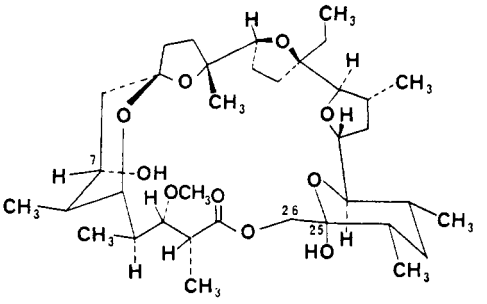

7

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.

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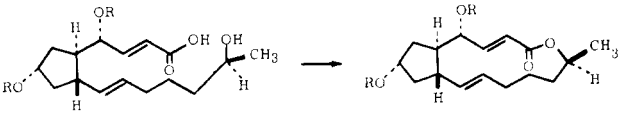
Synthesis of Brefeldin A, Carpaine, Vertaline, and Erythronolide B from Nonmacrocyclic Precursors

Sir:

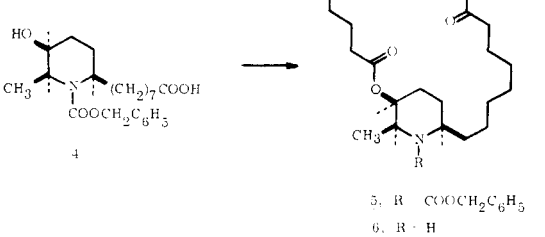
An effective new method for the synthesis of macrocyclic lactones has recently been developed in these laboratories based on a strategy of simultaneous activation of both hydroxyl and carboxyl groups toward lactonization.[1,2] We describe herein the application of this "double activation" method to the 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

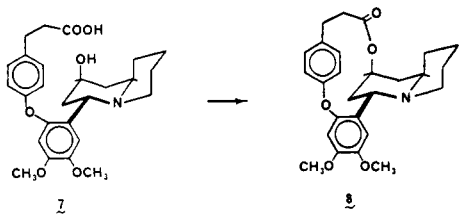
N-Benzyloxycarbonyl carpamic acid,[4,6] $[\alpha]^{20}D$ −9.36° (c = 4.40 in $CHCl_3$), a colorless oil, when subjected to the lactonization process described above for **1** → **2** yielded the bisbenzyloxycarbonyl derivative of carpaine **5**[4] in >50% yield. Hydrogenation of **5** in absolute ethanol 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

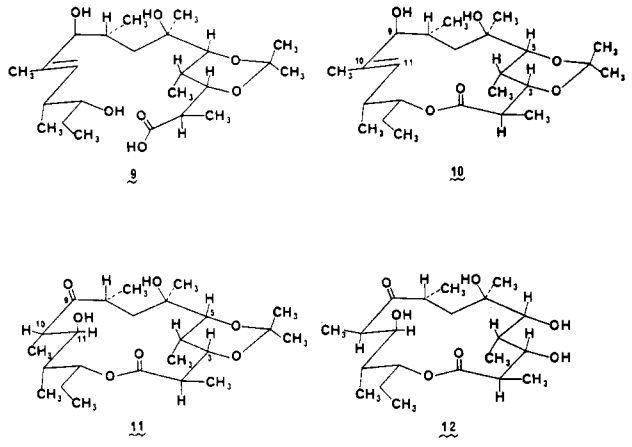
5, R = $COOCH_2C_6H_5$
6, R = H

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]



7 8

Erythronolide B (**12**), the aglycone of the antibiotic erythromycin, has been synthesized from the protected acyclic hydroxy acid **9** by application of the double activation method.[11] Treatment of **9** in THF with 2 equiv of 2,2′-dipyridyl disulfide and 2 equiv of triphenylphosphine for 22 hr at 25° led to the 2-pyridinethiol ester which could be isolated in 88% yield and which upon heating at reflux in xylene (under argon) at *ca.* 0.002 *M* concentration for 72 hr afforded the macrocyclic lactone **10,** identical with the material prepared in three steps from erythronolide[11] in 36% yield.[12] The conversion of **10** to erythronolide B[4] was effected by the sequence: (1) selective oxidation with manganese dioxide in methylene chloride to form the $\Delta^{10,11}$-en-9-one, mp 117°,[11] in 98% yield; (2) epoxidation of the 3,5-acetonide, $\Delta^{10,11}$-en-9-one by a large excess of 30% hydrogen peroxide in methanol containing 5 equiv of sodium hydroxide (per equivalent of enone) at 10° for 1 hr and 25° for 12 hr to form quantitatively 10(*R*), 11(*S*)-oxide,[4] mp 121–121.5°, $[\alpha]^{23}D$ +7.8° (*c* = 2 in CH_3OH); (3) reduction of the oxide with hydrogen (1 atm) over Pd–C catalyst in methanol containing a little sodium bicarbonate for 22 hr at 25° to form in 77% yield the 3,5-acetonide of 10-epi erythronolide B (**11**);[4] (4) epimerization of **11** at C-10 (potassium carbonate in aqueous methanol); and (5) acid-catalyzed hydrolysis of the acetonide (1:1 THF:1 *N* hydrochloric acid at 25°).



9 10

11 12

Studies in this area are continuing with the aim of achieving total syntheses of several naturally occurring macrocycles, including brefeldin A and erythronolide B, and also of improving and extending the double activation method.[13]

References and Notes

(1) E. J. Corey and K. C. Nicolaou, *J. Amer. Chem. Soc.*, **96,** 5614 (1974).
(2) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Amer. Chem. Soc.*, preceding paper.
(3) Prepared by treatment of brefeldin A (**3**) with 3 equiv of dihydropyran in methylene chloride in the presence of a catalytic amount of *p*-toluenesulfonic acid (initially at 0° then at 25° for 4 hr) to give the bis(tetrahydropyranyl) ether **2** (100%), followed by saponification of **2** with 0.13 *N* lithium hydroxide in 3:1 methanol:water at 50° for 20 hr (100%).
(4) Satisfactory infrared, proton magnetic resonance (pmr), and mass spectral data were obtained on a chromatographically homogeneous sample of this intermediate.
(5) See H. P. Weber, D. Hauser, and H. P. Sigg, *Helv. Chim. Acta*, **54,** 2763 (1971), for structure. We are indebted to Dr. Sigg for a generous gift of brefeldin A.
(6) Prepared from naturally derived carpaine (**6**) (gift of Dr. James L. Coke) by reaction with excess benzylchloroformate in 2:1 THF—4 *N* sodium hydroxide at 0° to form **5**,[4] $[\alpha]^{20}D$ −17.00° (*c* = 8.35 in $CHCl_3$), and subsequent hydrolysis with 0.3 *N* lithium hydroxide in 3:1 methanol—water at 70° for 20 hr.
(7) For the structure see (a) M. Spiteller-Friedman and G. Spiteller, *Monatsh. Chem.*, **95,** 1234 (1964); (b) J. L. Coke and W. Y. Rice, Jr., *J. Org. Chem.*, **30,** 3420 (1965), and references cited therein.
(8) Prepared from naturally derived vertaline (gift of Dr. James P. Ferris) by saponification with 20% aqueous sodium hydroxide:dimethyl sulfoxide (1:2) at 120° for 5 hr.
(9) For structure see (a) J. A. Hamilton and L. K. Steinrauf, *J. Amer. Chem. Soc.*, **93,** 2939 (1971); (b) J. P. Ferris, *J. Org. Chem.*, **27,** 2985 (1962); **28** 817 (1963).
(10) Since there was available to us only enough of the hydroxy acid **7** (15 mg) to permit a single small-scale cyclization experiment, it seems likely that substantially higher yield can be realized. The conversion of (±)-**7** to (±)-vertaline (**8**) in 41% yield by acid-catalyzed lactonization has recently been reported; see M. Hanaoka, N. Ogawa, and Y. Arata, *Chem. Pharm. Bull.*, **22,** 973 (1974). The acid–lactonization process has also been reported for other members of the Lythraceae series with yields being either low or unspecified; see (a) B. Loev, I. Lantos, and H. Van Hoeven, *Tetrahedron Lett.*, 1101 (1974); (b) M. Hanaoka, N. Ogawa, and Y. Arata, *ibid.*, 2355 (1973); and (c) M. Hanaoka, H. Sassa, N. Ogawa, Y. Arata, and J. P. Ferris, *ibid.*, 2533 (1974).
(11) The oily acid **9**[4] was prepared from naturally derived erythronolide B by the following sequence: (1) conversion of erythronolide B to the 3,5-acetonide,[4] mp 81.5°, $[\alpha]^{23}D$ −84.4° (*c* = 2 in CH_3OH), by reaction with 2-methoxypropene (4 equiv) in methylene chloride containing 0.7 mole % of phosphorus oxychloride at 25° for 168 hr; (2) dehydration at the β-ketol unit in the acetonide to form the $\Delta^{10,11}$ olefin,[4] mp 117°, uv_{max} 231 nm (ε 12,200); (3) reduction of the 9-keto group by 2 molar equiv of sodium borohydride in methanol at 0° to form the 3,5-acetonide, $\Delta^{10,11}$-en-9-ol **10**[4]; and (4) saponification using dimethyl sulfoxide—5.4 *N* sodium hydroxide (4:3) at 110° for 5 hr.
(12) Improvements in the efficiency of this process will be sought in further experimentation. It should be noted, however, that this represents the first successful cyclization to an erythromycin aglycone system and that, further, the cyclization was achieved without protection of the hydroxyl groups at C-6 or C-9.
(13) This investigation was assisted in part financially by a grant from the National Institutes of Health.

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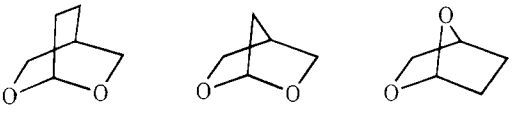
2,6- and 2,7-Dioxabicyclo[2.2.1]heptanes

Sir:

Recently[1] we reported the synthesis of a highly reactive bicyclic acetal, 2,6-dioxabicyclo[2.2.2]octane (**1**), the parent of a new ring system. We now report the synthesis of the next lower homolog, 2,6-dioxabicyclo[2.2.1]heptane (**2**), also the parent of a new ring system. Additionally we report the synthesis of the isomeric bicyclic acetal 2,7-dioxabicyclo[2.2.1]heptane (**3**), the parent of a much-investigated group of sugar derivatives.[2]



1 2 3

Alkylation of dimethyl malonate with bromoacetaldehyde diethyl acetal, followed by lithium aluminum hydride reduction, gave diol diacetal **4.** Bicyclization of this intermediate was performed in dilute dioctyl phthalate solution under high vacuum at 110° with a trace of *p*-toluenesulfonic acid as catalyst and condensation of the distillate at liquid nitrogen temperature. Compound **2** was obtained in 58% yield after distillation, bp 63–64° (30 mm).[3]

$$(HOCH_2)_2CHCH_2CH(OC_2H_5)_2 \xrightarrow{H^+} 2$$

4

Diol **5** was prepared according to the literature procedures used for the corresponding diethyl acetal.[4] Applica-