Soc., 86, 679 (1964); (b) J. P. Chesick, *ibid.*, 84, 3250 (1962).
(13) Syn and anti here refers to the stereochemistry of the fusion of the cyclopropane and cyclohexadiene rings to the central cyclobutane ring.
(14) (a) W. P. Lay and K. MacKenzie, *Chem. Commun.*, 398 (1970); (b) W. P. Lay, K. MacKenzie, and J. R. Telford, *J. Chem. Soc. C*, 3199 (1971).
(15) W. Grimme, *J. Amer. Chem. Soc.*, **95**, 2381 (1973).
(16) (a) S. W. Staley and T. J. Henry, *J. Amer. Chem. Soc.*, **91**, 1239 (1969); (b) *ibid.*, **91**, 7787 (1969).
(17) These facts have been rationalized by postulating that a methyl group of a dimethyl substituted bridge will be "sterically larger" than that in a monomethyl substituted bridge.[16]
(18) The ΔG^* for thermolysis of *anti*-CH_3-**2** is 27.4 kcal/mol[6b] while ΔG^* for the formation of *cis*-dihydroindenes from *syn*-CH_3-**2** can be estimated as 31.6 kcal/mol. Using this mechanistic model and these values of ΔG^* it can be estimated that *ca.* 0.4% of the *anti*-CH_3-**2** epimer is present after thermolysis of *syn*-CH_3-**2** for one half-life at 151°.

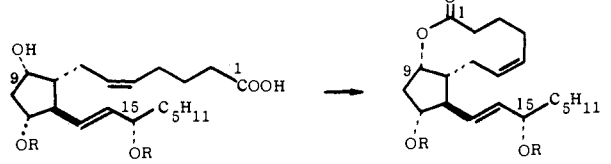
C. P. Lewis, Maurice Brookhart*
Department of Chemistry, University of North Carolina
Chapel Hill, North Carolina 27514
Received June 24, 1974

Synthesis of Novel Macrocyclic Lactones in the Prostaglandin and Polyether Antibiotic Series

Sir:

A highly effective method has recently been described for the conversion of a series of ω-hydroxyalkanoic acids to macrocyclic lactones under neutral, aprotic conditions.[1] The method is based on the strategy of forming from the hydroxy acid an ester which is subject to activation of *both* carboxyl and hydroxyl functions by internal proton transfer so as to result in an electrostatically driven cyclization to form the lactone. The extraordinary efficiency of this "double activation" process coupled with its operation without the need for basic or acidic catalysts opens for the first time the possibility of synthesizing a wide variety of complex and highly functionalized macrocyclic lactones. These include not only important naturally occurring lactones (*e.g.*, macrolide antibiotics) but also novel substances formed by lactonization of biologically active hydroxy acids. This communication discloses results on the synthesis of macrolactones in the prostaglandin series which are of special interest as stabilized *in vivo* equivalents of these easily metabolized and medically important substances. In addition, the conversion of the polyether antibiotic monensin to a novel and potentially useful cyclic form is described.

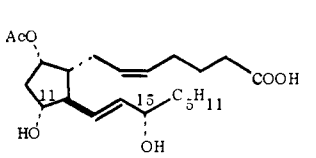
Prostaglandin $F_{2\alpha}$-11,15-bis(tetrahydropyranyl) (THP) ether (**1**),[2] upon treatment with 2,2′-dipyridyl disulfide (1.5 equiv) and triphenylphosphine (1.5 equiv)[1,3] in concentrated dry xylene solution for 15 hr at 25° followed by dilution with xylene and reluxing for 5 hr under an air-free (nitrogen) atmosphere, afforded the protected 1 → 9-lactone derivative of prostaglandin $F_{2\alpha}$ **2** in 90% yield. Removal of the protecting groups (HOAc-H_2O-THF, 3:1:1; 50°; 7 hr) proceeded smoothly to give prostaglandin $F_{2\alpha}$ 1 → 9-lactone **3** (ir_{max} 1740 cm^{-1}, $[\alpha]^{20}D$ + 80.87° (*c* 4 in $CHCl_3$)) as a colorless oil (92%) which solidifies upon refrigeration.[4] In agreement with the assigned structure, **3** underwent selective oxidation with manganese dioxide to form the corresponding 15-ketone,[4] uv_{max} 228 nm (ε 20,000) (EtOH). Apart from being of considerable interest with regard to biological activity, the lactone **3** represents an internally protected form of prostaglandin $F_{2\alpha}$ which allows a variety of useful selective transformations.[5]



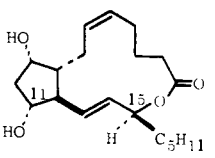
1, R = THP

2, R = THP
3, R = H

Reaction of the 9-acetate of prostaglandin $F_{2\alpha}$[4,6] (**4**) with 2,2′-dipyridyl disulfide (2 equiv) and triphenylphosphine (2 equiv) in concentrated xylene solution at 25° for 15 hr followed by dilution with xylene and heating at reflux for 15 hr afforded an oily acetoxy lactone (74%) which gave upon deacetylation (1 equiv of K_2CO_3 in methanol at 25° for 2.5 hr) and chromatography the 1→15-lactone of prostaglandin $F_{2\alpha}$ (**5**):[4] mp 111–112° (from ether–pentane); ir_{max}



4



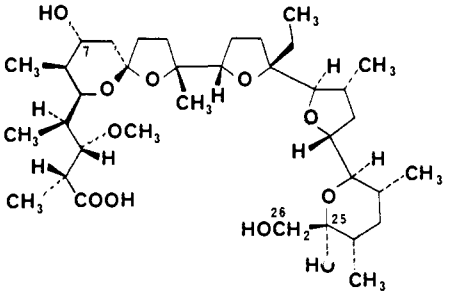
5

1730 cm^{-1}; $[\alpha]^{20}D$ −92.40° (*c* 1.2 in $CHCl_3$) (67%). The lactone **5** was unaffected by treatment with activated manganese dioxide under conditions which converted **3** to the corresponding 15-ketone providing chemical confirmation of the 1→15-lactone formulation (**5**) as opposed to a 1→11-lactone structure.[7]

Application of the lactonization method to prostaglandin $F_{2\alpha}$ itself (1.66 equiv of 2,2′-dipyridyl disulfide, 1.66 equiv of triphenylphosphine in concentrated xylene solution at 25° for 15 hr followed by dilution with xylene and heating at reflux for 8 hr) produced the 1→9-lactone **3** (60% yield) and the 1→15-lactone **5** (16% yield) as major products after chromatographic separation. The R_f values found for **3** and **5** on silica gel thin layer plates using 15% acetone in methylene chloride for development were 0.11 and 0.21, respectively.

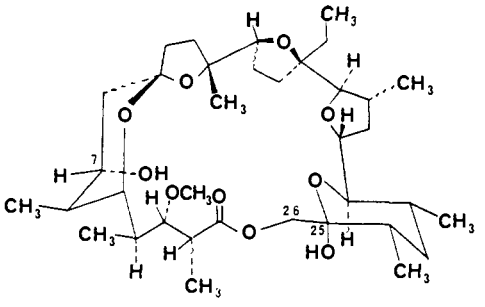
Starting from the 15-(*R*) epimer of **1** and using the same procedure as applied for the sequence **1→2→3**, there was produced in 91% overall yield the 15-(*R*) epimer of **3**[4] mp 117–118°, $[\alpha]^{20}D$ + 80.0° (*c* 2.6 in $CHCl_3$). Similarly starting from the 15-(*R*) epimer of **4** there was obtained the 15-(*R*) epimer of **5**,[4] oil, $[\alpha]^{20}D$ + 62.9° (*c* 0.4 in $CHCl_3$) (50% overall).

To illustrate the application of the macrolactonization process in an even more complex case, the cyclization of the polyether antibiotic monensin (**6**)[8] was chosen for study.



6

Treatment of monensin (free acid) with 2.5 equiv of 2,2′-dipyridyl disulfide and 2.5 equiv of triphenylphosphine in benzene for 17 hr at 25° followed by dilution with benzene and heating at reflux for 17 hr afforded the lactone **7**[4] as a clear, colorless oil soluble in all organic solvents, carbonyl absorption at 1726 ($CHCl_3$) or 1733 cm^{-1} (CCl_4), $[\alpha]^{23}D$ +41.8° (*c* 0.70 in CH_3OH), in 95% yield. The attachment



7

of the carbonyl group through oxygen to the C-26 methylene is clear from the occurrence in the pmr spectrum ($CDCl_3$, 100 MHz) of an AB doublet of doublets due to that methylene with doublet A at δ 3.62 and doublet B at δ 4.38 (J = 11 Hz).[9] Acetylation of **7** with acetic anhydride–pyridine at 80° for 1 hr and 110° for 2 hr affords a crystalline diacetate,[4] mp 225–228°, $[\alpha]^{23}D$ +50.1° (c 0.57 in CH_3OH).

The successful synthesis of the lactones **3**, **5**, and **7** described above demonstrates the utility and potential of the macrolactonization process used in these and earlier[1] studies. Applications to the synthesis of several complex *naturally occurring* macrocyclic lactones are reported in the accompanying paper.[10,11]

References and Notes

(1) E. J. Corey and K. C. Nicolaou, *J. Amer. Chem. Soc.*, **96**, 5614 (1974).
(2) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970).
(3) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Lett.*, 1901 (1970).
(4) Satisfactory (a) infrared and proton magnetic resonance (pmr) data and (b) high resolution mass spectra have been obtained using chromatographically homogeneous samples of this intermediate.
(5) To be described in a subsequent publication.
(6) Prepared from **1** by (a) acetylation with excess acetic anhydride–pyridine together with 0.1 equiv of 4-dimethylaminopyridine *in* methylene chloride at 25° for 15 hr and (b) subsequent depyranylation with HOAc–H_2O–THF (3:1:1) at 45° for 6 hr.
(7) The structure of **5** was also confirmed by the pmr spectrum of it and the mono- and diacetate derivatives.
(8) A. Agtrap, J. W. Chamberlain, M. Pinkerton, and L. Steinrauf, *J. Amer. Chem. Soc.*, **89**, 5737 (1967). We thank the Eli Lilly Co. for a generous supply of monensin.
(9) The observed chemical shift values for H_A and H_B of the C-26 methylene in monensin itself are δ 3.44 and 3.65 (J = 11 Hz). The downfield shift of the C-26 methylene protons of monensin lactone relative to monensin and also the large chemical shift between H_A and H_B in the lactone argue persuasively for structure **7** and against the isomeric 1→7 or 1→25 lactones. Structure **7** is also supported by the occurrence of a singlet due to one of the OH groups and a doublet due to the other in the pmr spectrum of **7** (in $CDCl_3$).
(10) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Amer. Chem. Soc.*, following paper.
(11) This research was assisted by a grant from the National Institutes of Health.

E. J. Corey,* K. C. Nicolaou, Lawrence S. Melvin, Jr.
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

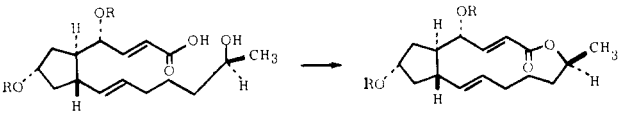
Received October 15, 1974

Synthesis of Brefeldin A, Carpaine, Vertaline, and Erythronolide B from Nonmacrocyclic Precursors

Sir:

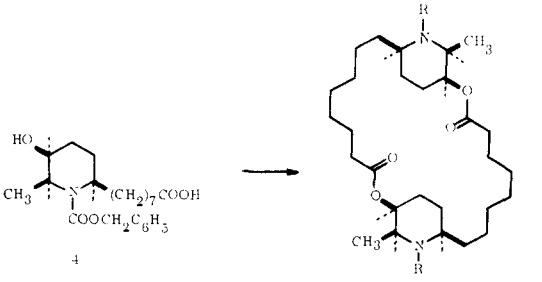
An effective new method for the synthesis of macrocyclic lactones has recently been developed in these laboratories based on a strategy of simultaneous activation of both hydroxyl and carboxyl groups toward lactonization.[1,2] We describe herein the application of this "double activation" method to the partial synthesis of four complex, naturally occurring macrocyclic substances from nonmacrocyclic hydroxy acids. These examples provide further evidence for the power of the double activation approach and, moreover, demonstrate that its use can lead to a profound simplification of the problem of synthesis of macrocyclic lactones, an increasingly important class of biologically active molecules.

The bistetrahydropyranyl ether of A-brefeldinoic acid **1**[3,4] was converted to brefeldin A (**3**)[5] in good yield in two steps. The 2-pyridinethiol ester of **1** was generated by reaction with 2,2′-dipyridyl disulfide (1.6 equiv) and triphenylphosphine[1] (1.6 equiv) in concentrated xylene solution at 25° for 15 hr, and the solution was diluted with xylene (100 ml/g of **1**) and added by motor-driven syringe over 10 hr with exclusion of oxygen (argon atmosphere) to refluxing xylene. The reaction was complete after an additional 10 hr at reflux and afforded after chromatography on silica gel the bis(tetrahydropyranyl) ether of brefeldin A (**2**) as a colorless oil,[4] $[\alpha]^{20}D$ +12.90° (c = 3.25 in $CHCl_3$), in 70% yield. Deprotection of **2** using acetic acid:water:tetrahydrofuran (THF) (3:3:2) at 50° for 5 hr gave in 97% yield brefeldin A, mp and mixed mp 204–205°, $[\alpha]^{20}D$ +91.15° (c = 1.3 in CH_3OH), which was chromatographically and spectroscopically[4] identical with an authentic specimen.



1, R = THP
2, R = THP
3, R = H

N-Benzyloxycarbonyl carpamic acid,[4,6] $[\alpha]^{20}D$ −9.36° (c = 4.40 in $CHCl_3$), a colorless oil, when subjected to the lactonization process described above for **1** → **2** yielded the bisbenzyloxycarbonyl derivative of carpaine **5**[4] in >50% yield. Hydrogenation of **5** in absolute ethanol containing a small amount of hydrochloric acid over Pd–C catalyst (1 atm H_2, 25°, 15 hr) quantitatively produced carpaine **6**,[7] mp and mmp 120–121°, $[\alpha]^{20}D$ +20.26° (c = 1.9 in $CHCl_3$), which was chromatographically and spectroscopically identical with an authentic sample. The preferential formation of cyclic diesters (dilides) such as carpaine has been observed previously[1] in special cases. There was no evidence for the formation of a monolactone in the cyclization of **4** described above.



4

5, R = $COOCH_2C_6H_5$
6, R = H

Exposure of the hydroxy acid **7**[4,8] to the lactonization process described above for **1** → **2** resulted in formation of the Lythraceae alkaloid vertaline (**8**),[4,9] mp, mmp 198–200°, $[\alpha]^{20}D$ −165.50° (c = 0.80 in $CHCl_3$), chromatographically and spectroscopically identical with an authentic specimen, in 67% yield.[10]