geometries for each compound.

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8-Bromoerythronolide 5,9:6,9-Spiroacetal B: Synthesis, Structure, Conformation, and Nucleophilic Substitution Reactivity

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The erythronolides are the aglycons of the erythromycins, important members of the macrolide class of antibiotics. Erythromycin A was first isolated from the fermentation broth of strains of *Saccharopolyspora erythraea* in 1952[1] and from that time on several of synthetic modifications have been investigated. Recently 8-fluoroerythronolides and 8-fluoroerythromicins have been synthesized by using electrophilic fluorinating agents.[2-4] The potential hazard connected with the use of these reagents is a considerable handicap for the industrial development of these derivatives. Alternative pathways, that make use of nucleophilic fluorinating agents, have not been reported in literature to date. Other 8-halogen derivatives, that may be used as substrates for nucleophilic substitution, are not reported in literature.

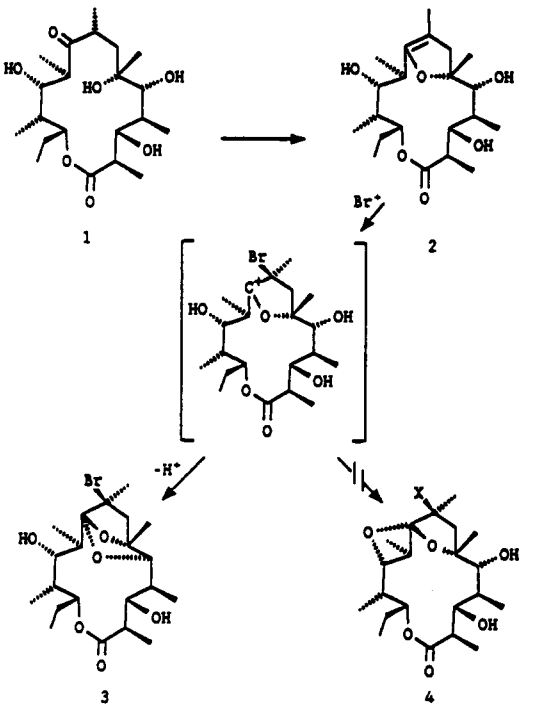
In this paper, we report our efforts for the synthesis of 8-bromoerythronolide B and its reactivity toward nucleophilic substitution. We have chosen as model erythronolide B rather than erythronolide A since the latter affords side products due to the presence of an additional hydroxyl group in position 12.

Results and Discussion

Conversion of erythronolide B (1) to the bromoerythronolide derivative 3 was performed with *N*-bromoacetamide in glacial acetic acid as solvent. The reaction is regio- and stereoselective.

In erythronolide B both positions α to the carbonyl are possibly subject to an easy bromination. Nevertheless the bromination of erythronolide B occurs quantitatively in position 8. This is not surprising, as indeed acid-catalyzed regioselective conversion of erythronolide (1) to its 8,9-anhydro 6,9-hemiacetal derivative 2 is well-known.[5] Derivative 2 is an intermediate of the reaction and is easily converted to bromo derivative 3 with several brominated agents (*N*-bromoacetamide, *N*-bromosuccinimide, sodium hypobromite) in several solvents (acetic acid, ethanol, chloroform) (Scheme I).

Scheme I



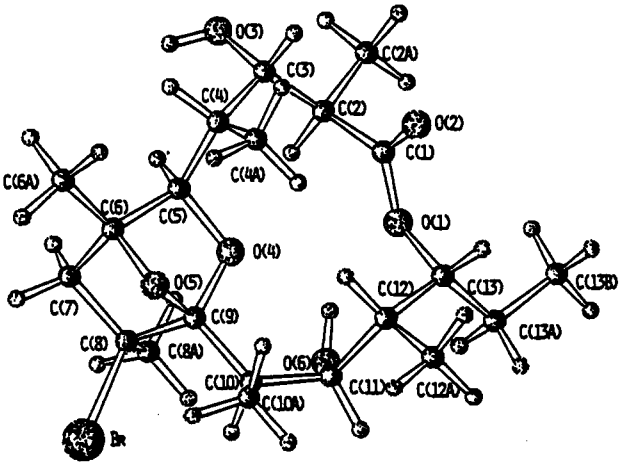


Figure 1. View of the crystal structure of 3.

A quantitative yield was obtained by the reaction of derivative 2 with *N*-bromoacetamide in acetic acid at room temperature. Precipitation of bromo derivative 3 from solvents with different polarity and moisture content yields mixtures in different proportions of two crystalline modifications. This conclusion is supported by the fact that while distinct IR, NMR, and X-ray spectra are obtained from the solids, dissolution of the precipitates gives products with identical IR and NMR spectra. In the present paper only the product crystallized from hexane is discussed; characterization of the second crystalline phase will be presented elsewhere.

Elemental analysis and the IR spectrum (no carbonyl absorption is apparent) of 3 were consistent with the formation of an internal acetal involving the C(9) ketone and the analysis of the X-ray and NMR spectral data proved to be consistent with a 5,9:6,9-spiroacetal.

This class of spiroacetals for the erythronolide ring was previously unknown. The formation of this structure is surprising with respect to what is published in the literature. The reported structures involving spiroacetals at C(9)

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Table I. Endocyclic Torsion Angles (deg) for 12-Membered Ring in Compound 3 (esd in Parentheses)

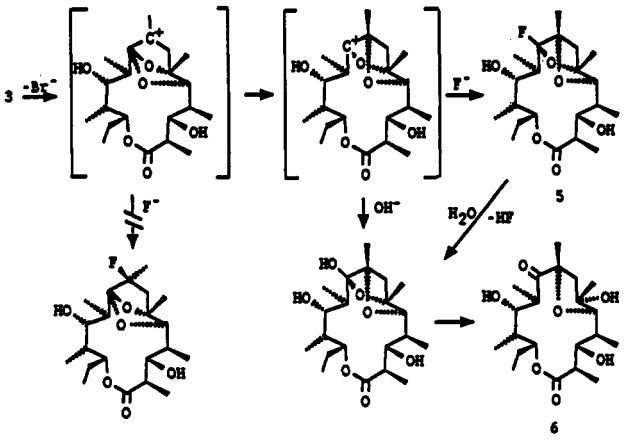
C(13)–O(1)–C(1)–C(2)	−166 (1)
O(1)–C(1)–C(2)–C(3)	132 (2)
C(1)–C(2)–C(3)–C(4)	−61 (2)
C(2)–C(3)–C(4)–C(5)	−52 (2)
C(3)–C(4)–C(5)–O(4)	80 (2)
C(4)–C(5)–O(4)–C(9)	127 (1)
C(5)–O(4)–C(9)–C(10)	−158 (1)
O(4)–C(9)–C(10)–C(11)	−13 (2)
C(9)–C(10)–C(11)–C(12)	80 (2)
C(10)–C(11)–C(12)–C(13)	−145 (1)
C(11)–C(12)–C(13)–O(1)	68 (2)
C(12)–C(13)–O(1)–C(1)	90 (2)

and deriving from electrophilic attack on 2 were formulated as 6,9:9,11-spiroacetals (Scheme I, 4: X = H, F).[3,5]

The absolute configuration and the solid state conformation of compound 3 [8(*S*)-8-bromo-9-deoxo-5,6-dideoxy-5,9:6,9-diepoxyerythronolide B] were determined by X-ray analysis. In Figure 1 an arbitrary view of compound 3 in its absolute configuration is shown. This molecule can be viewed for simplicity as a 12-membered ring, whose conformation is constrained by the condensation with the bicyclic acetal system. The endocyclic torsion angles of the 12-membered ring are reported in Table I. The value of −166° for the C(2)–C(1)–O(1)–C(13) torsion angle agrees with the expected s-trans planar conformation of the ester group,[6] the 14° distortion being also in an acceptable range. The reported value for dihedral angle C(12)–C(13)–O(1)–C(1) (92°) involves a C(1)–O(1)–C(13)–H(13) torsion angle of −25°, confirming the prediction of Schweizer and Dunitz[7] for secondary alcohols esters, which was also suggested to apply to macrocyclic lactones.[8] The conformation around the C(9)–C(10) bond (torsion angle O(4)–C(9)–C(10)–C(11) = −13°) is noteworthy: as a result atoms O(6) and O(5) are almost eclipsed respectively with atoms C(10A) and C(11). Short but not unacceptable contacts arise (O(5)···C(11) 2.83 Å and O(6)···C(10A) 2.68 Å). The nearly endocyclic positioning of the methyl group C(4A) is an unusual feature for macrocyclic substituents, determining somewhat close nonbonded interactions with sp^2 hybridized carbonyl atom C(1) (C(4A)···C(1) = 3.27 Å). A short contact (3.30 Å) is also observed between the C(10A) and the C(12A) methyls, which are in a 1–3 diaxial arrangement. The observed macrocyclic conformation is also characterized by an intramolecular three-center hydrogen bond involving the O(11) hydroxyl as donor and both O(5) and O(1) as acceptors (O(5)···O(6) = 2.74 Å and O(1)···O(6) = 2.77 Å); finally the O(3) hydroxyl appears to stabilize the intermolecular packing with a hydrogen bond to the O(6) atom of a molecule translated by one *c*-axis unit.

The ^1H and ^{13}C NMR data of compound 3 are reported in Table II. The values of the ring vicinal coupling constants for the bromo derivative suggest that the molecular conformation in solution is similar to that found in the solid state from X-ray analysis. In Table III some selected torsion angles derived from the X-ray results and calculated from the vicinal coupling constants on the basis of the generalized empirical Karplus equation proposed by Altona et al.[9] are collected. Variations up to 20° of the dihedral angles are observed between the solid state and

Scheme II. Formation of 5,8-Epoxy-8-*epi*-erythronolide B



the solution geometry. These changes and, in particular, the marked decrease of the torsion angle H(12)–C(12)–C(13)–H(13) may probably allow a release of the nonbonding repulsive interactions between the two methyl groups in positions 10 and 12, which according to the X-ray analysis are 1,3-diaxially oriented.

As pointed out above, two ring substituents are directed toward the inner part of the macrocyclic ring in the bromo compound, i.e., the hydroxyl group at C(11) and the methyl group in position 4. The large value of the coupling constant $^3J_{OH(11)-H(11)}$ (12 Hz) and the low-field chemical shift of the hydroxyl proton (3.69 ppm) suggest that the hydroxyl OH(11) must have a fixed conformation with the OH proton trans to H(11) and one or more hydrogen bonds to the ring oxygens as found in the crystal. Moreover, the close proximity between groups Me(4) and H(12) found in the solid state (Figure 1) can also be evidenced in solution from the strong NOE effect (ca. 10%) that can be observed between them.

In order to replace the bromine atom with fluorine, possible nucleophilic substitutions on compound 3 were investigated. However, all attempts with several reagents (e.g.: AgF or AgF_2 or tetrabutylammonium fluoride) failed. As shown by TLC and HPLC, the unstable compound 5 (Scheme II) was practically the only product of the reaction. Unfortunately, it was not possible to characterize fully compound 5 as, in the isolation process, 5 changes into compound 6. However, the elemental analysis of the crude product and the structural analysis of compound 6 make it possible to suggest 9-deoxo-5,6-dideoxy-5,8:6,9-diepoxy-9-fluoroerythronolide B to be probable structure of compound 5. The elemental analysis of 6 shows the loss of the bromine atom with respect to compound 3 while the IR spectrum indicates the presence of a carbonyl group. Finally the structure and the conformation of compound 6 have been elucidated from NMR data as 5-deoxy-5,8-epoxy-8-*epi*-erythronolide B (Figure 2). The ^1H and ^{13}C NMR data of the compound 6 are reported in Table II. The resonance at 218.3 ppm in the ^{13}C NMR spectrum can be safely assigned to the carbonyl group at carbon C(9). In addition, the proton spectrum shows three hydroxyl groups, which have been identified as OH(3), OH(11), and OH(6). Thus compound 6 is characterized by the presence of a new five-membered ring with an oxygen bridge between the carbons C(8) and C(5). Since this ring has only one protonated carbon and no vicinal coupling constants, the stereochemistry of the new chiral center C(8) can be deduced only on the basis of a set of NOE measurements. In fact the selective irradiation of H(5), Me(6), and Me(8) enhances the signal of the proton H(7a) (2.5, 3.1, and 4.8%, respectively) and not of H(7b); the enhancement of H(7b)

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Table II. ^1H and ^{13}C NMR Spectral Data of Compounds 3 and 6[a]

	3[b]	6[c]		3[b]	6[c]		3[b]	6[c]
H(2)	2.48	2.44	J(2,3)	10.4	10.1	C(1)	174.6	175.7
H(3)	3.74	4.20	J(3,4)	2.5	<0.5	C(2)	45.5	44.9
H(4)	1.93	2.26	J(4,5)	0.8	8.4	C(3)	76.9	71.5
H(5)	3.83	3.51	J(7,7')	13.6	12.6	C(4)	42.9	40.1
H(7b)	2.62	2.51	J(10,11)	6.0	1.2	C(5)	79.3	87.5
H(7a)	2.12	1.80	J(11,12)	7.5	10.0	C(6)	83.7	89.2
H(10)	3.29	3.43	J(12,13)	4.0	<0.5	C(7)	57.3	53.1
H(11)	3.64	4.34	J(13,13A)	11.4	9.0	C(8)	75.0	78.3
H(12)	2.50	1.50	J(13,13A')	2.6	5.6	C(9)	112.8	218.3
H(13)	4.91	5.21	J(13A,13A')	14.5	14.0	C(10)	40.9	39.3
H(13A)	2.19	1.60	J(2,Me)	6.7	6.6	C(11)	77.5	69.6
H(13A')	1.74	1.44	J(4,Me)	7.6	6.6	C(12)	37.5	40.7
Me(2A)	1.29	1.03	J(10,Me)	7.6	6.6	C(13)	80.4	76.7
Me(4A)	0.94	1.03	J(12,Me)	7.0	7.2	C(13A)	20.9	25.8
Me(6A)	1.45	1.25	J(13A,Me)	7.4	7.4	C(2A)	17.1	13.5
Me(8A)	1.91	1.09	J(13A',Me)	7.4	7.4	C(4A)	10.9	11.7
Me(10A)	1.16	0.82	$J(3,OH_3)$	4.0[d]	6.2	C(6A)	10.6	25.0
Me(12A)	1.01	0.88	$J(5,OH_6)$		1.7	C(8A)	28.3	25.1
Me(13B)	0.87	0.78	$J(11,OH_{11})$	12.0[d]	5.0	C(10A)	14.4	8.8
OH(3)	0.93[d]	4.64				C(12A)	19.5	9.1
OH(6)		4.41				C(13B)	9.9	10.5
OH(11)	3.69[d]	2.55						

[a] Chemical shifts in ppm from internal TMS; coupling constants in hertz. [b] Solvent $CDCl_3$. [c] Solvent $(CD_3)_2SO$. [d] Solvent C_6D_6.

Table III. Several Selected Torsion Angles (deg) for Compounds 3 and 6[a]

	torsional angle of 3		torsional angle of 6
angle	X-ray	NMR[b]	NMR[b]
H(2)-C(2)-C(3)-H(3)	174	174	174
H(3)-C(3)-C(4)-H(4)	78	67	-80
H(4)-C(4)-C(5)-H(5)	67	69	143
H(10)-C(10)-C(11)-H(11)	-54	-44	95
H(11)-C(11)-C(12)-H(12)	-144	-140	168
H(12)-C(12)-C(13)-H(13)	76	56	-90

[a] Torsional angles are given following the right-hand rule. [b] Calculated from the generalized empirical Karplus equation.[9]

(and not of H(7a)) has been observed by irradiation of the hydroxyl group OH(6). These experiments allow one to conclude that H(5), Me(6), and Me(8) lie on the same side of the five-membered ring and that the relative configuration at C(8) is inverted with respect to the native erythronolide B.

Moreover, the long-range coupling constant $^4J_{OH(6)-H(5)}$ of 1.7 Hz suggests that the two protons in the H-O-C-H fragment are in the W conformation,[10] with H(5) and OH(6) pseudoaxially oriented. The most probable conformation of the five-membered ring lies in the $^7T_6$, E_6, $_6T^5$ region of the twist-envelope pseudorotational cycle,[11] showing a pseudoaxial orientation of the groups OH(6), H(5), and H(7a) (Figure 2). This conformation is also consistent with the observed NOEs between Me(6) and H(3) (6.3%) and Me(8) and H(10) (4.1%).

As far as the conformation of the macrocyclic ring is concerned, we can observe that the values of the vicinal coupling constants are strictly comparable with those reported for erythronolide B.[12,13] The major difference occurs for J(4,5), which is 2.9 Hz in erythronolide B and is 8.4 Hz for compound 6. This variation is due to the formation of the five-membered ring that causes a rotation of the OH(5) group around the C(4)-C(5) bond and brings proton H(5) syn-periplanar to OH(3). The global conformation of compound 6 is qualitatively represented in Figure 2 on the basis of the dihedral angles calculated according to the generalized Karplus equation[9] and reported in Table III. The OH(6), H(11), and H(4) groups are oriented toward the center of the macrolide ring. The close spatial proximity of the protons H(4) and H(11) is unequivocally proved by the strong NOE (17-18%) observed between them. The two carbonyl groups at C(9) and C(1) are almost perpendicular to the plane of the macrolide ring and the hydroxyl OH(11) is sandwiched between them. This conformational arrangement can explain the unusual high-field chemical shift observed for OH(11) (2.55 ppm in DMSO solution, while OH-3 and OH-6 resonate at about 4.5 ppm), since this proton can be located in the shielding cone of one of the two carbonyl groups.

A product with the structure that we determined for compound 6 has been reported in the literature,[3] but the analytical data are apparently inconsistent with our data; specifically, the IR spectrum is very different and the attribution of the only signal reported for the ^{1}NMR spectrum, relative to proton at C(5) (δ 4.85 in pyridine $J_{4,5}$ = 10), is not coincident with our attribution (δ 4.03 in pyridine $J_{4,5}$ = 8.4). Scheme II shows the probable mechanism underlying the formation of compound 6. The bromine elimination is assisted by oxygen attack with inversion of configuration and formation of a carbocation at position 9. This carbocation reacts with nucleophiles, yielding the unstable compound 5, which easily hydrolyzes to yield 6.

In summary, we have prepared in a stereoselective mode (8S)-8-bromo-9-deoxo-5,6-dideoxy-5,9:6,9-diepoxyerythronolide B (3), but unfortunately this compounds is an unsuitable precursor for nucleophilic substitutions with fluorine at position 9; the intramolecular nucleophilic substitution is exceedingly favored so that intermolecular attack is impossible.

Experimental Section

Erythronolide B was obtained from PIERREL S.p.A. The ^{1}H and ^{13}C NMR experiments were performed on Bruker CXP 300 and AC 250 spectrometers, respectively, at room temperature. The sample concentration was ca. 5 mg/0.5 mL for the proton and ca. 20 mg/0.5 mL for the proton and carbon spectra. The spectral assignment was performed by bidimensional homo- and

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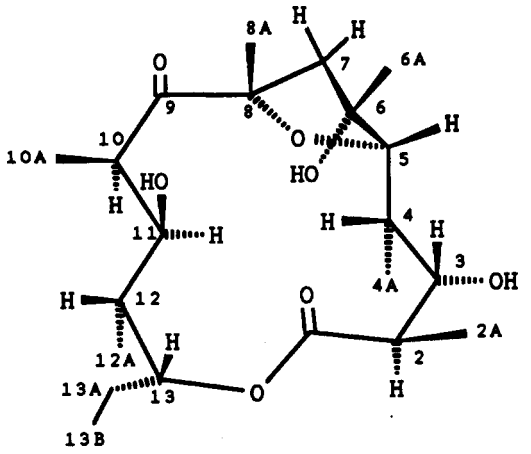

Figure 2. Proposed conformation of 6.

heterocorrelated spectroscopy. The ^1H NOE values were determined by using the monodimensional difference spectroscopy technique. Typically 5–7 experiments were performed with a selective irradiation of different protons and then subtracted from a control spectrum (off resonance irradiation). IR spectra were recorded on a Perkin-Elmer 467 spectrometer. Ultraviolet (UV) spectra were measured in methanol, using a Jasco UVIDEC-510 spectrophotometer. Optical rotations were determined at 20 °C in methanol solutions with a Jasco DIP-181 polarimeter. Mass spectra were recorded on a Finnigan MAT TSQ 70 spectrometer in the CI mode, using isobutane as reagent gas: source temperature 150 °C, isobutane pressure 4500 mTorr. HPLC analyses were carried out on a Jasco Twincle HPLC, equipped a UV detector (210 nm) and a chromatographic data system under the following conditions: reverse phase C-18 (2.5 × 100) Jasco column (7-μm particles); mobile phase acetonitrile–0.01 M phosphate buffer pH 7.0 (1:1); flow rate 1.5 mL/min at 40 °C. Thin-layer chromatography (TLC) was performed with aluminum-backed Merck silica gel 60 F254 plates. Melting points were determined on a Thomas hot-stage apparatus and are uncorrected.

(8*S*)-8-Bromo-9-deoxo-5,6-dideoxy-5,9:6,9-diepoxyerythronolide B (3). (A) A solution of erythronolide B (2.0 g, 5.2 mmol) in glacial acetic acid (30 mL) was stirred at room temperature for 1 h. *N*-Bromoacetamide (0.80 g) was slowly added. After being stirred at room temperature for 30 min, water was added and **3** precipitated as a pure white solid (2.0 g, 82%): mp 111 °C dec; after crystallization from hexane mp 115 °C dec; $[\alpha]_D$ +34.7°; UV (EtOH) λ_{max} 202 (ϵ 716); IR (KBr) 3535, 3445, 1732, 1170, 1050, 920 cm^{-1}; LRCIMS *m/z* 465–463 $(M + 1)^+$ (65), 447–445 (15), 401 (27), 384 (60), 383 (100), 365 (87), 347 (32), 285 (17), 205 (39). Anal. Calcd for $C_{21}H_{35}BrO_6$: C, 54.43; H, 7.61; Br, 17.24. Found: C, 54.21; H, 7.65; Br, 17.16.

(B) *N*-Bromoacetamide (0.4 g) was added to a solution of 8,9-didehydro-9-deoxo-6-deoxy-6,9-epoxyerythronolide B (**2**) (1.0 g, 2.5 mmol) in various solvents (15 mL) and the mixture was stirred for 30 min. Water was added and compound **3** precipitated. Solvent: (i) glacial acetic acid (1.15 g, 96%), mp 111 °C dec; IR (Nujol) 3560, 3525, 1720 cm^{-1}; (ii) chloroform/water (1.0 g, 83.4%), mp 111 °C dec; IR (Nujol) 3525, 3445, 1730 cm^{-1}; (iii) methanol (0.72 g, 60%), mp 115 °C dec; IR (Nujol) 3560, 3525, 3445, 1730, 1720 cm^{-1}.

5-Deoxy-5,8-epoxy-8-*epi*-erythronolide B (6). A solution of bromoerythronolide spiroacetal **3** (0.5 g) in acetonitrile (10 mL) was stirred with silver fluoride (or silver difluoride) (0.2 g) for 1 h at room temperature. The mixture was filtered and a solution of sodium bicarbonate was added. The mixture was extracted with ethyl acetate and the organic layer was dried, filtered, and evaporated. The crude product was purified by crystallization from toluene (0.39 g, 93%): mp 240 °C; $[\alpha]_D$ −72.8°; UV (EtOH) λ_{max} 290 nm (ϵ 71); IR (KBr) 3480, 3380, 3320, 3240, 1725, 1690, 1455, 1380, 1335, 1175, 1130 cm^{-1}; ^1H NMR (pyridine) δ 5.78 (1 H, dd, H-13, J(13,14) = 5.0 Hz, J(13,14′) = 9.0 Hz), 4.88 (2 H, d, H-3 and H-11, J(2,3) = J(11,12) = 9.6 Hz), 4.03 (1 H, d, H-5, J(4,5) = 8.4 Hz), 3.90 (1 H, q, H-10, J(10,Me) = 6.9 Hz), 3.00 (1 H, d, H-7a, J(7a,7b) = 12.3), 1.90 (1 H, d, H-7b)); LRCIMS *m/z* 401 $(M + 1)^+$ (45), 383 (100), 365 (10), 285 (10), 245 (10). Anal. Calcd for $C_{21}H_{36}O_7$: C, 62.97; H, 9.06. Found C, 62.85; H 8.91.

9-Deoxo-5,6-dideoxy-5,8:6,9-diepoxy-9-fluoro-8-*epi*-erythronolide B (5). A solution of bromoerythronolide spiroacetal **3** (0.5 g) in anhydrous acetonitrile (10 mL) was stirred with silver fluoride (or silver difluoride) (0.2 g) at room temperature under N_2 until the TLC analyses showed the disappearance of the starting material. The mixture was filtered and evaporated. Anal. (Crude product). Calcd for $C_{21}H_{35}FO_6$: C, 62.67; H, 8.77; F, 4.72. Found: C, 62.00; H, 8.60; F, 4.93. TLC analysis of the reaction solution, immediately at end of the reaction, showed **5** as the main product with traces of **6**; after 3 h, **6** was the only product present in solution. Analytical and spectroscopical data are not given because it was not possible to purify the product.

X-ray crystallographic analysis of 3: $C_{21}O_6H_{35}Br$, FW = 463.4, orthorhombic, space group $P2_12_12_1$, a = 23.985 (7), b = 11.202 (4), and c = 8.503 (3) Å, V = 2285 (1) Å^3, Z = 4, ρ = 1.35 g cm^{-3}, μ = 18.1 cm^{-1}, F(000) = 976, 0.35 × 0.15 × 0.03 mm, colorless, transparent crystal, Philips PW 1100 diffractometer, λ(Mo Kα) = 0.71063 Å, graphite monochromated, ambient temperature, lattice parameters from least-squares refinement of 16 reflections with $2\theta \geq 13°$, standard reflections (102, 102) measured every 90 min to check crystal stability and experimental conditions, no significant variations detected; 2037 unique reflections $(h, -k, l)$ with $5° \leq 2\theta \leq 48°$ were collected, 831 with $I \geq 2.5\sigma(I)$ being used for all analysis. $\theta/2\theta$ scans, constant scan speed 0.04° s^{-1}, two background counts of 7 s at each side of the peak and values averaged. Lorentz polarization but no absorption correction was applied. The position of the Br atom was determined from a Patterson synthesis, while other atoms were located by standard Fourier methods. The refinement was carried out by blocked-full-matrix least-squares, using SHELX76[14] using an optimized weighting scheme in the final cycles. Given the relative paucity of data, all atoms, except for the bromine, were refined isotropically. Hydrogen atom positions were refined in the riding mode with a common isotropic temperature factor, after inclusion at calculated positions, with the exception of hydroxyl hydrogens, which were located from Fourier difference maps. Final R, R_w, and goodness of fit values were 0.0627, 0.0485, and 1.86, respectively, while the maximum and minimum in the final difference map were 0.47 and −0.45 e Å^{-3}. The absolute configuration was determined by comparing the R values of the two enantiomeric structures at an early stage of the refinement, yielding R values of 0.102 and 0.094. The enantiomer with higher R value may be rejected at a high significance level.

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Supplementary Material Available: Atomic coordinates, equivalent isotropic displacement parameters, bond lengths, and bond angles from the X-ray crystallographic analyses of **3** (5 pages). Ordering information is given on any current masthead page.

(14) Sheldrick, G. M. 1976, SHELX76. Program for crystal structure determination. Univ. of Cambridge, England.

Trisannelated Benzene Synthesis by Zirconium Halide Catalyzed Cyclodehydration of Cycloalkanones

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The physical and chemical properties of trisannelated benzene derivatives, such as trindan (**1**) and dodecahydrotriphenylene (**2**), and its analogues have been extensively studied.[1] For example, the trindenyl trianion

