Palladium(II)-Catalyzed Cyclization of Urethanes and Total Synthesis of 1-Deoxymannojirimycin

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Supplemental material

General.

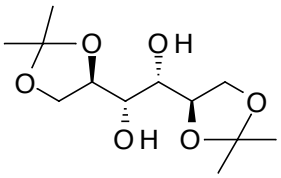
^{1}H-NMR spectra were measured with JEOL Model Mac-FX (90 MHz) or JEOL Model α-400 (400 MHz) spectrophotometer. Chemical shifts were relative to tetramethylsilane or chloroform (7.26 ppm) as an internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet) and br (broadened). Coupling constants were given in Hz.

Infrared spectra (IR) were recorded on a JASCO Model FT/IR-7300 spectrophotometer. List of infrared absorptions were diagnostic.

Elemental analyses were performed by micro analytical laboratory of Toyama University (Yanaco CHN corder MT-5).

Optical rotations ($[\alpha]_D$) were determined with a JASCO DIP-370 polarimeter.

1,2:5,6-Di-*O*-isopropylidene-D-mannitol.



To a suspension of $ZnCl_2$ (47.0 g, 0.34 mol) in acetone (300 mL) was added D-mannitol (30.0 g, 0.16 mol) at 0 ˚C under an argon atmosphere and the reaction mixture was stirred at room temperature for 24 h. After quenching with a solution of K_2CO_3 (47.7 g, 0.35 mol) in water (60 mL) at 0˚C, the resulting mixture was stirred at room temperature for 1 h. The acetone layer was collected by decantation and the precipitates were extracted with ethyl acetate (50 mL x 3). The conc. NH_4OH (1.0 mL) was added to acetone layer, and the resulting mixture was concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over K_2CO_3 and concentrated in vacuo. The resulting precipitates were recrystallized from ethyl acetate to afford 1,2:5,6-di-*O*-isopropylidene -D-mannitol (33.7 g, 78%) as colorless needles (mp 119.5 - 121˚C).

$[\alpha]^{25}D$ 2.4° (c 1.00, EtOH)

^1H NMR (400MHz, $CDCl_3$) δ = :

4.24-4.15 (m, 2H, C2,5H)

4.12 (dd, J = 6.4, 8.5 Hz, 2H, C1,6HH)

3.98 (dd, J = 5.6, 8.5 Hz, 2H, C1,6HH)

3.73-3.78 (brt, 2H, C3,4H)

2.57 (d, J = 6.6 Hz, 1.8H, OH)

1.42 (s, 6H, Me x 2)

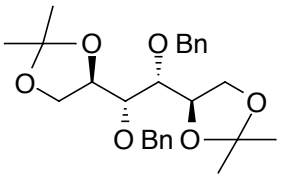
1.36 (s, 6H, Me x 2)

IR (neat) 3314(OH) cm^{-1}

Anal. Calcd for C12H22O6 : C, 54.95; H, 8.45; O, 36.60.

Found : C, 54.79; H, 8.51; O, 36.70.

3,4-Di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol.



To a suspension of NaH (4.12 g, 60% in mineral oil, 0.10 mol) in THF (170 mL) was added 1,2:5,6-di-*O*-isopropylidene-D-mannitol (8.89 g, 33.9 mmol) at 0 ˚C under an argon atmosphere and the reaction mixture was stirred for 2 h at same temperature. The benzyl bromide (9.5 mL, 79.7 mmol) and tetrabutylammonium iodide (4.0 mg, 0.01 mmol) were added to the mixture at 0 ˚C. The resulting mixture was stirred at room temperature for 6 h, then quenched with ice and extracted with diethyl ether. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (12.6 g, 84%) as a yellow oil.

$[\alpha]^{27}{}_D$ 37.7° (c 1.08, $CHCl_3$)

^1H NMR (400MHz, $CDCl_3$) δ = :

7.33-7.30 (m, 10H, Ph x 2)

4.70 (s, 4H, CH2Ph x 2)

4.24 (brq, 2H, C2,5H)

4.00 (dd, J = 6.3, 8.5 Hz, 2H, C1,6HH)

3.85 (dd, J = 6.3, 8.5 Hz, 2H, C1,6HH)

3.79 (d, J = 5.4 Hz, 2H, C3,4H)

1.41 (s, 6H, Me x 2)

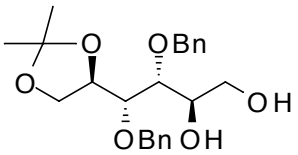
1.33 (s, 6H, Me x 2)

IR (neat) 1072(br, C-O) cm^{-1}

Anal. Calcd for C26H34O6 : C, 70.56; H, 7.74; O, 21.70.

Found : C, 70.30; H, 7.89; O, 21.81.

3,4-Di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol.



A solution of 3,4-di-*O*-benzyl-1,2:5,6-di-*O*-isopropylidene-D-mannitol (2.22 g, 5.0 mmol) in 60% acetic acid was stirred at room temperature for 3.5 h. The reaction mixture was diluted with ethyl acetate and alkalized with $NaHCO_3$. The sluggish mixture was filtered and the filterate was extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with $NaHCO_3$, 5%NaOH aq.and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed by silica gel column to give 3,4-di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol (761 mg, 38%)(eluent; Hex : AcOEt = 4 : 1) as a colorless oil and starting material (400 mg).

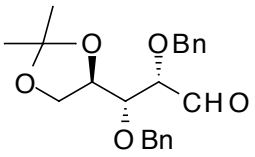
$[\alpha]^{31}{}_D$ 24.3° (c 1.06, CH_2Cl_2)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.36-7.25 (m, 10H, Ph x 2)
4.75 (d, J = 11.5 Hz, 1H, CHHPha)
4.70 (d, J = 11.5 Hz, 1H, CHHPha)
4.65 (d, J = 11.2 Hz, 1H, CHHPhb)
4.60 (d, J = 11.2 Hz, 1H, CHHPhb)
4.30 (dt, J = 5.9, 6.3 Hz, 1H, C5H)
4.05 (dd, J = 6.3, 8.3 Hz, 1H, C6HH)
3.96-3.92 (m, 2H, C6HH, C4H)
3.80 (ddd, J = 3.4, 4.6, 7.8 Hz, 1H, C2H)
3.72 (dd, J = 3.4, 11.5 Hz, 1H, C1HH)
3.66-3.61 (m, 2H, C1HH, C3H)
1.44 (s, 3H, Me)
1.34 (s, 3H, Me)

IR (neat) 3445(OH) cm^{-1}

(2*S*, 3*R*, 4*R*)-2,3-Dibenzyloxy-4,5-isopropylidenedioxypentanal.



To a solution of $NaIO_4$ (4.79g, 22.4 mmol) in water (45 mL) was added a solution of 3,4-di-*O*-benzyl-5,6-*O*-isopropylidene-D-mannitol (6.17 g, 15.3 mmol) in Et_2O (3 mL) at 0 ˚C and the reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex : AcOEt = 4 : 1) to afford (2*S*, 3*R*, 4*R*)-2,3-dibenzyloxy -4,5-isopropylidenedioxypentanal (4.51 g, 79%) as a colorless oil.

$[\alpha]^{26}{}_D$ 7.96˚ (c 1.06, CH_2Cl_2)

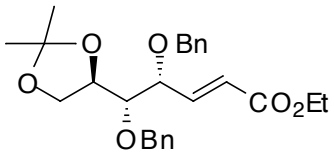
^{1}H NMR (400MHz, acetone-d_6) δ = :

9.81 (d, J = 1.0 Hz, 1H, CHO)
7.45-7.27 (m, 10H, Ph x 2)
4.82 (d, J = 11.7 Hz, 1H, CHHPha)
4.66 (d, J = 11.2 Hz, 1H, CHHPhb)
4.61 (d, J = 11.7 Hz, 1H, CHHPha)
4.55 (d, J = 11.2 Hz, 1H, CHHPhb)
4.31 (brq, 1H, C4H)
4.20 (dd, J = 1.0, 3.2 Hz, 1H, C2H)
4.13 (dd, J = 3.2, 5.9 Hz, 1H, C3H)
4.05 (dd, J = 6.3, 8.3 Hz, 1H, C5HH)
3.99 (dd, J = 6.3, 8.3 Hz, 1H, C5HH)
1.37 (s, 3H, Me)
1.29 (s, 3H, Me)

IR (neat) 1732(C=O) cm^{-1}

Anal. Calcd for C22H26O5 : C, 71.33; H, 7.07; O, 21.60.
Found : C, 71.05; H, 7.33; O, 21.62.

Ethyl (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-heptenoate.



To a suspension of NaH (0.12 g, 60% in mineral oil, 3.0 mmol) in THF (20 mL) was added diethyl ethoxycarbonylmethylphosphonate (0.7 mL, 3.5 mmol) at 0˚C under an argon atmosphere and the mixture was stirred at same temperature for 45 min. A solution of (2*S*, 3*R*, 4*R*)-2,3-dibenzyloxy-4,5-isopropylidenedioxypentanal (1.0 g, 2.7 mmol) in THF (7.0 mL) was added to the Wittig mixture at -78 ˚C and the reaction mixture was warmed to -20 ˚C for 3 h. The reaction mixture was quenched with water and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex : AcOEt = 9 : 1) to afford ethyl (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-heptenoate (1.06 g, 89%) as a colorless oil.

$[\alpha]^{31}{}_D$ -2.33° (c 1.03, CH_2Cl_2)

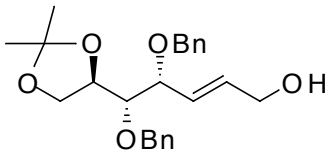
^{1}H NMR (400MHz, acetone-d_6) δ = :

7.40-7.25 (m, 10H, Ph x 2)
7.00 (dd, J = 5.9, 15.9 Hz, 1H, C3H)
6.13 (dd, J = 1.5, 15.9 Hz, 1H, C2H)
4.74 (d, J = 11.2 Hz, 1H, CHHPha)
4.67 (d, J = 11.2 Hz, 1H, CHHPha)
4.62 (d, J = 11.7 Hz, 1H, CHHPhb)
4.50 (d, J = 11.7 Hz, 1H, CHHPhb)
4.34 (ddd, J = 1.5, 4.2, 5.9 Hz, 1H, C4H)
4.29 (dt, J = 4.2, 6.6 Hz, 1H, C6H)
4.18 (dq, J = 11.0, 7.3 Hz, 1H, CHHCH3)
4.17 (dq, J = 11.0, 7.3 Hz, 1H, CHHCH3)
3.94 (dd, J = 1.5, 6.6 Hz, 2H, C7HH)
3.90 (t, J = 4.2 Hz, 1H, C5H)
1.37 (s, 3H, Me)
1.28 (s, 3H, Me)
1.26 (t, J = 7.3 Hz, 3H, CH2CH3)

IR (neat) 1715 (C=O), 1658 (C=C) cm^{-1}

Anal. Calcd for C26H32O6 : C, 70.89; H, 7.32; O, 21.79.
Found : C, 71.09; H, 7.57; O, 21.34.

(4*R*, 5*R*, 6*R*)-4,5-Dibenzyloxy-6,7-isopropylidenedioxy-2-hepten-1-ol.



To a solution of ethyl (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-heptenoate (1.02 g, 2.3 mmol) in THF (20 mL) was added diisobutylaluminum hydride (0.95M n-hexane solution)(7.3 mL, 6.9 mmol) at -78 ˚C under an argon atmosphere. The reaction mixture was warmed to -20 ˚C for 4 h. The reaction mixture was diluted with diethyl ether and quenched with saturated aqueous Na_2SO_4 at 0 ˚C and stirred at room temperature for 20 min. The mixture was dried over Na_2SO_4 and filtered through Celite. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluent; Hex : AcOEt = 4 : 1) to afford (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-hepten-1-ol (0.87 g, 94 %) as a colorless oil.

$[\alpha]^{31}{}_D$ -5.86° (c 0.99, CH_2Cl_2)

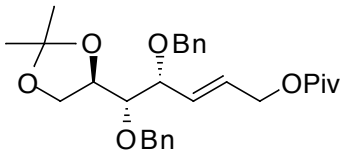
^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.35-7.25 (m, 10H, Ph x 2)
5.83 (dt, J = 5.1, 15.6 Hz, 1H, C2H)
5.67 (dd, J = 7.6, 15.6 Hz, 1H, C3H)
4.77 (d, J = 11.5 Hz, 1H, CHHPha)
4.66 (d, J = 11.5 Hz, 1H, CHHPha)
4.59 (d, J = 12.0 Hz, 1H, CHHPhb)
4.36 (d, J = 12.0 Hz, 1H, CHHPhb)
4.23 (dt, J = 3.9, 7.1 Hz, 1H, C6H)
4.10 (d, J = 5.1 Hz, 2H, C1HH)
3.98 (d, J = 7.1 Hz, 2H, C7H)
3.90 (dd, J = 3.9, 7.6 Hz, 1H, C4H)
3.74 (t, J = 3.9 Hz, 1H, C5H)
1.41 (s, 3H, Me)
1.34 (s, 3H, Me)

IR (neat) 3442(OH) cm^{-1}

Anal. Calcd for C24H30O5 : C, 72.34; H, 7.59; O, 20.07.
Found : C, 72.08; H, 7.74; O, 20.18.

(4*R*, 5*R*, 6*R*)-4,5-Dibenzyloxy-6,7-isopropylidenedioxy -1-pivaloyloxy-2-heptene.



To a solution of (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-2-hepten-1-ol (1.44 g, 3.6 mmol) in pyridine (3.6 mL) and THF (3.6 mL) was added pivaloyl chloride (0.6 mL, 0.59 g, 4.9 mmol) at 0 ˚C under an argon atmosphere and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with ethyl acetate and quenched with ice. The organic layer was washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex : AcOEt = 9 : 1) to afford (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-1-pivaloyloxy-2-heptene (1.63 g, 93%) as a colorless oil.

$[\alpha]^{29}{}_D$ -2.26˚ (c 0.93, CH_2Cl_2)

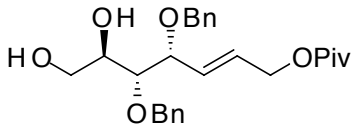
^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.36-7.24 (m, 10H, Ph x 2)
5.81 (dt, J = 4.4, 15.6 Hz, 1H, C2H)
5.76 (dd, J = 5.6, 15.6 Hz, 1H, C3H)
4.74 (d, J = 11.5 Hz, 1H, CHHPha)
4.67 (d, J = 11.5 Hz, 1H, CHHPha)
4.61-4.54 (m, 3H, C1HH, CHHPhb)
4.36 (d, J = 12.0 Hz, 1H, CHHPhb)
4.23 (dt, J = 3.9, 7.0 Hz, 1H, C6H)
3.98-3.90 (m, 3H, C4H, C7HH)
3.74 (t, J = 3.9 Hz, 1H, C5H)
1.43 (s, 3H, Me)
1.37 (s, 3H, Me)
1.21 (s, 9H, t-Bu)

IR (neat) 1731(C=O) cm^{-1}

Anal. Calcd for C29H38O6 : C, 72.17; H, 7.94; O, 19.89.
Found : C, 71.94; H, 8.17; O, 19.89.

(2*R*, 3*R*, 4*R*)-3,4-Dibenzyloxy-7-pivaloyloxy-5-heptene-1,2-diol.



To a solution of (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-6,7-isopropylidenedioxy-1-pivaloyloxy -2-heptene (0.55 g, 1.1 mmol) in THF (10 mL) was added 10% aqueous HCl (2 mL). The solution was stirred at 40 ˚C for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex : AcOEt = 3 : 2) to afford (2*R*, 3*R*, 4*R*)-3,4-dibenzyloxy-7- pivaloyloxy-5-heptene-1,2-diol (0.48 g, 95%) as a colorless oil.

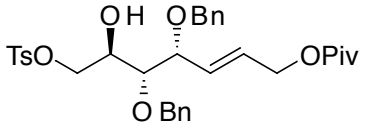
$[\alpha]^{29}_{D}$ -7.61˚ (c 1.03, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.38-7.26 (m, 10H, Ph x 2)
5.92-5.80 (m, 2H, C5,6H)
4.66-4.59 (m, 5H)
4.38 (d, J = 11.7 Hz, 1H, CHHPhb)
4.13 (t, J = 4.6 Hz, 1H, C4H)
3.80 (ddd, J = 3.7, 4.4, 7.3 Hz, 1H, C2H)
3.70 (dd, J = 3.7, 11.5 Hz, 1H, C1HH)
3.65 (dd, J = 4.4, 11.5 Hz, 1H, C1HH)
3.63 (dd, J = 4.6, 7.3 Hz, 1H, C3H)
2.60-2.20 (brs, 2H, OH x 2)
1.22 (s, 9H, t-Bu)

IR (neat) 3445(OH), 1729(C=O) cm^{-1}

(2*R*, 3*R*, 4*R*)-3,4-Dibenzyloxy-7-pivaloyloxy-1-tosyloxy-5-hepten-2-ol.



To a solution of (2*R*, 3*R*, 4*R*)-3,4-dibenzyloxy-7-pivaloyloxy-5-heptene-1,2-diol (2.19 g, 5.0 mmol) in pyridine (1.0 mL) and CH_2Cl_2 (5.0 mL) was added p-toluenesulfonyl chloride (1.05 g, 5.5 mmol) at 0 ˚C under an argon atmosphere and the mixture was stirred at room temperature for 23 h. The reaction mixture was quenched with 10% aqueous HCl. The aqueous layer was extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed by silica gel column to give (2*R*, 3*R*, 4*R*)-3,4-dibenzyloxy-7-pivaloyloxy-1- tosyloxy-5-hepten-2-ol (2.52 g , 85%)(eluent; Hex : AcOEt = 4 : 1) as a pale yellow oil and starting material (0.21 g).

$[\alpha]^{31}{}_D$ 0.95° (c 0.99, CH_2Cl_2)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.76 (d, J = 8.3 Hz, 2H, Ar-H (o- to S O_2) x 2)

7.36-7.20 (m, 12H, Ph x 2, Ar-H (m- to S O_2) x 2)

5.88-5.75 (m, 2H, C5,6H)

4.63-4.53 (m, 4H, C7HH, CHHPha,b)

4.51 (d, J = 11.2 Hz, 1H, CHHPha)

4.33 (d, J = 12.0 Hz, 1H, CHHPhb)

4.15-4.07 (m, 3H, C1HH, C4H)

3.96 (dt, J = 3.7, 7.6 Hz, 1H, C2H)

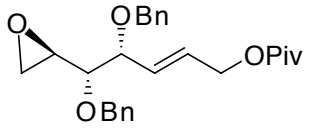
3.58 (dd, J = 3.7, 7.6 Hz, 1H, C3H)

2.44 (s, 3H, Ar-Me)

1.21 (s, 9H, t-Bu)

IR (neat) 3501(OH), 1728(C=O), 1362 and 1177(S=O) cm^{-1}

(4*R*, 5*R*, 6*R*)-6,7-Epoxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene.



To a solution of (2*R*, 3*R*, 4*R*)-3,4-dibenzyloxy-7-pivaloyloxy-1-tosyloxy-5-hepten-2-ol (0.29 g, 0.49 mmol) in MeOH (0.5 mL) was added K_2CO_3 (0.14 g, 1.0 mmol) at 0 ˚C under an argon atmosphere and the reaction mixture was stirred at the same temperature for 2 h. The suspension was diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 9 : 1) to afford (4*R*, 5*R*, 6*R*)-6,7-Epoxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene (0.18 g, 89%) as a colorless oil.

$[\alpha]^{29}_{D}$ -15.5° (c 1.05, $CHCl_3$)

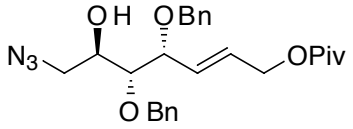
^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.36-7.24 (m, 10H, Ph x 2)
5.87-5.77 (m, 2H, C2,3H)
4.67 (d, J = 12.0 Hz, 1H, CHHPha)
4.66 (d, J = 12.0 Hz, 1H, CHHPhb)
4.64-4.54 (m, 3H, C1HH, CHHPha)
4.42 (d, J = 12.0 Hz, 1H, CHHPhb)
4.01 (dt, J = 2.4, 4.2 Hz, 1H, C4H)
3.38 (dd, J = 4.2, 4.9 Hz, 1H, C5H)
3.14 (ddd, J = 2.7, 3.9, 4.9 Hz, 1H, C6H)
2.75 (dd, J = 3.9, 5.4 Hz, 1H, C7HH)
2.68 (dd, J = 2.7, 5.4 Hz, 1H, C7HH)
1.22 (s, 9H, t-Bu)

IR (neat) 1729(C=O) cm^{-1}

Anal. Calcd for C26H32O5 : C, 73.56; H, 7.60; O, 18.84.
Found : C, 73.49; H, 7.66; O, 18.85.

(2*R*, 3*R*, 4*R*)-1-Azido-3,4-dibenzyloxy-7-pivaloyloxy-5-hepten-2-ol.



To a solution of (4*R*, 5*R*, 6*R*)-6,7-epoxy-4,5-dibenzyloxy-1-pivaloyloxy-2-heptene (0.79 g, 1.86 mmol) in DMF (9.5 mL) was added NaN_3 (0.36 g, 5.54 mmol), NH_4Cl (0.30 g, 5.61 mmol) and 15-crown-5 (0.04 mL, 0.2 mmol) at room temperature under an argon atmosphere and the mixture was stirred at 55 ˚C for 10 h. The suspension was diluted with ethyl acetate and added to water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed by silica gel column to give (2*R*, 3*R*, 4*R*)-1-azido-3,4-dibenzyloxy-7-pivaloyloxy-5-hepten-2-ol (0.41 g, 47%)(eluent ; Hex : AcOEt = 9 : 1) as a colorless oil and starting material (0.35 g).

$[\alpha]^{29}{}_D$ 6.84° (c 2.85, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

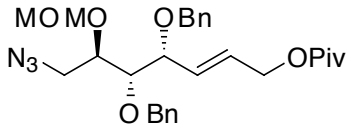
7.38-7.25 (m, 10H, Ph x 2)
5.92-5.80 (m, 2H, C5,6H)
4.65 (d, J = 12.0 Hz, 1H, CHHPha)
4.63-4.56 (m, 3H, CHHPhb, C7HH)
4.53 (d, J = 11.5 Hz, 1H, CHHPhb)
4.38 (d, J = 12.0 Hz, 1H, CHHPha)
4.17-4.13 (m, 1H, C4H)
3.96-3.90 (m, 1H, C2H)
3.57 (dd, J = 4.2, 7.8 Hz, 1H, C3H)
3.44 (dd, J = 2.9, 12.7 Hz, 1H, C1HH)
3.31 (dd, J = 5.6, 12.7 Hz, 1H, C1HH)
3.03 (d, J = 3.7 Hz, 1H, OH)
1.22 (s, 9H, t-Bu)

IR (neat) 3493(OH), 2102(N_3), 1731(C=O) cm^{-1}

Anal. Calcd for C26H33N3O5 : C, 66.79; H, 7.11; N, 8.99; O, 17.11.

Found : C, 66.75; H, 7.31; N, 8.54; O, 17.40.

(4R, 5R, 6R)-7-Azido-4,5-dibenzyloxy-6-methoxymethyloxy -1-pivaloyloxy-2-heptene.



To a solution of (2*R*, 3*R*, 4*R*)-1-azido-3,4-dibenzyloxy-7-pivaloyloxy-5-hepten-2-ol (0.27 g, 0.57 mmol) in ethyldiisopropylamine (0.15 mL, 0.86 mmol) was added chloromethyl methyl ether (0.06 mL, 0.79 mmol) at 0 ˚C under an argon atmosphere and the mixture was stirred at room temperature for 6.5 h. The reaction mixture was diluted with ethyl acetate and added to ice. The aqueous layer was extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, dried over K_2CO_3 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 9 : 1) to afford (4*R*, 5*R*, 6*R*)-7-azido-4,5-dibenzyloxy-6-methoxymethyloxy-1-pivaloyloxy-2-heptene (0.24 g, 83%) as a colorless oil.

$[\alpha]^{29}_{D}$ -2.08˚ (c 1.85, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

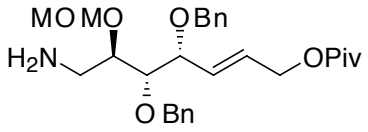
7.36-7.24 (m, 10H, Ph x 2)
5.86 (dt, J = 4.9, 15.9 Hz, 1H, C2H)
5.78 (dd, J = 7.1, 15.9 Hz, 1H, C3H)
4.69 (d, J = 11.7 Hz, 1H, CHHPha)
4.66 (d, J = 11.7 Hz, 1H, CHHPha)
4.60 (d, J = 12.0 Hz, 1H, CHHPhb)
4.57 (d, J = 4.9 Hz, 2H, C1HH)
4.54 (d, J = 6.8 Hz, 1H, OCHHO)
4.51 (d, J = 6.8 Hz, 1H, OCHHO)
4.32 (d, J = 12.0 Hz, 1H, CHHPhb)
4.02 (dd, J = 4.2, 7.1 Hz, 1H, C4H)
3.86 (td, J = 2.7, 5.4 Hz, 1H, C6H)
3.66 (dd, J = 4.2, 5.4 Hz, 1H, C5H)
3.62 (dd, J = 2.7, 12.9 Hz, 1H, C7HH)
3.51 (dd, J = 5.4, 12.9 Hz, 1H, C7HH)
3.38 and 3.37 (two s, 3H, OMe)
1.21 and 1.20 (two s, 9H, t-Bu)

IR (neat) 2102(N_3), 1731(C=O) cm^{-1}

Anal. Calcd for C26H33N3O5 : C, 65.73; H, 7.29; N, 8.21; O, 18.76.

Found : C, 65.34; H, 7.38; N, 7.82; O, 19.46

(2*R*, 3*R*, 4*R*)-3,4-Dibenzyloxy-2-methoxymethyloxy-7-pivaloyloxy-5-heptenamine.



To a solution of (4*R*, 5*R*, 6*R*)-7-azido-4,5-dibenzyloxy-6-methoxymethyloxy-1-pivaloyloxy -2-heptene (73 mg, 0.28 mmol) in THF (0.8 mL) was added triphenylphosphine (22 mg, 0.082 mmol) in THF(2.7 mL) and a drop of water at room temperature, the mixture was stirred at same temperature for 16 h. The mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography (eluent ; $CHCl_3$: MeOH = 19 : 1) to afford (2*R*, 3*R*, 4*R*)-3,4-dibenzyloxy-2- methoxymethyloxy-7-pivaloyloxy-5-heptenamine (10 mg, 46%) as a colorless oil.

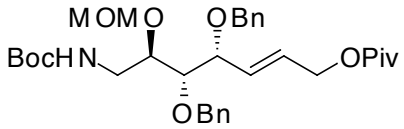
$[\alpha]^{28}{}_D$ -3.95° (c 1.85, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.35-7.24 (m, 10H, Ph x 2)
5.86 (dt, J = 4.9, 15.9 Hz, 1H, C6H)
5.80 (dd, J = 6.8, 15.9 Hz, 1H, C5H)
4.72 (d, J = 11.5 Hz, 1H, CHHPha)
4.69 (d, J = 11.5 Hz, 1H, CHHPha)
4.63-4.58 (m, 3H, C7HH, CHHPhb)
4.56 (d, J = 6.8 Hz, 1H, OCHHO)
4.51 (d, J = 6.8 Hz, 1H, OCHHO)
4.35 (d, J = 12.0 Hz, 1H, CHHPhb)
4.03 (dd, J = 3.9, 6.8 Hz, 1H, C4H)
3.69-3.64 (m, 2H, C2H, C3H)
3.34 (s, 3H, OMe)
2.97-2.86 (m, 2H, C1HH)
1.21 (s, 9H, t-Bu)

IR (neat) 3384 and 3320(NH_2), 1731(C=O) cm^{-1}

(4*R*, 5*R*, 6*R*)-4,5-Dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy-1-pivaloyloxy-2-heptene.



To a solution of (2*R*, 3*R*, 4*R*)-3,4-dibenzyloxy-2-methoxymethyloxy-7-pivaloyloxy -5-heptenamine (0.384 g, 0.79mmol) and triethylamine (0.11 mL, 0.79 mmol) in CH_2Cl_2 (1.5 mL) was added di-tert-butyl dicarbonate (0.20 mL, 0.87 mmol) at room temperature under an argon atmosphere and the mixture was stirred at the same temperature for 4 h. The reaction mixture was quenched with 10% aqueous HCl at 0 ˚C and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 4 : 1) to afford (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl) -amino]-6-methoxymethyloxy-1-pivaloyloxy-2-heptene (0.438 g, 95%) as a colorless oil.

$[\alpha]^{30}_{D}$ 0.59° (c 2.10, $CHCl_3$)

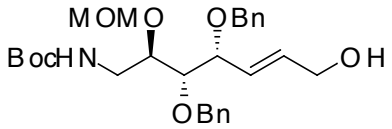
^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.36-7.25 (m, 10H, Ph x 2)
5.88 (dt, J = 5.1, 15.6 Hz, 1H, C2H)
5.77 (dd, J = 7.6, 15.6 Hz, 1H, C3H)
5.16-5.08 (m, 1H, NH)
4.71 (d, J = 11.2 Hz, 1H, CHHPha)
4.68 (d, J = 11.2 Hz, 1H, CHHPha)
4.62-4.56 (m, 3H, C1HH, CHHPhb)
4.54-4.47 (m, 2H, OCH2O)
4.35 (d, J = 11.7 Hz, 1H, CHHPhb)
4.01 (dd, J = 5.1, 7.6 Hz, 1H, C4H)
3.76 (dt, J = 3.9, 5.1 Hz, 1H, C6H)
3.60 (t, J = 5.1 Hz, 1H, C5H)
3.47 (ddd, J = 3.9, 5.9, 13.9 Hz, 1H, C7HH)
3.38-3.27 (m, 4H, C7HH, OMe)
1.52 (s, 9H, O-t-Bu)
1.21 (s, 9H, t-Bu)

IR (neat) 3405(NH), 1715(C=O) cm^{-1}

Anal. Calcd for C33H47NO8 : C, 67.67; H, 8.09; N, 2.39; O, 21.85.
Found : C, 67.41; H, 8.22; N, 2.29; O, 22.08.

(4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy-2-hepten-1-ol.



To a solution of (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy-1-pivaloyloxy-2-heptene (0.185 g, 0.32 mmol) in MeOH (1.6 mL) was added K_2CO_3 (85 mg, 0.62 mmol) at room temperature under an argon atmosphere and the mixture was stirred at same temperature for 14 h. The reaction mixture was diluted with ethyl acetate and the resulting solution was filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 2 : 3) to afford (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy -2-hepten-1-ol (0.158 g, quant.) as a colorless oil.

$[\alpha]^{28}{}_D$ 35.1° (c 1.15, $CHCl_3$)

^{1}H NMR (400MHz, $CDCl_3$) δ = :

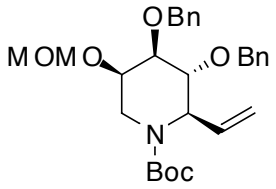
7.36-7.24 (m, 10H, Ph x 2)
5.99 (ddd, J = 4.6, 5.9, 15.6 Hz, 1H, C2H)
5.66 (dd, J = 8.1, 15.6 Hz, 1H, C3H)
5.14-5.06 (m, 1H, NH)
4.76 (d, J = 12.0 Hz, 1H, CHHPha)
4.73 (d, J = 12.0 Hz, 1H, CHHPha)
4.61 (d, J = 6.8 Hz, 1H, OCHHO)
4.59 (d, J = 11.7 Hz, 1H, CHHPhb)
4.54 (d, J = 6.8 Hz, 1H, OCHHO)
4.38 (d, J = 11.7 Hz, 1H, CHHPhb)
4.20 (dd, J = 4.6, 13.4 Hz, 1H, C1HH)
4.14 (dd, J = 5.9, 13.4 Hz, 1H, C1HH)
3.97 (brt, 1H, C4H)
3.81-3.74 (m, 2H, C5,6H)
3.53 (ddd, J = 2.4, 8.1, 14.4 Hz, 1H, C7HH)
3.36 (s, 3H, OMe)
3.13 (ddd, J = 4.4, 8.1, 14.4 Hz, 1H, C7HH)
1.41 (s, 9H, O-t-Bu)

IR (neat) 3434(NH, OH), 1695(C=O) cm^{-1}

Anal. Calcd for C28H39NO7 : C, 67.04; H, 7.84; N, 2.79; O, 22.33.
Found : C, 67.22; H, 8.08; N, 2.54; O, 22.16.

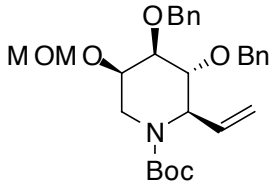
Pd(II) catalyzed cyclization

(2*R*, 3*R*, 4*R*, 5*R*)-3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine.



To a solution of (4*R*, 5*R*, 6*R*)-4,5-dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino] -6-methoxymethyloxy-2-hepten-1-ol (0.11 g, 0.22 mmol) in THF (4.0 mL) was added a catalytic amount of $PdCl_2(CH_3CN)_2$ (8.0 mg, 0.031 mmol) at 0 ˚C under an argon atmosphere and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 9 : 1) to afford the mixture of (2*R*, 3*R*, 4*R*, 5*R*) and (2*S*, 3*R*, 4*R*, 5*R*)-3,4-dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine (0.091 g, 86%) as a colorless oil. The diastereomeric ratio (2R) : (2S) was determined to >26 : 1 by 400MHz ^{1}H NMR analysis.

(2*R*, 3*R*, 4*R*, 5*R*)-3,4-dibenzyloxy
-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine



$[\alpha]^{26}_{D}$ -1.21° (c 1.16, $CHCl_3$)

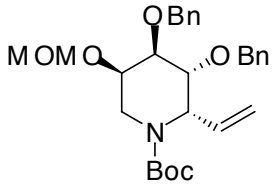
^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.39-7.22 (m, 10H, Ph x 2)
6.00 (ddd, J = 6.2, 10.0, 17.6 Hz, 1H, C1'HH)
5.08 (dd, J =2.5, 11,7 Hz, 1H, C1'HH)
5.00-4.75 (br, 1H, C2H)
4.73-4.62 (m, 4H, CHHPha, CHHPhb, OCH2O)
4.58 (d, J = 12.2 Hz, 1H, CHHPha)
4.43 (d, J = 12.0 Hz, 1H, CHHPhb)
4.06 (brd, 1H, C6Heq)
3.94 (ddd, J = 3.0, 4.9, 11.2, Hz, 1H, C5H)
3.82 (t, J = 3.1 Hz, 1H, C4H)
3.72-3.61 (m, 1H, C3H)
3.35 and 3.34 (two s, 3H, OMe)
3.23 (t, J = 12.0 Hz, 1H, C6Hax)
1.45 (s, 9H, O-t-Bu)

IR (neat) 1694(C=O) cm^{-1}

Anal. Calcd for C28H37NO6 : C, 69.54; H, 7.71; N, 2.90.
Found : C, 69.54; H, 7.70; N, 2.66

(2*S*, 3*R*, 4*R*, 5*R*)-3,4-dibenzyloxy -*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine



^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.41-7.21 (m, 10H, Ph x 2)

6.08 (ddd, J = 3.7, 10.7, 17.6 Hz)

5.27 (brd, 1H)

5.13 (brd, 1H)

4.86-4.66 (m, 7H, OCH2O)

4.20-4.03 (m, 2H)

3.99-3.92 (m, 1H)

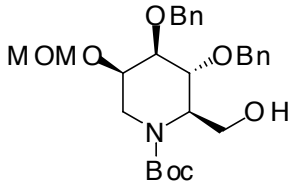
3.45 (dd, J = 3.2, 10.2 Hz, 1H)

3.41 (s, 3H, OMe)

2.96-2.73 (m, 1H)

1.45 (s, 9H, O-t-Bu)

(2*R*, 3*R*, 4*R*, 5*R*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-piperidinyl)methanol.



A gas of O_3 in O_2 was bubbled into a solution of (2*R*, 3*R*, 4*R*, 5*R*)-3,4-dibenzyloxy-N-tert- butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine (71 mg, 0.147 mmol) in CH_2Cl_2-MeOH (4:1, 1.5 mL) at -78 ˚C until the solution was turned to blue. Then an argon gas was bubbled through the solution until its color was cleared. To the reaction solution was added $NaBH_4$ (23 mg, 0.608 mmol) at -78 ˚C and the mixture was warmed slowly to room temperature, and stirred for additonal 21 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 7 : 3) to afford (2*R*, 3*R*, 4*R*, 5*R*)-(3,4-Dibenzyloxy-*N*-tert- butoxycarbonyl-5-methoxymethyloxy-2-piperidinyl)methanol (66 mg, 92%) as a colorless oil.

$[\alpha]^{30}_{D}$ -52.1˚ (c 1.05, $CHCl_3$)

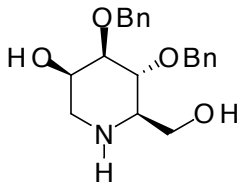
^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.36-7.25 (m, 10H, Ph x 2)
4.78 (d, J = 12.0 Hz, 1H, CHHPh1)
4.70-4.65 (m, 2H, OCH2O)
4.62 (d, J = 11.7 Hz, 1H, CHHPh2)
4.57 (d, J = 11.7 Hz, 1H, CHHPh2)
4.43 (d, J = 12.0 Hz, 1H, CHHPh1)
4.40-4.34 (m, 1H, C2H)
3.95 (ddd, J = 2.9, 4.6, 10.7 Hz, 1H, C5H)
3.91 (dd, J = 7.6, 11.5 Hz, 1H, C1HH)
3.82 (brs, 1H, C4H)
3.72 (dd, J = 5.6, 11.5 Hz, 1H, C1HH)
3.65 (brs, 1H, C3H)
3.40-3.20 (m, 5H, C6'HH, OMe)
1.45 (s, 9H, O-t-Bu)

IR (neat) 3459(OH), 1694(C=O) cm^{-1}

Anal. Calcd for C27H37NO7 : C, 66.51; H, 7.65; N, 2.87; O, 22.97.

3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-mannnitol

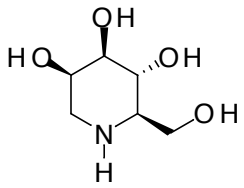


To a solution of (2*R*, 3*R*, 4*R*, 5*R*)-(3,4-Dibenzyloxy-*N*-tert-butoxycarbonyl-5-methoxymethyloxy-2-piperidinyl)methanol (17 mg, 0.035 mmol) in CH_2Cl_2 (0.4 mL) was added dropwise trifluoroacetic acid (0.01 mL, 0.13 mmol) at 0 ˚C under an argon atmosphere and the resulting mixture was stirred at the room temperature for 8 h. Then to this reaction mixture was added dropwise trifluoroacetic acid (0.04 mL, 0.52 mmol) at 0 ˚C, and the mixture was stirred at room temperature for 13.5 h. The mixture was alkalified with 2 N NaOH at 0 ˚C. The aqueous layer was extracted with CH_2Cl_2 (95 mL x 3). The combined organic layers were dried over K_2CO_3 and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; $CHCl_3$: ^{i}PrOH) to afford 3,4-Di-*O*-benzyl -1,5-dideoxy-1,5-imino-D-mannnitol (4 mg, 33%) as a colorless oil.

^{1}H NMR (400MHz, $CDCl_3$) δ = :

7.47-7.25 (m, 10H, Ph x 2)
4.89 (d, J = 11.0 Hz, 1H, CHHPha)
4.71 (d, J = 11.7 Hz, 1H, CHHPhb)
4.68 (d, J = 11.5 Hz, 1H, CHHPhb)
4.65 (d, J = 11.2 Hz, 1H, CHHPha)
4.06 (brs, 1H, C5H)
3.82 (dd, J = 2.8, 11.1 Hz, 1H, C1H)
3.60-3.70 (m, 2H)
3.53 (dd, J = 2.9, 9.3 Hz, 1H, C4H)
3.21 (dd, J = 3.3, 13.9 Hz, 1H, C6Heq)
2.40-2.70 (m, 2H)

Deoxymannojirimycin (1,5-Dideoxy-1,5-imino-D-mannitol)



To a solution of 3,4-Di-*O*-benzyl-1,5-dideoxy-1,5-imino-D-mannnitol (4 mg, 1.16 x 10^{-2} mmol) in EtOH (0.1 mL) was added concentrated HCl (0.01 mL) and 10 % Palladium on actived carbon (1.1 mg) at room temperature, and the mixture was stirred under H_2 gas atmosphere at same temperature for 5 h. The reaction mixture was filtered through Celite and the filtrate was concentrated in vacuo. The residue was Deoxymannojirimycin (1,5-Dideoxy -1,5-imino-D-mannitol) (6mg, quant.) as the hydrochloride salt, white solid.

^{1}H NMR (400MHz, D_2O) δ = :

4.10 (brs, 1H, C5H)
3.85 (dd, J = 3.2, 12.7 Hz, 1H, C1HH)
3.72 (t, J = 9.9 Hz, 1H, C3H)
3.69 (dd, J = 7.0, 12.7 Hz, 1H, C1HH)
3.54 (dd, J = 2.9, 9.5 Hz, 1H, C4H)
3.27 (dd, J = 2.8, 13.7 Hz, 1H, C6Heq)
3.10 (d, J = 13.7 Hz, 1H, C6Hax)
3.01 (ddd, J = 3.2, 6.7, 10.3 Hz, 1H, C2H)

Pd(II) catalyzed cyclization of pivaloyl compounds

To a solution of (4*R*, 5*R*, 6*R*)-4,5-Dibenzyloxy-7-[*N*-(tert-butoxycarbonyl)amino]-6-methoxymethyloxy-1-pivaloyloxy-2-heptene (17 mg, 0.029 mmol) in THF (0.6 mL) was added a catalitic amount of $PdCl_2(CH_3CN)_2$ (2 mg, 0.077 mmol) at r.t. under an argon atmosphere and the mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent ; Hex : AcOEt = 9 : 1) to afford the mixture of (2*R*, 3*R*, 4*R*, 5*R*) and (2*S*, 3*R*, 4*R*, 5*R*)-3,4-dibenzyloxy-*N*-tert- butoxycarbonyl-5-methoxymethyloxy-2-vinylpiperidine (5 mg, 36%) as a colorless oil. The diastereomeric ratio (2*R*) : (2*S*) was determined to 1 : 4.5 by 400MHz ^{1}H NMR analysis.