Short synthesis of the furanofuran sub-unit of the toxin erythroskyrine

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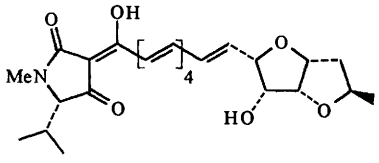
1 PERKIN COMMUNICATION

The synthesis of diol 16 from L-xylose is reported as a potential synthetic route to the furanofuran sub-unit of the toxin erythroskyrine 1.

Furanofurans, furanopyrans, pyranopyrans and related fused systems are common sub-units found in many natural products, including the potent toxin erythroskyrine[1] **1**. This material was



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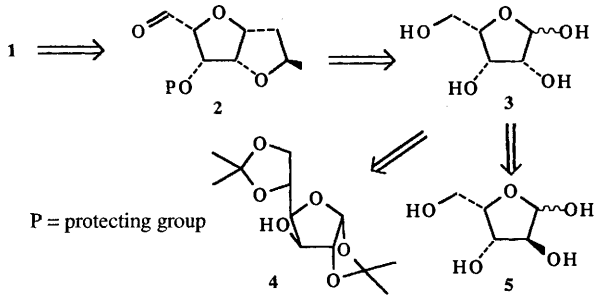
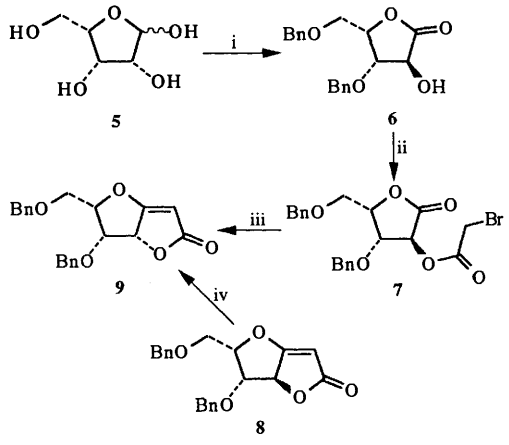
first isolated by Shoji *et al.*[1] and subsequently by Beutler *et al.*[2] who correctly redetermined its structure, and assigned the absolute configuration as **1** using NMR methods. As yet the total synthesis of **1** has not been realised, however, one synthesis of the furanofuran portion of this metabolite has been reported.[3]

Retrosynthesis of **1** by removal of the tetramic acid portion gives rise to the aldehyde **2** which can be considered as a key intermediate in any total synthesis. Further analysis of **2** reveals that the A ring of this intermediate has the absolute configuration found in the pentafuranose sugar L-lyxose **3**; access to derivatives of which is normally achieved *via* other more readily accessible or cheaper carbohydrates. Indeed the previously reported synthetic approach to erythroskyrine used D-glucose **4** as its starting material and accessed the L-lyxose intermediate by epimerisation at the C-3 and C-4 positions. An alternative retrosynthetic approach is to access a L-lyxose derivative from L-xylose **5** by effecting epimerisation at the C-2 position; it is efforts towards this eventuality which we now report (Scheme 1).



Scheme 1

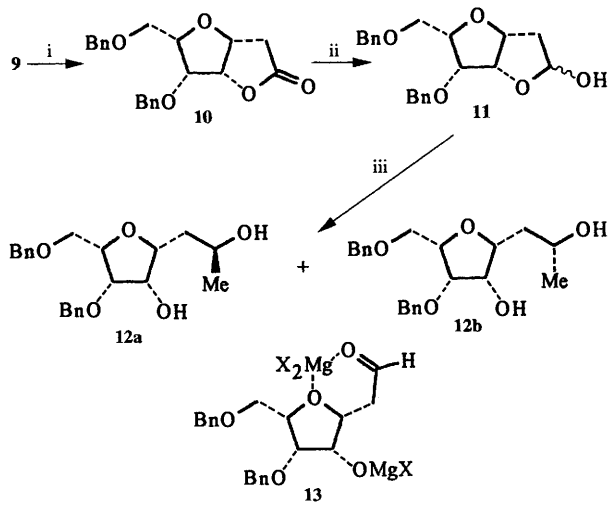
In order to test this possibility, L-xylose **5** was converted to the lactone **6** using a previously reported 4-step procedure;[4] this lactone was then bromoacetylated in 55% yield to give **7** in preparation for the crucial intramolecular non-classical Wittig reaction.[5] Thus **7** was treated with triphenylphosphine (2 h, MeCN, 40 °C), which was followed by the careful addition of 0.95 equivalents of DBU (−10 °C) and the reaction mixture heated to reflux for 30 min; this procedure gave the bicyclic tetronate **8** as judged by TLC. At this point the reaction mixture was cooled to room temperature, a further catalytic amount (*ca.* 0.05 equiv.) of DBU was added the reaction mixture refluxed for a further 3 min; two products were obtained from this reaction, the epimeric tetronate **9** in 55% yield together with the previously observed product **8** in 27% yield. The undesired product **8** can be epimerised to give further **9** by treatment with a further catalytic amount of DBU in refluxing acetonitrile, bringing the overall yield for this step to *ca.* ~65% (Scheme 2).



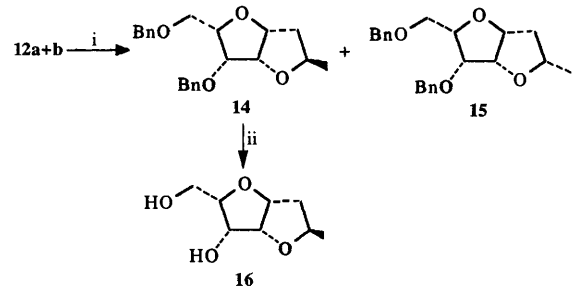
Scheme 2 *Reagents and conditions:* i, see ref. 4; ii, BrAcBr, pyridine, Et_2O (55%); iii, PPh_3, CH_3CN, then 0.95 equiv. DBU, reflux, 30 min, then 0.05 equiv. DBU, reflux, 3 min (**9**, 55%; **8**, 27%); iv, catalytic DBU, CH_3CN, reflux

Selective hydrogenation of the double bond in **9** was effected smoothly over rhodium on alumina (97%) to give **10**; subsequent diisobutylaluminium hydride (DIBAH) reduction of the lactone gave the hemiacetal **11** as a mixture of anomers. Treatment of this material with an excess of methylmagnesium bromide in a THF–TMEDA co-solvent gave an inseparable mixture (2.5–3:1) of alcohols **12a** and **b** in 81% overall yield from **10**. The major alcohol is presumed to be **12a** (*vide infra*) and may have arisen *via* a chelate such as **13** with the Grignard addition occurring from the most accessible face of this complex (Scheme 3).

Treatment of this mixture of diols under Mitsunobu conditions (PPh_3, DEAD, CH_2Cl_2, 24 h) effected efficient ring closure, to give two isomeric furanofurans **14** and **15** in an identical ratio to that observed for the starting materials; this observation is indicative of the reaction proceeding with inversion of stereochemistry for each diol. The required furanofuran **14** was easily isolated from this mixture by chromatography in 47% yield (*ca.* 70% based on content of **12a** in the starting mixture) and comparison of its spectral data with that reported for the furanofuran portion of erythroskyrine indicated an excellent level of correlation between the two substances. In addition, diol **16** ($[\alpha]_D^{24}$ +21.9 [*c* 0.58, chloroform]) was obtained on hydrogenation of **14** (70%), which again displayed excellent correlation with erythroskyrine in both its ^1H and ^{13}C spectra; these data were also in total



Scheme 3 *Reagents and conditions:* i, H_2, 5% Rh on alumina (97%); ii, DIBAH, PhMe, −78 °C; iii, 10 equiv. MeMgCl, THF–TMEDA (10:1), 0 °C–RT, 20 h (81%, 2 steps)



Scheme 4 *Reagents and conditions:* i, PPh_3, DEAD, CH_2Cl_2, 24 h [**14**; 47% (70% based on **12a**)]; ii, H_2, 10% Pd on charcoal, 5 h (97%)

agreement with previously reported literature information[3,6] (Scheme 4).

In conclusion, the synthesis of furanofuran **16** and its dibenzyl derivative **14** *via* this methodology offers a rapid, efficient and convenient stereoselective access to the furanofuran sub-unit of erythroskyrine. The application of similar chemistry, in conjunction with the construction of the acyl tetramic acid portion of the molecule will hopefully lead to the total synthesis of erythroskyrine.

Experimental

Column chromatography was carried out on Kieselgel (230–400 mesh) with the eluent specified in each case. TLC was conducted on precoated Kieselgel 60 F254 (Art. 5554; Merck) glass plates. All non-aqueous reactions were conducted in oven-dried apparatus under a static atmosphere of argon. Light petroleum refers to the fraction boiling in the range 35–60 °C. Dichloromethane and acetonitrile were dried and distilled before use using standard methods. Chemical shifts are reported as δ values relative to tetramethylsilane as an internal standard and J values are given in Hz. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform (unless otherwise stated) on a Brüker AC250 spectrometer. IR spectra were recorded as thin films (oils) or as chloroform solutions on a Perkin-Elmer 1600 series instrument. Mass spectra were recorded on a VG Masslab Model 12/253 spectrometer using chemical ionisation (with ammonia as the reagent gas). Accurate mass determinations were recorded on a VG Analytical ZAB-E spectrometer using chemical ionisation (with ammonia as the reagent gas). Optical rotations were determined on a POLAAR 2001 instrument and are determined as chloroform solutions and are given in units of 10^{-1} deg cm^2 g^{-1}.

Preparation of compounds 8 and 9

Triphenylphosphine (267.9 mg, 1.02 mmol, 1.2 equiv.) was added to a stirred solution of **7** (382.3 mg, 0.85 mmol) in dry acetonitrile (4 ml) and the resulting solution heated under an argon atmosphere at 50 °C, until TLC (ethyl acetate–petrol, 25:75) showed full conversion to the phosphonium salt (~2 h). The reaction mixture was cooled to 0 °C and 1,8-diazabicyclo[5.4.0]undec-5-ene (DBU; 122.6 mg, 0.806 mmol, 0.95 equiv.) was added. After stirring for 5 min., the reaction mixture was heated at reflux for 30 min and cooled again (0 °C). Further DBU was added (*ca.* 10 mg) and the mixture rapidly reheated in the oil bath for a further 3 min whereupon it was seen to darken considerably. The reaction was then cooled to 0 °C, diluted with ether (30 ml) and filtered through a silica plug, which was washed with further ether. Evaporation and chromatography (ethyl acetate–petrol, 20:80) of the filtrate gave **8** (80.6 mg, 27%) as an oil and **9** (162.5 mg, 55%) as a solid.

(1*S*,7*S*,8*R*)-8-Benzyloxy-7-benzyloxymethyl-2,6-dioxabicyclo-[3.3.0]oct-4-en-3-one 8. δ_H 3.81, 3.85 (2 H, 2 × dd, J 11.6, 3.0, 2.8, CH_2), 4.31 (1 H, dd, J 9.0, 8.1, CH), 4.56, 4.60 (2 H, 2 × d, J 12.0, CH_2), 4.60, 4.84 (2 H, 2 × d, J 11.8, CH_2), 4.60, 4.84 (2 H, 2 × d, J 11.8, CH_2), 4.94 (1 H, ddd, J 8.1, 3.0, 2.8, CH), 5.04 (1 H, d, J 1.8, vinyl CH), 5.53 (1 H, dd, J 9.0, 1.8, CH), 7.25–7.38 (10 H, m, 2 × Ph); δ_C 67.30, 72.26, 73.78 (3 × CH_2), 78.52, 81.98, 88.23, 89.67 (4 × CH), 127.61–128.58 (10 × PhCH), 136.56, 137.40 (2 × PhC), 174.32, 183.21 (2 × C); ν_{max} 1771 (C=O), 1656 (C=C); m/z 370 (100%, $[M + NH_4]^+$), 353 (80%, $[M + H]^+$); {$C_{21}H_{21}O_5$ ($[M + H]^+$) requires 353.1389; found 353.1389} $[\alpha]_D^{24}$ −52.4 (*c* 0.87).

(1*R*,7*S*,8*R*)-8-Benzyloxy-7-benzyloxymethyl-2,6-dioxabicyclo-[3.3.0]oct-4-en-3-one 9. Mp 90 °C; $\delta_H(C_6D_6)$ 3.36 (1 H, ddd, J 3.9, 2.3, 0.7, CH), 3.47, 3.60 (2 H, 2 × dd, J 10.8, 6.9, 5.0, CH_2), 4.09 (1 H, dd, J 3.9, 1.8, CH), 4.13, 4.22 (2 H, 2 × d, J 11.9, CH_2), 4.14, 4.56 (2 H, 2 × d, J 11.7, CH_2), 4.26 (1 H, ddd, J 6.9, 5.0, 2.3, CH), 4.86 (1 H, dd, J 1.8, 0.7, CH), 7.01–7.20 (10 H, m, 2 × Ph); δ_C 67.14, 73.51, 74.59 (3 × CH_2), 73.61, 80.56, 86.76, 92.22 (4 × CH_2), 127.66–128.38 (10 × PhCH), 136.59, 137.23 (2 × PhC), 174.84, 182.96 (2 × C); ν_{max} 1769 (C=O), 1652 (C=C); m/z 370 (100%, $[M + NH_4]^+$), 353 (55%, $[M + H]^+$); {$C_{21}H_{21}O_5$ ($[M + H]^+$) requires 353.1389; found 353.1389} $[\alpha]_D^{24}$ −12.4 (*c* 0.39).

Preparation of (1*S*,3*R*,5*R*,7*S*,8*R*)-8-benzyloxy-7-benzyloxymethyl-3-methyl-2,6-dioxabicyclo[3.3.0]octane 14

A mixture of diols **13a** and **13b** (50.0 mg, 0.1377 mmol) was dissolved in dry dichloromethane (2 ml) and triphenylphosphine (54.1 mg, 0.2065 mmol, 1.5 equiv.) was added. The mixture was stirred for 10 min then diethyl azodicarboxylate (DEAD; 0.033 ml, 0.2065 mmol, 1.5 equiv.) was added. The reaction was then stirred until TLC (ethyl acetate–petrol, 60:40 and diethyl ether–petrol, 50:50) indicated that no starting material remained (*ca.* 24 h). After adding water (10 ml) the product was extracted with diethyl ether (3 × 20 ml), dried ($MgSO_4$) and purified by flash chromatography (diethyl ether–petrol, 25:75). This procedure gave **14** (22.2 mg, 0.063 mmol, 47%) and a mixture (*ca.* 1:1) of **14** and **15** (14.2 mg, 0.040 mmol, 30%) as gums. Data for **14**: δ_H 1.26 (3 H, d, J 6.1, CH_3), 1.43 (1 H, ddd, J 5.4, 10.8, 13.3, CH), 2.18 (1 H, dd, J 4.6, 13.3, CH), 3.74 (2 H, m, $BnOCH_2$), 3.85 (1 H, dt, J 4.5, 6.0, CH), 3.94 (1 H, dd, J 4.5, 4.3, CH), 4.23 (1 H, m, CH), 4.49 (3 H, m, 2 × PhCH, and CH), 4.64 (1 H, d, J 12.0, PhCH), 4.70 (1 H, t, J 5.4, CH), 4.88 (1 H, d, J 11.8, PhCH), 7.25–7.34 (10 H, m, 2 × Ph); δ_C 19.88 (CH_3), 40.76, 68.70, 73.14, 73.48 (4 × CH_2), 76.21, 79.17, 81.25, 83.69, 83.80 (5 × CH), 127.47, 127.62, 127.88, 128.26, 138.22 (10 × CH), 138.18, 138.62 (2 × C); ν_{max} 2929, 2856 (C–H), 1096 (C–O); m/z 372 (45%, $[M + NH_4]^+$), 355 (100%, $[M + H]^+$) {$C_{22}H_{27}O_4$ ($[M + H]^+$) requires 355.1909; found 353.1909}; $[\alpha]_D^{24}$ +70.9 (*c* 0.73).

Selected data for (1*S*,3*R*,5*R*,7*S*,8*R*)-7-hydroxymethyl-3-methyl-2,6-dioxabicyclo[3.3.0]octan-8-ol 16

$[\alpha]_D^{24}$ +21.9 (*c* 0.58); δ_H 1.32 (3 H, d, *J* 6.0, CH_3), 1.57 (1 H, ddd, *J* 4.7, 10.7, 13.5, CH), 2.28 (1 H, dd, *J* 4.5, 13.5, CH), 2.75, 3.12 (2 × 1 H, br s, 2 × OH), 3.71 (1 H, app. q, *J* 4.6, CH), 3.95 (2 H, m, $HOCH_2$), 4.23 (2 H, m, CH and CH), 4.50 (1 H, app. t, *J* 4.7, CH), 4.63 (1 H, dd, *J* 4.7, 6.3, CH); δ_C 19.79 (CH_3), 40.43, 61.18 (2 × CH_2), 72.40, 77.17, 83.07, 83.09, 83.75 (5 × CH); ν_{max} 3480 (O–H), 2977, 2932 (C–H); *m*/*z* 192 ($[M + NH_4]^+$, 95%), 175 ($[M + H]^+$, 100%) {$C_8H_{15}O_4$ ($[M + H^+]$) requires 175.0970; found 175.0970}.

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