Total synthesis of trioxilins 11,12-*threo*-(8,11,12)-A_3 through type B_3 trioxilins†

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The total synthesis of trioxilins 11,12-*threo*-TrXB_3 has been extended to the corresponding trioxilins of the (8,11,12)-A_3 type. The synthesis involves the allylic rearrangement of a protected TrXB_3 derivative with a free 10-hydroxyl group under the Mitsunobu reaction conditions as the key step.

Previously,[1] we described the use of enantiodirected olefin dihydroxylation reaction for the total synthesis of 10-epimers and enantiomers of trioxilins (TrX) 11,12-*threo*-B_3.‡ The efficiency of this synthesis (9–10 steps) makes it possible to extend it for the synthesis of type A_3 trioxilins, which, along with TrXB_3, are the products of an oxidative metabolism of arachidonic acid in animals.[2,3]

Two subtypes, *viz*., (8,9,12)- and (8,11,12)-TrXA_3, are known for trioxilins A_3; these differ in the indicated arrangement of hydroxyl groups in the molecules. Both of these subtypes (their stereoisomers with respect to the configurations of the 8- and 9- or 11-hydroxyl groups) have been identified as both endogenous metabolites[2] and products of the acid hydrolysis of hepoxilins A_3.[4] According to their structures, (8,11,12)-TrXA_3 are allylic isomers of TrXB_3 and can formally be obtained from the latter by an allylic rearrangement. For this reason, the principal problem of this synthesis was to implement this rearrangement experimentally.

As starting compounds, we used 10-O-BMS derivatives of TrXB_3 (**1a**), both 10-epimers of which have been obtained in the synthesis of TrXB_3, each as two individual enantiomers.[1] It was more convenient to use the unseparated mixtures of 10-epimers **1a** and to separate epimers at a later stage of the synthesis. A two-step transformation of the protective groups under standard conditions (Scheme 1) produced from a mixture of 10-epimers (10*R*/*S*,11*S*,12*R*)-**1a** (10*R*:10*S* = 3:1) acetonides (10*R*/*S*)-**1c** with a free allylic hydroxyl group.§,¶

At this step, the enantiomeric purity of the products was analysed by HPLC on a chiral phase.†† Measurements gave ee ≥ 94.5% (12*R*) for (10*R*)-**1c** obtained from products of enantiodirected dihydroxylation performed by treatment with AD-mix-β, and ee ≥ 95.2% for its 12*S*-enantiomer (synthesised in a similar way using AD-mix-α as the source of chirality). The same excesses of the corresponding enantiomers should exist in all the subsequent products since the asymmetric centre at C^{12} was not affected in the chemical transformations.

Secondary allyl alcohols have been successfully rearranged by Pd^{II}-catalysed rearrangement of the corresponding acetates in the prostaglandin series[5] or by hydrolysis of the corresponding mesylates in the hepoxilin series.[6] Both of these methods failed in our case: the 10-acetate obtained from (10*R*/*S*)-**1c** did not isomerise under catalysis with $PdCl_2{\cdot}(MeCN)_2$, while mesylation of (10*R*/*S*)-**1c** mainly resulted in the elimination of the allylic hydroxyl group (an analogous situation was reported[7]). It was found more successful to use the anomalous Mitsunobu reaction, which occurs with a considerable proportion of allylic rearrangement and which we have used previously in the hepoxilin series.[8]

The Mitsunobu reaction of individual epimers (10*R*)- and (10*S*)-**1c** with benzoic acid proceeded with a 31–43% degree of the allylic rearrangement and gave (after hydrolysis of intermediate benzoates) a separable mixture of TrXA_3 acetonides (8*R*/*S*)-**2** and the inverted starting compounds (Scheme 1).‡‡ In each case, the replacement with allylic rearrangement proceeded with a 85–95% retention of the 'real'§§ configuration of the hydroxyl group, whereas replacement without the rearrangement resulted in a complete inversion. Owing to these stereochemical features, in preparative runs this reaction starting from the 3:1 (10*R*:10*S*) epimer mixture (10*R*/*S*)-**1c** resulted in an (8*R*/*S*)-**2** mixture with a significant predominance of the 8*R*-epimer, whereas the ratio of the 10-epimers in the recovered (10*R*/*S*)-**1c** mixture was opposite to the original one. The Mitsunobu reaction performed for the second time with this recovered mixture resulted again in an (8*R*/*S*)-**2** mixture, but now with predomi-

† Communication 12 from the series 'Synthetic study of hepoxilins'. For communication 11, see ref. 1.

‡ See ref. 1 for trivial names and abbreviations.

§ The present synthesis is exemplified by compounds with the 12*R* absolute configuration; these lead to (12*R*)-TrXA_3, which have not been described before. Some similar conversions were also performed in the 12*S*-series.

¶ A solution of a mixture of epimeric diols (10*R*/*S*,11*S*,12*R*)-**1a** (287 mg, 0.59 mmol) and *rac*-camphorsulfonic acid (28 mg) in 2,2-dimethoxypropane (2.5 g, 23.6 mmol) was kept for 24 h at 20 °C, diluted with ether and filtered through 3 g of Al_2O_3 (Brockman activity grade II, pH 7.0). The filtrate was concentrated to give a mixture of acetonides (10*R*/*S*)-**1b**; yield, 298 mg (96%); light yellow oil; R_f 0.48 (system A: Silufol UV_{254} silica gel plates, hexane–EtOAc, 8:2), which was dissolved without additional purification in THF (5 ml). To this solution, Bu^n_4NF (0.55 g, 2.08 mmol) was added, the mixture was kept for 3 h at 20 °C, diluted with water (5 ml) and extracted with EtOAc. Filtration of the extract through 3 g of SiO_2 followed by concentration gave of a mixture of acetonides (10*R*/*S*)-**1c**; yield, 200 mg (86%); light yellow oil; HPLC (Silasorb SPH-300 column, 6 μm, 200×4 mm; system, 0.6% Pr^iOH in *n*-hexane, 1.5 ml min^{-1}; UV detector at 210 nm): RT 5.7 (main peak) and 6.7 min. The individual epimers were isolated by preparative HPLC.

Major epimer (10*R*)-**1c**: colourless oil, R_f 0.18 (system A), 0.55 (system B: Silufol UV_{254} silica gel plates; hexane–EtOAc, 6:4), $[\alpha]_D^{25}$ –18.6° (*c* 0.81, $CHCl_3$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: 0.86 (t, 3H, $C^{20}H_3$, *J* 6.8 Hz), 1.22–1.36 (m, 6H, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.40 and 1.56 (2s, 2×3H, CMe_2), 1.68 (quint., 2H, C^3H_2, *J* 7.4 Hz), 1.96–2.03 (m, 2H, $C^{16}H_2$), 2.03–2.11 (m, 2H, C^4H_2), 2.28 (d, 1H, 10-OH, *J* 5.1 Hz), 2.26–2.44 (m, 2H, $C^{13}H_2$), 2.30 (t, 2H, C^2H_2, *J* 7.4 Hz), 2.78 (dt, 1H, H^{7A}, *J* 16.2 and 6.0 Hz), 2.92 (dt, 1H, H^{7B}, *J* 16.2 and 6.8 Hz), 3.62 (dd, 1H, H^{11}, *J* 5.1 and 7.8 Hz), 3.65 (s, 3H, OMe), 3.88 (ddd, 1H, H^{12}, *J* 5.2, 6.5 and 7.8 Hz), 4.40 (dt, 1H, H^{10}, *J* 8.9 and 5.1 Hz), 5.32–5.60 (m, 6H, H^5, H^6, H^8, H^9, H^{14}, H^{15}).

Minor epimer (10*S*)-**1c**: colourless oil, R_f 0.15 (system A), 0.50 (system B), $[\alpha]_D^{25}$ +27.9° (*c* 0.46, $CHCl_3$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: (only the differences from the spectrum of the other epimer are given): 1.39 and 1.40 (2s, 2×3H, CMe_2), 1.61 (br. s, 1H, 10-OH), 2.00 (q, 2H, $C^{16}H_2$, *J* 7.2 Hz), 2.09 (q, 2H, C^4H_2, *J* 7.4 Hz), 2.26–2.44 (m, 2H, $C^{13}H_2$), 3.73 (dd, 1H, H^{11}, *J* 4.6 and 7.8 Hz), 3.98 (ddd, 1H, H^{12}, *J* 5.2, 6.5 and 7.8 Hz), 4.59 (dd, 1H, H^{10}, *J* 4.6 and 8.9 Hz).

†† Chiracel OD column, 4.6×250 mm; system, 1% Pr^iOH in hexane, 1.5 ml min^{-1}; UV detector at 210 nm; retention times: (10*R*)-**1c**, 7.80 min; its enantiomer, 9.85 min.

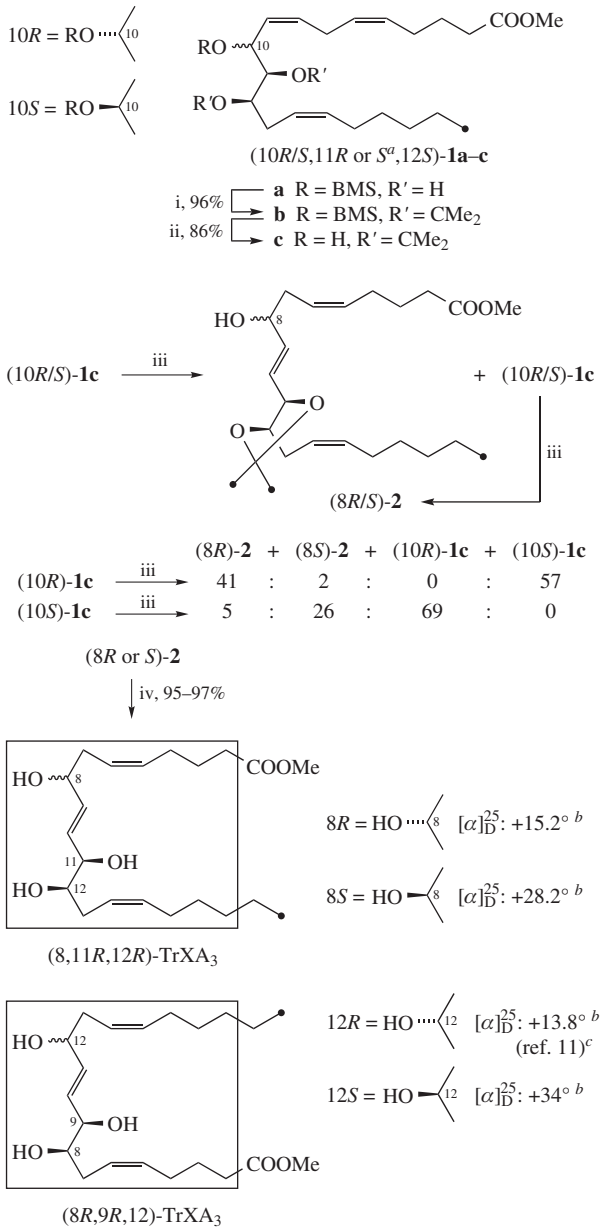
‡‡ The 'palladium-assisted Mitsunobu allylic shift',[9] *i.e.*, the same reaction performed in the presence of $PdCl_2{\cdot}(MeCN)_2$, did not increase the proportion of the allylic rearrangement.

§§ That is, spatial arrangement with respect to the double bond plane. The allylic shift of the hydroxyl group occurs with the inversion of the 'real' configuration (an attack from the opposite side of the *Z*-double bond), but the simultaneous change in the double bond configuration from *Z* to *E* is equivalent to a second inversion. In our cases, the retention (or change) of the *R*/*S* designation of the configuration does not imply that retention (or change) of the configuration has occured: upon the transformation of **1a** into **2**, which does not affect the configuration at C^{11}, the designation of the configuration at this centre changes from *S* to *R*.

nance of the 8*S*-epimer. Such a Mitsunobu reaction carried out sequentially two times not only increases the overall yield of $TrXA_3$ derivatives (8*R*/*S*)-**2** but also supplies a mixture of approximately equal amounts of 8-epimers, which have been separated by high-performance flash chromatography (HPFC).[10,¶¶,†††]

Removal of the protective acetonide moiety from individual epimers (8*R*)- and (8*S*)-**2** completes the synthesis of two isomers of trioxilin A_3 (8*R* and 8*S*,11*R*,12*R*)-$TrXA_3$,[‡‡‡] which have not been described before. Obviously, the enantiomers of these compounds can also be obtained if required from equally accessible[1] enantiomeric (10*R*/*S*,11*R*,12*S*)-**1a**.

The configuration of the resulting $TrXA_3$ at the asymmetric C^{11} and C^{12} centres was not affected in the above transformations; hence, it follows from the configuration of the starting compounds. The *E*-configuration of the 9,10-double bond is proved by the value of $^3J_{9,10}$ = 15.6 Hz in the ^{1}H NMR spectra. We assigned the configurations at C^8 based on the following considerations: trioxilins (8,9,12)-$TrXA_3$, which are the regioisomers of (8,11,12)-$TrXA_3$ synthesized here, have been reported previously.[11] In the molecules of these regioisomers, the environment of the C^8–C^{12} sections, which contain all the asymmetry and which are identical in structure, is also identical over a length of six carbon–carbon bonds on each side (see the framed identical parts of the molecules in Scheme 1). Therefore, it can be expected that pairs of such regioisomers having identical configurations of the C^8–C^{12} sections should have similar optical rotations and *vice versa*. Recently, we gave an experimental confirmation of a similar rule in the hepoxilin series.[12] One



Scheme 1 *Reagents and conditions*: i, $Me_2C(OMe)_2$, CSA, 20 °C, 24 h; ii, Bu^n_4NF, THF, 20 °C, 3 h; iii, BzOH, DEAD, PPh_3, PhH, 20 °C, 30 min, then K_2CO_3, MeOH, 20 °C, 24 h; iv, 80% aq. AcOH, 55 °C, 3 h. [a]Depends on substitution at neighbouring oxygen atoms. [b]In acetone. [c][α] of the corresponding enantiomer wih opposite sign.

¶¶ The following solutions were added in sequence to a solution of 190 mg (0.47 mmol) of a mixture of (10*R*/*S*)-**1c** (10*R*:10*S* = 3:1) in benzene (3 ml): PPh_3 (306 mg, 1.17 mmol) in benzene (2 ml), benzoic acid (143 mg, 1.17 mmol) in benzene (2 ml) and diethyl azodicarboxylate (203 mg, 1.17 mmol) in benzene (2 ml). The resulting bright yellow homogeneous solution was stirred for 30 min at 20 °C. The solution discoloured after 3 min, and the formation of a white finely-crystalline precipitate began. The mixture was evaporated to dryness, the semi-crystalline residue was triturated in 4 ml of diethyl ether–hexane mixture (8:2), and the precipitate (Ph_3PO and diethyl hydrazodicarboxylate) was filtered off. The filtrate was evaporated; the residue was dissolved in benzene and filtered through 10 g of SiO_2. Benzene was evaporated to give 439 mg of a contaminated mixture of intermediate 8- and 10-benzoates, light yellow oil; R_f 0.35 and 0.41 (system A), 0.65 and 0.68 (system B). This mixture was dissolved in a suspension of K_2CO_3 (100 mg, 0.72 mmol) in methanol (5 ml), stirred for 24 h at 20 °C, diluted with a phosphate buffer (30 ml, pH 6) and extracted with EtOAc. Concentration of the dried extract followed by chromatography on 30 g of SiO_2 (benzene, then EtOAc–hexane, 5:95 → 20:80) gave 41 mg (22%) of a mixture of (8*R*/*S*)-**2** (with predominance of the 8*R*-epimer); R_f 0.34 and 0.39 (main spot) (system B) and 109 mg (57%) of a mixture (10*R*/*S*)-**1c** (with predominance of the 10*S*-epimer); R_f 0.51 and 0.55 (main spot) (system B), light yellow oils. All the recovered mixture of (10*R*/*S*)-**1c** was treated again under the same conditions to give additionally 30 mg of a mixture of (8*R*/*S*)-**2** (with predominance of the 8*S*-epimer) and 63 mg of a mixture of (10*R*/*S*)-**1c** (with predominance of the 10*R*-epimer). Thus, the overall conversion of the starting compound was 67%, while the yield of the combined mixture of (8*R*/*S*)-**2** (with similar contents of the 8-epimers) was 56% with respect to the unrecovered starting compound. The individual epimers were isolated by HPFC (benzene, then EtOAc–hexane, 5:95 → 15:85).

Epimer (8*R*)-**2**: colourless oil, R_f 0.39 (system B), $[\alpha]_D^{25}$ +13.7° (*c* 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: 0.86 (t, 3H, $C^{20}H_3$, *J* 6.8 Hz), 1.21–1.38 (m, 6H, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.39 and 1.40 (2s, 2×3H, CMe_2), 1.58 (br. s, 1H, 8-OH), 1.68 (quint., 2H, C^3H_2, *J* 7.4 Hz), 2.01 (q, 2H, $C^{16}H_2$, *J* 7.4 Hz), 2.08 (q, 2H, C^4H_2, *J* 7.4 Hz), 2.26–2.40 (m, 4H, C^7H_2, $C^{13}H_2$), 2.30 (t, 2H, C^2H_2, *J* 7.4 Hz), 3.65 (s, 3H, OMe), 3.73 (dt, 1H, H^{12}, *J* 8.0 and 5.6 Hz), 4.05 (t, 1H, H^{11}, *J* 8.0 Hz), 4.19 (q, 1H, H^8, *J* 5.6 Hz), 5.36–5.56 (m, 4H, H^5, H^6, H^{14}, H^{15}), 5.68 (ddd, 1H, H^{10}, *J* 1.6, 8.0 and 15.6 Hz), 5.84 (ddd, 1H, H^9, *J* 1.0, 5.6 and 15.6 Hz).

Epimer (8*S*)-**2**: colourless oil, R_f 0.34 (system B), $[a]_D^{25}$ +6.5° (*c* 0.82, $CHCl_3$). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: (very similar; differences only) 3.72 (dt, 1H, H^{12}, *J* 7.6 and 5.6 Hz), 4.04 (t, 1H, H^{11}, *J* 7.6 Hz), 4.16 (q, 1H, H^8, *J* 5.6 Hz), 5.66 (ddd, 1H, H^{10}, *J* 1.2, 7.6 and 15.6 Hz), 5.82 (ddd, 1H, H^9, *J* 0.8, 5.6 and 15.6 Hz).

††† The mixtures of benzoates obtained in similar Mitsunobu reactions with individual epimers of (10*R*/*S*)-**1c** were analysed by HPLC (Silasorb SPH-300 column, 6 μm, 200×4 mm; system, 0.15% Pr^iOH in *n*-hexane, 2 ml min^{-1}; UV detector at 220 nm): RT 4.5, 4.9, 11.5 and 16.2 min for the benzoates of (10*R*)-**1c**, (10*S*)-**1c**, (8*S*)-**2** and (8*R*)-**2**, respectively. The product ratios are indicated in Scheme 1.

‡‡‡ (8*R*,11*R*,12*R*)-$TrXA_3$: light yellow oil, R_f 0.10 (system B, three developments), $[\alpha]_D^{25}$ +19.3° (*c* 1.38, $CHCl_3$), +15.2° (*c* 1.27, acetone). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: 0.86 (t, 3H, $C^{20}H_3$, *J* 6.8 Hz), 1.22–1.40 (m, 6H, $C^{17}H_2$, $C^{18}H_2$, $C^{19}H_2$), 1.68 (quint., 2H, C^3H_2, *J* 7.4 Hz), 2.03 (q, 2H, $C^{16}H_2$, *J* 7.4 Hz), 2.07 (q, 2H, C^4H_2, *J* 7.4 Hz), 2.20–2.32 (m, 4H, C^7H_2, $C^{13}H_2$), 2.30 (t, 2H, C^2H_2, *J* 7.4 Hz), 3.50 (dt, 1H, H^{12}, *J* 8.0 and 6.0 Hz), 3.65 (s, 3H, OMe), 3.99 (t, 1H, H^{11}, *J* 6.0 Hz), 4.19 (q, 1H, H^8, *J* 5.6 Hz), 5.36–5.59 (m, 4H, H^5, H^6, H^{14}, H^{15}), 5.74 (ddd, 1H, H^{10}, *J* 1.0, 6.0 and 15.6 Hz), 5.83 (ddd, 1H, H^9, *J* 0.8, 5.6 and 15.6 Hz).

(8*S*,11*R*,12*R*)-$TrXA_3$: light yellow oil, R_f 0.08 (system B, three developments), $[\alpha]_D^{25}$ +13.1° (*c* 0.74, $CHCl_3$), +28.6° (*c* 0.70, acetone). ^{1}H NMR (400 MHz, COSY, $CDCl_3$) δ: (very similar, differences only) 3.50 (dt, 1H, H^{12}, *J* 7.6 and 5.6 Hz), 3.98 (t, 1H, H^{11}, *J* 5.6 Hz), 4.17 (q, 1H, H^8, *J* 6.0 Hz), 5.73 (ddd, 1H, H^{10}, *J* 0.8, 5.6 and 15.6 Hz), 5.82 (ddd, 1H, H^9, *J* 0.8, 6.0 and 15.6 Hz).

can see in Scheme 1 that the rotation values for two epimers of (8*R*/*S*,11*R*,12*R*)-$TrXA_3$ match rather well the published data for two epimers of (8*R*,9*R*,12*R*/*S*)-$TrXA_3$. Based on this fact, we have derived the configurations at C^8 for the $TrXA_3$ synthesised. The same comparison confirms the absolute $C^{11,12}$-configurations of all the compounds obtained; previously,[1] this configuration was accepted on the basis of the enantiodirection of the chiral olefin dihydroxylation reaction.[13]

The four-stage conversion of the $TrXB_3$ derivative into (8,11,12)-$TrXA_3$ carried out with an overall yield of about 45% [taking into account the (10*R*/*S*)-**1c** recyclisation] generalizes the previously reported[1] enantiodirected total synthesis of trioxilins by the Sharpless enantioselective dihydroxylation of olefins to include A_3-type trioxilins. Unlike syntheses from natural homochiral starting compounds (carbohydrates, quinic acid, *etc*.), this synthetic scheme makes it possible to obtain, equally successfully, trioxilins of any enantiomeric series.

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