+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.
(2) B. K. Wasson, C. H. Gleson, I. Levi, J. M. Parker, L. M. Thompson, and C. H. Yates, *Can. J. Chem.*, **39**, 923 (1961).
(3) Satisfactory spectroscopic data (mass spectrum, ^1H NMR, IR, etc.) were obtained for this substance.
(4) P. A. Levene and A. Rothen, *J. Org. Chem.*, **1**, 76 (1936).
(5) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(6) Contamination of the minor epoxide, if any, should be <5%, judged from the results of the following transformations.
(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).
(8) T. Fukuyama, B. Vranesic, D. P. Negri, and Y. Kishi, *Tetrahedron Lett.*, 2741 (1978).
(9) The best conditions found in the model series (see ref 8) could not be applied for this case, since the tosyl group was not reduced under these conditions. Studies to improve the stereospecificity of this step are in progress.
(10) J. von Braun and W. Haensel, *Chem. Ber.*, **59**, 1999 (1926); N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 232 (1959).
(11) N. Cohen, W. F. Eichel, R. J. Lopresti, C. Neukom, and G. Saucy, *J. Org. Chem.*, **41**, 3505 (1976).
(12) The bishomoallylic alcohol **9** was not epoxidized under the conditions we used for the synthesis of lasalocid A.[8,13]
(13) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978); T. Nakata and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978).
(14) E. J. Corey, K. C. Nicolaou, M. Shibasaki, Y. Machida, and C. S. Shiner, *Tetrahedron Lett.*, 3183 (1975).
(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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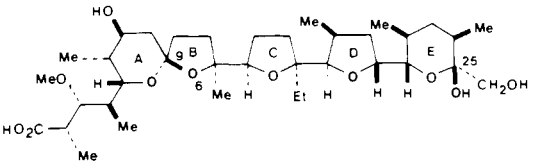
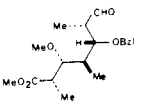
Total Synthesis of Monensin. 3. Stereocontrolled Total Synthesis of Monensin[1]

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



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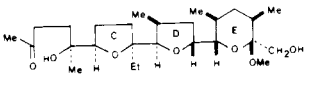

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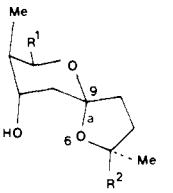
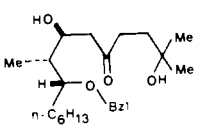


A

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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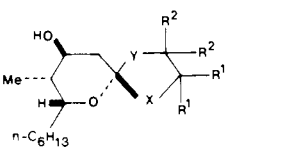
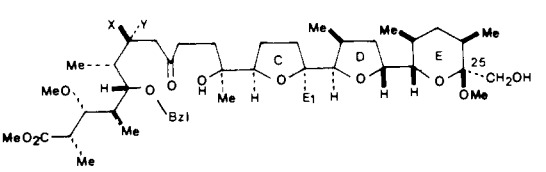


5 X=O, Y=CH_2, R^1=CH_3, R^2=H
6 X=CH_2, Y=O, R^1=H, R^2=CH_3



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

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a new mixture favoring the less polar isomer **5** by a ratio of at least 20:1 was produced. The spectroscopic studies on the spiro ketals and their acetates established the structure for **5** and **6** as indicated.[6]

Being encouraged by our successful total synthesis of lasalocid A,[7] we planned to form the crucial carbon–carbon bond between the left and right halves **2** and **3** by aldol reaction. After many unsuccessful attempts, we have found that this aldol reaction is nicely effected by freshly prepared $(i\text{-}C_3H_7)_2NMgBr$[8] in THF and furthermore that the ratio of the two diastereomeric aldols **7** and **8** is sensitive to the reaction temperature. The following ratios of **7** and **8** were observed at the indicated temperature: ~1:1 at 0 °C (71% yield; 90% yield based on the consumed ketone **3**), ~2:1 at −20 °C (60%; 91%), >5:1 at −50 °C (30%; 90%), and >8:1 at −78 °C (21%; 92%). The diastereomeric aldols **7**[5] (^{1}H NMR ($CDCl_3$) δ 3.25 (3 H, s), 3.27 (3 H, s), 3.68 (3 H, s), 4.60 (2 H, s), 7.31 (5 H, s); α^{22}_D +36.3° (*c* 0.95, CH_2Cl_2)[9]) and **8**[5] (^{1}H NMR ($CDCl_3$) δ 3.25 (6 H, s), 3.67 (3 H, s), 4.61 (2 H, a very close AB), 7.30 (5 H, s); α^{22}_D +46.1° (*c* 0.52, CH_2Cl_2)[9]) could be separated by preparative layer chromatography (Merck silica gel plate (0.5 mm), ether–pentane (5:4), five developments). Based on Cram's rule, the desired stereochemistry was tentatively assigned to the major aldol, which was later confirmed by successful transformation of **7** into monensin (**1**).

Following the conditions that we established in the model series, we subjected the aldol **7** to the following sequence of reactions: (1) 1 atm of H_2, 10% Pd/C, CH_3OH–AcOH (100:5), RT, 30 min; (2) CSA, wet CH_2Cl_2–Et_2O (3:1), RT, 1 h; (3) 1 N NaOH–CH_3OH (1:5), 60 °C, 1 h. Step 2 in this sequence was required to equilibrate the spiro ketal center and also to hydrolyze the tertiary methoxy group at the C(25)[2] position. Preparative layer chromatography (Merck silica gel plate (0.5 mm), ether, three developments) allowed isolation of synthetic monensin (**1**)[10] as its sodium salt. The overall yield from **7** to **1** was 53%. The synthetic substance was found to be identical with natural monensin in every respect (NMR, IR, α_D, mass spectrum, melting point, mixture melting point, TLC).

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References and Notes

(1) Part 6 of the series Synthetic Studies on Polyether Antibiotics. For part 5, see T. Fukuyama, C.-L. J. Wang, and Y. Kishi, *J. Am. Chem. Soc.*, preceding paper in this issue
(2) The numbering corresponds to that of monensin.
(3) For X-ray analysis of silver salt of monensin, see A. Agtarap, J. W. Chamberlin, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, **89**, 5737 (1967), and M. Pinkerton and L. K. Steinrauf, *J. Mol. Biol.*, **49**, 533 (1970); for X-ray analysis of free acid of monensin, see W. K. Lutz, F. K. Winkler, and J. D. Dunitz, *Helv. Chim. Acta*, **54**, 1103 (1971).
(4) Compound **4** was synthesized by the aldol reaction analogous to **2** + **3** → **7** + (**8**): D. S. Karanewsky, T. Fukuyama, and Y. Kishi, unpublished results.
(5) Satisfactory spectroscopic data (NMR, mass spectrum, IR, etc.) were obtained for this substance.
(6) Details of the structure assignment for **5** and **6** will be reported later.
(7) T. Nakata, G. Schmid, B. Vranesic, M. Okigawa, T. Smith-Palmer, and Y. Kishi, *J. Am. Chem. Soc.*, **100**, 2933 (1978); T. Nakata and Y. Kishi, *Tetrahedron Lett.*, 2745 (1978).
(8) This base (1.5 M) was prepared from EtMgBr and diisopropylamine in THF at 80 °C and kept at ~50 °C. The aldol reaction was carried out as follows. The aldehyde **2** (prepared from 38.2 mg of the alcohol (see part 2 of this series) just before use) and ketone (21.5 mg) were dissolved in 10 mL of anhydrous THF under an argon atmosphere, and cooled to −50 °C. To this solution was added 100 μL of the freshly prepared base. At ~5-min intervals, additional base (9 × 25 μL) was added. The reaction was monitored by TLC after each addition of the base. After the base was quenched with saturated ammonium chloride solution at −50 °C, the products were extracted with ether and then with methylene chloride. Preparative layer chromatography (Merck silica gel (0.5 mm), ether–pentane (5:4), five developments) gave 11.1 mg of **7** (30% yield; 90% yield based on the consumed **3**), 2.0 mg of **8** (contaminated by an unknown compound), and 14.3 mg of the recovered ketone **3**.
(9) It takes some time for this substance to give the steady rotation, perhaps owing to the phenomenon similar to mutarotation known for carbohydrates.
(10) We are indebted to Dr. Chamberlin, Eli Lilly & Co., and Dr. Westley, Hoffmann-La Roche Inc., for samples of sodium salt of monensin.

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Synthesis of Monomeric Niobium- and Tantalum–Benzyne Complexes and the Molecular Structure of $Ta(\eta^5\text{-}C_5Me_5)(C_6H_4)Me_2$

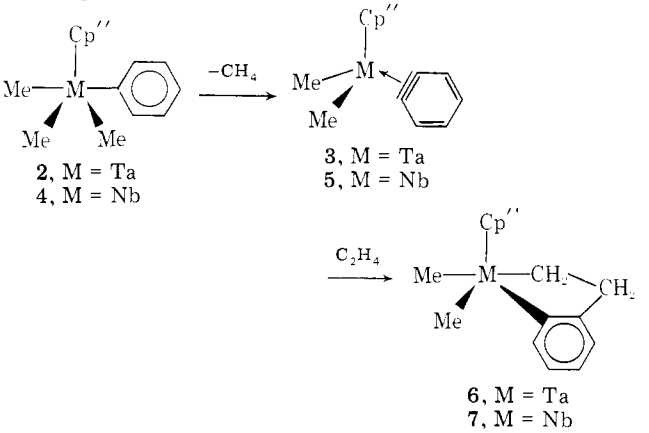
Sir:

Many transition metal complexes contain organic ligands which are highly reactive or unknown in the free state (e.g., cyclobutadiene,[1] trimethylenemethane,[2] carbenes,[3] and small-ring acetylenes[4]). A benzyne (C_6H_4) complex has been postulated as an intermediate in the thermal decomposition of $Ti(\eta^5\text{-}C_5H_5)_2(C_6H_5)_2$ on the basis of labeling and trapping experiments,[5] and recent results by Erker[6] support the formation of a benzyne intermediate, $Zr(\eta^5\text{-}C_5H_5)_2(C_6H_4)$, in the thermal exchange of aryl groups between $Zr(\eta^5\text{-}C_5H_5)_2(aryl)_2$ and aromatic solvents. To our knowledge, however, no compounds containing a benzyne molecule η^2 bonded to a single transition metal have been isolated.[7] Our studies of metallocyclopentane complexes[12] led us to develop a synthesis of tantalum–olefin complexes, $Ta(\eta^5\text{-}C_5Me_5)(CH_2{=}CHR)Cl_2$, by decomposition of thermally unstable dialkyl complexes, $Ta(\eta^5\text{-}C_5Me_5)(CH_2CMe_3)(CH_2CH_2R)Cl_2$ (R = H, Me).[13] We now report the extension of this principle, a form of the β-hydride elimination process by which many transition metal alkyl complexes decompose,[14] to the preparation of stable benzyne complexes.[15]

$Ta(\eta^5\text{-}C_5Me_5)(CH_2CMe_3)Cl_2$[13] reacts slowly (~24 h) with 1 equiv of $Zn(C_6H_5)_2$ in benzene to give neopentane and a dark brown solution containing $Ta(\eta^5\text{-}C_5Me_5)(C_6H_4)Cl_2$ (**1**); no intermediates can be observed by ^{1}H NMR. $Ta(\eta^5\text{-}C_5Me_5)(C_6H_4)Cl_2$ can be isolated as yellow crystals in 44% yield by removing the benzene in vacuo and recrystallizing the gummy residue from toluene at −30 °C. The ^{1}H NMR spectrum of **1** (τ, C_6H_6) shows a singlet for the $\eta^5\text{-}C_5Me_5$ group at 8.26 (relative area 15) and a symmetric AA′BB′ pattern consisting of two multiplets at 2.07 and 2.78 (relative area 4), consistent with its formulation as a benzyne complex. Since **1** is not soluble enough for ^{13}C NMR or a cryoscopic molecular weight determination, we sought a more soluble derivative.

Adding 1 mol of phenyllithium to a suspension of $Ta(\eta^5\text{-}C_5Me_5)Me_3Cl$[13] in ether at −78 °C initially produces a ho-

Scheme I



2, M = Ta
4, M = Nb

3, M = Ta
5, M = Nb

6, M = Ta
7, M = Nb

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