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ENANTIOSPECIFIC SYNTHESIS OF METHYL 11,12- AND 14,15-EPOXYEICOSATRIENOATE

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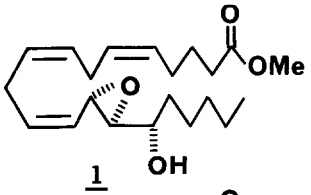
Summary: The methyl esters of the cytochrome P-450 epoxygenase metabolites 11(S),12(R)-and 14(R),15(S)-epoxyeicosatrienoic acid and some analogues were prepared enantiospecifically from 15(S)-HETE derived precursors.

Recent studies[1] have revealed an alternative mode of eicosanoid production mediated by cytochrome P-450 which results in a tantalizing array of oxygenated metabolites[2] including four regioisomeric cis-epoxyeicosatrienoic acids[3] (EETs). The EETs display potent in vitro biological activity[4] and their presence in mammalian tissue has been confirmed[5]. We have also determined the absolute configuration of the EETs generated by a reconstituted enzymatic system containing a purified preparation of the major phenobarbital inducible form of rat liver microsomal cytochrome P-450[6]. Since these eicosanoids are available in only minute amounts from natural sources, we report herein the first enantiospecific synthesis[7] of the cytochrome P-450 epoxygenase metabolites 11(S),12(R)- and 14(R),15(S)-EET and some analogues in sufficient amounts to aid in determining their role, if any, in biological processes.

A convenient route to the EETs exploits our previously reported conversion[8] of methyl 15(S)-HETE to methyl erythro and threo 15(S)-hydroxy-13,14-E-oxido-5,8,11-Z-eicosatrienoates 1 and 2, respectively. Mesylation ($MsCl,Et_3N,-20°C$) of 1 followed by regiospecific $NaBH_4$ reduction[8] (DMSO,90°C,90 min) generated trans-14(R),15(R)-EET 3[9] (57%).NMR($CDCl_3$,90MHz) δ: 0.94(3H,t), 1.16-1.92(10H,m), 1.96-2.20(2H,m), 2.36(2H,t,J ~ 7Hz), 2.60-3.12(6H,m), 3.68(3H,s), 4.96-5.82(6H,m); TLC: SiO_2,Et_2O/hexane 1:4 , R_f ~0.39. In contrast, the same sequence using 2 was less satisfactory and afforded 14(S),15(R)-EET 4 (10-22%), $[\alpha]_D^{24}$+2.77° (c = 0.65, $CHCl_3$), accompanied by several by-products. Likewise, borohydride reduction of mesylate 5 and tosylate 6, prepared directly from 1 by Still's modification[10] of the Mitsunobu inversion procedure, also gave a low yield of the cytochrome metabolite methyl 14(R),15(S)-EET 7[6], $[\alpha]_D^{24}$-2.75°(C = 0.70, $CHCl_3$), spectrally and chromatographically identical with an authentic (racemic) sample[7a].



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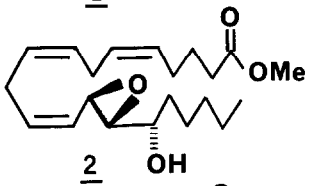

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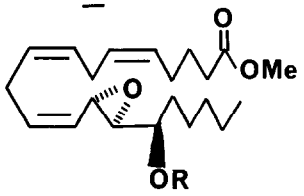

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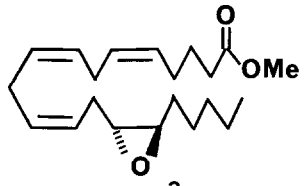
6 : R = Ts



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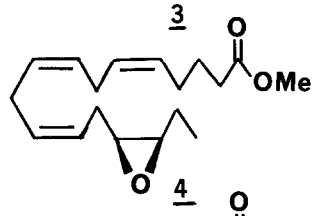

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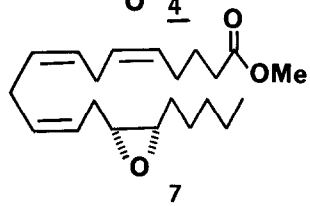

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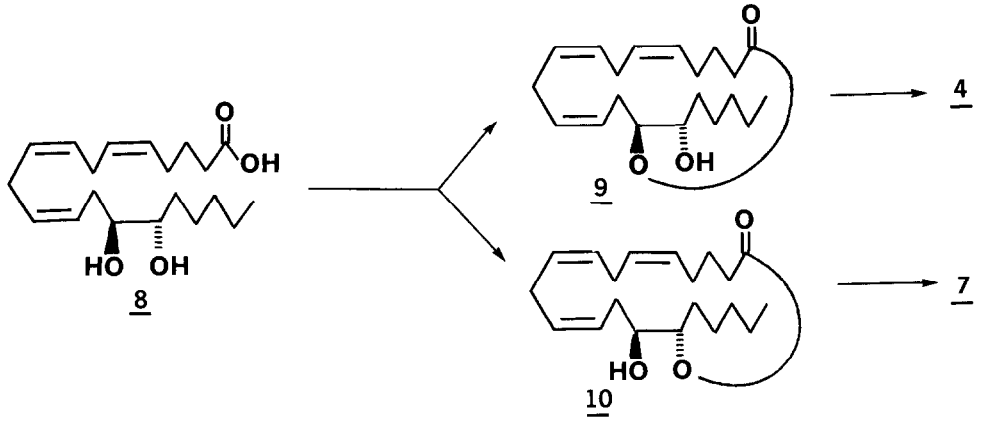
Alternatively, 14(S),15(S)-dihydroxyeicosatrienoic acid 8[8] could be lactonized[11] ($PhCH_3$, 115°C, 24h) via its 2-pyridinethiol ester[12] (2-thiopyridylchloroformate, Et_3N, -20°C) to a mixture of 9 and 10 (1:1.5, 50%) which were separated chromatographically (Et_2O/hexane 1:1, $R_f \sim 0.44$ and 0.55, respectively). 9 NMR($CDCl_3$, 90MHz): δ 0.88(3H,t), 1.10-2.60(17H,m), 2.62-2.96(4H,m), 3.48-3.80(1H,m), 4.80-5.04(1H,m), 5.06-5.68(6H,m); IR($CHCl_3$): 1725 cm^{-1}; mass spectrum of saturated TMS ether m/e (%): 392(M^+, 5), 173(100). 10 NMR: δ 0.88(3H,t), 1.08-2.52(17H,m), 2.60-2.92(4H,m), 3.50-3.84(1H,m), 4.76-5.00(1H,m), 5.04-5.80(6H,m); IR: 1730 cm^{-1}; mass spectrum of saturated TMS ether: 392(6), 257(10), 202(35). Sequential mesylation, saponification and esterification (CH_2N_2) evolved 4 (70%), $[\alpha]_D^{24}$+2.78°(C=0.82,$CHCl_3$), and 7 (80%), $[\alpha]_{24}^{D}$-2.73°(C = 0.90,$CHCl_3$).



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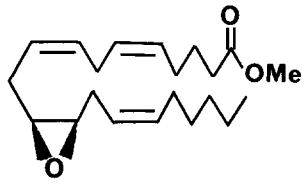
The ready availability of 4 provided easy access to the cytochrome metabolite methyl 11(S),12(R)-EET 11[6] (50% from 4), $[\alpha]_D^{24}$ -2.34° (c = 0.66, $CHCl_3$), using Corey's method[7b] of bromohydrin formation (HOAc/aq. KBr/THF, 0°), $^tBuOOH/VO(acac)_2$ epoxidation, and olefin regeneration (Tf_2O/py, 0°; then $(Me_2N)_3P$). This chirality transfer takes advantage of the high erythro preference inherent in vanadium catalyzed acyclic homoallylic epoxidations[13]. In principle, the antipode of 11 could be prepared analogously from 7.



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References:

1. J. Capdevila, L. Parkhill, N. Chacos, R. Okita, B.S.S. Masters, and R.W. Estabrook, Biochem. biophys. Res. Comm., 101, 1357-1363 (1981); J. Capdevila, N. Chacos, J. Werringloer, R.A. Prough, and R.W. Estabrook, Proc. Natl. Acad. USA, 78, 5362-5366 (1981).

2. S. Manna, J.R. Falck, N. Chacos, and J. Capdevila, Tetrahedron Letters, 24, 33-36 (1983); J. Capdevila, L.J. Marnett, N. Chacos, R.A. Prough, and R.W. Estabrook, Proc. Natl. Acad. Sci. USA, 79, 767-770 (1982); A.R. Morrison and N. Pascoe, ibid., 78, 7375-7378 (1981); E.H. Oliw, J.A. Lawson, A.R. Brash, and J.A. Oates, J. Biol. Chem., 256, 9924-9931 (1981); E.H. Oliw, F.P. Guengerich, and J.A. Oates, ibid., 257, 3771-3781 (1982); E.H. Oliw and J.A. Oates, Prostaglandins, 22, 863-871 (1981).

3. N. Chacos, J.R. Falck, C. Wixtrom, and J. Capdevila, Biochem. Biophys. Res. Comm., 104, 916-922 (1982).

4. J.R. Falck, S. Manna, J. Moltz, N. Chacos, and J. Capdevila, Biochem. Biophys. Res. Comm., 114, 743-749 (1983); J. Capdevila, N. Chacos, J.R. Falck, S. Manna, A. Negro-Vilar, and S.R. Ojeda, Endocrinology, 113, 421-423 (1983); G.D. Snyder, J. Capdevila, N. Chacos, S. Manna, and J.R. Falck, Proc. Natl. Acad. Sci. USA, 80, 3504-3507 (1983); P. Kutsky, J.R. Falck, G.B. Weiss, S. Manna, N. Chacos, and J. Capdevila, Prostaglandins, 26, 13-21 (1983).

5. J. Capdevila, B. Pramanik, J.L. Napoli, S. Manna, and J.R. Falck, Arch. Biochem. Biophys., in press. Also consult, A. Sevanian, J.F. Mead, and R.A. Stein, Lipids, 14, 634-643 (1979).

6. J.R. Falck, S. Manna, H.R. Jacobson, R.W. Estabrook, N. Chacos, and J. Capdevila, J. Amer. Chem. Soc., in press.

7. Achiral syntheses: (a) E.J. Corey, H. Niwa, and J.R. Falck, J. Amer. Chem. Soc., 101, 1586-1587 (1979); (b) E.J. Corey, A. Marfat, J.R. Falck, and J.O. Albright, ibid., 102, 1433-1435 (1980); (c) J.R. Falck and S. Manna, Tetrahedron Letters, 23, 1755-1756 (1982).

8. J.R. Falck, S. Manna, A.K. Siddhanta, J. Capdevila, and J.D. Buynak, Tetrahedron Letters, 24, 5715-5718 (1983).

9. Satisfactory spectral data (nmr, ir, mass spectroscopy) were obtained for all new compounds using chromatographically homogeneous samples. Stereochemical analysis[6] confirmed that the products reflect the original isomeric composition of the 15(S)-HETE[8].

10. I. Galynker and W.C. Still, Tetrahedron Letters, 23, 4461-4464 (1982). Zinc mesylate was prepared and used in the same manner.

11. E.J. Corey, S. Iguchi, J.O. Albright, and B. De, Tetrahedron Letters, 24, 37-40 (1983).

12. E.J. Corey and D.A. Clark, Tetrahedron Letters, 2875 (1979).

13. E.D. Mihelich, K. Daniels, and D.J. Eickhoff, J. Amer. Chem. Soc., 103, 7690-7692 (1981).

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