Table I. Heats of Neutralization at 25 °C for α-Phenethylamine and Mandelic Acid

base	acid	$-\Delta H$, kcal/mol in dimethyl sulfoxide	dioxane	water
R	R	7.630 ± 0.013	8.757 ± 0.026	12.67 ± 0.01
S	S	7.612 ± 0.035	8.759 ± 0.023	12.61 ± 0.02
R	S	7.431 ± 0.014	8.416 ± 0.028	12.63 ± 0.02
S	R	7.374 ± 0.024	8.409 ± 0.024	12.63 ± 0.02

Table II. Heats of Neutralization at 25 °C in Me_2SO for Ephedrine and Pseudoephedrine [$C_6H_5CH(OH)CH(CH_3)NHCH_3$] and Mandelic Acid

compd	base	acid	$-\Delta H$, kcal/mol
ephedrine	1R,2S	R	7.294 ± 0.017
	1S,2R	S	7.325 ± 0.030
	1R,2S	S	7.550 ± 0.029
	1S,2R	R	7.607 ± 0.028
pseudoephedrine	1R,2R	R	6.672 ± 0.025
	1S,2S	S	6.657 ± 0.018
	1R,2R	S	6.401 ± 0.019
	1S,2S	R	6.380 ± 0.017

titration (0–9.5 × 10^{-3} M), this experiment is simply a check on the purity of the compounds and the consistency of the technique.

In dimethyl sulfoxide all three bases, α-phenethylamine (Table I), ephedrine, and pseudoephedrine (Table II), show clear differences, well outside experimental error, between diastereomeric combinations. For each case, enantiomeric combinations agree within experimental error. The average difference between diastereomeric combinations of α-phenethylamine with the mandelic acid antipodes is 225 cal/mol compared to 265 cal/mol for ephedrine and 274 cal/mol for pseudoephedrine, suggesting that the larger number of hydrogen-bonding sites in the latter two bases provides a slightly greater opportunity for chiral discrimination in ion aggregation. Conductance could be detected for all three mandelate salts in dimethyl sulfoxide by using a standard Jones-type cell with a 1% bridge.[4] This indicates the presence of free ammonium and carboxylate ions in dimethyl sulfoxide solutions which are probably in equilibrium with the hydrogen-bonded ion pair.

In dioxane the diastereomeric salts of α-phenethylammonium mandelate do not dissociate enough to give measurable conductance. The chiral discrimination factor for these salts in this solvent is now 345 cal/mol compared to 225 cal/mol in Me_2SO where it is less associated.

The question of structures of the ion aggregates is presently being examined by high field (300 and 600 MHz) ^1H NMR spectroscopy. The concentration dependence of the chemical shifts of different protons in diastereomeric solutions in Me_2SO is clearly different and behaves in a manner consistent with the notion that the diastereomeric ion pairs vary both in structure and in their ion-pairing association constants. We would expect the entropies of association to be nearly identical for diastereomeric ion pairs. If this were so, the observed differences in heats of neutralization in Me_2SO are determined both by the inherent enthalpy of ion pairing for each combination and by their different degrees of association. Since association in dioxane is virtually complete, the measured enthalpy difference should be uncomplicated by association differences.

Heats of neutralization were determined by thermometric titration of solutions of the base (or acid) in the solvent introduced into a solution of the acid (or base). Both the usual single buret method[5] and the double buret method[6] were used with comparable results.

(4) Precise conductance studies are currently under way using a high quality Jones bridge.

(5) Christensen, J. J; Ruckman, J.; Eatough, D. J.; Izatt, R. M. *Thermochim. Acta* **1972**, *3*, 203–218. Eatough, D. J.; Christensen, J. J.; Izatt, R. M. *Ibid.* **1972**, *3*, 219–246.

(6) Arnett, E. M.; Chawla, B. *J. Am. Chem. Soc.* **1978**, *100*, 217–221.

Acknowledgment. This work was supported by NIH Grant GM-23086 and NSF Grant CHE-7622369 for which we are most grateful. We appreciate the help of Robin Avery and Ismene Petrakis in checking the thermometric titrations.

Synthesis of 16-Membered-Ring Macrolide Antibiotics. 3.[1] Carbomycin B and Leucomycin A_3: Retrosynthetic Studies

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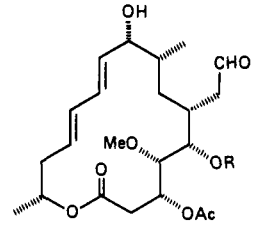
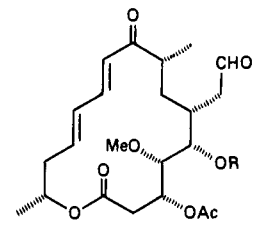
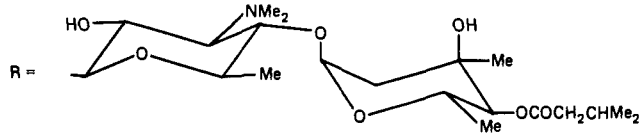
The 16-membered-ring macrolide antibiotics constitute an important, clinically useful series of naturally occurring compounds within the macrolide class of antibiotics.[2] Their rather complex molecular structures with the characteristic diene and polyoxygenated systems may be regarded as "structural turning points" from the lower ring size macrolide antibiotics (e.g., erythromycins)[2] to the higher size polyene macrolides (e.g., amphotericin).[2] Due to the complexity of these molecules, serious synthetic efforts in this area have only recently been reported.[1,3,4] In this series of papers we report the synthesis of carbomycin B (**1**)[5,7] (magnamycin B) and leucomycin A_3 (**2**)[6,7] (josamycin) in their optically active



(1)



(2)



forms from α-D-glucose by a strategy first outlined by us in 1979.[1,8]

† Fellow of the A. P. Sloan Foundation, 1979–1983; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985.

(1) (a) Part 1: Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327. (b) Part 2: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011. (c) This work was partially described at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979.

(2) For recent reviews, see: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (c) Back, T. G. *Tetrahedron* **1977**, *33*, 3041.

(3) Ziegler, F. E.; Gilligan, P. J.; Chakraborty, U. R. *Tetrahedron Lett.* **1979**, 3371.

(4) (a) Tatsuta, K.; Tanaka, A.; Fujimoto, K.; Kinoshita, M.; Umezawa, S. *J. Am. Chem. Soc.* **1977**, *99*, 5826. (b) Tatsuta, K.; Yamauchi, T.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3035.

(5) Isolated from *Streptomyces halstedii*: Hochstein, F. A.; Murai, K. *J. Am. Chem. Soc.* **1954**, *76*, 5080.

(6) Isolated from *Streptomyces kitasatoensis*: Hata, T.; Sano, Y.; Ohki, N.; Yokoyama, Y.; Matsumae, A.; Ito, S. *J. Antibiot.* **1953**, *A6*, B7.

(7) (a) Omura, S.; Katagiri, M.; Ogura, H.; Hata, T. *Chem. Pharmacol. Bull.* **1967**, *15*, 1529 (chemical correlation of carbomycin B and leucomycin A_3). (b) Hiramatsu, M.; Furusaki, A.; Noda, T.; Naya, K.; Tomiie, Y.; Nitta, I.; Watanabe, T.; Take, T.; Abe, J.; Omura, S.; Hata, T. *Bull. Chem. Soc. Jpn.* **1970**, *43* (7), 1966 (X-ray). (c) Omura, S.; Nakagawa, A. *J. Antibiot.* **1975**, *28*, 401 (review). (d) Freiberg, L. A.; Egan, R. S.; Washburn, W. H. *J. Org. Chem.* **1975**, *39*, 2474 (correction of C-9 configuration and conversion of carbomycin B to leucomycin A_3).

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This communication describes retrosynthetic studies designed to explore the chemistry of the aglycones of these sugar-containing macrolide antibiotics and assist in realizing the final steps of the projected synthesis. In the following paper[9] we report the total synthesis of a cyclic, subtarget molecule used as a common intermediate for the construction of both carbomycin B (**1**) and leucomycin A_3 (**2**).

The retrosynthetically derived plan for the synthesis of **1** and **2** required the construction of the advanced intermediate **10** and its conversion to **17**, a compound previously used in a partial synthesis of carbomycin B[4a] and leucomycin A_3.[4a,7d] Our degradation studies, therefore, were directed toward an efficient route to **10** from leucomycin A_3 in order to secure an authentic sample and enrich our supplies of this valuable intermediate needed to solidify and encourage our synthetic efforts. The chemistry developed during this investigation and described herein includes some highly selective and novel transformations.

The first operation in these studies was to detach the sugar units from the aglycon of these antibiotics, a task of considerable challenge because of the difficulties associated with the hydrolysis of the glycoside linkage of amino sugars and the sensitivity of the aglycon and its peripheral functions. These considerations and the failure of the reported procedures[10] to afford consistent and efficient results prompted us to turn our attention to a modified Polonovski–Masamune[11] reaction on a stable leucomycin A_3 derivative lacking the labile aldehyde function.

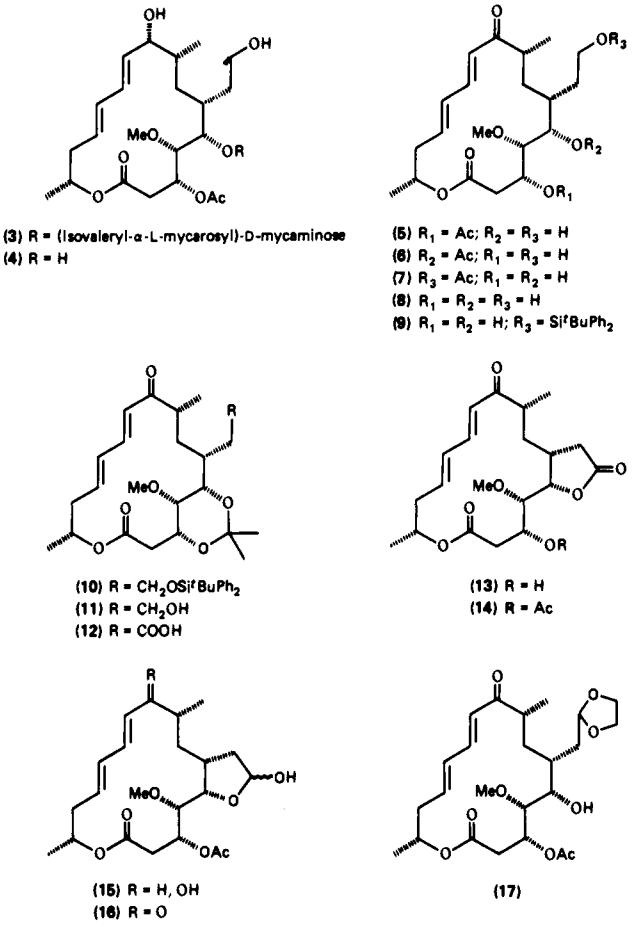
Leucomycin A_3 (**1**) was reduced with $LiAl(O\text{-}t\text{-}Bu)_3H$ (1.5 equiv, THF, 0 °C) to the alcohol **3**[12] (92%) (Scheme I) and then subjected to the following degradation sequence:[11] (1). *m*-chloroperbenzoic acid (1.1 equiv), CH_2Cl_2, 0 °C (to form the *N*-oxide), (2. $(CF_3CO)_2O$ (8 equiv)–pyridine (8 equiv), CH_2Cl_2, 0–25 °C (to remove the sugars), and (3. K_2CO_3 (1.0 equiv), CH_3OH, −10 °C, 10 min (to remove the trifluoroacetates) to afford reproducibly the triol acetate **4**[13] in 45–55% overall yield. Selective oxidation of **4** (1.3 equiv of DDQ, benzene, 25 °C) led cleanly to the dienone **5** (80%).

Removal of the C-3 acetate from **5** under a variety of basic or acidic conditions proved to be exceptionally difficult. Steric congestion around this side is presumably responsible for limited approach and predominance of side reactions such as β elimination and lactone cleavage. In search for an alternative approach to overcome this problem, it was speculated that migration of the acetate to a less sterically hindered site prior to its final hydrolytic removal might provide a solution. To test this hypothesis, conditions were found for the selective migration of the C-3 acetate to either the C-5 hydroxyl (3 equiv of NaSH,[14] EtOH, 0 °C) or the C-6″ hydroxyl (0.75 equiv of *p*-TsOH, THF, 60 °C) leading to **6** (90%) and **7** (89% based on 75% conversion), respectively. The three acetates **5**–**7** could be distinguished chromatographically (silica, 10% CH_3OH in CH_2Cl_2, **5**, R_f = 0.29; **6**, R_f = 0.32; **7**, R_f = 0.34) and spectroscopically. While attempted basic hydrolysis of **6** still presented problems, it was pleasing to discover that the primary acetate **7** suffered smooth cleavage to the triol **8** (70%) under mild basic conditions (1.5 equiv of anhydrous K_2CO_3 in absolute CH_3OH, 0 °C, 5 h).

Selective silylation of the primary hydroxyl group of **8** proceeded uneventfully as expected (1.5 equiv of Ph_2-*t*-BuSiCl, 1.5 equiv of Et_3N, 0.1 equiv of 4-(dimethylamino)pyridine, CH_2Cl_2, 25 °C)[15] leading to the diphenyl-*tert*-butylsilyl ether **9** in 90% yield. Finally, the target molecule, key intermediate **10**[13] was prepared from **9** by acetonide formation (8 equiv of 2,2-dimethoxypropane, 0.1 equiv of camphorsulfonic acid, acetone, 25 °C, 95%). This retrosynthetically derived intermediate was identical in all respects to a sample obtained synthetically as described in the accompanying communication.[9]

Having secured the identity of the retrosynthetic and totally synthetic samples of **10**, its transformation to the second key intermediate hydroxy ketal **17**[4a] was then undertaken. In addition to the manipulation of the functional groups required in this conversion, the problem of differentiating between the two ring hydroxyls (C-3 and C-5) had to be addressed. For this purpose it was necessary to modify the C-6-bound side chain in order to engage temporarily the C-5 hydroxyl group while the C-3 hydroxyl was functionalized. Thus, the silyl ether was first removed under

Scheme I



(8) After the completion of these syntheses in our laboratories and while these manuscripts were in preparation, a separate synthesis of these molecules appeared from Professor Tatsuta's laboratories: Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 2837.

(9) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1981**, *103*, following paper in this issue.

(10) (a) Omura, S.; Nakogawa, A.; Suzuki, K.; Hata, T.; Jakuboski, A.; Tishler, M. *J. Antibiot.* **1974**, *27*, 147. (b) Girotra, N. N.; Wendler, N. L. *Tetrahedron Lett.* **1975**, 227.

(11) Masamune, S.; Hayase, Y.; Chan, W. K.; Sobczak, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 7874.

(12) All new compounds exhibited satisfactory IR, ^1H and ^{13}C NMR, and mass spectral properties as well as analytical and/or exact mass data. All yields refer to isolated chromatographically homogeneous and spectroscopically pure materials.

(13) Important properties of selected key intermediates. **4**: R_f = 0.29 (silica, 10% MeOH in CH_2Cl_2); $[\alpha]^{25}_D$ +14.36° (*c* 1.82, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3440 (OH), 1728, and 1719 cm^{-1} (CO); ^1H NMR (250 MHz, $CDCl_3$, Me_4Si) δ 6.49 (dd, J = 15.5 and 10.5 Hz, 1 H, H-11), 6.06 (dd, J = 15.5 and 10.5 Hz, 1 H, H-12), 5.70 (dd, J = 15.5 and 10.5 Hz, 1 H, H-10), 5.67 (m, 1 H, H-13), 4.26 (dd, J = 11.0 and 4.5 Hz, 1 H, H-9), 3.57 (s, 3 H, OCH_3), 2.13 (s, 3 H, $OCOCH_3$), 1.27 (d, J = 6 Hz, 3 H, 15-CH_3), 1.02 (d, J = 6.5 Hz, 3 H, 8-CH_3). **10**: R_f = 0.23 (silica, 35% ether in petroleum ether); $[\alpha]^{25}_D$ +5.63 (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1718 (lactone) and 1678 cm^{-1} (dienone); ^1H NMR (250 MHz, CCl_3, Me_4Si) δ 6.99 (dd, J = 15.6 and 10 Hz, 1 H, H-11), 6.37 (d, J = 15.6 Hz, 1 H, H-10), 6.19 (dd, J = 15.0 and 9.7 Hz, 1 H, H-12), 6.03 (ddd, J = 15, 6.2, and 4.6 Hz, 1 H, H-13), 3.55 (s, 3 H, OCH_3), 2.63 (m, 1 H, H-8), 1.37, 1.27 (s, 3 H each, acetonide). **16**: R_f = 0.19 (silica, 5% MeOH in CH_2Cl_2); IR ($CHCl_3$) ν_{max} 3420 (OH), 1730, 1675, and 1632 cm^{-1}; NMR (250 MHz, $CDCl_3$, Me_4Si) δ 7.25 (dd, J = 16.0 and 11.5 Hz, 1 H, H-11), 6.34 (d, J = 16.0 Hz, H-10), 6.20 (m, 2 H, H-12 and H-13), 5.58 (t, J = 6.0 Hz, 1 H, H-6″), 5.06 (d, J = 11.0 Hz, 1 H, H-3), 3.54 (s, 3 H, OCH_3) 2.08 (s, 3 H, $COOCH_3$), 1.28 (d, J = 5.5 Hz, 3 H, 15-CH_3), 1.22 (d, J = 6.0 Hz, 3 H, 9-CH_3).

(14) This reagent was freshly prepared by dissolving Na in absolute ethanol followed by H_2S saturation at 0 °C and removal of solvent to dryness.

(15) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

carefully defined conditions (excess HF-pyridine complex, THF, 25 °C) to provide the primary alcohol **11** (70%) which was then oxidized to the carboxylic acid **12** by using Jones reagent (acetone, 0 °C, 95%). The use of the mildly acidic HF-pyridine complex[1b,16] reagent for the above desilylation provided a successful alternative to the basic, and in this case destructive, *n*-Bu_4NF reagent, and it should be useful in other cases as well. Acid treatment (10% aqueous HCl-THF, 1:1, 60 °C) of **12** or its methyl ester (CH_2N_2) gave the hydroxylactone **13** in 70% yield. The sterically demanding acetate **14** was smoothly formed by exposing **13** to excess Ac_2O (10 equiv), pyridine (10 equiv), and 4-(dimethylamino)-pyridine (1 equiv) in CH_2Cl_2 (25 °C, 85%). Treatment of **14** with $LiAl(O\text{-}t\text{-}Bu)_3H$ (2.1 equiv, THF, 25 °C) reduced both the ketone and the γ-lactone functions but not the macrolactone,[10b] giving rise to **15** (mixture of diastereoisomers, 40-50% yield based on ca. 50% conversion). DDQ (1.3 equiv, benzene, 25 °C) oxidation of **15** furnished selectively the dienone lactol **16** (86% yield). The lactone acetate **14** was more easily and directly prepared from the triol **8** by selective oxidation of the primary alcohol with Pt-O_2 in EtOAc (25 °C, 100%). Furthermore, this reaction provided considerable amounts of lactol **16** (30-40% yield based on ca. 50% conversion) by quenching prior to completion. The transformation of **16** to the final key intermediate **17** was smoothly achieved by ketalization ($HOCH_2CH_2OH$, camphorsulfonic acid, 25 °C).[17] Since **17** has already been converted to carbomycin B (**1**) and leucomycin A_3 (**2**),[4a,7d] the described sequence completes the synthesis of these macrolide antibiotics.

The total synthesis of the key intermediate **10** used in this synthesis is described in the accompanying paper.[9,18,19]

(16) For a related desilylation method using HF-H_2O-CH_3CN, see: Newton, R. F.; Reynolds, D. P.; Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3981.

(17) Accompanying **17** in this ketalization procedure is the isomeric hydroxyethyl furanoside. The two products can be separated chromatographically.

(18) We are indebted to Professor S. Omura (Kitasato University, Japan) and Dr. H. Yamada (Yamanouchi Pharmaceutical Co., Japan) for generous gifts of leucomycin A_3.

(19) This work was financially supported by the National Institutes of Health (Grant GM26879), Merck Sharp and Dohme, and the A. P. Sloan Foundation.

Synthesis of 16-Membered-Ring Marcolide Antibiotics. 4.[1] Carbomycin B and Leucomycin A_3: Total Synthesis of Cyclic Key Intermediate

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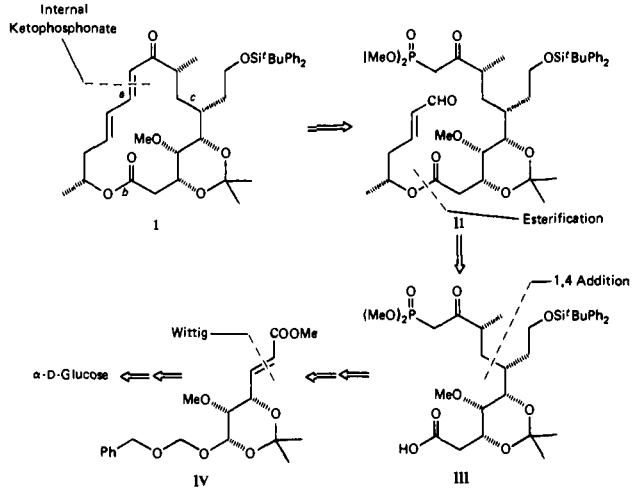
Received August 28, 1980

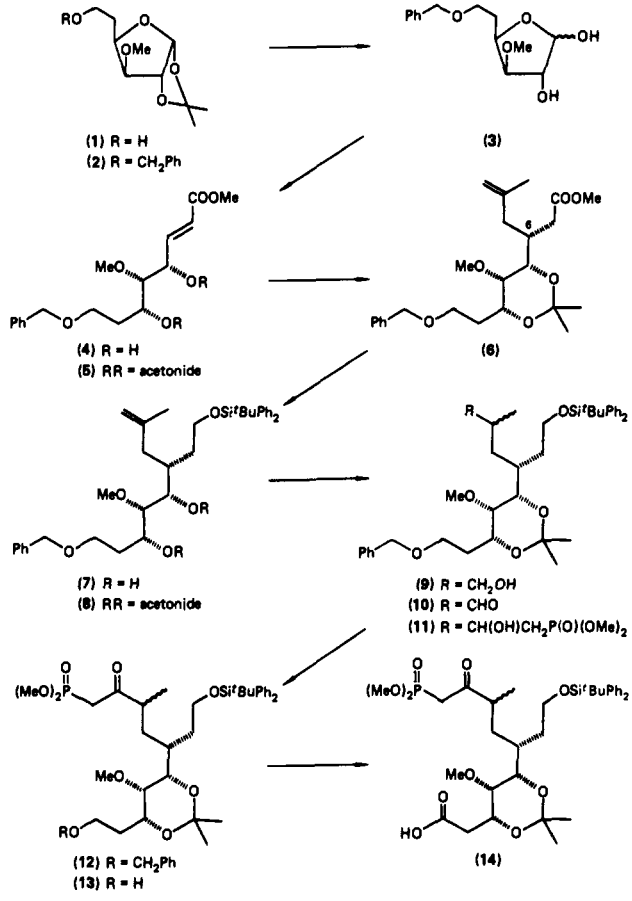
In the preceding paper[1] we described the partial synthesis of carbomycin B and leucomycin A_3 from the cyclic key intermediate I (Scheme I). In this paper we describe the total synthesis of this intermediate from α-D-glucose.

The synthesis of I was based on the retrosynthetic analysis depicted in Scheme I. Thus, careful inspection of structure I revealed three strategic bonds a, b, and c which upon sequential disconnection led to the progressively simpler intermediates II (internal ketophosphonate reaction), III (esterification), and IV (1,4 addition). Strategies for the synthesis of IV[3-5] from α-D-glucose and the stereoselective construction of bonds a[6] and c[3] were first reported by us[3,6] and subsequently by others.[4,5] Our convergent synthesis utilizes optically active starting materials and, therefore, produces I in its naturally occurring enantiomeric form.

Scheme I. Retrosynthetic Analysis of Cyclic Key Intermediate I



Scheme II



The synthesis of the C-1 to C-10 fragment (**14**, Scheme II) of these antibiotics started with α-D-glucose and proceeded via the readily available alcohol **1** (Scheme II) prepared as previously described.[3,5] Benzylation of **1** (1.3 equiv of $PhCH_2Br$, 1.3 equiv of NaH, DME, 60 °C) proceeded smoothly to afford **2**[7] (88%

† Fellow of the A. P. Sloan Foundation, 1979-1983; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980-1985.

(1) Part 3: Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, preceding paper in this issue.

(2) The total synthesis of this intermediate (I) was first reported at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979.

(3) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327.

(4) Ziegler, F. E.; Gilligan, P. J.; Chakraborty, U. R. *Tetrahedron Lett.* **1979**, 3371.

(5) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, 2837.

(6) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *43*, 4011.

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