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Enantiospecific Total Synthesis of a Novel Arachidonic Acid Metabolite 3-Hydroxyeicosatetraenoic acid

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Abstract: The enantiomers *R*- and *S*-3-hydroxyeicosatetraenoic acid **11a, 11b** were synthesized from coupling of a chiral aldehyde **7** with a Wittig salt **4**, which were derived from 2-deoxy-D-ribose and arachidonic acid, respectively.

A large number of unsaturated hydroxy fatty acids (oxylipins), which are formed by either lipoxygenase, dioxygenase or cytochrome P-450-mediated pathways are found in fungal species[1-6]. While the majority of fungal oxylipins are formed from oleic or linoleic acid, there are also few examples of arachidonic acid (AA)-derived oxylipins in fungi. In earlier communications, we have reported on the formation of novel 3-hydroxy fatty acids by the yeast *Dipodascopsis uninucleata* from polyenoic fatty acids provided that they contained a 5*Z*,8*Z*-diene system[7-9]. AA is converted by this yeast to 3*R*-hydroxy-5*Z*, 8*Z*, 11*Z*, 14*Z*-eicosatetraenoic acid (3-HETE). With respect to its double bond structure, this eicosanoid differs basically from the lipoxygenase-derived hydroxy-eicosatetraenoic acids 5-HETE, 12-HETE and 15-HETE, which are abundant in mammalian cells, and for which chemical total syntheses have been reported earlier[10]. Our investigations with 3*R*-HETE revealed remarkable alterations of intracellular signalling processes in inflammatory and tumour cells[11]. In connection with a programme in our laboratories directed toward the biological role of lipid second messengers in intracellular signal transduction pathways, syntheses of 3-hydroxy-polyenoic fatty acids in reasonable quantities became mandatory[12]. In the present report, we describe the convergent total synthesis of 3-HETE enantiomers **11a, 11b.**

Our synthetic strategy involved a convergent approach coupling of a chiral aldehyde with a Wittig salt, which were derived from 2-deoxy-D-ribose and AA, respectively (see schemes 1-3). Methyl ester of 5,6-dihydroxyeicosatetraenoic acid **1** was prepared from AA according to a procedure described previously[13]. The lead tetraacetate oxidation of **1** gave an aldehyde **2** as a light yellow oil. The reduction of **2** with sodium borohydride resulted in the colourless alcohol **3**. After conversion of **3** to bromide a phosphonium salt **4** was obtained by the addition of triphenylphosphine to the bromide and heating the mixture in argon atmosphere for 2 days.

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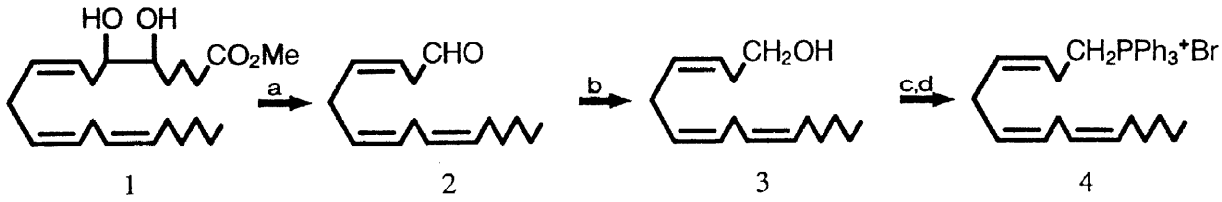
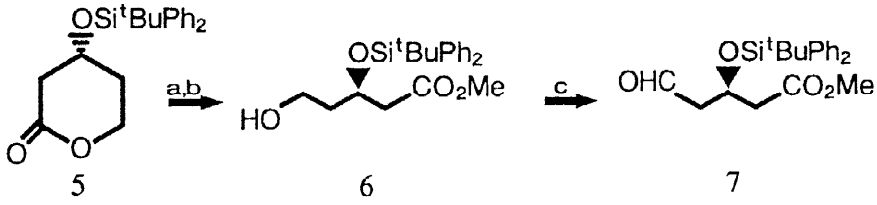


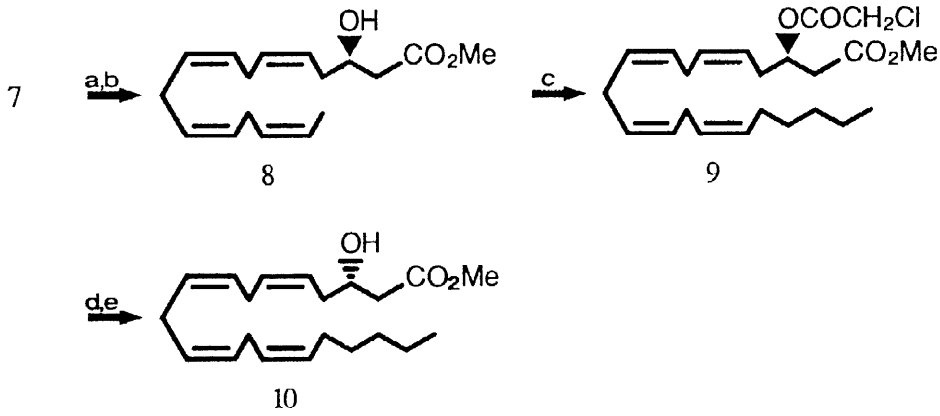
(a) $Pb(OAc)_4$, CH_2Cl_2, -40° C, 30 min.; (b) $NaBH_4$, EtOH-CH_2 Cl_2, 24° C, 30 min.;
(c) CBr_4, PPh_3, CH_2Cl_2, 0° C, 1 h.; (d) PPh_3, CH_3CN, 75° C, 2 days.

Scheme 1



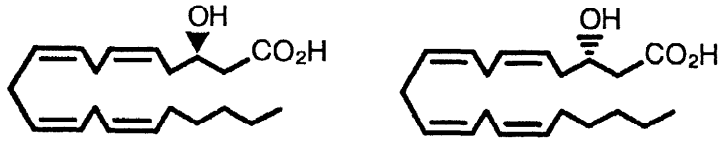
(a) 1N NaOH, THF-H_2O, 0° C, 30 min.; (b) CH_2N_2, MeOH-Et_2O, 0° C;
(c) PCC, CH_2Cl_2, 24° C, 6 h.

Scheme 2



(a) 4, $NaN(SiMe_3)_2$, THF, -78° C to -45° C, 3 h.; (b) Bu_4NF, $3H_2O/CH_3COOH$, THF, 45° C, 32 h.;
(c) $ClCH_2COOH$, PPh_3, DEAD, toluene, 24° C; 1 h.; (d) 1N LIOH, THF-H_2O, 0° C, 3 h.;
(e) CH_2N_2, MeOH-Et_2O, 0° C, 15 min.

Scheme 3



11 a 11 b

Fig. 1

For the preparation of chiral aldehyde 3*R*-t-butyldiphenylsilyloxy-d-valerolactone **5** was prepared from 2-deoxy-D-ribose as described previously[14] and converted to methyl ester **6** via saponification and treatment with ethereal diazomethane. The pyridinium chlorochromate oxidation (PCC) of **6** yielded chiral aldehyde **7** as a colourless oil.

The condensation of **7** with the ylide of **4**, which was obtained by the treatment of **4** solution in anhydrous THF at -78°C with sodium bis(trimethylsilyl)amide, gave following fluoride-mediated deprotection and HPLC purification methyl-3*R*-hydroxy-5,8,11,14-eicosatetraenoate **8** as a colourless oil. Mitsunobu inversion[15] of **8** using chloroacetic acid and triphenylphosphine yielded an ester **9.** The saponification followed by diazomethane esterification of **9** resulted in the synthesis of methyl-3*S*-hydroxy-5,8,11,14-eicosatetraenoate **10.** The corresponding free acids **11a, 11b**[16] shown in Figure 1 were prepared by saponification of the respective methyl esters using 1N LiOH in THF/H_2O at 0°C.

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16. Spectroscopic data (NMR, IR and Mass spectra) of all relevant compounds during the total synthesis of 3-HETE enantiomers were satisfactory and are as follows: **2:** ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.7 (t, J = 1.8 Hz, 1H).

3: ^{1}H NMR δ 5.31 - 5.59 (m, 6H), 3.67 (br s, 2H), 2.80 - 2.89 (m, 4H), 2.34 - 2.42 (m, 2H), 2.02 - 2.08 (m, 2H), 1.31 - 1.40 (m, 6H), 0.90 (t, J = 6.5 Hz, 3H); ^{13}C NMR (C_6D_6) δ 131.14, 130.48, 128.66, 127.64, 127.43, 125.60, 62.17, 31.47, 30.75, 29.27, 27.18, 25.70, 25.60, 22.54, 14.04. **4:** ^{1}H NMR δ 7.65 - 7.80 (m, 15H), 5.21 - 5.62 (m, 6H), 3.78 - 3.82 (m, 2H), 2.40 - 2.65 (m, 4H), 1.90 - 2.05 (m, 2H), 1.20 - 1.42 (m, 6H) 0.88 (t, J = 6.5 Hz, 3H). **6:**^{1}H NMR δ 7.55 - 7.75 (m, 4H), 7.30 - 7.45 (m, 6H), 4.35 - 4.40 (m, 1H), 3.65 (br s, 2H), 3.52 (s, 3H), 2.56 (δ J = 6.48 Hz, 2H), 1.61 - 1.87 (m, 2H), 1.04 (s, 9H);^{13}C NMR (C_6D_6) δ 171.80, 135.81, 135.70, 133.31, 129.82, 129.75, 127.65, 127.58, 68.50, 59.15, 51.41, 41.70, 38.95, 26.82, 19.16. **7:** ^{1}H NMR δ 9.62 (t, J = 2.44 Hz, 1H), 7.52 - 7.74 (m, 4H), 7.31 - 7.43 (m, 6H), 4.56 - 4.62 (m, 1H), 3.56 (s, 3H), 2.42 - 2.65 (m, 4H), 1.02 (s, 9H);^{13}C NMR (C_6D_6) δ 200.60, 170.87, 135.78, 135.71, 133.14, 132.99, 129.96, 128.86, 127.73, 127.63, 65.86, 51.48, 50.29 41.68, 26.74, 18.12. **8:** ^{1}H NMR δ 5.25 - 5.50 (m, 8H), 4.00 - 4.14 (m, 1H), 3.62 (s, 3H), 2.65 - 2.85 (m, 6H), 2.50 (dd, J = 8.70, 3.7 Hz, 2H), 2.20 - 2.42 (m, 4H), 1.90 - 2.06 (m, 4H), 1.22 - 1.40 (m, 6H);^{13}C NMR (C_6D_6) δ 173.25, 131.20, 130.52, 128.66, 128.51, 127.72, 127.71, 127.21, 124.79, 67.82, 51.77, 40.41, 34.33, 31.51, 29.31, 27.22, 25.78, 25.64, 22.57, 14.06. **9:** ^{1}H NMR δ 5.55 - 5.61 (m, 1H), 5.30 - 5.53 (m, 8H), 4.10 (s, 2H), 3.72 (s, 3H), 2.80 - 2.94 (m, 6H), 2.70 - 2.76 (m, 2H), 2.00 - 2.20 (m, 2H), 1.20 - 1.40 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H). **10:** ^{1}H NMR δ 5.20 - 5.38 (m, 8H), 4.04 - 4.12 (m, 1H), 3.72 (s, 3H), 2.78 - 2.84 (m, 6H), 2.40 - 2.60 (m, 2H), 2.22 - 2.40 (m, 2H), 1.94 - 2.10 (m, 2H), 1.20 - 1.40 (m, 6H), 0.83 (t, J = 6.8 Hz, 3H). **11a, 11b:** see reference 8 above.