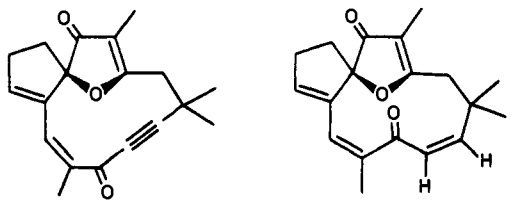
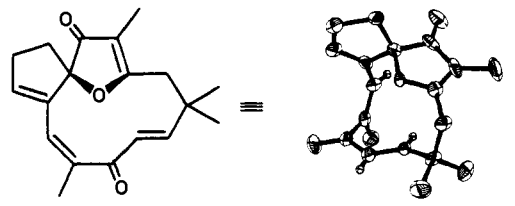
of the 250-MHz ^1H NMR spectral data of the normethyl system with that of authentic jatrophone[7,17] as well as by completion of a single-crystal X-ray analysis; that result is illustrated below.[12]



(13) (14)



Normethyljatrophone

In summation, the total synthesis of normethyljatrophone has been achieved in 15 steps and in 5.6% overall yield from cyclopentenone (**7**). Four X-ray crystallographic analyses were completed during this venture, thereby confirming the structure of **11**, **12**, **15** and that of normethyljatrophone (**2**). Studies to improve the overall sequence, as well as to effect the total synthesis of jatrophone paralleling the above strategy, will be reported in due course.

Note Added in Proof. *Since acceptance of the manuscript, we have successfully completed the first stereocontrolled total synthesis of both (+)-jatrophone (**1**) and that of its epimer (+)-epijatrophone, exploiting the synthetic strategy outlined above; **5a** and its epimer served, respectively, as starting materials. A complete account of this effort will be forthcoming in the near future.*

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant No. CA-22807. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania where the 220- and 360-MHz spectra were recorded.

(17) We thank Dr. Matthew Suffness of the National Cancer Institutes and Dr. Jeffrey Cordell, University of Illinois, Chicago Circle—Medical Center, for providing us with a generous sample of jatrophone.

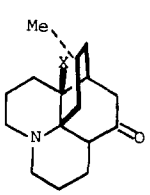
Total Synthesis of (±)-Lycodoline

Clayton H. Heathcock* and Edward F. Kleinman

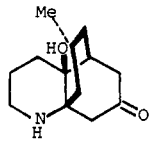
Department of Chemistry, University of California Berkeley, California 94720

Received September 5, 1980

Lycodoline (**1**, "alkaloid L.8") is the second most widely occurring of the lycopodium alkaloids.[1] It was first isolated in 1943 by Manske and Marion from *L. annotinum* Linn[2] and its structure was established in 1961 by Ayer and Iverbach.[3] In an attempted synthesis, Horii and co-workers succeeded in preparing tricyclic amino ketone **2**[4] but were unable to add the final ring.[5] Because



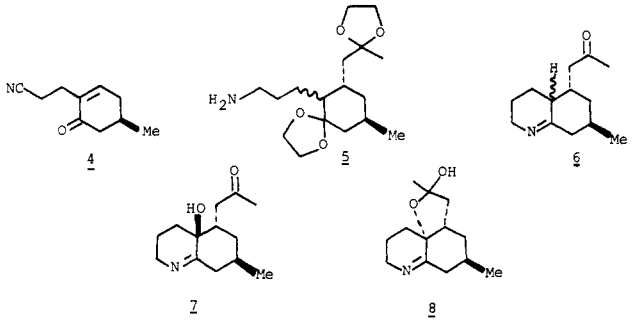
1: X = OH
3: X = H



2

of the close structural resemblance between lycodoline and lycopodine (**3**), we have examined the use of intermediates employed in our lycopodine synthesis[6] for construction of alkaloid **1**. However, the presence of the sensitive tertiary alcohol function in lycodoline precludes the use of the acidic conditions required to effect the key Mannich cyclization in the synthesis of **3**.[6] In this communication, we report an interesting solution to this problem, which has culminated in the first total synthesis of (±)-lycodoline.

Amino diketal **5**, available in three steps (58% overall yield) from cyano enone **4**,[6] is treated briefly with 10% aqueous HCl, and the resulting solution is made basic with NaOH. The unstable



4 **5** **6** **7** **8**

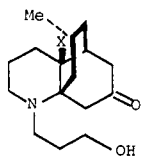
octahydroquinoline (**6**) is extracted with ethyl acetate, and the resulting solution is treated with oxygen gas and then hydrogen and Pd/C to obtain a mixture of alcohol **7** (mp 164–65 °C, 43%) and hemiketal **8** (oil, 4%). This interesting autoxidation finds precedent in the work of Cohen and Witkop on the parent octahydroquinoline.[7] In the present case, it is noteworthy that the diastereomer having the angular oxygen and the neighboring acetonyl group trans predominates by a factor of 10:1. We postulate that this stereoselectivity arises from simple steric hindrance of approach of an oxygen molecule to the intermediate free radical.

The third ring is smoothly formed by heating a dilute solution of compound **7** (0.075 M) in a 5:1 mixture of toluene and 3-bromopropanol at reflux for 24 h. Neutralization of the resulting hydrobromide salt (which crystallizes from the hot solution) provides amino ketone **2** (mp 165–166 °C) in 85% yield. Many other attempts to accomplish this cyclization were unsuccessful. Since the product is a hydrobromide salt, a full equivalent of HBr is required. However, it appears to be crucial to the success of the reaction that the acid be added exceedingly slowly. Thus, if the hydrobromide salt of imine **7** is heated for 24 h in toluene, no cyclization occurs. 3-Bromopropanol functions as a source of HBr by slowly polymerizing under the reaction conditions. It is interesting to note that 3-bromopropanol is superior to 2-bromoethanol for this purpose.

(1) D. B. MacLean, *Alkaloids*, **14**, 347 (1973).
(2) R. H. Manske and L. Marion, *Can. J. Res., Sect. B*, **21**, 92 (1943).
(3) (a) W. A. Ayer and G. G. Iverbach, *Tetrahedron Lett.*, No. 3, 87 (1961); (b) W. A. Ayer and G. G. Iverbach, *Can. J. Chem.*, **42**, 2514 (1964).
(4) Z.-i. Horii, S.-W. Kim, T. Imanishi, and T. Momose, *Chem. Pharm. Bull.*, **18**, 2235 (1970).
(5) S.-W. Kim, Y. Bando, and Z.-i. Horii, *Tetrahedron Lett.*, 2293 (1978).
(6) C. H. Heathcock, E. Kleinman, and E. S. Binkley, *J. Am. Chem. Soc.*, **100**, 8036 (1978).
(7) L. A. Cohen and B. Witkop, *J. Am. Chem. Soc.*, 77, 6595 (1955).

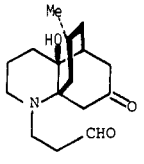
0002-7863/81/1503-222$01.00/0

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

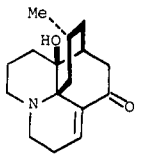


9: X = OH

10: X = H



11



12

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 (±)-dehydrolycodoline (**12**, mp 155–157 °C dec) is produced in 45% yield. The synthesis of (±)-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 ^{1}H NMR with the natural alkaloid.

Acknowledgment. This research was supported by a grant from the National Science Foundation (CHE 79-06344). We thank Professor Ayer for a sample of natural lycodoline.

(8) H. Rapoport, R. Nauman, E. R. Bissell, and R. M. Bonner, *J. Org. Chem.*, **15**, 1103 (1950).

Isolation and Characterization of Bicyclo Endoperoxides Derived from Methyl Linolenate

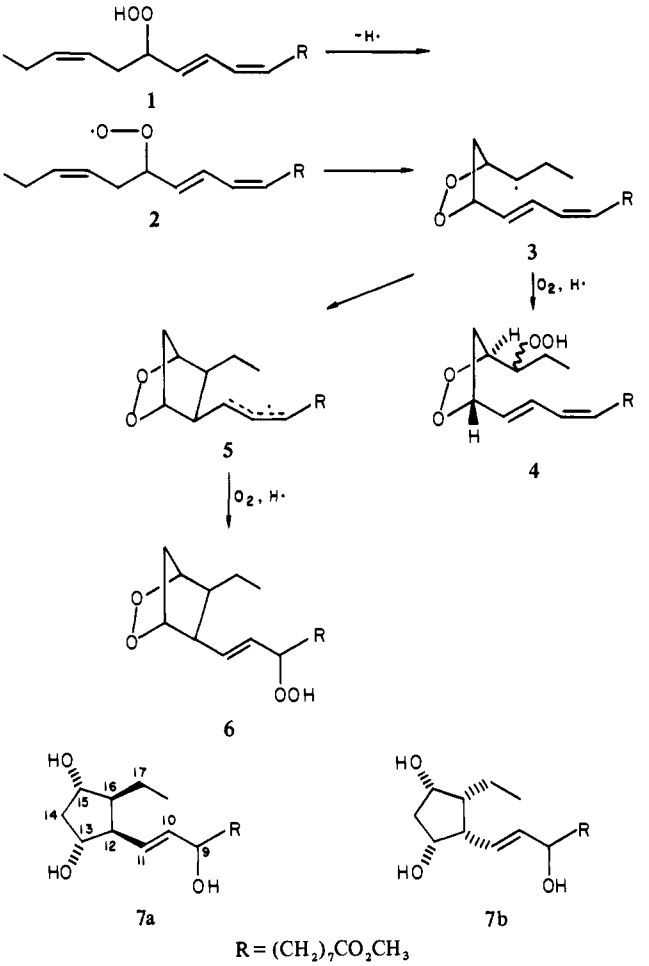
David E. O'Connor,* Edward D. Mihelich,* and Milton C. Coleman

The Procter & Gamble Company
Miami Valley Laboratories, Cincinnati, Ohio 45247

Received September 22, 1980

Over a decade ago Nugteren, Vonkeman, and Van Dorp[1] 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 discovery[4] 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 acid[5] 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

(1) Nugteren, D. H.; Vonkeman, H.; Van Dorp, D. A. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1237–1245.
(2) Porter, N. A.; Funk, M. O. *J. Org. Chem.* **1975**, *40*, 3614–3615. Porter, N. A., et al. In "Biochemical Aspects of Prostaglandins and Thromboxanes"; Kharasch, N., Fried, J., Eds.; Academic Press: New York, 1977; pp 39–53.
(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.

0002-7863/81/1503-223$01.00/0