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Intramolecular hydrogen abstraction reaction in carbohydrate chemistry. Synthesis of chiral 2,7-dioxabicyclo[2.2.1]heptane and 6,8-dioxabicyclo[3.2.1]octane ring systems

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Abstract

The reaction of specifically protected alditols with (diacetoxyiodo)benzene or iodosylbenzene and iodine is a mild and selective procedure for the synthesis of chiral 6,8-dioxabicyclo[3.2.1]octane and 2,7-dioxabicyclo[2.2.1]heptane ring systems under neutral conditions. This methodology can be useful not only for the preparation of chiral synthons but also for the selective oxidation of specific carbons of the carbohydrate skeleton, constituting a good procedure for the synthesis of protected uloses. This reaction could be considered to be an intramolecular glycosidation that proceeds through an oxycarbenium ion.

The 1,6-anhydropyranoses and 1,5-anhydrofuranoses, the so-called *glycosans* are the most representative examples of the 6,8-dioxabicyclo[3.2.1]octane and 2,7-dioxabicyclo[2.2.1]heptane systems, respectively.[1] They are generally formed by acid treatment of the corresponding sugars, by thermal depolymerization of some polysaccharides, and by specific glycosidation reactions by O-6 attack of a good leaving group at the anomeric centre. In this latter case the opposite reaction may also be possible.[2]

These compounds are considered intramolecular glycosides and are important in organic synthesis as chiral building blocks for the preparation of enantiomerically pure non-carbohydrate compounds.[3] Another important feature of these dioxabicycles is that they are suitable starting materials for the synthesis of oxepanes and other oxygen heterocyclic ring systems, by stereoselective reduction of the acetal group,[4] and for the preparation of cyclitols.[5]

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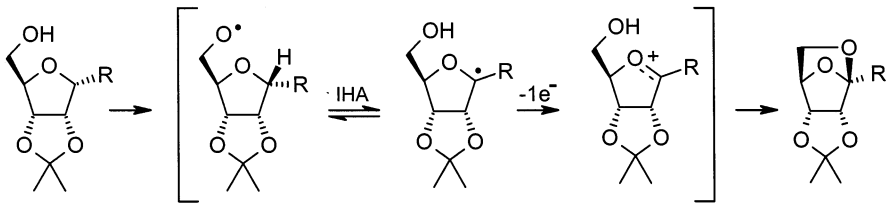
On the other hand, the 6,8-dioxabicyclo[3.2.1]octane unit is a widespread substructure in many natural metabolites with interesting biological activities. These products can have relatively simple structures such as the pheromones frontalin,[6] multistriatin, and *exo*-brevicomin[7] or can be very complex substances isolated from marine organisms such as pinnatoxin A,[8] palytoxin,[9] didemniserinolipid A,[10] and cyclodidemniserinol.[11] The general route to the synthesis of this dioxabicyclic unit is the acid-catalysed cyclisation starting from the corresponding dihydroxyketone. In this communication we describe an alternative methodology for the synthesis of the chiral 2,7-dioxabicyclo[2.2.1]heptane and 6,8-dioxabicyclo[3.2.1]octane ring systems, under neutral conditions, using an intramolecular hydrogen abstraction (IHA) reaction.[12] The IHA reaction was promoted by alkoxyl radicals generated in situ by reaction of alcohols with (diacetoxyiodo)benzene or iodosylbenzene and iodine under the conditions summarised in Table 1.[13]

A plausible mechanism for the reaction is shown in Scheme 1. The IHA reaction is followed by an oxidation of the C-radical with an excess of the reagent, and subsequent addition of the alcohol to the formed oxycarbenium ion. This process could then be conceptually considered to be an intramolecular glycosidation.



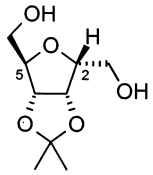
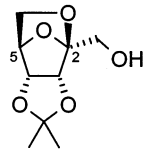
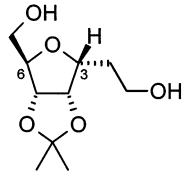
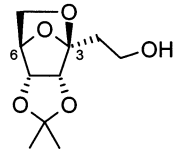
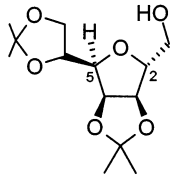
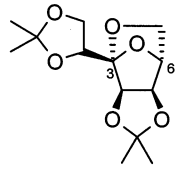
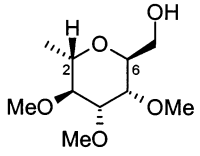
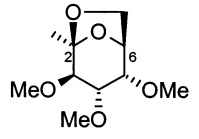
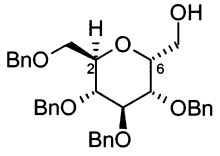
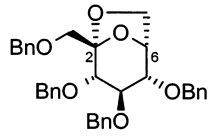
Scheme 1.

The D-altritol derivative **1** was obtained by reaction of 5-*O*-(*tert*-butyldimethyl)silyl-2,3-*O*-isopropylidene-D-ribofuranose with trimethylsulfoxonium iodide.[14] The IHA reaction of diol **1** (Entry 1) gave exclusively 2,5-anhydro-3,4-*O*-isopropyliden-β-D-psicopyranose (**2**)[15] by selective abstraction of the hydrogen at C-2. It is worth noting that no product coming from the alternative abstraction of the hydrogen at C-5 by the alkoxyl radical at C-1 was detected in the crude reaction.

The distance between the alkoxyl radical and the abstractable hydrogen, measured in a minimised structure of their respective transition states, are very similar (C_6–O···H–C_2 = 2.7 Å and C_1–O···H–C_5 = 2.8 Å), and both are within the range where this reaction occurs.[16] Nevertheless, the energy of the six-membered transition state for the H–C_5 abstraction calculated by using a MM2 forcefield model was found to be approx. 1 kcal/mol higher than the corresponding energy for the abstraction of H–C_2.[17] This can explain the observed regioselectivity of the reaction.

The mentioned regioselectivity was also observed with compound **3**[18] (Entry 2). The cyclisation through the most favourable six-membered transition state gave exclusively 2-deoxy-D-*ribo*-hept-3-ulose **4**.[15] The IHA reaction of D-*glycero*-D-*talo*-heptitol **5**, easily prepared from 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose,[14] takes place by the α-side of the molecule to yield L-*altro*-hept-3-ulose **6**[15] (Entry 3). This constitutes another approach to the fully substituted hept-3-ulose system.

Table 1
Synthesis of chiral 2,7-dioxabicyclo[2.2.1]heptane and 6,8-dioxabicyclo[3.2.1]octane systems by IHA reaction[a]

Entry	Substrate	Reagent[b] (mmol)	I_2 (mmol)	Solvent	Time min	Product	Yield %
1	 **1**	DIB (1.1)	0.5	CH_3CN	40	 **2**	70
2	 **3**	DIB (1.1)	1	CH_2Cl_2	30	 **4**	65
3	 **5**	DIB (2)	0.5	CH_2Cl_2	90	 **6**	86
4	 **7**	PhIO (2)	1	CH_2Cl_2	90	 **8**	90
5	 **9**	PhIO (2)	1.2	Cy/CH_2Cl_2	50	 **10**	60

[a]All reactions were performed in dry solvents (20 mL/mmol) at room temperature. [b]Per mmol of substrate.
DIB = (diacetoxyiodo)benzene; Cy = cyclohexane; Bn = benzyl.

The 6,8-dioxabicyclo[3.2.1]octane system can also be obtained from a conveniently functionalised carbohydrate precursor in excellent yield. Thus, the L-*glycero*-L-*manno*-heptitol derivative **7**[19] reacts with iodosylbenzene and iodine to give 2,7-anhydro-1-deoxy-3,4,5-tri-*O*-methyl-α-L-*altro*-hept-2-ulopyranose (**8**)[15] (Entry 4). The IHA reaction occurs under a more stable $^1C_4$ chair conformation allowing a 1,3-diaxial interaction between the implicated substituents, the hydro-

gen atom at C-2 and the hydroxymethyl group at C-6. Under similar conditions D-*glycero*-L-*gulo*-heptitol **9**[20] was cyclised to 2,7-anhydro-1,3,4,5-tetra-*O*-benzyl-β-D-*ido*-hept-2-ulopyranose (**10**)[15] (Entry 5). In this case, through its more stable $^4C_1$ chair conformation, which allows the maximum approximation between the alkoxyl radical at C-7 and the hydrogen at C-2.

Although Bols et al.[21] recently used the DIB/I_2 system for the deprotection of carbohydrate benzyl ethers in the presence of an appropriately located hydroxyl group, we have not detected debenzylation or formation of benzylidene to an appreciable extent in the case of compound **9**.

With these examples we have demonstrated the utility of the IHA reaction in the synthesis of these dioxabicyclic ring systems. The obtained products could be of interest as chiral synthons in the preparation of more complex molecules. As observed, the reaction may also be useful for the selective oxidation of specific carbons of the carbohydrate skeleton and constitutes a mild procedure for the synthesis of protected uloses, which are not readily accessible by other methods.

Acknowledgements

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15. Selected physical and spectroscopic data. **2**: mp 118–119°C; $[\alpha]_D$ −58 ($c=0.222$, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 3.42 (1H, d, $J=7.2$ Hz), 3.56 (1H, dd, $J=3.8$, 7.2 Hz), 4.03 (1H, dd, $J=6.6$, 12.5 Hz), 4.07 (1H, dd, $J=5.9$, 12.5 Hz), 4.29 (1H, d, $J=5.5$ Hz), 4.42 (1H, d, $J=5.5$ Hz), 4.69 (1H, d, $J=3.8$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) 25.2, 25.9, 59.1, 64.4, 78.3, 80.3, 81.2, 107.1, 112.6. **4**: syrup; $[\alpha]_D$ −68 ($c=0.116$); ^1H NMR 2.20 (1H, ddd, $J=15.1$, 6.2, 4.0 Hz), 2.28 (1H, ddd, $J=15.3$, 7.1, 4.2 Hz), 3.40 (1H, d, $J=7.4$ Hz), 3.55 (1H, dd, $J=7.1$, 3.9 Hz), 3.88 (2H, m), 4.20 (1H, d, $J=5.7$ Hz), 4.41 (1H, d, $J=5.4$ Hz), 4.66 (1H, d, $J=3.7$ Hz); ^{13}C NMR 25.2, 25.9, 30.7, 58.2, 64.3, 77.9, 80.2, 82.0, 108.6, 112.2. **6**: syrup; $[\alpha]_D$ −59.4 ($c=0.16$); ^1H NMR 3.44 (1H, d, $J=7.3$ Hz), 3.54 (1H, dd, $J=7.3$, 3.9 Hz), 4.09 (1H, dd, $J=8.3$, 7.0 Hz), 4.14 (1H, dd, $J=8.5$, 5.3 Hz), 4.37 (1H, d, $J=5.5$ Hz), 4.39 (1H, d, $J=5.5$ Hz), 4.61 (1H, dd, $J=6.9$, 5.3 Hz), 4.64 (1H, d, $J=3.9$ Hz); ^{13}C NMR 25.1 (2×), 25.8, 25.9, 64.68, 64.63, 71.4, 78.4, 80.1, 81.2, 107.0, 110.0, 112.3. **8**: syrup; $[\alpha]_D$ +122.4 ($c=0.42$); ^1H NMR 1.49 (3H, s), 3.24 (1H, d, $J=8.7$ Hz), 3.38 (1H, dd, $J=4.5$, 8.7 Hz), 3.55 (1H, dd, $J=2.5$, 4.5 Hz), 3.62 (1H, d, $J=7.9$ Hz), 3.83 (1H, dd, $J=5.7$, 7.9 Hz), 4.65 (1H, dd, $J=2.4$, 5.6 Hz); ^{13}C NMR 19.8, 57.8, 57.8, 61.0, 65.9, 73.6, 77.0, 80.2, 84.5, 107.9. **10**: syrup; $[\alpha]_D$ −10.5 ($c=1.49$); ^1H NMR 3.44 (1H, d, $J=10.5$ Hz), 3.72 (1H, dd, $J=5.0$, 7.6 Hz), 3.78 (1H, d, $J=7.9$ Hz), 3.79 (1H, dd, $J=4.2$, 7.8 Hz), 3.83 (1H, dd, $J=7.9$, 7.9 Hz), 3.90 (1H, d, $J=10.5$ Hz), 4.15 (1H, d, $J=7.6$ Hz), 4.42 (1H, dd, $J=4.4$, 4.4 Hz); ^{13}C NMR 65.9, 69.2, 72.9, 73.6, 74.2, 74.7, 75.3, 79.9, 81.4, 83.2, 107.5.
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