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Synthesis of Chiral Spiroacetals from Carbohydrates

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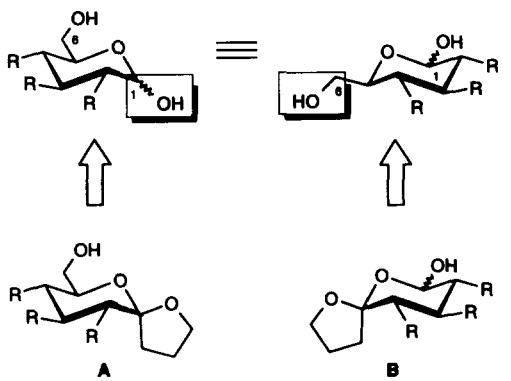
Abstract: *Optically active spiroacetals are prepared from carbohydrates with an intramolecular hydrogen abstraction reaction as the key step. Both spiroacetal enantiomers are formally available from the same sugar.*

A large variety of natural products of biological interest, particularly insect pheromones and polyether antibiotics, contain spiroacetal moieties in their structures. These spiroacetal metabolites are produced in Nature by a large number of insect species, plants, and fungi.[1] The most common synthetic approaches are based on the acid catalyzed cyclization of dihydroxyketone equivalents prepared by aldol chemistry, and on the addition of appropriate organometallic derivatives to lactones.[2]

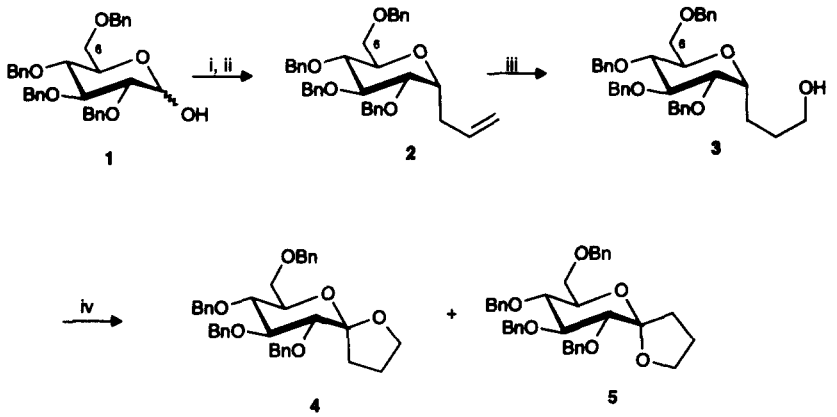
We wish to report here on a convenient methodology for the synthesis of optically active spiroacetals from carbohydrates by intramolecular hydrogen abstraction reactions promoted by alkoxy radicals. Thus, dioxaspiro-[5.5]undecanes, -[4.5]decanes, and -[4.4]nonanes are prepared in good yields.



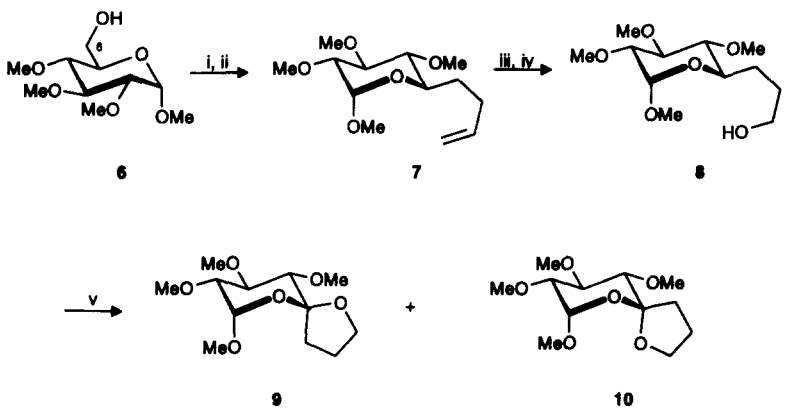
Scheme 1

As depicted in Scheme 1, both spiroacetal enantiomers could be formally obtained from the same carbohydrate depending on the carbon atom (C-1 or C-6) in which the additional side chain is formed, since a hydroxymethylenation[3] of the anomeric carbon of **B** gives rise to the optical isomer of **A**. Taking into account the relatively limited variety in Nature of sugars, particularly hexoses, this latter feature is synthetically interesting because it allows the required absolute configuration of the stereogenic centres in natural spiroacetals to be achieved.

The allylation of the tetrabenzylglucopyranose **1** was performed according to Kishi methodology[4] by



Scheme 2 i) *p*-NO_2-C_6H_4COCl; ii) CH_2=$CHCH_2TMS$, $BF_3.Et_2O$; iii) BH_3.THF, then NaOH, H_2O_2; iv) see table 1.



Scheme 3 i) TsCl, Py; ii) CH_2=$CHCH_2MgBr$, Et_2O; iii) O_3, $MeOH/CH_2Cl_2$; iv) $NaBH_4$; v) see table 1.

treatment with allyltrimethylsilane and boron trifluoride etherate, after activation of the C-1 anomeric carbon by formation of the *p*-nitrobenzoate ester, to yield a 9:1 (α:β) mixture of allylglucopyrans **2** in 85% yield (Scheme 2). Hydroboration-oxidation of the major stereoisomer (α-allyl derivative) gave rise to alcohol **3** (73%) which underwent intramolecular hydrogen abstraction when submitted to reaction with (diacetoxyiodo)benzene (DIB) and iodine[5] in cyclohexane at 40 °C under irradiation with two 100W tungsten-filament lamps for 1 h, yielding the isomeric spiroacetals **4** and **5** in 68% combined yield (Table 1, entry 1).[6]

The minor compound **5** is the thermodynamically favoured one (stabilizing anomeric effect),[7] as indicated by the acid-catalyzed isomerization of **4** to **5** (heating at 50 °C in AcOH with traces of HCl for 6h, 100% yield, ratio **4**:**5**=1:4). The structures of **4** and **5** and the configuration of the spirocentres were also unambiguously established by HETCOR and ROESY experiments.

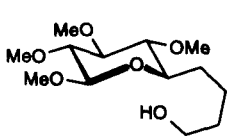
The elaboration of the corresponding three-carbon side chain through C-6 was accomplished from commercially available methyl α-D-glucopyranoside as follows (Scheme 3): Compound **6**, obtained in three steps[8] from the above-mentioned glucopyranose in 60% overall yield, was allylated by reaction of the corresponding 6-tosyl derivative with freshly prepared allylmagnesium bromide in ether (88%).[9]

Table 1. Synthesis of Chiral Spiroacetals.[a]

Entry	Substrate	Reagents[b] (mmol)	Conditions		Products (yield %)
			Time (h)	T (°C)	
1	**3**	DIB/I_2(1.1/1)	1	40	**4**(51); **5**(17)
2	**8**	DIB/I_2(1.1/1)	0.6	40	**9**(47); **10**(28)
3	**11**	HgO/I_2(2.5/2.5)	5	20	**12**(18); **13**(33)
4	**11**	AHDS/I_2(2.3/1.1)	5	80	**12**(33); **13**(24)
5	**11**	DIB/I_2(1.1/1)	0.5	40	**12**(53); **13**(33)
6	**14**	DIB/I_2(1.2/1)	3	40	**15**(42); **16**(25)

[a] All reactions were performed in cyclohexane by irradiation with two 100W tungsten-filament lamps. [b] Per mmol of substrate; DIB = (diacetoxyiodo)benzene; AHDS = acetoxyhydroxydiphenylselenurane.

The required alcohol **8**, prepared by ozonolysis of **7** in a 1/1 mixture of CH_2Cl_2/MeOH followed by *in situ* reduction with $NaBH_4$ (91%), was also cyclised with the DIB/iodine system, as shown in Table 1 (entry 2), to yield the isomers **9** and **10** (75%). In this case, the thermodynamically less favoured spiroacetal was **10** (minor component of the reaction) probably caused by 1,3-diaxial interactions between the oxygen of the tetrahydrofuran ring and the methoxyl group of the anomeric carbon.[1] Compound **10** underwent slow isomerization to **9** in the presence of acid (AcOH/*p*-TsOH 0.1 M, 18 °C, 7 h; ratio **10**/**9**=1/1); attempts to improve the reaction conditions by increasing the reaction temperature or the *p*-TsOH concentration led to decomposition products.



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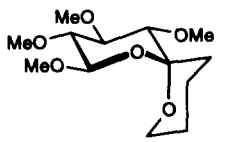

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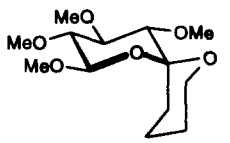

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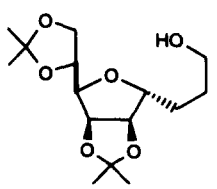

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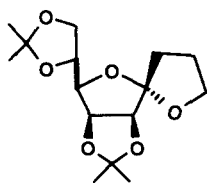

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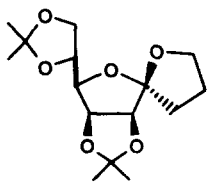

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The preparations of dioxaspiro[5.5]undecanes are shown in Table 1 (entries 3-5). The required alcohol **11** was obtained by hydroboration-oxidation of the corresponding olefin, which in turn was synthesized from methyl β-D-glucopyranoside in a similar way to compound **7**. To accomplish the intramolecular hydrogen abstraction three systems were tested: HgO, acetoxyhydroxydiphenylselenurane,[10] and DIB, all combined with I_2, the best result (86%) being obtained with the last one. The structure of isomeric spiroacetals **12** and **13** was deduced from their spectroscopic data: NOe, COSY, HETCOR, and ROESY experiments.[11]

Finally, the dioxaspiro[4.4]nonanes **15** and **16**[12] were synthesized by radical spirocyclization of the pentose derivative **14**[13] in an overall yield of 67% (Table 1, entry 6).

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REFERENCES AND NOTES

1. For reviews see: Vaillancourt, V.; Praft, N. E.; Perron, F.; Albizati, K. F. In *The Total Synthesis of Natural Products;* Vol. 8; ApSimon, J., Ed.; Wiley: New York, 1992; p 533. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
2. For radical approaches to racemic spiroacetals see: Kay, I. T.; Williams, E. G. *Tetrahedron Lett.* **1983**, *24*, 5915. Kay, I. T.; Bartholomew, D. *Tetrahedron Lett.* **1984**, *25*, 2035. Baker, R.; Brimble, M. A. *J. Chem. Soc., Perkin I* **1988**, 125.
3. Chatani, N.; Ikeda, T.; Sano, T.; Sonoda, N.; Kurosawa, H.; Kawasaki, Y.; Murai, S. *J. Org. Chem.* **1988**, *53*, 3387.
4. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.
5. Concepción, J. J.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1984**, *25*, 1953.
6. Compound **4**: m.p. 70-71°C (acetone-*n*-hexane); $[\alpha]_D$ +30° ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.96 (2H, m), 2.04 (1H, m), 2.19 (1H, m), 3.47 (1H, m), 3.54-3.63 (2H), 3.66-3.74 (3H, m), 3.95 (1H, dd, *J* 6.8, 13.6 Hz), 4.10 (1H, dd, *J* 7.5, 13.6 Hz), 4.52 (1H, d, J 10.7 Hz), 4.83 (1H, d, *J* 10.7 Hz), 4.55 (1H, d, *J* 11.9 Hz), 4.61 (1H, d, *J* 11.9 Hz), 4.74 (1H, d, *J* 11.1 Hz), 4.86 (1H, d, *J* 11.1 Hz), 4.78, (1H, d, *J* 10.9 Hz), 4.92 (1H, d, *J* 10.9 Hz), 7.14-7.36 (20H); ^{13}C NMR ($CDCl_3$) δ *inter alia* 109.88 (C), 73.83, 78.13, 82.28, 84.40 (CH), 25.02, 27.73, 68.20, 69.46 (CH_2); MS m/z 580.2827 (M^+, 1%). Compound **5**: ^1H NMR ($CDCl_3$) δ 1.78-1.98 (4H), 3.55 (1H, d, *J* 9.5 Hz), 3.62 (1H, dd, *J* 1.9, 10.8 Hz), 3.72 (1H, dd, *J* 3.7, 10.8 Hz), 3.68 (1H, t, *J* 9.5 Hz), 3.82-3.89 (2H), 3.99 (1H, m), 4.02 (1H, t, *J* 9.5 Hz), 4.52 (1H, d, J 12.2 Hz), 4.58 (1H, d, *J* 12.2 Hz), 4.54 (1H, d, J 10.9 Hz), 4.83 (2H, d, *J* 10.9 Hz), 4.68 (1H, d, *J* 11.4 Hz), 4.95 (1H, d, *J* 11.4 Hz), 4.88 (1H, d, *J* 11.0 Hz), 4.91 (1H, d, *J* 11.0 Hz), 7.15-7.34 (20H); ^{13}C NMR ($CDCl_3$) δ *inter alia* 107.34 (C), 71.24, 78.50, 80.05, 84.52 (CH), 24.02, 33.44, 68.13, 68.74 (CH_2); MS m/z 580.2826 (M^+, 1%).
7. Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.
8. Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990. Hirst, E. L.; Percival, E. In *Methods in Carbohydrate Chemistry*; Vol. 2; Whistler, R. L.; Wolfrom, M. L.; Eds.; Academic Press: New York, 1963; p 147.
9. Aged solutions of allylmagnesium bromide, addition of CuI, or changing the solvent to tetrahydrofuran, lead to complex mixtures.
10. Dorta, R. L.; Francisco, C. G.; Freire, R.; Suárez, E. *Tetrahedron Lett.* **1988**, *29*, 5429.
11. Compound **12**: ^1H NMR ($CDCl_3$) δ 1.51 (2H, m), 1.66 (2H, m), 1.87 (2H, m), 2.83 (1H, d, *J* 9.6 Hz), 2.99 (1H, t, *J* 8.6 Hz), 3.50 (1H, t, *J* 9.4 Hz), 3.56 (3H, s), 3.57 (3H, s), 3.58 (3H, s), 3.60 (3H, s), 3.71 (2H, m), 4.42 (1H, d, *J* 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ *inter alia* 97.25 (C), 82.65, 84.10, 85.17, 98.99 (CH), 18.11, 24.41, 30.05, 61.15 (CH_2); MS m/z 245.1389 (M^+-OMe, 71%). Compound **13**: ^1H NMR ($CDCl_3$) δ 1.53-1.76 (6H), 3.12 (1H, d, *J* 7.1 Hz), 3.16 (1H, t, *J* 7.2 Hz), 3.52 (3H, s), 3.54 (6H, s), 3.56 (3H, s), 3.71 (1H, m), 4.02 (1H, ddd, *J* 2.6, 11.7, 11.7 Hz), 4.38 (1H, d, *J* 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ *inter* alia 98.99 (C), 82.96, 83.37, 85.75, 100.57 (CH), 17.88, 25.11, 27.07, 61.72 (CH_2); MS m/z 245.1391 (M^+-OMe, 6%).
12. Compound **15**: ^1H NMR ($CDCl_3$) δ 1.34 (3H, s), 1.37 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 1.88 (1H, m), 1.98 (2H, m), 2.14 (1H, m), 3.85 (1H, dd, *J* 3.7, 8.2 Hz), 3.91 (2H, t, *J* 6.6 Hz), 4.01 (1H, dd, *J* 4.4, 8.8 Hz), 4.08 (1H, dd, *J* 6.4, 8.8 Hz), 4.35 (1H, ddd, *J* 4.4, 6.4, 8.4 Hz), 4.52 (1H, d, *J* 6.0 Hz), 4.81 (1H, dd, *J* 3.7, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ *inter alia* 115.08 (C), 73.12, 78.99, 80.08, 84.98 (CH), 23.53, 31.01, 67.01, 67.91 (CH_2); MS m/z 285.1333 (M^+-Me, 100%). Compound **16**: ^1H NMR ($CDCl_3$) δ 1.33, (6H, s), 1.41 (3H, s), 1.43 (3H, s), 1.74 (1H, m), 2.00 (3H, m), 3.48 (1H, dd, *J* 4.0, 8.0 Hz), 3.95 (1H, ddd, *J* 0.8, 7.0, 15.0 Hz), 4.02 (1H, dd, *J* 4.2, 8.8 Hz), 4.07 (1H, dd, *J* 6.0, 8.8 Hz), 4.08 (1H), 4.43 (1H, m), 4.48 (1H, d, *J* 6.0 Hz), 4.75(1H, dd, *J* 4.0, 6.0 Hz); ^{13}C NMR ($CDCl_3$) δ *inter alia* 113.48 (C), 73.28, 77.04, 79.20, 83.01 (CH), 24.20, 34.08, 67.08, 69.18 (CH_2); MS m/z 285.1350 (M^+-Me, 51%).
13. Compound **14** was prepared according to: Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079.

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