New Organic Chemistry of Sulfur Dioxide

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ABSTRACT

Simple 1,3-dienes undergo highly stereoselective hetero-Diels–Alder additions with SO_2 at low temperature giving sultines. These reactions that are faster than the more exothermic cheletropic additions of SO_2-producing sulfolenes. This has led to the invention of a new C–C bond-forming reaction combining electron-rich dienes and alkenes with SO_2. The reaction cascade has been exploited to develop combinatorial, one-pot, four-component syntheses of polyfunctional sulfones, sulfonamides, and sulfonic esters. It also allows us to generate, in one-pot operations, enantiomerically enriched polypropionate fragments containing up to three contiguous stereogenic centers and a (*E*)-alkene unit. These fragments can be used directly in further C–C bond-forming reactions, such as cross-aldol condensations, thus permitting the expeditious construction of complicated natural products of biological interest (e.g., Baconipyrones, Rifamycin S, Apoptolidinone) and analogues. New ene reactions of SO_2 have also been discovered; they open new avenues to organic synthesis.

1. Introduction

After wood burning, man discovered that sulfur burning in jars or other containers would help preserve food and beverages. Today, the U.S. demand for SO_2 amounts to ca. 300×10^3 tons per year at ca. $230/ton. It is used mostly as a beverage and food preservative (E220, ca. 25%), for bleaching paper and cloths (15%), gypsum manufacture (20%), corn processing (15%), water and waste treatment (10%), ore refining (6%), oil recovery (4%), and sulfonylation of oils and aromatic compounds (5%). Organic chemistry of SO_2 has been limited to the Friedel–Crafts sulfinylation, copolymerization of SO_2 with alkenes and alkynes, the synthesis of sulfinates and sulfones from polar organometallic species, the ring opening of epoxides and oxetanes leading to polysulfites, the isomerization of alkenes, and the formation of sulfolenes by cheletropic

additions with 1,3-dienes (for examples of classical organic reactions of sulfur dioxide reviews, see ref 1 and refs 1–13 cited therein; see also refs 2 and 3), a reaction reported first in 1914.[4] Other cycloadditions of SO_2 have been described for the reaction of ketenes and ketimines,[5–8] cyclic polyenes,[9,10] and quadricyclane.[11] Homocheletropic additions of SO_2 to 1,4-dienes have been reported.[12–14] The first examples of hetero-Diels–Alder additions of SO_2 involved highly reactive dienes **1**[15] and **3**.[16] In 1992, we reported that simple 1,3-dienes undergo hetero-Diels–s–Alder addition below −60 °C in the presence of a large excess of SO_2 and 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.[17]

This led us to investigate the factors affecting the competition between the hetero-Diels–Alder and the cheletropic addition of SO_2.[18–20] Our studies have been reviewed.[18–21] Apart from sultines resulting from reactions of SO_2 with 1-fluoro-1,3-dienes,[22] sultines are less stable than their sulfolene isomers. They decompose into the corresponding 1,3-dienes and SO_2 above −50 °C.[23–25] With 1-alkoxy- and 1-silyloxy-1,3-dienes **9**, the sultines **10** are not seen at −100 °C because these dienes generate the corresponding sulfolenes **11** at this temperature.[26] 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 electro-rich alkenes **13**, thus realizing a new C–C bond-forming reaction (Scheme 2), forming silyl sulfinates **14**.

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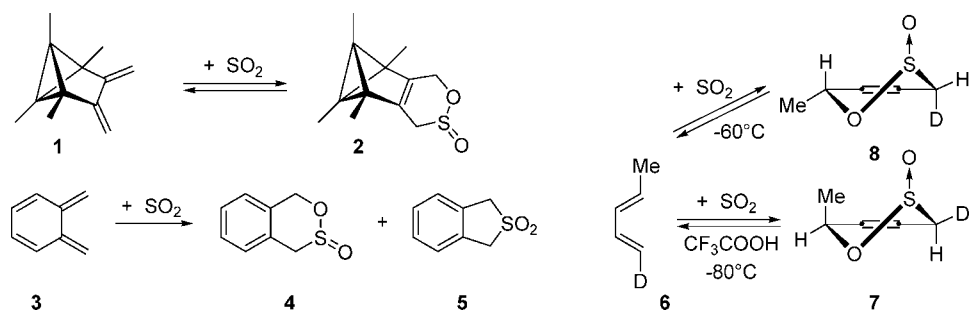‡ Universidad de Oviedo.

Scheme 1. Early Examples of Hetero-Diels–Alder Additions of SO$_2$

Scheme 2. New C–C Bond-Forming Reaction between Electron-Rich Dienes and Alkenes, via Umpolung with Sulfur Dioxide
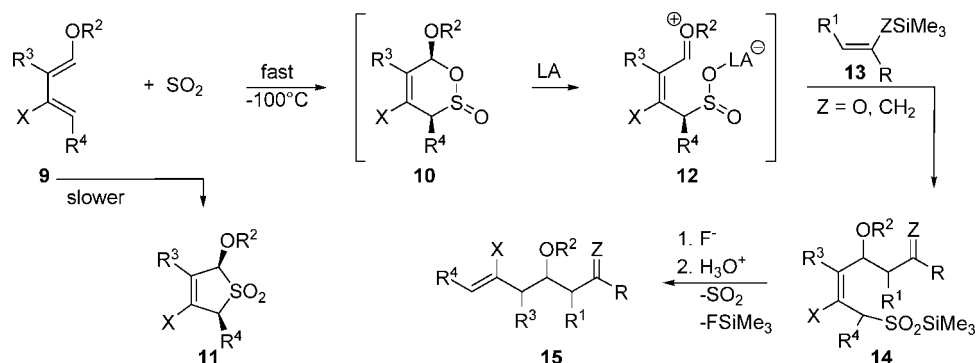
Scheme 3. SO$_2$-Induced Alkene Isomerization: (a) the Ene Mechanism and (b) the Sulfonyl Radical-Catalyzed Process
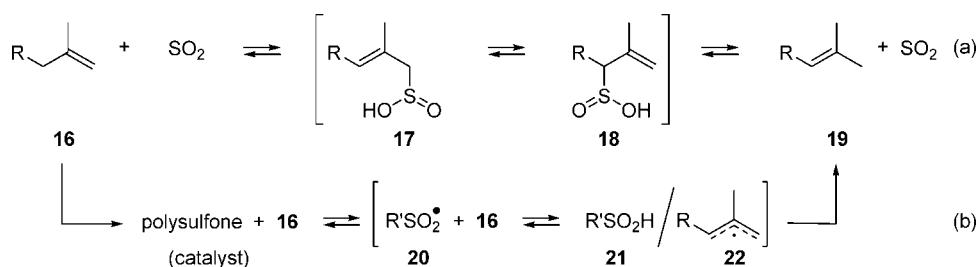
In situ desilylation and desulfinylation via retro-ene elimination of SO$_2$ generates in one-pot operations compounds **15** containing up to three contiguous stereogenic centers and one (*E*)-alkene unit.[27,28] We review the characteristics of this reaction cascade and some applications to the asymmetric synthesis of polypropionate antibiotics and other compounds of biological interest. Because step **14** → **15** implies a retro-ene elimination of SO$_2$, we have explored the ene reactions of SO$_2$. These studies have also led us to discover new organic chemistry of SO$_2$ that is reviewed here.

2. A Revisited Mechanism for the Sulfur-Dioxide-Induced Alkene Isomerization

Double-bond migration in alkenes **16** can be induced by SO$_2$ (Scheme 3). The process is explained by an ene reaction **16** + SO$_2$ → **17** followed by a [1,3]-sigmatropic shift **17** → **18** and subsequent retro-ene reaction that gives SO$_2$ and the isomeric alkenes **19**.[29–34]

In the case of methylidenecyclopentane and related alkyl substituted alkenes, we have found that their isomerizations are inhibited by radical-scavenging agents, such as 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and Bu$_3$SnH. Kinetic measurements showed induction periods

Scheme 4. Selectivity of SO$_2$ and Polysulfone-Catalyzed Alkene Isomerization
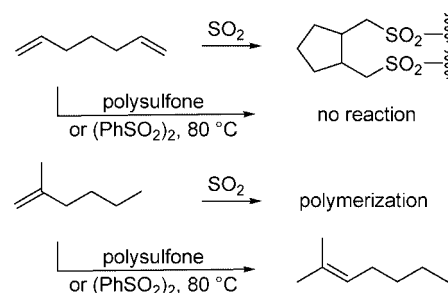
followed by zeroth-order reactions. During the induction period, a white precipitate of a 1:1 copolymer of the alkene and SO$_2$, a polysulfone,[35,36] forms. In the absence of SO$_2$, the latter catalyzes the alkene isomerizations.[37] The electron spin resonance (ESR) spectrum of the polysulfones showed typical signals for carbon-centered and sulfonyl radicals (e.g., **20**).[38–40] Alkene isomerization **16** → **19** is also induced upon heating (80–120 °C) or UV irradiation of **16** in the presence of a catalytic amount of diphenyldisulfone.[41–43] Both the polysulfone- and diphenyldisulfone-catalyzed alkene isomerizations follow zeroth-order rate laws and are inhibited by radical scavenging agents. Importantly, these reactions are

Scheme 5. Polysulfone PS Made of SO₂ and Methylidenecyclopentane Catalyzes the Cleavage of Methyl-Substituted Allyl Ethers
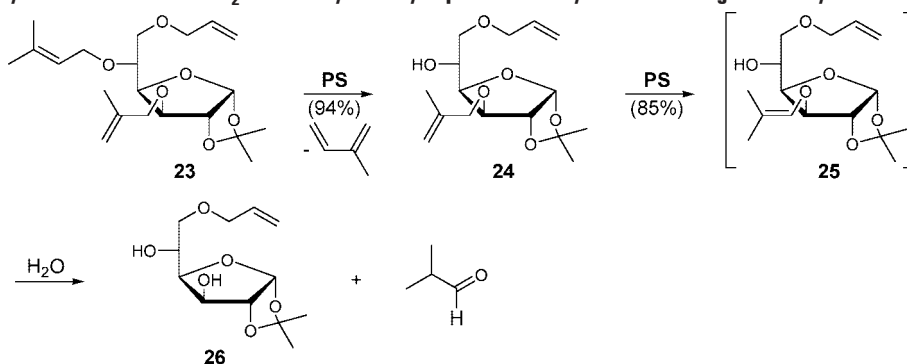
ᵃ The reaction is faster for prenyl than methallyl ethers and does not occur for allyl ethers.

Scheme 6. Plausible Mechanisms for the Isomerization of Alkenes in the Presence of Sulfonyl Radicals (See the Text)
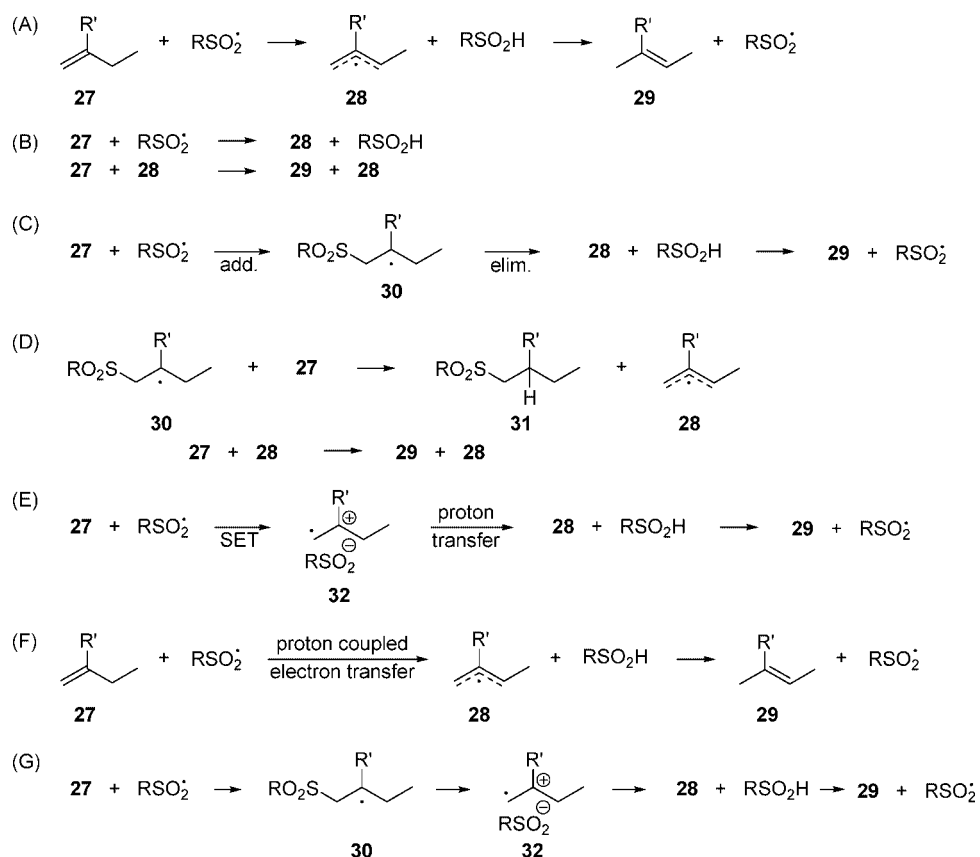
much better yielded than the SO₂-induced isomerizations, with the latter being accompanied by polymer formation.[37] Furthermore, the polysulfone- and diphenyldisulfone-catalyzed alkene isomerizations are highly chemoselective in the sense that linear, terminal alkenes (1-alkyl-substituted ethenes) and 1,2-dialkylethenes are not isomerized at all, whereas 2-alkyl-substituted alk-1-enes are isomerized (Scheme 4).

This discovery led us to invent new strategies for the protection and deprotection of alcohols and the semiprotection of polyols. Methallyl, prenyl, and methylprenyl ethers undergo selective cleavages catalyzed either by (PhSO₂)₂[44] or by the solid polysulfone PS (generated from the copolymerization of SO₂ with methylidenecyclopentane) under neutral conditions, without the use of transition-metal catalysts (Scheme 5).[45]

A number of different routes to rationalize the isomerization of alkenes **27 → 29** in the presence of sulfonyl radicals have been considered (Scheme 6). In mechanism A, one-step hydrogen abstraction gives RSO₂H and radical **28**. The latter diffuses away from the solvent cage and is reduced by a sulfinic acid moiety. Another channel is the direct hydrogen transfer RSO₃H + **28** → **29** in the initial solvent cage (B). In mechanism C, **28** is formed through a two-step mechanism: first, the addition of the sulfonyl radical onto the alkene **27** produces the alkyl radical **30**, and then, elimination of RSO₂H forms the allyl radical **28**. As a variant (D), the intermediate tertiary alkyl radical **30** abstracts a hydrogen atom from **27** and generates the corresponding allyl radical **28**. This starts a chain process as that described for mechanism B. As found for polar radicals, the hydrogen atom transfer can proceed through

Scheme 7. One-Pot, Three-Component Synthesis of Polyfunctional Sulfones

33 X = O   R' = H, alkyl, aryl   **35** X = O   **37** X = O
34 X = CH₂   **36** X = CH₂   **38** X = CH₂

Scheme 8. Possible Mechanism of the Sila-ene Reaction of SO₂ with Enoxysilanes

39 R = Me
40 R = *i*-Pr   fast for R = Me, slow for R = *i*-Pr

     41   **42**   **43**

a two-step process starting by an electron transfer to generate a radical cation **32**, followed by proton transfer to the sulfinate anion (E). This latter mechanism might also proceed through a single-step proton-coupled electron-transfer process (F). Finally, the sulfonyl radical addition to the alkene might be followed by heterolytic fragmentation, giving radical cation **32** and sulfinate anion (G), thus connecting with mechanism E. Calculations [CCSD(T)/6–311++6(d,p)/B3LYP/6–311++6/d,p] suggested that a mechanism involving the reaction between allyl radical and the alkene (B and D) requires energy barriers 5–6 kcal/mol higher than those for mechanism A, in which the hydrogen atom is transferred via the sulfinic acid. On the other hand, the addition of the sulfonyl radical to the alkene (C) involves energy barriers notably lower than for the hydrogen abstraction (A). However, as for the case of the abstraction of an allylic hydrogen in the chlorine atom reactions with alkene,[46] *ab initio* calculations failed to locate any transition structure for the elimination channel.

Ionic mechanisms, such as E or G, imply solvent effects on the rates or reactions. *Ab initio* calculations, including one and two solvent molecules explicitly, showed only a slight increase in charge separation between the alkene and sulfonyl radical. Thus, quantum calculations[47] strongly suggest that the isomerization of alkenes in the presence of sulfonyl radicals proceeds through one-step hydrogen abstraction (mechanism A). The chemoselectivity is not governed by an exothermicity difference but by a difference in ionization energies of the alkenes. Calculations for MeSO₂• plus propene and MeSO₂• plus 2-methylpropene show a charge transfer of 0.34 and 0.38 electron, respectively, from the alkene to the sulfonyl radical in the transition state of these hydrogen transfers.[47]

3. New Ene Reactions of Sulfur Dioxide

Before our work, metallo-ene reactions with SO₂ had been reported for allyltrialkyltin compounds,[48] enoxysilanes derived from esters,[49] and allyl germanes.[50] We have found that enoxysilanes **33**, derived from ketones and aldehydes, as well as allylsilanes **34** react with SO₂ to give silyl sulfinates **35** and **36**, respectively, that can be reacted in the same pot with a variety of electrophiles generating the corresponding

Scheme 9. Stereoselectivity of the Sila-ene Reactions of Sulfur Dioxide Promoted by TBSOTf = LA

47

     major | minor

     48   **49**

     ↓ Bu₄NF/BrCH₂COOEt   ↓

     50   **51** (4:1, 74%)

polyfunctional sulfones **37** and **38**, respectively (Scheme 7).[51]

The reactions are promoted by Lewis acids in agreement with a mechanism involving either zwitterionic intermediates of type **41** or a one-step process in which **41** is only a limiting structure of the transition state **42** (Scheme 8).

The reactions of allylsilanes **44** with SO₂/CH₂Cl₂/TBSOTf provide the corresponding trimethylsilyl alkene-sulfinates **45** that can be reacted with Bu₄NF and electrophiles R′X (e.g., MeI and BrCH₂COOEt) to generate the corresponding sulfones **46**. The ene reaction is the slowest for **44**, with R = COOEt, and the fastest for **44**, with R = Me. With silane **47**, a 4:1 mixture of (*E*)- and (*Z*)-alkene **50** and **51** is obtained after workup with Bu₄NF and BrCH₂COOEt. This can be interpreted in terms of transition states **48** and **49** that adopt chair-like structures, the most stable one (**48**) with a pseudo-equatorial methyl substituent (Scheme 9). One key question is whether the S=O bonds in these transition states adopt pseudo-axial positions (conformational anomeric effect as in sultines **18**) or prefer pseudo-equatorial positions.

A spin-off of our studies has been the invention of a new method for the chemoselective silylation of alcohols, polyols, phenols, and carboxylic acids under nonbasic conditions and with the formation of volatile coproducts (SO₂ isobutylene).[52]

44

45

46 R = H, R' = Me: 70%
R = Me, R' = CH$_2$COOEt: 60%
R = COOEt, R' = CH$_2$COOEt: 60%

The trimethylsilyl (**52**), triethylsilyl (**53**), and (*tert*-butyl)dimethylsilyl 2-methylprop-2-enesulfinates (**54**) (prepared as shown in Scheme 10) react with alcohols, phenols, and carboxylic acids to give the corresponding silyl ethers and esters in high yields. Reaction rates follow the order **52** ≫ **53** ≫ **54** and the order primary > secondary > tertiary alcohols and then allow chemoselective silylation as illustrated with **55** → **56** + SO$_2$ + isobutylene.

Our silylation reaction is inhibited by Et$_3$N but accelerated by a small amount of SO$_2$. As the kinetic deuterium isotope effect $k_H/k_D = 1.00 \pm 0.05$ for the reactions *t*-BuOH(D) + **54** → *t*-BuO-Si(*t*-Bu)Me$_3$ + SO$_2$ + isobutylene, we proposed the mechanism shown in Scheme 10. The alcohols add to SO$_2$, forming hydrogenosulfites **57** that react with the silyl sulfinates, forming intermediates **58**. Entropy-driven fragmentation occurs, which does not seem to be assisted by proton transfer. Because acids or bases are not required in these silylation techniques, they can be applied to fragile structures. Furthermore, sterically hindered alcohols can be silylated, including (*tert*-butyl)dimethylsilyl ethers.[52]

Prop-2-ene-1-boronate (**60**) adds SO$_2$, giving mixed anhydride **61**, which reacts with Grignard reagents, producing allylsulfoxide **62**. It is noteworthy that the Grignard reagents prefer the sulfur electrophilic center rather than the boron center, in most cases. Using enantiomerically pure alk-2-ene-1-boronic esters, enantiomerically or diastereomerically enriched sulfoxides can be obtained as shown in Scheme 11.[53]

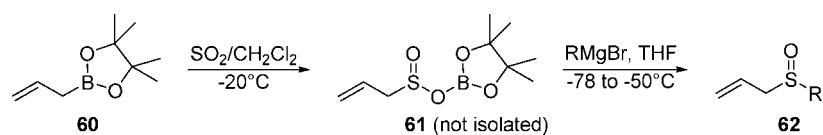## 4. A New C–C Bond-Forming Reaction: Umpolung with Sulfur Dioxide

When (*E*)-1-methoxybutadiene (**68**) is reacted with a large excess of SO$_2$, in the absence or presence of a Lewis acid catalyst (e.g., TBSOTf), only sulfolene **69** is formed between −100 and −60 °C. At 0–20 °C, quick polymerization occurs. However, when a mixture of **68** and enoxysilane **72** is reacted with SO$_2$ + TBSOTf at −100 °C, silyl sulfinate **73** forms. After solvent evaporation (recovery of SO$_2$) and treatment with Bu$_4$NF and MeI, a 81:19 mixture of methyl sulfones **74** and **75** is obtained [100% (*Z*) stereoselectivity].[27,28]

The formation of **73** is explained by invoking the fast hetero-Diels–Alder **68** + SO$_2$, giving sultine **70** that is immediately heterolyzed into zwitterion **71**. In the absence of enoxysilane, it equilibrates back to **68**, which finally undergoes the cheletropic addition with SO$_2$. In the presence of **72**, oxyallylation occurs, producing **73** and then **74** + **75** (Scheme 12). In the reaction of enantiomerically enriched diene (+)-**76** (Greene's chiral auxiliary;[54] ee >99%) and enoxysilane **77** in SO$_2$ and Yb(OTf)$_3$ as the catalyst, the same one-pot sequence of the reaction generates (−)-**78** in 79% yield and 25:1 diastereoselectivity. Similarly, diene (−)-**79** and enoxysilane **80** [with (CF$_3$SO$_2$)$_2$NH as the catalyst] give a 93% yield of a 14.1:1 mixture of (−)-**81** and **82** (Scheme 13).[55–57]

The results are interpreted (Scheme 14) in terms of the formation of sultines **83** that are ionized into zwitterions **84**. The least sterically hindered face of the diene undergoes suprafacial cycloaddition, leading to an *unlike* relative configuration between the β-alkoxy and ε-methyl groups in (−)-**81** and **82**. The face of the zwitterionic intermediate *anti* with respect to the sulfinyl moiety (which is not allowed to rotate freely because of Colombic interactions between it and the oxycarbenium moiety of **84**) adds to the enoxysilane preferentially on the face, realizing a minimal steric interaction with **84**. In these C–C bond-formation reactions that condense two electron-rich unsaturated systems, sulfur dioxide realizes an Umpolung by converting the 1-oxy-1,3-dienes into 1-oxyallylic cationic intermediates that react with high regio- and face selectivity onto their C1

Scheme 10. Preparation of New Silylating Agents and Possible Mechanism for the SO$_2$-Catalyzed Silylation of Alcohols by Silyl 2-Methylprop-2-ene-sulfinates
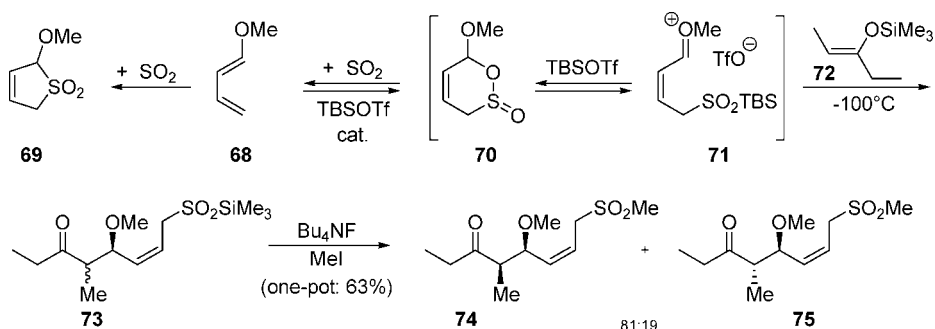

52 R = Me (54%)
53 R = Et (50%)
54 SiR$_3$ = (*t*-Bu)Me$_2$Si (40%)

55 **56** (95%)

57 **58** **59**
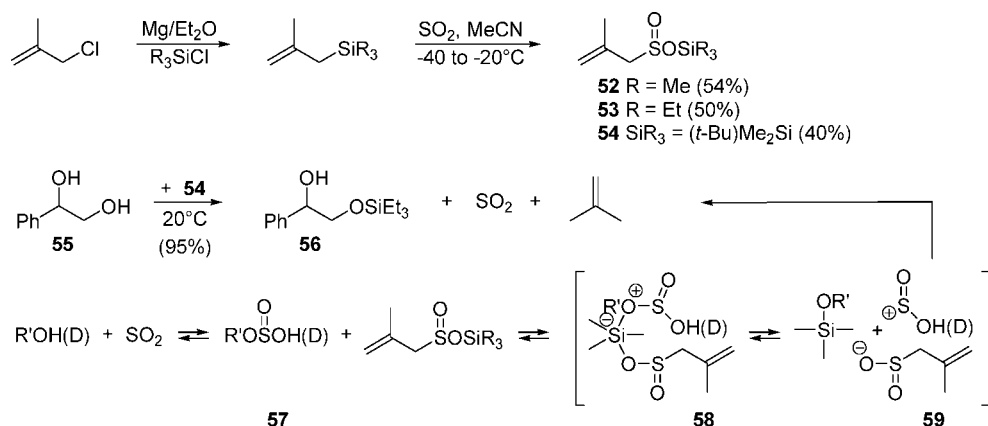
Scheme 11. Bora-ene Reactions of SO$_2$: New Route to Sulfoxides

R = Ph (62%), 4-MeC$_6$H$_4$ (61%), 3-MeC$_6$H$_4$ (60%), 1-naphthyl (50%), 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$ (36%), Bn (48%), etc.
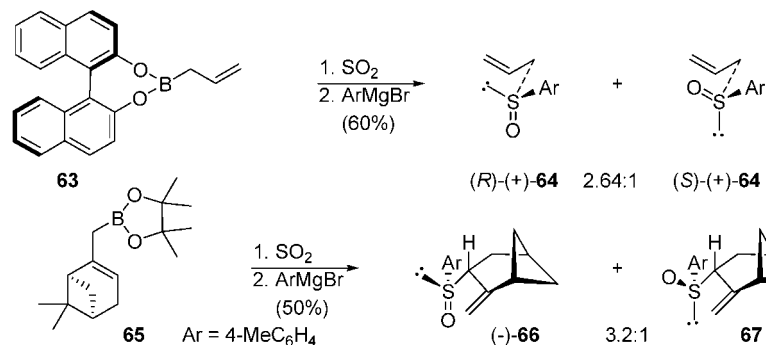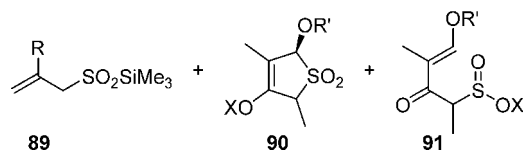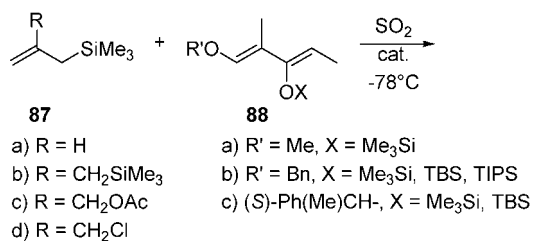

Scheme 12. Oxyallylation of Enoxysilanes

Scheme 13. Examples of One-Pot, Asymmetric and Diastereoselective Four-Component Synthesis of Polyfunctional (Z)-Alkenyl Methyl Sulfones Containing up to Three Stereogenic Centers
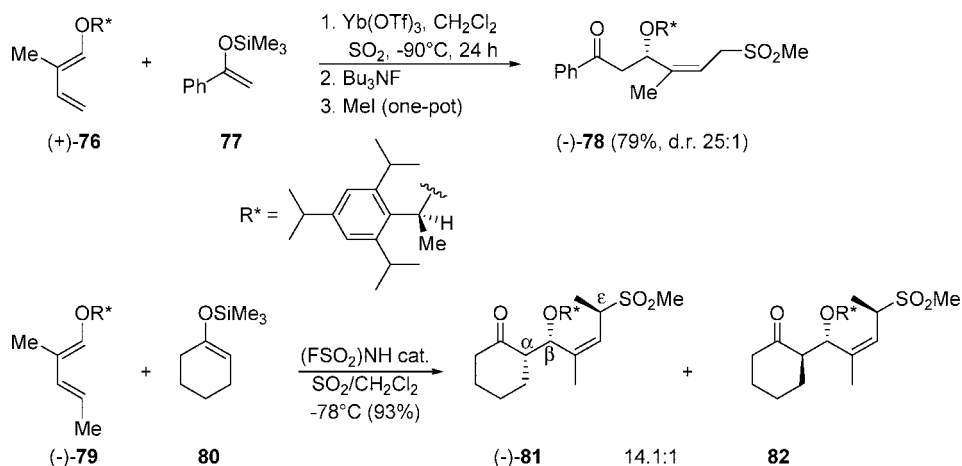

centers with nucleophilic alkenes. No direct experimental proof has been provided yet for the mechanism proposed in Scheme 14.

When diene (−)-**79** and allylsilanes **87** are reacted with an excess of SO$_2$ in the presence of a Lewis acid [e.g., Yb(OTf)$_3$, (*t*-Bu)Me$_2$SiOTf, and (CF$_3$SO$_2$)$_2$NSiMe$_3$] or protic acid (e.g., (CF$_3$SO$_2$)$_2$NH), no product of condensation is observed. Not unexpectedly (see above), the allylsilane reacts rapidly with SO$_2$ in ene reactions, giving the corresponding silyl sulfinates (see e.g., **34** + SO$_2$ → **36**),

thus allowing no chance for the allylsilanes to react with intermediate zwitterions **84**. When (−)-**79** is substituted for the more electron-rich (*E*,*E*)-1-alkoxy-3-trialkylsilyloxypenta-1,3-dienes (**88**), their reactions with **87** and SO$_2$ do not produce the desired products of C–C coupling between the dienes and allylsilanes. Apart from the ene reaction of SO$_2$ with allylsilanes **87**, giving **89**, dienes **88** react with SO$_2$, giving mixtures of sulfolenes **90** and silyl β-oxosulfinates **91**, with the latter resulting from ene reactions of **88** with their enoxysilane moieties.

87

a) R = H
b) R = CH$_2$SiMe$_3$
c) R = CH$_2$OAc
d) R = CH$_2$Cl

88

a) R' = Me, X = Me$_3$Si
b) R' = Bn, X = Me$_3$Si, TBS, TIPS
c) (S)-Ph(Me)CH-, X = Me$_3$Si, TBS

89   **90**   **91**

To suppress the latter ene reactions, the reactivity of 1-alkoxy-3-acyloxy-1,3-dienes toward **87** in SO$_2$ was explored. They were found to give products of C–C coupling. For instance, diene **92** reacts with **87d** in an excess of SO$_2$ and in the presence of the (CF$_3$SO$_2$)$_2$-NSiMe$_3$ catalyst, giving silyl sulfinate **93** as a unique product.[58]

92   **87d**   **93**
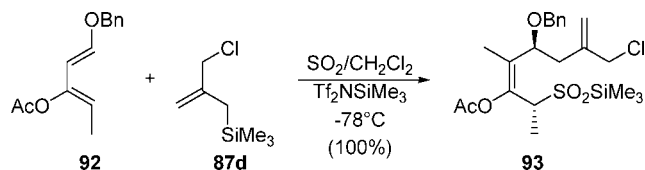
5. One-Pot, Four-Component Synthesis of Sulfones, Sulfonamides, and Sulfonic Esters

Organosulfones and sulfonamides are important compounds because of their chemical and biological properties.[59] Other electrophiles, EX, than MeI (e.g., allyl, methallyl, and arylmethyl bromides, BrCH$_2$COOEt,[60] alkyl iodides, and 2,4-dinitrofluorobenzene) combine with a large variety of 1-alkoxy- or 1-trialkylsilyloxy-1,3-diene **94**, SO$_2$, and enoxysilanes or allylsilanes **95**, thus realizing a combinatorial, one-pot, four-component synthesis of polyfunctional sulfones **97**. If the crude silyl sulfinates **96** are oxidized with Cl$_2$ or *N*-chlorosucciminide (NCS), the corresponding sulfonyl chlorides **98** are formed that can be reacted *in situ* with primary or secondary amines to generate polyfunctional sulfonamides **99** or with alcohols to give the corresponding sulfonic esters **100** (Scheme 15).

We have shown that enoxysilanes and allylsilanes undergo ene reactions with SO$_2$. The silyl sulfinates thus obtained can be converted also into sulfones, sulfonamides, and sulfonic esters, thus realizing one-pot, three-component syntheses of these compounds.[61]

For the first time, new medium-size heterocyclic systems, such as (+)-**103**, have been prepared (Scheme 16). The reaction of **87c** with diene (−)-**101** [97% enantiomeric excess (ee)] in SO$_2$/toluene premixed with 0.3 equiv of Tf$_2$NSiMe$_3$ at −78 °C gives a single silyl sulfinate **102**. Starting with (+)-**101** and **87c** and by treatment of the intermediate silyl sulfinate (*ent*-**102**) with Pd(Ph$_3$P), the

2*H*-thiocene derivative (+)-**103** is obtained in 41% overall yield (Scheme 16).[62]

6. Stereoselective Synthesis of (*E,Z*)- and (*E,E*)-2,4-Diene-1-ones. Synthesis of the C1–C11 Polyene Fragment of Apoptolidine

The oxo-sulfones of type **97** (Z = O; R* = R$_3$Si, Bn; X = H) eliminate R*OH readily under acidic conditions, giving (*E,Z*)-dienones (Scheme 17).

When the acid promoter HNTf$_2$ is used in a higher concentration (ca. 50% equiv) or when using TfOH (3%), the *s-trans* conformer of the 1-oxydiene **106** reacts with the activated SO$_2$ (SO$_2$H$^+$), generating the zwitterionic intermediate **110** with an (*E*)-alkene moiety. The latter is then quenched by the enoxysilane **107**, leading to (*E,E*)-dienone **109** after desilylation, arylation with 1-fluoro-2,4-dinitrobenzene, and treatment with triflic acid (Scheme 18).[63]
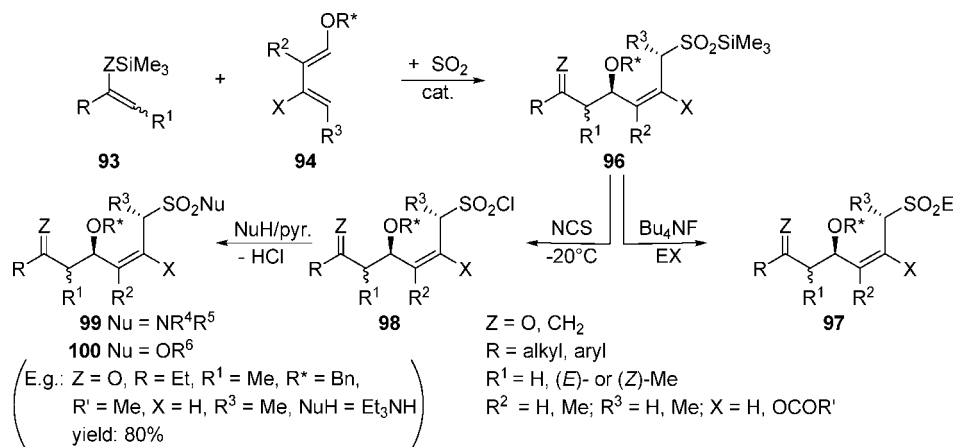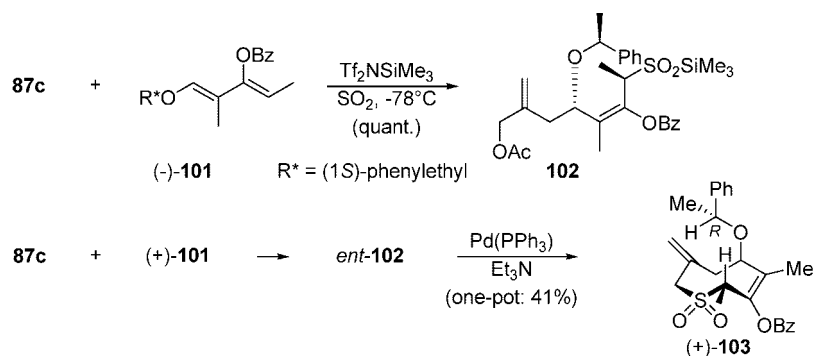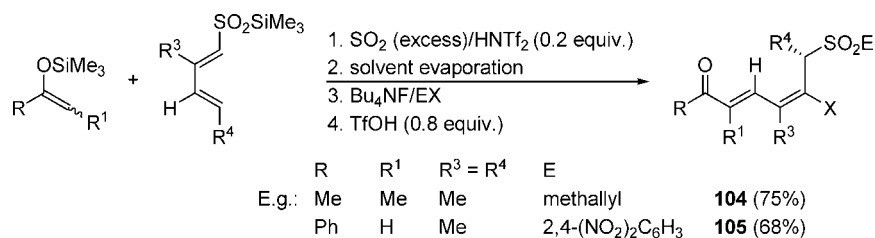
The usefulness of our one-pot synthesis of (*E,E*)-dienones is illustrated in Scheme 19 by a short synthesis[64] (requiring the isolation of only three synthetic intermediates) of Nicolaou's C$_1$–C$_{11}$ fragment of Apoptolidin,[65] a promising antitumor agent.[66]

7. One-Pot Synthesis of Polypropionate Stereotriads: Total Asymmetric Syntheses of Natural Polyketide Antibiotics

The thermal desulfinylation of α-substituted β,γ-unsaturated sulfinic acids is stereoselective.[67,68] This is also observed with **117** → **118** + SO$_2$.

115   **116**

**117**

118 (for R = Ph; yield: 95%, one-pot)
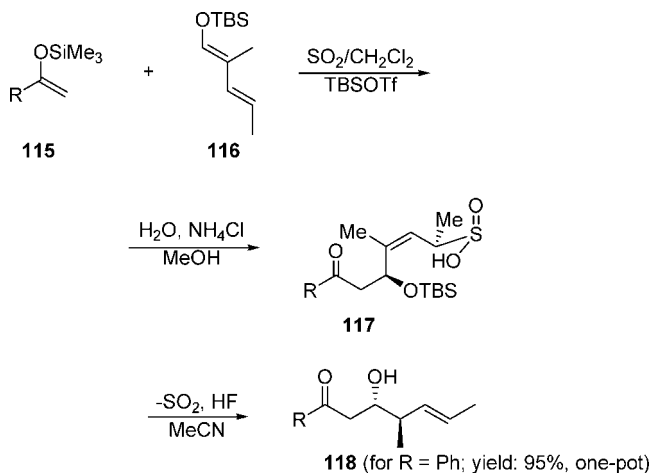
Because the desulfinylation of β,γ-unsaturated sulfinic acids requires acidic conditions (to form the sulfinic acids), it is often accompanied by elimination and/or retro-aldol reactions. Furthermore, sulfinic acids undergo disproportion.[67] We have found that the silyl sulfinate intermediates of type **96** (Scheme 15) can be desilylated by the 1:1 Pd(OAc)$_2$/PPh$_3$ catalyst, liberating the corresponding β,γ-unsaturated sulfinic acids that undergo a palladium-catalyzed desulfinylation in the

Scheme 14. Possible Interpretation of the Diastereoselectivity of the Reaction Cascade Hetero-Diels–Alder Addition, Zwitterion Formation, and Its Quenching by Enoxysilanes

(α:β *syn*, β:ε *unlike*)
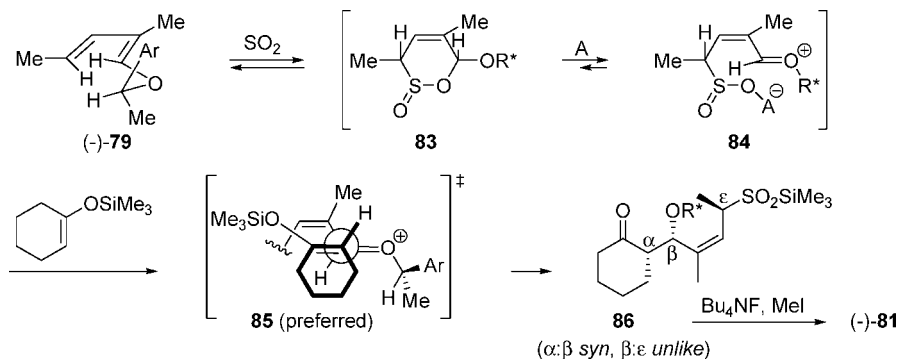
Scheme 15. Combinatorial, One-Pot, Four-Component Syntheses of Sulfones, Sulfonamides, and Sulfonic Esters

99 Nu = NR^4R^5
100 Nu = OR^6

$\left(\begin{array}{l}\text{E.g.: } Z = O, R = Et, R^1 = Me, R^* = Bn,\\ R' = Me, X = H, R^3 = Me, NuH = Et_3NH\\ \text{yield: 80\%}\end{array}\right)$

Z = O, CH_2
R = alkyl, aryl
R^1 = H, (*E*)- or (*Z*)-Me
R^2 = H, Me; R^3 = H, Me; X = H, OCOR'

Scheme 16. Syntheses of a Tetrahydro-2H-thiocene Derivative

Scheme 17. One-Pot Synthesis of (*E,Z*)-Dienones

|	R	R^1	$R^3 = R^4$	E	
E.g.:	Me	Me	Me	methallyl	**104** (75%)
	Ph	H	Me	2,4-$(NO_2)_2C_6H_3$	**105** (68%)

presence of K_2CO_3 and isopropanol with high yield and stereoselectivity.[69] The mechanism of the latter reaction is under investigation.

The usefulness of our one-pot polypropionate synthesis is demonstrated in the expeditious assemblies of the cyclohexanone unit **125** of baconipyrones A and B

Scheme 18. One-Pot Synthesis of (*E,E*)-Dienones
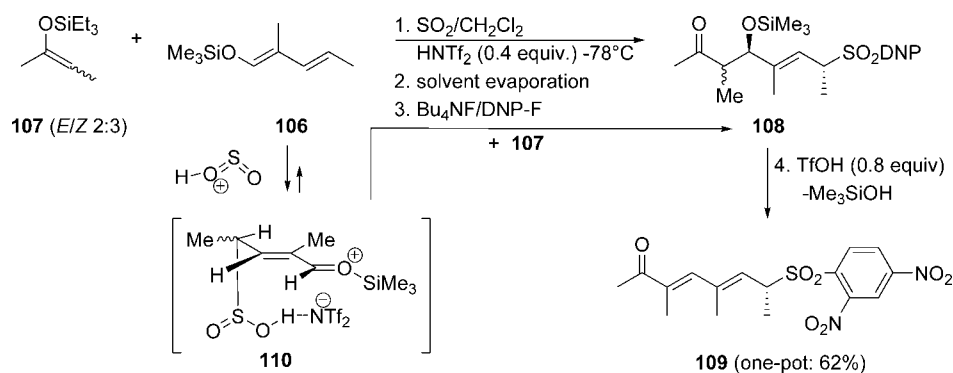
Scheme 19. Synthesis of Nicolaou's C_1–C_{11} Fragment of Apoptolidin
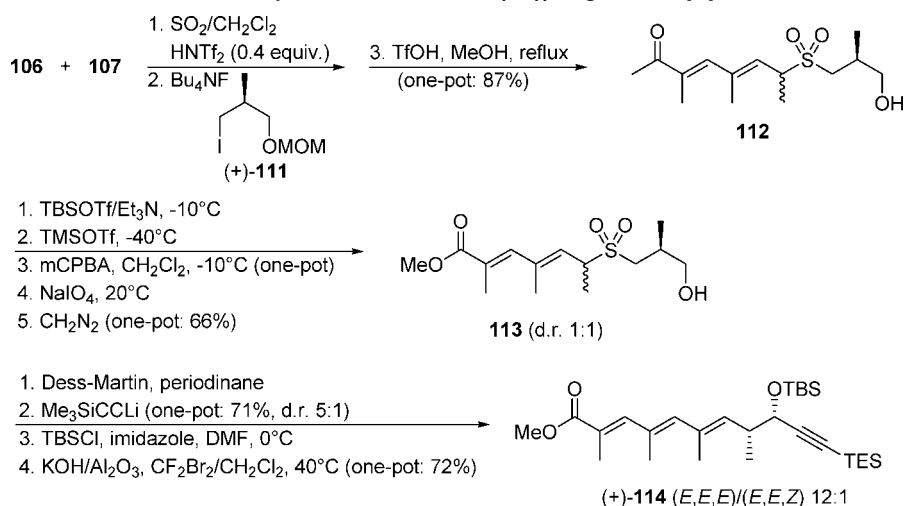
## Scheme 20. Three-Step Synthesis of the Cyclohexanone Subunit of Baconipyrones A and B
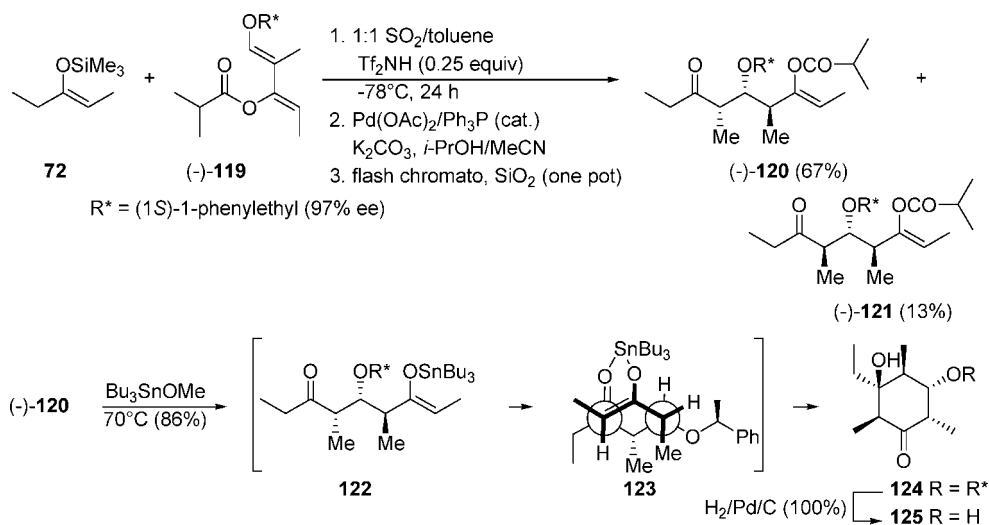
(Scheme 20)[70] and of a stereoheptad (−)-**130** corresponding to the C_{19}–C_{27}-ansa chain of Rifamycins (Scheme 21).[71]

Reaction of **72** and (−)-**119** (97% ee) with SO_2 in toluene and Tf_2NH provides a silyl sulfinate. The residue is treated with the $Pd(OAc)_2/Ph_3P$ catalyst in the presence of K_2CO_3, isopropanol, and acetonitrile, providing pure stereotriads (−)-**120** (67% yield) and (−)-**121** (13%).

Treatment of (−)-**120** with Bu_3SnOMe at 70 °C promotes a highly stereoselective intramolecular aldol reaction, giving **124**. Hydrogenolysis of **124** affords **125**. In this case, inexpensive (1*S*)-1-phenylethanol is used as a chiral auxiliary to generate the starting diene (−)-**119**.

The silyl (*Z*)-enol ether **126** derived from (−)-**120** reacts with 9-bromo-9-borabicyclo[3.3.1]nonane (Br-BBN) in CH_2Cl_2 (silyl/boron exchange) and then with

Scheme 21. Expeditious Asymmetric Synthesis of C₁₉–C₂₇-ansa Chain of Rifamycins: Formal Total Synthesis of Rifamycin S

8. Conclusion
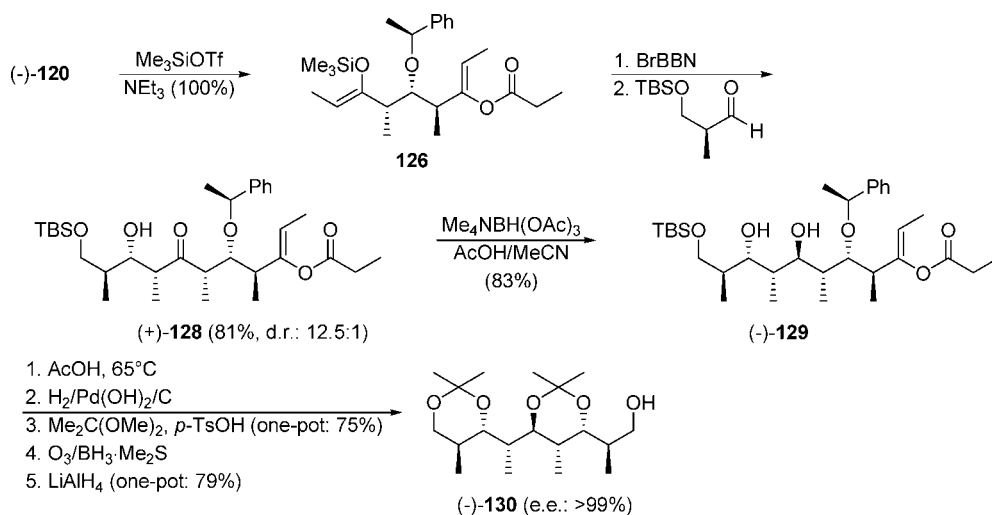
aldehyde (+)-**127** to produce a 12.5:1 mixture of aldols (+)-**128** and 9-epimer in 81% yield. Pure (+)-**128** is reduced under Evans' conditions to give diol (−)-**129** (83%), a stereoheptad equivalent to Kishi's intermediate (−)-**130** of the asymmetric synthesis of Ryfamycin S. The latter was derived from (−)-**129** (does not have to be purified for the next step) as shown in Scheme 21. Thus, Kishi's advanced intermediate is obtained in 25% overall yield in eight steps starting from inexpensive diene (−)-**119**. The synthesis requires the isolation of only four synthetic intermediates.[71] Application of our reaction cascade to the asymmetric synthesis of the polypropionate fragment of Apoptolidine is underway.[72]

8. Conclusion

After 10 000 years of use as a food and beverage preservative and about 100 years in industrial applications, sulfur dioxide is just starting to show its potential in fine organic chemistry as a solvent, reagent, and catalyst. With the help of quantum calculations, little known reactions, such as the hetero-Diels–Alder of SO_2 and sulfonyl radical-induced alkene isomerization, have delivered some of their characteristics and opened new avenues to organic synthesis. Particularly interesting is the use of SO_2 as an Umpolung device, permitting the formation of C–C bonds between electron-rich dienes and alkenes. Before our studies, chemists looked down on SO_2 because it was just useful to induce polymerization of unsaturated hydrocarbons or produce polymers. Apart from its use as a sulfinylation agent of benzene derivatives and polar organometallic reagents, SO_2 had little applications in organic chemistry. A new reaction cascade combining enantiomerically enriched 1-(1-phenylethyl)oxy-1,3-dienes, enoxysilanes, or allylsilanes and SO_2 allows for the one-pot synthesis of enantiomerically pure polyfunctional sulfones, sulfonamides, and sulfonic esters, as well as polypropionate stereotriads that can be used without activation or transformation, in further C–C bond-forming reactions, thus realizing expeditious constructions of complicated natural products of biological interest and analogues. Our studies have produced spin-offs, such as new chemoselective silylation agents that do not require basic media or acidic activation and new polysulfones that are solid catalysts for the chemoselective cleavage of methyl-substituted allyl ethers (new methods for the protection of alcohols and semiprotection of polyols).

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