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Synthesis of Long-Chain Polyketide Fragments by Reaction of 1,3-Dioxy-1,3-dienes with Allylsilanes: Umpolung with Sulfur Dioxide

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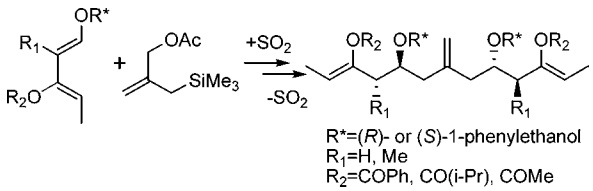
ABSTRACT



In the presence of a Lewis or protic acid and at low temperature, 1,3-dioxy-1,3-dienes add to sulfur dioxide generating zwitterionic intermediates that can react with carbon nucleophiles such as allylsilanes. After a retro-ene elimination of SO_2, valuable polyketide precursors are obtained.

Natural polyketides show important biological activity. A large number of methodologies toward these targets have already been developed.[1] Nevertheless, more efficient and versatile synthetic strategies are needed. We recently reported[2,3] a new asymmetric C−C bond-forming reaction **1** + **2**→**3** (Scheme 1). The strategy involves a cascade of reactions starting with the hetero-Diels−Alder addition of SO_2 to a 1,3-dienyl ether **1**, giving the corresponding sultine **4**[4] that is ionized to zwitterionic intermediate **5**, which is then added to enoxysilanes (oxyallylation) to give silyl sulfinates **6** that can be alkylated or allylated in situ to provide the corresponding sulfones.[5] We wish to report here the logical extension of this strategy to allylsilanes and to the synthesis of polyketide fragments via two-directional chain elongation.[6]

Unfortunately, when dienes **1** and various allylsilanes (see Table 1) were reacted with an excess of SO_2 in the presence of a Lewis or protic acid promoter, no product of condensation was observed. The allylsilanes reacted too rapidly with SO_2 in ene reactions giving the corresponding β,γ-unsaturated silyl sulfinates,[7] thus giving no chance to the allylsilanes to react with the intermediate zwitterions **5**.

In an exploratory study with achiral 1-benzyloxy-3-acetoxydiene **8**[3a] and allylsilanes **9** and **10**, we found that the best acid promoter is $(CF_3SO_2)_2NSiMe_3$ (Tf_2NTMS).[8] In a typical experiment, diene **8** and allylsilane **9** or **10** (1−3 equiv) were mixed together in a 1:1 mixture of SO_2/CH_2Cl_2

Scheme 1

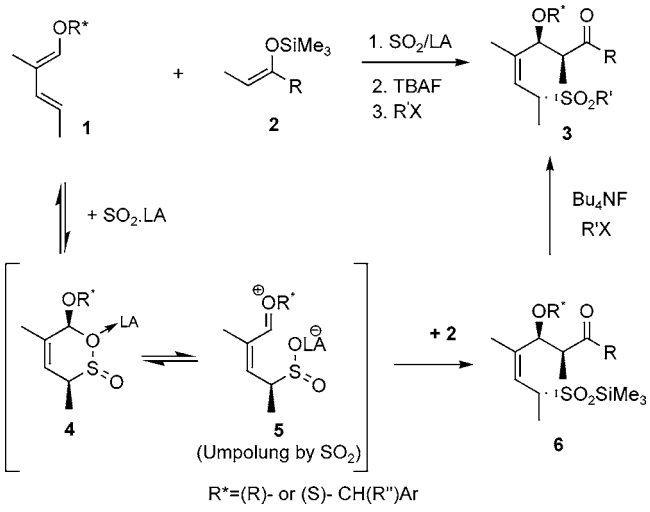


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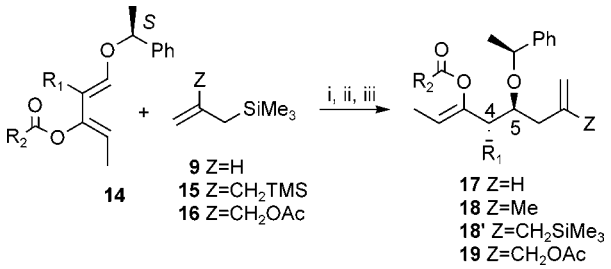
Table 1. Hydroallylation of Diene **14**[a]



entry	diene	R_1	R_2	allylsilane	product	yield (%)
1	**14a**[b]	Me	^{i}Pr	**9**	**17a**	68[d]
2	**14b**	Me	Ph	**9**	**17b**	70[d]
3	**ent-14c**[c]	H	Ph	**15**	**18a**	69[g]
4	**14b**	Me	Ph	**15**	**18b**	74[d]
5	**14a**[b]	Me	^{i}Pr	**16**	**19a**	69[e,f]
6	**14b**	Me	Ph	**16**	**19b**	71[e,f]
7	**ent-14c**[c]	H	Ph	**16**	**ent-19c**	52[e,f]

[a] Reaction conditions: (i) $CH_2Cl_2/SO_2/Tf_2NTMS$, −78 °C; (ii) evaporation of SO_2; (iii) $MeOH/Et_3NH^+TfO^-$, −78 °C. [b] Racemic. [c] Opposite enantiomer starting from (*R*)-1-phenylethanol. [d] Anti:syn = 11:1. [e] Single product. [f] Using PhMe instead of CH_2Cl_2 as a cosolvent with SO_2. [g] Diastereoselectivity = 9:1.

containing the acid promoter and cooled to −78 °C. The mixture was allowed to react for ca. 16 h at −78 °C, followed by evaporation of SO_2 and addition of MeOH containing $Et_3NH^+TfO^-$. After aqueous workup and flash chromatography, products **13a** and **13b** were obtained in 68 and 34% yields, respectively, with an anti/syn (centers C(4), C(5)) ratio of 11:1. To our knowledge, this is the first time that a buffer such as $Et_3NH^+TfO^-$ has been used to desilylate silyl sulfinates (**11** identified by ^{1}H and ^{13}C NMR when running the reaction in an NMR tube) and to induce the subsequent desulfitations **12**→**13** by retro-ene elimination of SO_2 at low temperature.[5a,9]

With acid promoters such as $Yb(OTf)_3$, $BF_3{\cdot}Et_2O$, and (*t*-Bu)Me_2SiOTf, reactions **8** + **9** and **8** + **10** failed to give any trace of the desired products **13**. With $TiCl_4$, these reactions had low yields of 10 and 5%, respectively. As $(CF_3SO_2)_2NH$ promoted reaction **8** + **9**→**13a** with a yield of 19%, other protic acids ($HClO_4$, FSO_3H, CF_3SO_3H, TsOH) have been explored as promoters but with little success, except for 1:1 (*R*)-1,1′-bi-2-naphthol/$SbCl_5$, where reaction **8** + **9** gave **13a** in 28% yield (same anti/syn diastereoselectivity, no chiral induction by HPLC).

We then turned to an asymmetric version of our process and identified (*R*)- and (*S*)-1-phenylethanol (relatively cheap and commercially available) as appropriate chiral auxiliaries. Dienes **14a**−**c**[10] were used in our study together with allylsilanes **9**, **15**, and **16** (Table 1). Using Tf_2NTMS as an acidic promoter, all our reactions led to the same anti/syn (centers C(4), C(5)) diastereoselectivity of 11:1[11] and products **17**−**19** were isolated in good yields. There were no other detectable (<3%) diastereomeric products, showing that (*R*)- and (*S*)-1-phenylethanol are good chiral auxiliaries for the preparation of these polyketide fragments. With allylsilane **15**, we had hoped to be able to isolate intermediates **18′** with Z = CH_2SiMe_3 useful for a second hydroallylation reaction (see below). Unfortunately, due to the competing ene-reaction with SO_2, the latter were rapidly converted into the corresponding β,γ-unsaturated silyl sulfinates. Under our aqueous workup conditions the latter were rapidly hydrolyzed and desulfitated (retro-ene elimination of SO_2) to give exclusively products **18** (Z = CH_2SiMe_3→Z = CH_3). With [2-(acetoxymethyl)allyl]trimethylsilane (**16**),[12] dienes **14a**, **14b**, and **ent-14c** gave products **19a**, **19b**, and **ent-19c**, respectively, that were isolated as single, pure diastereoisomers in 69, 71, and 52% yields after flash chromatography on silica gel.

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(11) For details, see Supporting Information.

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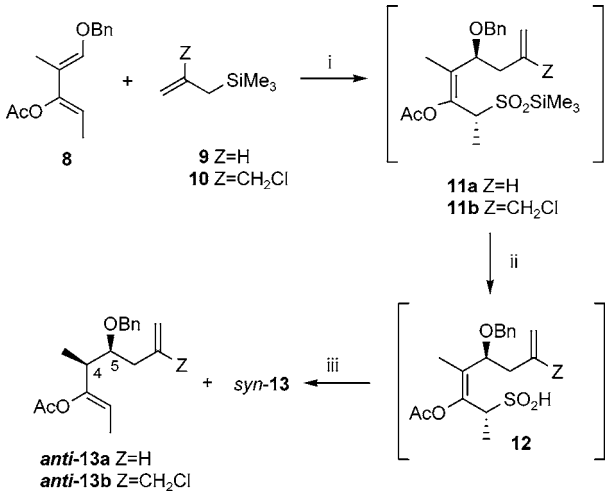
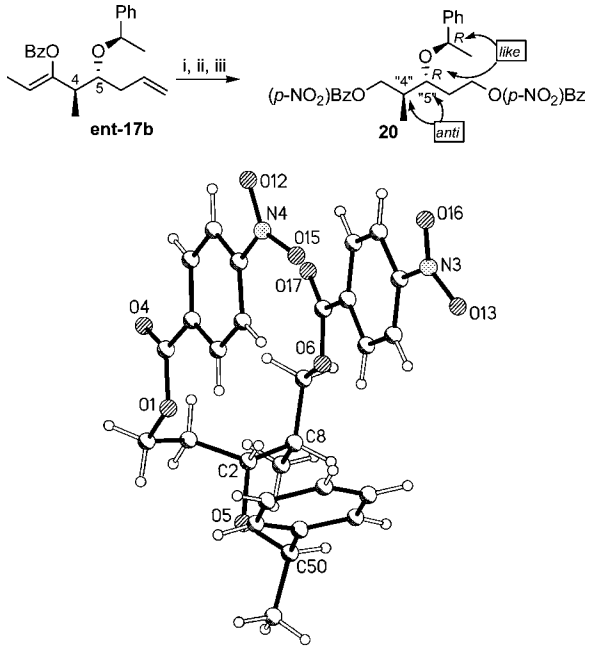
Scheme 2 [a]



[a] Conditions: (i) excess SO_2/CH_2Cl_2, acid promoter (LA), −78 °C; (ii) evaporation of SO_2; (iii) MeOH/$Et_3NH^+TfO^-$, −78 °C.

The relative configuration between the C(5) center and the phenethyl chiral auxiliary in products **17**−**19** has not been established unambiguously. However, in the case of **ent-17b** (derived from (*R*)-1-phenylethanol), its ozonolysis and subsequent reduction with $LiAlH_4$ followed by double esterification with *p*-nitrobenzoyl chloride provided a crystalline derivative **20**,[13] the stucture of which could be determined by X-ray crystallography (Scheme 3). As for all other cases reported so far,[2,3] a like relationship (*R*,*R* or *S*,*S*) between the benzylic center of the chiral auxiliary and the adjacent

Scheme 3 [a]

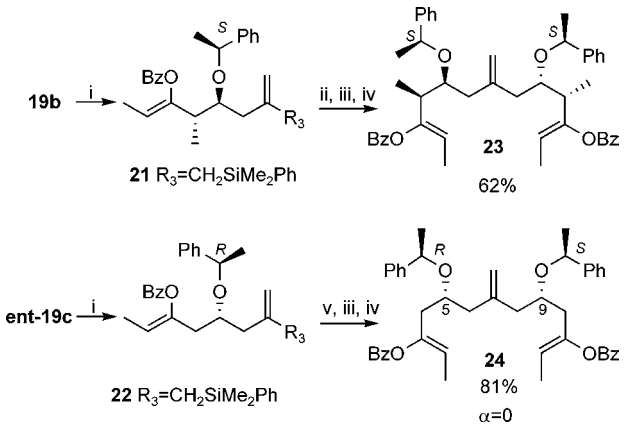


[a] Conditions: (i) (a) O_3/Et_2O/−78 °C, (b) DMS; (ii) LAH/Et_2O, 70%; (iii) (*p*-NO_2)BzCl/DMAP, 81%.

carbon center C(5) was observed. Moreover, this structure confirmed the C(4)/C(5) anti relationship. It is thus proposed that the same stereocontrol occurs in all reactions **14**→**17**, **18**, **19**.

Ally acetates **19b** and **ent-19c** underwent quantitative substitutions with $(Me_2PhSi)_2Cu(CN)Li_2$,[14] providing allylsilanes **21** and **22**, respectively (Scheme 4).

Scheme 4 [a]

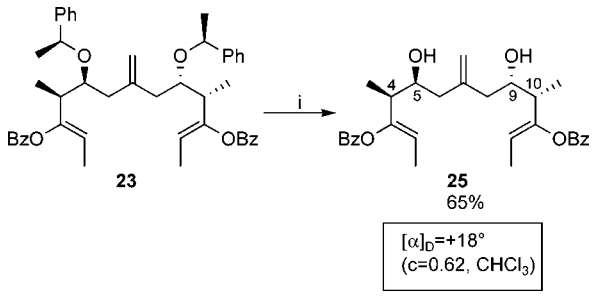


[a] Conditions: (i) $(Me_2PhSi)_2Cu(CN)Li_2$, quant.; (ii) **14b**/SO_2/Tf_2NTMS/PhMe, −78 °C; (iii) evaporation of SO_2; (iv) MeOH/$Et_3NH^+TfO^-$, −78 °C; (v) **14c**/SO_2/Tf_2NTMS/PhMe, −78 °C; (vi) $BF_3{\cdot}OEt_2$/EtSH.

In the presence of 2 equiv of diene **14b**, **21** reacted with SO_2 to give the pseudo-C_2-symmetrical product **23** in 62% yield (Scheme 4). Polyketide fragment **24** was prepared in the same way from **22** in 81% yield.

The relative configuration of products **23** and **24** was determined by measurements of the optical rotation (α). Centers C(4)/C(5) and C(9)/C(10) always have an anti relationship, which arises from highly stereoselective retro-*ene* reactions. Optical rotation measured for diol **25** (α ≠ 0) demonstrates the 5,9-anti relationship of the diol moiety (Scheme 5). In contrast, α = 0 found for product **24** is consistent with the 5,9-syn relative configuration. In both cases, the configuration of the newly created stereogenic centers is controlled by the chiral auxiliary.

Scheme 5 [a]



[a] Conditions: (i) $BF_3{\cdot}OEt_2$/EtSH.

Our C−C bond-forming reaction (reaction cascade: hetero-Diels−Alder addition of SO_2, ionization of intermediate sultine, electrophilic addition to enoxysilane (and now allylsilanes), silyl-sulfinate hydrolysis, and desulfitation via retro-*ene* elimination of SO_2) allows one to prepare diastereomerically pure, long-chain polyketide and polypropionate fragments by double-chain elongation. This is possible only with (*E*,*E*)-1-benzyloxy-3-acyloxypenta-1,3-dienes reacting with [2-(acetoxymethyl)allyl]trimethylsilane **16** in an excess of SO_2 and in the presence of Tf_2NTMS as a promoter. The method should prove to be useful for the construction of natural products and analogues. Full details will be published in due course.

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Supporting Information Available: Experimental procedures, spectral data, and stereochemical proofs for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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