Synthesis of series 2 trioxilins from trioxilin B_3 by selective hydrogenation

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Trioxilins (as methyl esters) (10*S*,11*S*,12*S*)-$TrXB_2$ and its (8*E*)-isomer were obtained by selective hydrogenation of the 5,6-double bond in (10*S*,11*S*,12*S*)-$TrXB_3$ 11,12-acetonide followed by deprotection.

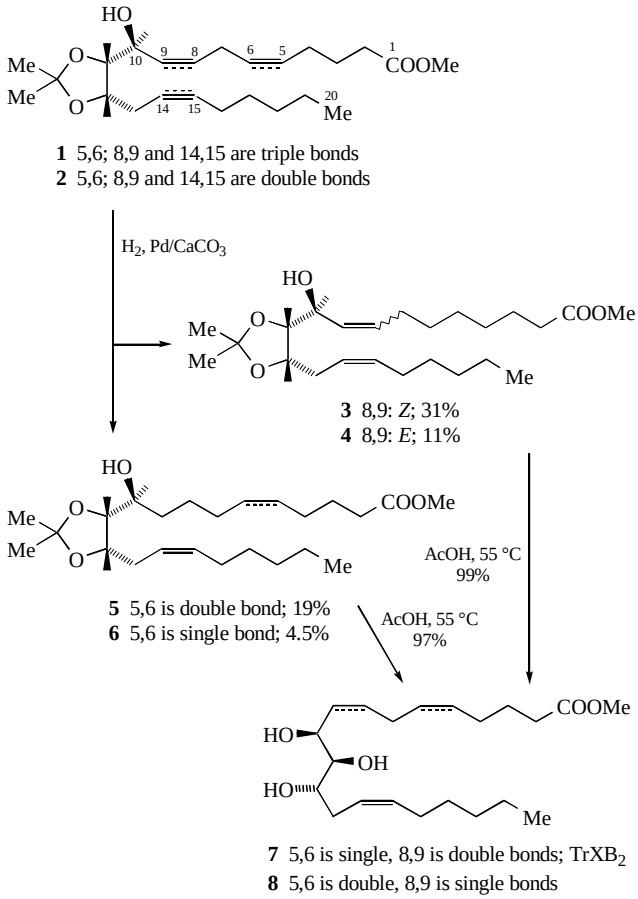
Hepoxilins and their immediate metabolites, trioxilins (TrX)[1] of series 3† (*i.e.*, with three double bonds at the 5,6-, 8,9- or 9,10-, and 14,15-positions), are metabolites formed from arachidonic acid *via* a 12-lipoxygenase pathway.[1] During the last years, hepoxilins attracted significant attention of biochemists mainly because of their regulatory role in an insulin secretion and hence in connection with diabetes. However, these studies were limited to series 3 hepoxilins, although series 4 hepoxilins, derived from (all-*Z*)-5,8,11,14,17-eicosapentaenoic acid were identified as endogenous metabolites.[2]

Other eicosanoids, prostaglandins (PG), are biosynthesised not only from the two above polyunsaturated fatty acids (PGs of series 2 and 3), but to the same extent from bis-homo-γ-linolenic acid (PGs of series 1).[3] Therefore, the occurrence of the corresponding series 2 hepoxilins and trioxilins in organisms seems to be very probable. To identify these potential endogenous 12-lipoxygenase eicosanoids, an independent chemical synthesis is desirable.

The total syntheses of prostaglandins of different series were accomplished by different, frequently independent, synthetic procedures.[3] However, the conversion of PG_2 into PG_1 was described.[4] This conversion is based on the selective hydrogenation of the 5,6(*Z*)-double bond in protected PG_2 derivatives, which is possible because of a diminished reactivity of the 13,14-double bond resulting from the (*E*)-configuration and steric hindrances from protective groups. Such a situation is not characteristic of series 3 hepoxilins/trioxilins, in which 5,6(*Z*)- and 14,15(*Z*)-double bonds together with their surroundings are very similar, and the third 8,9(*Z*)-double bond is present. Nevertheless, we have found a new means to differentiate these three double bonds thus making possible a direct conversion of series 3 trioxilins into series 2.

In the recent total synthesis of (10*S*,11*S*,12*S*)-$TrXB_3$ we observed[5] a striking selectivity in catalytic hydrogenation of 5,8,14-triacetylenic precursor 11,12-acetonide **1** into corresponding triene **2** (Scheme 1). The ease of hydrogenation of triple bonds in this triacetylene decreased in the order 5,6 > > 8,9 >> 14,15. The selectivity was explained by a hairpin conformation of the molecule due to the presence of a *cis*-substituted acetonide ring (as evident from the semi-empirical PM3 calculations). The $C^{9,10}$-fragment of molecule **1** in this conformation screens the 14,15-triple bond to reduce its reactivity. We surmised that the same selectivity could be held in some extent in triene **2** as well, thus opening the way to corresponding eicosanoids of series 2. This assumption has happened to be the case.

The catalytic hydrogenation of triene **2** over $Pd/CaCO_3$‡ in the presence of pyridine produced a product mixture, which was separated by high-performance flash chromatography[6] (HPFC). The main products were desired 5,6-dihydro derivative **3**, isolated in 31% yield, and 8,9-dihydro derivative **5** (19%). Two minor products were unexpected (8*E*)-5,6-dihydro derivative **4** (11%) and tetrahydro derivative **6** (4.5%).§



1 5,6; 8,9 and 14,15 are triple bonds
2 5,6; 8,9 and 14,15 are double bonds
3 8,9: *Z*; 31%
4 8,9: *E*; 11%
5 5,6 is double bond; 19%
6 5,6 is single bond; 4.5%
7 5,6 is single, 8,9 is double bonds; $TrXB_2$
8 5,6 is double, 8,9 is single bonds

Scheme 1

The positions of double bonds in hydrogenation products **3**–**6** were determined from single- and two-dimensional (H–H COSY) ^1H NMR data,¶ because the mass spectra provided information on the number rather than the position of double bonds because of the complexity of skeletal fragmentation.†† The NMR spectra of all compounds do not contain a multiplet of the C^7H_2 group separating 5,6- and 8,9-double bonds, which is characteristic of starting triene **2**; therefore, one (or both) of these double bonds was hydrogenated. The presence of the 8,9-double bond in **3**

† Trivial names and abbreviations: arachidonic acid is (all-*Z*)-5,8,11,14-eicosatetraenoic acid; bis-homo-γ-linolenic acid is (all-*Z*)-8,11,14-eicosatrienoic acid; eicosanoids of series 1, 2, 3 or 4 are eicosanoids with 1, 2, 3 or 4 double bonds in a molecule, respectively; hepoxilins (of types A_3/B_3) are stereoisomers of 8/10-hydroxy-11,12-epoxyeicosa-5(*Z*),9(*E*)/8(*Z*),14(*Z*)-trienoic acids; PG is prostaglandin; $TrXB_3$ are stereoisomers of 10,11,12-trihydroxyeicosa-5(*Z*),8(*Z*),14(*Z*)-trienoic acid (each compound can occur as a free acid or its methyl ester).

‡ Hydrogenation over the Lindlar catalyst proceeded very slowly.

§ Triene **2** (23 mg) in a benzene solution (2.2 ml) containing pyridine (0.2% v/v) was hydrogenated over a prereduced 5% $Pd/CaCO_3$ catalyst (5 mg, Aldrich) at 20 °C and 1 atm until all starting material was converted (5 h, TLC). The mixture was filtered and evaporated to dryness, and the residual oil was separated by HPFC on a Kieselgel 60 (Fluka) column (24×2 cm, over 2000 theoretical plates; gradient elution with EtOAc–hexane, 5:95 → 20:80). In the order of elution, the following compounds were isolated: 1 mg (4.5%) of **6** [R_f 0.67, silica gel plates (Merck), quadruple development by EtOAc–hexane, 20:80, for starting triene **2** R_f 0.43], 2.5 mg (11%) of a **5** + **6** mixture, 4.4 mg (19%) of **5** {R_f 0.63, $[\alpha]_D^{31}$ –11° (*c* 0.29, $CHCl_3$)}, 2.5 mg (11%) of **4** (R_f 0.52) and 7.1 mg (31%) of **3** {R_f 0.48, $[\alpha]_D^{31}$ –2.5° (*c* 0.47, $CHCl_3$)}.

and **4** is evident from the chemical shifts and multiplicities of $C^{10}HOH$ signals, as well as their COSY correlations with the signal of a vinylic proton in each case. In **4**, this signal (=C^8H) is shifted to low field and splitted with the coupling constant $^3J_{8–9}$ = 15.5 Hz so this double bond has (*E*)-configuration. Compounds **5** and **6** do not possess 8,9-double bonds, as evident from a significant ($\Delta\delta$ –0.8 ppm) shift of non-allylic $C^{10}HOH$ signals to high field. The intactness of 14,15-double bonds in all hydrogenation products **3**–**6** follows from the similarity of $C^{13}H_2$ signals (multiplet centered at near 2.4 ppm) in their spectra. Some other features of the NMR spectra also support the conclusions that dihydro compounds **3** and **4** are formed by hydrogenation of the 5,6-double bond of **2**; dihydro compound **5** is the result of 8,9-double bond hydrogenation, and both hydrogenations simultaneously lead to tetrahydro compound **6**.

It follows from the yields of hydrogenation products **3** + **4** and **5** that the hydrogenation reactivities of 5,6- and 8,9-double bonds in triene **2** are in a ratio of 2.2 : 1. The 14,15-double bond is not hydrogenated at all under the conditions used. All these findings are in a qualitative agreement with expectations based on the reactivity of triyne **1**. The formation of (8*E*)-product **4** may be understood as the possibility of (*Z*) → (*E*) isomerization of disubstituted double bonds in the course of Pd-catalyzed hydrogenations is long known.[7] Dobson *et al.*[7] found that the extent of this isomerization is unpredictable and depends (for Pd/C) on the origin of the catalyst.

The acetic acid hydrolysis of acetonides **3** and **5** cleanly produced trioxilins (10*S*,11*S*,12*S*)-TrXB$_2$ **7**‡‡ and 8,9-dihydro-(10*S*,11*S*,12*S*)-TrXB$_3$ **8**§§ (as methyl esters). Although the total yield of series 2 trioxilin **7** is not high, this straightforward method of partial synthesis is much simpler and gives higher yields than any independent total synthesis. The similar protocol, *e.g.*, hydroxyl group protection to shield the neighbouring double bonds — partial catalytic hydrogenation — deprotection, seems to be applicable to the synthesis of other less unsaturated 12-lipoxygenase eicosanoids from the corresponding series 3 congeners already obtained by total synthesis.

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¶ ^{1}H NMR spectra were measured in $CDCl_3$ on a Bruker DRX500 spectrometer at 500.13 MHz for **3**, **4** and Bruker AC-200 at 200.13 MHz for **5**, **6** (δ/ppm).

For **3**: 0.89 (t, 3H, $C^{20}H_3$), 1.26–1.43 (m, 12H, $C^{4–6,17–19}H_2$), 1.38 and 1.52 (2s, 2×3H, O_2CMe_2), 1.58–1.66 (m, 2H, C^3H_2), 1.99–2.07 (m, 2H, $C^{16}H_2$), 2.10 (dqd, 1H, $C^7H^aH^b$), 2.21 (dq, 1H, $C^7H^aH^b$), 2.27–2.42 (m, 2H, $C^{13}H_2$), 2.31 (t, 2H, C^2H_2), 3.68 (s, 3H, COOMe), 4.00 (t, 1H, $C^{11}H$), 4.14 (ddd, 1H, $C^{12}H$), 4.45 (ddd, 1H, $C^{10}H$), 5.38–5.45 (m, 2H, $C^{9,14}H$), 5.48–5.56 (m, 1H, $C^{15}H$), 5.63 (dt, 1H, C^8H); $^3J_{2–3}$ 7.5 Hz, $^3J_{6–7a}$ 7.5 Hz, $^3J_{6-7b}$ 7.5 Hz, $^2J_{7a–7b}$ 15.0 Hz, $^3J_{7a–8}$ 7.5 Hz, $^4J_{7a–9}$ 2.0 Hz, $^3J_{7b–8}$ 7.5 Hz, $^3J_{8–9}$ 11.0 Hz, $^3J_{9–10}$ 9.2 Hz, $^3J_{10–11}$ 5.9 Hz, $^3J_{10–OH}$ 3.5 Hz, $^3J_{11–12}$ 5.9 Hz, $^3J_{12–13a}$ 5.2 Hz, $^3J_{12–13b}$ 8.9 Hz, $^3J_{19–20}$ 6.4 Hz.

For **4**: 0.89 (t, 3H, $C^{20}H_3$), 1.26–1.42 (m, 12H, $C^{4–6,17–19}H_2$), 1.38 and 1.51 (2s, 2×3H, O_2CMe_2), 1.62 (quintet, 2H, C^3H_2), 2.01–2.09 (m, 4H, $C^{7,16}H_2$), 2.29–2.44 (m, 2H, $C^{13}H_2$), 2.31 (t, 2H, C^2H_2), 3.68 (s, 3H, COOMe), 3.99 (t, 1H, $C^{11}H$), 4.11–4.16 (m, 2H, $C^{10,12}H$), 5.42 (ddt, 1H, $C^{14}H$), 5.47 (ddt, 1H, C^9H), 5.52 (dtt, 1H, $C^{15}H$), 5.81 (dt, 1H, C^8H); $^3J_{2–3}$ 7.6 Hz, $^3J_{3–4}$ 7.6 Hz, $^3J_{7–8}$ 6.5 Hz, $^4J_{7–9}$ 1.5 Hz, $^3J_{8–9}$ 15.5 Hz, $^3J_{9–10}$ 7.5 Hz, $^3J_{10–11}$ 6.2 Hz, $^3J_{11–12}$ 6.2 Hz, $^3J_{13–14}$ 6.8 Hz, $^4J_{13–15}$ 1.5 Hz, $^3J_{14–15}$ 10.7 Hz, $^4J_{14–16}$ 1.5 Hz, $^3J_{15–16}$ 7.3 Hz, $^3J_{19–20}$ 6.5 Hz.

For **5**: 0.89 (t, 3H, $C^{20}H_3$), 1.23–1.65 (m, 10H, $C^{8,9,17–19}H_2$), 1.38 and 1.51 (2s, 2×3H, O_2CMe_2), 1.70 (quintet, 2H, C^3H_2), 1.96–2.15 (m, 2H, $C^{4,7,16}H_2$), 2.28–2.56 (m, 2H, $C^{13}H_2$), 2.32 (t, 2H, C^2H_2), 3.58–3.72 (m, 1H, $C^{10}H$), 3.68 (s, 3H, COOMe), 3.95 (dd, 1H, $C^{11}H$), 4.18 (dt, 1H, $C^{12}H$), 5.28–5.60 (m, 4H, $C^{5,6,14,15}H$); $^3J_{2–3}$ 7.3 Hz, $^3J_{3–4}$ 7.3 Hz, $^3J_{10–11}$ 4.5 Hz, $^3J_{11–12}$ 6.2 Hz, $^3J_{12–13a}$ 6.2 Hz, $^3J_{12–13b}$ 8.9 Hz, $^3J_{19–20}$ 6.5 Hz.

For **6**: 0.89 (t, 3H, $C^{20}H_3$), 1.23–1.64 (m, 20H, $C^{3–9,17–19}H_2$), 1.38 and 1.51 (2s, 2×3H, O_2CMe_2), 2.06 (dt, 2H, $C^{16}H_2$), 2.20–2.56 (m, 2H, $C^{13}H_2$), 2.31 (t, 2H, C^2H_2), 3.58–3.72 (m, 1H, $C^{10}H$), 3.68 (s, 3H, COOMe), 3.96 (dd, 1H, $C^{11}H$), 4.18 (dt, 1H, H_{12}), 5.34–5.62 (m, 2H, $C^{14,15}H$); $^3J_{2–3}$ 7.4 Hz, $^3J_{10–11}$ 4.6 Hz, $^3J_{11–12}$ 5.9 Hz, $^3J_{12–13a}$ 5.9 Hz, $^3J_{12–13b}$ 8.5 Hz, $^3J_{15–16}$ 6.4 Hz, $^3J_{16–17}$ 6.4 Hz, $^3J_{19–20}$ 6.5 Hz.

†† High ion MS [Kratos MS 890 instrument, direct inlet at 150 °C, EI, 30 eV, m/z (%)].

For **3**: 410 (2.2) $[M]^+$, 395 (19) $[M – Me]^+$, 392 (2.1) $[M – H_2O]^+$, 377 (1.5) $[M – Me – H_2O]^+$, 352 (4.1) $[M – Me_2CO]^+$, 335 (8.8) $[M – Me_2CO – – OH]^+$, 321 (8.4) $[M – Me_2CO – MeO]^+$, 303 (20) $[M – Me_2CO – H_2O – – MeO]^+$.

For **4**: 410 (0.7) $[M]^+$, 395 (11) $[M – Me]^+$, 392 (0.8) $[M – H_2O]^+$, 377 (0.6) $[M – Me – H_2O]^+$, 352 (2.7) $[M – Me_2CO]^+$, 335 (9.2) $[M – Me_2CO – – OH]^+$, 321 (7.8) $[M – Me_2CO – MeO]^+$, 303 (15) $[M – Me_2CO – H_2O – – MeO]^+$.

For **5**: 410 (3.1) $[M]^+$, 395 (45) $[M – Me]^+$, 352 (12) $[M – Me_2CO]^+$, 335 (15) $[M – Me_2CO – OH]^+$, 321 (14) $[M – Me_2CO – MeO]^+$, 303 (8.9) $[M – Me_2CO – H_2O – MeO]^+$.

For **6**: 412 (1.2) $[M]^+$, 397 (19) $[M – Me]^+$, 354 (1.3) $[M – Me_2CO]^+$, 337 (2.5) $[M – Me_2CO – OH]^+$, 323 (7.7) $[M – Me_2CO – MeO]^+$.

‡‡ A solution of acetonide **3** (5.6 mg) in 80% aqueous AcOH (500 µl) was heated at 55 °C for 5 h and then evaporated in a vacuum to dryness producing triol **7** (5.0 mg, 99%) as a clear oil, R_f 0.18 (EtOAc–hexane, 30:70, triple development), $[\alpha]_D^{30}$ +4.9° (*c* 0.38, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 0.90 (t, 3H, $C^{20}H_3$, *J* 6.7 Hz), 1.15–1.45 (m, 12H, $C^{4–6,17–19}H_2$), 1.64 (quintet, 2H, C^3H_2, *J* 7.2 Hz), 1.95–2.15 (m, 3H, $C^{16}H_2$ and $C^7H^aH^b$), 2.31 (t overlapping m, 2H, C^2H_2, *J* 7.4 Hz), 2.22–2.47 (m, 3H, $C^7H^aH^b$ and $C^{13}H_2$), 3.48 (br. s, 1H, $C^{11}H$), 3.69 (s, 3H, COOMe), 3.76 (br. t, 1H, $C^{12}H$, *J* 6.5 Hz), 4.67 (br. s, 1H, $C^{10}H$), 5.33–5.70 (m, 4H, $C^{8,9,14,15}H$).

§§ Triol **8** was obtained from acetonide **5** analogously to triol **7**. For **8**: yield 97%, R_f 0.26 (EtOAc–hexane, 30:70, triple development), $[\alpha]_D^{30}$ –13° (*c* 0.25, $CHCl_3$). ^{1}H NMR (200.13 MHz, $CDCl_3$) δ: 0.90 (t, 3H, $C^{20}H_3$, *J* 6.1 Hz), 1.20–1.65 (m, 10H, $C^{8,9,17–19}H_2$), 1.68 (quintet, 2H, C^3H_2, *J* 7.1 Hz), 1.95–2.38 (m, 10H, $C^{2,4,7,13,16}H_2$), 3.35–4.05 (m, 3H, $C^{10–12}H$), 3.69 (s over-lapping m, 3H, COOMe), 5.25–5.65 (m, 4H, $C^{4,5,14,15}H$).