JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

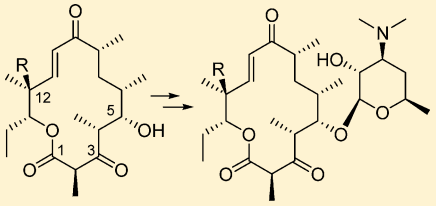
Total Synthesis of Pikromycin

Hong-Se Oh and Han-Young Kang*

Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea

Supporting Information

ABSTRACT: The total synthesis of pikromycin (**6**), the first isolated macrolide antibiotic, was achieved. The target macrolide was retrosynthetically divided into two parts, pikronolide (**6a**) (aglycon) and D-desosamine. The aglycon was synthesized using key reactions such as an asymmetric aldol reaction, Yamaguchi esterification, and ring-closing metathesis. The aglycon was coupled successfully with the trichloroacetimidate derivative of D-desosamine under Lewis acidic conditions to afford pikromycin. Narbomycin (**5**) was also synthesized from narbonolide (**5a**) under identical conditions.



Macrolide antibiotics belong to a class of polyketide natural products that exhibit clinically important biological activities.[1,2] They usually possess a macrolactone ring to which are attached one or more sugars; these antibiotics are usually produced by certain species of *Streptomyces*. Pikromycin was the first known macrolide antibiotic that was isolated in 1950 and originally considered to be an isomer of methymycin, which has a 12-membered lactone ring. The correct structure was identified by Brockmann and co-workers in 1957 to be a 14-membered lactone attached with a sugar called D-desosamine.[3] *Streptomyces venezuelae* produces a series of macrolides, which belong to two families, methymycin and pikromycin. A macrolide belonging to the methymycin family, such as methymycin (**2**),[4] has a 12-membered lactone ring, whereas a macrolide belonging to the pikromycin family, such as pikromycin (**6**), contains a 14-membered macrolactone ring (Figure 1). Pikromycin polyketide synthase (Pik PKS) is a gigantic enzyme that is responsible for producing many macrolactones such as 10-deoxymethynolide (**1a**)[5] and narbonolide (**5a**). Glycosylation of these two macrolactones with desosamine, which is the first post-PKS modification, is catalyzed by enzymes encoded by the *des* genes to provide YC-17 (**1**) and narbomycin (**5**), respectively. Hydroxylation, another post-PKS modification, of these two macrolides by cytochrome P450 oxygenase (Pik C), leads to the generation of a variety of macrolides, depending upon the site of oxidation. Hydroxylation of the C-10 and C-12 positions of **1** generates **2** and neomethymycin (**3**),[4] respectively. YC-17 (**1**) is hydroxylated at both C-10 and C-12 positions to afford novamethymycin (**4**).[6] Similarly, hydroxylation of **5** at C-12 or C-14 positions provides **6** and neopikromycin (**7**), respectively. The oxidation of both C-12 and C-14 positions affords novapikromycin (**8**).[7] As a result, a total of eight macrolides, four with 12-membered macrolactones and the other four with 14-membered macrolactones, are produced with the involvement of PKS, Des, and Pik C enzymes.

Chemical synthesis of these macrolides has attracted considerable attention; as a result, synthetic studies have been conducted on aglycons such as **1a**,[8] methynolide (**2a**),[9] neomethynolide (**3a**),[10] novamethynolide (**4a**), **5a**,[11] and pikronolide (**6a**)[12] as well as macrolides such as **2**. Surprisingly, even though pikromycin is the representative molecule in this series of macrolides that appear in the pikromycin biosynthetic pathway in *Streptomyces venezuelae* and is important structurally and historically, the total synthesis of pikromycin by chemical means has not been reported.

We have been involved in the synthesis of the macrolides that appear in the pikromycin pathway. We have successfully reported the syntheses of aglycons of these macrolides, such as **1a** and **5a**,[13] as well as macrolides such as **2**,[14] **3**, and **4**.[15] In this paper, we report the first successful total synthesis of pikromycin.

Our retrosynthetic analysis for pikromycin (**6**), which is based on our previously reported synthetic experiences,[13−15] is shown in Figure 2. Pikromycin can be derived from **6a** through glycosylation. Pikronolide (**6a**) can, in turn, be retrosynthetically divided into three parts. Aldol reaction, Yamaguchi esterification, and ring-closing metathesis could be used for the construction of **6a**. Our synthesis of **6a** is summarized in Scheme 1.

Carboxylic acid **9**[13] was prepared according to a procedure similar to that reported for the synthesis of **5a**. Esterification with the fragment **10**[14] through the Yamaguchi protocol afforded an ester **11**, which was subjected to the deprotection of the TBS group under acidic conditions (CSA, MeOH) to yield **12**. Oxidation followed by Grignard addition and another oxidation with DMP offered vinyl ketone **15** as a precursor for the critical ring-closing metathesis (RCM). Cyclization of **15** with the second-generation Grubbs catalyst successfully provided a 14-membered lactone **16** in good yield. Deprotection of the hydroxy group at C-3 with TBAF followed by the Dess−Martin oxidation provided a PMB-protected ketone **18**. Deprotection of the PMB group to free the hydroxy group at C-5 is the only remaining step for the completion of the total synthesis of **6a**. The usual deprotection condition employing

Received: June 18, 2011
Published: December 14, 2011

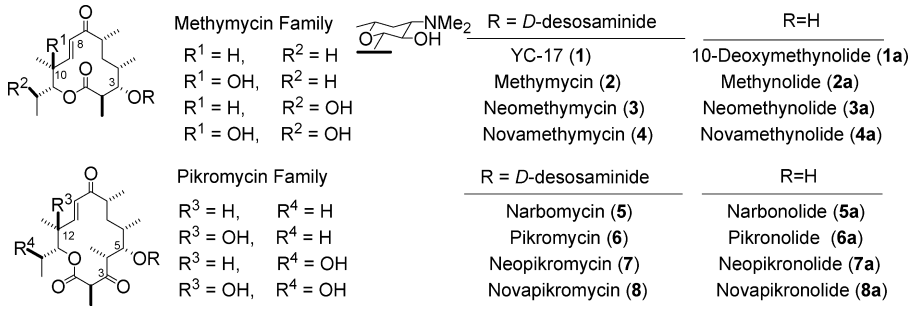


Figure 1. Methymycin and pikromycin families of macrolide antibiotics.

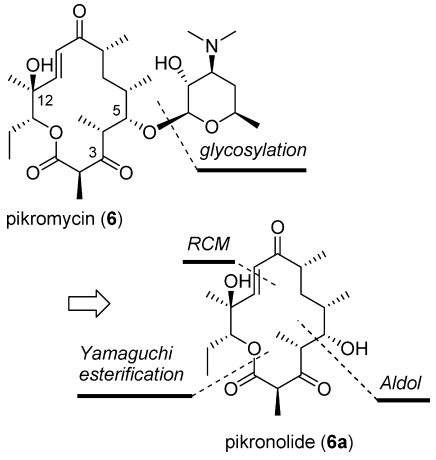


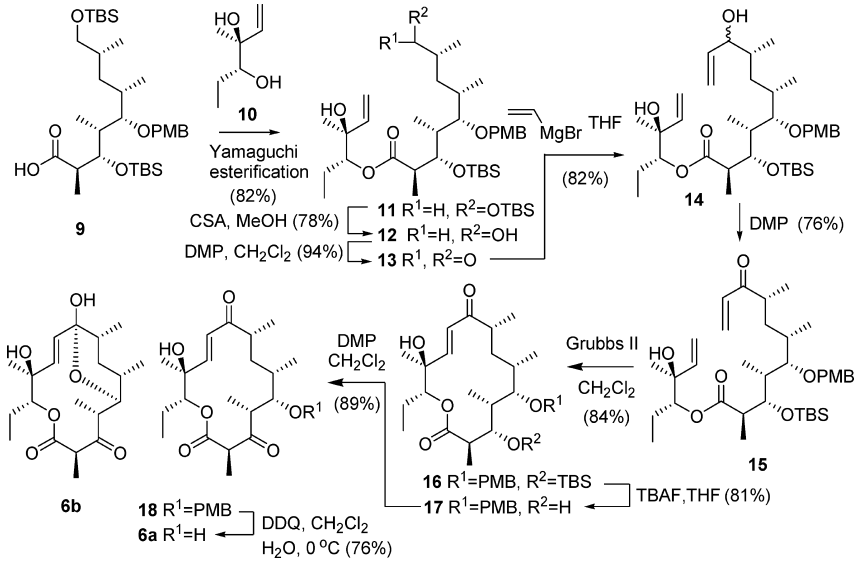
Figure 2. Retrosynthetic analysis.

DDQ at 0 °C affords **6a** (76%); the ^{1}H NMR spectrum of thus prepared **6a** reasonably matched with that reported by Yonemitsu and co-workers.[12] Careful analysis of the NMR spectrum shows that the deprotection provided a 4:1 mixture of pikronolide (**6a**) and another compound which is identified as the corresponding 5−9-hemiacetal **6b**. Although this mixture was inseparable, the structure of the hemiacetal **6b** was strongly supported by COSY and HSQC spectra. The ^{1}H NMR spectrum revealed that the ratio of the mixture was changed to 1: 1 by altering the solvent from $CDCl_3$ to CD_3OD. Although Yonemitsu and co-workers who reported the synthesis of pikronolide (**6a**) did not mention the formation of pikronolide-5,9-hemiacetal (**6b**), possibility of the hemiacetal formation through the reactions between the free hydroxy and the 9-keto group had already been reported in erythromycin[16] and telithromycin cases.[17]

Having pikronolide in our hands, glycosylation of **6a** with D-desosamine is required in order to achieve our goal, the synthesis of pikromycin. As a test for finding optimum conditions for the desired glycosylation, we first performed glycosylation of **5a**. Narbonolide (**5a**), which was prepared previously,[13] did not suffer from the contamination of an unidentified minor product and was also slightly more easily accessible due to the absence of the C-12 hydroxy group. To the best of our knowledge, total synthesis of narbomycin has never been reported either.

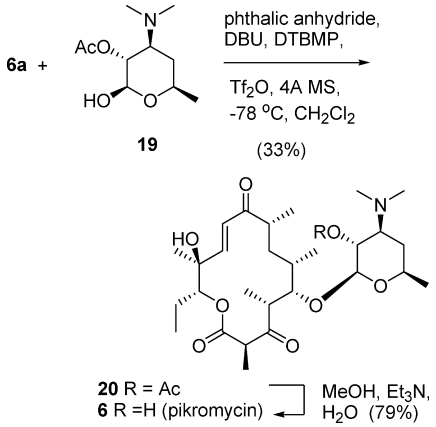
Even though we had a successful test glycosylation with a narbonolide derivative under the Lewis acidic conditions, we could not achieve the desired glycosylation of **6a** with a D-desosamine trichloroacetimidate derivative[18] under the Lewis acidic conditions such as BF_3 OEt or TMSOTf. Searching for a better glycosylation method, we found that stereoselective direct glycosylation developed by Kim,[19] which includes activation with phthalic anhydride and Tf_2O, is effective for the coupling of desosamine with **6a** (Scheme 2).

Scheme 1. Synthesis of Pikronolide (6a)



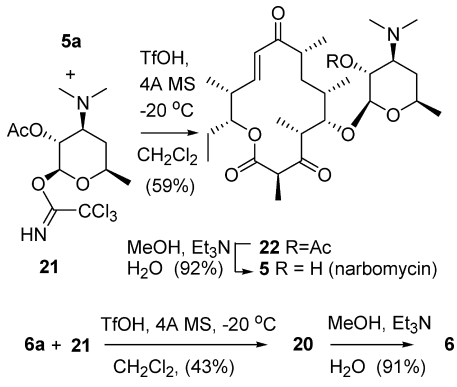
dx.doi.org/10.1021/jo201158q | J. Org. Chem. 2012, 77, 1125−1130

Scheme 2. Synthesis of Pikromycin (6)



In fact, glycosylation of **6a** with Ac-protected desosamine **19**[14] was achieved through activation with phthalic anhydride (phthalic anhydride, DBU, DTBMP, Tf_2O, 4 Å MS, −78 °C) in reasonable yield (33%). Deacetylation (MeOH, Et_3N, H_2O) afforded the desired pikromycin in 79% yield. Encouraged with this success in glycosylation via activation with phthalic anhydride, we also applied this method to the synthesis of **5** from **5a**. The phthalic anhydride method, however, resulted in the decomposition of **5a**. This was unexpected, since **6a** seemed to be more sensitive than narbonolide **5a** owing to the existence of an extra tertiary hydroxy group in **6a**. After experimentation, we finally found that the glycosylation of **5a** with the corresponding trichloroacetimidate **21**[14,15,18] using TfOH effectively afforded the desired glycosylated product, which was further subjected to deacetylation to yield **5**. This comprises the successful total synthesis of **5**. Under this glycosylation condition using TfOH we were also able to perform the successful glycosylation of **6** (Scheme 3). The

Scheme 3. Synthesis of Narbomycin (5) and Pikromycin (6)



spectroscopic properties (both ^1H NMR and ^{13}C NMR) of **6** thus prepared are identical to those of **6** isolated from the cell culture.

In conclusion, the first chemical total syntheses of pikromycin (**6**) and narbomycin (**5**) have been achieved via glycosylation of pikronolide (**6a**) and narbonolide (**5a**), respectively, with the trichloroacetimidate derivative of D-desosamine. Pikronolide was synthesized through the coupling of the corresponding fragments using asymmetric aldol reactions, Yamaguchi esterification, and ring-closing metathesis using Grubbs' second-generation catalyst.

EXPERIMENTAL SECTION

General Methods. ^1H NMR spectra were recorded on a 300, 400, or 500 MHz spectrometer at ambient temperature with $CDCl_3$ as the solvent unless otherwise stated. ^{13}C NMR spectra were recorded on a 75, 100, or 125 MHz spectrometer (with complete proton decoupling) at ambient temperature. High-resolution mass spectrometry (HRMS) was performed using a FAB technique. Flash chromatography was performed using 230−400 mesh silica gel.

(3*S*,4*R*)-3-Hydroxy-3-methylhex-1-en-4-yl (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3,9-Bis-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethylnonanoate (11). To a solution of carboxylic acid 9 (611 mg, 1.00 mmol) in THF (10 mL) at room temperature were added triethylamine (209 μL, 1.50 mmol) and 2,4,6-trichlorobenzoyl chloride (203 μL, 1.30 mmol). The mixture was stirred for 3 h at room temperature, and the solids were filtered off and washed with hexane (2 × 5 mL). The combined solution was concentrated under reduced pressure. The residue was dissolved in benzene (5 mL), and to this solution a solution of alcohol **10** (196 mg, 1.50 mmol) and 4-(dimethlamino)pyridine (DMAP) (171 mg, 1.40 mmol) in benzene (2 mL) was added. After being stirred for 15 h, the reaction mixture was diluted with ether (10 mL), washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc = 5:1) afforded the desired ester **11** (590 mg, 82%) as a colorless oil: $[\alpha]^{29}_D$ +8.12 (*c* 1.08, $CHCl_3$); IR (film) 3453, 2972, 2932, 1729, 1610, 1512, 1455, 1370, 1249, 1170, 1037 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.05 (d, *J* = 3.4 Hz, 6H), 0.83 (m, 12H), 0.88 (m, 12H), 0.94 (d, *J* = 6.8 Hz, 6H), 1.19 (m, 6H), 1.34 (m, 1H), 1.48 (m, 1H), 1.63 (m, 2H), 1.84 (m, 3H), 2.80 (dddd, *J* = 7.0, 7.0, 7.0, 13.9 Hz, 1H), 3.23 (m, 2H), 3.56 (dd, *J* = 4.5, 9.8, Hz, 1H), 3.75 (s, 3H), 3.98 (dd, *J* = 4.2, 6.2 Hz, 1H), 4.43 (q, *J* = 10.8 Hz, 2H), 4.71 (dd, *J* = 2.9, 9.8 Hz, 1H), 5.06 (dd, *J* = 0.7, 10.9 Hz, 1H), 5.24 (d, *J* = 17.3 Hz, 1H), 5.81 (dd, *J* = 10.8, 17.3 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0, 158.9, 140.9, 131.3, 128.9, 114.1, 113.6, 83.8, 80.3, 74.8, 73.9, 73.6, 67.8, 55.2, 43.3, 40.4, 35.7, 33.2, 33.1, 26.2, 26.0, 24.9, 22.7, 19.0, 18.5, 18.3, 17.5, 17.2, 14.9, 10.8, 10.7, −3.7, −3.8, −5.3; HRMS (FAB) calcd for $C_{40}H_{74}O_7Si_2$ + H 723.5051, found 723.5046.

(3*S*,4*R*)-3-Hydroxy-3-methylhex-1-en-4-yl (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(*tert*-Butyldimethylsilyloxy)-9-hydroxy-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethylnonanoate (12). Ester **11** (590 mg, 0.82 mmol) was dissolved in MeOH (10 mL). To this solution was added DL-10-camphorsulfonic acid (38 mg, 0.16 mmol). The resulting solution was stirred at 0 °C for 1 h. The reaction was terminated by addition of Et_3N (114 μL, 0.82 mmol). After the solution was concentrated, purification by flash chromatography (hexane/EtOAc = 3:1) gave the desired primary alcohol **12** (385 mg, 78%) as a colorless oil: $[\alpha]^{29}_D$ +7.59 (*c* 1.36, $CHCl_3$); IR (film) 3480, 2932, 1745, 1695, 1613, 1514, 1460, 1379, 1299, 1249, 1193, 1080, 983, 823 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (d, *J* = 7.0 Hz, 6H), 0.74 (t, *J* = 7.3 Hz, 3H), 0.84 (m, 12H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 1.12 (d, *J* = 7.8 Hz, 3H), 1.14 (s, 3H), 1.39 (m, 2H), 1.56 (m, 2H), 1.76 (m, 2H), 2.42 (bs, 1H), 2.68 (dddd, *J* = 7.1, 7.1, 7.1, 14.3 Hz, 1H), 2.82 (bs, 1H), 3.12 (dd, *J* = 1.5, 9.0 Hz, 1H), 3.30 (dd, *J* = 4.2, 11.1 Hz, 1H), 3.54 (dd, *J* = 3.5, 11.1 Hz, 1H), 3.68 (s, 3H), 3.82 (d, *J* = 7.9 Hz, 1H), 4.38 (q, *J* = 10.8 Hz, 2H), 4.65 (dd, *J* = 2.6, 9.6 Hz, 1H), 5.03 (dd, *J* = 0.9, 10.8 Hz, 1H), 5.18 (dd, *J* = 1.0, 17.3 Hz, 1H), 5.75 (dd, *J* = 10.8, 17.4 Hz, 1H), 6.75 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 158.9, 140.4, 131.3, 128.9, 114.5, 113.6, 85.2, 80.6, 75.0, 74.3, 73.6, 65.9, 55.2, 44.6, 40.8, 33.0, 32.8, 32.6, 32.2, 26.2, 24.5, 22.6, 18.7, 18.6, 18.5, 16.3, 10.5, 9.8, −3.3, −3.4; HRMS (FAB) calcd for $C_{34}H_{60}O_7Si$ + H 609.4187, found 609.4182.

(3*S*,4*R*)-3-Hydroxy-3-methylhex-1-en-4-yl (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethyl-9-oxononanoate (13). The alcohol **12** (290 mg, 0.48 mmol) was dissolved in CH_2Cl_2 (8 mL). To this solution was added Dess−Martin periodinane (DMP) (404 mg, 0.95 mmol). The resulting solution was stirred for 30 min at room

dx.doi.org/10.1021/jo201158q | J. Org. Chem. 2012, 77, 1125−1130

temperature. After the reaction was completed, aqueous saturated $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc = 5:1) offered the desired aldehyde **13** (271 mg, 94% yield) as a colorless liquid: $[\alpha]^{32}_D$ +15.3 (*c* 1.10, $CHCl_3$); IR (film) 3487, 2958, 2933, 2856, 1721, 1613, 1586, 1514, 1461, 1373, 1302, 1249, 1172, 1103, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.09 (d, *J* = 2.6 Hz, 6H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.93 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 6H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 7.3 Hz, 3H), 1.25 (s, 3H), 1.53 (m, 2H), 1.70 (m, 1H), 1.84 (m, 3H), 2.07 (s, 1H), 2.43 (m, 1H), 2.79 (q, *J* = 7.2 Hz, 1H), 3.24 (dd, *J* = 2.5, 7.9 Hz, 1H), 3.80 (s, 3H), 3.95 (dd, *J* = 2.2, 7.6 Hz, 1H), 4.48 (q, *J* = 10.7 Hz, 2H), 4.78 (dd, *J* = 2.8, 10.2 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 5.30 (d, *J* = 17.3 Hz, 1H), 5.88 (dd, *J* = 10.8, 17.3 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 9.59 (d, *J* = 3.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 175.9, 158.9, 140.7, 131.0, 128.9, 114.2, 113.6, 84.5, 80.2, 74.7, 74.6, 73.3, 55.2, 44.2, 44.1, 40.9, 33.0, 31.7, 26.2, 24.7, 22.6, 18.5, 17.7, 15.7, 15.0, 10.6, 10.2, −3.6, −3.7; HRMS (FAB) calcd for $C_{34}H_{58}O_7Si$ + Na 629.3850, found 629.3851.

(3*S*,4*R*)-3-Hydroxy-3-methylhex-1-en-4-yl (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(*tert*-Butyldimethylsilyloxy)-9-hydroxy-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethylundec-10-enoate (14). To a stirred solution of the aldehyde **13** (271 mg, 0.45 mmol) in THF (6 mL) was added 1 M vinylmagnesium bromide (890 μL, 0.89 mmol) at room temperature. After 20 min, the reaction mixture was diluted by adding Et_2O (10 mL), and then a saturated aqueous NH_4Cl solution (10 mL) was added. The organic solution was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc = 4:1) afforded the desired vinyl alcohol **14** (231 mg, 82%, dr = 1:1) as a colorless oil: IR (film) 3479, 2957, 2929, 2855, 1713, 1613, 1586, 1514, 1461, 1373, 1301, 1249, 1173, 1038, 957 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (m, 6H), 0.87 (m, 3H), 0.94 (m, 9H), 1.04 (m, 6H), 1.24 (m, 9H), 1.53 (m, 2H), 1.93 (m, 2H), 2.40 (m, 1H), 2.77 (m, 1H), 3.25 (m, 1H), 3.80 (s, 3H), 3.61−3.99 (m, 2H), 4.50 (q, *J* = 10.7 Hz, 2H), 4.79 (m, 1H), 5.14 (m, 2H), 5.29 (d, *J* = 17.5 Hz, 2H), 5.87 (m, 2H), 6.87 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 176.7, 158.9, 140.4, 140.3, 140.2, 139.9, 131.4, 128.9, 128.6, 128.4, 128.0, 127.8, 127.7, 115.1, 114.7, 114.5, 114.0, 113.6, 85.4, 85.0, 80.7, 80.6, 77.8, 77.2, 75.2, 74.6, 74.5, 74.4, 73.7, 73.6, 72.4, 55.3, 44.8, 44.4, 40.8, 40.6, 37.3, 35.8, 34.2, 34.0, 32.5, 31.9, 29.7, 26.3, 24.8, 24.7, 22.8, 22.7, 18.6, 18.5, 18.5, 18.1, 16.5, 15.8, 14.9, 10.6, 10.5, 10.3, 9.8, −3.2, −3.3, −3.4, −3.5; HRMS (FAB) calcd for $C_{36}H_{62}O_7Si$ + H 635.4343, found 635.4346.

(3*S*,4*R*)-3-Hydroxy-3-methylhex-1-en-4-yl (2*R*,3*S*,4*R*,5*S*,6*S*,8*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4,6,8-tetramethyl-9-oxoundec-10-enoate (15). The vinyl alcohol **14** (231 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (10 mL). To this solution was added Dess−Martin periodinane (DMP) (305 mg, 0.72 mmol), and the resulting solution was stirred for 30 min at room temperature. After the same workup procedure as described for the preparation of **13**, purification by flash chromatography (hexane/EtOAc = 4:1) offered the desired vinyl ketone **15** (174 mg, 76%) as a yellow liquid: $[\alpha]^{26}_D$ +13.12 (*c* 1.35, $CHCl_3$); IR (film) 3293, 2924, 2853, 1739, 1461, 1379, 1246, 1170, 1077, 983, 819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (d, *J* = 6.6 Hz, 6H), 0.81 (m, 12H), 0.94 (m, 6H), 1.05 (d, *J* = 6.9 Hz, 3H), 1.19 (m, 6H), 1.55 (m, 3H), 1.86 (m, 2H), 2.55 (bs, 1H), 2.71 (q, *J* = 6.8 Hz, 1H), 2.88 (m, 1H), 3.14 (dd, *J* = 2.7, 7.6 Hz, 1H), 3.72 (s, 3H), 3.88 (dd, *J* = 2.3, 6.9 Hz, 1H), 4.40 (q, *J* = 5.3 Hz, 2H), 4.74 (dd, *J* = 2.9, 9.8 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 5.24 (d, *J* = 17.3 Hz, 1H), 5.70 (d, *J* = 5.6 Hz, 1H), 5.81 (dd, *J* = 10.8, 17.3 Hz, 1H), 6.23 (d, *J* = 17.4 Hz, 1H), 6.48 (dd, *J* = 10.5, 17.4 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 175.8, 158.9, 104.8, 135.0, 131.2, 128.8, 128.3, 114.0, 113.6, 84.7, 80.6, 74.6, 74.5, 73.4, 55.2, 44.6, 41.3, 40.8, 33.6, 33.1, 26.2, 25.0, 22.8, 18.5, 18.4, 17.4, 15.5, 10.8, 10.5, −3.6, −3.8; HRMS (FAB) calcd for $C_{36}H_{60}O_7Si$ + Na 655.4006, found 655.4003.

(*E*)-(3*R*,4*S*,5*R*,6*S*,7*S*,9*R*,13*S*,14*R*)-4-(*tert*-Butyldimethylsilyloxy)-14-ethyl-13-hydroxy-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyloxacyclotetradec-11-ene-2,10-dione (16). A flame-dried round-bottomed flask was charged with vinyl ketone **15** (171 mg, 0.27 mmol) and CH_2Cl_2 (20 mL). Grubbs catalyst (second generation) (46 mg, 0.054 mmol) was subsequently added as a solid, producing a light brown solution which was stirred for 18 h at room temperature. The mixture was then concentrated. Purification of this residue by flash chromatography (hexane/EtOAc = 4:1) afforded the lactone **16** (137 mg, 84%) as a yellow liquid: $[\alpha]^{25}_D$ +24.0 (*c* 1.00, $CHCl_3$); IR (film) 3346, 2925, 2853, 1739, 1673, 1544, 1462, 1378, 1246, 1161, 1078, 822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (d, *J* = 13.2 Hz, 6H), 0.80 (m, 3H), 0.86 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H), 1.05 (m, 9H), 1.16 (m, 2H), 1.25 (s, 3H), 1.48 (m, 3H), 1.74 (m, 2H), 2.11 (bs, 1H), 2.52 (m, 2H), 3.12 (d, *J* = 9.4 Hz, 1H), 3.72 (s, 3H), 3.87 (dd, *J* = 1.9, 3.7 Hz, 1H), 4.38 (q, *J* = 10.6 Hz, 2H), 4.73 (dd, *J* = 2.2, 10.9 Hz, 1H), 6.25 (d, *J* = 15.6 Hz, 1H), 6.79 (m, 3H), 7.17 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 177.1, 159.0, 148.1, 131.0, 129.0, 124.7, 113.7, 84.7, 80.0, 75.3, 74.6, 71.5, 55.3, 45.2, 45.0, 44.4, 34.7, 34.4, 26.2, 22.2, 18.6, 18.4, 17.4, 13.5, 10.7, 9.6, −3.1, −4.3; HRMS (FAB) calcd for $C_{34}H_{56}O_7Si$ + H 605.3874, found 605.3868.

(*E*)-(3*R*,4*S*,5*S*,6*S*,7*S*,9*R*,13*S*,14*R*)-14-Ethyl-4,13-dihydroxy-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyloxacyclotetradec-11-ene-2,10-dione (17). To a stirred solution of lactone **16** (93 mg, 0.15 mmol) in dry THF (7 mL) at room temperature was added 1.0 M TBAF (460 μL, 0.46 mmol) via a syringe. After 2.5 h, the reaction mixture was concentrated. Purification by flash chromatography on a silica gel column (hexane/EtOAc = 2:1) afforded alcohol **17** (61 mg, 81%) as a colorless oil: $[\alpha]^{29}_D$ +26.8 (*c* 1.12, $CHCl_3$); IR (film) 3457, 2972, 2930, 1731, 1668, 1613, 1514, 1462, 1370, 1249, 1273 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.05 (m, 9H), 1.26 (d, *J* = 5.1 Hz, 3H), 1.31 (m, 6H), 1.54 (m, 1H), 1.73 (m, 1H), 1.92 (m, 1H), 2.14 (m, 2H), 2.64 (m, 1H), 2.78 (m, 1H), 3.05 (s, 1H), 3.59 (t, *J* = 3.4 Hz, 1H), 3.81 (s, 3H), 3.90 (d, *J* = 8.9 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H), 4.85 (d, *J* = 10.9 Hz, 1H), 6.22 (d, *J* = 16.3 Hz, 1H), 6.79 (d, *J* = 16.3 Hz, 1H), 6.89 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 176.2, 159.4, 149.1, 129.8, 129.5, 126.8, 114.0, 83.8 79.1, 73.6, 71.3, 55.3, 44.0, 40.0, 38.7, 37.9, 31.3, 29.7, 21.4, 21.4, 16.8, 14.8, 14.4, 10.4, 8.5; HRMS (FAB) calcd for $C_{28}H_{42}O_7$ + Na 513.2828, found 513.2833.

(*E*)-(3*R*,5*R*,6*S*,7*S*,9*R*,13*S*,14*R*)-14-Ethyl-13-hydroxy-6-(4-methoxybenzyloxy)-3,5,7,9,13-pentamethyloxacyclotetradec-11-ene-2,4,10-trione (18). The alcohol **17** (61 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (5 mL). To this solution was added Dess−Martin periodinane (DMP) (105 mg, 0.25 mmol). The resulting solution was stirred for 30 min at room temperature. After the same workup as described for the preparation of **13**, purification by flash chromatography (hexane/EtOAc = 2:1) offered the desired ketone **18** (54 mg, 89%) as a colorless oil: $[\alpha]^{25}_D$ −26.9 (*c* 0.32, $CHCl_3$); IR (film) 3476, 2972, 2929, 1746, 1692, 1619, 1514, 1462, 1370, 1249, 1185, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.04 (m, 6H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.45 (d, *J* = 7.3 Hz, 3H), 1.57 (s, 3H), 1.72 (m, 1H), 2.02 (m, 1H), 2.56 (m, 1H), 3.10 (dddd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 1H), 3.62 (s, 1H), 3.74 (m, 2H), 3.81 (s, 3H), 4.50 (s, 2H), 5.01 (dd, *J* = 1.7, 10.9 Hz, 1H), 6.28 (d, *J* = 15.7 Hz, 1H), 6.65 (d, *J* = 15.7 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H),7.26 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 203.3, 170.3, 159.3, 145.6, 130.1, 129.4, 128.9, 113.8, 83.5, 77.2, 75.1, 72.9, 55.3, 53.2, 46.3, 43.2, 37.2, 34.7, 29.7, 23.2, 23.1, 17.9, 14.9, 14.8, 13.4, 10.8; HRMS (FAB) calcd for $C_{28}H_{40}O_7$ + Na 511.2672, found 511.2675.

Pikronolide (6a). To a solution of ketone **18** (54 mg, 0.11 mmol) in CH_2Cl_2/H_2O [10:1(v/v), 3 mL] was added dichlorodicynoquinone (DDQ) (50 mg, 0.22 mmol) at 0 °C. The solution was stirred for 2 h. After the reaction was completed, the solution was filtered through a pad of Celite. The Celite pad was washed with CH_2Cl_2 (3 × 10 mL). After the combined filtrate was concentrated, purification by flash chromatography (hexane/EtOAc = 1:1) provided the desired product as a white solid (31 mg, 76%) which turned out to be a 4:1 inseparable mixture of pikronolide (**6a**) and its 5−9-hemiacetal **6b** by ^1H NMR

dx.doi.org/10.1021/jo201158q | *J. Org. Chem.* 2012, 77, 1125−1130

($CDCl_3$): mp 136−139 °C; $[\alpha]^{26}_D$ +79.6 (*c* 0.25, $CHCl_3$); IR (film) 3345, 2972, 2782, 1743, 1632, 1456, 1373, 1241, 1163, 1112, 1055, 826 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{32}O_6$ + Na 391.2097, found 391.2094.

6a: ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.34 (s, 3H), 1.43 (d, *J* = 7.3 Hz, 3H), 1.47−1.54 (m, 3H), 1.79 (m, 1H), 1.94 (m, 1H), 2.83 (q, *J* = 6.6 Hz, 1H), 2.94 (m, 1H), 2.94 (bs, 1H), 3.78 (q, *J* = 7.3 Hz, 1H), 3.98 (m, 1H), 5.00 (dd, *J* = 2.4, 11.2 Hz, 1H), 6.30 (d, *J* = 15.9 Hz, 1H), 6.71 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 204.0, 170.5, 146.9, 129.0, 83.0, 74.9, 73.6, 52.0, 48.5, 42.0, 37.0, 35.8, 23.1, 22.9, 17.7, 16.4, 13.7, 12.9, 10.6.

6b: ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.6, 3H), 0.89 (m, 3H), 1.06 (d, *J* = 6.6, 3H), 1.37 (s, 3H), 1.38 (m, 3H), 1.72 (m, 1H), 1.88 (m, 1H), 2.58 (dd, *J* = 2.8, 6.7 Hz, 1H), 3.77 (m, 1H), 3.85 (dd, *J* = 2.8, 10.2 Hz, 1H), 4.73 (dd, *J* = 1.9, 8.7 Hz, 1H), 5.98 (s, 1H), 5.99 (s, 1H); other protons are not assignable due to heavy overlap; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 169.3, 137.7, 126.9, 97.6, 78.1, 77.7, 74.6, 49.6, 47.5, 40.1, 38.3, 32.3, 29.7, 21.2, 19.0, 17.6, 16.5, 15.8, 10.9.

Ac-Protected Pikromycin 20. Method A:[19] A solution of alcohol **19**[14] (36 mg, 0.17 mmol), phthalic anhydride (30 mg, 0.20 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (28 μL, 0.015 mmol) in CH_2Cl_2 (2 mL) in the presences of 4 A molecular sieves was stirred for 15 min at room temperature. After 15 min the mixture was cooled to −78 °C, di-*tert*-butylmethylpyridine (DTBMP) (75 mg, 0.36) and Tf_2O (1.3 μL, 0.015 mmol) were added sequentially at −78 °C, and the resulting mixture was stirred for a further 15 min. After dropwise addition of a solution of pikronolide (**6a**) (8.4 mg, 0.023 mmol) in CH_2Cl_2 (2 mL) to the above solution via cannula, the reaction mixture was stirred at −78 °C for 15 min before it was allowed to the warm over 1 h to 0 °C. After additional stirring for 12 h at room temperature $NaHCO_3$ (20 mg) was added to the mixture. After filtration through a pad of Celite with CH_2Cl_2 (3 × 10 mL), the solution was concentrated. Purification of the residue by flash chromatography (EtOAc/MeOH = 10:1) afforded the Ac-protected pikromycin **20** (4.3 mg, 33%) as a colorless oil.

Method B: To a solution of trichloroacetimidate **21**[14,15,18] (11 mg, 0.030 mmol) and pikronolide (**6a**) (3.5 mg, 0.010 mmol) in CH_2Cl_2 (2 mL) was added 4 A molecular sieves (200 mg), and the resulting solution was stirred at room temperature. After 30 min, the mixture was cooled −20 °C, and then TfOH (1.3 μL, 0.015 mmol) was added. The resulting mixture was stirred for 2 h at −20 °C before it was warmed to room temperature. After additional stirring for 12 h at room temperature $NaHCO_3$ (10 mg) was added to the mixture. After filtration through a pad of Celite with CH_2Cl_2 (3 × 5 mL), the solution was concentrated. Purification of the residue by flash chromatography (EtOAc/MeOH = 10:1) afforded the Ac-protected pikromycin **20** (4.2 mg, 43%) as a colorless oil: $[\alpha]^{27}_D$ +50.2 (*c* 0.17, $CHCl_3$); IR (film) 3346, 2972, 2934, 2861, 2776, 1743, 1668, 1631, 1457, 1373, 1240, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.25 (m, 3H), 1.33 (s, 3H), 1.47 (d, *J* = 7.4 Hz, 3H), 1.53 (m, 1H), 1.68−1.77 (m, 3H), 2.04 (s, 3H), 2.09 (m, 1H), 2.28 (s, 6H), 2.77 (m, 2H), 2.99 (m, 1H), 3.56 (s, 1H), 3.59 (m, 1H), 3.74 (q, *J* = 7.3 Hz, 1H), 4.15 (s, 1H), 4.51 (d, *J* = 7.6 Hz, 1H), 4.83 (dd, *J* = 7.7, 10.3 Hz, 1H), 5.01 (dd, *J* = 2.3, 11.4 Hz, 1H), 6.22 (d, *J* = 16.0 Hz, 1H), 6.56 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.2, 203.6, 170.2, 169.8, 145.5, 129.4, 103.5, 83.6, 75.3, 71.1, 69.3, 63.3, 61.2, 52.2, 46.3, 42.3, 40.6, 37.9, 36.4, 30.5, 23.2, 23.1, 21.3, 21.1, 16.9, 14.2, 14.1, 13.4, 10.7; HRMS (FAB) calcd for $C_{30}H_{49}NO_9$ + Na 590.3305, found 590.3301.

Pikromycin (6). To a stirred solution of Ac-protected pikromycin **20** (4.2 mg, 0.0082 mmol) in MeOH (1 mL) at room temperature was added H_2O (200 μL) and triethylamine (200 μL). After 3 h, the reaction mixture was concentrated. Purification of the residue by flash chromatography (EtOAc/MeOH = 10:1) afforded pikromycin (**6**) (3.5 mg, 91%) as a colorless oil: $[\alpha]^{27}_D$ −13.7 (*c* 0.34, $CHCl_3$); IR (film) 3343, 2925, 2852, 1735, 1632, 1461, 1378, 1265, 1122, 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.3 Hz, 3H), 1.05 (d, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.48 (d, *J* = 7.4 Hz, 3H), 1.55 (m, 2H), 1.68 (m, 2H), 1.73 (m, 1H), 2.17 (m, 1H), 2.28 (s, 6H), 2.49 (ddd, *J* = 3.9, 10.2, 12.3 Hz, 1H), 2.71 (m, 1H), 3.23 (m, 2H), 3.57 (m, 2H), 3.80 (m, 1H), 3.88 (m, 1H), 3.97 (bs, 1H), 4.37 (d, *J* = 7.3 Hz, 1H), 5.03 (dd, *J* = 2.4, 11.4 Hz, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 6.63 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 203.8, 170.5, 145.2, 129.4, 105.1, 83.6, 75.2, 69.8, 67.0, 65.8, 53.5, 46.3, 40.3, 40.0, 37.7, 29.7, 28.2, 23.3, 23.1, 21.2, 17.5, 16.2, 15.1, 14.1, 13.2, 10.7; HRMS (FAB) calcd for $C_{28}H_{47}NO_8$ + Na 548.3199, found 548.3196.

Narbomycin (5). To a solution of trichloroacetimidate **21** (22 mg, 0.060 mmol) and narbonolide (**5a**)[13](7.2 mg, 0.020 mmol) in CH_2Cl_2 (3 mL) was added 4 A molecular sieves (200 mg), and the resulting solution was stirred at room temperature. After 30 min, the mixture was cooled −20 °C, and then TfOH (3.0 μL, 0.026 mmol) was added. The resulting mixture was stirred for 2 h at −20 °C before it was warmed to room temperature. After additional stirring for 12 h at room temperature, $NaHCO_3$ (10 mg) was added to the mixture. After filtration through a pad of Celite with CH_2Cl_2 (3 × 5 mL), the solution was concentrated. Purification of the residue by flash chromatography (EtOAc/MeOH = 10:1) afforded the Ac-protected narbomycin **22** (6.5 mg, 59%) as a colorless oil: $[\alpha]^{27}_D$ +58.3 (*c* 0.68, $CHCl_3$); IR (film) 2924, 2851, 1739, 1712, 1624, 1460, 1378, 1259, 1164, 1110, 1078, 1031, 977 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, *J* = 7.4 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.23 (d, *J* = 7.5 Hz, 3H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.58 (m, 1H), 1.73 (m, 3H), 2.02 (s, 3H), 2.07 (dd, *J* = 4.2, 11.5 Hz, 1H), 2.26 (s, 6H), 2.72 (m, 2H), 2.84 (m, 2H), 3.56 (m, 1H), 3.82 (q, *J* = 7.0 Hz, 1H), 4.27 (s, 1H), 4.46 (d, *J* = 7.7 Hz, 1H), 4.81 (dd, *J* = 7.6, 10.5 Hz, 1H), 4.89 (ddd, *J* = 3.6, 3.6, 9.9 Hz, 1H), 6.03 (d, *J* = 16.1 Hz, 1H), 6.60 (dd, *J* = 6.0, 16.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.5, 203.6, 169.8, 169.3, 146.7, 128.9, 102.9, 79.0, 71.2, 69.1, 63.3, 50.0, 48.3, 41.3, 40.6, 38.3, 37.1, 36.4, 30.7, 29.7, 22.2, 21.4, 21.1, 16.6, 14.9, 14.1, 12.9, 10.5; HRMS (FAB) calcd for $C_{30}H_{49}NO_8$ + Na 574.3356, found 574.3360.

To a stirred solution of Ac-protected narbomycin **22** (2.3 mg, 0.0042 mmol) in MeOH (1 mL) at room temperature was added H_2O (200 μL) and triethylamine (200 μL). After 3 h, the reaction mixture was concentrated. Purification of the residue by flash chromatography (EtOAc/MeOH = 10:1) afforded narbomycin (**5**) (2.0 mg, 94%) as a colorless oil: $[\alpha]^{25}_D$ +61.3 (*c* 0.32, $CHCl_3$); IR (film) 3397, 2962, 2924, 2852, 1739, 1704, 1632, 1461, 1377, 1261, 1164, 1078, 1031, 984 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.25 (m, 3H), 1.37 (d, *J* = 7.4 Hz, 6H), 1.51 (m, 2H), 1.58 (m, 2H), 1.67 (m, 2H), 1.85 (m, 1H), 2.29 (s, 6H), 2.51 (m, 2H), 2.74 (m, 2H), 2.94 (m, 1H), 3.26 (m, 1H), 3.55 (m, 1H), 3.86 (q, *J* = 7.1 Hz, 1H), 4.17 (bs, 1H), 4.32 (d, *J* = 7.4 Hz, 1H), 4.92 (ddd, *J* = 3.6, 3.6, 9.2 Hz, 1H), 6.13 (d, *J* = 15.8 Hz, 1H), 6.67 (d, *J* = 5.7, 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.7, 203.6, 169.4, 146.8, 123.2, 104.6, 78.7, 70.2, 69.6, 65.7, 50.8, 42.3, 40.3, 38.4, 36.7, 36.4, 29.7, 28.5, 25.6, 22.7, 21.2, 17.0, 14.3, 14.1, 13.8, 12.5, 10.5; HRMS (FAB) calcd for $C_{28}H_{47}NO_7$ + Na 532.3250, found 532.3254.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra (^1H and ^{13}C) for **5**, **6**, **6a**, **11**−**18**, **20**, and **22**; COSY and HSQC spectra for **6a** (and **6b**). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hykang@chungbuk.ac.kr.

■ ACKNOWLEDGMENTS

This work was supported by the Korea Research Foundation (KRF) grant funded by the Korea Government (MEST) (2009-0074078). The authentic sample of pikromycin with

which NMR spectra was taken was isolated from the cell culture provided by Prof. Yeo Joon Yoon (Ewha Womans University, Seoul, Korea). The NMR spectra of pikromycin were also kindly provided by Prof. David H. Sherman (University of Michigan). We thank Professors Yoon and Sherman.

■ REFERENCES

(1) For recent reviews on biology and the application to the total synthesis of macrocyclic natural products, see: (a) Omura, S. *Macrolide Antibiotics: Chemistry, Biology, and Practice*, 2nd ed.; Academic Press: Boston, 2002. (b) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

(2) For seminal synthetic studies on macrolide synthesis, see: (a) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3213. (c) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3215. (d) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921. (e) Masamune, S.; Hirama, M.; Mori, S.; Asrof Ali, S.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568.

(3) (a) Brockmann, H.; Henkel, W. *Naturwissenschaften* **1950**, *37*, 138. (b) Brockman, H.; Henkel, W. *Chem. Ber.* **1951**, *84*, 284. (c) Muxfeldt, H.; Shrader, S.; Hansen, P.; Brockmann, H. *J. Am. Chem. Soc.* **1968**, *90*, 4748.

(4) Isolation of methymycin and neomethymycin: (a) Djerassi, C.; Harpern, O. *J. Am. Chem. Soc.* **1957**, *79*, 2022. (b) Djerassi, C.; Halpern, O. *Tetrahedron* **1958**, *3*, 255.

(5) Isolation of 10-deoxymethynolide from *Streptomyces venezuelae* ATCC 15439: (a) Kinumaki, A.; Suzuki, M. *J. Chem. Soc., Chem. Commun.* **1972**, 744. (b) Lambalot, R. H.; Cane, D. E. *J. Antibiot.* **1992**, *45*, 1981.

(6) Zhang, Q.; Sherman, D. H. *J. Nat. Prod.* **2001**, *64*, 1447.

(7) Isolation of neopikromycinand novapikromycin: Lee, S. K.; Park, J. W.; Kim, J. W.; Jung, W. S.; Park, S. R.; Choi, C. Y.; Kim, E. S.; Kim, B. S.; Ahn, J. S.; Sherman, D. H.; Yoon, Y. J. *J. Nat. Prod.* **2006**, *69*, 847.

(8) Total synthesis of 10-deoxymethynolide: (a) Pilli, R. A.; de Andrade, C. K.; Souto, C. R.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 7811. (b) Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312.

(9) Total synthesis of methynolide: (a) Nakano, A.; Takimoto, S.; Inanaga, J.; Katsuki, T.; Ouchida, S.; Inoue, K.; Aiga, M.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1019. (b) Inanaga, J.; Katuski, T.; Takimoto, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021. (c) Tanaka, T.; Oikawa, Y.; Nakajima, N.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2203. (d) Oikawa, Y.; Tanaka, T.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2196. (e) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647. (f) Vedejs, E.; Buchanan, R. A.; Conrad, P.; Meier, G. P.; Mullins, M. J.; Watanabe, Y. *J. Am. Chem. Soc.* **1987**, *109*, 5878. (g) Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8430. (h) Ditrich, K. *Liebigs Ann. Chem.* **1990**, 789. (i) Cossy, J.; Bauer, D.; Bellosta, V. *Synlett* **2002**, 715. (j) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron* **2002**, *58*, 5909.

(10) Total synthesis of neomethynolide: (a) Inanaga, J.; Kawanami, Y.; Yamaguchi, M. *Chem. Lett.* **1981**, 1415. (b) Inanaga, J.; Kawanami, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1521.

(11) Total synthesis of narbonolide: (a) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612. (b) Venkatraman, L.; Aldrich, C. C.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2005**, *70*, 7267. (c) Venkatraman, L.; Salomon, C. E.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2006**, *71*, 9853.

(12) Total synthesis of pikronolide: (a) Nakajima, N.; Hamada, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1986**, *108*, 4645. (b) Nakajima, N.; Tanaka, T.; Hamada, T.; Oikawa, Y.; Yonemitsu. *Chem. Pharm. Bull.* **1987**, *35*, 2228. (c) Nakajima, N.; Ubukata, M.; Yonemistu, O. *Heterocycles* **1997**, *46*, 105.

(13) Xuan, R.; Oh, H.-S.; Lee, Y.; Kang, H.-Y. *J. Org. Chem.* **2008**, *73*, 1456.

(14) Oh, H.-S.; Xuan, R.; Kang, H.-Y. *Org. Biomol. Chem.* **2009**, *7*, 4458.

(15) Oh, H.-S.; Kang, H.-Y. *Tetrahedron* **2010**, *66*, 4307.

(16) (a) Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* **1971**, *27*, 362. (b) Atkins, P. J.; Herbert, T. O.; Jones, N. B. *Int. J. Pharm.* **1986**, *30*, 199. (c) Cachet, T.; Van den Mooter, G.; Hauchecorne, R.; Vinckier, C.; Hoogmartens, J. *Int. J. Pharm.* **1989**, *55*, 59. (d) Pariza, R. J.; Freiberg, L. A. *Pure Appl. Chem.* **1994**, *66*, 2365. (e) Kim, Y.-H.; Heinze, T. M.; Berger, R.; Pothuluri, J. V.; Cerniglia, C. E. *Int. J. Pharm.* **2004**, *271*, 63.

(17) (a) Velvadapu, V.; Paul, T.; Wagh, B.; Klepacki, D.; Guvench, O.; MacKerell, A. Jr.; Andrade, R. B. *ACS Med. Chem. Lett.* **2011**, *2*, 68. (b) Velvadapu, V.; Paul, T.; Wagh, B.; Glassford, I.; DeBrosse, C.; Andrade, R. B. *J. Org. Chem.* **2011**, *76*, 7516.

(18) Schmidt, R. R.; Jung, K.-H. Oligosaccharide Synthesis with Trichloroacetimidates. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker: New York, 1997; p 283.

(19) Kim, K. S.; Fulse, D. B.; Baek, J. Y.; Lee, B.-Y.; Jeon, H. B. *J. Am. Chem. Soc.* **2008**, *130*, 8537.