Diastereomeric 10,11-Epoxyerythromycins B and the Preparation of 10-*epi*-Erythromycin B[1]

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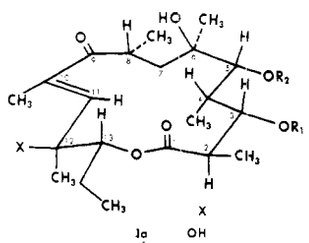
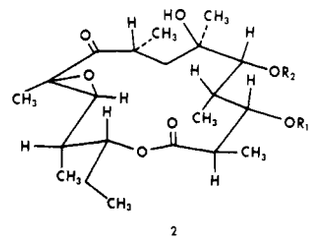
Received October 7, 1977

Epoxidation of 10,11-anhydroerythromycin B (**1b**) with either *m*-chloroperbenzoic acid or alkaline hydrogen peroxide gave, after reduction of the resulting *N*-oxide to the free amine, 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**). Catalytic hydrogenation of **2** gave a mixture of 10-*epi*-erythromycin B (**3**) and erythromycin B (**4d**). Sodium borohydride reduction of **1b** followed by epoxidation of the resulting allylic alcohol **12** with m-chloroperbenzoic acid gave, after reduction of the resulting *N*-oxide to the free amine, 9(*R*)-dihydro-10,11-anhydro-10(*R*),-11(*R*)-epoxyerythromycin B (**13**). The latter (**13**) readily rearranged to 9(*R*)-dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (**14**). Jones oxidation of both **13** and **14** gave 6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16a**). Albright–Goldman oxidation of **13** gave the 2′-*O*-acetyl-4″-oxo enol ether **17**, which was converted to 8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal (**18**) by methanolysis and sodium borohydride reduction.

We have previously reported studies of the chemistry of the erythromycin antibiotics which have been directed toward chemical and stereochemical modification of the erythromycin lactone rings.[2] Our general approach has involved initial introduction into the lactone rings of functionalizable sites of unsaturation. The present report is concerned with selective preparation from 10,11-anhydroerythromycin B (**1b**)[2a] of diastereomeric 10,11-epoxyerythromycins and some of their characteristic reactions, including the catalytic reduction of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) to 10-*epi*-erythromycin B (**3**).



	X
1a	OH
1b	H



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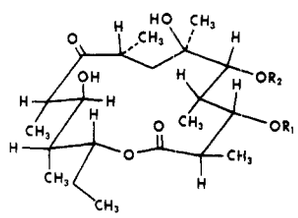

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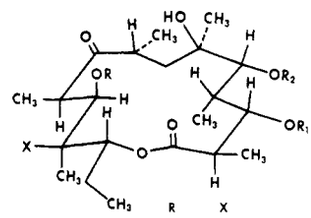
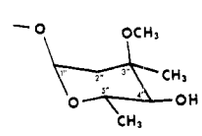
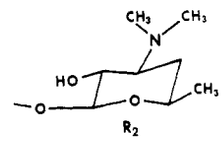


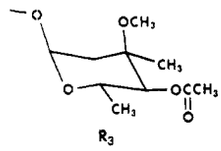
	R	X
4a	SO_2CH_3	OH
4b	SO_2CH_3	H
4c	H	OH
4d	H	H



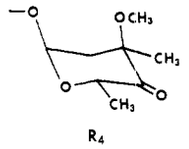
R_1



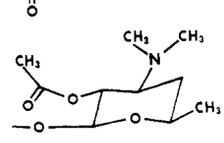
R_2



R_3



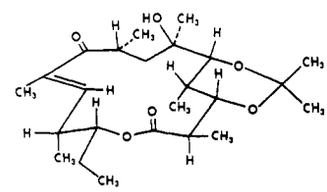
R_4



R_5

NMR and CD studies[4] of the erythromycin antibiotics have shown that the solution conformation of their aglycone rings is essentially identical with that found in the crystal for the hydriodide dihydrate of erythromycin A (**4c**).[6] Assignment of geometry to the 10,11-double bonds of the 10,11-anhydroerythromycins A and B (**1a** and **1b**), formed by base-catalyzed elimination of the elements of methanesulfonic acid from the corresponding 11-*O*-methanesulfonylerythromycins A and B[2a] (**4a** and **4b**, respectively), is based on the assumption of trans elimination of the antiperiplanar C_{10} protons and C_{11} methanesulfonate groups. The newly introduced trans double bonds of **1a** and **1b** are accommodated with minimal conformational change in the remainder of the lactone rings.[4]

Epoxidation of 10,11-anhydroerythromycin B (**1b**) with either *m*-chloroperbenzoic acid or alkaline hydrogen peroxide, followed by catalytic reduction of the resulting *N*-oxide to the free amine, gave, as shown below, 10,11-anhydro-10(*R*),-11(*S*)-epoxyerythromycin B (**2**). The stereochemistry of epoxidation of **1b** is thus the same as that reported by Corey, Nicolaou, and Melvin for the alkaline hydrogen peroxide oxidation of the 3,5-acetonide of 10,11-anhydroerythronolide B (**5**) to the 10(*R*),11(*S*)-epoxy ketone (**6**).[3] The structure of **6** was determined[3] by catalytic hydrogenation of **6** to the 10-*epi*-erythronolide derivative **7**, followed by C_{10} epimerization of the latter with potassium carbonate in methanol, and hydrolysis of the 3,5-acetonide of the resulting product to give erythronolide B (**8**).



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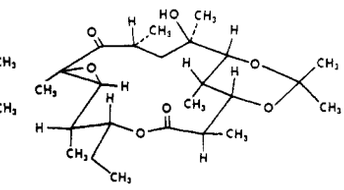

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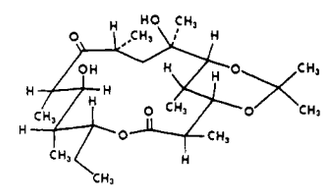

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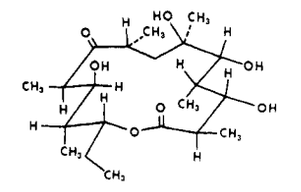

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Catalytic hydrogenation of epoxide ring of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) was favored when the reaction was carried out with the *N*-oxide of **2** rather than the free amine. For the hydrogenation, the *N*-oxide was prepared from pure **2** with hydrogen peroxide in methanol–water

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solution. Hydrogenation of the resulting *N*-oxide under 3 atm of hydrogen in methanol for 22 h in the presence of 5% Pd–C and sodium bicarbonate gave, in 22% yield, a 4:1 mixture of 10-*epi*-erythromycin B (**3**) and erythromycin B (**4d**), based on recovered epoxy ketone **2**. Since catalytic hydrogenation of the epoxy ketone **2** to the hydroxy ketones **3** and **4d** must occur with retention at C_{11}, isolation of erythromycin B (**4d**) established the configuration at C_{11} for both the epoxy ketone **2** and 10-*epi*-erythromycin B (**3**). In addition, since *m*-chloroperbenzoic acid epoxidations of olefins, in contrast to alkaline hydrogen peroxide epoxidations, are known to occur with stereospecific cis addition of oxygen to the double bond,[7] the configuration of the epoxy ketone **2** could be assigned.

Examination of Prentiss–Hall molecular models showed that 10-*epi*-erythromycin B (**3**) would have a 1,3-diaxial interaction between the C_{10} and C_{12} methyl groups if the conformation of its lactone ring were identical with that of erythromycin B (**4d**).[4] This interaction may be readily relieved by rotations about the C_{10}–C_{11} and C_{11}–C_{12} bonds, which place the C_{10} and C_{12} methyl groups in a 1,3-gauche relationship with the C_{12} methyl group in an equatorial orientation and the C_{10} methyl group in an axial orientation. In the resulting conformation, the conformation of the C_2–C_8 segment of the lactone ring remains the same as that of erythromycin B. The change in conformation of the C_{10}–C_{13} segment should also be favored, since the C_{11} hydroxyl group is closer to the C_6 hydroxyl group than is the case for erythromycin B and should thus result in a stronger intramolecular hydrogen bond. The dihedral angles between the H_{10} and H_{11} protons and the H_{11} and H_{12} protons of 10-*epi*-erythromycin B appear to be about 140–150°. The observed coupling constants of 10-*epi*-erythromycin B ($J_{10,11} = J_{11,12} = 6$ Hz) are compatible with the values ($J^{140} = 5.3$ and $J^{150} = 6.8$ Hz) calculated from the original Karplus equation.[8] The contrast between the above values and the corresponding coupling constants ($J_{10,11} = 1$ and $J_{11,12} = 9.8$ Hz)[2a] of erythromycin B, which has dihedral angles of about 90 and 180°, respectively, is consistent with the structure and conformation of 10-*epi*-erythromycin B.

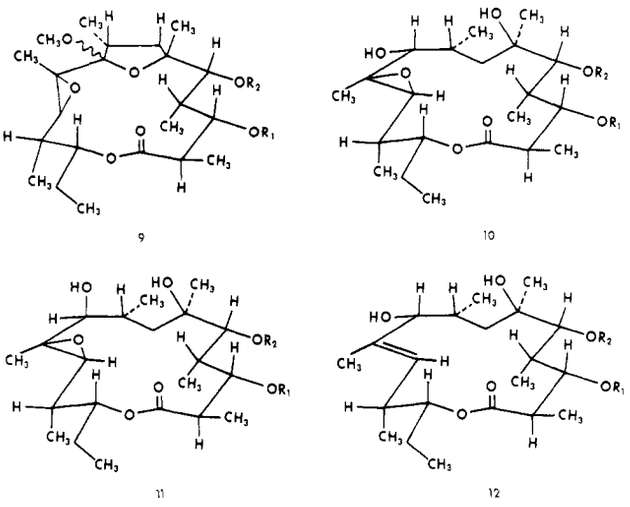
In our hands, attempted C_{10} epimerization of **3** with potassium carbonate in methanol gave only 10,11-anhydroerythromycin B (**1b**). Presumably the difference between the nature of the reactions of **3** and the 3,5-acetonide derivative (**7**) of 10-*epi*-erythronolide B described by Corey et. al.[3] is a consequence of the difference in lactone ring strain imposed by the different C_3 and C_5 substituents of **3** and **7**.

An attempt to convert the epoxy ketone **2** to 10-*epi*-erythromycin B (**3**) with chromous acetate gave only 10,11-anhydroerythromycin B (**1b**).

When the catalytic hydrogenation of the *N*-oxide of **2** was attempted with a sample which had not been rigorously freed of chloroform introduced during its isolation, the product obtained was the 6,9ξ-methyl acetal **9**. Formation of **9** from **2** is believed to be a consequence of the generation of hydrogen chloride under the hydrogenation conditions[9] from the chloroform present in the *N*-oxide. The 6,9ξ-methyl acetal **9** was readily converted to the epoxy ketone **2** on treatment with 1:1 (v/v) acetic acid–water solution.

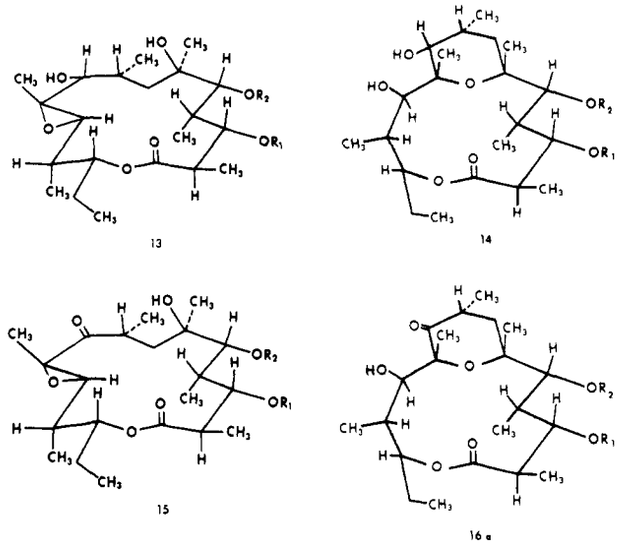
Sodium borohydride reduction of **2** gave a mixture of the C_9 epimeric alcohols **10** and **11**, which were separated by chromatography, but were not distinguished structurally.

Sodium borohydride reduction of 10,11-anhydroerythromycin B (**1b**) gave the allylic alcohol **12**. Epoxidation of **12** with *m*-chloroperbenzoic acid in a sodium bicarbonate buffered chloroform–water system, followed by catalytic reduction of the *N*-oxide product to the free amine, gave a 10:1 mixture of the 10,11-epoxy alcohol **13** and the 6,10-epoxy alcohol **14**, which were separated chromatographically. The epoxy alcohol **13** was assigned the 10(*R*),11(*R*) stereochemistry, since it



differed from the C_9 epimeric 10(*S*),11(*S*)-epoxy alcohols **10** and **11**.

The contrast in the stereochemistry of the epoxidations of the allylic alcohol **12** and the α,β-unsaturated ketone **1b** suggests a directing effect of the C_9 hydroxyl group of **12**, which results in epoxidation cis to the C_9 hydroxyl.[10] This consideration together with the 10(*R*),11(*R*) stereochemistry of the epoxy alcohol **13** led to the assignments of the 9(*R*) configurations to the allylic alcohol **12** and to both of the derived epoxy alcohols **13** and **14**.



An attempt to open the 10,11-epoxide ring of **13** with sodium azide in dimethylformamide in the presence of boric acid[11] led instead to quantitative rearrangement to the 6,10-epoxide **14**. The same product, **14**, was formed on treatment of the 10,11-epoxy alcohol **13** with 1:1 (v/v) acetic acid–water at room temperature. The latter rearrangement was shown by thin-layer chromatography to be complete within 0.5 h. In contrast, the diastereomeric epoxy alcohols **10** and **11** appeared to be stable for 24 h in 1:1 (v/v) acetic acid–water solution.

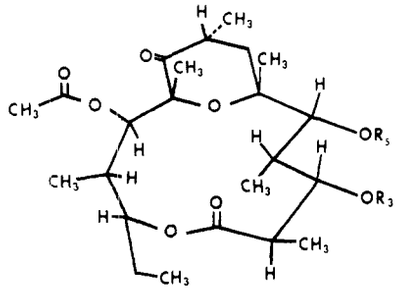
The facile acid-catalyzed rearrangement of the 10,11-epoxy alcohol **13** to the 6,10-epoxide **14** is compatible with backside attack of the C_6 hydroxyl group of **13** at C_{10} of the 10,11-epoxide ring. This rearrangement thus confirms the stereochemical assignment of the epoxide ring of **13**, and thus the stereochemical assignment of the diastereomeric epoxy alcohols **10** and **11** and the epoxy ketone **6** from which the latter two alcohols are derived.

An attempt to oxidize the 10(*R*),11(*R*)-epoxy alcohol **13** to the 10(*S*),11(*R*)-epoxy ketone **15** with Jones reagent gave instead 6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16a**). The same

product was formed by Jones oxidation of the 6,10-epoxide **14**, and it seems likely that formation of **15** from the 10,11-epoxy alcohol **13** occurs via initial acid-catalyzed rearrangement of **13** to **14** under the acidic Jones conditions. In contrast to the behavior of **13**, Jones oxidation of both the diastereomeric epoxy alcohols **10** and **11** regenerated the epoxy ketone **2**.

Our assignment of structure to the oxidation product **16a** as the C_9 rather than the C_{11} ketone is based on our assumption that the internally directed axial C_{11} proton of **14** would be hindered to attack by base in an intermediate 11-*O*-chromate ester. Preferential oxidation of axial over equatorial steroid alcohols has been similarly attributed to steric hindrance of axial protons, since the rate-determining step for chromic acid oxidation of alcohols is normally attack by base on the geminal proton of intermediate chromate esters.[12]

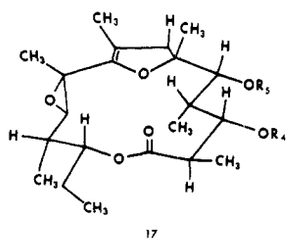
The ketone **16a** was converted into the 11,2′,4″-tri-*O*-acetyl derivative **16b** with acetic anhydride in pyridine. The latter,



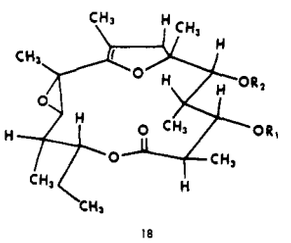
16b

16b, showed the absence of hydroxyl absorption in the infrared. Comparison of the NMR absorptions of the C_{11} protons of **16a** and **16b** (δ 4.03 and 5.20, respectively) showed that the expected paramagnetic shift on acetylation of the C_{11} hydroxyl group occurred. In addition, the C_{11} proton absorptions of both **16a** and **16b** appeared as slightly broadened singlets ($W_{1/2}$ = 3 and 2 Hz, respectively) which were compatible with the coupling constants $J_{11,12} \simeq 0$, which was expected since models indicated the dihedral angles between the C_{11} and C_{12} protons of **16a** and **16b** to be ~90°.

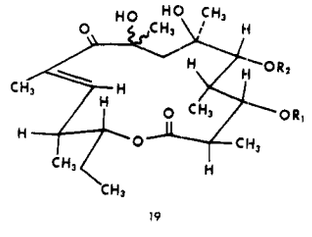
An attempt to convert the epoxy alcohol **13** to the epoxy ketone **15** by the Albright–Goldman modification of the Moffatt oxidation gave the 2′-*O*-acetyl-4″-oxoepoxy enol ether **17**, which was converted to the epoxy enol ether **18** by methanolysis of the 2′-*O*-acetyl group and sodium borohydride reduction[13] of the 4″-oxo group of **17**. The epoxy enol



17



18



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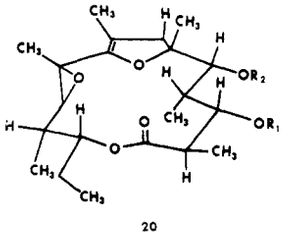

20

ether is most likely formed from the desired epoxy ketone **15** under the Albright–Goldman conditions. Enol ether formation from **15** contrasts with the behavior of erythromycin B (**4d**) under the Albright–Goldman conditions, which yields 2′-*O*-acetyl-4″-oxo-11-*O*-methylthiomethylerythromycin B[14] rather than the corresponding 8,9-anhydro 6,9-hemiacetal.

An attempt to convert the epoxy enol ether **18** to the epoxy ketone **15** by hydration of the enol ether double bond in 1:1 (v/v) acetic acid–water gave a mixture from which the major product was isolated with difficulty by chromatography. Spectral properties (IR, NMR) suggested that this material was one of the C_8 epimeric 8-hydorxy-10,11-anhydroerythromycins (**19**). Formation of the latter (**19**) from **18** may be formulated as shown in Scheme I.

An attempt to form the enol ether **20** from the epoxy ketone **2** under conditions which readily convert both erythromycin A and erythromycin B to their corresponding enol ethers (glacial acetic acid, 4 h, room temperature)[15] gave predominantly recovered starting material (~75%), while after 24 h extensive decomposition had occurred, leading to a multicomponent mixture. Under Albright–Goldman conditions **2** gave an intractable mixture. An examination of molecular models showed that the enol ether **20** would have a severe steric interaction between the C_8 and C_{10} methyl groups. No such interaction is present either in the diastereomeric enol ether **18** formed by Albright–Goldman oxidation of the epoxy alcohol **13**, or in either of the two possible C_9 epimers of the 9 ξ-methyl acetal **9** formed from the epoxy ketone **2** under the hydrochloric acid generating hydrogenation conditions.

The in vitro antibacterial activities of compounds **4c**, **4b**, **1b**, **2**, **3**, **10–14**, **16a**, **18**, and **19** are shown in Table I together with those of erythromycin A (**4c**), erythromycin B (**4d**), and the 9-dihydroerythromycins A and B (**21** and **22**). Although none of the derivatives reported have activities approaching those of the naturally occurring antibiotics **4c** and **4d**, it is of interest that both of the C_9 epimeric 9-dihydro-10(*S*),-11(*S*)-epoxy ketones **10** and **11** are much more active than the 10(*S*),11(*S*)-epoxy ketone **2** from which they were prepared. This contrasts with the greatly reduced activities of the 9-dihydroerythromycins A and B (**21** and **22**) compared with the parent antibiotics **4c** and **4d**. In addition, it may be noted that both of the C_9 epimeric 9-dihydro-10(*S*),11(*S*)-epoxyerythromycins (**10** and **11**) are much more active than the diastereomeric 9(*R*)-dihydro-10(*R*),11(*R*)- epoxyerythromycin (**13**). The importance of the stereochemistry of the erythromycin lactone rings is dramatically illustrated by the observation that 10-*epi*-erythromycin B (**3**), like 8-*epi*-erythromycin B reported previously,[2a] has greatly reduced antibacterial activity.

Experimental Section

The purity of all compounds was established spectroscopically and by TLC.[16] All compounds reported were characterized by M^+ peaks in their mass spectra. Optical rotations were determined with a Hilger and Watts polarimeter. IR spectra were obtained on deuteriochloroform solutions using a Perkin-Elmer Model 521 grating spectrometer. NMR spectra were determined at 100 MHz with a Varian HA-100 spectrometer with deuteriochloroform solutions. Chemicals shifts are reported in parts per million from internal tetramethylsilane (δ 0) and coupling constants are reported in hertz. Partition column chromatographies were carried out by the method of Oleinick and Corcoran[17] using silica gel (Merck, Darmstadt).

10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). A. To a magnetically stirred solution of 8.0 g of 10,11-anhydroerythromycin B (**1b**) in 160 mL of CH_2Cl_2 was added, portionwise, 8.0 g of *m*-chloroperbenzoic acid. After the addition was complete, stirring was continued at room temperature for 25 h. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 was evaporated under reduced pressure and residual CH_2Cl_2 was removed by codistillation with CH_3OH under reduced pressure, leaving the *N*-oxide (8.4 g) of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) as a light yellow foam.

Scheme I

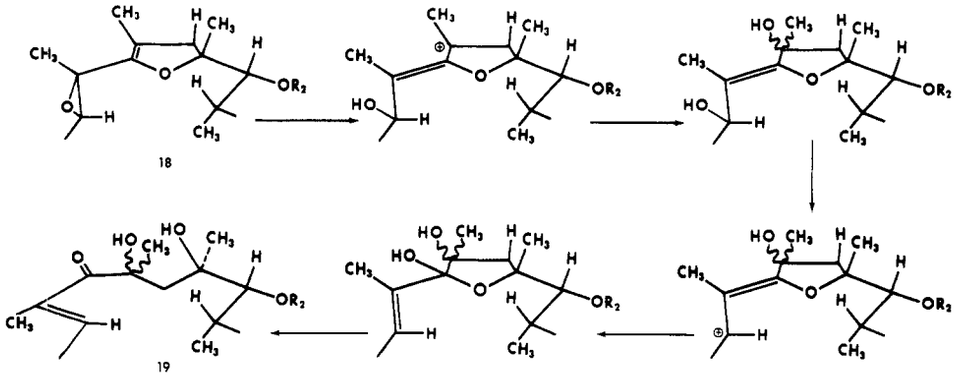

Table I. Antibacterial Activity of Selected Erythromycins

	Minimum inhibitory concentration, mcg/mL[a]						
Structure	*Staphylococcus aureus* 9144	*Staphylococcus aureus* Smith ER	*Streptococcus faecalis* 10541	*Klebsiella pneumoniae* 10031	*Shigella sonnei* 9290	*Haemophilus influenzae* 9334	*Mycoplasma pneumoniae* FH
4c	0.2	>100	0.05	3.1	12.5	1.56	0.05
4d	0.39	>100	0.05	6.2	25	3.1	0.1
1b	6.2	>100	1.56	25	>100		
2	6.2	>100	1.56	12.5	>100	50	0.25
3	3.1	>100	1.56	25	>100		
10	3.1	>100	0.39	3.1	50	12.5	0.5
11	1.56	>100	0.39	6.2	25	12.5	0.25
12	>100	>100	50	25	>100	>100	5.0
13	>100	>100	>100	>100	>100	>100	5.0
14	>100	>100	100	>100	>100	>100	5.0
16a	50	>100	50	>100	>100	>100	50.0
18	25	>100	1.56	100	>100	>100	10
19	6.2	>100	3.1	12.5	>100		
21	3.1	>100	0.2	12.5		25	0.5
22	3.1	>100	0.39	12.5		50	1.0

[a] Determined by an agar dilution method using brain heart infusion medium.

A portion (4.1 g) of the product thus obtained was hydrogenated under 3 atm of hydrogen for 2 h in 250 mL of C_2H_5OH in the presence of 1.25 g of 5% Pd–C to yield 3.6 g of the free amine **2**. Partition column chromatography of 2.6 g of the free amine gave 1.25 g of colorless glass. Crystallization from ethyl acetate–hexane gave 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) as prisms: mp 126.5–129 °C; $[\alpha]^{22}_D$ −36.4° (*c* 1.01, CH_3OH); IR 3610, 3510, 1727, and 1702 cm^{-1}; NMR δ 1.61 (C_6Me), 2.29 (NMe_2), 2.99 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz), 3.30 (OMe), 4.50 ($C_1{}'H$), 4.96 ($C_1{}''H$), 5.18 ($C_{13}H$); M^+ 715.4512, calcd for $C_{37}H_{65}NO_{12}$ 715.4506.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; H, 9.15; N, 1.95. Found: C, 61.97; H, 9.36; N, 1.90.

B. To a solution prepared from 2.0 g of 10,11-anhydroerythromycin B (**1b**), 0.57 g of NaOH, and 80 mL of CH_3OH, cooled in an ice bath, was added 12 mL of 30% aqueous H_2O_2. The resulting solution was stirred at 4 °C for 1 h and then overnight at room temperature. The major portion of the CH_3OH was evaporated under reduced pressure and the product was isolated by $CHCl_3$ extraction. The $CHCl_3$ extract was dried ($MgSO_4$) and the $CHCl_3$ was evaporated under reduced pressure, leaving 1.55 g of *N*-oxide. The catalytic reduction of the *N*-oxide to the free amine was carried out in C_2H_5OH under 3 atm of hydrogen in the presence of 5% Pd–C to yield 1.26 g of free amine. Partition column chromatography of the product gave 0.50 g of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) identical with that prepared as described above.

9(*R*)-Dihydro-10,11-anhydro-10(*S*),11(*S*)-epoxyerythromycin B (10) and 9(*S*)-Dihydro-10,11-anhydro-10(*S*),11(*S*)-epoxyerythromycin B (11). To a stirred solution of 6.2 g of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) in 124 mL of CH_3OH, cooled to −10 °C in a salt–ice bath, was added a freshly prepared solution of 4.0 g of $NaBH_4$ in 11 mL of water over a period of 20 min. Stirring was then continued at −10 °C for 4 h. The product was isolated by $CHCl_3$ extraction. The $CHCl_3$ extract was dried ($MgSO_4$) and the $CHCl_3$ was evaporated under reduced pressure, leaving 6.5 g of product as a glass. Partition column chromatography gave the pure epoxy alcohols **10** and **11**. The minor product (0.81 g) was eluted first. Crystallization from methanol–water gave the analytical sample: mp 182.5–183.5 °C; $[\alpha]^{23}_D$ −53.2° (*c* 1.0, CH_3OH); IR 3380 and 1725 cm^{-1}; NMR δ 2.28 (NMe_2), 3.32 (OMe), 3.40 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz), 3.70 (C_9H, $J_{8,9}$ = 3.0 Hz), 4.44 ($C_1{}'H$), 4.94 ($C_1{}''H$), 5.22 ($C_{13}H$); M^+ 717.4614, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.40; N, 1.95. Found: C, 61.08; H, 9.55; N, 2.04.

The major product (3.6 g) was eluted in subsequent fractions and isolated as a glass: $[\alpha]^{23}_D$ −53.7° (*c* 1.0, CH_3OH); IR 3603, 3500, and 1727 cm^{-1}; NMR δ 2.28 (NMe_2), 3.08 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz), 3.32 (OMe), 3.66 (C_9H, $J_{8,9}$ = 3.0 Hz), 4.44 ($C_1{}'H$), 4.91 ($C_1{}''H$), 5.14 ($C_{13}H$); M^+ 717.4651, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.40; N, 1.95. Found: C, 61.56; H, 9.43; N, 1.70.

9(*R*)-Dihydro-10,11-anhydroerythromycin B (12). To a stirred solution of 5.0 g of 10,11-anhydroerythromycin B (**1b**) in 100 mL of CH_3OH, cooled to −8 °C in a salt–ice bath, was added a freshly prepared solution of 3.3 g of $NaBH_4$ in 10 mL of water over a period of 10 min. After the addition was complete, stirring was continued in the cold for 4 h, and 3 mL of acetone was then added. The product was isolated by $CHCl_3$ extraction. The $CHCl_3$ extract was dried ($MgSO_4$) and the $CHCl_3$ was evaporated under reduced pressure, leaving 5.37 g of colorless foam. Partition column chromatography of 2.37 g of the product thus obtained gave 1.8 g of pure 9(*R*)-dihydro-10,11-anhydroerythromycin B (**12**) as a colorless glass: $[\alpha]^{22}_D$ −53.8° (*c* 1.0, CH_3OH); IR 3605, 3430, and 1718 cm^{-1}; NMR δ 1.60 ($C_{10}Me$), 2.32 (NMe_2), 3.29 (OMe), 3.54 (C_9H, $J_{8,9}$ = 3.0 Hz), 4.50 ($C_1{}'H$), 4.74 ($C_1{}''H$), 4.82 ($C_{13}H$), 5.46 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz); M^+ 701.4689, calcd for $C_{37}H_{67}NO_{11}$ 701.4714.

Anal. Calcd for $C_{37}H_{67}NO_{11}$: C, 63.31; H, 9.62; N, 1.99. Found: C, 61.78; H, 9.67; N, 1.83.

9(*R*)-Dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (13). A. To a vigorously stirred mixture of 7.5 g of 9(*R*)-dihydro-10,11-anhydroerythromycin B (**12**) in 190 mL of $CHCl_3$ and 300 mL of 5% $NaHCO_3$ was added, dropwise, a freshly prepared solution of 7.7 g of *m*-chloroperbenzoic acid in 90 mL of $CHCl_3$ over a period

of 1 h. After the addition was complete, stirring was continued for 20 h. To the resulting stirred mixture was added dropwise a solution of 22 mL of cyclohexene in 75 mL of $CHCl_3$ over a period of 1.5 h. After the addition was complete stirring was continued at room temperature for 3 h. The product was isolated by $CHCl_3$ extraction. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract under reduced pressure left 8.0 g of an *N*-oxide as a white glass.

Catalytic reduction of 4.09 g of the *N*-oxide in 250 mL of C_2H_5OH for 2 h under 3 atm of hydrogen in the presence of 1.4 g of 5% Pd–C yielded 3.91 g of free amine. This product (3.82 g) was chromatographed on a partition column. Early fractions contained 705 mg of a less polar product.

Further elution gave 2.16 g of a two-component mixture which upon chromatography on Sephadex LH20 in $CHCl_3$–hexane 1:1 (v/v) gave, in the initial fractions, 1.64 g of 9(*R*)-dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (**13**): $[\alpha]^{23}_D$ −60.6° (*c* 1.0, CH_3OH); IR 3545, 3420, and 1721 cm^{-1}; NMR δ 2.36 (NMe_2), 3.36 (OMe), 3.53 ($C_{11}H$, $J_{11,12}$ = 2.0 Hz), 3.64 (C_9H, $J_{8,9}$ = 2.5 Hz), 4.41 ($C_{1'}H$), 4.70 ($C_{13}H$), 4.79 ($C_{1''}H$); M^+ 717.4644, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.40; N, 1.95. Found: C, 59.54; H, 9.37; N, 1.68.

Subsequent fractions contained 0.24 g of 9(*R*)-dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (**14**), identical with that prepared from 9(*R*)-dihydro-10,11-anhydro-10-(*R*),11(*R*)-epoxyerythromycin B (**13**) as described below.

9(*R*)-Dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (14). A. A solution prepared from 1.51 g of 9(*R*)-dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (**13**), 25 mL of glacial acetic acid, and 25 mL of water was allowed to stand at room temperature for 1 h. The resulting solution was carefully added to a solution of 22.5 g of Na_2CO_3 in 225 mL of water with vigorous stirring. After the addition was complete, water (200 mL) was added followed by excess solid $NaHCO_3$. The product was isolated by $CHCl_3$ extraction. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract under reduced pressure left 1.54 g of pale yellow glass. Partition column chromatography of the product gave 0.67 g of colorless foam. Crystallization from CH_3OH–water gave an analytical sample of 9(*R*)-dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (**14**): mp 266–268 °C; $[\alpha]^{24}_D$ −41.6° (*c* 1.0, CH_3OH); IR 3600, 3570, 3450, and 1722 cm^{-1}; NMR δ 1.46 (C_6Me), 2.29 (NMe_2), 3.33 (OMe), 3.39 (C_9H, $J_{8,9}$ = 2.0 Hz), 4.25 ($C_{11}H$, $J_{11,12}$ = 1.0 Hz), 4.51 ($C_{1'}H$), 4.72 ($C_{13}H$), 4.84 ($C_{1''}H$); M^+ 717.4644, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.41; C, 1.95. Found: C, 61.64; H, 9.79; N, 1.85.

B. A mixture prepared from 103 mg of **13**, 101 mg of NaN_3, 109 mg of H_3BO_3, and 2 mL of DMF was stirred at room temperature for 23 h. The product was isolated by $CHCl_3$ extraction, and residual DMF was removed by codistillation with benzene to yield 103 mg of **14** as a white glass, identical in all respects with that described above.

6,10(*S*)-Epoxy-11-*epi*-erythromycin B (16a). A. From 9(*R*)-Dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (13). To a stirred solution of 2.0 g of **13** in 250 mL of acetone, cooled to −8 °C, was added 1.52 mL of Jones reagent. Stirring was continued at −8 °C for 3 min, after which time 5 mL of CH_3OH was added. The resulting solution was poured into 1.5 L of 5% aqueous $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with water and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure left 1.6 g of yellow foam. Partition column chromatography of this material gave 0.68 g of **16a**. An analytical sample was prepared by chromatography on Sephadex LH20 in $CHCl_3$–hexane 1:1 (v/v) followed by crystallization from ether: mp 169.5–170.5 °C; $[\alpha]^{23}_D$ −37.4° (*c* 1.0, CH_3OH); IR 3560, 3450, and 1726 cm^{-1}; NMR δ 1.67 (C_6Me), 2.29 (NMe_2), 3.33 (C_4H), 3.35 (OMe), 4.01 ($C_{11}H$, $W_{1/2}$ = 3 Hz, $J_{11,12}$ = 0 Hz), 4.56 ($C_{1'}H$), 4.69 ($C_{13}H$), 4.80 ($C_{1''}H$). M^+ 715.4488, calcd for $C_{37}H_{65}NO_{12}$ 715.4507.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; H, 9.15; N, 1.96. Found: C, 61.71; H, 9.28; N, 1.79.

B. From 9(*R*)-Dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (14). To a stirred solution of 1.45 g of **14** in 230 mL of acetone, cooled to −8 °C, was added 1.05 mL of Jones reagent. Stirring was continued at −8 °C for 6 min and then 10 mL of CH_3OH was added. The product (1.14 g) was isolated as described in part A above. Partition column chromatography of this material gave 0.85 g of **16a** in about 80% purity (TLC). Chromatography of 0.34 g of this material on Sephadex LH20 in $CHCl_3$–hexane 1:1 (v/v) gave 0.27 g of pure **16a**, identical with that described above.

11,2′,4″-Tri-*O*-Acetyl-6,10(*S*)-epoxy-11-*epi*-erythromycin B (16b). A solution prepared from 235 mg of 6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16a**), 6 mL of pyridine, and 1 mL of acetic anhydride was kept at room temperature for 15 days. The product (256 mg of orange glass) was isolated by $CHCl_3$ extraction, but TLC and NMR showed the acetylation was incomplete. The recovered material was treated with 1 mL of acetic anhydride in 6 mL of pyridine at 50 °C for 43 h. Isolation of the product by $CHCl_3$ extraction gave 241 mg of 11,2′,4″-tri-*O*-acetyl-6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16b**) as an orange glass: IR 1722 cm^{-1}; NMR δ 2.29 (NMe_2), 3.36 (OCH_3), 2.06, 1.96 (CH_3CO), 5.20 ($C_{11}H$, $W_{1/2}$ = 2 Hz, $J_{11,12}$ = 0 Hz); M^+ 841.4829, calcd for $C_{43}H_{71}NO_{15}$ 841.4824.

8,9:10,11-Dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-Hemiacetal (18). A solution prepared from 2.31 g of 9(*R*)-dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (**13**), 16 mL of acetic anhydride, and 23 mL of dimethyl sulfoxide was allowed to stand at room temperature for 20.5 h. The resulting solution was added dropwise, by pipet, to a suspension of 8 g of Na_2CO_3 in 80 mL of water. After the addition was complete, 80 mL of water was added, followed by careful addition of excess solid $NaHCO_3$. The product was isolated by $CHCl_3$ extraction. The $CHCl_3$ was evaporated from the $CHCl_3$ extract under reduced pressure. Residual dimethyl sulfoxide was removed by codistillation with benzene under reduced pressure. The residue [2′-*O*-acetyl-4″-oxo-8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal (**17**)] was allowed to stand for 23 h in a solution prepared from 70 mL of CH_3OH and 7 mL of 5% aqueous $NaHCO_3$. The product, 2.23 g of 4″-oxo-8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal, was isolated by $CHCl_3$ extraction in the usual manner.

To a solution of 2.18 g of the product thus obtained in 46 mL of CH_3OH, cooled in an ice bath, was added a freshly prepared solution of 1.4 g of $NaBH_4$ in 5 mL of water. Stirring was continued at 0 °C for 4 h. The product was isolated by $CHCl_3$ extraction in the usual manner. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract gave 2.29 g of white foam. A sample (2.0 g) of product prepared in this manner was chromatographed on a silica gel column prepared by benzene and eluted with increasing amounts of acetone in benzene to yield 0.985 g of 8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal (**18**): $[\alpha]^{25}_D$ −78.4° (*c* 0.94, CH_3OH); IR 3550, 3450, and 1726 cm^{-1}; NMR δ 1.68 (C_6Me), 2.49 (NMe_2), 3.01 ($C_{4''}H$, $J_{4,5}$ = 9.0 Hz), 3.32 (OMe), 4.42 ($C_{1'}H$), 4.82 ($C_{13}H$), 5.29 ($C_{1''}H$); M^+ 697.4394, calcd for $C_{37}H_{63}NO_{11}$ 697.4401.

Anal. Calcd for $C_{37}H_{63}NO_{11}$: C, 63.68; H, 9.10; N, 2.01. Found: C, 63.61; H, 9.39; N, 1.87.

Treatment of 8,9:10,11-Dianhydro-10(*S*),11(*R*)-epoxyerythromycin B (18) with 1:1 (v/v) Acetic Acid–Water. A solution prepared from 2.2 g of **18**, 36 mL of glacial acetic acid, and 36 mL of water was allowed to stand at room temperature for 0.5 h. The resulting solution was added dropwise to a stirred solution of 36 g of Na_2CO_3 in 360 mL of water. Water (60 mL) was added, and the product was isolated by $CHCl_3$ extraction. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract under reduced pressure left 2.2 g of white glass. Partition column chromatography of 0.97 g of this material gave 0.45 g of a two-component mixture in a ratio of about 3:1 as estimated from TLC. A purified sample of the major component, **19**, taken from the earlier fractions, had the following spectral characteristics: $[\alpha]^{25}_D$ −54.2° (*c* 1.05, CH_3OH); IR 3420, 1719, and 1648 cm^{-1}; NMR δ 1.60 (C_6Me), 1.86 ($C_{10}Me$), 2.29 (NMe_2), 3.27 (OMe), 4.37 ($C_{1'}H$), 4.77 ($C_{1''}H$), 4.85 ($C_{13}H$), 6.16 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz); M^+ 715.4513, calcd for $C_{37}H_{65}NO_{12}$ 715.4507.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; h, 9.15; N, 1.96. Found: C, 61.27; H, 9.30; N. 1.89.

Chromous Acetate Reduction of 10,11 Anhydro-10(*R*),-11(*S*)-epoxyerythromycin B (2). A mixture of 0.79 g of **2**, 2.4 g of freshly prepared chromous acetate, and 60 mL of ethanol was stirred under nitrogen for 42 h. Insoluble material was removed by filtration through a Celite mat. Evaporation of the C_2H_5OH from the filtrate under reduced pressure left a deep blue glass. The product was shaken with a mixture of 5% aqueous $NaHCO_3$ and $CHCl_3$ (severe emulsions developed which were broken with difficulty). The $CHCl_3$ extract was washed with water and the $CHCl_3$ was evaporated under reduced pressure.

Partition column chromatography of the product gave in the early fractions 0.36 g of 10,11-anhydroerythromycin B (**16**). Subsequent fractions yielded 0.24 g of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**).

The *N*-Oxide of 10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). To a magnetically stirred solution of 324 mg of pure **2**, 7.64 mL of CH_3OH, and 6.18 mL of water was added 1.85 mL of 30% H_2O_2. Stirring was continued for 22 h at room temperature. The resulting solution was shaken with a mixture of 50 mL of 5% aqueous $NaHCO_3$ and 30 mL of $CHCl_3$. The $CHCl_3$ solution was separated, washed with water, and dried ($MgSO_4$). Evaporation of the $CHCl_3$

left 319 mg of the *N*-oxide of **2**: NMR δ 1.42 (C_6Me), 3.20 ($NMe_2 \rightarrow O$), 3.35 (OMe), 4.96 ($C_{1''}H$), 5.18 ($C_{13}H$).

Conversion of 10-*epi*-Erythromycin B (3) to 10,11-Anhydroerythromycin B (1b). A solution of 86 mg of 10-*epi*-erythromycin B (**3**) in 17 mL of a saturated methanolic K_2CO_3 solution was heated at 43 °C for 1.25 h. The product, 58 mg of 10,11-anhydroerythromycin B (**1b**), was isolated by $CHCl_3$ extraction and identified by NMR and TLC comparisons with an authentic sample of **1b**.

10-*epi*-Erythromycin B (3). Chloroform was removed from a sample (1.8 g) of the *N*-oxide of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) by repeated codistillation under reduced pressure with CH_3OH. The product thus obtained was hydrogenated in 250 mL of CH_3OH for 22 h under 3 atm of hydrogen in the presence of 110 mg of $NaHCO_3$ and 2.7 g of 5% Pd–C. After removal of the catalyst by filtration, the major portion of the CH_3OH was evaporated under reduced pressure. The residue was shaken with a mixture of 250 mL of 5% $NaHCO_3$ and 200 mL of $CHCl_3$. The $CHCl_3$ solution was washed with three 125-mL portions of water. The aqueous solutions were washed in series with two 100-mL portions of $CHCl_3$. The $CHCl_3$ solutions were combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure left 1.35 g of product. Partition column chromatography of this material gave 306 mg (17%) of 10,11 anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) and 328 mg (22% based on recovered **2**) of a 4:1 mixture of 10-*epi*-erythromycin B (**3**) and erythromycin B (**4d**) as estimated by TLC. Repeated chromatography of the latter mixture of **3** and **4d** on a Sephadex LH20 column in $CHCl_3$–hexane 1:1 (v/v) led to isolation of 16 mg of pure erythromycin B (**4d**), identified by comparison of its NMR spectrum and TLC behavior with an authentic sample, and 91 mg of pure 10-*epi*-erythromycin B (**3**): $[\alpha]^{25}_D$ −68.2° (*c* 1.0, CH_3OH); IR 3610, 3450, and 1713 cm^{-1}; λ_{max} 280 (ε 56); NMR δ 2.32 (NMe_2), 3.32 (OMe), 3.79 (C_5H, $J_{4,5}$ = 5.0 Hz), 3.86 ($C_{11}H$, $J_{10,11}$ = ~6 Hz, $J_{11,12}$ = ~6 Hz), 4.16 (C_3H) 4.57 ($C_{1'}H$, $J_{1',2'}$ = 7.2 Hz), 4.86 ($C_{1''}H$, $J_{1'',2a''}$ = 4.5 Hz, $J_{1'',2e''}$ = ~1 Hz), 5.09 ($C_{13}H$, $J_{12,13}$ = ~1 Hz); M^+ 717.4673, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.41; N, 1.95. Found: C, 61.09; H, 9.19; N, 1.93.

6,9ξ-Methyl Acetal (9) of 10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). The $CHCl_3$ of a $CHCl_3$ solution of the *N*-oxide of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) was evaporated under reduced pressure and the residue was dried overnight at room temperature under high vacuum. A 0.293-g sample of the *N*-oxide thus obtained in 40 mL of CH_3OH was hydrogenated for 45 h under 3 atm of hydrogen in the presence of 441 mg of 5% Pd–C and 18.1 mg of $NaHCO_3$. After removal of the catalyst by filtration, the major portion of the CH_3OH was evaporated under reduced pressure. The residue was shaken with a mixture of 50 mL of 5% $NaHCO_3$ solution and 30 mL of $CHCl_3$. The $CHCl_3$ solution was separated and washed with three 35-mL portions of water. The aqueous solutions were washed in series with 30 mL of $CHCl_3$. The $CHCl_3$ solutions were combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ left 235 mg of the 6,9ξ-methyl acetal **9**: $[\alpha]^{24}_D$ −83° (*c* 1.0, CH_3OH); IR 3560 and 1726 cm^{-1}; NMR δ 1.57 (C_6Me), 2.29 (NMe_2), 3.30, 3.36 (OMe), 4.46 ($C_{1'}H$), 5.11 ($C_{13}H$), 5.25 ($C_{1''}H$); M^+ 729.4637, calcd for $C_{38}H_{67}NO_{12}$ 729.4663.

Anal. Calcd for $C_{38}H_{67}NO_{12}$: C, 62.53; H, 9.25; N, 1.92. Found: C, 61.92; H, 9.41; N, 1.91.

Conversion of the 6,9ξ-Methyl Acetal (9) to 10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). A solution of 50 mg of **9** in 1.66 mL of 1:1 acetic acid–water solution was allowed to stand at room temperature for 3 h. The resulting solution was slowly added to a suspension of excess Na_2CO_3 in water. The resulting aqueous suspension was extracted with several portions of $CHCl_3$. The $CHCl_3$ solutions were washed with water, combined, and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure left 51 mg of **2**, which was identified by comparison of its IR and NMR spectra and TLC behavior with those of an authentic sample.

Acknowledgments. The authors are indebted to Ms. R. Stanaszek and Mr. M. Cirovic for determining the NMR spectra and to Ms. S. Mueller for measuring the mass spectra. We wish to thank Dr. R. Girolami and Ms. C. Vojtko for determining antibacterial activities, Mr. W. Washburn for IR spectra, Mr. J. Leonard for many thin-layer chromatographies, Ms. J. Hood for microanalyses, and Dr. R. Egan for helpful discussions of NMR spectra and erythromycin lactone ring conformations. We wish to express our appreciation to Ms. Ginny Giovenco and Ms. Judy Fritz for typing the manuscript.

Registry No.—**1b,** 66101-01-7; **2,** 66027-58-5; **2** *N*-oxide, 66027-59-6; **3,** 66101-02-8; **4c,** 114-07-8; **4d,** 527-75-3; **9,** 66027-60-9; **10,** 66027-57-4; **11,** 66068-82-4; **12,** 66027-65-4; **13,** 66068-83-5; **13** *N*-oxide, 66027-61-0; **14,** 66027-62-1; **16a,** 66027-63-2; **16b,** 66027-55-2; **17,** 66027-54-1; **18,** 66027-56-3; **19,** 66027-64-3; **21,** 13200-64-1; **22,** 33442-49-8.

References and Notes

(1) The stereochemical relationships among the compounds reported are best illustrated with the conformational representations used here rather than with plane projections we have employed previously.[2] Such conformational representations have been used by Corey et al.[3] in the case of some related erythronolide B derivatives. However, a referee suggested that desirability of pointing out that, unless otherwise stated, the conformational representations of the new products reported here are based on the conformation of erythromycin B[4] and have not been determined experimentally. Since it has been shown[5] that the 14-membered lactone rings of a variety of 14-membered macrolides have approximately the same conformations, these conformational representations are probably reasonable approximations.

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