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SYNTHESIS AND METABOLISM OF (±)-EICOSA-CIS-14,15-EPOXY-CIS-8,11-DIENOIC ACID

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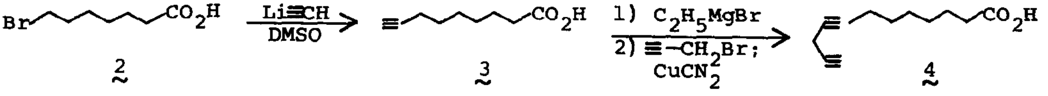
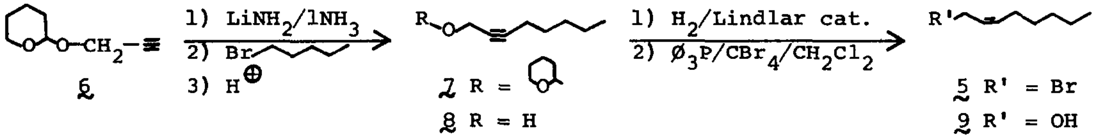
Epoxy polyunsaturated fatty acids have been proposed as possible intermediates in the enzymatic cyclization of polyunsaturated fatty acids into prostaglandins.[1] We wish to report a convenient synthesis of (±)-eicosa-cis-14,15-epoxy-cis-8,11-dienoic acid (1), and results of our incubation studies of this compound in a prostaglandin synthesizing system of bovine origin.

Reaction of 7-bromoheptanoic acid[2] (2) with lithium acetylide (ethylenediamine complex) in dry DMSO afforded 8-nonynoic acid[3] (3), b.p. 110-115°/0.05 mm (95% yield). The di-Grignard complex of 3 was condensed with propargyl bromide (15 hours at r.t.; Cu_2CN_2 as catalyst[4]) to give dodeca-8,11-diynoic acid, (4), b.p. 138-140°/0.05 mm, (52% yield)[16]; Pmr[5]: δ 3.2 (2H, m, $-\equiv-CH_2-\equiv-$), 2.08 (1H, m, $-C\equiv\underline{H}$); IR[6]: 3300 cm^{-1} ($-C\equiv C-\underline{H}$), 1705 ($-C=O$); λ_{max} (MeOH), 260 nm (ϵ 842).



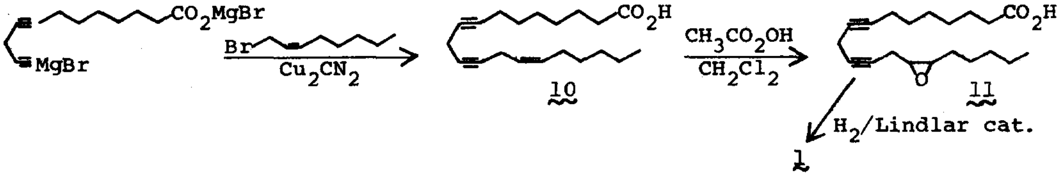
The complementary synthon, 1-bromo-oct-cis-2-ene (5) was prepared as follows: Tetrahydro-2-(prop-2'-ynyloxy)pyran[7] (6) was treated with lithium amide in (ℓ) NH_3 and coupled with 1-bromopentane to yield 7 (85% yield). Oct-2-yn-1-ol, (8), b.p. 78-80°/2 mm (lit.[8], b.p. 74-78°/2 mm), obtained via acidic hydrolysis of 7, was hydrogenated over Lindlar's catalyst in Skelly B to give oct-cis-2-en-1-ol[9], (9). Addition of triphenylphosphine to a mixture of 9 and carbon tetrabromide in dichloromethane[10] afforded 5, b.p. 58-60°/0.1 mm (81% yield). IR spectrum showed only traces of trans double bond at 965 cm^{-1}.

The di-Grignard reagent from 4 was condensed[9] with 5 in THF (20 hrs, r.t., Cu_2CN_2 as catalyst) to give eicosa-cis-14-ene-8,11-diynoic acid (10) in 40% yield[16]; Pmr: δ 2.91 (2H, m, C-13), δ 3.13 (2H, m, C-10) and δ 5.46 (2H, m, vinylic protons at C-14 and C-15); IR[6]: 2205 cm^{-1} ($-C\equiv C-$), 1705 ($-C=O$), 1310 ($-CH_2-C\equiv C-$);



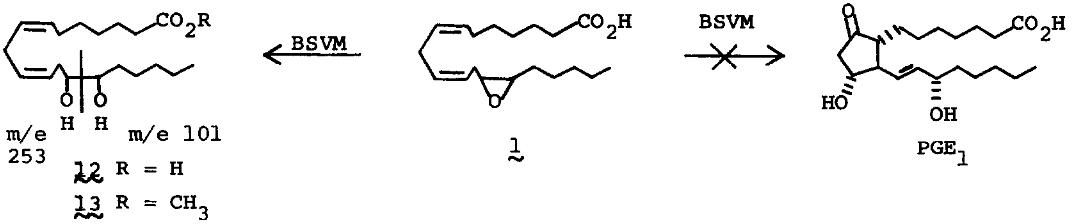
λ_{max} (MeOH): 272 nm (ϵ 409), 310 (ϵ 210). Treatment of **10** with peroxyacetic acid in dichloromethane (30 hr, 0° C) gave the crystalline epoxide, **11**, m.p. 42-45° (30% yield)[16]. In the pmr, the C-14 and C-15 methine protons were located between δ 2.64-3.68 overlapping the multiplet of the C-10 methylene at δ 3.16, IR[6]: 2200 cm^{-1} (—C≡C—), 1705 (—C=O), and 1310 ($—CH_2—C≡C—$).

Hydrogenation[11] of **11** over Lindlar catalyst afforded the desired (±)-eicosa-cis-14,15-epoxy-8,11-dienoic acid (**1**) (43% yield).[12] Pmr: δ 5.40 (4H, m, olefinic protons), 2.56-3.08 (m, 4H, C-10, C-14, C-15); IR[6]: 1705 (—C=O), 965 cm^{-1} (traces, trans double bond), 680 cm^{-1} (cis double bond); λ_{max} (MeOH): 230 nm (ϵ 695), 272 (ϵ 128). Mass spectrum of its methyl ester gave peaks at m/e 305 (M-31) and m/e 222 (M-114).



When **1** was exposed to bovine seminal vesicle microsomes[13] (BSVM) in the presence of GSH and epinephrine, no significant quantities of PGE_1 was detectable[14]; in contrast, under these conditions, all cis-8,11,14-eicosatrienoic acid (**12**) was readily converted into PGE_1 in efficient yields (65%). Instead, **1** (14 mg) was converted to a more polar product, (2.5 mg) characterized as eicosa-14, 15-dihydroxy-cis-8,11-dienoic acid (**13**).[15] The mass spectrum of its methyl ester, **13** gave the parent ion at m/e 354 with other pertinent peaks at m/e 305 (M-49; $-(CH_3O+H_2O)$); m/e 253 (M-101; $-(HOCH-(CH_2)_4CH_3)$).

This observation suggests that cis-epoxy polyunsaturated fatty acids are unlikely free biosynthetic prostaglandin intermediates in the mammalian system. The synthesis of (±)-eicosa-trans-14,15-epoxy-cis-8,11-dienoic acid is currently in progress.



Acknowledgment

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Footnotes and References

1. F. D. Gunstone, *Chem. and Ind.*, 1551 (1966).
2. D. E. Ames, R. E. Bowman and K. G. Mason, *J. Chem. Soc.*, 174 (1950).
3. 8-Nonynoic acid had previously been prepared in 35% yield by coupling 7-bromoheptanoic acid with sodium acetylide in liq. NH_3 (see A. A. Kraevskii, G. I. Myagbova, V. V. Dorogor, I. B. Afanosev, I. K. Sarycheva, and N. A. Pereobrazhenskii, *J. Gen. Chem.*, U.S.S.R. *34*, 1171 (1964)).
4. J. B. Osbond, P. G. Philpott and J. C. Wickens, *J. Chem. Soc.*, 2779 (1961).
5. Pmr were recorded on a 60 Mc Varian spectrometer in $CDCl_3$ with TMS as internal standard. Spectral data were in complete agreement with assigned structures.
6. IR showed no allenic impurity in the region 2100-1900 cm^{-1} and around 850 cm^{-1} (characteristic of terminal allenes).
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    b) J. S. McKennis, L. Brener, J. S. Ward, and R. Pettit, *J. Amer. Chem. Soc.*, *93*, 4957 (1971).
11. A. Steenhoek, B. H. Van Wijngaarden, and H. J. J. Pabon, *Rec. Trav. Chim.*, *90*, 961 (1971).
12. The compound was chromatographed on silica gel and its homogeneity was established by developing the silver nitrate impregnated thin layer plates using chloroform-acetone (8:2) and EtOAc-isooctane-HOAc-H_2O (110:50:20:100).
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14. The sensitivity limit of our detection method for PGE_1 is in the order of 5 µg (see ref. 13).
15. The enzymatic nature of this conversion was established by the observation that boiled BSVM failed to convert **1** into **13**.
16. Owing to the rapid autoxidation, several samples gave unsatisfactory C and H analyses.