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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. 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. Pharmacologically 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. 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.

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 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.
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 stereotetrad 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, anti, anti stereotetrad, but no polyketide with this fragment was found.

2 Stereotetrad 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 conglobatus 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 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 KH\(_{2}\)PO\(_4\), 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, \(\alpha\)-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 alkenne 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 Calyculins C. Calyculins form a class of highly cytotoxic metabolites originally isolated from the marine sponge...
**Discodermia calyx.** Calyculins have proven to be strong serine/threonine protein phosphatase inhibitors. The C₉–C₁₉ 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. Several syntheses of the lactone-dipropionate fragment have been published with varying strategies. The C₉–C₁₉ 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).

The remaining steps for the C₉–C₁₉ fragment of Calyculin C are shown in Scheme 5. The lactone aldehyde 43 was first allowed to react with a chiral crotyl borane reagent 44 yielding...
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 Aplyrone 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
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 to produce the desired anti, anti, syn stereochemistry.

Paterson et al. have also been working on the synthesis of alyronines. Although their total synthesis of alyronines 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 and aldehyde (Scheme 8). The desired anti, anti aldol product 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.

Paterson et al. also completed the synthesis of the C(21)–C(34) subunit of alyronines. 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 alyronines. The key step in the syntheses of the anti, syn,
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. 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 7  
\[ a \text{ Bu}_{2}BOTf, \text{Et}_{3}N, \text{CH}_{2}\text{Cl}_{2}, 0^\circ \text{C}, \text{then } 59, -78^\circ \text{C}, 2 \text{ h to } >0^\circ \text{C}, 2 \text{ h}; \text{b } \text{Me}_{2}\text{Al, MeONHMe-HCl, THF, toluene, CH}_{2}\text{Cl}_{2}, -10 \text{ to } >0^\circ \text{C}, 1.5 \text{ h}; \text{c } \text{TESCl, imidazole, DMF, 23}^\circ \text{C, 35 min;} \text{d } \text{DIBAL-H, THF, hexane, -78}^\circ \text{C, 2 h;} \text{e } \text{(chiral aldehydes), TESOTf, 2,6-lutidine, CH}_{2}\text{Cl}_{2}, 23^\circ \text{C, 2 h.}\]
K. C. Nicolaou and his group were the first ones to develop a total synthesis for amphotericin B and amphoteronolide B. 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).

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. and us. 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. 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  
\[ a \] LiBH₄, THF, 0 °C, 0.5 h, then t-BuCOCl, pyridine, 3 h; 2. Me₂-t-BuSiOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 1 h, then AcOH–THF–H₂O (3 : 1 : 1), 50 °C, 2 h; 3. PhSSPh, n-Bu₃P, THF, 0–25 °C, 3 h, then Raney Ni, EtOH, 12 h;  
\[ b \] dihydropyran, cat. CSA, CH₂Cl₂, 0–25 °C, 3 h; 2. DIBAL-H, CH₂Cl₂, −78 °C, 0.5 h, then CrO₃, HCl-pyr, NaOAc, CH₂Cl₂, 25 °C, 4 h.

Scheme 13  
\[ a \] (DHQD)₂PHAL, K₂OsO₄·2H₂O, K₂CO₃, K₃Fe(CN)₆, MeSO₂NH₂, t-BuOH–H₂O, 0 °C, 48 h;  
\[ b \] MsCl, pyridine, CH₂Cl₂, 0 °C, 48 h;  
\[ c \] NaH, MeCN, 0–23 °C, 3 h;  
\[ d \] [Pd₂(dba)₃]·CHCl₃, Bu₃P, HCO₂H, Et₃N, THF, 23 °C, 3 h;  
\[ e \] PhCHO, t-BuOK, THF, 0 °C, 1 h;  
\[ f \] Pd(OH)₂, H₂, EtOH, 23 °C;  
\[ g \] LDA, MeI, HMPS–THF, −278 °C, 16 h;  
\[ h \] DIBAL-H, THF, −78 °C, 2 h;  
\[ i \] (i-Pr)₃SiOTf, pyridine, 0–23 °C, 3 h;  
\[ j \] PhCHO, TFA–MeCN, 23 °C, 12 h;  
\[ k \] 1. (i-Pr)₃SiOTf, pyridine, 0–23 °C, 3 h; 2. O₃, CH₂Cl₂, −40 °C;  
\[ l \] DIBAL-H, THF, −78 °C, 2 h;  
\[ m \] H₂NNMe₂, TsOH·H₂O, EtOH, reflux, 12 h;  
\[ n \] Raney Ni, IPA, 24 h, 70 °C.

Scheme 14  
\[ a \] ZnCl₂, CH₂Cl₂, 55, 21 h, rt;  
\[ b \] LiHMDS, THF, TMSCl, 1 h, −78 °C to >0 °C;  
\[ c \] CH₃CHO, TiCl₄, CH₂Cl₂, 5 min, −78 °C;  
\[ d \] Et₂BOMe, NaBH₄, THF–MeOH, 1 h, −78 °C;  
\[ e \] Raney Ni, IPA, 24 h, 70 °C.
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). 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. Their synthesis began with a Ti(IV) mediated diastereoselective non-Evans syn aldol reaction using a 2-oxazolidinethione based chiral auxiliary (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.

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**Scheme 15**

\[ \begin{align*}
125 & \xrightarrow{a} 126 \\
128 & \xrightarrow{b} 127 \\
129 & \xrightarrow{c} 130
\end{align*} \]

*Steps a, b, and c.*

**Scheme 16**

\[ \begin{align*}
131 & \xrightarrow{a} 132 \\
134 & \xrightarrow{b} 135
\end{align*} \]

*Steps a, b, and c.*
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). 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). Chida’s synthesis of the stereotetrad of pironetin was started from L-quebrachitol 149 (Scheme 19). The intermediate 150 was prepared in five steps. 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). 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 (TiCl₄) addition of (Z)-crotyltri-n-butyllstannane 165 to the β-benzzyloxy aldehyde ent-15 to give the anti, syn homoallylic alcohol 166 (Scheme 21). 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 BF₃·OEt as the Lewis acid. The desired diastereomer 169

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**Scheme 17**

a 1. PhCH₂OC(=NH)CCl₃, CF₃SO₂H; 2. LiAlH₄; 3. Swern oxidation; b 1. (CF₃CH₂O)₂P(=O)CH₂CO₂Me, KN(TMS)₂, 18-Crown-6; 2. DIBAL-H; c MCPBA; d Me₂CuLi; e n-BuLi; f B₂H₆, H₂O₂.

**Scheme 18**

a 1. IBX, DMSO, rt, 30 min; 2. Ph₃CHCO₂Et, benzene, rt, 3 h; 3. DIBAL-H, CH₃Cl₂, –20 °C, 30 min; b TBHP, Ti(OPr)₄, (–)-DIPT, CH₂Cl₂, –20 °C, 20 h; c 1. Me₂CuLi, Et₂O, –78 °C, 8 h; 2. TBSCI, imidazole, CH₂Cl₂, rt, 3 h; 3. KH, MeI, Et₂O, rt, 30 min; 4. Bu₄NF, THF, rt, 2 h; d 1. TBHP, Ti(OPr)₄, (+)-DIPT, CH₂Cl₂, –20 °C, 18 h; 2. Red-Al, THF, 0 °C, 4 h.

**Scheme 19**

a 1. ref. 36; 2. Bu₄SnO, MeOH, reflux, then TsCl, DMAP; 3. 1,4-dioxane, rt; b MeONa, MeOH, reflux; c 1. Me₃Al, CH₂Cl₂ : hexanes, rt; 2. BzCl, pyridine, DMAP, rt; d 10-camphorsulfonic acid, MeOH, rt; e NaIO₄, acetone–H₂O, 0 °C, then NaBH₄, MeOH, 0 °C.
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). 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, 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.

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.

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).
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 dehyrdation. The desired enantiomer (+)-191 crystallized out from the enantiomeric mixture and the synthesis was continued with optically pure material. Then, NaBH₄ reduction and OsO₄ 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. The Evans all-syn-stereotetrad synthesis was very short and highly stereoselective (Scheme 25). The β-ketoimide 196 was allowed to react with methacrolein (TiCl₄ 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). 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, anti, syn, anti; anti, syn, anti, syn; anti, 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
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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