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## Synthesis of Dispiroacetals from Carbohydrates by Intramolecular Hydrogen Abstractions

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Abstract: The synthesis of 1,6,8-trioxadispiro[4.1.5.3]pentadecanes 15 and 16 from D-galactopyranose is described. The key steps are two intramolecular hydrogen abstraction reactions promoted by alkoxy radicals. Copyright © 1996 Elsevier Science Ltd

The dispiroacetal system is a basic substructure present in a number of natural polyether antibiotics such as, for example, narasin, salinomycin and CP 44,661.<sup>1</sup> Most of the reported syntheses of these dispiroacetals<sup>2</sup> involve at least an acid-catalyzed intramolecular acetalization to establish one of the spiroacetal centres, which may prove to be unsuitable in the presence of acid-sensitive functional groups.<sup>3</sup>



Recently<sup>4</sup> we have reported on the synthesis of several optically active spiroacetals from carbohydrates with an intramolecular hydrogen abstraction reaction as the key step for the spiroacetal ring system formation. We wish to report here on an extension of this methodology for the synthesis of trioxadispiro systems of type A starting from D-galactopyranose 1 (Scheme 1).



Scheme 2 i: a) 2,2-Dimethoxypropane/p-TsOH and then Ac2O/Py (56%); b) 80% AcOH/H<sub>2</sub>O, 50  $^{\circ}$ C (80%). ii: a) (imid)<sub>2</sub>C=S/CH<sub>3</sub>CN (90%); b) P(OMe)<sub>3</sub> (80%); c) H<sub>2</sub>/Pd(OH)<sub>2</sub>/C (85%). iii: BCl<sub>3</sub>.Me<sub>2</sub>S (80%). iv: a) K<sub>2</sub>CO<sub>3</sub> (100%); b) 'BuPh<sub>2</sub>SiCl/imidazole (79%). v: Me<sub>2</sub>SO<sub>4</sub>/NaOH (87%).



Scheme 3 i) CCl4/Ph<sub>3</sub>P and then 4-pentenylmagnesium bromide (74%). ii) O<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>/MeOH and then NaBH<sub>4</sub> (81%). iii) DIB/I<sub>2</sub>, hv (52%). iv) AcOH/HCl (100%).

The 3,4-dideoxy-D-galactopyranose derivative 5 was prepared as depicted in Scheme 2. The protection of the hydroxyl groups at C-3 and C-4 of the benzyl  $\alpha$ -D-galactopyranose 2, main anomer obtained by benzylation of 1, by treatment with 2,2-dimethoxypropane followed by acetylation and deprotection of the acetonide under acidic conditions gave the diol 3 in 45% overall yield. This *cis*-diol was then transformed into the corresponding cyclic thionocarbonate and subsequently removed with trimethyl phosphite.<sup>5</sup> Further reduction of the resulting olefin with H<sub>2</sub>/Pd(OH)<sub>2</sub>/C gave 4, which underwent selective deprotection of the hydroxyl group at the anomeric centre (BCl<sub>3</sub>-Me<sub>2</sub>S)<sup>6</sup> to afford the required compound 5.

The following step is the preparation of the suitable side chain at the anomeric carbon for performing the subsequent cyclization. We have previously observed<sup>7</sup> that 1,3-steric interactions prevent the 1,6-intramolecular hydrogen abstraction; thus, the tetrahydropyran ring must be the first cycle to be formed. All the attempts at the homologation at C-1 of 5 by reaction with  $CCl_4/Ph_3P$  followed by treatment with 4-pentenylmagnesium bromide,<sup>8</sup> under different reaction conditions, were unsuccessful.<sup>9</sup>

The diacetyl derivative 4 was then transformed into the *O*-methyl protected compound 8 in a 51% overall yield, as shown in Scheme 2. Homologation of 8 by reaction with  $CCl_4/Ph_3P$  (THF, reflux, 3h) followed by treatment of the crude chloride derivative with freshly prepared 4-pentenylmagnesium bromide (Et<sub>2</sub>O, 0 °C, 1h) was now a clean reaction leading to a ( $\alpha$ : $\beta$ =3.6:1) mixture of C-1 pentenyl derivatives 9a and 9b in 74% yield (Scheme 3). Ozonolysis of the major isomer 9a followed by NaBH<sub>4</sub> reduction gave rise to alcohol 10 (81%).





The intramolecular hydrogen abstraction reaction was achieved by reaction of 10 with (diacetoxyiodo)benzene (DIB) and iodine<sup>10</sup> (1.6 mmol and 1 mmol, respectively, per mmol of substrate) in cyclohexane at 40 °C under irradiation with two 100W tungsten-filament lamps for 70 minutes, yielding the spiroacetal 11 (30%)<sup>11</sup> besides its epimer at C-1 12 (22%). The minor component 12 was quantitatively transformed into 11 by acid treatment (AcOH with traces of HCl, r.t., 2 h).

The spectroscopic data of both compounds agree with the proposed structures. The stereochemistry at C-1 of the spiroacetal 11 was solved by single crystal X-ray analysis (Figure).<sup>12</sup>



Scheme 4 i: a) Bu4NF (88%); b) TsCl/Py (100%); Allylmagnesium bromide/Et<sub>2</sub>O (0  $^{\circ}$ C to r.t.) (85%). ii: O<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>/MeOH and then NaBH<sub>4</sub> (85%). iii: DIB/I<sub>2</sub>, hv (56%).

To prepare the five-membered ring in 11 a suitable homologation at C-6 of the original carbohydrate is needed. Hydrolysis of the silyl protecting group and subsequent allylation of the corresponding 6-tosyl derivative with freshly prepared allylmagnesium bromide in ether gave the butenyl derivative 13 in 75% overall yield (Scheme 4).

The required alcohol 14, obtained by ozonolysis and NaBH<sub>4</sub> reduction of 13, underwent cyclization by reaction with DIB/I<sub>2</sub> in cyclohexane at room temperature and under sunlight for 4 h, yielding the isomeric dispiroacetals 15 and 16 in 56% yield (ratio 15:16=1.4:1).<sup>13</sup> The structures of 15 and 16 and the configuration of the spirocentres were unambiguously established by COSY, HMQC and HMBC experiments, the observed ROESY interactions being indicated in Scheme 4.

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- Compound 11: m.p. 100-102 °C (acetone-n-hexane); [α]<sub>D</sub> +5.3 (CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.07 (9H, s), 1.27-1.48 (3H), 1.56-1.84 (4H); 1.89-2.14 (3H), 2.93 (1H, dd, *J* 4.8, 11.0 Hz), 3.38 (3H, s), 3.60 (1H, dd, *J* 4.5, 10.0 Hz), 3.66-3.85 (3H), 3.70 (1H, dd, *J* 5.9, 10.1 Hz), 7.36-7.44 (6H), 7.70-7.78 (4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 19.23, 96.47, 2x133.76 (C), 69.43, 81.57, 2x127.61, 2x127.72, 129.57, 129.58, 2x135.66, 2x135.68 (CH), 18.26, 22.43, 24.93, 27.03, 30.64, 60.57, 66.87 (CH<sub>2</sub>), 3x26.78, 57.19 (CH<sub>3</sub>); MS m/z 423 (M<sup>+</sup>-MeO, 1%).

Compound 12:  $[\alpha]_D$  -29.5 (CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.07 (9H, s), 1.25-1.81 (8H), 1.93-2.05 (2H), 3.03 (1H, dd, J 4.7, 10.8 Hz), 3.44 (3H, s), 3.54-3.83 (4H), 4.10 (1H, ddd, J 2.6, 11.4, 11.4 Hz), 7.34-7.44 (6H), 7.66-7.73 (4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  19.15, 99.16, 2x133.57 (C), 72.67, 81.81, 4x127.60, 2x129.57, 4x135.55 (CH), 17.25, 22.64, 24.80, 25.31, 26.75, 61.42, 66.80 (CH<sub>2</sub>), 3x26.75, 57.95 (CH<sub>3</sub>); MS m/z 454 (M<sup>+</sup>, 1%).

- 12. The data were measured on a Philips PW 1100 automatic four-circle diffractometer operating with Cu-K<sub> $\alpha$ </sub> radiation ( $\lambda$  = 1.5418 Å) monochromated by graphite. Crystal structure data for 11: C<sub>27</sub>H<sub>38</sub>O<sub>4</sub>Si, monoclinic, space group P2<sub>1</sub>, Z = 2, a = 14.015(3), b = 9.024(1), c = 11.204(5) Å,  $\beta$  = 113.19(3)°, R(%) = 3.56 for 2159 reflections with I>4 $\sigma$ (I). Detailed X-ray crystallographic data are available, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
- 13. Compound 15: <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>) δ 1.36 (1H, bd, J 14.3 Hz), 1.52-1.75 (7H), 1.93 (1H, ddd, J 2.7, 2.7, 13.2 Hz), 1.97-2.07 (3H), 2.30 (1H, ddd, J 4.4, 13.3, 13.3 Hz), 2.63 (1H, dddd, J 3.3, 11.7, 13.8, 13.8 Hz), 2.97 (1H, dd, J 3.8, 11.7 Hz), 3.28 (3H, s), 3.80-3.89 (2H), 4.01-4.08 (2H); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>) δ 97.6, 105.9 (C), 82.5 (CH), 19.3, 19.8, 24.7, 25.8, 32.3, 34.9, 40.0, 61.5, 69.2 CH<sub>2</sub>), 56.0 (CH<sub>3</sub>); MS m/z 241 (M<sup>+</sup>-1, 1%).

Compound 16: <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  1.27 (1H, d, J 11.8 Hz), 1.42-1.49 (1H), 1.50-1.62 (3H), 1.75 (1H, bd, J 12.7 Hz), 1.82-1.89 (1H), 1.91-2.00 (4H), 2.04-2.12 (2H), 2.31 (1H, ddd, J 3.1, 7.9, 12.3 Hz), 3.25 (3H, s), 3.26 (1H, dd, J 5.4, 8.8 Hz), 3.63-3.69 (1H), 3.73 (1H, ddd, J 7.3, 7.3, 7.3 Hz), 3.86 (1H, ddd, J 2.4, 12.5, 12.5 Hz), 4.02 (1H, ddd, J 4.8, 8.3, 8.3 Hz); <sup>13</sup>C NMR (C<sub>6</sub>D<sub>6</sub>)  $\delta$  98.0, 107.0 (C), 80.4 (CH), 19.1, 21.4, 24.8, 25.7, 31.9, 32.8, 37.4, 60.8, 67.4 (CH<sub>2</sub>), 57.2 (CH<sub>3</sub>).

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