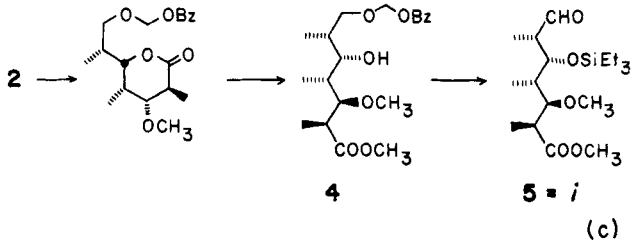
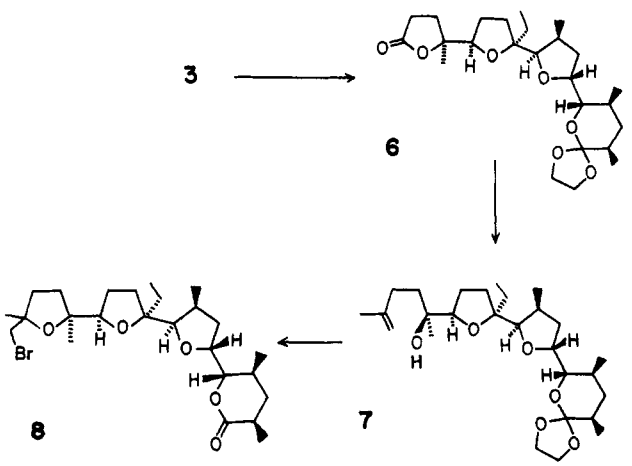


To convert the tetracyclic dilactone **3** into intermediates in our synthetic scheme, it was first necessary to chemically distinguish the γ- and the δ-lactone. This operation was readily effected with ethylene glycol (*p*-TsOH, $HC(OMe)_3$, 25 °C) to give a monoortho lactone (**6**, 60%[13]). As outlined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

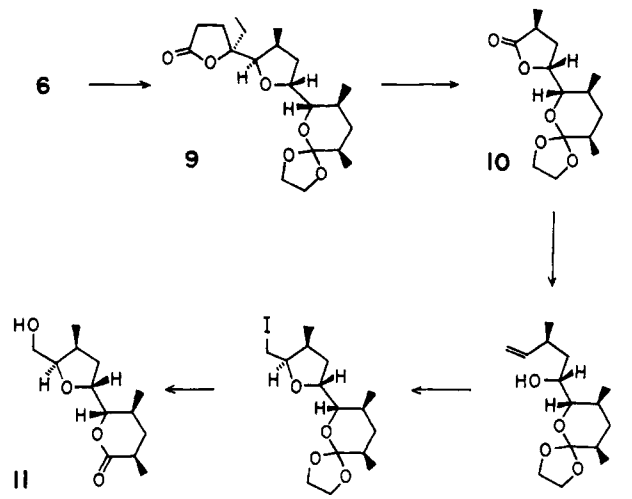
Tetracyclic ortho lactone **6** is also useful for preparation of the lower level bicyclic intermediate iv (Scheme I). The required degradation was accomplished by two sequential oxidative cleavages of a 1,2-hydroxy ether. Thus addition of excess methyllithium to **6** (Et_2O, 80%) gave a dimethylcarbinol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

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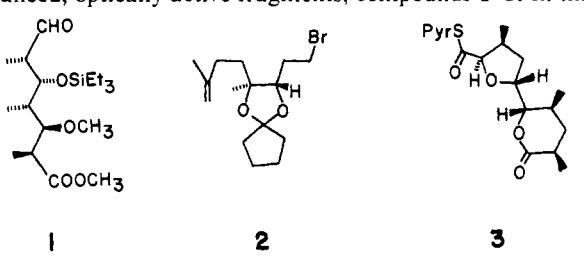
Synthesis of the Polyether Antibiotic Monensin. 2. Preparation of Intermediates[1]

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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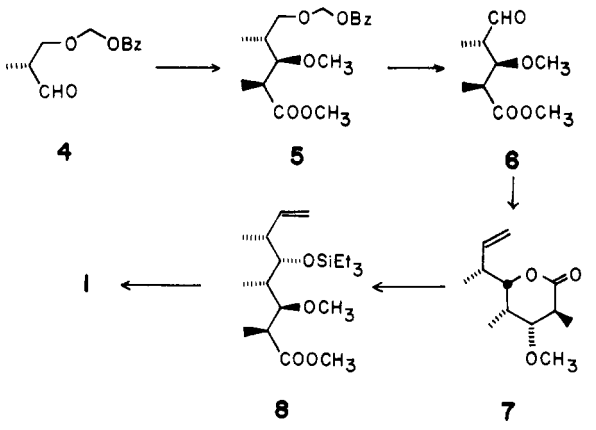
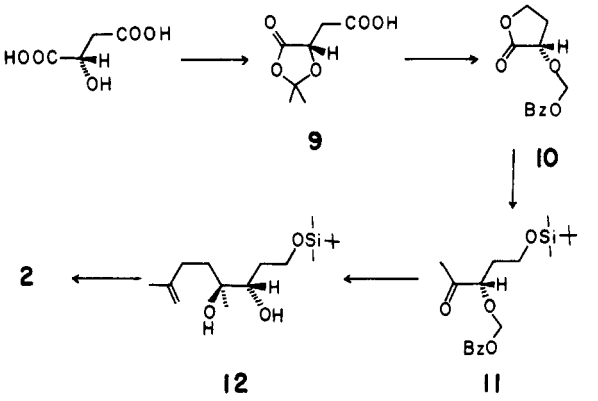
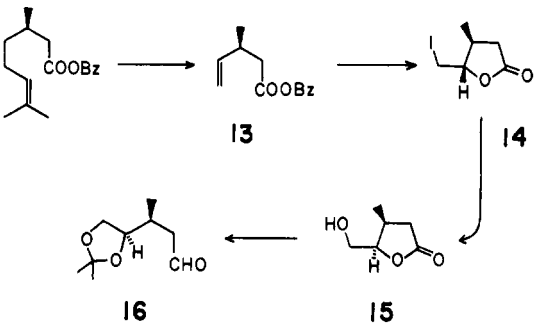
Scheme I



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.

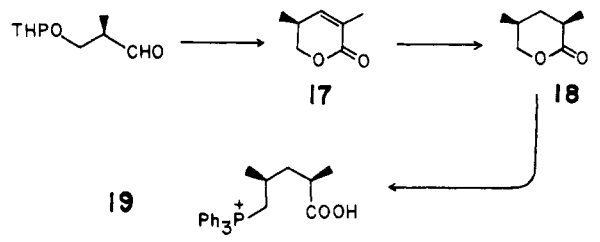
The central fragment (**2**) of monensin was prepared from (*S*)-(−)-malic acid as outlined in Scheme II. Thus the highly crystalline acetonide **9** (mp 107–108 °C, CCl_4) was obtained in 75–85% yield using 2,2-dimethoxypropane and *p*-toluenesulfonic acid. Reduction of the terminal carboxylic acid (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.

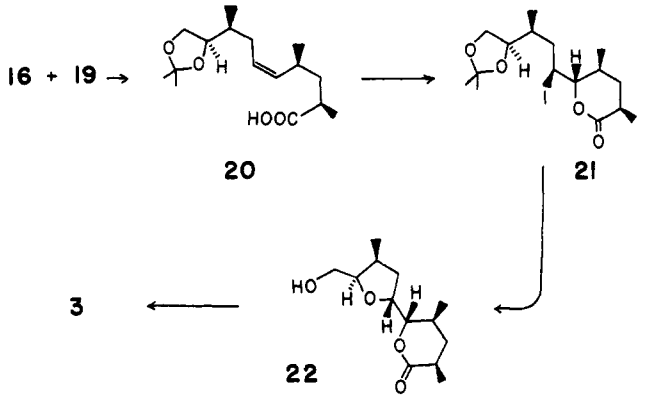
The first subfragment (**16**) corresponding to C-16–C-20 of monensin was prepared starting with the benzyl ester of (*R*)-citronellic acid (Scheme III).[13] Ozonolysis in acetone (−78 °C), followed by oxidative workup (Jones reagent, −78 → 0 °C), gave an acid which was oxidatively decarboxylated [$Pb(OAc)_4$, $Cu(OAc)_2$, 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

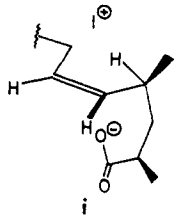


Scheme V



valerolactone quantitatively as an 8:1 cis-trans mixture of isomers. The desired cis compound **18** was readily secured by low-temperature recrystallization from ether–pentane.[17] Conversion into the phosphonium salt **19** was then effected via an intermediate iodo acid (concentrated HI, 130 °C, 10 min) by treatment with triphenylphosphine (1.2 equiv, neat, 130 °C, 3 h).

Coupling of **16** and **19** was accomplished using 1.5 equiv of the deep red dianion of **19** (NaH, Me_2SO, 25 °C, 18 h) and led to **20**[18] in 70% yield (based on **16**) (Scheme V). Our plan at this point was to hydroxylate the cis olefin intramolecularly using the oxygen substituents at C-17 and C-25. It was anticipated that if lactonization preceded etherification in the hydroxylation, then the correct asymmetry at C-20 and C-21 would be produced. This prediction follows from steric considerations of the required lactonization in which the cis olefin and the adjacent asymmetric center (C-22) would be expected to constrain the carboxylate-bearing appendage to the space below the olefin plane (i). Thus, the product of iodolactonization (KI_3, $NaHCO_3$, H_2O) is assigned structure **21** (87%). Subsequent treatment with silver trifluoroacetate (CH_2Cl_2, 25 °C) caused tetrahydrofuran formation with loss of acetone to produce **22** (50%) which was shown to be identical with authentic material prepared by degradation of monensin as described previously. Finally, oxidation (Jones reagent) and conversion (2-PyrSH, $COCl_2$, Et_3N)[19] to the corresponding thiopyridyl ester **3** completed preparation of the required fragments of monensin.



In the following paper, we describe the coupling of intermediates **1–3** to complete our synthesis of monensin.

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) Prepared by standard methods from (+)-β-hydroxyisobutyric acid: C. T. Goodhue and J. R. Schaeffer, *Biotechnol. Bioeng.*, **13**, 203 (1971).
(3) The kinetic nature of this reaction was verified by isolation of the minor aldol. Thus resubmission of that material to the aldol reaction conditions gave no detectable change in the product composition.
(4) C. T. Buse and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8109 (1977).
(5) W. C. Still and J. Schneider, unpublished work. Cf. R. W. Hoffmann and H.-J. Zeiss, *Angew. Chem., Int. Ed. Engl.*, **18**, 306 (1979). In contrast to the butenylaluminum used here, Hoffmann's butenylborane only gave slow epimerization of **6**.
(6) W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
(7) A. Agtarap, J. W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, **89**, 5737 (1967).
(8) T. J. Barton and C. R. Tully, *J. Org. Chem.*, **43**, 3049 (1978).
(9) The ratio given is by high pressure LC. Reversal of the order of the two Grignard additions gave the opposite (erythro) stereoisomer as the major product (stereoselectivity also 50:1).
(10) The stereochemical assignment follows by analogy to numerous model studies on closely related α-benzyloxymethyloxy ketones (W. C. Still, J. H. McDonald, and J. Schneider, *Tetrahedron Lett.*, in press) and was ultimately confirmed in this instance by a successful synthesis of monensin.
(11) Diol protection was accompanied by desilylation. The more familiar acetonide corresponding to **2** turned out to be too stable for subsequent removal.
(12) Optical purity was verified by conversion of **12** into the corresponding MTPA ester and high pressure LC comparison with the analogous MTPA esters of authentic racemic **12**. See J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.* **34**, 2543 (1969).
(13) J. Plesek, *Collect. Czech. Chem. Soc.*, **22**, 644 (1957).
(14) J. D. Bacha and J. K. Kochi, *Tetrahedron*, **24**, 2215 (1968).
(15) P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
(16) Reduction ($LiAlH_4$, Et_2O) allowed preparation of a bis-MTPA derivative which clearly distinguished racemic material from optically active **17** in the NMR.
(17) That racemization had not occurred was demonstrated by conversion of **18** back into **17** [(1) $LiNiPr_2$, PhSeBr; (2) O_3–CH_2Cl_2] followed by enantiomeric analysis as described above.[16]
(18) The product contained ~20% of the undesired trans olefin.
(19) E. J. Corey and D. A. Clark, *Tetrahedron Lett.*, 2875 (1979).
(20) Alfred P. Sloan Fellow, 1978–1980.

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

Sir:

In the preceding two papers we outlined a synthetic pathway to the polyether antibiotic monensin and described how certain key intermediates were prepared in optically active form both by synthesis and by degradation of natural material.[2] We now detail the methods used to join these intermediates and to complete our asymmetric synthesis of monensin.

The first coupling proceeded via a Grignard reaction which joined the central fragment **1** (C-8–C-15) to the right-hand fragment **2** (C-16–C-25). Although it was difficult to prevent overaddition with the simple magnesium salt, use of cuprous iodide (CuI·Bu_3P, THF, −78 °C) with the Grignard reagent[3] resulted in clean formation of ketolactone **3** (Scheme I). This monoadduct is special in the sense that it contains a ketonic carbonyl with an α-asymmetric center bearing a basic heteroatom substituent. Thus a nucleophilic addition to the carbonyl could be expected to be chelation controlled and would lead to the product having the required stereochemistry at C-16.[4] In fact, addition of ethylmagnesium bromide (THF, −78 °C) to **3** yielded a single[5] adduct (**4**) subsequently shown to result from the desired α attack (70% from **2**). At this point in the synthesis, the C-13–C-16 tetrahydrofuran ring was closed in 67% yield by (1) deketalization with differentiation

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