Expeditious Asymmetric Synthesis of Polypropionates Relying on Sulfur Dioxide-Induced C–C Bond Forming Reactions

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Abstract: For a long time, the organic chemistry of sulfur dioxide (SO_2) consisted of sulfinates that react with carbon electrophiles to generate sulfones. With alkenes and other unsaturated compounds, SO_2 generates polymeric materials such as polysulfones. More recently, H-ene, sila-ene and hetero-Diels–Alder reactions of SO_2 have been realized under conditions that avoid polymer formation. Sultines resulting from the hetero-Diels–Alder reactions of conjugated dienes and SO_2 are formed more rapidly than the corresponding more stable sulfolenes resulting from the cheletropic additions. In the presence of a protic or Lewis acid catalyst, the sultines derived from 1-alkoxydienes are ionized into zwitterionic intermediates bearing 1-alkoxyallylic cation moieties which react with electro-rich alkenes such as enol silyl ethers and allylsilanes with high stereoselectivity. (C–C-bond formation through Umpolung induced by SO_2). This produces silyl sulfinates that react with carbon electrophiles to give sulfones (one-pot four component asymmetric synthesis of sulfones), or with Cl_2, generating the corresponding sulfonamides that can be reacted in situ with primary and secondary amines (one-pot four component asymmetric synthesis of sulfonamides). Alternatively, Pd-catalyzed desulfinylation generates enantiomerically pure polypropionate stereotriads in one-pot operations. The chirons so obtained are flanked by an ethyl ketone moiety on one side and by a prop-1-en-1-yl carboxylate group on the other. They are ready for two-directional chain elongations, realizing expeditious synthesis of long-chain polypropionates and polyketides. The stereotriads have also been converted into simpler polypropionates such as the cyclohexanone moiety of baconipyrone A and B, Kishi's stereoheptad unit of rifamycin S, Nicolaou's C_1–C_{11}-fragment and Koert's C_{16}–C_I fragment of apoptolidin A. This has also permitted the first total synthesis of (-)-dolabriferol.

Keywords: aldol reactions; alkoxyallylic cation intermediates; apoptolidin A; baconipyrones; dolabriferol; hetero-Diels–Alder reactions; long-chain polyketides; retro-ene reaction; rifamycin S; Umpolung with SO_2

1. Introduction

Natural polypropionates are a large subgroup of polyketides (1,3-polyols) constructed by C_3-units. They are found in marine organisms including mollusks, sponges, fungi and actinomycetes [1–5], while some of them are also isolated from terrestrial resources [6]. Polypropionates interspace methyl groups in the polyketide chain which arise biochemically directly from the propionate unit or from the acetate–methionine motif [7–9]. They are characterized by abundant structural diversities and are important building blocks in the biosynthesis of several kinds of antibiotics such as macrolides, polyethers and cyclic peptides [10]. Most of them exhibit various kinds of bioactivities, especially antitumor and antimicrobial effects [11]. Examples of natural products containing polypropionate fragments are collected in Figure 1.
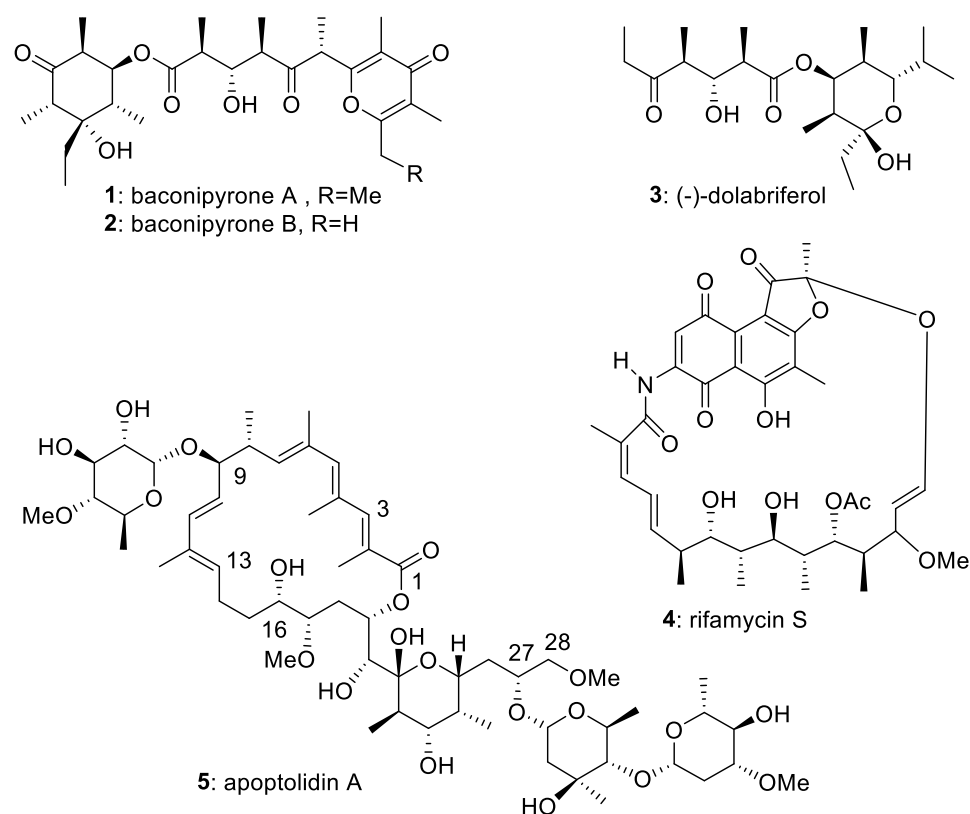
Figure 1. Examples of natural products containing polypropionate fragments, their synthesis being presented in this report.

The stereoselective construction of polypropionates is challenging, mainly because of stereochemical issues. Aldol reactions, crotylations, allenylation and propargylation of aldehydes R^1CHO have been used extensively to construct the four possible stereoisomeric R^1CH(OH)-CH(Me)-R^2 units [12–19]. More recently, the same fragments have been prepared through the transition metal catalyzed enantioselective hydro(hydroxycarbation) of terminal alkene R^2CH=CH$_2$ with alcohols R^1CH$_2$OH or aldehydes R^1CHO + H$_2$ [20]. The latter methods developed by Krische and co-workers have permitted significant shortening of the total syntheses of many natural polyketides and polypropionates [21–28]. The stereoselective construction of all possible stereoisomers of stereotriads R^3CH(Me)-CH(OH)-CH(Me)-R^4 (**6**, Figure 2) has been achieved by many methods [29] including those based on aldol or crotylation reactions of an aldehyde or its metallic enolate analogue bearing an α-methyl substituent [30–36].
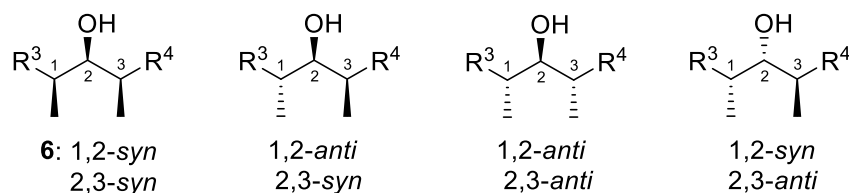
Figure 2. Four possible diastereomeric polypropionate stereotriads of type R^3-CH(Me)-CH(OH)-CH(Me)-R^4. Their enantiomers are not shown. Other stereotriads could be of the type R^3-CH(OH)-CH(Me)-CH(OH)-R^4.

Non-aldol formation of stereotriads has been proposed, such as the Sharpless asymmetric epoxidation of allyl alcohol followed by Pd-catalyzed hydrogenolysis of alkenyl oxirane with HCOOH [37,38] and the cuprate addition to epoxides [39–41]. A method applying an intramolecular Rh-catalyzed silylformylation/crotylsilylation/"aprotic" Tamao oxidation sequence has been developed by Leighton and co-workers [42–44]. Stereotriads

have been prepared through double oxidative hydroboration of allenyl alcohols [45]. Carreira and co-workers used enantiomerically pure chiral nitrile oxides and allylic alcohols to generate enantiomerically pure isoxazolines [46,47]. This permitted the preparation of all four possible dipropionates diastereoisomers, in a protected form, starting with the same set of reagents. Erythronolide A has been obtained by this method [48]. The Diels–Alder additions of alkenes to 1,3-dienes produce cyclohexenes containing up to four stereocenters. Danishefsky and co-workers have generated polypropionates via the Diels–Alder reaction. Cycloadditions of aldehydes to 1-methoxy-2-methyl-3-silyloxypenta-1,3-diene produce pyrans, a molecular fragment in many polypropionates [49,50]. The Diels–Alder reaction between 2,4-dimethylfuran and enantiomerically pure 1-cyanovinyl carboxylates produces enantiomerically pure 2-cyano-1,5-dimethyl-7-oxabicyclo[2.2.1]hept-5-en-2-yl esters. The alkaline hydrolysis of the latter liberates the chiral auxiliary (a carboxylic acid) which can be recycled. The bicyclic compounds so obtained permitted Vogel and co-workers to prepare several stereotetrads [51,52]. Alternatively, Plumet and Arjona used a Diels–Alder reaction between furan and acrylic acid which provided, after several transformations, a complete library of all possible stereotetrads [53,54]. Hunt and Grieco obtained polypropionates starting with the opening at the bridgehead of oxabicyclo[3.2.1]octenes employing silyl ketene acetals [55]. On their side, Toste and co-workers applied the enantioselective amine-catalyzed Kornblum–DeLaMare rearrangement, a reaction first described by Hagenbuch and Vogel in 1980 [56], on a 3-benzyloxy-2,4,8-trimethyl-6,7-dioxabicyclo[3.2.2]non-8-ene derivative to generate the two polypropionate fragments of dolabriferol (Figure 1) [57].

2. One-Pot Synthesis of Polypropionate Stereotriads Ready for Bidirectional Chain Elongations

For the stereotriads **6** and their enantiomeric forms (Figure 2) to become useful chirons (enantiomericallly pure synthetic intermediates) in the constructions of complicated polypropionates and analogues, their alcoholic moiety must be protected adequately and their R^3 et R^4 terminus should be functions that can enter directly in stereoselective C–C bond forming reactions, typically metal aldol reactions. Chirons of type **7** and **8** (and their enantiomers) have been obtained in one-pot operations (Scheme 1) [16]. Their group R^3 is an ethyl ketone which can be elongated into a system containing up to two further stereogenic centers via a direct aldol reaction, while the R^4 terminus is a protected ethyl ketone under the form of (Z)-prop-1-en-1-yl carboxylate (ethyl ketone enol carboxylate) that stays intact and can be used in the second chain elongation reaction, also producing up to two further stereogenic centers (see below Section 4).
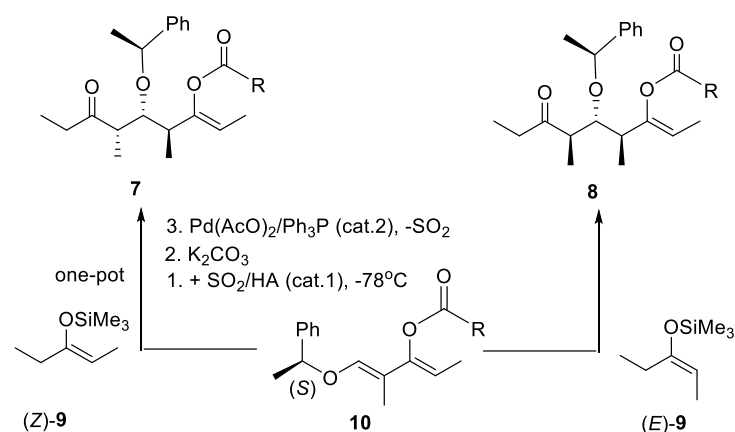
Scheme 1. One-pot synthesis of *syn,anti* and *anti,anti* stereotriads **7** and **8** through C–C bond formation between an 1-((1S)-phenylethyloxy)-2-methylpenta-1,3-dien-3-yl carboxylic esters **10** and the (E)- or (Z)-enoxysilane derived from butan-3-one ((E)-**9**, (Z)-**9**). HA is either a protic (e.g., (CF₃SO₂)₂NH) or Lewis acid (e.g.,: Me₃SiOSO₂CF₃) catalyst.

The enantiomers of stereotriads **7** and **8** are obtained in the same way using (*R*)-1-phenylethanol instead of (*S*)-1-phenylethanol to generate dienes **10**. Other 1-arylethanols can be used to generate more enantiomerically pure dienes (see below). The SO_2 is recovered at the end of the process. With the acid catalyst (e.g., HA = $(CF_3SO_2)_2NH$) it induces the Umpolung of the electron-rich diene into an alkoxyallylic cation intermediate (see below Section 3). R can be an alkyl (e.g., Me_2CH) or an aryl group (e.g., Ph).

3. Sulfur Dioxide as Umpolung Agent to Promote Carbon–Carbon Bond Forming Reactions between Alkenes and Dienes

In the presence of SO_2, alkenes, alkynes and polyenes produce polymeric materials, including polysulfones (copolymer with sulfur dioxide) [58–60]. Competing with these reactions, SO_2-catalyzed alkene isomerization can be observed. We have demonstrated that the latter reaction may not imply a hetero-ene reaction of the alkene with SO_2, followed by a fast [1,3]-sigmatropic shift of the intermediate β,γ-sulfinic acid and retro-ene reaction [61,62]. Instead, an allylic hydrogen atom is abstracted form the alkene by an alkanesulfonyl radical intermediate equilibrating with the polysulfone [63–65]. Since 1914 [66] it has been well-known that 1,3-dienes (that can adopt a *s-cis*-conformation) and sulfur dioxide equilibrate with their sulfolenes (cheletropic additions). On heating (>100 °C) the sulfolenes undergo cheletropic eliminations giving back the 1,3-dienes and SO_2. The first examples of hetero-Diels–Alder additions of SO_2 involved highly reactive dienes such as 1,4,5,6-tetramethyl-2,3-dimethylidenetriclo[2.1.1.0^{5,6}]hexane [67] and orthoquinodimethane [68]. Below −60 °C simple 1,3-dienes such as isoprene and piperylene react with SO_2 equilibrating with their sultines resulting from hetero-Diels–Alder reactions that are much faster than the corresponding cheletropic additions. Deguin and Vogel showed in 1992 that (*E,E*)-deuteriopiperylene (**11**) equilibrates with sultine **12** at −80 °C in the presence of an acid catalyst such as CF_3COOH. At −60 °C **12** is isomerized into the more stable isomeric sultine **13**, by cycloreversion into the initial cycloaddents and re-addition in a second hetero-Diels–Alder reaction (Scheme 2). Both the [4+2]-cycloadditions **11** + SO_2 → **12** and **11** + SO_2 → **13** are highly regio- and stereoselective [69]. As for many Diels–Alder reactions, the acid-catalyzed hetero-Diels–Alder reactions of SO_2 adheres to the Alder-endo rule and to the Woodward–Hoffmann rule of suprafaciality for the diene [69]. Sulfur dioxide itself catalyzes its cycloadditions [70–73]. In the absence of acid, the secondary deuterium kinetic isotopic effects of the SO_2 reaction with the dideuterodiene **15**-d$_2$ induced a regioselectivity opposite to the equilibrium isotopic regioselectivity. Sultine *ortho*-**17** formed faster than regioisomer *meta*-**17**. On staying at −55 °C, *ortho*-**17** was slowly isomerized into *meta*-**17** (Scheme 2). This demonstrates that the hetero-Diels–Alder reaction of SO_2 follows a mechanism with asynchronous formation of the C–S and C–O bonds in the transition state: the C–S bond is formed to a greater extent than the C–O bond [74].

The sulfolenes arising from the cheletropic additions of SO_2 to alkyl substituted 1,3-dienes are about 10 kcal mol^{-1} more stable than their isomeric sultines. In contrast, fluorosultines that result from the hetero-Diels–Alder reactions of SO_2 with 1-fluoro-1,3-dienes are more stable than their isomeric sulfolenes. This is assigned to an enthalpic anomeric effect of the F–C–O(S=O) moiety in the sultines [75].

With 1-alkoxy- 3-acyloxy-1,3-dienes **10** (prepared in four steps from butan-3-one and (*S*)-1-phenylethanol [76], the corresponding sultines **19** are not seen at −100 °C (large excess of SO_2, CH_2Cl_2 or toluene as co-solvent) as these dienes generate the corresponding sulfolenes at this temperature already. Nevertheless, sultines **19** are believed to be formed as intermediates before the isomeric sulfolenes (Scheme 3). In the presence of an acid catalyst (protic acid or Lewis acid), they equilibrate with zwitterionic intermediates **20** that can be reacted with electron-rich alkenes such as enoxysilane (*Z*)-**9**. This generates the silyl sulfinates **24**. The role of SO_2 is to convert the electron-rich dienes into 1-alkoxyallyl cation intermediates, realizing an inversion of polarity (Umpolung) that make possible the C–C coupling reaction between the two nucleophilic partners **10** and (*Z*)-**9** [77].
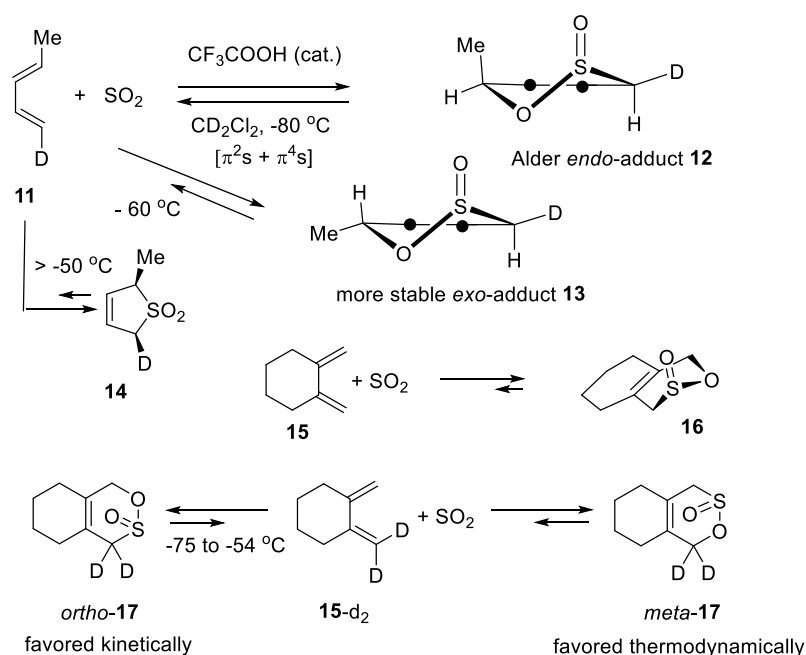
Scheme 2. Simple dienes that can adopt a *s-cis* conformation undergo SO$_2$ and acid-catalyzed hetero-Diels–Alder reactions with SO$_2$ at low temperature, giving sultines that are about 10 kcal mol^{-1} less stable than the corresponding sulfolenes.
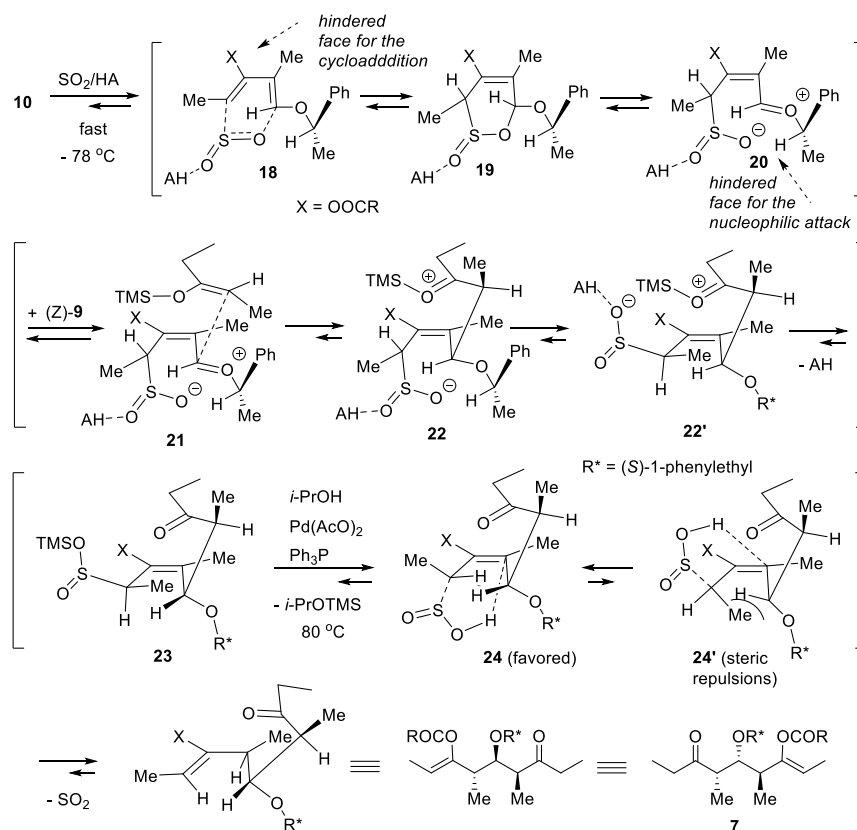
Scheme 3. Proposed mechanism for the reaction cascade producing the *syn,anti*-stereotriad 7 as major product: (1) face-selective acid-catalyzed hetero-Diels–Alder reaction of SO$_2$, (2) immediate ionization of the sultine so-obtained into a zwitterion, (3) face-selective quenching of the alkoxyallyl cation intermediate by the enoxysilane, (4) intramolecular or intermolecular silyl transfer forming a silyl sulfinate (can be isolated), (5) its Pd-catalyzed alcoholysis with isopropanol forming the corresponding, β,γ-unsaturated sulfinic acid which (6) undergoes a face-selective H-retro-ene reaction.

After removal of SO_2 in excess and solvent under vacuum, enough K_2CO_3 in CH_3CN was added to neutralize the acid catalyst. Then a 1:1 mixture of $Pd(AcO)_2/Ph_3P$ and isopropanol was added, and heating to 80 °C produced the final stereotriads. The stereoselectivity of the reaction cascade is explained in the following way (Scheme 3). The hetero-Diels–Alder reaction of SO_2 is face selective because the chiral auxiliary (1-alkoxy substituent of the diene) favors transition structure **18**, the least encumbered face of the diene reacting preferentially. The acid catalyzed ionization of the resulting sultines **19** generate ion-pairs **20** in which the sulfinate anion remains closed to the 1-alkoxyallyl cation moieties. This forces the nucleophile (e.g., enoxysilane (Z)-**12**) to attack **20** on the face opposite to that occupied by the sulfinate anion (transition structure **21**). The resulting adducts **22** undergo intramolecular silyl group transfers via conformations **22'**. Alternatively, two molecules of **22** could undergo a double intramolecular silyl group transfer giving the silyl sulfinates **23**. Alcoholysis of **23** gives sulfinic acids **24** which undergo H-retro-ene reactions generating **7**, the stereoselectivity of which is controlled by steric factors making transition structures **24** preferred to **24'**. For the reaction cascade using enoxysilane (Z)-**9** and diene **10** with R = *i*-Pr, R* = (S)-1-phenylethyl) (1:1 SO_2/toluene, catalyst AH = $(CF_3SO_2)_2NH$) the corresponding stereotriads **7** and **8** were isolated in 67 and 13 % yield, respectively, after column chromatography. Using Greene's chiral auxiliaries ((S)-1-[2,4,6- tris(isopropyl)phenyl]ethanol) [78]) instead of inexpensive (S)-1-phenylethanol the diastereoselectivity *syn,anti* vs. *anti,anti*-stereotriad was better than 95:5 [79].

The silyl sulfinates **23** can be isolated, or converted in situ into sulfinate salts that are quenched by all kinds of electrophiles to give sulfones (four-component synthesis of polyfunctional sulfones [80]), or converted in situ (with Cl_2 or *N*-chlorosuccinimide) into sulfonyl chlorides that react with amines to produce sulfonamides (four-component synthesis of polyfunctional sulfonamides [81,82]). Acidic treatment of **23** also leads to desulfinylation producing the stereotriads in a lower yield, due to elimination of 1-phenylethanol-generating dienes **26** and aldols **27**, the latter undergoing retro-aldol decomposition into penta-3-one and aldehydes **28** (Scheme 4). This is avoided when the silyl sulfinates are treated under neutral or slightly basic conditions (K_2CO_3) in isopropanol in the presence of a catalytic amount of $Pd(AcO)_2$ and Ph_3P. Without Ph_3P the reaction does not occur (formation of $Pd^{(0)}$ species as catalyst). One can envisage a $Pd^{(0)}$ complex intermediate which adds oxidatively (retention of configuration) into the allylic $C–SO_2SiMe_3$ bond of **23**. Subsequent desulfinylation and protolysis of the $Pd–SiMe_3$ bond gives *i*-$PrOSiMe_3$ (driving force) and an (allyl)palladium hydride that undergoes regioselective and stereoselective β-insertion of hydride into another (allyl)Pd intermediate. An alternative mechanism (Scheme 3) is to invoke that the $Pd^{(0)}$ role is just to promote the Si-sulfinate bond cleavage under non-acidic conditions generating the corresponding β,γ-unsaturated sulfinic acids that, in turn, undergo H-retro-ene elimination of SO_2 [83].
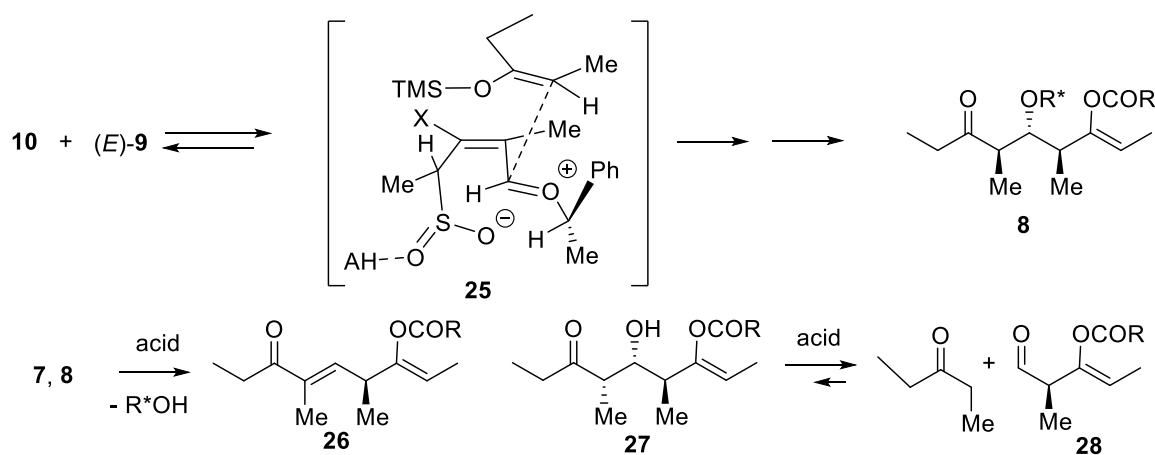
Scheme 4. Mechanism for the preparation of the *anti,anti*-stereotriad **8** and formation of co-products under acid-induced desulfinylation.

## 4. Long-Chain Polypropionates through Bidirectional Chain Elongation

The polypropionate **31** (a stereodecad) containing 10 contiguous stereogenic centers has been obtained by two successive metal-aldol reactions of stereotriad **7** (Scheme 5) [84]. Applying Paterson's method for direct formation of enoxyboranes [85–87] the dicyclohexyl(enoxy)borane derived from **7** reacted with acetaldehyde giving an boron *anti*-2-methylaldolate that was reduced directly with NaBH$_4$ generating a *anti,anti*-2-methyl-1,3-diol moiety, which was protected as the acetonide **29** (a stereohexad in one pot operation) in 61% overall yield. The (*Z*)-enol isobutyrate group of **29** was converted with retention into the (*Z*) lithium enolate **30** by reaction with MeLi·LiBr in ether. The latter added to the acetonide of D-glyceraldehyde giving a major lithium aldolate. Its phenylethyl ether was hydrogenolyzed under standard conditions and the aldol was reduced with Me$_4$NB(AcO)$_3$H [88,89] selectively into the corresponding *anti*-1,3-diol **31** (67% overall yield).
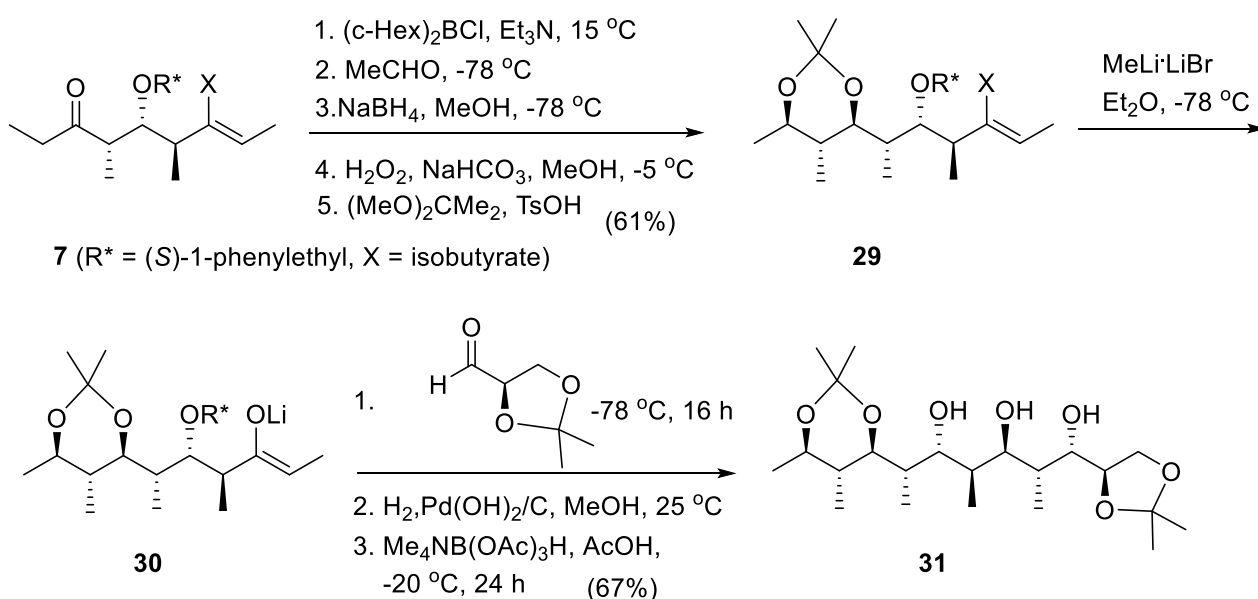
Scheme 5. An example of bidirectional chain elongation of stereotriad 7 by two successive metal-aldol reactions; synthesis of a stereodecad from a stereotriad requiring the isolation of one synthetic intermediate.

5. First Total Asymmetric Synthesis of the Cyclohexanol Subunit of Baconipyrones A and B

Baconipyrones A-D were isolated in 1989 by Faulkner and co-workers from *Siphonaria baconi* [90]. The stereotriad **7** (R = *i*-Pr, R* = (*S*)-1-phenylethyl) has been converted in two steps into cyclohexanone **34** (overall yield: 86%), subunit of baconipyrones A and B (Figure 1) [91]. Transesterification of enol isobutyrate **7** (Scheme 6) with Bu$_3$SnOMe [92,93] induced the desired stereoselective intramolecular aldol reaction, giving **33**. Transition structure **32** was proposed to explain the stereoselectivity hydrogenolysis of **33** and provided **34** quantitatively.
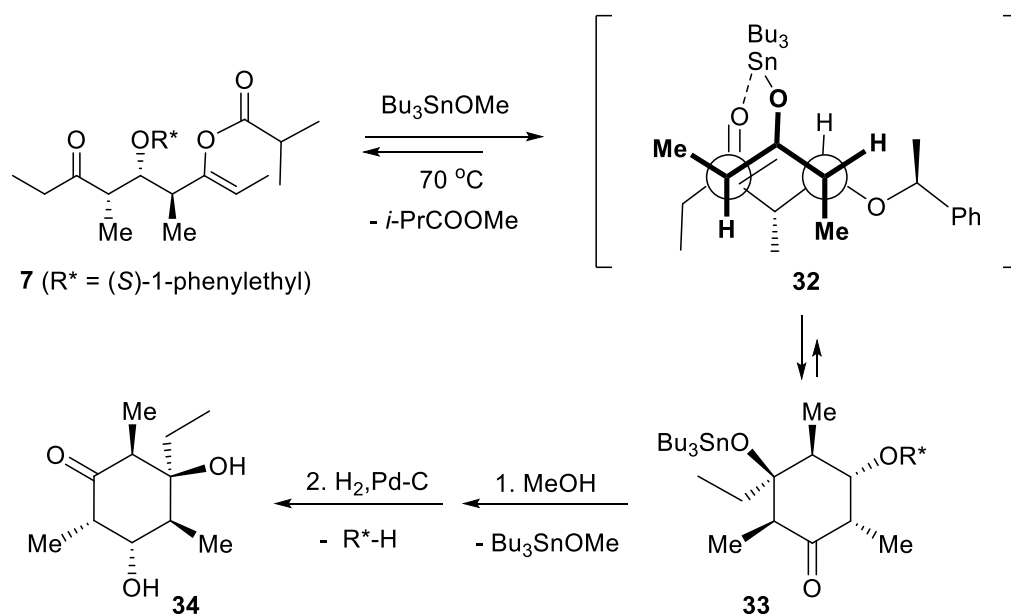
Scheme 6. Synthesis of the cyclohexanone subunit of baconipyrones A and B.

6. First Total Asymmetric Synthesis of (-)-Dolabriferol

(-)-Dolabriferol was isolated from *Dolabrifera dolabrifera*, a shell-less mollusk. (-)- Dolabriferol is assumed to protect the mollusk from predators [94]. This natural product is made of two polypropionates subunits linked by an ester function, a structural motif which is also found in baconipyrones (Figure 1). Ozonolysis of pure **35** arising from the reaction of diene **13** (R' = (R)-1-phenylethyl) and enoxysilane (E)-**9** provided the carboxylic subunit (+)-**36** of (-)-dolabriferol (two steps from diene **13**). Similarly, reaction of diene **37** with enoxysilane **38** resulted in a stereotriad **39** (67%, single diastereomer, diasteroselectivity better than 95:5), that was reduced with stereoselectivity into alcohol **40** (a stereotetrad in two steps from diene **37**). Protection as an allyl carbonate (alloc), followed by TiCl$_4$-induced E$_1$ cleavage of the 1-phenylethyl ether moiety furnished alcohol **41**. The esterification of **41** with carboxylic acid (+)-**36** using Paterson's protocol [95] produced **42** (DMAP = 4-dimethylaminopyridine). Selective removal of the acetyl group was realized by treatment in pure Bu$_3$SnOMe at 70 °C, followed by KF/H$_2$O work-up. Subsequent treatment with CF$_3$COOH removed the phenylethyl ether, giving **43**. Final deprotection of the alloc group (TPPS = 3,3′,3″-phosphinidynetris(benzenesulfonic acid) trisodium salt) and formation of the cyclic hemiacetal gave (-)-dolabriferol (Scheme 7).[96] Since this first total synthesis which established the absolute configuration of (-)-dolabriferol, several other synthetic approaches have been proposed, sometimes requiring more steps [57,97–100].
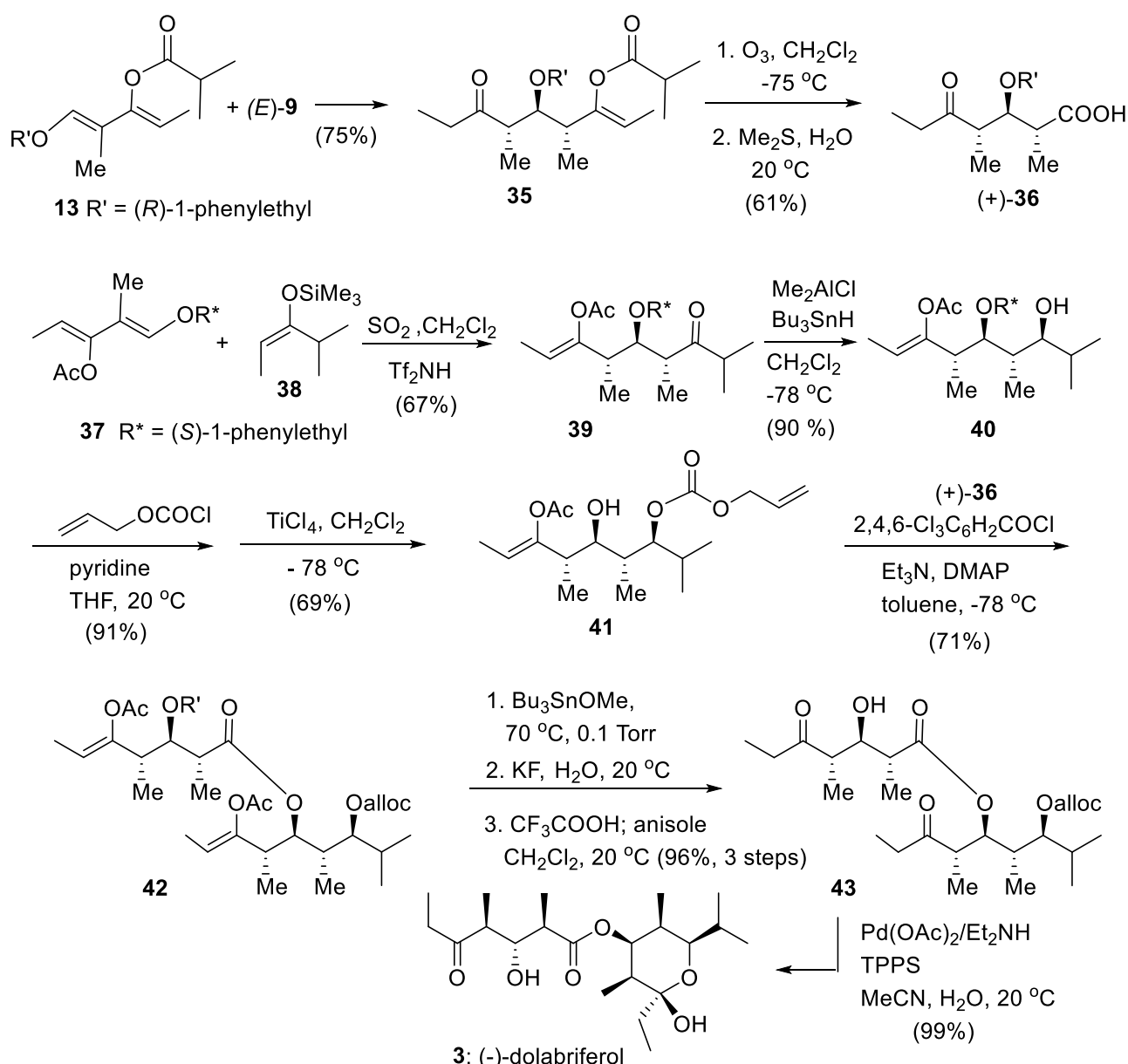
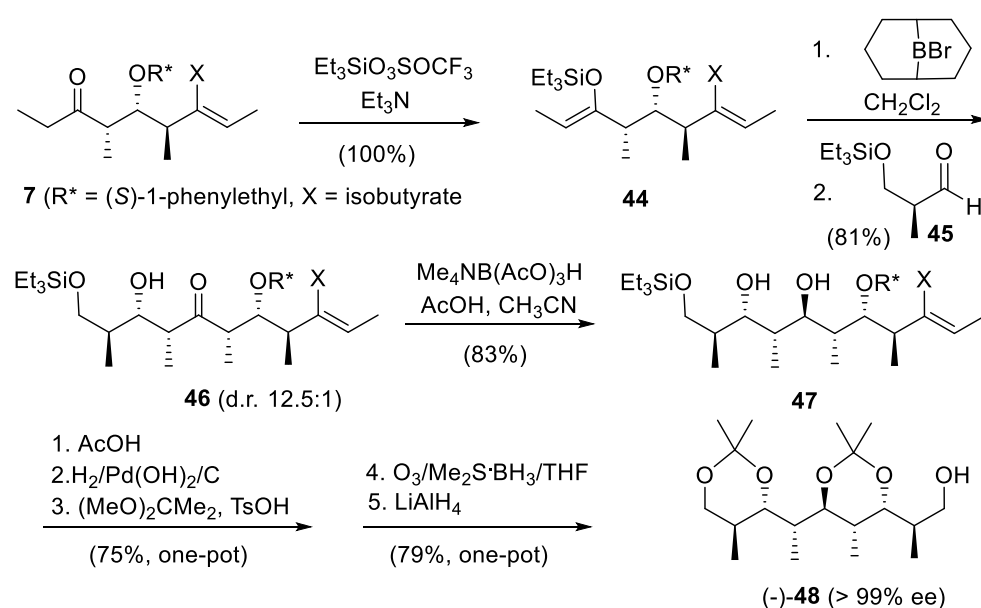**Scheme 7.** Total asymmetric synthesis of (-)-dolabriferol.

7. Expeditious Asymmetric Synthesis of the Stereoheptad C_{19}–C_{27} of Rifamycins: Formal Total Synthesis of Rifamycin S

Rifamycins [101–103] are antibiotics belonging to the group of naphthalenic ansamycins [104] characterized by an aliphatic bridge (polypropionate chain) linking two non-adjacent centers of an aromatic moiety. They are produced from *Streptomyces mediterranei* [105] and are active against a large variety of organisms, including bacteria, eukaryotes and viruses [106]. Rifamycins have shown also antitumour activity [107] and anti-inflammatory activity [108]. At present, rifamycins and analogues are applied in the treatment of tuberculosis. They inhibit bacterial DNA-dependent RNA polymerase [109–111]. Rifamycin S (**4**) and several analogues showing promising activities have been prepared [112–115].

The first total synthesis of rifamycin S (**4**) was reported by Kishi and co-workers in 1980 [116–119]. The stereoheptad (-)-**48** is a key intermediate for the construction of the ansa chain. It was obtained in 26 steps and 5.2% overall yield from (2S)-3-benzyloxy-2-methylpropanal. Since then, several total asymmetric syntheses of the polypropionate fragment have been proposed [120–123]. The construction of the C_{19}–C_{27} fragment ((-)-**48**

and analogues) of this antibiotic has become a challenging target for the testing of asymmetric synthetic methods and strategies [50,124–141].

Starting from the readily available diene **10** (R* = (*S*)-1-phenylethyl, X = isobutyrate, Scheme 1) Kishi's intermediate (-)-**48** was obtained in 25% yield requiring the isolation of only four synthetic intermediates (Scheme 8). The (*Z*)-enol ether **44** resulting from the silylation of ethyl ketone **7** (derived from diene **10**) reacted with 9-bromo-9-borabicyclo[3.3.1]nonane (BrBBN) in CH_2Cl_2 (silyl/boron exchange) and then with aldehyde **45** to produce a 12.5:1 mixture of **46** and 9-epimer in 81% yield. Pure **46** was reduced under Evans' conditions [88,89] to give diol **47**. The next five operations were carried out in the same pot without isolating any intermediate. Treatment of **47** with AcOH cleaved the silyl ether. Then hydrogenolysis removed the phenylethyl group. The crude tetrol so obtained was converted into the corresponding diacetonide. Ozonolysis of the enol isobutyrate moiety gave a mixed anhydride that was reduced with $LiAlH_4$ into (-)-**48** [142].


Scheme 8. Expeditious asymmetric synthesis of Kishi's stereoheptad: formal total synthesis of rifamycin S.

8. Generalization of the SO_2-Induced Umpolung. Short Synthesis of the C_{16}–C_{28} Fragment of Apoptolidinone: Formal Total Synthesis of Apoptolidin A

Apoptolidin A (isolated from *Nocardiopsis sp.*) [143,144] and the natural analogues B, C, D, E and F [145–147] are leads for the chemotherapy of cancers [148–151]. They selectively induce apoptosis in cancer cells. The groups of Nicolaou [152,153] and Koert [154,155] have presented the first syntheses of apoptolidin A. The groups of Sulikowsky [156,157] and Crimmins [158] have reported syntheses of the aglycon apoptolidinone A. Fragments of this aglycon has been prepared by other groups [159].

Applying our SO_2-induced Umpolung reaction, rapid access (nine steps) to Koert's C_{16}–C_{28} polyketide fragment **57** (Scheme 9) of apoptolidinones A has been realized [160]. This work illustrates that other dienes and enoxysilanes than those presented in Scheme 1 can be used in our reaction cascade. Fragment **57** is adequately protected for the glycosidation steps necessary in the construction of apoptolidin A.
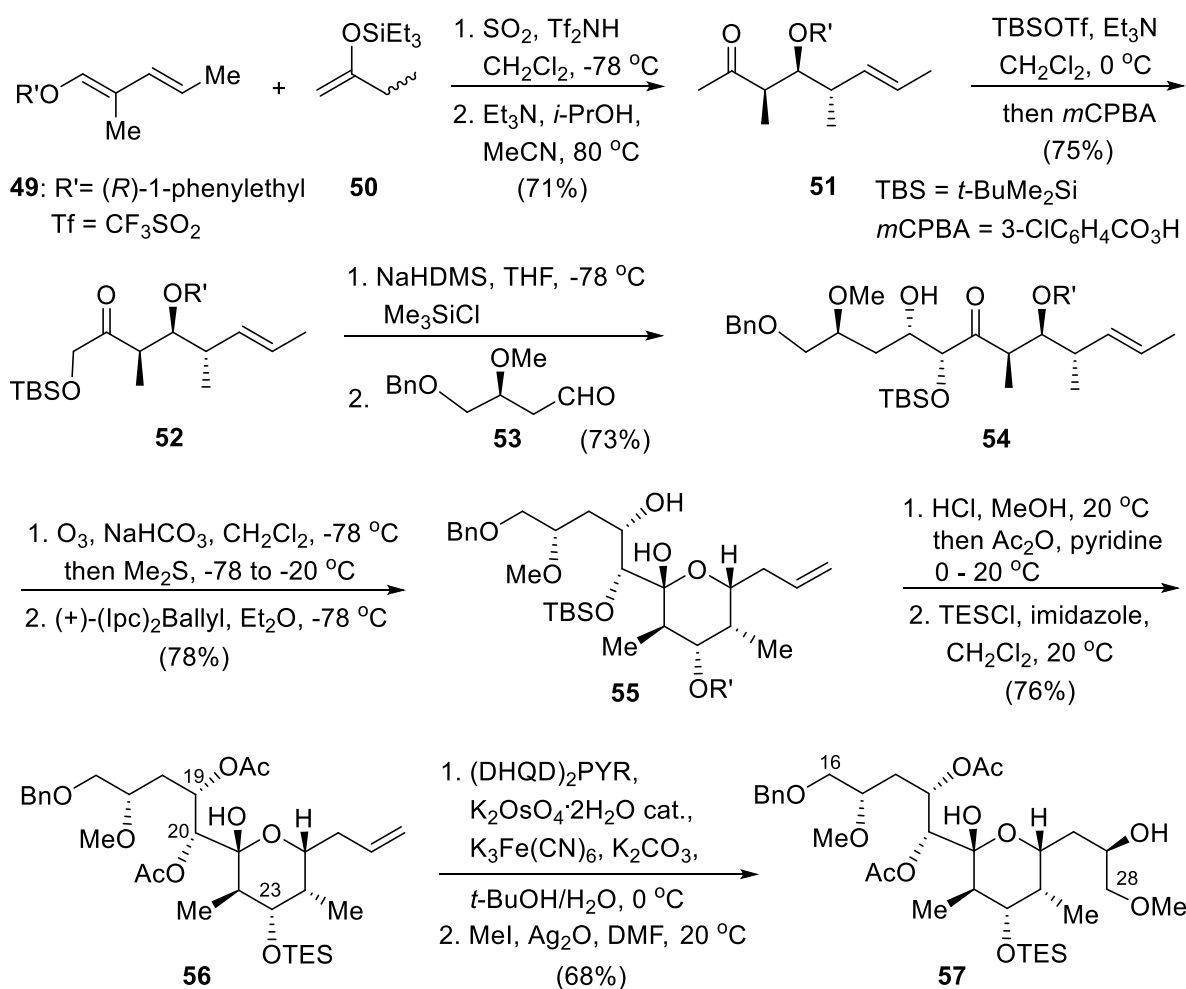
Scheme 9. Synthesis of Koert's C_{16}–C_{28} polyketide fragment of apoptolidin A.

Diene **49** (derived from inexpensive (*R*)-1-phenylethanol) and silyl ethers **50** (1:1 *E/Z* mixture) were reacted with a catalytic amount of $(CF_3SO_2)_2NH$ in SO_2/CH_2Cl_2 (5:1) cooled to −78 °C. After neutralization of the acid catalyst with Et_3N and solvent evaporation, alcoholysis with *i*-PrOH (80 °C) gave a 4:1 mixture of stereotriad **51** and its α,β,γ–*anti,anti* stereomer. This mixture was converted into their kinetic silyl enol ethers and oxidized with *m*CPBA (Rubottom oxidation [161]) giving **52** that underwent Mukaiyama aldol coupling with aldehyde **53** [162,163], producing alkene **54**. Ozonolysis of **54** followed by treatment with Me_2S gave an aldehyde that was allylated under Brown's conditions [164]. The resulting homoallylic alcohol was equilibrated with the hemiacetal **55** that underwent desilylation, debenzylation and Fischer glycosidation on treatment with HCl/MeOH at 50 °C. The resulting triol was then acetylated selectively into a diacetate (at C_{19} and C_{20}); the most sterically hindered alcohol at C_{23} was then silylated giving **56**. Sharpless asymmetric dihydroxylation [165] of **56** furnished a 4.5:1 mixture of the corresponding diol that was selectively monomethylated with MeI/Ag_2O giving Koert's intermediate **57**.

9. The One-Pot Four-Component Synthesis of Polyfunctional Sulfones: Application to a Short Synthesis of the C_1–C_{11} Fragment of Apoptolidin A

Another key intermediate in the total synthesis of apoptolidin A is the Nicolaou's C_1–C_{11}-fragment (+)-**65** the preparation of which requires 11 steps [152]. Applying our SO_2-induced Umpolung reaction, an expeditious synthesis of this intermediate was realized with an overall yield of 29% starting with simple diene **58**, enoxysilane **59** and the known enantiomerically pure (*S*)-3-methoxymethoxy-2-methylprop-1-yl iodide. The method required the isolation of only three synthetic intermediates (Scheme 10) [166]. In the

presence of 0.4 equivalent of a strong acid such as $(CF_3SO_2)_2NH$ sulfur dioxide adds to the *s-trans* form of diene **58** equilibrating with a zwitterionic intermediate **60** that was quenched by the enoxysilane **59**. One assumes that another zwitterionic intermediate **61** was formed, which after treatment with tetrabutylammonium fluoride generated the dihydroxyketone **62**, an aldol that loses one equivalent of water under acidic conditions (*p*-TsOH, MeOH, 70 °C) to give the (*E,E*)-dienone **63** (one pot: 87% yield). Silyl ether and enol silyl ether formation was followed by oxidation with *m*CPBA. This generated an α-hydroxyketone which was not isolated but directly submitted to the Malaprade oxidation, giving a carboxylic acid that was esterified in situ with diazomethane-producing ester **64**. Dess–Martin oxidation of the primary alcohol of **64** gave an aldehyde that was reacted, without purification, with Et_3SiCC-Li to give a 5:1 mixture of diastereomeric propargylic alcohols. They were silylated and the sulfone moiety underwent a Ramberg–Bäcklund rearrangement [167–169] providing a 12:1 mixture of (*E,E,E*)-/(*E,E,Z*)-triene-ester (+)-**65**.
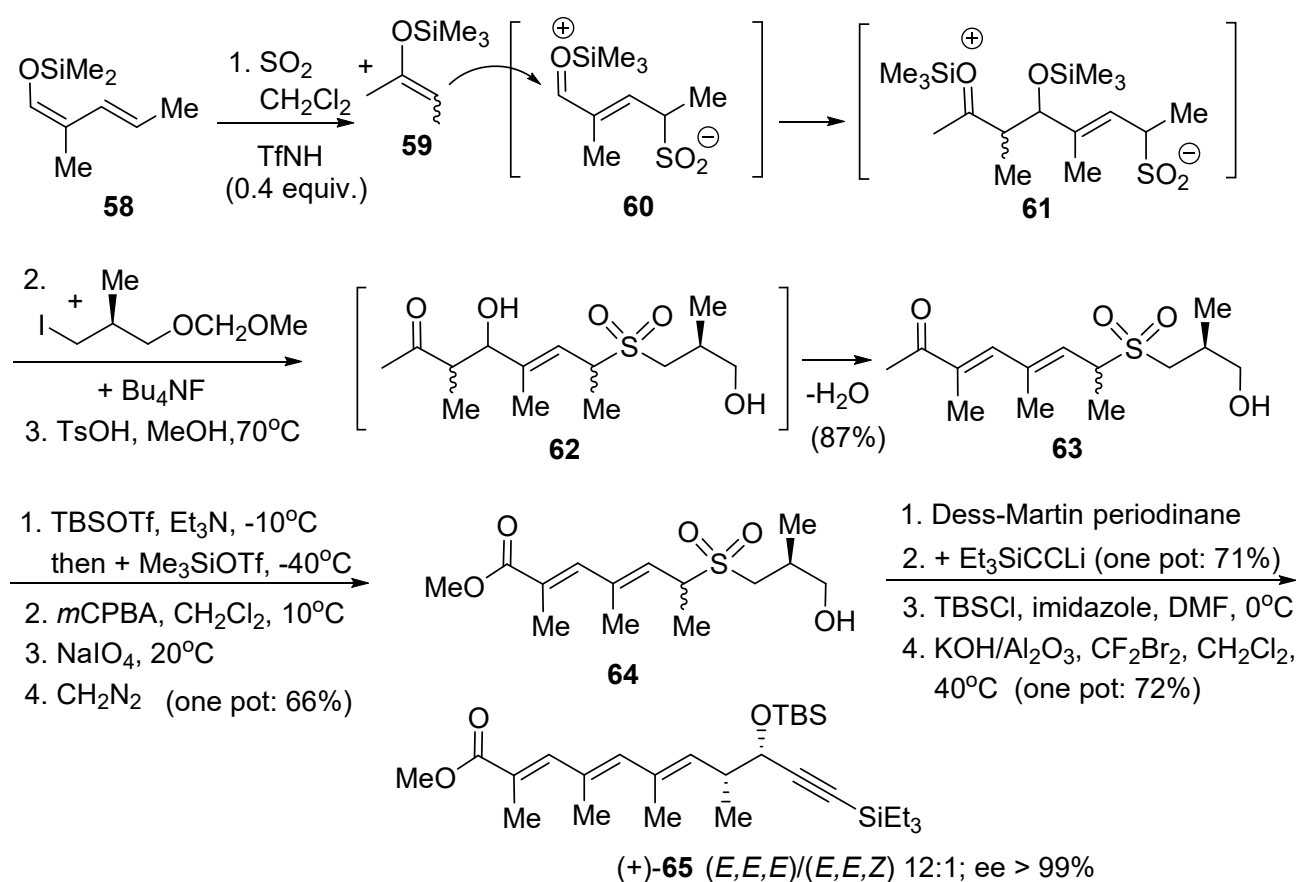
Scheme 10. An expeditious synthesis of the Nicolaou's C_1–C_{11} fragment of apoptolidin A.

10. Allylsilanes as Nucleophiles: Development of Two-Directional Polypropionate–Polyketide Synthesis

Like enol silyl ethers, allylsilanes are nucleophiles that can be used in our SO_2-induced CC bond-forming reaction. Using allyldisilane **67** and two different dienes, **66** and **69**, the stereotetrads **70** can be prepared in one-pot operations (Scheme 11). Diene **66** possesses a 1-(1-phenyl)ethoxy group whereas diene bears a 1-[1-(4-fluorophenyl]ethoxy substituent. The S_N1 and E_1 cleavage of the benzylic C–O ether bond of the 1-phenylethoxy group are faster than the S_N1 and E_1 C–O benzylic bond cleavage of the 1-(4-fluorophenyl)ethoxy group; the pseudo-symmetrical stereotetrad is suitable for two successive aldol reactions on both their chain terminus. This permits the expeditious syntheses of long-chain polyketides and polypropionates.
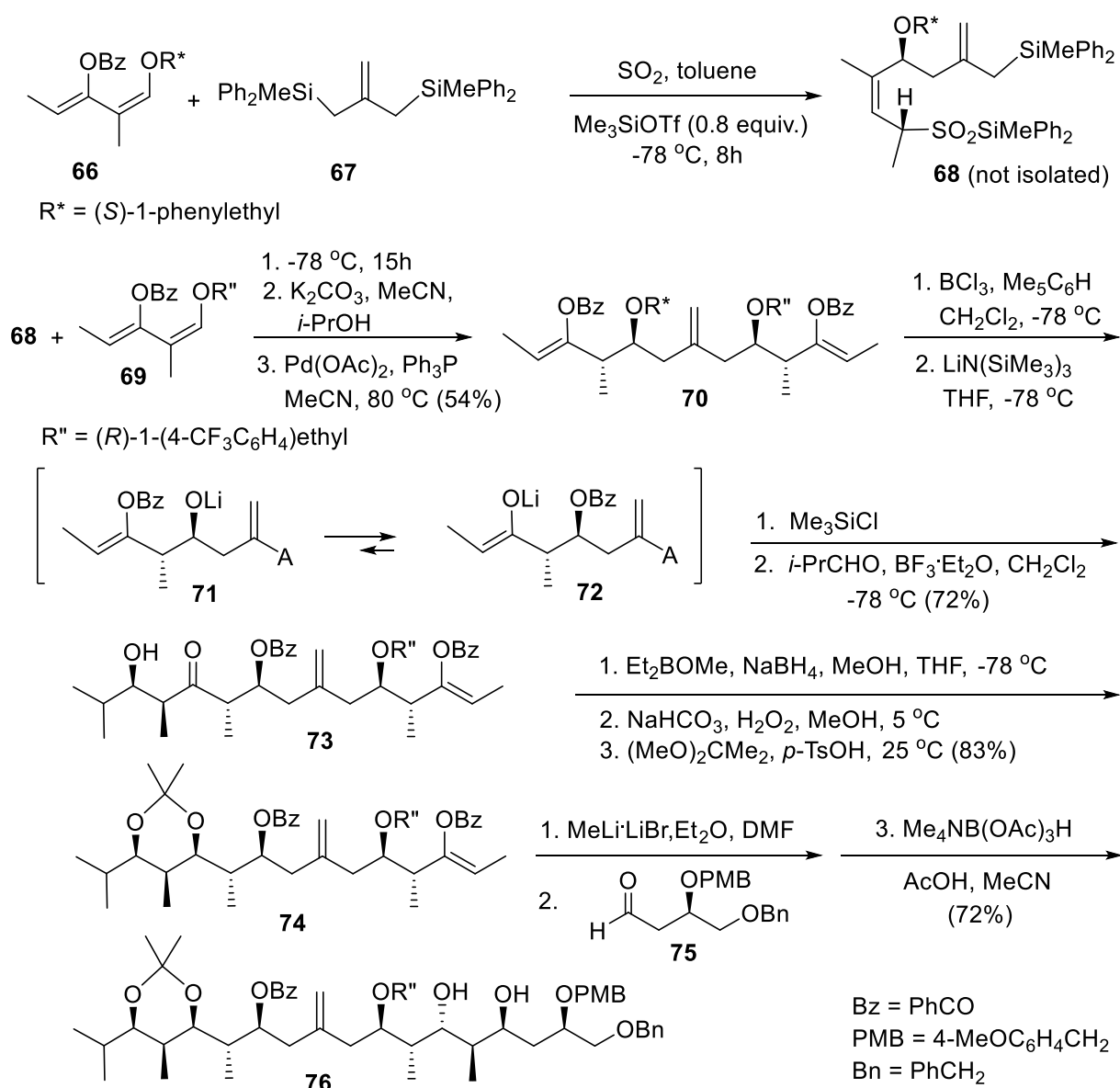
Scheme 11. Convergent synthesis of complicated polypropionate–polyketide fragments through dissymmetrical two-directional chain elongation.

Reaction of diene **66** with **67** and SO$_2$ promoted by Me$_3$SiOTf generated the product of mono-alkoxyallylation **68**. The reaction **66** + **67** → **68** is faster than the reaction of monoallylsilane **68** with diene **67** + SO$_2$ because bisallylsilane **66** enjoys twice the β-silicon effect. In the presence of one equivalent of diene **66** the product of double oxyallytion is not formed; only sulfinate **68** is formed. It can be reacted without purification with SO$_2$ and diene **69**, providing a bis(silyl sulfinate) which is not isolated but submitted directly to the double Pd$^{(0)}$-catalyzed desilylation and desulfitation reactions, furnishing the stereotetrad **70**, isolated in 54% yield (one-pot). Selective debenzylation of **70** with BCl$_3$/pentamethylbenzene eliminated the phenylethyl group, giving a homoallylic alcohol that was not isolated but treated directly with (Me$_3$Si)$_2$NLi to engender the corresponding lithium alcoholate **71** (one pot). The latter underwent rapid acyl group migration from the neighboring enol benzoate forming lithium enolate **72**. Without isolation, the latter enolate reacted with Me$_3$SiCl giving a (Z)-enoxysilane that was reacted in situ with isobutyraldehyde and BF$_3$ etherate, providing aldol **73** which was a single stereomer isolated in 72% yield. Reduction of aldol **72** under Narasaka's conditions [170] gave the corresponding *syn*-1,3-diol that was converted in situ into its acetonide **74** (83%, overall). The treatment

of enol benzoate **74** with MeLi·LiBr furnished the corresponding lithium (*Z*)-enolate. It was quenched by the chiral aldehyde **75** producing a major aldol that was not isolated but directly reduced under Evans' conditions [88,89]. This furnished **76**, a polyketides containing 11 stereogenic centers. As the configuration of the 1-oxydienes **66** and **69** can be either (*R*) or (*S*) and since the two successive aldol reactions on the intermediate stereotetrad can used a wide variety of aldehydes under well-chosen conditions, a very large library of polyketides can be prepared applying our method illustrated in Scheme 11 [171,172].

11. Conclusions

At low temperature, and in the presence of a protic or Lewis acid catalyst, 1-alkoxy-1,3-dienes undergo fast hetero-Diels–Alder reactions with SO_2, forming unstable sultines that are converted rapidly into zwitterionic intermediates containing 1-oxyallyl cation moieties. The latter are quenched in situ by electron-rich alkenes such as silyl enol ethers generating β,γ-unsaturated silyl sulfinates. Sufur dioxide induces a stereoselective C–C bond forming reactions between electron-rich dienes and alkenes (Umpolung through SO_2). The silyl sulfinates so obtained can be converted in situ into stereotriads that are flanked by an ethyl ketone group at one side and by an enol ester of an ethyl ketone on the other side. In a few synthetic steps the synthesis of the cyclohexanone unit of baconipyrones and of the two fragments of (-)-dolabriferol have been realized. With the first total synthesis of (-)-dolabriferol we could establish its absolute configuration. Aldol condensation of the ethyl ketone group of one of our stereotriads has opened a very short route to Kishi's stereoheptad, which he used to construct rifamycin-S. A similar strategy has permitted us to obtain the Koert's C_{16}–C_{28} polyketide fragment of apoptolidin A. Under strongly acidic conditions, *s-trans*-1-alkoxydienes and enoxysilanes react with SO_2 forming sulfinates that are quenched in situ with electrophiles to generate polyfunctional sulfones with a conjugated (*E,E*)-dienone moiety. The method has permitted an efficient synthesis of Nicolaou's C_1–C_{11} fragment of apoptolidin A. The stereotriads undergo two successive metal aldol reactions that produce complicated polyketides and polypropionates in a few steps. Allylsilanes can be used instead of enoxysilanes in our SO_2-induced Umpolung reaction. With 2-[(methyldiphenyl)methyl]allylmethyl(diphenyl)silane), two successive alkoxyallylations with two different 1-alkoxydienes can be run in the same pot, thus generating stereotetrads ready for two successive aldol reactions (two-directional chain elongations). The strategy permits us to construct, in a few steps, complicated polyketides and polypropionates in a combinatorial fashion.

Conflicts of Interest: The authors declare no conflict of interest.

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