A Concise Synthesis of the Methyl Esters of (10*S*)-Hepoxilin B_3 and (10*S*)-Trioxilin B_3

Wen-Lian Wu and Yu-Lin Wu*

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

Received December 3, 1992

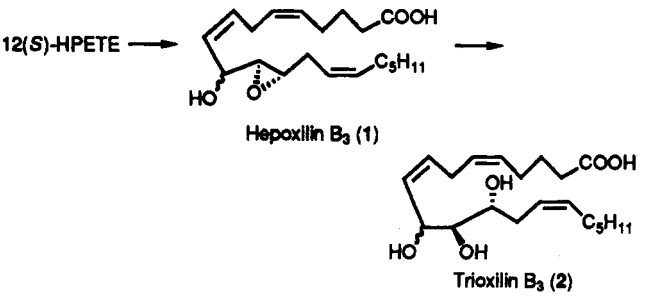
2,3:4,5-Di-*O*-Isopropylidene-D-mannose was converted to lactol 2,3-*O*-isopropylidene-6(*Z*)-dodecene-L-ribofuranose (**6**) by Grignard addition with propargyl magnesium bromide, alkylation of the resulting terminal alkyne, partial hydrogenation of the triple bond, and finally chemoselective cleavage of the 1,2-*O*-isopropylidene and subsequent periodate cleavage of the glycol. Wittig olefination of **6** led to methyl 10(*S*),11(*R*)-*O*-isopropylidene-10,11,12(*R*)-trihydroxyeicosa-5,8,14(*Z*)-trienoate (**5**), which could be converted to (10*S*)-trioxilin B_3 methyl ester (**3**) in one step or to (10*S*)-hepoxilin B_3 methyl ester (**4**) in three steps.

There is a great deal of current interest in hydroxylated eicosatetraenoic acids produced from arachidonic acid by the lipoxygenase pathway.[1] Hepoxilin B_3 (**1**), which arises from 12(*S*)-hydroperoxyeicosatetraenoic acid [12(*S*)-HPETE], is regiospecifically hydrated at C(12) to yield the corresponding triols, namely trioxilin B_3 (**2**), by an epoxide hydratase enzyme present in rat lung homogenate. Both hepoxilin B_3 and trioxilin B_3 consists of two C(10) diastereoisomers.[2] Recent findings show that the arachidonic metabolites of the hepoxilin/trioxilin pathways are of current interest as presynaptic messengers in Aplysia sensory cells[3] and as pancreatic insulin secretagogues.[4] Due to the biological importance and the difficulty in isolating hepoxilin B_3 and trioxilin B_3 in adequate quantity from biological material, several groups[5] have developed strategies for synthesis of these compounds. In the previous synthesis[5a,b] of hepoxilin B_3, the key addition step is not stereoselective, and isolation of the two C(10) diastereoisomers by HPLC is required.

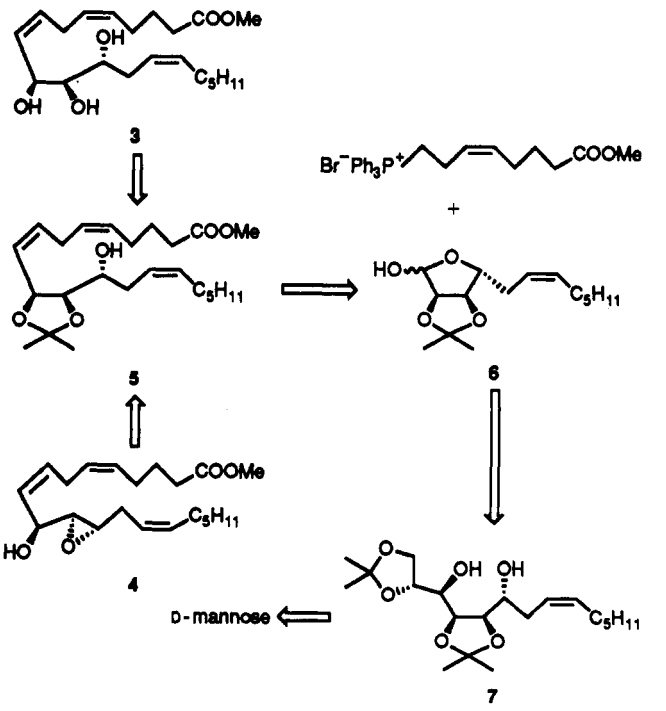
Our approach to the synthesis of (10*S*)-hepoxilin B_3 and (10*S*)-trioxilin B_3 is based on the following retrosynthetic scheme (Scheme II). The 10,11-*O*-isopropylidene trihydroxy compound **5** serves as the common intermediate for the synthesis of both **3** and **4**. **5** can be realized by Wittig olefination of lactols **6**, which are prepared from D-mannose-derived precursor **7**.

The readily available 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**8**) was prepared from D-mannose according to Nolan.[6] Treatment of **8** with $BrMgCH_2C{\equiv}CH$[7] in ether gave quantitatively diastereoisomeric mixture **9**, which was inseparable by chromatography. Alkylation of the anion of terminal alkyne **9** formed by use of *n*-BuLi in the presence of HMPA with *n*-pentyl bromide afforded **10a** (64%) and **10b** (6%), which were separated by flash chromatography. Hydrogenation of **10a** produced the alkene **7** in 97% yield (Scheme III). Chemoselective cleavage of the terminal 1,2-*O*-isopropylidene group with 70% AcOH followed by $NaIO_4$ cleavage of the resulting diol, furnished lactol **6** in 52% yield in two steps. Recently

Scheme I



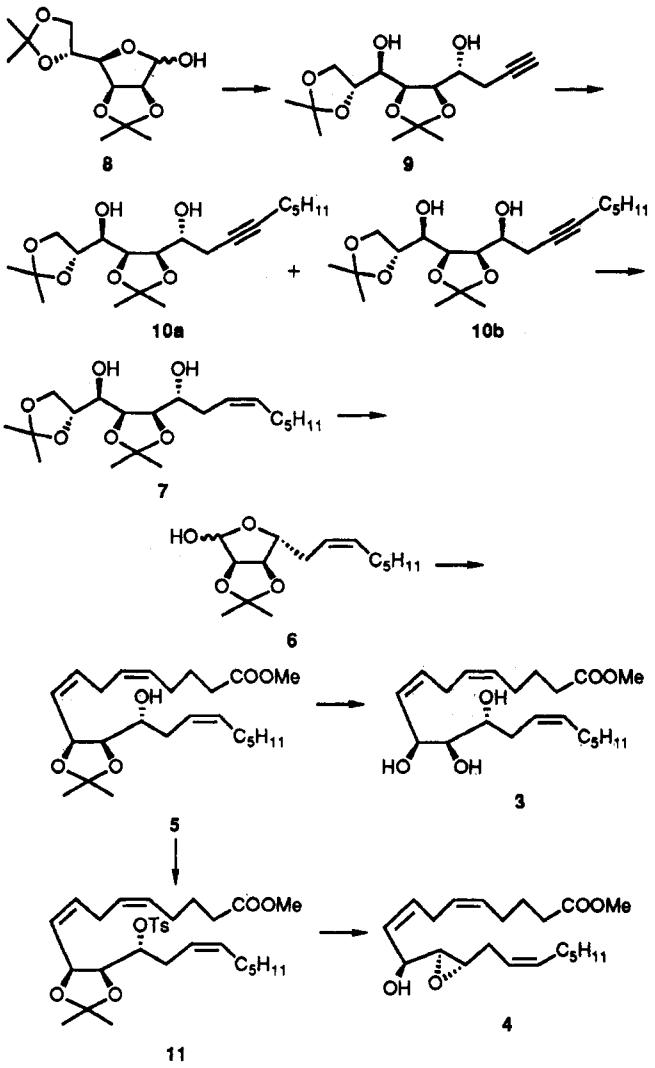
Scheme II



(1) For a review, see: Rokach, J.; Guindon, Y.; Yong, R. N.; Adams, J.; Atkinson, J. G. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1987; Vol. 7, p 141.
(2) Lumin, S.; Yadagiri, P.; Falck, J. R. *Tetrahedron Lett.* **1988**, *29*, 4237, and references cited therein.
(3) Piomelli, D.; Greengard, P. *Trends Pharmacol. Sci.* **1990**, *11*, 367.
(4) Pace-Asciak, C. R.; Martin, J. M.; Corey, E. J. *Prog. Lipid Res.* **1986**, *25*, 625.
(5) For total synthesis of hepoxilin B_3, see: (a) Corey, E. J.; Kang, J.; Laguzza, B. C.; Jones, R. L. *Tetrahedron Lett.* **1983**, *24*, 4913. (b) Demin, P. M.; Vasil'eva, L. L.; Lapitskaya, M. A.; Belosludtsev, Yu. Yu.; Myagkova, G. I.; Pivnitskii, K. K. *Bioorg. Khim.* **1990**, *16*, 127. *Chem. Abstr.* **1990** *113*, 40257; for trioxilin B_3, see: (c) ref 2. (d) Yadav, J. S.; Chander, M. C.; Reddy, K. K. *Tetrahedron Lett.* **1992**, *33*, 135. (e) Wu, W.-L.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2705.
(6) Lee, B.; Nolan, T. J. *Tetrahedron* **1967**, 2789.
(7) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Jannders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

0022-3263/93/1958-2760$04.00/0

Scheme III



we[8] found that this conversion was also realized in one pot by simple treatment of **7** with periodic acid in dry ether and an excellent yield (85%) was obtained. Wittig reaction of lactol **6** and the ylide prepared from [8-(methoxycarbonyl)-3(*Z*)-octenyl]triphenylphosphonium bromide[9] under cis-olefination conditions led to the key intermediate **5** in 64% yield. Acidic deketalization of **5** in MeOH gave the known triol trienoate **3** in 81% yield. Tosylation of **5**, deketalization of **11** with *p*-toluenesulfonic acid in MeOH, followed by treatment with K_2CO_3 afforded (10*S*)-hepoxilin B_3 methyl ester **4** in 61% overall yield from **5**.

In conclusion, both (10*S*)-hepoxilin B_3 and (10*S*)-trioxilin B_3 have been synthesized as their methyl esters from D-mannose in a short and convenient route.

Experimental Section

General Procedures. Melting points are uncorrected. IR spectra were run on a Schimadzu 440 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard at 200 MHz or 300 MHz. MS spectra (EI) were obtained on a Finnigan 4201 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 Autopol polarimeter. Flash column chromatography was performed on silica gel H (10–40 μm) and with petroleum ether/ethyl acetate system as eluent.

Terminal Alkyne (diastereomeric mixture) (9). About $^1/_{10}$ quantity of propargyl bromide (22.0 g, 0.185 mol) was added to magnesium (4.0 g, 0.167 mol) and mercuric chloride (0.3 g, 0.083 mol) in ether (50 mL). Once the reaction had been initiated by gentle heating, the solution was cooled to 0 °C and the remainder of propargyl bromide in ether (150 mL) was slowly added. The solution was cooled to −70 °C, then the starting material **8** (13.0 g, 50 mmol) was added portionwise, and the reaction mixture was stirred at −70 °C for 2 h and −70 °C to 0 °C for additional 2 h and then poured into a saturated solution of NH_4Cl. Usual workup and chromatography gave **9** (15 g, 100%) as a mixture of diastereoisomers: IR (film) 3450 (OH), 3290 (≡H), 2100 (C≡C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 1.36 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 3H), 1.47 (s, 3 H), 2.09 (t, J = 2.2 Hz, 1 H), 2.4–2.60 (m, 2 H), 3.9–4.20 (m, 6 H), 4.43 (m, 1 H); MS (*m/z*) 301 (M^+ +1, 40%), 285 (M^+ − Me, 30), 283 (M^+ + 1 − H_2O, 3); HRMS calcd for $C_{14}H_{21}O_6$ (M^+ − Me) 285.1338, obsd 285.1305.

1,2:4,5-Di-*O*-isopropylidene-8-tetradecyne-D-*glycero*-D-*manno*-1,2,3,4,5,6-hexol (10a) and (6*S*)-isomer (10b). To a stirred solution of **9** (12.0 g, 40 mmol) in dry THF (220 mL) was added *n*-BuLi (130 mmol) dropwise at −30 °C. After 30 min, a solution of BrC_5H_{11} (9.0 g, 56 mmol) in HMPA (30 mL) was added. Stirring was continued for 1 h at −50 °C and −50 °C to 20 °C overnight. The reaction was quenched with saturated NH_4Cl solution, and the aqueous layer was extracted with ether. The organic layers were combined, washed with brine, dried, and evaporated. The residue was chromatographed to give the anti-isomer **10a** (9.5 g, 64%), $[\alpha]_D$ −14.3° (*c* 0.5, $CHCl_3$); IR (film) 3450 (OH), 2100 (C≡C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.90 (t, J = 7.2 Hz, 3 H), 1.36 (s, 3 H), 1.38 (s, 3 H), 1.42 (s, 3 H), 1.47 (s, 3 H), 1.3–1.60 (m, 6 H), 2.20 (m, 2 H), 2.3–2.7 (m, 2 H), 3.8–4.44 (m, 7 H); MS (*m/z*) 371 (M^+ + 1, 1%), 355 (M^+ − Me, 5), 352 (M^+ − H_2O). Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.52; H, 9.48. Syn-isomer **10b** (0.87 g, 6%): mp 74–75 °C; $[\alpha]_D$ −1.4° (*c* 0.5, $CHCl_3$); IR (KBr) 3450 (OH), 2100 (C≡C) cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) 0.90 (t, J = 7.2 Hz, 3 H), 1.31 (s, 3 H), 1.35 (s, 3 H), 1.37 (s, 3 H), 1.45 (s, 3 H), 1.3–1.60 (m, 6 H), 2.15 (m, 2 H), 2.48 (m, 2 H), 3.70 (m, 1 H), 3.9–4.20 (m, 4 H), 4.42 (m, 2 H); MS (*m/z*) 371 (M^+ + 1, 1%), 355, 352. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.83; H, 9.47.

1,2:4,5-Di-*O*-isopropylidene-8(*Z*)-tetradecene-D-*glycero*-D-*manno*-1,2,3,4,5,6-hexol (7). The alkyne **10a** (6.0 g, 16.2 mmol) was hydrogenated under atmospheric pressure using Lindlar catalyst (0.8 g) in ethyl acetate (120 mL) in the presence of quinoline (0.4 g). After uptake of the theoretical amount of hydrogen, the mixture was filtered, and the filtrate was washed with 2 N HCl and aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated in vacuo. Chromatography of the residue produced **7** (5.9 g, 97%), $[\alpha]_D$ −23.1° (*c* 0.5, $CHCl_3$); IR (film) 3450 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.88 (t, J = 7.2 Hz, 3 H), 1.30 (m, 6 H), 1.36 (s, 3 H), 1.39 (s, 3 H), 1.41 (s, 3 H), 1.49 (s, 3 H), 2.2–2.4 (m, 4 H), 3.80–4.40 (m, 7 H), 5.45 (m, 1 H), 5.65 (m, 1 H); MS (*m/z*) 373 (M^+ + 1, 9%), 357 (M^+ − Me, 12%), 355 (M^+ + 1 − H_2O, 6%). Anal. Calcd for $C_{20}H_{36}O_6$: C, 64.49; H, 9.74. Found: C, 64.63; H, 9.90.

2,3-*O*-Isopropylidene-6(*Z*)-dodecene-L-ribofuranose (6). Procedure A. Alkene **7** (3.72 g, 10 mmol) was dissolved in 75% AcOH (60 mL), and the mixture was stirred for 1.5 h at 50 °C. After removal of the solvent under reduced pressure, the residue was dissolved in MeOH (10 mL) and added to a solution of $NaIO_4$ (5.35 g, 25 mmol) in H_2O (50 mL). The mixture was stirred for 4 h at room temperature and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated. Chromatography of the residue afforded lactol **6** (1.41 g, 52%): $[\alpha]_D$ −6.5° (*c* 0.75, $CHCl_3$); IR (film) 3450 (OH), 1660 (C=C), 1380, 1370 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 0.89 (t, J = 6.5 Hz, 3 H), 1.2–1.7 (m, 12 H), 2.05 (m, 2 H), 2.3–2.45 (m, 2 H), 4.0–4.2 (m, 1 H), 4.4–4.70 (m, 2 H), 5.5–5.65 (m, 3 H); MS (*m/z*) 271 (M^+ + 1, 1%), 255 (M^+ − Me, 12), 253 (M^+ + 1 − H_2O, 60). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.62; H, 9.74.

Procedure B. To a solution of H_5IO_6 (5.0 g, 22 mmol) in dry ether (30 mL) was added alkene **7** (2.60 g, 7 mmol) and the mixture was stirred at room temperature for 4 h. The organic layer was decanted and washed with aqueous $NaHCO_3$, brine, dried, and evaporated. Chromatography gave lactol **6** (1.60 g, 85%).

Methyl 10(*S*),11(*R*)-*O*-Isopropylidene-10,11,12(*R*)-trihydroxyeicosa-5,8,14(*Z*)-trienoate (5). To a suspension of [8(methoxycarbonyl)-3(*Z*)-octenyl]triphenylphosphonium bro-

(8) Wu, W.-L.; Wu, Y.-L., to be published.
(9) Pfister, J. R.; Merthy, D. V. K. *J. Med. Chem.* **1983**, *26*, 1099.

mide (1.8 g, 3.6 mmol) in THF (15 mL) was added dropwise potassium bis(trimethylsilyl)amide [$KN(SiMe_3)_2$] (1 M, 3.0 mmol) at −20 °C. A red solution was obtained after stirring for an additional 1 h at −20 °C. After HMPA (2 mL) was added, the solution was cooled to −70 °C, and a solution of lactol **6** (0.27 g, 1 mmol) was added dropwise. The reaction mixture was stirred at −70 °C to −15 °C over 3 h. After addition of saturated solution of NH_4Cl it was extracted with ether/petroleum ether (1:1). The combined extracts were washed with brine, dried, and evaporated. The oily residue was chromatographed to give **5** (0.26 g, 64%): TLC (ethyl acetate/hexane 1:4), R_f 0.78; $[\alpha]_D$ +24.6° (*c* 0.77, $CHCl_3$); IR (film) 3450 (OH, 1735 (COOMe), 1660 (C=C), 1380, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.91 (t, J = 6.5 Hz, 3 H), 1.30 (m, 6 H), 1.40 (s, 3 H), 1.49 (s, 3 H), 1.6–1.80 (m, 4 H), 2.0–2.59 (m, 8 H, H_2 and allylic), 2.92 (m, 2 H, H_7), 3.65–3.77 (m with methyl ester singlet at 3.68, 4 H), 4.02 (dd, J = 6.2, 8.5 Hz, 1 H, H_{11}), 5.03 (dd, J = 8.5, 5.8 Hz, 1 H, H_{10}), 5.4–5.75 (m, 6 H, olefinic); MS (*m/z*) 408 (M^+, 1.5%), 391 ($M^+ + 1 - H_2O$, 7.5), 351 ($M^+ + 1 - H_2O - C_3H_4$, 25), 333 (76), 315 (47), 97 (100); HRMS calcd for $C_{24}H_{38}O_4$ ($M^+ - H_2O$) 390.2770, obsd 390.2723.

Methyl 10(*S*),11(*R*)-Trihydroxyeicosa-5,8,14(*Z*)-trienoate (3). To a stirred solution of **5** (0.14 g, 0.34 mmol) in MeOH (5 mL) was added *p*-toluenesulfonic acid (0.1 g). After stirring for 24 h at room temperature the reaction mixture was worked up as usual. Purification by flash chromatography gave unreacted **5** (16 mg) and **3** (103 mg, 81%): TLC (ethyl acetate/hexane 2:3), R_f 0.33; $[\alpha]_D$ +29.6° (*c* 0.9, acetone) (lit.[2] $[\alpha]_D$ +29.2° (*c* 2.0, acetone)); IR (film) 3450 (OH), 1735 (COOMe), 1660 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (t, J = 6.5 Hz, 3 H), 1.26–1.36 (m, 6 H), 1.70 (m, 2 H), 2.04–2.62 (complex m, 11 H), 2.74–3.03 (m, 2 H), 3.54 (dd, J = 5.8, 6.3 Hz, 1 H, H_{11}), 3.60–3.72 (m with methyl ester singlet at 3.67, 4 H), 4.67 (dd, J = 9.0, 5.8 Hz, 1 H, H_{10}), 5.32–5.75 (m, 6 H, olefinic); MS (*m/z*) 369 ($M^+ + 1$, 4%), 351 ($M^+ + 1 - H_2O$, 9), 333 ($M^+ + 1 - 2\ H_2O$, 36), 315 ($M^+ + 1 - 3\ H_2O$, 22), 81 (100).

Methyl 10(*S*)-Hydroxy-11(*S*),12(*S*)-epoxyeicosa-5,8,14(*Z*)-trienoate (4). To a solution of **5** (0.1 g, 0.25 mmol) in dry CH_2Cl_2 (2 mL) was added *p*-TsCl (0.1 g) and pyridine (0.1 mL). After the mixture was stirred at room temperature overnight, the usual workup furnished crude **11**. To a solution of this **11** in MeOH (5 mL) was added *p*-toluenesulfonic acid (0.1 g). After stirring for 24 h at room temperature, K_2CO_3 (0.4 g) was added, and the reaction mixture was stirred for additional 30 min and diluted with ether. The organic layer was evaporated in vacuo and chromatographed to give **4** (52 mg, 61% from **5**): TLC (ethyl acetate/hexane 1:4) R_f 0.52; $[\alpha]_D$ +34.1° (*c* 0.5, acetone); IR (film) 3450 (OH), 1735 (COOMe), 1660 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 0.89 (*t*, J = 6.8 Hz, 3 H), 1.26–1.40 (m, 6 H), 1.68 (m, 2 H), 1.93–2.50 (complex m, 9 H), 2.85 (m, H_7 and H_{11}, 3 H), 3.05 (dt, J = 5.5, 2.3 Hz, 1 H, H_{12}), 4.68 (dd, J = 8.4, 2.9 Hz, 1 H, H_{10}), 5.32–5.68 (m, 6 H, olefinic); MS (*m/z*) 351 ($M^+ + 1$, 0.2%), 333 ($M^+ + 1 - H_2O$, 3), 315, 283, 239, 221.

Acknowledgment. Thanks to the Chinese Academy of Sciences and the State Committee of Science and Technology of China for the financial support.

Supplementary Material Available: Copies of ^1H NMR spectra of **3–5** and **9** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.