Enantiospecific Synthesis of the Hexahydrofuran Unit of Erythroskyrine, a Pentaenoyltetramic Acid Metabolite

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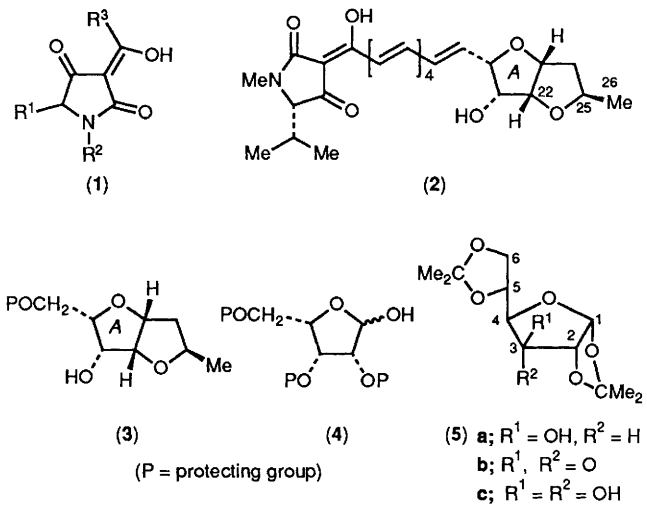
A hexahydrofuro[3,2-*b*]furan unit suitably functionalised for incorporation into the synthesis of erythroskyrine has been prepared in homochiral form from diacetone-D-glucose.

The 3-acyltetramic acids form a structurally diverse family of biologically active natural products sharing the 3-acylpyrrolidine-2,4-dione moiety (**1**). Amongst the 3-polyenoyl sub-class, the highly toxic pigment erythroskyrine (**2**), isolated from *Penicillium islandicum*,[1] is unique in carrying a hexahydrofuro[3,2-*b*]furan at the terminus of a pentaenoyl chain.[2] Continuing our interest in the 3-acyltetramic acids,[3] we report herein the first synthesis of the homochiral furofuran unit (**3**) suitable for incorporation into the synthesis of erythroskyrine.

The recently defined relative and absolute stereochemistry

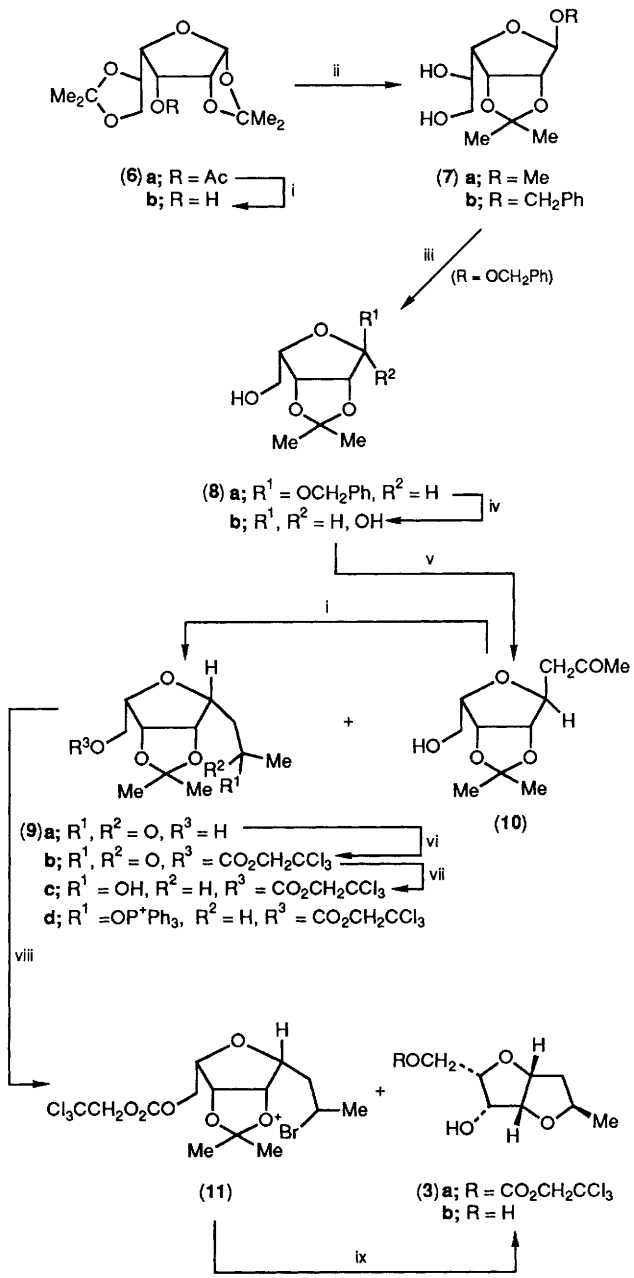


of erythroskyrine (**2**)[4] reveals that ring *A* correlates to a derivative (**4**) of L-lyxose which we planned to access from the readily available diacetone-D-glucose (**5a**). 1,2 : 5,6-Di-*O*-isopropylidene glucose (**5a**) was oxidised by ruthenium(VIII) (RuO_2, $NaIO_4$, CCl_4–MeCN–H_2O)[5] to afford a mixture (87%) of ketone (**5b**) and its hydrate (**5c**) which was converted into the gulose derivative (**6a**) as reported,[7,8] and thence into the alcohol (**6b**) (NaOEt, EtOH, 20 °C; 94%), to accomplish the necessary inversions of C-3 and C-4.

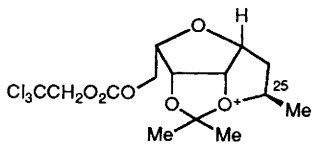
After extensive investigations, selective deprotection at O-5 and O-6 was developed from the acetonide rearrangement of alcohol (**6b**) (2,2-dimethoxypropane, Me_2CO–MeOH, conc. HCl, reflux) which gave diol (**7a**) (Scheme 1) as the β-glycoside in good yield (71%).[8] The significance of a cyclic protecting group at C-2, C-3 of sugars during condensations at C-1 to form *C*-glycosides[9] led us to modify the rearrangement to permit subsequent selective unmasking of C-1. When acetate (**6a**) was treated with benzyl alcohol (Me_2CO, conc. HCl, 20 → 60 °C) the benzyl glycoside (**7b**)† was produced (59%). Excision of C-6 by periodate cleavage–borohydride reduction ($NaIO_4$, H_2O–EtOH, then $NaBH_4$) occurred smoothly to afford (**8a**) (91%) and deprotection at C-1 gave the hemiacetal (**8b**) [20% $Pd(OH)_2$–C, EtOH, 1 atm H_2; 96%], an L-lyxose derivative suitably protected for incorporation of a C_3-fragment.

Condensation of hemiacetal (**8b**) with dimethyl acetylmethylphosphonate [NaH, $MeO(CH_2)_2OMe$, reflux] led to a mixture of furanose *C*-glycosides (**9a,10**), separable by chromatography, from which base-mediated epimerisation (NaOEt, EtOH, reflux) afforded the more stable[10] α-anomer (**9a**) (78% overall) subsequently protected as its 2,2,2-trichloroethyl carbonate (**9b**) [Cl_3CCH_2OCOCl, pyridine–dimethylformamide (DMF), 0 °C; 100%].

The remaining objective was cyclisation to generate the hexahydrofuro[3,2-*b*]furan unit. Reduction of ketone (**9b**) [$LiAlH(OBu^t)_3$, tetrahydrofuran (THF)] afforded the corresponding alcohols (**9c**) (77%; 2 : 1 epimer mixture). Treatment of the alcohols under bromination conditions (Ph_3P, $BrCCl_2CCl_2Br$, Et_2O) led to the expected bromide (**11**) (40%) as a *single stereoisomer* along with a second product (14%) which proved to be the required furofuran (**3a**), *again as a single stereoisomer*. Exposure of the bromide (**11**) to acid



Scheme 1. *Reagents*: i, NaOEt, EtOH; ii, $(MeO)_2CMe_2$, Me_2CO–MeOH, conc. HCl [from (**6b**)]; or $PhCH_2OH$, Me_2CO, conc. HCl [from (**6a**)]; iii, $NaIO_4$, H_2O–EtOH, then $NaBH_4$, EtOH; iv, H_2, $Pd(OH)_2$–C; v, NaH, $MeCOCH_2P(O)(OMe)_2$; vi, Cl_3CCH_2OCOCl, pyridine–DMF; vii, $LiAlH(OBu^t)_3$, THF; viii, Ph_3P, $Br(CCl_2)_2Br$; ix, aq. AcOH [to (**3a**)], or aq. HBr–Et_2O [to (**3b**)].



(70% aq. AcOH, reflux) resulted in acetonide cleavage and cyclisation to afford the bis-furan (**3a**) (66%), stereochemically identical to the earlier sample. Alternatively treatment of the bromide (**11**) with aq. HBr (Et_2O, reflux) led to the bicyclic diol (**3b**) (46%). The structure of (**3a**) was fully

† All new compounds gave spectral data (IR, UV, NMR, MS) in accord with the assigned structure, and satisfactory combustion analysis or accurate mass measurement.

supported by analytical and spectroscopic data, including NMR COSY measurements. Comparison of the ^1H and ^{13}C NMR information for (**3a**) with that reported[4] for the furofuran portion of erythroskyrine indicated excellent correlation for C-22 to C-26 (erythroskyrine numbering).‡ We have thus completed the first synthesis in homochiral form of the hexahydrofuro[3,2-*b*]furan unit of erythroskyrine.

Halogenation under the conditions used involves diastereoisomeric alkoxyphosphonium salts (**9d**).[11] A possible rationale for the formation of (**3a**) in both reactions invokes intramolecular participation[12] in the minor epimer of (**9d**) leading directly to (**3a**) *via* oxycation (**12**) (with an *exo*-Me at C-25) and cleavage of the isopropylidene moiety on work-up. Attack by bromide ion on the major epimer of (**9d**) affords bromide (**11**) and thence, by acid treatment, furofuran (**3a**) of the same configuration.§

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‡ *Selected data* for (**3a**): m.p. 63.5—65 °C; δ_H ($CDCl_3$) 1.33 (3H, d, *J* 6 Hz, H-26), 1.55 (1H, ddd, *J* 13.5, 11, and 4.5 Hz, H-24a), 2.28 (1H, dd, *J* 13.5 and 4.5 Hz, H-24b), 4.22 (2H, m, H-25, 21), 4.5 (1H, t, *J* 4.5 Hz, H-23), and 4.63 (2H, m, H-22, 19a); δ_C ($CDCl_3$) 19.8 (C-26), 40.3 (C-24), 77.2 (C-25), 82.9 (C-23), and 84.2 (C-22).

§ This rationale implies that the major alcohol (**9c**) has the (*R*)-configuration, which is consistent with chelation control in the reduction of ketone (**9b**).

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