Total Synthesis of Methymycin

Hong-Se Oh, Richeng Xuan and Han-Young Kang*

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

hykang@chungbuk.ac.kr

Supplementary Information

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**General Methods**

$^1$H 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 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 diethylamide was distilled before use. Flash chromatography was carried out on Woelm 32-64 μm silica packed in glass columns.
Experimental Section

(2R)-1-Benzylxoy-2-(methoxymethoxy)butane (4)

To a solution of (2R)-1-benzyloxybutan-2-ol (3) (1.70 g, 9.43 mmol) obtained as described in the previous procedure in CH₂Cl₂ (20 mL) was added N,N-diisopropylethylamine (10.1 mL, 56.6 mmol) at 0 °C. The resulting solution was stirred for 30 min at 0 °C, and to this solution was added the chloromethylmethyl ether (2.14 mL, 28.3 mmol). After stirred for 10 min at 0 °C and the solution was warmed to room temperature, stirred for 16 h. After the reaction was completed, saturated aqueous NH₄Cl solution (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The organic solutions were combined, dried (MgSO₄), and concentrated. Purification of the residue by flash chromatography (hexane:EtOAc=7:1) afforded (2R)-1-Benzylxoy-2-(methoxymethoxy)butane (4) (1.69 g, 80%) as a colorless oil: [α]D²⁵ 19.6 (c 1.62, CHCl₃); IR (film): 2932.2, 1723.1, 1455.0, 1365.4, 1273.8, 1210.1, 1103.1, 1040.4, 918.9, 846.6 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.99 (t, J = 7.5 Hz, 3H), 1.72~1.55 (m, 2H), 3.42 (s, 3H), 3.55 (d, J = 5.0 Hz, 2H), 3.76 (m, 1H), 4.58 (s, 2H), 4.72 (d, J = 6.8 Hz, 1H), 4.81 (d, J = 6.8 Hz, 1H), 7.38~7.27 (m, 5H); ¹³C NMR (75 MHz, CDCl₃): δ 138.3, 128.2, 127.5, 127.4, 95.9, 77.4, 73.2, 72.3, 55.3, 24.8, 9.7; HRMS: m/z calcd for C₁₃H₂₁O₃(M+H)+, 225.1491, found: 225.1486.

(2R)-2-(Methoxymethoxy)butan-1-ol (5)

A solution of (2R)-1-benzyloxy-2-(methoxymethoxy)butane (4) (1.69 g, 7.53 mmol) in MeOH (30 mL) was stirred under hydrogen (1 atm, balloon) at room temperature in the presence of 5% palladium on charcoal (3.4 g). The resulting mixture was stirred at room temperature for 18 h. After filtration through a pad of Celite with ether (3 × 30 mL), the solution was concentrated.
Purification by flash chromatography (pentane:ether = 1:1) afforded the alcohol 5 (1.01 g, 92%) as a colorless oil: \([\alpha]_D^{26.6} \ 66.1 \ (c \ 1.36, \ CHCl_3)\); IR (film): 3419.2, 2936.1, 1648.8, 1463.7, 1214.0, 1038.5, 918.0, 836.0, 419.4 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta \ 0.87 \ (t, \ J = 7.5 \ Hz, \ 3H), \ 1.52\text{-}1.40 \ (m, \ 2H), \ 3.16 \ (s, \ 1H), \ 3.33 \ (s, \ 1H), \ 3.45 \ (m, \ 2H), \ 3.53 \ (m, \ 1H), \ 4.67 \ (dd, \ J = 17.0, \ 6.9 \ Hz, \ 2H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta \ 96.5, \ 82.5, \ 64.8, \ 55.3, \ 24.3, \ 9.7\); HRMS: m/z calcd for C\(_6\)H\(_{15}\)O\(_3\)(M+H)+, 135.1021, found:135.1025

\((4R)\)-4-(Methoxymethoxy)hex-1-en-3-one (7)

\[
\begin{align*}
\text{OH} & \quad \text{(COCl)}_2, \text{DMSO, Et}_3\text{N} \\
\text{OMOM} & \quad \text{CH}_2\text{Cl}_2, -78 ^\circ\text{C} \\
5 & \quad \text{1) VinylMgBr, THF, - 0 ^\circ\text{C}} \\
& \quad \text{2) Swern oxidation} \\
\text{OMOM} & \quad \text{CH}_2\text{Cl}_2, -78 ^\circ\text{C} \\
6 & \quad \text{OMOM} \\
7 & \quad \text{OMOM}
\end{align*}
\]

A flame-dried round-bottomed flask was charged with a solution of oxalyl chloride (4.20 mL, 48.1 mmol) in CH\(_2\)Cl\(_2\) (30 mL) at -78 °C. The mixture was added dimethyl sulfoxide (3.94 mL, 55.5 mmol) at -78 °C. This mixture was stirred for 30 min before alcohol 5 (1.66 g, 12.3 mmol) in CH\(_2\)Cl\(_2\) (6 mL) was added. After 10 min, the reaction mixture was added triethylamine (25.8 mL, 185 mmol) and stirred for 10 min. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with ether (40 mL) and saturated aqueous NH\(_4\)Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 40 mL), and washed with saturated aqueous NaCl (50 mL). The organic solutions were combined, dried (MgSO\(_4\)), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired vinyl alcohol (791 mg, 40%, 2 steps) as a colorless oil.

To a stirred solution of the aldehyde 6 (1.63 g, 12.3 mmol) prepared as described in the previous procedure and THF (30 mL) was added vinylmagnesium bromide (1.00 M, 24.7 mL, 24.7 mmol) at 0 °C. After stirred for 1 h, the reaction mixture was diluted with ether (10 mL) and saturated aqueous NH\(_4\)Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The organic solutions were combined, dried (MgSO\(_4\)), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired vinyl alcohol (791 mg, 40%, 2 steps) as a colorless oil.

A flame-dried round-bottomed flask was charged with a solution of oxalyl chloride (1.03 mL, 11.9 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at -78 °C. The mixture was added dimethyl sulfoxide (0.95 mL,
13.3 mmol) at -78 °C. This mixture was stirred for 30 min before the vinyl alcohol (791 mg, 4.95 mmol), which was prepared as described in the previous procedure, in CH₂Cl₂ (3 mL) was added. After 10 min, the reaction mixture was added N,N-disopropyl ethylamine (4.41 mL, 24.7 mmol) and stirred for 10 min. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with ether (40 mL) and saturated aqueous NH₄Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL), and washed with saturated aqueous NaCl (50 mL). The organic solutions were combined, dried (MgSO₄), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired vinyl ketone 7 (578 mg, 74%) as a colorless oil: [α]D^24.4 66.1 (c 1.36, CHCl₃); IR (film): 2938.0, 1700.9, 1614.1, 1462.7, 1403.0, 1159.0, 1103.1, 919.9 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.97 (t, J = 7.4 Hz, 3H), 1.76 (m, 2H), 3.34 (s, 3H), 3.33 (s, 1H), 4.13 (J = 6.5 Hz, 1H), 4.66–4.59 (dd, J = 14.0, 6.9 Hz, 2H), 6.40–5.79 (ddd, J = 17.4, 10.5, 1.6 Hz, 2H), 6.71–6.62 (dd, J = 17.4, 10.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 200.0, 131.9, 129.3, 96.2, 82.4, 56.0, 25.4, 9.5.

(3S, 4R)-4-(Methoxymethoxy)-3-methylhex-1-en-3-ol (8)

To a stirred solution of vinyl ketone 7 (578 mg, 3.65 mmol) in THF (15 mL) was added methylmagnesium bromide (3 M, 1.83 mL, 5.49 mmol) at -78 °C. After stirred for 1 h, the reaction mixture was diluted with Et₂O (10 mL) and saturated aqueous NH₄Cl 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 (MgSO₄), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired alcohol 8 (625 mg, 98%) as a colorless oil: [α]D^24.9 -23.4 (c 1.50, CHCl₃); IR (film): 3449.1, 2967.9, 1716.3, 1641.1, 1462.7, 1367.3, 1103.1, 1034.6, 920.8 (film): cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.97 (t, J = 7.4 Hz, 3H), 1.20 (s, 3H), 1.66–1.34 (m, 2H), 3.23–3.19 (dd, J = 9.9, 2.7 Hz, 1H), 3.40 (s, 3H), 3.72 (s, 1H), 4.64 (d, J = 6.8 Hz, 1H), 4.76 (d, J = 6.8 Hz, 1H), 5.32–5.11 (ddd, J = 17.3, 10.7, 1.6 Hz, 2H), 6.00–5.90 (dd, J = 17.3, 10.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 141.1, 113.5, 99.0, 91.9, 74.5, 56.0, 24.5, 24.2, 11.0; HRMS: m/z calcd for C₇H₁₄O₂(M+H-H₂O)^+ 157.1229, found:157.1235.
To a stirred solution of alcohol 8 (625 mg, 3.59 mmol) in dry THF (3 mL) at room temperature was added 6 N HCl (3 mL). After stirred for 2 h, the reaction mixture was diluted with ether (10 mL) and aqueous saturated NaHCO₃ (10 mL). The layers were then separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), and dried (MgSO₄). After being concentrated, purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired diol 9 (322 mg, 69%) as a colorless oil: [α]D²⁴⁺ 18.5 (c 1.28, CHCl₃); IR (film): 3427.9, 2974.7, 2878.2, 1644.0, 1456.0, 1414.5, 1099.2, 976.8, 922.8, 883.2 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.96 (t, J = 7.4 Hz, 3H), 1.21 (s, 3H), 1.57~1.11 (m, 2H), 2.93 (s, 2H), 3.26 (dd, J = 10.5, 2.2 Hz, 1H), 5.26~5.08 (ddd, J = 10.8, 10.0, 1.3 Hz, 2H), 5.91~5.81 (dd, J = 17.4, 10.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 140.7, 114.3, 79.7, 75.5, 24.5, 24.1, 11.1, 10.8; HRMS: m/z calcd for C₇H₁₃O(M+H-H₂O)+, 113.0966, found:113.0965.

A flame-dried round-bottomed flask was charged with a solution of oxalyl chloride (2.54 mL, 29.1 mmol) in CH₂Cl₂ (20 mL) at -78 °C. To the mixture was added dimethyl sulfoxide (2.38 mL, 33.5 mmol) at -78 °C. This mixture was stirred for 30 min before alcohol 5 (1.00 g 7.45 mmol) in CH₂Cl₂ (5 mL) was added. After stirred for 10 min, triethylamine (15.6 mL, 111.8 mmol) was added to the reaction mixture and the resulting mixture was stirred for 10 min. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with ether (30 mL) and saturated aqueous NH₄Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL), and washed with saturated aqueous NaCl (40 mL). The organic solutions were combined, dried (MgSO₄), and
concentrated to provide the desired aldehyde 6 which was used for the next step without further purification.

To a stirred solution of the aldehyde 6, which was prepared as described in the previous procedure, in THF (20 mL) was added methylmagnesium bromide (3 M, 7.45 mL, 22.4 mmol) at 0 °C. The reaction mixture was stirred for 1 h before it was diluted with ether (10 mL). To this, then, was added a saturated aqueous NH₄Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The organic solutions were combined, dried (MgSO₄), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired alcohol (376 mg, 34%, 2 steps) as a colorless oil.

A flame-dried round-bottomed flask was charged with a solution of oxalyl chloride (0.861 mL, 9.87 mmol) in CH₂Cl₂ (10 mL) at -78 °C. To the mixture was added dimethyl sulfoxide (0.808 mL, 11.4 mmol) at -78 °C. This mixture was stirred for 30 min before the alcohol (376 mg, 2.53 mmol), which was prepared in the previous step, in CH₂Cl₂ (3 mL) was added. After 10 min, the reaction mixture was added triethylamine (5.29 mL, 38.0 mmol) and stirred for 10 min. The mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was diluted with ether (10 mL) and saturated aqueous NH₄Cl solution (10 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 20 mL), and washed with saturated aqueous NaCl (30 mL). The organic solutions were combined, dried (MgSO₄), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired methyl ketone 10 (296 mg, 80%) as a colorless oil: [α]D<sub>24</sub> 45.2 (c 1.13, CHCl₃); IR (film): 2938.0, 1716.3, 1463.7, 1354.8, 1215.9, 1155.2, 1122.4, 1035.6, 918.9 cm⁻¹; <sup>1</sup>H NMR (300 MHz, CDCl₃): δ 0.97 (t, J = 7.4 Hz, 3H), 1.75~1.65 (m, 2H), 2.15 (s, 3H), 3.37 (s, 3H), 3.93 (t, J = 6.2 Hz, 1H), 4.67 (m, 1H); <sup>13</sup>C NMR (75 MHz, CDCl₃): δ 209.9, 96.3, 83.8, 55.9, 26.0, 25.0, 9.5.

(3R, 4R)-4-(Methoxymethoxy)-3-methylhex-1-en-3-ol (11)

![Chemical structure](image)

To a stirred solution of methyl ketone 10 (296 mg, 2.02 mmol), prepared as described in the
previous procedure, in THF (10 ml) was added vinylmagnesium bromide (1.0 M, 3.03 mL, 3.03 mmol) at -78 °C. After stirred for 1 h, the reaction mixture was diluted with Et₂O (10 mL) and saturated aqueous NH₄Cl 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 (MgSO₄), and concentrated. Purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired alcohol 11 (218 mg, 62%) as a colorless oil: [α]D^26.2 - 19.3 (c 1.18, CHCl₃); IR (film): 3449.1, 2967.9, 1642.7, 1367.3, 1103.1, 1034.6, 920.8 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.97 (t, J = 7.4 Hz, 3H), 1.18 (s, 3H), 1.63–1.27 (m, 2H), 3.17–3.13 (dd, J = 9.6, 2.7 Hz, 1H), 3.40 (s, 3H), 3.45 (s, 1H), 4.62 (d, J = 6.7 Hz, 1H), 4.75 (d, J = 6.7 Hz, 1H) 5.34–5.06 (ddd, J = 17.3, 10.7, 1.5 Hz, 2H), 5.87–5.78 (dd, J = 17.3, 10.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 142.5, 113.8, 98.8, 90.1, 74.5, 55.9, 24.0, 21.8, 11.0; HRMS: m/z calcd for C₉H₁₇O₂(M+H-H₂O)+, 157.1229, found:157.1231.

(3R, 4R)-3-Methylhex-1-ene-3,4-diol (12)

\[
\begin{align*}
\text{OMOM} & \quad \text{6N HCl:THF=1:1} \\
\text{11} & \quad \text{OH} \\
\end{align*}
\]

To a stirred solution of alcohol 11 (218 mg, 1.25 mmol) in dry THF (2 mL) at room temperature was added 6 N HCl (2 mL). After 2 h, the reaction mixture was diluted with ether (10 mL), then to this mixture was added aqueous saturated NaHCO₃ (5 mL). The layers were then separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), and dried (MgSO₄). After being concentrated, purification of the residue by flash chromatography (pentane:ether = 1:1) afforded the desired diol 12 (86 mg, 53%) as a colorless oil: [α]D^24.7 15.7 (c 0.61, CHCl₃); IR (film): 3406.6, 2975.6, 2878.2, 1643.1, 1458.9, 1414.5, 1094.4, 975.8, 923.7 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.03 (t, J = 7.4 Hz, 3H), 1.23 (s, 3H), 1.63–1.28 (m, 2H), 2.22 (s, 2H), 3.34 (d, J = 10.0 Hz, 1H), 5.36–5.15 (ddd, J = 17.4, 10.8, 1.2 Hz, 2H), 5.96–5.86 (dd, J = 17.4, 10.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 142.7, 114.2, 78.7, 75.5, 23.7, 21.4, 11.1; HRMS: m/z calcd for C₇H₁₃O(M+H-H₂O)+, 113.0966, found:113.0968.

(1R,2R)-1-Ethyl-2-hydroxy-2-methylbut-3-enyl-(2R,3S,4S,6R)-3-(tertbutyldimethylsilanyloxy)-7-(4-methoxybenzyloxy)-2,4,6-trimethylheptanoate (14b)
To a solution of carboxylic acid 13 (56 mg, 0.13 mmol) in THF (2 mL) at room temperature were added triethylamine (27 µL, 0.19 mmol) and 2,4,6-trichlorobenzoyl chloride (25 µL, 0.16 mmol). The mixture was stirred for 3 h at room temperature, and the solids were filtered off and washed with hexane (5 mL). The combined solution was concentrated under reduced pressure. The residue was dissolved in benzene (2 mL), and to this solution a solution of alcohol 12 (20 mg, 0.15 mmol) and DMAP (22 mg, 0.18 mmol) in benzene (2 mL) was added. After being stirred for 16 h, the reaction mixture was diluted with ether (10 ml), and washed with saturated NaHCO₃ (5 mL) and saturated NaCl (5 mL), dried (MgSO₄), and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc = 4:1) afforded the desired ester 14b (57 mg, 81%) as a colorless oil: \([\alpha]_D^{22.3} 16.8 (c 1.17, \text{CHCl}_3); \text{IR (film)}: 3449.1, 2956.3, 1731.8, 1613.2, 1513.9, 1461.8, 1248.7, 1172.5, 1058.7, 836.0, 774.3 \text{ cm}^{-1}; \text{^1H NMR (300 MHz, CDCl}_3):} \delta 0.05 (s, 6H), 0.89 (m, 21H), 1.17 (d, \text{ } J = 7.1 \text{ Hz, 3H}), 1.21 (m, 3H), 1.40 (m, 2H), 1.70 (m, 2H), 1.81 (dddd, \text{ } J = 13.1, 6.6, 6.6, 6.6 \text{ Hz, 1H}), 2.29 (s, 1H), 2.62 (dddd, \text{ } J = 13.8, 6.9, 6.9 \text{ Hz, 1H}), 3.21 (dddd, \text{ } J = 32.0, 9.0, 5.6 \text{ Hz, 2H}), 3.80 (s, 3H), 3.89 (dd, \text{ } J = 5.6, 3.1 \text{ Hz, 1H}), 4.42 (d, \text{ } J = 12.5 \text{ Hz, 2H}), 4.78 (dd, \text{ } J = 10.0, 2.8 \text{ Hz, 1H}), 5.10 (d, \text{ } J = 10.7 \text{ Hz, 1H}), 5.32 (d, \text{ } J = 17.3 \text{ Hz, 1H}), 5.89 (dd, \text{ } J = 17.2, 10.7 \text{ Hz, 1H}), 6.87 (d, \text{ } J = 8.5 \text{ Hz, 2H}), 7.26 (d, \text{ } J = 8.5 \text{ Hz, 2H}); \text{^13C NMR (75 MHz, CDCl}_3):} \delta 176.1, 159.0, 142.8, 130.7, 129.1, 113.6, 113.5, 79.8, 75.4, 75.0, 72.6, 55.2, 42.1, 36.9, 36.3, 31.0, 26.0, 23.3, 22.3, 18.5, 16.6, 14.6, 10.6, -4.1, -4.2; \text{HRMS: m/z calcld for C}_{31}H_{55}O_6Si(M+H)^+, 551.3768, found: 551.3766.}

(1R,2R)-1-Ethyl-2-hydroxy-2-methyl-but-3-enyl (2R,3S,4S,6R)-3-(tertbutyldimethylsilanyloxy)-2,4,6-trimethyl-7-oxonon-8-enoate (15b)
To a stirred solution of ester 14b (54 mg, 0.098 mmol) in H2O (0.3 mL) and CH2Cl2 (3 mL) was added the DDQ (45 mg, 0.196 mmol) at 0 °C. After 2.5 h, the reaction mixture was diluted with CH2Cl2 (5 mL), then to this mixture was added aqueous saturated NaHCO3 (5 mL). The layers were then separated and the aqueous layer was extracted with CH2Cl2 (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaHCO3 (5 mL), water (5 mL), and dried (MgSO4). After being concentrated, purification of the residue by flash chromatography (hexane:EtOAc = 3:1) afforded the desired primary alcohol (39 mg, 93%) as a colorless oil: [α]D26 -26.6 21.4 (c 1.09, CHCl3); IR (film): 3374.8, 2929.3, 1731.8, 1461.8, 1375.0, 1253.5, 1176.4, 1057.8, 836.0, 774.3 cm\(^{-1}\); 1H NMR (300 MHz, CDCl3): δ 0.08 (s, 6H), 0.90 (m, 21H), 1.19 (d, J = 7.1 Hz, 3H), 1.24 (s, 3H), 1.61 (m, 6H), 2.22 (dddd, J = 14.3, 7.1, 7.1, 7.1 Hz, 1H), 3.42 (dddd, J = 45.6, 10.8, 10.8 Hz, 2H), 3.86 (dd, J = 7.3, 2.2 Hz, 1H), 4.79 (dd, J = 10.2, 2.5 Hz, 1H), 5.13 (d, J = 10.7 Hz, 1H), 5.33 (d, J = 17.3 Hz, 1H), 5.91 (dd, J = 17.3, 10.7 Hz, 1H); 13C NMR (75 MHz, CDCl3): δ 176.8, 142.4, 113.9, 80.1, 75.9, 75.0, 66.9, 42.8, 35.9, 34.6, 32.6, 29.7, 26.0, 22.7, 22.3, 18.4, 18.0, 17.1, 15.7, 10.7, -4.0, -4.0; HRMS: m/z calcd for C23H47O5Si (M+H)+: 431.3193, found: 431.3197.

To a solution of the primary alcohol (35.0 mg, 0.081 mmol) obtained as described in the previous procedure and CH2Cl2 (4 mL) was added Dess-Martin periodinane (68.9 mg, 0.162 mmol) at 0 °C. The resulting solution was stirred for 1.5 h and was diluted with CH2Cl2 (10 mL). After the reaction was completed, aqueous saturated NaHCO3 (10 mL) and aqueous saturated Na2S2O3 (5 mL) were added. The resulting mixture was stirred and the organic layer was extracted and washed with saturated aqueous NaHCO3 (10 mL), water (10 mL), dried (MgSO4), and concentrated. Purification of the residue by flash chromatography (hexane:EtOAc = 5:1) afforded the desired aldehyde (27 mg, 79%): 1H NMR (300 MHz, CDCl3): δ 0.07 (s, 6H), 0.88 (m, 3H), 0.90 (s, 9H), 0.93 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 7.1 Hz, 3H), 1.25 (s, 3H), 1.63 (m, 3H), 1.86 (dddd, J = 13.8, 9.5, 3.7 Hz, 1H), 2.43 (m, 2H), 2.72 (ddddd, J = 14.5, 7.3, 7.3 Hz, 1H), 3.85 (dd, J = 7.8, 2.3 Hz, 1H), 4.80 (dd, J = 10.1, 2.8 Hz, 1H), 5.11 (d, J = 11.4 Hz, 1H), 5.32 (dd, J = 17.3 Hz, 1H), 5.90 (dd, J = 17.3, 10.8 Hz, 1H), 9.56 (d, J = 2.2 Hz, 1H); 13C NMR (75 MHz, CDCl3): δ 205.8, 176.0, 142.5, 113.7, 80.1, 76.4, 75.0, 44.1, 43.4, 36.2, 32.3, 26.1, 22.8, 22.5, 18.4, 17.2, 15.5, 14.8, 10.6, -3.9, -3.9.

To a stirred solution of the aldehyde (27 mg, 0.063 mmol) prepared as described in the previous procedure and THF (5 ml) was added vinylmagnesium bromide (1 M, 94 µL, 0.094 mmol) at 0 °C. After stirred for 1 h, the reaction mixture was diluted with Et2O (5 mL) and saturated aqueous NH4Cl 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 (MgSO₄), and concentrated. Purification of the residue by flash chromatography (hexane:EtOAc = 3:1) afforded the desired vinyl alcohol (22.7 mg, 79%) as a colorless oil.

To a stirred solution of the alcohol (22.7 mg, 0.050 mmol), which was prepared as described in the previous procedure, in CH₂Cl₂ (3 mL) was added Dess-Martin periodinane (42 mg, 0.099 mmol) at 0 °C. The resulting solution was stirred for 2 h and diluted with CH₂Cl₂ (5 mL). After the reaction was completed, aqueous saturated NaHCO₃ (10 mL) and aqueous saturated Na₂S₂O₃ (5 mL) were added. The resulting mixture was stirred and the organic layer was separated and washed with saturated aqueous NaHCO₃ (5 mL), water (5 mL), and finally dried (MgSO₄). Concentration followed by purification of the residue by flash chromatography (hexane:EtOAc = 10:1) afforded the desired vinylketone 15b as a colorless oil (22 mg, 97%): [α]D²⁶ -16.5 (c 1.79, CHCl₃); IR (film): 3486.7, 2928.4, 2856.1, 1730.8, 1612.2, 1461.8, 1377.9, 1255.4, 1174.4, 1055.8, 837.0, 775.2 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.06 (s, 6H), 0.88 (m, 3H), 0.90 (s, 9H), 1.12 (d, J = 7.1 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3H), 1.25 (m, 3H), 1.29 (s, 3H), 1.38 (m, 2H), 1.63 (m, 3H), 1.93 (m, 3H), 2.84 (m, 1H), 2.94 (m, 1H), 3.18 (s, 1H), 3.81 (d, J = 8.2 Hz, 1H), 4.81 (dd, J = 9.8, 2.7 Hz, 1H), 5.06 (d, J = 10.8 Hz, 1H), 5.27 (d, J = 17.3 Hz, 1H), 5.87 (m, 2H), 6.37 (m, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 205.1, 176.3, 142.7, 135.3, 128.9, 113.6, 80.2, 76.7, 74.7, 43.3, 40.8, 36.2, 33.8, 29.7, 26.1, 22.6, 18.8, 18.4, 17.6, 15.8, 10.7, -3.8, -3.8.; HRMS: m/z calcd for C₂₅H₄₇O₅Si(M+H)+, 455.3193, found: 455.3196.


A flame-dried round-bottomed flask was charged with a solution of vinylketone 15b (4.7 mg, 0.0097 mol) in CH₂Cl₂ (3 mL). Grubbs Catalyst (2nd-Generation) (0.4 mg, 0.48 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 = 5:1) afforded the lactone 16b (3.5 mg, 85%) as a white solid: mp 194.0–196.0 °C; [α]D²⁶ 73.8 (c 1.45, CHCl₃); IR (film): 3397.0,
epi-Methynolide (2b)

To a stirred solution of lactone 16b (3.5 mg, 0.0082 mmol) in dry THF (1 mL) at room temperature was added 1.0 M TBAF (80 µL, 0.082 mmol) via a syringe. After 2.5 h, the reaction mixture was concentrated. Purification by flash chromatography (hexane:EtOAc = 1:2) afforded epi-methynolide (2b) (2.0 mg, 78%) as a white solid: mp 163.5~166.0 °C; [α]D26 74.7 (c 0.20, CHCl3); IR (film): 3446.2, 2969.8, 2936.1, 1707.7, 1686.4, 1632.5, 1458.9, 1375.0, 1312.3, 1153.2, 1080.9, 994.1 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 0.91 (t, J = 7.4 Hz, 3H), 1.01 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.33 (d, J = 7.0 Hz, 3H), 1.37 (s, 3H), 1.32-1.52 (m, 2H), 1.48-1.68 (m, 2H), 1.74-1.84(m, 2H), 1.95 (s, 1H), 2.56 (dd, J = 7.1, 6.9, 3.6 Hz, 1H)), 2.67(dq, J = 10.4, 6.8 Hz, 1H), 3.57(dd, J = 10.4, 5.6 Hz, 1H)), 4.85(dd, J = 8.3, 5.7 Hz, 1H)), 6.46(d, J = 15.4 Hz, 1H), 6.67 (d, J = 15.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl3): δ 204.9, 174.4, 148.0, 124.6, 77.9, 76.6, 75.4, 45.2, 43.4, 33.2, 33.1, 20.4, 19.3, 17.4, 6.3, 16.6, 10.0; HRMS: m/z calcd for C₁₇H₂₃O₆Si(M+H)+, 312.1937, found: 312.1945.

Methyl 2,3-anhydro-4,6-dideoxy-α-D-ribo-hexopyranoside (18)
To a solution of diol 17 (1.79 mg, 11.04 mmol) in benzene (30 mL) at room temperature were added PPh₃ (4.34 g, 16.56 mmol) and DEAD (40% in toluene, 7.2 mL, 16.56 mmol). The resulting solution was stirred for 30 min at room temperature before it was warmed to 100 °C. After additional stirring for 16 h at 100 °C, the solution was cooled to room temperature. After 30 min, the reaction mixture benzene was evaporated and concentrated. Purification of the residue by flash chromatography (pentane:Et₂O=1:1) afforded the epoxide 18 (1.41 mg, 89 %) as a colorless oil: [α]D²⁵ 74.2 (c 0.80, CHCl₃); IR (film): 2974.6, 1445.4, 1394.3, 1258.3, 1192.8, 1160.9, 1132.0, 1069.3, 1029.8, 981.6, 945.6 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.03 (d, J = 8.9 Hz, 3H), 1.48 (dd, J = 14.5, 11.1 Hz, 1H), 1.93 (d, J = 14.6 Hz, 1H), 3.22 (t, J = 3.6 Hz, 1H), 3.26 (s, 1H), 3.34 (s, 3H), 3.78 (m, 1H), 4.81 (d, J = 3.2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 95.3, 60.0, 55.0, 50.8, 50.5, 32.1, 20.4; HRMS: m/z calcd for C₇H₁₂O₃, 144.0786, found: 144.0788.

Methyl α-D-desosaminide (19)

Epoxide 18 (1.41 mg, 9.78 mmol) was added to a solution of 40 % aqueous dimethylamine (30 mL) and the resulting mixture was stirred for 60 h at room temperature. After the mixture was concentrated under reduced pressure, purification of the residue by flash chromatography (CH₂Cl₂:MeOH=7:1) afforded the methyl α-D-desosaminide 19 (1.21 g, 65 %) as a colorless oil: [α]D²⁵ 160.6 (c 1.47, CHCl₃); IR (film): 3463.5, 2935.1, 1456.0, 1382.7, 1277.6, 1202.4, 1099.2, 1052.9, 981.6, 940.1, 837.0 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.20 (d, J = 6.3 Hz, 3H), 1.25 (m, 1H), 1.72 (ddd, J = 5.8, 3.0, 3.0 Hz, 1H), 2.28 (s, 6H), 2.92 (ddd, J = 12.0, 3.8 Hz, 1H), 3.43 (s, 3H), 3.54 (dd, J = 10.6, 3.7 Hz, 1H), 3.90 (dd, J = 6.2, 6.2, 2.0 Hz, 1H), 4.85 (d, J = 3.6 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 99.5, 68.5, 60.3, 54.9, 39.8, 29.0, 21.2;
HRMS: m/z calcd for C₉H₁₉NO₃, 189.1365, found: 189.1363.

Methyl 2-O-acetyl-3-dimethylamino-3,4,6-trIDEOxy-α-D-xylohexopyranoside (20)

To a solution of Methyl α-D-desosaminide 19 (1.00 mg, 5.28 mmol) CH₂Cl₂ (10 mL) at 0 °C were added DMAP (322 mg, 2.64 mmol), triethylamine (2.2 mL, 15.8 mmol) and acetic anhydride (1.5 mL, 15.8 mmol). 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 NaHCO₃ solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The organic solutions were combined, dried (MgSO₄), and concentrated. Purification of the residue by flash chromatography (EtOAc:MeOH = 10:1) afforded 20 (990 mg, 72%) as a colorless oil: [α]D<sup>25.2</sup> 152.5 (c 1.97, CHCl₃); IR (film): 2940.9, 2782.8, 2133.9, 1744.3, 1455.0, 1372.1, 1246.8, 1128.2, 1042.3, 945.0, 923.7, 903.5, 870.7 cm⁻¹; <sup>1</sup>H NMR (300 MHz, CDCl₃): δ 1.02 (d, J = 6.3 Hz, 3H), 1.19 (ddd, J = 12.2, 12.2, 12.2 Hz, 1H), 1.61 (ddd, J = 13.0, 4.0, 2.2 Hz, 1H), 1.93 (s, 3H), 2.10 (s, 6H), 2.95 (ddd, J = 12.0, 12.0, 4.2 Hz, 1H), 3.20 (s, 3H), 3.74 (ddddd, J = 12.5, 6.2, 6.2, 6.2, 2.0 Hz, 1H), 4.60 (d, J = 3.6 Hz, 1H), 4.71 (dd, J = 11.0, 3.7 Hz, 1H); <sup>13</sup>C NMR (75 MHz, CDCl₃): δ 170.0, 97.4, 70.3, 63.8, 57.3, 54.5, 40.1, 32.1, 20.7, 20.4; HRMS: m/z calcd for C₁₁H₂₁NO₄, 231.1471, found: 231.1470.

1, 2-Di-O-acetyl-D-desosamine (21)

To a stirred solution of 20 (990 mg, 4.28 mmol) in acetic anhydride (6 mL) was added the
H$_2$SO$_4$ solution [H$_2$SO$_4$ (8 drops) in acetic anhydride (1 mL)] (0.5 mL) 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 NaHCO$_3$ (300 mg) was added to the mixture. After 30 min, Et$_2$O (20 mL) and a saturated aqueous NaHCO$_3$ solution (20 mL) were added to the mixture. The resulting mixture was stirred for 2 h at room temperature. The organic layer was separated, and the aqueous layer was extracted with ether (5 × 15 mL). The organic solutions were combined, dried (MgSO$_4$), and concentrated. Purification of the residue by flash chromatography (EtOAc:MeOH = 10:1) afforded the desired product 21 (α:β=5:1, 810 mg, 74 %) as a colorless oil. IR (film): 2975.6, 1748.2, 1373.1, 1243.9, 1139.7, 1058.7, 1012.5, 925.7, 843.7 cm$^{-1}$; major (α) $^1$H NMR (300 MHz, CDCl$_3$): δ 1.17 (d, J = 6.2 Hz, 3H), 1.37 (dd, J = 12.0, 12.0, 12.0 Hz, 1H), 1.83 (ddd, J = 13.1, 3.7, 2.4 Hz, 1H), 2.00 (s, 3H), 2.09 (s, 3H), 2.26 (s, 6H), 3.12 (ddd, J = 11.5, 11.5, 4.0 Hz, 1H), 4.00 (m, 1H), 4.99 (dd, J = 11.1, 3.6 Hz, 1H), 6.18 (dd, J = 3.6 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 170.2, 169.5, 90.6, 68.7, 67.1, 57.5, 40.1, 31.4, 21.0, 20.9; minor (β) $^1$H NMR (300 MHz, CDCl$_3$): δ 1.47 (d, J = 6.1 Hz, 3H), 1.35 (m, 1H), 1.75 (m, 1H), 1.95 (s, 3H), 2.04 (s, 3H), 2.24 (s, 6H), 2.79 (ddd, J = 10.8, 10.8, 4.3 Hz, 1H), 3.68 (m, 1H), 4.89 (dd, J = 10.5, 8.0 Hz, 1H), 5.55 (d, J = 7.9 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 169.0, 169.4, 93.5, 70.4, 69.6, 62.9, 40.4, 30.3, 21.4, 20.9; HRMS: m/z calcd for C$_{12}$H$_{21}$NO$_5$, 259.1420, found: 259.1423.

2-O-acetyl-D-desosamine (22)

To a stirred solution of 21 (810 mg, 3.12 mmol) in dry THF (10 mL) at room temperature was added benzylamine (683 µL, 6.24 mmol) via a syringe. After 18 h, the reaction mixture was concentrated. Purification by flash chromatography (CH$_2$Cl$_2$:MeOH= 7:1) afforded 2-O-acetyl-D-desosamine (22) (α:β = 0.7:1, 480 mg, 71%) as a colorless oil: major (β) $^1$H NMR (300 MHz, CDCl$_3$): δ 1.28 (d, J = 6.2 Hz, 3H), 1.39 (m, 1H), 1.80 (m, 1H), 2.13 (s, 3H), 2.29 (s, 6H), 2.82 (ddd, J = 12.1, 10.5, 4.3 Hz, 1H), 3.62 (ddddd, J = 12.2, 6.2, 6.2, 6.2, 2.0 Hz, 1H), 4.54 (d, J = 7.7 Hz, 1H), 4.71 (dd, J = 10.4, 7.7 Hz, 1H); minor (β) $^1$H NMR (300 MHz, CDCl$_3$): δ 1.20 (d, J = 6.2 Hz, 3H), 1.39 (m, 1H), 1.80 (m, 1H), 2.13 (s, 3H), 2.30 (s, 6H), 3.20 (ddd, J = 12.1, 12.1, 4.1 Hz, 1H), 4.18 (ddddd, J = 12.7, 6.5, 6.5, 6.5, 2.4 Hz, 1H), 4.91 (dd, J = 11.1, 3.6 Hz, 1H),
5.32 (d, J = 3.5 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 171.7, 170.6, 96.8, 91.0, 73.2, 70.8, 69.5, 64.4, 62.4, 57.1, 40.6, 40.5, 32.2, 31.5, 21.4, 21.1.
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