Total synthesis of methymycin†

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Methynolide and 10-*epi*-methynolide were synthesized from the necessary segments, which were prepared by the addition of Grignard reagents to the corresponding α-alkoxyketones utilizing 1,2-stereochemical selection based on Cram chelation control. Ring-closing metathesis, as the key reaction, was carried out to combine the segments for the synthesis of methynolide and 10-*epi*-methynolide. The total synthesis of methymycin was also achieved by the glycosylation of methynolide with the trichloroimidate derivative of D-desosamine.

Introduction

Macrolide antibiotics have attracted the attention of synthetic chemists not only for the complex stereochemical relationship around the macrocylic ring skeleton but also for their significant biological activities.[1] The pikromycin biosynthetic pathway involves a series of macrolide antibiotics, such as methymycin and pikromycin, which contain 12- and 14-membered macrolactones as the core structures, respectively.[2]

Pikromycin polyketide synthase (Pik PKS) from *Streptomyces venezulae* is a gigantic enzyme that is responsible for producing these macrolide lactones. Pik PKS produces two macrolactones, that is, 10-deoxymethynolide and narbonolide, which undergo post-PKS modifications to produce methymycin and pikromycin macrolactone antibiotics. The post-PKS modifications include glycosylation followed by regiospecific oxidations which are caused by Des VII and cytochrome P450 hydroxylase (PikC).

Among the macrolides formed from the pikromycin biosynthetic pathway, methymycin and pikromycin are two of the major macrolides. Methymycin contains a macrolactone called methynolide as an aglycone. A great deal of effort has been directed towards the total synthesis of methynolide[3] and its seco-derivative.[4] The first and only total synthesis of methymycin was reported by Masamune and co-workers.[5] We have been interested in the pikromycin biosynthetic pathways in connection with the possibility of generating a wide variety of biologically active derivatives through a combination of genetic and chemical methods.[6] In order to facilitate the investigation of the biosynthetic mechanisms and explore macrolactone derivatives with new chemical structures using these techniques, it is important to identify and secure the expected macrolides. This requirement for biosynthetic studies, as well as interest in structural complexity, prompted this study of the synthesis of macrolides that appear in the pikromycin biosynthetic pathway.

Successful synthetic routes for the total synthesis of typical 12- and 14-membered macrolactones, 10-deoxymethynolide and narbonolide, have already been reported.[7] Success in the syntheses of these macrolactones encouraged us to investigate the synthesis of related macrolide antibiotics. Methymycin was chosen as a synthetic target because it is one of the most abundant macrolides that belongs to the methymycin family of macrolides, and no total synthesis of this macrolide antibiotic has been reported since Masamune *et al.* reported their synthesis in 1975.[5] The synthesis of methymycin would provide a good opportunity to facilitate biosynthetic research as well as to evaluate the efficiency of modern synthetic methods.

Results and discussion

Fig. 1 shows the retrosynthetic analysis of methymycin (**1**). Methymycin could be synthesized by combining methynolide (**2a**), the corresponding aglycone part, and D-desosamine, the sugar moiety. Following the successful synthetic route developed for 10-deoxymethynolide,[7] methynolide was disassembled retrosynthetically into the parts shown in Fig. 1 ensuring that the implementation of segment **A** would lead to the synthesis of methynolide (**2a**), and eventually to methymycin (**1**).

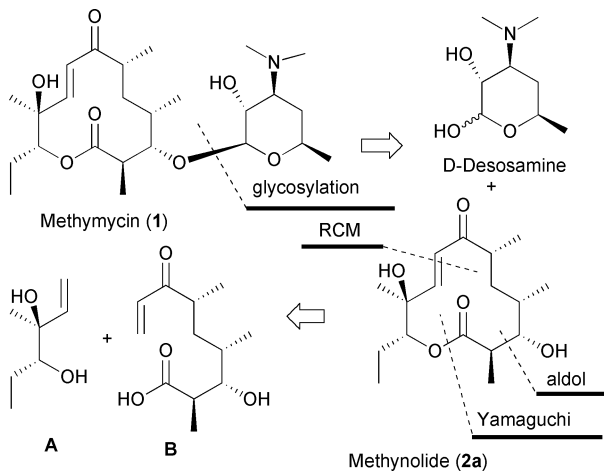

Fig. 1 Retrosynthesis of methymycin (**1**).

Our synthetic efforts towards methymycin started with the preparation of segment **A**. Scheme 1 summarizes the synthesis of segment **A**. The synthesis started from benzyl-protected diol **3**

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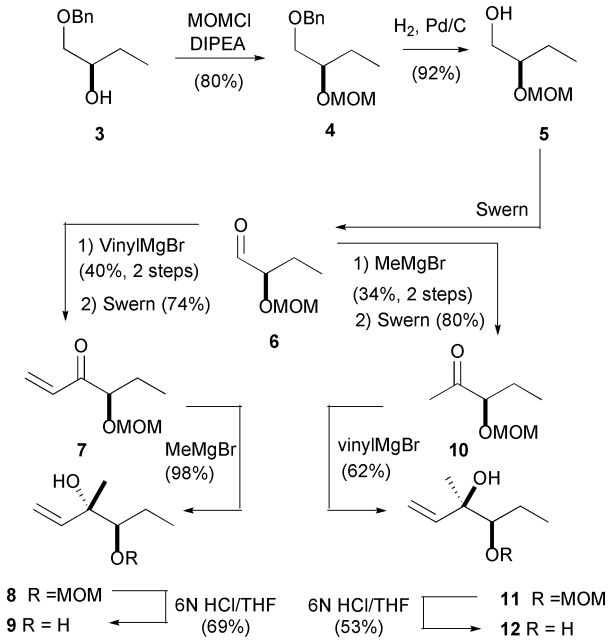
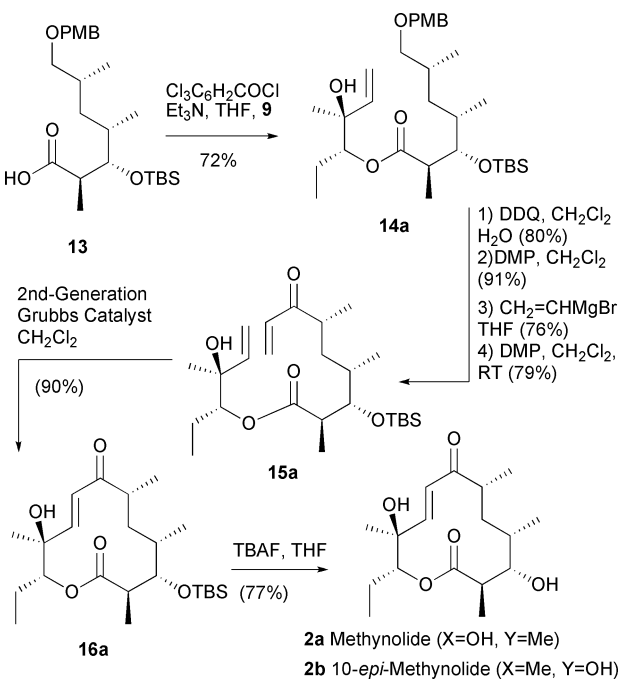


Scheme 1 Synthesis of the segment **A**.

which was prepared from (*S*)-glycidol according to the procedure reported in the literature.[8] After the secondary hydroxy group was protected with MOM group, the primary alcohol **5** was synthesized by debenzylation (Pd/C, H_2). Cram chelation control is the key to implementing the necessary stereochemistry at the carbon that contains a tertiary hydroxy group. Oxidation of alcohol **5** provided the aldehyde **6**, which was used for the chelation-controlled nucleophilic addition for the implementation of the 1,2-stereochemical relationship. It is well known in the literature that highly effective asymmetric induction can be achieved by the reaction of organometallic compounds, such as Grignard reagents, with α-alkoxyketones.[9]

Changing the order of addition of the nucleophiles that attack the carbonyl group can allow preparation of the desired segment **A** with the correct stereochemistry for the synthesis of methynolide as well as the segment with the epimeric stereochemistry for preparing 10-*epi*-methynolide. Therefore, the addition of vinyl Grignard reagent to the aldehyde **6** first provided a *sec*-alcohol as a diastereomeric mixture, which was then oxidized without separation to give the vinyl ketone **7**. Methyl Grignard (MeMgBr) addition to this vinyl ketone occurred in a chelation-controlled manner to produce the desired diol derivative **8** with excellent selectivity. The addition occurred in an almost completely controlled manner and with no formation of the corresponding diastereomeric diol derivative **11**. After acid hydrolysis, the desired diol **9** possessing the correct stereochemistry for the synthesis of methynolide (**1**) was synthesized. Alternatively, the aldehyde **6** was subjected to an addition reaction with methyl Grignard reagent (MeMgBr) to provide the corresponding MOM-protected diol. Oxidation followed by vinyl Grignard (vinylMgBr) addition under the chelation-controlled conditions provided the MOM-protected diol **11** exclusively. No formation of the diastereomeric diol derivative **8** was observed. The diastereomeric diol segment **12** was obtained by the deprotection of compound **11** by hydrolysis under acidic conditions. In summary, the utilization of 1,2-stereochemical selection by chelation control resulted in the successful implementation of the required diol stereochemistry for the synthesis of the segment.

The synthesis of methynolide was then achieved based on the route developed previously for the synthesis of 10-deoxymethynolide (Scheme 2). Carboxylic acid **13**[7] was subjected to esterification with **9** (**a** series) using the Yamaguchi protocol. Removal of the protecting group (DDQ) followed by the Dess-Martin oxidation provided an aldehyde, which was further subjected to a Grignard reaction with vinyl Grignard reagent. The resulting alcohol was oxidized to furnish vinyl ketone **15a**. The successful synthesis of vinyl ketone **15a** set the stage for testing the key ring-closing metathesis (RCM) reaction. There were two issues regarding the key RCM reaction with compound **15a**. The bulkiness of the quaternary carbon center next to the vinyl group and the instability of the unprotected allylic hydroxy group raised concern for the success of the RCM reaction. The inability to protect the tertiary allylic hydroxyl group (*e.g.* benzylation) led us to examine the RCM reaction of compound **15a** with the hydroxy group intact. The critical RCM reaction with Grubbs' second-generation catalyst was carried out uneventfully in good yield. Masamune *et al.* used the protection of the corresponding tertiary hydroxy group with a benzyl group during their total synthesis of methynolide.[5] This presents another example of the mildness and superiority of the RCM reaction with Grubbs' catalyst. The total synthesis of methynolide (**2a**) was achieved after deprotection. The successful synthesis of methynolide demonstrated the efficiency and generality of the synthetic strategy reported previously for the synthesis of 12-membered macrolactones.



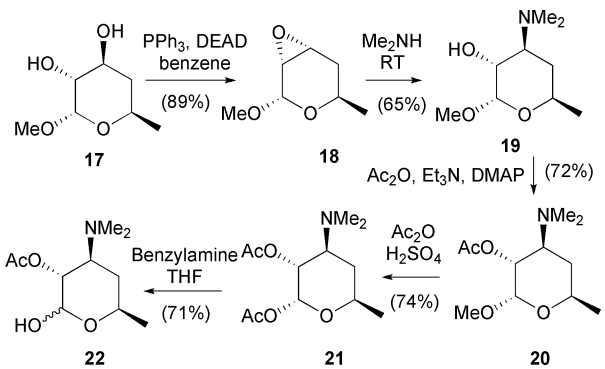
Scheme 2 Synthesis of methynolide and 10-*epi*-methynolide.

10-*epi*-Methynolide (**2b**) was also prepared successfully through the same reaction sequences, using compound **12** as the corresponding segment **A** (**b** series) for the esterification of carboxylic acid **13**. The structure was confirmed by a comparison with the NMR data reported in the literature for racemic

10-*epi*-methynolide (**2b**).[10] The synthesis of methynolide and 10-*epi*-methynolide assures our assignment of the correct stereochemistry for the chelation-controlled attack of the Grignard reagents during the synthesis of segment **A**, as shown in Scheme 1.

After the synthesis of methynolide, we then turned our attention to methymycin. In order to pursue the total synthesis of methymycin, it is important to secure the corresponding sugar, D-desosamine. During their synthesis of methymycin, the Masamune group exploited the sugar part derived from the degradation of the natural product.[11] In the present study, we decided to prepare the D-desosamine derivative required for the glycosylation of methynolide by chemical synthesis.[12] D-Desosamine belongs to a class of naturally occurring deoxy amino sugars which frequently show a variety of biological activities and are found in several important macrolide antibiotics.[13]

The synthesis started with compound **17** that was prepared from commercially available methyl α-D-glycopyranoside (Scheme 3).[14] The epoxide **18** was prepared from compound **17** by the Mitsunobu reaction, and it was opened with dimethylamine to provide methyl α-D-desosamine **19**. From compound **19**, the diacetate derivative **21** was synthesized in a two-step sequence ((a) Ac_2O, Et_3N; (b) Ac_2O, H_2SO_4). Deacetylation was achieved by a treatment with benzylamine to provide compound **22**.[15]

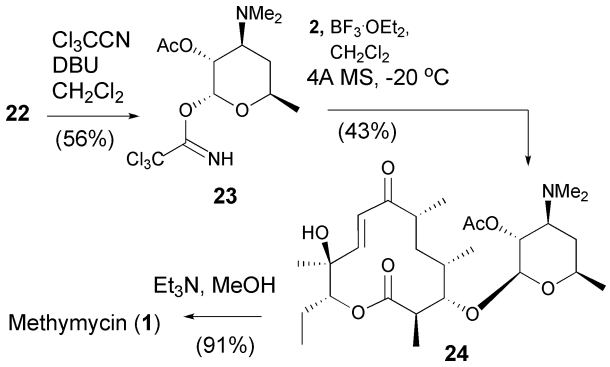


Scheme 3 Synthesis of the D-desosamine derivative.

The remaining task for the total synthesis of methymycin was glycosylation. Careful selection of the glycosylation conditions was needed due to the potential instability of methynolide, particularly under acidic glycosylation conditions because it has a tertiary allylic hydroxy group. After considerable experimentation, we decided to use the trichloroimidate method for glycosylation (Scheme 4).[16] Acetylated desosamine **22** was converted to the corresponding trichloroimidate **23**. The critical glycosylation of methynolide (**2**) with compound **23** was carried out successfully in the presence of $BF_3{\cdot}OEt_2$ to offer compound **24**. Final deacetylation completed the total synthesis of methymycin (**1**). The spectral data matched with those reported in the literature.[17]

Conclusion

A total synthesis of methymycin has been achieved, which is the only synthesis reported since the Masamune group reported their result.[5] Methynolide, the aglycone, was synthesized by combining segments based on the route developed previously by us. In principle, all the polyketide macrolactones in the pikromycin biosynthetic pathway can be synthesized by switching the key



Scheme 4 Total synthesis of methymycin.

segment due to the modular nature of the approach. The key segment for the synthesis of methynolide was prepared utilizing 1,2-stereochemical selection based on Cram chelation control, which allowed adjustment of the stereochemical relationship by variation of the order of addition of the nucleophiles to the carbonyl group. As a result, the corresponding segments for both the synthesis of methynolide and 10-*epi*-methynolide could be prepared. The stereoselective preparation of methynolide as well as 10-*epi*-methynolide is a strong advantage of this synthetic route. D-Desosamine, which is the sugar part of various natural products, was synthesized and used for the glycosylation of methynolide, which led to the successful synthesis of methymycin (**1**). The modular approach for the synthesis of macrolactones, and the glycosylation method developed in this study, will be useful for synthesizing other polyketide macrolides in the methymycin family.

Experimental

^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 ppm on a 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 a JASCO DIP-1000 digital polarimeter in solution in a 1 dm cell. High resolution mass spectra were recorded on a Jeol JMS700 by using FAB method. All reagents 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 diethylamide was distilled before use. Flash chromatography was carried out on Woelm 32–64 μm silica packed in glass columns.

(1*R*,2*S*)-1-Ethyl-2-hydroxy-2-methylbut-3-enyl (2*R*,3*S*,4*S*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-7-(4-methoxybenzyloxy)-2,4,6-trimethylheptanoate (14a)

To a solution of carboxylic acid **13** (45 mg, 0.10 mmol) in THF (1.5 mL) at room temperature were added triethylamine (19 μL, 0.13 mmol) and 2,4,6-trichlorobenzoyl chloride (20 μL,

0.12 mmol). The mixture was stirred for 3 h at room temperature, and the solids were filtered off and washed with hexane (3 mL). The combined solution was concentrated under reduced pressure. The residue was dissolved in benzene (1 mL), and to this solution a solution of alcohol **9** (21 mg, 0.16 mmol) and DMAP (17 mg, 0.14 mmol) in benzene (2 mL) was added. After being stirred for 13 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 = 4:1) afforded the desired ester **14a** (40 mg, 72%) as a colorless oil: $[\alpha]_D^{25.8}$ +10.5 (*c* 1.32, $CHCl_3$); IR (film): 3486.7, 2954.4, 2858.0, 1727.9, 1612.2, 1511.9, 1461.8, 1369.2, 1299.8, 1172.5, 1056.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.85 (t, J = 7. 6 Hz, 3H), 0.89 (s, 9H), 0.92 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.90–1.10 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 1.23 (s, 3H), 1.40–1.90 (m, 5H), 2.18 (s, 1H), 2.65 (quintet, J = 7.0 Hz, 1H), 3.14 (dd, J = 9.0, 6.8 Hz, 1H), 3.28 (dd, J = 9.0, 5.3 Hz, 1H), 3.80 (s, 3H), 3.92 (dd, J = 6.0, 2.1 Hz, 1H), 4.41 (s, 2H), 4.76 (dd, J = 10.0, 2.9 Hz, 1H), 5.13 (dd, J = 10.8, 1.2 Hz, 1H), 5.30 (dd, J = 17.3, 1.2 Hz, 1H), 5.87 (dd, J = 17.3, 10.8 Hz, 1H), 6.86 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 159.0, 140.8, 130.7, 129.1, 114.0, 113.6, 80.3, 75.4, 75.3, 74.8, 72.6, 55.2, 42.3, 36.9, 36.2, 31.1, 26.0, 25.1, 22.7, 18.3, 16.6, 14.7, 10.7, –4.1, –4.2; HRMS: m/z calcd for $C_{31}H_{54}O_6Si$, 550.3690; found, 550.3677.

(1*R*,2*S*)-1-Ethyl-2-hydroxy-2-methylbut-3-enyl (2*R*,3*S*,4*S*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-2,4,6-trimethyl-7-oxonon-8-enoate (15a)

To a stirred solution of ester **14a** (102 mg, 0.185 mmol) in H_2O (0.2 mL) and CH_2Cl_2 (2 mL) was added DDQ (84 mg, 0.370 mmol) at 0 °C. After 2.5 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL). Then, aqueous saturated $NaHCO_3$ (5 mL) was added to the mixture. The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and dried ($MgSO_4$). After being concentrated, purification of the residue by flash chromatography (hexane:EtOAc = 3:1) afforded the desired primary alcohol (64 mg, 80%) as a colorless oil: $[\alpha]_D^{25.7}$ +19.2 (*c* 1.41, $CHCl_3$); IR (film): 3401.8, 2958.3, 1724.1, 1461.8, 1376.9, 1257.4, 1180.2, 1052.9, 929.5, 837.0 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.93 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 6.8 Hz, 3H), 0.90–1.00 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H), 1.27 (s, 3H), 1.40–1.80 (m, 5H), 2.25 (bs, 2H), 2.73 (quintet, J = 7.1, 1H), 3.37 (dd, J = 10.8, 5.1 Hz, 1H), 3.48 (dd, J = 10.8, 4.6 Hz, 1H), 3.88 (dd, J = 7.3, 2.4 Hz, 1H), 4.80 (dd, J = 10.0, 2.9 Hz, 1H), 5.16 (dd, J = 10.8, 1.0 Hz, 1H), 5.30 (dd, J = 17.3, 1.0 Hz, 1H), 5.90 (dd, J = 17.3, 10.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 140.4, 114.2, 80.6, 76.1, 74.7, 66.8, 42.9, 36.0, 34.5, 32.6, 26.0, 25.0, 22.8, 18.3, 18.0, 17.2, 15.5, 10.6, –3.9, –4.0; HRMS: m/z calcd for $C_{23}H_{47}O_5Si$ $(M + H)^+$, 431.3193; found, 431.3196.

To a solution of the primary alcohol (61.4 mg, 0.142 mmol) obtained as described in the previous procedure and CH_2Cl_2 (5 mL) was added the Dess-Martin periodinane (121 mg, 0.285 mmol) at 0 °C. The resulting solution was stirred for 1.5 h and was diluted with CH_2Cl_2 (10 mL). After the reaction was completed, aqueous saturated $NaHCO_3$ (10 mL) and aqueous saturated $Na_2S_2O_3$ (5 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 = 5:1) afforded the desired aldehyde (55 mg, 91%): $[\alpha]_D^{27.3}$ +32.7 (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (t, J = 7.4 Hz, 3H), 0.89 (s, 9H), 0.93 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 1.05–1.16 (m, 1H), 1.20 (d, J = 7.1 Hz, 3H), 1.24 (s, 3H), 1.42–1.75 (m, 3H), 1.86 (ddd, J = 13.7, 9.6, 3.6 Hz, 1H), 2.38–3.50 (m, 1H), 2.63 (bs, 1H), 2.74 (quintet, J = 7.3 Hz, 1H), 3.86 (dd, J = 7.8, 2.2 Hz, 1H), 4.79 (dd, J = 10.0, 2.9 Hz, 1H), 5.16 (dd, J = 10.8, 1.0 Hz, 1H), 5.32 (dd, J = 17.3, 1.0 Hz, 1H), 5.90 (dd, J = 17.3, 10.8 Hz, 1H), 9.54 (d, J = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.7, 176.1, 140.6, 114.0, 80.6, 76.3, 74.6, 44.0, 43.4, 36.3, 32.3, 26.0, 25.0, 22.8, 18.3, 17.2, 15.5, 14.8, 10.6, –3.8, –3.9.

To a stirred solution of the aldehyde (36.1 mg, 0.084 mmol) prepared as described in the previous procedure and THF (2 mL) was added vinylmagnesium bromide (1 M, 420 μL, 0.420 mmol) at 0 °C. After stirring for 20 min, the reaction mixture was diluted with Et_2O (5 mL) and saturated aqueous NH_4Cl solution (5 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 5 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography (hexane:EtOAc = 3:1) afforded the desired vinyl alcohol (32 mg, 76%) as a colorless oil.

To a stirred solution of the alcohol (16.7 mg, 0.0365 mmol) prepared as described in the previous procedure in CH_2Cl_2 (2 mL) was added Dess-Martin periodinane (31 mg, 0.073 mmol) at 0 °C. The resulting solution was stirred for 5 h and diluted with CH_2Cl_2 (5 mL). After the reaction was completed, aqueous saturated $NaHCO_3$ (10 mL) and aqueous saturated $Na_2S_2O_3$ (5 mL) were added. The resulting mixture was stirred and the organic layer was separated and washed with saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and finally dried ($MgSO_4$). Concentration followed by purification of the residue by flash chromatography (hexane:EtOAc = 10:1) afforded the desired vinyl ketone **15a** as a colorless oil (13.2 mg, 79%): $[\alpha]_D^{25.6}$ +25.9 (*c* 1.50, $CHCl_3$); IR (film): 3506.0, 2962.1, 1727.9, 1616.1, 1401.8, 1376.9, 1253.5, 1176.4, 1052.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 6H), 0.87 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.93 (d, J = 7.1 Hz, 3H), 1.20 (s, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.30–1.50 (m, 1H), 1.50–1.70 (m, 2H), 1.97 (ddd, J = 13.7, 10.8, 2.8 Hz, 1H), 2.82–3.10 (m, 1H), 3.36 (s, 1H), 3.84 (dd, J = 8.5, 1.5 Hz, 1H), 4.79 (dd, J = 9.6, 3.5 Hz, 1H), 5.16 (dd, J = 10.8, 1.3 Hz, 1H), 5.36 (dd, J = 17.3, 1.3 Hz, 1H), 5.82 (dd, J = 10.1, 1.6 Hz, 1H), 5.97 (dd, J = 17.3, 10.8 Hz, 1H), 6.29 (dd, J = 17.6, 1.5 Hz, 1H), 6.41 (dd, J = 17.6, 10.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.1, 176.4, 140.7, 135.4, 128.9, 113.9, 80.9, 76.5, 74.5, 43.3, 40.6, 36.4, 33.8, 26.1, 25.1, 23.1, 18.8, 18.4, 17.8, 16.0, 10.7, -3.7, -3.8.; HRMS: m/z calcd for $C_{25}H_{47}O_5Si$ $(M + H)^+$, 455.3193; found, 455.3193.

(*E*)-(3*R*,4*S*,5*S*,7*R*,11*S*,12*R*)-4-(*tert*-Butyldimethylsilanyloxy)-12-ethyl-3,5,7,11-tetramethyloxacyclododec-9-ene-2,8-dione (16a)

A flame-dried round-bottomed flask was charged with a solution of vinyl ketone **15a** (16.0 mg, 35.2 μmol) in CH_2Cl_2 (7 mL). Grubbs' Catalyst (2nd-Generation) (3.0 mg, 3.52 μmol) was

subsequently added as a solid, producing a light brown solution, which was stirred for 12 h at room temperature. The mixture was then concentrated to give a dark brown oil. Purification of this residue by flash chromatography (hexane:EtOAc = 7:1) afforded the lactone **16a** (13.6 mg, 90%) as a white solid: mp 184.2–186.5 °C; $[\alpha]_D^{23.7}$ +75.5 (*c* 1.45, $CHCl_3$); IR (film): 3397.0, 2969.8, 1727.9, 1681.6, 1630.5, 1461.8, 1251.6, 1088.6, 1056.8, 973.9, 836.0, 774.3 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85–1.00 (ovlp m, 15H), 1.20 (d, $J = 6.9$ Hz, 3H), 1.24 (d, $J = 7.0$ Hz, 3H), 1.34 (s, 3H), 1.28–1.36 (m, 1H), 1.40–1.70 (m, 3H), 1.89–1.97 (m, 1H), 2.11 (s, 1H), 2.50–2.67 (ovlp m, 2H), 3.64 (d, $J = 10.0$ Hz, 1H), 4.75 (dd, $J = 2.0$, 10.7 Hz, 1H), 6.34 (d, $J = 15.9$ Hz, 1H), 6.59 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.2, 175.4, 148.7, 125.6, 79.0, 76.5, 76.1, 74.4, 45.0, 44.4, 34.4, 33.4, 26.2, 21.2, 19.4, 18.5, 18.4, 17.7, 17.3, 10.6, −3.1, −3.3; HRMS: m/z calcd for $C_{23}H_{43}O_5Si$ $(M + H)^+$, 427.2880; found, 427.2878.

Methynolide (2a)

To a stirred solution of lactone **16a** (3.4 mg, 0.0079 mmol) in dry THF (1 mL) at room temperature was added 1.0 M TBAF (200 μL, 0.200 mmol) *via* a syringe. After 2.5 h, the reaction mixture was concentrated. Purification by flash chromatography (hexane:EtOAc = 1:2) afforded methynolide (**2a**) (1.9 mg, 77%) as a white solid: mp 164.0–167.2 °C; $[\alpha]_D^{21.7}$ +74.9 (*c* 0.07, $CHCl_3$); IR (film): 3428.8, 2966.0, 1724.1, 1627.6, 1457.9, 1373.1, 1272.8, 1160.9, 987.4 cm^{-1}: 3428.8, 2965.0, 1724.1, 1627.6, 1457.9, 1373.1, 1272.8, 1160.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.91 (t, $J =$ 7.4 Hz, 3H), 1.01 (d, $J = 5.9$ Hz, 3H), 1.25–1.40 (m, 1H), 1.21 (d, $J = 7.0$ Hz, 3H), 1.33 (d, $J = 6.8$ Hz, 3H), 1.38 (s, 3H), 1.46–1.67 (m, 3H), 1.94 (s, broad, 1H), 1.94 (ddq, $J = 14.0$, 7.5, 2.0 Hz, 1H), 2.50–2.66 (m, 2H), 3.58 (brd, $J = 10.5$ Hz, 1H), 4.78 (dd, $J = 11.0$, 2.0 Hz, 1H), 6.34 (d, $J = 15.9$ Hz, 1H), 6.59 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.9, 174.8, 148.6, 125.5, 78.0, 76.5, 74.5, 45.2, 43.5, 33.4, 33.1, 21.2, 19.5, 17.6, 17.4, 16.5, 10.7; HRMS: m/z calcd for $C_{17}H_{28}O_5$, 312.1937; found, 312.1937.

2-*O*-Acetyl-3-dimethylamino-3,4,6-trideoxy-α-D-xylohexopyranosyl trichloroacetimidate (23)

To a solution of **22** (27 mg, 0.12 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added Cl_3CCN (149 μL, 1.49 mmol) and DBU (5.00 μL, 0.036 mmol). After stirring for 1 h at 0 °C, the reaction mixture was concentrated. Purification by flash chromatography (EtOAc:MeOH = 10:1) afforded the desired trichloroacetimidate **23** (α:β = 1:1, 24 mg, 56%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (d, $J = 6.2$ Hz, 3H), 1.29 (d, $J = 6.1$ Hz, 3H), 1.46 (m, 2H), 1.82 (m, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.10 (m, 1H), 2.28 (s, 6H), 2.29 (s, 6H), 2.83 (m, 1H), 3.24 (m, 1H), 3.76 (dddd, $J = 10.8$, 6.2, 6.2, 6.2 Hz, 1H), 4.11 (m, 1H), 5.06 (m, 2H), 5.70 (d, $J = 7.7$ Hz, 1H), 6.38 (d, $J = 3.4$ Hz, 1H), 8.49 (s, 1H), 8.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 169.6, 161.4, 161.3, 97.7, 94.9, 91.3, 90.8, 70.6, 69.6, 69.4, 67.6, 62.9, 57.6, 40.6, 40.4, 31.7, 30.4, 21.1, 21.0, 21.0.

Methymycin (1)

To a solution of trichloroacetimidate **23** (13. 7mg, 0.038 mmol) and methynolide (**2a**) (6 mg, 0.019 mmol) in CH_2Cl_2 (2 mL) was added molecular sieves (200 mg), and the reaction was stirred for 30 min at room temperature. After 30 min the mixture was cooled to −20 °C and then $BF_3{\cdot}OEt_2$ (3.5 μL, 0.0247 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 protected methymycin **24** (4.2 mg, 43%) as a colorless oil. $[\alpha]_D^{27.0}$ +50.2 (*c* 0.17, $CHCl_3$); IR (film): 3453.9, 2925.9, 2854.1, 1731.8, 1692.2, 1628.6, 1459.9, 1373.1, 1238.1, 1162.9, 1109.8, 1059.7, 989.3, 903.5 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (t, $J = 7.4$ Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 1.18 (d, $J = 7.0$ Hz, 3H), 1.23 (d, $J = 6.1$ Hz, 3H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.37 (s, 3H) 1.43 (m, 1H), 1.73 (bd, $J = 11.4$ Hz, 1H), 1.93 (ddd, $J = 14.1$, 7.6, 2.3 Hz, 1H), 2.03 (s, 1H), 2.08 (s, 3H), 2.26 (s, 6H), 2.55 (m, 1H), 2.71 (m, 2H), 3.47 (m, 1H), 3.55 (d, $J = 10.3$ Hz, 1H), 4.31 (d, $J = 7.6$ Hz, 1H), 4.77 (m, 2H), 6.34 (d, $J = 16.0$ Hz, 1H), 6.57 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.3, 174.9, 169.9, 148.3, 125.9, 102.9, 85.3, 74.5, 71.6, 69.1, 63.5, 45.1, 44.1, 40.6, 33.7, 33.5, 30.4, 29.7, 21.4, 21.0, 19.5, 17.6, 17.3, 16.0, 10.7; HRMS: m/z calcd for $C_{27}H_{46}NO_8$ $(M + H)^+$, 512.3223; found, 512.3226.

To a stirred solution of **24** (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 methymycin (**1**) (3.5 mg, 91%) as a colorless oil. $[\alpha]_D^{24.9}$ +79.7 (*c* 0.11, $CHCl_3$); IR (film): 3432.7, 2924.5, 2852.2, 2345.0, 2081.8, 1729.8, 1686.4, 1631.5, 1461.8, 1376.9, 1268.0, 1161.9 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.4$ Hz, 3H), 1.02 (d, $J = 6.7$ Hz, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 1.23 (d, $J = 6.1$ Hz, 3H), 1.37 (s, 3H), 1.44 (d, $J = 6.9$ Hz, 3H), 1.51 (m, 2H), 1.67 (m, 1H), 1.92 (ddd, $J = 14.1$, 7.6, 2.2 Hz, 1H), 2.28 (s, 6H), 2.50 (m, 1H), 2.56 (m, 1H), 2.87 (m, 1H), 3.22 (dd, $J = 10.2$, 7.4 Hz, 1H), 3.48 (m, 1H), 3.61 (d, $J = 10.4$ Hz, 1H), 4.24 (d, $J = 7.3$ Hz, 1H), 4.75 (dd, $J = 10.8$, 2.2 Hz, 1H), 6.35 (d, $J = 15.9$ Hz, 1H), 6.59 (d, $J = 15.9$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.4, 175.2, 148.4, 125.8, 105.0, 85.5, 76.2, 74.5, 70.3, 69.5, 65.9, 45.1, 44.2, 40.2, 33.9, 33.6, 29.7, 21.3, 21.1, 19.5, 17.6, 17.4, 16.2, 10.7; HRMS: m/z calcd for $C_{25}H_{44}NO_7$ $(M + H)^+$, 470.3118; found, 470.3121.

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