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SYNTHESIS AND STEREOCHEMICAL REVISION OF A BIOACTIVE DIHYDROXYEICOSANOID ISOLATED FROM THE RED MARINE ALGA FARLOWIA MOLLIS

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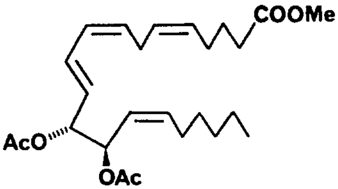
Summary: Chiral *trans*-enals derived from 2-deoxypyranoses by ylide-induced β-elimination were exploited for the synthesis and stereochemical revision of a novel, marine eicosanoid.

Recently, Gerwick and colleagues[1] isolated three homologous dihydroxylated fatty acid metabolites from a previously unstudied temperate red marine alga, *Farlowia mollis*. One of these was characterized as 12(**R**),13(**R**)-dihydroxyeicosa-5(**Z**),8(**Z**),10(**E**),14(**Z**)-tetraenoic acid based on detailed spectroscopic analysis of its more stable diacetate methyl ester 1. Its congeners, derived from γ-linolenic and eicosapentaenoic acids, were assigned comparable structures partly in analogy with 1.

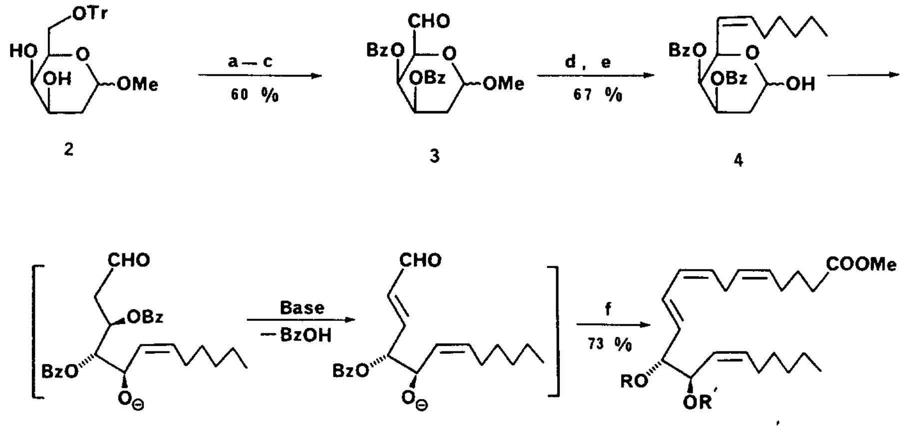


1

To confirm these assignments and to expedite further evaluation of the reported biological activities, we describe herein a versatile synthesis of this novel class[2] of eicosanoids utilizing chiral *trans*-enals generated from functionalized carbohydrate precursors[4]. Also, as a consequence of comparisons between natural and synthetic material, we propose the stereochemical revision of the *Farlowia* diols.

Methyl pyranoside 2, obtained[5] as an anomeric mixture in 2 steps (80%) from 2-deoxy-D-galactose, was converted to aldehyde 3[6] by successive benzoylation of the secondary alcohols, zinc bromide mediated detritylation[7], and pyridinium dichromate (PDC) oxidation (Scheme). Elaboration of 3 with hexylidenetriphenylphosphorane (7)[generated at 0°C in THF using sodium bis(trimethylsilyl)amide, 3h] followed by exposure to excess trimethylsilyl iodide[8] afforded lactol 4. The key transformation, i.e., the one-pot construction of the Z,E-diene, exploits the facile, ylide-induced elimination of benzoate from the open-chain tautomer of 4 under the conditions used for Wittig olefination. Preferential condensation *in situ* of the resultant *trans*-enal with 7-carbomethoxyhepta-3(Z)-en-1-ylidenetriphenylphosphorane[5](8) furnished benzoate 5 and its transesterification product 6 as an 1:1 mixture in good yield after chromatographic purification [TLC: SiO_2, EtOAc/hexane (1:4), R_f = 0.32 and 0.38, respectively]. Solvolysis (NaOMe, MeOH, 25°C, 12h) of 5 and 6 gave rise to the same diol which upon acetylation yielded 1, $[\alpha]^{24}_D$ -49° (c 0.50, CCl_4). Although similar to derivatized natural material, 1[9] was clearly distinct chromatographically and spectrally.

Scheme

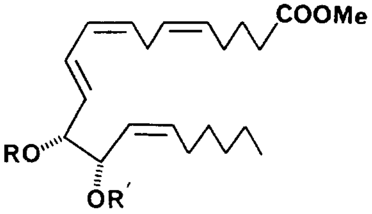


5 : R = Bz, R′ = H

6 : R = H, R′ = Bz

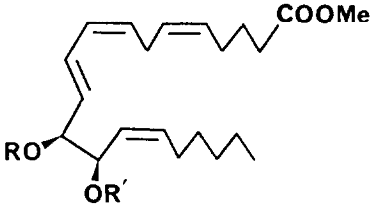
[a] PhCOCl, C_5H_5N/CH_2Cl_2 (1:5), 24°C, 4h. [b] $ZnBr_2$ (3 equiv), $MeOH/CH_2Cl_2$ (1:10), 24°C, 1h. [c] PDC (1.5 equiv), CH_2Cl_2, 24°C, 1h. [d] 7 (2 equiv), $THF/PhCH_3$ (1:3), -78°C, 0.5h. [e] NaI/Me_3SiCl (10 equiv each), CH_3CN, 0°C, 1h; $NaHCO_3$. [f] 8 (4 equiv), THF/HMPA (10:1), -40°C, 1h.

Reappraisal of the original data[1] suggested the *Farlowia* diols may possess an erythro rather than a threo configuration. Confirmation was obtained by Mitsunobu inversion[10] of 5 using diethyl azodicarboxylate/triphenylphosphine/chloroacetic acid (4 equiv each) in THF at room temperature for 10 min which led to 9 (76%). Removal of the protecting groups (NaOMe, MeOH, 23°C, 10h) and acetylation yielded 10, $[\alpha]^{24}_{D}+ 9.2°$ (c 0.42, CCl_4) [lit.[1] $[\alpha]^{24}_{D}$ + 2.24° (c 0.63, CCl_4)][11], identical by HPLC and NMR (250, 400 MHz[12]) with similarly derivatized natural material. The enantiomer 12, $[\alpha]^{24}_{D}-9.4°$ (c 0.63, CCl_4), was prepared in the same manner from 6 via epimerized ester 11. Thus, the arachidonate metabolite isolated from *F. mollis* should be formulated as 12(**R**),13(**S**)-dihydroxyeicosa-5(**Z**),8(**Z**),10(**E**),14(**Z**)-tetraenoic acid and the structures of its companion diols revised accordingly.



9 : R = Bz, R′ = $COCH_2Cl$

10 : R = R′ = Ac



11 : R = $COCH_2Cl$, R′ = Bz

12 : R = R′ = Ac

The results of the Mitsunobu sequence were corroborated by repetition of the synthesis in the Scheme starting with 2-deoxy-**D**-glucose. This afforded the C(12)-epimers of 5 and 6 which were transformed to 12 upon methanolysis of the benzoate and acetylation.

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References and Notes

1. M.L. Solem, Z.D. Jiang, and W.H. Gerwick, *Lipids* **24**: 256-260 (1989).
2. At present, their biogenesis is obscure. One plausible pathway which accounts for the unusual oxygenation pattern involves rearrangement of a hydroperoxide, e.g., 11-HPETE, to an oxiranyl carbinol[3]. The epoxide undergoes ring opening with loss of the adjacent proton or, alternatively, hydrates to the corresponding triol which then suffers dehydration.
3. For a related transformation see, C.R. Pace-Asciak, E. Granstrom, and B. Samuelsson, *J. Biol. Chem.* **258**: 6835-6840 (1983).
4. Cf., Y. Guidon, D. Delorme, C.K. Lau, and R. Zamboni, *J. Org. Chem.* **53**: 267-275 (1988).
5. S. Lumin, P.Yadagiri, and J.R. Falck, *Tetrahedron Lett.* **29**: 4237-4240 (1988).
6. Satisfactory spectral data were obtained for all new compounds using chromatographically homogeneous samples.
7. V. Kohli, H. Blocker, and H. Koster, *Tetrahedron Lett.* **21**: 2683-2686 1980).
8. M.E. Jung and M.A. Lyster, *J. Org. Chem.* **42**: 3761-3764 (1977).
9. ^{1}H NMR (C_6D_6, 250 MHz) of **1**: δ 0.85 (t,J 6.6 Hz, 3H), 1.10-1.38 (m,6H), 1.56 (tt, J 7.3, 7.3 Hz, 2H), 1.69 (s,3H), 1.74 (s,3H), 1.92 (dt, J 7.3, 7.3 Hz, 2H) 2.09 (t,J 7.3 Hz, 2H), 2.18 - 2.30 (m,2H), 2.80 (t, J 6.8 Hz, 2H), 3.37 (s,3H), 5.18-5.42 (m,4H), 5.46-5.68 (m,2H), 5.80 (t,J 7.3Hz, 1H), 5.93 (t,J 11.1 Hz, 1H), 6.05 (dd, J 7.2, 9.1 Hz, 1H), 6.83 (dd, J 11.1, 15.1Hz, 1H). **10**: δ 0.85 (t, J 6.6 Hz, 3H) 1.14-1.38 (m,6H), 1.56 (tt, J 7.3, 7.3Hz, 2H), 1.71 (s,3H), 1.74 (s,3H), 1.90 (dt, J 7.3, 7.3 Hz, 2H), 2.09 (t, J 7.3 Hz, 2H), 2.20 (tt, J 6.6, 6.6Hz, 2H), 2.77 (t, J 6.8Hz, 2H), 3.37 (s, 3H), 5.18-5.44 (m,3H), 5.52-5.65 (m,2H), 5.75 (t, J 8.1Hz, 1H), 5.80-5.88 (m,1H), 5.97 (t, J 11.1 Hz, 1H), 6.18 (dd, J 3.5, 8.1Hz, 1H), 6.81 (dd, J 11.1, 14.6Hz, 1H).
10. O. Mitsunobu, *Synthesis*: 1-28 (1981).
11. Samples obtained from later harvests displayed significantly higher rotation values. W.H. Gerwick, personal communication.
12. The comparison at 400 MHz was performed by Prof. W.H. Gerwick (Oregon State Univ.)

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