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 iodide (concentrated H1, 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, Me2SO, 25 °C, 18 h) and led to 2018 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 hydroxylations, 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 (1). Thus, the product of iodolactonization (KI3, NaHCO3, H2O) is assigned structure 21 (87%). Subsequent treatment with silver trifluoroacetate (CH2C12, 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 natural material.2 We now detail the methods used to join these intermediates and to complete our asymmetric synthesis of monensin.

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

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-Bu3Sn, THF, -78 °C) with the Grignard reagent1 resulted in clean formation of ketolactone 3 (Scheme I). This monoaduct 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-16.16 In fact, addition of ethylmagnesium bromide (THF, -78 °C) to 3 yielded a single1 adduct (4) subsequently shown to result from the desired 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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Scheme I

1 \[\text{Br} \rightarrow \text{Pyr S} \rightarrow \text{CHO} \]

2

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4

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6

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8

of the C-12, C-16-tertiary hydroxyls (NBS, p-TsOH, CH₂Cl₂, 0 °C); (2) mesylation of the C-13 secondary hydroxyl (MsCl, Et₂N, CH₂Cl₂, 0 °C); and (3) solvolysis in buffered trifluoroethanol (NaOAc, 60 °C). The resulting tetracyclic lactone was shown to be identical with material derived from natural monensin as described previously.

There remained several operations to be carried out on 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 benzylmagnesium bromide (THF, -78 °C), followed by treatment with acidic methanol \[\text{HC(OOMe)_3, p-TsOH}\], led to \[\text{in 80% yield (Scheme II)}.\]

Subsequent reductive elimination \[\text{Zn(Cu), NaI, DMF, 60 °C}\], protection \[\text{Et₂SiOC(OEt), C₅H₅N, CH₃CN, 25 °C}\], and ozonolysis \[\text{CH₂Cl₂, -78 °C; Me₂S, CS₂SN}\] 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. This proposal appears to have been borne out. When the magnesium enolate of 8 (LDA, THF, -78 °C; MgBr₂) was reacted with 1.2 equiv of 9 at low temperature, a 3:1 mixture of diastereomeric alcohols was produced in 75% yield. 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. Thus hydrogolysis (10% Pd/C, Et₂O), equilibrating spiroketalization (p-TsOH, CH₂Cl₂, Et₂O, H₂O), and saponification (NaOH, H₂O, MeOH) gave monensin sodium which was identical with natural material by all the usual criteria.

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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.
(3) We were unable to prepare the Grignard reagent of 1 without substantial (≈30%) dimerization.
(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 (CuH/Bu₃P) and the Grignard reagent derived from 1.
(6) Identity was established by NMR, IR, MS, and TLC comparison.
(8) This proposition is supported by the stereochemical results obtained by Kishi and co-workers on a similar aldol.
(9) The lithium enolate gave approximately the same stereochemical results as the Grignard enolate derived from 1.
(10) We were unable to effect the aldol reaction using unsilylated 8 by analogy to the aldol coupling reported in the previous monensin synthesis. Under the published conditions (nPr₄N/MgBr, THF, -40 °C), 8 was recovered unchanged and 8 was largely reduced to the corresponding primary alcohol.
(12) The final product was also correlated with natural material as the methyl ester and the methyl ester diacetate.

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