Tetrahedron 66 (2010) 4307–4317

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total synthesis of neomethymycin and novamethymycin

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ARTICLE INFO

Article history:
Received 2 March 2010
Received in revised form 8 April 2010
Accepted 8 April 2010
Available online 14 April 2010

Keywords:
Neomethymycin
Novamethymycin
Pikromycin
Total synthesis
Macrolides

ABSTRACT

Total synthesis of neomethymycin and novamethymycin has been achieved. These two macrolides contains 12-membered macrolactones as aglycones and belong to the methymycin family of antibiotics, which appears in the pikromycin biosynthetic pathway. The segments in the 12-membered macrolactone that are responsible for causing structural difference in neomethymycin and novamethymycin were synthesized by starting with methyl D-(+)-lactate and D-glucose, for neomethynolide, and for novamethynolide, respectively. The key steps in synthesis of neomethynolide and novamethynolide, which are aglycones for neomethymycin and novamethymycin, respectively, were asymmetric aldol reactions, Yamaguchi esterification, and ring-closing metathesis using Grubbs' second generation catalyst. Finally, the coupling of agylcones with the corresponding trichloroacetimidates, followed by deprotection, completed the total synthesis of these two macrolide antibiotics.

1. Introduction

Macrolides belong to a large class of natural products that have attracted considerable attention due to not only their biological activities but also their structural diversity.[1] Pikromycin was the first macrolide antibiotic to be isolated and this has led to a new era in natural product chemistry and has introduced new synthetic challenges. In the course of biosynthetic pathway leading to pikromycin, *Streptomyces venezuelae* produces two major types of macrolide antibiotics, that is, the methymycin and pikromycin families, which contain the 12- and the 14-membered macrolactones as aglycones, respectively. The methymycin family of macrolide antibiotics is biosynthetically produced from 10-deoxymethynolide (**1a**).[2–4] The post-PKS (polyketide synthase) modification of 10-deoxymethynolide (**1a**) converts it into a total of four compounds, that is, YC-17 (**1**),[5] methymycin (**2**),[6] neomethymycin (**3**),[6] and novamethymycin (**4**)[7] (Fig. 1). The aglycones of the methymycin family of polyketides are 10-deoxymethyolide (**1a**), methynolide (**2a**),[8,9] neomethynolide (**3a**),[10] and novamethynolide (**4a**). Another family of macrolide antibiotics is also produced: the pikromycin family. This family is made up of four macrolides, which include narbomycin (**5**), pikromycin (**6**), neopikromycin (**7**),[11] and novapikromycin (**8**).[11] Aglycones of the pikromycin family that have 14-membered lactones are narbonolide (**5a**),[12] pikronolide (**6a**),[13] neopikronolide (**7a**), and novapikronolide (**8a**), respectively. The structures of these macrolides vary depending on the oxidation pattern during the post-PKS modification of 10-deoxymethynolide (**1a**) and narbonolide (**5a**).

For the synthesis of 10-deoxymethynolide (**1a**) and narbonolide (**5a**) these lactones were retrosynthetically divided into segments. Each segment was synthesized and assembled to achieve the total synthesis.[14] All the macrolactones shown in Figure 1 could, in theory, be synthesized by switching their structurally different segments (modules). This synthetic approach has been successfully applied to the synthesis of methymycin (**2**). After methynolide (**2a**), the aglycone of methymycin (**2**), was synthesized, glycosylation with desosamine successfully afforded methymycin.[15]

Neomethymycin (**3**), belonging to one of the methymycin families of macrolide antibiotics, has been isolated and its structure identified by Djerassi and Halpren.[6] Although the synthesis of neomethynolide (**3a**), the aglycone of neomethymycin (**3**), has been reported by Yamaguchi, the chemical synthesis of neomethymycin (**3**) has never been reported previously. Recently, Zang and Sherman reported the isolation of novamethymycin (**4**) from *S. venezuelae*, which has been known to produce methymycin (**2**) and neomethymycin (**3**).[7] This also shows the broad substrate flexibility of the PikC cytochrome P450 hydroxylase, in accepting not only the 12- and 14-membered-ring macrolides but also those with additional hydroxyl groups.

Neomethymycin (**3**) and novamethymycin (**4**) are members of the methymycin family of antibiotics and have never been chemically synthesized. Since our approach for synthesizing methymycin (**2**) was successful, we decided to apply this approach to the synthesis of neomethymycin (**3**) and novamethymycin (**4**). This would not only prove the generality of our modular route but also provide

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doi:10.1016/j.tet.2010.04.039

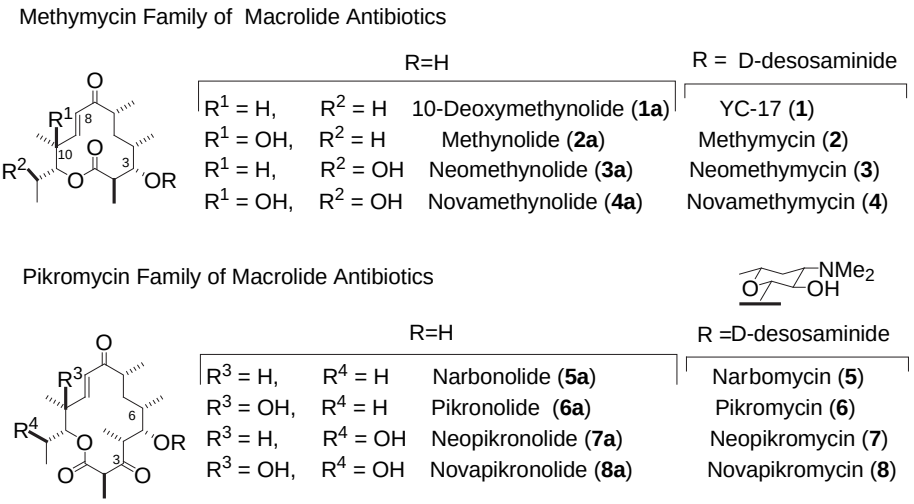


Figure 1. Methymycin and Pikromycin families of macrolide antibiotics.

an example of efficiency of modern synthetic methodology to prepare these types of polyketide macrolides. Here, we report the total synthesis of neomethymycin (**3**) and novamethymycin (**4**).

2. Results and discussion

According to the modular approaches we have previously developed for the synthesis of methymycin (**2**), neomethymycin (**3**), and novamethymycin (**4**) can be divided into segments, as shown in Figure 2.

First, we focused on the synthesis of the segment **9a** for neomethynolide (**3a**) as summarized in Scheme 1.

The synthesis was started with the commercially available methyl D-(+)-lactate. Aldehyde **10** was prepared according to the reported procedure.[16] Then, aldehyde **10** was subjected to the asymmetric aldol reaction[17] with **11**[18] to afford aldol adduct **12**. After the newly formed hydroxy group was protected with TES, $LiBH_4$ reduction followed by oxidation (Parikh–Doering) yielded aldehyde **15**. The Wittig reaction followed by deprotection (HF, CH_3CN) provided the required protected segment **9a** for the synthesis of neomethynolide.

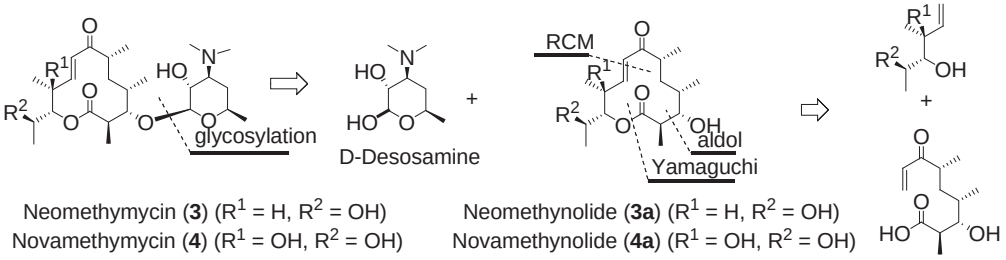


Figure 2. Retrosynthesis of neomethymycin (**3**) and novamethymycin (**4**).

Neomethymycin (**3**) and novamethymycin (**4**) could be synthesized from the corresponding aglycones, neomethynolide (**3a**) and novamethynolide (**4a**), respectively, via glycosylation. We expected that optimum conditions for successful glycosylation must be found for the synthesis of these two macrolides. Aglycones could be prepared by the coupling of segments, as shown in Figure 2, and eventually total synthesis could be started from the synthesis of the corresponding segment **9**. Specifically, segments **9a** and **9b** (as suitably protected forms) are required for the synthesis of neomethymycin (**3**) and novamethymycin (**4**), respectively (Fig. 3).

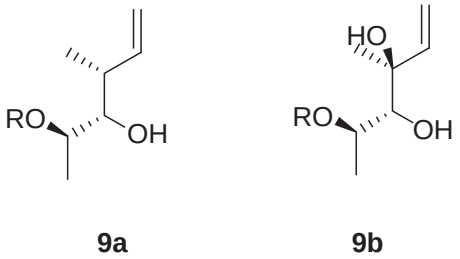
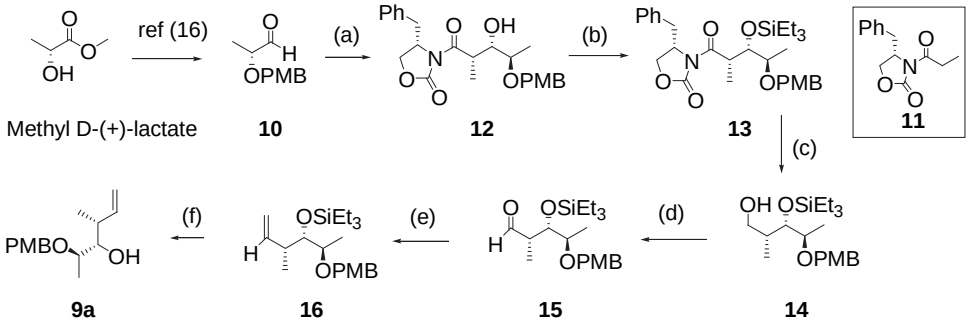


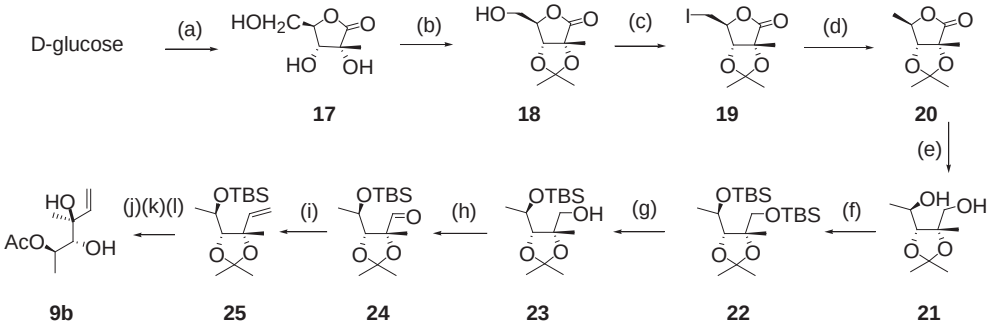
Figure 3. Fragments required for modular approaches.

The synthesis of segment **9b** for novamethynolide (**4a**) is summarized in Scheme 2.

We noted that glucosaccharinic acid lactone **17** would be a key component in the preparation of the suitably protected segment **9b** for the synthesis of novamethynolide (**4a**). The synthesis of glucosaccharinic acid lactone **17** by original procedure was hampered by low yield and long reaction time.[19] Fortunately, a recent report on the improvement of this procedure based on the Amadori rearrangement encouraged us to adopt lactone **17** as the starting material for segment **9b**.[20] Due to a handling problem, we had to purify after converting it to acetonide **18**. Although the yield was lower than that reported previously (**18** from D-glucose, 8.3% yield), we still concluded that this procedure was very competitive because it was efficient and an inexpensive starting material (D-glucose) was used (one-pot with short reaction time). We then synthesized segment **9b** using the procedure summarized in Scheme 2. Protection of diol functionality as an acetonide, iodination, and subsequent radical reduction (Bu_3SnH, AIBN, toluene) provided the compound **20** in good yield. Reduction ($LiBH_4$) was performed to provide diol **21**; this was followed by protection with the TBS group, to produce TBS-protected diol **22**. Selective deprotection with HF·pyridine

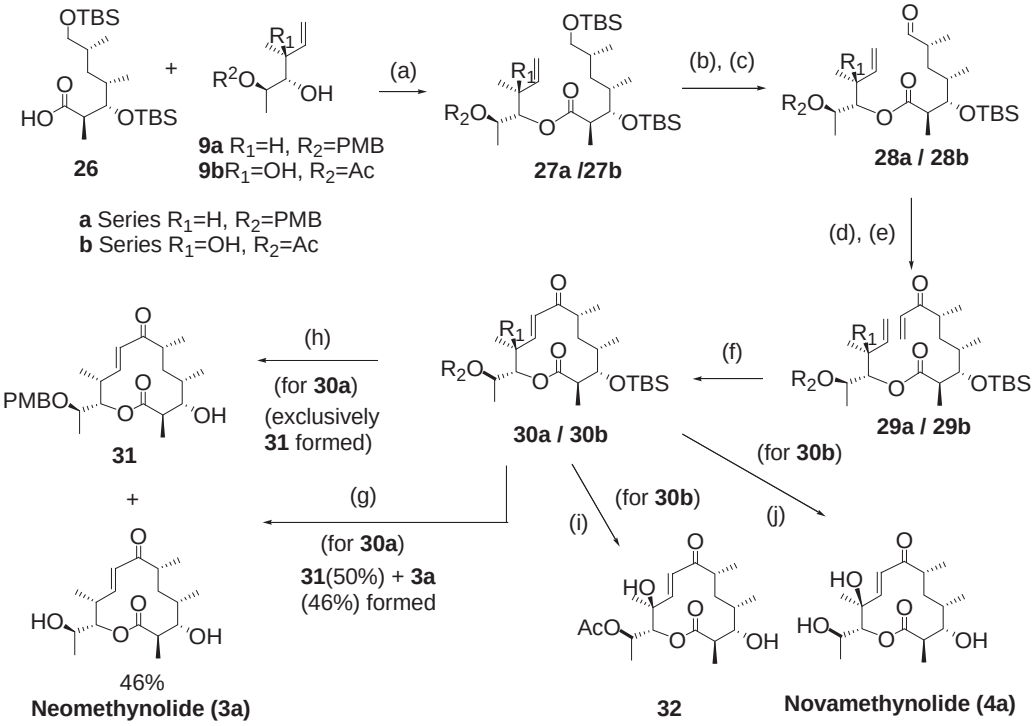


Scheme 1. (a) Compound **11**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C (75%); (b)Et_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (97%); (c) $LiBH_4{\cdot}H_2O$, ether (73%); (d) $SO_3{\cdot}$pyridine, CH_2Cl_2, DMSO, Et_3N (75%); (e) $H_2C{=}PPh_3$, THF (80%); (f) HF, CH_3CN, rt (98%).



Scheme 2. (a) Me_2NH, EtOH, AcOH then $Ca(OH)_2$, H_2O (b) H_2SO_4, acetone (8.3%, two steps); (c) Ph_3P, I_2, imidazole, CH_2Cl_2 (73%); (d) Bu_3SnH, AIBN, toluene (87%); (e) $LiBH_4$, H_2O, ether, 0 °C to rt (62%); (f) TBSOTf, 2,6-lutidine, CH_2Cl_2 (87%); (g) HF·pyridine,THF, pyridine, 0 °C (81%); (h) DMP, CH_2Cl_2 (74%); (i) $MePh_3Br$, *n*-BuLi, THF, −78 °C to 0 °C (83%); (j) TBAF, THF (96%); (k) Ac_2O, Et_3N, DMAP (81%); (l) 80% AcOH, 80 °C (69%).

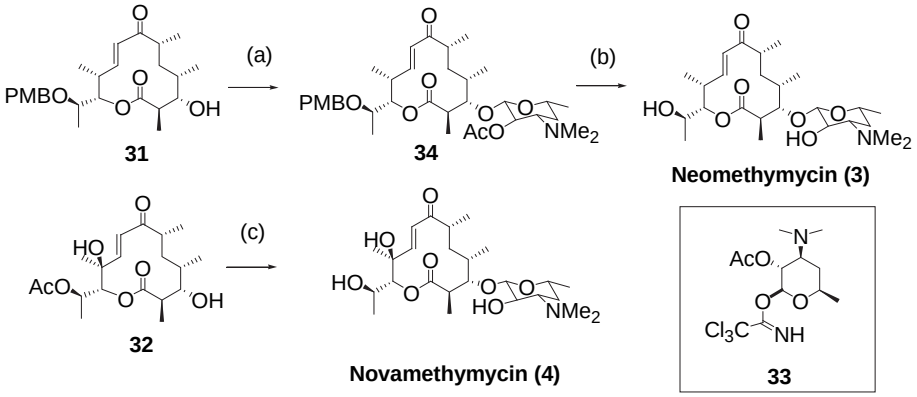
generated a primary alcohol **23**. Subsequent oxidation followed by the Wittig olefination provided olefin **25**. Finally, the removal of the acetonide group under acidic conditions provided segment **9b** in a properly protected form. After the required segments **9a** and **9b** were obtained, we proceeded to synthesize the aglycones for neomethynolide (**3a**) and novamethynolides (**4a**). The synthesis of neomethynolide (**a** series) and novamethynolide (**b** series) is summarized in Scheme 3.



Scheme 3. (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, DMAP, benzene (97%(**a**)/76%(**b**)); (b) CSA, MeOH, (98%(**a**)/86%(**b**)); (c) DMP, CH_2Cl_2, (97%(**a**)/92%(**b**)); (d) vinylMgBr, THF (82%(**a**)/85%(**b**)); (e) DMP, CH_2Cl_2, (95%(**a**)/92%(**b**)); (f) Grubbs' second generation catalyst, CH_2Cl_2 (85%(**a**)/85%(**b**)); (g) HF, CH_3CN (for **30a**)(**31**(50%)+**3a**(46%)); (h) TBAF, THF (for **30a**)(exclusively **31** formed (85%)); (i) 48% HF/CH_3CN/H_2O=1: 8.5: 0.5 (for **30b**)(77%); (j) TBAF, THF (for **30b**)(67%).

Carboxylic acid **26**[14] was esterified with **9a** by means of Yamaguchi's protocol[21] to afford ester **27a**, which was further subjected to deprotection of TBS and oxidation to yield aldehyde **28a**. The precursor for the critical ring-closing metathesis (RCM) reaction[1,22] was prepared by the addition of vinyl Grignard reagent followed by Dess–Martin oxidation. The key RCM reaction with the Grubbs' second generation catalyst, took place efficiently to afford the protected form of neomethynolide **30a**. Selective deprotection of the TBS group with HF in CH_3CN in the presence of the PMB-protected hydroxyl group occurred with moderate efficiency producing the desired protected neomethynolide **31** (50%) as well as neomethynolde (**3a**) (46%). Employing TBAF, however, enabled us to deprotect selectively and exclusive formation of the protected neomethymycin **31** was achieved. A similar synthetic sequence was adopted for the synthesis of the required protected novamethynolide, as shown in Scheme 3. Starting with the Yamaguchi esterification of **26** with **9b**, the key RCM precursor **29b** was prepared. The RCM reaction with the Grubbs' second generation catalyst then provided lactone **30b**. The protected novamethynolide **30b** was converted into novamethynolide (**4a**) with TBAF, which completed the first total synthesis of novamethynolide (**4a**). Lactone **30b** was also transformed into the protected novamethynolide **32**, in which the hydroxyl group at the side chain was protected by the acetyl group.[23]

The final stages of the total syntheses are illustrated in Scheme 4. Glycosylation of the PMB-protected neomethynolide **31** with trichloroacetimidate **33**[24] was performed in the presence of a Lewis acid ($BF_3 \cdot OEt_2$) to produce compound **34**.[25] Deprotection of the PMB group and deacetylation provided the desired neomethymycin (**3**).[26] The total synthesis of novamethymycin (**4**) was also achieved under similar conditions. Glycosylation of the Ac-protected novamethynolide **32** with trichloroacetimidate **33**, followed by deacetylation provided novamethymycin (**4**). The spectroscopic properties of the synthesized neomethymycin (**3**) and novamethymycin (**4**) were identical to those of an authentic sample or reported in the literatures.[6,7]



Scheme 4. (a) Compound **33**, $BF_3 \cdot OEt$, CH_2Cl_2, 4 Å MS, −20 °C (46%); (b) (1) DDQ, CH_2Cl_2/H_2O=10:1 (79%); (2) Et_3N, H_2O, MeOH (80%); (c) (1) **33**, $BF_3 \cdot OEt$, CH_2Cl_2, 4 Å MS, −20 °C (52%); (2) Et_3N, H_2O, MeOH (75%).

3. Conclusion

The first total synthesis of two members of methymycin families of macrolide antibiotics, neomethymycin and novamethymycin was achieved. These two macrolides were retrosynthetically divided into two parts: sugar and aglycone. The corresponding aglycones were also divided into two parts, with one part of each of the two macrolides different from each other, and the other identical, which has already prepared previously during the synthesis of methymycin. Segment **9a** for neomethymycin was synthesized using methyl D-(+)-lactate as a starting material, which is commercially available, in eight steps. The synthesis of the segment **9b** for novamethymycin was started with glucose, utilizing the recently reported procedure based on the Amadori rearrangement. The synthesis of this segment was achieved efficiently in twelve steps. Syntheses of these two segments were achieved efficiently and will be useful for the syntheses of many related natural products. In particular, the synthetic sequences developed for the segment required for novamethymycin **9b** is unique and will be useful for the synthesis of natural products.

4. Experimental

4.1. General

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 and Brucker Avance 500 NMR Spectrometer. The chemical shifts are reported in parts per million on scale downfield from TMS, and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad peak. IR spectra were recorded on JASCO FT/IR-300E. Optical rotations were measured by JASCO DIP-1000 digital polarometer in solution in a 1-dm cell. High resolution mass spectra were recorded on a Jeol JMS700 by using FAB method. All reagent and solvents were reagent grade and used without further purification unless specified otherwise. Technical grade ethyl acetate, hexane, and pentane used for column chromatography were distilled prior to use. Tetrahydrofuran (THF) and diethyl ether, when used as solvents for reactions, were freshly distilled from sodium–benzophenone ketyl. Dimethylformamide (DMF) was stored over 4-Å molecular sieves, and triethylamine was distilled before use. Flash chromatography was carried out on Woelm 32–64 μm silica packed in glass columns.

*4.1.1. (S)-4-Benzyl-3-[(2S,3S,4R)-3-hydroxy-4-(4-methoxybenzyloxy)-2-methylpentanoyl]-1,3-oxazolidin-2-one (**12**).* To a solution of (4*S*)-3-propionyl-4-benzyl-2-oxazolidinone (1.40 g, 5.96 mmol) in CH_2Cl_2 (20 mL) was added dibutylboron triflate (7.94 mL of a 1.0 M solution in CH_2Cl_2, 7.94 mmol) and triethylamine (1.40 mL, 9.93 mmol) dropwise at 0 °C. The solution was cooled down to −78 °C. To this solution was added a solution of (2*R*)-2-(4-methoxybenzyloxy)propanal **10** (1.30 g, 6.62 mmol) in CH_2Cl_2 (5 mL) at −78 °C. The resulting solution was stirred for 1 h at −78 °C. The solution was then warmed to 0 °C and stirred for 1 h additionally. The reaction was terminated by adding a pH 7 aqueous phosphate buffer solution (0.2 M-sodium hydrogen phosphate: 0.1 M citric acid=82:18, 20 mL) and methanol (20 mL). To this cloudy solution was added a solution of methanol and 30% hydrogen peroxide (2:1, 20 mL) and the resulting solution was stirred for 2 h at 0 °C. After the solution was concentrated, it was extracted

with CH_2Cl_2 (3×20 mL). The organic layer was washed with saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=4:1) provided the desired aldol product **12** (1.90 g, 75%) as a colorless oil: $[\alpha]_D^{27.8}$ +32.5 (*c* 1.85, $CHCl_3$); IR (film): 3515, 2933, 1779, 1695, 1611, 1513, 1455, 1386, 1248, 1106, 1028, 824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (m, 5H), 6.97 (d, *J*=6.5 Hz, 2H), 6.68 (d, *J*=8.7 Hz, 2H), 4.39 (d, *J*=11.1 Hz, 1H), 4.28 (m, 1H), 4.13 (d, *J*=11.1 Hz, 1H), 3.91 (m, 1H), 3.81 (dd, *J*=2.8, 9.0 Hz, 1H), 3.71 (m, 1H), 3.59 (m, 1H), 3.55 (s, 3H), 3.28 (dddd, *J*=6.0, 6.0, 6.0, 12.1 Hz, 1H), 3.07 (s, 1H), 2.96 (dd, *J*=3.2, 13.4 Hz, 1H), 2.54 (dd, *J*=9.2, 13.4 Hz, 1H), 1.14 (d, *J*=6.0 Hz, 3H), 1.06 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 158.8, 152.6, 134.9, 130.1, 129.1, 129.0, 128.6, 127.0, 113.4, 75.2, 74.3, 70.0, 65.6, 54.9, 54.5, 39.2, 37.4, 15.8, 12.0; HRMS: *m*/*z* calcd for $C_{24}H_{29}NO_6[M+Na]^+$: 450.1893; found, 450.1889.

*4.1.2. (S)-4-Benzyl-3-[(2S,3S,4R)-4-(4-methoxybenzyloxy)-2-methyl-3-(triethylsilyloxy)pentanoyl]-1,3-oxazolidin-2-one (**13**).* To a stirred solution of aldol product **12** (1.90 g, 4.45 mmol), 2,6-lutidine (1.03 mL, 8.90 mmol) in CH_2Cl_2 (20 ml) was added triethylsilyl trifluoromethanesulfonate (TESOTf)(1.50 mL, 6.68 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. After reaction was completed, aqueous saturated NaCl (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=5:1) afforded the TES-protected product **13** (2.36 g, 97%) as a colorless oil: $[\alpha]_D^{27.8}$ +37.6 (*c* 1.41, $CHCl_3$); IR (film): 2955, 2876, 1781, 1696, 1612, 1513, 1456, 1385, 1351, 1248, 1111, 1038, 971, 824, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.09 (m, 5H), 6.96 (d, *J*=7.5 Hz, 2H), 6.64 (d, *J*=8.6 Hz, 2H), 4.33 (d, *J*=11.3 Hz, 1H), 4.13 (d, *J*=11.3 Hz, 1H), 4.09 (m, 1H), 3.97 (m, 1H), 3.74 (m, 2H), 3.53 (s, 3H), 3.28 (t, *J*=8.7 Hz, 1H), 3.17 (m, 1H), 2.97 (dd, *J*=2.5, 13.3 Hz, 1H), 2.48 (dd, *J*=9.5, 13.1 Hz, 1H), 1.06 (m, 6H), 0.83 (t, *J*=7.8 Hz, 9H), 0.52 (q, *J*=7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 158.7, 152.7, 128.6, 130.6, 129.6, 129.2, 128.7, 128.6, 113.3, 78.3, 76.4, 70.1, 65.3, 54.9, 54.8, 41.4, 37.5, 15.6, 14.9, 6.9, 5.2; HRMS: *m*/*z* calcd for $C_{30}H_{43}NO_6Si[M+Na]^+$: 564.2757; found, 564.2760.

*4.1.3. (2R,3S,4R)-4-(4-Methoxybenzyloxy)-2-methyl-3-(triethylsilyloxy)pentan-1-ol (**14**).* To a solution of TES-protected product **13** (1.63 g, 3.00 mmol) in ether (30 mL) was added distilled water (81 μL, 4.5 mmol) at room temperature. After the solution was cooled to 0 °C, lithium borohydride (3.0 mL of a 2.0 M solution in THF, 6.00 mmol) was added slowly with stirring. After 10 min, the temperature of the solution was raised to room temperature, and stirred for additional 2 h. The reaction was terminated with addition of an aqueous NaOH solution (1.0 M, 20 mL) and extracted with ether (3×30 mL). After the organic layer was washed with saturated NaCl (30 mL), the ethereal solution was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (hexane/EtOAc=2:1) provided the desired alcohol **14** (798 mg, 73%) as a colorless oil: $[\alpha]_D^{27.3}$ −11.2 (*c* 1.18, $CHCl_3$); IR (film): 3417, 2955, 2876, 1613, 1513, 1461, 1302, 1248, 1037, 803, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.02 (d, *J*=8.6 Hz, 2H), 6.63 (d, *J*=8.6 Hz, 2H), 3.54 (dd, *J*=11.3, 37.9 Hz, 2H), 3.55 (s, 3H), 3.54 (m, 1H), 3.28 (m, 3H), 2.26 (br t, *J*=4.9 Hz, 1H), 1.75 (m, 1H), 0.99 (d, *J*=6.2 Hz, 3H), 0.74 (t, *J*=8.1 Hz, 9H), 0.41 (q, *J*=7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 130.6, 129.2, 113.5, 76.5, 76.0, 70.4, 65.5, 55.0, 38.6, 16.0, 11.9, 6.9, 5.1; HRMS: *m*/*z* calcd for $C_{20}H_{36}O_4Si[M+Na]^+$: 369.2461; found, 369.2457.

*4.1.4. (2S,3S,4R)-4-(4-Methoxybenzyloxy)-2-methyl-3-(triethylsilyloxy)pentanal (**15**).* To a solution of the alcohol **14** (743 mg, 2.02 mmol) and triethylamine (844 μL, 6.06 mmol) in CH_2Cl_2 (10 mL) was added a solution of pyridine−SO_3 complex (1.13 g, 7.07 mmol) in DMSO (10 mL) under room temperature with stirring. After 1 h, the reaction mixture was terminated by addition of aqueous saturated NaCl (20 mL). The mixture was extracted with CH_2Cl_2 (3×20 mL) and the organic solution was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=5:1) afforded the desired aldehyde **15** (554 mg, 75%) as a colorless liquid: ^1H NMR (300 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.00 (d, *J*=8.4 Hz, 2H), 6.64 (d, *J*=8.2 Hz, 2H), 4.30 (d, *J*=11.2 Hz, 1H), 4.11 (d, *J*=11.2 Hz, 1H), 3.85 (dd, *J*=3.8, 6.7 Hz, 1H), 3.55 (s, 3H), 3.19 (dddd, *J*=6.2, 6.2, 6.2, 12.4 Hz, 1H), 2.48 (m, 1H), 1.01 (d, *J*=6.1 Hz, 3H), 0.82 (d, *J*=7.0 Hz, 3H), 0.71 (t, *J*=8.0 Hz, 9H), 0.36 (q, *J*=7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 159.1, 130.2, 129.3, 113.6, 75.6, 74.6, 70.4, 55.0, 49.8, 16.0, 7.9, 6.8, 5.1.

*4.1.5. (2R,3S,4R)-2-(4-Methoxybenzyloxy)-4-methyl-3-(triethylsilyloxy)hex-5-ene (**16**).* To a solution of $MePh_3PBr$ (1.74 g, 4.86 mmol) in THF (10 mL) was added *n*-BuLi (3.38 mL, 1.6 M in hexanes, 5.40 mmol) at 0 °C. The solution was cooled to −78 °C, after which aldehyde **15** (496 mg, 1.35 mmol) was added. After 30 min, the temperature of the solution was raised to room temperature, and stirred for additional 1 h. After reaction was completed, saturated NH_4Cl (20 mL) was added. The organic layer 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=15:1) afforded the alkene **16** (394 mg, 80%) as a colorless oil: $[\alpha]_D^{25.9}$ −8.4 (*c* 1.62, $CHCl_3$); IR (film): 2955, 2875, 1613, 1513, 1460, 1382, 1301, 1248, 1155, 1108, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J*=8.1 Hz, 2H), 6.82 (d, *J*=8.7 Hz, 2H), 5.68 (ddd, *J*=8.0, 10.3, 17.3 Hz, 1H), 4.94 (m, 2H), 4.37 (dd, *J*=11.4, 32.0 Hz, 2H), 3.76 (s, 3H), 3.54 (dd, *J*=4.1, 6.5 Hz, 1H), 3.43 (dddd, *J*=4.1, 8.3, 8.3, 8.3 Hz, 1H), 2.28 (m, 1H), 1.09 (d, *J*=6.2 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 0.90 (t, *J*=8.1 Hz, 9H), 0.57 (q, *J*=7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 141.9, 131.0, 129.2, 114.1, 113.6, 78.6, 76.0, 70.2, 55.2, 41.5, 15.9, 14.0, 7.0, 5.3.

*4.1.6. (2R,3S,4R)-2-(4-Methoxybenzyloxy)-4-methylhex-5-en-3-ol (**9a**).* To a solution of alkene **16** (394 mg, 1.08 mmol) and CH_3CN (10 mL) at room temperature, was added a solution of [HF/H_2O/CH_3CN(v/v/v)=1:0.5:8.5] (5 mL). After the mixture was stirred for 3 h, it was neutralized with saturated $NaHCO_3$ (5 mL) and extracted with ether (3×10 mL). The combined organic solution was washed with saturated NaCl (10 mL) and dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=7:1) afforded the desired alcohol **9a** (264 mg, 98%) as a colorless oil: $[\alpha]_D^{27.4}$ −12.5 (*c* 1.50, $CHCl_3$); IR (film): 3464, 2974, 1613, 1513, 1459, 1379, 1301, 1248, 1174, 1036, 986, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.16 (d, *J*=8.4 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 5.57 (ddd, *J*=8.3, 10.3, 17.3 Hz, 1H), 4.94 (m, 2H), 4.36 (dd, *J*=11.2, 28.1 Hz, 2H), 3.70 (s, 3H), 3.45 (m, 2H), 2.20 (m, 2H), 1.08 (d, *J*=6.1 Hz, 3H), 1.00 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 140.4, 130.5, 129.2, 114.9, 113.7, 75.6, 75.5, 70.1, 55.1, 40.2, 16.3, 12.8; HRMS: *m*/*z* calcd for $C_{15}H_{22}O_3[M+Na]^+$: 273.1467; found, 273.1469.

*4.1.7. 2-C-Methyl-D-ribono-1,4-lactone (**17**)*[17]. To a solution of D-Glucose (15 g, 83 mmol) in ethanol (25 mL) and glacial acetic acid (4.8 mL) was added dimethylamine (40% solution in water, 16 mL, 141 mmol) at room temperature. The solution was stirred for 1.5 h at 80 °C. The resulting dark orange solution was concentrated. The dark oil was dissolved in water (200 mL), and to this was added calcium oxide (26.2 g, 467 mmol) at room temperature. The mixture was stirred for 24 h at 70 °C. The mixture was cooled to room temperature, and to this was added oxalic acid dehydrate (31.5 g, 250 mmol). After 10 min, filtration through a pad of Celite with MeOH (2×100 mL) and the solution was passed through Amberlite

IR 120 ion exchange resin. After the solution was concentrated, the concentrate was then dissolved in water (200 mL). The solution was stirred for 15 min at 40 °C. The water was removed under vacuum afforded the desired crude product **17** (10 g).

*4.1.8. 2,3-O-Isopropylidene-2-C-methyl-D-ribono-1,4-lactone (**18**)*[17]. To a mixture of crude product **17** (10 g, 61.7 mmol) in acetone (100 mL) at room temperature was added concentrated sulfuric acid (1.26 mL, 12.34 mmol). After the mixture was stirred for 30 h at room temperature, the reaction mixture was added to aqueous ammonia (1 mL). The resulting mixture was filtered and concentrated. Purification by flash chromatography (pentane/ether=1:5) afforded the desired lactone **18** (1.4 g, 8.3%, two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.51 (s, 2H), 3.92 (d, J=12.3 Hz, 1H), 3.77 (d, J=13.7 Hz, 1H), 3.37 (s, 3H), 1.60 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 112.7, 83.6, 82.8, 82.4, 61.8, 26.7, 26.5, 19.6.

*4.1.9. 5-Iodo-2,3-O-isopropylidene-2-C-methyl-D-ribolactone (**19**).* To a solution of alcohol **18** (1.52 g, 7.50 mmol) in CH_2Cl_2 (30 mL) at room temperature were added PPh_3 (2.95 g, 11.3 mmol), imidazole (1.53 g, 22.5 mmol) and I_2 (2.66 g, 10.5 mmol). The mixture was stirred for 2 h at room temperature. After the reaction was completed, the solution was filtered through a pad of silica gel. The silica gel pad was washed with CH_2Cl_2 (3×20 mL). After the combined filtrate was concentrated, purification by flash chromatography (hexane/EtOAc=3:1) afforded the desired iodolactone **19** (1.70 g, 73%) as a colorless oil: $[\alpha]_D^{25.2}$ −46.6 (*c* 1.47, $CHCl_3$); IR (film): 2989, 1789, 1453, 1378, 1346, 1217, 1167, 1099, 1009, 930, 862 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.53 (dd, J=5.6, 8.6 Hz, 1H), 4.32 (d, J=0.6 Hz, 1H), 3.31 (dd, J=5.2, 10.8 Hz, 1H), 3.13 (dd, J=8.6, 10.8 Hz, 1H), 1.54 (s, 3H), 1.31 (d, J=2.3 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.0, 113.1, 83.3, 81.7, 81.1, 26.6, 20.7, 2.8; HRMS: *m*/*z* calcd for $C_9H_{13}IO_4[M+H]^+$: 312.9937; found, 312.9939.

*4.1.10. 5-Deoxy-2,3-O-isopropylidene-2-C-methyl-D-ribolactone (**20**).* To a solution of iodolactone **19** (1.62 g, 5.19 mmol) in toluene (30 mL) at room temperature were added AIBN (85 mg, 0.52 mmol) and Bu_3SnH (3.00 mL, 10.4 mmol). The solution was stirred for 16 h at 120 °C. After the reaction was completed, the solution was cooled at room temperature. The solution was then concentrated to give a yellow oil. Purification of this residue by flash chromatography (hexane/EtOAc=5:1) afforded desired the lactone **20** (843 mg, 87%) as a white solid: mp: 87–89 °C; $[\alpha]_D^{26.2}$ −68.0 (*c* 1.28, $CHCl_3$); IR (film): 2997, 2941, 1772, 1453, 1377, 1292, 1213, 1107, 1062, 1031, 989, 955 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (q, J=7.1 Hz, 1H), 4.11 (s, 1H), 1.53 (s, 3H), 1.33 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 112.5, 84.5, 81.6, 78.2, 26.7, 26.3, 20.6, 18.9; HRMS: *m*/*z* calcd for $C_9H_{14}O_4[M+H]^+$: 187.0970; found, 187.0971.

*4.1.11. 5-Deoxy-2,3-O-isopropylidene-2-C-methyl-ribitol (**21**).* To a solution of lactone **20** (780 mg, 4.19 mmol) in ether (30 mL) was added distilled water (226 μL, 12.6 mmol) at room temperature. After the solution was cooled to 0 °C, lithium borohydride (8.4 mL of a 2.0 M solution in THF, 16.8 mmol) was added slowly with stirring. After 10 min, the temperature of the solution was raised to room temperature, and stirred for additional 2 h. The reaction was terminated by addition of an aqueous NaOH solution (1.0 M, 20 mL) and extracted with ether (3×30 mL). After the organic layer was washed with aqueous saturated NaCl (30 mL), the ethereal solution was dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=1:1) provided the desired diol **21** (496 mg, 62%) as a white solid: mp 67–70 °C; $[\alpha]_D^{25.6}$ −30.8 (*c* 0.93, $CHCl_3$); IR (film): 3259, 2983, 2932, 2872, 1444, 1367, 1249, 1216, 1187, 1100, 1064, 986, 913 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$,): δ 4.23 (s, 1H), 4.10 (s, 1H), 3.94 (m, 1H), 3.70 (d, J=10.5 Hz, 1H), 3.53 (d, J=8.6 Hz, 1H), 3.30 (d, J=10.4 Hz, 1H), 1.38 (s, 3H), 1.32 (s, 6H), 1.28 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.2, 86.4, 81.9, 66.3, 64.7, 28.3, 26.3, 23.8, 20.8; HRMS: *m*/*z* calcd for $C_9H_{18}O_4[M+Na]^+$: 213.1103; found, 213.1107.

*4.1.12. (4S,5R)-5-[(R)-1-(tert-Butyldimethylsilyloxy)ethyl]-4-[(tert-butyldimethylsilyloxy)methyl]-2,2,4-trimethyl-1,3-dioxolane (**22**).* To a stirred solution of diol **21** (482 mg, 2.53 mmol), 2,6-lutidine (943 μL, 8.10 mmol) in CH_2Cl_2 (10 ml) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf)(943 μL, 8.10 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. After reaction was completed, aqueous saturated NaCl (20 mL) and aqueous saturated NH_4Cl solution (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=7:1) afforded the TBS-protected product **22** (920 mg, 87%) as a colorless oil: $[\alpha]_D^{24.6}$ −26.4 (*c* 1.31, $CHCl_3$); IR (film): 2931, 2858, 1463, 1369, 1255, 1214, 1103, 993, 962, 930, 909, 838, 775, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (q, J=6.1 Hz, 1H), 3.58 (m, 3H), 1.39 (s, 3H), 1.31 (d, J=10.2 Hz, 6H), 1.24 (d, J=6.1 Hz, 3H), 0.87 (d, J=4.6 Hz, 18H), 0.05 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.8, 86.7, 82.1, 66.9, 65.9, 28.0, 26.6, 26.0, 25.9, 23.0, 21.8, 18.3, 18.0, −3.5, −4.6, −5.4, −5.4; HRMS: *m*/*z* calcd for $C_{21}H_{46}O_4Si_2[M+H]^+$: 419.3013; found, 419.3009.

*4.1.13. (4S,5R)-5-[(R)-1-(tert-Butyldimethylsilyloxy)ethyl]-4-hydroxymethyl-2,2,4-trimethyl-1,3-dioxolane (**23**).* The TBS-protected product **22** (910 mg, 2.17 mmol) was dissolved in THF (15 mL). To this solution was added HF·pyridine/pyridine(v/v)=1:1 (4 mL). The resulting solution was stirred at 0 °C for 16 h. After the reaction was completed, aqueous saturated $NaHCO_3$ (20 mL) was added and the mixture was extracted with ether (3×15 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=4:1) offered the desired alcohol **23** (535 mg, 81%) as a colorless oil: $[\alpha]_D^{25.2}$ −26.5 (*c* 0.87, $CHCl_3$); IR (film): 3493, 2932, 2858, 1735, 1463, 1371, 1255, 1215, 1106, 1062, 988, 959, 932 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.16 (q, J=6.3 Hz, 1H), 3.60 (m, 2H), 3.43 (dd, J=10.2, 17.0 Hz, 1H), 2.88 (t, J=6.9 Hz, 1H), 1.41 (s, 3H), 1.36 (d, J=6.9 Hz, 6H), 1.29 (d, J=6.4 Hz, 3H), 0.89 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 106.6, 85.7, 82.2, 67.3, 65.2, 28.2, 26.5, 25.8, 23.1, 21.5, 18.0, −4.1, −4.6; HRMS: *m*/*z* calcd for $C_{15}H_{32}O_4Si[M+H]^+$: 305.2148; found, 305.22151.

*4.1.14. (4R,5R)-5-[(R)-1-(tert-Butyldimethylsilyloxy)ethyl]-2,2,4-trimethyl-1,3-dioxolane-4-carbaldehyde (**24**).* To a solution of the alcohol **23** (300 mg, 0.99 mmol) obtained as described in the previous procedure in CH_2Cl_2 (10 mL) was added the Dess–Martin periodinane (840 mg, 1.98 mmol) at room temperature. The resulting solution was stirred for 2 h and was diluted with CH_2Cl_2 (10 mL). After the reaction was completed, aqueous saturated $NaHCO_3$ (20 mL) and aqueous saturated $Na_2S_2O_3$ (10 mL) were added. The resulting mixture was stirred and the organic layer was extracted and washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=10:1) afforded the desired aldehyde **24** (220 mg, 74%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H), 4.08 (dddd, J=5.0, 6.5, 6.5, 6.5 Hz, 1H), 3.80 (d, J=5.0 Hz, 1H), 1.51 (s, 3H), 1.40 (d, J=4.5 Hz, 6H), 1.19 (d, J=6.5 Hz, 3H), 0.84 (s, 9H), 0.03 (d, J=1.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.5, 109.3, 89.1, 84.7, 66.8, 27.8, 26.4, 25.7, 21.0, 20.7, 18.0, −4.6, −4.7.

*4.1.15. (4S,5R)-5-[(R)-1-(tert-Butyldimethylsilyloxy)ethyl]- 2,2,4-trimethyl-4-vinyl-1,3-dioxolane (**25**).* To a solution of $MePh_3PBr$ (1.30 g, 3.65 mmol) in THF (10 mL) was added *n*-BuLi (2.28 mL,

1.6 M in hexanes, 3.65 mmol) at 0 °C. The solution was cooled to −78 °C, after which aldehyde **24** (220 mg, 0.73 mmol) was added. After 30 min, the temperature of the solution was raised to room temperature, and stirred for additional 1 h. After reaction was completed, aqueous saturated NH_4Cl (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3×15 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=15:1) afforded the desired alkene **25** (182 mg, 83%) as a colorless oil: $[\alpha]_D^{25.3}$ −20.2 (*c* 1.71, $CHCl_3$); IR (film): 2928, 2857, 1642, 1471, 1368, 1256, 1213, 1108, 1065, 1005, 986, 945 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.91 (dd, *J*=10.7, 17.3 Hz, 1H), 5.31 (dd, *J*=1.6, 17.3 Hz, 1H), 5.09 (dd, *J*=1.5, 10.7 Hz, 1H), 3.78 (m, 1H), 3.53 (d, *J*=8.6 Hz, 1H), 1.39 (d, *J*=5.5 Hz, 6H), 1.33 (s, 3H), 1.21 (d, *J*=6.0 Hz, 3H), 0.83 (s, 9H), 0.02 (d, *J*=7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.5, 114.2, 107.2, 87.5, 82.6, 68.3, 27.8, 26.5, 26.4, 26.0, 22.3, 18.0, −3.2, −4.5; HRMS: *m*/*z* calcd for $C_{16}H_{32}O_3Si[M+H]^+$: 301.2199; found, 301.2204.

*4.1.16. (2R,3R,4S)-3,4-Dihydroxy-4-methylhex-5-en-2-yl acetate (**9b**).* To a stirred solution of alkene **25** (182 mg, 0.61 mmol) in dry THF (10 mL) at room temperature was added 1.0 M tetrabutylammonium fluoride (TBAF) (1.22 mL, 1.22 mmol). After 2.5 h, the reaction mixture was concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=4:1) afforded alcohol (110 mg, 96%) as a colorless oil: $[\alpha]_D^{25.5}$ −29.0 (*c* 1.61, $CHCl_3$); IR (film): 3416, 2982, 1373, 1208, 1059, 929, 874 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.01 (dd, *J*=11.0, 17.5 Hz, 1H), 5.32 (dd, *J*=2.0, 17.5 Hz, 1H), 5.14 (dd, *J*=1.5, 11.0 Hz, 1H), 3.76 (m, 1H), 3.55 (d, *J*=8.5 Hz, 1H), 1.91 (s, 3H), 1.43 (d, *J*=1.5 Hz, 6H), 1.37 (s, 3H), 1.27 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 114.2, 107.9, 87.3, 82.6, 66.7, 28.0, 26.6, 26.0, 21.6.

To a solution of the alcohol (110 mg, 0.59 mmol) prepared as described in the previous procedure in CH_2Cl_2 (10 mL) were added DMAP (36 mg, 0.30 mmol), triethylamine (246 μL, 1.77 mmol) and acetic anhydride (167 μL, 1.77 mmol at 0 °C). The resulting solution was stirred for 10 min at 0 °C before it was warmed to room temperature. After additional stirring for 1 h at room temperature and then to this was added a saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3×15 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=7:1) afforded the desired acetylated product (110 mg, 81%) as a colorless oil: $[\alpha]_D^{25.7}$ −16.9 (*c* 1.98, $CHCl_3$); IR (film): 2983, 2936, 2870, 1739, 1643, 1456, 1371, 1240, 1131, 1094, 1060, 929 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.69 (dd, *J*=11.0, 17.5 Hz, 1H), 5.22 (dd, *J*=1.5, 17.5 Hz, 1H), 5.07 (dd, *J*=1.5, 10.5 Hz, 1H), 4.76 (dddd, *J*=6.0, 6.0, 6.0, 9.0 Hz, 1H), 3.76 (d, *J*=8.5 Hz, 1H), 1.96 (s, 3H), 1.41 (s, 3H), 1.36 (d, *J*=7.0 Hz, 6H), 1.25 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 138.7, 114.6, 108.2, 85.1, 82.3, 69.6, 28.0, 26.6, 25.4, 20.9, 17.9; HRMS: *m*/*z* calcd for $C_{12}H_{20}O_4Si[M+H]^+$: 229.1440; found, 229.1443.

The acetylated product (110 mg, 0.48 mmol) obtained as described in the previous procedure was dissolved in 80% acetic acid (10 mL). The solution was stirred at 80 °C for 4 h. After the reaction was completed, the solution was cooled at room temperature. The solution was then concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=2:1) offered the desired diol **9b** (62 mg, 69%) as a colorless oil: $[\alpha]_D^{26.0}$ +16.7 (*c* 1.25, $CHCl_3$); IR (film): 3449, 2982, 1723, 1373, 1252, 1044, 923 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.83 (dd, *J*=10.5, 17.0 Hz, 1H), 5.22 (dd, *J*=1.5, 17.5 Hz, 1H), 5.04 (dd, *J*=1.0, 11.0 Hz, 1H), 4.88 (dddd, *J*=4.5, 6.5, 6.5, 6.5 Hz, 1H), 3.46 (d, *J*=4.5 Hz, 1H), 2.50 (br s, 2H), 1.92 (s, 3H), 1.25 (s, 3H), 1.18 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 140.5, 113.1, 77.7, 74.5, 71.3, 26.4, 21.4, 15.4; HRMS: *m*/*z* calcd for $C_9H_{16}O_4[M+H]^+$: 189.1127; found, 189.1129.

*4.1.17. (2R,3S,4R)-2-(4-Methoxybenzyloxy)-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3,7-bis(tert-butyldimethylsilyloxy)-2,4,6-trimethylheptanoate (**27a**).* To a solution of carboxylic acid **26** (583 mg, 1.33 mmol) in THF (10 mL) at room temperature were added triethylamine (278 μL, 2.00 mmol) and 2,4,6-trichlorobenzoyl chloride (270 μL, 1.73 mmol). The mixture was stirred for 3 h at room temperature, and the solids were filtered off and washed with hexane (10 mL). The combined solution was concentrated. The residue was dissolved in benzene (10 mL), and to this solution, a solution of alcohol **9a** (500 mg, 2.00 mmol) and DMAP (227 mg, 1.86 mmol) in benzene (3 mL) was added. After being stirred for 15 h, the reaction mixture was diluted with ether (20 mL), and 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=10:1) afforded the desired ester **27a** (860 mg, 97%) as a colorless oil: $[\alpha]_D^{29.1}$ +9.0 (*c* 1.46, $CHCl_3$); IR (film): 2954, 2857, 1735, 1613, 1514, 1462, 1377, 1251, 1170, 1059, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, *J*=8.7 Hz, 2H), 6.83 (d, *J*=8.7 Hz, 2H), 5.66 (ddd, *J*=8.3, 10.3, 17.3 Hz, 1H), 5.01 (m, 3H), 4.40 (q, *J*=11.3 Hz, 2H), 3.89 (dd, *J*=5.1, 8.1 Hz, 1H), 3.77 (s, 3H), 3.57 (m, 1H), 3.46 (dd, *J*=4.6, 9.7 Hz, 1H), 3.21 (dd, *J*=7.2, 9.7 Hz, 1H), 2.59 (q, *J*=7.1 Hz, 1H), 2.48 (q, *J*=7.4 Hz, 1H), 1.64 (m, 2H), 1.38 (m, 1H), 1.12 (d, *J*=6.4 Hz, 6H), 0.98 (d, *J*=6.7 Hz, 3H), 0.87 (m, 24H), 0.03 (d, *J*=4.5 Hz, 6H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 159.6, 139.9, 130.6, 129.3, 115.2, 113.6, 76.0, 75.8, 73.8, 70.0, 67.8, 55.2, 42.6, 39.0, 36.9, 35.4, 33.5, 26.0, 25.9, 18.3, 18.3, 18.3, 16.9, 16.1, 14.8, 14.7, −4.0, −4.1, −5.4; HRMS: *m*/*z* calcd for $C_{37}H_{69}O_6Si_2[M+H]^+$: 665.4633; found, 665.4630.

*4.1.18. (2R,3S,4R)-2-(4-Methoxybenzyloxy)-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3-(tert-butyldimethylsilyloxy)-2,4,6-trimethyl-7-oxoheptanoate (**28a**).* Ester **27a** (860 mg, 1.29 mmol) was dissolved in MeOH (15 mL). To this solution was added DL-10-camphorsulfonic acid (60 mg, 0.26 mmol). The resulting solution was stirred at 0 °C for 2 h. The reaction was terminated by addition of triethylamine (93 μL, 0.67 mmol). After the solution was concentrated, purification by flash chromatography (hexane/EtOAc=5:1) gave the desired primary alcohol (700 mg, 98%) as a colorless oil: $[\alpha]_D^{30.1}$ +21.6 (*c* 1.20, $CHCl_3$); IR (film): 3453, 2955, 1732, 1613, 1514, 1461, 1378, 1302, 1251, 1174, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.15 (d, *J*=8.7 Hz, 2H), 6.78 (d, *J*=8.7 Hz, 2H), 5.60 (ddd, *J*=8.2, 10.3, 17.2 Hz, 1H), 4.98 (m, 3H), 4.34 (q, *J*=11.4 Hz, 2H), 3.74 (dd, *J*=2.2, 7.9 Hz, 1H), 3.71 (s, 3H), 3.54 (ddddd, *J*=3.7, 6.3, 6.3, 6.3, 12.6 Hz, 1H), 3.25 (m, 1H), 2.62 (q, *J*=7.1 Hz, 1H), 2.39 (q, *J*=6.9 Hz, 1H), 2.10 (br s, 1H), 1.63 (m, 1H), 1.43 (m, 2H), 1.18 (d, *J*=7.0 Hz, 3H), 1.07 (d, *J*=6.3 Hz, 3H), 0.93 (d, *J*=6.7 Hz, 3H), 0.83 (m, 15H), 0.00 (d, *J*=1.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.7, 159.0, 139.5, 130.4, 129.3, 115.4, 113.6, 77.0, 76.0, 73.8, 70.0, 66.4, 55.1, 44.0, 39.3, 35.4, 34.1, 32.8, 26.0, 18.3, 18.3, 17.5, 16.4, 15.4, 14.2, −3.9, −4.0; HRMS: *m*/*z* calcd for $C_{31}H_{54}O_6Si[M+H]^+$: 573.3587; found, 573.3590.

The alcohol (700 mg, 1.27 mmol) obtained as described in the previous procedure was dissolved in CH_2Cl_2 (20 mL). To this solution was added Dess–Martin periodinane (DMP) (1.10 g, 2.54 mmol). The resulting solution was stirred for 1 h at room temperature. After the reaction was completed, saturated $NaHCO_3$ (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=7:1) offered the desired aldehyde **28a** (680 mg, 97%) as a colorless liquid: ^1H NMR (300 MHz, $CDCl_3$): δ 9.51 (d, *J*=2.5 Hz, 1H), 7.22 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 5.67 (ddd, *J*=8.1, 10.2, 17.8 Hz, 1H), 5.04 (m, 3H), 4.41 (q, *J*=11.3 Hz, 2H), 3.86 (dd, *J*=2.6, 7.6 Hz, 1H), 3.79 (s, 3H), 3.60 (m, 1H), 2.65 (q, *J*=7.2 Hz, 1H), 2.49 (q, *J*=7.0 Hz, 1H), 2.34 (m, 1H), 1.83 (ddd, *J*=4.1, 8.9, 13.7 Hz, 1H), 1.65 (m, 1H), 1.17 (d, *J*=7.1 Hz, 3H), 1.14 (d, *J*=6.3 Hz, 3H), 1.05 (d, *J*=6.9 Hz, 3H), 0.99 (d, *J*=6.7 Hz, 3H), 0.90 (m, 12H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2, 175.2, 159.0, 139.7, 130.5, 129.3,

115.4, 113.6, 76.4, 76.0, 73.8, 70.0, 55.2, 44.1, 43.5, 39.1, 36.3, 32.5, 26.0, 18.3, 16.9, 15.3, 14.5, 14.5, −3.9, −4,0.

*4.1.19. (2R,3S,4R)-2-(4-Methoxybenzyloxy)-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3-(tert-butyldimethylsilyloxy)-2,4,6-trimethyl-7-oxonon-8-enoate (**29a**).* To a stirred solution of the aldehyde **28a** (680 mg, 1.24 mmol) and THF (10 mL) was added vinylmagnesium bromide (1 M in THF, 1.49 mL, 1.49 mmol) at 0 °C. After 1 h, the reaction mixture was diluted by adding Et_2O (10 mL), and then to this was added a saturated aqueous NH_4Cl solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3×20 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc=7:1) afforded a mixture of vinyl alcohols (590 mg, 82%) as a colorless oil.

The mixture of vinyl alcohols (590 mg, 1.02 mmol) obtained as described in the previous procedure was dissolved in CH_2Cl_2 (20 mL). To this solution was added Dess–Martin periodinane (DMP) (867 mg, 2.04 mmol). The resulting solution was stirred for 1 h at room temperature. After the reaction was completed, saturated $NaHCO_3$ (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=7:1) offered the desired vinyl ketone **29a** (560 mg, 95%) as a colorless liquid: $[\alpha]_D^{27.6}$ +21.6 (*c* 1.04, $CHCl_3$); IR (film): 2931, 2861, 1732, 1698, 1612, 1524, 1461, 1378, 1294, 1250, 1173, 1056 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.22 (d, *J*=8.5 Hz, 2H), 6.85 (d, *J*=8.5 Hz, 2H), 6.43 (dd, *J*=11.0, 17.5 Hz, 1H), 6.26 (dd, *J*=1.0, 17.5 Hz, 1H), 5.74 (dd, *J*=1.5, 10.5 Hz, 1H), 5.68 (ddd, *J*=8.0, 10.5, 17.5 Hz, 1H), 5.02 (m, 3H), 4.42 (q, *J*=11.5 Hz, 2H), 3.89 (dd, *J*=3.0, 7.0 Hz, 1H), 3.79 (s, 3H), 3.60 (dd, *J*=4.0, 6.0 Hz, 1H), 2.86 (m, 1H), 2.63 (q, *J*=7.0 Hz, 1H), 2.50 (dddd, *J*=7.0, 7.0, 7.0, 14.5 Hz, 1H), 1.86 (ddd, *J*=4.0, 8.5, 13.5 Hz, 1H), 1.54 (m, 1H), 1.16 (t, *J*=7.0 Hz, 6H), 1.08 (d, *J*=7.0 Hz, 3H), 1.00 (d, *J*=7.0 Hz, 3H), 0.91 (d, *J*=7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 175.4, 159.0, 139.9, 135.0, 130.6, 129.3, 128.0, 115.2, 113.6, 76.0, 76.0, 73.9, 70.1, 55.2, 42.9, 41.4, 39.1, 37.1, 35.0, 26.0, 18.3, 17.7, 16.5, 16.1, 15.1, 14.7, -4.1, -4.1; HRMS: *m*/*z* calcd for $C_{33}H_{54}O_6Si[M+H]^+$:597.3587; found, 597.3585.

*4.1.20. (E)-(3R,4S,5S,7R,11R,12S)-4-(tert-Butyldimethylsilyloxy)-12-[(R)-1-(4-methoxybenzyloxy)ethyl]-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione (**30a**).* A flame-dried round-bottomed flask was charged with a solution of vinyl ketone **29a** (560 mg, 0.97 mmol) in CH_2Cl_2 (30 mL). Grubbs catalyst (second generation) (82 mg, 0.097 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 to give a dark brown oil. Purification of this residue by flash chromatography (hexane/EtOAc=5:1) afforded the lactone **30a** (450 mg, 85%) as a colorless oil: $[\alpha]_D^{25.5}$ +45.1 (*c* 1.85, $CHCl_3$); IR (film): 2933, 2864, 1732, 1692, 1629, 1514, 1462, 1375, 1324, 1253, 1162, 1090, 1056, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.5 Hz, 2H), 6.89 (d, *J*=8.5 Hz, 2H), 6.74 (dd, *J*=5.5, 15.7 Hz, 1H), 6.40 (d, *J*=15.7 Hz, 1H), 4.92 (dd, *J*=2.1, 9.3 Hz, 1H), 4.61 (d, *J*=11.0 Hz, 1H), 4.35 (d, *J*=11.0 Hz, 1H), 3.80 (s, 3H), 3.59 (m, 1H), 3.05 (m, 1H), 2.63 (dddd, *J*=7.0, 7.0, 7.0, 10.0 Hz, 1H), 2.48 (m, 1H), 1.62 (m, 1H), 1.31 (m, 1H), 1.20 (d, *J*=7.0 Hz, 6H), 1.16 (d, *J*=6.0 Hz, 3H), 1.00 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.3 Hz, 3H), 0.90 (s, 9H), 0.06 (d, *J*=4.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 174.8, 159.3, 147.4, 129.9, 125.9, 113.8, 79.0, 74.2, 72.2, 70.3, 55.2, 45.0, 44.0, 35.2, 34.1, 33.6, 26.2, 18.5, 18.5, 17.7, 16.9, 16.3, 9.7, −3.2, −3.4; HRMS: *m*/*z* calcd for $C_{31}H_{50}O_6Si[M+Na]^+$: 569.3274; found, 569.3272.

*4.1.21. (E)-(3R,4S,5S,7R,11R,12S)-4-Hydroxy-12-[(R)-1-(4-methoxybenzyloxy)ethyl]-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione (**31**) and neomethynolide (**3a**). Method* 1. To a solution of lactone **30a** (330 mg, 0.60 mmol) and CH_3CN (5 mL) at room temperature, was added a solution of [HF/H_2O/CH_3CN(v/v/v)=1:0.5:8.5 (10 mL). After the mixture was stirred for 17 h, it was neutralized with saturated $NaHCO_3$ (10 mL) and extracted with ether (3×20 mL). The combined organic solution was washed with aqueous saturated NaCl (10 mL) and dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=2:1) afforded the desired alcohol **31** (130 mg, 50%) as a colorless oil and neomethynolide (**3a**) (86 mg, 46%) as a white solid: **31**: $[\alpha]_D^{25.5}$ 27.9 (*c* 1.40, $CHCl_3$); IR (film): 3478, 2969, 1731, 1688, 1626, 1513, 1460, 1376, 1251, 1162, 1031, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26 (d, *J*=8.3 Hz, 2H), 6.89 (d, *J*=8.3 Hz, 2H), 6.74 (dd, *J*=5.4, 15.7 Hz, 1H), 6.39 (dd, *J*=1.2, 15.7 Hz, 1H), 4.95 (dd, *J*=2.3, 9.3 Hz, 1H), 4.62 (d, *J*=11.1 Hz, 1H), 4.36 (d, *J*=11.1 Hz, 1H), 3.81 (s, 3H), 3.60 (m, 2H), 3.05 (m, 1H), 2.55 (m, 2H), 1.59 (m, 2H), 1.31 (m, 3H), 1.30 (d, *J*=6.9 Hz, 3H), 1.21 (d, *J*=7.0 Hz, 3H), 1.17 (d, *J*=6.0 Hz, 3H), 1.01 (d, *J*=6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 174.2, 159.4, 147.7, 129.9, 125.7, 113.9, 77.9, 77.2, 74.4, 72.1, 70.4, 55.3, 45.2, 43.1, 35.4, 33.3, 33.0, 17.7, 17.5, 16.3, 16.2, 9.7; HRMS: *m*/*z* calcd for $C_{25}H_{36}O_6[M+Na]^+$: 455.2410; found, 455.2406: **3a** mp 101–104 °C; $[\alpha]_D^{22.1}$ 73.8 (*c* 1.52, $CHCl_3$); IR (film): 3439, 2970, 1728, 1684, 1627, 1458, 1377, 1155, 996, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$,): δ 6.75 (dd, *J*=5.4, 15.7 Hz, 1H), 6.53 (dd, *J*=1.3, 15.7 Hz, 1H), 4.83 (dd, *J*=2.3, 9.0 Hz, 1H), 3.89 (dddd, *J*=6.1, 6.1, 6.1, 12.4 Hz, 1H), 3.56 (d, *J*=10.4 Hz, 1H), 3.07 (m, 1H), 2.62 (dddd, *J*=6.9, 6.9, 6.9, 10.4 Hz, 1H), 2.52 (m, 1H), 1.63 (t, *J*=12.8 Hz, 1H), 1.51 (br s, 2H), 1.35–1.22 (m, 2H), 1.30 (d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=6.7 Hz, 3H), 1.21 (d, *J*=5.9 Hz, 3H), 1.17 (d, *J*=6.9 Hz, 3H), 1.01 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.7, 174.3, 147.4, 125.9, 78.0, 75.4, 66.4, 45.2, 43.2, 35.5, 33.3, 33.1, 21.0, 17.7, 17.5, 16.2, 9.8; HRMS: *m*/*z* calcd for $C_{17}H_{28}O_5$: 312.1937; found, 312.1936.

Method 2. To a stirred solution of lactone **30a** (17 mg, 0.031 mmol) in dry THF (2 mL) at room temperature was added 1.0 M TBAF (60 μL, 0.062 mmol) via a syringe. After 3 h, the reaction mixture was concentrated. Purification by flash chromatography (hexane/EtOAc=3:1) afforded alcohol **31** (11 mg, 85%) as a colorless oil.

*4.1.22. (2R,3R,4S)-2-Acetoxy-4-hydroxy-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3,7-bis(tert-butyldimethylsilyloxy)-2,4,6-trimethylheptanoate (**27b**).* To a solution of carboxylic acid **26** (144 mg, 0.33 mmol) in THF (5 mL) at room temperature were added triethylamine (69 μL, 0.50 mmol) and 2,4,6-trichlorobenzoyl chloride (67 μL, 0.43 mmol). The mixture was stirred for 3 h at room temperature, and the solids were filtered off and washed with hexane (10 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 **9b** (62 mg, 0.33 mmol) and DMAP (20 mg, 0.17 mmol) in benzene (2 mL) was added. After being stirred for 15 h, the reaction mixture was diluted with ether (10 mL), and 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=7:1) afforded the desired ester **27b** (151 mg, 76%) as a colorless oil: $[\alpha]_D^{25.0}$ +12.8 (*c* 0.96, $CHCl_3$); IR (film): 3516, 2955, 1740, 1462, 1371, 1255, 1156, 1078, 928, 839, 809 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.92 (dd, *J*=11.0, 17.0 Hz, 1H), 5.38 (dd, *J*=1.0, 17.5 Hz, 1H), 5.16 (m, 2H), 5.05 (d, *J*=3.5 Hz, 1H), 3.95 (dd, *J*=3.5, 6.5 Hz, 1H), 3.45 (dd, *J*=5.0, 10.0 Hz, 1H), 3.26 (dd, *J*=7.0, 9.5 Hz, 1H), 2.71 (m, 1H), 2.09 (s, 1H), 1.95 (s, 3H), 1.67 (m, 2H), 1.43 (ddd, *J*=5.0, 7.5, 14.0 Hz, 1H), 1.24 (m, 9H), 0.94 (d, *J*=7.0 Hz, 3H), 0.89 (m, 21H), 0.06 (d, *J*=7.0 Hz, 6H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.3, 170.3, 140.1, 113.9, 77.1, 75.4, 74.0, 69.7, 67.8, 42.2, 37.0, 35.7, 33.6, 26.7, 25.9, 25.9, 21.2, 18.3, 18.1, 16.7, 15.3, 14.8, −4.1, −4.2, −5.4; HRMS: *m*/*z* calcd for $C_{31}H_{62}O_7Si_2[M+H]^+$: 603.4112; found, 603.4114.

*4.1.23. (2R,3R,4S)-2-Acetoxy-4-hydroxy-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3-(tert-butyldimethylsilyloxy)-2,4,6-trimethyl-7-oxoheptanoate (**28b**).* Ester **27b** (143 mg, 0.24 mmol) was dissolved in

MeOH (5 mL). To this solution was added DL-10-camphorsulfonic acid (11 mg, 0.05 mmol). The resulting solution was stirred at 0 °C for 2 h. The reaction was terminated by addition of Et_3N (35 μL, 0.24 mmol). After the solution was concentrated, purification by flash chromatography (hexane/EtOAc=2:1) gave the desired primary alcohol (100 mg, 86%) as a colorless oil: $[\alpha]_D^{25.9}$ +19.1 (*c* 1.56, $CHCl_3$); IR (film): 3430, 2955, 1739, 1461, 1372, 1254, 1164, 1055, 927, 837 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.94 (dd, *J*=10.0, 17.0 Hz, 1H), 5.38 (dd, *J*=1.0, 17.5 Hz, 1H), 5.18 (dd, *J*=1.5, 11.0 Hz, 1H), 5.14 (dddd, *J*=3.5, 6.5, 6.5, 6.5 Hz, 1H), 5.06 (d, *J*=3.5 Hz, 1H), 3.89 (dd, *J*=2.5, 7.5 Hz, 1H), 3.50 (dd, *J*=4.5, 11.0 Hz, 1H), 3.40 (dd, *J*=5.0, 11.0 Hz, 1H), 2.81 (q, *J*=7.0 Hz, 1H), 1.96 (s, 3H), 1.70 (m, 3H), 1.59 (m, 1H), 1.26 (s, 3H), 1.24 (d, *J*=6.5 Hz, 3H), 1.23 (d, *J*=7.0 Hz, 3H), 0.96 (d, *J*=7.5 Hz, 3H), 0.94 (d, *J*=6.5 Hz, 3H), 0.91 (s, 9H), 0.08 (d, *J*=2.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.9, 170.3, 139.9, 114.0, 77.6, 76.3, 73.8, 69.8, 66.8, 43.1, 36.1, 34.3, 32.6, 26.6, 26.0, 21.2, 18.4, 18.2, 17.5, 15.5, 15.3, −3.9, −4.0; HRMS: *m*/*z* calcd for $C_{25}H_{48}O_7Si[M+H]^+$: 489.3248; found, 489.3246.

The alcohol (87 mg, 0.18 mmol) obtained as described in the previous procedure was dissolved in CH_2Cl_2 (10 mL). To this solution was added Dess–Martin periodinane (DMP) (151 mg, 0.36 mmol). The resulting solution was stirred for 1 h at room temperature. After the reaction was completed, 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=7:1) offered the desired aldehyde **28b** (80 mg, 92%) as a colorless liquid: ^1H NMR (500 MHz, $CDCl_3$): δ 9.54 (d, *J*=2.3 Hz, 1H), 5.92 (dd, *J*=10.8, 17.2 Hz, 1H), 5.39 (dd, *J*=1.3, 17.2 Hz, 1H), 5.16 (dd, *J*=1.3, 10.8 Hz, 1H), 5.13 (dddd, *J*=3.2, 6.6, 6.6, 6.6 Hz, 1H), 5.03 (d, *J*=3.2 Hz, 1H), 3.86 (dd, *J*=2.1, 8.4 Hz, 1H), 2.84 (m, 2H), 2.44 (m, 1H), 1.93 (s, 3H), 1.89 (ddd, *J*=3.2, 10.1, 13.7 Hz, 1H), 1.53 (m, 1H), 1.25 (d, *J*=6.6 Hz, 3H), 1.23 (d, *J*=7.2 Hz, 3H), 1.21 (s, 3H), 1.11 (d, *J*=7.2 Hz, 3H), 0.94 (d, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.07 (d, *J*=1.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.7, 175.4, 170.2, 139.9, 113.9, 77.5, 76.6, 73.7, 69.9, 44.1, 43.7, 36.4, 32.2, 26.7, 26.1, 21.1, 18.4, 17.6, 15.7, 15.1, 15.0, −3.8, −3.9.

*4.1.24. (2R,3R,4S)-2-Acetoxy-4-hydroxy-4-methylhex-5-en-3-yl (2R,3S,4S,6R)-3-(tert-butyldimethylsilyloxy)-2,4,6-trimethyl-7-oxonon-8-enoate (**29b**).* To a stirred solution of the aldehyde **28b** (80 mg, 0.16 mmol) and THF (10 ml) was added vinylmagnesium bromide (1 M in THF, 250 μL, 0.25 mmol) at 0 °C. After 1 h, the reaction mixture was diluted by adding Et_2O (10 mL), and then to this was added a saturated aqueous NH_4Cl solution (10 mL). The organic layer 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=7:1) afforded a mixture of vinyl alcohols (71 mg, 85%) as a colorless oil.

The mixture of vinyl alcohols (71 mg, 0.14 mmol) obtained as described in the previous procedure was dissolved in CH_2Cl_2 (10 mL). To this solution was added Dess–Martin periodinane (DMP) (117 mg, 0.28 mmol). The resulting solution was stirred for 1 h at room 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=7:1) offered the desired vinyl ketone **29b** (65 mg, 92%) as a colorless liquid: $[\alpha]_D^{25.5}$ +29.0 (*c* 1.16, $CHCl_3$); IR (film): 3493, 2932, 2857, 1737, 1673, 1612, 1461, 1409, 1371, 1247, 1161, 1093, 1050, 926 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.39 (dd, *J*=10.0, 17.5 Hz, 1H), 6.28 (dd, *J*=1.0, 17.5 Hz, 1H), 5.95 (dd, *J*=11.0, 17.5 Hz, 1H), 5.38 (dd, *J*=1.0, 10.5 Hz, 1H), 5.44 (dd, *J*=1.5, 17.5 Hz, 1H), 5.18 (dd, *J*=1.5, 11.0 Hz, 1H), 5.15 (dddd, *J*=3.0, 6.5, 6.5, 6.5 Hz, 1H), 5.02 (d, *J*=3.0 Hz, 1H), 3.82 (dd, *J*=1.0, 9.0 Hz, 1H), 3.74 (s, 1H), 2.98 (m, 2H), 2.04 (ddd, *J*=2.0, 11.0, 13.5 Hz, 1H), 1.94 (s, 3H), 1.66 (s, 1H), 1.31 (d, *J*=6.5 Hz, 3H), 1.24 (d, *J*=7.5 Hz, 3H), 1.13 (d, *J*=7.0 Hz, 3H), 1.13 (s, 3H), 0.94 (d, *J*=7.0 Hz, 3H), 0.91 (s, 9H), 0.08 (d, *J*=2.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 176.0, 170.2, 139.8, 135.5, 129.2, 113.8, 77.6, 77.1, 73.5, 70.2, 43.7, 40.6, 36.5, 33.6, 26.9, 26.1, 21.2, 19.1, 18.5, 18.3, 16.1, 14.9, −3.6, −3.7; HRMS: *m*/*z* calcd for $C_{27}H_{48}O_7Si[M+H]^+$: 535.3067; found, 535.3071.

*4.1.25. (E)-(3R,4S,5S,7R,11S,12R)-4-(tert-Butyldimethylsilyloxy)-12-[(R)-1-acetoxyethyl]-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione (**30b**).* A flame-dried round-bottomed flask was charged with a solution of vinyl ketone **29b** (65 mg, 0.13 mmol) in CH_2Cl_2 (15 mL). Grubbs catalyst (second generation) (22 mg, 0.026 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 to give a dark brown oil. Purification of this residue by flash chromatography (hexane/EtOAc=3:1) afforded the lactone **30b** (51 mg, 85%) as a colorless oil: $[\alpha]_D^{30.7}$ +62.1 (*c* 1.65, $CHCl_3$); IR (film): 3483, 2930, 2856, 1741, 1694, 1630, 1461, 1371, 1318, 1251, 1137, 1089, 1061, 979, 894 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.59 (d, *J*=16.0 Hz, 1H), 6.31 (d, *J*=16.0 Hz, 1H), 5.28 (m, 1H), 4.90 (d, *J*=5.0 Hz, 1H), 3.63 (d, *J*=10.0 Hz, 1H), 3.02 (s, 1H), 2.70 (dddd, *J*=7.0, 7.0, 7.0, 10.0 Hz, 1H), 2.53 (ddddd, *J*=4.5, 7.0, 7.0, 7.0, 11.5 Hz, 1H), 2.06 (s, 3H), 1.72 (s, 1H), 1.64 (t, *J*=13.5 Hz, 1H), 1.40 (s, 3H), 1.24 (d, *J*=7.0 Hz, 3H), 1.23 (d, *J*=6.5 Hz, 3H), 1.19 (d, *J*=7.0 Hz, 3H), 0.93 (d, *J*=6.5 Hz, 3H), 0.90 (s, 9H), 0.07 (d, *J*=3.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.0, 174.6, 170.7, 148.8, 125.8, 79.1, 74.5, 69.2, 45.3, 44.4, 38.8, 33.6, 26.4, 21.5, 20.4, 18.7, 18.7, 17.9, 17.3, 17.0, −2.9, −3.2; HRMS: *m*/*z* calcd for $C_{25}H_{44}O_7Si[M+Na]^+$: 507.2754; found, 507.2759.

*4.1.26. Novamethynolide (**4a**).* To a stirred solution of lactone **30b** (20 mg, 0.041 mmol) in dry THF (3 mL) at room temperature was added 1.0 M TBAF (160 μL, 0.16 mmol) via a syringe. After 5 h, the reaction mixture was concentrated. Purification by flash chromatography (hexane/EtOAc=1:1) afforded novamethynolide (**4a**) (9.0 mg, 67%) as a white solid: mp 143–146 °C; $[\alpha]_D^{26.2}$ +39.5 (*c* 0.74, $CHCl_3$); IR (film): 3441, 2924, 1735, 1688, 1633, 1459, 1377, 1271, 1133, 991 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.64 (d, *J*=16.0 Hz, 1H), 6.31 (d, *J*=16.0 Hz, 1H), 4.70 (d, *J*=9.4 Hz, 1H), 4.14 (m, 1H), 4.02 (s, 3H), 3.58 (d, *J*=8.9 Hz, 1H), 3.14 (s, 1H), 2.58 (m, 2H), 1.61 (m, 2H), 1.52 (s, 3H), 1.32 (m, 1H), 1.30 (d, *J*=6.9 Hz, 3H), 1.25 (m, 1H), 1.21 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.0 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 173.7, 148.3, 125.2, 77.7, 75.5, 74.3, 67.8, 45.3, 43.2, 33.3, 33.0, 21.0, 17.6, 17.4, 16.2; HRMS: *m*/*z* calcd for $C_{17}H_{28}O_6[M+Na]^+$: 351.1784; found, 351.1781.

*4.1.27. (E)-(3R,4S,5S,7R,11S,12R)-12-[(R)-1-Acetoxyethyl]-4-hydroxy-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione (**32**).* To a solution of lactone **30b** (40 mg, 0.083 mmol) and CH_3CN (2 mL) at room temperature, was added a solution of [$HF/H_2O/CH_3CN$(v/v/v)= 1:0.5:8.5] (5 mL). After the mixture was stirred for 17 h, it was neutralized with saturated $NaHCO_3$ (10 mL) and extracted with ether (3×10 mL). The combined organic solution was washed with aqueous saturated NaCl (10 mL) and dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc=1:1) afforded the desired compound **32** (24 mg, 77%) as a white solid: mp 87–90 °C; $[\alpha]_D^{27.7}$ 72.4 (*c* 1.08, $CHCl_3$); IR (film): 3407, 2968, 2924, 1727, 1633, 1464, 1375, 1244, 1133, 1072, 983 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.59 (d, *J*=16.0 Hz, 1H), 6.32 (d, *J*=16.0 Hz, 1H), 5.29 (dddd, *J*=6.5, 6.5, 6.5, 12.0 Hz, 1H), 4.93 (d, *J*=5.0 Hz, 1H), 3.58 (d, *J*=10.0 Hz, 1H), 3.03 (s, 1H), 2.66 (dddd, *J*=7.0, 7.0, 7.0, 10.5 Hz, 1H), 2.57 (m, 1H), 2.07 (s, 3H), 1.74 (s, 2H), 1.63 (t, *J*=13.0 Hz, 1H), 1.42 (s, 3H), 1.33 (m, 2H), 1.33 (d, *J*=7.0 Hz, 3H), 1.25 (d, *J*=6.5 Hz, 3H), 1.20 (d, *J*=7.0 Hz, 3H), 1.00 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.6, 173.8, 170.5, 148.6, 125.4, 77.8, 74.4, 74.3,

69.0, 45.2, 43.3, 33.5, 32.9, 21.3, 20.1, 17.6, 17.4, 16.9, 16.2; HRMS: *m*/*z* calcd for $C_{19}H_{30}O_7[M+Na]^+$: 393.1889; found, 393.1891.

4.1.28. Protected neomethymycin ***34***. To a solution of trichloroacetimidate **33** (50 mg, 0.14 mmol) and PMB-protected-neomethynolide **31** (30 mg, 0.069 mmol) in CH_2Cl_2 (5 mL) was added molecular sieves (300 mg). The resulting solution was stirred at room temperature. After 30 min the mixture was cooled to −20 °C and then $BF_3{\cdot}OEt_2$ (12 μL, 0.083 mmol) was added. The resulting mixture was stirred for 3 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 protected **34** (20 mg, 46%) as a colorless oil: $[\alpha]_D^{26.1}$ +50.7 (*c* 0.94, $CHCl_3$); IR (film): 2933, 1734, 1686, 1624, 1513, 1455, 1375, 1242, 1156, 1103, 1056, 987 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J*=8.6 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 6.71 (dd, *J*=5.5, 15.7 Hz, 1H), 6.39 (dd, *J*=1.0, 15.7 Hz, 1H), 4.90 (dd, *J*=2.3, 9.3 Hz, 1H), 4.77 (dd, *J*=7.6, 10.6 Hz, 1H), 4.61 (d, *J*=11.1 Hz, 1H), 4.35 (d, *J*=11.1 Hz, 1H), 4.29 (d, *J*=7.6 Hz, 1H), 3.81 (s, 3H), 3.59 (m, 1H), 3.53 (d, *J*=10.5 Hz, 1H), 3.46 (m, 1H), 3.04 (m, 1H), 2.69 (m, 2H), 2.52 (m, 1H), 2.26 (s, 6H), 2.08 (s, 3H), 1.81 (m, 3H), 1.73 (m, 2H), 1.54 (t, *J*=12.7 Hz, 1H), 1.37 (m, 4H), 1.28 (d, *J*=6.9 Hz, 3H), 1.23 (d, *J*=6.1 Hz, 3H), 1.17 (d, *J*=7.0 Hz, 3H), 1.15 (d, *J*=6.1 Hz, 3H), 0.99 (d, *J*=6.8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.1, 174.4, 169.9, 159.4, 147.2, 129.9, 129.5, 126.1, 113.9, 102.9, 85.5, 74.5, 72.2, 71.6, 70.4, 69.1, 63.5, 52.3, 45.1, 43.7, 40.6, 35.3, 33.6, 33.4, 30.3, 21.3, 20.9, 17.6, 17.4, 16.3, 15.7, 9.7; HRMS: *m*/*z* calcd for $C_{35}H_{53}NO_9[M+H]^+$: 632.3799; found, 632.3796.

*4.1.29. Neomethymycin (****3****).* To a solution of product **34** (15 mg, 0.024 mmol) in CH_2Cl_2/H_2O [10:1(v/v), 3 mL] was added dichlorodicynoquinone (DDQ) (16 mg, 0.072 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 (EtOAc/MeOH=10:1) provided the desired alcohol product (9.7 mg, 79%) as a colorless oil: $[\alpha]_D^{25.7}$ +59.4 (*c* 0.54, $CHCl_3$); IR (film): 3388, 2924, 2853, 2333, 1730, 1686, 1626, 1462, 1378, 1246, 1162, 1062 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.74 (dd, *J*=5.6, 15.7 Hz, 1H), 6.43 (dd, *J*=1.3, 15.7 Hz, 1H), 4.78 (m, 2H), 4.30 (d, *J*=7.6 Hz, 1H), 3.88 (m, 1H), 3.53 (d, *J*=10.5 Hz, 1H), 3.47 (ddd, *J*=1.8, 6.2, 11.0 Hz, 1H), 3.05 (m, 1H), 2.70 (m, 2H), 2.52 (m, 1H), 2.26 (s, 6H), 2.08 (s, 3H), 1.73 (m, 2H), 1.56 (t, *J*=14.2 Hz, 1H), 1.43 (m, 2H), 1.34 (m, 2H), 1.29 (d, *J*=7.0 Hz, 3H), 1.23 (d, *J*=6.1 Hz, 3H), 1.20 (d, *J*=6.1 Hz, 3H), 1.19 (d, *J*=7.0 Hz, 3H), 1.16 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 174.5, 169.9, 146.8, 126.3, 102.9, 85.4, 75.4, 71.6, 69.1, 66.5, 63.5, 45.1, 43.7, 40.6, 35.4, 33.6, 33.5, 30.3, 29.7, 21.4, 21.0, 21.0, 17.6, 17.3, 15.7, 9.8.

To a stirred solution of the alcohol product (7.0 mg, 0.014 mmol) (prepared as described in the previous procedure) in MeOH (2 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 neomethymycin (**3**) (5.3 mg, 80%) as a colorless oil: $[\alpha]_D^{18.3}$ 124.6 (*c* 0.35, $CHCl_3$); IR (film): 3385, 2925, 2858, 1732, 1685, 1625, 1460, 1377, 1255, 1158, 1109, 1050, 994 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.76 (dd, *J*=5.5, 15.7 Hz, 1H), 6.44 (dd, *J*=1.2, 15.7 Hz, 1H), 4.79 (dd, *J*=2.2, 9.0 Hz, 1H), 4.24 (d, *J*=7.3 Hz, 1H), 3.89 (dddd, *J*=6.1, 6.1, 6.1, 8.8 Hz, 1H), 3.77 (d, *J*=2.5 Hz, 1H), 3.59 (d, *J*=10.5 Hz, 1H), 3.48 (m, 1H), 3.23 (dd, *J*=7.4, 10.2 Hz, 1H), 3.05 (m, 1H), 2.88 (dddd, *J*=7.1, 7.1, 7.1, 10.6 Hz, 1H), 2.54 (m, 2H), 2.36 (s, 1H), 2.29 (s, 6H), 1.86 (m, 2H), 1.69 (m, 4H), 1.46 (m, 2H), 1.41 (d, *J*=7.0 Hz, 3H), 1.28 (m, 2H), 1.23 (d, *J*=6.2 Hz, 3H), 1.20 (d, *J*=6.2 Hz, 3H), 1.19 (d, *J*=7.1 Hz, 3H), 1.16 (d, *J*=6.8 Hz, 3H), 1.02 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 174.8, 147.0, 126.2, 105.0, 85.6, 75.4, 70.3, 69.5, 66.5, 65.9, 45.1, 43.9, 40.2, 35.4, 34.1, 33.4, 29.7, 28.4, 22.7, 21.1, 21.0, 17.6, 17.4, 15.9, 14.1, 9.8; HRMS: *m*/*z* calcd for $C_{25}H_{43}NO_7[M+H]^+$: 470.3118; found, 470.3120.

*4.1.30. Novamethymycin (****4****).* To a solution of trichloroacetimidate **33** (22 mg, 0.060 mmol) and the protected novamethynolide **32** (13 mg, 0.030 mmol) in CH_2Cl_2 (4 mL) was added molecular sieves (200 mg). The resulting solution was stirred for 30 min at room temperature. The mixture was cooled −20 °C and then $BF_3{\cdot}OEt_2$ (6 μL, 0.045 mmol) was added. The resulting mixture was stirred for 3 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 diacetyl−protected novamethymycin (8.8 mg, 52%) as a colorless oil: $[\alpha]_D^{25.3}$ +67.4 (*c* 0.53, $CHCl_3$); IR (film): 3353, 2925, 2852, 1739, 1630, 1459, 1378, 1243, 1127, 1056, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.58 (d, *J*=16.0 Hz, 1H), 6.31 (d, *J*=16.0 Hz, 1H), 5.27 (m, 1H), 4.89 (d, *J*=5.3 Hz, 1H), 4.79 (m, 1H), 4.31 (d, *J*=7.5 Hz, 1H), 4.12 (q, *J*=7.1 Hz, 1H), 3.56 (d, *J*=10.5 Hz, 1H), 3.48 (m, 1H), 3.35 (m, 1H), 2.75 (dd, *J*=6.8, 10.4 Hz, 1H), 2.56 (m, 2H), 2.29 (s, 6H), 2.09 (s, 3H), 2.08 (s, 3H), 2.05 (m, 1H), 1.68 (m, 2H), 1.57 (m, 2H), 1.42 (s, 3H), 1.36 (m, 2H), 1.31 (d, *J*=6.9 Hz, 3H), 1.25 (d, *J*=5.9 Hz, 3H), 1.24 (d, *J*=8.1 Hz, 3H), 1.18 (d, *J*=7.0 Hz, 3H), 0.98 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 173.9, 169.8, 169.6, 148.2, 125.9, 102.9, 85.0, 74.4, 74.3, 70.5, 69.7, 69.0, 63.5, 63.1, 45.1, 43.9, 40.6, 33.9, 33.3, 30.5, 30.3, 21.4, 21.1, 20.9. 20.2, 17.3, 16.9, 15.7; HRMS: *m*/*z* calcd for $C_{29}H_{47}NO_{10}[M+H]^+$: 570.3278; found, 570.3285.

To a stirred solution of diacetyl−protected novamethymycin (5.1 mg, 0.0090 mmol) prepared as described in the previous procedure in MeOH (1 mL) at room temperature was added H_2O (100 μL) and triethylamine (100 μL). After stirred for 5 h, the reaction mixture was concentrated. Purification of the residue by flash chromatography (EtOAc/MeOH=10:1) afforded novamethymycin (**4**) (3.3 mg, 75%) as a colorless oil: $[\alpha]_D^{21.8}$ +97.3 (*c* 0.13, $CHCl_3$); IR (film): 3402, 2925, 1736, 1693, 1633, 1460, 1377, 1271, 1159, 1111, 1051, 989 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.64 (d, *J*=16.0 Hz, 1H), 6.32 (d, *J*=16.0 Hz, 1H), 4.68 (d, *J*=9.3 Hz, 1H), 4.23 (d, *J*=7.3 Hz, 1H), 4.13 (m, 1H), 3.61 (d, *J*=10.7 Hz, 1H), 3.49 (m, 1H), 3.23 (dd, *J*=7.4, 10.2 Hz, 1H), 2.86 (dddd, *J*=7.0, 7.0, 7.0, 10.7 Hz, 1H), 2.58 (m, 1H), 2.52 (m, 1H), 2.29 (s, 6H), 1.68 (m, 2H), 1.52 (s, 3H), 1.46 (m, 1H), 1.41 (d, *J*=7.0 Hz, 3H), 1.23 (d, *J*=6.2 Hz, 3H), 1.20 (d, *J*=6.2 Hz, 3H), 1.17 (d, *J*=7.0 Hz, 3H), 1.02 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 174.1, 147.9, 125.6, 105.0, 85.3, 75.5, 74.2, 70.3, 69.5, 67.9, 65.9, 45.2, 44.0, 40.2, 33.8, 33.6, 39.7, 21.1, 21.1, 20.3, 17.6, 17.4, 15.8; HRMS: *m*/*z* calcd for $C_{25}H_{43}NO_8[M+H]^+$: 486.3067; found, 486.3070.

Acknowledgements

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2007-521-C00152). The authors are grateful to Prof. Yeo Joon Yoon (Ewha Womans University) for supplying the cell culture from which an authentic sample of neomethymycin was isolated.

Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.04.039.

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