Pure Appl. Chem., Vol. 80, No. 4, pp. 791–805, 2008.
doi:10.1351/pac200880040791

Use of sultines in the asymmetric synthesis of polypropionate antibiotics*

Pierre Vogel‡, Maris Turks, Laure Bouchez, Cotinica Craita, Xiaogen Huang, M. Carmen Murcia, Freddy Fonquerne, Charles Didier, and Christopher Flowers

Laboratory of Glycochemistry and Asymmetric Synthesis (LGSA), Swiss Federal Institute of Technology (EPFL), Batochime, CH-1015 Lausanne, Switzerland

Abstract: At low temperature and in the presence of an acid catalyst, SO_2 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 SO_2 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 enoxysilanes 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 enantiomerically enriched dienes such as 1-[(*R*)- or 1-(*S*)-phenylethyloxy]-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.

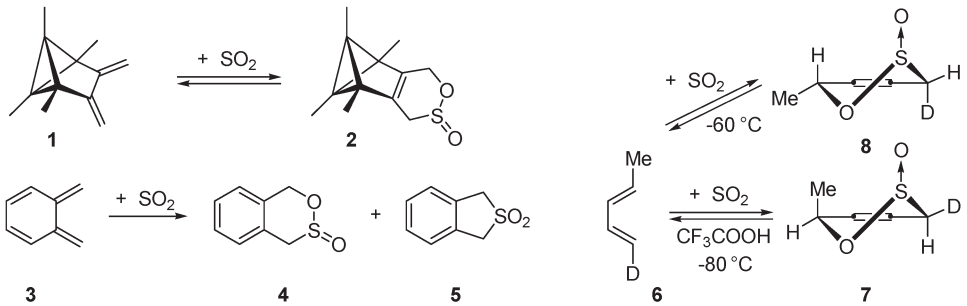
INTRODUCTION

The organic chemistry of SO_2 has been limited to the formation of arenesulfinic acids (Friedel–Crafts sulfinylation [1,2]), the copolymerization of SO_2 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 sulfones [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-

*Paper based on a presentation at the 21st International Congress for Heterocyclic Chemistry (ICHC 21), 15–20 July 2007, Sydney, Australia. Other presentations are published in this issue, pp. 669–805.
‡Corresponding author

dition of SO_2 to isoprene producing 2,5-dihydro-3-methylthiophene-1,1-dioxide (sulfolene), a reaction known since 1914 [26,27].

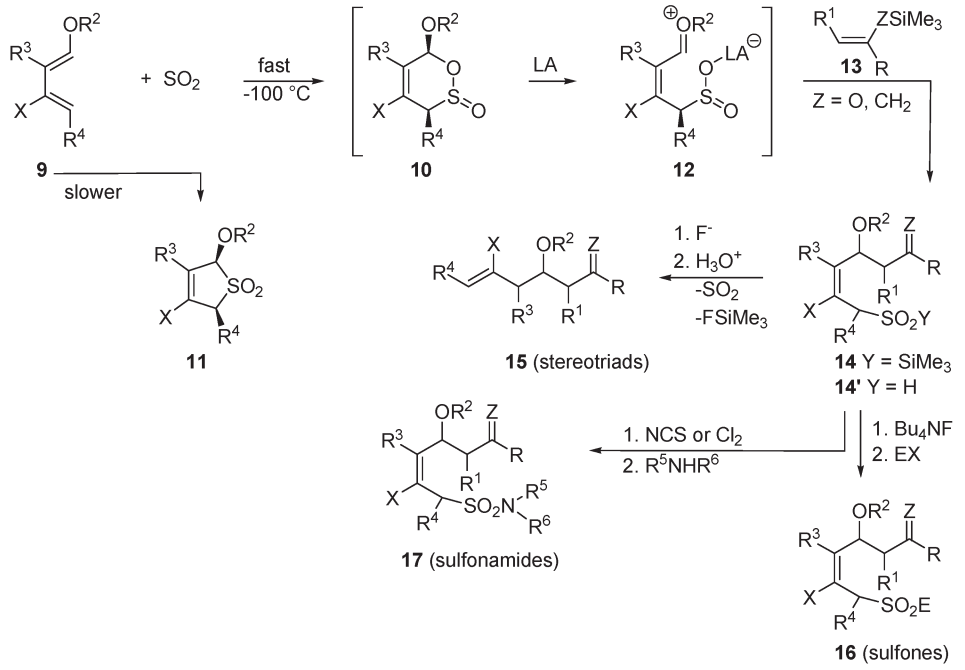
Other cycloadditions of SO_2 have been described for the reaction of ketenes and ketimines [28–31], cyclic polyenes [32–34], and quadricyclane [35]. Homocheletropic additions of SO_2 to 1,4-dienes have been reported [36–38]. The first examples of hetero-Diels–Alder additions of SO_2 involved highly reactive 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 SO_2 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].



Scheme 1 Examples of hetero-Diels–Alder additions of sulfur dioxide.

This led us to investigate the factors affecting the competition between the hetero-Diels–Alder and the cheletropic addition of SO_2. Our studies have been reviewed [42–45]. Apart from sultines resulting from reactions of SO_2 with 1-fluoro-1,3-dienes [46], sultines are less stable than their sulfolene isomers. They decompose into the corresponding 1,3-dienes and SO_2 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].

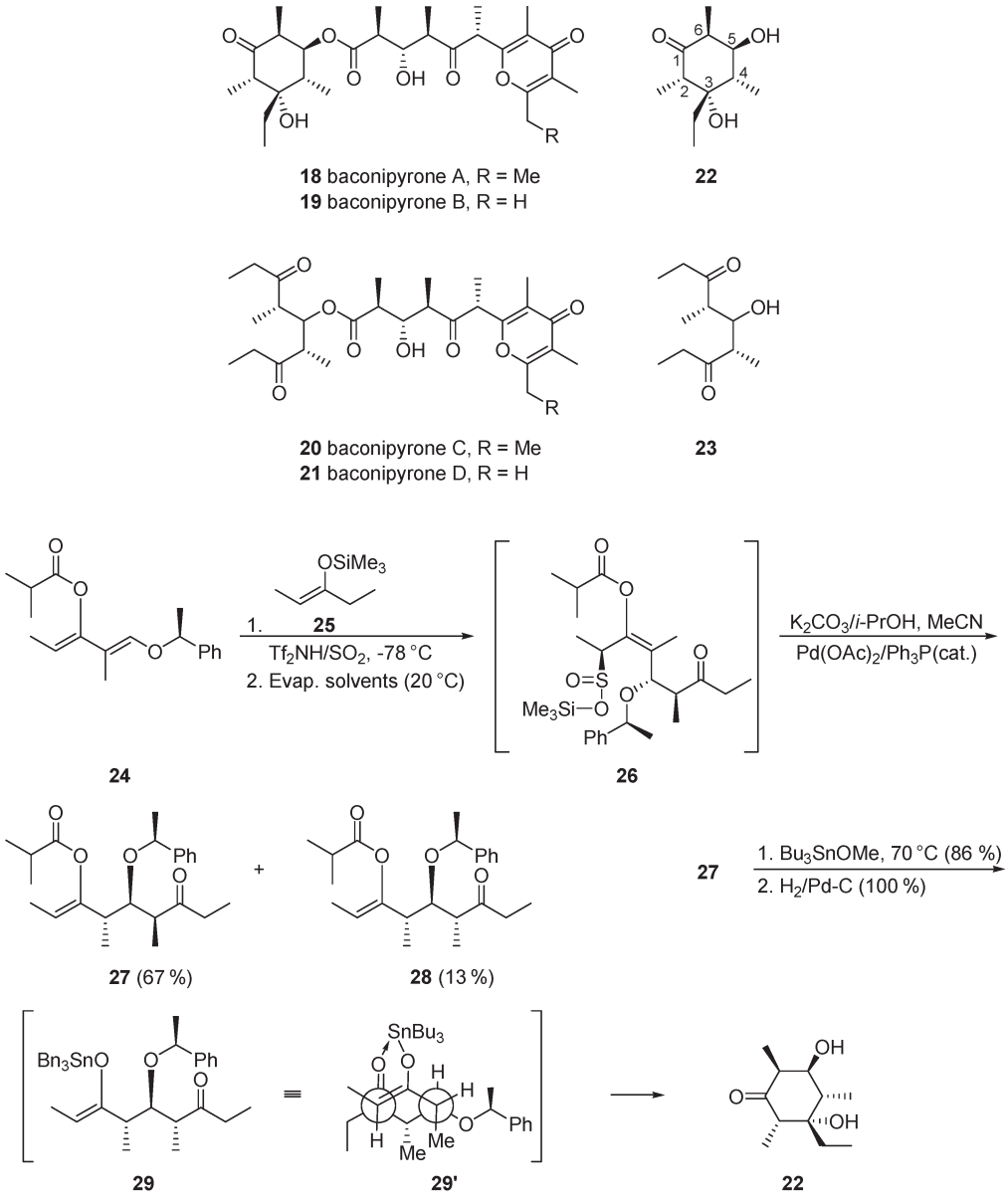
In situ desilylation and stereoselective desulfination via retro-ene elimination of SO_2 from the β,γ-unsaturated sulfinic acids **14'** [53–55] generates, in a one-pot operation, compounds **15** containing up to three contiguous stereogenic centers and one (*E*)-alkene unit [52]. The polypropionate 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 Cl_2 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 suflonamides [60,61]. We review here applications of our reaction cascade **9** + SO_2 → **10** → **12** + **13** → **14** → **15** to the asymmetric total synthesis of polypropionate antibiotics [62] and disclose further chemistry of sultines with allylsilanes [63].



Scheme 2 Reaction cascades via sultine ionization (umpolung with sulfur dioxide) permitting the one-pot syntheses of polypropionate stereotriades, polyfunctional sulfones, and sulfonamides.

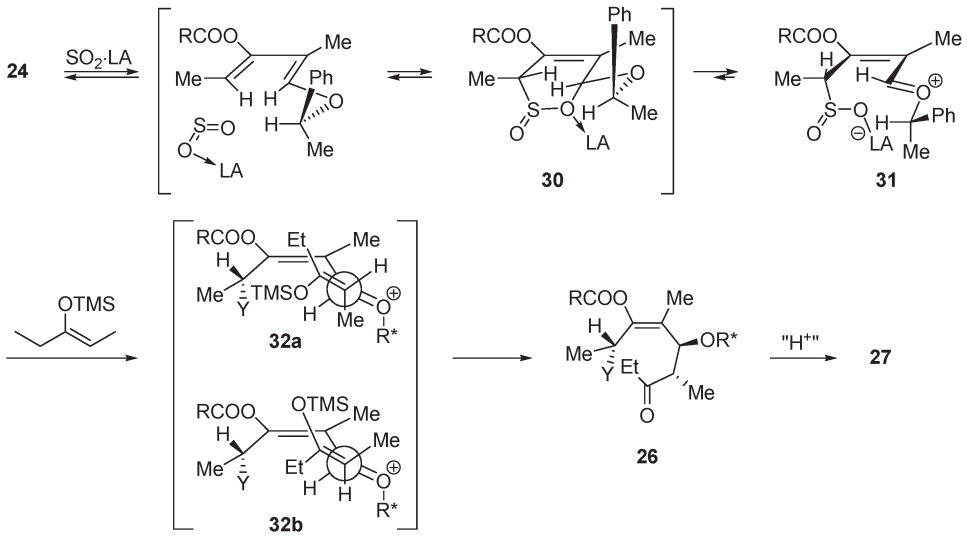
Synthesis of the cyclohexanone subunit of baconipyrones A and B and of the hydroxydiketone subunit of baconipyrones C and D

Baconipyrones A–D (**18–21**) were isolated in 1989 by Faulkner and coworkers from *Siphonaria baconi* [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 SO_2/toluene containing 0.25 equiv of Tf_2NH cooled to –78 °C, a very intense yellow color appears (formation of diene·SO_2 complex) which disappears after 24 h at –78 °C. After evaporation of the solvents (recovery of SO_2), the residue is treated with K_2CO_3 in *i*-PrOH/MeCN and heated to 80 °C in the presence of a catalytical amount of $Pd(OAc)_2$ and Ph_3P. 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 Bu_3SnOMe [77,78] induces the desired stereoselective intramolecular aldol reaction (probably via **29** $\rightleftarrows$ **29'**) and furnishes **22** after quantitative debenzylation.



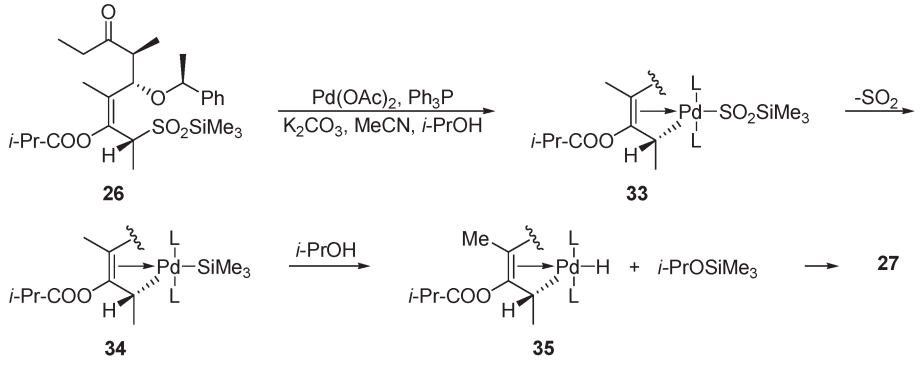
Scheme 3 First total asymmetric synthesis of cyclohexanone subunit of baconipyrones A and B.

The high diastereoselectivity observed in the reaction of **24** → **27** + **28** (Scheme 3) can be interpreted in terms of a highly diastereoselective (suprafacial) hetero-Diels–Alder addition of SO_2 to diene **24** in which the C–H bond of the phenylethyl ether resides in the π-plane of the *cis*-butadiene moiety (Scheme 4). Thus, the SO_2 coordinated to the Lewis acid promoter attacks the face of the diene *syn* with respect to the methyl group of the phenylethyl ether group, giving sultine **30** that is ionized irreversibly into zwitterion **31**. There are two possible orientations, **32a** and **32b**, for the enoxysilane that command the α,β-relative configuration in **33**. As **27** is the major product, orientation **32a** must be favored.



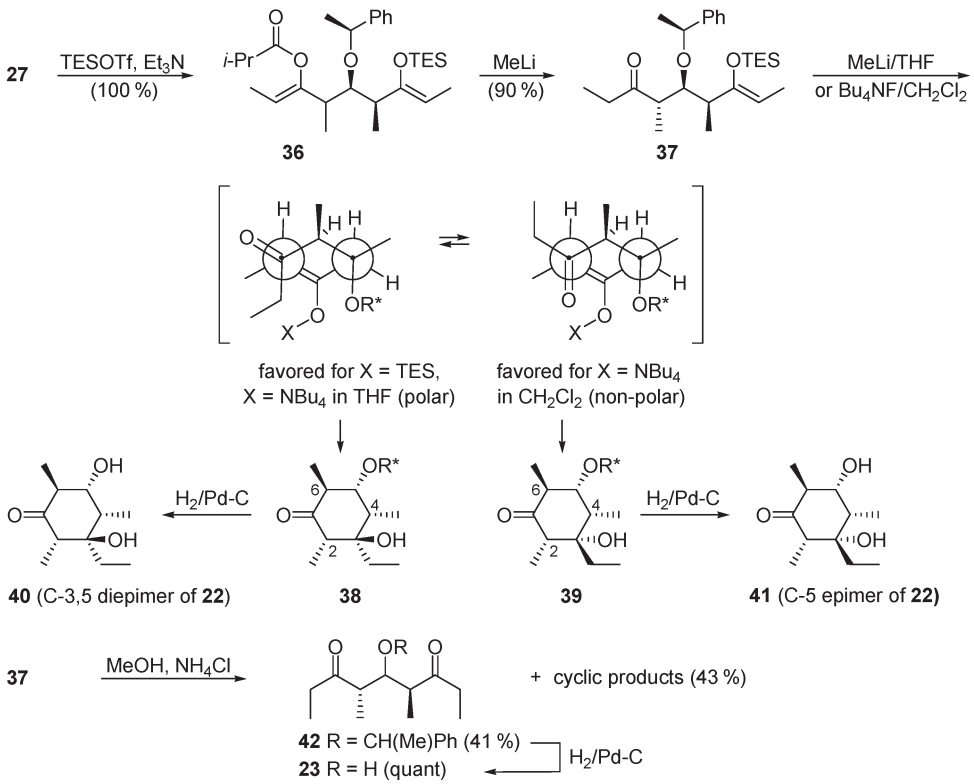
Scheme 4 Face-selective hetero-Diels–Alder addition of SO_2, stereoselective zwitterionic intermediate quenching with enoxysilane.

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 Ph_3P 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–SO_2SiMe_3 bond of **26** producing **33**. Subsequent desulfinylation into **34** and protolysis of the Pd–$SiMe_3$ bond giving *i*-PrOSiMe_3 (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 SO_2 producing **27** [76]. Further studies are obviously necessary for a better view.



Scheme 5 Possible mechanism for the Pd(0)-catalyzed desulfination of silyl sulfinates.

Enolization of ethylketone **27** with Et_3SiOTf/NEt_3 gives silyl enol ether **36** quantitatively (Scheme 6). Treatment of **36** with MeLi provides **37** (90 %), which undergoes intramolecular Mukaiyama aldol reaction promoted by $BF_3{\cdot}Et_2O$ giving a 9:1 mixture of **38** and **39**, two stereoisomers of **22**. With Bu_4NF in THF at –15 °C, **37** furnishes a 5:1 mixture of **38** and **39**, whereas in CH_2Cl_2 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 $MeOH/NH_4Cl$ 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 C_{19}–C_{27} 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].

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 (2*S*)-3-benzyloxy-2-methylpropanal (**45**). Since then, several total asymmetric synthesis of **43** have been proposed [101–104], and the construction of the C_{19}–C_{27} 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 CH_2Cl_2 (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].

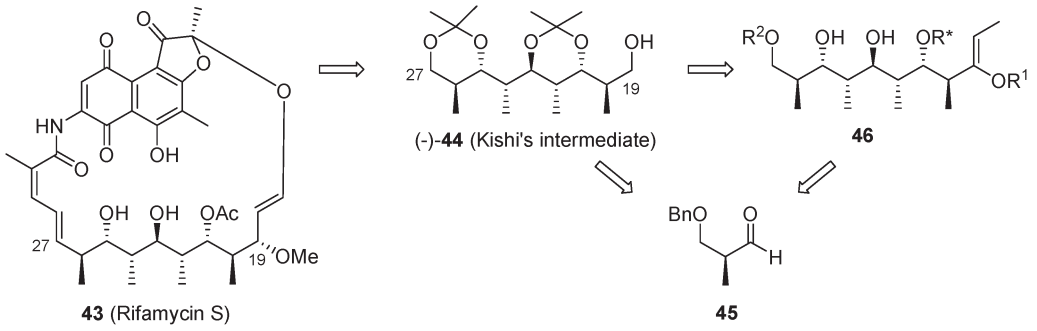
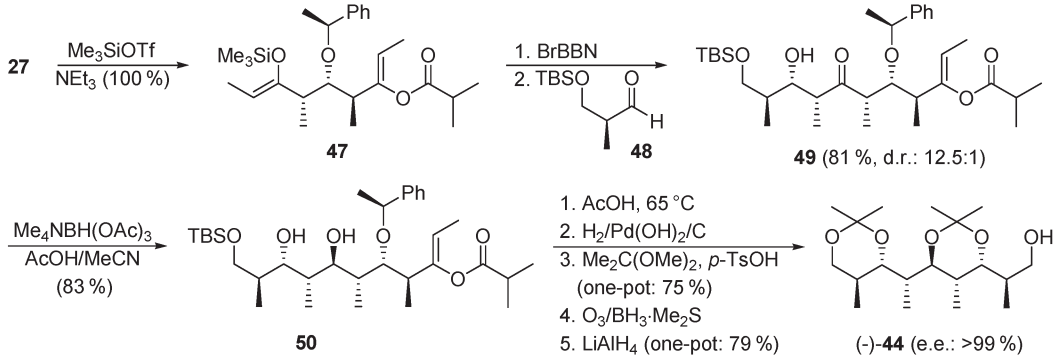


Fig. 1 Kishi's retrosynthesis of rifamycin S.



Scheme 7 Expeditious asymmetric synthesis of a stereoheptad: formal total synthesis of rifamycin S.

Short synthesis of the C_1–C_{11} and C_{16}–C_{28} 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].

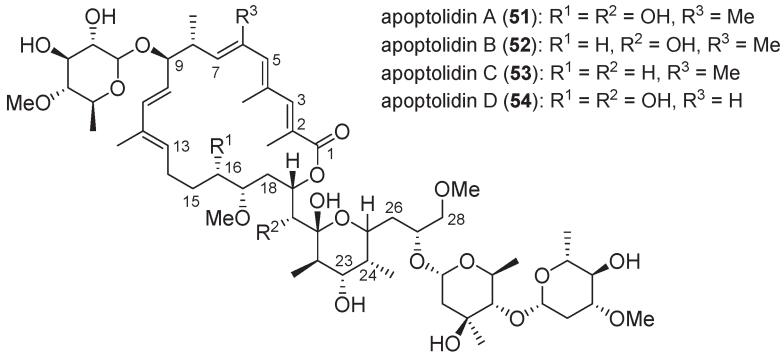
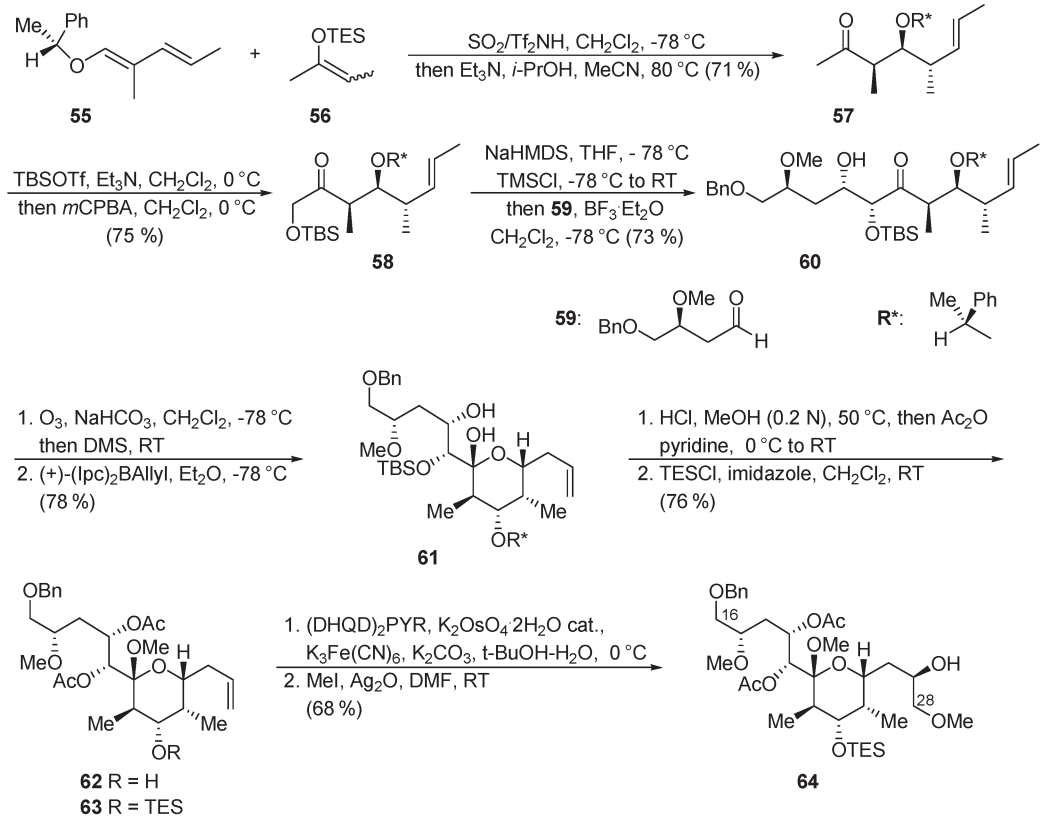


Fig. 2 Structures of apoptolidins.

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].

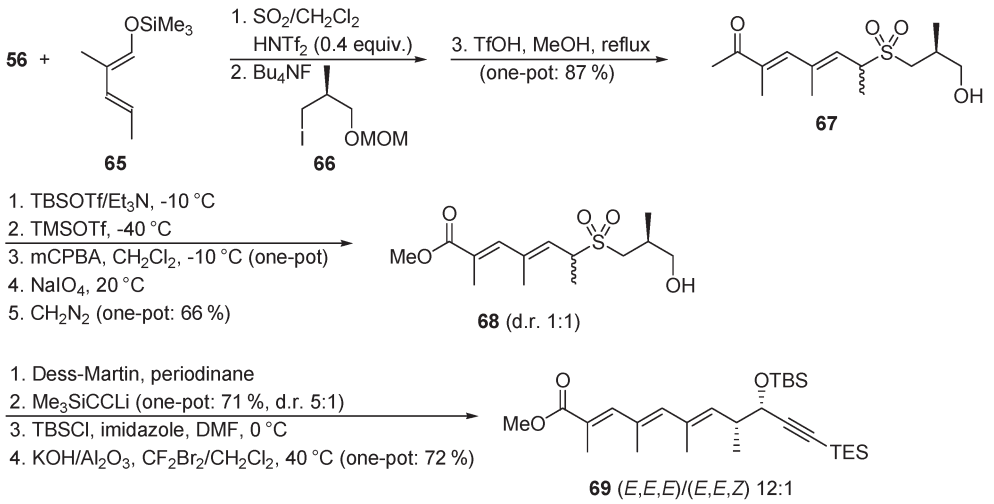
Applying our reaction cascade to diene **55** and enoxysilane **56**, we have realized a rapid access (9 steps) to Koert's C_{16}–C_{28} polyketide fragment **64** (Scheme 8) of apoptolidinones A and D [156]. This fragment is adequately protected for the glycosidation steps necessary in the construction of **51**.



Scheme 8 Synthesis of Koert's C16–C28 polyketide fragment.

The enantiomerically enriched (97 % ee) diene **55** [59] [derived from inexpensive (*R*)-1-phenylethanol] and silyl ethers **56** (1:1 *E*/*Z* mixture) are reacted with $(CF_3SO_2)_2NH$ in SO_2/CH_2Cl_2 (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 alkene **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** (Ac_2O/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 MeI/Ag_2O 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 C_1–C_{11} 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**, SO_2, 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 $Me_3SiC{\equiv}C$–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].

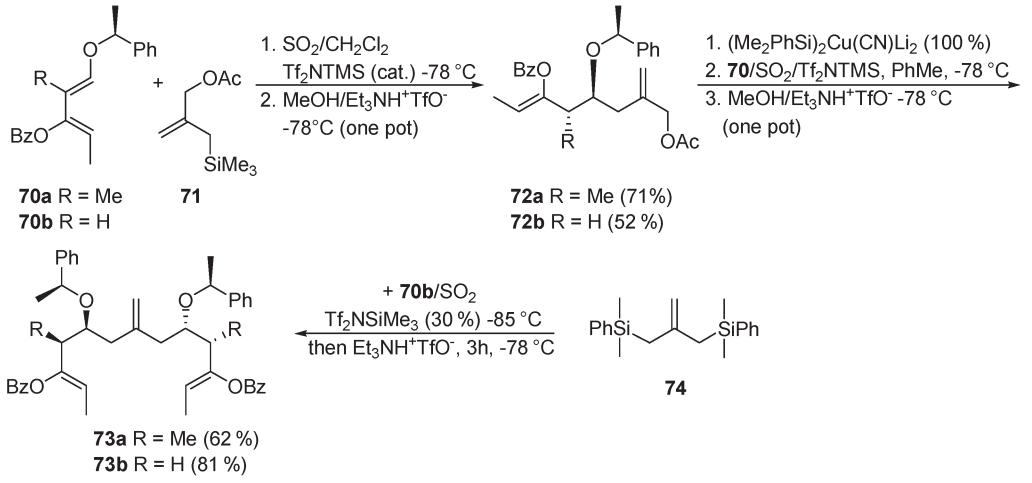


Scheme 9 Expeditious synthesis of the Nicolaou's C_1–C_{11} fragment of apoptolidin A.

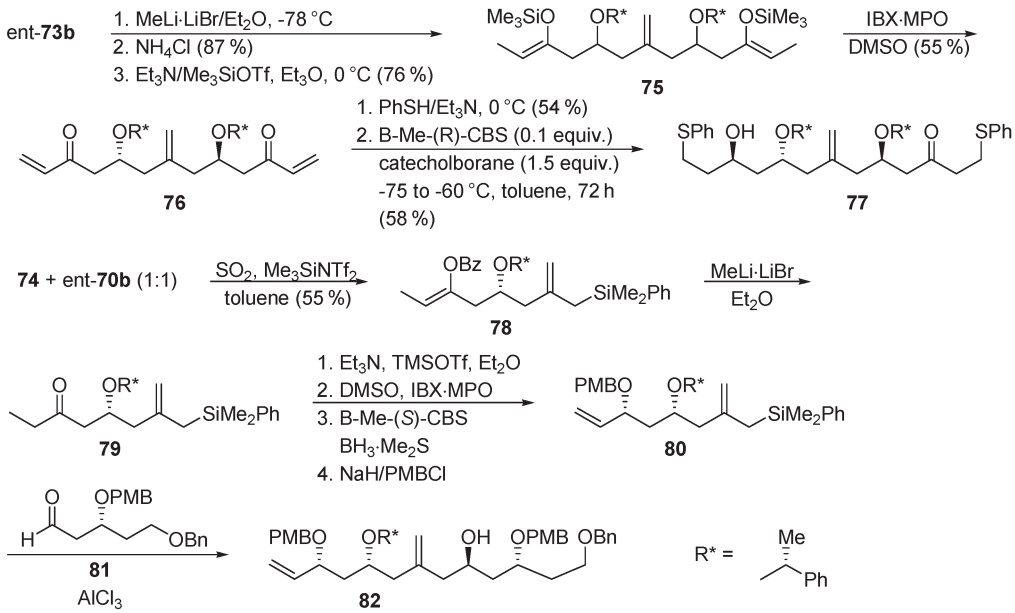
Synthesis of long-chain polyketide fragments using allylsilanes

When 1-oxy-1,3-dienes are mixed with allylsilanes and SO_2 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 SO_2 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 $SO_2/CH_2Cl_2/Tf_2NSiMe_3$ (cat.) at –78 °C producing **72** after work-up with $Et_3NH^+TfO^-$ in MeOH (Scheme 10). This induces retro-ene eliminations of SO_2 from β,γ-unsaturated sulfinic acid intermediates (see Scheme 2). S_N2' Substitution of allyl acetates **72** with $(Me_2PhSi)_2Cu(CN)Li_2$ 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-enoxysilane **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 SO_2 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-phenylethyloxy)-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 sulfinates 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 baconipyrones A and B, of the Kishi's stereoheptads of rifamycin S, of the Nicolaou's C_1–C_{11} fragment of apoptolidin A, and of the Koert's C_{16}–C_{28} 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 sulfinates resulting from our reaction cascade (hetero-Diels–Alder addition of SO_2, 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 polyfunctionnal sulfones. By converting them into sulfonyl chloride intermediates, one-pot, four component syntheses of polyfunctional sulfonamides are possible.

ACKNOWLEDGMENTS

We are grateful to the Swiss National Science Foundation (Bern), the Roche Research Foundation (Basel), the "Secrétariat d'Etat à l'Education et à la Recherche" (SER) (European FP6 project TRIoH), and the CSCS (Manno, Switzerland) for financial support.

REFERENCES

1. C. Friedel, J. Crafts. *Ann.* **14**, 442 (1888).
2. E. Knoevenagel, H. Kenner. *Ber. Dtsch. Chem.* **41**, 3318 (1908).
3. C. S. Marvel, F. J. Glavis. *J. Am. Chem. Soc.* **60**, 2622 (1938).
4. C. S. Marvel, L. F. Audrieth, W. H. Sharkey. *J. Am. Chem. Soc.* **64**, 1229 (1942).
5. Z. Florjanczyk. *Prog. Polym. Sci.* **16**, 509 (1991).
6. W. Kitching, C. W. Fong. *Organomet. Chem. Rev., Sect. A: Sub. Rev.* **5**, 281 (1970).
7. A. Wojcicki. *Adv. Organomet. Chem.* **12**, 31 (1974).
8. Z. Florjanczyk, D. Raducha. *Pol. J. Chem.* **69**, 481 (1995).
9. Z. Florjanczyk, D. Raducha. *Makromol. Chem.* **194**, 2605 (1993).
10. K. Soga, I. Hattori, J. Kinoshita, S. Ikeda. *J. Polym. Sci., Part A: Polym. Chem.* **15**, 745 (1977).
11. K. Soga, K. Kiyohara, I. Hattori, S. Ikeda. *Makromol. Chem.* **181**, 2151 (1980).

12. J. G. Tillett. *Chem. Rev.* **76**, 747 (1976).
13. N. S. Simpkins. In *Tetrahedron Chemistry Series*, Pergamon Press, Elmsford, NY (1993).
14. H. Takeuchi, T. Nagai, N. Tokura. *Bull. Chem. Soc. Jpn.* **46**, 695 (1973).
15. D. H. R. Barton, B. Lacher, B. Misterkiewicz, S. Z. Zard. *Tetrahedron* **44**, 1153 (1988).
16. M. M. Rogic, D. Masilamani. *J. Am. Chem. Soc.* **99**, 5219 (1977).
17. D. Masilamani, M. M. Rogic. *J. Am. Chem. Soc.* **100**, 4634 (1978).
18. G. Capozzi, V. Lucchini, F. Marcuzzi, G. Melloni. *Tetrahedron Lett.* **21**, 3289 (1980).
19. D. Markovic, P. Vogel. *Angew. Chem., Int. Ed.* **43**, 2928 (2004).
20. D. Markovic, P. Steunenberg, M. Ekstrand, P. Vogel. *Chem. Commun.* 2444 (2004).
21. D. Markovic, P. Vogel. *Org. Lett.* **6**, 2693 (2004).
22. D. Markovic, A. Varela-Alvarez, J. A. Sordo, P. Vogel. *J. Am. Chem. Soc.* **128**, 7782 (2006).
23. R. B. Woodward, R. Hoffmann. *The Conservation of Orbital Symmetry*, Academic Press, New York (1970).
24. S. D. Turk, R. L. Cobb. In *1,4-Cycloaddition Reactions*, J. Hamer (Ed.), p. 13, Academic Press, New York (1967).
25. M. J. S. Dewar. *J. Am. Chem. Soc.* **106**, 209 (1984).
26. G. de Bruin. *Proc. K. Ned. Akad. Wet.* **17**, 585 (1914).
27. H. J. Backer, J. Strating. *Recl. Trav. Chim. Pays-Bas* **53**, 525 (1934).
28. A. Gomes, M. M. Joullie. *Chem. Commun.* 935 (1967).
29. J. M. Bohen, M. M. Joullie. *Tetrahedron Lett.* **12**, 1815 (1971).
30. J. M. Decazes, J. L. Luche, H. B. Kagan, R. Parthasarathy, J. Ohrt. *Tetrahedron Lett.* **13**, 3633 (1972).
31. D. Bellus. *Helv. Chim. Acta* **58**, 2509 (1975).
32. L. A. Paquette, U. Jacobsson, M. Oku. *J. Chem. Soc., Chem. Commun.* 115 (1975).
33. H. Hogeveen, H. Jorritsma, P. W. Kwant. *Tetrahedron Lett.* **16**, 1795 (1975).
34. J. Gasteiger, R. Huisgen. *J. Am. Chem. Soc.* **94**, 6541 (1972).
35. O. De Lucchi, V. Lucchini. *J. Chem. Soc., Chem. Commun.* 464 (1982).
36. O. De Lucchi, V. Lucchini. *J. Chem. Soc., Chem. Commun.* 1105 (1982).
37. J. M. Roulet, B. Deguin, P. Vogel. *J. Am. Chem. Soc.* **116**, 3639 (1994).
38. J. M. Roulet, P. Vogel, F. Wiesemann, A. A. Pinkerton. *Tetrahedron* **51**, 1685 (1995).
39. R. F. Heldeweg, H. Hogeveen. *J. Am. Chem. Soc.* **98**, 2341 (1976).
40. T. Durst, L. Tetreault-Ryan. *Tetrahedron Lett.* **19**, 2353 (1978).
41. B. Deguin, P. Vogel. *J. Am. Chem. Soc.* **114**, 9210 (1992).
42. P. Vogel, J. A. Sordo. *Curr. Org. Chem.* **10**, 2007 (2006).
43. D. Suarez, T. L. Sordo, J. A. Sordo. *J. Org. Chem.* **60**, 2848 (1995).
44. D. Suarez, J. Gonzalez, T. L. Sordo, J. A. Sordo. *J. Org. Chem.* **59**, 8058 (1994).
45. D. Suarez, T. L. Sordo, J. A. Sordo. *J. Am. Chem. Soc.* **116**, 763 (1994).
46. E. Roversi, R. Scopelliti, E. Solari, R. Estoppey, P. Vogel, P. Brana, B. Menendez, J. A. Sordo. *Chem.—Eur. J.* **8**, 1336 (2002).
47. F. Monnat, P. Vogel, J. A. Sordo. *Helv. Chim. Acta* **85**, 712 (2002).
48. E. Roversi, F. Monnat, P. Vogel, K. Schenk, P. Roversi. *Helv. Chim. Acta* **85**, 733 (2002).
49. E. Roversi, P. Vogel. *Helv. Chim. Acta* **85**, 761 (2002).
50. F. Monnat, P. Vogel, V. M. Rayon, J. A. Sordo. *J. Org. Chem.* **67**, 1882 (2002).
51. B. Deguin, J. M. Roulet, P. Vogel. *Tetrahedron Lett.* **38**, 6197 (1997).
52. J. M. Roulet, G. Puhr, P. Vogel. *Tetrahedron Lett.* **38**, 6201 (1997).
53. J. B. Baudin, S. Julia. *Bull. Soc. Chim. Fr.* **132**, 196 (1995).
54. W. L. Mock, R. M. Nugent. *J. Org. Chem.* **43**, 3433 (1978).
55. R. S. Garigipati, J. A. Morton, S. M. Weinreb. *Tetrahedron Lett.* **24**, 987 (1983).
56. V. Narkevitch, K. Schenk, P. Vogel. *Angew. Chem., Int. Ed.* **39**, 1806 (2000).
57. V. Narkevitch, S. Megevand, K. Schenk, P. Vogel. *J. Org. Chem.* **66**, 5080 (2001).

58. V. Narkevitch, P. Vogel, K. Schenk. *Helv. Chim. Acta* **85**, 1674 (2002).
59. X. G. Huang, P. Vogel. *Synthesis* 232 (2002).
60. L. Bouchez, M. Turks, S. R. Dubbaka, F. Fonquerne, C. Craita, S. Laclef, P. Vogel. *Tetrahedron* **61**, 11473 (2005).
61. L. C. Bouchez, S. R. Dubbaka, M. Turks, P. Vogel. *J. Org. Chem.* **69**, 6413 (2004).
62. P. Vogel, M. Turks, L. C. Bouchez, D. Markovic, A. Varela-Alvarez, J. A. Sordo. *Acc. Chem. Res.* **40**, 931 (2007).
63. M. Turks, F. Fonquerne, P. Vogel. *Org. Lett.* **6**, 1053 (2004).
64. D. C. Manker, D. J. Faulkner, T. J. Stout, J. Clardy. *J. Org. Chem.* **54**, 5371 (1989).
65. D. J. Brecknell, L. A. Collett, M. T. Davies-Coleman, M. J. Garson, D. D. Jones. *Tetrahedron* **56**, 2497 (2000).
66. I. Paterson, D. Y. K. Chen, J. L. Acena, A. S. Franklin. *Org. Lett.* **2**, 1513 (2000).
67. D. G. Gillingham, A. H. Hoveyda. *Angew. Chem., Int. Ed.* **46**, 3860 (2007).
68. K. A. Black, P. Vogel. *J. Org. Chem.* **51**, 5341 (1986).
69. A. Warm, P. Vogel. *J. Org. Chem.* **51**, 5348 (1986).
70. P. Vogel, D. Fattori, F. Gasparini, C. Ledrian. *Synlett* 173 (1990).
71. P. Vogel, J. Cossy, J. Plumet, O. Arjona. *Tetrahedron* **55**, 13521 (1999).
72. O. Arjona, R. Menchaca, J. Plumet. *Org. Lett.* **3**, 107 (2001).
73. M. Turks, M. C. Murcia, R. Scopelliti, P. Vogel. *Org. Lett.* **6**, 3031 (2004).
74. S. Danishefsky, M. Bednarski, T. Izawa, C. Maring. *J. Org. Chem.* **49**, 2290 (1984).
75. S. Danishefsky, T. Kitahara. *J. Am. Chem. Soc.* **96**, 7807 (1974).
76. X. G. Huang, C. Craita, P. Vogel. *J. Org. Chem.* **69**, 4272 (2004).
77. M. Pereyre, B. Bellegarde, J. Mendelsohn, J. Valade. *J. Organomet. Chem.* **11**, 97 (1968).
78. S. S. Labadie, J. K. Stille. *Tetrahedron* **40**, 2329 (1984).
79. K. L. Rinehart. *Acc. Chem. Res.* **5**, 57 (1972).
80. K. L. Rinehart, S. Shield. *Fortsch. Chem. Org. Naturst.* **33**, 231 (1976).
81. W. Wehrli. *Top. Curr. Chem.* **72**, 21 (1977).
82. V. Prelog. *Pure Appl. Chem.* **6**, 545 (1963).
83. P. Sensi, S. Furesz, G. Maggi, G. Maffi. *Antimicrob. Agents Chemother.* 699 (1966).
84. S. K. Arora. *J. Med. Chem.* **28**, 1099 (1985).
85. U. R. Joss, A. M. Hughes, M. Calvin. *Nature—New Biology* **242**, 88 (1973).
86. C. Gurgo, M. Green, R. Ray. *J. Natl. Cancer Inst.* **49**, 61 (1972).
87. S. S. Yang, R. G. Smith, R. C. Ting, G. Lancini, M. S. Reitz, R. C. Gallo, F. M. Herrera. *J. Natl. Cancer Inst.* **49**, 7 (1972).
88. S. Spisani, S. Traniello, C. Martuccio, O. Rizzuti, L. Cellai. *Inflammation* **21**, 391 (1977).
89. G. Hartmann, K. O. Honikel, F. Knusel, J. Nuesch. *Biochem. Biophys. Acta* **145**, 843 (1967).
90. H. Umezawa, S. Mizuno, H. Yamazaki, K. Nitta. *J. Antibiot.* **21**, 234 (1968).
91. A. Bacchi, G. Pelizzi, M. Nebuloni, P. Ferrari. *J. Med. Chem.* **41**, 2319 (1998).
92. G. Lancini, M. Cavallari. *Drugs and the Pharmaceutical Sciences*, Marcel Dekker, New York (1997).
93. R. J. O'Brien, M. A. Lyle, D. E. Snider Jr. *Rev. Infect. Dis.* **9**, 519 (1987).
94. R. N. Brogden, A. Fitton. *Drugs* **47**, 983 (1994).
95. J. Barluenga, F. Aznar, A. B. Garcia, M. P. Cabal, J. J. Palacios, M. A. Menendez. *Bioorg. Med. Chem. Lett.* **16**, 5717 (2006).
96. A. H. Jobanputra, G. D. Patil, R. Z. Sayyed, A. B. Chaudhari, S. B. Chincholkar. *Indian J. Biotechnol.* **2**, 370 (2003).
97. H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson, Y. Kishi. *J. Am. Chem. Soc.* **102**, 7962 (1980).
98. H. Iio, H. Nagaoka, Y. Kishi. *J. Am. Chem. Soc.* **102**, 7965 (1980).
99. Y. Kishi. *Pure Appl. Chem.* **53**, 1163 (1981).

100. H. Nagaoka, Y. Kishi. *Tetrahedron* **37**, 3873 (1981).
101. S. Hanessian, J. R. Pougny, I. K. Boessenkool. *J. Am. Chem. Soc.* **104**, 6164 (1982).
102. T. Katsuki, T. Hanamoto, M. Yamaguchi. *Chem. Lett.* 117 (1989).
103. I. Paterson, C. K. Mcclure, R. C. Schumann. *Tetrahedron Lett.* **30**, 1293 (1989).
104. R. Chenevert, Y. S. Rose. *J. Org. Chem.* **65**, 1707 (2000).
105. E. J. Corey, T. Hase. *Tetrahedron Lett.* **20**, 335 (1979).
106. S. Masamune, B. Imperiali, D. S. Garvey. *J. Am. Chem. Soc.* **104**, 5528 (1982).
107. S. Masamune, P. A. McCarthy. In *Macrolide Antibiotics*, S. Omura (Ed.), pp. 127–198, Academic Press, New York (1984).
108. I. Paterson, M. M. Mansuri. *Tetrahedron* **41**, 3569 (1985).
109. A. V. R. Rao, J. S. Yadav, V. Vidyasagar. *J. Chem. Soc., Chem. Commun.* 55 (1985).
110. A. V. R. Rao, J. S. Yadav, C. S. Rao. *Tetrahedron Lett.* **27**, 3297 (1986).
111. W. R. Roush, A. D. Palkowitz. *J. Am. Chem. Soc.* **109**, 953 (1987).
112. S. J. Danishefsky, D. C. Myles, D. F. Harvey. *J. Am. Chem. Soc.* **109**, 862 (1987).
113. F. E. Ziegler, A. Kneisley. *Tetrahedron Lett.* **28**, 1725 (1987).
114. F. E. Ziegler, W. T. Cain, A. Kneisley, E. P. Stirchak, R. T. Wester. *J. Am. Chem. Soc.* **110**, 5442 (1988).
115. G. Tarara, D. Hoppe. *Synthesis* 89 (1989).
116. M. Born, C. Tamm. *Helv. Chim. Acta* **73**, 2242 (1990).
117. W. R. Roush, A. D. Palkowitz, K. Ando. *J. Am. Chem. Soc.* **112**, 6348 (1990).
118. T. Harada, Y. Kagamihara, S. Tanaka, K. Sakamoto, A. Oku. *J. Org. Chem.* **57**, 1637 (1992).
119. M. Lautens, R. K. Belter. *Tetrahedron Lett.* **33**, 2617 (1992).
120. M. Miyashita, K. Yoshihara, K. Kawamine, M. Hoshino, H. Irie. *Tetrahedron Lett.* **34**, 6285 (1993).
121. T. Harada, A. Oku. *Synlett* 95 (1994).
122. J. S. Yadav, C. S. Rao, S. Chandrasekhar, A. V. R. Rao. *Tetrahedron Lett.* **36**, 7717 (1995).
123. S. Hanessian, W. G. Wang, Y. H. Gai, E. Olivier. *J. Am. Chem. Soc.* **119**, 10034 (1997).
124. J. A. Marshall, M. R. Palovich. *J. Org. Chem.* **63**, 3701 (1998).
125. K. W. Hunt, P. A. Grieco. *Org. Lett.* **3**, 481 (2001).
126. S. BouzBouz, J. Cossy. *Org. Lett.* **3**, 3995 (2001).
127. D. A. Evans, K. T. Chapman, E. M. Carreira. *J. Am. Chem. Soc.* **110**, 3560 (1988).
128. M. Turks, X. G. Huang, P. Vogel. *Chem.—Eur. J.* **11**, 465 (2005).
129. J. W. Kim, H. Adachi, K. ShinYa, Y. Hayakawa, H. Seto. *J. Antibiot.* **50**, 628 (1997).
130. Y. Hayakawa, J. W. Kim, H. Adachi, K. ShinYa, K. Fujita, H. Seto. *J. Am. Chem. Soc.* **120**, 3524 (1998).
131. P. A. Wender, M. Sukopp, K. E. Longcore. *Org. Lett.* **7**, 3025 (2005).
132. P. A. Wender, K. E. Longcore. *Org. Lett.* **9**, 691 (2007).
133. A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla. *Proc. Natl. Acad. Sci. USA* **97**, 14766 (2000).
134. A. R. Salomon, D. W. Voehringer, L. A. Herzenberg, C. Khosla. *Chem. Biol.* **8**, 71 (2001).
135. A. R. Salomon, Y. B. Zhang, H. Seto, C. Khosla. *Org. Lett.* **3**, 57 (2001).
136. L. Benitez-Bribiesca. In *When Cells Die*, R. A. Lockshin, Z. Zakeri, J. L. Tilly (Eds.), pp. 453–492, Wiley-Liss, New York (1998).
137. P. T. Daniel, U. Koert, J. Schuppan. *Angew. Chem., Int. Ed.* **45**, 872 (2006).
138. K. C. Nicolaou, Y. W. Li, K. C. Fylaktakidou, H. J. Mitchell, K. Sugita. *Angew. Chem., Int. Ed.* **40**, 3854 (2001).
139. K. C. Nicolaou, K. C. Fylaktakidou, H. Monenschein, Y. W. Li, B. Weyershausen, H. J. Mitchell, H. X. Wei, P. Guntupalli, D. Hepworth, K. Sugita. *J. Am. Chem. Soc.* **125**, 15433 (2003).
140. K. C. Nicolaou, Y. W. Li, K. Sugita, H. Monenschein, P. Guntupalli, H. J. Mitchell, K. C. Fylaktakidou, D. Vourloumis, P. Giannakakou, A. O'Brate. *J. Am. Chem. Soc.* **125**, 15443 (2003).

141. H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, R. Mahrwald, B. Ziemer, M. E. J. Garcia, U. Koert. *Angew. Chem., Int. Ed.* **43**, 4597 (2004).
142. H. Wehlan, M. Dauber, M. T. M. Fernaud, J. Schuppan, S. Keiper, R. Mahrwald, M. E. J. Garcia, U. Koert. *Chem.—Eur. J.* **12**, 7378 (2006).
143. B. Wu, Q. S. Liu, G. A. Sulikowski. *Angew. Chem., Int. Ed.* **43**, 6673 (2004).
144. M. T. Crimmins, H. S. Christie, K. Chaudhary, A. Long. *J. Am. Chem. Soc.* **127**, 13810 (2005).
145. J. Schuppan, B. Ziemer, U. Koert. *Tetrahedron Lett.* **41**, 621 (2000).
146. K. C. Nicolaou, Y. W. Li, B. Weyershausen, H. X. Wei. *Chem. Commun.* 307 (2000).
147. G. A. Sulikowski, W. M. Lee, B. Jin, B. Wu. *Org. Lett.* **2**, 1439 (2000).
148. K. Toshima, T. Arita, K. Kato, D. Tanaka, S. Matsumura. *Tetrahedron Lett.* **42**, 8873 (2001).
149. Y. Z. Chen, J. B. Evarts, E. Torres, P. L. Fuchs. *Org. Lett.* **4**, 3571 (2002).
150. J. D. Pennington, H. J. Williams, A. R. Salomon, G. A. Sulikowski. *Org. Lett.* **4**, 3823 (2002).
151. P. A. Wender, O. D. Jankowski, E. A. Tabet, H. Seto. *Org. Lett.* **5**, 2299 (2003).
152. K. Abe, K. Kato, T. Arai, M. A. Rahim, I. Sultana, S. Matsumura, K. Toshima. *Tetrahedron Lett.* **45**, 8849 (2004).
153. M. T. Crimmins, A. Long. *Org. Lett.* **7**, 4157 (2005).
154. B. H. Jin, Q. S. Liu, G. A. Sulikowski. *Tetrahedron* **61**, 401 (2005).
155. Y. Kim, P. L. Fuchs. *Org. Lett.* **9**, 2445 (2007).
156. C. Craita, C. Didier, P. Vogel. *Chem. Commun.* 2411 (2007).
157. G. M. Rubottom, M. A. Vazquez, D. R. Pelegrina. *Tetrahedron Lett.* **15**, 4319 (1974).
158. C. Bonini, L. Chiummiento, M. Pullez, G. Solladie, F. Colobert. *J. Org. Chem.* **69**, 5015 (2004).
159. I. V. Hartung, B. Niess, L. O. Haustedt, H. M. R. Hoffmann. *Org. Lett.* **4**, 3239 (2002).
160. G. A. Sulikowski, W. M. Lee, B. Jin, B. Wu. *Org. Lett.* **2**, 1439 (2000).
161. H. C. Brown, K. S. Bhat, R. S. Randad. *J. Org. Chem.* **54**, 1570 (1989).
162. H. C. Kolb, M. S. Vannieuwenhze, K. B. Sharpless. *Chem. Rev.* **94**, 2483 (1994).
163. L. C. Bouchez, P. Vogel. *Chem.—Eur. J.* **11**, 4609 (2005).
164. T. L. Chan, S. Fong, Y. Li, T. O. Man, C. D. Poon. *J. Chem. Soc., Chem. Commun.* 1771 (1994).
165. X. P. Cao, T. L. Chan, H. F. Chow, J. G. Tu. *J. Chem. Soc., Chem. Commun.* 1297 (1995).
166. X. P. Cao. *Tetrahedron* **58**, 1301 (2002).
167. K. C. Nicolaou, D. L. F. Gray, T. Montagnon, S. T. Harrison. *Angew. Chem., Int. Ed.* **41**, 996 (2002).
168. E. J. Corey, S. Shibata, R. K. Bakshi. *J. Org. Chem.* **53**, 2861 (1988).
169. E. J. Corey, R. K. Bakshi, S. Shibata, C. P. Chen, V. K. Singh. *J. Am. Chem. Soc.* **109**, 7925 (1987).
170. E. J. Corey, R. K. Bakshi, S. Shibata. *J. Am. Chem. Soc.* **109**, 5551 (1987).
171. E. J. Corey, C. J. Helal. *Angew. Chem., Int. Ed.* **37**, 1986 (1998).
172. J. L. Duffy, T. P. Yoon, D. A. Evans. *Tetrahedron Lett.* **36**, 9245 (1995).