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Polyketide stereotetrads in natural products

Ari M. P. Koskinen and Kaisa Karisalmi

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Natural products (or secondary metabolites) remain as the most important source for discovery of new and potential drug molecules. With high resolution data of their structures, and the advancement of synthesis possibilities, analysis of the natural products based on their specific structural features is valuable to those entering the field. In this *tutorial review* we attempt such an analysis indicating the salient features of the structural classes with examples of the synthesis of each one of them. As the particular class of natural products, we have chosen polyketides.

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 (Fig. 1). 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 five 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.

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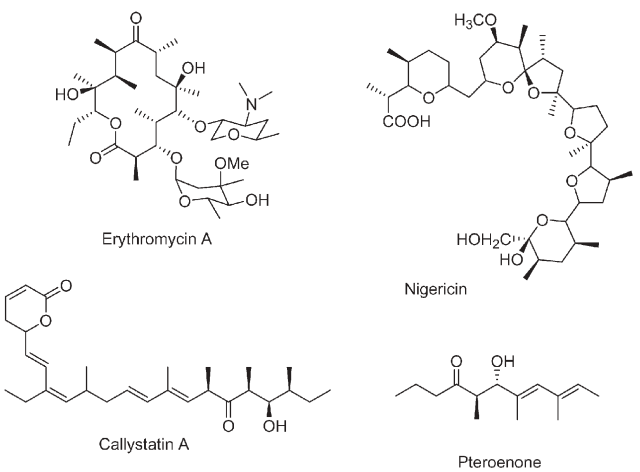


Fig. 1 Examples of naturally occurring polyketides.

Ari M. P. Koskinen

Professor Ari M. P. Koskinen was born in Hyvinkää, Finland in 1956 and received his Doctor of Technology in 1983. After postdoctoral studies at the University of California, Berkeley, he joined the University of Surrey, England, as a lecturer in 1989. He moved to the University of Oulu, Finland in 1992 as Professor of Chemistry, and transferred to his current position at the Helsinki University of Technology in August, 1999 as Professor of Organic Chemistry. Prof. Koskinen has been a member of the Finnish Academy of Sciences and Letters since 2003, and a member of the Novartis Foundation International Scientific Advisory Panel since 2004.

Kaisa Karisalmi

Kaisa Karisalmi was born in Helsinki, Finland, in 1975. She started her studies at the University of Helsinki and received an MSc in organic chemistry in 2000. In the same year she joined the research group of Professor Ari Koskinen at the Helsinki University of Technology as a PhD student. Her PhD work focused on asymmetric synthesis of natural products. After receiving her PhD in 2004 she started to work at Karyon as a manager of organic synthesis.

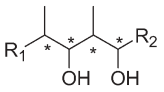


Fig. 2 General structure of a stereotetrad.

The stereotetrad (Fig. 2) is a common substructure in polyketides. Four stereogenic centers, next to each other, result in eight possible diastereomeric combinations of this structure (Fig. 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**).

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

2.1.1 Ionomycin. The polyether antibiotic ionomycin (Fig. 4) was isolated 1978 from the fermentation broths of *Streptomyces congoblatus* and its structure, including absolute stereochemistry, was resolved one year later. As an ionophore, ionomycin 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.[4]

Three total syntheses of ionomycin have been published; Evans (1990),[5] Hanessian (1990)[6] and Lautens (2002),[7] each

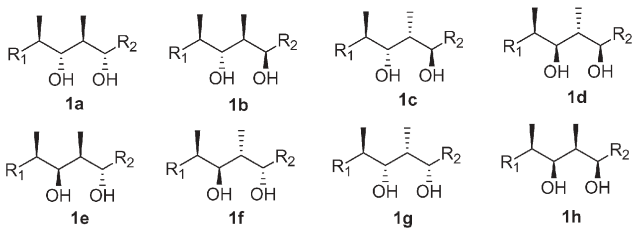


Fig. 3

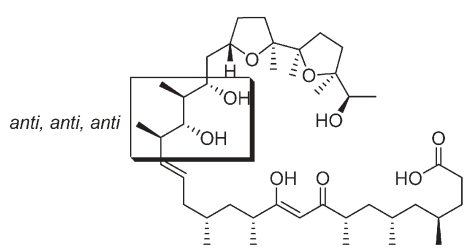


Fig. 4

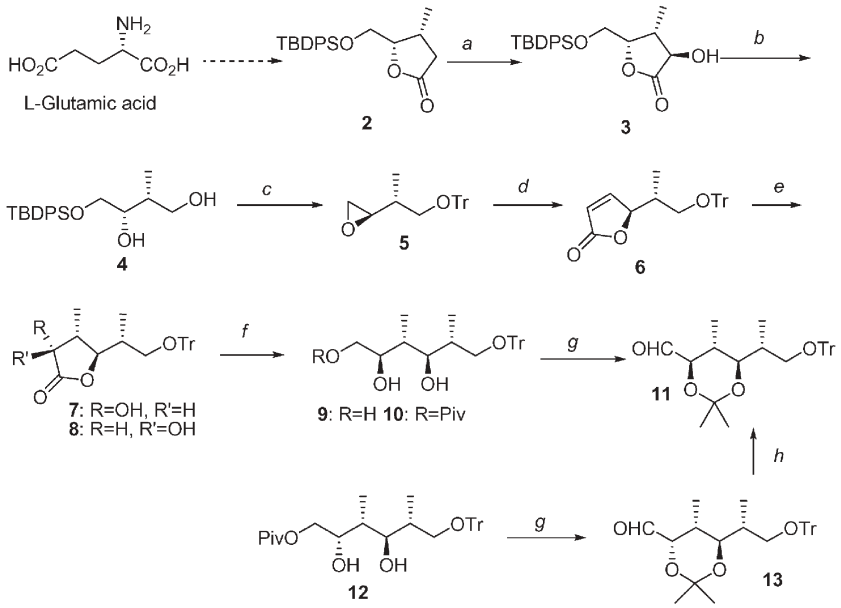
with different strategies for the synthesis of the *anti*, *anti*, *anti* dipropionate fragment (boxed in Fig. 4).

Hanessian *et al.* based the synthesis of the stereotetrad fragment on L-glutamic acid as the chiral progenitor (Scheme 1).[8] Glutamic acid was first converted to the butyrolactone derivative **2**, with a sequence involving deamination, lactonisation, oxidation and conjugate addition. The lactone was then treated with KHMDS, and the resulting enolate was oxygenated with oxodiperoxymolybdenum pyridine to produce the hydroxy lactone **3**. The trisubstituted lactone was then opened and converted to the acyclic diol **4**, which was selectively protected and converted to the epoxide **5**. The epoxide **5** was enlarged to the unsaturated lactone **6** by selenoacetate extension oxidation. Then a second conjugate addition was conducted followed by an oxygenation step leading to a 1 : 1.7 mixture of epimeric alcohols **7** and **8**, the minor epimer **7** being the desired one. Lactone **7** was reduced, the primary alcohol **9** was protected as the pivalate ester **10**, followed by ketal formation, deesterification and Swern oxidation. The major epimer **8** was subjected to the same protocol as **7** to afford the thermodynamically less stable aldehyde **13**. Aldehyde **13** was equilibrated to the desired aldehyde **11**.

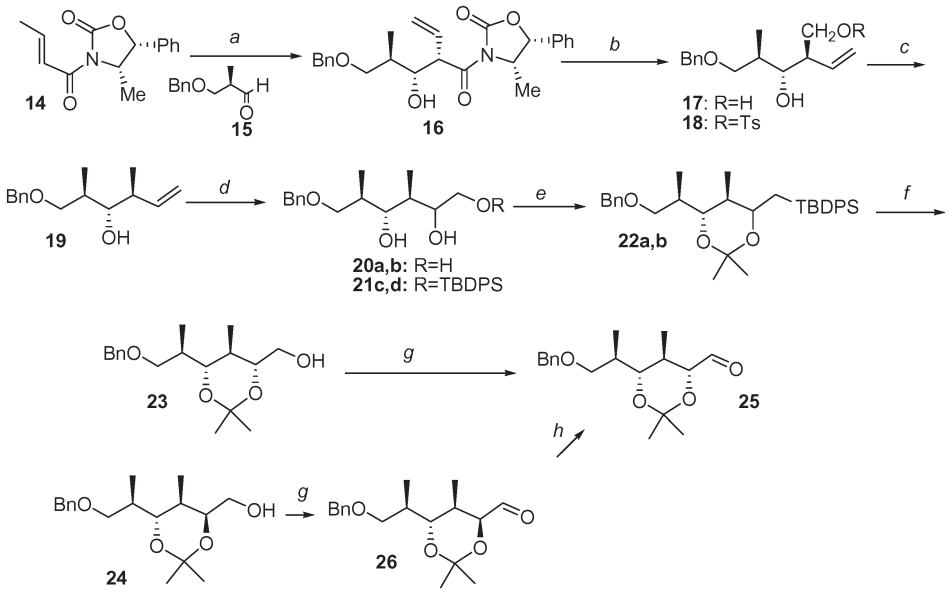
Evans *et al.* published the total synthesis of ionomycin also in 1990,[5] based on the chiral auxiliary strategy (oxazolidinone) for creating the first asymmetric centers (Scheme 2). Aldol addition of the boryl enolate derived from crotonimide **14** with aldehyde **15** provided the crystalline *syn*, α-vinyl adduct **16**. The chiral auxiliary was reductively removed to give the corresponding alcohol **17**. Deoxygenation was then achieved by tosylation and hydride reduction to produce the stereotriad **19**. After OsO_4 oxidation of the double bond two epimeric alcohols **20a,b** were obtained in a 78 : 22 ratio. Selective TBDPS protection of the primary alcohol, followed by ketal formation and removal of the TBDPS group, produced two separable diastereomeric alcohols **23** and **24**. The major diastereomer **23** was directly oxidized to the desired aldehyde **25**. The minor diastereomer **24** was also oxidized, followed by base mediated epimerization to produce the thermodynamically more stable aldehyde **25**.

The most recent total synthesis of ionomycin has been published in 2002 by Lautens *et al.*[7] Their synthesis was based on the ring-opening methodology, which had been developed earlier in their laboratory. The synthesis of the dipropionate fragment began with the [3.2.1] oxabicyclic alkene **27**, which was reductively opened to give the substituted cycloheptene **28** in excellent yield (95%) and enantioselectivity (93–95% ee) (Scheme 3). One stereocenter in **28** needed inversion for achieving the desired stereochemistry (step *b*). Cycloheptene **29** was then opened ozonolytically and reductive work-up produced the diol **30**. 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 **33** with the correct stereochemistry.

2.1.2 Calyculin C. Calyculins form a class of highly cytotoxic metabolites originally isolated from the marine sponge



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



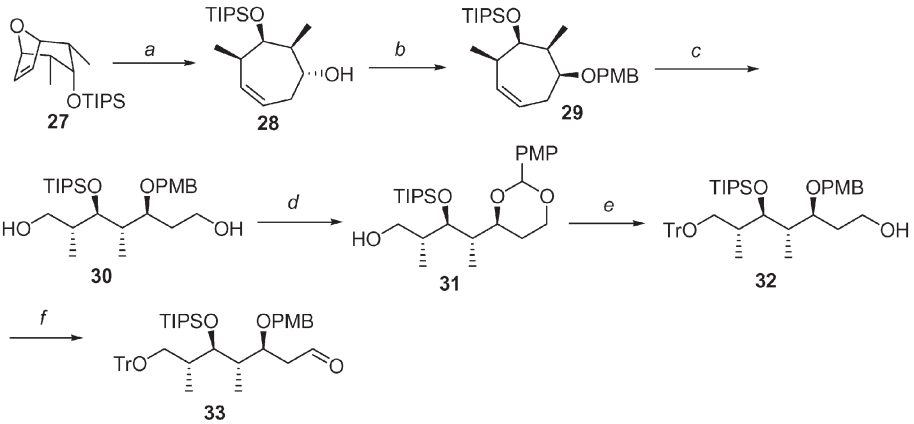
Scheme 2 *a* Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C, **15**, −78 °C, H_2O_2, MeOH; *b* 1. Bu_3B, HOAc, THF; 2. $LiBH_4$, THF, 0 °C; 3. H_2O_2, MeOH; *c* 1. *p*-$TolSO_2Cl$, pyridine, 5 °C; 2. $Li(Et)_3BH$, THF; 3. H_2O_2, NaOH (aq), MeOH; *d* 1. OsO_4, R_3N–O, H_2O/Me_2CO; 2. TBDPSCl, Et_3N, DMAP, CH_2Cl_2; *e* $Me_2C(OMe)_2$, CSA, acetone; *f* (*n*-$Bu)_4NF$, THF; *g* Pyr·SO_3, Et_3N, DMSO; *h* K_2CO_3, MeOH.

Discodermia calyx. Calyculins have proven to be strong serine/threonine protein phosphatase inhibitors.[8]

The C_9–C_{19} dipropionate lactone fragment of calyculin C (boxed in Fig. 5) 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.[9] Several syntheses of the lactone-dipropionate fragment have been published with varying strategies.[10] The C_9–C_{19} fragment is an *anti*, *anti*, *anti* stereotetrad, which can be reached either by linear or by convergent approaches.

In our own work, we adopted a linear approach for the construction of the *anti*, *anti*, *anti* stereotetrad. First, a short and highly enantio- and diastereoselective synthesis of the key intermediate **43** was realised (Scheme 4).[11]

The remaining steps for the C_9–C_{19} fragment of Calyculin C are shown in Scheme 5.[12] The lactone aldehyde **43** was first allowed to react with a chiral crotyl borane reagent **44** yielding



Scheme 3 *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.

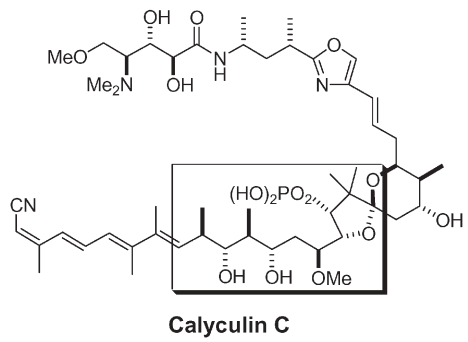


Fig. 5

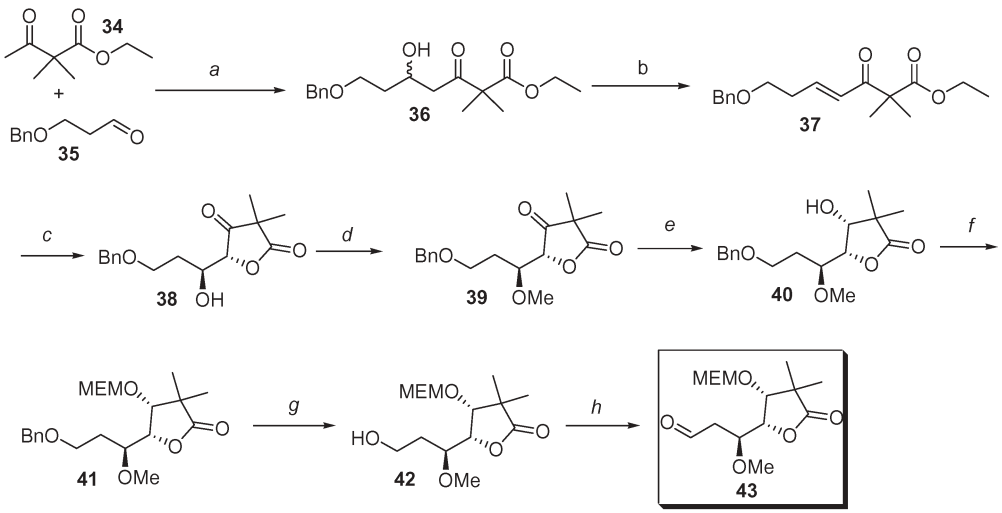
a 6 : 1 diastereomeric mixture of two *anti* homoallylic alcohols. The major diastereomer **45** was isolated with simple flash chromatography, followed by ozonolysis to yield the unstable β-hydroxy aldehyde **46**. The second crotylation was realized with *Z*-crotyl trifluorosilane, giving a single diastereomer **47**. Finally the diol was converted to the corresponding ketal **48**.

2.2 *anti*, *anti*, *syn* and *anti*, *syn*, *anti*: Aplyronines A/B/C

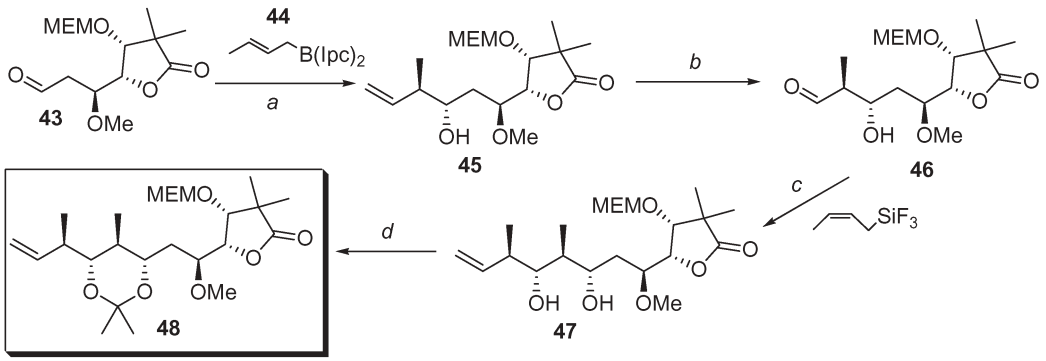
Aplyronines A, B and C (Fig. 6), 24-membered cytotoxic marine macrolides, were isolated from the sea hare *Aplysia kurodai* in 1993.

Aplyronines contain three stereotetrads: one with *anti*, *syn*, *anti* and two with *anti*, *anti*, *syn* stereochemistries. Yamada published the first total synthesis of Aplyronine A in 1996, only three years after the isolation.[13] Their retrosynthetic analysis revealed each of the three stereotetrads to represent an individual substructure in the total synthesis.

The synthesis of the *anti*, *syn*, *anti* stereotetrad (Scheme 6) began with an Evans aldol reaction between **49** and **15** in which two new stereogenic centers were created. The fourth stereocenter was introduced successfully through Sharpless asymmetric epoxidation (step *d*). The final stages in the



Scheme 4 *a* LDA, the ketone **34**, 1 h., then the aldehyde **35**, 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* LS-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.



Scheme 5 *a* the crotyl reagent was prepared from (+)-IpcBOMe and *trans*-butene in THF at −78 °C, then BF_3·OEt, the aldehyde **43**, −78 °C, 1 h, then ethanolamine; *b* O_3, CH_2Cl_2, −78 °C, then triphenyphosphine, rt, 3 h; *c* aldehyde **46**, 4 Å MS, CH_2Cl_2, rt, 0.5 h, then 0 °C, DIPEA, (*Z*)- crotyl trifluorosilane, 4 h; *d* 2-methoxy propene, pyridinium *p*-toluenesulfonate (PPTS) (cat.), CH_2Cl_2, rt, 0.5 h.

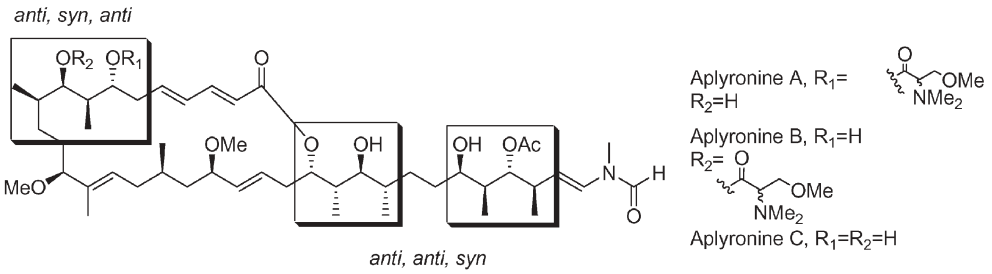
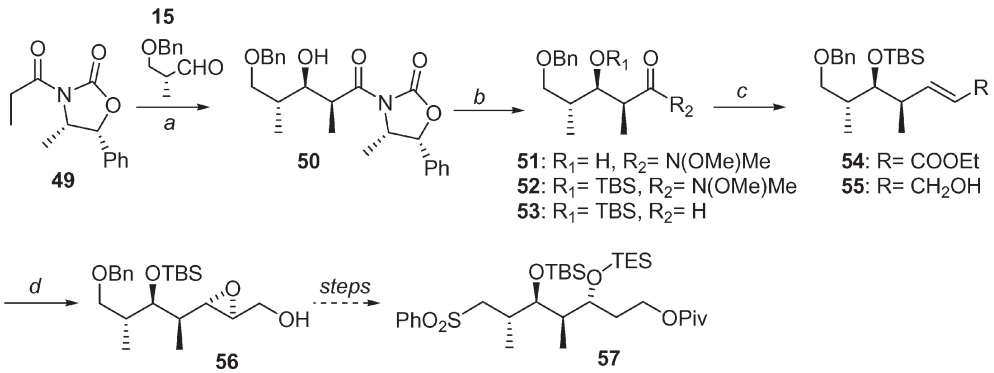


Fig. 6



Scheme 6 *a* Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then **15**, −78 °C, 3 h – >0 °C, 20 min; *b* 1. Me_3Al, MeONHMe·HCl, THF, toluene, CH_2Cl_2, −10 to >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*-PrO)$_2$P(O)CH_2COOEt, *t*-BuOK, THF, −78 °C, 1 h to >0 °C, 1.5 h; 2. DIBAL-H, CH_2Cl_2, hexane, −78 °C, 1 h; *d* Ti(O-*i*-Pr)$_4$, (+)-DET, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −23 °C, 1 h.

synthesis included protection of the hydroxyl groups and conversion of the leftward hydroxyl group to the sulfone **57**.

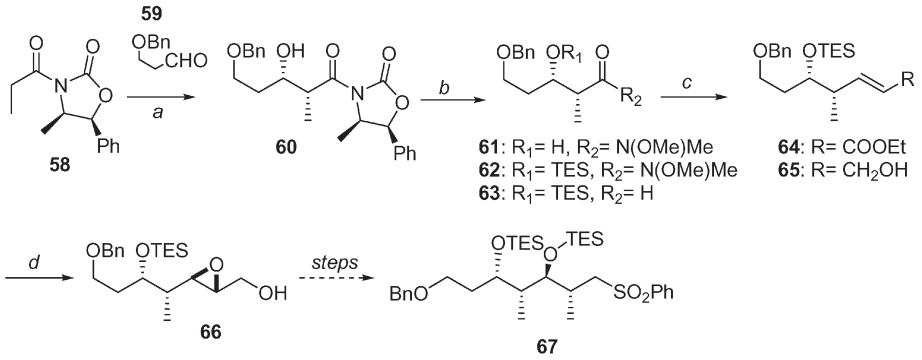
The syntheses of the C(21)–C(27) (Scheme 7) and C(28)–C(34) *anti*, *anti*, *syn*, stereotetrads were both also based on the Evans aldol chemistry and the Sharpless asymmetric epoxidation. The fourth stereogenic center was created through nucleophilic attack of methylcuprate onto the epoxide **66** to produce the desired *anti*, *anti*, *syn* stereochemistry.

Paterson *et al.* have also been working on the synthesis of aplyronines.[14] Although their total synthesis of aplyronines is still incomplete, the syntheses of the stereotetrad subunits have been published.

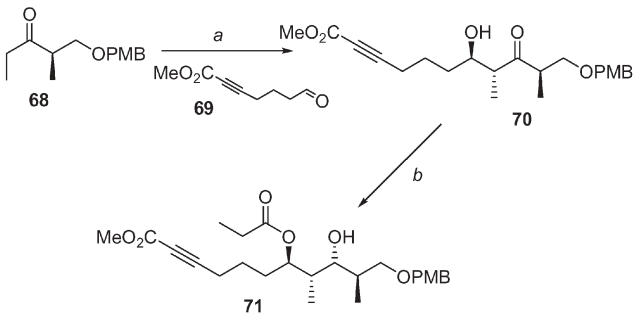
The synthesis of the *anti*, *syn*, *anti* stereotetrad began with an aldol reaction between the *E*-boron enolate of the chiral precursor **68** and aldehyde **69** (Scheme 8). The desired *anti*, *anti* aldol product **70** was obtained with high diastereoselection (⩽97% ds). The ketone was then reduced in a 1,3-*anti* manner to produce the desired *anti*, *syn*, *anti* stereochemistry in **71**.

Paterson *et al.* also completed the synthesis of the C(21)–C(34) subunit of aplyronines.[14] This southern segment contains two *anti*, *anti*, *syn* stereotetrads and the syntheses of both fragments were based on the chiral starting materials (**72**, **73**, **76**), diastereoselective aldol reactions (steps *a* and *c*) and stereoselective 1,3-*anti* diol reduction (steps *d* and *g*) (Scheme 9).

Synthetic methodology developed in the laboratory of Marshall suited perfectly for the synthesis of the stereotetrads of aplyronines.[15] The key step in the syntheses of the *anti*, *syn*,



Scheme 7 *a* Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, then **59**, −78 °C, 2 h to >0 °C, 2 h; *b* 1. Me_3Al, MeONHMe·HCl, THF, toluene, CH_2Cl_2, −10 to >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 to >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.

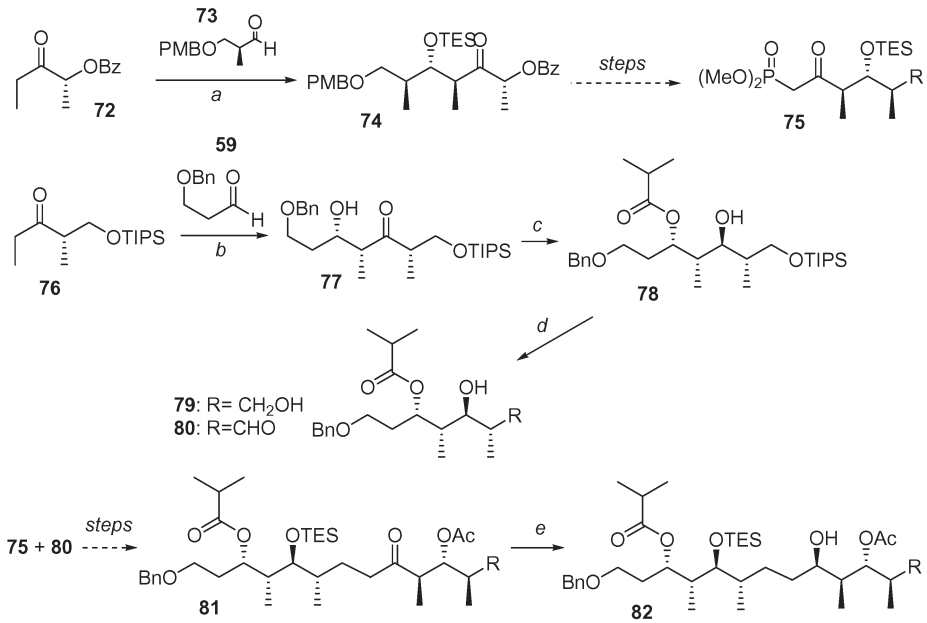


Scheme 8 *a* $(c\text{-Hex})_2BCl$, Et_3N, Et_2O, 0 °C, 1 h, then −78 °C and **69** to >−20 °C, 12 h, oxidative work-up; *b* SmI_2, EtCHO, THF, 0 °C, 15 min, then **70**, 0 °C, 2 h.

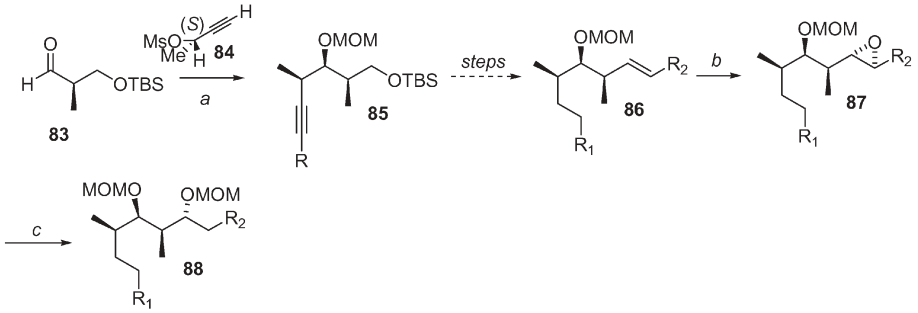
anti (Scheme 10) and both *anti*, *anti*, *syn* (Scheme 11) stereotetrads was the first reaction; an *in situ* prepared chiral allenylindium reagent reacted with a chiral α-methyl aldehyde (Scheme 10, step *a*; Scheme 11, steps *a* and *c*) creating two new stereogenic centers with high diastereoselectivity.[16] The fourth stereocenter of the stereotetrads was created either *via* Sharpless asymmetric epoxidation (Scheme 10, step *b*; Scheme 11, step *d*) or by aldol reaction (Scheme 11, step *b*). In the synthesis of the rightward *anti*, *anti*, *syn* stereotetrad, the aldol reaction (Scheme 11, step *d*) produced two separable diastereomers **95** and **96** in a 60 : 40 ratio. The desired diastereomer **96** proved to be the minor one, but the major diastereomer **95** was inverted to the desired diastereomer **96** and elaborated to the intermediate **100**.

2.3 *syn*, *anti*, *anti*: Amphotericin B/Amphoteronolide B

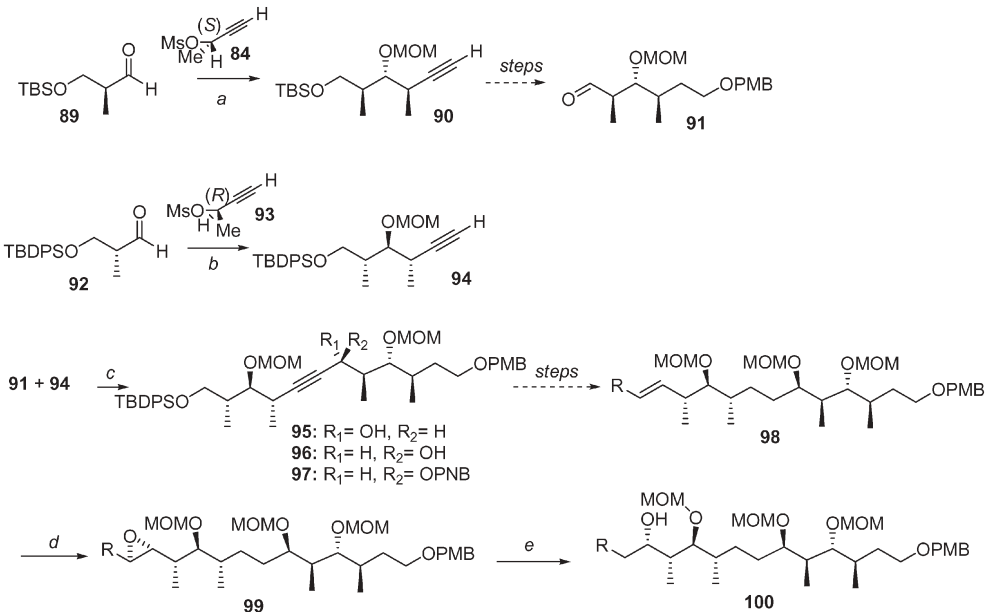
The antifungal macrolide antibiotic amphotericin B (Fig. 7) was isolated from *Streptomyces nodosus* in 1956 and its stereochemical structure was resolved 15 years later by X-ray analysis.



Scheme 9 *a* 1. $(c\text{-Hex})_2BCl$, Me_2NEt, Et_2O, 0 °C, 1 h, then −78 °C, **73**, to >−20 °C, 16 h; 2. TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 2 h; *b* $Sn(OTf)_2$, Et_3N, CH_2Cl_2, **59**, −78 °C, 2 h; *c* isobutyraldehyde, SmI_2, THF, 0 °C, 2.5 h; *d* 1. HF·pyridine, THF, rt, 7 h; 2. cat. TEMPO, $PhI(OAc)_2$, rt, 2 h; *e* SmI_2, CH_3CHO, THF, −5 °C, 2.5 h.



Scheme 10 *a* 1. $Pd(dppf)Cl_2$, InI, THF–HMPA; 2. MOMCl, Bu_4NI, *i*-Pr_2Net; *b* (+)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH; *c* 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* 1. $Pd(dppf)Cl_2$, InI, THF–HMPA; 2. MOMCl, Bu_4NI, *i*-Pr_2Net; *c* lithiation of **94**, then **91**; *d* (−)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH; *e* Zn, MeOH, △.

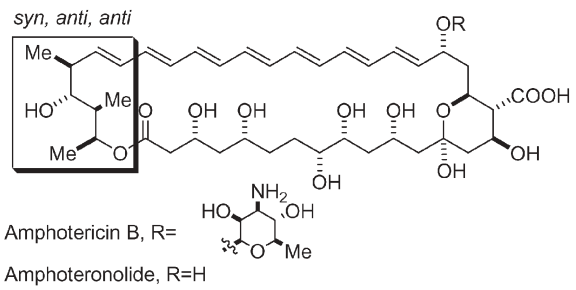


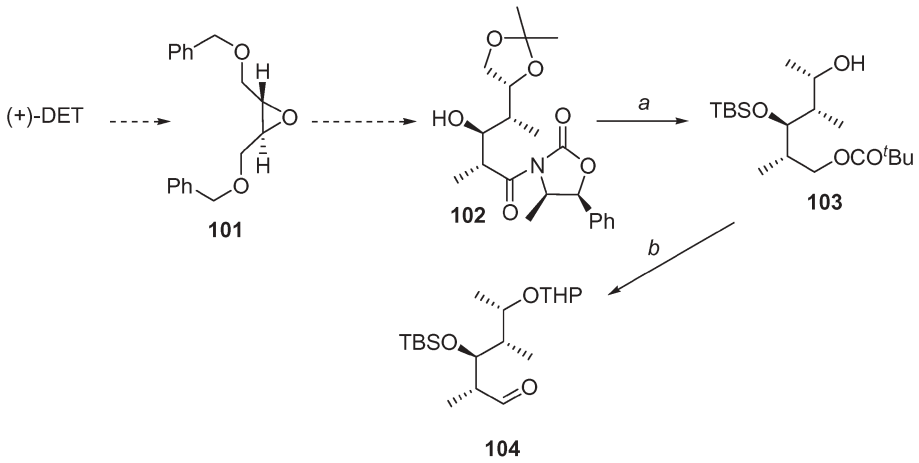
Fig. 7

K. C. Nicolaou and his group were the first ones to develop a total synthesis for amphotericin B and amphoteronolide B.[17] In their retrosynthetic analysis the *syn*, *anti*, *anti* stereotetrad (boxed in Fig. 7) was an independent building block. The keys for asymmetry and stereoselectivity in their synthesis of this dipropionate were the chiral starting material (+)-diethyl tartrate and Evans aldol methodology (Scheme 12).[18]

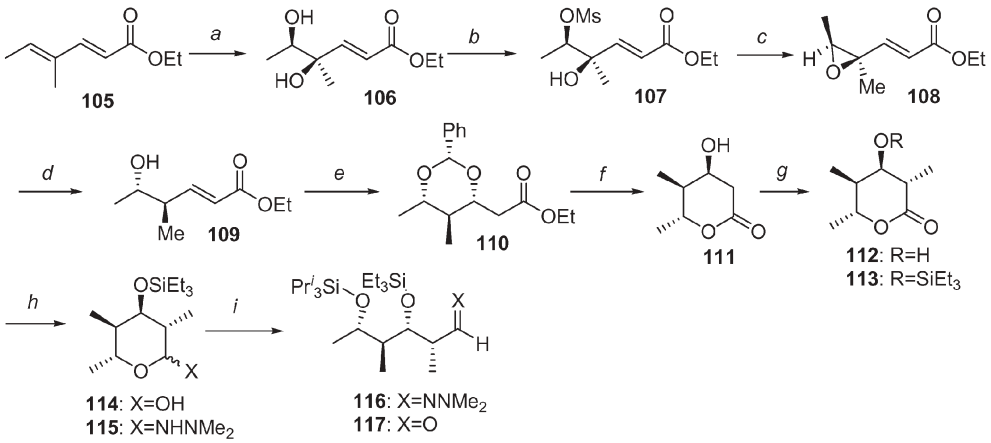
The enantiomerically pure epoxide **101** was readily available from (+)-diethyl tartrate. At first the epoxide **101** was converted to the Evans oxazolidinone derivative **102**, the chiral auxiliary was removed and the aldehyde was masked as a pivalate. Finally, the hydroxyl groups were protected and the pivalate ester was reduced and the intermediate alcohol oxidized to produce the desired aldehyde **104**.

The C(33)–C(37) dipropionate fragment of amphotericin B has also been the target for Carreira *et al.*[19] and us.[20] Carreira's enantioselective synthesis of the stereotetrad consisted of 14 steps in 16% overall yield (Scheme 13). 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.

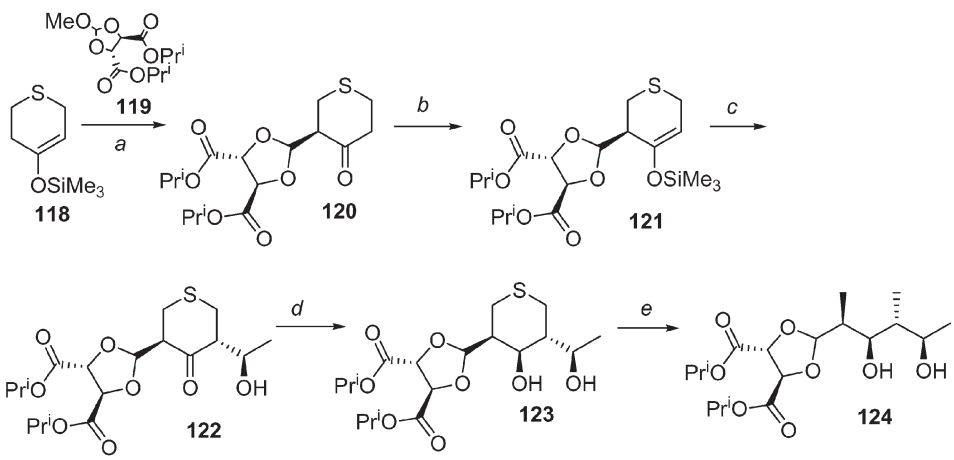
Our own synthesis of this *syn*, *anti*, *anti* stereotetrad was based on the thiopyran ring strategy.[21,22] Commercially available tetrahydrothiopyran-4-one was first converted to the corresponding silyl enol ether **118** (Scheme 14). The asymmetry was then introduced into the ring with the help of the tartrate derived orthoester **119**. Two diastereomers were



Scheme 12 *a* 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; *b* 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 13 *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, HCO_2H, 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*-Pr)$_3$SiOTf, pyridine, 0–23 °C, 3 h; 2. O_3, CH_2Cl_2, −78 °C, Me_2S.



Scheme 14 *a* $ZnCl_2$, CH_2Cl_2, **55**, 21 h, rt; *b* LiHMDS, THF, TMSCl, 1 h, −78 °C to >0 °C; *c* CH_3CHO, $TiCl_4$, CH_2Cl_2, 5 min, −78 °C; *d* Et_2BOMe, $NaBH_4$, THF–MeOH, 1 h, −78 °C; *e* Raney Ni, IPA, 24 h, 70 °C.

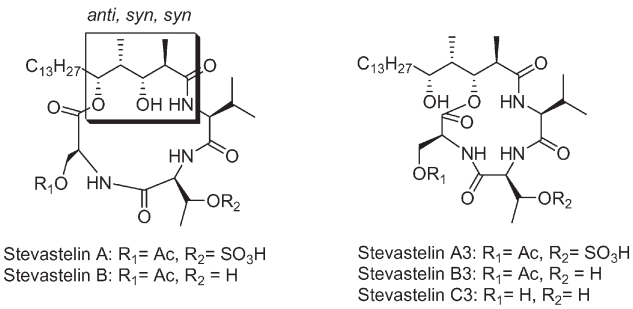


Fig. 8

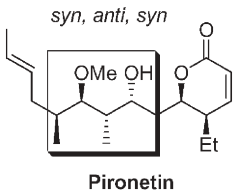


Fig. 9

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 **120**. The next aldol reaction *via* the kinetic silyl enol ether **121** was highly diastereoselective and the desired aldol product **122** 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 **119**, which actually worked as a chiral auxiliary (masked aldehyde).

2.4 *anti*, *syn*, *syn*: Stevastelins

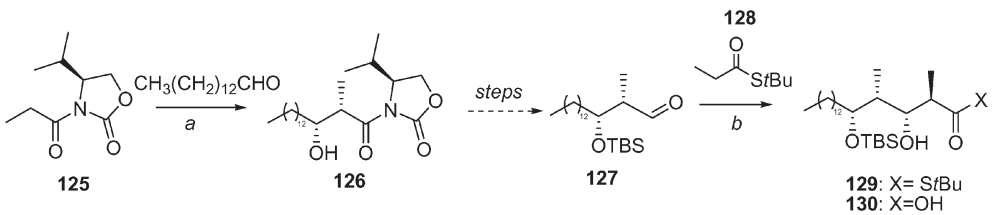
Stevastelins (Fig. 8) represent a family of novel depsipeptides isolated from a culture of *Penicillium* sp. NK374186 and they are potent immunosuppressive agents.

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 15).[22] The other two stereocenters were created *via* an aldol reaction of the *E*-boron enolate of **128** and the chiral aldehyde **127** (step *c*). Only one diastereomer, the desired *anti*, *syn*, *syn* product **130** was obtained.

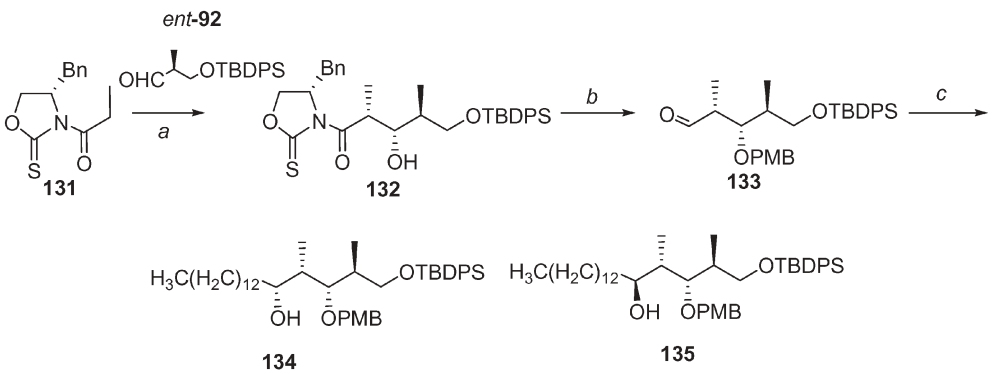
Chakraborty *et al.* have reported the synthesis of the subunits of stevastelin B.[23] Their synthesis began with a Ti(IV) mediated diastereoselective non-Evans *syn* aldol reaction using a 2-oxazolidinethione based chiral auxiliary[24] (Scheme 16). This reaction produced the desired stereotriad as the only isolable diastereomer. The fourth stereocenter was created *via* nucleophilic addition of the long chain Grignard reagent onto the aldehyde **133**. The diastereoselectivity of this step was low: after purification the desired product **134** was obtained only in 40% yield.

2.5 *syn*, *anti*, *syn*: Pironetin (PA-48153C)

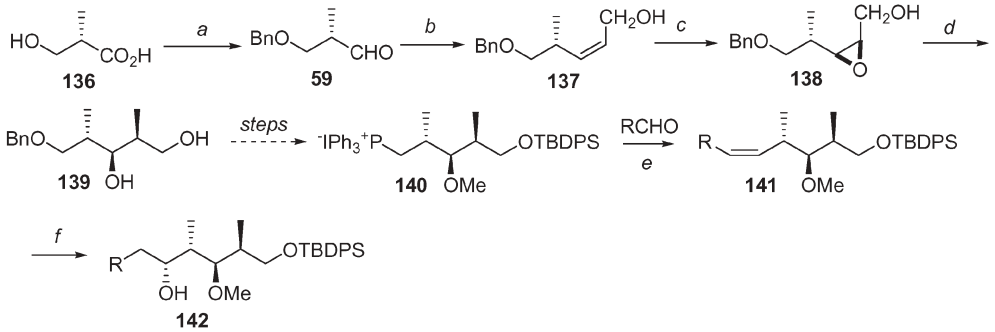
Pironetin (PA-48153C) (Fig. 9) was isolated in 1993 independently by two Japanese research groups from the fermentation broths of *Streptomyces* sp. NK10958 and *Streptomyces prunicolor* PA-48153.



Scheme 15 *a* n-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, then −78 °C, tetradecanal, 12 h; *b* **128**, $(Chx)_2BCl$, Et_3N, CH_2Cl_2, 0 °C, 2 h, then −78 °C, **127**, 12 h, oxidative work-up.



Scheme 16 *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 to >0 °C; 4. Swern oxidation; *c* $CH_3(CH_2)_{12}MgBr$, THF, 0 °C to >rt.



Scheme 17 *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* *n*-BuLi; *f* B_2H_6, H_2O_2.

The structure of pironetin, 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.

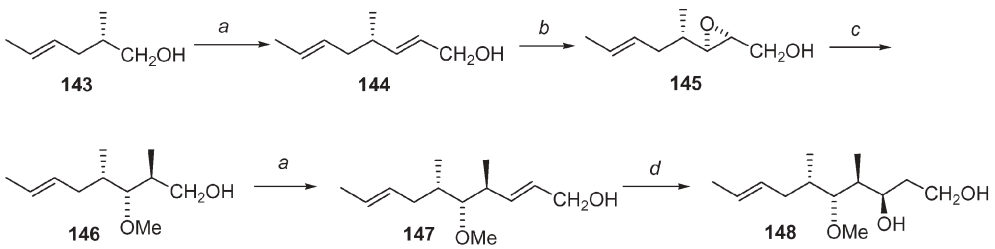
The first total synthesis of pironetin by Yasui *et al.* was published two years after its isolation (Scheme 17).[25] The synthesis of the stereotetrad was very straightforward and the keys in the synthesis were the chiral precursor **136**, asymmetric epoxidation (step *c*) and hydroboration (step *f*).

Gurjar *et al* based their synthesis of the dipropionate of pironetin on the chiral precursor **143** and Sharpless asymmetric epoxidation (Scheme 18).[26]

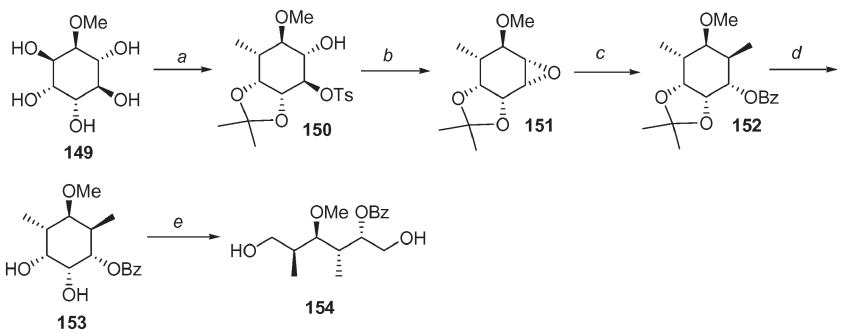
Chida's synthesis of the stereotetrad of pironetin was started from L-quebrachitol **149** (Scheme 19). The intermediate **150** was prepared in five steps.[27] Two stereocenters were inverted *via* base treatment of **150** to produce the epoxide **151** followed by *trans*-diaxial opening of the epoxide with the methyl nucleophile and protection. Intermediate **152** already had the desired stereochemistry. Finally, **152** was deketalized and opened to produce the acyclic *syn*, *anti*, *syn* stereotetrad **154** of pironetin.

Watanabe *et al.* used the chiral precursor **155** as the starting material in their synthesis of the stereotetrad fragment of pironetin (Scheme 20).[28] All stereochemical information emanated from the chiral cyclohexanone derivative **155** and the chiral R chain, which was coupled to **161** in high yield and diastereoselectivity (step *g*).

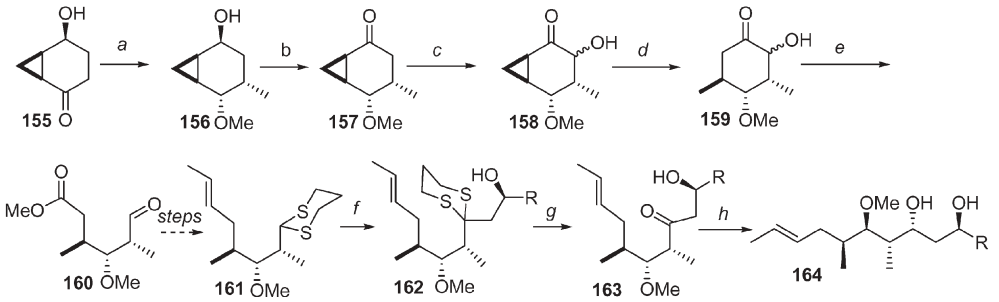
Keck *et al.* initiated their synthesis with chelation controlled ($TiCl_4$) addition of (*Z*)-crotyltri-*n*-butylstannane **165** to the β-benzyloxy aldehyde *ent*-**15** to give the *anti*, *syn* homoallylic alcohol **166** (Scheme 21).[29] The fourth stereocenter of the stereotetrad was created *via* an aldol reaction between the stereotriad aldehyde **167** and the chiral TMS enol ether **168** using $BF_3{\cdot}OEt$ as the Lewis acid. The desired diastereomer **169**



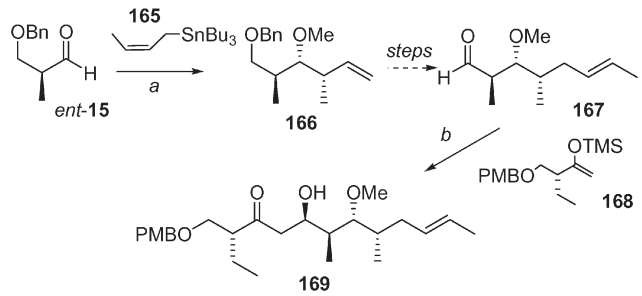
Scheme 18 *a* 1. IBX, DMSO, rt, 30 min; 2. $Ph_3{=}CHCO_2Et$, benzene, rt, 3 h; 3. DIBAL-H, CH_2Cl_2, −20 °C, 30 min; *b* TBHP, $Ti(OiPr)_4$, (−)-DIPT, CH_2Cl_2, −20 °C, 20 h; *c* 1. Me_2CuLi, Et_2O, −78 °C, 8 h; 2. TBSCl, imidazole, CH_2Cl_2, rt, 3 h; 3. KH, MeI, Et_2O, rt, 30 min; 4. Bu_4NF, THF, rt,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



Scheme 19 *a* 1. ref. 36; 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-camphorsulfonic acid, MeOH, rt; *e* $NaIO_4$, acetone–H_2O, 0 °C, then $NaBH_4$, MeOH, 0 °C.



Scheme 20 *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* *n*-BuLi, HMPA, THF, 0 °C, then RX; *g* $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, rt; *h* $LiAlH(OtBu)_3$, LiI, ether, −78 °C to >0 °C.



Scheme 21 *a* 1. **165**, $TiCl_4$ 2. KH, MeI; *b* **168**, $BF_3{\cdot}OEt$.

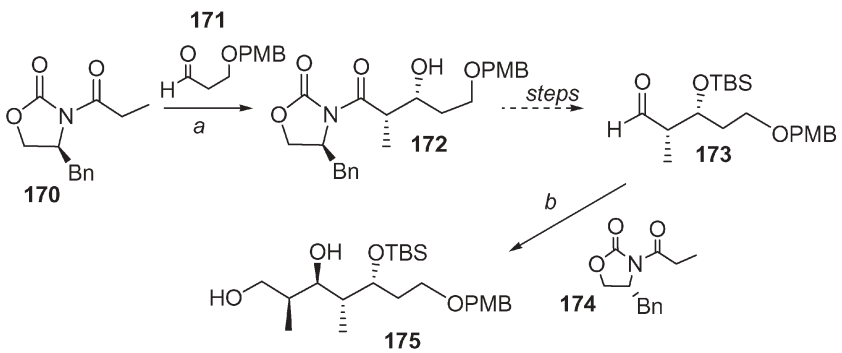
was the only product in this reaction; none of the other diastereomers was detected.

The most recently published total synthesis of pironetin by Dias *et al.* was based on the Evans aldol chemistry (Scheme 22).[30] This route was very short and efficient but it needed external chiral information twice for building up the desired stereochemistry (steps *a* and *c*).

2.6 *syn*, *syn*, *syn*: Erythromycin A/B and Erythronolide A/B

Erythromycins and erythronolides (Fig. 10), and their derivatives belong to macrolide antibiotics. Erythromycin A was isolated in the early 1950's from a strain of *Streptomyces erythraeus*, and its complete structure was revealed in 1965 by X-ray analysis. The antibiotic activity of erythromycins is related to their ability to inhibit ribosomal-dependent protein biosynthesis.[31]

For over four decades the challenging structures of erythromycins and erythronolides have attracted many research groups,[32] but only a few total syntheses have been reported so far. In this chapter, the first two and



Scheme 22 *a* *n*-Bu_2BOTf, CH_2Cl_2, Et_3N, −5 °C, then −78 °C, **171**; *b* 1. **174**, *n*-Bu_2BOTf, CH_2Cl_2, Et_3N, −5 °C, then −78 °C, **173**; 2. $LiBH_4$, THF–MeOH, 0 °C.

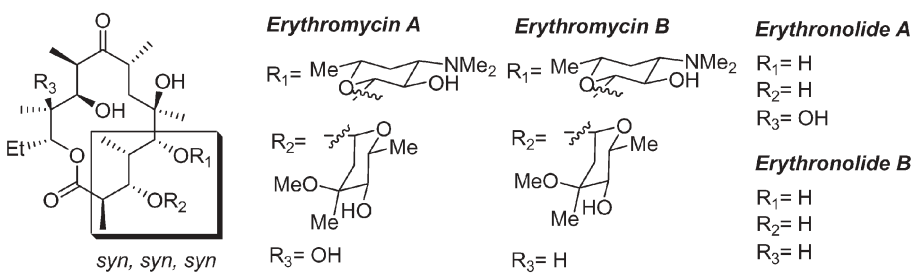
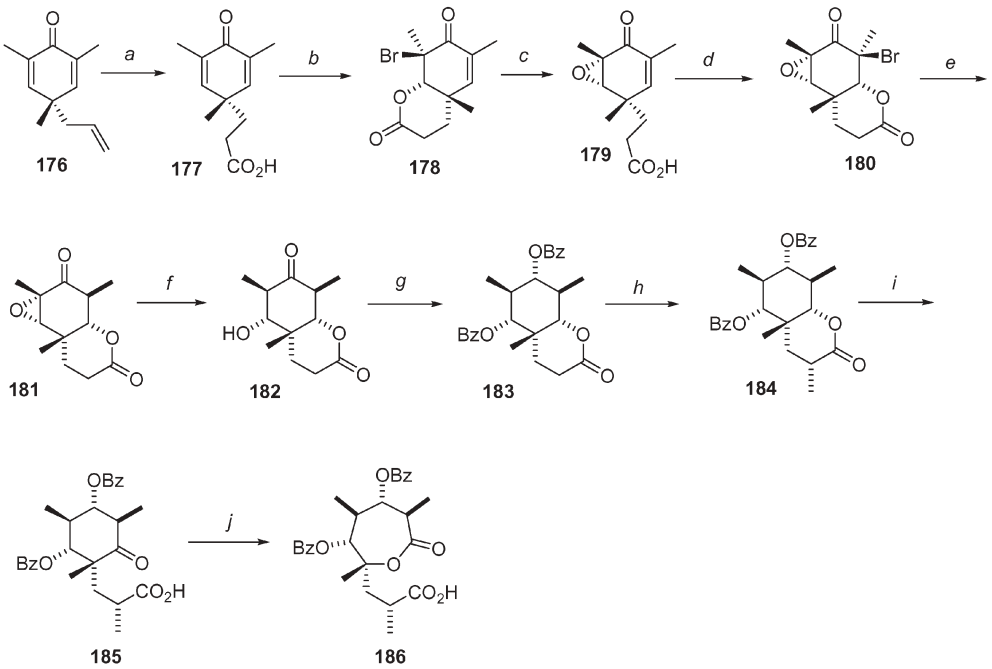


Fig. 10

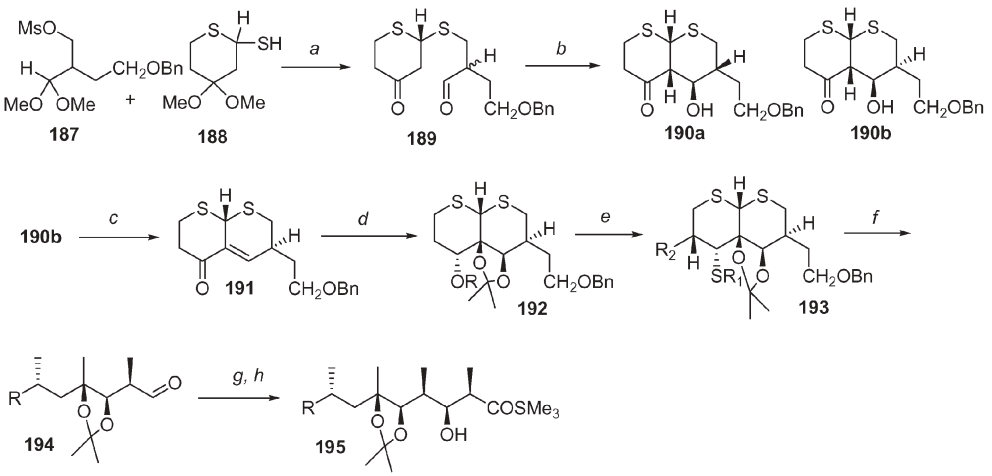


Scheme 23 *a* 1. B_2H_6, THF, 0–10 °C; 2. Jones chromic acid, 0–−10 °C; *b* Br_2, KBr, H_2O; *c* aq. KOH, THF; *d* Br_2, KBr, H_2O; *e* Bu_3SnH, AIBN, PhH; *f* Al/Hg, THF, H_20, 0 to −10 °C; *g* 1. H_2, Raney Ni, DME, −20 °C; 2. BzCl, pyridine; *h* LDA, THF, −78 °C, then MeI, HMPA, −78 °C to >−45 °C; *i* 1. LiOH, H_2O; 2. CrO_3, H_2SO_4, acetone, −10 °C; *j* $MeCO_3H$, EtOAc, 55 °C.

the two most recent syntheses of the stereotetrad of erythromycins/erythronolides (boxed in Fig. 10) are discussed in detail.

E. J. Corey *et al.* published in 1978 the first total synthesis of (±)-erythronolide B (Scheme 23).[33] The creation of the *syn*, *syn*, *syn* stereotetrad began from the achiral dienone **176** by hydroboration followed by oxidation, to produce the dienone acid **177**. Treatment with bromine–potassium bromide solution yielded the bromo lactone **178**, which was then converted under basic reaction conditions to the epoxy acid **179**. The epoxy acid **179** was then converted to the bromo epoxy lactone **180**, from which the bromine was cleaved *via* radical reaction to produce the epoxy lactone **181**. Epoxide **181** was reductively opened and the ketone **182** was then stereoselectively reduced. The hydroxyl groups were then protected to produce the dibenzoate **183**, which already possessed the all-*syn* stereochemistry. Dibenzoate **183** was finally transformed to lactone **186**, which was one of the key intermediates in the first total synthesis of erythronolide A.

Woodward *et al.* completed the first (and also so far the only one) total synthesis of Erythromycin A in 1981.[34] Thiopyranone ring strategy was the key for the successful total synthesis as well as for the synthesis of the *syn*, *syn*, *syn* stereotetrad (Scheme 24).



Scheme 24 *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 °C; 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*-$NO_2PhSeCN$, nBu_3P, THF, 30% H_2O_2, THF, rt; 3. O_3, MeOH, CH_2Cl_2, −78 °C, then Me_2S, $NaHCO_3$; *g* 1. $EtCOSCMe_3$, LDA, THF, −110 °C; 2. *t*-BuLi, THF, −110 °C, then AcOH, −110 °C; *h* 1. *t*-BuLi, $(CH_2NMe_2)_2$, THF, −110 °C; 2. AcOH, −110 °C.

The synthesis of the *syn*, *syn*, *syn* stereotetrad began from the racemic starting materials **187** and **188**. The racemic intermediate **189** was allowed to undergo an intramolecular aldol reaction catalyzed by D-proline, and a 1 : 1 mixture of enantiomerically enriched diastereomers **190a** and **190b** were obtained (36% ee for both diastereomers). The synthesis was continued with **190b** and the enantiomerically enriched enone **191** was obtained after dehydration. The desired enantiomer (+)-**191** 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 **192** 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 **194** 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 **195**.

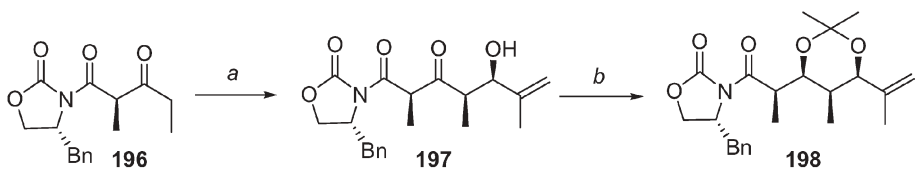
Evans and Kim published the total synthesis of 6-deoxyerythronolide B (biosynthetic precursor of erythromycins) in 1997.[35] The Evans all-*syn*-stereotetrad synthesis was very short and highly stereoselective (Scheme 25). The β-ketoimide **196** was allowed to react with methacrolein ($TiCl_4$ as the Lewis acid) followed by a 1,3-*syn* reduction and ketal protection of the diol to produce the stereotetrad **198** in excellent yield and stereoselectivity.

The most recent total synthesis of erythromycins was published in 2003 by Martin *et al.* (Scheme 26).[36] The synthesis of the *syn*, *syn*, *syn* stereotetrad fragment started with Evans aldol chemistry to give the aldol adduct **201** as the only isomer (step *a*). After several reaction steps, 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 (step *e*).

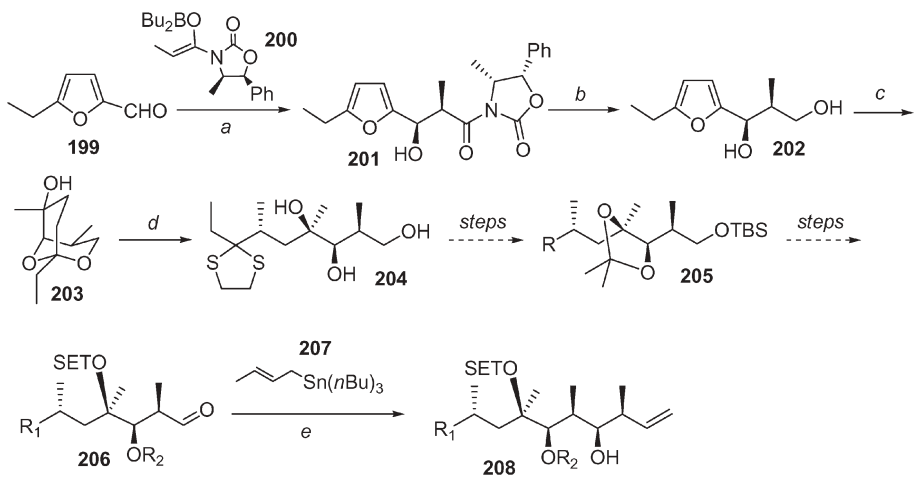
3 Conclusions

The stereotetrad is a common substructure in polypropionate natural products. Four stereogenic centers next to each other result 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 the 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 a minimum.

Some interesting points can be noted. 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



Scheme 25 *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 26 *a* **200**, CH_2Cl_2, **199**; *b* $LiBH_4$, THF; *c* 1. Br_2, MeCN, H_2O; 2. Me_2CuLi; 3. MeLi, $CeCl_3$; *d* $TMSSCH_2CH_2STMS$, $TiCl_4$; *e* **206**, **207**, $BF_3{\cdot}OEt$, CH_2Cl_2.

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.

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