58 mmol, 205 mol-%) was dissolved in dry THF (9.5 mL) and added in small portions into a flask equipped with a reflux condenser, which contained magnesium chips (0.26 g, 10.6 mmol, 330 mol-%). Heat generation was noticed during the addition and the mixture was stirred for 1 hour. In a separate 2-neck flask equipped with an argon balloon, 1-(*tert*-Butyldimethylsilanyloxy)-hexa-2*E*,4*E*-diene-6-acetate **425** (0.87 g, 3.2 mmol, 100 mol-%) was dissolved in dry THF (4.5 mL).. A 0.1 M solution of Li_2CuCl_4 in THF (1.44 mL, 0.14 mmol, 4.5 mmol-%) was added and the resulting mixture was immersed in a cooling bath (acetone/ice) at –15 °C. The freshly prepared Grignard solution from above was added dropwise with a syringe into the orange reaction mixture. The colors of the reaction mixture changed during the addition in a following sequence: orange-brown-green-yellow/green-brown-purple red. The reaction was followed by TLC (20 % MTBE/hexane, PMA). After the addition, which took 45 minutes, the purple solution was immersed in an ice bath for 2.5 hours. At this time period, the reaction mixture turned yellowish. The reaction mixture was diluted with ether (25 mL) and washed with a saturated solution of NH_4Cl (2 x 10 mL). pH of the NH_4Cl solution was adjusted to 10 with NH_4OH before washings. The layers were separated and the water layer was extracted three times with ether (30, 20, 10 mL). The organic layer was separated and dried with Na_2SO_4 overnight. The organic layer was filtered and the solvents were evaporated to give 1.09 g of yellow liquid. The crude product was purified by a gradient flash chromatography (5 %, 10 %, 100 % MTBE/ hexane) to give **426** (0.55 g, 55 %) as a clear oil. R_f (20 % MTBE/ hexane) = 0.28. ^{1}H NMR ($CDCl_3$/TMS, 399.99 MHz) δ 6.21-6.01 (m, 2 H), 5.68-5.61 (m, 2 H), 4.85 (t, 1 H, *J* = 4.8 Hz), 4.19 (d, 2 H, *J* = 5.2 Hz), 3.98-3.92 (m, 2 H), 3.89-3.83 (m, 2 H), 2.11 (q, 2 H, *J* = 7.2 Hz), 1.70-1.64 (m, 2 H), 1.56-1.49 (m, 2 H), 0.92-0.88 (m, 9 H), 0.08 – 0.06

(m, 6 H). ^{13}C NMR ($CDCl_3$, 100.59 MHz) δ 134.4, 131.1, 130.9, 130.8, 105.2, 65.5, 64.3, 34.0, 33.1, 26.7, 24.3, 19.1, -4.8. LRMS (EI) 312, 255, 211, 173, 137, 119, 93, 75, 73 (100). HRMS (EI) calculated for $C_{17}H_{32}O_3Si$: 312.2121, found 312.2029.

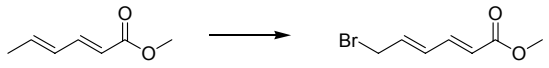
6.1.3 2-(Octa-4*E*,6*E*-dien-8-ol)-1,3-dioxolane (427)



426 **427**

2-(8-(*tert*-Butyldimethylsilanyloxy)-octa-*4E,6E*-diene)-1,3-dioxolane **426** (0.13 g, 0.41 mmol, 100 mol-%) was dissolved in acetone (7.5 mL). *para*-Toluenesulfonic acid monohydrate (12 mg, 0.06 mmol, 15 mol-%) and H_2O (0.2 mL) were added to the mixture. The mixture was stirred at room temperature and followed by TLC (30 % MTBE/hexane, PMA). Stirring was continued for 35 minutes until the starting material had disappeared. An ice cold solution of $NaHCO_3$ (5 mL) was added and stirring was continued for 5 minutes. The product was diluted with ether (35 mL). The layers were separated and the water layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL). The organic layer was dried with $MgSO_4$ for 30 minutes and the solvents were evaporated to give 0.125 g of clear oil. The crude product was purified by flash chromatography (25 % EtOAc/hexane) to yield **427** (60 mg, 74%) as a clear oil. R_f (50% EtOAc/hexane) = 0.27. ^{1}H NMR ($CDCl_3$/TMS, 399.99 MHz) δ 6.22-6.05 (m, 2 H), 5.75-5.67 (m, 2 H), 4.86 (t, 1 H, *J* = 4.7 Hz), 4.16 (d, 2 H, *J* = 5.3 Hz), 3.97-3.95 (m, 2 H), 3.86-3.83 (m, 2 H), 2.14 (q, 2 H, *J* = 7.0 Hz), 1.67-1.64 (m, 2 H), 1.57-1.49 (m, 2 H), 1.40 (s, 1 H). ^{13}C NMR ($CDCl_3$, 100.59 MHz) δ 135.3, 132.3, 130.3, 130.1, 104.8, 65.3, 63.9, 33.7, 32.8, 23.9. LRMS (EI) 198, 181, 167, 110, 99, 82, 73(100), 55. HRMS (EI) calculated for $C_{11}H_{18}O_3$: 198.1256, found 198.1256.

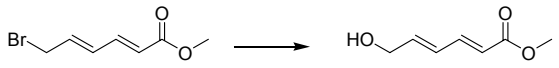
6.1.4 Methyl 6-bromohexa-2*E*,4*E*-dienoate (429)



428 **429**

Methyl sorbate **428** (3.16 g, 25 mmol, 100 mol-%) was dissolved in chlorobenzene (21 mL) in an oven dried. flask. *N*-Bromosuccinimide (NBS) (4.63 g, 26 mmol, 104 mol-%) was added into the reaction mixture. The reaction flask was equipped with a reflux condenser and was warmed in an oil bath (110 °C) for 15 minutes and benzoyl peroxide (0.28 g, 1.2 mmol, 4.6 mol-%) was added in a small portions. The oil bath temperature was raised to 150 °C and the reaction mixture was stirred vigorously. The reaction was followed by TLC (60 % MTBE/hexane). At 135 °C, NBS dissolved totally into the yellow reaction mixture. After 1 hour at 150 °C (oil bath temperature), the reaction mixture had changed to brown. After 2 hours, the reaction mixture was allowed to cool to room temperature. The reaction was not complete by TLC. Chlorobenzene was evaporated (15 mmHg/45-50 °C). Some of the product had evaporated with chlorobenzene. Chlorobenzene, which contained some product was mixed with the rest of the product mixture. Ether (100 mL) was added and the mixture was washed with a 5 w-% NaOH solution (10 x 20 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated by evaporation. Chlorobenzene was distilled from the crude product under reduced pressure (30-32 °C/12-14 mmHg). The crude product was analyzed by ^{1}H NMR. The ratio of compounds (6-bromo **429**: *anti*-dibromo **430**:*syn*-dibromo **431**:methyl sorbate **428**) was (5.23 : 1.64 : 1 : 2.89). The impure product fractions were combined to give 2.85 g of yellow oil (70-100 °C/0.2 mmHg). R_f **429** (30% MTBE/C_6) = 0.43. ^{1}H NMR of **429** ($CDCl_3$/TMS, 400.13 MHz) δ 7.27 (dd, 1 H, *J* = 15.6, 10.8 Hz), 6.43-6.36 (m, 1 H), 6.28-6.22 (m, 1 H), 5.94 (d, 1 H, *J* = 15.5 Hz), 3.76 (s, 3 H). LRMS (EI) 205, 173, 147, 125, 111, 93, 79, 66 (100). Ref: (108)

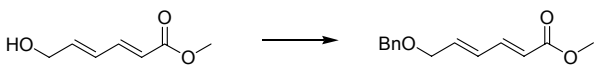
6.1.5 Methyl 6-hydroxyhexa-2*E*,4*E*-dienoate (435)



429 **435**

Impure methyl 6-bromohexa-2E,4E-dienoate **429** 12 (0.92 g) was dissolved in acetone (12 mL) and a saturated solution of $NaHCO_3$ (8 mL) was added. A yellowish slurry was formed. The reaction flask was equipped with a reflux condenser and a magnetic stirring bar. The reaction mixture was refluxed until TLC (30 % MTBE/hexane) showed the absence of the starting material. Refluxing was continued for 3 hours and 3 drops of 5 w-% HCl solution was added to neutralize the mixture. Acetone was evaporated and 20 mL of EtOAc was added. The layers didn't separate and thus H_2O (5 mL) was added. The layers were separated and the water layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (2 x 15 mL), dried overnight with Na_2SO_4, filtered and concentrated to give 0.45 g of yellow oil. The crude product was purified by a flash chromatography (25% EtOAc/hexane) to yield a white solid (0.27 g, 42 %). Mp. = 56-58 °C. R_f (50% EtOAc/hexane) = 0.20. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.34-7.27 (m, 1 H), 6.46-6.39 (m, 1 H), 6.27-6.21 (m, 1 H), 5.90 (d, 1 H, *J* = 16.0 Hz), 4.31 (d, 2 H, *J* = 4.0 Hz), 3.77 (s, 3 H), 1.7 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 168.1, 144.6, 141.8, 128.4, 121.6, 63.3, 52.3. LRMS (EI) 142, 113, 98, 81(100), 55. Ref: (108) mp. = 52-54 °C.

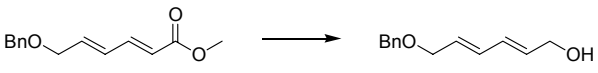
6.1.6 6-Benzyloxy-hexa-2*E*,4*E*-dienoic acid methyl ester (437)



435 **437**

Benzyl alcohol (0.649 g, 6.00 mmol, 536 mol-%) was dissolved in dry CH_2Cl_2 (5 mL) in a dry argon flushed flask and 2,6-dimethylpyridine (0.643 g, 6.00 mmol, 536 mol-%) was added. A second dry argon flushed flask was charged with methyl 6-hydroxyhexa-*2E,4E*-dienoate **435** (0.160 g, 1.12 mmol, 100 mol-%), dry CH_2Cl_2 (9 mL) and 2,6-dimethylpyridine (0.484 g, 4.52 mmol, 404 mol-%). A third dry argon flushed flask was charged with dry CH_2Cl_2 (15 mL) and trifluoromethanesulfonic anhydride (1.693 g, 6.00 mmol, 536 mol-%). The third flask was cooled to –78 °C with a cooling bath (acetone/CO_2(s)). After this, the contents of the first flask were transferred into the cooled flask dropwise. The addition took 10 minutes and the reaction was followed by TLC (50 % EtOAc/hexane). Stirring was continued for 25 minutes and the reagents from the second flask were transferred dropwise into the reaction mixture. The addition took 15 minutes. Stirring was continued for 40 minutes at -78 °C and then the reaction mixture was immersed into a cooling bath at – 25 °C (ethylene glycol/CO_2). After stirring for 1.5 hours, pyridine (2 mL) was added followed by H_2O (10 mL). The organic layer was washed with H_2O (2 x 10 mL). The organic phase was stored in a refrigerator over weekend. The organic phase was dried with Na_2SO_4, filtered and concentrated to give 2.62 g of yellow oil. The crude product was purified by flash chromatography (5 % EtOAc/hexane) to give **437** (0.244 g, 93%) as a clear oil. R_f (25% EtOAc/hexane) = 0.35. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.36 (m, 6 H), 6.46-6.39 (m, 1 H), 6.22-6.15 (m, 1 H), 5.89 (dt, 1 H, *J* = 15.4, 0.7 Hz), 4.55 (s, 2 H), 4.14 (dd, 2 H, *J* = 5.2, 1.6 Hz), 3.75 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 168.1, 144.7, 139.4, 138.5, 129.8, 129.1, 128.5, 128.4, 121.7, 73.3, 70.3, 52.2. Ref: (108).

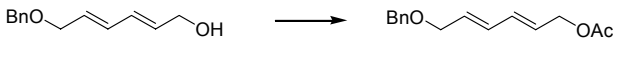
6.1.7 1-Benzyloxy-6-hydroxyhexa-2*E*,4*E*-diene (438)



437 **438**

Methyl 6-benzyloxyhexa-*2E,4E*-dienoate **437** (8.15 g, 35.1 mmol, 100 mol-%) was dissolved in dry toluene (250 mL) and the resulting mixture was cooled to –75 °C (ethyl acetate/N_2). A 1 M solution of diisobutylaluminum hydride in toluene (110 mL, 110 mmol, 314 mol-%) was added dropwise in portions (30 mL) to keep the inside temperature between –70 – 75 °C. After stirring for 10 minutes, acetone (6 mL) and MeOH (2 mL) were added to quench the reaction. The reaction mixture was poured into a beaker, which contained 1 M solution of HCl (300 mL) The mixture was stirred for 15 minutes. The layers were separated and the water layer was extracted with ether (3 x 200 mL). The combined organic layers were washed twice with brine (150, 100 mL), dried with Na_2SO_4 and filtered. The solvents were evaporated to give 7.7 g of clear oil. The crude product was purified by flash chromatography (20% EtOAc/hexane) to yield **438** (0.80 g, 80%) as a clear oil. R_f (25% EtOAc/hexane) = 0.11. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.35 – 7.26 (m, 5 H), 6.32-6.23 (m, 2 H), 5.87-5.78 (m, 2 H), 4.52 (s, 2 H), 4.18 (t, 2 H, *J* = 5.5 Hz), 4.06 (d, 2 H, *J* = 5.4 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 138.9, 133.1, 132.6, 131.2, 130.6, 129.1, 128.4, 128.3, 72.8, 70.9, 63.9. LRMS (EI) 204, 186, 169, 160, 130, 107, 97, 83(100), 69, 55. HRMS (EI) calculated for $C_{13}H_{16}O_2$: 204.1150, found 204.1166.

6.1.8 1-Acetoxy-6-benzyloxyhexa-2*E*,4*E*-diene (439)

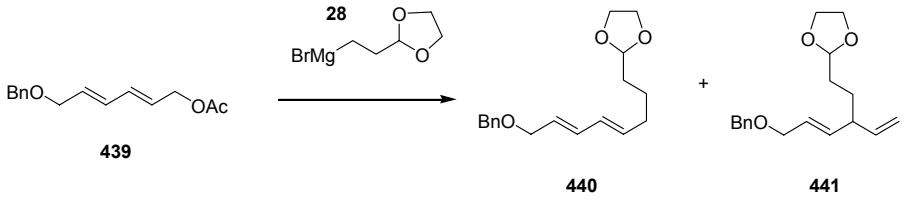


438 **439**

1-Benzyloxy-6-hydroxyhexa-*2E,4E*-diene **438** (0.71 g, 3.5 mmol, 100 mol-%) was dissolved in pyridine (2.75 g, 34.7 mmol, 1000 mol-%) and acetic anhydride (3.54 g, 34.7 mmol, 1000 mol-%) was added. The orange reaction mixture was followed by TLC (50 % EtOAc/hexane) and stirred for 2 hours. Excess pyridine and acetic anhydride was

distilled from the reaction mixture (24-40 °C/9-10 mmHg). The distillation residue was diluted with ether (30 mL) and washed with a 0.5 M solution of H_3PO_4 (15 mL). The layers were separated and the water layer was extracted with ether (10 mL). The combined organic layers were washed with brine (10 mL), dried with Na_2SO_4 and filtered. The evaporation of the solvents gave 1.0 g of yellow oil. The crude product was purified by flash chromatography (10% EtOAc/hexane) to give **439** (0.78 g, 91%) as a clear oil. R_f (50% EtOAc/hexane) = 0.57. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.28-7.26 (m, 5 H), 6.34-6.24 (m, 2 H), 5.88-5.73 (m, 2 H), 4.60 (d, 2 H, *J* = 6.2 Hz), 4.52 (s, 2 H), 4.07 (d, 2 H, *J* = 5.5 Hz), 2.07 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 171.4, 138.9, 134.2, 132.0, 131.9, 129.1, 128.4, 128.3, 127.5, 72.9, 70.8, 65.3, 21.6. LRMS (EI) 246, 235, 220, 202, 168, 155, 142, 130, 108, 91, 79, 67(100), 51. HRMS (EI) calculated for $C_{15}H_{18}O_3$: 246.1256, found 246.1258.

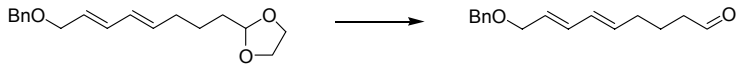
6.1.9 2-(8-Benzyloxyocta-4*E*,6*E*-diene)-1,3-dioxolane (440)



Grignard reagent **28** was prepared as follows. 2-(2-Bromoethyl)-1,3-dioxolane **28** (1.12 g, 6.19 mmol, 205 mol-%) was diluted with dry THF (9 mL). This mixture was added into a flask equipped with a reflux condenser, which contained magnesium chips (0.24 g, 9.97 mmol, 330 mol-%). The addition was done in portions to avoid over boiling of THF. Stirring was continued for 60 minutes. 1-Acetoxy-6-benzyloxyhexa-*2E,4E*-diene **439** (0.74 g, 3.02 mmol, 100 mol-%) was dissolved in dry THF (4 mL) and a 0.1 M solution of Li_2CuCl_4 (1.4 mL, 0.14 mmol, 4.5 mol-%) in THF was added. This resulted formation of orange mixture. The Grignard reagent was added in portions into the reaction flask.

The color of the reaction mixture changed in the following order: orange-brown-green-yellow-brown-purple. The addition took 35 minutes. The reaction was followed by TLC (50 % EtOAc/hexane). The reaction mixture was immersed in an ice bath. Stirring was continued for 1.5 hours and after this, the reaction mixture was allowed to warm to r.t. Stirring was continued for 14 hours and the reaction mixture was diluted with ether (25 mL). The mixture was washed with a saturated solution of NH_4Cl (2 x 10 mL), which was made basic (pH ≈ 8) with NH_4OH before use. The combined water layers were extracted once with ether (20 mL). The combined organic layers were washed with brine (15 mL), dried with Na_2SO_4 and filtered to give 1.0 g of yellowish oil. The crude product was purified by flash chromatography (10 % MTBE/hexane) to yield **440**/**441** (0.57 g, 65%) as a clear oil. The ratio of **440**/**441** was (84:16). The products **440**/**441** were inseparable by flash chromatography. R_f **440**/**441** (20% MTBE/hexane) = 0.25. ^{1}H NMR **440** ($CDCl_3$/TMS, 400.13 MHz) δ 7.35-7.26 (m, 6 H), 6.23 (dd, 1 H, *J* = 14.8, 10.4 Hz), 6.07 (dd, 1 H, *J* = 14.7, 10.2 Hz), 5.69 (dt, 2 H, *J* = 14.7, 7.0 Hz), 4.86 (t, 1 H, *J* = 4.6 Hz), 4.51 (s, 2 H), 4.04 (d, 2 H, *J* = 6.6 Hz), 3.96-3.94 (m, 2 H), 3.86-3.83 (m, 2 H), 2.14 (q, 2 H, *J* = 7.5 Hz), 1.70-1.64 (m, 2 H), 1.57-1.49 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 139.1, 135.5, 134.0, 130.7, 129.0, 128.5, 128.2, 127.9, 105.1, 72.6, 71.2, 65.5, 34.0, 33.1, 24.2. LRMS (EI) 287, 197, 181, 153, 99, 91(100), 73, 65, 51. HMRS (EI+) calculated for $C_{18}H_{24}O_3Na$: 311.1628, found 311.1623.

6.1.10 9-Benzyloxynona-5*E*,7*E*-dien-1-al (442)

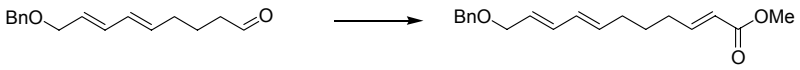


440 **442**

2-(8-Benzyloxyocta-*4E,6E*-diene)-1,3-dioxolane mixture **440**/**441** (2.49 g, 8.64 mmol, 100 mol-%) was dissolved in acetone (150 mL) and a 0.5 M solution of HCl (150 mL) was added. The reaction mixture was stirred for 17 hours at r.t. The reaction was followed by TLC (40 % MTBE/hexane, ninhydrin) and a small samples were worked up

and analyzed by ^{1}H NMR during the reaction. The mixture was diluted with ether (200 mL) and the layers were separated. The water phase was extracted with ether (100, 50 mL). The combined organic phases were washed with brine (150 mL), dried with $MgSO_4$, filtered and concentrated to give 2.7 g of the product as an oil. The crude product was purified by flash chromatography (13 % MTBE/hexane) to yield **442** (1.84 g, 87 %) as a clear oil. R_f (40 % MTBE/hexane) = 0.34. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 9.78 (s, 1 H), 7.35-7.33 (m, 5 H), 7.29-7.25 (m, 1 H), 6.95 (dt, 1 H, *J* = 15.7, 7.0 Hz), 6.23 (dd, 1 H, *J* = 15.2, 10.4 Hz), 6.06 (dd, 1H, *J* = 15.0, 10.4 Hz), 5.82 (dt, 1 H, *J* = 15.5, 1.6 Hz), 5.72-5.62 (m, 2 H), 4.51 (s, 2 H), 4.04 (d, 2 H, *J* = 6.3 Hz), 3.72 (s, 3 H), 2.20 (qd, 2 H, *J* = 7.2, 1.5 Hz), 2.11 (q, 2 H, *J* = 7.0 Hz), 1.56 (q, 2 H, *J* = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 203.0, 139.0, 134.3, 133.5, 131.4, 129.1, 128.5, 128.4, 128.3, 72.7, 71.1, 43.8, 32.5, 22.2. LRMS (EI+) 244, 200, 181, 170, 153, 135, 107, 91, 81(100), 65. HRMS (EI+) calculated for $C_{16}H_{20}O_2$: 244.1463, found 244.1468.

6.1.11 11-Benzyloxyundeca-2*E*,7*E*,9*E*-triene methyl ester (443)

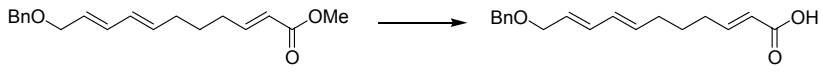


442 **443**

9-Benzyloxynona-*5E,7E*-dien-1-al **442** (133 mg, 0.55 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (2 mL) and methyl (tri-phenyl-phosphoranylidene) (195 mg, 0.58 mmol, 105 mol-%) was added The reaction was followed by TLC (40 % MTBE/hexane, PMA). The reaction mixture was stirred for 21 hours at r.t. At this point, a second portion of methyl (tri-phenyl-phosphoranylidene) (18 mg, 0.055 mmol, 10 mol-%) was added. Stirring was continued for 2 hours and the mixture was diluted with CH_2Cl_2 (10 mL). The mixture was washed with brine (5 mL) and the layers were separated. The water layer was extracted once with EtOAc (5 mL) and the combined organics were dried with Na_2SO_4, filtered and the solvents were evaporated to give 161 mg of yellow oil. Hexane

(5 mL) was added and the mixture was stirred vigorously for 30 minutes. The white precipitate was filtered and washed with hexane (2 x 5 mL). The solvents were evaporated to give 161 mg of clear oil. The crude product was purified by flash chromatography (7 % MTBE/hexane) to yield **443** (33 mg, 80 %) as a clear oil. R_f (50 % MTBE/hexane) = 0.51. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.34-7.26 (m, 5 H), 6.23 (dd, 1 H, *J* = 15.2, 10.6 Hz), 6.07 (dd, 1 H, *J* = 15.0, 10.6 Hz), 5.66 (m, 2 H), 4.51 (s, 2 H), 4.04 (d, 2 H, *J* = 6.2 Hz), 2.44 (td, 2 H, *J* = 7.4, 1.7 Hz), 2.14 (q, 2 H, *J* = 7.2 Hz), 1.74 (q, 2 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 167.5, 149.5, 138.8, 134.5, 133.4, 130.7, 128.8, 128.2, 121.6, 72.6, 71.0, 51.8, 32.3, 32.0, 28.3, 27.3, 23.1. LRMS (EI+) 299 (M-1), 209, 181, 165, 136, 105, 91(100), 81, 67, 55. HRMS (EI+) calculated for $C_{19}H_{24}O_3$: 300.1726, found (M-1) 299.1733. The yield of 2*Z*,7*E*,9*E*-isomer of the product was 11 mg (6%).

6.1.12 11-Benzyloxyundeca-2*E*,7*E*,9*E*-triene acid (444)

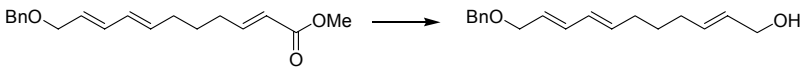


443 **444**

11-Benzyloxyundeca-*2E,7E,9E*-triene methyl ester **443** (133 mg, 0.44 mmol, 100 mol-%) was dissolved in THF (2 mL) and a 1 M solution of NaOH (7 mL) was added. The reaction was followed by TLC (40% MTBE/hexane, PMA). The reaction mixture was stirred for 16 hours at r.t. After this, the reaction mixture was immersed in an oil bath to 60-70 ^{o}C. Stirring was continued for 3 hours and the mixture was diluted with ether (10 mL). The layers were separated and the water layer was extracted with ether (20 mL). The aqueous layer was acidified with 5 M HCl until the pH was 1-2. The aqueous was extracted with CH_2Cl_2 (2 x 10 mL). The combined organics were dried with Na_2SO_4. Na_2SO_4 was filtered and the solvents were evaporated to give **444** (97 mg, 77%) as a yellow oil. R_f (50% EtOAc/hexane) = 0.18. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.35-

7.26 (m, 5 H), 7.06 (dt, 1 H, *J* = 15.7, 6.8 Hz), 6.23 (dd, 1 H, *J* = 14.7, 10.4 Hz), 6.07 (dd, 1 H, *J* = 15.0, 10.8 Hz), 5.83 (dt, 1 H, *J* = 15.7, 1.5 Hz), 5.74-5.62 (m, 2 H), 4.51 (s, 2 H), 4.05 (dd, 2 H, *J* = 6.2, 0.9 Hz), 2.25 (qd, 2 H, *J* = 7.2, 1.6 Hz), 2.13 (q, 2 H, *J* = 7.2 Hz), 1.58 (q, 2 H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 172.4, 152.4, 134.7, 133.7, 131.1, 129.0, 128.3, 121.6, 72.8, 71.1, 32.6, 32.3, 28.0. LRMS (EI+) 285 (M-1), 195, 181, 165, 141, 119, 105, 91(100), 79, 67, 55. HRMS (EI+) calculated for $C_{18}H_{22}O_3$: 286.1569, found 286.1572.

6.1.13 11-Benzyloxy-undeca-2*E*,7*E*,9*E*-trien-1-ol (469)

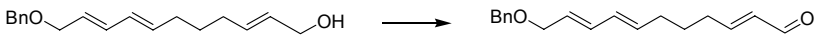


443 **469**

11-Benzyloxy-undeca-2,7,9-trienoic acid methyl ester **443** (0.352 g, 1.17 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (10 mL) and cooled to – 78 °C. DIBAL-H (3.6 mL, 3.60 mmol, 308 mol-%) was added dropwise. Stirring was continued for 70 minutes and MeOH (1 mL) was added to quench the reaction. The mixture was allowed to warm to 0 °C. After 10 minutes of stirring, a 1 M solution of HCl (10 mL) was added and stirring was continued at room temperature for 30 minutes. The layers were separated and the water layer was extracted with ether (3 x 10 mL). The combined organics were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated to give 0.332 g of **469** as a clear oil. The product was was pure enough for the next reaction. R_f (40 % MTBE in hexanes) = 0.16. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.34 – 7.26 (m, 7 H), 6.23 (dd, 1 H, *J* = 15.0, 10.5 Hz), 6.06 (dd, 1 H, *J* = 15.1, 11.0 Hz), 5.72 – 5.65 (m, 4 H), 4.51 (s, 2 H), 4.09 (br s, 2 H), 4.04 (d, 2 H, *J* = 6.3 Hz), 2.13 – 2.03 (m, 4 H), 1.52 – 1.45 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 139.0, 135.6, 134.0, 133.5, 130.6, 130.0, 129.0, 128.4, 128.2, 127.8, 72.7, 71.2, 64.4, 32.7, 32.3, 29.3. LRMS (EI+) 271 (M-1), 197, 181, 165,

129, 119, 105, 91(100), 79, 67, 55. HRMS (EI+) calculated for $C_{18}H_{24}O_2$: 272.1776, found 272.1786.

6.1.14 11-Benzyloxy-undeca-2*E*,7*E*,9*E*-trienal (470)

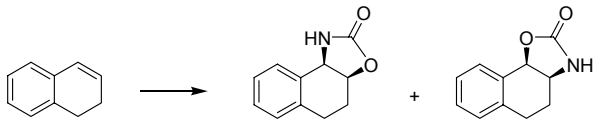


469 **470**

Crude 11-Benzyloxy-undeca-2,7,9-trien-1-ol **469** (0.313 g, 1.15 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (20 mL) and MnO_2 (0.600 g, 6.9 mmol, 600 mol-%) was added. Stirring was continued for 15 hours and a second portion of MnO_2 (0.102 g, 1.17 mmol, 102 mol-%) was added. Stirring was continued for 3.5 hours and a third portion of MnO_2 (0.298 g, 3.43 mmol, 298 mol-%) was added. Stirring was continued for 5 hours and the reaction mixture was filtered through a thin pad of Celite. The product was concentrated to give 0.461 g of yellowish oil. The crude product was purified by flash chromatography (14 % MTBE/hexane) to yield **470** (0.264 g, 89 % over 2 steps) as a clear oil. R_f (40 % MTBE in hexanes) = 0.22. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ) 9.51 (d, 1 H, *J* = 7.8 Hz), 7.35 – 7.26 (m, 5 H), 6.83 (dt, 1 H, *J* = 15.6, 6.8 Hz), 6.24 (dd, 1 H, *J* = 14.8, 10.8 Hz), 6.15 – 6.04 (m, 2 H), 5.75 – 5.61 (m, 2 H), 4.51 (s, 2 H), 4.05 (d, 2 H, *J* = 6.0 Hz), 2.34 (qd, 2 H, *J* = 7.3, 1.4 Hz), 2.15 (q, 2 H, *J* = 7.3 Hz), 1.62 (q, 2 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 194.7, 158.9, 140.8, 139.0, 136.0, 134.4, 133.8, 133.5, 131.2, 129.0, 128.3, 72.7, 71.1, 32.7, 32.6, 28.0. LRMS (EI+) 270, 180, 105, 91(100), 79, 65. HRMS (EI+) calculated for [M-43] 227.1435, found 227.1491.

6.2 Chiral auxiliary induced preparation of bicyclo[4.3.0]nonene derivatives and their reactions

6.2.1 (3a*R*',9b*S*')-3a,4,5,9b-Tetrahydro-1*H*-naphtho[1,2-*d*]oxazol-2-one (449)

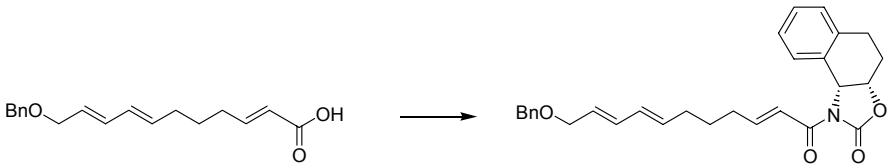


446 **449** **450**

Urethane (0.552 g, 6.2 mmol, 310 mol-%) was dissolved in 1-PrOH (8 mL). NaOH (0.244 g, 6.1 mmol, 305 mol-%) in H_2O (15 mL) was added, which was followed by *t*-BuOCl (0.669 g, 6.1 mmol, 305 mol-%) and H_2O (5 mL). After 5 minutes of stirring, the reaction mixture was immersed in an ice bath and $(DHQD)_2PHAL$ (83 mg, 0.1 mmol, 5 mol-%) in 1-PrOH (7 mL) was added. The reaction mixture was homogeneous at this point. 1,2-Dihydronaphthalene **446** (0.262 g, 2.0 mmol, 100 mol-%) in 1-PrOH (5 mL) was added to the reaction mixture. This was followed by $K_2OsO_2(OH)_4$ (31 mg, 0.08 mmol, 4 mol-%). The reaction was followed by TLC (25 % EtOAc/hexane). At first, the reaction mixture was green. After 1.5 hours of stirring, the reaction mixture was taken to r.t. After 30 minutes of stirring, the color of the mixture turned to yellow and the complete formation of amino alcohols were noticed by TLC. After 2 hours and 15 minutes of stirring, NaOH (0.318 g, 7.8 mmol, 390 mol-%) was added. This resulted in a slow formation of black/brown mixture. After 4.5 hours of stirring, the amino alcohols had disappeared and the reaction mixture was red. H_2O (20 mL) was added and the mixture was extracted with EtOAc (3 x 20, 15 mL). The combined organic layers were washed with brine (50 mL), dried with $MgSO_4$ and filtered. The solvents were evaporated to give 0.79 g of brown oil. The crude product was purified by flash chromatography (50 % EtOAc/hexane) to yield **449** (0.205 g, 54%, 78 %ee) and **450** (0.134 g, 37%, 79 %ee). A part of the product **449** (76 mg) was recrystallized from boiling CH_2Cl_2 (3 mL) to yield

449 (41 mg, 54%, >99 %ee). Mp. 182-186 °C. $[\alpha]_D^{20}$ = -217.9 (c 0.94 , $CHCl_3$). The HPLC retention times were (**449**) = 21.2 min and it's enantiomer was 28.0 min. The retention time of product **450** was 27.6 min and it's enantiomer 31.9 min. R_f **449** (50% EtOAc/hexane) = 0.15. ^{1}H NMR **449** ($CDCl_3$/TMS, 400.13 MHz) δ 7.26-7.15 (m, 4 H), 6.39 (s, 1 H), 5.16-5.12 (m, 1 H), 4.94 (d, 1 H, *J* = 8.3 Hz), 2.95-2.91 (m, 1 H), 2.64-2.60 (m, 1 H), 2.32-2.27 (m, 1 H), 1.86-1.77 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 159.9, 138.0, 133.9, 129.3, 128.6, 127.6, 76.0, 53.6, 27.9, 24.3, 23.3. LRMS (EI) 189, 161, 146, 128(100), 117, 104, 77, 51. HRMS (EI) calculated for $C_{11}H_{11}NO_2$: 189.0790, found 189.0789. R_f **450** (50% EtOAc/hexane) = 0.09. ^{1}H NMR **450** ($CDCl_3$/TMS, 400.13 MHz) δ 7.44-7.17 (m, 4 H), 5.90 (s, 1 H), 5.61 (d, 1 H, *J* = 8.0 Hz), 4.30-4.26 (m, 1 H), 2.91-2.88 (m, 1 H), 2.64-2.59 (m, 1 H), 1.94-1.87 (m, 2 H). ^{13}C NMR **450** ($CDCl_3$, 100.62 MHz) 160.0, 138.7, 131.0, 129.4, 128.8, 127.4, 122.0, 76.1, 52.0, 28.6, 25.3, 23.3. LRMS (EI) 189, 161, 145, 128(100), 115(100), 104, 91, 77, 65. HRMS (EI) calculated for $C_{11}H_{11}NO_2$: 189.0790, found 189.0796.

6.2.2 (3a*R*', 9b*S*')-1-(11-Benzyloxy-undeca-2*E*,7*E*,9*E*-trienoyl)-3a,4,5,9b-tetrahydro-1H-naphtho[1,2-*d*]oxazol-2-one (452)

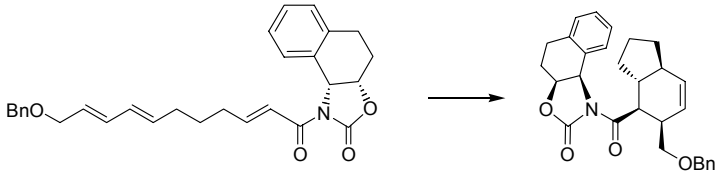


444 **452**

The triene acid **444** (0.327 g, 1.13 mmol, 110 mol-%) was dissolved in dry THF (3.2 mL). Distilled triethyl amine (0.168 g, 1.66 mmol, 148 mol-%) was added. The resulting mixture was immersed in a cooling bath to – 45 °C (CH_3CN/N_2). Distilled pivaloyl chloride (0.14 mL, 1.13 mmol, 110 mol-%) was injected into the reaction flask in a

dropwise manner. The mixture was stirred at – 40 – 45 ^{o}C for 1.5 hours. During this period, oxazolidinone **449** was dissolved in dry THF (5 mL) with warming (+ 50 ^{o}C). The dissolved oxazolidinone solution was cooled to – 78 ^{o}C (acetone/CO_2) and *n*-BuLi (2.104 M in hexanes, 0.5 mL, 1.05 mmol, 103 mol-%) was added dropwise. A slurry formed and a 1 mL of dry THF was added to increase solubility. The mixture was immersed in an ice bath to increase the solubility. At this point, a brown homogeneous solution was obtained. The mixture was cooled again to – 78 ^{o}C. The lithiated oxazolidinone **449** was then transferred dropwise with a syringe into the reaction flask, which contained the acid. The lithiated oxazolidinone solution partially precipitated at – 78 ^{o}C during the addition. The addition resulted in the formation of a slurry. The reaction mixture was allowed to warm slowly. After 2.5 hours of stirring, the reaction mixture was immersed in an ice bath for 1.5 hours. After this, the reaction mixture was allowed to warm to r.t. for 1.5 hours. A saturated solution of NH_4Cl (8 mL) and EtOAc (10 mL) was added. The organic layer was separated and washed with a saturated solution of $NaHCO_3$ (11 mL) and brine (20 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated to give 0.523 g of yellow oil. The crude product was purified by flash chromatography (20-23 % EtOAc/hexane) to yield **452** (0.272 g, 71 %) as a white solid. R_f (30 % MTBE/hexane) = 0.16. $[\alpha]^{20}_{D}$ = + 99.7 (c 0.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.79-7.76 (m, 1 H), 7.34-7.11 (m, 9 H), 6.22 (dd, 1 H, *J* = 15.1, 10.4 Hz), 6.06 (dd, 1 H, *J* = 15.0, 10.5 Hz), 5.81 (d, 1 H, *J* = 7.8 Hz), 5.72-5.59 (m, 2 H), 5.08-5.04 (m, 1 H), 4.50 (s, 2 H), 4.04 (d, 2 H, *J* = 5.6 Hz), 2.99 (td, 1 H, *J* = 12.5, 3.8 Hz), 2.64 (dt, 1 H, *J* = 16.0, 3.2 Hz), 2.41 (dq, 1 H, *J* = 14.5, 3.4 Hz), 2.25 (q, 2 H, *J* = 7.2 Hz), 2.11 (q, 2 H, *J* = 7.1 Hz), 1.86-1.78 (m, 1 H), 1.57 (q, 2 H, *J* = 7.7 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 166.2, 154.4, 151.5, 139.0, 138.5, 134.8, 133.7, 132.8, 132.4, 131.0, 129.2, 129.0, 128.9, 128.4, 128.2, 128.1, 127.6, 121.8, 74.7, 72.6, 71.1, 55.1, 32.6, 28.2, 27.6, 23.9. LRMS (EI+) 457, 336, 268, 238, 190, 177, 160, 147, 130, 105, 91(100), 79. HRMS (EI+) calculated for $C_{29}H_{31}NO_4$: 457.2253, found 457.2283.

6.2.3 [(3a*S*',4*R*', 5*S*',7a*R*'), 3a*R*', 9b*S*']-1-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbonyl)-3a,4,5,9b-tetrahydro-1*H*-naphtho[1,2-*d*]oxazol-2-one (454)

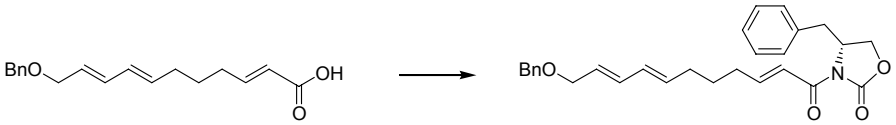


452 **454**

Triene oxazolidinone **452** (0.272 g, 0.59 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (12 mL) and cooled to – 45 °C. Diethylaluminum chloride in hexanes (1.0 M, 0.83 mL, 0.83 mmol, 140 mol-%) was added dropwise in 20 minutes. Stirring was continued for 6 hours between – 45 – 20 °C and then the reaction mixture was allowed to warm slowly to r.t. After 19 hours of stirring, the reaction mixture was cooled to – 45 °C and more DEAC (0.65 mL, 0.65 mmol, 110 mol-%) was added dropwise. The addition took 20 minutes and it resulted formation of white gas. Stirring was continued for 2 days and the reaction mixture was cannulated to ice cool solution of 1M HCl (10 mL). This resulted formation of white/yellow slurry. The layers were separated and the water layer was extracted with CH_2Cl_2 (5 mL). The combined organics were washed with 5 w-% $NaHCO_3$ solution (10 mL) and dried with Na_2SO_4. The filtration and concentration gave 0.278 g of orange oil. The crude product was purified by flash chromatography (5-15 % EtOAc/hexane) to yield **454** (62 mg, 23 %) as a white solid. R_f (30 % EtOAc/hexane) = 0.36. $[\alpha]^{20}_D$ = + 182.2 (c 0.995, $CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.86-7.84 (m, 1 H), 7.28-7.09 (m, 9 H), 5.86 (d, 1 H, *J* = 9.9 Hz), 5.80 (d, 1 H, *J* = 8.3 Hz), 5.56 (ddd, 1 H, *J* = 9.9, 3.6, 2.6 Hz), 5.81 (dtd, 1 H, *J* = 6.7, 3.9, 1.1 Hz), 3.81 (d, 2 H, *J* = 3.7 Hz), 3.07-2.94 (m, 3 H), 2.83 (dd, 1 H, *J* = 8.6, 5.4 Hz), 2.63 (m, 1 H), 2.44 (dq, 1 H, *J* = 14.6, 2.9 Hz), 2.05 (m, 1H), 1.95-1.65 (m, 6 H), 1.26-1.05 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 174.6, 153.9, 139.2, 138.9, 133.3, 132.0, 130.8, 128.9, 128.5, 128.4, 127.7, 127.6, 127.0, 74.3, 72.6, 71.7, 55.5, 47.6, 45.0, 42.0, 38.8, 29.3, 28.8, 28.4, 23.9, 22.5. LRMS (EI+) 457,

349, 336, 268, 238, 220, 190, 177, 160, 147, 129, 105, 91(100), 79, 55. HRMS (EI+) calculated for $C_{29}H_{31}NO_4$: 457.2253, found 457.2218.

6.2.4 (4*R*)-4-Benzyl-3-(11-benzyloxy-undeca-2*E*,7*E*,9*E*-trienoyl)-oxazolidin-2-one (453)

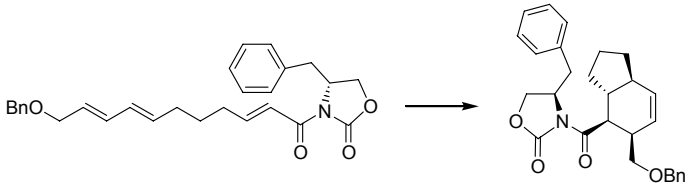


444 **453**

The triene acid **444** (0.286 g, 1.0 mmol, 105 mol-%) was dissolved in dry THF (5 mL) and triethylamine (0.152 g, 1.5 mmol, 150 mol-%) was added. The resulting mixture was cooled to – 40 °C (acetonitrile/N_2). Pivaloyl chloride (0.121 g, 1.0 mmol, 105-%) was added dropwise in to reaction mixture. After the addition, the reaction mixture was immersed in a cooling bath to – 25 °C (ethylene glycol/CO_2). Stirring was continued for 40 minutes. During this period (*R*)-4-benzyl-2-oxazolidinone (0.168 g, 0.95 mmol, 100 mol-%) was dissolved in dry THF (4 mL) and the mixture was cooled to – 78 °C (acetone/CO_2) and *n*-BuLi (492 µl, 0.98 mmol, 103 mol-%) was added dropwise. The addition resulted formation of orange solution. Stirring was continued for 30 minutes. Both reaction flasks were cooled to - 78°C and the lithiated oxazolidinone was slowly cannulated into the flask, which contained previously formed triene anhydride. The slurry was stirred for 1 hour and then the mixture was stirred for 20 minutes at – 30 °C. After this, the reaction mixture was warmed to 0 °C for 30 minutes and finally the reaction mixture was allowed to warm to r.t. A saturated solution of NH_4Cl (4 mL) and EtOAc (5 mL) was added. The layers were separated and the water layer was extracted with EtOAc (10 mL). The combined organics were washed with a saturated solution of $NaHCO_3$ (10 mL) and brine (10 mL). The organic phase was dried with Na_2SO_4, filtered and

concentrated to give 0.486 g of yellow oil. The crude product was purified by flash chromatography (15 % EtOAc/hexane) to yield **453** (0.358 g, 85 %) as a clear oil. R_f (20 % EtOAc/hexane) = 0.14. $[\alpha]^{20}_D$ = - 41.5 (c 1.18, $CHCl_3$). ^1H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.34-7.20 (m, 12 H), 6.24 (dd, 1 H, *J* = 15.4, 10.7 Hz), 6.08 (dd, 1 H, *J* = 15.0, 10.4 Hz), 5.74-5.64 (m, 2 H), 4.74-4.68 (m, 1 H), 4.50 (s, 2 H), 4.20-4.13 (m, 2 H), 4.04 (dd, 2 H, *J* = 6.3, 0.9 Hz), 3.32 (dd, 1 H, *J* = 13.3, 3.1 Hz), 2.79 (dd, 1 H, *J* = 13.5, 9.6 Hz), 2.31 (q, 2 H, *J* = 7.3 Hz), 2.15 (q, 2 H, *J* = 7.2 Hz), 1.61 (q, 2 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 165.5, 153.8, 151.6, 138.8, 135.8, 134.6, 133.5, 130.8, 129.9, 129.4, 128.8, 128.2, 128.0, 127.9, 127.7, 121.1, 72.4, 71.0, 66.5, 55.7, 38.3, 32.5, 28.0. LRMS (EI+) 445, 354, 324, 268, 238, 204, 178, 160, 147(100), 133, 117, 105, 91, 79, 53. HRMS (EI+) calculated for $C_{28}H_{31}NO_4$: 445.2253, found 445.2169.

6.2.5 [4*R*,(3a*R*',4*S*', 5*R*',7a*S*')]-4-Benzyl-3-(5-benzyloxymethyl-2,3,3a,4,5,7a - hexahydro-1*H*-indene-4-carbonyl)-oxazolidin-2-one (455)

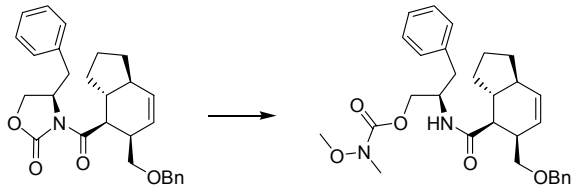


453 **455**

Triene oxazolidinone **453** (0.959 g, 2.15 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (35 mL) and cooled to – 41 °C (CH_3CN/N_2(l)). Diethylaluminum chloride in hexanes (1.0 M, 3.12 mL, 3.12 mmol, 145 mol-%) was added dropwise. The addition resulted in the formation of a yellowish solution. The reaction mixture was allowed to warm slowly to – 10 – 18 °C in a cold room. After 53 hours of stirring, the reaction mixture was cannulated to ice cool solution of 1M HCl (30 mL). This resulted formation of a white slurry. Stirring was continued for 10 minutes and the layers were separated. The water layer was

extracted with CH_2Cl_2 (30, 2 x 20 mL). The combined organics were washed with 5 w-% $NaHCO_3$ solution (2 x 30 mL). The water slurry was extracted with CH_2Cl_2 (2 x 30 mL). The combined organics were washed with brine (30 mL), dried with Na_2SO_4, filtered and concentrated to give 0.973 g of thick yellow oil. The crude product was purified by flash chromatography (6-15% EtOAc/hexane) to give **455** (0.686 g, 72%) as a white solid. The product was recrystallized from MeOH. mp. 92-93 °C. $[\alpha]^{20}_D$ = - 153.9 (c 1.00, $CHCl_3$). R_f (50 % MTBE/hexane) = 0.52. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.56-7.07 (m, 10 H), 5.92 (d, 1 H, *J* = 9.8 Hz), 5.50 (ddd, 1 H, *J* = 9.8, 4.0, 2.6 Hz), 4.59-4.53 (m, 1H), 4.41 (q, 2 H, *J* = 12.1 Hz), 4.07 (td, 1 H, *J* = 8.8, 0.8 Hz), 3.98 (dd, 1 H, *J* = 9.0, 2.5 Hz), 3.73 (dd, 1 H, *J* = 11.3, 6.3 Hz), 3.54 (dd, 1 H, *J* = 9.7, 8.6 Hz), 3.42-3.37 (m, 1 H), 3.33-3.27 (m, 2 H), 2.05 (dd, 1 H, *J* = 13.5, 11.0 Hz), 2.00-1.96 (m, 1 H), 1.90-1.69 (m, 5 H), 1.27-1.19 (m, 1 H), 1.12-1.02 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 174.2, 153.8, 138.6, 136.7, 131.7, 129.8, 129.2, 128.7, 128.3, 127.9, 127.6, 127.4, 73.0, 71.2, 66.6, 56.2, 47.3, 44.9, 42.1, 39.3, 37.7, 29.3, 22.5. LRMS (EI+) 445, 354, 324, 238, 178, 160, 147, 117, 105, 91(100), 65, 55. HRMS (EI+) calculated for $C_{28}H_{31}NO_4$: 445.2253, found 445.2259.

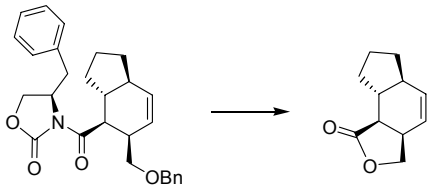
6.2.6 [2*R*,(3a*R*',4*S*', 5*R*',7a*S*')]-*N*-Methoxy-*N*-methyl-carbamic acid 2-benzyl-3-[(5-benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbonyl)-amino]-propyl ester (457)



455 **457**

MeONHMe·HCl (37 mg, 0.383 mmol, 240 mol-%) was treated with dry CH_2Cl_2 (2 mL). The mixture was cooled to – 10 – 12 °C (acetone/ice). Trimethyl aluminum in hexanes (0.18 mL, 0.359 mmol, 224 mol-%) was added dropwise, which resulted in the formation of white smoke. Stirring was continued for 10 minutes at – 10 °C and 30 minutes at room temperature. The reaction mixture was cooled to – 10 °C and adduct **455** (71 mg, 0.160 mmol, 100 mol-%) in dry CH_2Cl_2 (2 mL) was added dropwise. Stirring was continued 20 minutes and the reaction mixture was immersed in an ice bath for 1.5 hours. After this the reaction mixture was taken to r.t. for 16 hours. The reaction mixture was warmed with an oil bath (+ 50 °C) for 24 hours. A mixture of 0.5 M HCl (2 mL) and CH_2Cl_2 (1 mL) was added at 0 °C. Stirring was continued for 2.5 hours and CH_2Cl_2 (3 mL) was added. The layers were separated and the water layer was extracted with CH_2Cl_2 (2 x 3 mL). The combined organics were washed with brine (3 mL), dried with Na_2SO_4, filtered and concentrated to give **457** (63 mg, 78 %) as a white solid. $[\alpha]_{20}^{D}$ = -119.2 (c 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.31-7.12 (m, 10 H), 6.02 (d, 1 H, *J* = 8.2 Hz), 5.93 (d, 1 H, *J* = 9.9 Hz), 5.63 (ddd, 1 H, *J* = 9.9, 3.9, 2.8 Hz), 4.42 (s, 3 H), 4.11 (d, 2 H, *J* = 5.5 Hz), 3.69 (s, 3 H), 3.44 (dd, 2 H, *J* = 5.6, 1.9 Hz), 3.14 (s, 3 H), 2.81-2.65 (m, 3 H), 2.42 (dd, 1 H, *J* = 11.4, 7.0 Hz), 1.82-1.61 (m, 7 H), 1.19-1.14 (m, 1H), 1.01-0.97 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 173.5, 157.8, 139.1, 137.8, 131.7, 130.0, 129.2, 128.9, 128.3, 128.1, 127.3, 73.7, 72.4, 67.0, 62.3, 54.1, 50.9, 50.4, 45.6, 42.9, 40.3, 37.9, 36.2, 29.5, 28.5, 22.8. IR (FT-IR) 3019, 2400, 1671, 1513, 1427, 1211, 1046, 929, 758, 670. LRMS (EI+) 506, 476, 415, 310, 280, 237, 176, 147, 117, 105, 91, 65. HRMS (ES+) calculated for $C_{30}H_{38}N_2O_5Na$: 529.2678, found 529.2698.

6.2.7 (3a*R*',5a*S*',8a*R*',8b*S*')-3,3a,5a,6,7,8,8a,8b-Octahydro-indeno[4,5-*c*]furan-1-one (458)



455 **458**

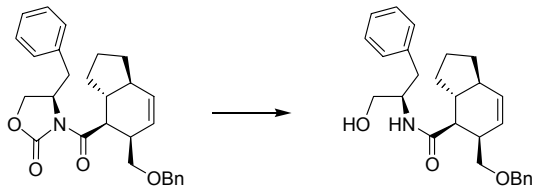
Hexahydroindene oxazolidinone **455** (12 mg, 0.027 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (0.5 mL) and H_2O (0.025 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (10 mg, 0.044 mmol, 163 mol-%) was added. Stirring was continued for 3 days at r.t. and then the reaction mixture was warmed with a water bath (+30-35 °C). Stirring was continued for 1 day at this temperature and CH_2Cl_2 (2 mL) was added. The organics were washed with a saturated solution of $NaHCO_3$ (2 mL). The water layer was extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated to give 9.3 mg of yellow oil and brown precipitate. The crude product was purified by flash chromatography (10 % EtOAc/hexane) to give **458** (1.9 mg, 40%) as a white solid. R_f (50% EtOAc/hexane) = 0.33. ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 6.04 (d, 1 H, *J* = 9.9 Hz), 5.55 (dt, 1 H, *J* = 9.9, 2.9 Hz), 4.52 (t, 1H, *J* = 8.7 Hz), 3.90 (dd, 1 H, *J* = 10.7, 8.7 Hz), 3.21 (q, 1 H, *J* = 7.2 Hz), 2.55 (dd, 1 H, *J* = 12.1, 8.5 Hz), 2.02-1.93 (m, 3 H), 1.79-1.75 (m, 2 H), 1.51-1.41 (m, 2 H), 1.26-1.20 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 179.0, 133.4, 124.4, 72.5, 44.6, 43.8, 42.1, 37.5, 28.9, 28.5, 22.4. LRMS (EI+) 178, 149, 133(100), 120, 105, 91, 79, 65, 51. HRMS (EI+) calculated for $C_{11}H_{14}O_2$: 178.0994. found 178.0994.

6.2.8 (3a*R*',5a*S*',8a*R*',8b*S*')-3,3a,5a,6,7,8,8a,8b-Octahydro-indeno[4,5-*c*]furan-1-one (458)

IMDA adduct **455** (0.136 g, 0.305 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (4 mL). A 2.0 M solution of $BCl_3{\cdot}SMe_2$ (1.06 mL, 2.120 mmol, 700 mol-%) was added

dropwise. Stirring was continued for 5 hours and a saturated solution of $NaHCO_3$ (10 mL) was added cautiously. A formation of CO_2 was noticed. A 20 mL of sat. $NaHCO_3$ and CH_2Cl_2 (20 mL) was added. The layers were separated and the water layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with a solution of 1M HCl (2 x 10 mL). The water phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated to give 0.123 g of brown oil. The crude product was purified by flash chromatography (15 % to 85 % EtOAc in hexanes). to yield **458** (45 mg, 84%). 40 mg (74 %) of chiral auxiliary was recovered. R_f (25 % EtOAc/hexane) = 0.29. $[\alpha]_{20}^{D}$= +54.4 (c 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 6.05 (d, 1 H, *J* = 9.7 Hz), 5.55 (dt, 1 H, *J* = 9.9, 3.2 Hz), 4.52 (t, 1 H, *J* = 8.9 Hz), 3.90 (dd, 1 H, *J* = 10.8, 8.7 Hz), 3.23-3.21 (m, 1 H), 2.55 (dd, 1 H, *J* = 12.1, 8.4 Hz), 2.05-1.20 (m, 8 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 179.1, 133.6, 124.6, 72.8, 44.8, 44.0, 42.3, 37.8, 29.1, 28.8, 22.6. HRMS see above.

6.2.9 [3a*R*',4*S*', 5*R*',7a*S*',(1*R*)]-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxylic acid (1-benzyl-2-hydroxy-ethyl)-amide (456)



455 **456**

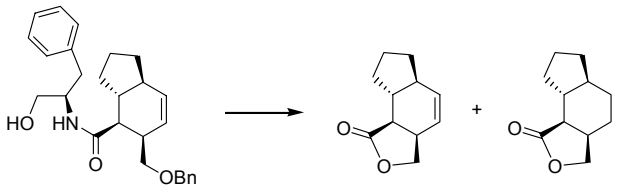
Hexahydroindene oxazolidinone **455** (26 mg, 0.059 mmol, 100 mol-%) was dissolved in MeOH (5 mL) and KOH (31 mg, 0.556 mmol, 942 mol-%) was added. Stirring was continued for 1 hour at r.t. and then the reaction mixture was acidified with 2 M $KHSO_4$ (10 drops) until the pH was 4. MeOH was evaporated to give a white slurry. CH_2Cl_2 (10 mL) was added ant the organic phase was washed with 2 M $KHSO_4$ (3 mL). The layers

were separated and the water phase was diluted with water (10 mL). The water layer was extracted with CH_2Cl_2 (4 x 5 mL). The combined organics were washed with brine (5 mL), dried with Na_2SO_4, filtered and concentrated to give 36 mg of white solid. The crude product was purified by recrystallization from 60 % hexane/CH_2Cl_2 to give **456** (9 mg, 53 %) as a white solid. R_f (100% EtOAc) = 0.43. $[\alpha]_{20}^{D}$ = -120.1 (c 1.00, CH_2Cl_2). ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.35-7.05 (m, 10 H), 5.93 (d, 1 H, *J* = 9.9 Hz), 5.86 (d, 1 H, *J* = 6.6 Hz), 5.53 (ddd, 1 H, *J* = 9.9, 3.8, 2.7 Hz), 4.46 (q, 2 H, *J* = 12.0 Hz), 4.09-4.02 (m, 1 H), 3.71-3.66 (m, 1 H), 3.58-3.49 (m, 4 H), 2.77-2.65 (m, 3 H), 2.44 (dd, 1 H, *J* = 11.8, 7.0 Hz), 1.82-1.77 (m, 2 H), 1.62-1.58 (m, 4 H), 1.44-1.38 (m, 1 H), 1.19-1.14 (m, 1H), 0.99-0.88 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 175.2, 138.8, 138.3, 132.0, 129.8, 129.3, 129.1, 128.7, 128.5, 128.4, 127.3, 73.8, 72.1, 65.7, 54.5, 51.2, 45.7, 42.9, 40.3, 37.4, 29.5, 28.5, 22.9. HRMS (ES+) calculated for $C_{27}H_{33}NO_3Na$: 442.2358, found 442.2363.

6.2.10 [3a*R*',4*S*', 5*R*',7a*S*',(1*R*)]-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carboxylic acid (1-benzyl-2-hydroxy-ethyl)-amide (456)

IMDA adduct **455** (52 mg, 0.116 mmol, 100 mol-%) was dissolved in dry THF (3 mL). H_2O (2.3 µl, 0.128 mmol, 110 mol-%) was added and the mixture was cooled to 0 °C. A 2.0 M solution of $LiBH_4$ in THF (64µl, 0.128 mmol, 110 mol-%) was added. Stirring was continued for 3.5 hours and a second portion of $LiBH_4$ in THF (65µl, 0.130 mmol, 112 mol-%) was added. The whitish cloudy reaction mixture was stirred 17 hours at room temperature. A 5 w-% solution of citric acid (5 mL) was added cautiously. The water layer was extracted with ether (4 x 10 mL). The combined organics were washed with brine (5 mL), filtered and concentrated to give 54 mg of white solid. The crude product was purified by flash chromatography (50-100% EtOAc in hexanes) to yield **456** (30 mg, 62%). For analytical details, see 6.2.9.

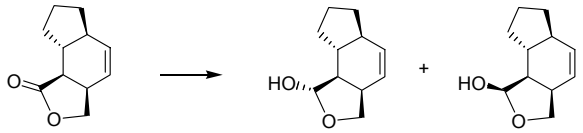
6.2.11 (3a*R*',5a*S*',8a*R*',8b*S*')-3,3a,5a,6,7,8,8a,8b-Octahydro-indeno[4,5-*c*]furan-1-one (458)



456 **458** **459**

Amide **456** (32 mg, 0.076 mmol, 100 mol-%) was dissolved in dioxane (2 mL) and 6 M HCl (2 mL) was added, which resulted in precipitation. The reaction mixture was warmed in an oil bath (100-105 °C). Stirring was continued for 18.5 hours and the reaction mixture was cooled to r.t. The product was partitioned between H_2O (10 mL) and CH_2Cl_2 (15 mL). The water layer was extracted with CH_2Cl_2 (6 x 5 mL). The organic layer was dried with Na_2SO_4, filtered and concentrated to give 22 mg of white solid. The crude product was purified by flash chromatography. The column was 2.5 g, 1 x 14 cm. The eluent was 13 % EtOAc in hexanes to 100 % EtOAc. The yield was 11 mg (82%) of lactone mixture **458** and **459**. The ratio of **458** to **459** was 2.5:1 by 1H NMR. R_f **458**/**459** (50 % EtOAc/hexane) = 0.56. ^{1}H NMR **458** ($CDCl_3$/TMS, 400.13 MHz) δ 6.05 (d, 1 H, *J* = 9.9 Hz), 5.55 (d, 1 H, *J* = 9.9 Hz), 4.52 (t, 1 H, *J* = 8.9 Hz), 3.90 (dd, 1 H, *J* = 10.8, 8.7 Hz), 3.23-3.20 (m, 1 H), 2.55 (dd, 1 H, *J* = 12.1, 8.4 Hz), 2.52 (m, 1 H) 2.05-1.70 (m, 7 H), 1.57-1.40 (m, 1H), 1.30-1.18 (m, 1 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 179.2, 133.7, 124.6, 72.8, 44.9, 44.1, 42.3, 37.8, 29.2, 28.8, 22.7. LRMS (EI+) 178, 149, 133, 119, 105, 91(100), 79, 65, 51. For HRMS see chapter 6.2.7.

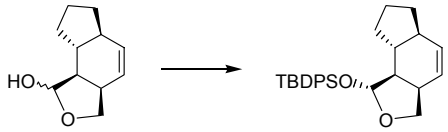
6.2.12 [(3a*R*',5a*S*',8a*R*',8b*S*'),1*R/S*]-3,3a,5a,6,7,8,8a,8b,-Octahydro-1*H*-indeno[4,5-*c*]furan-1-ol (460a,b)



458 460a 460b

3,3a,5a,6,7,8,8a,8b-Octahydro-indeno[4,5-*c*]furan-1-one **458** (44 mg, 0.25 mmol, 100 mol-%) was dissolved in dry toluene (4 mL). The resulting mixture was cooled to – 78 °C. A 1.0 M solution of DIBAL-H (0.3 mL, 0.300 mmol, 120 mol-%) in toluene was added dropwise. Stirring was continued for 30 minutes and saturated solution of NH_4Cl (5 mL) was added. The reaction mixture was allowed to warm to room temperature. A saturated solution of Rochelle's salt was added (10 mL). Stirring was continued for 15 minutes and the water phase was extracted with ether (4 x 20 mL). The combined organics were washed with brine (20 mL), dried with Na_2SO_4, filtered and concentrated to give 43 mg of clear oil. The crude product was purified by flash chromatography (15 % EtOAc/hexane) to yield **460a**/**460b** (33 mg, 72 %) in ratio 20:1. R_f (50% EtOAc/hexane) = 0.28. $[\alpha]_{20}^{D}$ = +16.2 (c 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 5.92 (d, 1 H, *J* = 9.7 Hz), 5.60 (dt, 1 H, *J* = 9.9, 3.0 Hz), 5.40 (d, 1 H, *J* = 2.9 Hz), 4.30 (dd, 1 H, *J* = 9.5, 7.8 Hz), 3.58 (t, 1 H, *J* = 8.0 Hz), 3.12 (m, 1 H), 3.04 (d, 1 H, *J* = 3.1 Hz), 2.16 (dd, 1 H, *J* = 12.1, 7.7 Hz), 1.87 (m, 3 H), 1.73 (m, 2 H), 1.21 (m, 3 H). ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 131.8, 127.5, 102.8, 73.6, 51.4, 43.6, 43.6, 38.4, 29.8, 29.1, 22.9. LRMS (EI+) 180, 162, 150, 134, 119(100), 105, 91, 790, 67, 53. HRMS (EI+) calculated for $C_{11}H_{16}O_2$: 180.1150, found 180.1140.

6.2.13 [1*S*,(3a*R*',5a*S*',8a*R*',8b*S*')]-1-*tert*-Butyl-(3,3a,5a,6,7,8,8a,8b-octahydro-1*H*-indeno[4,5-*c*]furan-1-yloxy)-diphenyl-silane (467)

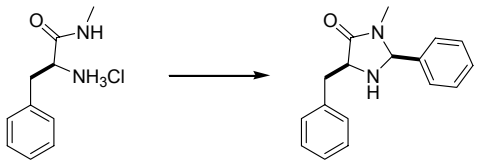


460a,b **467**

Lactol **460a,b** (16.1 mg, 0.089 mmol, 100 mol-%) was dissolved in dry DMF (1 mL) and imidazole (6.8 mg, 0.100 mmol, 112 mol-%) was added. *tert*-Butyldiphenylsilyl chloride (23 µl, 0.088 mmol, 99 mol-%) was added and stirring was continued at 50-55 °C (oil bath). After 45 minutes of stirring, a second portion of imidazole (7.2 mg, 0.106 mmol, 118 mol-%) and *tert*-butyldiphenylsilyl chloride (24 µl, 0.092 mmol, 103 mol-%) was added. Stirring was continued for 90 minutes and a third portion of imidazole (6.6 mg, 0.097 mmol, 109 mol-%) and *tert*-butyldiphenylsilyl chloride (24 µl, 0.092 mmol, 103 mol-%) was added. Stirring was continued for 19 hours at 55 °C. The organic phase was diluted with ether (20 mL), washed with H_2O (5 mL), brine (5 mL) and dried with $MgSO_4$. The filtration and concentration gave 84 mg of clear oil. The crude product was purified by flash chromatography (2 - 10 % MTBE/hexane) to yield **467** (15 mg, 39 %). R_f (5 % MTBE in hexanes) = 0.38. $[\alpha]_{20}^{D}$ = +38.1 (c 1.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.75-7.35 (m, 10 H), 5.88 (d, 1 H, *J* = 9.6 Hz), 5.64 (dt, 1 H, *J* = 9.7, 3.0 Hz), 5.36 (s, 1H), 4.31 (dd, 1 H, *J* = 9.7, 7.7 Hz), 3.55 (t, 1 H, *J* = 7.9 Hz), 3.25-3.20 (m, 1H), 2.19 (dd, 1 H, *J* = 11.8, 7.4 Hz), 1.90 – 1.50 (m, 5 H), 1.07 (s, 9H), 1.00-0.80 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 136.4, 136.3, 135.9, 134.8, 134.5, 133.2, 131.5, 130.9, 130.3, 130.3, 128.6, 128.3, 128.3, 128.1, 103.2, 73.6, 53.3, 43.6, 38.3, 29.8, 28.9, 27.5, 27.2, 22.9, 19.9. LRMS (EI+) 418, 362, 332, 283, 274, 253, 239, 217(100), 199, 181, 163, 145, 135, 117, 105, 91, 77, 63, 57, 51. HRMS (EI+) (M-(t-Bu)) calculated 361.1624, found 361.1640.

6.3 Organocatalytic preparation of bicyclo[4.3.0]nonane derivatives

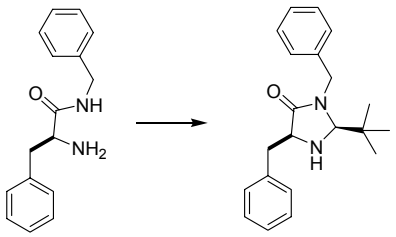
6.3.1 (2*S*,5*S*)-5-Benzyl-3-methyl-2-phenyl-imidazolidin-4-one (474a)



472 **474**

A HCl salt of amine **472** (2.37 g, 11.1 mmol, 100 mol-%) was treated with a saturated solution of $NaHCO_3$ (45 mL). The free amine was extracted with $CHCl_3$ (3 x 50 mL). The organics were dried with Na_2SO_4, filtered and concentrated to give 2.05 g of yellowish oil. Methanol (20 mL), benzaldehyde (1.29 g, 12.2 mmol, 110 mol-%) and *para*-toluenesulphonic acid monohydrate (0.21 g, 1.1 mmol, 10 mol-%) was added and the reaction mixture was warmed with an oil bath to +75 °C. Stirring was continued for 3 days and the reaction mixture was allowed to cool to r.t. The solvents were evaporated to give 3.26 g of orange oil. The crude product was purified by flash chromatography (50-100 % EtOAc/hexane) to yield **474** (0.31 g, 11 %) as a yellowish oil. The ratio of (*S,S*):(*S,R/R,S*)-products were 1:3.1 by 1H NMR. R_f (*S,S*)-**474** (75% EtOAc in hexanes) = 0.16. $[\alpha]_{20}^{D}$ = -46.5 (c 1.12, $CHCl_3$). R_f (*S,R/R,S*) (75 % EtOAc in hexanes) = 0.33. The product was analyzed by chiral HPLC (10 % i-PrOH in hexane, flow rate 1.0 mL/min) The retention times were (*S,S*) 13.59 min and (*S,R*) 11.8 min. RT (*R,S*) 9.4 min. ^{1}H NMR **474** ($CDCl_3$, 400.132 MHz) δ 7.32-7.24 (m, 8H), 6.85-6.83 (m, 2H), 5.14 (d, 1H, *J* = 1.5 Hz), 3.88 (t, 1H, *J* = 0.5 Hz), 3.28-3.16 (m, 2H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 174.4, 138.4, 136.7, 129.8, 129.5, 129.0, 128.8, 127.1, 126.9, 77.6, 60.4, 36.8, 27.3. HRMS (ES+) calculated for [M+1] $C_{17}H_{19}N_2O$: 267.1497, found 267.1484.

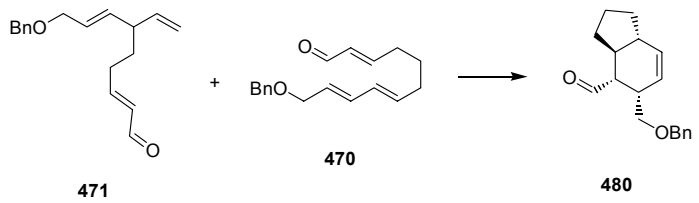
6.3.2 (2*S*,5*S*)-3,5-Dibenzyl-2-*tert*-butyl-imidazolidin-4-one (479a)



478 **479a**

Free amine **478** (2.22 g, 8.73 mmol, 100 mol-%) was dissolved in MeOH (15 mL). Trimethylacetaldehyde (0.83 g, 9.60 mmol, 110 mol-%) and *para*-toluenesulphonic acid monohydrate (0.17 g, 0.87 mmol, 10 mol-%) was added. The resulting mixture was warmed with an oil bath to + 75 °C. Stirring was continued under reflux for 2 days and the reaction mixture was allowed to cool to r.t. The solvents were evaporated to give 2.72 g of yellow oil. The crude product was purified by flash chromatography (32 % EtOAc/hexane) to yield **479a** (0.52 g, 18 %) as a clear oil. The ratio of (*S,S*) to (*S,R/R,S*) was 1:2 by 1H NMR. R_f (*S,S*)-**479a** (70% EtOAc/hexane) = 0.49. $[\alpha]_{20}^{D}$ = -128.0 (c 1.11, $CHCl_3$). R_f (*S,R/R,S*) (70% EtOAc/hexane) = 0.65. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.32-7.13 (m, 10H), 5.06 (d, 1H, *J* = 15.7), 4.25 (d, 1H, *J* = 15.7 Hz), 4.13 (s, 1H), 3.85 (ddd, 1H, *J* = 7.5, 4.1, 1.4 Hz), 3.22 (dd, 1H, *J* = 13.7, 4.1 Hz), 3.04 (dd, 1H, *J* = 13.7, 7.5 Hz), 0.76 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 174.4, 138.4, 136.7, 129.8, 129.5, 129.0, 128.8, 127.1, 126.9, 77.6, 60.4, 36.8, 27.3. (*S,S*)-Configuration was confirmed by COSYGPGF (coupling between 4.13 and 3.85 was noticed). HRMS (EI) calculated for $C_{21}H_{26}N_2O$: 322.2045, found [M-1] 321.1994.

6.3.3 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (38)



471 470 480

(2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one **475** (128 mg, 0.52 mmol, 6 mol-%) was dissolved in CH_3CN (20 mL) and a 0.1 M aqueous solution of HCl (5.2 mL) was added. The resulting mixture was stirred for 5 minutes and a 65 w-% triene aldehyde **470** (2.50 g, 9.25 mmol, 100 mol-%) in CH_3CN (32 mL) was added. The reaction mixture was stirred for 20 hours and the reaction mixture was diluted with ether (200 mL) and washed with H_2O (50 mL) and brine (50 mL) mixture. The organic phase was dried with $MgSO_4$, filtered and concentrated to give 2.8 g of yellow oil. The crude product was purified by flash chromatography (5 % EtOAc/hexane) to give **480** (1.23 g, 79 %, 72 %ee) as a clear oil. The branched triene aldehyde **471** was easily separated by flash chromatography. The enantiomeric excess was determined by chiral HPLC from the corresponding alcohol. R_f (20 % MTBE in hexanes) = 0.34. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 9.77 (d, 1H, *J* = 2.8 Hz), 7.34-7.27 (m, 5H), 5.96 (d, 1H, *J* = 9.9 Hz), 5.47 (ddd, 1H, *J* = 9.9, 3.9, 2.6 Hz), 4.41 (d, 1H, *J* = 11.6 Hz), 4.33 (d, 1H, *J* = 11.6 Hz), 3.44 (dd, 1H, *J* = 9.9, 3.6 Hz), 3.37 (t, 1H, *J* = 9.4 Hz), 3.09 (m, 1H), 2.61 (ddd, 1H, *J* = 11.6, 6.5, 2.7 Hz), 2.06 (m, 1H), 1.84-1.61 (m, 5H), 1.17-1.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 203.2, 137.7, 132.3, 128.4, 127.8, 127.7, 126.2, 72.8, 70.7, 55.3, 45.0, 39.8, 39.6, 28.4, 27.6, 22.4. LRMS (EI+) 270, 180, 105, 91(100), 79, 65. HRMS (EI) calculated for $C_{18}H_{22}O_2$: 270.1620, found 270.1624.

6.3.4 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one **475** (10 mg, 0.04 mmol, 20 mol-%) was treated with a 0.4 M solution of HCl (0.1 mL). A 73 w-% 11-benzyloxy-undeca-2*E*,7*E*,9*E*-trienal **470** (54 mg, 0.20 mmol, 100 mol-%) was dissolved in MeOH (1.9 mL) and added into the reaction flask. After 2 minutes of stirring, the reaction mixture was yellowish solution. The reaction mixture was stirred for 5 hours and the reaction mixture was diluted with ether and the combined organics were washed with brine (10 mL). The water layer was extracted once with ether (5 mL) and the combined organics were dried with Na_2SO_4. The filtration and concentration of the organics gave 0.182 g of yellow emulsion. The dimethyl acetal product was hydrolyzed by treating the product with TFA:H_2O:$CHCl_3$ (1:1:2) (4 mL). Stirring was continued for 2 hours and the reaction mixture was neutralized by adding a saturated solution of $NaHCO_3$ (12 mL). The layers were separated and the water layer was extracted with ether (3 x 20 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated to give 0.140 g of clear oil. The crude product was purified by flash chromatography (5 – 20 % EtOAc in hexanes) to yield **480** (21 mg, 54 %). The enantiomeric excess was determined by HPLC (1.6 % i-PrOH in hexanes, flow rate 0.7 mL/min, λ = 230 nm). Only the *endo*-cycloadduct was observed by ^{1}H NMR. The enantiomeric excess was determined to be 74 %. For analytical details, see 6.3.3.

6.3.5 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

A 68 w-% 11-benzyloxy-undeca-2*E*,7*E*,9*E*-trienal **470** (56 mg, 0.21 mmol, 100 mol-%) was dissolved in MeOH (1.9 mL) and (5*S*)-5-benzyl-2,2,3-trimethyl-imidazolidin-4-one **476** (9 mg, 0.04 mmol, 20 mol-%) was added. The mixture was cooled to 0 °C. After this, a 0.4 M solution of HCl (0.1 mL) was added. The reaction mixture was stirred for 4 hours and the reaction mixture was allowed to warm to room temperature. Stirring was continued for 44 hours and the reaction mixture diluted with ether (20 mL) and the combined organics were washed with brine (10 mL). The water layer was extracted once with ether (5 mL) and the combined organics were dried with Na_2SO_4. The crude product

was filtered and concentrated to give yellow emulsion. The dimethyl acetal product was hydrolyzed by treating the product with TFA:H_2O:$CHCl_3$ (1:1:2) (4 mL). Stirring was continued for 2 hours and the reaction mixture was neutralized by adding a saturated solution of $NaHCO_3$ (15 mL). The layers were separated and the water layer was extracted with ether (3 x 20 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated to give 93 mg of clear oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (11 mg, 28%). The *endo/exo* ratio was determined by ^{1}H NMR to be 3.3:1. The enantiomeric excess was not determined.

6.3.6 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-5-Benzyl-3-methyl-2-phenyl-imidazolidin-4-one **474a** (6 mg, 0.023 mmol, 20 mol-%) was dissolved in CH_3CN (1 mL) and treated with a 0.1 M solution of HCl (0.23 mL). Because linear triene **470** polymerized more rapidly than the branched triene **471**, only the ratio of branched triene was higher. It was not possible to separate the trienes **470** and **471** by flash chromatography, although several eluent mixtures were tested. A 21 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (31 mg, 0.111 mmol, 100 mol-%) was dissolved in CH_3CN (1 mL) and added into the reaction flask. After 30 minutes of stirring, the reaction mixture was yellowish solution. The reaction mixture was stirred for 44 hours and the reaction mixture was diluted with ether (5 mL) and the combined organics were washed with brine (3 mL), dried with $MgSO_4$, filtered and concentrated to give 40 mg of yellow oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (3.6 mg, 59 %). The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5 % i-PrOH in hexanes). The enantiomeric excess was 10 %. Only *endo*-adduct was observed by 1H NMR.

6.3.7 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one **475** (6 mg, 0.025 mmol, 20 mol-%) was dissolved in CH_3CN (1 mL) and treated with a 0.1 M solution of HCl (0.25 mL). A 21 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (33 mg, 0.124 mmol, 100 mol-%) was dissolved in CH_3CN (1.5 mL) and added into the reaction flask. After 30 minutes of stirring, the reaction mixture was yellowish solution. The reaction mixture was stirred for 17 hours and diluted with ether (5 mL). The combined organics were washed with brine (3 mL). The combined organics were dried with $MgSO_4$, filtered and concentrated to give 44 mg of yellow oil. The crude product was purified by flash chromatography (5 - 25 % EtOAc in hexanes) to yield **480** (7 mg, 99 %) as a clear oil. The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5% i-PrOH in hexanes). The enantiomeric excess was 72 %. $[\alpha]_{20}^{D}$ = +23.3 (c 1.33, $CDCl_3$). Only *endo*-adduct was observed by ^{1}H NMR.

6.3.8 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one **475** (6.0 mg, 0.024 mmol, 20 mol-%) was dissolved in CH_3CN (1 mL) and a 0.1 M solution of HCl (0.25 mL) was added. A 65 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (32.6 mg, 0.121 mmol, 100 mol-%) was dissolved in CH_3CN (1.5 mL) and added into the reaction flask. The reaction mixture was stored in a freezer at –20 °C for 25.5 hours. After this, the mixture was allowed to stand for 44 hours at 6 °C (cold room). The reaction mixture was diluted with ether (5 mL) and the combined organics were washed with brine (3 mL). The water layer was extracted once with ether (3 mL) and the combined organics were dried with $MgSO_4$. The filtration and concentration of the organics gave 38 mg of clear oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (7

mg, 54 %) as a clear oil. The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5 % i-PrOH in hexanes). The enantiomeric excess was 66 %. Only *endo*-adduct was observed by ^{1}H NMR.

6.3.9 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-5-Benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one **475** (5.9 mg, 0.024 mmol, 18 mol-%) was dissolved in CH_2Cl_2 (1.5 mL) and i-PrOH (0.25 mL) was added. *p*-Toluenesulfonic acid monohydrate (4.6 mg, 0.024 mmol, 18 mol-%) was added. A 65 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (35.2 mg, 0.130 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (1.0 mL) and added into the reaction flask. The reaction mixture was stored in a freezer at –20 °C for 25.5 hours. After this, the reaction mixture was allowed to stand for 67 hours at 6 °C (cold room). The reaction mixture was diluted with ether (5 mL) and the combined organics were washed with brine (3 mL). The water layer was extracted once with ether (3 mL) and the combined organics were dried with $MgSO_4$. The filtration and concentration of the organics gave 41 mg of clear oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (10.2 mg ,45 %). The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5% i-PrOH in hexanes). The enantiomeric excess was 41 %. *Endo/exo* ratio was determined by ^{1}H NMR to be 25:1.

6.3.10 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-3,5-Dibenzyl-2-*tert*-butyl-imidazolidin-4-one **479a** (8.3 mg, 0.026 mmol, 20 mol-%) was dissolved in CH_3CN (1 mL) and a 0.1 M solution of HCl (0.25 mL) was

added. A 65 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (35.6 mg, 0.132 mmol, 100 mol-%) was dissolved in CH_3CN (1.5 mL) and added into the reaction flask. The reaction mixture was stored in a freezer at –20 °C for 25.5 hours. After this, the reaction mixture was allowed to stand for 68 hours at 6 °C (cold room). The reaction mixture was diluted with ether (5 mL) and the combined organics were washed with brine (3 mL). The water layer was extracted once with ether (2 mL) and the combined organics were dried with $MgSO_4$. Filtration and concentration of the organics gave 60 mg of yellow oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (9.3 mg, 40%). The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5% i-PrOH in hexanes). The enantiomeric excess was 56 %. *Endo/exo* ratio was determined by ^{1}H NMR to be 17:1.

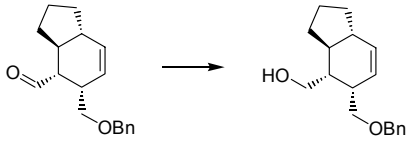
6.3.11 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-3,5-Dibenzyl-2-*tert*-butyl-imidazolidin-4-one **479a** (8.3 mg, 0.026 mmol, 19 mol-%) was dissolved in CH_2Cl_2 (1.5 mL) and i-PrOH (0.25 mL) was added. *p*-Toluenesulfonic acid monohydrate (4.9 mg, 0.026 mmol, 19 mol-%) was added. A 65 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (37.3 mg, 0.138 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (1.0 mL) and added into the reaction flask. The reaction mixture was stored in a freezer at –20 °C for 25.5 hours. After this, the reaction mixture was allowed to stand for 68 hours at 6 °C (cold room). The reaction mixture was diluted with ether (5 mL) and the combined organics were washed with brine (3 mL). The water layer was extracted once with ether (2 mL) and the combined organics were dried with $MgSO_4$. The filtration and concentration of the organics gave 48 mg of clear oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (9.1 mg, 38 %). The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5 % i-PrOH in hexanes). The enantiomeric excess was 12 %. *Endo/exo* ratio was determined by ^{1}H NMR to be 14:1.

6.3.12 (3a*S*',4*R*',5*S*',7a*R*')-5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-4-carbaldehyde (480)

(2*S*,5*S*)-3,5-Dibenzyl-2-*tert*-butyl-imidazolidin-4-one **479a** (8.3 mg, 0.026 mmol, 19 mol-%) was dissolved in CH_3CN (1 mL) and a 0.1 M solution of HCl (0.25 mL) was added. A 65 w-% 11-benzyloxy-undeca-2,7,9-trienal **470** (36.9 mg, 0.136 mmol, 100 mol-%) was dissolved in CH_3CN (1.5 mL) and added into the reaction flask. The reaction mixture was stirred for 72 hours. The reaction mixture was diluted with ether (5 mL) and the combined organics were washed with brine (3 mL). The water layer was extracted once with ether (2 mL) and the combined organics were dried with $MgSO_4$. The filtration and concentration of the organics gave 45 mg of yellow oil. The crude product was purified by flash chromatography (5 % EtOAc in hexanes) to yield **480** (13.0 mg, 54 %). The enantiomeric excess was determined from the corresponding alcohol by chiral HPLC (5 % i-PrOH in hexanes). The enantiomeric excess was 47 %. Only *endo*-cycloadduct was observed by ^1H NMR.

6.3.13 (3a*S*',4*R*',5*S*',7a*R*')-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-methanol (481)



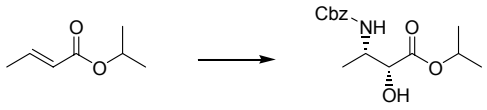
480 **481**

The cyclic aldehyde **480** (9 mg, 0.033 mmol, 100 mol-%) was dissolved in EtOH (1 mL) and $NaBH_4$ (excess) was added at r.t. The reaction mixture was stirred for 1 hour and quenched with 5 w-% aqueous solution of citric acid (1 mL). The product was extracted

with ether (3 x 2 mL) and washed with brine (2 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated to give 9.3 mg of **481** as a clear oil. R_f (40 % MTBE in hexanes) = 0.35. UV(max) = 239 nm. HPLC (5 % i-PrOH in hexanes). RT (minor diastereomer) = 11.4 min, RT (major diastereomer) = 13.7 min. The enantiomeric excess was 72 %. $[\alpha]_{20}^{D}$ = +92.5 (*c* 0.32, MeOH). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.33 (m, 5H), 5.90 (d, 1H, *J* = 9.8 Hz), 5.45 (ddd, 1H, *J* = 9.6, 4.3, 2.4 Hz), 4.52 (s, 2H), 3.67-3.51 (m, 4H), 3.35 (dd, 1H, *J* = 9.6, 1.7 Hz), 2.84 (m, 1H), 2.02 (m, 1H), 1.80-1.68 (m, 6H), 1.22-1.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 137.2, 132.2, 128.6, 128.1, 128.0, 127.4, 73.6, 71.2, 63.2, 46.1, 44.5, 41.7, 38.7, 28.7, 27.1, 22.5. HRMS (EI) calculated for $C_{18}H_{24}O_2$: 272.1776, found 272.1786.

6.4 Preparation of amino alcohol side chain by oxyamination

6.4.1 (2*R*,3*S*)-Isopropyl 3-(benzyloxycarbonylamino)-2-hydroxybutanoate (497)

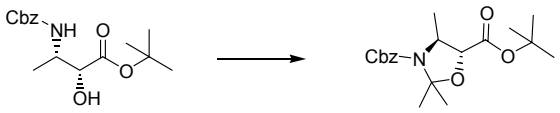


493 **497**

Benzyl carbamate (0.470 g, 3.10 mmol, 310 mol-%) was dissolved in CH_3CN (4 mL). NaOH (0.122 g, 3.05 mmol, 305 mol-%) in H_2O (7.5 mL) was added. After 5 minutes of stirring, 1,3-dichloro-5,5-dimethyl hydantoin (0.300 g, 1.52 mmol, 152 mol-%) was added. After 15 minutes of stirring, $(DHQD)_2PHAL$ (40 mg, 0.05 mmol, 5 mol-%) and *trans*-isopropyl crotonate **493** (0.129 g, 1.00 mmol, 100 mol-%) was dissolved in CH_3CN (3.5 mL) and added to the reaction mixture. This was followed by $K_2OsO_2(OH)_4$ (15 mg, 0.04 mmol, 4 mol-%). The reaction was followed by TLC (50 % EtOAc/hexane). The starting material consumption was followed by coloring the TLC plates with permanganate solution. The reaction mixture was brown at start. After 1 hour of stirring,

Na_2SO_3 (1 g) was added to the yellow reaction mixture to quench the reaction. After 30 minutes of stirring, the product was extracted with EtOAc (4 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried with Na_2SO_4 and filtered. The solvents were evaporated and the product was concentrated to give 0.791 g of yellowish solid. The crude product was purified by flash chromatography (25 % EtOAc/hexane) to give **497** (0.137 g, 46 %) as a white solid. Chlorinated ethyl carbamate was the main byproduct. R_f (50 % EtOAc in hexanes) = 0.40. HPLC (0.9 mL/min, 10 % i-PrOH in hexanes) RT (major) 10.94 min, (minor) 12.41 min. The enantiomeric excess was 91 %. $[\alpha]_{20}^{D}$ = -1.0 (c 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.36 – 7.30 (m, 5 H), 5.08 – 5.02 (m, 3 H), 4.97 (d, 1 H, *J* = 9.4 Hz), 4.26 (qv, 1 H, *J* = 7.2 Hz), 4.07 (dd, 1 H, *J* = 4.1, 2.2 Hz), 3.12 (d, 1 H, *J* = 4.1 Hz), 1.60 (s, 1 H), 1.27 (d, 6 H, *J* = 6.8 Hz), 1.21 (d, 3 H, *J* = 6.2 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 172.8, 155.5, 136.5, 128.5, 128.1, 128.0, 73.2, 70.5, 66.7, 49.0, 21.7, 21.4, 18.2. LRMS (EI+) 295, 236, 208, 178, 149, 134 (100), 121, 107, 91, 79, 65, 57. HRMS (EI+) calculated for $C_{15}H_{21}NO_5$: 295.1420, found 295.1416.

6.4.2 (4*R*,5*S*)-Benzyl 4-(*tert*-butoxycarbonyl)-2,2,4-trimethyl-3-oxazolidinecarboxylate (498)

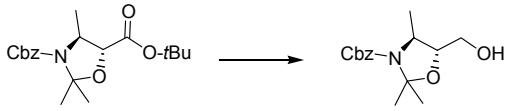


494 **498**

Benzene was dried by passing it through a pad of active alumina. *tert*-Butyl (*2R,3S*)-3-(benzyloxycarbonylamino)-2-hydroxybutanoate **494** (90 mg, 0.29 mmol, 100 mol-%) was dissolved in previously dried benzene (2 mL). 2,2-Dimethoxypropane (68 mg, 0.64 mmol, 221 mol-%) and *para*-toluenesulfonic acid monohydrate (1 mg, 0.005 mmol, 2 mol-%) was added and the resulting mixture was refluxed. The oil bath temperature was 80-88 °C. The reaction was followed by TLC (50 % EtOAc/hexane). After 2 hours of

refluxing, the reaction mixture was treated with H_2O (2 mL) and the product was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (5 mL). The organic layer was dried with Na_2SO_4 and filtered. The solvents were evaporated to give 0.1 g of yellow oil. The crude product was purified by flash chromatography (15 % EtOAc/hexane) to give **498** (85 mg, 83 %) as a white solid. M.p. 64-66 °C. R_f (50 % EtOAc/hexane) = 0.53. $[\alpha]_{20}^{D}$ = -10.9 (c 1.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.37-7.33 (m, 5 H), 5.16 (t, 2 H, *J* = 12.4 Hz), 4.26 (m, 1 H), 4.16 (d, 1 H, *J* = 4.1 Hz), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.48 (s, 9 H), 1.42 (s, 3 H). 13C NMR ($CDCl_3$, 100.62 MHz) 129.2, 128.7, 128.6, 83.0, 28.6. IR ($CHCl_3$) 3020, 1746, 1700, 1410, 1353, 1221, 1217, 1213, 1210, 1087, 759. LRMS (EI) 349, 334, 292, 278, 258, 248, 234, 204, 181, 158, 114, 91, 84, 77, 65(100). HRMS (EI) calculated for $C_{19}H_{27}NO_5$: 349.1889, found 349.1824.

6.4.3 (4*R*,5*S*)-5-Hydroxymethyl-2,2,4-trimethyl-oxazolidine-3-carboxylic acid benzyl ester (500)

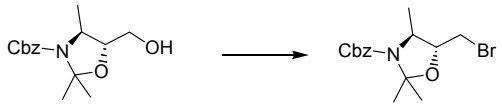


498 **500**

tert-Butyl oxazolidine derivative **498** (1.76 g, 5.03 mmol, 100 mol-%) in dry THF (50 mL) was cooled to 0 °C and $LiAlH_4$ (0.57 g, 19.13 mmol, 380 mol-%) was added in portions. The resulting mixture was stirred for 1.5 hours and the reaction was quenched with H_2O (0.6 mL). This was followed by NaOH (0.6 mL, 15 w-%) and H_2O (1.7 mL). The resulting mixture was stirred for 20 minutes and dried with Na_2SO_4. The mixture was filtered and treated with diethyl ether (20 mL). The mixture was filtered through a Celite pad and the pad was washed with ether (200 mL). The filtrate was dried with Na_2SO_4, filtered, concentrated and purified by flash chromatography (20 % EtOAc in hexanes) to

give **500** (1.22 g, 87 %) as a colorless oil. R_f (50 % EtOAc in hexanes) = 0.27. $[\alpha]_D^{20}$ = + 9.05 (c 1.00, $CHCl_3$). IR ($CHCl_3$) ν 3684, 3608, 3019, 2400, 1698, 1410, 1352, 1222, 1076, 757, 669 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34 (m, 5H), 5.15 (m, 2H), 3.84 (m, 2H), 3.75 (m, 1H), 3.62 (m, 1H), 2.04 (s, 1H), 1.65 (s, 3H), 1.54 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 137.1, 129.2, 128.8, 128.7, 101.2, 82.7, 67.4, 63.1, 54.4, 27.6, 26.9, 20.3, 14.9. LRMS (EI) m/z [M+1] 278, 264, 220, 105, 91(100), 84, 65, 59. HRMS (EI) calculated for $C_{15}H_{21}NO_4$: 279.1471, found 279.1385.

6.4.4 (4*R*,5*S*)-Benzyl 5-bromomethane-2,2,4-trimethyl-3-oxazolidine (501)

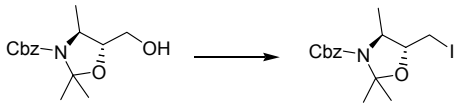


500 **501**

Crude benzyl (4*S*,5*R*)-4-hydroxymethyl-2,2,4-trimethyl-3-oxazolidine **500** (≈0.53 mmol, 100 mol-%) from the reaction above was dissolved in dry THF (10 mL). Triphenylphosphine (0.324 g, 1.24 mmol, 200 mol-%), carbon tetrabromide (0.408 g, 1.23 mmol, 200 mol-%) and diisopropylethylamine (0.158 g, 1.22 mmol, 200 mol-%) was added. The resulting mixture was stirred for 1 hour and the mixture was diluted with ether (50 mL). The organics were washed with 0.5 M H_3PO_4 (2 x 25 mL). The combined water layers were extracted with ether (25 mL). The organics were washed with a saturated solution of $NaHCO_3$. The water layer was extracted with ether (25 mL). The combined organics were washed with brine (25 mL), filtered and concentrated to give 0.577 g of brown oil. The crude product was purified by flash chromatography (6 % EtOAc/C_6) to give **501** (0.136 g, 75 % from **498**) as a clear oil. R_f **501** (50 % EtOAc/hexane) = 0.55. $[\alpha]_{20}^D$ = +9.5 (c 1.59, $CHCl_3$). ^1H NMR ($CDCl_3$/TMS, 400.13 MHz) δ 7.38-7.31 (m, 5 H), 5.20 (m, 2 H), 4.01 (m, 2 H), 3.42 (d, 2 H, *J* = 6.0 Hz), 3.21

(q, 1 H, *J* = 7.2 Hz), 1.65 (s, 3 H), 1.56 (s, 3 H), 1.36 (s, 3 H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) 153.0, 137.0, 129.2, 128.8, 128.7, 96.3, 82.3, 67.4, 57.4, 33.7, 28.4, 27.7, 21.1. LRMS (EI+) 341, 326, 282, 248, 236, 204, 164, 135, 107, 92(100), 77, 65, 51. HRMS (EI) calculated for $C_{15}H_{20}BrNO_3$: 341.0627, found [M-1] 340.0578.

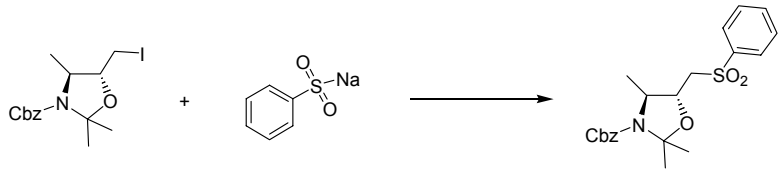
6.4.5 (4*R*,5*S*)-5-Iodomethyl-2,2,4-trimethyl-oxazolidine-3-carboxylic acid benzyl ester (502)



500 **502**

Triphenyl phosphine (1.56 g, 5.94 mmol, 150 mol-%) and imidazole (0.40 g, 5.94 mmol, 150 mol-%) was added into a solution of alcohol **500** (1.11 g, 5.03 mmol, 100 mol-%) in dry CH_2Cl_2 (40 mL). Iodine (1.51 g, 5.94 mmol, 150 mol.%) was added into the mixture and the reaction mixture was stirred for 5 hours. The reaction mixture was diluted with diethyl ether (100 mL) and washed with 0.5 M H_3PO_4 (50 mL). The product was extracted with diethyl ether (3 x 50 mL) and washed with a saturated solution of $NaHCO_3$ (50 mL) and brine (50 mL). The organics were dried with Na_2SO_4, filtered and concentrated to give white solid. The crude product was purified by flash chromatography (10 % EtOAc in hexanes) to give **502** (1.16 g, 76 %) as a clear oil. R_f **502** (50 % EtOAc in hexanes) = 0.62. $[\alpha]_D^{20}$ = + 6.9 (c 1.00, $CHCl_3$). IR ($CHCl_3$) ν 3682, 3492, 3017, 2401, 1698, 1409, 1353, 1211, 1093, 770, 668 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.34 (m, 5H), 5.11 (m, 2H), 3.92 (m, 2H), 3.25 (m, 2H), 1.67 (s, 3H), 1.55 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 153.0, 137.0, 129.2, 128.8, 128.7, 96.4, 82.5, 67.4, 58.5, 28.5, 27.9, 21.1, 8.3. LRMS (EI) m/z [M+1] 390, 374(100), 330, 282, 224, 181, 148, 107, 91, 84, 77, 65, 59, 51. HRMS (EI) calculated for $C_{15}H_{20}NIO_4$: 389.0488, found 389.0465.

6.4.6 (4*R*,5*S*)-Benzyl 5-sulfonylphenylmethane-2,2,4-trimethyl-3-oxazolidine (504)

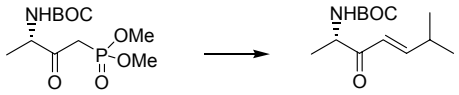


502 **503** **504**

Benzyl (4*S*,5*R*)-4-iodomethane-2,2,4-trimethyl-3-oxazolidine **502** (45 mg, 0.12 mmol, 100 mol-%) was dissolved in dry DMF (2 mL) and sodium phenylsulfone **503** (57 mg, 0.35 mmol, 292 mol-%) was added at r.t. and stirring was continued for 30 minutes. After this, the reaction mixture was warmed with an oil bath to + 50 °C. Stirring was continued for 13 hours. A second portion of sodium phenylsulfone (30 mg, 0.02 mmol, 17 mol-%) was added and stirring was continued for 7 hours. The third portion of sodium phenylsulfone (27 mg, 0.02 mmol, 17 mol-%) was added and stirring was continued for 16 hours. The reaction mixture was cooled to r.t. and the product was partitioned between H_2O (10 mL) and ether (10 mL). The layers were separated and the water phase was extracted with ether (3 x 10 mL). The combined organics were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated to give 46 mg of clear oil. The product was purified by flash chromatography (40 % MTBE in hexanes) to give **504** (35 mg, 76 %) as a clear oil. R_f (40 % MTBE/hexane) = 0.15. $[\alpha]_{20}^{D}$ = - 22.2 (c 0.99, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.93 – 7.34 (m, 10H), 5.17 – 5.09 (m, 2H), 4.25 (dt, 1H, *J* = 4.1, 6.1 Hz), 3.90 (s, 1H), 3.37 (qd, 2H, *J* = 14.3, 6.1 Hz), 1.47 (s, 3H), 1.40 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100.613 MHz) δ 152.8, 140.2, 136.9, 134.6, 129.9, 129.2, 129.0, 128.8, 128.7, 96.0, 67.5, 60.9, 58.5, 28.0, 27.5, 20.3. LRMS (EI+) 403, 388, 344, 312, 268, 204, 181, 160, 141, 126, 112, 91, 77(100), 65, 51. HRMS (EI+) calculated for [M+1] $C_{21}H_{26}NO_5S$: 404.1533, found 404.1541.

6.5 Preparation of amino alcohol side chain by HWE and Wittig approaches

6.5.1 (1*S*)-(1,5-Dimethyl-2-oxo-hex-3-enyl)-carbamic acid *tert*-butyl ester (463)



413 **463**

Ethanol was distilled from $Mg(OEt)_2$ to 3 Å molecular sieve powder. (3*S*)-(3-*tert*-Butoxycarbonylamino-2-oxo-butyl)-phosphonic acid dimethyl ester **413** (63 mg, 0.21 mmol, 100 mol-%) was dissolved in dry EtOH (2 mL) and K_2CO_3 (30 mg, 0.22 mmol, 102 mol-%) was added. Stirring was continued for 15 minutes and isobutyraldehyde (17 mg, 0.24 mmol, 111 mol-%) in dry EtOH (2 mL) was added. The reaction mixture was stirred for 40 minutes and reaction was not noticed. A drop of water was added. A slow reaction was noticed. Stirring was continued for 2 hours and 2 drops of water was added. Stirring was continued for 25.5 hours and the reaction mixture was filtered. The reaction mixture was concentrated and EtOAc (5 mL) was added. The organics were washed with a 10 w-% aqueous solution of citric acid (5 mL). The water phase was extracted with EtOAc (2 x 5 mL). The combined organics were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated to give 86 mg of white precipitate. The crude product was purified by flash chromatography (10 % EtOAc in hexanes) to give **463** (36 mg, 69 %) as a white solid. M.p. 49-51 °C. $[\alpha]_{20}^{D}$ = +10.5 (c 1.0, $CHCl_3$). R_f (15 % EtOAc in hexane) = 0.22. The product was analyzed by chiral HPLC (flow rate 0.6 mL/min, 5 % i-PrOH in hexanes). The retention times with HPLC were (**463**) 10.44 min, (enantiomer) 13.96 min. GLC (Supelco γ-dex) (inj. 240 °C, vel. 28 cm/sec, 100-220 °C, 8 °C/min, det. 270 °C. The retention times with GLC were (**463**) 14.85 min, (enantiomer) 15.49 min. The enantiomeric excess was >99 %ee. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 6.97 (dd, 1 H,

J = 15.8, 6.7 Hz), 6.13 (d, 1 H, *J* = 15.9 Hz), 5.40 (s, 1H), 4.58 (t, 1 H, *J* = 7.2 Hz), 2.49 (m, 1H), 1.44 (s, 9 H), 1.33 (d, 3 H, *J* = 7.0 Hz), 1.08 (d, 6 H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 199.1, 156.2, 155.5, 124.0, 79.9, 53.6, 31.7, 28.7, 21.5, 21.5, 19.2. LRMS (EI+) 242 (M+1), 168, 144, 125, 97, 88, 57(100). HRMS (EI+) calculated for [M+1] $C_{13}H_{24}NO_3$: 242.1758, found 242.1704.

6.5.2 (1*S*)-(1,5-Dimethyl-2-oxo-hex-3-enyl)-carbamic acid *tert*-butyl ester (463)

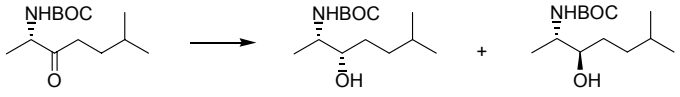
(3*S*)-(3-*tert*-Butoxycarbonylamino-2-oxo-butyl)-phosphonic acid dimethyl ester **413** (151 mg, 0.51 mmol, 100 mol-%) was dissolved in CH_3CN (5 mL) and K_2CO_3 (141 mg, 1.02 mmol, 200 mol-%) was added. The reaction mixture was stirred for 2 minutes and isobutyraldehyde (55 mg, 0.75 mmol, 150 mol-%) was added. Stirring was continued in an argon atmosphere for 5 days and the reaction mixture was neutralized by adding a 10 w-% aqueous solution of citric acid. The product was extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated to give 0.236 g of yellow oil. The crude product was purified by flash chromatography (10 % EtOAc in hexanes) to give **463** (75 mg, 61 %) as a white solid. The enantiopurity was determined by GLC. The temperature program was 240 °C (inj.), oven 100-220 °C/8 °C/min, 28 cm (vel.), 240 °C (det.). The retention times with GLC were (**463**) 14.8 min, (enantiomer) 15.4 min. The enantiomeric excess was 97 %. See chapter 6.5.1. for analytical details.

6.5.3 (1*S*)-(1,5-Dimethyl-2-oxo-hexyl)-carbamic acid *tert*-butyl ester (485)

463 **485**

Enone (**463**) (56 mg, 0.232 mmol, 100 mol-%) was dissolved in THF (6 mL). Freshly prepared Raney Ni (W2) in EtOH (100 pipette drops) was added. Stirring was continued for 40 minutes at room temperature. After this, the reaction mixture was filtered through a short pad (2 cm) of silica. Ether (3 x 4 mL) was used for flushing the pad. The solvents were evaporated to give 61 mg of clear oil. The crude product was purified by flash chromatography. The eluent was 10% EtOAc in hexanes. The yield of **485** was 50 mg (89 %) as a white solid. R_f **485** (32 % EtOAc in hexanes) = 0.45. GLC (Supelco γ-dex) (inj. 250 °C, vel. 28 cm/sec, 100-200 8 °C/min, det. 240 °C). The retention times were (**485**) 14.0 min, (enantiomer) 14.3 min. The enantiomeric excess was 96 %. $[\alpha]_{20}^{D}$ = -0.4 (c 1.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 5.31 (s, 1H), 4.32 (t, 1H, *J* = 7.0 Hz), 2.50 (m, 2H), 1.53 (m, 3H), 1.44 (s, 9H), 1.33 (d, 3H, *J* = 7.2 Hz), 0.89 (dd, 6H, *J* = 6.2, 1.1 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 209.8, 155.1, 79.6, 55.0, 37.1, 32.3, 28.3, 27.6, 22.3, 22.2, 17.9. HRMS (ES+) calculated for $C_{13}H_{25}NO_3Na$: 266.1732, found 266.1717.

6.5.4 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)



485 **486a** **486b**

$ZnBr_2$ (13.0 mg, 0.058 mmol, 123 mol-%) was dissolved in dry ether (1 mL). Amino ketone **485** (11.4 mg, 0.047 mmol, 100 mol-%) in dry ether (1.5 mL) was added at 0 °C. The resulting mixture was stirred for 40 minutes. After this, the reaction mixture was cooled to – 78 °C and 1.0 M solution of DIBAL-H in toluene (140 µl, 0.140 mmol, 300 mol-%) was added dropwise. Stirring was continued for 35 minutes at – 78 °C and MeOH (0.5 mL) was added to quench the reaction. This was followed by a 1 M solution of HCl (2 mL). The reaction mixture was allowed to warm to r.t. and the stirring was continued for 15 minutes. The product was extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine (2 mL), dried with $MgSO_4$, filtered and concentrated to give 10 mg (77 %) of **486a,b** as a white solid. R_f (32 % EtOAc in hexanes) = 0.20. GLC (Supelco γ-dex) (inj. 240 °C, vel. 28 cm/sec, 100-200 8 °C/min, det. 270 °C). RT (*S,R*-**486b**) 15.20 min, RT(*S,S*-**486a**) = 15.70 min. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:7.1 The enantiomeric excess was 75 %. ^{1}H NMR **486a** ($CDCl_3$, 400.132 MHz) δ 4.78 (m, 1H), 3.70 (m, 1H), 3.62 (m, 1H), 2.14 (m, 1H), 1.65-1.18 (m, H), 1.44 (s, 9H), 1.09 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 6H, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 155.8, 79.4, 74.7, 50.5, 35.1, 31.3, 28.4, 28.1, 22.5 (d), 14.3. HRMS (ES+) calculated for $C_{13}H_{27}NO_3Na$: 268.1889, found 268.1883.

6.5.5 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

Amino ketone **485** (13.5 mg, 0.055 mmol, 100 mol-%) was dissolved in dry THF (2 mL). $ZnBr_2$ (15.4 mg, 0.068 mmol, 123 mol-%) was added at 0 °C. The resulting mixture was stirred for 60 minutes. After this, the reaction mixture was cooled to – 78 °C and a 1.0 M solution of DIBAL-H in toluene (280 µl, 0.280 mmol, 500 mol-%) was added dropwise. Stirring was continued for 45 minutes at – 78 °C and MeOH (0.5 mL) was added to quench the reaction. This was followed by a 1 M solution of HCl (2 mL). The reaction mixture was allowed to warm to r.t. and stirring was continued for 15 minutes.

The product was extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine (2 mL), dried with $MgSO_4$, filtered and concentrated to give 17 mg of crude product. The product was analyzed by chiral GLC. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:4.1. For analytical data see 6.5.4.

6.5.6 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

Amino ketone **485** (10.3 mg, 0.042 mmol, 100 mol-%) was dissolved in dry THF (1.5 mL). The reaction mixture was cooled to – 95 °C ($MeOH/N_2(l)$) and 1.0 M solution of *L*-Selectride in THF (150 µl, 0.150 mmol, 355 mol-%) was added dropwise. Stirring was continued for 35 minutes at – 95 °C and H_2O (0.5 mL) was added to quench the reaction. The reaction mixture was allowed to warm to room temperature. The product was extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine (2 mL), dried with $MgSO_4$, filtered and concentrated to give 26 mg of clear oil. The crude product was purified by flash chromatography (15 % EtOAc in hexanes) to give **486a,b** was (11.5 mg, >99 %) as a white solid. The product was analyzed by chiral GLC. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:3.5. $[\alpha]_{20}^{D}$ = -1.0 (c 0.99, $CHCl_3$). For analytical data see 6.5.4.

6.5.7 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

Amino ketone **485** (34.9 mg, 0.143 mmol, 100 mol-%) was dissolved in dry THF (1 mL) and freshly prepared *D*-*B*-Me-CBS catalyst in toluene (143 µl, 0.143 mmol, 100 mol-%) was added. The reaction mixture was cooled to – 24 °C (ethylene glycol/CO_2). A 2.0 M solution of $BH_3 \cdot SMe_2$ in THF (80 µl, 0.160 mmol, 112 mol-%) was added dropwise. Stirring was continued for 1 hour and MeOH (0.5 mL) was added to quench the reaction.

This was followed by 1M HCl (1 mL). The reaction mixture was allowed to warm to room temperature. The product was extracted with EtOAc (4 x 3 mL). The combined organics were washed with brine (3 mL), dried with $MgSO_4$, filtered and concentrated to give 47 mg of white solid. The product was analyzed by GLC. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:1.4. For analytical data see 6.5.4.

6.5.8 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

$ZnBr_2$ (11.0 mg, 0.058 mmol, 123 mol-%) was dissolved in dry THF (1 mL). Amino ketone **485** (9.5 mg, 0.039 mmol, 100 mol-%) in dry ether (1.5 mL) was added at 0 °C. The resulting mixture was stirred for 55 minutes. After this, the reaction mixture was cooled to – 78 °C and a 1.0 M solution of *L*-Selectride in THF (140 µl, 0.140 mmol, 300 mol-%) was added dropwise. Stirring was continued for 30 minutes at – 78 °C and 1M HCl (1 mL) was added to quench the reaction. The reaction mixture was allowed to warm to r.t. and stirring was continued for 15 minutes. The product was extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine (2 mL), dried with Na_2SO_4, filtered and concentrated to give 9.1 mg (95 %) of pure product. The product was analyzed by chiral GLC. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:3.8. For analytical data see 1.5.3.

6.5.9 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

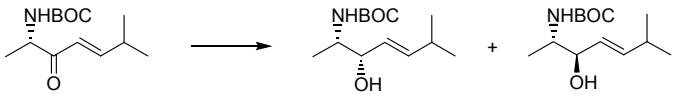
Amino ketone **485** (12.0 mg, 0.049 mmol, 100 mol-%) was dissolved in dry toluene (2 mL). The reaction mixture was cooled to – 78 °C and a 1.0 M solution of DIBAL-H in toluene (148 µl, 0.148 mmol, 300 mol-%) was added dropwise. Stirring was continued for 20 minutes at – 78 °C and MeOH (0.5 mL) was added to quench the reaction. This was followed by a 1 M solution of HCl (2 mL). The reaction mixture was allowed to

warm to r.t. and stirring was continued for 15 minutes. The product was extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine (2 mL), dried with $MgSO_4$, filtered and concentrated to give 12.2 mg (>99 %) of **486a,b**. The product was analyzed by chiral GC. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:3.3. For analytical data see 6.5.4.

6.5.10 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

Amino ketone **485** (10.9 mg, 0.045 mmol, 100 mol-%) was dissolved in MeOH (1 mL). $CeCl_3 \cdot 7H_2O$ (18.4 mg, 0.049 mmol, 120 mol-%) was added. The mixture was stirred until $CeCl_3$ dissolved. $NaBH_4$ (4.3 mg, 0.114 mmol, 276 mol-%) was added and stirring was continued for 20 minutes. After this, a 5 w-% solution of citric acid (2 mL) was added and stirring was continued for 5 minutes. The product was extracted with EtOAc (3 x 3 mL). The combined organics were washed with brine (2 mL), dried with $MgSO_4$, filtered and concentrated to give 13.9 mg crude product. The product was analyzed by chiral GC. The ratio of (*S,R*-**486b**) to (*S,S*-**486a**) was 1:5.3. For analytical data see 6.5.4.

6.5.11 (1*S*,2*S/R*)-(2-Hydroxy-1,5-dimethyl-hex-3-enyl)-carbamic acid *tert*-butyl ester (487a,b)

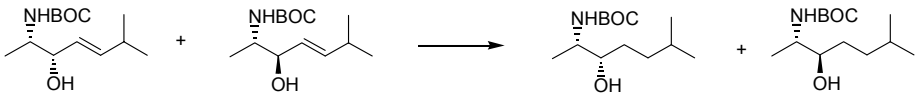


463 **487a** **487b**

Ether was distilled from Na/benzophenone to 4Å molecular sieves. A 10 mL flask was flame dried and filled with argon. (1,5-Dimethyl-2-oxo-hex-3-enyl)-carbamic acid *tert*-

butyl ester **463** (16 mg, 0.065 mmol, 100 mol-%) was dissolved in dry ether (3 mL) and the resulting mixture was cooled to – 78 °C (acetone/CO_2(s)). A 1.0 M solution of *L*-selectride® in THF (200 µl, 0.200 mmol, 310 mol-%) was added dropwise into the reaction mixture. The reaction mixture was stirred for 1 hour and H_2O (0.5 mL) was added dropwise and the mixture was allowed to warm to r.t. Ether was evaporated and the product was partitioned between CH_2Cl_2 (10 mL) and brine (5 mL). The water layer was extracted thrice with CH_2Cl_2 (3 x 5 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated to give 23 mg of clear oil. The crude product was purified by flash chromatography (13 % EtOAc in hexanes) to give **487a,b** (15 mg, 92 %) as a clear oil. R_f (50 % EtOAc in hexanes) = 0.44. $[\alpha]_{20}^{d}$ = - 8.0 (c 1.00, $CHCl_3$). λ_{max} = 202 nm. HPLC (5 % i-PrOH in hexanes, λ = 235 nm). RT (*S,R*-**487b**) 4.45 min, RT (*S,S*-**487a**) 6.34 min. The ratio of (*S,R*-**487b**) to (*S,S*-**487a**) was 1:1.1. ^{1}H NMR (*S,R*-**487a**) ($CDCl_3$, 400.132 MHz) δ 5.69 (dddd, 1H, *J* = 15.5, 6.7, 2.9, 1.2 Hz), 5.41 (dddd, 1H, *J* = 15.5, 14.7, 7.2, 1.4 Hz), 4.65 (s, 1H), 4.11 (m, 1H), 3.65 (q, 1H, *J* = 6.6 Hz) 2.30 (m, 2H), 1.44 (s, 9H), 1.07 (d, 3H, *J* = 6.8 Hz),1.00 (dd, 6H, *J* = 6.8, 1.9 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 157.0, 141.6, 126.1, 80.3, 76.5, 51.8, 31.6, 29.1, 23.0, 22.9, 16.2. LRMS (EI+) 240, 205, 172, 144, 128, 109, 99, 88, 81, 69, 57(100). HRMS (EI+) calculated for $C_{13}H_{25}NO_3$: 244.1913, found 244.1914.

6.5.12 (1*S*,2*S/R*)- (2-Hydroxy-1,5-dimethyl-hexyl)-carbamic acid *tert*-butyl ester (486a,b)

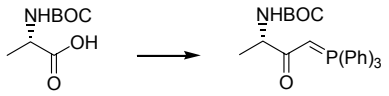


487a **487b** **486a** **486b**

A mixture diastereomers **487a,b** (7.1 mg, 0.03 mmol, 100 mol-%) was dissolved in MeOH (1 mL). Cyclohexene (2.2 mg, 0.03 mmol, 100 mol-%) was added in THF (0.5 mL). The reaction mixture was bubbled with argon to remove oxygen for 5 minutes. 5%

Pd on $CaCO_3$ was added and the reaction flask was flushed with H_2 gas. The reaction mixture was stirred for 21 hours under H_2 atmosphere. After this, the reaction mixture was filtered through a Celite pad. The Celite pad was flushed with MeOH. The solvents were evaporated to give 6.3 mg of clear oil. Cyclohexene reacted to cyclohexane during the reaction. R_f **486a,b** (23 % EtOAc in hexanes) = 0.27. For analytical data see 6.5.4.

6.5.13 (1*S*)-[1-Methyl-2-oxo-3-(triphenyl-Λ-phosphanylidene)-propyl]-carbamic acid *tert*-butyl ester (465)

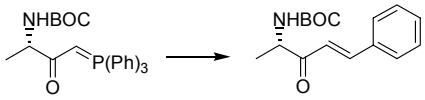


464 **465**

Methyltriphenylphosphonium bromide (2.19 g, 6.0 mmol, 300 mol-%) was diluted with dry benzene (60 mL) in a flame dried flask, filled with argon. The previously prepared phenyllithium (0.758 M, 8.0 mL, 6.1 mmol, 305 mol-%) was added dropwise in 10 minutes. The white slurry changed to brownish yellow clear solution during the addition. *N*-BOC-(*L*)-alanine **464** (0.38 g, 2.0 mmol, 100 mol-%) was dissolved in dry benzene (23 mL). To this flask, 1,1-carbonyldiimidazole (0.40 g, 2.5 mmol, 125 mol-%) was added in one portion. The flask containing methylene phosphorane was cooled to – 78 °C, this resulted freezing of the mixture. The reaction mixture was allowed to warm until the solution was homogenous. After this, the solution of imidazole derivative of **464** was added dropwise into the cooled flask containing methylene phosphorane in 15 minutes. Stirring was continued at r.t. for 1 hour. The product was partitioned between brine (100 mL) and EtOAc (100 mL). The layers were separated and the water phase was extracted once with EtOAc (50 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated to give 1.72 g of brown oil and clear oil in two different phases. The crude product was purified by flash chromatography (85 % EtOAc in hexanes) to yield **465** (0.49 g, 54 %) as an yellow solid. M.p. 48-50 °C. R_f (EtOAc) = 0.19. $[\alpha]_{20}^{D}$ = - 1.5 (c

1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 400.132 MHz) δ 7.63-7.46 (m, 15 H), 5.73 (d, 1 H, *J* = 6.5 Hz), 4.33-4.30 (m, 1 H), 3.71 (d, 1 H, *J* = 24.4 Hz), 1.42 (s, 12 H). ^{13}C NMR ($CDCl_3$, 100.613 MHz) δ 191.6, 156.2, 133.7, 133.6, 132.8, 132.8, 132.7, 132.6, 129.6, 129.5, 129.2, 129.1, 127.9, 127.0, 79.0, 61.0, 53.6, 53.4, 29.1, 22.0, 21.7. LRMS (EI+) 447, 374, 304(100), 277, 262, 228, 201, 183, 165, 152, 108, 77, 57. HRMS (EI+) calculated for [M+1] $C_{27}H_{31}NO_3P$: 448.2042, found 448.2075.

6.5.14 (1*S*)-(1-Methyl-2-oxo-4-phenyl-but-3-enyl)-carbamic acid *tert*-butyl ester (466)



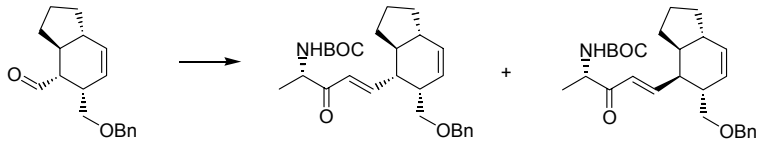
465 **466**

Benzaldehyde was distilled in reduced pressure (bp = 8 mmHg/61 °C). Benzaldehyde (11 mg, 0.16 mmol, 100 mol-%) was diluted with dry benzene (2 mL). (*1S*)-[1-Methyl-2-oxo-3-(triphenyl-Λ-phosphanylidene)-propyl]-carbamic acid *tert*-butyl ester **465** (104 mg, 0.23 mmol, 150 mol-%) was added and the reaction mixture was refluxed for 46 hours under argon atmosphere. Benzene evaporated during the reflux period and the residue was treated with EtOAc (5 mL). The organics were washed with brine (5 mL) and the separated water phase was extracted twice with EtOAc (5 mL). The combined organics were dried with Na_2SO_4, filtered and concentrated to give 122 mg of orange oil. The crude product was purified by flash chromatography (15 % MTBE in hexanes) to yield **466** (33 mg, 76%) as a thick clear oil. R_f (30 % MTBE in hexanes) = 0.26. $[\alpha]_{20}^{D}$ = +6.5 (c 1.57, $CHCl_3$). ^1H NMR ($CDCl_3$, 400.132 MHz) δ 7.71 (d, 1 H, *J* = 16.0 Hz), 7.58 – 7.40 (m, 5 H), 6.82 (d, 1 H, *J* = 16.0 Hz), 5.46 (d, 1 H, *J* = 6.5 Hz), 4.68 (t, 1 H, *J* = 7.2 Hz), 1.46 (s, 9 H), 1.41 (d, 3 H, *J* = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 199.0, 155.9, 145.1, 134.9, 131.5, 129.7, 129.2, 123.0, 80.4, 54.5, 29.0, 19.3. LRMS (EI+) 276

(M+1), 202, 158, 144, 131, 103, 88, 77, 57(100), 51. HRMS (EI+) calculated for [M+1] $C_{16}H_{22}NO_3$: 276.1600, found 276.1591.

6.6 Synthesis of amaminol analog by HWE and Kociensky-Julia approach

6.6.1 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*]-[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-1-methyl-2-oxo-but-3-enyl]-carbamic acid *tert*-butyl ester (489a,b)

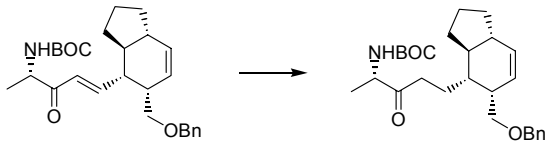


480 **489a** **489b**

(3-*tert*-Butoxycarbonylamino-2-oxo-butyl)-phosphonic acid dimethyl ester **413** (1.15 g, 3.89 mmol, 105 mol-%) was dissolved in EtOH (94 w-%) (15 mL) and K_2CO_3 (0.54 g, 3.89 mmol, 105 mol-%) was added. The reaction mixture was stirred for 2 minutes and 5-benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-*1H*-indene-4-carbaldehyde **480** (0.96 g, 3.55 mmol, 100 mol-%, 72% ee) in EtOH (94 w-%) (22 mL) was added. Stirring was continued for 29 hours. A second portion of K_2CO_3 (0.23 g, 1.67 mmol, 47 mol-%) was added. Stirring was continued for 18 hours and the reaction mixture was filtered. The solids were washed with EtOH (Aa-grade) (20 mL). The solvents were evaporated and the resulting orange oil was diluted with $CHCl_3$ (70 mL) and the organic phase was

washed twice with a saturated aqueous solution of NH_4Cl (2 x 25 mL). PH of the aqueous phase was 4 at this point. The combined organics were washed with H_2O (20 mL), dried with $MgSO_4$, filtered and concentrated to give 2.05 g of yellow oil. The crude product was purified by flash chromatography (10 % EtOAc in hexanes) to give **489a,b** (1.24 g, 79 %) as a clear oil. The product was a mixture of diastereomers (**489a:489b**) with ratio 1.3:1. This was determined by ^{1}H NMR. It was possible to separate diastereomers, but the separation of conformers was not achieved by flash chromatography or chiral HPLC. The yield of **489a** was 44 % as a clear oil. R_f (20 % MTBE in hexanes) = 0.43. $[\alpha]_{20}^{D}$ = + 33.2 (c 1.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.33-7.26 (m, 5H), 7.01 (dd, 1H, *J* = 15.9, 8.9 Hz), 6.19 (d, 1H, *J* = 15.9 Hz), 5.96 (d, 1H, *J* = 10.0 Hz), 5.49 (dt, 1H, *J* = 10.1, 2.9 Hz), 5.42 (d, 1H, *J* = 5.0 Hz), 4.59-4.45 (m, 3H), 3.46-3.34 (m, 2H), 2.88 (d, 1H, *J* = 8.8 Hz), 2.50 (m, 1H), 1.83 (m, 2H), 1.70-1.55 (m, 4H), 1.44 (s, 9H), 1.32 (d, 3H, *J* = 7.0 Hz), 1.28-1.10 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 198.2, 155.1, 149.5, 138.3, 132.5 (d), 128.4, 127.6 (d), 126.0 (d), 79.5, 72.9 (d), 72.7 (d), 53.2, 42.9 (d), 41.8, 39.8, 39.2 (d), 28.7 (d), 28.3, 26.1, 22.0, 19.0. LRMS (EI+) 440 (M+1), 383, 339, 295, 275, 248, 231, 218, 187, 159, 144, 131, 105, 91, 79, 65, 57(100). HRMS (ES+) calculated for $C_{27}H_{37}NO_4Na$: 462.2620, found 462.2624.

6.6.2 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*]-[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-1-methyl-2-oxo-butyl]-carbamic acid *tert*-butyl ester (512)

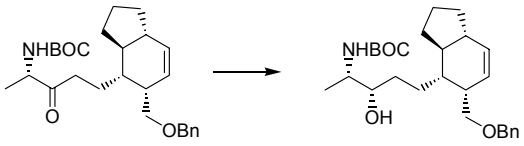


489a **512**

[*4*-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1H-inden-4-yl)-1-methyl-2-oxo-but-3-enyl]-carbamic acid *tert*-butyl ester **489a** (171 mg, 0.39 mmol, 100 mol-%) was dissolved

in THF (23 mL) and the mixture was cooled to 0 °C. A suspension of Raney Ni in EtOH (0.6 g/mL) (5 mL) was added dropwise in 10 minutes. The resulting mixture was stirred for 90 minutes at 0 °C. A second portion of Raney Ni in EtOH (2 mL) was added and stirring was continued for 15 minutes at 0 °C. After this, the cooling bath was removed for 15 minutes and the reaction mixture was filtered through a thin pad of silica (3 cm). Ether (3 x 5 mL) was used for washing the pad. The solvents were evaporated to give 167 mg of clear oil. The crude product was purified by flash chromatography (15% MTBE in hexanes) to give **512** (154 mg, 89 %) as a clear oil. R_f (20 % MTBE in hexanes) = 0.20. $[\alpha]_{20}^{D}$ = + 8.9 (c 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.32 (m, 5H), 5.90 (d, 1H, *J* = 9.8 Hz), 5.41 (dt, 1H, *J* = 9.7, 3.2 Hz), 5.25 (m, 1H), 4.51 (m, 2H), 4.29 (m, 1H), 3.37 (m, 1H), 3.28 (t, 1H, *J* = 9.2 Hz), 2.56 (m, 2H), 2.31 (m, 1H), 1.85-1.44 (m, 9H), 1.43 (s, 9H), 1.26 (m, 5H). 13C NMR ($CDCl_3$, 100.62 MHz) δ 210.0 (d), 155.2, 138.6, 138.5, 132.6, 128.4 (d), 127.6 (d), 126.3, 79.6, 73.3, 73.0, 55.1 (d), 43.6, 41.9, 38.5 (d), 37.3 (d), 35.5, 29.2, 28.3, 25.7, 22.3, 20.9 (d), 17.8. LRMS (EI+) 442 (M+1), 385, 342, 297, 277(100), 259, 246, 233, 220, 198, 185, 171, 159, 144, 119, 105, 91, 79, 65, 57. HRMS (ES+) calculated for $C_{27}H_{39}NO_4Na$: 464.2777, found 464.2774.

6.6.3 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*,2*S*]-[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-2-hydroxy-1-methyl-butyl]-carbamic acid *tert*-butyl ester (513)

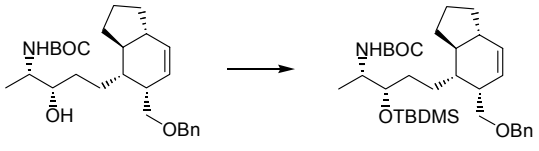


512 **513**

$ZnBr_2$ (96 mg, 0.424 mmol, 123 mol-%) was dissolved in dry ether (7 mL) and cooled with an ice bath to 0 °C. [4-(5-Benzyloxymethyl-2,3,3aR,4S,5R,7aS-hexahydro-1H-inden-4-yl)-1S-methyl-2-oxo-butyl]-carbamic acid tert-butyl ester **512** (153 mg, 0.346

mmol, 100 mol-%) in dry ether (11 mL) was added. The resulting mixture was stirred for 50 minutes at 0 °C. After this, the reaction mixture was cooled to – 78 °C. A 1.0 M solution of DIBAL-H in toluene (1.9 mL, 1.90 mmol, 549 mol-%) was added dropwise into the reaction mixture in portions until the reaction was ready by TLC (32% EtOAc in hexanes). The reaction was ready after addition by TLC. After 1 hour, the reaction mixture was quenched with MeOH (3 mL) and a solution of 1 M HCl (5 mL). The cooling bath was removed and stirring was continued for 25 minutes. The product was extracted with EtOAc (3 x 15 mL), washed with brine (15 mL), dried with Na_2SO_4, filtered and concentrated to give 160 mg of yellowish oil. The crude product was purified by flash chromatography (6 % *i*-PrOH in hexanes) to yield **513** (130 mg, 85 %) as a clear oil. R_f (10% *i*-PrOH in hexanes) = 0.27. $[\alpha]_{20}^{D}$ = + 5.4 (c 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.33-7.26 (m, 5H), 5.89 (d, 1H, *J* = 9.9 Hz), 5.43 (m, 1H), 4.77 (m, 1H), 4.56-4.47 (m, 2H), 3.62 (m, 2H), 3.41-3.38 (m, 1H), 3.33 (t, 1H, *J* = 9.2 Hz), 2.41 (m, 1H), 1.90-1.44 (m, 11H), 1.44 (s, 9H), 1.14-1.08 (m, 2H), 1.05 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 155.8, 138.6 (d), 132.3 (d), 128.3, 127.5 (d), 126.7 (d), 79.4, 74.9, 74.5, 73.6, 72.9, 50.6, 43.8, 41.6 (d), 38.6 (d), 35.6 (d), 31.6 (d), 29.2, 28.4, 25.7, 23.8, 23.3, 22.3, 14.3 (d). HRMS (ES+) calculated for $C_{27}H_{41}NO_4Na$: 466.2933, found 466.2913.

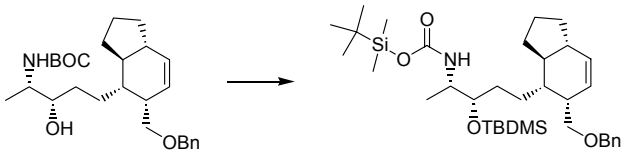
6.6.4 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*,2*S*]-[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-butyl]-carbamic acid *tert*-butyl ester (515)



513 **515**

[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1H-inden-4-yl)-2-hydroxy-1-methyl-butyl]-carbamic acid tert-butyl ester **513** (40 mg, 0.090 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (2 mL). The mixture was cooled to 0 °C and 2,6-lutidine (24 mg, 0.225 mmol, 250 mol-%) was added. The resulting mixture was stirred for 5 minutes and neat *tert*-butyldimethylsiloxy triflate (48 mg, 0.180 mmol, 200 mol-%) was added dropwise. The mixture was stirred for 20 minutes at 0 °C. After this, a saturated solution of K_2CO_3 (2 mL) was added. Stirring was continued for 15 minutes at 0 °C. The layers were separated and the water layer was extracted with ether (3 x 5 mL). The combined organics were washed with 0.5 M H_3PO_4 (3 x 10 mL). The combined organics were washed with brine (10 mL), dried with $MgSO_4$, filtered and concentrated to give 79 mg of yellowish oil. The crude product was purified by flash chromatography (5-20 % MTBE in hexanes) to yield **515** (40 mg, 80 %) as a clear oil. R_f (32 % EtOAc in hexanes) = 0.58. $[\alpha]_{20}^{D}$ = + 7.2 (c 1.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.33-7.26 (m, 5H), 5.89 (d, 1H, *J* = 9.9 Hz), 5.44 (m, 1H), 4.65-4.50 (m, 1H), 4.52 (q, 2H, *J* = 13.3 Hz), 3.73-3.60 (m, 2H), 3.41-3.32 (m, 2H), 2.39 (m, 1H), 1.82-1.61 (m, 6H), 1.44 (s, 9H), 1.44-1.20 (m, 5H), 1.04 (dd, 3H, *J* = 6.6, 5.3 Hz), 0.92-0.87 (m, 11H), 0.05-0.04 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 154.3 (d), 138.7, 132.3, 128.3, 127.4 (d), 126.8 (d), 74.6, 74.4, 73.7, 72.7, 50.0, 49.6, 43.8, 41.6 (d), 38.7 (d), 36.1 (d), 31.8 (d), 29.7, 29.2, 28.4, 25.9, 25.6 (d), 23.0 (d), 22.3, 18.1, 17.5, 13.2 (d), -3.0, -3.6, -4.1, -4.6. HRMS (ES+) calculated for $C_{33}H_{55}NO_4NaSi$: 580.3798, found 580.3795.

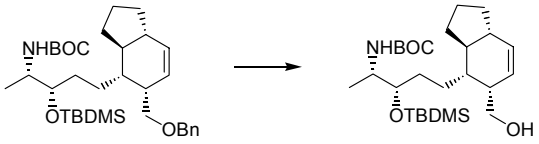
6.6.5 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*,2*S*]-[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-butyl]-carbamic acid *tert*-butyl-dimethyl-silyl ester (514)



513 **514**

[4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-2-hydroxy-1-methyl-butyl]-carbamic acid *tert*-butyl ester **513** (130 mg, 0.294 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (6 mL). The mixture was cooled to 0 °C and 2,6-lutidine (110 mg, 1.029 mmol, 350 mol-%) was added. The resulting mixture was stirred for 5 minutes and *tert*-butyldimethylsiloxy triflate (233 mg, 0.882 mmol, 300 mol-%) was added dropwise. The mixture was stirred for 20 minutes at 0 °C. After this, a saturated solution of K_2CO_3 (10 mL) and ether (10 mL) was added. The layers were separated and the water layer was extracted with ether (3 x 15 mL). The combined organics were washed with 0.5 M H_3PO_4 (3 x 10 mL). The water phase was extracted once with ether (15 mL). The combined organics were washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated to give 189 mg of yellowish oil. The crude product was purified by rapid filtration through a silica pad (2 cm). The pad was flushed with CH_2Cl_2 to yield **514** (176 mg, 97 %). R_f (32 % EtOAc in hexanes) = 0.57. $[\alpha]_{20}^{D}$ = + 2.0 (c 1.37, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.33-7.26 (m, 5H), 5.89 (d, 1H, *J* = 9.9 Hz), 5.43 (m, 1H), 4.78 (m, 1H), 4.51 (q, 2H, *J* = 12.0 Hz), 3.72-3.66 (m, 2H), 3.41-3.32 (m, 2H), 2.39 (m, 1H), 1.85-1.25 (m, 11H), 1.14-1.08 (m, 2H), 1.04 (dd, 3H, *J* = 6.6, 5.3 Hz), 0.92-0.87 (m, 20H), 0.27-0.26 (m, 6 H), 0.10-0.02 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 155.1 (d), 138.7, 132.2 (d), 128.3, 127.3 (d), 126.8, 78.9, 74.6, 73.7, 72.7, 49.4 (d), 43.9 (d), 42.0, 41.7 (d), 41.4, 38.7 (d), 36.1 (d), 32.7, 29.2, 28.4, 25.9 (d), 25.7 (d), 22.9, 22.0, 18.1 (d), 14.3 (d), 0.68, -2.3, -3.5, -3.9. HRMS (ES+) calculated for $C_{35}H_{61}NO_4NaSi_2$: 638.4037, found 638.4050.

6.6.6 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*,2*S*]-[2-(*tert*-Butyl-dimethyl-silanyloxy)-4-(5-hydroxymethyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-1-methyl-butyl]-carbamic acid *tert*-butyl ester (516)

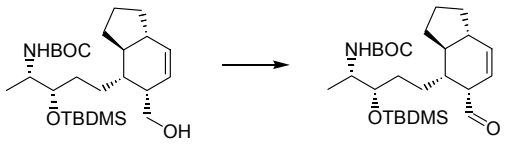


515 **516**

Gaseous ammonia was condensed into a flask immersed in a cooling bath to – 78 °C. A small sodium peaces was added into ammonia liquid (5 mL) until blue color developed. Dried ammonia was condensed into the reaction flask, which was cooled to –78 °C. A small sodium peaces were added until blue color developed. After this, [4-(5-Benzyloxymethyl-2,3,3a,4,5,7a-hexahydro-*1H*-inden-4-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-butyl]-carbamic acid *tert*-butyl ester **515** (17 mg, 0.031 mmol, 100 mol-%) in dry THF (1 mL) was added. This resulted decoloration of the reaction mixture. Sodium peaces were added until blue color developed. The addition was repeated if color disappeared. The reaction mixture was stirred for 80 minutes and solid NH_4Cl was added until blue color disappeared. Excess ammonia was allowed to evaporate. Water (25 mL) was added and the product was extracted with ether (3 x 75 mL). The combined organics were washed with 0.5 M solution of H_3PO_4 (20 mL) and brine (40 mL). The organics were dried with $MgSO_4$, filtered and concentrated to give 27 mg of white solid. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to yield **516** (8 mg, 56 %) as a clear oil. R_f (20 % EtOAc in hexanes) = 0.17. $[\alpha]_{20}^{D}$ = -7.2 (c 1.07, MeOH). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 5.93 (d, 1H, *J* = 9.9 Hz), 5.43 (m, 1H), 4.58 (d, 1H, *J* = 7.3 Hz), 3.78 (m, 1H), 3.65 (m, 1H), 3.62-3.42 (m, 2H), 2.25 (m, 1H), 1.85-1.33 (m, 11H), 1.44 (s, 9H), 1.14-1.08 (m, 2H), 1.03 (d, 3H, *J* = 7.1 Hz), 0.90-0.89 (m, 9H), 0.05 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 155.3 (d), 132.7 (d), 126.3 (d), 79.2, 74.1 (d), 66.3 (d), 49.6 (d), 44.0 (d), 38.6, 35.6, 35.1, 32.4, 29.1 (d), 28.4, 25.9 (d),

25.7, 22.2, 18.1 (d), 14.3 (d), -4.1. HRMS (ES+) calculated for $C_{26}H_{49}NO_4NaSi$: 490.3329, found 490.3350.

6.6.7 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*,2*S*]-[2-(*tert*-Butyl-dimethyl-silanyloxy)-4-(5-formyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-1-methyl-butyl]-carbamic acid *tert*-butyl ester (517)

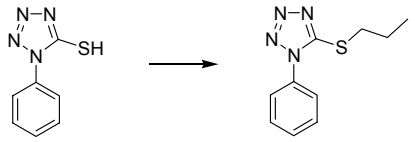


516 **517**

Oxalyl chloride (5 mg, 0.040 mmol, 120 mol-%) was diluted with dry CH_2Cl_2 (0.5 mL) and cooled to –78 °C. Dry DMSO (6 mg, 0.080 mmol, 240 mol-%) was diluted with dry CH_2Cl_2 (0.2 mL) and added into the flask containing oxalyl chloride. 2-(*tert*-Butyl-dimethyl-silanyloxy)-4-(5-hydroxymethyl-2,3,3a,4,5,7a-hexahydro-*1H*-inden-4-yl)-1-methyl-butyl]-carbamic acid *tert*-butyl ester **516** (16 mg, 0.033 mmol, 100 mol-%) was dissolved in dry CH_2Cl_2 (0.6 mL) and added into the reaction flask. Stirring was continued for 40 minutes at –78 °C and triethylamine (17 mg, 0.167 mmol, 506 mol-%) was added. The mixture was stirred for 5 minutes and the cooling bath was removed for 1 hour. CH_2Cl_2 (3 mL) was added and the organics were washed with 0.5 M H_3PO_4 (2 x 1.5 mL). The combined water layers were extracted with CH_2Cl_2 (2 x 3 mL). The combined organics were washed with brine (2 mL), dried with Na_2SO_4, filtered and concentrated to give 15 mg (97 %) of **517** as pure product. The product was highly volatile. R_f (32 % EtOAc in hexanes) = 0.49. $[\alpha]_{20}^{D}$ = + 30.7 (c 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 9.63 (d, 1H, *J* = 2.0 Hz), 6.12 (d, 1H, *J* = 9.9 Hz), 5.62 (m, 1H), 4.55 (m, 1H), 3.74-3.64 (m, 2H), 2.91 (m, 1H), 2.25 (t, 1H, *J* = 9.7 Hz), 1.90-1.80 (m, 2H), 1.72-1.64 (m, 2H), 1.60-1.47 (m, 3H), 1.44 (s, 9H), 1.38-1.32 (m, 3H), 1.15-1.06 (m, 2H), 1.03 (dd, 3H, *J* = 10.4, 6.8 Hz), 0.90-0.89 (m, 9H), 0.07-0.03 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.62

MHz) δ 201.4 (d), 155.1 (d), 134.9 (d), 120.9 (d), 79.1, 74.5 (d), 54.7 (d), 44.8, 38.4, 34.5 (d), 32.9, 28.7, 28.4, 25.9 (d), 25.7, 22.2, 21.9, 18.1, 14.3 (d), -4.2 (d), -4.50, -4.58. HRMS (ES+) calculated for $C_{26}H_{47}NO_4NaSi$: 488.3172, found 488.3155.

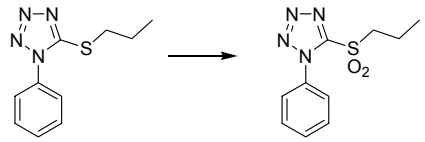
6.6.8 1-Phenyl-5-propylsulfanyl-1*H*-tetrazole (508)



507 **508**

Triphenyl phosphine (0.87 g, 3.3 mmol, 110 mol-%), 1-PrOH (0.18 g, 3.0 mmol, 100 mol-%) and 1-phenyl-*1H*-tetrazole-5-thiol **507** (0.59 g, 3.3 mmol, 110 mol-%) was dissolved in dry THF (45 mL) and the resulting mixture was cooled to 0 °C. Diethyl azodicarboxylate (0.58 g, 3.3 mmol, 110 mol-%) was diluted with dry THF (3 mL) and added dropwise into the reaction mixture. Stirring was continued for 1.5 hours and the reaction mixture was taken to room temperature. Stirring was continued for 18 hours. The solvents were evaporated and the product was partitioned between a 5 w-% solution of $NaHCO_3$ (50 mL) and ether (100 mL). The organics were washed with brine (50 mL), dried with $MgSO_4$, filtered and concentrated to give 2.38 g of white solid. The crude product was purified by flash chromatography (10 % EtOAc in hexanes) to yield **508** (0.58 g, 87 %) as a clear oil. R_f (50 % EtOAc in hexanes) = 0.48. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.60-7.53 (m, 5 H), 3.38 (t, 2 H, *J* = 7.3 Hz), 1.86 (s, 2 H, *J* = 7.3 Hz), 1.06 (t, 3 H, *J* = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 155.1, 134.4, 130.7, 130.4, 124.5, 35.9, 23.2, 13.8. LRMS (EI+) 220, 192, 150, 136, 118(100), 104, 91, 77, 65, 51. HRMS (ES+) calculated for $C_{10}H_{13}N_4S$: 221.0861, found 221.0841.

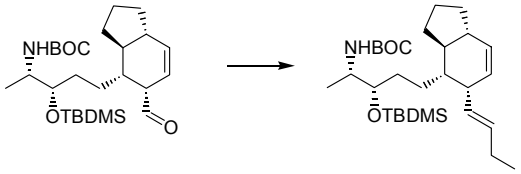
6.6.9 1-Phenyl-5-(propane-1-sulfonyl)-1*H*-tetrazole (509)



508 **509**

1-Phenyl-5-propylsulfanyl-1H-tetrazole **508** (0.51 g, 2.3 mmol, 100 mol-%) was dissolved in CH_2Cl_2 (23 mL). $NaHCO_3$ (1.93 g, 23.0 mmol, 1000 mol-%) and partially dissolved 70 w-% aqueous slurry of m-chloroperbenzoic acid (2.84 g, 11.5 mmol, 500 mol-%) treated with CH_2Cl_2 (15 mL) was added. Stirring was continued for 2.5 hours and CH_2Cl_2 (20 mL) was added. Stirring was continued for 20.5 hours and a saturated aqueous solution of $NaHCO_3$ (30 mL) and a saturated aqueous solution of $Na_2S_2O_3$ was added. The layers were separated and the organic layer was washed with brine/H_2O (1:1) (80 mL). The organics were dried with Na_2SO_4, filtered and concentrated to give 1.08 g of white solid. The crude product was purified by flash chromatography (15 % EtOAc in hexanes) to yield **509** (0.48 g, 83 %) as an yellowish solid. Mp. 49-51 °C. R_f (20 % EtOAc in hexanes) = 0.32. ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 7.70-7.60 (m, 5 H), 3.74-3.70 (m, 2 H), 2.06-1.96 (m, 2 H), 1.14 (t, 3 H, *J* = 7.5 Hz). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 154.2, 133.7, 132.1, 130.4, 125.8, 58.2, 16.6, 13.5. FT-IR (cm-1) 3338, 3019, 2400, 1599, 1520, 1424, 1223, 1215, 1208, 1153, 1046, 929, 748, 668. LRMS (EI+) 253 (M+1), 145, 131, 119(100), 103, 91, 77, 65, 51. HRMS (EI+) calculated for $C_{10}H_{13}O_2N_4S$. 252.0681, found 252.0666.

6.6.10 [(3a*S*',4*R*',5*S*',7a*R*'),1*S*,2*S*]-[4-(5-But-1-enyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-butyl]-carbamic acid *tert*-butyl ester (518)

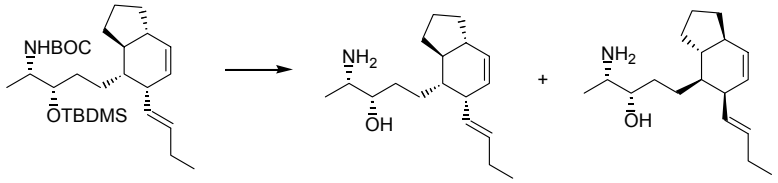


517 **518**

Potassium hexamethyldisilazane (16 mg, 0.082 mmol, 117 mol-%) was dissolved in dry DME (0.5 mL) and cooled to –55 °C ($CHCl_3/N_2$(l)). 1-Phenyl-5-(propane-1-sulfonyl)-1H-tetrazole **509** (21 mg, 0.084, 120 mol-%) in dry DME (0.8 mL) was added into the reaction flask, which resulted formation of yellowish solution. Stirring was continued for 30 minutes and aldehyde **517** (33 mg, 0.070 mmol, 100 mol-%) in dry DME (1.0 mL) was added. A clear solution was obtained. Stirring was continued for 2.5 hours at –35 – 55 °C. After this, the reaction mixture was immersed in an ice bath for 2 hours. The reaction was not complete at this point and more KHMDS (15 mg, 0.073 mmol, 104 mol-%) was dissolved in dry DME (0.5 mL) and added into the reaction mixture at –55 °C. The reaction mixture turned from colorless to yellowish solution at this point. Stirring was continued for 30 minutes and a saturated solution of $NaHCO_3$ (1 mL) was added. This resulted formation of clear solution. The mixture was stirred 25 minutes at r.t. and the mixture was diluted with EtOAc (5 mL). The layers were separated and the water layer was extracted with EtOAc (2 x 3 mL). NaCl was added to help the phase separation. The combined organics were washed with brine (3 mL), dried with Na_2SO_4, filtered and concentrated to give 46 mg of yellow oil/slurry. The crude product was purified by flash chromatography (4-10 % EtOAc in hexanes) to yield **518** (24 mg, 70 %) as a clear oil. The product was highly volatile and it was easily evaporated in an oil pump vacuo. R_f(20 % EtOAc in hexanes) = 0.61. $[\alpha]_{20}^{D}$ = +41.3 (c 1.21, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400.132 MHz) δ 5.84 (d, 1H, *J* = 9.9 Hz), 5.42-5.36 (m, 3H), 4.58 (m, 1H), 3.69 (m, 2H), 2.67 (m, 1H), 2.01 (m, 2H), 1.81-1.44 (m, 6H), 1.44 (s, 9H), 1.38-1.32 (m, 5H), 1.15-1.06 (m, 2H),

1.03 (dd, 3H, *J* = 10.4, 6.8 Hz), 0.97 (t, 3H, *J* = 7.3 Hz), 0.90-0.89 (m, 9H), 0.06-0.04 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 155.2, 133.0, 131.8, 130.1 (d), 128.7 (d), 120.9 (d), 79.0, 74.7, 49.0 (d), 43.9 (d), 42.8, 40.5, 38.6, 38.4, 33.0, 29.7, 29.2, 28.5, 26.0, 25.6, 23.1, 22.2, 18.2, 14.2, 13.9, -4.1 (d), -4.50, -4.59. HRMS (ES+) calculated for $C_{29}H_{53}NO_3NaSi$: 514.3692, found 514.3704.

6.6.11 [(3a*S*',4*R*',5*S*',7a*R*'),3*S*,4*S*]-4-Amino-1-(5-but-1-enyl-2,3,3a,4,5,7a-hexahydro-1*H*-inden-4-yl)-pentan-3-ol (519)



518 **519** **1**

[4-(5-But-1-enyl-2,3,3a,4,5,7a-hexahydro-*1H*-inden-4-yl)-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-butyl]-carbamic acid *tert*-butyl ester **518** (12 mg, 0.024 mmol, 100 mol-%) was dissolved in dioxane (0.9 mL) and 32 w-% HCl (1.1 mL) was added. The reaction mixture was stirred at r.t. for 3.5 hours. Water (2 mL) and ether (4 mL) was added. The layers were separated and the water phase was basified with a sat. solution of $NaHCO_3$ until pH was 8-9. The free amine product was extracted with $CHCl_3$ (4 x 10 mL). The water phase was saturated with NaCl to help the product isolation. The combined organics were dried with Na_2SO_4, filtered and concentrated to give 3.9 mg (58 %) of **519** and amaminol A **1** as a yellowish oil. Data for **519**: $[\alpha]_{20}^{D}$ = +62.0 (c 0.39, MeOH). ^{1}H NMR (MeOD/TMS, 400.132 MHz) δ 5.85 (d, 1H, *J* = 9.9 Hz), 5.49-5.42 (m, 3H), 3.40 (m, 1H), 2.84 (m, 1H), 2.76 (m, 1H), 2.00 (m, 2H), 1.86-0.97 (m, 16H), 1.03 (dd, 3H, *J* = 10.4, 6.8 Hz), 0.97 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (MeOD, 100.62 MHz) δ 134.4 (d), 132.9 (d), 131.0 (d), 129.9 (d), 76.4 (d), 52.3 (d), 45.1 (d), 44.1, 41.6 (d), 39.9 (d), 32.5 (d), 30.3 (d), 26.9 (d), 26.6, 24.7 (d), 23.1, 17.1 (d), 14.4. HRMS (ES+)

calculated for (M+1) $C_{18}H_{32}NO$: 278.2484, found 278.2463. Amaminol A **1**: ^{1}H NMR (MeOD/TMS, 400.132 MHz) δ 3.48 (dd, 1H), 3.13 (m). Other peaks were not observed, because of overlapping with peaks of the product **519**.

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