A Route to Unsaturated Spiroketals from Phenylthio Hex-2-enopyranosides *via* Sequential Alkylation, Allylic Rearrangement and Intramolecular Glycosidation

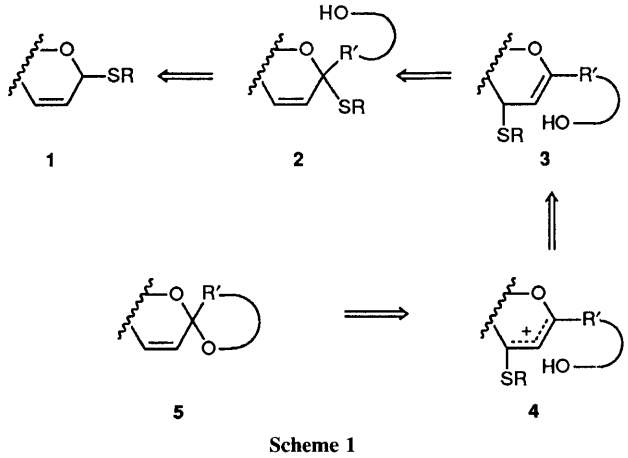
Ana M. Gomez,[a,b] Serafin Valverde*[a] and Bert Fraser-Reid*[b]

[a] *Instituto de Quimica Organica General, 28006 Madrid, Spain*
[b] *Paul M. Gross Chemical Laboratory, Department of Chemistry Duke University, Durham, North Carolina 27706, USA*

Alkylated phenylthio hex-2-enopyranosides readily undergo 1,3-phenylthio migration, and treatment of the resulting enol ether with *N*-iodosuccinimide gives an allyl-oxocarbenium ion which can be trapped intramolecularly by a suitably located hydroxy group to yield an unsaturated spiroketal.

Spiroketals are important subunits of a variety of naturally occurring compounds of biological and synthetic interest[1] and although several methods have been developed for the syntheses of saturated members, only a few are available for preparation of the unsaturated counterparts,[1a,2] of which avermectin[3] is a prominent example. A novel strategy for this synthetic objective (Scheme 1) takes advantage of recent developments in the chemistry of phenylthio hex-2-enopyranosides: the ability to alkylate the anomeric centre,[4] *e.g.* **1** → **2**, and the facile 1,3-sigmatropic thioallylic rearrangement,[5] *e.g.* **2** → **3**, of the 4-deoxy species.† The availability of the latter, a 3-deoxy-3-phenylthio glycal, promised ready access to a delocalized allyl oxo-carbenium ion[6] **4**, which, in keeping with ample precedent,[1] should suffer nucleophilic attack α to the ring oxygen.[6,7] Thus if a suitably located hydroxy group were present **4**, the product should be an unsaturated spiroketal, *e.g.* **4** → **5**. In this manuscript, we report on the implementation of this strategy as a route to 1,7-dioxaspiro[5.5]undec-3-enes and 1,7-dioxaspiro[5.5]undeca-4,10-dienes.

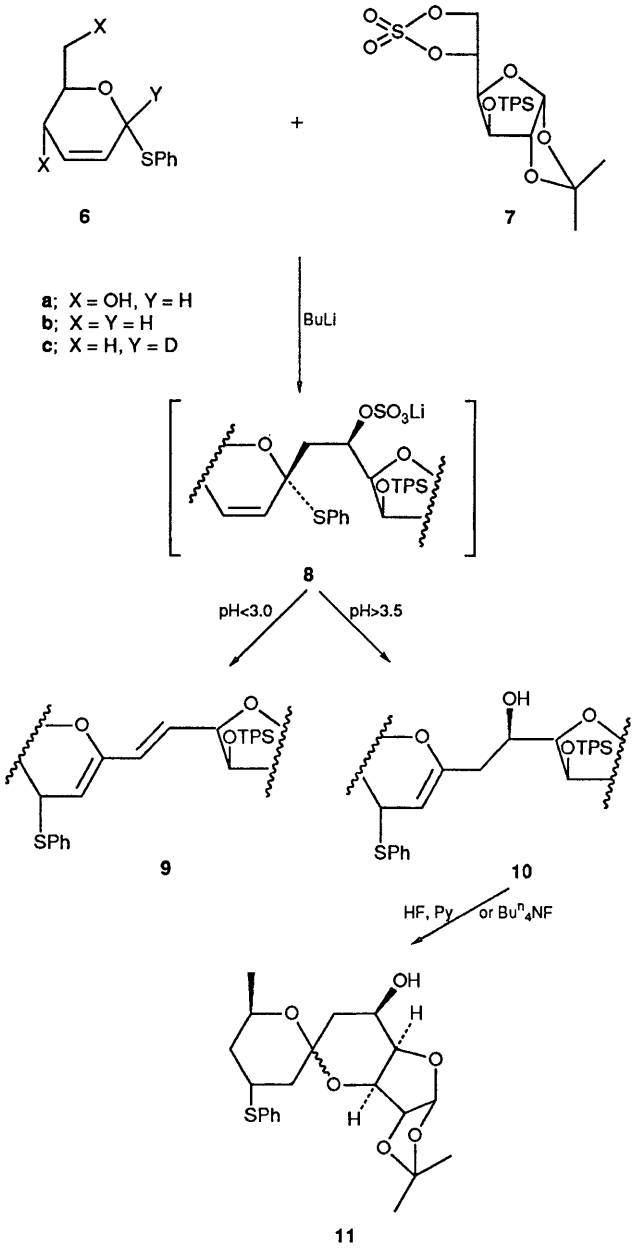
Compound **6b** was readily prepared by C4 and C6 dideoxygenation of the known phenylthio-2,3-dideoxy-α-D-*erythro*-hex-2-eno-pyranoside **6a**.[4] For the alkylating agent we chose to examine cyclic sulphates‡ whose utility has been demonstrated by Moon Kim and Sharpless.[8] Thus compound **7**, prepared from diacetone glucose by routine transformations, was chosen for preliminary investigation. Indeed reaction with the anion of **6b** gave rise to a very polar product, presumably **8**, which was treated *in situ* with a catalytic amount of concentrated sulphuric acid in the presence of 0.5 equivalents of water following the procedure of Sharpless.[8b] When the hydrolysis was carried out at pH > 3.5, the product was the enol ether **10** along with the small amount of the diene **9** (Scheme 2). However when the hydrolysis was done at pH < 3.0, the reaction gave rise only to diene **9**, this being a single



Scheme 1

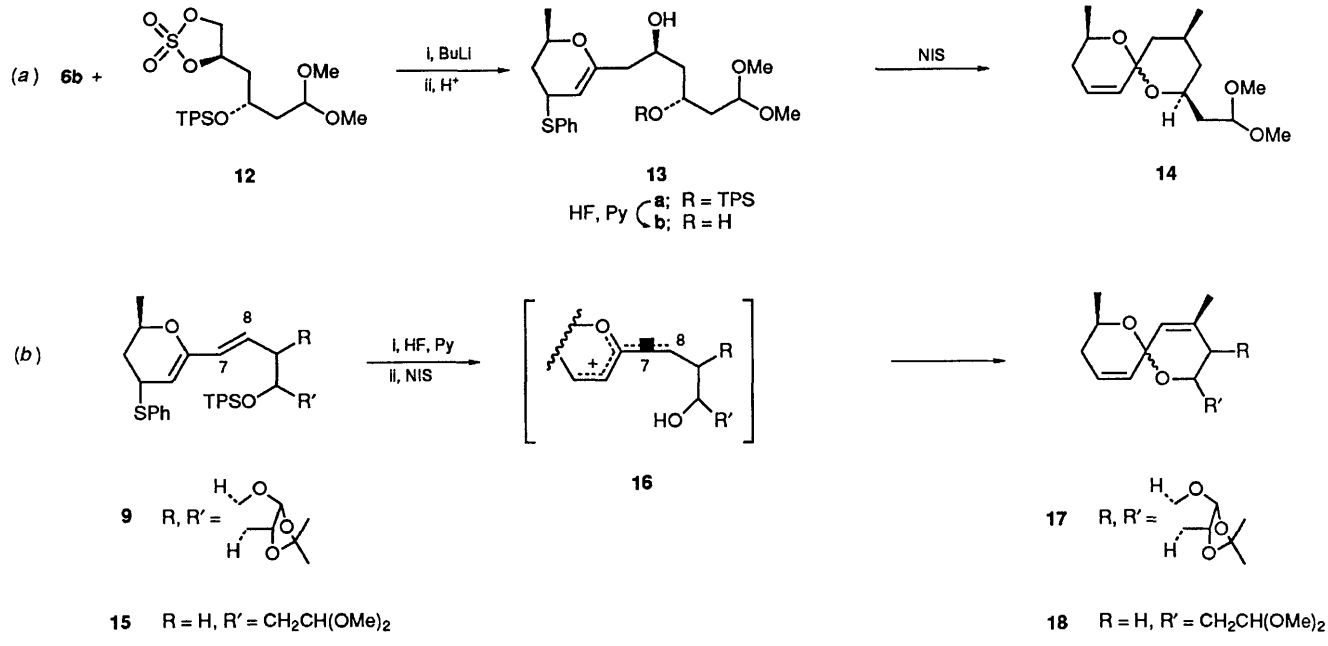
† 1,3-Sigmatropic rearrangement is observed only in the case of the 4-deoxy pyranosides. The 4-oxygenated analogues do not suffer rearrangement.

‡ Previous attempts to use the corresponding epoxides were unsuccessful.



Scheme 2§ TPS = Bu^tPh_2Si

§ All new compounds gave satisfactory spectroscopic and elemental or high-resolution mass spectral data.



Scheme 3§

geometric isomer ($J_{7,8}$ = 15.6 Hz). The isolation of **9** and **10** indicated that a 1,3-sigmatropic rearrangement had indeed occurred to give the more substituted double bond. The ^{1}H NMR spectra of these compounds showed that only one of the C3 epimers was formed.

The stereochemical course of alkylation was checked by treating the metallated product from **6b** with D_2O. A single deuteriated phenylthio glycoside was obtained whose structure was assigned as **6c** on the basis of ^{1}H NMR comparison of the chemical shifts of the unsaturated protons of the deuteriated compound with those of the corresponding non-deuteriated phenylthio α- and β-glycosides. Notably, during deuteriation, thioallylic rearrangement had *not* occurred, probably because the double bonds for both possible products would be equally substituted. However, on the basis of this result it was possible to assume that the alkylation step had taken place with retention of configuration at C1 (as in **8**).

Retention of configuration in low temperature alkylation of α-lithiated ethers[9] and glycosoyl lithiums[10] has been reported.

Compound **10** was treated with HF–pyridine to cleave the silyl ether and this led directly to the saturated spiroketal **11**. When desilylation was effected with tetra-*N*-butylammonium fluoride, spiroketal **11** was also obtained directly. These results showed that the spirocyclization of this substrate was an extremely facile process, even in basic media.

The reaction of cyclic sulphate **12**¶ was next studied, and the alcohol **13a** or diene **15** was obtained as the major product under similar conditions as those described in Scheme 2. However, with **13a**, formation of the spiroketal did not occur spontaneously upon desilylation as had occurred in **10**. Instead the diol **13b** required treatment with *N*-iodosuccinimide (NIS) for cyclization to be effected leading to the spiroketal **14**.

The dienes **9** and **15** represented an interesting case in that the *trans*-nature of the C7–C8 double bond should preclude formation of a spiroketal. However, a mechanism for double bond isomerization was conceivable *via* the delocalization of the allyl oxo-carbenium ion, represented by **16**, obtainable by iodinolysis of the phenylthio group. Indeed, treatment of the crude alcohols with NIS in methylene chloride in the presence of molecular sieves gave the unsaturated spiroketals **17** and **18** as 3 : 1 α–β mixtures in *ca.* 65% overall yield [Scheme 3(*b*)].

The last results might be explained by assuming that the reaction takes places through chemoselective attack by the electrophile at the phenylthio group of **9** and **15** rather than at the electron-rich enol ether leading to the allyl oxo-carbenium ion.

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¶ Cyclic sulphate **12** was prepared from D-glucose. Details of its preparation will be published shortly.

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