4.30 (m, 1, H-3'), 4.14 (dt, 1, H-4'), 3.46 (ddd, B part of an ABMX spin system, 1, H-5'b), 3.13 (dd, A part of an ABMX spin system, 1, H-5'a), 2.72 (ddd, 1, H-2'b), 2.17 and 2.16 (d, 1, 5-CH_3 and ddd, 1, H-2'a); MS, m/z 224 $(M + 1)^+$. Anal. ($C_{10}H_{13}N_3O_3 \cdot 0.4H_2O$) C, H, N.

(B) Reaction of 2a with Ammonia. A stirred mixture of **2a** (1.00 g, 2.64 mmol), Me_2SO (10 mL), and liquid NH_3 (40 mL) was heated at 78 °C in a glass-lined stainless steel pressure vessel for 20 h. The reaction mixture was evaporated to dryness under high vacuum and an extract of the residue in 5:1 $CHCl_3$–MeOH (3 mL) applied to a flash column of 45 g of silica gel, which was then developed with the same solvent mixture. The product fraction was evaporated to dryness and the residue (617 mg) further purified as above on a second column of silica gel (80 g) to give crude **4b** (610 mg). A solution of this solid in MeOH (50 mL) was stirred with Dowex IX8 ($^-$OH) resin (2.0 g), filtered, and evaporated to a solid, which was triturated with EtOAc (1 mL), collected, and dried: yield 369 mg (61%); mp ca. 230 °C dec (Mel-Temp). The properties of this compound were identical with those described in A.

1-[2,5-Dideoxy-5-(methylamino)-β-D-*threo*-pentofuranosyl]thymine (5a). A stirred solution of **4a** (254 mg, 1.09 mmol) in 1 N NaOH (2.5 mL, 2.5 mmol) was heated in an oil bath at 70–75 °C for 20 h, adjusted to pH 8.5 with 1 N HCl, refrigerated, filtered, and evaporated to dryness under high vacuum. An EtOH (2 × 5 mL) extract of the residue was evaporated to an oil, which was purified on a flash column of 10 g of silica gel with MeOH as the eluting solvent. The product fraction was evaporated to dryness and further purified on a flash column of 45 g of silica gel with 20:10:1 $CHCl_3$–MeOH–NH_4OH as the eluting solvent. The product fraction was evaporated to dryness and the residue triturated with EtOAc (2 mL) to give a white powder, which was collected, washed with EtOAc, and dried at 56 °C: yield 64 mg (23%); mp 184 °C; UV (MeOH) [λ_{max}, nm ($\epsilon \times 10^{-3}$)] (pH 1) 266 (9.67), (pH 7) 266 (9.74), (pH 13) 266 (7.46); ^{1}H NMR δ 7.83 (q, 1, H-6, J = 1.0 Hz), 6.06 (dd, 1, H-1'), 4.22 (dd, 1, H-3'), 3.82 (dt, 1, H-4'), 2.84 (dd, B part of an ABX spin system, 1, H-5'b), 2.78 (dd, A part of an ABX spin system, 1, H-5'a), 2.55 (ddd, 1, H-2'b), 2.31 (s, 3, NCH_3), 1.84 (dd, 1, H-2'a), 1.77 (d, 3, 5-CH_3, J = 1.0 Hz); MS, m/z 256 $(M + 1)^+$. Anal. ($C_{11}H_{17}N_3O_4 \cdot 0.2H_2O$) C, H, N.

1-(5-Amino-2,5-dideoxy-β-D-*threo*-pentofuranosyl)thymine (5b). A stirred suspension of **4b** (585 mg, 2.62 mmol) and 1 N NaOH (6 mL) was heated in an oil bath at 80 °C for 11 h, adjusted to pH 8.5 with 1 N HCl, and evaporated to dryness in vacuo. The residue was evaporated with EtOH (2 × 25 mL) to remove H_2O. A solution of the residue in 20:10:1 $CHCl_3$–MeOH–NH_4OH (10 mL) was applied to a flash column of 125 g of silica gel and developed with the same solvent. The evaporated product was further purified on a second flash column of silica gel (45 g) to give, after evaporation of the product fraction, an oil, which was dissolved in 1:1 $CHCl_3$–EtOH (3 mL), filtered, and evaporated to an oil that solidified. The crystalline mass was triturated with $CHCl_3$, collected, washed with $CHCl_3$, and dried: yield 60 mg (9%); mp 190–195 °C (Mel-Temp); UV (MeOH) [λ_{max}, nm ($\epsilon \times 10^{-3}$)] (pH 1) 266 (9.41), (pH 7) 266 (9.33), (pH 13) 266 (7.20); ^{1}H NMR δ 7.82 (q, 1, H-6, J = 1.0 Hz), 6.06 (dd, 1, H-1'), 4.25 (dd, 1, H-3'), 3.69 (td, 1, H-4'), 3.44 (q, CH_2 of EtOH), 2.89 (dd, B part of an ABX spin system, 1, H-5'b), 2.83 (dd, A part of an ABX spin system, 1, H-5'a), 2.55 (ddd, 1, H-2'b), 1.84 (dd, 1, H-2'a), 1.76 (d, 3, 5-CH_3, J = 1.0 Hz), 1.06 (t, CH_3 of EtOH); MS, m/z 242 $(M + 1)^+$. Anal. ($C_{10}H_{15}N_3O_4 \cdot 0.2C_2H_5OH \cdot 0.7H_2O$) C, H, N.

Acknowledgment. This investigation was supported by Grant CA23173 awarded by the National Cancer Institute, National Institutes of Health. We are indebted to Dr. W. C. Coburn, Jr., and other members of the Molecular Spectroscopy Section of Southern Research Institute, who performed the microanalytical and spectral determinations.

Registry No. **1a**, 63914-08-9; **2a**, 26922-45-2; **4a**, 108169-93-3; **4b**, 108169-94-4; **5a**, 108169-95-5; **5b**, 108169-96-6; $MeNH_2$, 74-89-5; thymidine, 50-89-5.

Stereochemical Studies of Polyols from the Polyene Macrolide Lienomycin

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Received December 30, 1986

Because the polyene macrolides are characterized by noncrystallinity and the presence of numerous chiral hydroxyl groups, elucidation of their stereochemistry has constantly been a challenging problem; to date the full stereochemistry of only amphotericin B is known. Taking lienomycin as an example, we have devised methods to determine the relative and absolute configurations of acyclic polyols. This has resulted in clarifying 10 of the 15 chiral centers in the aglycone.

Taking lienomycin, a polyene antibiotic with 15 chiral centers in the macrolactone ring, as an example, we have attempted to devise general approaches for determining the relative and absolute configurations of their polyol moieties. The method consists of (a) preparation of cleaved fragments by ozonolysis, etc.; (b) conversion of the 1,3-diol groups into 6-membered isopropylidenes to determine the relative configurations of *sec*-hydroxyl and *sec*-methyl groups; and (c) conversion of cleaved fragments into 6-membered hemiacetal dibenzoates to establish their absolute configurations by the dibenzoate chirality method. The absolute configurations of simpler fragments are determined by direct correlation with known or synthetic specimen.

The macrolide antibiotic lienomycin is produced by *Actinomyces diastatochromogenes* var. lienomycine[1] and

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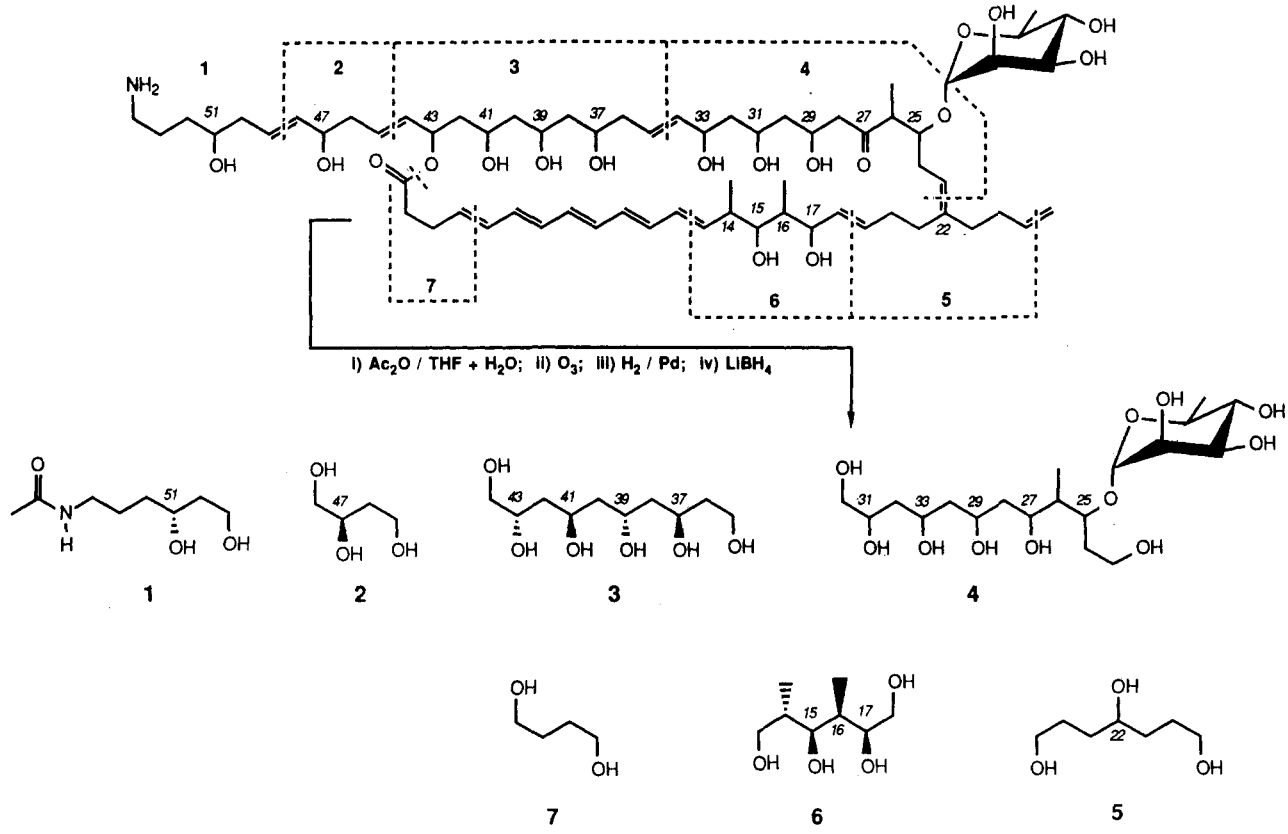

Figure 1. Degradation of lienomycin and structures of products 1–7.

exhibits antibacterial[2] and antitumor[3] as well as antifungal activity typical for polyene macrolides. Although the gross structure of leinomycin has been reported,[4-6] its stereochemistry remains unknown. The amorphous nature of the macro ring and the multitude of chiral centers have been major obstacles in structural elucidation of macrolides. Thus, although numerous members of the polyene macrolide family[7] are known, most of them are characterized only by partial structures. Moreover, amphotericin B is the only member of this family with the absolute configuration assigned.[8] We report the results of stereochemical studies on lienomycin in view of the increased interest in the chemistry of polyene macrolides as exemplified by the recent studies by Nicolau[9] and Fraser-Reid.[10]

The studies were performed on its degradation products obtained by the reaction sequence presented in Figure 1: (i) N-acetylation; (ii) ozonolysis of the 11 double bonds; (iii) catalytic hydrogenation of ozonides; (iv) lithium borohydride reduction of the ester moiety, 27-one, and aldehyde groups resulting from ozonolysis. It was assumed that the degradation products thus obtained retained all chiral centers originally present. Here we report determination of the absolute configurations at 10 of these centers, namely C-51 (**1**), C-47 (**2**), C-43/C-41/C-39/C-37 (**3**), and C-14/C-15/C-16/C-17 (**6**) (Figure 1).

I. Absolute Configuration of Butane-1,2,4-triol (2) and 1-Acetamidohexane-4,6-diol (1) (Figure 1). Degradation products **1** and **2** were examined by chemical correlation with (*S*)-(−)-malic acid (**8**) as shown in Figure 2. Esterification of **8** followed by reduction with sodium borohydride yielded (*S*)-(−)-butane-1,2,4-triol (**9**), its specific rotation $[\alpha]_D$ −24.3° indicating that the absolute configuration at C-47 in **2**, $[\alpha]_D$ +24.5°, is *R*.

S-(−)-Butane-1,2,4-triol (**9**), protected as its 2,4-*O*-benzylidene derivative **10**, was oxidized to 2,4-*O*-benzylidene-1-oxobutane-2,4-diol (**11**), which was then reacted with diethyl cyanomethyl phosphonate to yield 1-cyano-2,4-*O*-benzylidenepent-1-ene-2,4-diol (**12**); catalytic hydrogenation of **12** in acetic anhydride gave 1-acetamido-2,4-*O*-benzylidenehexane-2,4-diol (**13**), $[\alpha]_D$ +32°, the structure of which was elucidated by ^1H NMR. In benzylidene derivatives **10–13**, only the more stable of the two possible diastereomers (i.e., with equatorial phenyl group) was formed. Degradation product **1** from lienomycin was converted into benzylidene derivative **1a**, $[\alpha]_D$ +31.6°, having an ^1H NMR identical with that of **13**; the absolute configuration at C-51 is thus *R*.

II. Absolute Configuration of 3. (a) Relative Configurations at C-43/41 and C-39/37 in 3. Relative configurations at C-43/41 and C-39/37 in **3** were established by ^1H NMR studies of **3c** (Figure 3), which was prepared by reaction of dipivaloyl ester **3a** with 2,2-dimethoxypropane (to **3b**) and deprotection. The ^1H NMR studies leading to full proton assignments (Figure 4) included COSY, homonuclear difference decoupling, and simulations (1180 ITRCAL).

(1) Gauze, G. F.; Maksimova, T. S.; Olchovatova, O. L.; Kudrina, E. S.; Kochetkova, G. V.; Volkova, L. Ya. *Antibiotiki* **1971**, 387–390.
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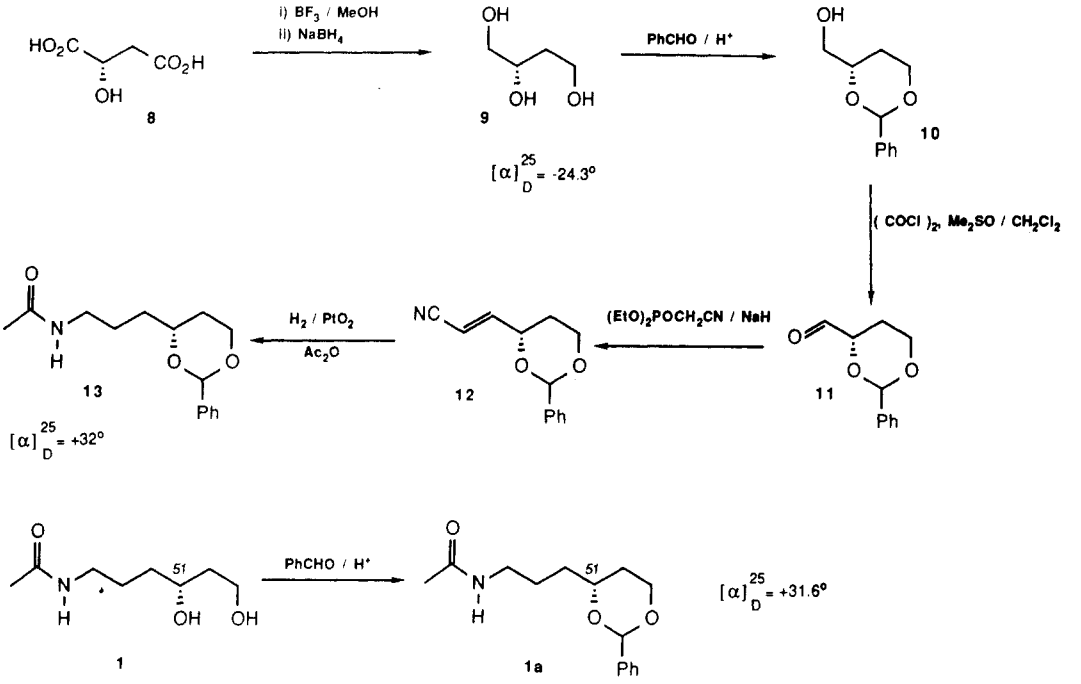


Figure 2. Determination of absolute configurations at C-47 and C-51.

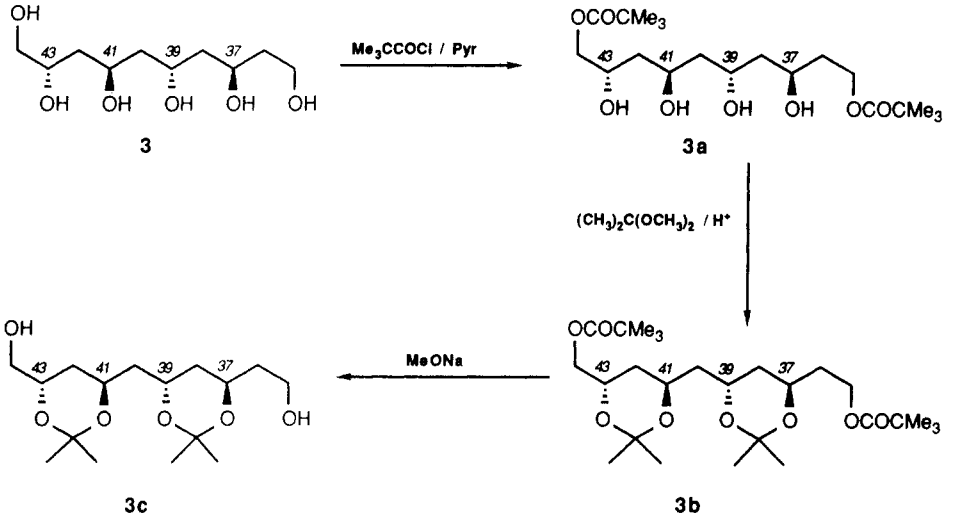


Figure 3. Derivatization of 3 into the diisopropylidene derivative 3c.

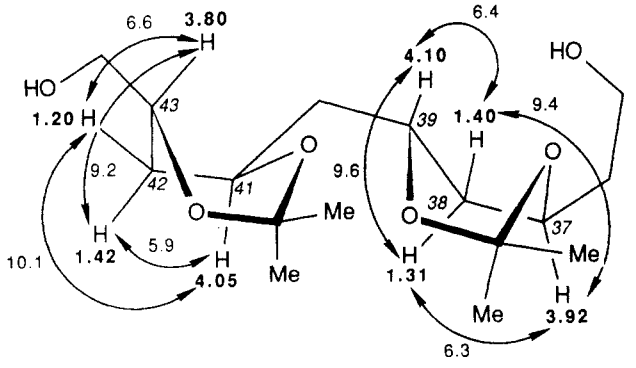


Figure 4. Assignments of relative configurations at C-43/C-41 and C-39/C-37.

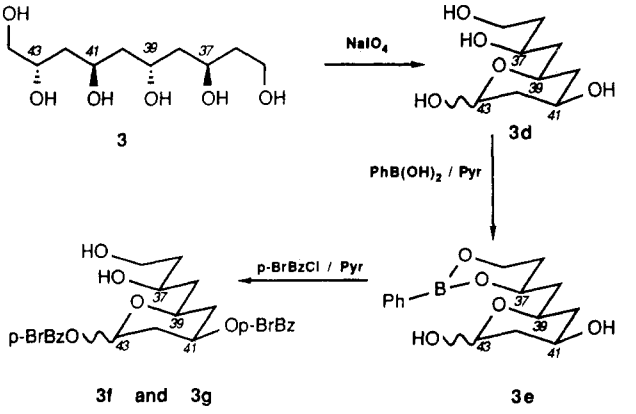
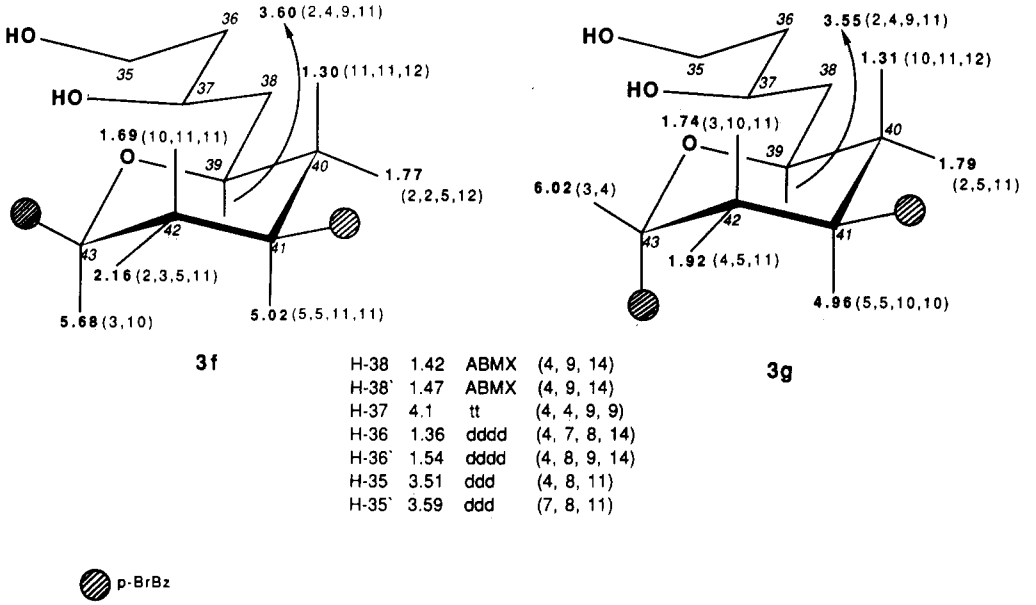


Figure 5. Transformation of 3 into 3f and 3g.

The vicinal coupling constants of protons 43/42/41 and protons 38/37 indicated that both 4,6-disubstituted 1,3-dioxane rings existed in nonchair conformations. Namely, half the sum of all vicinal coupling constants between the protons in 4,6-disubstituted 1,3-dioxanes is 11 and 15 Hz for chair and nonchair (or twist-boat) conformations, respectively.[11] In 3c this value is 15.6 Hz for both rings. The twist-boat conformations of both 1,3-dioxane rings lead to relative configurations $R/S(S/R)$ for C-43/41 and R/S-(S/R) for C-39/37.

(11) Tavernier, D.; Anteunis, M. *Bull. Soc. Chim. Belges* **1973**, *76*, 157.



H-38	1.42	ABMX	(4, 9, 14)
H-38`	1.47	ABMX	(4, 9, 14)
H-37	4.1	tt	(4, 4, 9, 9)
H-36	1.36	dddd	(4, 7, 8, 14)
H-36`	1.54	dddd	(4, 8, 9, 14)
H-35	3.51	ddd	(4, 8, 11)
H-35`	3.59	ddd	(7, 8, 11)

Figure 6. Conformations of **3f** and **3g**.

(b) Relative Configurations at C-41/39 in 3. Relative configurations at C-41/39 were assigned by ^{1}H NMR studies of **3f** obtained by chemical transformations presented in Figure 5. The first step was periodate oxidation of **3** which yielded **3d**. The next two steps shown in Figure 5 were performed sequentially as a one-pot reaction, i.e. phenyl boronate formation followed by p-bromobenzoylation (accompanied by deprotection), yield **3f** and **3g**. The NMR results leading to full stereochemical assignments and chair conformation for **3f** are shown in Figure 6. Thus, *R*/*S*(*S*/*R*) are assigned to C-41/39; namely, the 3-substituents on the pyran ring are equatorial.

(c) Absolute Configuration of 3g. The scheme in Figure 5 gave rise to a minor product **3g**. Despite the limited amount of 100 μg it was possible to clarify the ^{1}H NMR signals as depicted in Figure 6 by homonuclear decoupling and comparison with the spectrum of **3f**. The vicinal coupling constants between the ring protons clearly indicated that the pyran ring adopts a chair conformation and that the two benzoate groups at C-41/43 are equatorial/axial; namely, unlike the diequatorial benzoates in **3f** the spatial disposition of the benzoates in **3g** is suited for analysis by the exciton chirality method.[12] The circular dichroic spectrum of **3g** exhibited a typical negatively split curve: (in MeOH) 250 nm (Δε −15.7), and 234 (Δε +5.9). This leads to the absolute configuration shown in **3g**, or 43*S*/41*R*/39*S*/37*R* in **3**.

III. Absolute Configurations at C-14, C-15, C-16, and C-17 in 6. Relative and absolute configurations of fragment **6** (Figure 1) were assigned by a scheme similar to that described above for **3**. Thus, pivaloylation, isopropylidene formation, and deprotection afforded **6c** (Figure 7). The coupling constants between protons 15/16/17 (**6c**, Figure 8) indicated that the 1,3-dioxane ring adopts a chair conformation and established the relative configurations at these centers.

The relative configurations at C-15/14 and the absolute configuration of **6** were next determined from the spectroscopic data of **6d** obtained by periodate cleavage of **6** followed by p-bromobenzoylation (Figure 7). The NMR data (Figure 8) showed the pyran ring to be in the chair

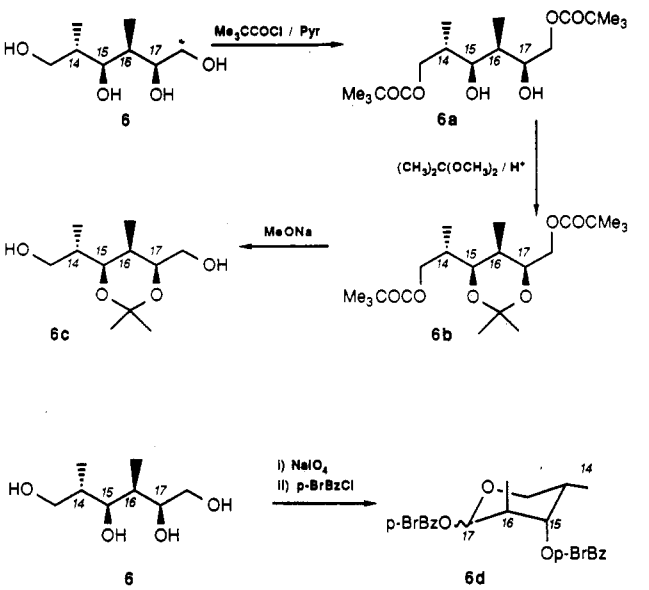


Figure 7. Derivatization of **6** into the isopropylidene derivative **6c** and bis(*p*-bromobenzoate) **6d**.

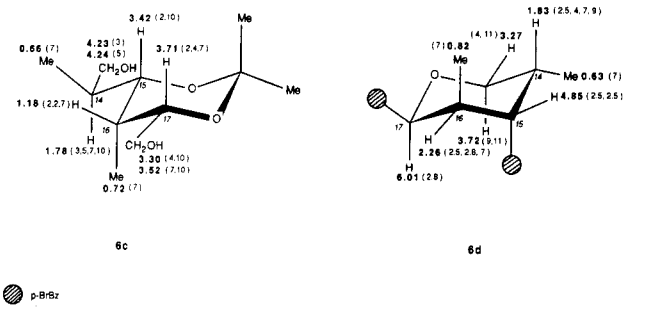


Figure 8. Conformations of **6c** and **6d**.

conformation and the benzoate groups at C-15/17 to be axial/equatorial.

The positively split CD spectrum of **6d** (in MeOH) [250 nm (Δε +9.6), 234 (Δε −4.8)] established the absolute configuration of **6d** as shown. The absolute configurations of moiety **6** are thus 14*S*, 15*S*, 16*R*, and 17*S*.

This leaves fragment **4** containing five of the remaining chiral centers in the lienomycin aglycone (C-27 originates

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Table I. Proton Assignments for 3c (C_6D_6)

H/C	δ	mult	coupling partner (^3J, Hz)
H-44	3.37	ddd	OH (4.0), H-43 (6.6), H-44′ (11.5)
H-44′	3.42	ddd	OH (7.5), H-43 (3.5), H-44 (11.5)
H-43	3.80	dddd	H-44′ (3.5), H-44 (6.6), H-42 (6.6), H-42′ (9.2)
H-42	1.20	ddd	H-43 (6.6), H-41 (10.1), H-42′ (12.6)
H-42′	1.42	ddd	H-43 (9.2), H-41 (5.9), H-42 (12.6)
H-41	4.05	dddd	H-42′ (5.9), H-40 (7.2), H-42 (10.1), H-40′ (4.0)
H-40	1.40	ddd	H-41 (7.2), H-39 (4.1), H-40′ (13.6)
H-40′	1.45	ddd	H-41 (4.0), H-39 (7.2), H-40 (13.6)
H-39	4.10	dddd	H-40 (4.1), H-40 (7.2), H-38 (9.6), H-38′ (6.4)
H-38	1.31	ddd	H-39 (9.6), H-38′ (12.6), H-37 (6.3)
H-38′	1.40	ddd	H-39 (6.4), H-38 (12.6), H-37 (9.5)
H-37	3.92	dddd	H-38 (6.3), H-38′ (9.5), H-36 (3.7), H-36′ (8.8)
H-36	1.43	dddd	H-37 (3.7), H-36′ (14.3), H-35 (5.0), H-35′ (6.5)
H-36′	1.64	dddd	H-37 (8.8), H-36 (14.3), H-35 (7.3), H-35′ (4.5)
H-35	3.59	dddd	H-36 (5.0), H-36′ (7.3), H-35′ (11.0), OH (0.3)
H-35′	3.66	dddd	H-36 (5.0), H-36′ (4.5), H-35 (11.0), OH (5.0)
C-Me	1.33	s	
C-Me	1.35	s	

from reduction of the 27-one). However, despite several attempts it was not possible to elucidate its stereochemistry due to the following reasons: (i) formation of unseparable epimers at C-27; (ii) failure to cleave the glycosidic bond under mild conditions to leave the aglycon intact; (iii) the limited supply of lienomycin.

In summary, we have degraded the polyene antibiotic into several acyclic polyol fragments and have determined the absolute as well as relative configurations by (a) direct chemical correlations or (b) conversion to cyclic 6-membered 1,3-dioxanes amenable to ^1H NMR and CD analyses. In order to avoid formation of more than one dioxane from a particular acyclic polyol, it is *desirable that the polyol to be reacted contains an even number of hydroxyl functions.*

Experimental Section

Specific rotations were measured at 25 °C on a Perkin-Elmer 141 polarimeter. CD spectra were recorded on a Jasco 500A spectropolarimeter driven by a Jasco DP500N data processor. The COSY spectra of **3f** and **3g** were obtained at 360 MHz on a Nicolet NT-360 spectrometer equipped with NIC 1280/293B data system. Simulations of ^1H NMR spectra were carried out with the 1180 ITRCAL program on a NIC 1280/293B data system. Routine ^1H NMR spectra were obtained at 250 MHz on a Brucker WM-250 spectrometer.

DCI/CI and FAB mass spectra were measured on Ribermag 10-10-C and VG-70EQ spectrometers, respectively. Purifications of the end products were performed by silica gel flash chromatography unless stated otherwise.

Acylation of Primary Hydroxyl Groups with Pivaloyl Chloride (Procedure a). The compound (0.04 mM) was dissolved in 1.5 mL of pyridine, and 0.09 mM of pivaloyl chloride was added. After 6 h 0.5 mL of MeOH and 5 mL of heptane were added, and the reaction mixture was evaporated to dryness.

Acetonization (Procedure b). The compound (10 mg) was dissolved in 1 mL of $Me_2C(OMe)_2$, and a catalytic amount of TsOH was added. After 2 h the reaction mixture was diluted with 5 mL of Et_2O and passed through a short column packed with basic Al_2O_3. The eluent was evaporated to dryness.

Deprotection of Primary Hydroxyl Groups (Procedure c). The compound (10 mg) was dissolved in 1 mL of dry MeOH, and 15 mg of MeONa was added. After 2 h the reaction mixture was evaporated to dryness.

Periodate Oxidation (Procedure d). The compound (10 mg) was dissolved in 1 mL of H_2O, and 10 mg of $NaIO_4$ was added. After 30 min the reaction mixture was diluted with 4 mL of H_2O and passed through a short column packed with two beds of resin RG501-X8. The eluent was evaporated to dryness.

Acylation with *p*-Bromobenzoyl Chloride (Procedure e). The sample (10 mg) was dissolved in 1 mL of pyridine, and 30 mg of *p*-BrBzCl was added. After 1 h 0.5 mL of MeOH and 5 mL of heptane were added, and the reaction mixture was evaporated to dryness.

Protection of 1,3-Diols as 1,3-*O*-Benzylidene Derivatives (Procedure f). The 1,3-diol (X mM) was dissolved in $5X$ mL of $PhCH(OMe)_2$, and a catalytic amount of TsOH was added. After 1 h the reaction mixture was diluted 5-fold with Et_2O and passed through a short column of basic Al_2O_3. The Et_2O was evaporated from the eluent, and the residue was applied to a silica gel column and eluted with 50 mL of hexane in order to remove $PhCH(OMe)_2$. The residue on top of the column was then flash chromatographed.

Degradation of Lienomycin. Degradation products 1–7 were obtained, separated, and identified by the procedure previously described.[6]

(*S*)-(−)-Dimethyl Malate. 8 (1 g) was subjected to Fisher esterification to give 1.19 g of dimethyl malate.

(*S*)-(−)-Butane-1,2,4-triol (9). Dimethyl malate (600 mg, 3.7 mmol) was dissolved in 15 mL of THF/H_2O (1:1), and 200 mg (5.3 mmol) of $NaBH_4$ was added. After 20 min the reaction mixture was diluted with 30 mL of MeOH, and Dowex 50WX8 [H^+] was added to pH 7. The reaction mixture was then filtered, and the filtrate was evaporated to dryness. The residue was twice dissolved in 10 mL of MeOH and evaporated to dryness. The crude product was purified by flash chromatography with CH_2Cl_2/MeOH (10:1): yield 380 mg (96%); FAB-MS, m/e 107 $[M + H]^+$; NMR (pyridine-d_5) δ 2.14 (2 H, m), 3.97 (2 H, dd), 4.17 (2 H, dt), 5.38 (1 H, m), 6.05 (3 H, m); $[\alpha]_D$ −24.3° (*c* 2, MeOH).

2,4-*O*-Benzylidenebutane-1,2,4-triol (10). **10** was prepared from 300 mg of **9** by procedure f and purified with Hex/AcOEt (3:1): yield 330 mg (60%); CI-MS, m/e 195 $[M + H]^+$; NMR (C_6D_6) δ 0.65 (1 H, ddt), 1.55 (1 H, ddt), 3.30–3.50 (4 H, m), 3.85 (1 H, ddd), 5.27 (1 H, s), 7.08–7.20 (3 H, m), 7.55 (2 H, m).

2,4-*O*-Benzylidene-1-oxobutane-2,4-diol (11). **10** (200 mg) was subjected to Swern oxidation[13] and purified with Hex/AcOEt (3:1): yield 170 mg (86%); CI-MS, m/e 193 $[M + H]^+$; NMR (C_6H_6) δ 1.10 (1 H, ddt), 1.54 (1 H, dddd), 3.25 (1 H, ddd), 3.53 (1 H, dd), 3.76 (1 H, dd), 5.17 (1 H, s), 7.10–7.25 (3 H, m), 7.62 (2 H, m), 9.43 (1 H, br s).

1-Cyano-3,5-*O*-benzylidenepent-1-ene-3,5-diol (12). **11** (150 mg) was reacted with $(EtO)_2POCH_2CN$ and puified with Hex/AcOEt (4:1): yield 136 mg (82%); CI-MS, m/e 216 $[M + H]^+$; NMR (C_6D_6) (cis isomer) δ 1.00 (1 H, ddt), 1.48 (1 H, dddd), 3.34 (1 H, dt), 3.78 (1 H, ddd), 4.44 (1 H, dd), 4.54 (1 H, ddt), 5.20 (1 H, s), 5.81 (1 H, dd), 7.05–7.25 (3 H, m), 7.61 (2 H, m), (trans isomer) δ 0.53 (1 H, ddt), 1.18 (1 H, dddd), 3.21 (1 H, dt), 3.48 (1 H, dddd), 3.74 (1 H, ddd), 5.14 (1 H, s), 5.81 (1 H, dd), 7.10 (3 H, m), 7.55 (2 H, m).

1-Acetamido-4,6-*O*-benzylidenehexane-4,6-diol (13, 1a). **12** (50 mg) was dissolved in 1 mL of Ac_2O, and 5 mg of PtO_2 was added. The reaction mixture was hydrogenated in a closed system under slight hydrogen pressure. After 16 h the catalyst was

(13) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

filtered, and the filtrate was diluted with 15 mL of toluene and evaporated to dryness. The crude product was purified CH_2Cl_2/AcOEt (2:1): yield 37 mg (61%); DCI-MS, m/e 264 [M + H]$^+$; NMR (C_6D_6) δ 0.88 (1 H, br d), 1.15–1.65 (5 H, m), 1.55 (3 H, s), 3.12 (2 H, m), 3.40 (1 H, dddd), 3.52 (1 H, dt), 3.98 (1 H, dd), 4.65 (1 H, br s), 5.38 (1 H, s), 7.05–7.25 (3 H, m), 7.65 (2 H, m); $[\alpha]_d$ +32° (c 1, MeOH).

1 (10 mg) was derivatized to **1a** by procedure f and purified as described above: yield 9 mg (60%); 1 $[\alpha]_D$ +31.6°; other spectral data, identical with those of **13**.

Compound 3c. **3** (10 mg) was acylated by procedure a, acetonized by procedure b, deprotected by procedure c, and purified with hex/AcOEt (5:2): yield 7 mg of **3c**; CI-MS, m/e 319 [M + H]$^+$.

Compounds 3f and 3g. **3** (10 mg) was subjected to periodate oxidation by procedure d. The product obtained was dissolved in 1 mL of dry pyridine, and 6 mg of $PhB(OH)_2$ and molecular sieves type 4A were added. After 1 h molecular sieves were removed, and 20 mg of *p*-BrBzCl was added. After 2 h 0.5 mL of MeOH and 5 mL of heptane were added, and the reaction mixture was evaporated to dryness. The residue was dissolved in 5 mL of Et_2O and passed through a short column packed with basic Al_2O_3. The column was eluted sequentialy with 8 mL of Et_2O and 5 mL of MeOH, and the MeOH eluent was evaporated to dryness. The residue was purified by HPLC with CH_2Cl_2/AcOEt (3:1): yield 4 mg of **3f** and 0.1 mg of **3g** (estimated from UV); DCI-MS for **3f** and **3g**, m/e 575 (50%), 573 (100%), 571 (50%) [M + H]$^+$.

Compound 6c. **6** (10 mg) was acrylated by procedure a, acetonized by procedure b, deprotected by procedure c, and purified with hex/AcOEt (2:1): yield 6 mg; CI-MS, m/e 179 [M + H]$^+$.

Compound 6d. **6** (10 mg) was oxidized by procedure d, acylated by procedure e, and purified by HPLC with hex/AcOEt (10:1): yield 4 mg; DCI-MS, m/e 515 (50%), 513 (100%), 511 (50%) [M + H]$^+$.

Acknowledgment. Current studies were supported by NIH Grant AI 10187 and in part by the Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Project CPBP 01.13.

Relative Stabilities of the Desmotroposantonins

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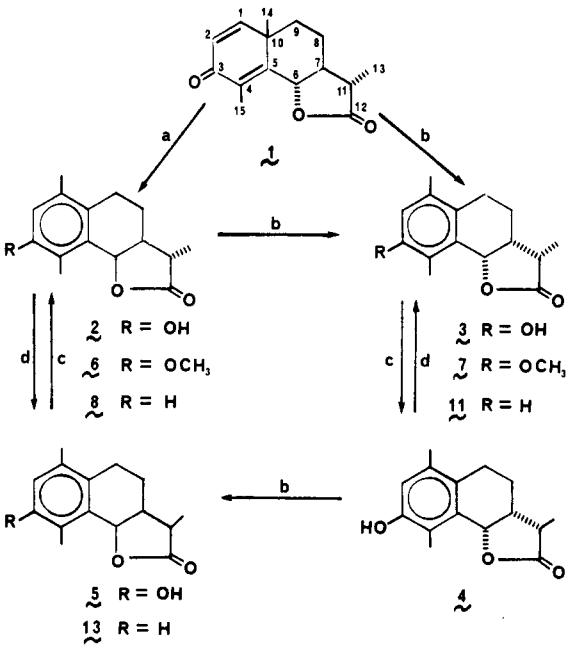
Received September 17, 1986

Equilibration of (−)-α-desmotroposantonin methyl ether (**6**), (+)-β-desmotroposantonin methyl ether (**7**), and isohyposantonin (**8**) with K_2CO_3 in xylene gives the same 56:44 mixture of isomers at C-11. Although acid-catalyzed isomerization of (−)-α-desmotroposantonin (**2**) affords (+)-β-desmotroposantonin (**3**) in good yield, the deoxy analogue of **2**, isohyposantonin (**8**), gives an approximately 1 to 1 mixture of **8** and the β-desmotroposantonin analogue (**11**) with acid **10** as the major product. These results indicate that the published data which indicate that the β-isomers are significantly more stable than their α-epimers are based on reactions in which equilibrium was not reached. NMR studies at 200 MHz show that the conformation of the lactone ring in the α- and β-isomers is not the same. A conformation is suggested for α-desmotroposantonin on the basis of the NMR data, and an explanation is offered for the stability relationships in the desmotroposantonin series.

The gross structure of the well-known and readily available sesquiterpene lactone α-santonin (**1**, no stereochemistry implied) was determined many years ago by Clemo, Haworth, and Walton.[1] Just over 30 years ago, in nearly simultaneous publications, Woodward and Corey presented reasonable arguments which strongly suggested that the stereochemistry of santonin is that depicted in **1** but with the configuration at C-11 reversed.[2] A few years later on the basis of crystallographic and degradative work the stereochemistry at C-11 was corrected and structure **1** was established for this historically important natural product.[3]

The incorrect stereochemical assignments were based on the unique cycle in which (−)-α-desmotroposantonin (**2**)[4] and (+)-β-DTS (**3**), dienone phenol rearrangement products of santonin, undergo further isomerizations under the conditions outlined in Scheme I (**2** to **5**).[5,6] Woodward and

Scheme I[a]



[a] (a) Ac_2O/H_2SO_4, 30 min, 90 °C, and then 10% aqueous NaOH/EtOH, 5 h, reflux; (b) 40% aqueous H_2SO_4, 12 h, 85 °C; (c) KOH, 1 h, 210 °C and then acidify; (d) K_2CO_3/xylene, 24 h, reflux.

Corey assumed that the vigorous acid treatment which affords the β-isomers is thermodynamically controlled and

(1) Clemo, G. R.; Haworth, R. D.; Walton, E. J. *J. Chem. Soc.* **1930**, 1110.

(2) (a) Woodward, R. B.; Yates, P. *Chem. Ind. (London)* **1954**, 1391. (b) Corey, E. J. *J. Am. Chem. Soc.* **1955**, *77*, 1044. (c) For a summarization of the arguments, see: Cocker, W.; McMurry, T. B. H. *Tetrahedron*, **1960**, *8*, 181.

(3) (a) Nakazaki, M.; Arakawa, H. *Proc. Chem. Soc.* **1962**, 151. (b) Asher, J. D. M.; Sim, G. A. *Ibid.* **1962**, 111. (c) Barton, D. H. R.; Miki, T.; Pinhey, J. T.; Wells, R. J. *Ibid.* **1962**, 112.

(4) The abbreviation DTS will be used to denote desmotroposantonin. The terms α and β refer to the relative stereochemistry at C-7 and C-11.

(5) Huang-Minlon (Huang-Minlon. *J. Am. Chem. Soc.* **1948**, 70, 611) summarizes these conversions in detail, and Barton (Barton, D. H. R. *J. Org. Chem.* **1950**, 15, 467) provides additional mechanistic rationalizations.

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