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Stereoselective SmI_2-mediated Conversion of Carbohydrates into Cyclopentanols

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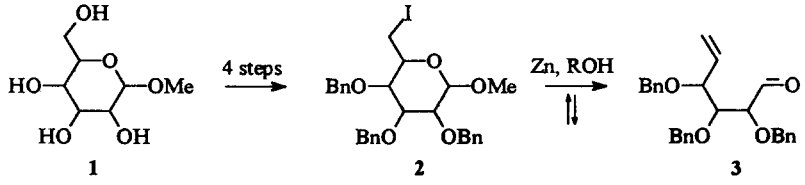
Abstract: Carbohydrate derivatives were employed as precursors in the synthesis of stereodefined cyclopentanols. This rapid conversion was effected by a zinc-assisted Grob-fragmentation, followed by a stereocontrolled SmI_2-mediated cyclisation.

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.

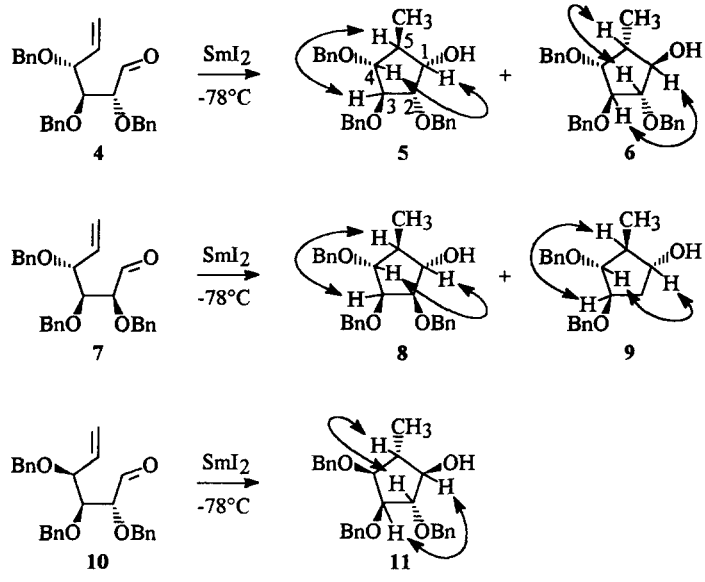
In our approach to highly oxygenated stereodefined cyclopentanols, we sought a rapid means of preparing the derivatised 5-hexenals (3), which would be employed as substrates for the SmI_2-mediated radical cyclisation thereof. These hexenals[7] were obtained by treatment of the corresponding methyl 6-deoxy-6-iodoglycoside (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).

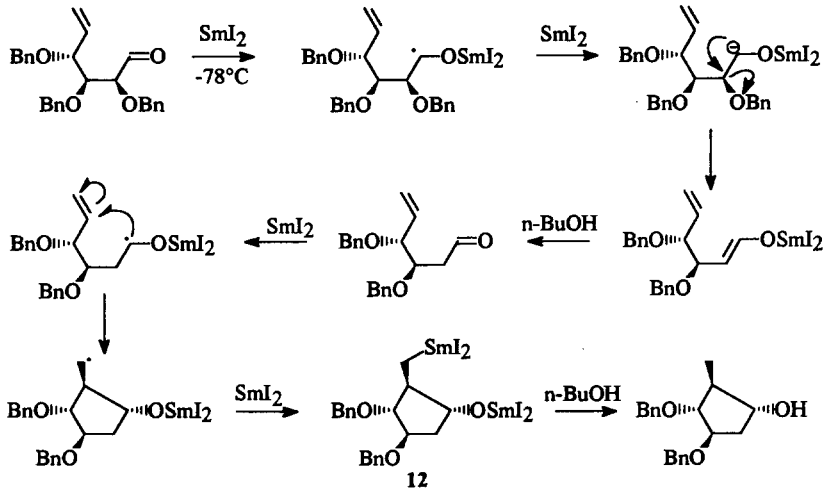


Scheme 2

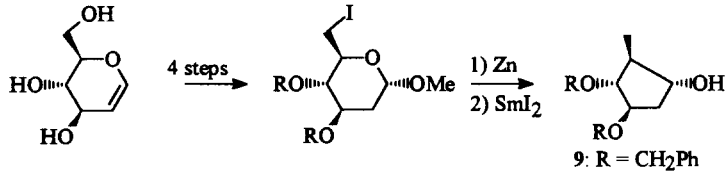
Cyclic products 5 and 6 were isolated individually in a 2:1 ratio. That two products are obtained is the result of the existing stereochemistry precluding a 1,2- and 4,5-*trans* configuration. In the other cases (*i.e.* products from 7 and 10) this type of configuration is possible, and the reaction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

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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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