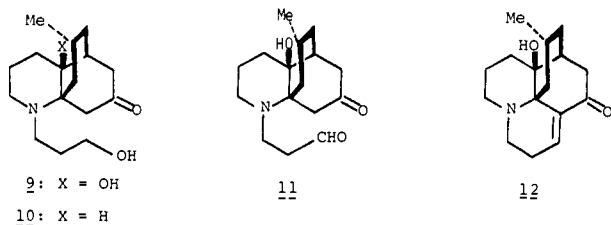


The requisite three-carbon unit necessary for elaboration of the final ring is conveniently introduced by treating **2** with 5 equiv of 3-iodopropanol in refluxing acetone in the presence of potassium carbonate and sodium bicarbonate; alcohol **9** (mp 140–140.5 °C) is obtained in 72% yield. In our lycopodine synthesis,⁶ we were



able to form ring D from an analogous hydroxy ketone (**10**) by Rapoport's modification of the Oppenauer oxidation.⁸ However, treatment of **9** with potassium *tert*-butoxide and benzophenone in refluxing toluene gives only a trace of enone **1**; the major product is the dealkylated amino ketone **2**. Thus in this case, the intermediate keto aldehyde **11** suffers retro-Michael reaction faster than it undergoes intramolecular aldol condensation. The culprit appears to be the hydroxy group, which is known to be strongly hydrogen bonded to the nitrogen in compound **1** itself.^{3b} Apparently, this hydrogen bond reduces the basicity of the leaving amide ion sufficiently so that elimination becomes the dominant reaction. Various attempts to convert the offending alcohol into an ether or ester were unsuccessful. However, a simple modification of Rapoport's method neatly solves the problem. If the Oppenauer oxidation is carried out by using potassium hydride, rather than potassium *tert*-butoxide, the tertiary hydroxy is deprotonated throughout the reaction. Under these conditions (\pm)-dehydrolycodoline (**12**, mp 155–157 °C dec) is produced in 45% yield. The synthesis of (\pm)-lycodoline (**1**, mp 192–194 °C dec) is completed by hydrogenation of **12** using Adam's catalyst in ethanol. The synthetic material, obtained in 78% yield, is identical by infrared and 250-MHz ¹H NMR with the natural alkaloid.

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Isolation and Characterization of Bicyclic Endoperoxides Derived from Methyl Linolenate

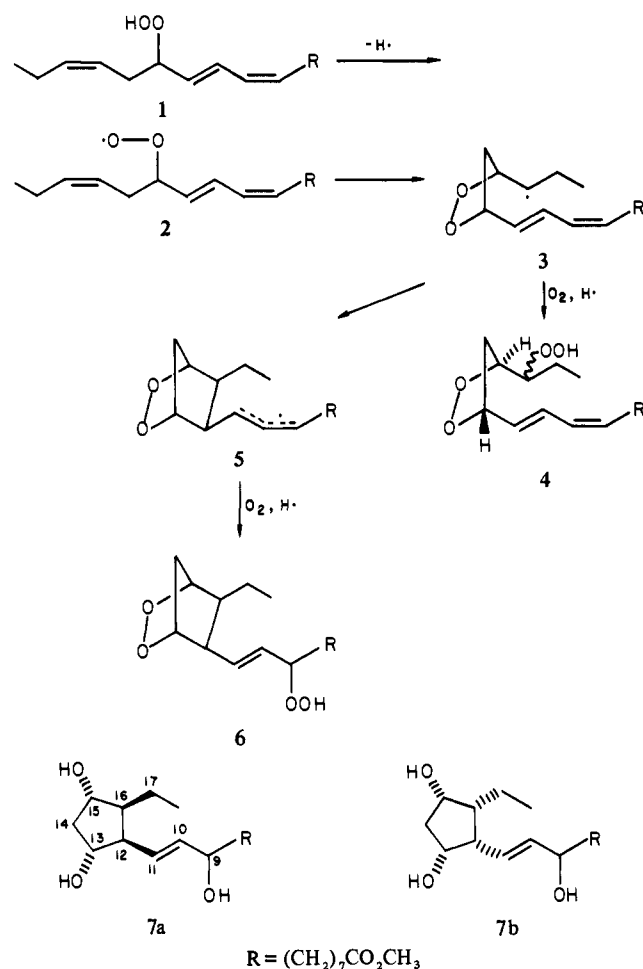
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Over a decade ago Nugteren, Vonkeman, and Van Dorp¹ demonstrated that small amounts of racemic prostaglandins are formed during the autoxidation of triunsaturated fatty acids, presumably by a sequence analogous to **1** → **2** → **3** → **5** → **6** (Scheme I). While more recent work further supports the generality of such nonenzymatic conversions,^{2,3} little attention has

Scheme I



been given to the stereochemical aspects of this transformation. Generally, the low yields of natural prostaglandins or their close structural analogues have been regarded by previous investigators as evidence for the stereorandom nature of these autoxidations. The recent discovery⁴ that ring closure of β,γ -unsaturated peroxy radicals (**2** → **3**) highly favors *cis*-dioxolane formation (as is required for further conversion to prostaglandins) led us to investigate in detail the stereochemical features of the later events in bicyclic endoperoxide formation (**3** → **5** → **6**). We now report the isolation and stereochemical characterization of such bicyclic peroxides from autoxidized methyl 13-hydroperoxy-*cis*-9,*trans*-11,*cis*-15-octadecatrienoate (**1**), indicating stereoselection is operative in these steps as well. In particular, formation of endoperoxides possessing the natural prostaglandin ring stereochemistry appears to be highly disfavored.

The hydroperoxide **1** was prepared in 70% yield (after chromatography) by the lipoxygenase-catalyzed oxidation of α -linolenic acid⁵ and subsequent esterification of the product with diazomethane, following a procedure of Porter.⁶ A solution of **1** (1.05 g) in 15 mL of carbon tetrachloride was then saturated with oxygen and was allowed to stand at room temperature for 10 days, during which time it was periodically resaturated with oxygen. Medium-pressure liquid chromatography (silica gel, 70:30 (v/v) hexane-ethyl acetate) of the reaction product gave 182 mg of recovered **1** (*R_f* 0.76),⁷ 200 mg of a second fraction (*R_f* 0.55–0.60) consisting of two monocyclic peroxides (**4**),⁸ 218 mg of a third

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(3) (a) Pryor, W. A.; Stanley, J. P. *J. Org. Chem.* **1975**, *40*, 3615–3617. (b) Pryor, W. A.; Stanley, J. P.; Blair, E. *Lipids* **1976**, *11*, 370–379.

(4) (a) Beckwith, A. L. J.; Wagner, R. D. *J. Am. Chem. Soc.* **1979**, *101*, 7099–7100. (b) *J. Chem. Soc., Chem. Commun.* **1980**, 485–486. (c) Mihelich, E. D. *J. Am. Chem. Soc.* **1980**, *102*, 7141–7143.

(5) Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5329–5335.

(6) Funk, M. O.; Isaac, R.; Porter, N. A. *Lipids* **1976**, *11*, 113–117.

(7) Thin layer chromatography (TLC) was done on silica gel eluting with 50:50 (v/v) pentane-ether.

fraction of bicyclo endoperoxides (R_f 0.25-0.37), and 328 mg of more polar components.⁹ Two subfractions of the R_f 0.25-0.37 fraction were obtained as pure compounds and were shown by further analysis to be isomers of structure 6, with R_f 's of 0.37 (**6a**) and 0.34 (**6b**). Each showed a single peak on analytical high-pressure liquid chromatography (LC) μ -Porasil, 75:25 (v/v) hexane-ethyl acetate) with capacity factors of 1.1 and 1.4 for **6a** and **6b**, respectively.

¹H and ¹³C NMR spectroscopic analyses^{10,11} confirm the structure assignments shown in Scheme I. Thus, proton decoupling experiments established that the hydroperoxy group in each isomer is attached to C-9. The δ 35-50 region of the ¹³C spectra shows a unique set of three peaks for each isomer (48.7, 48.1, and 39.3 for **6a**; 46.0, 45.4, and 44.1 for **6b**). These peaks are due to carbons 12, 14, and 16 and reflect differences in ring stereochemistry. Although each isomer is spectroscopically unique, it is difficult to assign the specific stereochemistry of either on the basis of NMR spectral analysis, because no model compounds for comparison exist. Stereochemical assignments, however, could be made with the corresponding triols for which there are several appropriate models available.

Reduction of **6a** and **6b** with stannous chloride¹² gave triols which were shown to have structures **7a** and **7b**, respectively. Mass spectral analysis¹³ of their trimethylsilyl derivatives revealed the expected fragmentation patterns^{13b,14} and gave the correct exact masses for selected large fragments of the assigned structures. ¹H and ¹³C NMR spectral analysis of **7a** and **7b** and their acetate

derivatives allowed the assignment of ring stereochemistry. In the ¹³C spectra the exocyclic methylene carbons (C-17) differ significantly in chemical shift (22.1 for **7a** vs. 19.3 for **7b**); the C-11 carbons show similar differences (128.7 for **7a** vs. 128.0 for **7b**). By analogy with the results of Mizsak and Slomp¹⁶ in a study of isomeric prostaglandins, we conclude that in each case the higher field absorbance indicates a cis relationship and the lower field absorbance a trans relationship between that carbon and the ring hydroxyls. De Clerq and Samson¹⁷ have also established an easy method of ring configuration assignment based on high-field ¹H NMR studies of acetate derivatives. For each of the four possible ring isomers, there is a unique combination of $J_{12,16}$ and the chemical shifts of H-14 β and H-13 (H-15). We found ¹H NMR data for the triacetate of **7a** to be 4.89 ppm (H-13 and H-15), 2.70 ppm (H-14 β), $J_{12,16} = 6.8$ Hz and for the triacetate of **7b** to be 5.02 ppm (H-13), 2.62 ppm (H-14 β), $J_{12,16} = 6.6$ Hz. These data show that **7a** has both alkyl substituents on the ring trans to the hydroxyls and **7b** has the alkyl substituents and hydroxyls cis. On the basis of these assignments the structures of the bicyclo endoperoxides must therefore be both substituents exo for **6a** and both substituents endo for **6b**.

The bicyclo endoperoxide fraction (R_f 0.25-0.37) contains additional components that appear to be other isomers of 6, but the ring stereochemistries of **6a** and **6b** account for a large percentage of the total fraction. Our data indicate that **6a** and **6b** actually are each single diastereoisomers whose C-9 epimers are chromatographically separated from them. They appear on high-pressure LC to comprise about half of the total bicyclo endoperoxide fraction; however, the combination of **6a** and **6b** and their C-9 epimers constitute >75% of the total.¹⁸

The selectivities shown in this reaction are quite remarkable: the dioxolane ring formation (2 \rightarrow 3) gives exclusively cis substitution; the oxygenation of intermediate 5 occurs predominantly at C-9; perhaps most noteworthy, the ring closure (3 \rightarrow 5) primarily forms bicyclo endoperoxides with cis substituents. This last feature departs radically from enzyme-mediated endoperoxide formation in that the natural prostaglandin stereochemistry is disfavored.

Acknowledgment. We thank Drs. A. J. De Stefano and T. W. Keough for mass spectral analyses and Dr. F. S. Ezra, Dr. J. P. Yesinowski, and Ms. C. S. Yeakle for the 300-MHz ¹H NMR data.

(8) These two cyclic peroxides were further separated by chromatography (silica gel, 65:30:5 (v/v) hexane-ether-chloroform) and their complete structures were determined as described in ref 4c. For earlier work see: (a) Chan, H. W.-S.; Matthew, J. A.; Coxon, D. T. *J. Chem. Soc., Chem. Commun.* 1980, 235-236. (b) Roza, M.; Francke, A. *Biochim. Biophys. Acta* 1978, 528, 119-126. (c) Begemann, P. H.; Woestenbergh, W. J.; Leer, S. *J. Agric. Food Chem.* 1968, 16, 679-684.

(9) In a number of runs we have isolated ~20% of a monocyclic peroxide fraction, 15-20% of a bicyclo endoperoxide fraction and 40-50% of a more polar residue. However, TLC suggests that the two peroxide fractions constitute the major part of the reaction mixture and shows little of the more polar materials. These peroxides are not very stable to the chromatographic conditions and, we believe, are converted to more polar materials during chromatography.

(10) All NMR spectra were taken in dilute solutions of deuteriochloroform and are referenced to tetramethylsilane internal standard. Proton assignments were substantiated by homonuclear decoupling experiments.

(11) Selected NMR absorption bands. **6a**: ¹H NMR (300 MHz) δ 7.94 (s br, 1, OOH), 5.52 (dd, 1, $J = 15.5, 7.2$ Hz, H-10), 5.44 (dd, 1, $J = 15.5, 9.8$ Hz, H-11), 4.53 (s br, 1, H-15), 4.42 (s br, 1, H-13), 4.26 (m, 1, H-9), 2.92 (m, 1, H-12), 2.16 (m, 2, contains H-16), 0.95 (t, 3, $J = 7.2$ Hz, H-18); ¹³C (22.5 MHz) δ 174.3 (C-1), 132.5, 131.1 (C-10, C-11), 86.3 (C-9), 81.7, 80.5 (C-13, C-15), 51.4 (CO₂CH₃), 48.7, 48.1, 39.3 (C-12, C-14, C-16), 21.9 (C-17), 13.2 (C-18). **6b**: ¹H NMR (300 MHz) δ 7.89 (s br, 1, OOH), 6.02 (dd, 1, $J = 15.5, 9.9$ Hz, H-11), 5.47 (dd, 1, $J = 15.5, 7.5$ Hz, H-10), 4.64 (s br, 1, H-15), 4.47 (s br, 1, H-13), 4.33 (m, 1, H-9), 2.66 (m, 1, H-12) 1.90 (m, 1, H-16), 0.88 (t, 3, $J = 7.3$ Hz, H-18); ¹³C (22.5 MHz) δ 174.3 (C-1), 132.8, 132.2 (C-10, C-11), 86.6 (C-9), 83.0, 80.1 (C-13, C-15), 51.4 (CO₂CH₃), 46.0, 45.4, 44.1 (C-12, C-14, C-16), 18.8 (C-17), 13.0 (C-18).

(12) Hamberg, M.; Svensson, J.; Wakabayshi, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* 1974, 71, 345-349.

(13) Mass spectra were obtained on an AEI/Kratos MS-30 dual beam, double focusing mass spectrometer. Principal fragments were (mass, % of base peak) **7a**: 543, 0.3; 468, 10; 401, 7; 378, 7.8; 352, 10; 323, 3; 311, 40; 285, 24; 259, 6; 217, 13; 195, 45; 73, 100. **7b**: 558, 0.2; 543, 1; 468, 48; 401, 28; 378, 12; 352, 31; 323, 22; 311, 48; 285, 31; 259, 15; 217, 16; 195, 32; 73, 100. Parent ions were too weak for their exact masses to be determined. However, the exact masses of fragments derived from the well-established loss of one and two trimethylsilylanol units were obtained. For the fragments C₂₅H₄₀O₄Si₂ (M - (CH₃)₃SiOH) and C₂₂H₃₆O₃Si (M - 2(CH₃)₃SiOH): calcd, 468.3091, 378.2590; found, **7a**, 468.3186, 378.2643; **7b**, 468.3140, 378.2630.

(14) Wlodawer, P.; Samuelsson, B. *J. Biol. Chem.* 1973, 248, 5673-5678.

(15) Selected NMR absorption bands. **7a**: ¹H NMR (300 MHz) δ 5.59 (dd, 1, $J = 15.4, 6.3$ Hz, H-10), 5.42 (dd, 1, $J = 15.4, 9.0$ Hz, H-11), 4.15 (m, 3, H-9, -13, -15), 2.79 (m, 1, H-12), 2.41 (m, 1, H-14 β), 2.03 (m, 1, H-16), 1.66 (m, 1, H-14 α); ¹³C (22.5 MHz) 174.3 (C-1), 135.8 (C-10), 128.7 (C-11), 76.5, 76.4, 72.7 (C-9, C-13, C-15), 51.4 (CO₂CH₃), 53.6, 52.5, 42.8 (C-12, C-14, C-16), 22.1 (C-17), 12.8 (C-18). **7b**: ¹H NMR (300 MHz) δ 5.85 (dd, 1, $J = 15.5, 10.4$ Hz, H-11), 5.59 (dd, 1, $J = 15.5, 6.2$ Hz, H-10), 4.19 (m, 3, H-9, -13, -15), 2.76 (ddd, 1, $J = 10.4, 8.8, 6.3$ Hz, H-12), 2.17 (ddd, 1, $J = 14.5, 6.7, 5.6$ Hz, H-14 β), 1.85 (ddd, 1, $J = 14.5, 4.6, 2.0$ Hz, H-14 α), 1.82 (m, 1, $J_{12,16} = 8.8$ Hz, H-16); ¹³C (22.5 MHz) δ 174.3 (C-1), 137.7 (C-10), 128.0 (C-11), 76.3, 73.8, 72.5 (C-9, C-13, C-15), 51.5 (CO₂CH₃), 50.1, 49.0, 43.0 (C-12, C-14, C-16), 19.3 (C-17), 12.9 (C-18).

(16) Mizsak, S. A.; Slomp, G. *Prostaglandins* 1975, 10, 807-812.

(17) De Clerq, P.; Samson, M. *Org. Magn. Reson.* 1977, 9, 385-388.

(18) A high-pressure LC of the R_f 0.25-0.37 fraction shows four peaks containing endoperoxides; the **6a** and **6b** peaks (capacity factors, 1.1 and 1.4) are 17% and 38% of the total area, respectively, with the third peak (capacity factor, 1.7) and fourth peak (capacity factor, 2.4) accounting for 29% and 16%. A ¹³C NMR spectrum of the 2.4 capacity factor component was essentially identical with that of **6b**, suggesting it is the C-9 epimer; a ¹³C NMR spectrum of the 1.7 capacity factor component shows multiple peaks in the δ 35-50 region, with the major ones being identical with those of **6a**. Reduction of this 1.7 capacity factor material gave a mixture of triols; the ¹H NMR spectrum of the acetate derivative of one of these indicated it has the same ring stereochemistry as **7a** and thus must be its C-9 epimer. Further evidence for the great preponderance of two ring configurations lies in the ¹³C NMR spectrum of the crude reaction mixture. The δ 35-50 region shows as the only significant peaks those of **6a** and **6b** plus one each for the two monocyclic peroxides 4.

Influence of ¹⁴N on ¹³C NMR Spectra of Solids

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Resonances from carbons bonded to nitrogen are often broadened and split into asymmetric doublets in ¹³C NMR spectra of polycrystalline organic molecules obtained with proton decoupling and magic-angle sample spinning.¹⁻⁶ The influence of