$^{13}C$ NMR q at 22.6, 23.1, t at 21.0 (C-4), 23.4 (C-5), 35.2 (C-11), 37.0 (C-7), d at 35.1 (C-10), 42.1 (C-8), 123.0 (C-3), 129.2 (C-2), s at 24.2 (C-6), 28.3 (C-1), 43.8 (C-9); MS 131 (100), 91 (80), 145 (60), 117 (55), 159 (50), 118 and 174 ($M^{+\cdot}$, 43), 105 (32), 77 and 115 (28); exact mass calcd for $C_{13}H_{18}$ 174.1408, found 174.1433.

**9,9-Dimethyltetracyclo[6.2.1.0$^{1,6}$.0$^{6,10}$]undecane (13).** A mixture of 9,9-dimethyltetracyclo[6.2.1.0$^{1,6}$.0$^{6,10}$]undecan-2-one (**5**, 0.6 g), hydrazine hydrate (6 mL), diethylene glycol (12 mL), and ethanol (12 mL) was heated at reflux for 15 min. Potassium hydroxide pellets (3 g) were added, and heating at reflux was continued for 1 h. The mixture was then distilled very slowly, allowing the temperature to rise over 3 h. The distillate was extracted with water and pentane, and the residue in the distillation flask was extracted with pentane. The combined pentane phases were washed (10% HCl, water) and concentrated carefully with a distillation column. The residue (0.5 g) consisted mainly of the title product and was purified by preparative GC on Carbowax: $[\alpha]^{20}_D$ 0° (10% in $CHCl_3$); $^1H$ NMR $\delta$ 0.87 (s, 6 H), 0.46 (s, 1 H, HC-10), 1.09 and 1.69 (each 2 H, AB system, $J$ = 10 Hz, $H_2C$-7 and $H_2C$-11), 1.26 (HC-8) overlapping with 1.15 and 1.26 (mult, $H_2C$-3 and $H_2C$-4), 1.73 and 1.80 (each 2 H, mult, $H_2C$-2 and $H_2C$-5); $^{13}C$ NMR q at 23.3, t at 23.0 (C-3, C-4), 25.8 (C-2, C-5), 38.4 (C-7, C-11), d at 33.8 (C-10), 42.0 (C-8), s at 23.2 (C-1, C-6), 44.2 (C-9); MS 91 (100), 133 (78), 176 ($M^{+\cdot}$) and 105 (40), 119 (38), 161 (35), 41, 79, 93 (21); exact mass calcd for $C_{13}H_{20}$ 176.1564, found 176.1490.

## 15-Membered Macrolides via Translactonization in 14-Hydroxy-6-*O*-methylerythromycin A

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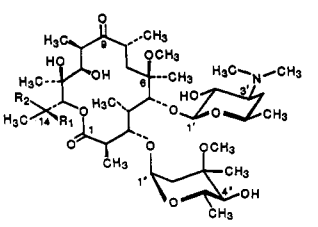
In our previous studies on the metabolism of 6-*O*-methylerythromycin A (**1**), a new semisynthetic macrolide antibiotic, several metabolites were isolated from human urine.[1] Among them, active metabolites M-5 (**2**) and M-6 (**3**) were determined to be (14*R*)- and (14*S*)-14-hydroxy-6-*O*-methylerythromycins A, respectively.[2]

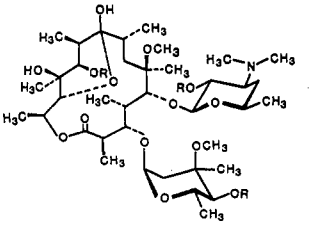
During the isolation and identification of the metabolites of **1**, **3** was found to be converted to a new polar compound when dissolved in protic solvents, methanol, or acetone–water, etc. This compound was identical with M-7 (**4**), previously isolated from human urine,[1] whose structure still remained to be identified. The latter has been determined to be a novel 15-membered macrolide having the 9,13-hemiketal structure, derived by a translactonization between the 14-hydroxyl and the lactone group. The translactonization from **3** to **4** is accelerated by reaction of **3** with potassium carbonate in methanol. The above results let us convert **2**, an epimer of **3** at C-14, into another type of translactonization product. The desired 15-membered macrolide **5** could readily be obtained from **2** by the use of potassium carbonate and exists as two tautomers having the 9-carbonyl (**5A**) and the 9,12-hemiketal (**5B**) structures. This paper describes the structure determination of the two novel 15-membered macrolides, **4** and **5**.

### Results and Discussion

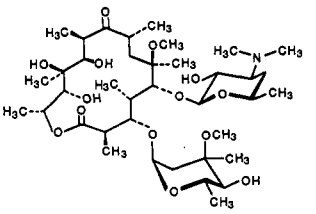
The molecular formula of **5** was determined as $C_{38}H_{69}NO_{14}$ from the elemental analysis and mass and $^{13}C$ NMR



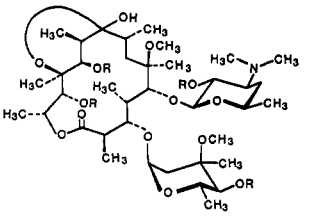
1 $R_1$ = H $R_2$ = H
2 $R_1$ = OH $R_2$ = H
3 $R_1$ = H $R_2$ = OH



4 R = H
7 R = Ac



5A



5B R = H
6 R = Ac

spectra, which is the same as that of **2**. The $^1H$ NMR spectrum of **5** in deuteriochloroform indicates that **5** contains two components (**5A** and **5B**, ca. 2:1, respectively) from several pairs of signals for H-1′, H-1″, H-14, 3″-$OCH_3$, 6-$OCH_3$, etc. In the $^{13}C$ NMR spectrum of **5** in deuteriochloroform, C-9 resonates at 222.4 ppm (**5A**, major) and 107.3 ppm (**5B**, minor), and these signals are ascribed to carbonyl and hemiketal structures at C-9, respectively. Compound **5** showed absorption at 1683 $cm^{-1}$ in the IR spectrum and absorption around 280 nm (shoulder) in the UV spectrum, consistent with a 9-carbonyl group. When the $^1H$ NMR spectrum of **5** was measured in deuteriopyridine, several pairs of signals converged. The signal of C-9 resonates only at 107.5 ppm, indicating that **5** exists as the hemiketal structure (**5B**) in deuteriopyridine. The $^1H$ NMR spectrum of the sample recovered from the solution of deuteriopyridine was measured in deuteriochloroform, and the same $^1H$ NMR spectrum as originally measured in deuteriochloroform was obtained. Therefore **5A** and **5B** are interconvertible tautomers.

Unambiguous NMR assignments of **5A** were made by means of homonuclear $^1H$–$^1H$ and heteronuclear $^1H$–$^{13}C$ 2D NMR spectroscopy. Tables I and II show that the chemical shifts of protons and carbons assigned to cladinose and desosamine were similar in **5A** and **2**. However, the chemical shifts of the aglycons are considerably different between **5A** and **2**. The signal of H-13 in **5A** is 1.71 ppm upfield from that in **2**, whereas H-14 and C-14 in **5A** resonate at lower field by 0.66 and 6.0 ppm, respectively, than those in **2**. The chemical shifts of H-14 (4.79 ppm) and C-14 (72.5 ppm) in **5A** are similar to those of H-13 (4.94 ppm) and C-13 (74.5 ppm) in **2**, respectively. These spectral data clearly indicate that **5A** is a 15-membered macrolide derived from **2** by a translactonization between the 14-hydroxyl and the lactone group.

The chemical shifts of protons and carbons of **5B** in deuteriopyridine were compared with those of **2**. The $^1H$ and $^{13}C$ NMR spectra of **2** were also measured in deuteriopyridine. The upfield shift of H-13 (−1.10 ppm) and the downfield shifts of H-14 (+1.19 ppm) and C-14 (+6.6 ppm) in **5B** with respect to **2** shows that **5B** is also a translactonization product between the 14-hydroxyl and the lactone group. The chemical shift of C-9 (107.5 ppm) indicates a hemiketal structure. In order to confirm the hemiketal structure, the hydroxy protons of **5B** were assigned. The signals at 8.04, 5.81, 5.55, and 5.06 ppm are

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(2) Adachi, T.; Morimoto, S.; Kondoh, H.; Nagate, T.; Watanabe, Y.; Sota, K. *J. Antibiot.* **1988**, *41*, 966.

0022-3263/89/1954-3507$01.50/0 

Table I. $^1$H NMR Chemical Shifts of Macrolide Derivatives in $CDCl_3$ and $C_5D_5N$

| position | 2[a,c] | 2[b] | 3[a,c] | 4[a] | 5A[a] | 5B[b] | 6[b] | 7[a] |
|---|---|---|---|---|---|---|---|---|
| 2 | 2.84 | 3.18 | 2.99 | 2.78 | 2.69 | 3.11 | 3.20 | 2.77 |
| 3 | 3.77 | 4.14 | 3.79 | 4.15 | 3.92 | 4.26 | 4.05 | 4.14 |
| 4 | 1.85 | 2.33 | 1.91 | 2.43 | 1.86 | 2.83 | 2.70 | 2.32 |
| 5 | 3.65 | 4.12 | 3.67 | 3.78 | 3.63 | 4.13 | 4.01 | 3.74 |
| 7 | 1.73/1.83 | 1.88/2.19 | 1.73/1.85 | NA/2.57 | 1.71/1.84 | 1.81/2.37 | NA/2.28 | 1.06/2.47 |
| 8 | 2.59 | 2.96 | 2.58 | 2.00 | 2.55 | 2.48 | 2.64 | 2.00 |
| 10 | 2.98 | 3.28 | NA | 1.72 | 3.07 | NA | 2.34 | 1.88 |
| 11 | 3.75 | 4.25 | 3.70 | 3.63 | 3.79 | 4.46 | 5.20 | 5.00 |
| 13 | 4.94 | 5.79 | 5.06 | 3.76 | 3.23 | 4.69 | 5.66 | 3.83 |
| 14 | 4.13 | 4.54 | 4.40 | 5.18 | 4.79 | 5.73 | 5.74 | 5.19 |
| 15(14-Me) | 1.10 | 1.41 | 1.13 | 1.28 | 1.41 | 1.71 | 1.20 | 1.28 |
| 16(2-Me) | 1.18 | 1.35 | 1.23 | 1.16 | 1.18 | 1.36 | 1.37 | 1.18 |
| 17(4-Me) | 1.08 | 1.65 | 1.10 | 1.21 | 1.04 | 1.65 | 1.49 | 1.11 |
| 18(6-Me) | 1.41 | 1.70 | 1.41 | 1.36 | 1.40 | 1.64 | 1.56 | 1.32 |
| 19(8-Me) | 1.13 | 1.11 | 1.13 | 0.90 | 1.16 | 1.34 | 1.19 | 0.90 |
| 20(10-Me) | 1.11 | 1.46 | 1.12 | 1.00 | 1.30 | 1.38 | 1.41 | 0.87 |
| 21(12-Me) | 1.27 | 1.51 | 1.36 | 1.14 | 1.31 | 1.60 | 1.51 | 1.12 |
| 6-OMe | 3.02 | 3.36 | 3.03 | 3.37 | 3.01 | 3.51 | 3.34 | 3.35 |
| 1′ | 4.43 | 4.92 | 4.45 | 4.37 | 4.44 | 4.93 | 5.11 | 4.46 |
| 2′ | 3.18 | 3.57 | 3.19 | 3.17 | 3.19 | 3.61 | 5.16 | 4.68 |
| 3′ | 2.41 | 2.61 | 2.41 | 2.51 | 2.43 | 2.55 | 2.91 | 2.73 |
| 4′ | NA[d]/1.66 | 1.15/NA | NA/1.66 | NA/1.66 | NA/1.66 | 1.15/NA | NA/1.82 | NA/1.69 |
| 5′ | 3.48 | 3.98 | 3.49 | 3.47 | 3.48 | 3.89 | 4.04 | 3.43 |
| 6′(5′-Me) | 1.23 | 1.32 | 1.23 | 1.22 | 1.22 | 1.32 | 1.37 | 1.19 |
| 3′-$NMe_2$ | 2.28 | 2.17 | 2.28 | 2.27 | 2.28 | 2.14 | 2.21 | 2.26 |
| 1″ | 4.91 | 5.12 | 4.93 | 4.75 | 4.96 | 5.18 | 5.27 | 4.81 |
| 2″ | 1.59/2.36 | 1.55/2.43 | 1.59/2.37 | 1.53/2.38 | 1.59/2.35 | 1.58/2.43 | 1.67/2.47 | 1.63/2.44 |
| 4″ | 3.03 | 3.30 | NA | 2.99 | 3.04 | 3.31 | 4.97 | 4.71 |
| 5″ | 4.00 | 4.54 | 4.01 | 4.06 | 4.03 | 4.61 | 4.68 | 4.44 |
| 6″(5″-Me) | 1.30 | 1.63 | 1.31 | 1.31 | 1.30 | 1.69 | 1.40 | 1.17 |
| 7″(3″-Me) | 1.25 | 1.33 | 1.26 | 1.22 | 1.24 | 1.33 | 1.20 | 1.12 |
| 3″-OMe | 3.33 | 3.49 | 3.33 | 3.25 | 3.33 | 3.41 | 3.52 | 3.30 |
| 9-OH | – | – | – | NA | – | 6.90 | NA | 6.77 |
| 11-OH | 3.93 | NA | 4.05 | 6.80 | NA | 8.04 | – | – |
| 12-OH | 4.23 | NA | NA | NA | NA | – | – | NA |
| 13-OH | – | – | – | – | NA | 5.81 | – | – |
| 14-OH | 4.49 | NA | NA | – | – | – | – | – |
| 2′-OH | 3.44–3.48 | NA | 3.45 | 3.43 | 3.56 | 5.06 | – | – |
| 4″-OH | 2.19 | NA | 2.19 | 2.38 | 2.22 | 5.55 | – | – |
| 11-OAc | | | | | | | 2.16 | 2.18 |
| 13-OAc | | | | | | | 2.28 | – |
| 2′-OAc | | | | | | | 2.06 | 2.06 |
| 4″-OAc | | | | | | | 2.13 | 2.13 |

[a] Measured in deuteriochloroform. [b] Measured in deuteriopyridine. [c] Reference 2. [d] NA means not assigned.

assigned to the 11-OH, 13-OH, 4″-OH, and 2′-OH, respectively, by means of $D_2O$ exchange and homonuclear $^1H$–$^1H$ 2D NMR experiments. The signal at 6.90 ppm is assigned to the 9-OH from the long-range coupling with C-10 by heteronuclear $^1H$–$^{13}C$ 2D spectroscopy. The hydroxy proton of the 12-OH was not observed. Furthermore, acetylation of **5** with acetic anhydride in pyridine at room temperature for 5 days afforded tetra-*O*-acetate **6**. In the $^1H$ NMR spectrum of **6**, four acetyl signals at 2.06, 2.13, 2.16, and 2.28 ppm together with the downfield shifts of H-2′ (3.61 → 5.16 ppm), H-4″ (3.31 → 4.97 ppm), H-11 (4.46 → 5.20 ppm), and H-13 (4.69 → 5.66 ppm) compared with **5B** clearly show that **6** is the 2′,4″,11,13-tetra-*O*-acetate of **5B**. The 9,12-hemiketal structure is therefore determined for **5B**.

The molecular formula of **4** was determined as $C_{38}H_{69}NO_{14}$ from mass and $^{13}C$ NMR spectra, which is the same as that of **3**. In the NMR spectrum, the upfield shift of H-13 (−1.30 ppm) and the downfield shifts of H-14 (+0.78 ppm) and C-14 (+5.2 ppm) in **4** with respect to **3** indicate a translactonization of **3** between the 14-hydroxyl and the lactone group. A signal at 97.9 ppm (C-9) in **4** is observed instead of original 9-carbonyl signal in **3** (221.3 ppm), indicating a hemiketal structure. This conclusion is consistent with the fact that neither the IR absorption around 1683 $cm^{-1}$ nor the UV absorption around 280 nm due to the 9-carbonyl group were observed in **4**. In the $^1H$ NMR spectrum of **4**, the signals for the 11-OH (6.80 ppm), 2′-OH (3.43 ppm), and 4″-OH (2.38 ppm) are assigned, but other hydroxy protons were not detected. Acetylation of **4** in a similar manner to that described above afforded the tri-*O*-acetate (**7**) of **4**. In the $^1H$ NMR spectrum of **7** in deuteriochloroform, three acetyl signals at 2.06, 2.13, and 2.18 ppm together with the downfield shifts of H-2′ (3.17 → 4.68 ppm), H-4″ (2.99 → 4.71 ppm), and H-11 (3.63 → 5.00 ppm) show that **7** is the 2′,4″,11-tri-*O*-acetate of **4**. Compound **7** was heated with acetic anhydride in pyridine at 100 °C for 4 h, but further acetylation of **7** was not observed. The secondary 13-hydroxyl group is thought to be blocked by the formation of 9,13-hemiketal. Compound **4** is consequently determined to be a 15-membered macrolide having the 9,13-hemiketal structure.

The antimicrobial activities of the 15-membered macrolides **4** and **5** were 63- to 250-fold less than those of **2**.

Translactonizations have been reported previously during the chemical modification of macrolide antibiotics, oleandomycin,[3] tylonolide derivatives[4] and CP-47,444,[5] and the total synthesis of erythromycin B.[6] Recently 12-

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(4) Tanaka, A.; Watanabe, A.; Kobayashi, R.; Tsuchiya, T.; Umezawa, S. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3837.
(5) Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203.

Table II. $^{13}C$ NMR Chemical Shifts of Macrolide Derivatives in $CDCl_3$ and $C_5D_5N$

| position | 2[a,c] | 2[b] | 3[a,c] | 4[a] | 5A[a] | 5B[b] | 6[b] | 7[a] |
|---|---|---|---|---|---|---|---|---|
| 1 | 175.1 | 175.6 | 175.7 | 173.0 | 176.1 | 175.4 | 174.3 | 173.2 |
| 2 | 45.0 | 45.6 | 44.9 | 46.9 | 45.4 | 45.5 | 45.1 | 47.0 |
| 3 | 78.2 | 78.7 | 78.5 | 82.5 | 77.5 | 79.6 | 79.8 | 82.6 |
| 4 | 39.5 | 39.8 | 39.2 | 38.8 | 40.5 | 38.4 | 38.1 | 38.6 |
| 5 | 80.6 | 80.6 | 80.8 | 77.6 | 81.2 | 80.2 | 80.8 | 77.1 |
| 6 | 78.4 | 79.1 | 78.5 | 81.2 | 78.5 | 80.2 | 81.5 | 81.2 |
| 7 | 39.5 | 39.5 | 39.5 | 36.7 | 39.8 | 37.0 | 35.9 | 36.4 |
| 8 | 45.2 | 44.4 | 45.3 | 35.9 | 45.2 | 37.6 | 37.2 | 35.7 |
| 9 | 220.8 | 219.0 | 221.3 | 97.9 | 222.4 | 107.5 | 109.5 | 97.7 |
| 10 | 36.9 | 39.3 | 36.5 | 40.0 | 37.5 | 44.9 | 47.0 | 38.7 |
| 11 | 68.9 | 70.1 | 69.9 | 79.1 | 74.2 | 88.1 | 86.4 | 81.3 |
| 12 | 76.8 | 77.5 | 74.8 | 73.6 | 74.3 | 79.4 | 79.2 | 73.5 |
| 13 | 74.5 | 76.1 | 75.8 | 73.7 | 83.1 | 76.7 | 75.9 | 74.3 |
| 14 | 66.5 | 66.9 | 66.2 | 71.4 | 72.5 | 73.5 | 71.5 | 71.7 |
| 15(14-Me) | 19.8 | 20.6 | 20.9 | 17.8 | 19.1 | 16.2 | 16.7 | 17.8 |
| 16(2-Me) | 15.5 | 16.0 | 16.0 | 15.9 | 15.1 | 15.3 | 15.7 | 16.0 |
| 17(4-Me) | 8.9 | 9.9 | 9.1 | 10.6 | 8.8 | 10.2 | 9.8 | 10.5 |
| 18(6-Me) | 19.7 | 20.8 | 19.8 | 21.0 | 19.7 | 21.8 | 22.2 | 21.0 |
| 19(8-Me) | 17.9 | 18.2 | 18.1 | 19.4 | 19.0 | 19.3 | 18.9 | 19.3 |
| 20(10-Me) | 12.3 | 12.4 | 12.2 | 11.0 | 13.3 | 13.6 | 15.5 | 10.9 |
| 21(12-Me) | 16.3 | 18.6 | 17.9 | 13.6 | 23.7 | 23.2 | 22.4 | 14.1 |
| 6-OMe | 50.6 | 51.1 | 50.7 | 49.8 | 50.9 | 51.0 | 51.1 | 49.8 |
| 1′ | 102.8 | 103.4 | 102.8 | 103.9 | 102.8 | 104.0 | 100.8 | 101.6 |
| 2′ | 70.9 | 71.8 | 71.0 | 70.9 | 70.9 | 71.8 | 72.2 | 71.7 |
| 3′ | 65.6 | 65.6 | 65.6 | 65.2 | 65.6 | 65.3 | 64.0 | 62.8 |
| 4′ | 28.5 | 30.3 | 28.6 | 28.5 | 28.6 | 30.8 | 30.5 | 31.0 |
| 5′ | 68.8 | 68.2 | 68.8 | 69.1 | 68.8 | 68.3 | 67.7 | 68.6 |
| 6′(5′-Me) | 21.4 | 22.0 | 21.5 | 21.3 | 21.5 | 21.5 | 21.8 | 21.1 |
| 3′-$NNe_2$ | 40.2 | 40.5 | 40.3 | 40.2 | 40.3 | 40.5 | 40.6 | 40.6 |
| 1″ | 96.1 | 96.9 | 96.1 | 98.5 | 95.3 | 97.0 | 96.7 | 98.7 |
| 2″ | 34.8 | 35.5 | 34.9 | 35.7 | 34.8 | 35.6 | 35.3 | 36.0 |
| 3″ | 72.7 | 73.5 | 72.7 | 72.6 | 72.8 | 73.4 | 73.0 | 73.0 |
| 4″ | 77.9 | 78.6 | 78.0 | 78.1 | 77.9 | 78.8 | 78.8 | 78.6 |
| 5″ | 65.7 | 66.3 | 65.8 | 65.7 | 65.7 | 66.2 | 63.6 | 63.1 |
| 6″(5″-Me) | 18.7 | 19.7 | 18.7 | 17.6 | 18.6 | 19.5 | 18.8 | 17.2 |
| 7″(3″-Me) | 21.4 | 21.5 | 21.5 | 21.5 | 21.4 | 21.9 | 21.1 | 21.1 |
| 3″-OMe | 49.5 | 49.7 | 49.5 | 49.2 | 49.5 | 49.6 | 49.5 | 49.6 |
| 11-OCO*Me* | | | | | | | 20.8 | 21.0 |
| 13-OCO*Me* | | | | | | | 21.2 | – |
| 2′-OCO*Me* | | | | | | | 21.5 | 21.4 |
| 4″-OCO*Me* | | | | | | | 20.7 | 20.9 |
| OCOMe | | | | | | | 170.6 | 172.9 |
| OCOMe | | | | | | | 170.3 | 170.7 |
| OCOMe | | | | | | | 169.8 | 169.8 |
| OCOMe | | | | | | | 169.3 | – |

[a] Measured in deuteriochloroform. [b] Measured in deuteriopyridine. [c] Reference 2.

membered erythromycin A derivatives were isolated by Kibwage et al. from fermentation residues of *Streptomyces erythreus*, which were derived as a result of a translactonization between the 11-hydroxyl and the lactone group.[7] Also this type of translactonization has been synthetically demonstrated by two groups, Kibwage et al.[8] and Kirst et al.[9] The 15-membered macrolides reported here are interesting examples of another type of translactonization in erythromycin derivatives. Translactonization represents a new approach to the synthesis of unusual macrolides.

## Experimental Section

$^1H$ and $^{13}C$ NMR spectra were recorded in deuteriochloroform and deuteriopyridine solutions at 400 and 100.4 MHz, respectively (Tables I and II). The signals of $^1H$ and $^{13}C$ NMR spectra were assigned by correlated $^1H$–$^1H$ homonuclear and $^1H$–$^{13}C$ heteronuclear 2D NMR spectroscopy. Melting points were measured using a Yanaco micromelting point apparatus and are uncorrected. TLC was performed on E. Merck plates of silica gel 60 $F_{254}$ and chloroform–methanol–concentrated ammonium hydroxide (9:1:0.1) as a developing solvent. The antibiotic susceptibility measurements were performed by agar dilution method.

**Translactonization of 2 to 5.** A solution of **2** (459 mg) and potassium carbonate (364 mg) in methanol (50 mL) was stirred at room temperature for 2 days. TLC of the reaction mixture indicated disappearance of the starting material ($R_f$ 0.48) and appearance of a new polar product ($R_f$ 0.25). The reaction mixture was poured into a mixture of water (200 mL) and ethyl acetate (100 mL). The two layers were separated, and the aqueous layer was further extracted twice with ethyl acetate (50 mL). The combined organic layer was washed three times with a saturated sodium chloride solution (100 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, LiChroprep Si 60 (E. Merck), with chloroform–methanol–concentrated ammonium hydroxide (20:1:0.1) as the eluant. Crystallization from acetone–water afforded **5** (350 mg) as colorless needles: mp 147–150 °C; $[\alpha]^{23}_D$ –50.3° (*c* 0.5, EtOH); $UV_{max}$ (EtOH) 217 ($\epsilon$ 391.3), 280 (shoulder); IR ($CHCl_3$) 3540, 3443, 3000–2700, 1725, 1683, 1458, 1379, 1347, 1326, 1266, 1245, 1167, 1110, 1088, 1070, 1053, 1035, 1013, 971 $cm^{-1}$; FAB-MS *m/z* ($MH^+$) 764; HR-MS *m/z* ($MH^+$) 764.4791 (calcd for $C_{38}H_{70}NO_{14}$ 764.4796). Anal. Calcd for $C_{38}H_{69}NO_{14}\cdot H_2O$: C, 58.37; H, 9.15; N, 1.79. Found: C, 58.53; H, 9.15; N, 1.68.

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**Translactonization of 3 to 4.** A solution of **3** (7.4 mg) and potassium carbonate (10 mg) in methanol (4 mL) was stirred at room temperature for 1 h. TLC of the reaction mixture indicated disappearance of the starting material ($R_f$ 0.38) and appearance of a new polar product ($R_f$ 0.28). By TLC, HPLC, and $^1$H NMR spectroscopy, the product was identical with a previously isolated metabolite (M-7) of 6-*O*-methylerythromycin A from human urine: mp 222–223 °C; $[\alpha]^{24}_D$ −34.4° (*c* 0.5, EtOH); $UV_{max}$ (EtOH) 217 (ε 379.4); IR ($CHCl_3$) 3551, 3442, 3206, 3000–2700, 1716, 1457, 1378, 1266, 1247, 1165, 1122, 1094, 1079, 1054, 1037, 1019, 998 cm$^{-1}$; FAB-MS *m/z* ($MH^+$) 764; HR-MS *m/z* ($MH^+$) 764.4761 (calcd for $C_{38}H_{70}NO_{14}$ 764.4796).

**Acetylation of 4.** A solution of **4** (89 mg) and acetic anhydride (3 mL) in pyridine (3 mL) was stirred at room temperature for 5 days. The solution was poured into a saturated sodium bicarbonate solution (30 mL) and extracted three times with ethyl acetate (30 mL × 3). The combined organic layer was washed with a saturated sodium chloride solution, dried ($MgSO_4$), and concentrated under reduced pressure. To the crude residue was added *n*-heptane (30 mL), and the solvent was distilled under reduced pressure to remove the remaining pyridine. Chromatography of the crude product on a silica gel column, LiChroprep 60 (E. Merck), with chloroform–methanol–concentrated ammonium hydroxide (40:1:0.1) as the eluant afforded the tri-*O*-acetate **7** (75 mg). Concentration of **7** in ethanol under reduced pressure gave a colorless crystalline solid: mp 207–210 °C; TLC $R_f$ 0.72; $[\alpha]^{23}_D$ −43.4 (*c* 0.5, EtOH); $UV_{max}$ (EtOH) 275 nm (ε 81.7), 222 nm (ε 457.9); IR ($CHCl_3$) 3474, 3210, 3000–2700, 1737, 1457, 1376, 1245, 1170, 1123, 1075, 1051, 1047, 1018, 986 cm$^{-1}$; FAB-MS *m/z* ($MH^+$) 890. Anal. Calcd for $C_{44}H_{75}NO_{17}$: C, 59.38; H, 8.49; N, 1.57. Found: C, 59.24; H, 8.60; N, 1.61.

**Acetylation of 5.** A solution of **5** (100 mg) and acetic anhydride (3 mL) in pyridine (3 mL) was stirred at room temperature for 5 days. The tetra-*O*-acetate **6** (84 mg) was obtained as a colorless glass by the similar procedure used in the acetylation of **4**: mp 143–147 °C; TLC $R_f$ 0.73; $[\alpha]^{25}_D$ −28.1° (*c* 0.5, EtOH); $UV_{max}$ (EtOH) 221 nm (ε 439.6), 270 (shoulder); IR ($CHCl_3$) 3000–2700, 1736, 1460, 1375, 1250, 1174, 1125, 1108, 1090, 1049, 1013 cm$^{-1}$; FAB-MS *m/z* ($MH^+$) 932. Anal. Calcd for $C_{46}H_{77}NO_{18}$: C, 59.28; H, 8.33; N, 1.50. Found: C, 59.34; H, 8.51; N, 1.38.

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