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One-pot SmI_2-promoted Transformation of Carbohydrate Derivatives into Cyclopentanols

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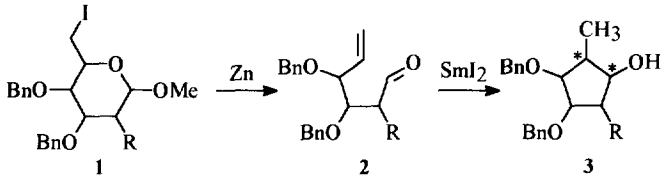
Abstract: Selectively functionalised carbohydrate derivatives underwent SmI_2-promoted Grob-fragmentation reactions. This was followed by an *in situ*, stereocontrolled SmI_2-mediated cyclisation to afford the corresponding cyclopentanols. Copyright © 1996 Published by Elsevier Science Ltd

There is currently significant interest in the construction of carbocycles from carbohydrates,[1] involving the use of SmI_2.[2] Much of this work has been directed toward the total or partial synthesis of natural products.[1]

We recently described a two-step procedure for converting various carbohydrate derivatives into stereodefined cyclopentanols.[3] Herein we report a modified, more efficient one-pot procedure for similar transformations. Our previous work[3] involved an initial zinc-assisted Grob-fragmentation[4] of methyl 6-deoxy-6-iodoglycosides (**1**), which afforded the corresponding 5-hexenals (**2**) (Scheme 1). These compounds were subsequently cyclised to stereodefined cyclopentanols (**3**) under the action of SmI_2.



1 **2** **3**

R = H, OBn.

Scheme 1

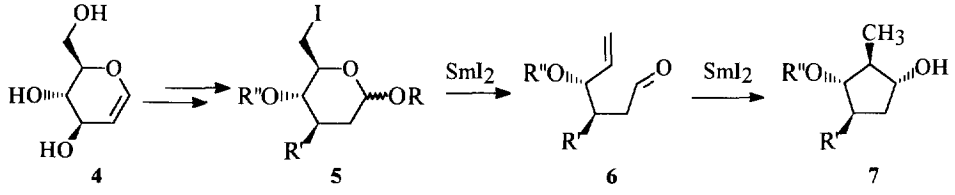
Hereafter, we sought to establish a protocol by which the Grob-fragmentation may be executed under the action of SmI_2. This transformation was found to be rather difficult in the case of methyl glycosides (**1**).

Although some of the requisite cyclopentanols (*ca.* 10%) were isolated, significant amounts of the products of simple reductive de-iodination were also obtained. Interestingly, the corresponding *t*-butyl glycosides furnished the desired cyclopentanols in noticeably improved yields (*ca.* 33%).

However, we believed that a better leaving group at the anomeric position may very well enhance the fragmentation reaction. To this end, the nucleofugal properties of the group at the anomeric position were increased by the incorporation of acetoxy- or phenoxy functionalities at that position. Thus, various functionalised phenyl 2,3,6-trideoxy-6-iodo-D-glucosides and acetyl 2,6-dideoxy-6-iodo-D-glucosides (**5**) were prepared in high-yielding steps from D-glucal (**4**).[5]

Treatment of iodoglucosides (**5**) with excess SmI_2-THF/HMPA under reflux[6] afforded the analogous stereodefined cyclopentanols (**7**), presumably *via* 5-hexenals (**6**), in good overall yields (Table 1, Scheme 2).[7] A complete mechanism for the two individual steps (fragmentation and cyclisation) is proposed in Scheme 3.

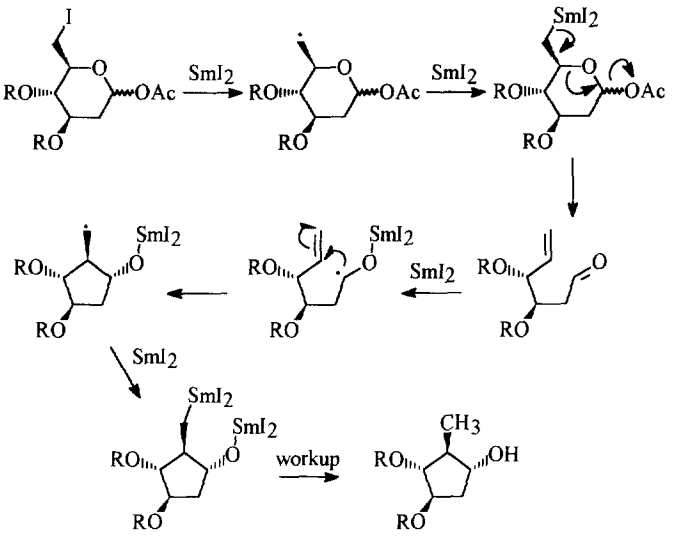
In all cases, the hydroxyl and methyl groups in the products possessed an *anti* relationship, in accordance with our previous results.[3] Confirmation of the *trans* stereochemistry was obtained from nuclear Overhauser effect data, making use of the existing stereochemistry as a reference.



Scheme 2

Table 1

Substrate				Product	Yield (%)
	R	R'	R"		
5a	Ac	OAc	Ac	**7a**	70
5b	Ac	OPiv	Piv	**7b**	72
5c	Ac	OBn	Bn	**7c**	76
5d	Ph	H	Piv	**7d**	72
5e	Ph	H	Bn	**7e**	71



Scheme 3

Although the corresponding 2-oxygenated substrates have not yet been investigated, our earlier results suggest that β-elimination will not compete significantly with cyclisation.[3]

In conclusion, we have discovered a facile, rapid means of converting appropriately functionalised carbohydrates into the corresponding stereodefined cyclopentanols. In conjunction with the use of electrophiles,[8] this methodology should allow easy access to a variety of precursor molecules of some natural products.

Our protocol nicely complements that of Sinaÿ,[9] whose methodology provides products in which the new exocyclic functionality posses a *syn* relationship.

Acknowledgements:

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5. Grové, J.J.C.; Holzapfel, C.W.; Williams, D.B.G. unpublished results. For example, synthesis of compound **5** (R = Ac, R' = OAc, R" = Ac): Selective tosylation of the primary hydroxyl group of **4**, followed by acetylation afforded the 3,4-di-*O*-acetyl-6-*O*-tolylsulphonyl-D-glucal. Addition of HOAc over the double bond (PPh_3·HBr, HOAc, CH_2Cl_2),[10] followed by iodonation (NaI, acetone, reflux), furnished the title compound in an overall yield of *ca.* 70%.

6. Typical experimental procedure: A solution of SmI_2 in THF (10.5 ml of a 0.1M solution) and HMPA (1.0 ml) was heated to reflux. Iodoglycoside (**5**) (0.21 mmol) in THF (10.0 ml) was added to this solution in a dropwise fashion during 10 min. The mixture was allowed to stir at that temperature for 2 h, after which it was allowed to cool to ambient temperature, and was diluted with 1:1 hexane/EtOAc (10.0 ml). Extraction (3×10 ml of a 5% aqueous citric acid, vacuum concentration and flash chromatography (5:1 hexane/ EtOAc) provided the pure cyclopentanol (**7**).

7. All products afforded satisfactory IR-, ^{1}H NMR-, ^{13}C NMR- and low- and high-resolution mass spectra. For example, compound **7** (R" = $COC(CH_3)_3$, R' = $OCOC(CH_3)_3$ (72%): $[\alpha]_D^{24}$ 32.2° (*c* = 1.0, in $CHCl_3$), IR (in $CHCl_3$) ν_{max} 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, Varian VXR 200) δ1.11 (3H, d, J = 7.0 Hz), 1.14 (9H, s), 1.16 (9H, s), 1.87 (1H, tq, J = 7.2 and J = 7.1 Hz), 1.93-2.18 (2H, m), 3.91 (1H, br dt, J = 6.9 and J = 6.9 Hz), 4.78 (1H, dd, J = 7.3 and J = 4.7 Hz), 5.11 (1H, dt, J = 8.1and J = 4.8 Hz); ^{13}C NMR δ 15.5, 26.99, 27.02, 38.9, 39.0, 46.8, 75.7, 76.1, 81.7, 177.7, 177.8; m/z (EI-MS, Finnigan-Matt 8200) 300 (M^+, 3%), 199 (M^+-$C_5H_9O_2$, 2%), 198 (M^+-$C_5H_9O_2$ and H, 3%), 57 (C_4H_9, 100%); HRMS found: 300.1935 calculated for $C_{16}H_{28}O_5$: 300.1937.

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