Helsinki University of Technology

Department of Chemical Technology

Laboratory of Organic Chemistry

ASYMMETRIC SYNTHESES OF THE STEREOTETRADS OF AMPHOTERICIN B AND CALYCULIN C

Kaisa Karisalmi

Dissertation for the degree of Doctor of Philosophy to be presented with due permission of the Department of Chemical Technology for public examination and debate in Auditorium KE 2 (Komppa Auditorium) at Helsinki University of Technology (Espoo, Finland) on the 13th of November, 2004, at 12 noon.

Espoo 2004

Distribution:
Helsinki University of Technology
Department Of Chemical Technology
Laboratory of Organic Chemistry
P.O. Box 6100
FIN-02015 HUT, FINLAND

ISBN 951-22-7299-7
ISSN 1236-2999

Valopaino, Helsinki 2004

Karisalmi, Kaisa. ***Asymmetric syntheses of the stereotetrads of Amphotericin B and Calyculin C.*** Espoo 2004. Helsinki University of Technology, Organic Chemistry Report 3/2004. 55 pages and the original papers.

ISBN 951-22-7299-7

ISSN 1236-2999

Keywords polyketides, polypropionates, asymmetric synthesis, stereotetrad, Calyculin C, Amphotericin B

ABSTRACT

Calyculin C and Amphotericin B are biologically active natural products. Amphotericin B is an antifungal agent, which has been a widely used drug in antifungal chemotherapy. Calyculin C is a potent protein phosphatase inhibitor and plays an important role in cancer research.

Calyculin C and Amphotericin B contain a stereotetrad fragment. The synthesis of the *syn, anti, anti* stereotetrad of Amphotericin B was based on the thiopyranone ring and a chiral auxiliary strategies. The synthesis began with the introduction of the asymmetry into the thiopyranone ring *via* a tartrate derived chiral ortho ester, followed by a highly diastereoselective Mukaiyama aldol reaction and 1,3-*syn* diol reduction. The synthesis was complete in only six steps with reasonable yield and diastereoselectivity.

The all-*anti* stereotetrad of Calyculin C was first approached through a convergent strategy but it yielded a wrong diastereomer as the major product. The linear synthesis began with a chiral boron crotylation followed by ozonolysis. The second crotylation with (*Z*)-crotyl trifluorosilane produced the desired *anti, anti, anti* stereochemistry with high diastereoselectivity.

ACKNOWLEDGEMENTS

The research work reported in this thesis was carried out in the Department of Chemical Technology, Helsinki University of Technology, during the years 2000-2004.

First, I wish to thank my supervisor Professor Ari Koskinen for providing me the opportunity to work as a member of his research group among a challenging topic of asymmetric synthesis. Under his guidance I have found the keys for understanding organic chemistry. His valuable advice and constantly open door have made it possible for me to carry this project all the way.

I am most grateful for Finnish Academy for financial support and Professor Hans-Joachim Knoelker and Dr Nick Greeves for careful revision of my manuscript. I wish to thank Professor Kari Rissanen, Dr. Maija Nissinen and Heidi Mansikkamäki for the cooperation with the X-ray crystallographic analyses and Päivi Joensuu for sharp work with HRMS analyses.

All members in the Laboratory of Organic Chemistry have done their bit for my PhD project. Petri has given me invaluable advice and supervision, his pointed and sudden questions have made me studying harder. Anna-Maija has always been ready for helping me with laboratory routines. Jari and Juho have helped me a lot with NMR experiments and I am very grateful for their patience. Vesa has been a good “Calyculin C team” mate; he has always been there when I have had problems with computers (=very often). Kati and Anniina E. have made me realize how difficult it is to be a good supervisor; they have also helped with the synthesis of the lactone fragment of Calyculin C. Larissa, Tatja and Ainoliisa have been the best possible teaching company

at Organic Chemistry I and II. Thank you Mervi, Saara, Anna, Tiina, Jatta, Taina, Antti P. and Mikko P. for your support, interesting discussions and friendship!

Special thanks go for all of my friends; thank you for being always so supportive and caring. Mami & Heljä and Jenni & Nina, with you I have always been able to forget my work and concentrate on more important things; analyzing reality-TV series and relationships!

My warmest thanks go for my parents, Seppo and Marja-Liisa, and my grandparents, Aimo-pappa and Teku-mummu. Without your encouragement and love I couldn't have done this. I also want to thank my brother Antti and his wife Katja, the moments we have spent together have been essential offsets by everyday routines.

Most of all, thank you Antti! Your care, support and love have been irreplaceable throughout this work.

I dedicate this thesis to my Mom.

Helsinki, September 2004 Kaisa Karisalmi

SYMBOLS AND ABBREVIATIONS

Ac	acetyl
Bz	benzoyl
BINAP	2,2'-(bisphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bu	butyl
t-Bu	*tert*-butyl
Chx(= c-Hex)	cyclohexyl
CSA	camphorsulfonic acid
DDQ	dicyclohexylcarbodiimide
de	diastereomeric excess
DET	diethyl tartrate
$(DHQD)_2PHAL$	dihydroquinidine 1,4-phthalazinediyl diether
$(DHQD)_2PYR$	dihydroquinidine 2,5-diphenyl-4,6-pyrimidinediyl diether
DHP	3,4-dihydro-2H-pyran
DIBAL-H	diisobutylaluminum hydride
DIPA	diisopropyl amine
DIPEA	diisopropylethylamine (Hünig's base)
DIPT	diisopropyl tartrate
DMAP	4-*N,N*-dimethylaminopyridine
DME	ethylene glycol dimethyl ether
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppf	1,1’-bis(diphenylphosphanyl)ferrocene
EDAC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

ee	enantiomeric excess
Et	ethyl
HMPA	hexamethylphosphoric triamide $(Me_2N)_3P=O$
IBX	*o*-iodoxybenzoic acid
IPA	isopropyl alcohol
Ipc	isopinocampheyl
KHMDS	potassium hexamethyldisilazide
L-Selectride	lithium tri-*sec*-butylborohydride
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MCPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MEM	methoxyethoxymethyl
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum(pyridine)hexamethyl-phosphoramide
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
NMO	*N*-methylmorpholine *N*-oxide
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
i-Pr	*iso*-propyl
Pyr	pyridine
Red-Al	sodium dihydrobis(2-methoxyethoxy) aluminate
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*t*-butyldiphenylsilyl
TBHP	*t*-butyl hydroperoxide

TBS=TBDMS	*t*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran(yl)
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMEDA	*N,N,N′,N′*-tetramethylethylenediamine
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl
Ts	*p*-toluenesulfonyl

LIST OF PUBLICATIOS

The thesis consists of a summary review and the following publications:

I) Karisalmi, K., Koskinen, A. M. P., Nissinen, M. and Rissanen, K. *Tetrahedron* **2003**, *59*, 1421.

II) Karisalmi, K., Rissanen, K. and Koskinen, A. M. P. *Org. Biomol. Chem.* **2003**, *1*, 3193.

III) Karisalmi, K. and Koskinen, A. M. P. *Synthesis* **2004**, (*9*), 1331.

IV) Karisalmi, K. and Koskinen, A. M. P. *Tetrahedron Lett.* **2004**, *45*, *in press*. (available on line at www.sciencedirect.com)

THE AUTHOR'S CONTRIBUTION

I) The author defined the research plan together with coauthors. The author carried out the experiments and analyses (except the X-ray crystallographic analyses), interpreted the results, and wrote the manuscript.

II) The author defined the research plan, carried out the experiments and analyses (except the X-ray crystallographic analysis), interpreted the results and wrote the manuscript.

III) The author defined the research plan together with coauthors. The author carried out the experiments and analyses (except the X-ray crystallographic analyses), interpreted the results, and wrote the manuscript.

IV) The author defined the research plan, carried out the experiments and analyses, interpreted the results and wrote the manuscript.

CONTENTS

PREFACE

Amphotericin B is a macrolide polyketide originally isolated from *Streptomyces nodosus* in 1956. Amphotericin B is a potent antifungal agent, which makes it an important target molecule for organic chemists.

Calyculin C is a highly cytotoxic polyketide metabolite isolated from the marine sponge *Discodermia calyx* by Fusetani *et al.* It has proven to be a strong serine/threonine protein phosphatase inhibitor and based on this property, might be a potential anti-cancer agent.

In chapter 1 naturally occurring polyketides are introduced. Chapter 2 deals with asymmetric syntheses of polyketide stereotetrads. Six different natural polyketides have been chosen to represent seven of the eight possible diastereomeric stereotetrads (the *syn, syn, anti* stereotetrad is a very uncommon structure in natural polyketides). The syntheses of the stereotetrad fragments, including my own synthesis of the dipropionate fragment of Amphotericin B, are discussed in detail. In chapter 3, my synthetic efforts towards the *anti, anti, anti* dipropionate-lactone fragment of Calyculin C are discussed.

1 Introduction

Polyketides form an enormous class of natural products synthesized by bacteria, fungi and plants through a condensation reaction of simple carboxylic acids.[1] Polyketides vary widely in structure; they can be cyclic, acyclic, small, large, simple or complex. They may also be linked to different sugars or aminosugars.

It is quite clear that because polyketides vary so much in structure, they also have many different biological activities. Between 5000 and 10000 polyketides are known and about 1% of them possess drug activity, which is 5 times as many as the average in natural products.[2] Pharmaceutically important polyketide drugs include antibiotics, cancer chemotherapeutics, cholesterol lowering agents and antifungals.

Polyketides can be grouped into smaller subgroups: fatty acids, polypropionates and aromatic polyketides.[3] Polypropionates are furthermore divided in three groups: polyether antibiotics, macrolides and spiroketals. These subgroups have structural similarities within each group, but there are also several structural features, which are universal among all polyketides.

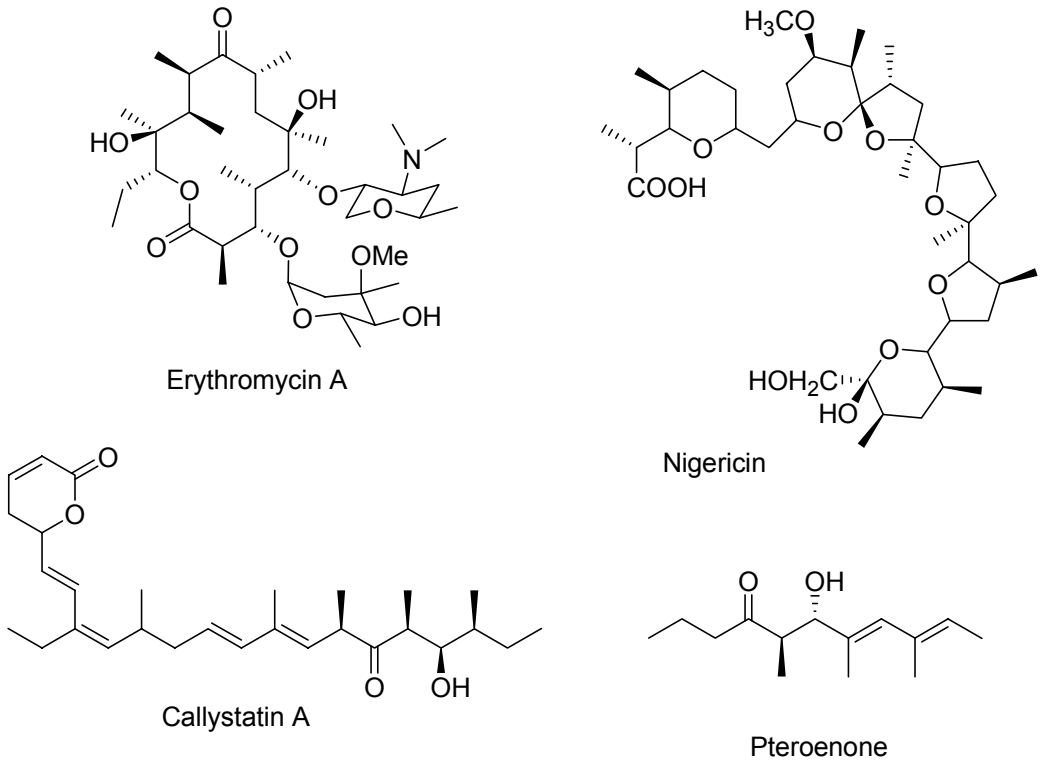


Figure 1. Examples of naturally occurring polyketides.

The stereotetrad (Figure 2) is a common substructure in polyketides. Four stereogenic centers, next to each other, results in eight possible diastereomeric combinations of this structure (Figure 3): *anti, anti, anti* (**1a**); *anti, anti, syn* (**1b**); *anti, syn, anti* (**1c**); *syn, anti*, *anti* (**1d**); *syn, syn, anti* (**1e**); *syn, anti, syn* (**1f**); *anti, syn, syn* (**1g**) and *syn, syn*, *syn* (**1h**).

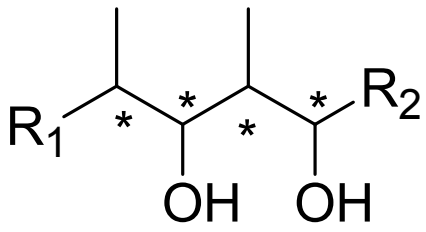


Figure 2. General structure of a stereotetrad.

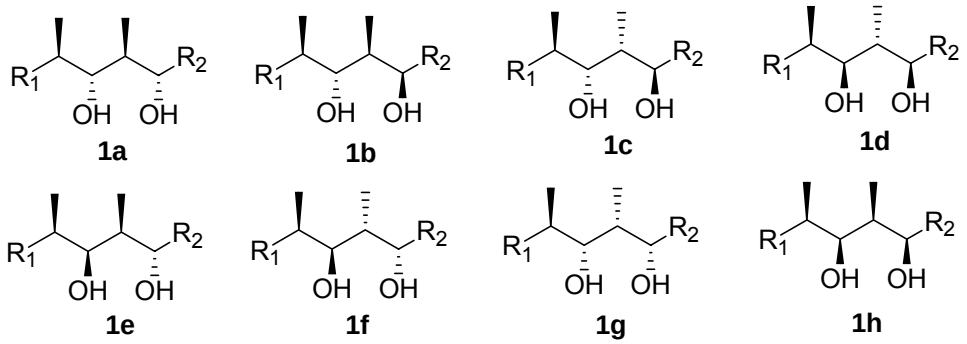


Figure 3

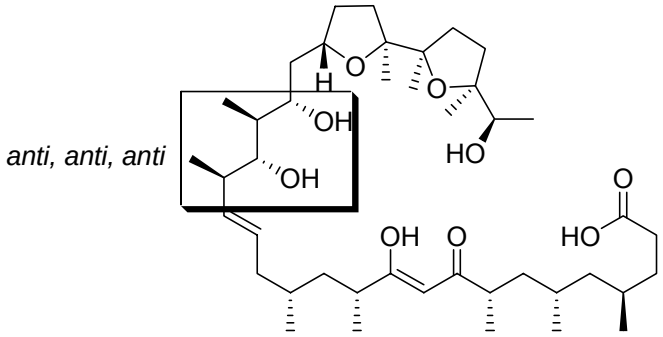
Polyketides containing a fragment like **1a-1d** and **1f-1h** are abundant in nature. These natural products are challenging target molecules for synthetic chemists; especially stereocontrol in the synthesis of stereotetrads shown in Figure 3 calls for accurate planning and realization in laboratory.

The stereotetrad **1e** proved to be a very uncommon structure in natural products. A literature search (Scifinder, Beilstein) returned several hits for this *syn, syn, anti* stereotetrad, but no polyketide with this fragment was found.

2 Stereotetrads in natural products

2.1 Ionomycin; anti, anti, anti

Ionomycin (**2**, Figure 4) belongs to the subgroup of polyether antibiotics. It was isolated 1978 from the fermentation broths of *Streptomyces congoblatus*[4] and its structure, including absolute stereochemistry, was resolved one year later.[5] Ionomycin is an ionophore, meaning that it chelates various inorganic cations and transports them across lipid membranes. This character, especially its high affinity for Ca^{2+} ions, has made it an important molecule in neurochemistry research.[6]



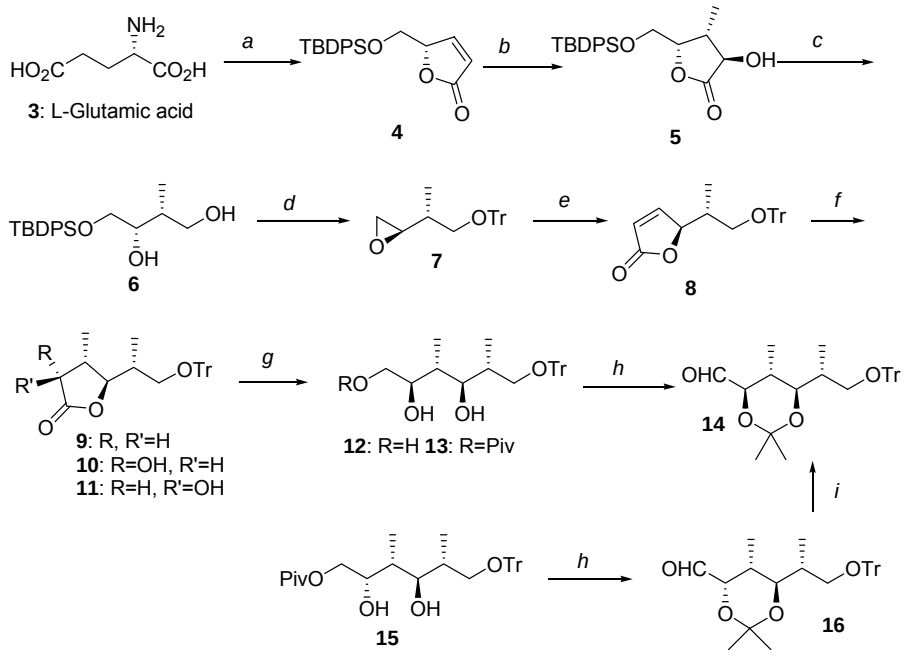
2: Ionomycin

Figure 4

Three different research groups have published total syntheses of Ionomycin; Evans (1990)[7], Hanessian (1990)[8] and Lautens (2002)[9]. Each of these research groups had their own strategies for the synthesis of the *anti, anti, anti* dipropionate fragment (boxed in Figure 4).

Hanessian *et al*. based the synthesis of the stereotetrad fragment on L-glutamic acid (**3**) as the chiral progenitor (Scheme 1).[8] First, glutamic acid was converted to the butyrolactone derivative **4**,[10] which was then allowed to undergo the first conjugate addition.[11] The lactone was then treated with KHMDS, and the resulting enolate was oxygenated with oxodiperoxymolybdenum pyridine to produce the hydroxy lactone **5**.[10, 11] The

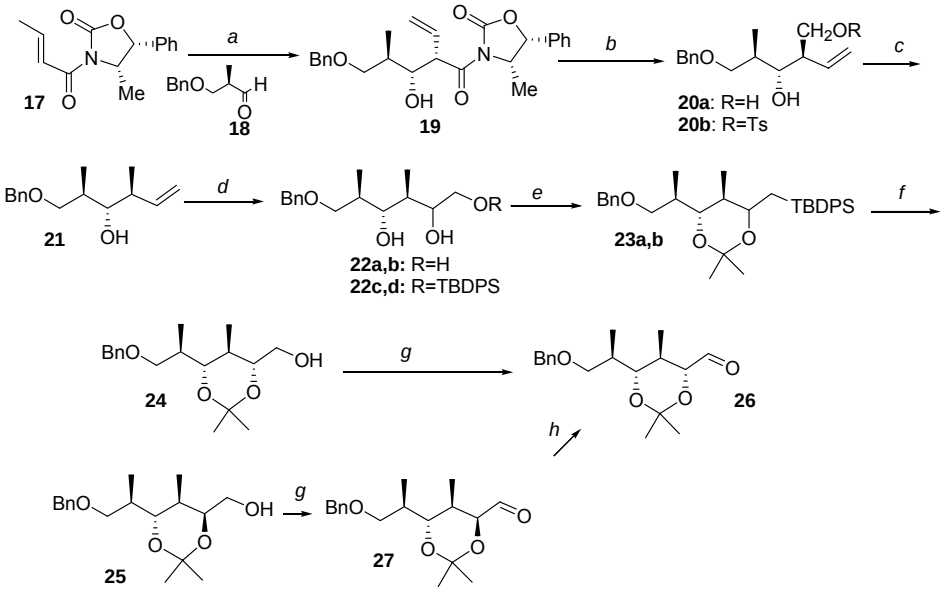
trisubstituted lactone was then opened and reduced to produce the acyclic diol **6**, which was selectively protected and converted to the epoxide **7**. The epoxide **7** was enlarged to the lactone **8** by acetate extension and the double bond was constructed as in the first step *a*. Then a second conjugate addition was conducted followed by an oxidation step leading to a 1:1.7 mixture of epimeric alcohols **10** and **11**, the minor epimer **10** being the desired one. Lactone **10** was reduced, the primary alcohol **12** was protected as the pivalate ester **13**, followed by ketal formation, diesterification and Swern oxidation. The major epimer **11** was subjected to the same protocol as **10** to afford the thermodynamically less stable aldehyde **16**. Aldehyde **16** was equilibrated to the desired aldehyde **14**, which was the desired stereotetrad fragment in the total synthesis of Ionomycin.



a) Ref. 10; *b*) Ref. 10 and 11 *c*) 1. $NaBH_4$, aq. THF; 2. $NaIO_4$, aq. MeOH *d*) 1. TrCl, Et_3N, DMAP, CH_2Cl_2; 2. MsCl, Et_3N, CH_2Cl_2, then *n*-Bu_4NF, THF *e*) 1. $PhSeCH_2CO_2H$, BuLi; 2. EDAC·HCl, DMAP; 3. 30% H_2O_2, CH_2Cl_2 *f*) 1. CuI, MeLi·LiBr, ether, -20 °C; 2. KHMDS, THF, -78 °C → -30 °C, MoOPH *g*) 1. $LiAlH_4$, THF; 2. pivaloyl chloride, pyridine *h*) 1. camphorsulfonic acid, acetone, 2,2-dimethoxypropane; 2. $LiAlH_4$, THF; 3. oxalyl chloride, DMSO, CH_2Cl_2, -78 °C → -30 °C *i*) K_2CO_3, MeOH.

Scheme 1

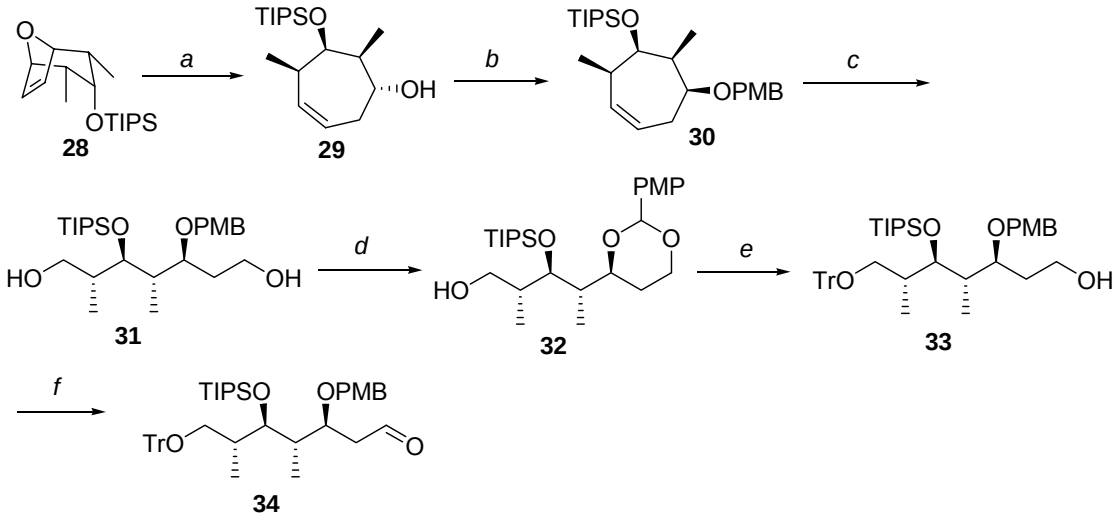
Evans *et al*. published the total synthesis of Ionomycin simultaneously with Hanessian *et al*. in 1990.[7] Evans used the chiral auxiliary strategy (oxazolidinone) for creating the first asymmetric centers (Scheme 2). Their previous studies had shown that the aldol addition of boryl enolates derived from crotonimide **17**[12] with aldehydes provided the crystalline *syn*, α-vinyl adducts such as **19**.[13] The desired *syn* adduct **19** was obtained also in this case. At this point the chiral auxiliary was removed and the aldehyde was reduced to the corresponding alcohol **20a**. Alcohol **20a** was then tosylated and the tosylate was reduced with hydride to produce the stereotriad **21** with the desired stereochemistry. After oxidation of the double bond with OsO_4 two epimeric alcohols **22a** and **22b** were obtained in a 78:22 ratio. Selective protection of the primary alcohol with TBDPS group, followed by ketal formation and removal of the TBDPS group, produced two separable diastereomeric alcohols **24** and **25**. The major diastereomer **24** was directly oxidized to the desired aldehyde **26**. The minor diastereomer **25** was also oxidized, after which it was epimerized to produce the thermodynamically more stable aldehyde **26**.



a) Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C, **18**, -78 °C, H_2O_2, MeOH *b*) 1. Bu_3B, HOAc, THF; 2. $LiBH_4$, THF, 0 °C; 3. H_2O_2, MeOH *c*) 1. *p*-$TolSO_2Cl$, pyridine, 5 °C; 2. $Li(Et)_3BH$, THF; 3. H_2O_2, NaOH (aq), MeOH *d*) 1. OsO_4, R_3N-O, H_2O/Me_2CO; 2. TBDPSCl, Et_3N, DMAP, CH_2Cl_2 *e*) $Me_2C(OMe)_2$, CSA, acetone *f*) (*n*-$Bu)_4NF$, THF *g*) $Pyr{\cdot}SO_3$, Et_3N, DMSO *h*) K_2CO_3, MeOH.

Scheme 2

The most recent total synthesis of Ionomycin has been published in 2002 by Lautens *et al.*[9] Their synthesis was based on the ring-opening methodology, which had been developed earlier in their laboratory.[14] The synthesis of the dipropionate fragment began with the [3.2.1] oxabicyclic alkene **28**[15], which was opened under reductive conditions (Scheme 3). The product, substituted cycloheptene **29** was obtained in excellent yield (95%) and enantioselectivity (93-95% ee). One stereocenter in **29** needed inversion for achieving the desired stereochemistry (Scheme 3, step *b*). Cycloheptene **30** was then opened ozonolytically and reductive work-up produced the diol **31**. The primary hydroxyl groups were differentiated with the help of PMP-acetal formation and finally the free hydroxyl group was oxidized by the Swern protocol producing the desired building block **34** with the correct stereochemistry.

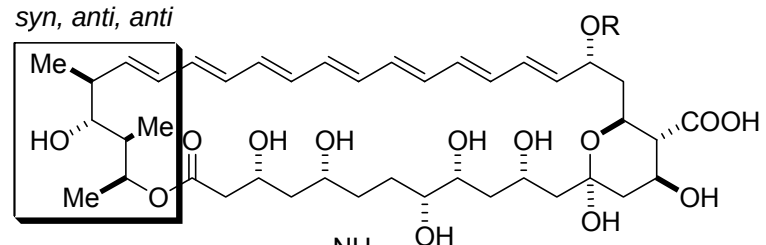


a) $Ni(COD)_2$, (*S*)-BINAP, toluene, 65 °C, DIBAL-H (added over 20 h) *b*) 1. DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -78 °C; 2. toluene, DIBAL-H, -78 °C; 3. THF, KHMDS, PMBCl *c*) O_3, MeOH/CH_2Cl_2, -78 °C then $NaBH_4$, rt *d*) CH_2Cl_2, DDQ, mol. sieves *e*) 1. TrCl, Et_3N, DMAP, CH_2Cl_2; 2. CH_2Cl_2, DIBAL-H, -78 °C -> 0 °C *f*) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -78 °C.

Scheme 3

2.2 Amphotericin B/Amphoteronolide B; syn, anti, anti

Amphotericin B (Figure 5) belongs to the macrolide subgroup of polyketides. It was isolated from *Streptomyces nodosus* in 1956 by Vandeputte *et al*.[16] and its stereochemical structure was resolved 15 years later by X-ray analysis.[17] Amphotericin B is a potent antifungal agent and is a widely used drug in antifungal chemotherapy.[18]



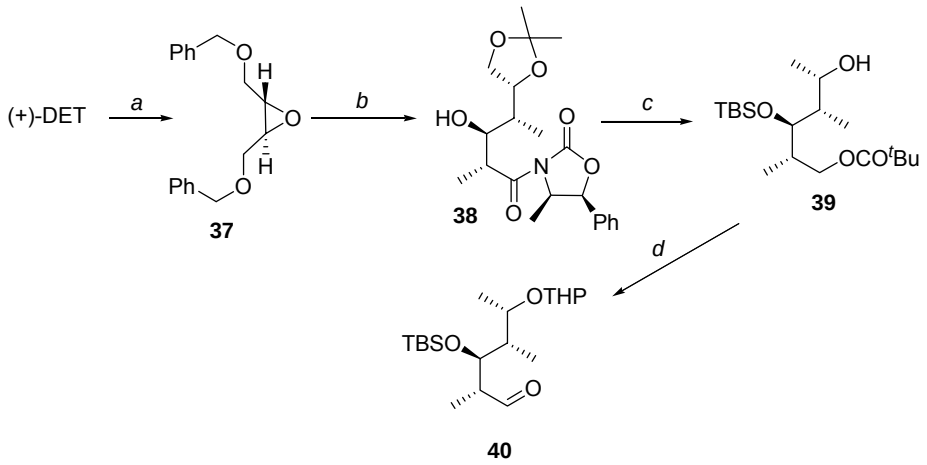
35: Amphotericin B, R=

36: Amphoteronolide, R=H

Figure 5

K. C. Nicolaou and his group were the first ones to develop a total synthesis for Amphotericin B and Amphoteronolide B.[19] In their retrosynthetic analysis the *syn*, *anti*, *anti* stereotetrad (boxed in Figure 5) was an independent building block.[20] The keys for asymmetry and stereoselectivity in their synthesis of this dipropionate were the chiral starting material (+)-diethyl tartrate and Evans aldol methodology[21] (Scheme 4).

The enantiomerically pure epoxide **37** was readily available from (+)-diethyl tartrate.[20] At first the epoxide **37** was converted to the Evans oxazolidinone derivative **38**,[22] the chiral auxiliary was removed and the aldehyde was masked as a *t*-butyl ester. Finally, the hydroxyl groups were protected and the *t*-butyl ester was successfully reduced to produce the desired aldehyde **40**.

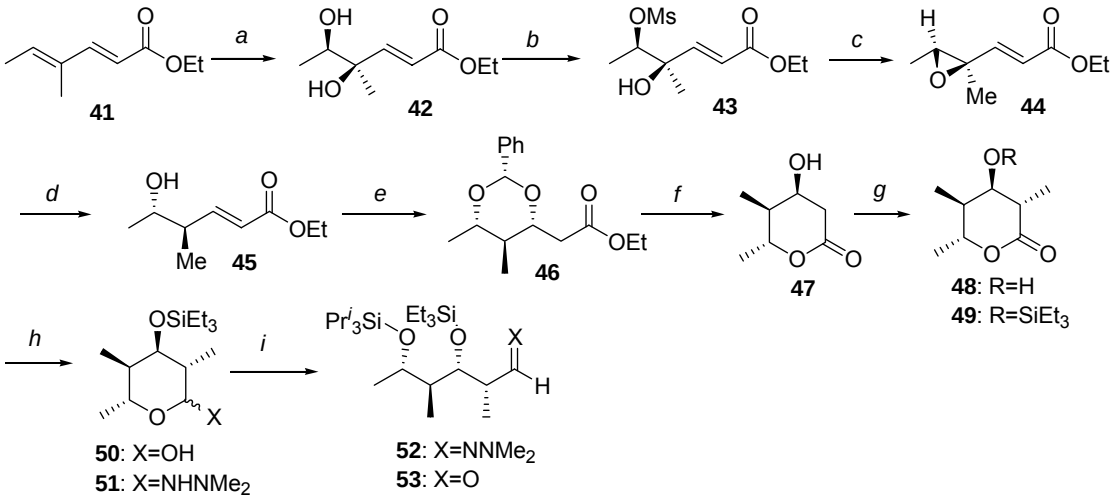


a) Ref. 20 *b*) Ref. 20 and 22 *c*) 1. $LiBH_4$, THF, 0 °C, 0.5 h, then *t*-BuCOCl, pyridine, 3 h; 2. Me_2-*t*-BuSiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, then AcOH-THF-H_2O (3:1:1), 50 °C, 2 h; 3. PhSSPh, *n*-Bu_3P, THF, 0-25 °C, 3 h, then Raney Ni, EtOH, 12 h *d*) 1. dihydropyran, cat. CSA, CH_2Cl_2, 0-25 °C, 3 h; 2. DIBAL-H, CH_2Cl_2, -78 °C, 0.5 h, then CrO_3, HCl·pyr, NaOAc, CH_2Cl_2, 25 °C, 4 h.

Scheme 4

The C(33)-C(37) dipropionate fragment of Amphotericin B has been also the target for us and Carreira *et al*. Carreira and Tholander published an enantioselective synthesis of this stereotetrad in 2001; the synthesis consisted of 14 steps in 16% overall yield.[23] Our enantioselective synthesis of the C(33)-C(37) fragment of Amphotericin B was published two years later and the complete synthesis contained only 6 steps.[24]

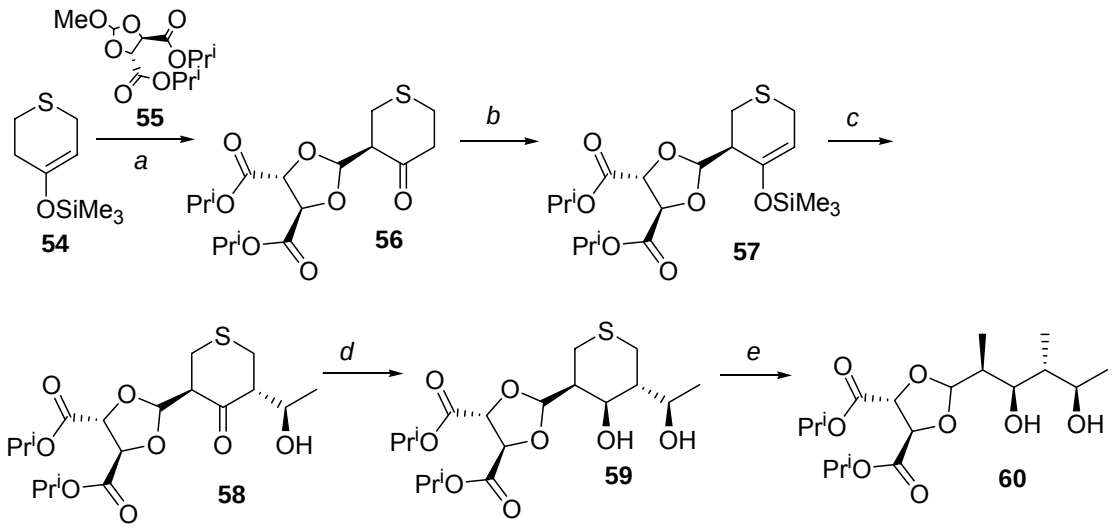
The synthetic route of Carreira *et al*. is shown in Scheme 5. The key reactions from the stereochemical point of view were steps *a* (Sharpless asymmetric dihydroxylation, >99% ee), *d* (> 95% de) and *g* (> 95% ee). Sharpless asymmetric dihydroxylation introduced the asymmetry into the molecule (step *a*) after which no extra external chiral information was needed.



a) $(DHQD)_2PHAL$, $K_2OsO_4 \cdot 2\ H_2O$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 °C, 48 h *b*) MsCl, pyridine, CH_2Cl_2, 0 °C, 48 h *c*) NaH, MeCN, 0-23 °C, 3 h *d*) $[Pd_2(dba)_3] \cdot CHCl_3$, Bu_3P, H_2O_2, Et_3N, THF, 23 °C, 3 h *e*) PhCHO, *t*-BuOK, THF, 0 °C, 1 h *f*) 1. $Pd(OH)_2$, H_2, EtOH, 23 °C; 2. TFA/MeCN, 23 °C, 12 h *g*) 1. LDA, MeI, HMPA/THF, -78 °C, 16 h; 2. 2,6-di(*tert*-butyl)-4-methylpyridine, Et_3SiOTf, CH_2Cl_2, -40 °C h) 1. DIBAL-H, THF, -78 °C, 2 h; 2. H_2NNMe_2, $TsOH \cdot H_2O$, EtOH, reflux, 12 h *i*) 1. $(i\text{-}Pr)_3SiOTf$, pyridine, 0-23 °C, 3 h; 2. O_3, CH_2Cl_2, -78 °C, Me_2S.

Scheme 5

Our synthesis of this *syn*, *anti*, *anti* stereotetrad was based on the thiopyrane ring strategy.[24,25] Commercially available tetrahydrothiopyran-4-one was first converted to the corresponding silyl enol ether **54** (Scheme 6). The asymmetry was then introduced into the ring with the help of the tartrate derived orthoester **55**. Two diastereomers were obtained in a 3:1 ratio and both diastereomers were successfully crystallized from the mixture. An X-ray structure of the minor diastereomer revealed the stereochemistry of **56**. The next aldol reaction *via* the kinetic silyl enol ether **57** was highly diastereoselective (10:1 according to ^1H NMR) and the desired aldol product **58** was obtained in reasonable yield. Finally, 1,3-*syn* diol reduction and removal of the sulfur with Raney Nickel produced the enantiomer of the stereotetrad of Amphotericin B. The sole source of asymmetry in the whole synthesis was the chiral tartrate derived orthoester **55**, which actually worked as a chiral auxiliary (masked aldehyde).



a) $ZnCl_2$, CH_2Cl_2, **55**, 21 h, rt *b*) LiHMDS, THF, TMSCl, 1 h, -78 ^oC -> 0 ^oC *c*) CH_3CHO, $TiCl_4$, CH_2Cl_2, 5 min., -78 ^oC *d*) Et_2BOMe, $NaBH_4$, THF/MeOH, 1 h, -78 ^oC *e*) Raney Ni, IPA, 24 h, 70 ^oC.

Scheme 6

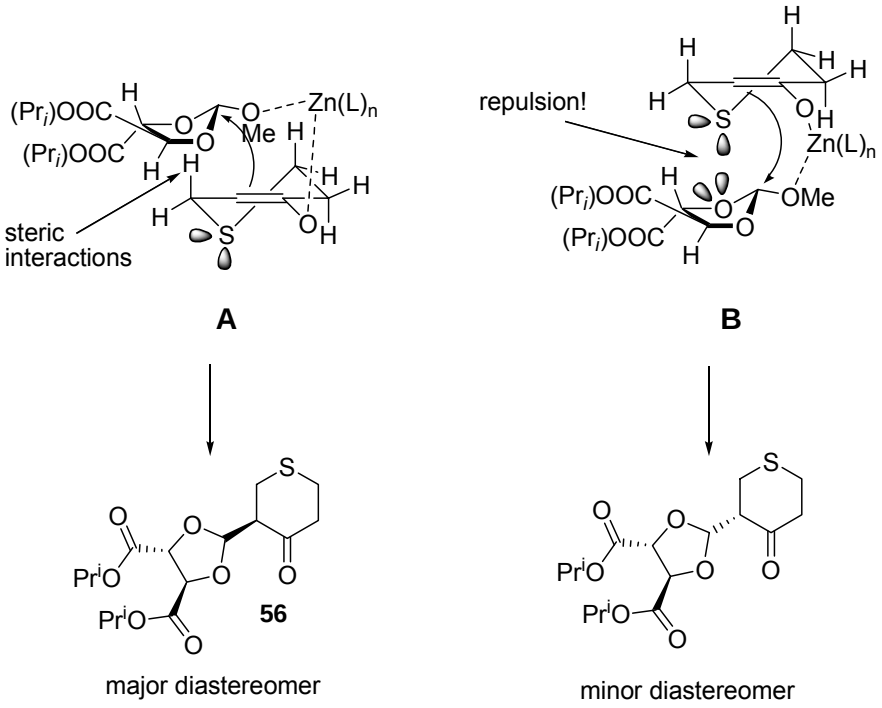


Figure 6

A mechanistic proposal for the first reaction step (Scheme 6, step *a*) is shown in Figure 6. Zinc coordinates the enolate and the orthoester near to each other and enhances the electrophilicity of the poor orthoester electrophile. The orthoester **55** can approach the nucleophilic enolate from the upper (**A**) or lower side (**B**) of the double bond (Figure 6). When it approaches from the upper side, there is only one axial hydrogen in the way. When the electrophile comes from the lower side, stereoelectronic interactions interfere in the reaction. The non-bonding free electron pairs of the thiopyranone ring sulfur and the orthoester repel each other and thus the energy of the transition state in case **B** is higher than in case **A**. This must be also the explanation for the diastereoselectivity. The electrophile's ester tails have also a small influence on the diastereoselectivity: the used *i*-propyl ester gave the 3:1 ratio while the corresponding ethyl ester gave a slightly slower 2.3:1 ratio of the diastereomers.

2.3 Aplyronine A/B/C; anti, syn, anti and anti, anti, syn

Aplyronines A, B and C (Figure 7), 24-membered marine macrolides, were isolated from the sea hare *Aplysia kurodai* in 1993 by Yamada and co-workers.[26] Aplyronines proved to be bioactive molecules; they have high degree of activity towards a variety of tumor cell lines.[26, 27]

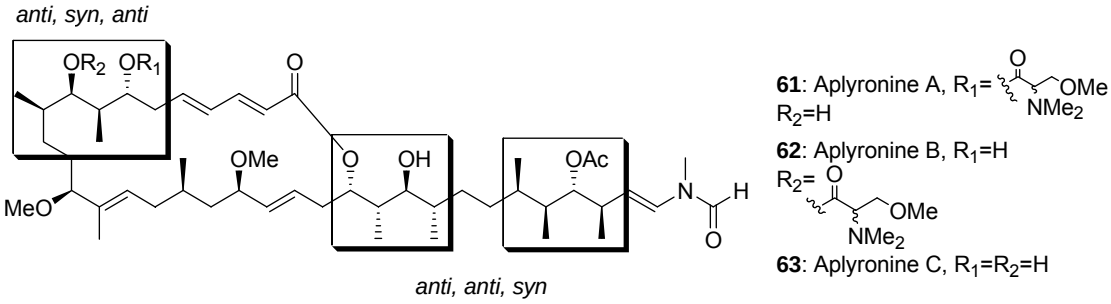
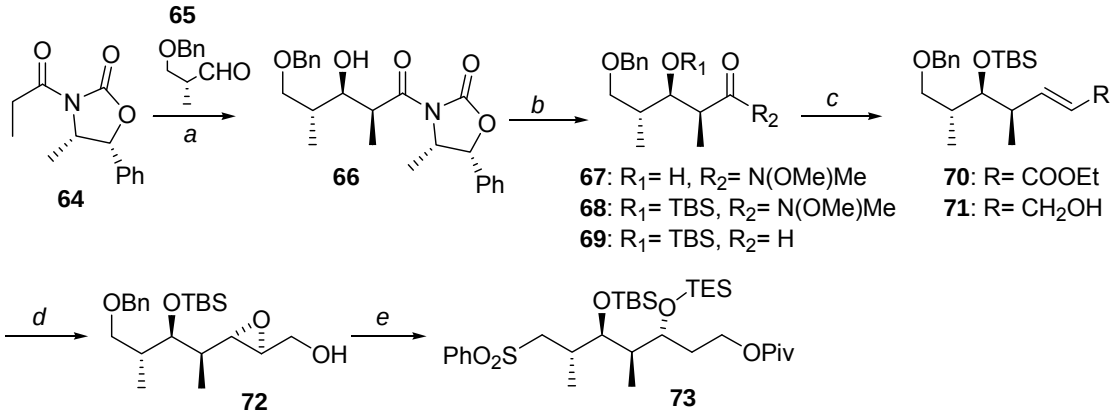


Figure 7

Aplyronines contain three stereotetrads: one with *anti, syn, anti* and two with *anti, anti, syn* stereochemistries.

Yamada and his group published the first total synthesis of Aplyronine A in 1996, only three years after the isolation.[27] Their retrosynthetic analysis was planned so that each of the three stereotetrads represented an individual substructure in the total synthesis.

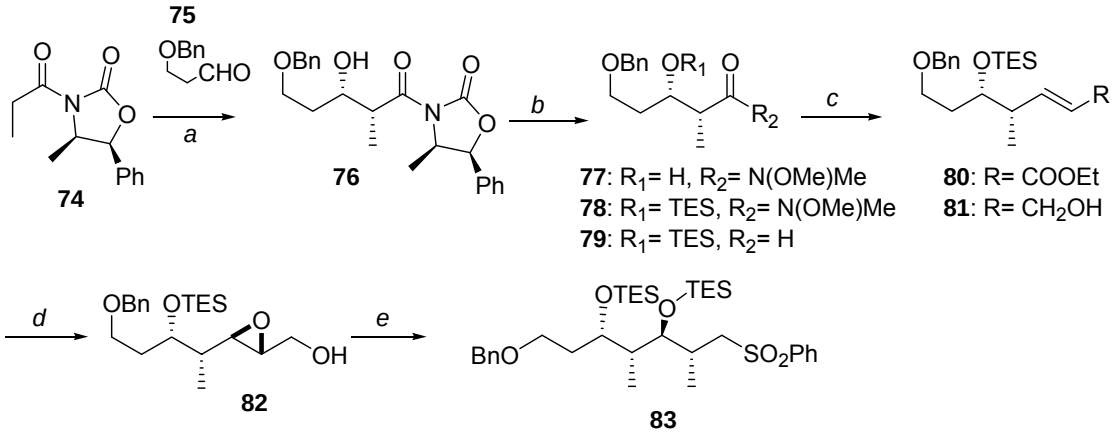
The synthesis of the *anti, syn, anti* stereotetrad (Scheme 7) began with an Evans aldol reaction between **64** and **65** in which two new stereogenic centers were created. The fourth stereocenter was introduced successfully through Sharpless asymmetric epoxidation (Scheme 7, step *d*). The final stages (step *e*) in the synthesis of the *anti, syn, anti* dipropionate included protection of the hydroxyl groups and conversion of the leftward hydroxyl group to the sulfone **73**.



a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then **65**, -78 °C, 3 h-> 0 °C, 20 min *b*) 1. Me_3Al, MeONHMe·HCl, THF, toluene, CH_2Cl_2, -10-> 0 °C, 1.6 h; 2. *t*-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; 3. DIBAL-H, THF, hexane, -78 °C, 2 h *c*) 1. $(i\text{-PrO})_2P(O)CH_2COOEt$, *t*-BuOK, THF, -78 °C, 1 h-> 0 °C, 1.5 h; 2. DIBAL-H, CH_2Cl_2, hexane, -78 °C, 1 h *d*) $Ti(O\text{-}i\text{-Pr})_4$, (+)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, -23 °C, 1 h *e*) Ref. 27.

Scheme 7

The syntheses of the C(21)-C(27) (Scheme 8) and C(28)-C(34) *anti, anti, syn*, stereotetrads were both also based on the Evans aldol chemistry and the Sharpless asymmetric epoxidation.[27] The fourth stereogenic center was created through nucleophilic attack of methylcuprate into the epoxide **82** to produce the desired *anti*, *anti, syn* stereochemistry.

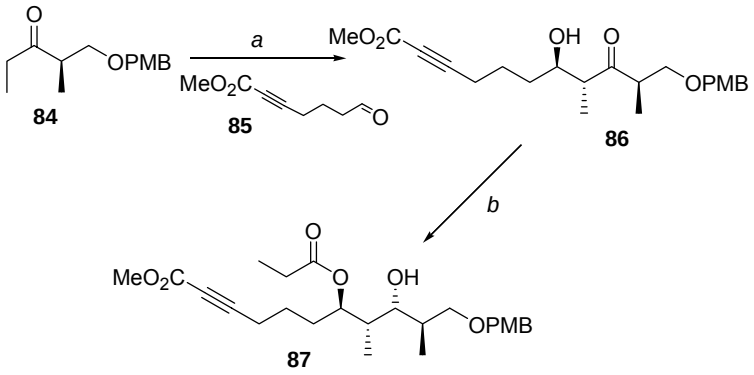


a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then **75**, -78 °C, 2 h-> 0 °C, 2 h *b*) 1. Me_3Al, MeONHMe·HCl, THF, toluene, CH_2Cl_2, -10-> 0 °C, 1.5 h; 2. TESCl, imidazole, DMF, 23 °C, 35 min. 3. DIBAL-H, THF, hexane, -78 °C, 2 h *c*) 1. $(i\text{-PrO})_2P(O)CH_2COOEt$, *t*-BuOK, THF, -78 °C, 1.5 h-> 0 °C, 1.5 h; 2. DIBAL-H, CH_2Cl_2, hexane, -78 °C, 1.5 h *d*) $Ti(O\text{-}i\text{-Pr})_4$, (-)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, -23 °C, 2 h *e*) Ref. 27.

Scheme 8

Paterson *et al*. have also been working on the total synthesis of aplyronines.[28] Although their total synthesis of aplyronines is still incomplete, the syntheses of the stereotetrad subunits have been published.[28]

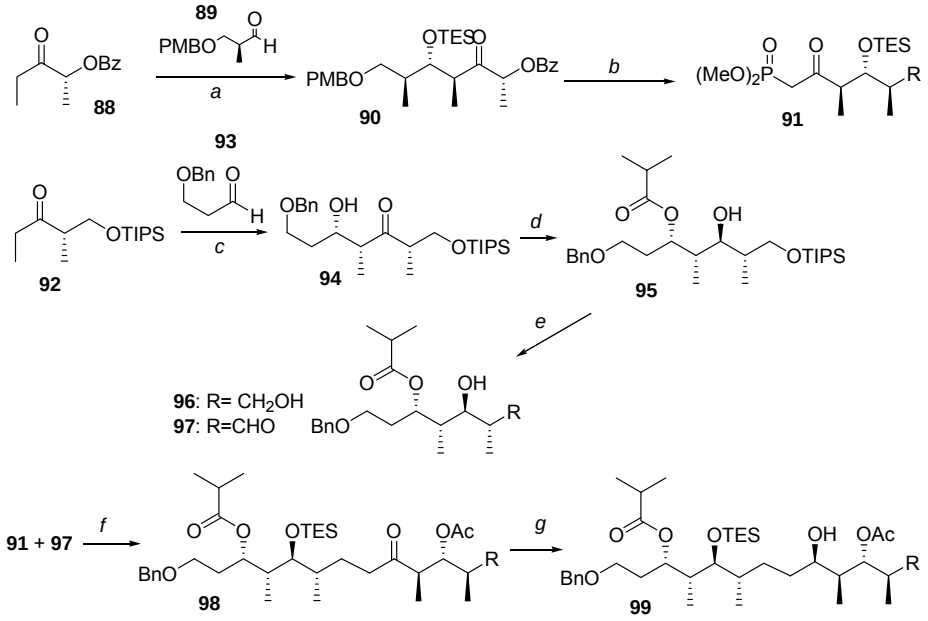
The synthesis of the *anti, syn, anti* stereotetrad began with an aldol reaction between the *E*-boron enolate of the chiral precursor **84** and aldehyde **85** (Scheme 9).[28a] The desired *anti, anti* aldol product **86** was obtained with high diastereoselection (≤ 97% ds). The ketone was then reduced in a 1,3-*anti* manner to produce the desired *anti, syn, anti* stereochemistry in **87**.



a) (c-Hex)$_2$BCl, Et$_3$N, Et$_2$O, 0 ^{o}C, 1 h, then –78 ^{o}C and **85** -> -20 ^{o}C, 12 h, oxidative work-up *b*) SmI$_2$, EtCHO, THF, 0 ^{o}C, 15 min., then **86**, 0 ^{o}C, 2 h.

Scheme 9

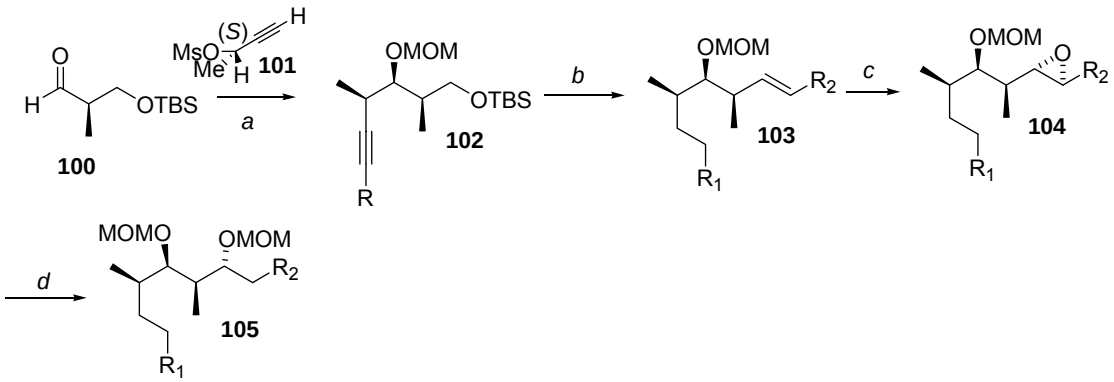
Paterson *et al*. also completed the synthesis of the C(21)-C(34) subunit of aplyronines.[28b] This southern segment contains two *anti, anti, syn* stereotetrads and the syntheses of both dipropionates were based on the chiral starting materials (**88**, **89**, **92**), diastereoselective aldol reactions (steps *a* and *c*) and stereoselective 1,3-*anti* diol reduction (steps *d* and *g*) (Scheme 10).



a) 1. $(c\text{-Hex})_2BCl$, Me_2NEt, Et_2O, 0 °C, 1h, then –78 °C, **89**, -> -20 °C, 16 h; 2. TESOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 2 h *b*) Ref. 28b *c*) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, **93**, -78 °C, 2 h *d*) isobutyraldehyde, SmI_2, THF, 0 °C, 2.5 h *e*) 1. HF·pyridine, THF, rt, 7 h; 2. cat. TEMPO, $PhI(OAc)_2$, rt, 2 h *f*) Ref. 28b *g*) SmI_2, CH_3CHO, THF, -5 °C, 2.5 h.

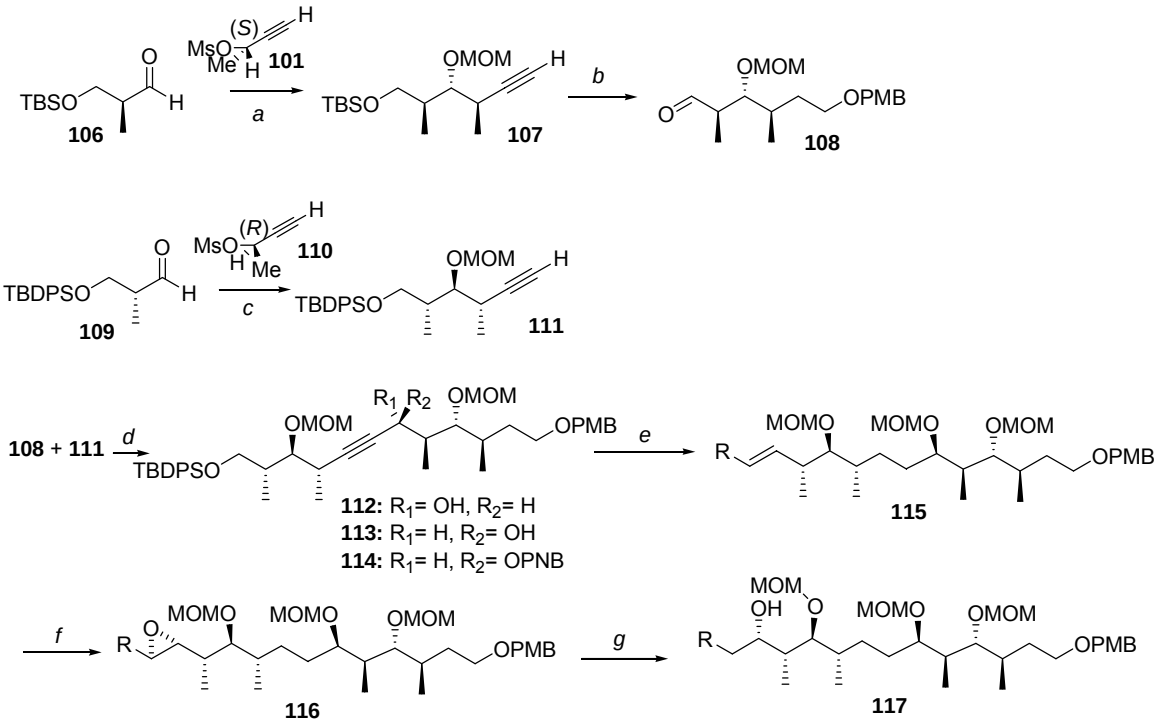
Scheme 10

Synthetic methodology developed in the laboratory of J. Marshall suited perfectly for the synthesis of the stereotetrads of aplyronines.[29] The key step in the syntheses of the *anti, syn, anti* (Scheme 11) and both *anti, anti, syn* (Scheme 12) dipropionates was the first reaction; an *in situ* prepared chiral allenylindium reagent reacted with a chiral α-methyl aldehyde (Scheme 11, step *a*; Scheme 12, steps *a* and *c*) creating two new stereogenic centers with high diastereoselectivity.[30] The fourth stereocenter of the stereotetrads was created either *via* Sharpless asymmetric epoxidation (Scheme 11, step *c*; Scheme 12, step *f*) or by aldol reaction (Scheme 12, step *d*). In the synthesis of the rightward *anti, anti, syn* stereotetrad, the aldol reaction (Scheme 12, step *d*) produced two separable diastereomers **112** and **113** in a 60:40 ratio. The desired diastereomer **113** proved to be the minor one, but the major diastereomer **112** was inverted *via* the Martin-Mitsunobu procedure[31] to the desired diastereomer **113**.



a) 1. Pd(dppf)Cl_2, InI, THF-HMPA; 2. MOMCl, Bu_4NI, *i*-Pr_2Net *b*) Ref. 29 *c*) (+)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH *d*) 1. Red-Al, THF; 2. MOMCl, Bu_4NI, *i*-Pr_2NEt.

Scheme 11

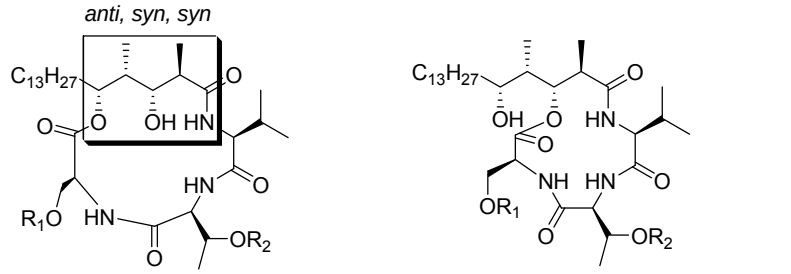


a) 1. Pd(dppf)Cl_2, InI, THF-HMPA; 2. MOMCl, Bu_4NI, *i*-Pr_2NEt *b*) Ref. 29 *c*) 1. Pd(dppf)Cl_2, InI, THF-HMPA; 2. MOMCl, Bu_4NI, *i*-Pr_2Net *d*) lithiation of **111**, then **106**, ref. 29 *e*) ref. 29 *f*) (-)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH g) Zn, MeOH, ∆.

Scheme 12

2.4 Stevastelins; anti, syn, syn

Stevastelins (Figure 8) represent a family of novel depsipeptides isolated from a culture of *Penicillium* sp. NK374186[32] and they have shown to be potent immunosuppressive agents.[33]

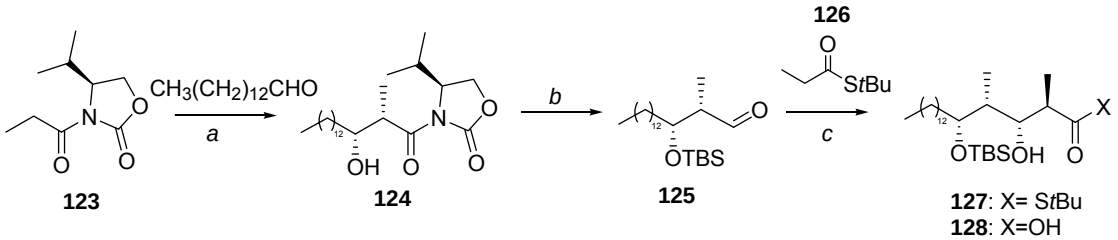


Stevastelin A **118**: R_1= Ac, R_2= SO_3H
Stevastelin B **119**: R_1= Ac, R_2 = H

Stevastelin A3 **120**: R_1= Ac, R_2= SO_3H
Stevastelin B3 **121**: R_1= Ac, R_2 = H
Stevastelin C3 **122**: R_1= H, R_2= H

Figure 8

Two research groups have aimed their studies towards the synthesis of stevastelins. Sarabia *et al.* began the synthesis of the stereotetrad of stevastelins with the Evans aldol methodology to create the first two stereocenters in a *syn* manner (Scheme 13).[34] The other two stereocenters were created via an aldol reaction of the *E*-boron enolate of **126** and the chiral aldehyde **125** (Scheme 13, step *c*). Only one diastereomer, the desired *anti, syn, syn* product **127** was obtained.



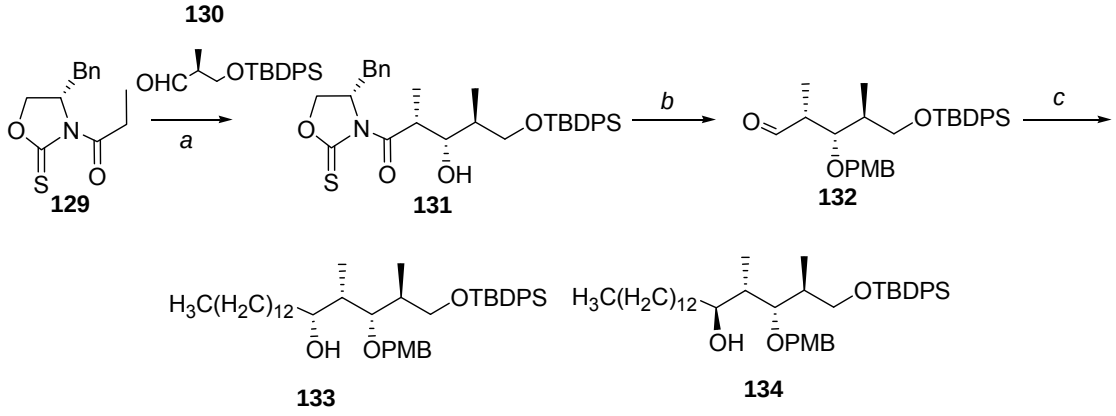
123 **124** **125**

127: X= S*t*Bu
128: X=OH

a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, then –78 °C, tetradecanal, 12 h *b*) Ref. 33 *c*) **126**, $(Chx)_2BCl$, EtN_3, CH_2Cl_2, 0 °C, 2 h, then –78 °C, **125**, 12 h, oxidative work-up.

Scheme 13

Chakraborty *et al*. have reported the synthesis of the subunits of stevastelin B.[35] Their synthesis began with a Ti(IV) mediated diastereoselective non-Evans *syn* aldol reaction[36] using a 2-oxazolidinethione based chiral auxiliary[37] (Scheme 14). This reaction produced the desired stereotriad as the only isolable diastereomer. The fourth stereocenter was created *via* nucleophilic addition of the long chain Grignard reagent onto the aldehyde **132**. The diastereoselectivity of this step was low: after purification the desired product **133** was obtained only in 40% yield.

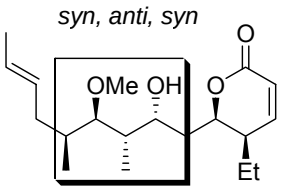


a) $TiCl_4$, DIPEA, CH_2Cl_2, -78 °C *b*) 1. $NaBH_4$, EtOH, 0 °C; 2. $MeOPhCH(OMe)_2$, CSA (cat.), CH_2Cl_2; 3. DIBAL-H, CH_2Cl_2, -78 °C-> 0 °C; 4. Swern oxidation *c*) $CH_3(CH_2)_{12}MgBr$, THF, 0 °C-> rt.

Scheme 14

2.5 Pironetin (PA-48153C); syn, anti, syn

Pironetin (PA-48153C) (Figure 9) was isolated in 1993 independently by two Japanese research groups from the fermentation broths of *Streptomyces* sp. NK10958[38] and *Streptomyces prunicolor* PA-48153.[39] Pironetin has shown immunosuppressive activity towards T and B lymphocytes.[39] Also, its potent activity as a plant growth regulator has been described by Kobayashi and coworkers.[38]

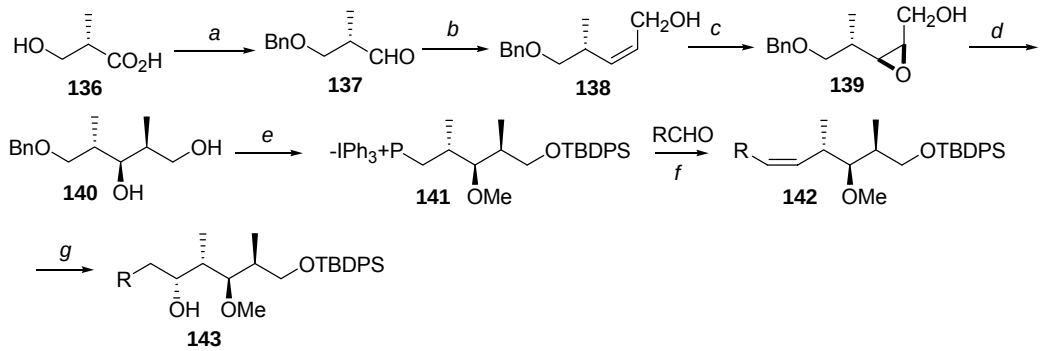


135: Pironetin

Figure 9

The structure of Pironetin (Figure 9), the unsaturated δ-lactone ring joined to the *syn, anti, syn* stereotetrad, has attracted many research groups since its isolation, and several total syntheses have been published so far.

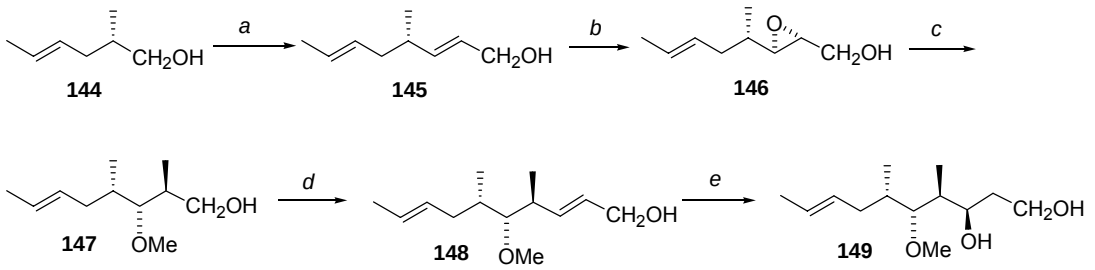
The first total synthesis of Pironetin by Yasui *et al*. was published two years after its isolation.[40] The synthesis of the stereotetrad was very straightforward and the keys in the synthesis were the chiral precursor **136**, asymmetric epoxidation (Scheme 15, step *c*) and hydroboration (Scheme 15, step *g*).



a) 1. $PhCH_2OC(=NH)CCl_3$, CF_3SO_3H; 2. $LiAlH_4$; 3. Swern oxidation *b*) 1. $(CF_3CH_2O)_2P(=O)CH_2CO_2Me$, $KN(TMS)_2$, 18-Crown-6; 2. DIBAL-H *c*) MCPBA *d*) Me_2CuLi *e*) ref. 39 *f*) *n*-BuLi *g*) B_2H_6, H_2O_2.

Scheme 15

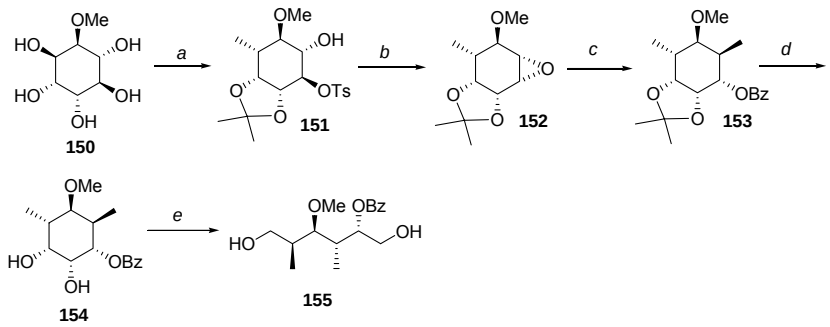
Gurjar *et. al* based their synthesis of the dipropionate of Pironetin on the chiral precursor **144** and Sharpless asymmetric epoxidation (Scheme 16).[41]



a) 1. IBX, DMSO, rt, 30 min.; 2. Ph_3=$CHCO_2Et$, benzene, rt, 3 h; 3. DIBAL-H, CH_2Cl_2, -20 °C, 30 min *b*) TBHP, Ti(O*i*Pr)$_4$, (-)-DIPT, CH_2Cl_2, -20 °C, 20 h *c*) 1. Me_2CuLi, Et_2O, -78 °C, 8 h; 2. TBSCl, imidazole, CH_2Cl_2, rt, 3 h; 3. KH, MeI, Et_2O, rt, 30 min.; 4. Bu_4NF, THF, rt, 2 h *d*) = *a*) *e*) 1. TBHP, Ti(O*i*Pr)$_4$, (+)-DIPT, CH_2Cl_2, -20 °C, 18 h; 2. Red-Al, THF, 0 °C, 4 h.

Scheme 16

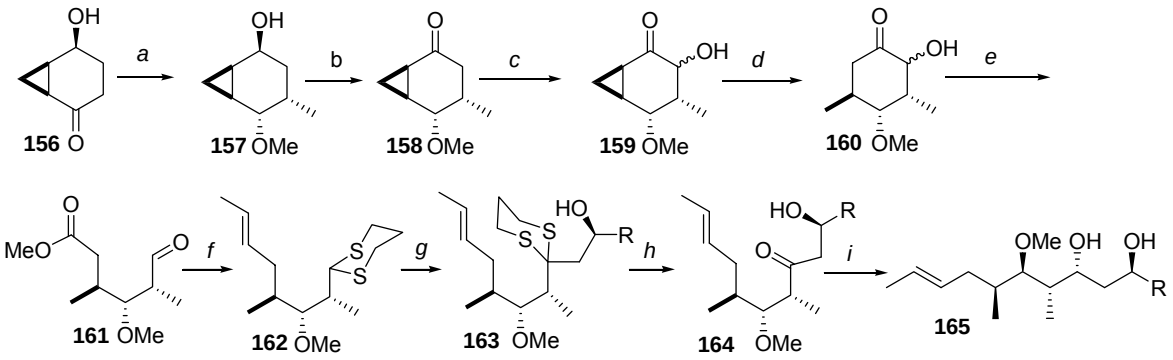
Chida *et al*. began the synthesis of the stereotetrad of Pironetin from L-quebrachitol **150**[42] (Scheme 17), which is an optically active cyclitol obtained in large quantities from the serum of rubber tree.[43] Intermediate **151** was prepared stereoselectively from L-quebrachitol **150** in five steps.[44] Two stereocenters were inverted via base treatment of **151** to produce the epoxide **152** followed by *trans*-diaxial opening of the epoxide with the methyl nucleophile and protection. Intermediate **153** already had the desired stereochemistry. Finally, **153** was deketalized and opened to produce the acyclic *syn*, *anti, syn* stereotetrad **155** of Pironetin.



a) 1. ref. 44; 2. Bu_2SnO, MeOH, reflux, then TsCl, DMAP; 3. 1,4-dioxane, rt b) MeONa, MeOH, reflux *c*) 1. Me_3Al, CH_2Cl_2:hexanes, rt; 2. BzCl, pyridine, DMAP, rt *d*) 10-caphorsulfonic acid, MeOH, rt *e*) $NaIO_4$, acetone:H_2O, 0 °C, then $NaBH_4$, MeOH, 0 °C.

Scheme 17

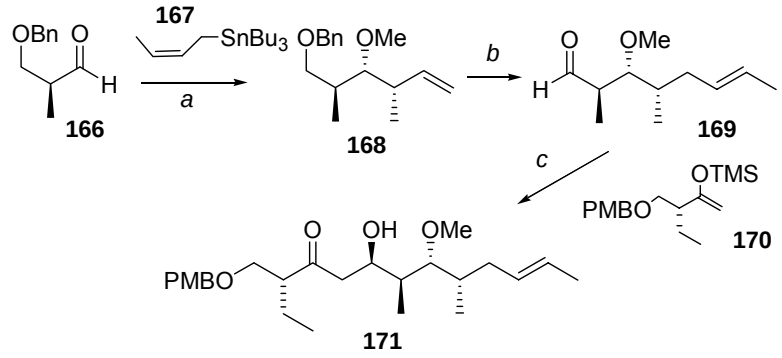
Watanabe *et al*. used the chiral precursor **156**[45] as the starting material in their synthesis of the dipropionate fragment of Pironetin (Scheme 18).[46] All stereochemical information came from the chiral cyclohexanone derivative **156** and the chiral R* chain, which was coupled to **162** in high yield and diastereoselectivity (Scheme 18, step *g*).



a) 1. DHP, PPTS, CH_2Cl_2, rt; 2. LDA, HMPA, THF, -78 °C, then MeI; 3. L-Selectride, THF, -78 °C; 4. NaH, MeI, TBAI, THF, 60 °C; 5. aq. HCl, MeOH, 0 °C *b*) Dess-Martin oxidation *c*) 1. TBSOTf, Et_3N, CH_2Cl_2, 0 °C; 2. cat. OsO_4, NMO, THF, H_2O, rt *d*) LHMDS, THF, -78 °C, then Li, liq. NH_3, then NH_4Cl *e*) $Pb(OAc)_4$, benzene, MeOH, rt *f*) ref. 45 *g*) *n*- BuLi, HMPA, THF, 0 °C, then R*X *h*) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, rt *i*) $LiAlH(OtBu)_3$, LiI, ether, -78 °C -> 0 °C.

Scheme 18

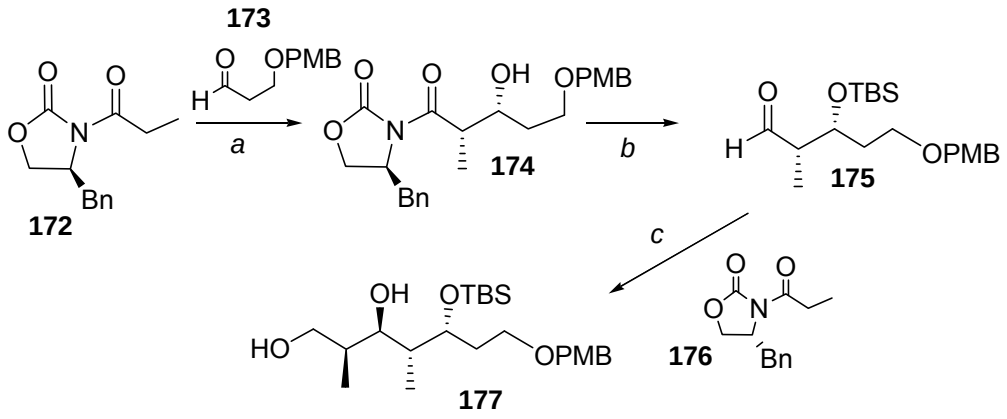
Keck *et al*. started their synthesis with chelation controlled ($TiCl_4$) addition of (*Z*)-crotyltri-*n*-butylstannane **167** to the β-benzyloxy aldehyde **166** to give the desired *anti, syn* homoallylic alcohol **168** (Scheme 19).[47] The fourth stereocenter of the stereotetrad was created *via* an aldol reaction between the stereotriad aldehyde **169** and the chiral TMS enol ether **170** using BF_3·OEt as the Lewis acid. The desired diastereomer **171** was the only product in this reaction; none of the other diastereomers was detected.



a) 1. **167**, $TiCl_4$ 2. KH, MeI *b*) ref. 46 *c*) **170**, $BF_3 \cdot OEt$.

Scheme 19

The most recently published total synthesis of Pironetin by Dias *et al*. was based on the Evans aldol chemistry (Scheme 20).[48] This route was very short and efficient but it needed external chiral information twice for building up the desired stereochemistry (Scheme 20, steps *a* and *c*).



a) n-Bu_2BOTf, CH_2Cl_2, Et_3N, - 5 °C, then –78 °C, **173** *b*) ref. 47 *c*) 1. **176**, n-Bu_2BOTf, CH_2Cl_2, Et_3N, - 5 °C, then –78 °C, **175**; 2. $LiBH_4$, THF/MeOH, 0 °C.

Scheme 20

2.6 Erythromycin A/B and Erythronolide A/B; syn, syn, syn

Erythromycins (Figure 10, **178**, **179**), erythronolides (Figure 10, **180**, **181**) and their derivatives belong to macrolide antibiotics. Erythromycin A was isolated in the early 50's by McGuire *et al*.[49] from a strain of *Streptomyces erytreus,* and its complete structure was revealed in 1965 by X-ray analysis.[50] The antibiotic activity of erythromycins is related to their ability to inhibit ribosomal-dependent protein biosynthesis.[51]

For over four decades the challenging structures of erythromycins and erythronolides have attracted many research groups,[52] but only a few total syntheses have been reported so far. In this chapter, the first two and the two most recent syntheses of the stereotetrad of erythromycins/erythronolides (boxed in Fig. 10) are discussed in detail.

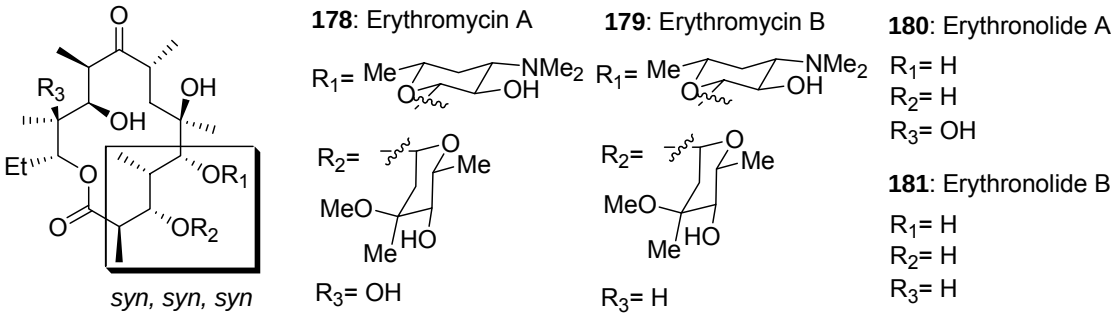
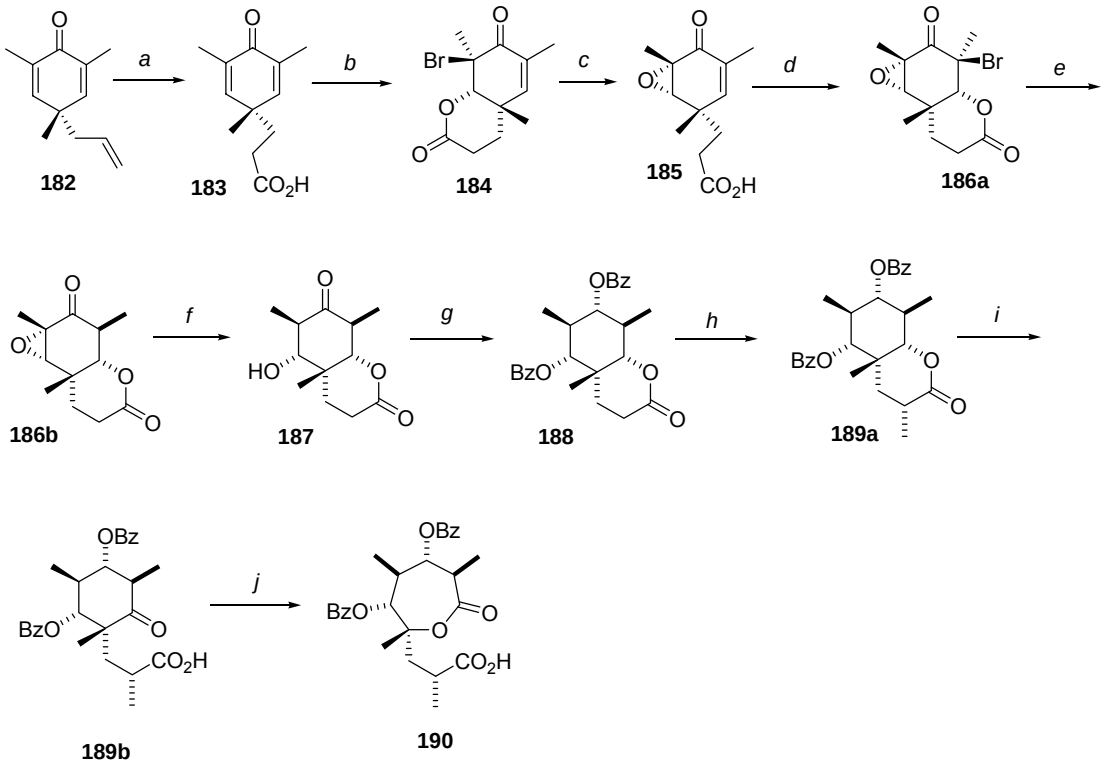


Figure 10

E. J. Corey *et al*. published in 1978 the first total synthesis of (+/-)-erythronolide B.[53] The creation of the *syn, syn, syn* stereotetrad began from dienone **182** (rac.) by hydroboration followed by oxidation, to produce the dienone acid **183**.[54] Treatment with bromine/potassium bromide solution yielded the bromo lactone **184**, which was then converted under basic reaction conditions to the epoxy acid **185**. The epoxy acid **185** was then converted to the bromo epoxy lactone **186a**, from which the bromine was cleaved away *via* radical reaction to produce the epoxy lactone **186b**. Epoxide **186b** was opened and the ketone **187** was then stereoselectively reduced with Raney Nickel. Then the hydroxyl groups were protected to produce the dibenzoate **188**, which already possessed the all-*syn* stereochemistry.

Dibenzoate **188** was finally transformed to lactone **190**, which was one of the key intermediates in the first total synthesis of erythronolide A.



a) 1. B_2H_6, THF, 0-10 °C; 2. Jones chromic acid, 0- -10 °C *b*) Br_2, KBr, H_2O *c*) aq. KOH, THF *d*) Br_2, KBr, H_2O *e*) NBu_3SnH, AIBN, PhH, *f*) Al/Hg, THF, H_20, 0- -10 °C *g*) 1. H_2, Raney Ni, DME, -20 °C; 2. BzCl, pyridine *h*) LDA, THF, -78 °C, then MeI, HMPA, -78 °C-> -45 °C *i*) 1. LiOH, H_2O; 2. CrO_3, H_2SO_4, acetone, -10 °C *j*) $MeCO_3H$, EtOAc, 55 °C.

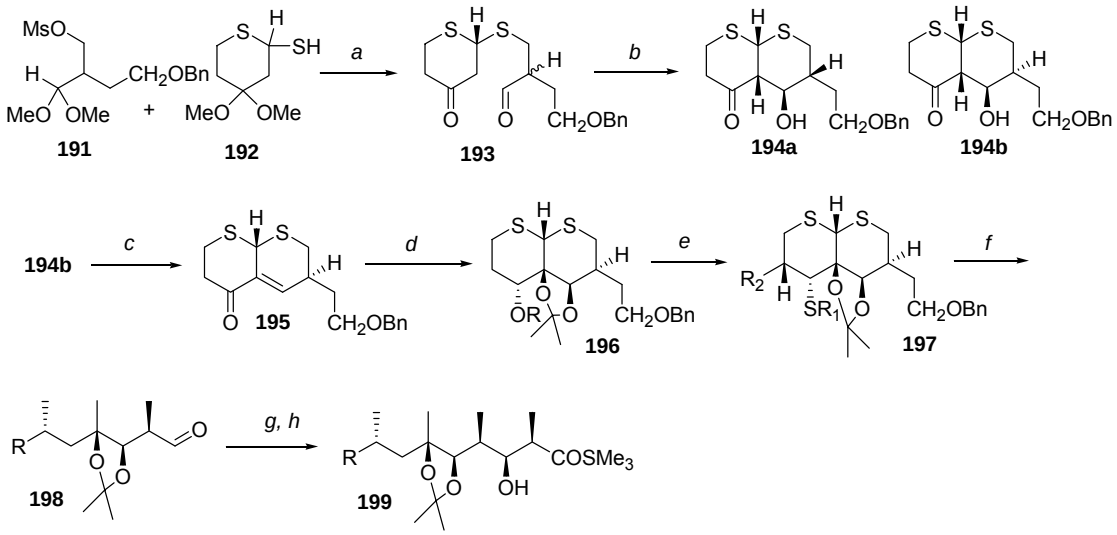
Scheme 21

Woodward *et al*. completed the first (and also the only one, so far) total synthesis of Erythromycin A in 1981.[52b] Thiopyranone ring strategy was the key for the successful total synthesis as well as for the synthesis of the *syn, syn, syn* stereotetrad (Scheme 22).

The synthesis of the *syn, syn, syn* stereotetrad began from the racemic starting materials **191** and **192**. The racemic intermediate **193** was allowed to undergo an intramolecular aldol reaction catalyzed by D-proline, and a 1:1 mixture of enantiomerically enriched diastereomers **194a** and **194b** were obtained (36% ee for both diastereomers). The synthesis was continued with **194b** and the enantiomerically enriched enone **195** was obtained after

dehydration. The desired enantiomer (+)-**195** crystallized out from the enantiomeric mixture and the synthesis was continued with optically pure material. Then, $NaBH_4$ reduction and OsO_4 oxidation gave stereospecifically the key intermediate **196** in good yield and stereoselectivity.

The final stages in building up the all-*syn*-stereotetrad were very straightforward. After desulfurisation, deprotection and oxidation (step *f*), aldehyde **198** was allowed to react with the enolate of *tert*-butyl thiopropionate. The product, the undesired Cram aldol adduct (wrong stereochemistry at C2) was finally inverted via kinetic protonation to the desired *syn, syn, syn* product **199**.



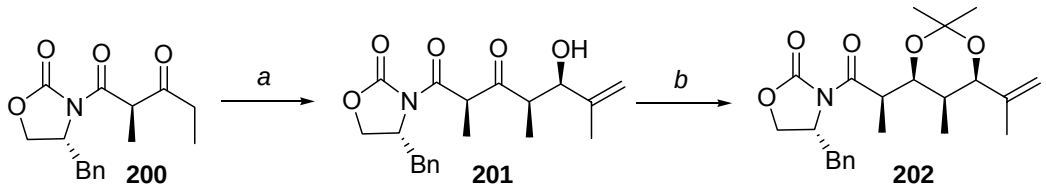
a) 1. NaH, THF, DMSO, rt; 2. AcOH, H_2O, rt *b)* D-Pro, PhH/MeOH, rt *c)* 1. MsCl, py; 2. Al_2O_3, EtOAc *d)* 1. $NaBH_4$, MeOH, 0 ^oC; 2. $MeOCH_2I$, KH, THF; 3. OsO_4, Et_2O, then $NaHSO_3$, py; 4. $Me_2C(OMe)_2$, TsOH, CH_2Cl_2 *e)* six steps; *f)* 1. Raney Ni (W2), EtOH, DMF, rfx; 2. *o*-$NO_2PhSeCN$, *n*Bu_3P, THF, 30% H_2O_2, THF, rt; 3. O_3, MeOH, CH_2Cl_2, -78 ^oC, then Me_2S, $NaHCO_3$ *g*) 1. $EtCOSCMe_3$, LDA, THF, -110 ^oC; 2. *t*-BuLi, THF, -110 ^oC, then AcOH, -110 ^oC *h*) 1. *t*-BuLi, $(CH_2NMe_2)_2$, THF, -110 ^oC; 2. AcOH, -110 ^oC.

Scheme 22

Evans *et. al* published the total synthesis of 6-deoxyerythronolide B (biosynthetic precursor of erythromycins) in 1997[55] and it is not surprising that the synthesis was based on the Evans aldol chemistry.

The Evans' all-*syn*-stereotetrad synthesis was very short and highly stereoselective (Scheme 23). The β-ketoimide **200** was allowed to react with methacrolein ($TiCl_4$ as the Lewis acid) followed by a 1,3-*syn* reduction and

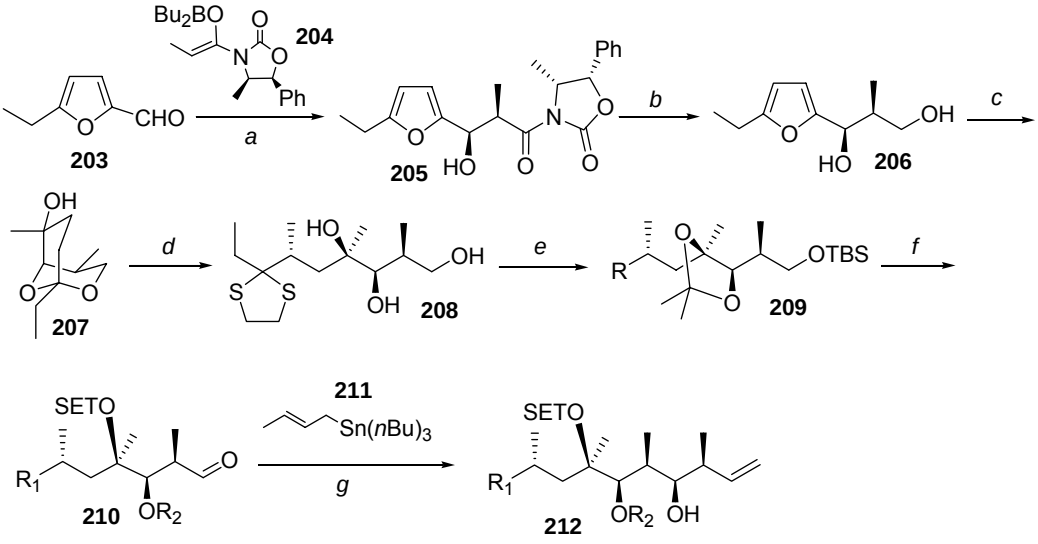
ketal protection of the diol to produce the stereotetrad **202** in excellent yield and stereoselectivity.



a) $TiCl_4$, *i*-Pr_2NEt, methacrolein, 0 °C, CH_2Cl_2 *b*) 1. $Zn(BH_4)_2$, -78 °C, CH_2Cl_2; 2. $Me_2C(OMe)_2$, CSA, 25 °C, CH_2Cl_2.

Scheme 23

The most recent total synthesis of erythromycins was published in 2003 when S. F. Martin *et al*. completed the total synthesis of Erythromycin B.[56] The synthesis of the *syn, syn, syn* stereotetrad fragment started with Evans aldol chemistry to give the aldol adduct **205** as the only isomer (Scheme 24, step *a*).[57] After several reaction steps (Scheme 24, steps *b*-*f*), which concentrated on the synthesis of the left half of Erythromycin B, two missing stereocenters of the *syn, syn, syn* stereotetrad were created *via* asymmetric crotylation (Scheme 24, step *g*).

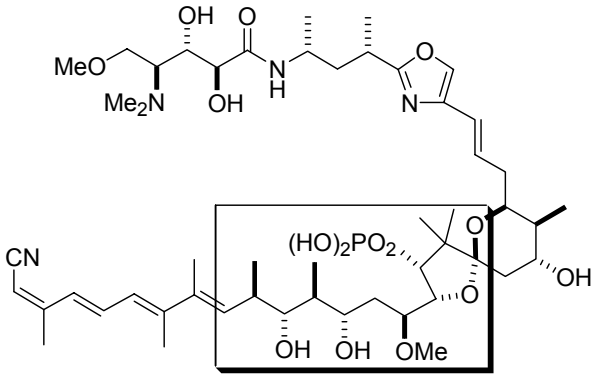


a) **204**, CH_2Cl_2, **203**; ref. 56 *b*) $LiBH_4$, THF; ref. 56 *c*) 1. Br_2, MeCN, H_2O; 2. Me_2CuLi; 3. MeLi, $CeCl_3$; ref. 56 *d*) $TMSSCH_2CH_2STMS$, $TiCl_4$; ref. 56 *e*) ref. 55 *f*) ref. 55 *g*) **210**, **211**, $BF_3{\cdot}OEt$, CH_2Cl_2, ref. 55.

Scheme 24

3 Preparation of the dipropionate-lactone fragment of Calyculin C

Calyculins form a class of highly cytotoxic metabolites originally isolated from the marine sponge *Discodermia calyx* by Fusetani *et al.*[58] Calyculins have proven to be strong serine/threonine protein phosphatase inhibitors[59] and based on this property, calyculins might be potential anti-cancer agents.[60]



213: Calyculin C

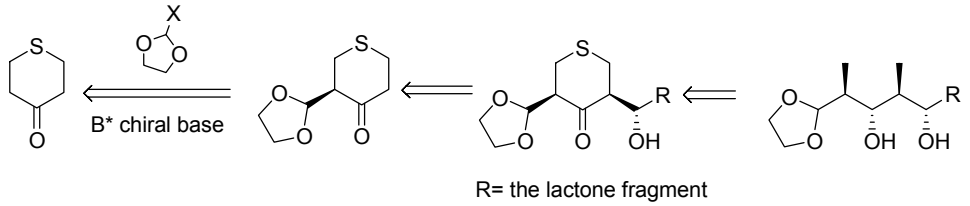
Figure 11

The C_9-C_{19} dipropionate lactone fragment of Calyculin C (boxed in Fig. 11) contains seven of the total fifteen stereogenic centers and is thereby a key substructure of this sponge metabolite.

Synthetic efforts towards calyculins have been recently reviewed.[61] Several syntheses of the lactone-dipropionate fragment have been published with varying strategies.[62] The most challenging part in the synthesis of this C_9-C_{19} fragment is the *anti*, *anti*, *anti* stereotetrad, which can be reached either by linear[62e-d] or by convergent[62a-c] approaches. However, the syntheses published so far have many weaknesses (too many steps, poor diastereoselectivity or need for inversion of stereocenters). Therefore, new routes for this fragment are still needed.

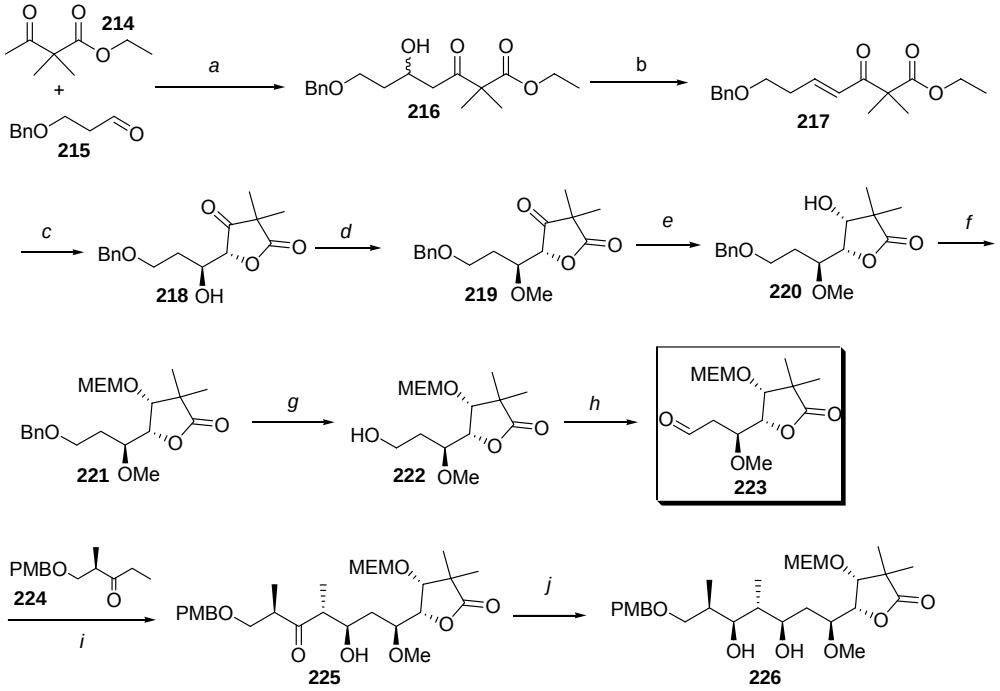
Our first retrosynthetic analysis of the C_9-C_{19} fragment was based on the thiopyranone ring strategy (Scheme 25), but unfortunately it did not lead us towards the stereotetrad of Calyculin C. Luckily those studies were not

fruitless: the results guided us to a short and enantioselective synthesis of the C(33)-C(37) fragment of Amphotericin B.[24, 25]



Scheme 25

The second approach towards the target fragment carried us two steps closer to the goal. We succeeded in realizing a short and highly enantio- and diastereoselective synthesis of the key intermediate **223** (Scheme 26).[63] Unfortunately, the convergent approach led us to a wrong diastereomer **226** of C_9-C_{19} fragment of Calyculin C.



a) LDA, the ketone **214**, 1 h., then the aldehyde **215**, THF, -78 °C, 1 h *b*) MsCl, NEt_3, CH_2Cl_2 0 °C, 4.5 h *c*) $(DHQD)_2PYR$, $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, OsO_4, H_2O/*t*-BuOH 0 °C, 17 h *d*) MeI, Ag_2O, Et_2O, reflux, 22 h *e*) L-Selectride, THF, -78 °C, 15 min. *f*) MEMCl, DIPEA, CH_2Cl_2, reflux, 48 h *g*) $Pd(OH)_2$/C, EtOH, H_2, 40 min. *h*) TPAP, CH_2Cl_2, 4 Å MS, 2 h *i*) NEt_3, the ketone **224**, $(Chx)_2BCl$, Et_2O, 0 °C, 1 h, then -78 °C, the aldehyde **223** -> -18 °C, 21 h *j*) 1. $(Et)_2BOMe$, $NaBH_4$, THF/MeOH, -78 °C, 4 h; 2. pinacol, MeOH, 40 °C, 72 h.

Scheme 26

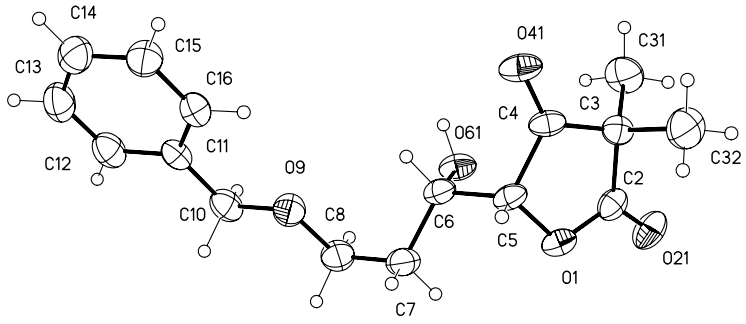
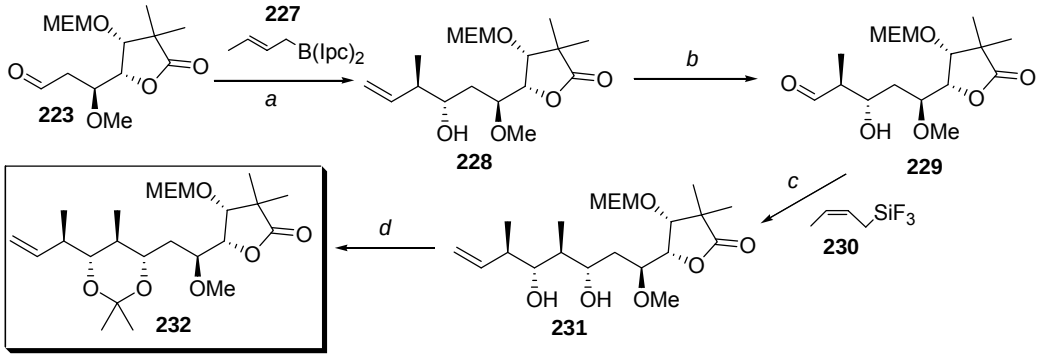


Figure 12 Crystal structure of the lactone intermediate **218**.[64]

Finally, the third plan was successful: a linear approach brought us to the end of the synthetic path of the C_9-C_{19} fragment of Calyculin C (Scheme 27).[65] The lactone aldehyde **223** was first allowed to react with a chiral crotyl borane reagent **227**[66] yielding a 6:1 diastereomeric mixture of two *anti* homo allylic alcohols. The major diastereomer **228** was isolated with simple flash chromatography, followed by ozonolysis to yield the unstable β-hydroxy aldehyde **229**. The second crotylation was realized with *Z*-crotyl trifluorosilane **230**.[67] The reaction succeeded perfectly: only one diastereomer **231** was obtained! Finally the diol was converted to the corresponding ketal **232**, which helped to confirm the stereochemistry of the stereotetrad.



a) the crotyl reagent was prepared from (+)-IpcBOMe and *trans*-butene in THF at -78 °C, then $BF_3{\cdot}OEt$, the aldehyde **223**, -78 °C, 1 h, then ethanol amine *b*) O_3, CH_2Cl_2, -78 °C, then triphenyphosphine, rt, 3 h *c*) the aldehyde **229**, 4 Å MS, CH_2Cl_2, rt, 0.5 h, then 0 °C, DIPEA, (*Z*)- crotyl trifluorosilane **230**, 4 h *d*) 2-methoxy propene, pyridinium *p*-toluenesulfonate (PPTS) (cat.), CH_2Cl_2, rt, 0.5 h.

Scheme 27

4 Conclusions

The stereotetrad is a common substructure in polypropionate natural products. Four stereogenic centers next to each other results in eight possible diastereomeric combinations of this structure. Thus, an asymmetric synthesis of each of these combinations (*anti, anti, anti*; *anti, anti, syn*; *anti, syn, anti*; *syn, anti*, *anti*; *syn, syn, anti*; *syn, anti, syn*; *anti, syn, syn* and *syn, syn*, *syn*) demands accurate planning and careful realization in laboratory. When the synthesis of a stereotetrad is a part of a total synthesis of a more complex molecule the situation becomes even more complicated. If the stereotetrad fragment can be cleaved retrosynthetically into an independent sub goal, its synthesis is often more straightforward than in the case where the stereochemistry of the stereotetrad is created by a linear approach. In the latter situation, the stereochemistry and structure of the remaining molecule has to be considered and it usually limits the possible strategies to minimum.

Some interesting points can be noted from chapter 2, which deals with syntheses of stereotetrads. It was a big surprise to discover, that the linear structure of the *syn, syn, anti* stereotetrad (as a fragment of a natural product) was not found with a database search. Even if the conclusion, that the *syn, syn, anti* stereotetrad does not exist in natural products, cannot be drawn, it is evident that this structure is very rare in nature. It was also interesting to notice that the syntheses of all different stereotetrads were mostly based on *i*) Evans asymmetric aldol methodology, *ii*) Sharpless asymmetric epoxidation and dihydroxylation, *iii*) asymmetric crotylations and *iv*) diastereoselective aldol reaction between an aldehyde and an *E*-enolate of a ketone.

The *syn*, *anti*, *anti* dipropionate fragment of Amphotericin B was synthesized *via* thiopyranone ring strategy. The asymmetry was introduced into the thiopyranone ring with the chiral tartrate derived orthoester **55**, which indeed played a role of a chiral auxiliary. The highly diastereoselective Mukaiyama aldol reaction created the next two stereogenic centers and finally the 1,3-*syn* selective reduction produced the last stereocenter with high diastereoselectivity. After Raney Nickel

desulfurisation the enantiomer of the C(33)-C(37) dipropionate fragment of Amphotericin B was ready; the synthesis needed only six reaction steps starting from a commercially available tetrahydro thiopyran-4-one.[24, 25]

The dipropionate-lactone fragment of Calyculin C was a challenging target molecule, above all because of the *anti, anti, anti* stereotetrad structure. The intermediate lactone aldehyde **223** was used in both realized synthetic approaches as the key precursor.

The convergent approach began with an *anti* aldol reaction between the *E*-$(Chx)_2$B-enolate of the chiral ketone **224** and the key aldehyde **223** followed by 1,3-*syn* selective reduction. The PMP-acetal of **226** revealed the stereochemistry of the stereotetrad to be the undesired *syn, anti, anti*.[62]

The linear approach towards the all-*anti* stereotetrad was more fruitful. First, asymmetric crotylation between the key lactone aldehyde **223** and the chiral crotyl borane **227** yielded a diastereomeric mixture (6:1) of *anti* homo allylic alcohols. After ozonolysis, the β-hydroxy aldehyde **229** was allowed to react with (*Z*)-crotyl trifluorosilane **230** and only one diastereomer **231** was obtained as the product. The diol was finally converted into the corresponding ketal **232**. NMR studies of the ketal confirmed the *anti, anti, anti* stereochemistry.

5 References

[1] Birch, A. J. *Science* **1967**, *156*, 202.

[2] Rohr, J. *Angew. Chem. Int. Ed*. **2000**, *39*, 2847.

[3] Koskinen, A. *Asymmetric Synthesis of Natural Products* John Wiley & Sons Ltd, Chichester, **1993**, 234 p.

[4] Liu, C.-M. and Hermann, T. E. *J. Biol. Chem* **1978**, *253*, 5892.; Liu, W.-C., Slusarchyk, D. S., Astle, G., Trejo, W. H., Brown, W. E and Meyers, E. *J. Antibiot*. **1978**, *31*, 815.

[5] Toeplitz, B. K, Cohen, A. I., Funke, P. T., Parker, W. L. and Gougoutas, J. Z. *J. Am. Chem. Soc*. **1979**, *101*, 3344.

[6] Parpura, V., Basrsky, T. A., Liu, F., Jeftinija, K., Jeftinija, S. and Haydon, P. G. *Nature* **1994**, *369*, 744.

[7] Evans, D. A., Dow, R. L., Shih, T. L., Takacs, J. M. and Zahler, R. *J. Am. Chem. Soc*. **1990**, *112*, 5290.

[8] Hanessian, S., Cooke, N. G., DeHoff, B. and Sakito, Y. *J. Am. Chem. Soc*. **1990**, *112*, 5276.

[9] Lautens, M., Colucci, J. T., Hiebert, S., Smith, N. D. and Bouchain, G. *Org. Lett*. **2002**, *4*, 1879.

[10] Hanessian, S., Murray, P. J. and Sahoo, S. P. *Tetrahedron Lett*. **1985**, *26*, 5631.

[11] Hanessian, S. and Murray, P. J. *Tetrahedron* **1987**, *43*, 5055.; *J. Org. Chem*. **1987**, *52*, 1170.

[12] Evans, D. A. Chapman, K. T. and Bisaha, J. *J. Am. Chem. Soc*. **1988**, *110*, 1238.

[13] Evans, D. A. and Sjogren, E. B. *Tetrahedron Lett*. **1986**, *27*, 4961.

[14] see references in ref. 9

[15] Lubineneau, A. and Bouchain, G. *Tetrahedron Lett*. **1997**, *38*, 8031.

[16] Vandeputte, J., Watchel, J. L. and Stiller E. T. *Antibiot. Annu.* **1956**, 587.

[17] Mechinski, W. Shaffner, C. P, Ganis P. and Avitabile, G.*Tetrahedron Lett*. **1970**, 3873.; Ganis, P., Avitabile, G. Mechinski, W. and Shaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560.

[18] Hunter, P. A. *Drug. Discov. Today* **1996**, *1*, 227.; Rychnowsky, S. D. *Chem. Rev*. **1995**, *95*, 2021.

[19] Nicolaou, K. C., Daines, R. A., Ogawa, Y. and Chakraborty, T. K. *J. Am. Chem. Soc*. **1988**, *110*, 4696 and references there in.

[20] Nicolaou, K. C., Papahatjis, D. P., Claremon, D. A., Magolda, R. L. and Dolle, R. E. *J. Org. Chem*. **1985**, *50*, 1440; Nicolaou, K. C., Daines, R. A. Uenishi, J. Li, W. S., Papahatjis, D. P. and Chakraborty T. K. *J. Am*. *Chem. Soc*. **1987**, *109*, 2205.

[21] Evans, D. A., Nelson, J. V. and Taber, T. R. in *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L. and Wilen, S. H., Eds. **1982**, *Vol 13*, p 1.

[22] Nicolaou, K. C., Petasis, N. A., Dolle, R. E., Li, W. S. Papahatjis, D. P. Uenishi, J. and Zipkin, R. E. in *New Methods in Drug Research*; Makriyanni, A. Ed.; Prous Science: Barcelona, Spain, **1985**, p 179.

[23] Tholander J. and Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 613.

[24] Karisalmi, K., Rissanen, K. and Koskinen, A. M. P. *Org. Biomol. Chem.* **2003**, *1*, 3193.

[25] Karisalmi, K., Koskinen, A. M. P., Nissinen, M. and Rissanen, K. *Tetrahedron* **2003**, *59*, 1421.

[26] Yamada, K., Ojika, M., Ishigaki, T., Yoshida, Y., Ekimoto, H. and Arakawa, M. *J. Am. Chem. Soc*. **1993**, *115*, 11020.

[27] Kigoshi, H., Suenaga, K., Mutou, T., Ishigaki, T., Atsumi, T., Ishiwata, H., Sakakura, A., Ogawa, T., Ojika, M. and Yamada, K. *J. Org. Chem*. **1996**, *61*, 5326.

[28] a) Pateron, I., Cowden, C. J. and Woodrow, M. D. *Tetrahedron Lett*. **1998**, *39*, 6037. b) Paterson, I., Blakey, S. B. and Cowden, C. J. *Tetrahedron Lett*. **2002**, *43*, 6005.

[29] Marshall, J. A. and Grant, C. M. *J. Org. Chem*. **1999**, *64*, 696.

[30] Marshall, J. A. and Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501.

[31] Martin, S. F. and Dodge, J. A. *Tetrahedron Lett*. **1991**, *32*, 3017.

[32] Morino, T., Shimada, K.-I., Masuda, A., Nishimoto, M and Saito, S. *J. Antibiot*. **1996**, *49*, 1049.; Morino, T., Masuda, A., Shimada, K.-I., Yamashita, N., Nishimoto, M., Nishikiori, T. and Saito, S. *J. Antibiot*. **1996**, *49*, 564.;

Shimada, K.-I., Morino, T., Masuda, A., Sato, M., Kitagawa, M.and Saito, S. *J. Antibiot*. **1996**, *49*, 569.

[33] Morino, T., Masuda, A., Yamada, M, Nishimoto, M., Nishikiori, T., Saito, S. and Shimada, N. *J. Antibiot*. **1994**, *47*, 1341.

[34] Sarbia, F., Chammaa, S. and Lopez-Herrera, J. *Tetrahedron Lett*. **2002**, *43*, 2961.

[35] Chakraborty, T. K, Ghosh, S. and Dutta, S. *Tetrahedron Lett*. **2001**, *42*, 5085.

[36] Crimmins, M. T., King, B. W. and Tabet, E. A. *J. Am Chem. Soc*. **1997**, *119*, 7883.

[37] Delaunay, D., Toupet, L. and Le Corre, M. *J. Org. Chem*. **1995**, *60*, 6604.

[38] Kobayashi, S., Tsuchiya, K., Kurokawa, T., Nakagawa, T. and Shimada, N. *J. Antibiot*. **1994**, *47*, 697.; Kobayashi, S., Tsuchiya, K. Kurokawa, T., Nakagawa, T. and Shimada, N. *J. Antibiot.* **1994**, *47*, 703.

[39] Yoshida, T., Koizumi, K. and Itazaki, H. *Japan Patent Kokai* **1993**, 5-310726.

[40] Yasui, K., Tamura, Y., Nakatani, T., Kawada, K. and Ohtani, M. *J. Org. Chem* **1995**, *60*, 7567.

[41] Gurjar, M. K., Henri Jr, J. T., Bose, D. S. and Rao, A. V. R. *Tetrahedron Lett*. **1996**, *37*, 6615.

[42] van Alphen, J. *Ind. Eng. Chem*. **1951**, *43*, 141.

[43] Chida, N., Yoshinaga, M., Tobe, T. and Ogawa, S. *Chem. Commun*. **1997**, 1043.

[44] Chida, N., Yamada, K. and Ogawa, S*. J. Chem. Soc., Perkin Trans. 1* **1993**, 1957.

[45] Kitahara, T., Kurata, H. and Mori, K. *Tetrahedron* **1988**, *44*, 4339.

[46] Watanabe, H., Watanabe, H. and Kitahara, T. *Tetrahedron Lett*. **1998**, *39*, 8313.

[47] Keck, G. E., Knutson, C. E. and Wiles, S. A. *Org. Lett*. **2001**, *3*, 707.

[48] Dias, L. C., Oliveira, L. G. and de Sousa, M. A. *Org. Lett*. **2003**, *5*, 265.

[49] McGuire, J. M., Bunch, R. L., Anderson, R. C., Boaz, H. E. Flynn, E. H., Powell, H. M. and Smith, J. W. *Antibiot. Chemother*. **1952**, *2*, 281.

[50] Harris, D. R., McGeachin, S. G. and Mills, H. H. *Tetrahedron Lett*. **1965**, 679.

[51] *Macrolide Antibiotics*, Omura, S. Ed., Academic Press: Orlando, FL, **1984**.

[52] For leading references and representative synthetic approaches see: a) Corey, E. J., Hopkins, P. B., Kim, S., Yoo, S.E., Nambiar, J. R. and Falck, J. R. *J. Am. Chem. Soc*. **1979**, *101*, 7131. b) Woodward, R. B., Logusch, E., Nambiar, K. P., Sakan, K., Ward, D. E., Au-Yeung, B.-W., Balaram, P., Browne, L. J., Card, P. J., Chen, C. H., Chênevert, R. B., Fliri, A., Frobel, K., Gais, H.-J., Garrat, D. G., Hayakawa, K., Heggie, W., Hesson, D. P., Hoppe, D., Hoppe, I., Hyatt, J. A., Ikeda, D., Jacobi, P. A., Kim, K. S., Kobuke, Y., Kojima, K., Krowicki, K., Lee, V. J., Leutert, T., Malchenko, S., Martens, J., Matthews, R. S., Ong, B. S., Press, J. B., Rajan Babu, T. V., Rousseau, G., Sauter, H. M., Suzuki, M., Tatsuta, K., Tolbert, L. M., Truesdale, E. A., Uchida, I., Ueda, Y., Uyehara, T., Vasella, A. T, Vladuchick, W. C., Wade, P. A., Williams, R. M. and Wong, H. N.-C*. J. Am. Chem. Soc.* **1981**, *103*, 3210. c) Masamune, S., Hirama, M., Mori, S., Ali, S. A. and Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. d) Bernet, B., Bishop, P. M., Caron, M., Kawamata, T., Roy, B. L., Ruest, L., Sauve, G., Soucy, P. and Deslongchamps, P. *Can. J. Chem*. **1985**, *63*, 2810. e) Stork, G. and Rychnovsky, S. D. *J. Am. Chem. Soc*. **1987**, *109*, 1564. f) Nakata, T., Fukui, M. and Oishi, T. *Tetrahedron Lett*. **1988**, *29*, 2219, 2223. g) Chamberlin, A. R., Dezube, M., Reich, S. H. and Sall, D. J. *J. Am. Chem. Soc*. **1989**, *111*, 6247. h) Paterson, I. and Rawson, D. J. *Tetrahedron Lett*. **1989**, *30*, 7463. i) Hikota, M., Tone, H., Horita, K. and Yonemitsu, O. *J. Org. Chem*. **1990**, 55, 7. j) Myles, D. C., Danishefsky, S. J. and Schulte, G. *J. Org. Chem*. **1990**, *55*, 1636. k) Sviridov, A. F., Borodkin, V. S., Ermolenko, M. S., Yashunsky, D. V. and Kochetkov, N. K. *Tetrahedron*, **1991**, *47*, 2291, 2317. l) Mulzer, J., Mareski, P. A., Buschmann, J. and Luger, P. *Synthesis* **1992**, 215. m) Sturmer, R., Ritter, K. and Hoffmann, R. W. *Angew. Chem*. **1993**, *105*, 112.; *Agew. Chem. Int. Ed. Engl*. **1993**, *32*, 101.

[53] Corey, E. J., Kim, S., Yoo, S., Nicolaou, K. C., Melvin, L. S. Jr., Brunelle, D. J, Falck, J. R., Trybulski, E. J., Lett, R. and Sheldrake, P. W. *J. Am. Chem. Soc*. **1978**, *100*, 4620.

[54] Corey, E. J., Trybulski, E. J., Melvin, L. S. Jr., Secrist, J. A., Lett, R., Sheldrake, P. W., Falck, J. R., Brunelle, D. J., Haslanger, M. F, Kim, S. and Yoo, S. *J. Am. Chem. Soc*. **1978**, *100*, 4618.

[55] Evans, D. A. and Kim, A. S. *Tetrahedron Lett*., **1997**, 38, 53.

[56] Hergenrother, P. J., Hodgson, A., Judd, A. S. Lee, W.-C. and Martin, S. *Angew. Chem. Int. Ed*. **2003**, *42*, 3278.

[57] Martin, S. F., Lee, W.-C., Pacofsky, G. J., Gist, R. P. and Mulhern, T. A. *J. Am. Chem. Soc* **1994**, *116*, 4674.

[58] Kato, Y.; Fusetani, N.; Matsunaga, S. and Hashimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 2780.

[59] Sheppeck, J. E.; II, Gauss, C.-M. and Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739.

[60] Bridges, A. J. *Chemtracts-Org. Chem.* **1995**, *8*, 73.

[61] Pihko, P., *PhD. Thesis* **1999**, Univ. Oulu, Dept. Chemistry.

[62] (a) Evans, D. A., Gage J. R. and Leighton J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. (b) Yokokawa, F., Hamada, Y. and Shiori, T. *Chem. Comm.* **1996**, 871. (c) Smith, A. B., Friestad, G. K., Duan, J. J.-W., Barbosa, J., Hull, K. G., Iwashima, M., Qui, Y., Spoors, P. G., Bertonesque, E. and Salvatore B. A. *J. Org. Chem.* **1998**, *63*, 7596. d) Ogawa, A. K. and Armstrong, R. W. *J. Am. Chem. Soc.* **1998**, *120*, 12435. e) Tanimoto N., Gerritz, S. W., Sawabe, A., Noda, T., Filla, S. A. and Masamune, S. *Angew. Chem. Int. Ed.* **1994**, *33*, 673.

[63] Karisalmi, K. and Koskinen, A. M. P. *Synthesis*, **2004**, *(9),* 1331.

[64] Mansikkamäki, H., University of Jyväskylä.

[65] Karisalmi, K. and Koskinen, A. M. P. *Tetrahedron Lett*, **2004**, *45*, *in press*.

[66] Brown, H. C. and Bhat, K. S. *J. Am. Chem. Soc*. **1986**, *108*, 5919.

[67] Chemler, S. R. and Roush, W. R. *J. Org. Chem.* **2003**, *68*, 1319.