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.

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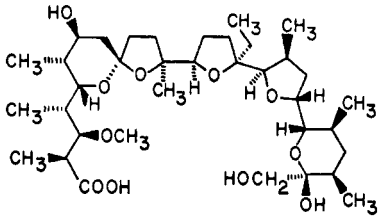
Synthesis of the Polyether Antibiotic Monensin. 1. Strategy and Degradations[1]

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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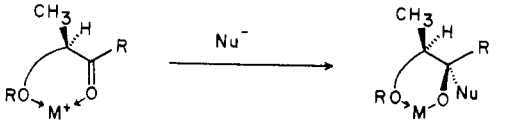
polyether antibiotic to have its structure determined and also to find its way to the marketplace.[3] The utility of monensin, as well as its challenging array of 17 asymmetric centers, has attracted considerable attention since its discovery, and during the years 1977–1978 serious synthetic programs 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.

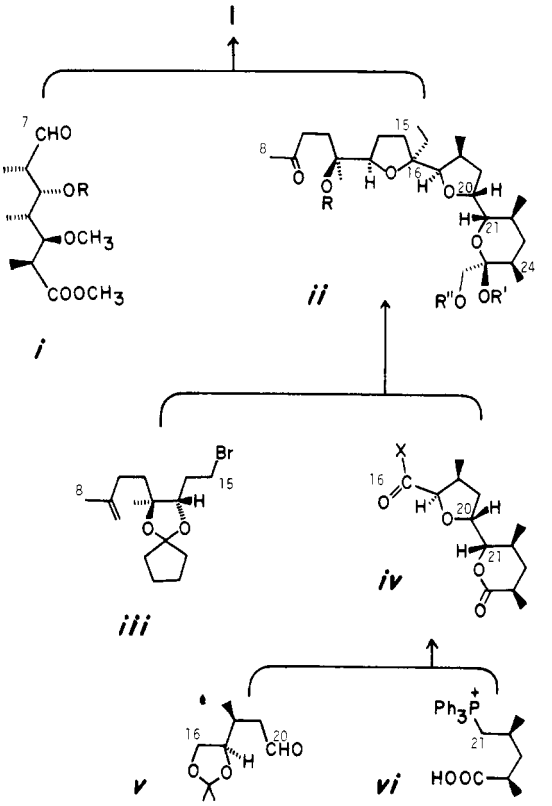
As outlined in the Scheme I, our synthesis is designed to be convergent at several levels. In addition to the usual logistical attractions of convergency, this scheme has a distinct stereochemical advantage. As applied here it allows monensin to be broken down retrosynthetically into fragments (i, iii, 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



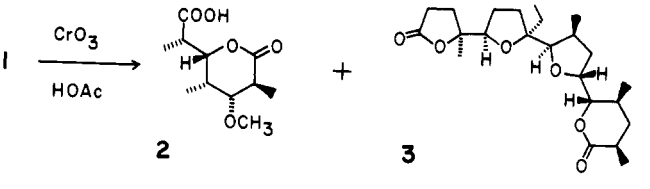
(a)

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·$2C_5H_5N$, CH_2Cl_2) gave the left fragment of monensin as the triethylsilyl ether **5**[14] (86% from **4**).

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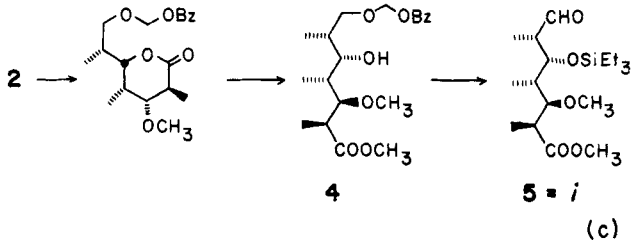
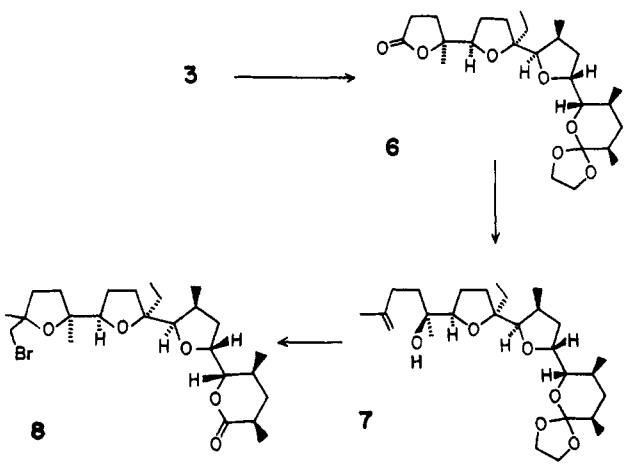


To convert the tetracyclic dilactone **3** into intermediates in our synthetic scheme, it was first necessary to chemically distinguish the γ- and the δ-lactone. This operation was readily effected with ethylene glycol (*p*-TsOH, $HC(OMe)_3$, 25 °C) to give a monoortho lactone (**6**, 60%[13]). As outlined 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%).

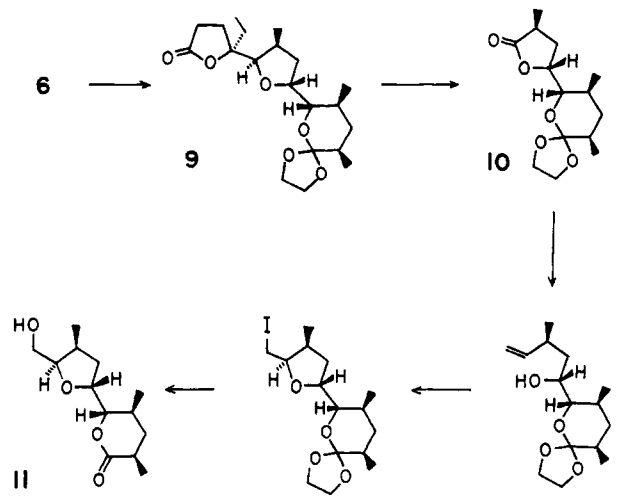
Tetracyclic ortho lactone **6** is also useful for preparation of the lower level bicyclic intermediate iv (Scheme I). The required degradation was accomplished by two sequential oxidative cleavages of a 1,2-hydroxy ether. Thus addition of excess methyllithium to **6** (Et_2O, 80%) gave a dimethylcarbinol 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).
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(16) Alfred P. Sloan Fellow, 1978–1980.

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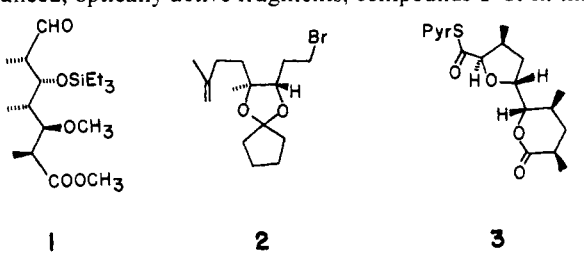
Synthesis of the Polyether Antibiotic Monensin. 2. Preparation of Intermediates[1]

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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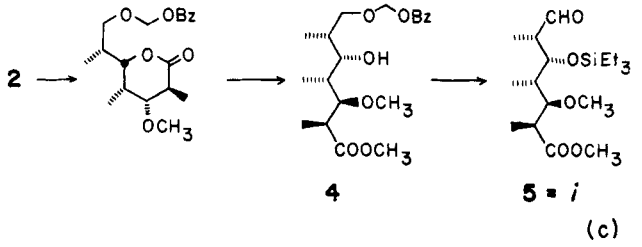

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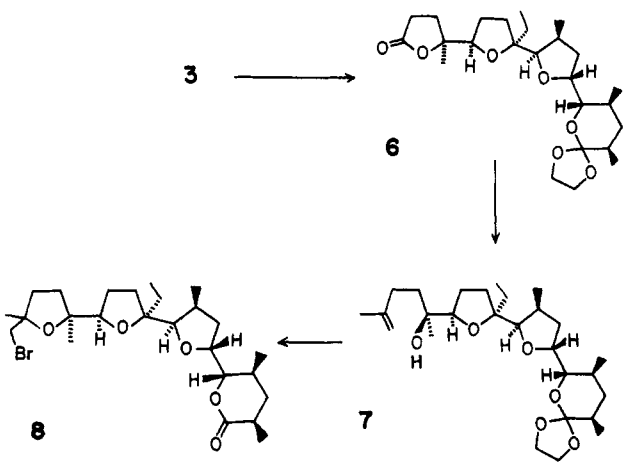
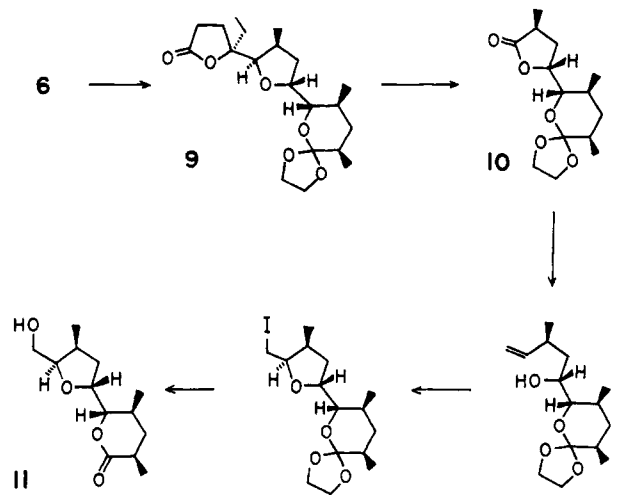
Scheme II



Scheme III



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

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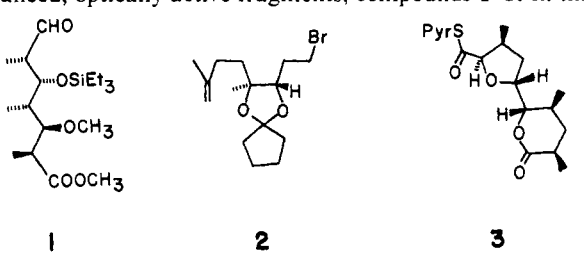
As described in the first paper of this series, our approach to monensin is based on the synthesis and coupling of three advanced, optically active fragments, compounds **1–3.** In this



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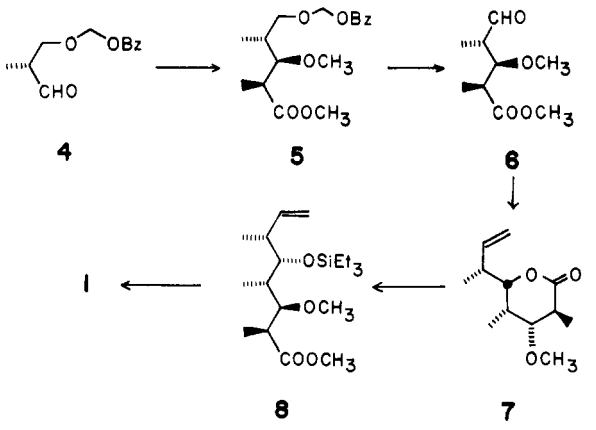
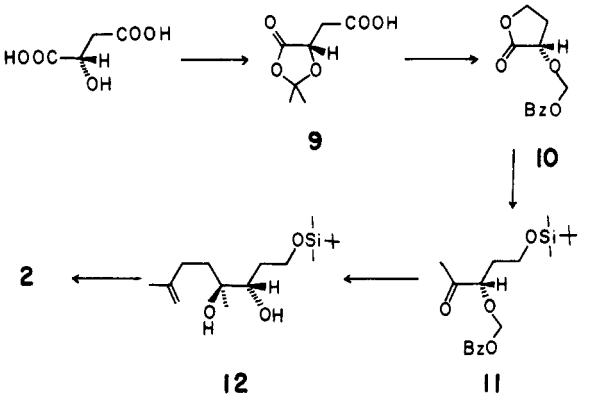
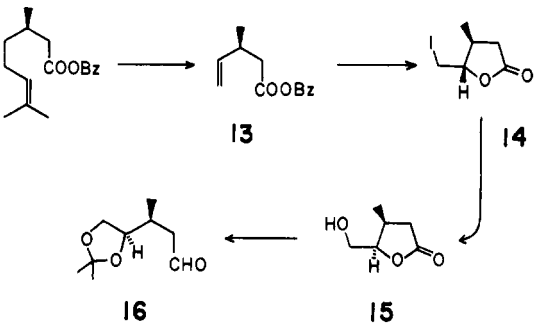
Scheme I



Scheme II



Scheme III



paper, we describe the preparation of these materials from simple, optically active starting materials.

Synthesis of the left-hand fragment (**1**) of monensin began with benzyloxymethyl-protected (*R*)-β-hydroxyisobutyraldehyde[2] (**4**) (Scheme I). Kinetic[3] aldolization with the magnesium bromide enolate [(a) $LiNiPr_2$, THF; (b) $MgBr_2$] of 2-methyl-2-trimethylsilyloxy-3-pentanone[4] at −110 °C produced a 5:1 mixture of diastereomeric aldols in which the major product was that predicted by chelation-controlled (anti-Cram) α induction (85% yield). The mixture was oxidatively converted (H_5IO_6, MeOH) into the corresponding β-hydroxy acid and methylated as the dianion [(a) $KN(TMS)_2$; (b) $(CH_3)_2SO_4$] to give **5** in 50% overall yield. Removal of the minor diastereomer was accomplished at this point by medium pressure LC on silica gel. Hydrogenolysis (10% Pd/C, H_2, THF) and oxidation ($CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2) then gave a new aldehyde, **6** (90%), suitable for a second aldol-type reaction. In contrast to the above conversion of **4** into **5**, this second aldol was required to proceed via Cram's rule (steric) α induction. Thus, the relatively bulky, branched nature of C-3 had to override the chelating ability of the C-3 methoxyl if the required stereochemistry at C-5 and C-6 was to be obtained. The aldol-like reaction was conducted using *cis*-2-butenyldiethylaluminum[5] (THF, −78 °C) as a propanal enolate equivalent and was found to produce an ~3:1 mixture of diastereomers. The major isomer was readily separated by flash chromatography[6] and was shown to have structure **7** by its conversion [(a) O_3, acetone; (b) Jones reagent] into the lactonic acid prepared previously by degradation of monensin.[7] Lactone **7** was then opened [(a) LiOH, THF, H_2O; (b) CH_2N_2] and silylated ($Et_3SiOClO_3$, CH_3CN, C_5H_5N)[8] to produce **8.** Finally, ozonolysis (MeOH, −78 °C) with a dimethyl sulfide–pyridine workup gave **1** (>95% from **7**). This material was shown to be identical with authentic **1** prepared from monensin as described in the first paper in this series.

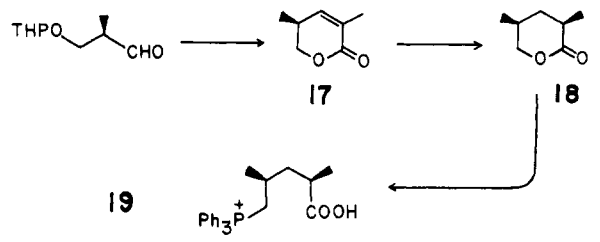
The central fragment (**2**) of monensin was prepared from (*S*)-(−)-malic acid as outlined in Scheme II. Thus the highly crystalline acetonide **9** (mp 107–108 °C, CCl_4) was obtained in 75–85% yield using 2,2-dimethoxypropane and *p*-toluenesulfonic acid. Reduction of the terminal carboxylic acid (BH_3, THF), followed by acidification, led to a hydroxybutyrolactone which was protected with benzyl chloromethyl ether (*i*-Pr_2NEt) to give **10** (75%). Reaction with methylmagnesium bromide (THF, −78 °C) stopped cleanly after the addition of 1 equiv of reagent and the product hemiketal was protected as the primary silyl ether (*t*-$BuMe_2SiCl$, DMF, imidazole) **11.** Since ketone **11** has the necessary features for chelation-controlled nucleophilic addition to the carbonyl, it would be expected that a Grignard reaction would produce largely the product resulting from the less-hindered β addition to the conformation shown. In fact, the addition of 3-methyl-3-butenylmagnesium bromide (THF, −78 °C) to **11** produced a 50:1 mixture of diastereomers[9] in which the major product had the anticipated threo stereochemistry.[10] Lithium–ammonia debenzylation (−78 °C, 3 min) gave diol **12** (70% from **10**). Finally, protection (cyclopentanone, *p*-TsOH, $CuSO_4$)[11] and bromination (NBS, Ph_3P) led to **2**[12] (71%).

Construction of the remaining substructure of monensin, the right-hand fragment **3,** was somewhat more involved than the syntheses described above since **3** contains remote as well as vicinal stereocenters. To obtain the desired remote stereochemical relationships as well as to facilitate overall construction, a convergent approach was adopted which involved coupling two optically active subfragments. These materials were synthesized as described below.

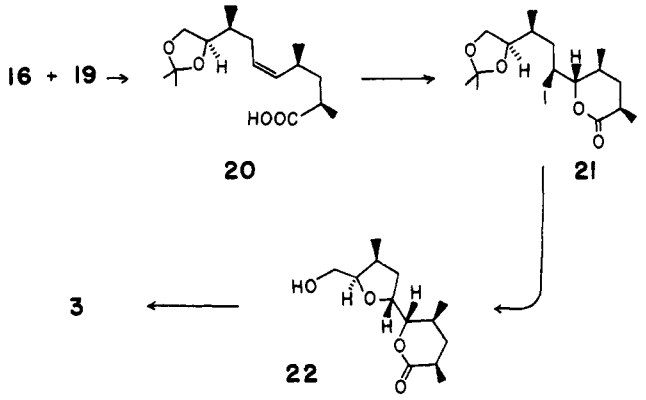
The first subfragment (**16**) corresponding to C-16–C-20 of monensin was prepared starting with the benzyl ester of (*R*)-citronellic acid (Scheme III).[13] Ozonolysis in acetone (−78 °C), followed by oxidative workup (Jones reagent, −78 → 0 °C), gave an acid which was oxidatively decarboxylated [$Pb(OAc)_4$, $Cu(OAc)_2$, C_6H_6, 80 °C][14] to **13** (72% at 80% conversion). Saponification (KOH, MeOH, H_2O) and thermodynamic iodolactonization[15] (I_2, CH_3CN, −15 °C, 72 h) gave **14** (89%) with stereoselectivity on the order of 20:1. Inversion at C-17 was effected by addition of the potassium salt of benzyl alcohol (THF, −20 °C) to produce an intermediate epoxy benzyl ester which spontaneously relactonized to **15** on hydrogenolysis (10% Pd/C, H_2, Et_2O) (84% yield). Finally reduction ($LiAlH_4$, Et_2O), acetonide formation [$(CH_3)_2CO$, $CuSO_4$, *p*-TsOH], and oxidation ($CrO_3{\cdot}C_5H_5N{\cdot}HCl$, CH_2Cl_2) gave the desired subfragment **16** (80% from **15**).

The second subfragment (**19**) corresponding to C-21–C-25 of monensin was prepared from the tetrahydropyranyl ether of (*R*)-β-hydroxyisobutyraldehyde (Scheme IV).[2] Addition of the lithium enolate of ethyl propionate ($LiNiPr_2$, THF, −78 °C) gave an aldol which was refluxed with excess *p*-toluenesulfonic acid in benzene for 8 h to produce the unsaturated lactone **17**[16] (50%). Catalytic reduction with 5% rhodium on alumina (Et_2O, −10 °C) gave the corresponding dimethyl-

Scheme IV



Scheme V



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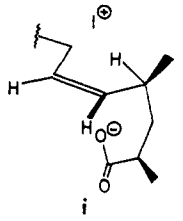

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Synthesis of the Polyether Antibiotic Monensin. 3. Coupling of Precursors and Transformation to Monensin[1]

Sir:

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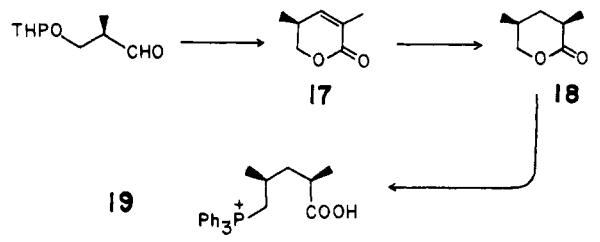
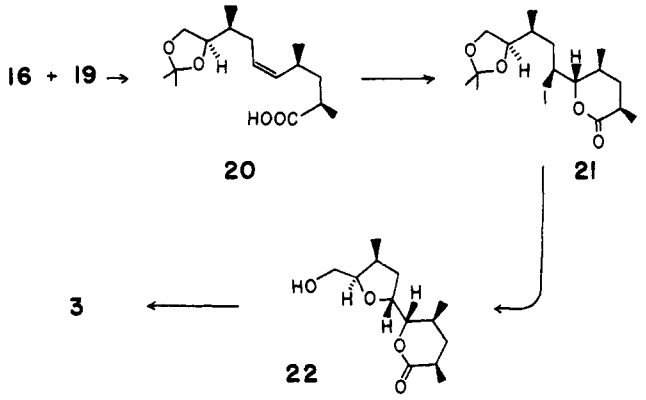
Scheme IV



Scheme V



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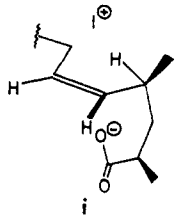

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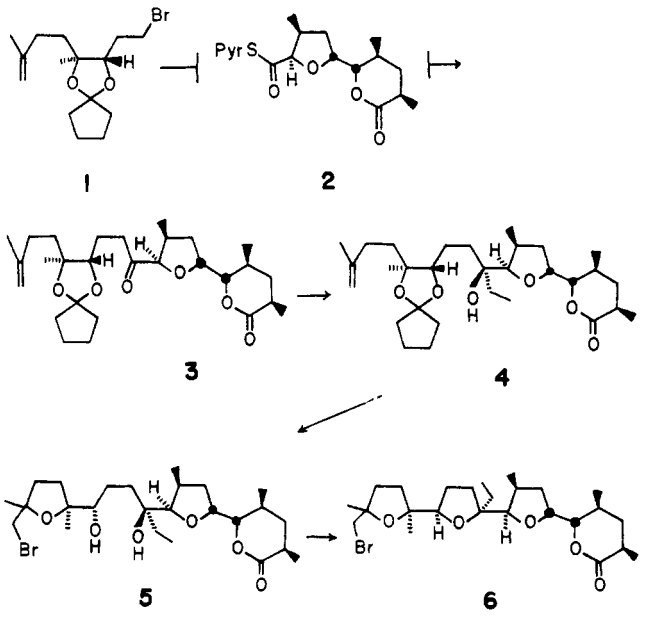
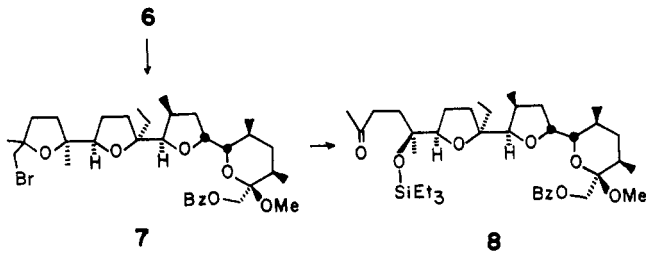
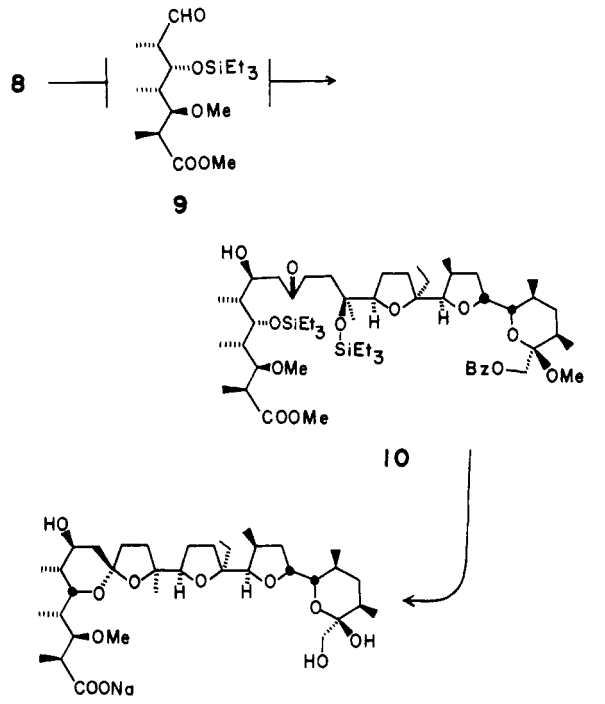


Scheme II



Scheme III



of the C-12,C-16-tertiary hydroxyls (NBS, *p*-TsOH, CH_2Cl_2, 0 °C); (2) mesylation of the C-13 secondary hydroxyl (MsCl, Et_3N, CH_2Cl_2, 0 °C); and (3) solvolysis in buffered trifluoroethanol (NaOAc, 60 °C). The resulting tetracyclic lactone **6** was shown to be identical[6] with material derived from natural monensin as described previously.[2]

There remained several operations to be carried out on **6** before the final coupling to the left-hand fragment (C-1–C-7) could be effected. These operations involved addition of a methanol carbanion equivalent (C-26) to the lactone and then conversion of the bromomethyl tetrahydrofuran into a methyl ketone. Thus the addition of benzyloxymethyllithium[7] (THF, −78 °C), followed by treatment with acidic methanol [$HC(OMe)_3$, *p*-TsOH], led to **7** in 80% yield (Scheme II). Subsequent reductive elimination [Zn(Cu), NaI, DMF, 60 °C], protection ($Et_3SiOClO_3$, C_5H_5N, CH_3CN, 25 °C), and ozonolysis (CH_2Cl_2, −78 °C; Me_2S, C_5H_5N) gave in 85% yield the required methyl ketone **8.**

The final coupling to link C-1–C-7 (**9**) with C-8–C-25 (**8**) was accomplished by a kinetic enolate aldol condensation (Scheme III). Although the asymmetry created at C-7 could not be predicted with certainty, it was anticipated, however, that the branched nature of C-5 and the bulk of the triethylsilyl protecting group would override chelation by the C-5 oxygen substituent and produce largely the Cram product **10.**[8] This proposal appears to have been borne out. When the magnesium[9] enolate of **8** (LDA, THF, −78 °C; $MgBr_2$) was reacted with 1.2 equiv of **9** at low temperature, a 3:1 mixture of diastereomeric aldols was produced in 75% yield.[10] The major product was shown to have the desired structure (**10**) by its conversion into monensin along the lines previously reported by Kishi and co-workers.[11] Thus hydrogenolysis (10% Pd/C, Et_2O), equilibrating spiroketalization (*p*-TsOH, CH_2Cl_2, Et_2O, H_2O), and saponification (NaOH, H_2O, MeOH) gave monensin sodium which was identical with natural material by all the usual criteria.[6,12]

Acknowledgment. We express our thanks to the NSF (CHE 78-01769), Eli Lilly, and Hoffmann-La Roche for their support and to Noam Glaser and Kevin Darst for their assistance in carrying out many of the large-scale degradations of monensin necessary for this work.

References and Notes

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(3) We were unable to prepare the Grignard reagent of **1** without substantial (~30%) dimerization.
(4) M. L. Wolfrom and S. Hanessian, *J. Org. Chem.*, **27,** 1800 (1962); T. D. Inch, *Carbohydr. Res.*, **5,** 45 (1967); S. Hanessian, G. Rancourt, and Y. Guindon, *Can. J. Chem.*, **56,** 1843 (1978); T. Nakata and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978); W. C. Still, J. H. McDonald, III, and J. Schneider, *Tetrahedron Lett.*, in press.
(5) None of the 16-epi compound could be detected by NMR. An authentic sample of 16-*epi*-**4** was prepared by sequential addition of ethylmagnesium bromide (CuI·Bu_3P) and the Grignard reagent derived from **1.**
(6) Identity was established by NMR, IR, MS, and TLC comparison.
(7) W. C. Still, *J. Am. Chem. Soc.*, **100,** 1481 (1978).
(8) This proposition is supported by the stereochemical results obtained by Kishi and co-workers on a similar aldol.[11]
(9) The lithium enolate gave approximately the same stereochemical results but the percent conversion was unacceptably low (~50%).
(10) We were unable to effect an aldol reaction using unsilylated **8** by analogy to the final coupling reported in the previous monensin synthesis.[11] Under the published conditions (*i*-Pr_2NMgBr, THF, −40 °C), **8** was recovered unchanged and **9** was largely reduced to the corresponding primary alcohol.
(11) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. J. Wang, G. Schmid, and Y. Kishi, *J. Am. Chem. So.*, **101,** 262 (1979).
(12) The final product was also correlated with natural material as the methyl ester and the methyl ester diacetate.
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