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OXIDATION PRODUCTS OF ARACHIDONIC ACID I. THE SYNTHESIS OF METHYL 8R,11R,15-TRIHYDROXY-9S,12-OXYEICOSA-5Z,13E-DIENOATE (19)[1]

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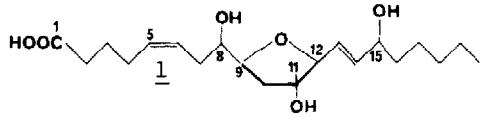
Diacetone glucose was converted in high yield to 3-deoxy-5-6-anhydro-1,2-O-isopropylidene-D-glucofuranose(3), which was transformed to title compound.[3] Its mass spectrum confirms the structure of a naturally occurring oxidation product of arachidonic acid first described by Wolfe and Pace-Asciak.[4]

Wolfe and Pace-Asciak[4] and Axelrod et al[5] isolated 1 of unknown stereochemistry from the enzymatic conversion of arachidonic acid by sheep seminal



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vesicles[4] and soybean lipoxygenase II[5] respectively. We wish to report the synthesis of one of the stereoisomers of 1, the choice of some of the chiral centers (C_9 and C_{11}) and double-bond geometries (Δ^5,Δ^{13}) being dictated by biogenetic considerations. This synthesis confirms the structure assigned to 1, which was based on a limited number of degradation studies and mass spectral data only.

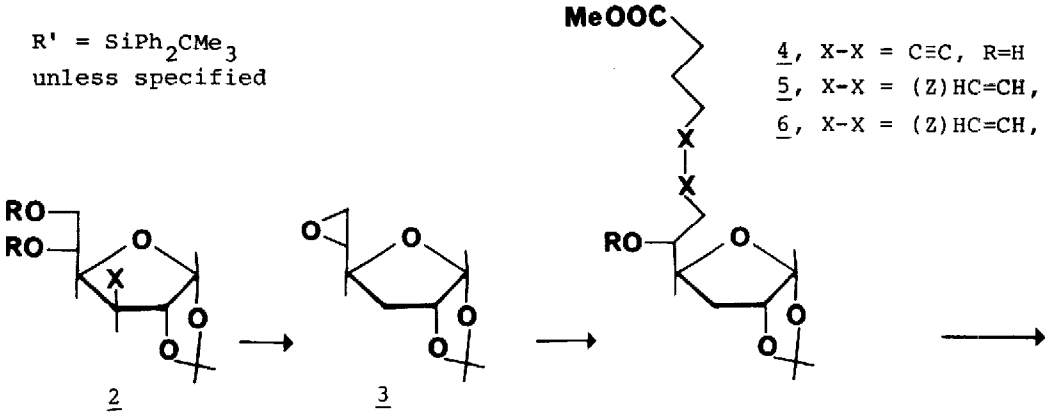
Diacetone glucose (2, X=OH, RR=CMe_2) was transformed to its xanthate[6,7]. Hydrolysis with methanolic sulfuric acid gave the corresponding diol[8], which was transformed to diacetate 2 (R=Ac, X=xanthate). Reduction with tributyltin hydride in toluene[6] gave 2 (R=Ac, X=H), which crystallized spontaneously upon partial evaporation of solvents. Methanolysis (NaOMe/MeOH) provided diol 2 (R=X=H), which was transformed to its 6-monotosylate, contaminated with ditosylate. Treatment of the tosylates with ∿1 eq of aqueous methanolic potassium hydroxide gave epoxide 3[9], b.p. 110°/3 mm, in 55% yield, based on diacetone glucose.

Addition of epoxide 3 in HMPA to 2 eq of the dianion of 5-hexynoic acid[10], generated with BuLi, followed by methylation (CH_2N_2) gave pure 4* in 47% yield. Catalytic hydrogenation using Brown's P-2 nickel boride catalyst[11] gave Z-olefin 5 only, as established by ^{13}C-n.m.r. and g.c.-mass spectrometry.

Silylation[12] afforded 6, which could be converted directly to diol dithioacetal 7 by reaction with EtSH-$ZnCl_2$ at -10°, and hence to acetonide 8* with dimethoxypropane-acetone-TsOH. Unstable aldehyde 9 was obtained by hydrolysis of 8 with HgO/$HgCl_2$ in acetone-water. Di-isopropylamine catalysed condensation of aldehyde 9 with 1-nitro-octan-3-one ethylene ketal[13] in DMF for 18 hrs, followed by acetylation (Ac_2O,4-Me_2N-pyridine) and elimination of the elements of acetic acid (K_2CO_3, benzene, 18-crown-6, 75°, 4 hrs) effected the conversion 9 → 12 in ∿55%, based on 4. Carefully controlled hydrolysis (MeOH/2NHCl (10:1), 2 hrs, 20°), and cyclisation of the resulting diol 13 with triethylamine in THF (20°, 18 hrs) gave 14. Hydrolysis of the ethylene ketal function (acetone, TsOH, 18 hrs, 20°), and elimination of HNO_2 from the resulting nitroketone 15 (NEt_3, $CHCl_3$, 20°, 18 hrs) gave α,β-unsaturated ketone 16* as one isomer only, as established by h.p.l.c. Its n.m.r. spectrums as well as that of the acetates of 16 and 16 (R'=Me) clearly indicated the presence of an AB quartet due to $H_{13}H_{14}$ (J=16.5 Hz), with $J_{12,13}$ = 4.5 Hz and $J_{12,14}$ = 1.5 Hz. The stereochemistry at C_{12} is tentatively assigned as depicted, based on the striking similarity of the n.m.r. pattern due to $H_{11,12,13,14}$ with that of a model substance (benzoate of 16, $CH_2CH{=}CH(CH_2)_3COOMe$ = H) prepared by a different route, in which there was no ambiguity with respect to the stereochemistry at C_{12}. The n.m.r. spectrum of the model compound was kindly provided by Professor S. Hanessian.

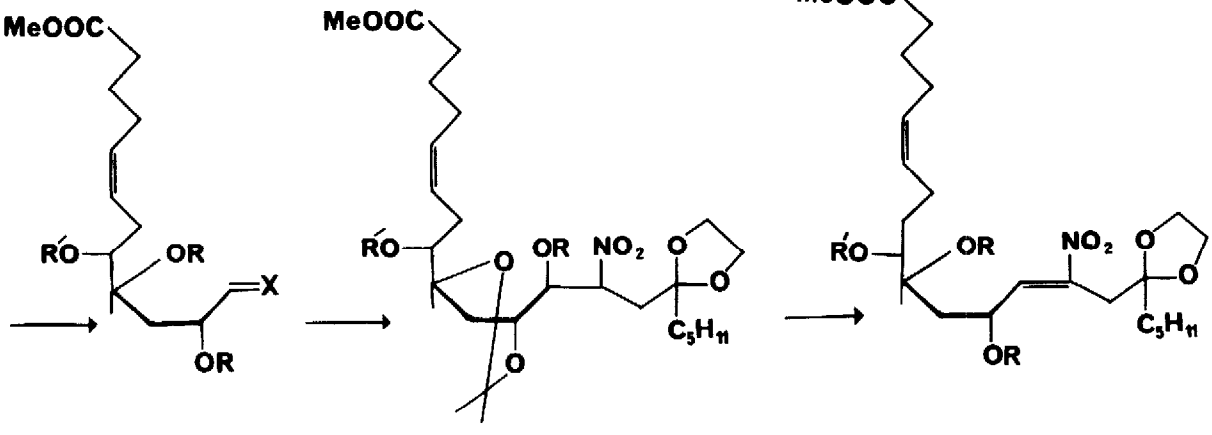
Sodium borohydride reduction of 16 gave 17 and 18, contaminated with products of 1,4-reduction. Chromatography gave a polar fraction consisting of 17 and dihydro-17/18, and a less polar fraction consisting of 18. The n.m.r. spectrum of 18 was in accord with the structure proposed; in particular, the ratio of the two sets of olefinic protons was 1:1. Removal of the silyl protecting group of 18 (n-Bu_4NF, THF, 60°, 18 hrs) gave 19 as one isomer of unknown stereochemistry. G.c. mass spectrometry of its tris-trimethylsilyl ether showed it to be >95% pure, and to have a mass spectrum identical to that of the tris-trimethylsilyl ether methyl ester of 1[4], except for some minor differences in intensity of some peaks. This synthesis therefore proves the structure of 1 proposed by Pace-Asciak and Wolfe.[4]

R' = $SiPh_2CMe_3$
unless specified



2 3

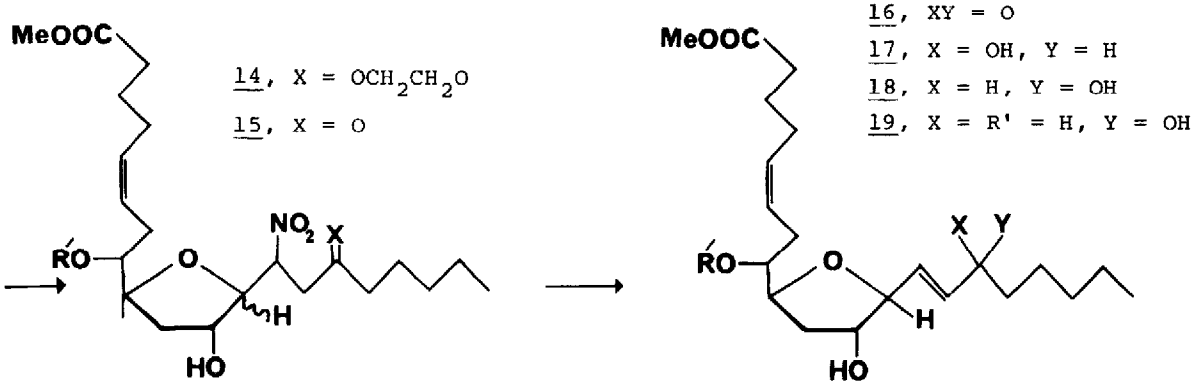
4, X-X = C≡C, R=H
5, X-X = (Z)HC=CH, R=H
6, X-X = (Z)HC=CH, R=$SiPh_2CMe_3$



7, R = H, X = $(SEt)_2$
8, RR = CMe_2, X = $(SEt)_2$
9, RR = CMe_2, X=O

10, R = H
11, R = Ac

12, RR = CMe_2
13, R = H



14, X = OCH_2CH_2O
15, X = O

16, XY = O
17, X = OH, Y = H
18, X = H, Y = OH
19, X = R' = H, Y = OH

References, notes, and analytical data of key compounds

1. We wish to thank the Natural Sciences and Engineering Research Council of Canada for financial support.
2. Holder of scholarships of N.S.E.R.C. and the Ministère de l'Education du Québec, 1977-1979.
3. S. Hanessian and G. Rancourt, 169th National Meeting of the American Chemical Society, Philadelphia, Pa., 1975, Abstr. CARB 26, as quoted in S. Hanessian, Accts. Chem. Res. 12, 160 (1979).
4. C. Pace-Asciak and L. Wolfe, Biochemistry 10, 3664 (1971), Chem. Comm. 1234, 1235 (1970).
5. a) G. Bild, S.G. Bhat, C.S. Ramadoss, B. Axelrod and C. Sweeley, Biochem. Biophys. Res. Comm. 81, 486 (1978). b) G. Bild, S.G. Bhat, C.S. Ramadoss and A. Axelrod, J. Biol. Chem., 253, 21 (1978).
6. H.R. Barton and S.W. McCombie, J.C.S. Perkin I, 1574 (1975).
7. K. Freudenberg and A. Wolf, Ber. der Deut. Chem. Gesell., 60, 232 (1927).
8. No base in work-up as it results in poorly defined mixtures.
9. P. Szabó and L. Szabó, J. Chem. Soc., 5139 (1964).
10. H. Gilman and B. Holland, Synthetic Comm., 199 (1974). See, however, G. Just, C. Luthe, H. Oh and J. Montgomery, Synthetic Comm. 613 (1979).
11. C.A. Brown and V.K. Ahuja, J. Chem. Soc. Chem. Comm. 553 (1973).
12. S. Hanessian and P. Lavallée, Can. J. Chem. 53, 2975 (1975).
13. Prepared according to the procedure of P. Bakuzis, L.F. Bakuzis and F. Weingartner, Tet. Lett. 2371 (1978).

4* M.p. 41-42°, δ: 4.74 (dd, 1H, $J_{1,2}$ ~ $J_{2,3}$ = 4 Hz, C_2H), 5.78 (d, 1H, $J_{1,2}$ = 4 Hz, C_1H). I.r. ($CHCl_3$) 1735 (C=O), 3480 (OH); (m/e 297 (M-15); $[\alpha]_D^{23}$-16.5°. Calcd. for $C_{16}H_{24}O_6$: C 61.54 H 7.69; found 61.77 H 7.50.

8* δ: 1.08 (s,9H), 1.10-2.92 (m,16H), 1.34 (s,6H,CMe_2), 2.70 (q, J = 7 Hz, 4H, 2S$\underline{CH_2}CH_3$), 3.60 (s,3H,CO_2CH_3), 3.60-4.20 (m,4H,H-CS,H-C-O), 5.19-5.44 (m,2H, Z HC=CH) 7.17-7.89 (m,10H,$SiPh_2$); I.r.: 1737 cm^{-1} (COOMe); e/m 584 (M^+-COOMe-CH_3), 135 ($CH(sEt)_2$). Calcd for $C_{36}H_{54}O_5S_2Si$: C 65.65 H 8.21 S 9.73; found C 65.69 H 7.96 S 9.49; $[\alpha]_D^{23}$-29.4°.

16* I.r. 3440 (OH), 1730 (COOMe), 1670, 1626 cm^{-1} (C=C-C=O), e/m 620 (M^+). Calcd for $C_{37}H_{52}O_6Si$ C 71.62 H 8.39. Found C 71.34 H 8.37.

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