Tetrahedron Letters, Vol.32, No.21, pp 2315-2318, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A CONCISE SYNTHESIS OF (*R*)-HYDROXY-E,Z-DIENE FATTY ACIDS: PREPARATION OF 12(*R*)-HETE, TETRANOR-12(*R*)-HETE, AND 13(*R*)-HODE

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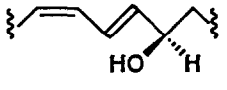
Summary: Chiral *E*-enals derived from functionalized 2-deoxy-D-ribofuranoses by ylide-induced β-elimination were exploited for the synthesis of fatty acid metabolites containing the (*R*)-hydroxy-*E*,*Z*-diene subunit.

The enzymatic conversion of polyunsaturated fatty acids to conjugated *E*,*Z*-dienols, e.g., arachidonic and linoleic acids to hydroxyeicosatetraenoic (HETE) and hydroxyoctadecadienoic (HODE) acids, respectively, is a prominent pathway to bioactive metabolites in plants and animals[1]. While the *S*-antipode generally prevails, recent studies have revealed several *R*-stereospecific systems[2]. Moreover, the *R*-series metabolites frequently display pharmacologic profiles that are qualitatively and/or quantitatively different from their *S*-counterparts. 12(*R*)-HETE (6), for instance, is a more potent chemotactic and chemokinetic factor than 12(*S*)-HETE[3]; additionally, it inhibits Na^+/K^+-ATPase activity in mammalian tissue whereas the 12(*S*)-enantiomer does not[4]. As endogenous constituents of the cornea, 6 and its metabolite 9 have been postulated to have a regulatory role in ocular function[5]. Likewise, both enantiomers of 13-HODE are naturally occurring[6]. The *S*-isomer has attracted considerable attention as an inhibitor of platelet and cancer cell adhesion to endothelium[7] and as a self-defense substance against rice-blast disease[8]. However, comparatively little is known about 13(*R*)-HODE (11), due in part to its limited availability from natural sources.



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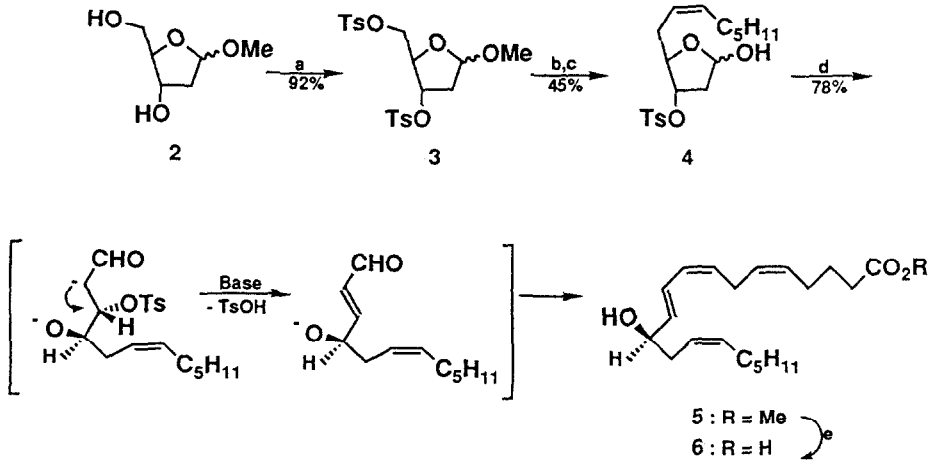
To satisfy the urgent need for sufficient amounts of enantiomerically homogenous standards[9] for biological evaluation, we describe herein a convergent strategy for the preparation of fatty acid metabolites containing the (*R*)-hydroxy-E,Z-diene subunit 1[10] and illustrate its versatility in concise syntheses of 6, 9, and 11.

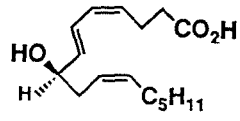
Methyl furanoside 2, obtained[11] as an anomeric mixture from commercial 2-deoxy-D-ribose (95%), was readily converted to lactol 4[12] via selective coupling of the bis-tosylate 3[13] with the higher order cuprate generated[14] from (Z)-1-iodo-1-heptene (7) in Et_2O and subsequent mild acid hydrolysis (Scheme I). Creation of the *E,Z*-diene exploited a facile, ylide-induced elimination of tosylate from the open-chain tantomer of 4 under the conditions utilized for Wittig olefination. *In situ* condensation of the resultant *E*-enal with 7-carbomethoxyhepta-3(*Z*)-en-1-ylidenetriphenylphosphorane[14] (8) furnished 12(*R*)-HETE methyl ester (5), identical in all respects with an authentic sample[15]. Saponification afforded the corresponding free acid 6.

Scheme I



[a]TsCl, C_5H_6N/CH_2Cl_2 (4:5), 0°C, 12 h. [b]7, BuLi, Et_2O, -40°C, 20 min; CuCN, -40°C → 0°C, 4h. [c]AcOH/THF/H_2O (2:1:1), 70°C, 8h. [d]8 (3 equiv), THF/HMPA (10:1), -20°C, 1h. [e]LiOH, MeOH, 24°C, 4h; HCl.

Analogous treatment of 4 with 3-carboxypropylidenetriphenylphosphorane[16] (3.5 equiv) yielded 8(*R*)-hydroxyhexadeca-4(*Z*),6(*E*),10(*Z*)-trienoic acid (9) as a colorless oil. Its chromatographic (capillary GC, HPLC) and mass spectroscopic characteristics were identical with the major metabolite of 12(*R*)-HETE produced by freshly isolated corneal tissue and cells in culture[5].



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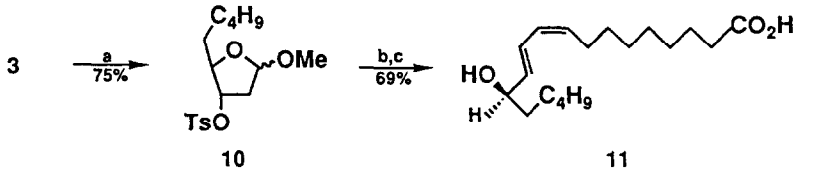
Extension of the general theme to 13(*R*)-HODE (11) required homologation of 3 to tosylate 10 with dibutyl copper lithium in Et_2O (Scheme II). Successive methyl lactol hydrolysis, generation of the corresponding *E*-enal as above, and *in situ* olefination using 8-carboxyoctylidenetriphenylphosporane[16,17] (12) smoothly evolved 11 whose spectral and chromatographic properties were comparable with a 13(*S*)-standard[17].

Scheme II



10 11

[a]BuLi, CuI, Et_2O, -40°C, 3h. [b]AcOH/THF/H_2O (1:1:1), 70°C, 12h. [c]12 (4 equiv), THF/HMPA (10:1), -20°C, 30 min.

Acknowledgment: Supported financially by the USPHS NIH (GM 31278, EY 06513) and the Robert A. Welch Foundation (I-782).

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12. Satisfactory spectral data were obtained for all new compounds using chromatographically homogeneous samples.

13. ^{1}H NMR ($CDCl_3$, 250 MHz) of 3 (less polar isomer): δ 2.16-2.24 (m,2H), 2.50 (s,6H), 3.23 (s,3H), 3.92 (dd,J~6,10 Hz,1H), 3.97 (dd,J~5.0,10 Hz,1H), 4.17-4.24 (m,1H), 4.86-4.94 (m,1H), 5.03 (dd,J~3,4.5 Hz,1H), 7.36 (d,J~7 Hz,4H), 7.75 (d,J~7 Hz,4H). 3 (more polar isomer): δ 2.10-2.22 (m,2H), 2.50 (s,6H), 3.30 (s,3H), 3.96 (dd,J~1.5,3 Hz,1H), 4.13 (dd,J~1.5,6 Hz,1H), 4.30-4.36 (m,1H), 4.78-4.84 (m,1H), 4.96 (d,J~6 Hz,1H), 7.36 (d,J~7 Hz,4H), 7.75 (d,J~7 Hz,4H). 4 (less polar isomer): δ 0.90 (t,J~7 Hz,3H), 1.20-1.48 (m,6H), 1.88-2.06 (m,2H), 2.13-2.32 (m,4H), 2.46 (s,3H), 3.34 (s,3H), 4.12-4.20 (m,1H), 4.54-4.63 (m,1H), 4.87 (dd,J~1.5,5 Hz,1H), 5.16-5.30 (complex m,1H), 5.39-5.52 (complex m,1H), 7.32 (d,J~7 Hz,2H), 7.79 (d,J~7 Hz,2H), 4 (more polar isomer): δ 0.90 (t,J~7 Hz,3H), 1.20-1.48 (m,6H), 1.88-2.08 (m,2H), 2.16-2.38 (m,4H), 2.47 (s,3H), 3.36 (s,3H), 4.00-4.07 (m,1H), 4.62-4.79 (m,1H), 5.05 (d,J~5 Hz,1H), 5.16-5.30 (complex m,1H), 5.40-5.52 (complex m,1H), 7.37 (d,J~7 Hz,2H), 7.80 (d,J~7 Hz,2H). 9 methyl ester: δ 0.89 (t,J~7Hz,3H), 1.20-1.42 (m,6H), 1.55-1.72 (m,2H), 1.93-2.11 (m,2H), 2.29-2.59 (m,4H), 3.68 (s,3H), 4.15-4.28 (m,1H), 5.30-5.67 (complex m,3H), 5.73 (dd,J~6,16 Hz,1H), 6.02 (apparent t,J~11 Hz,1H), 6.54 (dd,J~11,15 Hz,1H). 10 (less polar isomer): δ 0.90 (t,J~7 Hz,3H), 1.16-1.45 (m,6H), 1.68-2.23 (m,4H), 2.45 (s,3H), 3.35 (s,3H), 4.12-4.25 (m,1H), 4.53-4.62 (m,1H), 4.84 (dd,J~1.5,5 Hz,1H, 7.35 (d,J~7 Hz,2H), 7.75 (d,J~7 Hz,2H).

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16. Phosphonium salt prepared from corresponding commercial bromide using PPh_3 in CH_3CN at 70°C. A yellow-orange THF solution of the ylide was generated from the azeotropically dried salt by dropwise addition of $NaN(Me_3Si)_2$ (0.9 equiv) at -20°C

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(Received in USA 24 January 1991)