Pergamon

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Synthesis of a New Spiroacetal Based Herbicide

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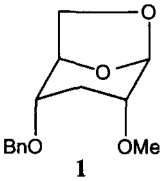
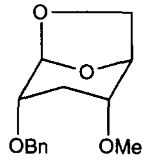
Abstract: [3R*, 5S*, 6S*]-3-Benzyloxy-5-methoxy-1,7-dioxaspiro[5.5]undecane **3** and [3R*, 5S*, 6S*]-3-methoxy-5-benzyloxy-1,7-dioxaspiro[5.5]undecane **4** were prepared making use of a base induced rearrangement of a 4,5-epoxy-1,7-dioxaspiro[5.5]undecane. © 1997 Elsevier Science Ltd.

Shell has evaluated and filed patents[1] for a range of herbicidal oxygen containing mono or bicyclic compounds which bear an aryloxy substituent β to the ring oxygen. It was established that locking of the heterocyclic ring so that the benzyloxy substituent was in an axial or pseudoaxial orientation maximised the herbicidal activity. Further examples of this cyclic ether class of herbicide based on an 8-oxabicyclo[3.2.1]octane ring system were later reported by Sammes *et al.*[2] They[3] synthesized a series of 1,6-anhydro-3-deoxyhexose derivatives in which the benzyloxy and methoxy groups were locked in axial positions by the oxymethylene bridge and found that *bis*-ethers **1** and **2**, exhibited significant herbicidal activity when applied pre-emergence.



1

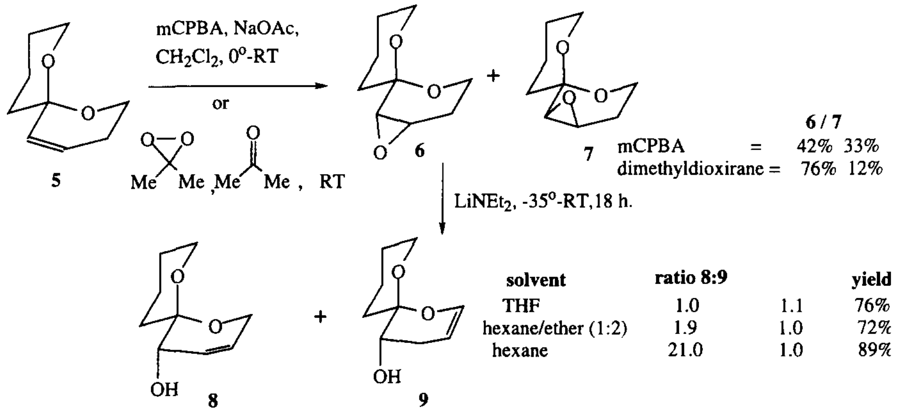


2

Given that the 1,7-dioxaspiro[5.5]undecane ring system is conformationally locked by the strong preference for the ring oxygens to adopt a bis-axial orientation with respect to each other,[4] it was decided to synthesize spiroacetal analogues of the ribosugars **1** and **2** in order to evaluate their herbicidal activity. Introduction of axial benzyloxy and methoxy groups at C-3 and C-5 on the spiroacetal ring provides spiroacetal analogues, **3** and **4**, of the ribosugars **1** and **2**, which maintain the two important structural features of the carbohydrate based herbicides: (i) the benzyloxy group is β to the ring oxygen and (ii) the C-O bond of the neighbouring ring occupies an axial position on the ring bearing the alkoxy groups.

The dominant synthetic approach to spiroacetals has focused on the acid catalysed cyclisation of dihydroxyketones or compounds containing a masked carbonyl group.[5] A synthesis of spiroacetals **3** and **4**, however, requires placement of axial alkoxy groups at C-3 and C-5. Acid catalyzed cyclisation of an appropriately functionalised dihydroxyketone precursor, however, would lead to competing formation of the corresponding diequatorial substituted ring system. The challenge of the present work therefore, was to devise a method for functionalizing a 1,7-dioxaspiro[5.5]undecane ring system avoiding acidic conditions which results in thermodynamically controlled equilibration of the spirocentre. We therefore report herein a synthesis of 3,5-diaxial substituted spiroacetals **3** and **4** making use of a stereoselective base induced rearrangement of epoxyspiroacetal **6** to axial allylic alcohol **8** (Scheme). This latter rearrangement has hitherto been unreported on a 1,7-dioxaspiro[5.5]undecane ring system and offers a versatile method to functionalise spiroacetals in a stereocontrolled manner.

Spiroacetal **5** was readily synthesized by the addition of the appropriate lithium acetylide to δ-valerolactone.[6] Subsequent epoxidation of olefin **5** using *m*-CPBA afforded the α-epoxide **6** and β-epoxide **7** with little selectivity (1.3:1, 75%), however use of dimethyldioxirane showed greater preference for the α-epoxide **6** over the β-epoxide **7** (6.3:1, 88%).[7] Dimethyldioxirane is sensitive to steric factors hence epoxidation occurs from the lower less hindered face of the olefin, however, *m*-CPBA is capable of hydrogen bonding to the oxygen of the neighbouring ring assisting competitive attack from the more hindered β-face of the molecule.

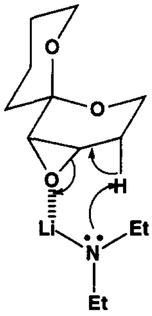


		6 / 7	
mCPBA	=	42%	33%
dimethyldioxirane	=	76%	12%

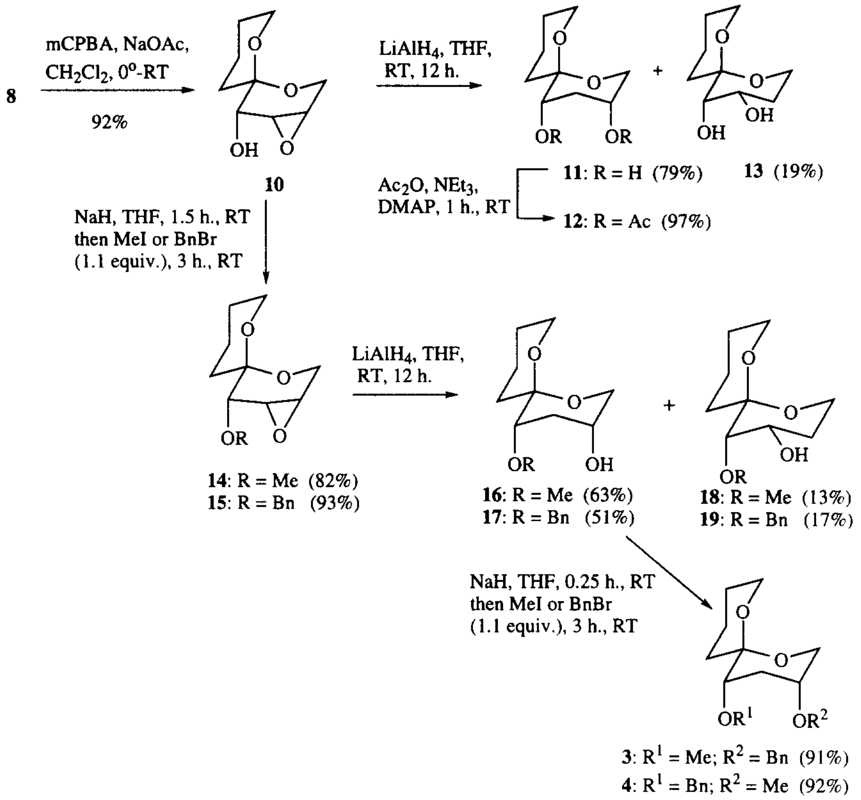
solvent	ratio 8:9		yield
THF	1.0	1.1	76%
hexane/ether (1:2)	1.9	1.0	72%
hexane	21.0	1.0	89%

Scheme 1

Treatment of the α-epoxide **6** with lithium diethylamide in THF afforded both the allylic alcohol **8** and the homoallylic alcohol **9** in approximately equal amounts however, use of a nonpolar solvent hexane suppressed the isomerization of the allylic alcohol **8** to the homoallylic alcohol **9** affording a 21:1 ratio of **8**:**9** in 89% yield. Coordination of an oxygen lone pair with the electron deficient lithium centre of the reagent sets up a transition state (Figure) in which abstraction of a *syn* proton and opening of the epoxide leads to stereoselective formation of allylic alcohol **8** with a pseudoaxial hydroxyl group at C-5.



Figure



Scheme 2

The hydroxyl group liberated in the epoxide rearrangement step was then used to direct a second epoxidation to the lower face of the alkene. Thus, treatment of alcohol **8** with *m*-CPBA buffered with sodium acetate afforded α-*syn*-epoxyalcohol **10** in 92% yield. Subsequent epoxide opening using lithium aluminium hydride proceeded smoothly affording *syn*-1,3-diaxial diol **11** in 71% yield and 4,5-diol **13** in 19% yield. Conversion of diol **11** to diacetate derivative **12** allowed ready assignment of the stereochemistry.[8]

5-H resonated as a double doublet at δ_H 4.68, $J_{5,4ax}$ 3.8 and $J_{5,4eq}$ 2.5 Hz supporting the assignment that 5-H was equatorial. 3-H resonated as a multiplet at δ_H 4.81-3.84 precluding direct assignment of the stereochemistry of 3-H, however indirect assignment of the stereochemistry for 3-H could be inferred from the clean coupling pattern for 4eq-H which resonated as a double double double doublet at δ_H 2.07, J_{gem} 15.8, $J_{4eq,5}$ 2.5, $J_{4eq,2eq}$ 2.5 and $J_{4eq,3}$ 2.5 Hz. The magnitude of the latter vicinal coupling constant established that 3-H is also pseudoequatorial.

Having established that epoxyalcohol **10** undergoes ready opening to the desired diaxial diol **11**, it then remained to introduce the appropriate alkoxy group at C-5 before the ring opening step. Thus epoxyalcohol **10** was treated with sodium hydride and methyl iodide or benzyl bromide affording methyl ether **14** or benzyl ether **15** respectively, in high yield. Reduction of methoxyepoxide **14** with lithium aluminium hydride then afforded alcohol **16** in 63% yield together with the regioisomeric alcohol **18** in 13% yield whereas benzyloxyepoxide **15** afforded alcohol **17** in 51% yield together with alcohol **19** in 17% yield. Finally benzylation of alcohol **16** afforded *bis*-ether **3** whereas methylation of alcohol **17** afforded *bis*-ether **4** in excellent yield (91 % and 92% respectively).

Spiroacetals **3** and **4** were screened for herbicidal activity and exhibited significant activity against the weeds *Avena fatua, Setaria viridis, Amaranthus retroflexus and Chenopodium album* when applied pre-emergence.[9] Bis-ethers **3** and **4** which contain alkoxy groups anchored in a 1,3-diaxial orientation on a spiroacetal ring represent the first examples of herbicides based on a spiroacetal ring system. These unusual structural features required introduction *via* a novel base induced rearrangement of an epoxyspiroacetal.

ACKNOWLEDGEMENT

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7. All new compounds were fully characterised by ^{1}H and ^{13}C NMR spectroscopy and by elemental analysis or high resolution mass spectroscopy.
8. Selected data for **12**; m.p. 96.5-97.5°C [Found: C, 57.15; H, 7.69%; M^+H (CI, NH_3), 273.1339. $C_{13}H_{20}O_6$ requires: C, 57.34; H, 7.40; M^+H, 273.1338]; υ_{max} (Nujol) cm^{-1} 1729 [s, C=O (ester)], 1089 (s, C-O); δ_H (400 MHz, $CDCl_3$) 1.31 (1H, ddd, $J_{11ax,11eq}$ 13.4, $J_{11ax,10ax}$ 13.4 and $J_{11ax,10eq}$ 4.5 Hz, 11ax-H), 1.56-1.88 (4H, m, 9-CH_2 and 10-CH_2), 1.93 (1H, dt, $J_{11eq,11ax}$ 13.4 and $J_{11eq,10}$ 3.1 Hz, 11eq-H), 2.07 (1H, dddd, $J_{4eq,4ax}$ 15.8, $J_{4eq,2eq}$ 2.5, $J_{4eq,3}$ 2.5 and $J_{4eq\ 5}$ 2.5 Hz, 4eq-H), 2.11 (6H, s, 2x Ac), 2.27 (1H, ddd, $J_{4ax,4eq}$ 15.8, $J_{4ax,3}$ 3.8 and $J_{4ax,5}$ 3.8 Hz, 4ax-H), 3.66-3.69 (2H, m, 8-CH_2), 3.82 (1H, ddd, $J_{2eq,2ax}$ 13.0, $J_{2eq,3}$ 2.5 and $J_{2eq,4eq}$ 2.5 Hz, 2eq-H), 3.91 (1H, dd, $J_{2ax,2eq}$ 13.0 and $J_{2ax,3}$ 2.1 Hz, 2ax-H), 4.68 (1H, dd, $J_{5,4ax}$ 3.8 and $J_{5,4eq}$ 2.5 Hz, 5-H), 4.81-4.84 (1H, m, 3-H).
9. Compounds were tested by Zeneca, Jealott's Hill Research Station, Berkshire, UK.

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