Synthesis of Ring-Contracted Derivatives of Erythromycin

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8,9-Anhydroerythromycin 6,9-hemiketal was converted by a translactonization process into a 12-membered-ring macrolide. Subsequent oxidative reactions have yielded several new derivatives which possess either 12-membered lactone or 11-membered dilactone rings.

Recent publications have reported the synthesis[1] and isolation[2] of some 12-membered macrolide derivatives utilizing 14-membered macrolide antibiotics as precursors. Such compounds represent a new approach to the synthesis of potentially useful antibiotics for clinical and/or veterinary medicine. Very few 12-membered macrolides have been isolated as natural products and very little structural modification has been performed within this class.[3] In this paper, we report our synthetic efforts toward several ring-contracted derivatives of erythromycin. After submission of our manuscript, a report concerning translactonization of erythromycins was published in which results analogous to some of our work were described.[4]

Results and Discussion

Acid-catalyzed conversion of erythromycin (**1**) to its 8,9-anhydro 6,9-hemiketal derivative (**2**) is well-known.[5] Under reaction conditions different from those of an independent group,[4] migration of the lactone carbonyl group in **2** from the C-13 hydroxyl to the C-11 hydroxyl group was achieved under a wide variety of acidic, basic, or thermal (refluxing toluene) conditions to yield the 12-membered-ring enol ether derivative **3** (Figure 1). Our preferred conditions for preparation of **3** utilize potassium carbonate in refluxing methanol; even though an approximate 6:1 ratio of **3**:**2** is obtained (HPLC analysis), isolation of **3** is relatively easy on a 10–12-g scale. Compound **3** is identical with a minor product recently isolated from mother liquor concentrates of erythromycin[2] and subsequently synthesized directly from erythromycin A.[4] However, our two-step synthesis on a 10-g scale yielded a less-complex reaction mixture and more readily purified product than did the single-vessel process. In addition, the equilibrium ratio of compounds **3**:**2** was somewhat higher under our conditions (6:1) than that reported for the single-vessel procedure (4:1);[4] in our hands, the latter process gave only a 3.1:1 ratio of compounds **3**:**2** on a 10-g scale.

Unfortunately, translactonization under these conditions (potassium carbonate in refluxing methanol) has been confined to the enol ether **2**; erythromycin itself as well as erythromycylamine, erythromycin 9-hydrazone, anhydroerythromycin 6,9;9,12-spiroketal, and 9-dihydroerythromycin all failed to give any detectable conversion to ring-contracted products, suggesting that the five-membered ring that is formed by cyclization of the 6-hydroxyl group into C-9 creates the ring conformation required for translactonization. The formation of the dihydrofuran ring overcomes the factors disfavoring 12-membered rings. The transformation of **2** to **3** has been effected by conditions as diverse as triethylamine in refluxing methanol, 9-BBN in THF, iron pentacarbonyl in refluxing toluene, or $(Ph_3P)_2Pd(OAc)_2$–Bu_3N–HCOOH in warm DMF,[6] with no apparent reaction other than translactonization. An attempt to reduce the double bond with BH_3 in THF yielded a mixture from which the descladinosyl derivative of **3** was isolated. Enol ether derivatives **2** and **3** were each interconverted by mercuric acetate in aqueous methanol without any noticeable hydrolysis of the vinyl ether moiety.

Although other hydrolytic and reductive procedures are still being studied, several selective oxidative transformations have been accomplished. Lead tetraacetate in toluene selectively cleaved the diol tail of **3** to give the methyl ketone **4**, as recently reported.[4] However, the reactions of **3** with other oxidizing agents have produced results different from the precedents reported for the reactions of erythromycin. Hydrogen peroxide selectively oxidized the amino sugar of **3** to the corresponding N-oxide **5**; epoxidation of the double bond by hydrogen peroxide was not observed, in contrast to results from the erythromycin series.[7] Oxidation of the double bond was successfully accomplished with either bromine, *N*-bromosuccinimide, or *N*-chlorosuccinimide in aqueous acetonitrile, yielding the 8-hydroxy 6,9-hemiketal derivative **6**; the stereochemistry at C-8 and C-9 of **6** has not yet been determined. No evidence for halogenated derivatives was found in these reactions. Disappointingly, the hemiketal **6** did not spontaneously open to the 6-hydroxy-9-keto isomer and attempts to catalyze such an isomerization have been unsuccessful. The synthesis of 8-hydroxyerythromycins by oxidation of their enol ether derivatives with different oxidizing agents and hydrolysis of the resultant hemiketals is well-known,[8-11] but the uncertainties influencing the equilibrium between the hydroxy ketone and hemiketal isomers have also been noted.[10] Further work is necessary to determine if the 12-membered 6,9-hemiketal derivatives can be isomerized to the respective 6-hydroxy-9-keto compounds.

Treatment of the ring-contracted enol ether **3** with *m*-chloroperbenzoic acid in dichloromethane at 0 °C produced a complex reaction mixture from which the 11-membered-ring diolide N-oxide **7** was isolated as the

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Table I. Proton NMR Chemical Shifts of Macrolide Derivatives[a]

position	2	3	4	6	7	8
2	2.74	2.83	2.80	2.81	2.81	2.85
3	4.09	4.29	4.23	4.00	4.08	4.03
4	1.88	1.7	1.72	2.02	2.14	2.13
5	3.89	3.70	3.67	3.48	3.74	3.80
7	2.65/1.97	2.78/2.03	2.75/2.01	2.81/2.00	3.15/2.84	3.18/3.02
10	2.79	2.93	3.19	3.04	2.84	3.13
11	3.47	5.06	5.25	5.02	5.25	5.44
13	4.86	2.83		3.03	2.98	
13-CH_2	1.88/1.47	~1.6/~1.3		1.72/1.24	1.89/1.31	
13-CH_3	0.88	0.98		1.02	0.97	
2-CH_3	1.15	1.27	1.30	1.23	1.28	1.35
4-CH_3	1.10	1.10	1.07	1.11	1.12	1.07
6-CH_3	1.35	1.42	1.39	1.52	1.76	1.77
8-CH_3	1.57	1.55	1.55	1.37	2.19	2.15
10-CH_3	1.06	~1.2	0.98	1.17	1.37	1.15
12-CH_3	1.06	~1.2	2.09	1.32	1.14	2.15
1′	4.44	4.33	4.31	4.23	4.46	4.40
2′	3.21	3.20	3.17	3.25	3.66	3.18
3′	2.44	2.48	2.46	2.56	3.34	2.45
4′	1.68/1.26	~1.6/~1.2	1.62/1.25	1.75/1.24	1.89/1.31	1.68/~1.20
5′	3.52	3.48	3.44	3.46	3.56	3.48
5′-CH_3	1.24	1.19	1.22	1.20	1.23	1.22
$N(CH_3)_2$	2.29	2.29	2.26	2.32	3.16/3.14	2.29
1″	5.09	4.89	4.90	4.77	4.90	4.93
2″	2.41/1.60	2.38/~1.5	2.35/1.55	2.33/1.54	2.35/1.53	2.36/1.57
4″	3.06	3.03	3.00	3.00	3.01	3.02
5″	4.09	4.05	4.02	4.05	3.94	3.99
5″-CH_3	1.32	1.33	1.30	1.23	1.27	1.29
3″-CH_3	1.26	1.21	1.22	1.20	1.23	1.24
3″-OCH_3	3.36	3.28	3.26	3.23	3.29	3.28
OH	3.09	NA[b]	NA	NA	NA	NA
4″-OH	2.19	NA	NA	NA	NA	NA

[a] Numbering of the carbon atoms in all compounds corresponds to their respective initial positions in 2. [b] NA means not assigned.

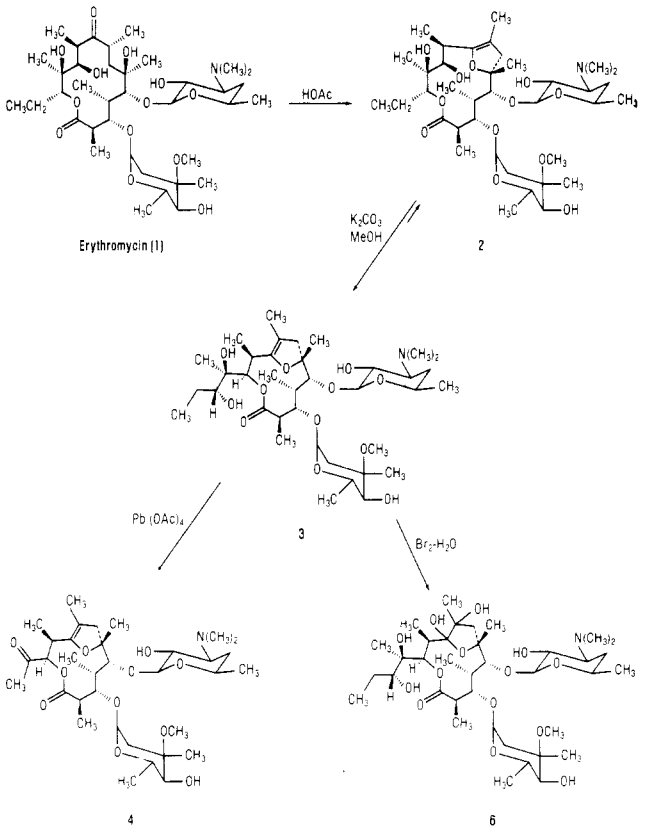

Figure 1. Formation of 12-membered-ring macrolides.

principal component, albeit in low yield. Analogous cleavage of the 8,9-double bond occurred simultaneously with cleavage of the diol upon treatment of 3 with sodium periodate in aqueous acetonitrile to produce the 11-membered diolide 8 (Figure 2). These reactions thereby provide a synthetic entry into a novel class of 11-membered-ring dilactone structures. Similar transformations have been previously accomplished with erythromycin A and B by using hydrogen peroxide and osmium tetraoxide.[10,11] Although the number of dilactone compounds found as natural products is still relatively low, most have possessed some degree of biological activity.[12,13] However, those that have been reported appear not to have saccharides attached to the dilactone ring.

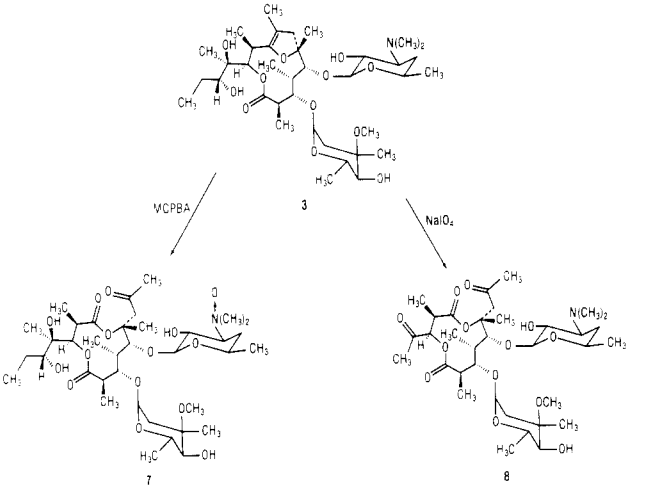

Figure 2. Formation of 11-membered-ring diolides.

The structures of compounds 3, 4, 6, 7, and 8 were determined by the techniques of ^1H NMR, proton homonuclear decoupling, ^{13}C NMR, DEPT, and decoupled and

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Table II. ^{13}C NMR Chemical Shifts of Macrolide Derivatives[a]

position	2	3	4	6	7	8
1	178.30	175.94	173.19	172.15	175.78	173.13
2	44.82	46.82	46.33	46.41	47.53	46.89
3	76.59	80.53	80.59	81.58	78.62	79.73
4	43.28	38.77	38.71	40.58	38.45	38.71
5	80.26	81.60	81.82	86.07	81.53	82.15
6	85.63	86.06	86.15	85.09	86.82	86.53
7	42.69	43.40	43.54	50.06	44.42	45.45
8	101.47	101.34	102.58	81.93	205.98	204.09
9	151.78	149.60	147.87	109.28	172.60	171.22
10	30.47	31.67	32.48	38.29	43.09	42.21
11	70.89	77.49	80.50	80.46	74.41	77.55
12	75.41	76.61	206.09	77.16	NA	206.12
13	78.28	76.70		78.28	76.82	
13-CH_2	21.07	22.50		22.79	22.86	
13-CH_3	10.58	11.82		11.60	11.63	
2-CH_3	13.50	15.14	14.78	14.70	14.33	14.57
4-CH_3	8.72	9.29	9.42	10.81	9.37	9.84
6-CH_3	26.23	26.69	26.92	32.11	23.72	24.95
8-CH_3	11.83	10.93	10.95	23.96	32.80	32.10
10-CH_3	14.81	11.20	10.60	15.11	11.51	11.19
12-CH_3	16.17	15.56	27.42	18.03	17.98	26.98
1′	102.99	103.99	103.97	105.03	102.91	103.47
2′	70.48	71.06	71.06	70.30	72.24	70.82
3′	65.88	65.37	65.44	65.39	76.15	65.47
4′	28.83	28.83	28.95	28.90	34.77	28.92
5′	68.81	68.97	69.00	69.51	67.41	69.15
5′-CH_3	21.30	21.18	21.25	20.94	20.98	21.25
$N(CH_3)_2$	40.33	40.25	40.30	40.36	59.06/52.09	40.33
1″	94.77	97.53	97.47	98.33	96.56	96.82
2″	34.73	35.25	35.33	35.41	34.86	35.15
3″	73.05	72.42	72.47	72.51	72.53	72.65
4″	78.21	78.13	78.18	78.06	77.91	77.91
5″	65.60	65.37	65.44	65.45	65.50	65.71
5″-CH_3	18.25	18.33	18.42	17.34	18.28	18.16
3″-CH_3	21.56	21.44	21.51	21.40	21.57	21.57
3″-OCH_3	49.50	49.30	49.36	49.08	49.48	49.36

[a] Numbering of the carbon atoms in all compounds corresponds to their respective initial positions in **2**. [b] NA means not assigned.

coupled heteronuclear correlations. The ^{13}C NMR data of some derivatives of erythromycin were also compared.[14] However, our data, based on heteronuclear correlations for **2**, require the reassignments of 2-Me, 8-Me, 10-Me, and 12-Me as recorded in Table II. Compound **3** was identified by comparison with **2** through the shift of H-13 to δ 2.83 from 4.86 and the downfield shift of H-11 to δ 5.06 from 3.47 (see Table I). This is consistent with a trans-esterified product as depicted in Figure 1.

The proton and ^{13}C NMR spectra of **4** show the loss of resonances for C-12, C-13, and 13-methyl. New resonances are observed which are consistent with a ketone (δ 206.09, ^{13}C) and an acetyl methyl (δ 27.42, ^{13}C, and 2.09, ^{1}H).

The ^{13}C NMR spectrum of **6** is consistent with its proposed structure through new resonances for quaternary carbon atoms at δ 109.28 (hemiketal) and 85.09 and the loss of the double bond resonances. In addition, C-7 and 8-methyl undergo downfield shifts, which are consistent with a β substitution.

The presence of the N-oxide in **7** was confirmed through the downfield shift (both ^{1}H and ^{13}C) of the N-methyl resonances (see Table I). Two new carbonyls which are seen at δ 172.60 and 205.98 are representative of a ketone and lactone. The ^{1}H resonance corresponding to 8-methyl is at δ 2.19, which is a normal position for an acetyl methyl. The structure of **8** was determined through a comparison of compounds **4** and **7**.

The ring-contracted macrolides **3**, **4**, **6**, and **8** possessed weak antimicrobial activity against *Streptococcus pyogenes*, *S. pneumoniae*, *S. faecalis*, and *Hemophilus influenzae*. The N-oxide derivatives **5** and **7** had no antimicrobial activity. In view of the facile isomerization of **2** to **3** that we have observed and the known formation of **2** as a metabolite of erythromycin,[15] we would anticipate that **3** may now also be identified as a metabolite of erythromycin.

Experimental Section

Proton and carbon-13 nuclear magnetic resonance spectra were obtained in deuteriochloroform solution on a Bruker WM-270 NMR spectrometer. Chemical shifts are reported in parts per million using internal tetramethylsilane (Table I) or chloroform (77.0 ppm, Table II). Field desorption mass spectra were determined on a Varian MAT 731 spectrometer using carbon dendrite emitters. Infrared spectra were recorded in chloroform solution on a Nicolet MX-1 FT-IR spectrometer. Ultraviolet spectra were obtained in 95% ethanol solution on a Cary 219 spectrometer. Optical rotations were measured in methanol solution on a Perkin-Elmer 241 polarimeter. Melting points were determined on a Mel-temp apparatus and are uncorrected.

All compounds were purified to homogeneity according to thin layer chromatographic (TLC), HPLC, and proton NMR analyses. TLC was performed on E. Merck plates of silica gel 60 with a fluorescent indicator (F-254) and dichloromethane–methanol–concentrated ammonium hydroxide (90:10:2) as developing solvent; visualization was effected with anisaldehyde–sulfuric acid spray reagent. Analytical HPLC was performed by utilizing an isocratic HPLC system consisting of a Waters 6000A solvent delivery unit, Rheodyne 7125 sample injector, Waters microbondapak C18 column with acetonitrile–methanol–1% ammonium acetate (30:30:40) as the mobile phase, and Waters 401 refractive index detector; data were recorded on a Hitachi D2000 computing integrator. Product purification by chromatography was per-

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formed on silica gel, using either flash chromatography techniques[16] (E. Merck grade 60 silica gel, 230–400 mesh) or a Waters Model 500 Prep LC system. The antibiotic susceptibility measurements were performed by agar dilution methods.

8,9-Anhydroerythromycin 6,9-Hemiketal (2). A solution of erythromycin (20.0 g, 27.3 mmol) in glacial acetic acid (100 mL) was stirred at room temperature for 1 h.[5] Sodium hydroxide (5 N) was slowly added until precipitation was complete after the mixture had cooled back to ambient temperature. The mixture was extracted twice with dichloromethane and the combined organic layers were extracted with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered, and evaporated. The crude product (18.9 g) was purified by preparative HPLC (linear gradient of dichloromethane to 7% methanol + 0.5% ammonium hydroxide in dichloromethane) to yield **2** (13.2 g, 68%) as a white solid: mp 135–139 °C (lit.[5] mp 133–135 °C); TLC R_f 0.60; HPLC t_R 10.78 min; $[\alpha]^{25}_D$ −41.7° (*c* 1.0, MeOH); UV (EtOH) λ_{max} 208 nm (ϵ 7112); IR ($CHCl_3$) 3450, 3000–2700, 1735 (lactone), 1450, 1370, 1180, 1050 cm^{-1}; FDMS, *m/e* 715 (M^+). Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; H, 9.15. N, 1.96. Found: C, 62.28; H, 8.92; N, 1.69.

Translactonization of 2 to 3. A solution of **2** (10.0 g, 14 mmol) in methanol (200 mL) was treated with potassium carbonate (1.9 g, 14 mmol) and the mixture was refluxed for 90 min. Solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. From the organic layer was obtained 9.6 g of a white foam which was purified by preparative HPLC (linear gradient of dichloromethane to 7.5% methanol + 0.5% ammonium hydroxide in dichloromethane) to yield **3** (5.4 g, 54%) as a white solid: mp 126–130 °C (lit.[4] mp 131–136 °C); TLC R_f 0.50; HPLC t_R 7.00 min; $[\alpha]^{25}_D$ −36.8° (*c* 1.0, MeOH); UV (EtOH) end absorption <210 nm; IR ($CHCl_3$) 3450, 3000–2700, 1710 (lactone), 1455, 1375, 1160, 1110, 1055, 1010 cm^{-1}; FDMS, *m/e* 715 (M^+). Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; H, 9.15; N, 1.96. Found: C, 61.81; H, 9.23; N, 2.15.

Lead Tetraacetate Cleavage of 3 to 4. **3** (2.0 g, 2.8 mmol) was dissolved in toluene (80 mL) and treated with lead tetraacetate (1.9 g, 4.2 mmol). After being stirred at room temperature for 50 min, the heterogeneous mixture was extracted twice with saturated sodium bicarbonate solution, dried (sodium sulfate), filtered, and evaporated. The crude product (1.8 g) was separated by flash chromatography, eluting with a gradient of dichloromethane to dichloromethane–methanol–ammonium hydroxide (96:4:0.5), to give **4** (780 mg, 43%) as a white foam: mp 110–116 °C (lit.[4] mp 110–114 °C); TLC R_f 0.62; HPLC t_R 7.72 min; $[\alpha]^{25}_D$ −39.0° (*c* 1.0, MeOH); UV (EtOH) end absorption <210 nm; IR ($CHCl_3$) 3400, 3000–2700, 1725 and 1720 (lactone and ketone), 1450, 1380, 1240, 1170, 1115, 1054 cm^{-1}; FDMS, *m/e* 655 (M^+). Anal. Calcd for $C_{34}H_{57}NO_{11}$: C, 62.27; H, 8.76; N, 2.14. Found: C, 62.04; H, 8.70; N, 2.11.

Oxidation of 3 to 5. **3** (100 mg, 0.14 mmol) was dissolved in acetonitrile (1 mL) and water (0.5 mL) and then treated with 30% hydrogen peroxide (0.014 mL) dropwise. After stirring at room temperature for 2 days, a white solid had precipitated. The heterogeneous mixture was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate) and evaporated to afford 60 mg (59%) of **5**: mp 156–161 °C; TLC R_f 0.29; HPLC t_R 5.95 min; UV (EtOH) λ_{max} 207 nm (ϵ 5930); IR ($CHCl_3$) 3450, 3000–2800, 1712 (lactone), 1458, 1380, 1260, 1170, 1125, 1015 cm^{-1}; ^1H NMR same as for **3** except δ 4.45 (1′), 3.76 (2′), 3.39 (3′), 1.96/1.38 (4′), 3.59 (5′), 1.27 (5′-CH_3), 3.20 (NMe_2); FDMS, *m/e* 731 (M^+).

Oxidation of 3 to 6. **3** (100 mg, 0.14 mmol) was dissolved in acetonitrile (1 mL) and water (0.5 mL) and cooled to 0 °C for 15 min. A solution of bromine (23 mg, 0.14 mmol) in water (1 mL) was added dropwise. After being stirred for 20 min at 0 °C, the reaction mixture was partitioned between dichloromethane and saturated bicarbonate solution. The organic layer was dried (sodium sulfate), filtered, and evaporated to give 85 mg of **6** (81%) as a white solid: mp 168–170 °C; TLC R_f 0.37; HPLC t_R 3.93 min; $[\alpha]^{25}_D$ −73.4° (*c* 1.0, MeOH); UV (EtOH) weak end absorption <210 nm; IR ($CHCl_3$) 3450, 3000–2700, 1720 (lactone), 1460, 1375, 1250, 1160, 1040 cm^{-1}; FDMS, *m/e* 749 (M^+). Anal. Calcd for $C_{37}H_{67}NO_{14}$: C, 59.26; H, 9.01; N, 1.87. Found: C, 59.48; H, 9.17; N, 1.91.

Diolide 7 from MCPBA Cleavage. **3** (1.0 g, 1.4 mmol) was dissolved in dichloromethane (10 mL) and cooled at 0 °C for 30 min. A solution of *m*-chloroperbenzoic acid (80%, 870 mg, 0.42 mmol) was added dropwise to the cooled solution. Since conversion was incomplete after 2 h at 0 °C (TLC), additional *m*-chloroperbenzoic acid (435 mg, 0.21 mmol) in dichloromethane (5 mL) was added. After an additional 2 h, no change was apparent by TLC. The mixture was extracted with 10% sodium bisulfite solution and then with saturated sodium bicarbonate solution. The organic layer was dried (sodium sulfate) and evaporated to give 390 mg of crude product, from which 98 mg (9%) of **7** was obtained by crystallization from dichloromethane: mp 176–179 °C; TLC R_f 0.21; HPLC t_R 2.86 min; UV (EtOH) weak end absorption <210 nm; IR ($CHCl_3$) 3500, 3000–2800, 1723 (lactones), 1460, 1380, 1250, 1175, 1080 cm^{-1}; FDMS, *m/e* 764 (M + H^+).

Diolide 8 from Sodium Periodate Cleavage of 3. **3** (100 mg, 0.14 mmol) was dissolved in methanol (1 mL) and water (0.5 mL). Sodium periodate (240 mg, 1.12 mmol) was dissolved with the aid of sonication in water (3 mL) and methanol (2 mL) and was then added dropwise, yielding a white precipitate. After stirring the heterogeneous mixture for 11 days at room temperature, it was partitioned between ethyl acetate and saturated sodium bicarbonate solution. After workup as usual, the crude product (60 mg) was purified by flash chromatography, eluting with a gradient of dichloromethane to dichloromethane–methanol (23:2), to yield **8** (45 mg, 47%) as a colorless glass: mp 90–93 °C; TLC R_f 0.57; HPLC t_R 3.86 min; $[\alpha]^{25}_D$ −27.4° (*c* 1.0, MeOH); UV (EtOH) end absorption <210 nm; IR ($CHCl_3$) 3400, 3000–2700, 1727 (lactone and ketone), 1465, 1245, 1165 cm^{-1}; FDMS, *m/e* 687 (M^+). Anal. Calcd for $C_{34}H_{57}NO_{13}$: C, 59.37; H, 8.35; N, 2.04. Found: C, 59.11; H, 8.07; N, 1.78.

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Registry No. **1**, 114-07-8; **2**, 33396-29-1; **3**, 105882-69-7; **4**, 105882-72-2; **5**, 109719-53-1; **6**, 109719-54-2; **7**, 109719-55-3; **8**, 109719-56-4.

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