syntheses such as the classical Fischer indole[8] and the recent Gassman indole[9] syntheses do not provide regiocontrolled entry into the 4-substituted indoles[10] (except for the case of an electron-withdrawing group such as nitro in the latter approach) which are important intermediates toward ergot alkaloids attaches special merit to this approach.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. M.R. thanks the Deutsches Forschungsgemeinschaft for partial support. M.C. thanks the Science Research Council of the United Kingdom for a postdoctoral fellowship.

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(1) Cf. deWaard, E. R.; Rens, H. R.; Huisman, H. O. *Tetrahedron Lett.* **1973,** 4315. Oikawa, Y.; Yonemitsu, O. *J. Org. Chem.* **1976,** *41,* 1118.
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(3) **2**: NMR δ 1.54 (s, 3 H), 1.76 (s, 3 H), 1.95 (m, 4 H), 2.70 (t, J = 6 Hz, 2 H), 3.69 (s, 3 H), 6.42 (d, J = 3 Hz, 1 H), 6.61 (dd, J = 9, 3 Hz, 1 H), 7.40 (d, J = 9 Hz, 1 H). **3**: NMR δ 7.0 (d, J = 8 Hz, 1 H), 6.58 (m, 2 H), 5.62 (br t, J = 4 Hz, 1 H), 3.74 (s, 3 H), 2.68 (m, 2 H), 2.2 (m, 2 H), 1.98 (br s, 3 H). **5a:** NMR δ 1.54 (s, 3 H), 1.80 (s, 3 H), 1.70–2.10 (m, 4 H), 2.63 (m, 2 H), 5.82 (s, 2 H), 6.36 (s, 1 H), 7.0 (s, 1 H). **9**: NMR δ 1.48 (s, 3 H), 1.78 (m, 4 H), 1.97 (s, 6 H), 2.56 (m, 2 H), 3.56 (s, 3 H), 5.80 (m, 1 H), 5.90 (t, J = 3 Hz, 1 H), 6.41 (m, 1 H). **10:** NMR δ 1.60 (s, 3 H), 1.67–2.40 (m, 6 H), 2.38 (s, 3 H), 3.40 (s, 3 H), 6.03 (d, J = 3 Hz, 1 H), 6.39 (d, J = 3 Hz, 1 H), 7.09 (d, J = 8 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H). **12:** NMR δ 0.92 (d, J = 7 Hz, 6 H), 1.16–164 (m, 9 H), 1.80 (s, 3 H), 1.87 (s, 3 H), 2.40 (s, 3 H), 3.42 (s, 3 H), 4.04 (dd, J = 11, 4 Hz, 1 H), 5.72 (m, 1 H), 5.88 (t, J = 3 Hz, 1 H), 6.44 (t, J = 2 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.30 (d, J = 8 Hz, 2 H). **13:** NMR δ 0.98 (d, J = 8 Hz, 6 H), 1.64 (m, 3 H), 2.89 (br t, J = 8 Hz, 2 H), 3.80 (s, 3 H), 6.43 (d, J = 3 Hz, 1 H), 6.83 (apparent, t, J = 4 Hz, 1 H), 6.93 (d, J = 3 Hz, 1 H), 7.06 (apparent d, J = 4 Hz, 2 H). **15:** NMR δ 1.76 (s, 6 H), 3.52 (d, J = 8 Hz, 2 H), 3.76 (s, 3 H), 5.37 (t, J = 8 Hz, 1 H), 6.36 (d, J = 3 Hz, 1 H), 6.76 (apparent t, J = 4 Hz, 1 H), 6.86 (d, J = 3 Hz, 1 H), 7.00 (apparent d, J = 4 Hz, 2 H). New compounds have been fully characterized by spectral means and have satisfactory elemental composition.
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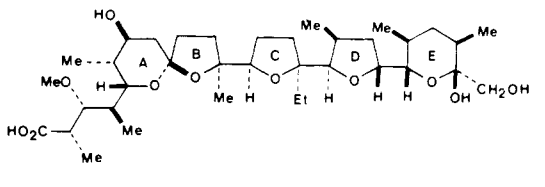
Total Synthesis of Monensin. 1. Stereocontrolled Synthesis of the Left Half of Monensin[1]

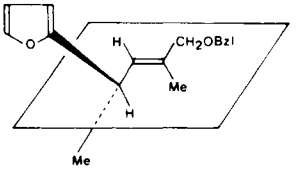
Sir:

Monensin (**1**),[2] produced by a strain of *Streptomyces cinnamonensis,* is perhaps the best known, most historical example from among a group of about 40 naturally occurring polyether antibiotics.[3] Monensin presents a formidable challenge to synthetic chemists; 17 asymmetric centers are present on the backbone of 26 carbon atoms, which means that in principle 131 072 stereoisomers exist for the antibiotic. In reporting the first total synthesis of monensin, we describe the synthesis of the left half of the antibiotic in this communication, the synthesis of the right half in the second,[4] and the total synthesis in the third.[5]



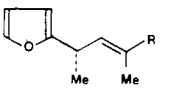
1 monensin

Wittig reaction of 2-(2-furyl)propionaldehyde[6] with carbethoxyethylidenetriphenylphosphorane in refluxing benzene afforded the trans ester **2**[7] (^{1}H NMR ($CDCl_3$) δ 1.38 (3 H, d, J = 7 Hz), 1.93 (3 H, d, J = 2 Hz), 6.70 (1 H, dq, J = 10, 2 Hz)) in 70% yield along with a small amount of the corresponding cis ester (<5% yield). Hydride reduction of **2** ($LiAlH_4$, Et_2O, RT), followed by benzylation ($C_6H_5CH_2Br$, KH, DMF-THF (1:4), 0 °C), gave the benzyl ether **3**[7] (^{1}H NMR ($CDCl_3$) δ 1.31 (3 H, d, J = 7 Hz), 1.75 (3 H, d, J = 1.5 Hz), 3.90 (2 H, br s), 4.43 (2 H, s), 5.43 (1 H, br d, J = 8 Hz)) in 95% overall yield. Hydroboration of **3** (B_2H_6, THF, 0 °C), followed by alkaline hydrogen peroxide workup, yielded the alcohol **4**[7] (^{1}H NMR ($CDCl_3$) δ 0.98 (3 H, d, J = 7 Hz), 1.29 (3 H, d, J = 7 Hz), 4.50 (2 H, s)) along with a small amount of its diastereomer in 85% yield. The ratio of **4** and its diastereomer was ~8:1. The structure assignment of **4** was made based on an example similar to this case.[8] The origin of the remarkable stereospecificity observed might be related to the conformational preference of **3**; based on the pioneering investigations by Wilson,[9] Herschbach,[10] Bothner-By,[11] and others,[12] the preferred conformation of **3** is assumed to be A. Therefore, hydroboration would take place preferentially from the sterically less hindered α face to yield **4**.

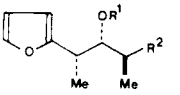


A

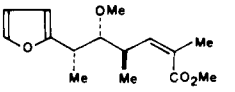
Methylation of **4** (CH_3I, KH, DMF-THF (1:4), 0 °C, followed by debenzylation (1 atm of H_2, 10% Pd/C, CH_3OH, RT), gave the alcohol **5**[7] (^{1}H NMR ($CDCl_3$) δ 0.96 (3 H, d, J = 7 Hz), 1.27 (3 H, d, J = 7 Hz), 3.21 (3 H, s)) in 88% overall yield. Optical resolution of **5** was achieved in a three-step sequence: (1) (−)-$C_6H_5CH(CH_3)N{=}C{=}O$, Et_3N at 50 °C; (2) separation of the resultant diastereomeric urethanes



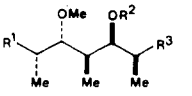
2 $R = CO_2C_2H_5$
3 $R = CH_2OCH_2C_6H_5$



4 $R^1 = H$, $R^2 = CH_2OCH_2C_6H_5$
5 $R^1 = CH_3$, $R^2 = CH_2OH$
6 $R^1 = CH_3$, $R^2 = CHO$



7



8 R^1 = 2-furyl, $R^2 = H$, $R^3 = CH_2OH$
9 R^1 = 2-furyl, $R^2 = CH_2C_6H_5$, $R^3 = CH_2OCH_2OCH_3$
10 $R^1 = CO_2CH_3$, $R^2 = CH_2C_6H_5$, $R^3 = CH_2OCH_2OCH_3$
11 $R^1 = CO_2CH_3$, $R^2 = CH_2C_6H_5$, $R^3 = CH_2OH$
12 $R^1 = CO_2CH_3$, $R^2 = CH_2C_6H_5$, $R^3 = CHO$

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by medium-pressure column chromatography (silica gel; hexane–methylene chloride–acetone (48:48:4)); (3) $LiAlH_4$ reduction of the separated diasteromeric urethanes to the levorotatory (α^{22}_D −11.07° (*c* 3.63, $CHCl_3$)) and dextrorotatory (α^{22}_D +11.13° (*c* 1.77,$CHCl_3$)) alcohols **5**, respectively.

Pyridinium chlorochromate oxidation[13] of the levorotatory alcohol **5** in methylene chloride at room temperature yielded the aldehyde **6**[7] (^{1}H NMR ($CDCl_3$) δ 1.11 (3 H, d, *J* = 7 Hz), 1.32 (3 H, d, *J* = 7 Hz), 3.28 (3 H, s), 9.41 (1 H, d, *J* = 1.8 Hz)) in 88% yield. Condensation of **6** in THF at −78 °C to −50 °C with the phosphonate anion prepared from $(MeO)_2P(O)CH(CH_3)CO_2CH_3$ gave exclusively[14] the cis ester **7**[7] (^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, d, *J* = 7 Hz), 1.28 (3 H, d, *J* = 7 Hz), 1.85 (3 H, d, *J* = 1.2 Hz), 3.40 (3 H, s), 3.65 (3 H, s), 5.76 (1 H, dq, *J* = 10, 1.2 Hz)) in 73% yield. Hydride reduction ($LiAlH_4$, Et_2O, RT), followed by hydroboration ((1) B_2H_6, THF, 0 °C; (2) H_2O_2, aqueous 10% KOH–THF, RT), afforded the alcohol **8**[7] (^{1}H NMR ($CDCl_3$) δ 1.05 (6 H, d, *J* = 7 Hz), 1.33 (3 H, d, *J* = 7 Hz), 3.46 (3 H, s)) in 80% yield along with a small amount of its diastereomer in a ratio of 12:1. Based on the aforementioned reason (note the geometry of the olefinic bond), the structure **8** was tentatively assigned to the major product, which was later confirmed by comparison of **12** with the authentic sample prepared by an alternative route.[15] The alcohol **8** was converted to the methoxymethyl benzyl ether **9**[7] (^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, d, *J* = 7 Hz), 1.06 (3 H, d, *J* = 7 Hz), 1.25 (3 H, d, *J* = 7 Hz), 3.05 (3 H, s), 3.35 (3 H, s)) in 2 steps ((1) $BrCH_2OCH_3$, $(CH_3)_2NC_6H_5$, CH_2Cl_2, 0 °C; (2) $C_6H_5CH_2Br$, KH, DMF–THF (1:4), 0 °C) in 68% overall yield. Ozonization of **9** (O_3, CH_3OH, −78 °C), followed by diazomethane esterification, gave the ester **10**[7] (^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, d, *J* = 7 Hz), 1.05 (3 H, d, *J* = 7 Hz), 1.13 (3 H, d, *J* = 7 Hz), 3.25 (3 H, s), 3.35 (3 H, s), 3.67 (3 H, s); α^{22}_D +32.5° (*c* 1.36, $CHCl_3$)) in 55% overall yield. Acid treatment of **10** (concentrated HCl–CH_3OH (1:150), reflux) yielded the alcohol **11**[7] (^{1}H NMR ($CDCl_3$) δ 0.98 (6 H, d, *J* = 7 Hz), 1.13 (3 H, d, *J* = 7 Hz), 3.25 (3 H, s), 3.68 (3 H, s); α^{22}_D +23.6° (*c* 1.35, $CHCl_3$)) in 94% yield. Pyridinium chlorochromate oxidation of **11** furnished the unstable aldehyde **12**[7,15,17] (^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, d, *J* = 7 Hz), 1.11 (3 H, d, *J* = 7 Hz), 1.15 (3 H, d, *J* = 7 Hz), 3.26 (3 H, s), 3.70 (3 H, s), 4.07 (1 H, dd, *J* = 6, 3 Hz), 4.57 (2 H, s), 9.77 (1 H, d, *J* = 2 Hz); α^{22}_D +74.2° (*c* 0.91, $CHCl_3$)) in ~95% yield.

Acknowledgment. We are appreciative of the efforts of Drs. Tatsumi Yamazaki and Donald S. Karanewsky in the early stages of this synthesis. Financial assistance from National Institutes of Health, National Science Foundation, and Hoffmann-La Roche Inc. is gratefully acknowledged.

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(4) T. Fukuyama, C.-L. J. Wang, and Y. Kishi, *J. Am. Chem. Soc.*, following paper in this issue.
(5) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. J. Wang, G. Schmid, and Y. Kishi, *J. Am. Chem. Soc.*, accompanying paper in this issue.
(6) We have studied several routes to 2-(2-furyl)propionaldehyde including the known method (U. Schmidt, J. Gombos, E. Haslinger, and H. Zak, *Chem. Ber.*, **109,** 2628 (1976)), and found that the following sequence of reactions is most practical for preparation of a large quantity of this substance: (1) methylation (*n*-BuLi (1.2 equiv), MeI, THF, −78 °C to RT) of (2-furyl)acetonitrile (K. Yu. Novitskii, Kh. Gresl, and Yu. K. Yur'ev, *Khim. Geterotsikl. Soedin.*, 829 (1966)); (2) hydrolysis (KOH, aqueous CH_3OH; reflux); (3) reduction ($LiAlH_4$, Et_2O, 0 °C); (4) oxidation (CrO_3PyHCl, CH_2Cl_2, RT).
(7) Satisfactory spectroscopic data (mass spectrum, ^{1}H NMR, IR, etc.) were obtained for this substance.
(8) T. Matsumoto, Y. Hosoda, K. Mori, and K. Fukui observed a highly stereospecific hydroboration on a very similar system to **3** (*Bull. Chem. Soc. Jpn.*, **45,** 3156 (1972)).
(9) R. W. Kilb, C. C. Lin, and E. B. Wilson, Jr., *J. Chem. Phys.*, **26,** 1695 (1957).
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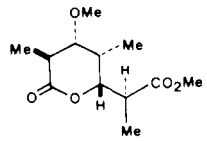
(11) A. A. Bothner-By, C. Naar-Colin, and H. Guenther, *J. Am. Chem. Soc.*, **84,** 2748 (1962).
(12) For example, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience Publishers, New York, 1965, p 19 ff.
(13) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(14) *The amount of the corresponding trans ester, if any, should be <2%.* Related to the synthesis of the polyether and some other antibiotics, we have studied the Horner–Emmons modification of the Wittig reaction to optimize the formation of cis-α,β-unsaturated esters like **7**, and realized that the ratio of the cis and trans esters is sensitive to the structure of the phosphonate anion, solvent, and reaction temperature: G. Schmid, Y. Oikawa, and Y. Kishi, unpublished results. Attempted application of the oxido ylide method (see E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, **92,** 226, (1970)) for the synthesis of cis-allylic alcohol (cf. **7**) directly from **6** was not successful.
(15) We first investigated an alternative route to **12** involving aldol reaction of **6** with the zinc enolate of 2-methyl-2-hydroxy-3-pentanone. Thus, **12** was synthesized from **6** in eight steps ((1) aldol reaction; (2) $LiAlH_4$, Et_2O, 0 °C; (3) $NaIO_4$, aqueous CH_3OH, RT; (4) $CH(OCH_3)_3$–CH_3OH, CSA, RT; (5) $C_6H_5CH_2Br$, KH, DMF–THF (1:4), 0 °C; (6) O_3, CH_3OH, −78 °C; (7) CH_2N_2, Et_2O, 0 °C; (8) aqueous AcOH, RT) with 13% overall yield. A disadvantage of this sequence is the fact that the best stereospecificity of the aldol reaction was 1.8:1 in favoring the desired product. The stereochemistry of the major aldol was confirmed by transforming it to the lactonic ester i,[16]



i

one of the degradation products of monensin, in three steps ((1) O_3, CH_3OH, −78 °C; (2) H_5IO_6, dioxane, RT, 24 h; (3) CH_2N_2, Et_2O, 0 °C).
(16) We are indebted to Dr. Chamberlin, Eli Lilly & Co., for a sample of the lactonic ester i.
(17) We have recently developed a method to convert the lactonic ester i (see ref 15 and 16) to **12** in 11 steps: T. Fukuyama, K. Akasaka, and Y. Kishi, unpublished results.

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Total Synthesis of Monensin. 2. Stereocontrolled Synthesis of the Right Half of Monensin[1]

Sir:

Here, continuing from the preceding communication on the synthesis of the left half of monensin, we describe the synthesis of the right half of the antibiotic.

Monobenzylation of 2-allyl-1,3-propanediol[2] was efficiently carried out in two steps ((1) C_6H_5CHO, CSA, C_6H_6, azeotropic conditions; (2) $LiAlH_4$–$AlCl_3$ (1:4), Et_2O, RT) in 93% overall yield. Optical resolution of the monobenzyl ether **1**[3] was achieved in a three-step sequence: (1) (+)-1-$C_{10}H_7CH(CH_3)N{=}C{=}O$, Et_3N, RT; (2) separation of the resultant diastereomeric urethanes by medium-pressure column chromatography (silica gel; hexane–methylene chloride–ether (10:10:1)), (3) $LiAlH_4$ reduction of the separated diastereomeric urethanes to the levorotatory (α^{22}_D −12.1° (*c* 0.68, $CHCl_3$)) and dextrorotatory (α^{22}_D +13.6° (*c* 0.92, $CHCl_3$)) monobenzyl ethers **1**, respectively. The *S* configuration was assigned to the levorotatory alcohol **1** based on the following experiment: (−)-**1** was converted to (−)-2-methylpentanoic acid (α^{22}_D −21.4°) in four steps ((1) MsCl, Py, 0 °C; (2) $LiAlH_4$, Et_2O, RT; (3) H_2, 10% Pd/C, CH_3OH, RT; (4) Jones oxidation), while the rotation of (*S*)-2-methylpen-

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