may curl back to protonate the leaving group or it may be hydrogen bonded to the charged phosphate oxygens. Evidence that the roles of the imidazolium ions are those shown in Figures 2 and 3 is the finding that the pH–rate maximum for **2** comes at approximately its titration pK_a, but that for **6** is almost 1 pH unit higher than its titration pK_a of 6.1. This would indicate stabilization of the imidazolium ion by the bound phosphate anion in **6**, but not in **2**. If the imidazolium ion in **6** catalyzes the hydrolysis by such phosphate binding, it would be playing the role of lysine-41 in ribonuclease. Because of the flexibility in **5** and **6**, the specificity in the cleavage of **1** is particularly striking.

(12) For an earlier example in which high specificity accompanied relatively modest catalytic acceleration, cf. Breslow, R.; Campbell, P. *Bioorg. Chem.* **1971**, *1*, 140–156.

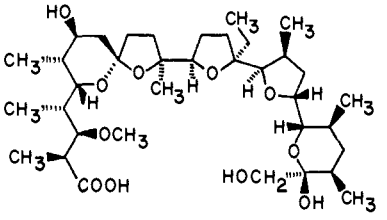
(13) Support of this work by the National Institutes of Health is gratefully acknowledged.

Ronald Breslow,* Philippe Bovy, Carol Lipsey Hersh
Department of Chemistry, Columbia University
New York, New York 10027
Received November 9, 1979

Synthesis of the Polyether Antibiotic Monensin. 1. Strategy and Degradations[1]

Sir:

The polyether antibiotics constitute a growing class of naturally occurring ionophores having a variety of useful biological properties and a degree of stereochemical complexity as yet unsurpassed by other natural products with an all-carbon backbone.[2] One of these materials, a compound named monensin (**1**), has acquired special significance since it was the first



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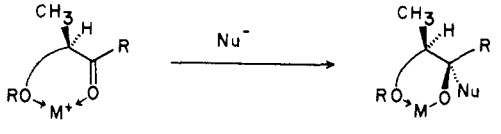
polyether antibiotic to have its structure determined and also to find its way to the marketplace.[3] The utility of monensin, as well as its challenging array of 17 asymmetric centers, has attracted considerable attention since its discovery, and during the years 1977–1978 serious synthetic programs started up at Harvard and here at Columbia. Earlier this year Kishi and co-workers reported their results.[4] In this series of papers we describe our work on a highly convergent synthesis of monensin starting from simple optically active compounds.

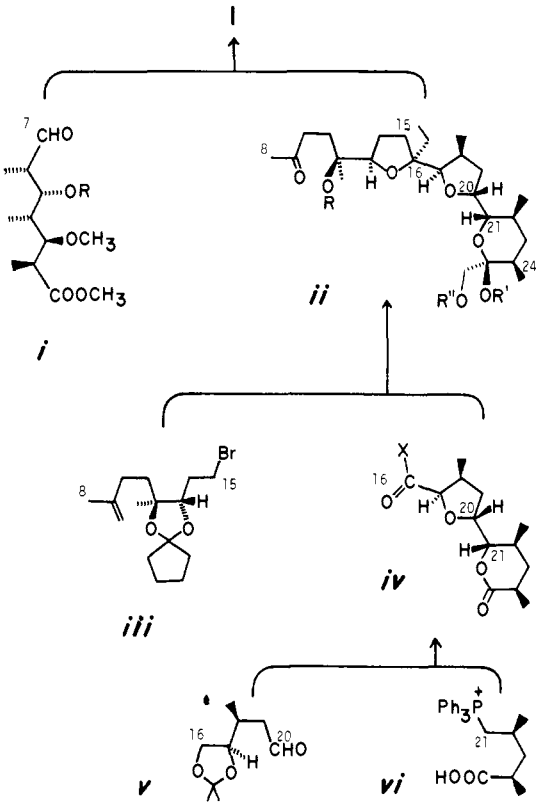
As outlined in the Scheme I, our synthesis is designed to be convergent at several levels. In addition to the usual logistical attractions of convergency, this scheme has a distinct stereochemical advantage. As applied here it allows monensin to be broken down retrosynthetically into fragments (i, iii, and v) containing only vicinal asymmetric centers so that most of the remote stereorelationships may be built up synthetically by coupling fragments having the proper absolute configuration. The remaining remote asymmetric centers (C-9 and C-24) are easily controlled by their environment on substituted six-membered rings. To avoid potentially tedious resolutions of the required intermediates, the synthesis begins with (−)-malic acid (→ iii) and (+)-β-hydroxyisobutyric acid[5] (→ i, v,[6] and vi).

The stereochemical problems in monensin are thus reduced to the formation of vicinal stereorelationships with control by preexisting asymmetric centers. One reaction which has proven especially useful in this context is the chelation-controlled nucleophilic addition shown in eq a.[7] We have studied this



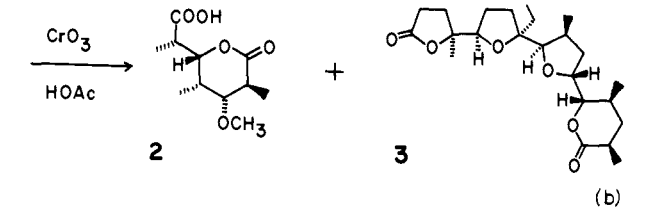
(a)

Scheme I



reaction in some detail and have found general methods for controlling the stereochemistry of the addition to the extent of ≥50:1 with Grignard reagents.[8] It should be noted that the stereochemistry produced by this type of operation is opposite to the usual Cram's rule[9] (steric control) prediction in cases where the chain bearing -OR is more sterically demanding than methyl. For this reason, stereoselection of the type shown has commonly been referred to as "anti-Cram" as well as "chelation controlled".

To secure materials for structure proof of advanced synthetic intermediates and to enrich our supplies of these valuable compounds, a monensin degradation–reconstruction program was undertaken. The primary degradation was achieved by chromic acid as reported with the original structure elucidation[10] (eq b).



(b)

The lactonic acid **2** was converted into the left fragment of monensin (i, Scheme I) in six steps. Reduction via the mixed carbonic anhydride (EtO_2CCl, Et_3N) with sodium borohydride in wet ether[11] (4 h, 25 °C) gave the corresponding primary alcohol which was protected with benzyl chloromethyl ether (*i*-Pr_2NEt). Saponification (LiOH-H_2O-THF) followed by acidification (excess NaH_2PO_4, 0 °C) and immediate in situ methylation (CH_2N_2) then gave the acylic ester **4** (78% from **2**) (eq c). Although the hindered secondary alcohol resisted protection with trialkylsilyl chlorides under the usual conditions, triethylsilyl perchlorate[12] (C_5H_5N, CH_3CN, 0 °C) added cleanly and rapidly. Finally hydrogenolysis (10% Pd/C, H_2, Et_2O) and oxidation ($CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2) gave the left fragment of monensin as the triethylsilyl ether **5**[14] (86% from **4**).

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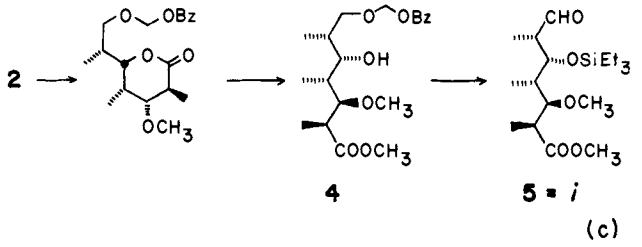
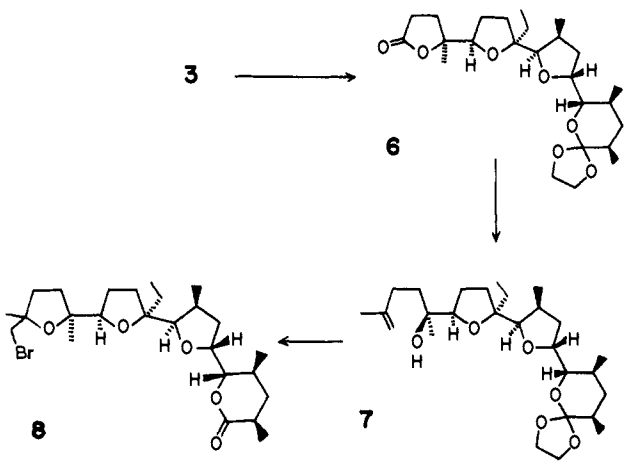


To convert the tetracyclic dilactone **3** into intermediates in our synthetic scheme, it was first necessary to chemically distinguish the γ- and the δ-lactone. This operation was readily effected with ethylene glycol (p-TsOH, $HC(OMe)_3$, 25 °C) to give a monoortho lactone (**6**, 60%[13]). As outlined in the Schemes II and III, **6** is a particularly useful material since it is readily transformed into advanced intermediates on our synthetic pathway. A key precursor of ii (Scheme I) was prepared as follows. Conversion into the methyl ketone (1.2 equiv of MeLi, THF, −78 °C) and methylenation (Ph_3PCH_3Br, BuLi, THF) gave the olefinic alcohol **7** in 73% yield. Simultaneous cyclization and deprotection was effected with N-bromosuccinimide and p-toluenesulfonic acid (CH_2Cl_2, 0 °C) to produce a synthetic intermediate,[14] the bromomethyl tetrahydrofuran **8** (96%).

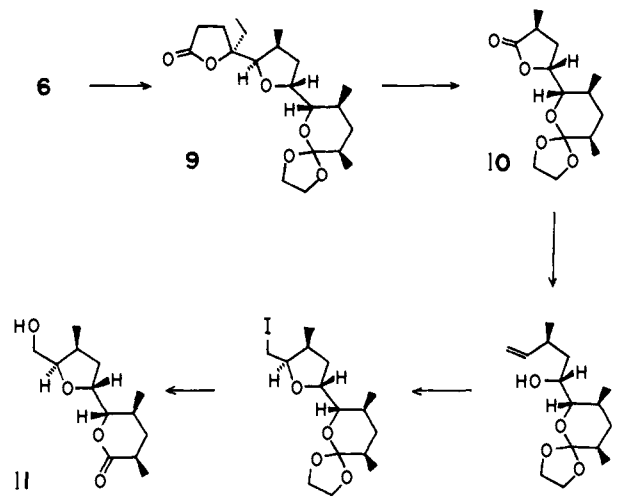
Tetracyclic ortho lactone **6** is also useful for preparation of the lower level bicyclic intermediate iv (Scheme I). The required degradation was accomplished by two sequential oxidative cleavages of a 1,2-hydroxy ether. Thus addition of excess methyllithium to **6** (Et_2O, 80%) gave a dimethylcarbinol which was fragmented (excess $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2, 10 h) into the corresponding tricyclic ortho lactone **9** (74%). Repetition of the degradation sequence gave the bicyclic ortho lactone **10** (74%). Replacement of the missing carbon was readily accomplished by reduction (Dibal, $PhCH_3$, −78 °C) and Wittig methylenation (Ph_3PCH_3Br, BuLi, THF) in 84% yield. Cyclization (N-iodosuccinimide, CH_2Cl_2, 0 °C) gave the β-iodomethyltetrahydrofuran with 4:1 stereoselectivity (β:α iodomethyl)[15] (94%). The major isomer was separated by medium pressure LC on silica gel and converted into the corresponding alcohol by benzoate displacement ($PhCO_2H$, DBU, DMF) and reduction ($LiAlH_4$, Et_2O) (40%). Finally, deprotection with p-toluenesulfonic acid in wet methylene chloride (0 °C) gave **11** (98%).[14]

The accompanying communications describe intermediates **5, 8,** and **11** in terms of their synthesis and use for the preparation of monensin.

Scheme II



Scheme III



References and Notes

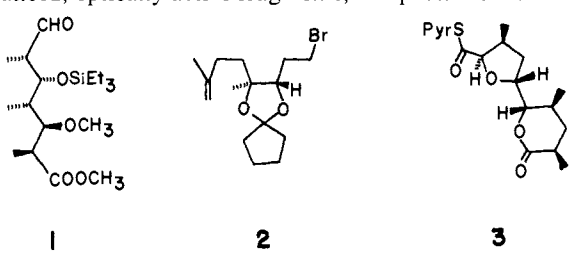
(1) This work was described at the Sixth International Symposium on Synthesis in Organic Chemistry in Cambridge, England, on July 25, 1979.
(2) Reviews: J. W. Westley, *Annu. Rep. Med. Chem.*, **10**, 246 (1975); B. C. Pressman, *Annu. Rev. Biochem.*, **45**, 601 (1976); J. W. Westley, *Adv. Appl. Microbiol.*, **22**, 177 (1977).
(3) A. Agtarap, J. W. Chamberlain, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, **89**, 5737 (1967).
(4) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979); T. Fukuyama, C.-L. J. Wang, and Y. Kishi, *ibid.*, **101**, 260 (1979); T. Fukuyama, K. Akasaka, D. S. Karanewsky, G. Schmid, and Y. Kishi, *ibid.*, **101**, 262 (1979).
(5) C. T. Goodhue, and J. R. Schaeffer, *Biotechnol. Bioeng.*, **13**, 203 (1971). We thank Dr. Noal Cohen of Hoffmann-La Roche for a generous supply of this material.
(6) Although we have prepared v from (+)-β-hydroxyisobutyric acid, a synthesis starting from (*R*)-citronellic acid [J. Plesek, *Collect. Czech. Chem. Soc.*, **22**, 644 (1957)] has proven much more serviceable.
(7) Cyclic chelation model: D. J. Cram, and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); D. J. Cram, and D. R. Wilson, *ibid.*, **85**, 1245 (1963).
(8) W. C. Still, J. H. McDonald, and J. Schneider, *Tetrahedron Lett.*, in press.
(9) N. T. Ahn, and O. Eisenstein, *Nouv. J. Chim.*, **1**, 61 (1977), and references cited therein; ref 7.
(10) We thank Dr. J. W. Chamberlain at Eli Lilly and Co. for the detailed experimental procedure.
(11) Alcoholic solvents caused extensive epimerization.
(12) T. J. Barton and C. R. Tully, *J. Org. Chem.*, **43**, 3049 (1978), and references cited therein.
(13) The actual yield may be considerably higher than 60% since the starting tetracyclic dilactone could not be totally purified.
(14) The synthesis of this compound as the enantiomer shown is described in the accompanying communication.
(15) The stereochemistry of the major isomer was proven by an alternate degradation of **9** which left the C-16,C-17 bond intact. Analogous stereoselectivity is observed in closely related kinetic iodolactonizations: P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
(16) Alfred P. Sloan Fellow, 1978–1980.

David B. Collum, John H. McDonald, III
W. Clark Still*[16]
Department of Chemistry, Columbia University
New York, New York 10027
Received October 22, 1979

Synthesis of the Polyether Antibiotic Monensin. 2. Preparation of Intermediates[1]

Sir:

As described in the first paper of this series, our approach to monensin is based on the synthesis and coupling of three advanced, optically active fragments, compounds **1–3.** In this



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