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Synthesis of chiral and highly functionalized cyclopentanes†

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Abstract—The unexpected reduction of the acetal moiety at the glycosidic C1–O-*exo* bond in the bis-heteroannulated-pyranosides **3** and **9** is a simple and new method for the synthesis of chiral and highly functionalized cyclopentanes.

For years we have been very interested in the synthesis of chiral, highly functionalized cyclopentanes via free radical mediated carbocyclization of conveniently functionalized precursors derived from sugars.[1] Simultaneously, we have also prepared a series of cyclopenta[*c*]pyrans by Pauson–Khand (PK) reaction[2] on pyranoside templates derived from carbohydrates.[3] This structural motif (**A**, Fig. 1) is widespread in nature in biologically interesting molecules.[4] As a consequence, a number of strategies have been devised for the synthesis of these natural products.[5] In a recent paper van Boom and co-workers reported on the synthesis of structural fragments of type **B** (Fig. 1).[6] This prompted us to describe here the unexpected results obtained in the reduction of the acetal moiety of the glycosidic C1–O-*exo* bond in the complex adducts (**3** and **9**). Compound **3** was obtained by PK reaction of the 2-(prop-2-ynyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1**); product **9** was prepared by manipulation of the PK reaction product **4**, synthesized from the corresponding 2-(prop-2-ynyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**2**).

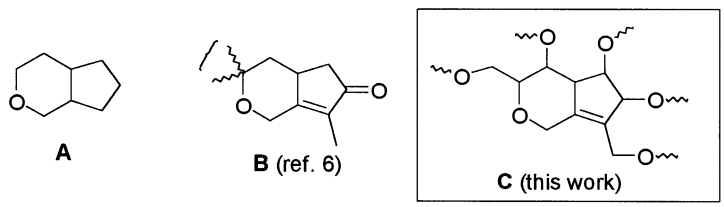
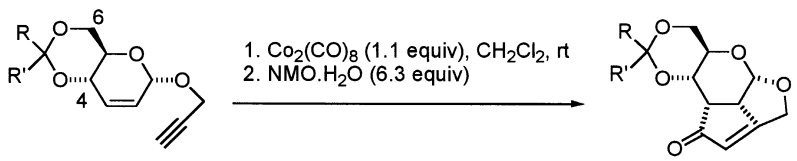


Figure 1.



Scheme 1.

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† Dedicated to Professor Joachim Thiem on the occasion of his 60th birthday.

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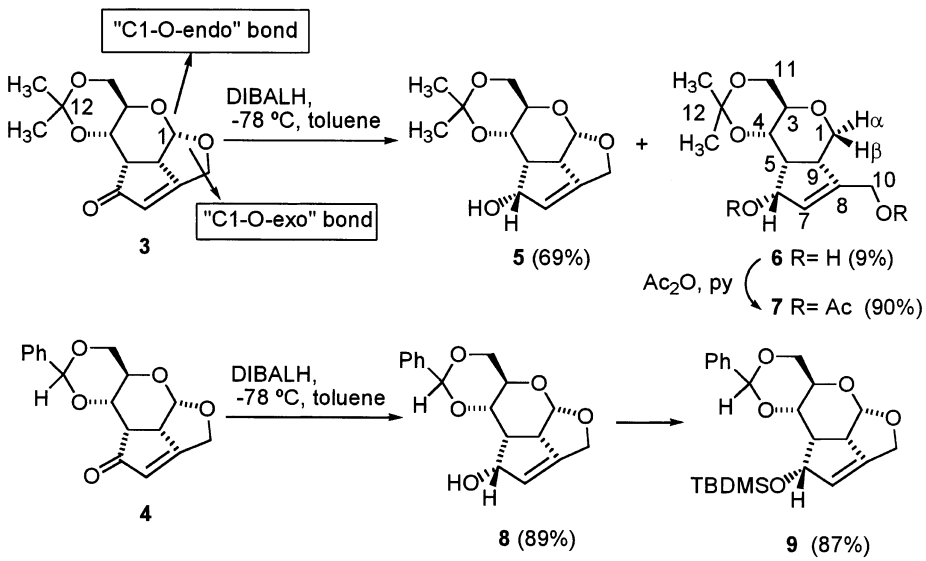
This protocol resulted in a new strategy for the synthesis of chiral, polyfunctionalized cyclopentanes of type **C** (Fig. 1), difficult to obtain by other procedures, and with wide potential synthetic interest.

In the course of our ongoing project for the synthesis of iridoids via PK reaction on carbohydrates,[3e] we considered the reduction of ketones **3** and **4**. These compounds were prepared by PK reaction of 2-(prop-2-ynyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides **1** and **2**, respectively (Scheme 1). It is interesting to point out that these compounds, having a 1,3-dioxane ring involving the oxygens at positions C6 and C4 in the pyranoside template, have given the best yields so far obtained by us for the PK reactions in sugar templates.[7]

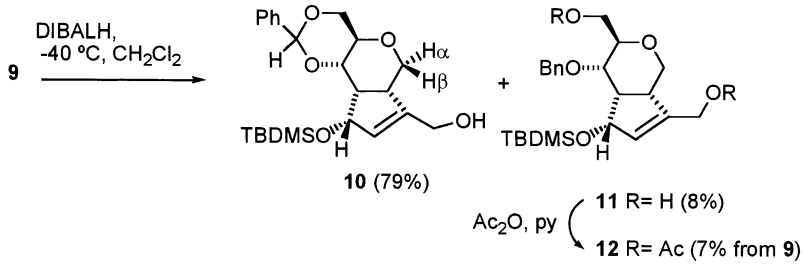
We have found that the reduction of the bis-heteroannulated-pyranoside **3** with DIBALH (2.0 equiv., 1.0 M in toluene), at −78°C, in toluene, afforded the allylic alcohols **5**[8] and **6**,[8] in 69 and 9% yields, respectively (Scheme 2). In both cases the ketone reduction proceeded stereoselectively from the less hindered β-face to give the expected compounds with *R* configuration at C6,[3] as determined by full spectroscopic analysis. The formation of product **6**,[8] albeit in low yield (9%), during the reduction of product **3**, was unexpected. Acetylation of product **6** gave a diacetate (**7**),[8] whose structure was confirmed by analytical and spectroscopic data. Particularly significant in this product (**7**) was the absence of the anomeric proton (H-1), which was substituted by two protons at 4.17 ppm (ddd, 1H, $J_{1\alpha,1\beta}=$ 11.5 Hz, $J_{1\beta,9}=6.6$ Hz, $J=0.5$ Hz, H-1β) and at 3.38 ppm (t, 1H, $J_{1\alpha,1\beta}=J_{1\alpha,9}=11.5$ Hz, H-1α), that led us to conclude that the glycosidic C1–O-*exo* bond was partially broken in the reduction of compound **3** to yield minor, but significant quantities of product **5**. Based on the chemical and spectroscopic evidence, the formation of product having a secondary alcohol, after cleavage of the C1–O-*endo* bond, was eliminated. The formation of product **6** from **3** is probably due to the presence of the sterically hindered isopropylidene acetal that prevents the attack at C12. However, it is well known that the regioselective cleavage of benzylidene acetals gives benzyl ethers using $AlCl_3/LiAH$[9] or $NaCNBH_3/HCl$.[10] The use of DIBALH for such a purpose has also been described.[11]

Continuing with our project, the benzylidene protected compound **4**, under the same experimental conditions (DIBALH, 2.0 equiv., 1.0 M in toluene, at −78°C; in toluene as solvent), afforded adduct **8** in 89% yield (Scheme 1). When the reduction was performed in THF, under the same conditions, compound **8** was isolated in 73% yield. Product **8** was transformed into intermediate **9**[8] by standard conditions (*t*-butyldimethylsilyl chloride, imidazole, methylene chloride, rt) in 87% yield (Scheme 2).

In order to test the benzylidene hydrogenolysis versus the C1–O glycosidic cleavage, we submitted compound **9** to reduction (Scheme 3). From compound **9**, with toluene as solvent and at −78°C,[12] alcohol **10** (26% (41%)) was the only isolated product; when the reaction was performed at −40°C, the regiochemistry was the same but the yield was better (57% (95%)). Repeating the process using methylene chloride, at −78°C,[12] alcohol **10** (21% (43%)) was obtained; when the reaction was performed at −40°C, a mixture of products **10** (79%) and **11** (8%) resulted. The analytical and spectroscopic data of compound **10** clearly showed this was again the result of the exclusive and regioselective cleavage of the glycosidic C1–O-*exo* bond. In fact, as in compounds **6**/**7** (Scheme 2), we readily noticed the absence of the anomeric proton, which was substituted by two new protons at 4.14 ppm (dd, 1H, $J_{1\alpha,1\beta}=11.0$ Hz, $J_{1\beta,9}=6.1$ Hz, H-1β) and at 3.56 ppm (t, 1H, $J_{1\alpha,1\beta}=J_{1\alpha,9}=11.0$ Hz, H-1α). Finally, peracetylation of alcohol **11** afforded product **12**[8] (7% overall yield from



Scheme 2.



Scheme 3.

9) (Scheme 3). Substrate **11**[13] was the result of the reduction of the benzylidene group plus the reduction of the C1–O-*exo* bond.

Overall, the reduction of the acetal at the glycosidic C1–O-*exo* bond, in molecules **3** and **9**, is worthy of note and unexpected. This is probably a consequence of the high tension in these bis-heteroannulated-pyranosides, coupled with the geometry of these products which present β-faces at C-1 free of steric constraints for any attacking reagent, as we can see by simple inspection of molecular models.

In summary, a series of unexpected results have afforded a new and simple protocol for the synthesis of chiral and highly polyfunctionalized cyclopentanes for further synthetic elaboration. Work is now in progress in our laboratory in order to explore the synthetic scope of this hydride-mediated regioselective glycosidic reduction. The results will be reported in due course.

Acknowledgements

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7. A large series of differently substituted 2-(prop-2-ynyl)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosides at C4-O and C6-O positions have been synthesized and submitted to PK reaction, showing the critical and important effects of these groups on the yields and in the structure of the resulting adducts (Marco-Contelles, J.; Ruiz-Caro, J., to be published).
8. All new compounds showed excellent analytical and spectroscopic data. *Selected spectroscopic data*. **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.34 (m, 5H, C_6H_5), 5.86 (br s, 1H, H-7), 5.58 (s, 1H, H-12), 4.82 (dd, 1H, $J_{6,5}=6.0$ Hz, $J_{6,7}=2.0$ Hz, H-6), 4.33 (dd, 1H, $J_{11',11}=10.0$ Hz, $J_{11',3}=5.0$ Hz, H-11′), 4.24 (td, 1H, $J_{3,4}=J_{3,11}=10.0$ Hz, $J_{3,11'}=5.0$ Hz, H-3), 4.20 (br s, 2H, 2H-10), 4.14 (dd, 1H, $J_{1',1}=11.0$ Hz, $J_{1',9}=6.0$ Hz, H-1′), 3.96 (dd, 1H, $J_{4,3}=10.0$ Hz, $J_{4,5}=6.0$ Hz, H-4), 3.59 (t, 1H, $J_{11,11'}=J_{11,3}=10.0$ Hz, H-11), 3.56 (t, 1H, $J_{1,1'}=J_{1,9}=11.0$ Hz, H-1), 2.91 (dt, 1H, $J_{9,1}=11.0$ Hz, $J_{9,1'}=J_{9,5}=6.0$ Hz, H-9), 2.56 (q, 1H, $J_{5,6}=J_{5,4}=J_{5,9}=6.0$ Hz, H-5), 1.59 (br s, 1H, OH), 0.89 [s, 9H, -C$(CH_3)_3$], 0.04 (s, 3H, -Si-CH_3), 0.03 (s, 3H, -Si-CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1 (C-8), 129.7 (C-7), 137.8–126.4 (C_6H_5), 102.6 (C-12), 80.1 (C-4), 75.1 (C-6), 71.7 (C-1), 70.3 (C-11), 68.8 (C-3), 61.1 (C-10), 45.3 (C-9)*, 43.9 (C-5)*, 25.9 [-C($CH_3)_3$], 17.9 [-C($CH_3)_3$], −4.5 (-Si-CH_3), −4.8 (-Si-CH_3) (* these values can be interchanged).
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12. In a typical experiment, product (**9**) was dissolved in dry toluene (or CH_2Cl_2) (0.15 M) and cooled at −78 (or −40°C) under argon and stirring. DIBALH (3 equiv., 1.0 M in toluene) was added. After 4 h, DIBALH (2 equiv., 1.0 M in toluene) was added again to the mixture. After 4 h the reaction was quenched with methanol and warmed at rt. The salts were filtered over Celite-545, and the filtrate was evaporated to give a residue which was submitted to chromatography.
13. Compound **11** presented the benzyl group at O-C4, in agreement with similar trends observed for the reduction of the benzylidene groups with $AlCl_3/LiAlH_4$ (see Ref. 9).