Pergamon

Tetrahedron Letters, Vol. 35, No. 4, pp. 539-542, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0269-P

CONVERSION OF ARACHIDONIC ACID TO THE PROSTAGLANDIN ENDOPEROXIDE PGG_2, A CHEMICAL ANALOG OF THE BIOSYNTHETIC PATHWAY

E. J. Corey and Zhe Wang

Department of Chemistry, Harvard University, Cambridge, Massachusetts, 02138

Summary: *Reaction of the methyl ester of (15S)-hydroperoxy-5,8,11Z,13E-eicosapentaenoic acid (7) with oxygen in benzene solution in the presence of a catalyst made from samarium (II) iodide and O_2 produces a mixture of the methyl esters of PGG_2 (12) and its 12-epimer (15) (ratio 1 : 3, yield 43% based on recovered starting material).*

The biosynthesis of prostaglandins (PG's) from arachidonic acid (**1**) is remarkable because it involves the formation in a single enzymic step of the structurally complex endoperoxides PGG_2 (**2**) and PGH_2 (**3**), possibly via an 11-peroxy radical intermediate.[1] These unstable endoperoxides serve as precursors of the other members of the prostanoid family, including the potent regulators $PGF_{2\alpha}$, PGE_2, PGI_2 and thromboxane A_2.[2] Although PGH_2 has been synthesized chemically from $PGF_{2\alpha}$ by a several step process involving nucleophilic displacement by H_2O_2 at C(9) and C(11) to established the endoperoxide bridge,[3-5] the biomimetic synthesis of PGG_2 or PGH_2 has never been realized in chemical systems.[6-8] One major problem is the tendency of monocyclic radicals such as **4** to form selectively the bicyclic products **5** and **6** in which the carbon appendages are *cis* to one another, *i.e.* either *exo,exo* or *endo,endo*.[6-8] Other key unsolved problems of free-radical-based approach include (1) the control of absolute stereochemistry, and relative stereochemistry at C(15), and (2) the enforcement of a single reaction mode for each essential reactive intermediate. This paper presents a successful conversion of arachidonic acid to PGG_2 (natural chirality) which utilizes a new strategy for the control of the complex, free-radical reaction pathway.

The specific concept which guided our investigations is outlined in Scheme I. The starting material **7**, the methyl ester of (15*S*)-hydroperoxy-5,8,11*Z*,13*E*-eicosatetraenoic acid (15-HPETE), is readily available from **1** by soybean lipoxygenase-catalyzed oxidation followed by methylation (CH_2N_2 in ether).[9] The mechanistic pathway from **7** involves (1) proton abstraction to form the peroxy radical **8**, (2) ring closure at C(14) to form a 14,15-dioxetane-11,13-allylic radical, (3) addition of O_2 at C(11) to form **9** (4) attack by oxygen of **9** at C(9) to afford dioxolane **10**, (5) cyclization of **10** to the endoperoxide **11** and hydrogen atom transfer from **7** to **11** to give the methyl ester of PGG_2 (**12**) and the chain-propagating peroxy radical **8**.

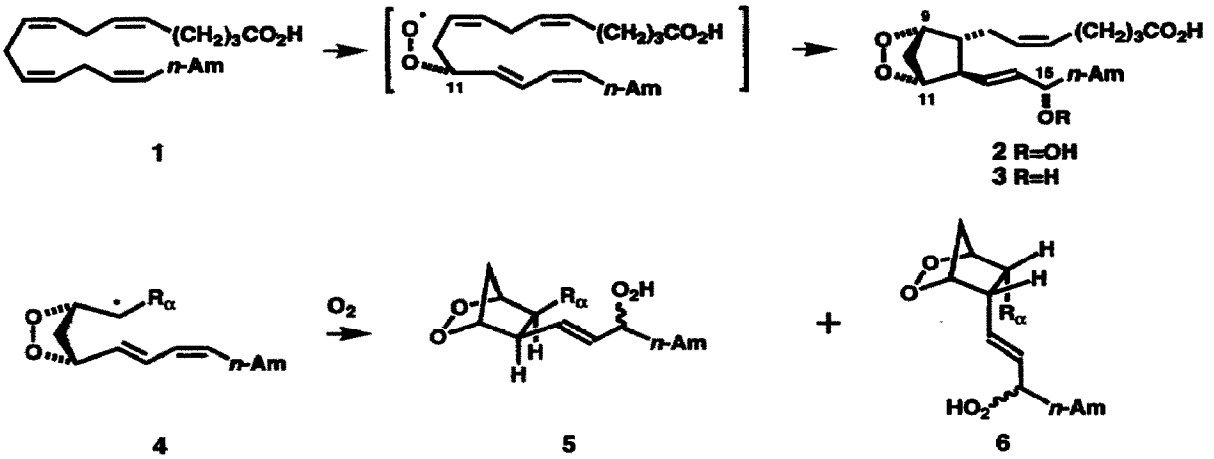
New methodology had to be devised for the initiating step **7** → **8**, since the literature is remarkably devoid of effective reagents for the conversion ROOH → ROO•, even though the reverse reaction is commonplace. A number of possible reagents for this transformation were tested using the model reaction **13** → **14** with only negative results.[10,11] However, reaction of **13** with $Mn_3O(OAc)_7$ in CH_3CN at 0 °C for 3 h in the presence of O_2

produced **14** in 50% yield (optimized conditions) in addition to 20% of 5-methyl-4-hexen-1-ol. Even better results were made using as initiator a colorless reagent, presumably I_2 SmOOSmI_2 or equivalent, prepared by the reaction of SmI_2 in THF with O_2. Addition of 0.1 equiv of this samarium peroxide initiator in THF[12] to a solution of **13** in benzene and reaction with excess O_2 at 23 °C for 15 h afforded the monocyclic hydroperoxide **14** in 70% yield.[13] The samarium peroxide reagent is to our knowledge the best currently available for effecting the conversion of hydroperoxides to peroxy radicals.

Using the samarium peroxide reagent it was possible to effect the transformation of 15-HPETE methyl ester **7** to a 1 : 3 mixture of PGG_2 methyl ester **12** and 12-*epi*-PGG_2, (**15**) (15%, 43% total yield corrected for 65% recovery of unreacted 7). The following experiment is illustrative. To a solution of **7**[9] (25 mg, 0.071 mmol) in dry benzene at 6 °C under N_2 was added 480 μl (0.3 eq) of O_2. A solution of 36 μl of 0.1 M SmI_2 in THF (Aldrich) was diluted to 0.5 ml with benzene and treated with 80 μl of O_2 gas at 10 °C (decolorization was immediate) and this solution was added to the solution of **7** dropwise over 15 min. The homogeneous reaction mixture was stirred at 23 °C for 40 h, diluted with cold (*ca.* -40 °C) hexane and subjected to rapid low temperature chromatography on silica gel (-10 °C or below) using a cold 2 : 1 to 1 : 1 hexane–ether gradient as eluant to give 16.3 mg of unreacted 15-HPETE methyl ester (**7**) and 4 mg (15%) of a 1 : 3 mixture of PGG_2 methyl ester (**12**) and 12-*epi*-PGG_2 methyl ester (**15**). More careful chromatography under the above conditions separated the mixture of **12** and **15** and afforded pure PGG_2 methyl ester (**12**) which was identical with an authentic sample, obtained by treatment of biosynthetic PGG_2 (Cayman Chemical) with ethereal diazomethane, by silica gel tlc analysis, and by 500 MHz NMR and infrared spectral analysis.[14,15] Reduction of synthetic **12** by 1.5 equiv of $SnCl_2$ in ethanol at 0-23 °C for 1 h afforded $PGF_{2\alpha}$ methyl ester, identical with an authentic sample by IR, 500 MHz ^1H NMR, ^{13}C NMR and chromatographic comparison.

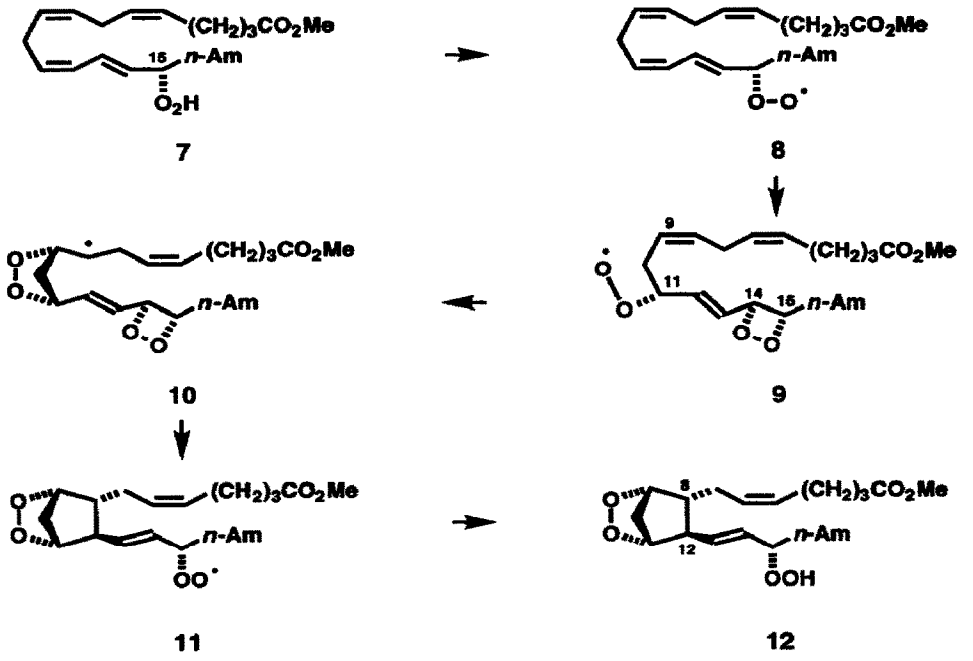
The synthesis of the methyl ester of PGG_2 (**12**) from **7** is of special interest as a chemical counterpart of a complex enzymic process which has not hitherto been realized in model non-enzymic systems and also as a significant step in the solution of a long standing and prominent synthetic problem. Its success is due to the discovery of a new and selective reagent for the generation of peroxy radicals from hydroperoxides (i.e. a samarium (III) peroxide)[16] and the strategy of introducing the (15*S*)-hydroperoxy group before the oxidative bis-cyclization step to control absolute configuration. The experimental demonstration of the concept outlined in Scheme I indicates that the dioxetane intermediates, i.e. **9** and its predecessor, are probably also beneficial in the control of relative stereochemistry. The cyclization of **10** to a 3 : 1 mixture of **15** and **12** produces a much high proportion of endoperoxide with the required *trans* arrangement of C(8) and C(12) appendages than was observed in previously studied cases,[6-8] although still below a desirable level.[17]

The biosynthesis of PGG_2 and PGH_2 has generally been thought to proceed by the initial conversion of arachidonic acid to an (11*R*)-hydroperoxy radical intermediate, as shown above. The results obtained in this investigation suggest that the possibility of biosynthesis from a (15*S*)-hydroperoxy radical should also be considered seriously since, to the best of our knowledge, such a pathway is consistent with presently available data.[18,19]

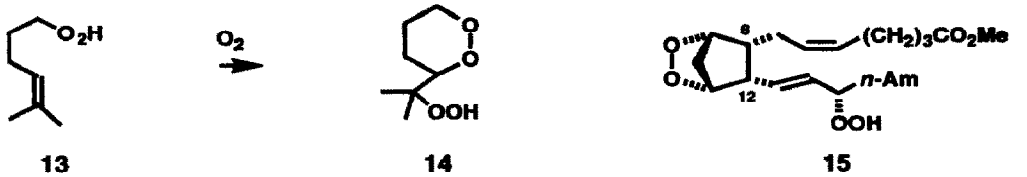


1 2 3 4 5 6

Scheme I



7 8 9 10 11 12



13 14 15

References and Notes

1. For recent reviews see (a) Smith, W. L.; Marnett, L. J. *Biochem. Biophys. Acta* **1991**, *1083*, 1. (b) Smith, W. L. *Am. J. Physiol.* **1992**, *263*, F181.
2. (a) Hamberg, M.; Samuelsson, B. *Proc. Nat. Acad. Sci. USA* **1973**, *70*, 899. (b) Nugteren, D. H.; Hazelhof, E. *Biochem. Biophys. Acta* **1973**, *326*, 448. (c) Hamberg, M.; Svensson, J.; Wakabayashi, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1974**, *71*, 345. (d) Hamberg, M.; Svensson, J.; Samuelsson, B. *Proc. Natl. Acad. Sci. USA* **1975**, *72*, 2994.
3. Johnson, R. A.; Nidy, E. G.; Baczynskyj, L.; Gorman, R. R. *J. Am. Chem. Soc.* **1977**, *99*, 7738.
4. Porter, N. A.; Byers, J. D.; Holden, K. M.; Menzel, D. B. *J. Am. Chem. Soc.* **1979**, *101*, 4319.
5. See also (a) Nicolaou, K. C.; Gasic, G. P.; Barnette, W. E. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 293. (b) Salomon, M. F.; Salomon, R. G. *J. Am. Chem. Soc.* **1977**, *99*, 3500. (c) Salomon, R. G.; Salomon, M. F. *J. Am. Chem. Soc.* **1977**, *99*, 3501. (d) Porter, N. A.; Gilmore, D. W. *J. Am. Chem. Soc.* **1977**, *99*, 3503.
6. O'Conner, D. E.; Mihelich, E. D.; Coleman, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 3577.
7. Corey, E. J.; Shimoji, K.; Shih, C. *J. Am. Chem. Soc.* **1984**, *106*, 6425.
8. Corey, E. J.; Shih, C.; Shih, N.-Y.; Shimoji, K. *Tetrahedron Lett.* **1984**, *25*, 5013.
9. (a) Baldwin, J. E.; Davies, D. I.; Hughes, L.; Gutteridge, N. J. A. *J. Chem. Soc. Perkin I* **1979**, 115. (b) Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5329.
10. Negative results were obtained with the following initiators in combination with O_2: Galvinoxyl (Aldrich), TEMPO (Aldrich), $Ph_3C^{\bullet}$, triethylborane, Mn(III) acetylacetonate, and MnO_2. The use of cupric triflate–O_2, recently recommended by R. K. Haynes and S. C. Vonwiller (*J. Chem. Soc. Chem. Commun.* **1990**, 449 and 551; see also Courtneidge, J. L. *J. Chem. Soc. Chem. Commun.* **1992**, 381), was also ineffective for the conversion **13** → **14**.
11. The hydroperoxide **13** was prepared from the corresponding primary alcohol by (1) conversion to the triflate (1.3 equiv of triflic anhydride, 1.5 equiv of 2,6-lutidine in CH_2Cl_2 at -78 °C for 45 min) and (2) addition at -78 °C of a solution of dry H_2O_2 in ether and reaction at 0 °C for 1 h and at 23 °C for 8 h, and (3) purification by flash chromatography on silica gel using CH_2Cl_2 as eluant (58% overall yield of pure **13**). 5-Methyl-4-hexen-1-ol was synthesized from 2,3-dihydrofuran by hydration to γ-butyrolactol (cat. TsOH in 25 : 1 ether–water at 23 °C for 14 h) and subsequent reaction with isopropylidenetriphenylphosphorane (generated by reaction of KO*t*-Bu and *i*-$PrPh_3P^+I^-$ in THF).
12. Solutions of the samarium peroxide reagent in THF at 23 °C retain their initiating activity even after 12 h at this temperature.
13. Although the mechanism of initiation by this reagent is unknown one possibility might be decomposition to $I_2SmO^{\bullet}$ and selective hydrogen abstraction from ROOH or I_2Sm transfer from $ROOSmI_2$.
14. 500 MHz ^1H NMR data for these endoperoxides were as follows. For PGG_2 methyl ester (**12**) (in $CDCl_3$, δ): 7.94 (1H, s, OOH), 5.56 (1H, dd, J=7.4, 15.8 Hz), 5.47 (1H, dd, J=7.9, 15.8 Hz), 5.39 (2H, m), 4.55 (1H, br.s), 4.47 (1H, br.), 4.27 (1H, dt, J=7.4, 5.8), 3.67 (3H, s), 2.32 (4H, m), 2.12 (4H, m), 1.71 - 1.22 (12H, m, aliphatic), 0.88 (3H, t, 6.1 Hz). For 12-*epi*-PGG_2 methyl ester (**15**) (in $CDCl_3$, δ): 6.04 (1H, dd, J=9.7, 15.7 Hz), 7.94 (1H, s, OOH), 5.48 (1H, dd, J=8.3, 15.7 Hz), 5.38 (2H, m), 4.56 (1H, br.s), 4.49 (1H, br.s), 4.34 (1H, dt, J=8.3, 7.9 Hz), 2.69 (1H, *endo*-12-H, dd, J=11.2, 10.7 Hz), 2.00 (1H, *endo*-8-H, dd, J=3.8, 7.1 Hz) and aliphatic hydrogens. A barely discernible doublet of doublets in the ^1H NMR spectrum of synthetic **12** centered at 3.93 δ may be due to the presence of a small amount of the methyl ester of 8-*epi*-PGG_2
15. Because of the instability of endoperoxides **12** and **15**, it is essential that chromatographic separations be carried out as rapidly as possible at low temperature, preferably with a refrigerated jacketed column and with pre-cooled silica gel and solvent.
16. Experiments in which $Mn_3O(OAc)_7$ was used as an initiator of oxidative cyclization did not lead to appreciable yields of the endoperoxides **12** and **15**.
17. There are two other significant problems. (1) Due to the instability and reactivity of the endoperoxides **12** and **15**, longer reaction times decrease the amount of unreacted starting material **7** but increase the formation of troublesome byproducts; and (2) larger amounts of O_2 lead to the formation of non-carbocyclic bis-dioxolanes of the type previously encountered in earlier attempts to mimic the PG biosynthetic route, see for example, Khan, J. A.; Porter, N. A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 217.
18. See for instance, Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5336.

19. This research was assisted financially by a grant from the National Institutes of Health.

(*Received in USA* 4 *October* 1993; *accepted* 17 *November* 1993)