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Synthesis of trioxilins B_3 from hepoxilins B_3†

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Four stereoisomeric hepoxilins B_3 are stereospecifically converted into the corresponding trioxilins B_3, with configurational inversion at two asymmetric centres, by prolonged treatment with aqueous alkali.

Trioxilins (TrX)‡ have been known since 1978[2] as endogenous metabolites of arachidonic acid formed in a 12-lipoxygenase pathway of metabolism through intermediate hepoxilins (Hx).[3] Data on the biological properties of trioxilins (activity, their role in the organism, *etc.*) are almost totally lacking. Only the biogenesis and (partly) the composition of mixtures of regio- and stereo-isomers, as well as incomplete configurations of trioxilins, have been established.[3] So, for endogenous trioxilins B_3 the 12*R*-configuration is commonly accepted on the basis of the proposed mechanism of their biosynthesis. On the other hand, hepoxilins that are the direct precursors of trioxilins have been investigated much more, and for them a number of interesting biological activities has been found (for recent reviews on this family of eicosanoids, see ref. 4). Moreover, unsaturated trihydroxy-C_{18}- and -C_{20}-acids, structurally very similar to trioxilins, have been identified as highly active natural bioregulators.[5]

With the aim of making available stereochemically individual samples for biological studies, a number of total syntheses of trioxilins A_3 and B_3 were accomplished from natural chiral starting materials (carbohydrates, quinic acid).[6] However, 'biomimetic' synthesis of trioxilins from hepoxilins has not yet been achieved, if we discount such a synthesis as the acidic hydrolysis of hepoxilins which results in inseparable mixtures of all theoretically possible regio- and stereo-isomers (up to 4 non-optical isomers from each of 4 hepoxilins).[7] In the present communication we describe a single-step stereoselective transformation of hepoxilins B_3 **1**, **2** into trioxilins B_3 **3**, **4**.

The discovery of a non-trivial and simple method has been greatly assisted by the observation of invariable formation of a side product upon a normal alkaline hydrolysis of (10*S*)-HxB_3 methyl ester **1a** into the corresponding free acid **1b** in aqueous methanol. Upon further study this side product was found to be the 10-*O*-methyl ether of $TrXB_3$ **5**. This becomes the main product (yield 67%) at more prolonged (3.5 h) reaction, being accompanied by the formation of a small amount of (10*R*,11*S*,12*S*)-$TrXB_3$ **3**. The simple replacement of the solvent for aqueous *tert*-butyl alcohol led to the formation (after carrying out the reaction for 2 days) of trioxilin **3** in high yield (88%) and as a single product.§ An analogous conversion of (10*R*)-HxB_3 methyl ester **2a** into epimeric (10*S*,11*S*,12*S*)-$TrXB_3$ **4** requires 9 days for completion but proceeds just as cleanly (yield 78%). These transformations can be accelerated by heating, and can be performed with the corresponding free acids **1b**, **2b** as well.

The specified relative and absolute configuration of the obtained trioxilin B_3 stereoisomers **3**, **4** has been reliably proven by comparison of optical rotations as well as of ^{1}H

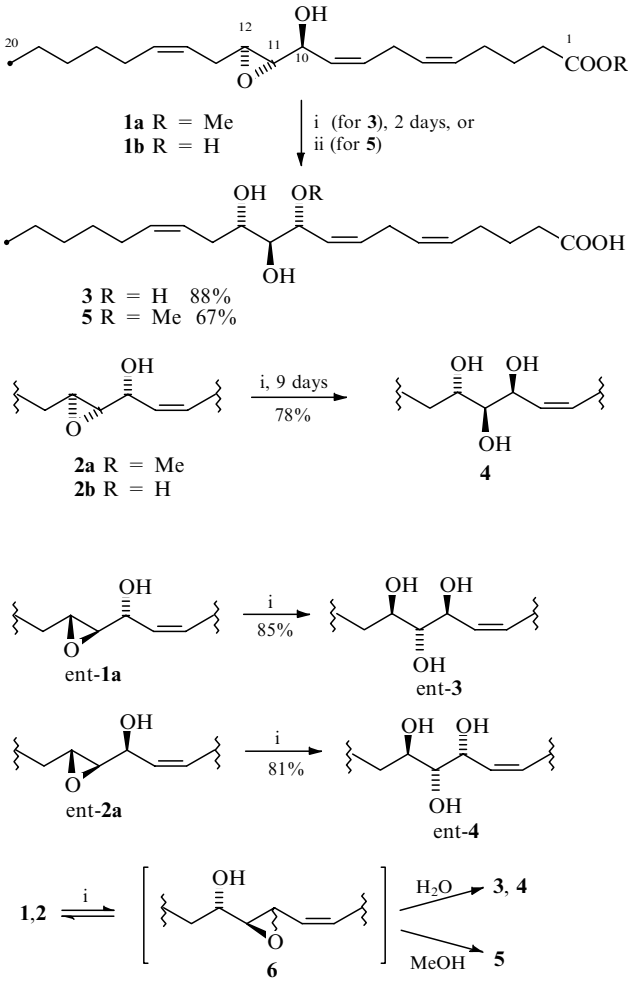
† Part 5 of a series 'Synthetic Research of Hepoxilins'. For part 4, see ref. 1.

‡ Trivial names and abbreviations: ent, enantio; $TrXA_3$, 8,9,12(*S*)- and 8,11,12(*S*)-trihydroxyeicosa-5(*Z*),10(*E*),14(*Z*)- and -5(*Z*),9(*E*),14(*Z*)-trienoic acids; $TrXB_3$, 10,11,12-trihydroxyeicosa-5(*Z*),8(*Z*),14(*Z*)-trienoic acids; HxA_3, 11(*S*),12(*S*)-epoxy-8(*R*)- and 8(*S*)-hydroxyeicosa-5(*Z*),9(*E*),14(*Z*)-trienoic acids; HxB_3, 11(*S*),12(*S*)-epoxy-10(*R*)- and 10(*S*)-hydroxyeicosa-5(*Z*),8(*Z*),14(*Z*)-trienoic acids.

§ *Synthesis of* **3**. Solutions of (10*S*)-HxB_3 methyl ester (5.85 mg) **1a** in Bu^tOH (0.5 ml) and of LiOH in water (1.6 M, 1 ml) were mixed and stirred under an argon atmosphere for 2 days at 23 °C, monitoring the disappearance of initially formed acid **1b** by TLC. After acidification to pH 3 and extraction (Et_2O) flash chromatography (silica gel 5–40 μm, EtOAc–hexane, 15:85→30:70) afforded 5.29 mg (88%) of trioxilin **3**.

¶ **3**: colourless oil, $[\alpha]_D^{25}$ −34.0° (*c* 0.31 in $CHCl_3$). TLC (Silufol): R_f 0.22 (EtOAc–hexane, 6:4). GLC of methyl ester of Bu^tMe_2Si *tris*-ether†† (a fused silica capillary column, 0.2 mm×25 m, 240 °C, stationary phase PEG-20M, helium as a carrier gas, 3.6×10^5 Pa, FID): retention time 14.53 min. IR (CCl_4, ν/cm^{-1}): 1711 (C=O), 3400 (OH). ^{1}H NMR (80 MHz, $CDCl_3$, δ, ppm): 0.89 (t, 3H, *J* 6.0 Hz, H_3^{20}), 1.26 (m, 6H, $H_2^{17+18+19}$), 1.74 (m, 2H, H_2^3), 2.08 (m, 4H, H_2^{4+16}), 2.36 (m, 4H, H_2^{2+13}), 2.97 (m, 5H, H_2^7 + 3×OH), 3.61 (m, 2H, H^{11+12}), 4.71 (dd, 1H, *J* 5.5 and 8.0 Hz, H^{10}), 5.34–5.72 (m, olefinic 6H). **4**: colourless oil, $[\alpha]_D^{25}$ +19.1° (*c* 0.99 in $CHCl_3$). TLC: R_f 0.18. GLC: 14.20 min. IR: 1711 (C=O), 3400 (OH). ^{1}H NMR (400 MHz, $CDCl_3$, COSY, δ, ppm): 0.87 (t, 3H, *J* 6.5 Hz, H_3^{20}), 1.23–1.37 (m, 6H, $H_2^{17+18+19}$), 1.66 and 1.68 (2 dquintet, 2H, *J* 14.6 and 7.3 Hz, H_2^3), 2.03 (q, 2H, *J* 7.1 Hz, H_2^{16}), 2.07 and 2.17 (2 dq, 2H, *J* 14.6 and 7.3 Hz, H_2^4), 2.33 (t, 2H, *J* 7.3 Hz, H_2^2), 2.33 (m, 2H, H_2^{13}), 2.75 (dt, 1H, *J* 16.2 and 4.9 Hz, H^7), 2.98 (dt, 1H, *J* 16.2 and 6.8 Hz, H^7), 3.47 (dd, 1H, *J* 4.1 and 5.5 Hz, H^{11}), 3.75 (dt, 1H, *J* 8.1 and 5.5 Hz, H^{12}), 4.70 (dd, 1H, J 4.1 and 7.7 Hz, H^{10}), 5.32–5.48 (m, 3H, H^{5+6+14}), 5.52–5.63 (m, 3H, H^{8+9+15}). **5**: colourless oil. TLC: R_f 0.48. IR: 1707 (C=O), 3425 and 3590 (OH). ^{1}H NMR (80 MHz): 0.88 (t, 3H, *J* 6.0 Hz, H_3^{20}), 1.27 (m, 6H, $H_2^{17+18+19}$), 1.75 (m, 2H, H_2^3), 2.07 (m, 4H, H_2^{4+16}), 2.36 (m, 4H, H_2^{2+13}), 2.92 (t, 2H, *J* 6.0 Hz, H_2^7), 3.29 (s, 3H, OMe), 3.66 (m, 4H, H^{11+12} + 2×OH), 4.25 (dd, 1H, *J* 4.5 and 9.5 Hz, H^{10}), 5.29–6.04 (m, olefinic 6H).

†† Obtained by treatment with CH_2N_2 in Et_2O followed by an excess of $CF_3SO_3SiMe_2Bu^t$ in Et_3N–C_6H_6 (1:4, 20 °C, 10 min).



Scheme 1 *Reagents and conditions:* i, 1.1 M LiOH in H_2O–Bu^{t}OH (2 : 1), 23 °C, several days; ii, 0.8 M LiOH in MeOH–H_2O (1 : 1), 23 °C, 3.5 h.

NMR spectral parameters of synthetic samples[¶] with the data published for the corresponding enantiomeric compounds.[6a,c‡‡] These configurations of trioxilins **3**, **4** indicate that their formation from the corresponding hepoxilins **1**, **2** proceeds with a simultaneous inversion of the configurations at the C^{10} and C^{11} asymmetric centres. Together with other peculiarities of the reaction mentioned above this stereochemistry specifies the following mechanism of transformation (ignoring trivial alkaline hydrolysis of the methyl ester group). As a result of the reversibility of the Payne rearrangement,[8] an equilibrium between hepoxilins B_3 **1**, **2** and their 12-hydroxy-10,11-epoxy-regioisomers **6** is established in alkaline medium (the configuration at C^{11} in the latter is already inverted). These allylic epoxides **6** are selectively attacked by hydroxide anion at the allylic C^{10}–O bond in accordance with an S_N2 mechanism, which results in configurational inversion at C^{10} and formation of trioxilins **3**, **4**. Although no detectable amounts of regioisomers **6** were observed in the reaction medium, their transient formation is suggested by the emergence of the 10-*O*-methyl ether of $TrXB_3$ **5** if the reaction is carried out in aqueous methanol, due to a competitive allylic epoxide opening by the more nucleophilic methoxide anion. In the case of (10*R*)-HxB_3 **2a** the reversible isomerization into regioisomer **6** requires the formation of a less stable *cis*-epoxide ring thus resulting in slower transformation into the corresponding trioxilin **4**.

As the 12*R*-configuration is accepted for enzymatically-formed trioxilins B_3,[3] the 12*S*-trioxilins B_3 **3**, **4**, obtained by the method described above from 'natural' (*i.e.* 12*S*-) enantiomers of hepoxilins B_3 **1**, **2**, are to be considered as 'unnatural' enantiomers. This is essential for a proposed study of their biological activity. The 'unnatural' enantiomers of hepoxilins, *ent*-**1a** and *ent*-**2a**, are necessary for additionally making available 'natural' 12*R*-enantiomers of trioxilins B_3. The former have been obtained according to our scheme of hepoxilin total synthesis[1] using D-(−)-diethyl tartrate at the Sharpless enantiodirected epoxidation step.[§§] Alkaline treatment (see above) of *ent*-**1a** and *ent*-**2a** afforded (10*S*,11*R*,12*R*)-$TrXB_3$ *ent*-**3** and (10*R*,11*R*,12*R*)-$TrXB_3$ *ent*-**4**, respectively, identical to enantiomeric **3** and **4** in all physical properties except for the signs of the optical rotations.[¶¶]

The transformation described in this communication can be considered as an extension of the previously described total syntheses[1,9] of hepoxilins B_3 into the corresponding trioxilins B_3. Moreover, as a number of (12*S*)-HxB_3 syntheses were performed from derivatives of (12*R*)-$TrXB_3$,[6b,d,10] it could also serve to obtain the enantiomers of the same trioxilins.

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‡‡ Literature data: (10*R*,11*R*,12*R*)-$TrXB_3$ methyl ester: $[\alpha]_D^{22}$ −16.4° (*c* 3.5 in Me_2CO);[6a] (10*S*,11*R*,12*R*)-$TrXB_3$: $[\alpha]_D$ +30.2° (*c* 1.8 in Me_2CO).[6c]

§§ *ent*-**1a**: $[\alpha]_D^{25}$ −71.6° (*c* 0.41 in $CHCl_3$); *ent*-**2a**: $[\alpha]_D^{25}$ +54.7° (*c* 0.78 in $CHCl_3$). Other physical properties are identical to those of **1a** and **2a**.

¶¶ *ent*-**3**: $[\alpha]_D^{25}$ +35.6° (*c* 0.27 in $CHCl_3$); *ent*-**4**: $[\alpha]_D^{25}$ −20.5° (*c* 0.56 in $CHCl_3$).

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