A simple construction of chiral fused benzoxocine ring ethers from D-glucose by regioselective 8-*endo*-aryl radical cyclisation

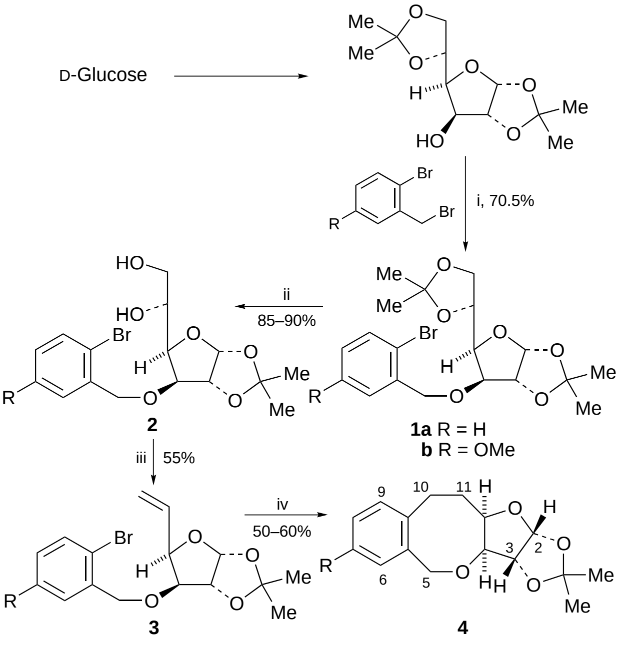
Partha Chattopadhyay,*[a] Monika Mukherjee[b] and Soma Ghosh[b]

[a] *Indian Institute of Chemical Biology, Calcutta-700 032, India*
[b] *Department of Solid State Physics, Indian Association for the Cultivation of Science, Jadavpur, Calcutta-700 032, India*

A regioselective 8-*endo-trig* aryl radical cyclisation of the 5,6-deoxy-D-*xylo*-5-enofuranosides 3a and 3b with tri-*n*-butyltin hydride provides the chiral furo[3,2-*c*][2]benzoxocines 4a and 4b in good yields; the crystal structure of 4a is reported.

The synthesis of condensed cyclic ethers incorporating medium size rings, a unique structural feature present in some highly bioactive marine natural products,[1] is a challenging problem. The development of new and general methodology for the synthesis of this class of compound,[2,3] especially in chiral form, has become an attractive area for investigation in recent years. The syntheses of chiral 5-, 6- and 7-membered cyclic ethers have been achieved from D-glucose by intramolecular nitrone cycloaddition reactions.[4] More recently, functionalised 9-membered chiral ethers have been prepared from D-glucose through oxy-Cope rearrangement.[5] We report herein a simple and convenient conversion of D-glucose to highly functionalised chiral condensed tricyclic benzoethers incorporating a *cis* 8-5 bicyclic system by regioselective 8-*endo-trig* aryl radical cyclisation.[6]

The transformation of the easily accessible 5,6-deoxy-*O*-isopropylidene-3-*O*-(*o*-bromobenzyl)-α-D-*xylo*-5-enofuranose **3a** and the corresponding 5′-methoxy derivative **3b** to the tricyclic furo[3,2-*c*][**2**]benzoxocines **4a** and **4b** is shown in Scheme 1. D-Glucose was converted to the 3-*O*-(*o*-bromobenzyl) ethers **1a**† and **1b** through *O*-benzylation of 1,2 : 5,6-diisopropylidene-α-*D*-glucofuranose with 50% aq. NaOH in a biphasic medium (CH_2Cl_2–H_2O) using Bu_4NBr as phase transfer catalyst. Under mild acidic condition, the 5,6-*O*-isopropylidene group in **1a**,**b** was selectively deprotected to give **2a**,**b** which on treatment with Ph_3P, I_2 and imidazole in boiling toluene[7] gave the desired dideoxy furanose derivatives **3a** and **3b**. Radical cyclisation of each of the alkenes **3a** and **3b** in refluxing benzene (0.008 mol dm^{-3}) for 8–10 h with Bu_3SnH (1.5 equiv.) and a catalytic amount of AIBN furnished the respective crystalline tricyclic ethers **4a** and **4b** in 50–60% yield as the only isolable products in each case after separation of the tin compounds[8] followed by chromatography on silica gel. The assigned structures of the products **4a** and **4b** resulting from 8-*endo-trig* aryl radical cyclisation were based upon spectroscopic data. Unequivocal confirmation of the structure of **4a** was obtained from an X-ray crystal structure‡ determination (Fig. 1).



Scheme 1 *Reagents and conditions*: Bu_4NBr, 50% NaOH, CH_2Cl_2, 25 °C, 12 h; ii, 75% AcOH, 25 °C, 12 h; iii, PPh_3, I_2, imidazole, PhMe, reflux, 2 h; iv, Bu_3SnH, AIBN, benzene, 200 W lamp, reflux, 10 h

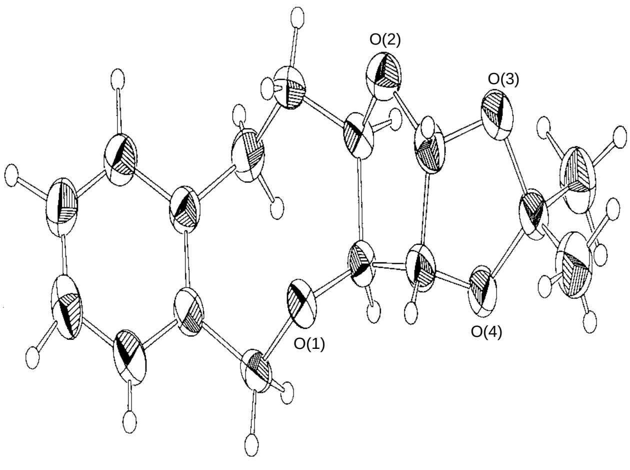


Fig. 1 ORTEP diagram of **4a**

In conclusion, the present investigation clearly shows the potential of regioselective aryl radical cyclisation from carbohydrate derived substrates in the synthesis of chiral condensed cyclic ethers incorporating medium sized rings.

Grateful acknowledgement is due to Professor U. R. Ghatak, INSA Senior Scientist, for his kind interest and valuable suggestions. We also extend our thanks to the Regional Sophisticated Instruments Center, Bose Institute, Calcutta, India, for the use of its single crystal diffractometer facility.

Footnotes and References

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* E-mail: iichbio@giasclo1.vsnl.net.in

† Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds. *Selected data* for **4a** mp 151–152 °C; $[\alpha]_D^{27}$ −20.6 (*c* 0.34, $CHCl_3$); $\delta_H(CDCl_3)$ 1.3 (s, 3 H), 1.46 (s, 3 H), 2.04–2.28 (m, 2 H), 2.44–2.68 (m, 1 H), 3.18–3.44 (m, 1 H), 4.04 (d, 1 H, *J* 4, H-3a), 4.28 (dt, 1 H, *J* 6 and 4, H-11a), 4.58 (d, 1 H, *J* 14), 4.62 (d, 1 H, *J* 4, H-3), 5.1 (d, *J* 14, 1 H), 5.90 (d, 1 H, *J* 4, H-2), 7.02–7.34 (m, 4 H, Ar-H); $\delta_C(CDCl_3)$ 26.2, 27.7, 28.6, 31.0, 75.0, 79.0, 84.5, 85.4, 104.0, 111.1, 126.1, 128.3, 128.8, 130.5, 135.7, 140.6; MS (EI) *m*/*z* 276 (M^+). For **4b**: mp 106–107 °C; $[\alpha]_D^{24}$ + 2.6 (*c* 0.23, $CHCl_3$); $\delta_H(CDCl_3)$ 1.31 (s, 3 H), 1.46 (s, 3 H),

2.09–2.21 (m, 2 H), 2.45–2.57 (m, 1 H), 3.17–3.31 (m, 1 H), 3.78 (s, 3 H, OMe), 4.02 (d, 1 H, *J* 4, H-3a), 4.22–4.29 (dt, 1 H, *J* 6 and 4, H-11a), 4.56 (d, 1 H, *J* 14), 4.62 (d, 1 H, *J* 4, H-3), 5.05 (d, *J* 14, 1 H), 5.89 (1 H, d, *J* 4, H-2), 6.64 (d, 1 H, *J* 2.5), 6.76–6.80 (1 H, dd, *J* 8 and 2.5), 7.08 (1 H, d, *J* 8); δ_C(CDCl$_3$) 26.2, 26.7, 27.8, 31.3, 55.2, 74.9, 78.9, 84.2, 85.4, 103.9, 111.2, 113.3, 114.4, 131.6, 134.6, 136.8, 157.8; MS (EI) *m*/*z* 360 (M$^+$).

‡ *Crystal data* for **4a**: C$_{16}$H$_{20}$O$_4$, $M = 276.33$, orthorhombic, space group $P2_12_12_1$, $a = 8.6733(6)$, $b = 9.1234(6)$, $c = 17.9110(11)$ Å, $U = 1417.3(2)$ Å^3, $Z = 4$, $D_c = 1.295$ g cm^{-3}, μ(Mo-Kα radiation, $\lambda = 0.71073$ Å) = 0.86 cm^{-1}, $2\theta_{max} = 50°$. 1412 reflections were recorded on an Enraf-Nonius CAD-4 diffractometer at 293 K. The structure was solved by direct method (MULTAN88) and refined by the full-matrix least-squares technique (SHELXL93). The function minimised was $\Sigma w(F_0^2 - F_c^2)$ [$w = 1/\sigma^2(F_0^2) + (0.06P)^2$ where $P = (F_0^2 + 2F_c^2)/3$]. Anisotropic refinement of nonhydrogen atoms and isotropic refinement of hydrogen atoms, located from difference Fourier maps, converged at $R_1 = 0.0415$ ($wR_2 = 0.0881$) for 1069 reflections with, $I > 2\sigma(I)$. Goodness of fit = 1.146 maximum/minimum residual electron densities +0.204/−0.244 e Å^{-3}. CCDC 182/616.

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Received in Cambridge, UK, 27th August 1997; 7/06249D