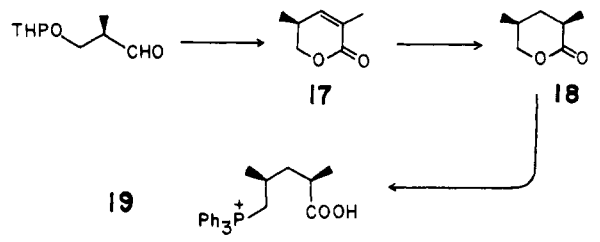
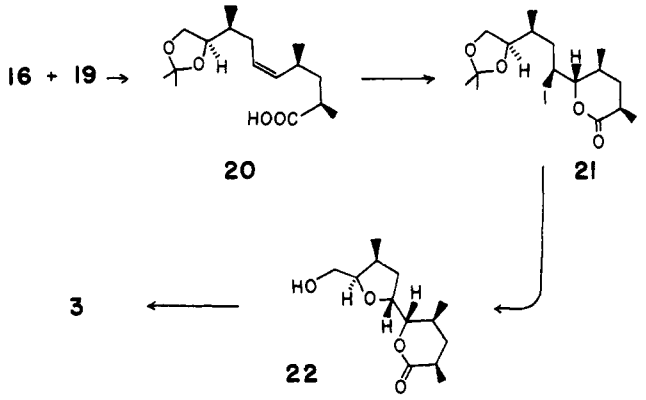
Scheme IV

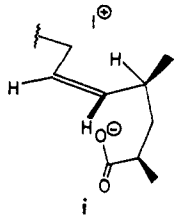


Scheme V



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.

David B. Collum, John H. McDonald, III
W. Clark Still* [20]
Department of Chemistry, Columbia University
New York, New York 10027
Received October 22, 1979

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

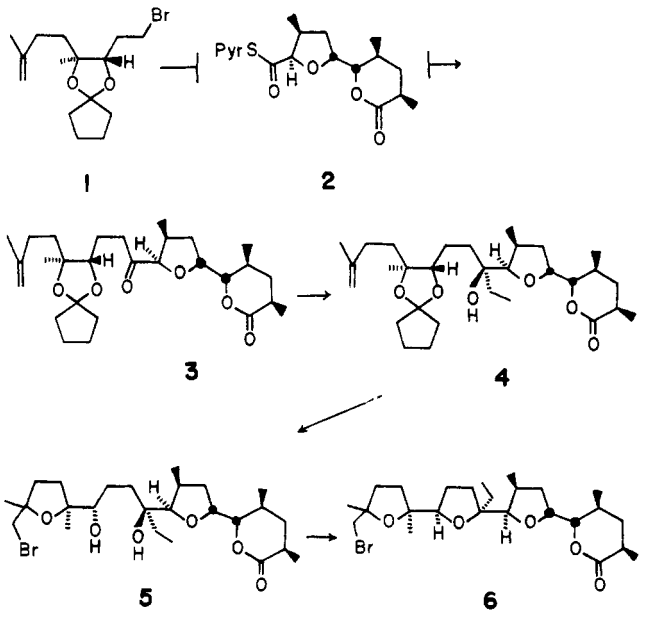
Sir:

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.

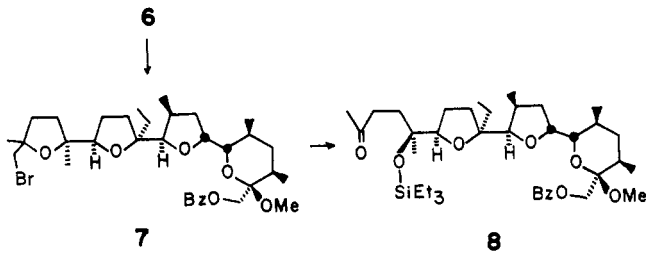
The first coupling proceeded via a Grignard reaction which joined the central fragment **1** (C-8–C-15) to the right-hand fragment **2** (C-16–C-25). Although it was difficult to prevent overaddition with the simple magnesium salt, use of cuprous iodide (CuI·Bu_3P, THF, −78 °C) with the Grignard reagent[3] 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

0002-7863/80/1502-2120$01.00/0

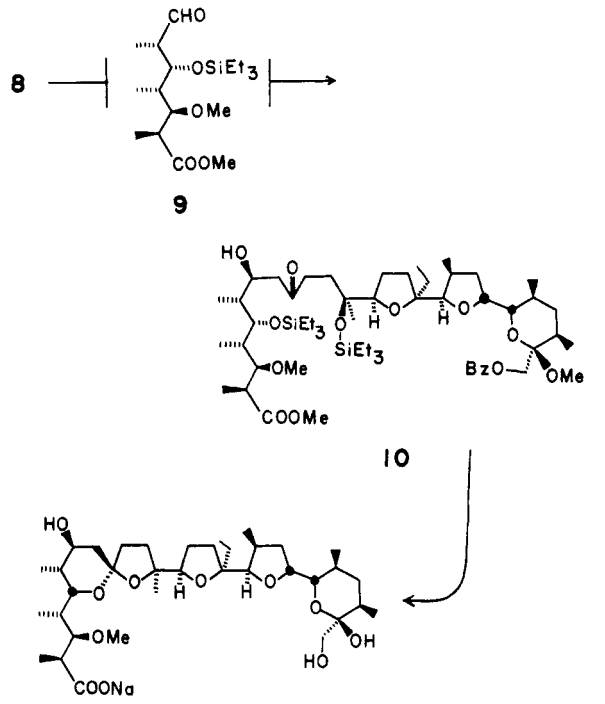
Scheme I



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

(1) This work was described at the Sixth International Symposium on Synthesis in Organic Chemistry in Cambridge, England, on July 25, 1979.
(2) D. B. Collum, J. H. McDonald, III, and W. C. Still, *J. Am. Chem. Soc.*, preceding two papers in this issue.
(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.
(13) Alfred P. Sloan Fellow, 1978–1980.

David B. Collum, John H. McDonald, III
W. Clark Still* [13]
Department of Chemistry, Columbia University
New York, New York 10027
Received October 22, 1979