Synthesis of 1,2-Cyclopropanated Sugars from Glycals

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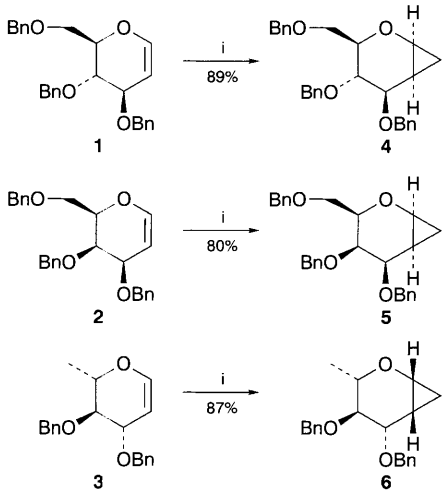
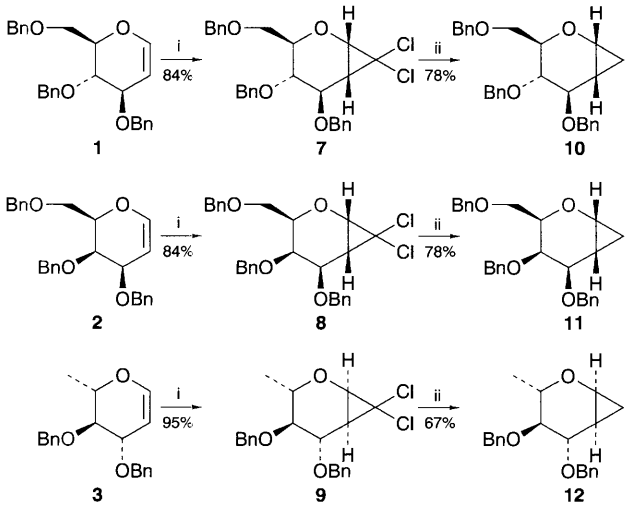
Syntheses of both forms of cyclopropanated sugars from glycals by (*i*) Simmons–Smith reaction and (*ii*) dichlorocarbene addition followed by dehalogenation are described.

Cyclopropanated sugars belong to the class of doubly branched carbohydrate derivatives. Their potential as useful intermediates in the synthesis of branched-chain sugars and natural products have not been fully explored as there are very few reports on their synthesis and practically none on the 1,2-cyclopropanated sugars except the one by Brimacombe *et al.*[1] In this communication, the results of the reactions of carbenes/carbenoids with glycals leading to cyclopropanated sugars are presented.

Tri-*O*-benzyl-D-glucal **1**, tri-*O*-benzyl-D-galactal **2** and di-*O*-benzyl-L-rhamnal **3** were chosen as representative examples. The direct cyclopropanation of glycals was investigated with **1–3**, using the modified Simmons–Smith procedure involving the use of acetyl chloride as activator.[2] This provided single cyclopropyl adducts **4–6** respectively, in excellent yields (Scheme 1). The product cyclopropanes were fully characterized by spectral and analytical methods.



Scheme 1 *Reagents and conditions*: i, CH_2I_2, Zn, CuCl, AcCl, diethyl ether, reflux



Scheme 2 *Reagents and conditions*: i, $CHCl_3$, 50% aq. NaOH, cat. $BnEt_3NCl$, room temp.; ii, $LiAlH_4$ (excess), THF, room temp.

It has been shown in the cyclopropanation of allylic alcohols/ethers that the organozinc species adds to the double bond from the same face as the hydroxy/alkoxy substituent. This has been explained by invoking coordination of the dimeric organozinc reagent to the oxygen atom of the substituent.[3] Based on this observation, it was rationalized that in the present case, the attack took place from the same side as the C-3 substituent. Detailed NMR analysis of the products confirmed the structures.† The C-3 hydrogen, in all cases, appeared as an apparent triplet in the ^1H NMR spectrum, suggesting that J_{23} and J_{34} are nearly equal. It is known in the case of glucose and rhamnose, that the C-3 and C-4 hydrogens, which are *trans* diaxial to one another, have large couplings. It is also known that in cyclopropyl systems, *cis* couplings are larger than *trans* ones.[4] Taken together, it is clear that the products obtained have the stereochemistry shown in Scheme 1.

Next, the possibility of synthesizing cyclopropanes having the opposite stereochemistry was explored. It was reasoned on steric grounds that carbenes like dichlorocarbene would approach the glycal double bond from the side opposite to that of the C-3 benzyloxy substituent, providing cyclopropanes **10–12** after reductive dehalogenation. The glycals **1–3** furnished single dichlorocarbene adducts **7–9** in high yields when treated with $CHCl_3$–aq. NaOH under phase-transfer catalysis (Scheme 2).

The stereochemistry of the adducts was determined from the coupling constant values for C-2 hydrogen in their ^1H NMR spectra.‡ Couplings J_{12} and J_{23} were different in all the three cases, which strongly suggested that H-2 and H-3 are *trans* to each other (by necessity H-1 and H-2 have to be *cis*). This indicates that the dichlorocyclopropanes **7–9** have a stereochemistry opposite to that present in **4–6**.

With the structure of the dichlorocyclopropanes secure, the reductive dechlorination of these were carried out using $LiAlH_4$. With excess $LiAlH_4$, the adducts **7–9** underwent clean reactions providing the corresponding fully reduced cyclopropanes **10–12** in very good yields. Compounds **10–12** were characterized by NMR spectroscopy as well as by analytical methods.§ Although the cyclopropanes **4–6** and **10–12** showed the same elemental composition, their ^1H and ^{13}C NMR spectra were different, thus indicating that they are different stereoisomers.

In this paper, it has been shown that both 1,2-glycocyclopropanes can be prepared in high yields, starting from the same glycal using readily available reagents. Further research on the utility of these cyclopropanes in the synthesis of various branched-chain sugars is in progress.

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Footnotes

† *Physical data for compound* **6**: ^1H NMR ($CDCl_3$): δ 0.75–0.80 (m, 2H, H-7), 1.21 (d, J = 6.6 Hz, 3H, H-6), 1.27–1.40 (m, 1H, H-2), 3.02 (dd, J = 9.7, 7.0 Hz, 1H, H-4), 3.36 (m, 1H, H-5), 3.79 (m, 1H, H-1), 4.14 (t, J = 6.9 Hz, 1H, H-3), 4.60 (dd, 2H, OCH_2Ph), 4.85 (dd, 2H, OCH_2Ph), 7.32 (m, 10H, ArH). ^{13}C NMR: δ 11.61, 15.30, 17.51, 54.42,

69.26, 73.63, 73.82, 78.24, 83.06, 127.11, 127.41, 127.86, 127.95, 138.41; $[\alpha]_D$: +89 (*c* 1.1, $CHCl_3$).

‡ *Physical data for compound* **9**: ^{1}H NMR ($CDCl_3$): δ 1.28 (d, *J* = 6.4 Hz, 3H, H-6), 1.80 (dd, *J* = 8.2, 4.2 Hz, 1H, H-2), 3.29 (t, *J* = 7.4 Hz, 1H, H-4), 3.56 (d, *J* = 8.2 Hz, 1H, H-1), 3.76 (dd, *J* = 4.2 Hz, 1H, H-3), 3.88 (m, 1H, H-5), 4.57–4.94 (m, 4H, OCH_2Ph), 7.32 (m, 10H, ArH). ^{13}C NMR: δ 19.84, 33.92, 57.86, 61.42, 71.99, 74.49, 76.06, 77.04, 81.07, 127.75, 127.92, 127.99, 128.36, 128.52, 137.73, 138.33; $[\alpha]_D$: −40 (*c* 1.2, $CHCl_3$).

§ *Physical data for compound* **12**: ^{1}H NMR ($CDCl_3$): δ 0.61 (m, 2H, H-7), 0.97 (m, 1H, H-2), 1.29 (d, *J* = 6.5 Hz, 3H,H-6), 3.24 (t, *J* = 6.6 Hz, H-4), 3.46 (m, 1H, H-1), 3.67 (m, 2H, H-3, H-5), 4.53 (m, 2H, OCH_2Ph), 4.70 (d, 2H, OCH_2Ph), 7.33 (m, 10H, ArH). ^{13}C NMR: δ 10.15, 14.33, 18.91, 49.34, 71.21, 71.99, 73.63, 79.93, 81.83, 127.68, 127.79, 127.96, 128.29, 128.42, 138.57, 138.74; $[\alpha]_D$: −11 (*c* 1, $CHCl_3$).

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