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.

References and Notes

(1) Part 4 of the series Synthetic Studies on Polyether Antibiotics. For part 3, see T. Nakata and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978).
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(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.
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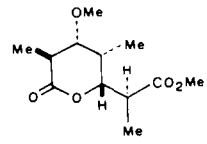
(13) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(14) The amount of the corresponding trans ester, if any, should be <2%. Related to the synthesis of the polyether and some other antibiotics, we have studied the Horner–Emmons modification of the Wittig reaction to optimize the formation 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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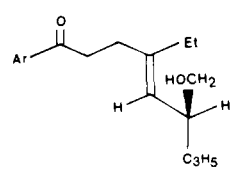
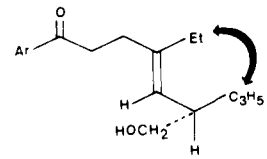
tanoic acid is known as α_D +21.4°.[4] The levorotatory monobenzyl ether **1** was converted to the *p*-methoxyacetophenone derivative **2**[3] (^{1}H NMR ($CDCl_3$) δ 1.01 (3 H, t, J = 7 Hz), 3.85 (3 H, s); α^{22}_D +4.0° (*c* 0.20, $CHCl_3$)) in 31% overall yield in eight steps ((1) CrO_3PyHCl,[5] CH_2Cl_2, RT; (2) $CH_3CH_2C(=CH_2)MgBr$, THF, 0 °C; (3) $CH_3C(OEt)_3$, $CH_3CH_2CO_2H$, 140 °C; (4) $LiAlH_4$, Et_2O, RT; (5) CrO_3PyHCl, CH_2Cl_2, RT; (6) *p*-$MeOC_6H_4MgBr$, Et_2O, 0 °C; (7) Jones oxidation; (8) BCl_3, CH_2Cl_2, 0 °C). The dextrorotatory monobenzyl ether **1** was also transformed to **2** with the same absolute configuration as that derived from the levorotatory monobenzyl ether **1** in 30% overall yield in 10 steps ((1) $BrCH_2OCH_3$, $(CH_3)_2NC_6H_5$, CH_2Cl_2, RT; (2) Li, liquid NH_3; (3-9) follow the steps 1-7 for the levorotatory series; (10) concentrated HCl, CH_3OH, 60 °C)—note the symmetry element of **1**.

We anticipated that epoxidation of **2** should afford the epoxide **3** as the major product, since the transition state A would experience less steric hindrance than the alternative transition state B (note the arrow in B), assuming that this epoxidation involves first complexation of an oxidant with the hydroxyl group of **2**. Indeed, *m*-chloroperbenzoic acid in methylene



A



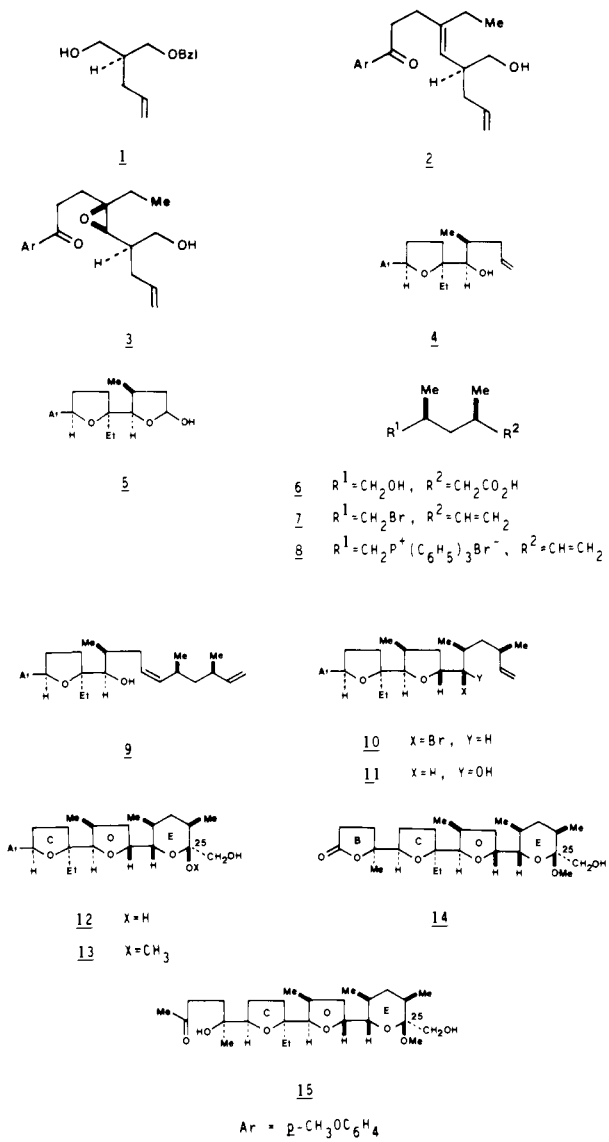
B

chloride-aqueous sodium bicarbonate (two phase) at room temperature gave almost quantitatively a single,[6] unstable[7] epoxide **3** (^{1}H NMR ($CDCl_3$) δ 1.05 (3 H, t, J = 7 Hz), 3.90 (3 H, s)). After tosylation (TsCl, Py, 0 °C), **3** was stereospecifically converted to the tetrahydrofuran **4** (^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, d, J = 7 Hz), 0.95 (3 H, t, J = 7 Hz), 3.68 (3 H, s); α^{22}_D +18.8° (*c* 1.20, $CHCl_3$)) by the method ((1) $LiAlH_4$, Et_2O, 0 °C; (2) CSA, CH_2Cl_2, RT) recently developed in our laboratory.[8] The best ratio of **4** and its diastereomer was 7:2.[9] Periodate-osmium tetroxide oxidation of **4** in aqueous dioxane at room temperature yielded the lactol **5** (^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, t, J = 7 Hz), 1.01 (3 H, d, J = 7 Hz), 3.76 (3 H, s); α^{22}_D +19.2° (*c* 2.62, $CHCl_3$)) in 36% overall yield from **3**.

Baeyer-Villiger oxidation of *cis*-3,5-dimethylcyclohexanone,[10] followed by aqueous potassium hydroxide workup, gave the hydroxy acid **6**.[3] Optical resolution of **6** was achieved by fractional crystallization (eight times from $CHCl_3$-Et_2O) of its (+)-α-methylbenzylamine salt.[3] The 3*R* configuration was tentatively assigned to the dextrorotatory hydroxy acid **6**, since (+)-**6** yielded (+)-3,5-dimethylhexan-1-ol (α^{22}_D +8.65° (*c* 0.45, $CHCl_3$)) in three steps ((1) CH_2N_2, Et_2O, 0 °C; (2) MsCl, Py, 0 °C; (3) $LiAlH_4$, Et_2O, RT), while (*R*)-(+)-3,7-dimethyloctan-1-ol is known to have α_D +4.20°.[11] The dextrorotatory hydroxy acid **6** was transformed to the bromide **7**[3] (^{1}H NMR ($CDCl_3$) δ 1.03 (6 H, d, J = 7 Hz); α^{22}_D −15.0° (*c* 0.71, $CHCl_3$)) in 10 steps ((1) H_2SO_4, EtOH, reflux; (2) $BrCH_2OCH_3$, $(CH_3)_2NC_6H_5$, CH_2Cl_2, RT; (3) $LiAlH_4$, Et_2O, RT; (4) MsCl, Py, 0 °C; (5) C_6H_5SNa, DMF, RT; (6) CH_3CO_3H, AcONa, AcOH-CH_2Cl_2, 0 °C; (7) Δ, $CaCO_3$, decaline; (8) concentrated HCl, EtOH, reflux; (9) MsCl, Py, 0 °C; (10) LiBr, DMF, 100 °C). Treatment of **7** with triphenylphosphine in DMF at 120 °C gave the phosphonium salt **8**[3] (^{1}H NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 7 Hz), 1.02 (3 H, br d, J = 7 Hz)). The overall yield from **6** to **8** was 36%.

Wittig reaction of **5** and **8** ($Me_2SO^-Na^+$, Me_2SO, RT) afforded the cis olefin **9**[3] (^{1}H NMR ($CDCl_3$) δ 0.94 (6 H, d, J = 7 Hz), 0.95 (3 H, d, J = 7 Hz), 3.79 (3 H, s); α^{22}_D +10.3° (*c* 0.71, $CHCl_3$)) in 78% yield along with a small amount of the corresponding trans olefin (<2% yield). NBS bromination[12] of **9** in acetonitrile at room temperature gave a single bromide **10**[3] (^{1}H NMR ($CDCl_3$) δ 0.98 (6 H, d, J = 7 Hz), 1.00 (3 H, d, J = 7 Hz), 1.03 (3 H, t, J = 7 Hz), 3.78 (3 H, s); α^{22}_D +1.3° (*c* 0.38, $CHCl_3$)) in 57% yield. The structure **10** was assigned for the product, based on our extensive studies in the lasalocid A synthesis.[13] Treatment of **10** with superoxide anion in Me_2SO containing crown ether[14] gave the alcohol **11**[3] (^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 7 Hz), 0.98 (3 H, t, J = 7 Hz), 1.02 (6 H, d, J = 7 Hz), 3.78 (3 H, s); α^{22}_D +19.5° (*c* 0.36, $CHCl_3$)) in 47% yield. Byproducts of this reaction were olefins formed from elimination of hydrogen bromide.

Functionalization of the vinyl group of **11** was accomplished in 53% overall yield by protection of the secondary alcoholic group as its trichloroacetate (Cl_3CCOCl, Py, 0 °C), osmylation (OsO_4, Py-THF, RT), monobenzoylation (C_6H_5COCl, Py-CH_2Cl_2, RT), Jones oxidation, and then hydrolysis of the trichloroacetyl and benzoyl groups (NaOMe, CH_3OH, RT). As a single hemiketal **12**[3] (^{1}H NMR ($CDCl_3$) δ 3.78 (3 H, s); α^{22}_D +74.7° (*c* 0.17, $CHCl_3$)) was produced on the base hydrolysis, the stereochemistry at C(25)[15] was concluded as indicated—note the stereochemistry of this center of monensin. The hemiketal group in **12** was protected as its methyl ketal **13**[3] (^{1}H NMR ($CDCl_3$) δ 3.26 (3 H, s), 3.76 (3 H, s); α^{22}_D



Ar = *p*-$CH_3OC_6H_4$

+85.5° (*c* 0.18, $CHCl_3$)) under the standard conditions ($CH(OCH_3)_3$-CH_3OH, CSA, CH_2Cl_2, RT) quantitatively.

Transformation of **13** to the lactone **14**[3] (^1H NMR ($CDCl_3$) δ 1.34 (3 H, s), 3.26 (3 H, s), 3.98 (1 H, d, J = 4 Hz); IR ($CHCl_3$) 1760 cm^{-1}; α^{22}_D +43.6° (*c* 1.69, $CHCl_3$)) was accomplished in seven steps ((1) Li, liquid NH_3, EtOH; (2) $CH(OCH_3)_3$-CH_3OH, CSA, CH_2Cl_2, RT; (3) O_3, CH_3OH, −78 °C; (4) $MgBr_2$, wet CH_2Cl_2, RT; (5) CH_3MgBr, Et_2O, RT; (6) O_3, CH_3OH, −78 °C; (7) concentrated HCl, CH_3OH, RT) in 22% overall yield. A few of these steps require a comment. First, magnesium bromide in wet methylene chloride (step 4) was found most satisfactory to form the enol ether of the β-ketoaldehyde. Second, highly stereospecific addition of a Grignard reagent to a ketonic group adjacent to a tetrahydrofuran (step 5) was demonstrated in our total synthesis of lasalocid A.[13] In this particular case **14** was the only product detected by NMR and TLC analysis. The structure of **14** was concluded from the following transformation; acid treatment of **14** (CSA, wet ether, RT), followed by periodate oxidation ($NaIO_4$, aqueous CH_3OH, 0 °C), gave the dilactone (i.e., the ring E[15] in the structure **14** is the δ-lactone), which was found to be identical with the authentic dilactone,[16,17] one of the degradation products of monensin, by comparison of spectroscopic (NMR, IR, α_D) and TLC data. Treatment of **14** with methyllithium in THF at −78 °C afforded the methyl ketone **15**[3] (^1H NMR ($CDCl_3$) δ 1.13 (3 H, s), 2.15 (3 H, s), 3.25 (3 H, s), 4.13 (1 H, d, J = 4 Hz); IR ($CHCl_3$) 1715 cm^{-1}; α^{22}_D +65.1° (*c* 1.78, $CHCl_3$)) almost quantitatively.

Acknowledgment. Financial assistance from National Institutes of Health, National Science Foundation, and Hoffmann-La Roche Inc. is gratefully acknowledged.

References and Notes

(1) Part 5 of the series Synthetic Studies on Polyether Antibiotics. For part 4, see G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, preceding paper in this issue.
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(7) This type of epoxy ketone is known to rearrange to a ketal under acidic conditions. For an example, see W. K. Anderson and T. Veysoglu, *J. Org. Chem.*, **38**, 2267 (1973).
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(15) The numbering corresponds to that of monensin (see ref 16).
(16) A. Agtarap, J. W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, **89**, 5737 (1967).
(17) We are indebted to Dr. Chamberlin, Eli Lilly & Co., and Dr. Westley, Hoffmann-La Roche Inc., for samples of natural monensin. The authentic sample of the dilactone was prepared from natural monensin by following the Lilly procedure. We thank Dr. Chamberlin for information on the details of this experiment.
(18) We have recently developed a method to convert the dilactone (see ref 16 and 17) to **15** in 13 steps: T. Fukuyama, K. Akasaka, and Y. Kishi, unpublished results.

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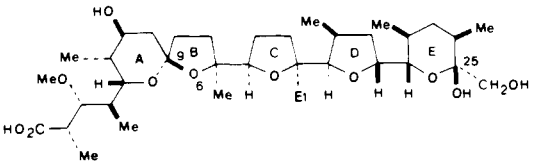
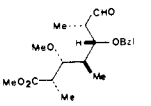
Total Synthesis of Monensin. 3. Stereocontrolled Total Synthesis of Monensin[1]

Sir:

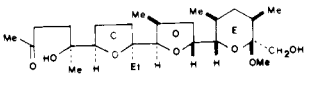
Having completed the synthesis of the left and right halves **2** and **3** of monensin (**1**), we now need to develop a method of constructing the spiro ketal moiety of the antibiotic. We anticipated that the asymmetric center at the C(9)[2] position should stereospecifically be introduced by intramolecular ketalization of the corresponding dihydroxy ketone, because the configuration and conformation around this center of monensin (**1**) has been shown by X-ray analysis[3] as A, in which the C(9)-O(6)[2] bond takes the axial position with respect to the tetrahydropyran ring. Therefore, this configuration must be thermodynamically more stable than the alternative one owing to the anomeric effect well known in carbohydrate chemistry.



1 monensin



2



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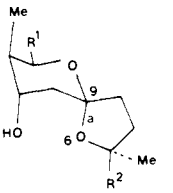
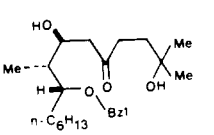


A

The proposed intramolecular ketalization, particularly its stereochemistry outcome, was investigated on the model compound **4**.[4,5] Hydrogenolysis of **4** (1 atm of H_2, 10% Pd/C, CH_3OH-AcOH (95:5), RT) yielded an ~1:1 mixture of spiro ketals **5**[5] and **6**[5] (Merck silica gel plate (0.25 mm), acetone-hexane (3:7); R_f 0.72 and 0.48, respectively). When this mixture was equilibrated with a catalytic amount of camphorsulfonic acid in methylene chloride at room temperature,



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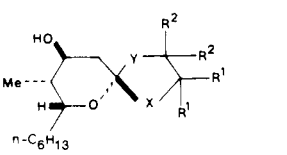
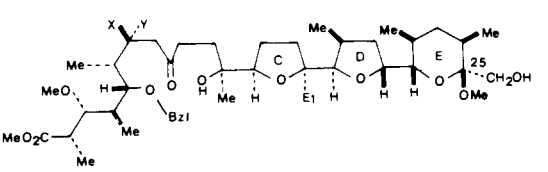


5 X=O, Y=CH_2, R^1=CH_3, R^2=H
6 X=CH_2, Y=O, R^1=H, R^2=CH_3



7 X=OH, Y=H
8 X=H, Y=OH

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