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Synthesis of 14,15-Dehydroerythromycin A Ketolides: Effects of the 13-Substituent on Erythromycin Tautomerism

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A ketolide was prepared from 14,15-dehydroerythromycin A by two different routes. The first approach involving oxidation of the 3-OH of 3-descladinosyl-14,15-dehydroerythromycin A 2′-*O*-acetate gave unexpectedly high levels of 3,11-double oxidation. This may be due to greater formation of the 9,12-hemiketal in 14,15-dehydroerythromycin A and concomitant exposure of the 11-OH group for oxidation. NMR studies of 14,15-dehydroerythromycin A support this hypothesis, revealing a 9 : 1 ratio of 9-ketone to 9,12-hemiketal in $CDCl_3$ and a 1 : 1 ratio in CD_3OD as contrasted with the corresponding tautomer ratios of 30 : 1 in $CDCl_3$, and 6 : 1 in CD_3OD with erythromycin A. Alteration of the 13-substituent on the erythronolide A ring from ethyl to vinyl thus favors formation of the 9,12-hemiketal. A second route to the ketolides was developed based on these findings, in which the 11-OH is eliminated prior to oxidation of the 3-OH.

Macrolide antibiotics such as erythromycin have long been used for treatment of upper and lower respiratory infections against Gram-positive bacteria. Such antibiotics have the advantage of a relatively small number of side effects. Degradation of erythromycin in the acidic environment of the stomach yields 8,9-anhydroerythromycin A 6,9-hemiketal, which causes gastrointestinal discomfort.[1] The analogs clarithromycin,[2] azithromycin[3] and roxithromycin[4] were developed to avoid formation of such by-products and improve pharmacokinetic properties of erythromycin.[5]

A more recent problem with erythromycin A and subsequent derivatives is the increasing incidence of resistance. A new class of macrolides known as ketolides show promising activity against erythromycin A-resistant microorganisms. Ketolides have been synthesized by replacing the 3-cladinosyl group with a carbonyl and addition of an *N*-alkylaromatic substituted C11-C12 cyclic carbamate which enhances ribosomal binding.[6] Synthesis and biological evaluation of a number of different ketolides with various aromatic substituents has proven useful in optimizing the effectiveness of such compounds. However, the effects of substitution at the 13-position of the erythromycin A derivatives on antibacterial activity have not been thoroughly investigated.

Technology developed by KHOSLA and co-workers allows manipulation of the polyketide synthases that generate a number of natural products.[7] This technique has been applied to make erythromycin analogues with different substituents at the 13 position such as 14,15-dehydroerythromycin.[8] We report here the synthesis of a 14,15-dehydroketolide and describe unexpected effects of the 13-substitution on the tautomeric equilibria of erythromycin A.

Results and Discussion

The 14,15-dehydroerythromycin A was prepared by precursor-directed biosynthesis.[8] A route previously reported for making erythromycin-based (13-ethyl) ketolides was initially used in an attempt to make the 14,15-dehydroketolide **7b**.[6] However, the conformational or

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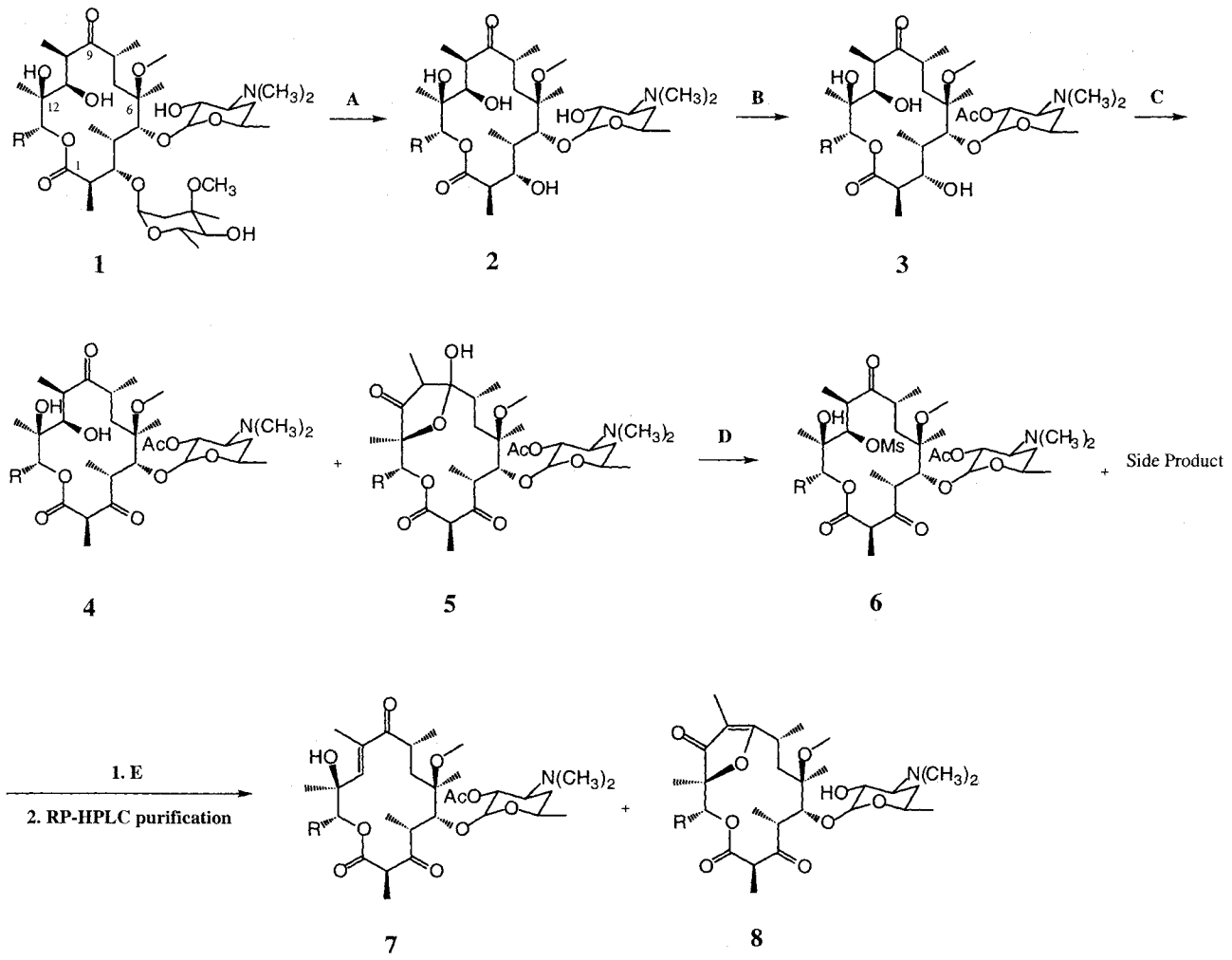
Fig. 1. Conversion of 6-*O*-methylerythromycin A (**1a**) and 6-*O*-methyl-14,15-dehydroerythromycin A (**1b**) to the corresponding ketolides by initial route.

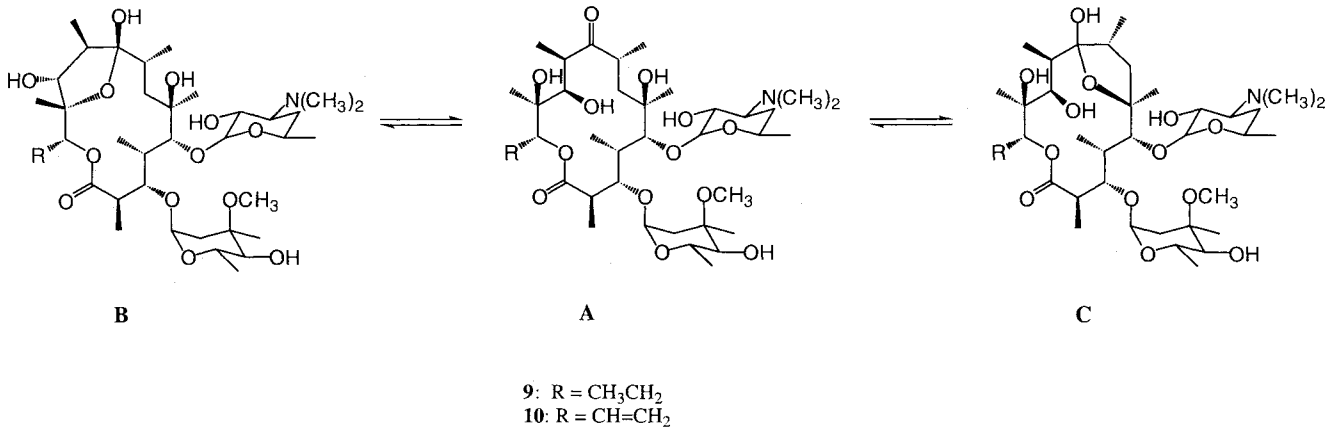


In all cases (**a**) R=CH_2CH_3, (**b**) R=CH=CH_2. Reagents: (A) HCl, H_2O; (B) acetic anhydride, K_2CO_3, CH_2Cl_2; (C) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, DMSO, pyridinium trifluoroacetate; (D) methanesulfonyl chloride, pyridine; (E) 1,8-diazabicyclo[5.4.0]undec-7-ene, acetone.

tautomeric differences between the 13-ethyl and the 13-vinyl macrolides required the development of a novel synthetic strategy.

Both 6-*O*-methylerythromycin A (**1a**) and 14,15-dehydro-6-*O*-methylerythromycin (**1b**) were prepared by alkylation of the corresponding erythromycins (Fig. 1).[9] Acid hydrolysis of the cladinose followed by acetylation of the 2′ position gave intermediate **3**. Moffat oxidation of **3a** provided the desired ketone **4a** along with a minor amount (3~5%) of a doubly-oxidized product, assumed to be **5a** (*vide infra*). Applying identical reaction conditions to **3b**, however, resulted in unacceptable levels of over-oxidation. Upon complete consumption of **3b**, the products **4b** and **5b** were detected in approximately equal amounts. Mass spectrometric analysis of partial reactions indicated a 1 : 2 : 1 mixture of starting material **3b**, product **4b**, and the doubly-oxidized product **5b**, suggesting that it would not be possible to control the formation of **5b** and still achieve acceptable levels of conversion. An efficient separation of **4b** and **5b** could not be achieved, so the mixture was carried forward. Treatment of a mix of **4b** and **5b** with methanesulfonyl chloride and subsequently with diazabicycloundecene provided **7b** and **8b**, which could be separated and fully characterized. Structural determination

Fig. 2. Tautomeric equilibria in erythromycins.



The 9-keto form (**A**) is in equilibrium with the 9,12-hemiketal (**B**) and 6,9-hemiketal (**C**) forms.

of **8b** corroborated the suspected structure of the doubly oxidized compound **5b**.

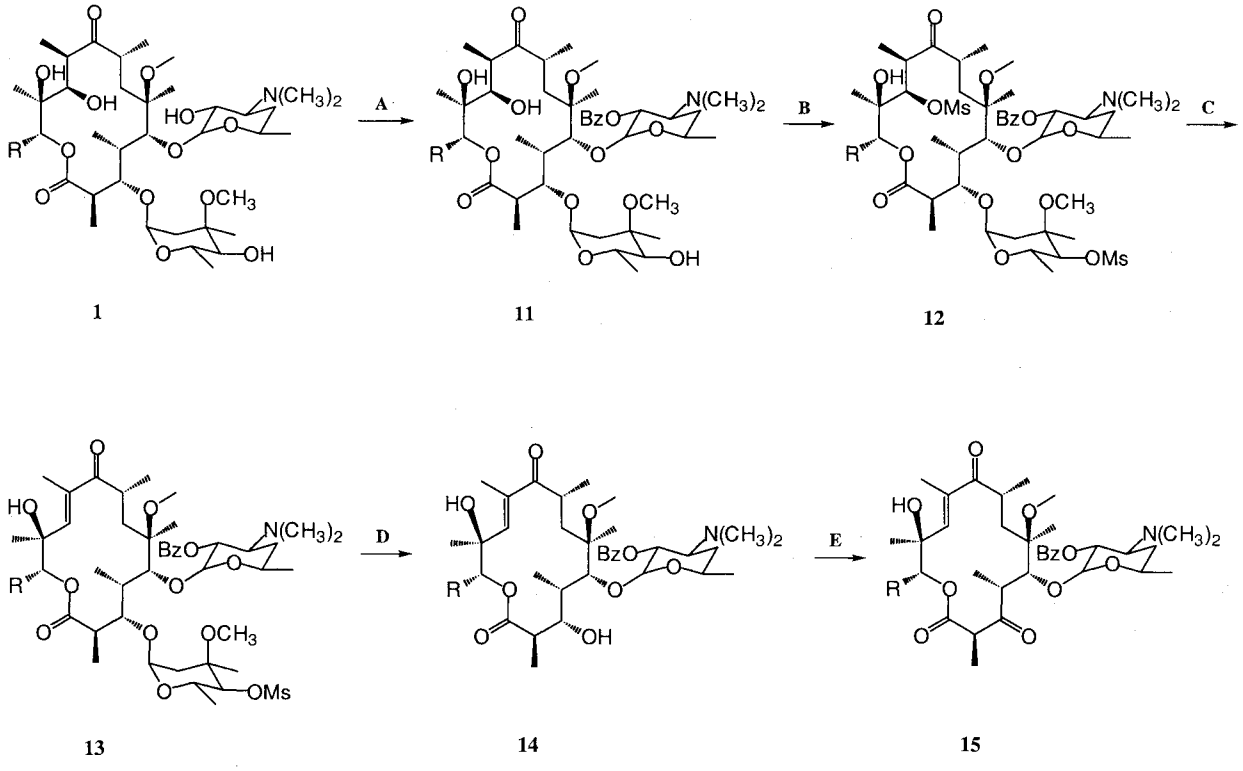
The observed difference in reactivity between **3a** and **3b** strongly suggests underlying conformational or tautomeric differences between the two molecules. Evidence for this hypothesis was obtained through NMR studies of the corresponding erythromycins. Erythromycin A has been shown to exist as a mixture of 9-keto- (**9A**), 9,12-hemiketal- (**9B**), and 6,9-hemiketal- (**9C**) forms, with the ratio of tautomers depending strongly upon the solvent (Fig. 2).[10] The ratio of **9A** to **9B** is approximately 30 : 1 in $CDCl_3$ but 6 : 1 in CD_3OD. Tautomer **9C** is very minor (2~5%) in both media. Examination of the NMR spectra of 14,15-dehydroerythromycin A (**10A**) revealed similar tautomeric forms, although with markedly different ratios of the tautomers. The ratio of **10A** to **10B** is 9 : 1 in $CDCl_3$ and 1 : 1 in CD_3OD. As with erythromycin, **10C** remains minor in both media. Tautomer **10B** was clearly identified as the major hemiketal in CD_3OD by NMR. The 9-keto tautomer **10A** shows resonances for C9, C12, and C6 at δ 219.9, 75.1, and 74.3, respectively, whereas the major hemiketal tautomer shows these signals at δ 107.0, 82.0, and 74.1, consistent with the 9,12-hemiketal **10B**. Assignments were made using HSQC and HMBC experiments, and agree with values reported for the tautomers of **9**.[10]

Formation of the 9,12-hemiketal is thus more favored when the 13-group is vinyl than when it is ethyl. The cause of this is uncertain, although a reduced steric demand for the vinyl group in the 9,12-hemiketal is a likely contributing factor. Formation of **9B** results in a syn-pentane-type interaction between the 14-CH_2 and 11-OH groups, which is lessened in **10B** due to the planarity of the 14-CH. We hypothesize that formation of the 9,12-hemiketal and concomitant exposure of the normally unreactive 11-OH may account for the different reactivities of **3a** and **3b** towards oxidation.

To avoid these difficulties, we developed a synthetic sequence in which the 10,11-alkene is introduced prior to the oxidation step (Fig. 3). Following protection of the 2′-hydroxyl of **1**, mesylation provides the 4″,11-*O*-mesylate **12** and the 11-*O*-mesyl group is eliminated by treatment with base to yield **13**. The 4-*O*-mesylcladinose is hydrolyzed, and the resulting 3-hydroxyl is oxidized to provide the ketolide **15**. When applied to **1b**, this sequence provided **15b** in 28% overall yield, substantially improved over the 14% yield obtained using the sequence in Figure 1. Hydrolysis of the 4-*O*-mesylated-cladinose from **13** requires harsher conditions than observed with **1**, yet provides **14** in good yield. This approach was also successful with R=CH_3CH_2, converting **1a** into ketolide **15a** in 35% overall yield compared with 25% yield obtained using the procedure of Figure 1.

These results demonstrate an unexpected effect of the 13-substituent on the tautomeric equilibria and consequent reactivity of erythromycin A. An alternate route for the preparation of the ketolides from clarithromycin and its analogs was developed to compensate for these effects which resulted in a higher overall yield and ease of

Fig. 3. Synthesis of ketolides **15a** and **15b** by an alternate route, avoiding 11-oxidation.



In all cases (**a**) R=CH_2CH_3, (**b**) R=CH=CH_2. Reagents: (A) benzoic anhydride, CH_2Cl_2, Et_3N; (B) methanesulfonyl chloride, pyridine (C) 1,8-diazabicyclo[5.4.0]undec-7-ene, acetone; (D) HCl, H_2O; (E) Dess-Martin periodinane, CH_2Cl_2.

purification of the intermediates.

Materials and Methods

General Experimental Procedures

14,15-Dehydroerythromycin A was produced by fermentation by precursor-directed biosynthesis.[8] All other materials were reagent grade and used as provided unless otherwise stated. All reactions were performed under N_2 atmosphere. Column chromatography was performed with Merck 60 230~400 mesh silica gel. Thin layer chromatography was performed on pre-coated glass with silica gel 60 and the spots were visualized by vanillin followed by heating. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solution at 300 K (Bruker DRX-400 spectrometer). Mass spectra were obtained using electrospray ionization with a PE/Sciex API-100LC mass spectrometer equipped with a Turbo Ion Spray source.

6-*O*-Methyl-14,15-dehydroerythromycin A (**1b**)

(A) 14,15-Dehydroerythromycin A 9-oxime (**IA**)

A solution of 14,15-dehydroerythromycin A (102 mg, 0.139 mmol) in 0.310 ml of 2-propanol, 50% aq hydroxylamine (0.101 ml, 1.53 mmol), and AcOH (32 μl, 0.556 mmol) was heated at 50°C for 24 hours. The reaction mixture was cooled to ambient temperature and satd aq $NaHCO_3$ was added to pH 12. The product was extracted with CH_2Cl_2 (4×30 ml) and the organic layer was washed with brine and dried to give **IA** (90 mg, 87%) as a white solid. MS *m/z* 748 $(M+H)^+$. The product was carried on without purification.

(B) 14,15-Dehydroerythromycin A 9-(*O*-(1-isopropoxycyclohexyl)oxime (**IB**)

A mixture of **IA** (312 mg, 0.418 mmol) in 2.09 ml of CH_2Cl_2 and 1,1-diisopropoxycyclohexane (418 mg, 2.09 mmol) was stirred with 158 mg (0.627 mmol) of pyridinium

p-toluenesulfonate for 2 days. Addition of 1 N NaOH to pH 12 and extraction with CH_2Cl_2 (4×50 ml) yielded crude product. Column chromatography (99 : 1 toluene/Et_3N to 70 : 29 : 1 toluene/Me_2CO/Et_3N) gave **IB** (308 mg, 83%) as a white solid. ^1H NMR δ 6.06 (1H, ddd, J=17.3, 10.9, 4.6 Hz), 5.59 (1H, m), 5.23 (1H, dt, J=10.9, 1.6 Hz), 5.17 (1H, dt, J=17.3, 1.6 Hz), 4.88 (1H, d, J=4.6 Hz), 4.42~4.47 (1H, m), 4.14~4.00 (3H, m), 3.82~3.75 (2H, m), 3.59 (1H, d, J=7.3 Hz), 3.55~3.47 (1H, m), 3.33 (3H, s), 3.23 (1H, dd, J=10.1, 7.3 Hz), 3.07~2.98 (1H, m), 2.90 (1H, dq, J= 7.5, 7.5 Hz), 2.70 (1H, q, J=7.0 Hz), 2.40~2.50 (1H, m), 2.37 (1H, d, J=15.4 Hz), 2.31 (6H, s), 2.09~2.01 (1H, m), 1.98~1.92 (1H, m), 1.90~1.81 (2H, m), 1.68~1.50 (9H, m), 1.49 (3H, s),1.40~1.33 (2H, m), 1.32~1.01 (31H, m). MS *m/z* 888 $(M+H)^+$.

(C) 2′,4″-bis-*O*-Trimethylsilyl-14,15-dehydroerythromycin A 9-[*O*-(1-isopropoxycyclohexyl)oxime] (**IC**)

A solution of **IB** (80 mg, 0.090 mmol) in CH_2Cl_2 (0.90 ml) was treated with 1-trimethylsilylimidazole (36 μl, 0.24 mmol) and chlorotrimethylsilane (20 μl, 0.153 mmol). The solution was stirred at ambient temperature for 10 minutes. The reaction mixture was diluted with 50 ml of CH_2Cl_2 and washed with 1 N NaOH solution. The aqueous layer was washed with CH_2Cl_2 (3×60 ml). The organic extracts were combined, dried, and evaporated to give the desired product as a white foam (90 mg, 97%). Analysis by LC-MS revealed the product to be more than 95% pure and was carried on without purification. MS *m/z* 1032 $(M+H)^+$.

(D) 2′,4″-bis-*O*-Trimethylsilyl-6-*O*-methyl-14,15-dehydroerythromycin A 9-[*O*-(1-isopropoxycyclohexyl)oxime] (**ID**)

A solution of **IC** (340 mg, 0.330 mmol) in 1.98 ml of 1 : 1 DMSO/THF was treated with 0.330 ml of a 2 M solution of methyl bromide in ether. The solution was cooled with an ice-water bath to 0°C. A mixture of 0.660 ml of a 1 M KO*t*-Bu in THF and 0.660 ml of DMSO was added dropwise over 4 hours until the reaction was completed as determined by TLC and MS. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N NaOH. The aqueous layer was further extracted with CH_2Cl_2 (4×50 ml). The organic extracts were combined, washed with brine, dried, and evaporated to give **ID** as a white foam. MS *m/z* 1045.7 $(M+H)^+$.

(E) 6-*O*-methyl-14,15-dehydroerythromycin A 9-oxime (**IE**)

A solution of **ID** (344 mg, 0.329 mmol) in 2 : 1 CH_3CN/H_2O (5.06 ml) and AcOH (1.83 ml, 31.9 mmol) was stirred at ambient temperature for 8 hours. The reaction was adjusted to pH 12 with 1 N NaOH and extracted with CH_2Cl_2 (4×50 ml). The organic extracts were combined, washed with brine, and dried to give **IE** as a white solid (245 mg). MS *m/z* 761.5 $(M+H)^+$.

(F) 6-*O*-Methyl-14,15-dehydroerythromycin A (**1b**)

A mixture of **IE** (245 mg, 0.322 mmol) in 3.22 ml of 1 : 1 EtOH/H_2O, sodium hydrosulfite (561 mg, 3.22 mmol) and 96% formic acid (121 μl, 3.22 mmol) was heated at 90°C for 2.5 hours. Partial evaporation of the solvent, addition of 1 N NaOH, extraction with CH_2Cl_2 (4×50 ml), and evaporation of the extract yielded **1b**. MS *m/z* 746.6 $(M+H)^+$.

5-*O*-Desosaminyl-6-*O*-methyl-14,15-dehydroerythronolide A (**2b**)

A solution of **1b** (170 mg, 0.227 mmol) in 5 ml of 5% aqueous HCl was stirred for 2.5 hours, then 1 N NaOH was added and the mix was extracted with CH_2Cl_2 (4×50 ml). The organic extracts were combined, washed with brine and concentrated. The residue was purified by column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N to 70 : 29 : 1) to give **2b** as a white solid (110 mg, 57% over 4 steps, from **ID**). ^1H NMR δ 6.08 (1H, ddd, J=17.2, 10.8, 4.8 Hz), 5.70 (1H, m), 5.25 (1H, dt, J=10.8, 1.6 Hz), 5.20 (1H, dt, J=17.3, 1.6 Hz), 4.40 (1H, d, J=7.3 Hz), 3.94 (1H br s), 3.86 (1H, br s), 3.69 (1H, s), 3.54 (1H, d, J=9.7 Hz), 3.54~3.47 (1H, m), 3.44~3.35 (1H, m), 3.24 (1H, dd, J=10.2, 7.4 Hz), 3.01 (1H, q, J=7.3 Hz), 2.97 (3H, s), 2.71 (1H, dq, J=10.4, 6.6 Hz), 2.65~2.55 (1H, m), 2.49 (1H, ddd, J=12.3, 10.3, 3.7 Hz), 2.26 (6H, s), 2.25~2.18 (1H, m), 2.02~1.88 (1H, m), 1.67 (1H, d, J=12.9 Hz), 1.57 (1H, d, J=13.5 Hz), 1.59 (3H, s), 1.35~1.09 (20H, m). ^{13}C NMR δ 220.5, 174.0, 133.4, 116.8, 106.7, 88.5, 79.0, 78.1, 74.6, 74.2, 70.6, 70.2, 69.6, 65.7, 49.5, 45.5, 44.3, 40.2, 38.7, 37.7, 35.8, 28.1, 21.2, 18.8, 17.7, 16.4, 14.6, 12.4, 8.2. MS: *m/z*=588.4 $([M+H]^+)$.

5-*O*-(2′-*O*-Acetyldesosaminyl)-6-*O*-methyl-14,15-dehydroerythronolide A (**3b**)

A mixture of **2b** (110 mg, 0.187 mmol) in 1.34 ml of CH_2Cl_2, potassium carbonate (77 mg, 0.561 mmol), and acetic anhydride (26 μl, 0.281 mmol) was stirred for 15 hours. The reaction was diluted with CH_2Cl_2 and washed with $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (5×50 ml) and the organic extracts were combined and dried to give **3b** as a white solid (100 mg, 85%). MS *m/z* 630.6 $(M+H)^+$.

Oxidation of **3b** (**4b**+**5b**)

A solution of pyridinium trifluoroacetate (107 mg, 0.553

mmol) in 0.245 ml of CH_2Cl_2 was added dropwise to a suspension of **3b** (52 mg, 0.083 mmol), 1-[(3-dimethylamino)propyl)]-3-ethylcarbodiimide hydrochloride (106 mg, 0.553 mmol), and DMSO (106 μl) in 0.550 ml of CH_2Cl_2 at 0°C over 6 hours. The reaction was stopped by addition of H_2O and stirring for 5 minutes. The product was extracted with CH_2Cl_2 (5×50 ml) and purified by column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N) to give 42 mg of a white solid. LC/MS shows a 3 : 2 ratio of *m/z* 628.5 (**4b** $(M+H)^+$ and *m/z* 626.5 (**5b** $(M+H)^+$ at the end of the reaction.

5-*O*-(2′-*O*-Acetyldesosaminyl)-10,11-anhydro-3-deoxy-3-oxo-6-*O*-methyl-14,15-dehydroerythronolide A (**7b**) and 5-*O*-(2′-*O*-Acetyldesosaminyl)-9,10-anhydro-3,11-dideoxy-3,11-dioxo-6-*O*-methyl-14,15-dehydroerythronolide A 9,12-Hemiketal (**8b**)

Methanesulfonyl chloride (26 μl, 0.337 mmol) is added to a solution of the mixture of **4b** and **5b** from above (42 mg, 0.067 mmol) in 0.25 ml of pyridine, and the solution was stirred at ambient temperature for 22 hours. The mixture was diluted with CH_2Cl_2 and washed sequentially with satd aq $NaHCO_3$ (4×30 ml) and brine. Column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N) gave 32 mg (68%) of the mesylate as a white film. MS: *m/z*=707 ($[M+H]^+$). A solution of this product (32 mg) in 0.16 ml of acetone and 1,8-diazabicyclo[5,4,0]undec-7-ene (35 μl, 0.23 mmol) was stirred for 20 hours. Column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N) to gave 20 mg (70%) of a 3 : 2 mixture of **7b** and **8b** as a white solid. The products were purified by HPLC (C_{18}, 40~60% CH_3CN in H_2O) to obtain 11 mg of **7b**: ^1H NMR δ 6.74 (1H, s), 5.91 (1H, ddd, *J*=17.2, 10.8, 6.4 Hz), 5.41 (1H, dt, *J*=10.8, 1.2 Hz), 5.32 (1H, dt, *J*=17.2, 1.2 Hz), 5.27 (1H, d, *J*=6.4 Hz), 4.72 (1H, dd, *J*=10.8, 7.6 Hz), 4.34 (1H, d, *J*=7.6 Hz), 4.15 (1H, d, *J*=8.4 Hz), 3.79 (1H, q, *J*=6.8 Hz), 3.57~3.47 (1H, m), 3.15 (1H, dq, *J*=7.6, 1.2 Hz), 2.85 (3H, s), 2.64 (1H, ddd, *J*=12.4, 10.4, 4.4 Hz), 2.33 (6H, s), 2.02 (6H, s), 1.80 (1H, dd, *J*=15.2, 4.4 Hz), 1.75~1.68 (1H, m), 1.64~1.52 (1H, m), 1.48 (3H, s), 1.44~1.35 (1H, m), 1.35~1.18 (10H, m), 1.16 (3H, d, *J*=6.8 Hz), 1.10 (3H, d, *J*=7.6 Hz). ^{13}C NMR δ 206.8, 203.1, 169.7, 168.2, 141.4, 139.6, 131.5, 120.2, 101.9, 80.7, 80.4, 78.7, 72.6, 71.5, 69.1, 63.4, 51.2, 50.5, 47.1, 40.6, 39.9, 30.4, 29.3, 22.7, 22.2, 21.3, 21.0, 18.6, 14.4, 14.0, 13.6. MS *m/z* 611 $(M+H)^+$.

The 2′-*O*-acetate was lost from **8b** during purification. ^1H NMR δ 6.13 (1H, ddd, *J*=17.2, 10.0, 8.8 Hz), 5.44~5.27 (3H, m), 4.30 (1H, d, *J*=7.2 Hz), 4.07 (1H, d, *J*=10.0 Hz), 3.55 (1H, q, *J*=6.8 Hz), 3.53~3.47 (1H, m), 2.92~2.85 (1H, m), 2.81 (3H, s), 2.68~2.55 (2H, m), 2.36 (6H, s), 2.25 (1H, dd, *J*=15.2, 14.8 Hz), 2.07 (3H, br s), 2.05~1.99 (1H, m), 1.81 (3H, s), 1.75~1.68 (1H, m), 1.60 (1H, d, *J*=14.8 Hz), 1.36~1.17 (16H, m). ^{13}C NMR δ 205.1, 203.9, 194.7, 168.0, 129.8, 122.1, 107.8, 104.3, 85.8, 82.3, 79.1, 77.8, 70.1, 69.1, 65.8, 51.8, 50.4, 49.7, 41.5, 39.9, 31.8, 30.0, 21.1, 19.9, 19.7, 19.6, 16.5, 14.1, 6.0.

2′-*O*-Benzoyl-6-*O*-methyl-14,15-dehydroerythromycin A (**11b**)

A solution of **1b** (668 mg, 0.895 mmol), benzoic anhydride (385 mg, 1.70 mmol) and Et_3N (0.250 ml, 1.79 mmol) was stirred in 3.6 ml of CH_2Cl_2 for 2 days. Satd aq $NaHCO_3$ was added and the product was extracted with CH_2Cl_2 (3×50 ml). The solvent was removed *in vacuo* and the residue was purified by column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N) to give 477 mg (58% over 4 steps from **ID**) of **11b** as a white solid. MS *m/z* 850.6 $(M+H)^+$.

2′-*O*-Benzoyl-6-*O*-methyl-4″,11-bis(*O*-methanesulfonyl)-14,15-dehydroerythromycin A (**12b**)

A solution of 549 mg (0.646 mmol) of **11b** in 2.39 ml of pyridine was stirred with methanesulfonyl chloride (0.500 ml, 6.46 mmol) for 1 day. The reaction was diluted with CH_2Cl_2 and quenched with satd aq $NaHCO_3$. The aqueous layer was extracted three times and the combined organic layer was dried *in vacuo*. Column chromatography (90 : 9 : 1 toluene/acetone/Et_3N) gave 530 mg (82%) of **12b** as a pale yellow foam. MS *m/z* 1006.5 $(M+H)^+$.

2′-*O*-Benzoyl-6-*O*-methyl-4″-*O*-methanesulfonyl-10,11-anhydro-14,15-dehydroerythromycin A (**13b**)

A solution of **12b** (59 mg, 0.059 mmol) in 0.195 ml of acetone was stirred with 18 μl (0.12 mmol) of DBU for 1 day. The residue was dried *in vacuo* and purified by column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N) to give 50 mg (75%) of **13b** as a white foam. MS *m/z* 910.5 $(M+H)^+$.

5-*O*-(2′-*O*-Benzoyldesosaminyl)-10,11-anhydro-6-*O*-methyl-14,15-dehydroerythronolide A (**14b**)

A mixture of **13b** (337 mg, 0.370 mmol) in 1.5 ml of CH_3CN and 6.9 ml of a 3 N aq HCl was stirred for 22 hours. The CH_3CN was removed *in vacuo* and 1 N NaOH was added to pH 12. The product was extracted with CH_2Cl_2 (4×40 ml), and the combined organic extracts were concentrated to dryness. Column chromatography using a gradient (96 : 4 CH_2Cl_2/MeOH to 95 : 4 : 1 CH_2Cl_2/MeOH/Et_3N) gave 197 mg (79%) of **14b** as a white foam. MS *m/z* 674.4 $(M+H)^+$.

5-*O*-(2′-*O*-Benzoyldesosaminyl)-10,11-anhydro-3-deoxy-3-oxo-6-*O*-methyl-14,15-dehydroerythronolide A (**15b**)

A suspension of **14b** (226 mg, 0.335 mmol) in CH_2Cl_2 (14.6 ml) was stirred with the Dess-Martin periodinane (427 mg) for 1 hours. The mix was diluted with CH_2Cl_2, satd aq $NaHCO_3$ was added, and the product was extracted with CH_2Cl_2 (4×40 ml). The combined extract was dried *in vacuo*. Column chromatography (90 : 9 : 1 toluene/Me_2CO/Et_3N) followed by a second column (CH_2Cl_2 to CH_2Cl_2+ 1% Et_3N) gave 168 mg (75%) of **15b** as a white foam. ^{1}H-NMR: δ 8.01 (2H, d, J=7.2 Hz), 7.54 (1H, t, J=7.2 Hz), 7.42 (2H, t, J=7.2 Hz), 6.69 (1H, s), 5.87 (1H, ddd, J=17.5, 10.8, 6.0 Hz), 5.38 (1H, d, J=10.8 Hz), 5.28 (1H, d, J=17.5 Hz), 5.23 (1H, d, J=6.0 Hz), 5.01 (1H, dd, J=10.4, 7.5 Hz), 4.51 (1H, d, J=7.5 Hz), 4.17 (1H, d, J=8.4 Hz), 3.68 (1H, q, J=6.8 Hz), 3.65~3.55 (1H, m), 3.18~3.08 (1H, m), 3.03 (1H, dq, J=8.0, 8.0 Hz), 2.83 (3H, s), 2.26 (6H, s), 2.00 (3H, s), 1.90~1.70 (2H, m), 1.60~1.42 (2H, m), 1.38 (3H, s), 1.35 (3H, s), 1.29~1.23 (7H, m), 1.16 (3H, d, J=6.8 Hz), 0.92 (3H, d, J=7.6 Hz). ^{13}C-NMR: δ 206.8, 203.1, 168.1, 165.1, 141.4, 139.6, 132.7, 131.5, 130.5, 129.8, 128.3, 120.2, 102.1, 80.8, 80.4, 78.7, 72.5, 71.9, 69.2, 63.8, 51.1, 50.5, 47.1, 40.7, 39.9, 37.8, 31.2, 22.2, 22.1, 21.0, 18.5, 14.3, 14.2, 13.6. MS *m/z* 672.4 $(M+H)^+$.

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