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PREFERENTIAL FORMATION OF 8-EPI-PROSTAGLANDIN $F_{2\alpha}$ VIA THE CORRESPONDING ENDOPEROXIDE BY A BIOMIMETIC CYCLIZATION

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Summary: Homolytic demercuration of the 1,2-dioxolanes 14a and 14b in the presence of oxygen leads preferentially to endoperoxide 17 (both epimers at C*) which upon reduction affords 8-epi-prostaglandin $F_{2\alpha}$ and the C(15)-epimer, a result in accord with a previous mechanistic proposal.

We recently described the first chemical synthesis of prostaglandins (PGs) by a biomimetic route involving free radical carbocyclization to form a 2,3-dioxabicyclo[2.2.1]heptane (endoperoxide) intermediate.[1] Each of the diastereomeric 1,2-dioxolanes 1 and 2 upon treatment with tri-n-butyltin hydride at -40° was converted to a reduced organomercurial which underwent gradual decomposition in the presence of air at -10 to 0° to form the endoperoxides 3 and 4 in a ratio of ca. 1 : 1 (each as a 1 : 1 mixture of diastereomers at the carbon corresponding to C(15) by PG numbering). Endoperoxide 3, formed in 35-45% yield, was converted to enone 5, a standard intermediate for PG synthesis by the sequence: (1) reduction with triphenylphosphine in isopropyl alcohol at 0°, (2) cyclic acetal formation catalyzed by pyridinium tosylate in methanol at 23°, (3) purification by chromatography, (4) oxidation to α,β-enone by manganese dioxide, and (5) epimerization at C(12) (morpholine, acetic acid, 75°, 48 hr).

The striking finding that the same 1 : 1 mixture of endoperoxides 3 and 4 was obtained starting from the two diastereomeric mercurials 1 and 2 was interpreted in terms of cyclization via a common radical conformer 6, stabilized in the geometry shown by delocalization into the radicaloid p orbital both from a β-peroxy oxygen lone pair and from the diene unit. Cyclization from 6 will involve rotation of syn p orbital lobes toward one another (disrotatory motion) and in consequence the endoperoxide which results will possess cis oriented appendages (either exo,exo or endo,endo). The present note describes a test of this model which predicts that cis disubstituted endoperoxide should also result with substrates having the full eicosanoid side chain and a 12,13(Z)-double bond regardless of whether the 14,15-double bond is E or Z. For this study the 12,13(Z)-isomer and the 12,13(Z), 14,15(E)-isomer of 11-HPETE methyl esters, 11 and 13, respectively, had to be synthesized.

The OBO ester 7[2] was metallated to the magnesium acetylide (1 equiv of ethylmagnesium bromide, ether, 0°) and coupled with 1-iodo-hex-2-yne-5-ene[3] in the presence of 1 mole % of cuprous chloride in tetrahydrofuran (THF) at 23° for 24 hr to afford a product which was hydroxylated (1.3 equiv N-methylmorpholine N-oxide, 5 mole % osmium tetroxide in 2 : 1 acetone-water for 3 hr at 23°) to give diol 8 (50%

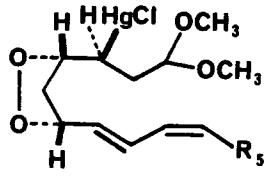
overall) after chromatography on silica gel (sg).[4] Aldehyde 9 was produced from 8 in 80% overall yield by the sequence: (1) Lindlar reduction using Pd-$CaCO_3$ and 1 atm H_2 in THF containing 1.5% of triethylamine, (2) exposure to 1 mM sulfuric acid-methanol at 0° for 20 min, addition of potassium carbonate to a net 0.01 M concentration and stirring at 23° for 1.6 hr (to convert OBO ester to methyl ester), and (3) glycol cleavage of the resulting diol methyl ester using 1.5 equiv of lead tetraacetate in methylene chloride (5 ml/g $Pb(OAc)_4$) at -30° for 50 min, (4) isolation by addition of ether, rapid filtration through a short column of sg, concentration in vacuo, and azeotroping in vacuo with n-heptane to remove traces of acetic acid. Reaction of 9 with the lithio derivative of non-1-yne-3(Z)-ene[5] (from 1 equiv of BuLi in hexane) in toluene-hexane at -78° for 1.5 hr gave after sg chromatography the corresponding acetylenic carbinol which upon Lindlar reduction (Pd-$CaCO_3$, 1 atm H_2, pyridine-toluene) and sg TLC purification afforded 12,13(Z)-11-HETE methyl ester (10).

Non-1-yne-3(E)-ene was synthesized from 1-heptyne by the sequence: (1) hydroboration with 1 equiv of disiamylborane (0°, THF, 2 hr), (2) vinyl copper formation by treatment with 1 equiv of sodium methoxide in THF (23°, 0.5 hr) followed by cuprous cyanide (-78°, 1 hr), (3) coupling with trimethylsilyliodoacetylene (-78 to -10°, 40 hr) to form trimethylsilyl-non-1-yne-3(E)-ene (45% overall), and (4) desilylation (sodium methoxide-methanol, 23°, 2 hr). Conversion of non-1-yne-3(E)-ene to the lithio acetylide (BuLi) and reaction with aldehyde 9 produced the corresponding acetylenic carbinol which was transformed by Lindlar reduction as described above into 12,13(Z), 14,15(E)-11-HETE methyl ester (12).

The 11-HETE isomers 10 and 12 were converted to the corresponding hydroperoxides, 11 and 13, respectively, by reaction of the mesylates with anhydrous hydrogen peroxide.[1,7] The mesylates were formed from the alcohols using mesyl chloride-triethylamine (3 equiv of each) at -78° in methylene chloride for 20 min and then treated with excess 20% dry hydrogen peroxide in ether at -110° for 30 min and then for a further 30 min at -110 to -78°. After quenching of the reaction mixture at -78° with deionized water, extractive isolation, and preparative sg TLC purification at 5° using 1 : 1 ether-hexane containing triethylamine for development, the hydroperoxides 11 and 13 were obtained as colorless oils in yields of 60-62%.

Separately the hydroperoxides 11 and 13 were transformed (in 83 and 74% yield, respectively) into the isomeric cis-3,5-disubstituted 1,2-dioxolanes 14a and 14b, respectively, by reaction at 0° in THF with mercury (II) chloroacetate (1.5 equiv for 2 hr) followed by extractive isolation from saturated aq. sodium chloride and sg TLC (20 : 1 CH_2Cl_2-ether for elution).[8] The chloromercurials 14a and 14b were then converted to endoperoxides by the following process: (1) reaction with 3 equiv of tri-n-butyltin hydride in chlorobenzene at -40° for 40 min (TLC analysis showed disappearance of 13 and formation of a new UV active spot of R_f 0.62 vs 0.48 for 14 using 20 : 1 CH_2Cl_2-ether), and (2) bubbling air through the reaction mixture which was allowed to warm slowly to 0° and then maintained at 0° for 1.5 hr (metallic mercury is deposited). The endoperoxides were not isolated but instead reduced in situ by reaction with methanolic triphenylphosphine (3 equiv, 0° for 0.5 hr and 23° for 3 hr).[9] Chromatographic analysis revealed that the mercurials 14a and 14b gave essentially the same mixture of products consisting of two $PGF_{2\alpha}$ methyl ester isomers, which however were definitely distinguishable from the methyl esters of $PGF_{2\alpha}$, and an array of much more polar products.[10] The two major products, each obtained in pure condition in 10%

yield after chromatography, were identified as C(15) epimers of triol 15. Oxidation of the epimers with dichlorodicyanobenzoquinone in 1 : 1 dioxane-methylene chloride at 40° for 6 hr afforded cleanly the same conjugated enone 16, UV_{max} 228 nm,[11] which was clearly distinguished from the 15-keto derivative of $PGF_{2\alpha}$ methyl ester (UV_{max} 232 nm) by HPLC and pmr comparison. That the C(13)-C(20) side chain of the enone is



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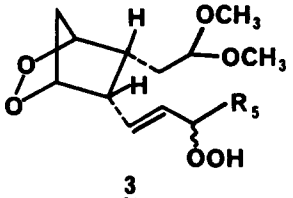

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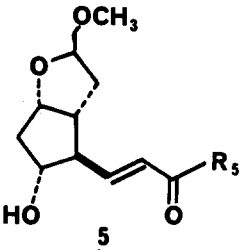

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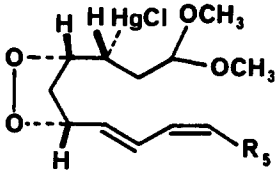

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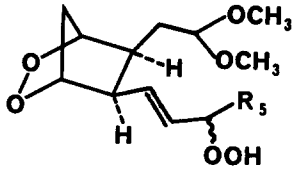

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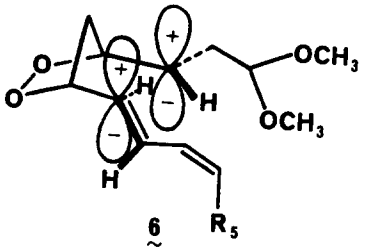

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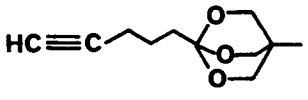

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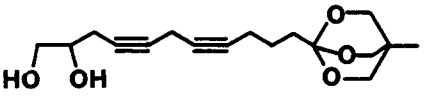

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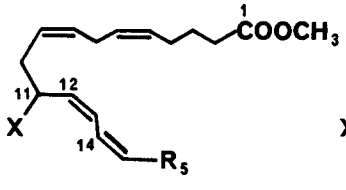
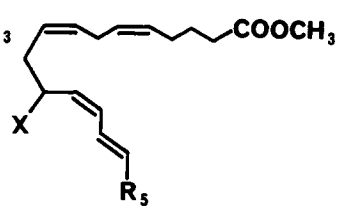
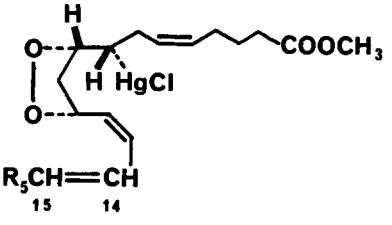


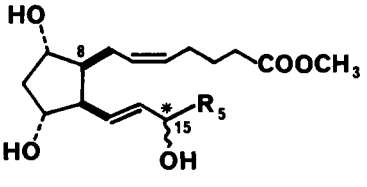
10, X=OH
11, X=OOH



12, X=OH
13, X=OOH



14 a, 14,15(Z)
14 b, 14,15(E)



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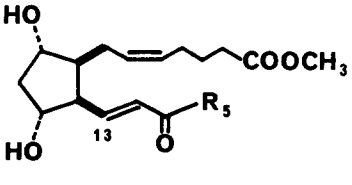

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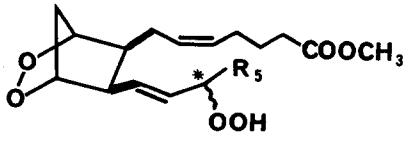

17

$R_5 = nC_5H_{11}$

trans to the C(11) hydroxyl as shown in 16 was indicated by the appearance of the C(13) proton at 6.65 δ in the PMR spectrum. This value is characteristic of the trans C(13)-C(11) OH arrangement. For example, the 15-ketone of $PGF_{2\alpha}$ methyl ester shows the C(13) proton at 6.70 δ whereas a number of analogs in which C(13) and C(11) OH are cis invariably show the corresponding C(13) proton below 7.0 δ in the PMR spectra.[1,12,13] The requirement that the 9- and 11-hydroxyls in 15 are cis to one another, the trans arrangement of C(13) and the 11-hydroxyl, and the demonstration that 16 is isomeric with the 15-ketone of $PGF_{2\alpha}$ methyl ester together lead unambiguously to the assignment of 15 and 16 to the products from cyclization of mercurials 14a and 14b. Finally, ketone 16 was shown to be identical (PMR, HPLC) with the 15-ketone obtained by oxidation of an authentic sample of 8-epi $PGF_{2\alpha}$ methyl ester (supplied by the Upjohn Co.). The intermediacy of endoperoxide 17 (both epimers at C*) logically follows.

These results are fully in accord with our earlier findings[1] and with the view that the transition state for endoperoxide formation is reached from a radical intermediate of conformation analogous to that shown for 6 by disrotatory closure. The favored formation of only the exo,exo-endoperoxide 17 from mercurials 14a and 14b can be understood as a result of the Z geometry of the 12,13-double bond which greatly disfavors the endo,endo pathway. That pathway would force the C(14)-H group and the nearby endoperoxide oxygen into strong steric repulsion. Our results and theory are also in accord with previous observations on the stereochemistry of dihydroxycyclopentanes generated by oxidation of linolenic acid.[12,14]

References and Notes

1. E. J. Corey, K. Shimoji, and C. Shih, J. Am. Chem. Soc., in press.
2. E. J. Corey and N. Raju, Tetrahedron Letters, 24, 5571 (1983).
3. Prepared in 80% yield from the corresponding alcohol by reaction with 1.5 equiv of triphenylphosphine, 1.5 equiv of imidazole and 1.5 equiv of iodine in acetonitrile at 0° for 30 min.
4. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained for each stable reaction product. All synthetic intermediates described herein were obtained in racemic form.
5. E. J. Corey and C. Rücker, Tetrahedron Letters, 23, 719 (1982).
6. This Lindlar reduction was especially difficult to control and invariably a by-product arising from further reduction of the 14,15-double bond (ca. 20%) was obtained.
7. E. J. Corey, A. Marfat, J. R. Falck, and J. O. Albright, J. Am. Chem. Soc., 102, 1433 (1980).
8. Under these conditions only the cis-substituted 1,2-dioxolane is formed.[1] No trans isomer can be detected by chromatographic analysis, or from the 270 MHz PMR spectra of 14a and 14b. PMR data (270 MHz, $CDCl_3$ δ) for 14a are as follows: 6.55 (t, J=10.9 Hz, 1H), 6.19 (t, J=10.9 Hz, 1H), 5.48 (m, 4H), 5.20 (m, 1H), 4.75 (m, 1H), 3.68 (s, 3H), 3.06 (m, 1H), 2.55 (m, 2H), 2.33 (t, J=7.3 Hz, 2H), 2.09 (m, 3H), 1.88 (m, 1H), 1.74 (quintet, 2H), 1.30 (m, 8H), 0.89 (t, J=7 Hz, 3H). The chloromercurials 14a and 14b show good stability.
9. The endoperoxide products were detected by sg TLC analysis using 20:1 CH_2Cl_2-ether as spots of R_f 0.30 and 0.22 which are each converted by R_3P-CH_3OH to more polar product.[10]
10. TLC-sg R_f values using 3% CH_3OH in ethyl acetate (3 developments) were as follows: $PGF_{2\alpha}$ methyl ester 0.45; 15-epi-$PGF_{2\alpha}$ methyl ester 0.64; reaction products (15) 0.54 and 0.41.
11. Enone products were identical by HPLC and 270 MHz PMR analysis. The HPLC retention time measured for 16 was found to be 20 min as compared to 16.5 min for the 15-ketone of $PGF_{2\alpha}$ methyl ester (DuPont Zorbax 4.6mm x 25cm column, 10% isopropyl alcohol in hexane, 2ml/min flow rate). The greater polarity of 16 is clearly in accord with the assigned structure.
12. D. E. O'Connor, E. D. Mihelich, and M. C. Coleman, J. Am. Chem. Soc., 103, 223 (1981); 106, 3577 (1984).
13. S. A. Mizsak and G. Slomp, Prostaglandins, 10, 807 (1975).

14. This research was assisted financially by a grant from the National Science Foundation.

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