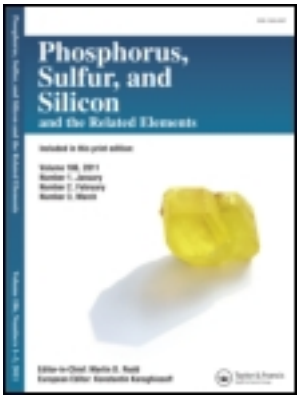

Phosphorus, Sulfur, and Silicon and the Related Elements

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Total Synthesis of Polypropionate Natural Products: Application of New Sulfur Dioxide Chemistry

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In the presence of a Lewis or protic acid at low temperature, electron-rich dienes add to sulfur dioxide and carbon nucleophiles generating silyl sulfinates. The latter can be transformed into valuable polyketide precursors.

Keywords Polypropionate; retro-ene reaction; sulfur dioxide; umpolung with SO_2

INTRODUCTION

Natural polyketides show important biological activity. A large number of methodologies for these targets have already been developed.[1] Nevertheless, more efficient and versatile synthetic strategies are needed. We recently reported a new asymmetric C–C bond forming reaction that condenses butadien-1-yl ethers **1**, enoxysilanes,[2] or allylsilanes[3] **4** and SO_2. The strategy involves a cascade of reactions starting with the hetero-Diels–Alder additions of SO_2 to a 1,3-dienyl ether **1**, giving the corresponding sultines **2** that are ionized into zwitterionic intermediates **3**, which are reacted with nucleophiles to give the corresponding silyl sulfinates **5a** (Scheme 1). The latter can be converted

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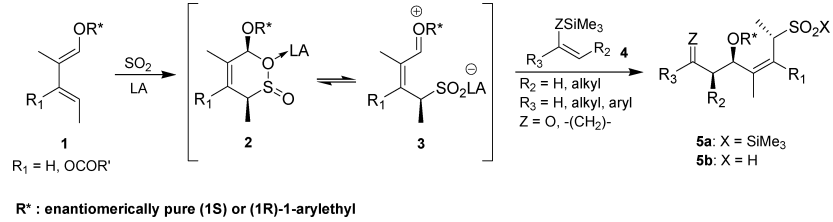
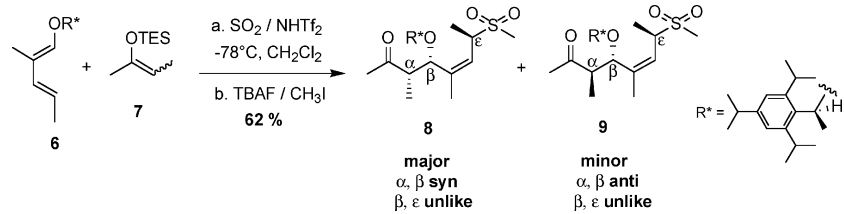


SCHEME 1 Umpolung with sulfur dioxide. R*: enantiomerically pure (1*S*) or (1*R*)-1-arylethyl.

into polyfunctional sulfones, sulfonamides, and sulfonic esters or into polypropionate fragments. Recent examples are disclosed in this article.

RESULTS AND DISCUSSION

The silyl sulfinates can be reacted with TBAF (Bu_4NF) and an electrophile to generate polyfunctional sulfones (Scheme 2) or be oxidized



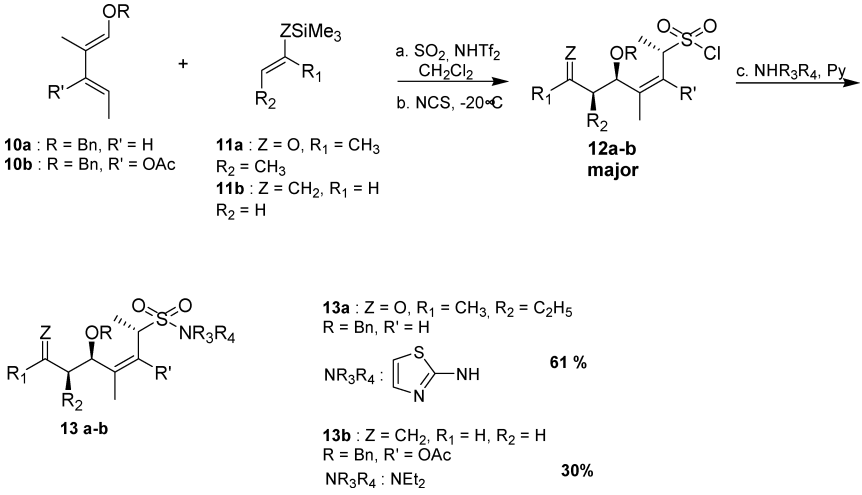
SCHEME 2 Synthesis of polyfunctional sulfones.

with Cl_2 (or NCS) or Br_2 (or NBS) to generate intermediate sulfonyl halides that react with nucleophiles such as amines to provide libraries of polyfunctional sulfonamides in one-pot operations (Scheme 3).

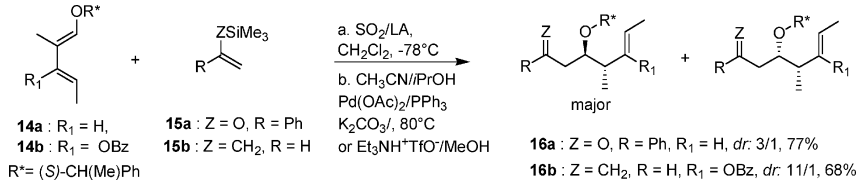
Alternatively, the silyl sulfinates **5a** can be converted into the corresponding sulfinic acids **5b** using catalytic amount of $Pd(OAc)_2$ or a buffer such as $Et_3NH^+TfO^-$. The desulfitation of the sulfinic acids **5b** allows the formation of the corresponding (*E*)-alkenes **16 a–b** (Scheme 4).

Our tandem oxyallylation (**1** + **2** + SO_2 →**5a**), hydrolysis (**5a** → **5b**), and retro-ene elimination of SO_2 realizes a one-pot synthesis of valuable enantiomerically pure polyketide fragments starting with enantiomerically pure ethers **1**, constructing up to three contiguous stereogenic centers and an alkene moiety.

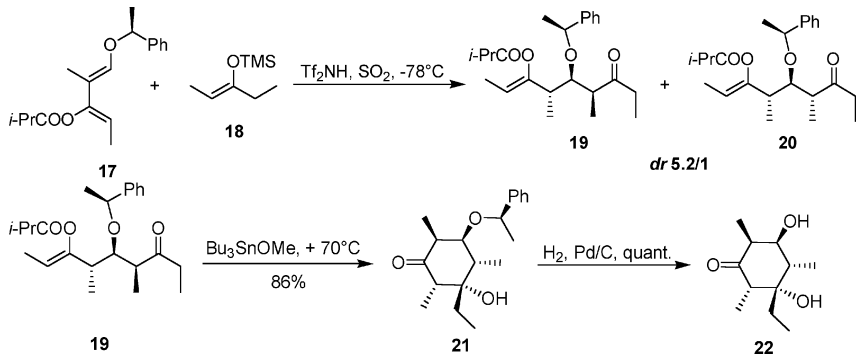
Applying our new C—C bond-forming reaction based on the sulfur dioxide-induced condensation of 1,3-dioxy-1,3-dienes to enoxysilanes, very short and stereoselective synthesis of (+)-(2*S*, 3*S*, 4*S*, 5*S*, 6*S*)-3-ethyl-3,5-dihydroxy-2,4,6-trimethylcyclohexanone (**22**), the cyclohexane unit of baconipyrones **A** and **B** (Scheme 5) has been realized.



SCHEME 3 One-pot, four-component synthesis of polyfunctional sulfonamides.

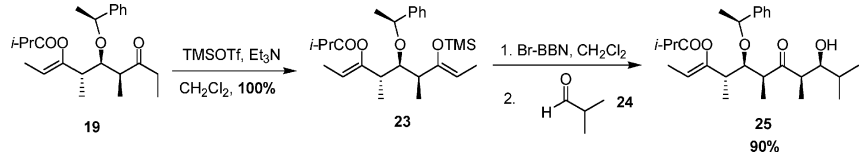


SCHEME 4 Desulfitation via retro-ene elimination of SO_2.



SCHEME 5 Synthesis of the cyclohexanone unit of baconipyrone A and B.

Another interesting application is to involve key building blocks from SO_2 chemistry in aldol condensation, which would generate more complex polypropionate fragments, as found in the structure of natural compounds. One of our preliminary results with model aldehyde **24** shows good stereoselectivity for the aldol condensation of boron enolate derived from **19** (Scheme 6).



SCHEME 6 Synthesis of long-chain polypropionates.

Our C—C bond-forming reaction allows us to prepare diastereomerically pure, long-chain polypropionate containing up to three contiguous stereogenic centers and an alkene moiety. Using enantiomerically pure butadiene-1-yl-1-arylethyl ethers, enantiomerically pure polyketides are readily obtained.

EXPERIMENTAL

Synthesis of Sulfonamides

$NHTf_2$ (0.3 equivalent (eq.)) in anhydrous (anh) CH_2Cl_2 was degassed by freeze–thaw cycles on the vacuum line. SO_2 (20 eq), dried by passing through a column packed with phosphorus pentoxide and aluminum oxide, was transferred on the vacuum line to the CH_2Cl_2 solution frozen at -196°C. The mixture was allowed to melt and to warm to -78°C. After 30 min at this temperature a solution of diene (1 eq) and the enoxysilane (1.3 eq) in CH_2Cl_2 were added dropwise under vigorous stirring and Ar atmosphere. The mixture was stirred at -78°C for 12 h. At this temperature, the excess of SO_2 and the solvent were evaporated under reduced pressure (10^{-1} Torr) to dryness (1 h) while temperature slowly reached 20°C. Halogenating agent (NCS, 1.1 eq) was added at -20°C. After 1 h at this temperature, the dark mixture was transferred into a solution of the amine (1.2 eq) in pyridine under Ar atmosphere. The mixture was finally stirred at this temperature for 2 h, and poured into a mixture of ice water and Et_2O. The organic phase was washed with an aqueous saturated solution of $CuSO_4$. The combined organic extracts were washed with brine, dried (Na_2SO_4), and the solvent evaporated under reduced pressure under reflux. Purification by flash column chromatography on silica gel gave a yellowish oil.

Synthesis of Polyketide Fragments

A two-necked flask was dried by flame and filled with Ar, and then CH_2Cl_2 and Lewis Acid (LA) were introduced. The mixture was cooled by liquid N_2 and connected to the vacuum. An excess of SO_2 was condensed into the flask, which was allowed to warm to -80°C by using an acetone–dry ice cooling system. After 30 min, the mixture of diene (1 eq) and enoxysilane (2 eq) in CH_2Cl_2 was added dropwise. Stirring was continued overnight at -84°C. Then, all the SO_2 and CH_2Cl_2 were evaporated under vacuum. The resulting viscous mixture was dissolved into anh. CH_3CN. In another flask, a mixture of $Pd(OAc)_2$ (0.1eq), PPh_3 (0.1eq), and anh. K_2CO_3 (1 eq to the LA) was prepared. The solution of the resulting mixture in CH_3CN was added, followed by the addition of isopropanol. The resulting mixture was heated to 80°C for 30 min. Then sat. aq. $NaHCO_3$ solution was added and the mixture was extracted by ether. The organic phase was separated and washed with brine and dried (Na_2SO_4). After solvent evaporation, flash column chromatography on silica gel gave the corresponding alkenes (polypropionate fragments).

(−)-(1*Z*,2*S*,3*R*,4*S*)-1-Ethylidene-2,4-dimethyl-5-oxo-3-((1″*S*)-1-phenylethoxy)-heptylisobutyrate (19)

$[\alpha]_{589}^{25} = -18$ (c = 0.5, $CHCl_3$); IR (film): 2966, 2879, 1756, 1710, 1612, 1460, 1383, 1135; ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.32–7.24 (m, 5H, arom), 5.21 (q, $J = 6.8$ Hz, 1H), 4.44 (q, $J = 6.8$ Hz, 1H), 3.77 (t, $J = 5.5$ Hz, 1H), 2.69 (dq, $J = 5.5$, 6.8 Hz, 1H), 2.64 (m, 2H), 2.19 (dq, AB-syst, $J = 17.9$, 7.4 Hz, 1H), 2.09 (dq, AB-syst, $J = 17.9$, 7.4 Hz, 1H), 1.45 (dd, $J = 6.8$, 1.2 Hz, 3H), 1.37 (d, $J = 7.4$ Hz, 3H), 1.22 (d, $J = 6.8$ Hz, 6H), 1.10 (d, $J = 7.4$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.82 (t, $J = 7.4$ Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100.6 MHz): 213.0, 174.1, 149.6, 143.6, 128.3, 127.5, 126.8, 112.5, 76.9, 76.7, 47.8, 40.9, 34.2, 33.9, 23.6, 19.2, 19.1, 13.3, 12.5, 10.9, 7.7; anal. calcd. for $C_{23}H_{34}O_4$ (374.51): C 73.76, H 9.15; found C 73.77, H 9.09; MALDI-HRMS calcd. for $C_{23}H_{34}O_4Na^+$ 397.2355; found 397.2345.

((±)-(4*RS*, 5*RS*,7*Z*,8*RS*)-5-(Benzyloxy)-*N*,*N*-diethyl-4,6-dimethyl-3-oxonon-7-ene-8-sulfonamide (13a)

IR (film): ν 2974, 2875, 1713, 1455, 1332, 1140, 1010, 937, 737 cm^{-1}; UV (CH_3CN): $\lambda_{max} = 230$ ($\varepsilon = 6432$);[1] H NMR (400 MHz, $CDCl_3$): δ 7.35–7.28 [m, 5H, Ph(Bn)], 6.95 (d, 1H, $J = 4.5$), 6.44 (d, 1H, $J = 4.5$), 5.57 (d, 1H, $^3J = 9.2$), 4.48 [d, 1H, $^2J = 12.0$, CH_2(Bn)], 4.34 (d, 1H,

$^3J = 8.0$), 4.24 [d, 1H, $^2J = 12.0$, CH_2(Bn)], 4.02 (qd, 1H, $^3J = 9.0$, $^3J = 6.8$), 2.98 (p, 1H, $^3J = 7.7$), 2.53 (qd, 1H, $^2J = 18.8$, $^3J = 7.1$), 2.41 (qd, 1H, $^2J = 18.8$, $^3J = 7.1$, H), 1.79 (s, 3H), 1.32 (d, 3H, $^3J = 6.8$), 1.03 (t, 3H, $^3J = 7.1$); ^{13} C NMR (100.6 MHz, $CDCl_3$): δ 213.2,140.1, 130.6, 125, 124.0, 122.7, 108.0, 70.1, 56.9, 49.3, 43.5, 36.4, 19.1, 16.7, 13.9, 7.4; CI-MS (NH_3): m/z = 454 [100, $(M + 18)^+$], 437 [20, $(M + 1)^+$].

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