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Stereoselective SmI_2-mediated Conversion of Carbohydrates into Cyclopentanols

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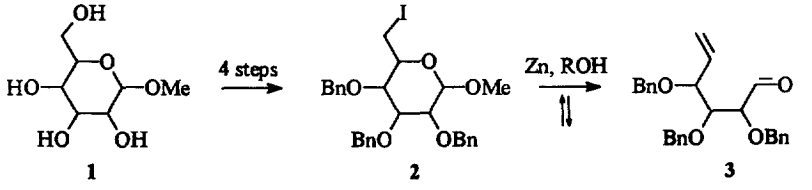
Abstract: Carbohydrate derivatives were employed as precursors in the synthesis of stereodefined cyclopentanols. This rapid conversion was effected by a zinc-assisted Grob-fragmentation, followed by a stereocontrolled SmI_2-mediated cyclisation.

The use of carbohydrates as precursors for the synthesis of cyclopentane derivatives has been explored only relatively recently.[1] Since then, significant attention has been paid to this strategy, resulting in many new syntheses of substituted, stereodefined cyclopentanes.[2] A number of these synthetic routes have been directed toward the synthesis of natural products, many of which are bioactive (and economically important).[3]

Several SmI_2-based protocols for such conversions (especially at the cyclisation step), which proceed through acyclic intermediates, have been forthcoming.[4] These reactions have, however, been limited to electron-deficient olefins (in δ,ε-unsaturated aldehydes), which minimises the propensity to undergo pinacol coupling reactions.[5] Although such cyclisations have been carried out using unactivated alkenes on simple substrates,[6] the use of analogous carbohydrate derivatives remains unknown.

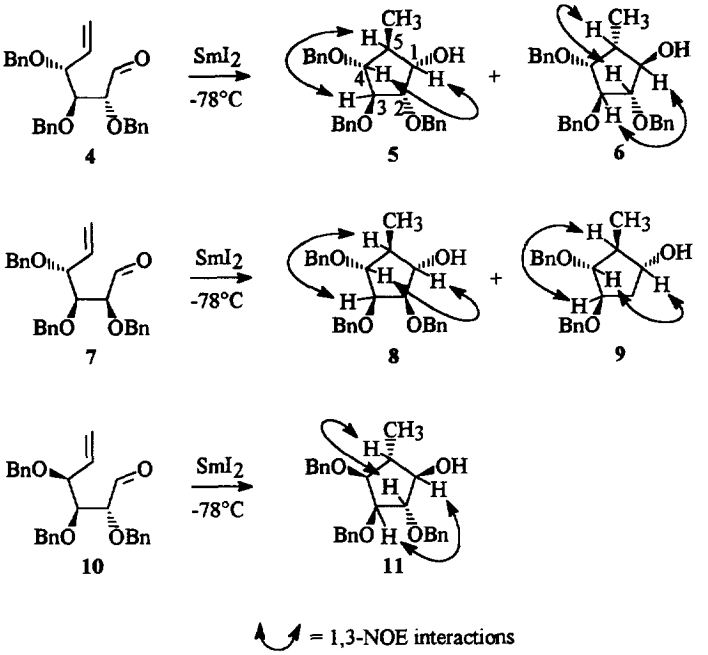
In our approach to highly oxygenated stereodefined cyclopentanols, we sought a rapid means of preparing the derivatised 5-hexenals (3), which would be employed as substrates for the SmI_2-mediated radical cyclisation thereof. These hexenals[7] were obtained by treatment of the corresponding methyl 6-deoxy-6-iodoglycoside (2) with powdered zinc in a 96% aqueous alcohol (ethanol or *n*-propanol),[8] in greater than 90% yield in all cases (see Scheme 1 for general reaction). The methyl 6-deoxy-6-iodoglycosides (2) were prepared in four high-yielding steps from the corresponding methyl glycosides (1).[9]



1 2 3

Scheme 1

Each 5-hexenal (3) was treated with SmI_2 under dilute conditions in the presence of a proton source,[10] to afford the desired cyclopentanols in good yield (typically above 65%). In this manner the cyclopentanols derived from glucose, mannose and galactose were prepared (Scheme 2).

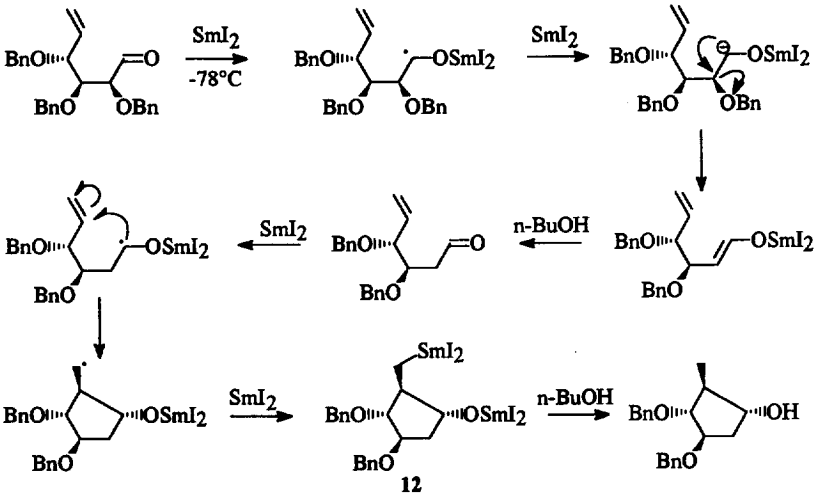


Scheme 2

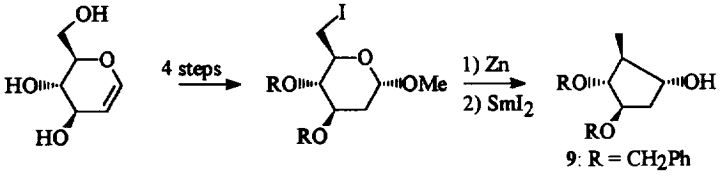
Cyclic products 5 and 6 were isolated individually in a 2:1 ratio. That two products are obtained is the result of the existing stereochemistry precluding a 1,2- **and** 4,5-*trans* configuration. In the other cases (*i.e.* products from 7 and 10) this type of configuration is possible, and the reaction furnishes these as exclusive products.

Cyclopentanol 9 arises *via* an initial SmI_2-induced elimination of the benzyloxy group α to the carbonyl functionality. This is the only case in which such an elimination was observed, and presumably occurs due to a preferred open-chain conformation that is not conducive to cyclisation. Elimination reactions of this type are not unknown in samarium(II) chemistry,[11] and have been used to effect the selective deoxygenation of certain carbohydrate derivatives.[12] A complete mechanism proposed for the establishment of cyclopentanol 9 is set out in Scheme 3.

Methyl 2,6-dideoxy-6-iodo-α,D-glucopyranosides were prepared in four high-yielding steps from D-glucal (Scheme 4).[9,13] These compounds were consecutively treated with zinc and SmI_2 as previously described, to afford the requisite deoxycyclopentanols in good yield, as single stereoisomers.



Scheme 3



R = $COC(CH_3)_3$ or CH_2Ph

Scheme 4

Subsequent manipulation at the exocyclic carbon (*e.g.* chain extension or oxidation), *via* the intermediate carbanionic species corresponding to **12** in Scheme 3, would allow a greater number and variety of products to be formed in these cyclisations. Such electrophile-quench reactions have been adequately described by others.[6,14]

In conclusion, we have devised a rapid and generally applicable means of converting selectively substituted carbohydrates into the analogous stereodefined cyclopentanols.

Acknowledgement. We thank the South African Foundation for Research and Development, AECI and SASOL for financial support.

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7. All products afforded satisfactory IR-, ^{1}H NMR-, ^{13}C NMR- and low- and high resolution mass spectra. For example, compound **11**: $[\alpha]_D^{23}$: -4.6° (*c* = 1.0, $CHCl_3$); mp.: 72-74°C; ^{1}H NMR ($CDCl_3$, Varian VXR 200): δ 1.10 (3H, d, J 7.0), 2.17 (1H, tq, J 6.9 and J 6.9), 3.50 (1H, dd, J 6.9 and J 4.4), 3.58 (1H, br dd, J 6.8 and J 4.2), 3.85 (1H, t, J 4.1), 3.90 (1H, t, J 4.1), 4.45 (1H, d, J 12.0), 4.57 (2H, s), 4.59 (1H, d, J 12.0), 4.63 (2H, s), 7.25-7.43 (15H, m); ^{13}C NMR: δ 16.4, 44.2, 71.7, 71.8, 72.1, 81.1, 82.5, 89.0, 127.6, 127.67, 127.74, 127.7, 127.8, 127.9, 128.3, 128.4, 138.15, 138.24; m/z (EI-MS, Finnigan-Matt 8200) 418 (M^+, 4%), 417 (M^+-H, 10%), 327 (M^+-C_7H_7 and H, 8%), 91 (C_7H_7, 100%); HRMS: found 418.2147, calculated for $C_{27}H_{30}O_4$ 418.2144.

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10. General procedure for the cyclisation of 5-hexenals (**3**): a solution of **3** (0.35 mmol) in THF (20 ml), HMPA (4 ml) and *n*-BuOH (1 ml) was cooled to -78°C, after which a solution of SmI_2 in THF (10.5 ml of a 0.1 M solution, 1.05 mmol) was added dropwise during 15 min. The reaction mixture was allowed to warm to 0°C during 30 min., at which time it was diluted with 1:1 hexane/EtOAc (30 ml) and washed with aqueous citric acid (20 ml of a 5% solution). The solvent was removed under reduced pressure, and the residue was chromatographed (4:1 hexane/EtOAc) on silica.

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