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Synthesis of Dispiroacetals from Carbohydrates by Intramolecular Hydrogen Abstractions

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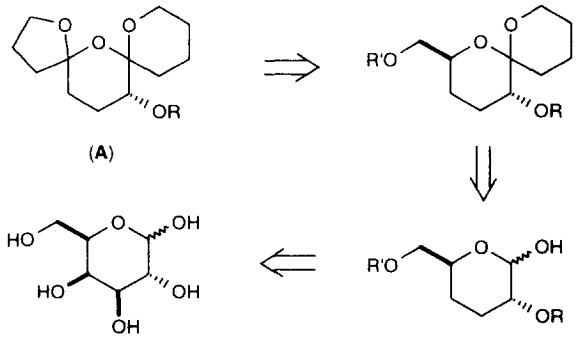
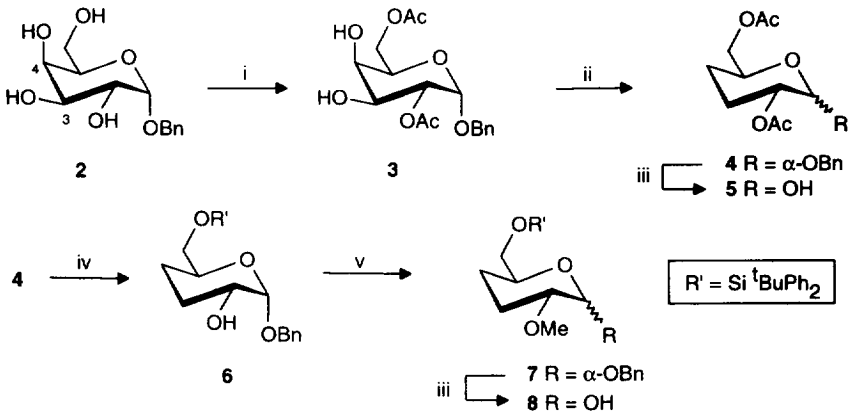
Abstract: The synthesis of 1,6,8-trioxadispiro[4.1.5.3]pentadecanes **15** and **16** from D-galactopyranose is described. The key steps are two intramolecular hydrogen abstraction reactions promoted by alkoxy radicals. Copyright © 1996 Elsevier Science Ltd

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.[1] Most of the reported syntheses of these dispiroacetals[2] 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.[3]

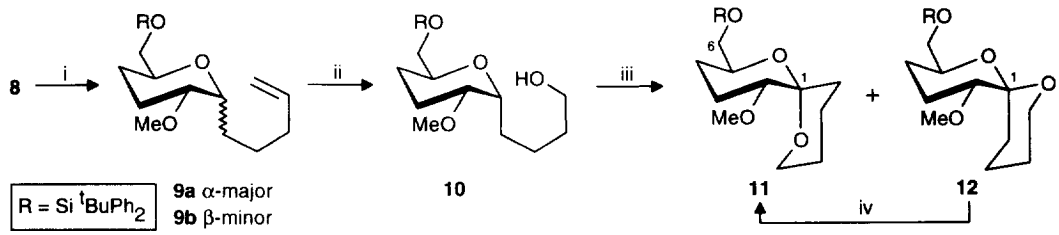
Scheme 1



Recently[4] 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 Ac_2O/Py (56%); b) 80% AcOH/H_2O, 50 °C (80%). ii: a) $(imid)_2C{=}S/CH_3CN$ (90%); b) $P(OMe)_3$ (80%); c) $H_2/Pd(OH)_2/C$ (85%). iii: $BCl_3{\cdot}Me_2S$ (80%). iv: a) K_2CO_3 (100%); b) $^tBuPh_2SiCl$/imidazole (79%). v: Me_2SO_4/NaOH (87%).



Scheme 3 i) CCl_4/Ph_3P and then 4-pentenylmagnesium bromide (74%). ii) O_3/CH_2Cl_2/MeOH and then $NaBH_4$ (81%). iii) DIB/I_2, 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 α-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.[5] Further reduction of the resulting olefin with $H_2/Pd(OH)_2/C$ gave **4**, which underwent selective deprotection of the hydroxyl group at the anomeric centre ($BCl_3{\cdot}Me_2S$)[6] 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[7] 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,[8] under different reaction conditions, were unsuccessful.[9]

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_2O, 0 °C, 1h) was now a clean reaction leading to a (α:β=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 $NaBH_4$ reduction gave rise to alcohol **10** (81%).

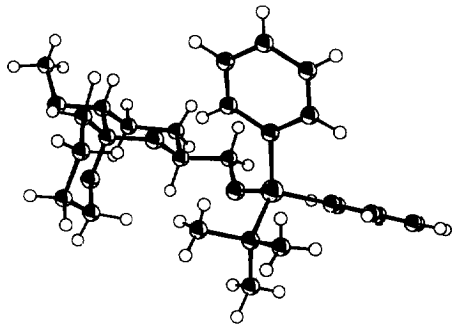
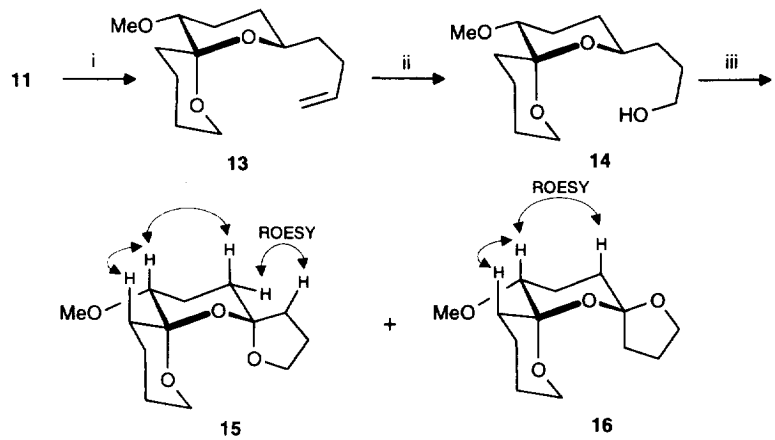


Figure X-Ray of compound **11**

The intramolecular hydrogen abstraction reaction was achieved by reaction of **10** with (diacetoxyiodo)benzene (DIB) and iodine[10] (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%)[11] 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).[12]



Scheme 4 i: a) Bu_4NF (88%); b) TsCl/Py (100%); Allylmagnesium bromide/Et_2O (0 °C to r.t.) (85%). ii: O_3/CH_2Cl_2/MeOH and then $NaBH_4$ (85%). iii: DIB/I_2, 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 $NaBH_4$ reduction of **13**, underwent cyclization by reaction with DIB/I_2 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).[13] 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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11. Compound **11**: m.p. 100-102 °C (acetone-n-hexane); $[\alpha]_D$ +5.3 ($CHCl_3$); ^1H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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_2), 3x26.78, 57.19 (CH_3); MS m/z 423 (M^+-MeO, 1%).

    Compound **12**: $[\alpha]_D$ -29.5 ($CHCl_3$); ^1H NMR ($CDCl_3$) δ 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); ^{13}C NMR ($CDCl_3$) δ 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_2), 3x26.75, 57.95 (CH_3); MS m/z 454 (M^+, 1%).
12. The data were measured on a Philips PW 1100 automatic four-circle diffractometer operating with Cu-Kα radiation (λ = 1.5418 Å) monochromated by graphite. Crystal structure data for **11**: $C_{27}H_{38}O_4Si$, monoclinic, space group $P2_1$, Z = 2, a = 14.015(3), b = 9.024(1), c = 11.204(5) Å, β = 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**: ^1H NMR (C_6D_6) 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); ^{13}C NMR (C_6D_6) 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_2), 56.0 (CH_3); MS m/z 241 (M^+-I, 1%).

    Compound **16**: ^1H NMR (C_6D_6) δ 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); ^{13}C NMR (C_6D_6) δ 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_2), 57.2 (CH_3).

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