Use of sultines in the asymmetric synthesis of polypropionate antibiotics*

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Abstract: At low temperature and in the presence of an acid catalyst, SO₂ adds to 1,3-dienes equilibrating with the corresponding 3,6-dihydro-1,2-oxathiin-2-oxides (sultines). These compounds are unstable above −60 °C and equilibrate with the more stable 2,5-dihydrothiophene 1,1-dioxides (sulfolenes). The hetero-Diels–Alder additions of SO₂ are suprafacial and follow the Alder endo rule. The sultines derived from 1-oxy-substituted and 1,3-dioxy-disubstituted 1,3-dienes cannot be observed at −100 °C but are believed to be formed faster than the corresponding sulfolenes. In the presence of acid catalysts, the 6-oxy-substituted sultines equilibrate with zwitterionic species that react with electron-rich alkenes such as exoeylsilanes and allylsilanes, generating β,γ-unsaturated silyl sulfinates that can be desilylated and desulfinylated to generate polypropionate fragments containing up to three contiguous stereogenic centers and an (E)-alkene unit. Alternatively, the silyl sulfinates can be reacted with electrophiles to generate polyfunctional sulfones (one-pot, four-component synthesis of sulfones), or oxidized into sulfonyl chlorides and reacted with amines, then realizing a one-pot, four-component synthesis of polyfunctional sulfonamides. Using enantioselectically enriched dienes such as 1-[(R)- or 1-[(S)-phenylethoxy]-2-methyl-(E,E)-penta-1,3-dien-3-yl isobutyrate, derived from inexpensive (R)- or (S)-1-phenylethanol, enantiomerically enriched stereotriads are obtained in one-pot operations. The latter are ready for further chain elongation. This has permitted the development of expeditious total asymmetric syntheses of important natural products of biological interest such as the baconipyrones, rifamycin S, and apoptolidin A.

Keywords: apoptolidine; baconipyrones; hetero-Diels–Alder; rifamycin S; sulfur dioxide.

INTRODUCTION

The organic chemistry of SO₂ has been limited to the formation of arenesulfinic acids (Friedel–Crafts sulfinylation [1,2]), the copolymerization of SO₂ with alkenes or alkynes (polysulfone synthesis [3–5]), the synthesis of sulfinates by reaction with organometallic compounds [6–8], the ring-opening of oxiranes and oxetanes [8,9] leading to polysulfites [8,10–12], the synthesis of sulfoxides [8,13–15], the isomerization of alkenes via ene reaction/sigmatropic shift/retro-ene elimination sequence [16–22], and the cheletropic additions of conjugated polyenes [23–25] forming cyclic sulfones, as the [ω2s+π4s] ad-

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dition of SO₂ to isoprene producing 2,5-dihydro-3-methylthiophene-1,1-dioxide (sulfolene), a reaction known since 1914 [26,27].

Other cycloadditions of SO₂ have been described for the reaction of ketenes and ketimines [28–31], cyclic polyenes [32–34], and quadricyclane [35]. Homocheletropic additions of SO₂ to 1,4-di- enes have been reported [36–38]. The first examples of hetero-Diels–Alder additions of SO₂ involved highly reactive dienes 1 [39] and 3 [40]. In 1992, we reported that simple 1,3-dienes undergo hetero-Diels–Alder addition below −60 °C in the presence of a large excess of SO₂ and of a protic or Lewis acid promoter (Scheme 1). We showed that (E,E)-5-deuteropiperylene (6) equilibrates with sultine 7 at −80 °C. At −60 °C, 7 is converted into the more stable isomeric sultine 8, thus demonstrating the suprafaciability of the acid-catalyzed cycloaddition that obeys the Alder (endo) rule [41].

This led us to investigate the factors affecting the competition between the hetero-Diels–Alder and the cheletropic addition of SO₂. Our studies have been reviewed [42–45]. Apart from sultines resulting from reactions of SO₂ with 1-fluoro-1,3-dienes [46], sultines are less stable than their sulfolene isomers. They decompose into the corresponding 1,3-dienes and SO₂ above −50 °C [47–49]. With 1-alkoxy and 1-silyloxy-1,3-dienes 9, the sultines 10 are not seen at −100 °C as these dienes generate the corresponding sulfolenes 11 at this temperature [50]. Nevertheless, sultines 10 are believed to be formed before the sulfolenes. In the presence of an acid catalyst, they equilibrate with zwitterionic intermediates 12 that can be reacted with electron-rich alkenes 13, thus realizing a new C–C bond-forming reaction (Scheme 2) forming silyl sulfinates 14 [51,52].

In situ desilylation and stereoselective desulfination via retro-ene elimination of SO₂ from the β,γ-unsaturated sulfinic acids 14' [53–55] generates, in a one-pot operation, compounds 15 containing up to three contiguous stereogenic centers and one (E)-alkene unit [52]. The polypropionate fragments 15 so-obtained have their two extremities ready for further chain elongation without requiring deprotection and activation. Alternatively, the intermediate sulfinates 14 can be converted in the same pot into sulfones 16, thus realizing a one-pot, four-component synthesis of polyfunctional sulfones [56–60]. In situ oxidation of sulfinates 14 with Cl₂ or NCS provides the corresponding sulfonyl chlorides that can be reacted with primary and secondary amines to provide the corresponding sulfonamides 17, thus realizing a one-pot, four-component synthesis of polyfunctional sulfonamides [60,61]. We review here applications of our reaction cascade 9 + SO₂ → 10 → 12 + 13 → 14 → 15 to the asymmetric total synthesis of polypropionate antibiotics [62] and disclose further chemistry of sultines with allylsilanes [63].

Scheme 1 Examples of hetero-Diels–Alder additions of sulfur dioxide.
Synthesis of the cyclohexanone subunit of baconipyrones A and B and of the hydroxydiketone subunit of baconipyrones C and D

Baconipyrones A–D (18–21) were isolated in 1989 by Faulkner and coworkers from *Siphonaria bassoni* [64]. They constitute an exception to the normal polypropionic skeleton with their noncontiguous, ester-type backbone [65]. The first total synthesis of (−)-baconipyrone C was presented by Paterson and coworkers [66] in 2000 [67]. Applying the “naked sugar” methodology [68–71], Plumet and coworkers [72] obtained a 3,5-dihydroxycyclohexanone, which we showed happens to be a stereoisomer of the cyclohexanone subunit 22 of baconipyrones A and B [73]. We have prepared 22 in only three steps (58 % overall yield) starting with the enantiomerically enriched diene 24 (derived from 2-methyl-3-oxopentanal and inexpensive (S)-1-phenyl ethanol (97 % ee), in four steps, 61 % overall yield, applying Danishefsky’s method [74,75]) and enoxysilanes 25 (derived from penta-3-one). Thus, when a 1:2 mixtures of 24 + 25 is added to a 1:1 mixtures of SO₂/toluene containing 0.25 equiv of Tf₂NH cooled to −78 °C, a very intense yellow color appears (formation of diene SO₂ complex) which disappears after 24 h at −78 °C. After evaporation of the solvents (recovery of SO₂), the residue is treated with K₂CO₃ in i-PrOH/MeCN and heated to 80 °C in the presence of a catalytic amount of Pd(OAc)₂ and Ph₃P. This induces a stereoselective desulfinylation of the silyl sulfinate intermediate 26 [76] with formation of 27 and 28 that are separated by flash chromatography on silica gel and isolated pure in 67 and 13 % yield, respectively (Scheme 3). Acidic treatment of 26 also leads to desulfitation, but giving 27 and 28 in lower yields, probably because of the intrinsic instability of these compounds under acidic conditions (elimination of phenylethanol, hydrolysis of phenylethyl ether and retro-aldol, see below). Transesterification of enol ester 27 with Bu₃SnOMe [77,78] induces the desired stereoselective intramolecular aldol reaction (probably via 29 and 29’) and furnishes 22 after quantitative debenzylation.

The high diastereoselectivity observed in the reaction of \(24 \rightarrow 27 + 28\) (Scheme 3) can be interpreted in terms of a highly diastereoselective (suprafacial) hetero-Diels–Alder addition of \(\text{SO}_2\) to diene 24 in which the C–H bond of the phenylethyl ether resides in the \(\pi\)-plane of the cis-butadiene moiety (Scheme 4). Thus, the \(\text{SO}_2\) coordinated to the Lewis acid promoter attacks the face of the diene \(\text{syn}\) with respect to the methyl group of the phenylethyl ether group, giving sulfoxide 30 that is ionized irreversibly into zwitterion 31. There are two possible orientations, 32a and 32b, for the enoxysilane that command the \(\alpha,\beta\)-relative configuration in 33. As 27 is the major product, orientation 32a must be favored.

Scheme 3 First total asymmetric synthesis of cyclohexanone subunit of baconipyrones A and B.

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The Pd-catalyzed desulfination of silyl sulfinate 26 follows probably the mechanism proposed in Scheme 5. Although we have no proof for it, studies with trimethylsilyl 2-methylprop-2-enesulfinate have shown that Pd(OAc)₂ alone in MeCN does not catalyze the reaction. The presence of Ph₃P and i-PrOH is crucial for success, and intermediacy of allyl-Pd species has been established [76]. The remarkable chirality transfer 26 to 27 strongly supports a mechanism in which Pd(0) adds oxidatively (retention of configuration) into the C–SO₂SiMe₃ bond of 26 producing 33. Subsequent desulfonylation into 34 and protolysis of the Pd–SiMe₃ bond giving i-PrOSiMe₃ (driving force) is expected to generate hydride 35 that undergoes regioselective and stereoselective β-insertion of hydride into the allyl-Pd intermediate. An alternative mechanism is to invoke that the Pd(0) catalyst role is just to promote the Si-sulfinate bond cleavage that generates the corresponding β,γ-unsaturated sulfinic acids that in turn undergo classical retro-ene elimination of SO₂ producing 27 [76]. Further studies are obviously necessary for a better view.

Scheme 4 Face-selective hetero-Diels–Alder addition of SO₂, stereoselective zwitterionic intermediate quenching with enoxysilane.

Scheme 5 Possible mechanism for the Pd(0)-catalyzed desulfination of silyl sulfinites.
Enolization of ethylketone 27 with Et₃SiOTf/NEt₃ gives silyl enol ether 36 quantitatively (Scheme 6). Treatment of 36 with MeLi provides 37 (90%), which undergoes intramolecular Mukaiyama aldol reaction promoted by BF₃⋅Et₂O giving a 9:1 mixture of 38 and 39, two stereoisomers of 22. With Bu₄NF in THF at −15 °C, 37 furnishes a 5:1 mixture of 38 and 39, whereas in CH₂Cl₂ at −50 °C, a 1:3.5 mixture of 38 and 39 is formed in 76% yield. Compounds 40 and 41 can be obtained pure by flash chromatography on silica gel. Heating 37 with MeOH/NH₄Cl to 130 °C provides diketone 42 (41%). Debenzylation gives the hydroxydiketone 23, subunit of baconipyrones C and D. These transformations demonstrate the high efficiency and diversity of our synthetic approach to the polypropionate subunits of the baconipyrones and their stereomers.

Scheme 6 Synthesis of stereoisomeric 3,5-dihydroxycyclohexanones and of the hydroxydiketone subunit of baconipyrones C and D.

Expeditious asymmetric synthesis of the stereoheptad C₁₉–C₂₇ of rifamycins: Formal total synthesis of rifamycin S

Rifamycins [79–81] are antibiotics belonging to the group of naphthalenic ansamycins [82] characterized by an aliphatic bridge (polypropionate chain) linking two nonadjacent centers of an aromatic moiety. They are produced from Streptomyces mediterranei [83] and are active against a large variety of organisms; including bacteria, eukaryotes, and viruses [84]. Rifamycins have shown also antitumor [85–87] and anti-inflammatory activity [88], but at present are mainly used for the treatment of tuberculosis. Their antimicrobial activity is due to the inhibition of bacterial DNA-dependent RNA polymerase [89–92]. Several derivatives of rifamycin S (43) have been prepared, and many of them have shown promising activities [93–96].

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The first total synthesis of rifamycin S was reported by Kishi and coworkers in 1980 (Fig. 1) [97–100]. The stereoheptad 44 was 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 (45). Since then, several total asymmetric synthesis of 43 have been proposed [101–104], and the construction of the C19–C27 fragment [(-)-44 and analogs] of this antibiotic has become a challenging target for the testing of asymmetric synthetic methods and strategies [102,105–126]. Applying our reaction cascade (Scheme 2), we have developed a synthesis of Kishi’s intermediate 44 in 25 % yield that requires the isolation of only four synthetic intermediates (Scheme 6), starting from the readily available diene 24 (Scheme 3). The (Z)-enol ether 47 derived from ethyl ketone 27 (Scheme 3) reacts with 9-bromo-9-borabicyclo[3.3.1]nonane (BrBBN) in CH2Cl2 (silyl/boron exchange) [172] and then with aldehyde 48 to produce a 12.5:1 mixture of 49 and 9-epimer in 81 % yield. Pure 49 is reduced under Evans’ conditions [127] to give diol 50 (83 %), a stereoheptad equivalent to 44 of the asymmetric synthesis of rifamycin S. The latter is derived from 50 (does not have to be purified) as shown in Scheme 7 [128].

![Fig. 1 Kishi’s retrosynthesis of rifamycin S.](image)

![Scheme 7 Expeditious asymmetric synthesis of a stereoheptad: formal total synthesis of rifamycin S.](image)

**Short synthesis of the C1–C11 and C16–C28 fragments of apoptolidinone: Formal total synthesis of apoptolidin A**

Apoptolidin A (51) isolated from Nocardiopsis sp [129,130], and natural analogs B (52) and D (54) [131,132] are among the most interesting leads for cancer chemotherapy [133] as they induce apoptosis selectively in cancer cells (Fig. 2) [134–137].

Successful total synthesis of 1 has been achieved by the groups of Nicolaou [138–140] and Koert [141,142]. Syntheses of apoptolidinone A, the aglycone of 1, were reported by the groups of Sulikowsky [143], Crimmins [144], Nicolaou [138–140], and Koert [141,142]. In addition, several studies on the synthesis of fragments of apoptolidinones have been reported [137,145–155]. Applying our reaction cascade to diene 55 and enoxysilane 56, we have realized a rapid access (9 steps) to Koert’s C_{16–C_{28}} polyketide fragment 64 (Scheme 8) of apoptolidinones A and D [156]. This fragment is adequately protected for the glycosidation steps necessary in the construction of 51.

Scheme 8 Synthesis of Koert’s C_{16–C_{28}} polyketide fragment.

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The enantiomerically enriched (97 % ee) diene 55 [derived from inexpensive (R)-1-phenylethanol] and silyl ethers 56 (1:1 E/Z mixture) are reacted with (CF₃SO₂)₂NH in SO₂/CH₂Cl₂ (5:1) cooled to −78 °C. Solvent evaporation, alcoholysis with i-PrOH (80 °C), gives a 4:1 mixture of stereotriade 57 and its α,β,γ-anti,anti stereomer. This mixture is converted into their kinetic silyl enol ethers and oxidized with mCPBA (Rubottom oxidation [157]), giving 58, which undergoes Mukaiyama aldol coupling with aldehyde 59 [158–160] producing alken 60 (73 %). Ozonolysis of 60 provides an aldehyde that is allylated under Brown’s conditions [161]. The resulting homoallylic alcohol is equilibrated with the hemiacetal 61, which undergoes desilylation, hydrolysis of the 1-phenylethyl ether, and Fischer glycosidation on treatment with HCl/MeOH at 50 °C. The resulting triol is then acetylated selectively into diacetate 62 (Ac₂O/pyridine, 0–20 °C). After silylation of 62 into 63, Sharpless asymmetric dihydroxylation [162] furnishes a 4.5:1 mixture of the corresponding diol that is selectively monomethylated with Me₃SiCl giving the Koert’s 64 (68 %, after purification by flash column chromatography on silica gel).

Another key intermediate in the total synthesis of apoptolidin A is the Nicolaou’s C₁–C₁₁ fragment 69 [140]. We have developed an expeditious synthesis of 69 that requires the isolation of only three synthetic intermediates (Scheme 9) [163] and is based on our one-pot, four-component synthesis of sulfones. The combination of enoxysilanes 56, diene 65, SO₂, and iodide 66 provides, after acidic work-up (induced elimination of the β-silyloxy moiety), the (E,E)-dienone 67. Silyl ether and enol silyl ether formation is followed by oxidation with mCPBA. This generates an α-hydroxyketone which is not isolated but directly submitted to the Malaprade oxidation giving a carboxylic acid that is esterified in situ with diazomethane producing 68 (1:1 mixture of diastereomers). Dess–Martin oxidation of the primary alcohol 68 gives an aldehyde that is reacted, without purification, with Me₃SiC≡C–Li to give a 5:1 mixture of propargylic alcohols. They are silylated, and the sulfone moiety undergoes a Ramberg–Bäcklund rearrangement providing a 12:1 mixture of (E,E,E)-(E,E,Z)-triene-ester 69 (99 % ee) [164–166].

**Scheme 9** Expeditious synthesis of the Nicolaou’s C₁–C₁₁ fragment of apoptolidin A.

**Synthesis of long-chain polyketide fragments using allylsilanes**

When 1-oxy-1,3-dienes are mixed with allylsilanes and SO₂ in the presence of an acid catalyst, only products of ene reaction of the allylsilanes are observed. In contrast, when using 1,3-dioxy-1,3-dienes, the hetero-Diels–Alder of SO₂ with the latter can be faster than the ene-reaction cascade (hetero-
Diels–Alder reaction, zwitterion formation, allylation). For instance, dienes 70 and allylsilane 71 react with SO$_2$/CH$_2$Cl$_2$/Tf$_2$NSiMe$_3$ (cat.) at –78 °C producing 72 after work-up with Et$_3$NH$^+$TfO$^-$ in MeOH (Scheme 10). This induces retro-ene eliminations of SO$_2$ from β,γ-unsaturated sulfinic acid intermediates (see Scheme 2). S$_2$O$_2^-$ Substitution of allyl acetates 72 with (Me$_2$PhSi)$_2$Cu(CN)Li$_2$ generates allylsilanes that can be reacted again with 1,3-dioxy-1,3-dienes and SO$_2$ to produce long-chain polyketide fragments of type 73. The same compound 73b has been obtained in 34 % yield by reacting 2.5 equiv of diene 70b with 74 (Scheme 11). Treatment of ent-73b with MeLi-LiBr in ether at –78 °C generates a diethyl ketone (87 %) which is converted into the bis-enoxy silane 75 (76 %), the oxidation of which with IBX-MPO complex [167] (IBX = idooxybenzoic acid; MPO = 4-methoxypyridine-N-oxide) gives

Scheme 10 Stereoselective double-chain elongation through two successive hetero-Diels–Alder/allylation/retro-ene desulfinylation cascades.

Scheme 11
76 in 55 % yield. Work is underway to improve yields of the reaction sequence 74 → 73 → 75 → 76, to desymmetrize 76 and to convert it into long-chain polyketides of natural products of biological interest. In preliminary studies we have found that the double adduct of PhSH to 76 can be reduced stereoselectively with catecholborane and the CBS catalyst B-Me-(S)-CBS [168–171] giving 77 in 58 % yield. Using a 1:1 mixture of 74 and ent-70b, a 55 % yield of 78 is obtained. It is converted into ethyl ketone 79, then Nicolaou’s oxidation gives the corresponding enone that is reduced with CBS catalyst into an allyl alcohol that is protected as paramethoxybenzyl ether 80. This compound undergoes Sakurai’s allylation of aldehydes. For instance, with aldehyde 81, allylic alcohol 82 is formed as major product.

CONCLUSION

The unstable sultines resulting from the hetero-Diels–Alder addition of SO₂ to 1-oxy and 1,3-dioxy-1,3-dienes are useful intermediates for the stereoselective synthesis of polyketide and polypropionate antibiotics. Using enantiomerically enriched 1-(1-phenylethoxy)-1,3-dienes, enantiomerically pure sultine intermediates are formed that can be reacted with enoxysilanes or allylsilanes, in the presence of an acid catalyst. This produces β,γ-unsaturated silyl sulfinites that can be desulfinylated into polyketide or polypropionate fragments containing up to three stereogenic centers and on (E)-alkene units. The extremities of these fragments do not require deprotection and/or functional activation and can be used as such in all kinds of cross-aldol reactions, thus allowing the rapid construction of long-chain polypropionates. The efficiency of the method has been demonstrated by the total asymmetric syntheses of the cyclohexane subunits of bacopiyrones A and B, of the Kishi’s stereoheptads of rifamycin S, of the Nicolaou’s C₁₁–C₄₁ fragment of apoptolidin A, and of the Koert’s C₁₆–C₂₈ polyketide fragments of the same target. At this moment, stereotriad with α,β,γ-syn,anti-relative configuration have been obtained. Work is underway to develop conditions permitting the one-pot synthesis of the other stereomers. Combining the intermediates β,γ-unsaturated sulfinites resulting from our reaction cascade (hetero-Diels–Alder addition of SO₂, ionization of the sultine into zwitterionic species, and their quenching by enoxysilane or allylsilanes) with electrophiles has allowed one to propose efficient, one-pot, four-component syntheses of polyfunctional sulfones. By converting them into sulfonyl chloride intermediates, one-pot, four component syntheses of polyfunctional sulfonamides are possible.

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