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 (SO2) consisted of sulfinates that react with carbon electrophiles to generate sulfones. With alkenes and other unsaturated compounds, SO2 generates polymeric materials such as polysulfones. More recently, H-ene, sila-ene and hetero-Diels–Alder reactions of SO2 have been realized under conditions that avoid polymer formation. Sultines resulting from the hetero-Diels–Alder reactions of conjugated dienes and SO2 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 SO2). This produces silyl sulfinates that react with carbon electrophiles to give sulfones (one-pot four component asymmetric synthesis of sulfones), or with Cl2, 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 baconipyrones A and B, Kishi’s stereoeheptad unit of rifamycin S, Nicolaou’s C1–C11-fragment and Koert’s C16–C1 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 SO2

1. Introduction

Natural polypropionates are a large subgroup of polyketides (1,3-polyols) constructed by C3-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.
The stereoselective construction of polypropionates is challenging, mainly because of stereochemical issues. Aldol reactions, crotylations, allenylation and propargylation of aldehydes R1CHO have been used extensively to construct the four possible stereoisomeric R1CH(OH)-CH(Me)-R2 units [12–19]. More recently, the same fragments have been prepared through the transition metal catalyzed enantioselective hydro(hydroxy)carbene) of terminal alkene R2CH=CH2 with alcohols R1CH2OH or aldehydes R1CHO + H2 [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 R3CH(Me)-CH(OH)-CH(Me)-R4 (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 1](image1.png)

Figure 1. Examples of natural products containing polypropionate fragments, their synthesis being presented in this report.

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 isoaxazolines [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-silyloxy-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 stereotetrad[s [51,52]. Alternatively, Plunet and Arjona used a Diels–Alder reaction between furan and acrylic acid which provided, after several transformations, a complete library of all possible stereotetrad[s [53,54]. Hunt and Grieco obtained polypropionates starting with the opening at the bridgehead of oxabicyclo[3.2.1]octenes employing silyl ketene acetics [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 chiron[s (enantiomerically pure synthetic intermediates) in the constructions of complicated polypropionates and analogues, their alcoholic moiety must be protected adequately and their R³ and R⁴ 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 R³ 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 R⁴ 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](image)

**Scheme 1.** One-pot synthesis of syn,anti and anti,anti stereotriads 7 and 8 through C–C bond formation between an 1-((1S)-phenylethylxyloxy)-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-arylethans can be used to generate more enantiomerically pure dienes (see below). The SO₂ is recovered at the end of the process. With the acid catalyst (e.g., HA = (CF₃SO₂)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., Me₂CH) 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 SO₂, alkenes, alkynes and polyenes produce polymeric materials, including polysulfones (copolymer with sulfur dioxide) [58–60]. Competing with these reactions, SO₂-catalyzed alkene isomerization can be observed. We have demonstrated that the latter reaction may not imply a hetero-ene reaction of the alkene with SO₂, 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 SO₂. The first examples of hetero-Diels–Alder additions of SO₂ involved highly reactive dienes such as 1,4,5,6-tetramethyl-2,3-dimethylenetriclo[2.1.1.0₂²]hexane [67] and orthoquinodimethane [68]. Below −60 °C simple 1,3-dienes such as isoprene and piperylene react with SO₂ 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 CF₃COOH. 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 + SO₂ → 12 and 11 + SO₂ → 13 are highly regio- and stereoselective [69]. As for many Diels–Alder reactions, the acid-catalyzed hetero-Diels–Alder reactions of SO₂ 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 SO₂ reaction with the didieterodiene 15-d₂ 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 SO₂ 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 SO₂ to alkyl substituted 1,3-dienes are about 10 kcal mol⁻¹ more stable than their isomeric sulfolenes. In contrast, fluorosultines that result from the hetero-Diels–Alder reactions of SO₂ 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 SO₂, CH₂Cl₂ 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 sulfimates 24. The role of SO₂ 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].
Proposed mechanism for the reaction cascade producing the catalyzed hetero-selective quenching of the alkoxyallyl cation intermediate by the enoxysilane, (4) intramolecular or intermolecular silyl transfer forming a silyl sulfinates that react with amines to produce sulfonamides (four functional sulfones [80]), or converted in situ (with Cl-sulfonyl chlorides that react with amines to produce sulfones (four as intermediates before the isomeric sulfolenes (Scheme 3). In the presence of an acid catalyst, the sulfolenes arising from the cheletropic additions of SO$_2$ are more stable than their isomeric sultines. This is assigned to an enthalpic anomic effect of the F-dienes are more stable than their isomeric sulfolenes. This is demonstrated when the hetero-Diels-Alder reactions with SO$_2$ follow a mechanism with asynchronous formation of the –C=O bond is formed to a greater extent than the S=O moiety in the sultines 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 sulfinates, (5) its Pd-catalyzed alcoholysis with isopropanol forming the corresponding, phenylethanol, (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.

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 SO₂ in excess and solvent under vacuum, enough K₂CO₃ in CH₃CN was added to neutralize the acid catalyst. Then a 1:1 mixture of Pd(AcO)₂/Ph₃P 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 SO₂ 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 sulfines 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 conformation 22'. Alternatively, two molecules of 22 could undergo a double intramolecular silyl group transfer giving the silyl sulfinites 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 SO₂/toluene, catalyst AH = (CF₃SO₂)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 sulfinites 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 Cl₂ 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 sulfinites are treated under neutral or slightly basic conditions (K₂CO₃) in isopropanol in the presence of a catalytic amount of Pd(AcO)₂ and Ph₃P. Without Ph₃P 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-SO₂SiMe₃ bond of 23. Subsequent desulfinylation and protolysis of the Pd-SiMe₃ bond gives i-PrOSiMe₃ (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 SO₂ [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 NaBH₄ 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 Me₄NB(AcO)₃H [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 Bu₃SnOMe [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 5. An example of bidirectional chain elongation of stereotriad by two successive metal-aldol reactions; synthesis of a stereodecad from a stereotriad requiring the isolation of one synthetic intermediate.

**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 TiCl4-induced E1 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 Bu3SnOMe at 70 °C, followed by KF/H2O work-up. Subsequent treatment with CF3COOH 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].
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 CH₂Cl₂ (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 LiAlH₄ into (−)-48 [142].

![Scheme 8](image)

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

8. Generalization of the SO₂-Induced Umpolung. Short Synthesis of the C₁₆−C₂₈ Fragment of Apoptolidinone: Formal Total Synthesis of Apoptolidin A

Apoptolidin A (isolated from *Nocardiosis 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 apoptolidinon A. Fragments of this aglycon have been proposed [120–123]. The construction of the C₂₈-fragment (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.
Diene 49 (derived from inexpensive (R)-1-phenylethanol) and silyl ethers 50 (1:1 E/Z mixture) were reacted with a catalytic amount of (CF₃SO₂)₂NH in SO₂/CH₂Cl₂ (5:1) cooled to −78 °C. After neutralization of the acid catalyst with Et₃N 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 mCPBA (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 Me₂S 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 C₁₉ and C₂₀); the most sterically hindered alcohol at C₂₃ 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 Mel/Ag₂O giving Koert’s intermediate 57.

Scheme 9. Synthesis of Koert’s C₁₆–C₂₃ polyketide fragment of apoptolidin A.

9. The One-Pot Four-Component Synthesis of Polyfunctional Sulfones: Application to a Short Synthesis of the C₁–C₁₁ Fragment of Apoptolidin A

Another key intermediate in the total synthesis of apoptolidin A is the Nicolaou’s C₁–C₁₁-fragment (+)-65 the preparation of which requires 11 steps [152]. Applying our SO₂-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$_3$SO$_2$)$_2$NH 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 tetrybutylammonium 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 mCPBA. 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$_3$SiCC-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.](image)

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 allylsilane 67 and two different dienes, 66 and 69, the stereotetrad 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$_{N}$1 and E$_{1}$ cleavage of the benzylic C–O ether bond of the 1-phenylethoxy group are faster than the S$_{N}$1 and E$_{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 SO₂ promoted by Me₃SiOTf generated the product of mono-alkoxyallylation 68. The reaction 66 + 67 → 68 is faster than the reaction of monoallylsilane 66 with diene 67 + SO₂ because bisallylsilane 66 enjoys twice the β-silicon effect. In the presence of one equivalent of diene 66 the product of double oxyallylation is not formed; only sulfinate 68 is formed. It can be reacted without purification with SO₂ 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 BCl₃/Me₂C₆H₅ eliminated the phenylethyl group, giving a homoallylic alcohol that was not isolated but treated directly with (Me₃Si)₂NLi 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 Me₃SiCl giving a (Z)-enoxysilane that was reacted in situ with isobutyraldehyde and BF₃ etherate, providing aldol 73 which was a single stereomer isolated in 72% yield. Reduction of aldol 73 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 SO₂, 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. Sulfur dioxide induces a stereoselective C=C bond forming reactions between electron-rich dienes and alkenes (Umpolung through SO₂). 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 stereohetrad, which he used to construct rifamycin-S. A similar strategy has permitted us to obtain the Koert’s C₁₆–C₂₈ polyketide fragment of apoptolidin A. Under strongly acidic conditions, s-trans-1-alkoxydienes and enoxysilanes react with SO₂ 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 Nicolau’s C₁₋C₁₁ 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 SO₂-induced Umpolung reaction. With 2-{[methyl(diphenyl)methyl]allyl}methyl(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.

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