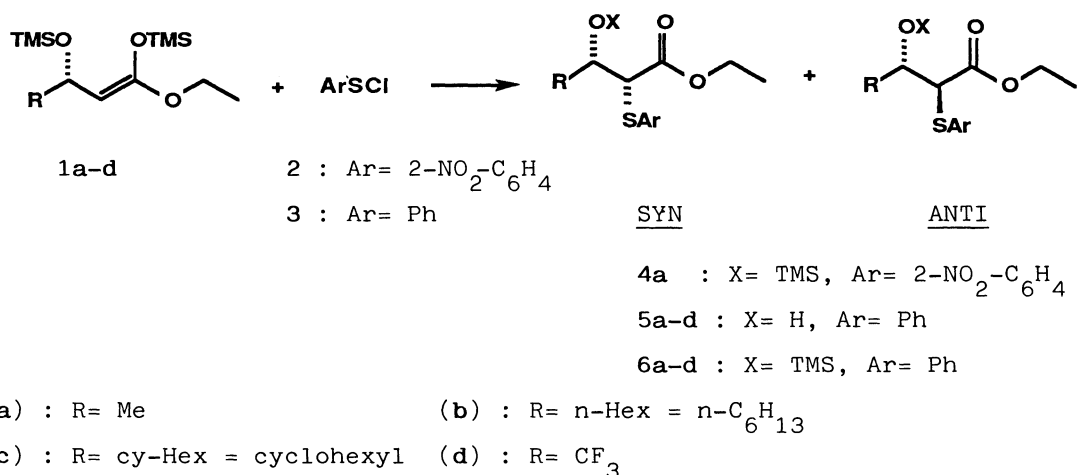


Electrophilic Sulphenylation of Silyl Ketene Acetals Derived from 3-Hydroxy-esters. Diastereoselective Synthesis of Protected Epoxyalcohols

Giuseppe GUANTI,* Luca BANFI, Enrica NARISANO, and Sergio THEA
Istituto di Chimica Organica e C.N.R., Centro di Studio sui Diariloidi,
corso Europa 26, 16132 Genova, Italy

Anti-3-Hydroxy-2-phenylsulphenyl esters are stereoselectively synthesized by reaction between silyl ketene acetals and phenyl sulphenyl chloride. Subsequent elaboration leads to protected epoxyalcohols.

Silyl ketene acetals¹⁾ are particularly useful intermediates in organic synthesis, since they can easily be generated and react with a variety of electrophiles under mild conditions. 3-Hydroxyesters, which are now available in optically pure form,²⁾ are attractive chiral starting materials, since they allow further functionalization at C-2 and chain elongation at C-1. Stereochemistry of functionalization at C-2 has been studied with some electrophiles mainly under basic conditions.³⁾ Recently, we examined both aminoalkylation under acidic conditions^{4a)} and amination^{4b)} under basic and acidic conditions.



Scheme 1.

Table 1.

Entry	R	ArSCl	mmol of ArSCl/ mmol of 1	Conditions	Yield/%	Diastereomeric ratio 4 ^{a,b)} : 5 ^{c)}
1	Me	(2)	1.1	CH ₂ Cl ₂ , r.t., 3 h	50	35 : 65
2	Me	(2)	1.1	CH ₂ Cl ₂ , 0 °C, 22 h	16	28 : 72
3	Me	(2)	2.0	PhMe, -65 °C, 3.5 h	38	21 : 79
4	Me	(3)	1.5	CH ₂ Cl ₂ , r.t., 1.5 h	66	26 : 74 ^{d)}
5	Me	(3)	1.5	CH ₂ Cl ₂ , -78 °C, 20 h	68	20 : 80 ^{d)}
6	Me	(3)	1.5	PhMe, r.t., 1.5 h	73	8 : 92 ^{d)}
7	Me	(3)	1.5	PhMe, -78 °C, 20 h	74	6 : 94 ^{d)}
8	n-Hex	(3)	1.5	PhMe, -50 °C, 20 h	66	15 : 85 ^{e)}
9	cy-Hex	(3)	1.5	PhMe, -85 °C, 20 h	62	18 : 82 ^{e)}
10	CF ₃	(3)	1.5	PhMe, -85 °C, 20 h	63	35 : 65 ^{f)}

a) Stereochemical attribution was not made. b) Determined by CGC. c) syn : anti ratio.

d) Determined by TLC spectrodensitometry (254 nm) and/or by weighing isolated isomers.

e) Determined by weighing isolated isomers. f) Determined by ¹H NMR spectroscopy.

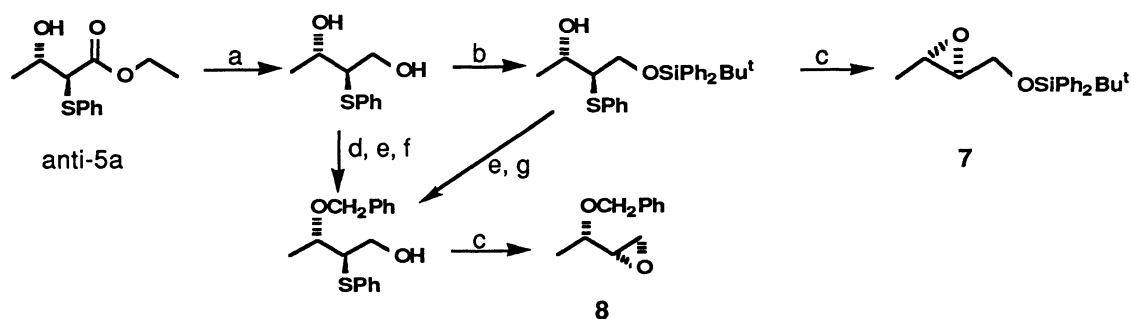
In order to extend our observations on the stereoselectivity of electrophilic additions to β -hydroxy esters, we decided to examine the course of sulphenylation of silyl ketene acetals⁵⁾ derived from 3-hydroxy esters, under neutral conditions. Arenesulphenyl chlorides were chosen as sulphur electrophiles (Scheme 1 and Table 1).⁶⁾ The reaction of 1-ethoxy-1,3-bis(trimethylsilyloxy)but-1-ene (1a) with 2-nitrosulphenyl chloride (2) was tried first under various conditions, but ethyl 3-trimethylsilyloxy-2-(2-nitrophenylthio)-butyrate (4a) was always obtained in rather disappointingly low chemical and stereochemical yield. On the contrary, phenylsulphenyl chloride (3) gave ethyl 3-hydroxy-2-(phenylthio)butyrate (5a) in good chemical and stereochemical yield.⁷⁾ Most likely 5a derives from desilylation of 6a under reaction work-up. The two stereoisomers could be easily separated by column chromatography and identified on the basis of coupling constants ³J_{2,3} in their ¹H NMR spectra.⁸⁾ Quite surprisingly, the major isomer was the anti one, opposite to the stereoselectivity observed in reaction of 1a with other electrophiles like benzylideneaniline^{4a)} (carbon electrophile) and benzenediazonium tetrafluoroborate^{4b)} (nitrogen electrophile). Solvent seems to influence to some extent the stereochemical outcome (entries 4,6 vs. 6,7). It must be stressed that in the present case, where no catalyst is required, the electrophile is a formally neutral species, while both diazonium salt and imine-trimethylsilyl triflate complex have cationic character; nevertheless, it has also been reported^{5c)} that phenylsulphenyl chloride and 1,3-dithienium tetrafluoroborate (cationic electrophile) attack in the

same stereochemical sense, when chiral O-silylated imide enolates (with the asymmetric centre located in the amine moiety) are used. Other electrophiles should be tried before any sound hypothesis could be drawn.

In a typical procedure, 6.15 mmol of **1a** were dissolved in dry PhMe (40 ml) at $-78\text{ }^{\circ}\text{C}$ and treated with phenylsulphenyl chloride (9.22 mmol) dissolved in 15 ml of dry PhMe. After 20 h, column chromatography of the crude reaction mixture afforded pure anti and syn **5a**.

In order to test the generality of this sulphenylation, the reaction was applied to various silyl ketene acetals (**1b,c**): chemical and stereochemical results are reported in entries 8-10 of Table 1. It must be stressed that, when **1c** and **1d** were used (entries 9 and 10), a mixture of **5** and **6** was obtained. Efforts to deprotect **6** to **5** in situ, adding a CH_2Cl_2 solution of $n\text{-Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$ (TBAF) after completion of the reaction at $-85\text{ }^{\circ}\text{C}$, were fruitless. Thus, **6** obtained from column chromatography of the crude reaction mixture was subsequently treated either with HCl in THF-water (for **6c**) or with TBAF in CH_2Cl_2 (for **6d**) for 1 min at room temperature to give **5** in quantitative yield. Yields and diastereomeric ratios reported in Table 1 are determined on deprotected product **5**. Low stereoselectivity of entry 10 could be due to the high reactivity of **1d**.

In order to show an application of these α -sulphenyl- β -hydroxyesters, we converted racemic anti-**5a** into both protected trans-2,3-epoxybutan-1-ol (**7**) and syn-3,4-epoxybutan-2-ol (**8**) following Scheme 2.⁹⁻¹⁰ It should be noted that, while epoxides like **7** can be synthesized enantioselectively through Sharpless epoxidation,¹¹ the preparation of **8** and its analogues by the epoxidation with kinetic resolution of racemic 3-hydroxy-1-alkenes is not feasible, since that method is known to afford anti-derivatives, which are diastereomeric to **8**.¹²



a) LiAlH_4 , THF, $0\text{ }^{\circ}\text{C}$, 60%; b) $t\text{-Bu}(\text{Ph})_2\text{SiCl}$, imidazole, CH_2Cl_2 , r.t., 85%; c) Me_3OBF_4 , CH_2Cl_2 , then 0.5 M NaOH, r.t., 40%; d) Ph_3CCl , pyridine, r.t., 48 h, 71%; e) PhCH_2Br , NaH, DMF, r.t., 30 min, 95%; f) CF_3COOH , $t\text{-BuOH}$, r.t., 69%; g) $n\text{-Bu}_4\text{NF}\cdot 3\text{H}_2\text{O}$, CH_2Cl_2 , r.t., 24 h, 51%.

Scheme 2.

We thank the C.N.R. and the Ministero della Pubblica Istruzione for financial support.

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- 6) Although racemates were used in this work, only one enantiomer is arbitrarily shown for the sake of clarity.
- 7) Diphenyldisulphide did not react with **1a** either in the presence or in the absence of a catalyst ($\text{Me}_3\text{Si}-\text{OTf}$ or TiCl_4). Reaction with PhSCl or PhSSPh via the enolate gave only poor yields.
- 8) 6.3 Hz for syn-5a and 7.3 Hz for anti-5a (see T. Fujisawa, T. Itoh, and T. Sato, *Tetrahedron Lett.*, 25, 5083 (1984)).
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(Received June 24, 1988)