Four Chiral Centers in a One Pot Procedure. Analogues of Isosorbide

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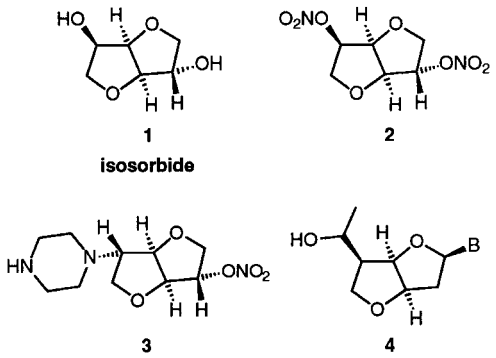
Abstract: Synthesis of analogues of isosorbide in one pot from 1-hydroxymethyl-4-phenylsulfonylbutadienes has been achieved.

In the previous paper, we have described a simple way to obtain 1-sulfonyl-1,3-dienes with adequate functionalization. These compounds have been the object of numerous studies in the last years, above all as dienes or dienophiles.[1] Furthermore, it should be noted that there are more examples with sulfoxides rather than sulfones due to the potential chirality that these substrates[2] can possess.

In our case, having developed a very easy way to get 1-sulfonyl-1,3-dienes with an allylic alcohol, we wanted to exploit this feature to produce chiral compounds by way of the Sharpless enantioselective epoxidation.[3]

In this way, we planned to develop a short synthesis of analogues of isosorbide **1**. Amino derivatives of **1** are being used as chiral auxiliaries[4] in asymmetric synthesis while the dinitro derivative **2** and the piperazine derivative **3** possess antianginal activity[5]. **1**, has been used recently as the starting material for the synthesis of novel bicyclic dideoxynucleosides as potential antiviral agents **4**.[6]



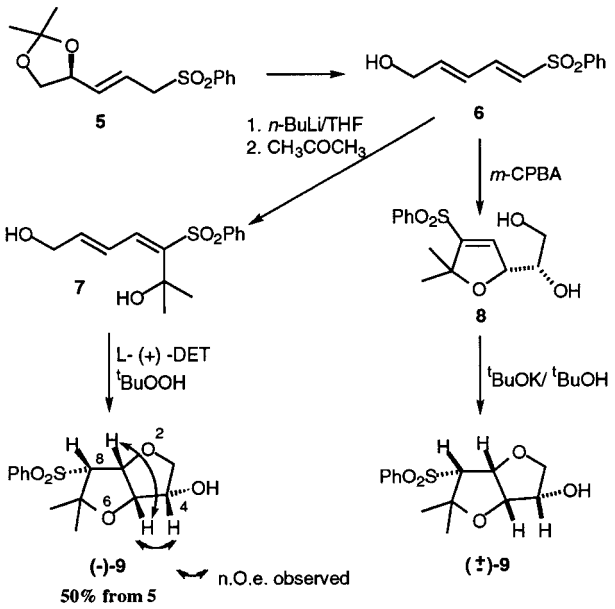
All different routes to isosorbide analogues start from isosorbide **1** as the starting material. In this context, we have found a new and versatile method to obtain analogues with different stereochemistry and functionalization, which allows not only the use of S_N2 type reactions but also the use electrophilic reagents.

Results and discussion

Compound **6** was easily obtained as described in the previous paper by treatment of sulfone **5** with *n*-BuLi/THF at -78° C (Scheme I).

Treatment of **6** with *n*-BuLi/THF followed by addition of acetone as the electrophile gives compound **7** in excellent yields (90%). When **7** reacts with *m*-CPBA it afford compound **8** directly (77%). The second cyclization proved to be difficult, with bases such as NaH or KH giving inconsistant results. However, use of Craig´s conditions[7] (^{t}BuOH/ ^{t}BuOK 5:1) gave satisfactory yields of **9** (83%).

When **7** reacts under Sharpless conditions with L-(+)-DET, after the usual work up of the reaction only homochiral (-)-**9**[8] is isolated. The stereochemistry was established by study of N.M.R. spectra and n.O.e. studies. The *CIS* relationship between H-4 and H-5 (mechanism) was confirmed by the n.O.e observed (Scheme I) and the same relationship of H-5 and H-1 was established for the existence of another n.O.e.



Scheme 1

between them. The stereochemistry of H-8 was based on its coupling constant with H-1 (J = 5.8 Hz), the other stereochemistry would give a nearly zero coupling constant, (see ref 4). This was confirmed by the existence of n.O.e between H-1 and H-8 in the bencil derivative.

So, in conclusion we have developed a short, and stereocontrolled way to obtain analogues of isosorbide. At the moment, we are trying to introduce further functionalization at C-8, and a range of electrophiles are being used in the addition step.

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(8) Spectral data for **9**:

(-)-9: $[\alpha]^{20}_{D}$= -39.9 (c=1.0, $CHCl_3$).; IR (cm^{-1}): 2930, 2857, 1719, 1290, 1152, 1084.; ^{1}H NMR (400MHz, $CDCl_3$): δ 1.60 (3H, s, Me-C7), 1.61 (3H, s, Me-C7), 3.29 (1H, d, J=5.8Hz, H-8), 3.46 (1H, dd, J=9.5 and 6.6Hz, H_B-3), 3.79 (1H, dd, J=9.5 and 5.5Hz, H_A-3), 4.08 (1H, m, H-4), 4.60 (1H, t, J=5.8Hz, H-5), 5.22 (1H, t, J=5.8Hz, H-1), 7.60 (2H, m, Ar), 7.66 (1H, m, Ar), 7.91 (2H, m, Ar); ^{13}C NMR (100Mhz, $CDCl_3$): δ 23.1 (Me-C7), 28.6 (Me-C7), 70.5 (C-8), 71.9 (C-3), 76.6 (C-4), 78.3 (C-5), 85.0 (C-1), 86.8 (C-7), 128.2 (2CH*ortho*, Ar), 129.2 (2CH*meta*, Ar), 133.9 (CH*para*, Ar), 134.0 (C*ipso*, Ar). Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08; Found: C, 56.35; H, 5.99.