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Total synthesis of (+)-dienomycin C

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ABSTRACT

Total synthesis of (+)-dienomycin C was achieved via Sharpless asymmetric epoxidation, Pd-catalyzed hydrogenolysis with formic salt, and Pd(II)-catalyzed cyclization of urethane.

1. Introduction

The piperidine alkaloids (ex (**1**), (**2**)), many of which have been isolated from the plant kingdom, have great potential as a source of new drugs. Dienomycin C **1** was isolated from the culture filtrate of the *Streptomyces* strain MC67-C1 by Umezawa in 1970.[1] This compound (Fig. 1) has a characteristic antibacterial activity against some strains of *Mycobacterium tuberculosis*. Racemic dienomycin C was synthesized by Troin's group in 1996.[2] In 1999, Comins's group reported the first total synthesis of (+)-dienomycin C[3] and in the same year, Troin's group independently achieved a total synthesis of (+)-dienomycin C.[4]

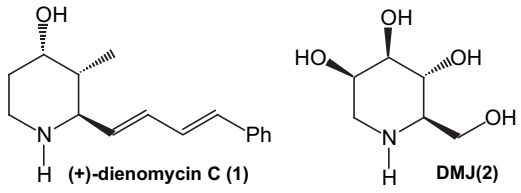
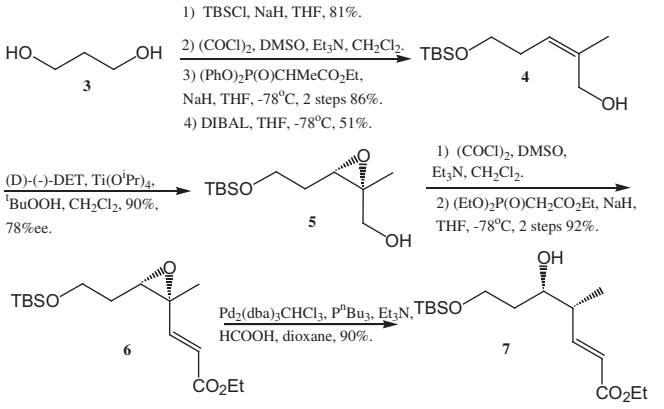


Fig. 1. The piperidine alkaloids.

2. Results and discussion

For many years, we have been studying the Pd(II)-catalyzed cyclization of urethane and its application to the total synthesis of natural products.[5] Here, we report the application of this cyclization to asymmetric synthesis of (+)-dienomycin C. The key synthetic problem for (+)-dienomycin C is the construction of three consecutive chiral centers on the piperidine ring. We planned to achieve this by using the combination of Sharpless asymmetric epoxidation,[6] Pd-catalyzed hydrogenolysis with formic salt[7] and Pd (II)-catalyzed cyclization of the urethane.[5]

Our starting material was 1,3-propanediol **3** (Scheme 1). Its hydroxy group was protected by TBS group in 81% yield. The protected alcohol was oxidized by Swern oxidation to afford the aldehyde and followed by *Z*-selective Wittig–Horner reaction to give the ester in 86% yield (two steps). The ester was treated with DIBAL in THF to give allyl alcohol **4** in 51% yield. Sharpless asymmetric epoxidation[6] of the allyl alcohol **4** with (D)-(−)-DET,



Scheme 1. Preparation of the alcohol **7**.

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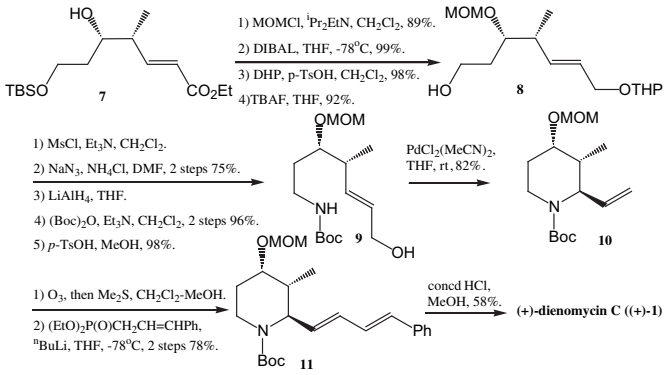
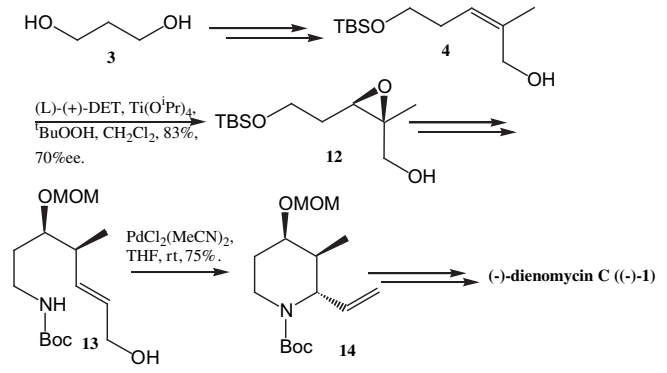
^{t}BuOOH, and Ti(O^{i}Pr)$_4$ in CH_2Cl_2 provided the epoxide **5** in 90% yield and 78%ee.[8] Oxidation of the epoxide **5** by means of Swern oxidation followed by Wittig–Horner reaction gave the α,β-unsaturated ester **6** in 92% yield. This ester **6** was treated with $Pd_2(dba)_3CHCl_3$, $^{n}Bu_3P$, HCO_2H, and Et_3N in dioxane to give the alcohol **7** as a single isomer in 90% yield.[7]

After protection of the alcohol **7** with MOMCl, reduction of the ester group with DIBAL followed by protection of the resulting allyl alcohol with DHP and deprotection of TBS group via TBAF treatment provided the alcohol **8** in 79% yield (Scheme 2). Mesylation of the hydroxyl moiety followed by continuous addition of NaN_3 gave the azide in 75% yield. Reduction of the azide moiety with $LiAlH_4$ and protection of the resulting amine with $(Boc)_2O$ provided the Boc-protected amine in 96% yield. Deprotection of the THP group gave the allyl alcohol **9** in 98% yield. Next the allyl alcohol **9** was treated with $PdCl_2(MeCN)_2$ in THF at rt to give the cyclized product **10** as a single isomer in 82% yield. Ozonolysis, followed by Wittig reaction with $(EtO)_2P(O)CH_2CH{=}CHPh$ provided the diene **11** in 78% yield(two steps).



Scheme 2. Last stage of synthesis of (+)-dienomycin C (+)-**1**.

Finally, deprotection with concd HCl gave (+)-dienomycin C (+)-**1** in 58% yield. All spectra data were in agreement with literature values.[4] Based on these mechanisms, we could determine the absolute configuration of (+)-dienomycin C (+)-**1** as (2*R*,3*R*,4*S*). Moreover we synthesized (−)-(2*S*,3*S*,4*R*)-dienomycin C (−)-**1** by using similar strategy (Scheme 3)[9] and reconfirmed the reported stereochemistry (2*R*,3*R*,4*S*) of (+)-dienomycin C.



Scheme 3. Synthesis of (−)-dienomycin C (−)-**1**.

The plausible reaction mechanism of the Pd(II)-catalyzed cyclization[10] is shown in Fig. 2. If the stereochemical outcome of this reaction could be explained in terms of six-membered transition state, the palladium complex **IA** and **IB** seem to be in equilibrium. The stereoselective formation of **10** could be explained by assuming the transition state **IA**. The transition state **IB** would be disadvantageous, because of non-bonding interaction between the carbamate moiety and π-allyl-oxy palladium complex. *anti*-Attack of nitrogen nucleophile to complex **IA** occurs from the opposite side of the complex **IA** to give the σ-Pd complex **II**. Consequently, *syn*-elimination of PdCl(OH) afforded the cyclized product **10**. Further mechanism's studies were in progress.[11]

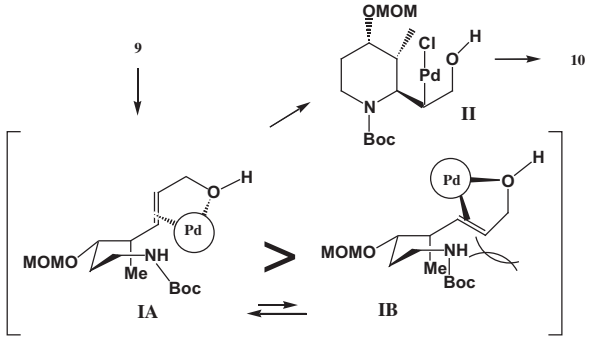


Fig. 2. The plausible reaction mechanism of the Pd(II)-catalyzed cyclization.

3. Conclusion

In conclusion, we have accomplished a total synthesis of natural (+)-dienomycin C. This reconfirms the reported stereochemistry (2*R*,3*R*,4*S*) of (+)-dienomycin C.

4. Experimental

4.1. General

^{1}H NMR spectra were measured with JEOL Model ECX-300/TRH(300 MHz), JEOL Model JNM-ECP600(600 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 hertz. ^{13}C NMR spectra were measured with JEOL Model ECX-300/TRH(75 MHz), JEOL Model JNM-ECP600(150 MHz) spectrophotometer. Chemical shifts were relative to tetramethylsilane or chloroform (77.0 ppm) as an internal standard. Infrared spectra (IR) were recorded on JASCO Model FT/IR-7300 or FT/IR-6100 spectrophotometer. List of infrared absorptions were diagnostic. High-resolution mass spectra were measured with JEOL Model JMS-700 mass spectrometer. Optical rotations ($[\alpha]_D$) were determined with JASCO Model P-1020 polarimeter.

4.2. 1-(*tert*-Butyldimethylsilyloxy)-propan-3-ol

To a solution of 1,3-propanediol (5.00 g, 65.7 mmol) in THF (66 mL) was added NaH (3.01 g, 69.0 mmol, 55% in dispersion oil) at 0 °C under an argon atmosphere and the reaction mixture was stirred for 1 h. The reaction mixture was cooled at 0 °C, then TBSCl (10.4 g, 69.0 mmol) added at same temperature. The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with ice and the resulting mixture was extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with water (20 mL×3) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex/AcOEt=19:1) to afford 1-(*tert*-butyldimethylsilyloxy)-propan-3-ol (10.1 g, 81%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.84 (t, *J*=5.5 Hz, 2H), 3.80 (t, *J*=5.5 Hz, 2H), 1.78 (tt, *J*=5.5, 5.5 Hz, 2H), 0.90 (s, 9H), 0.08 (s, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ: 62.9, 62.5, 34.1, 25.8, 18.2, −5.5; IR (neat): 3600–3050, 2930, 2858, 1472, 1256, 1098; HRMS *m*/*z* (EI) calcd for $C_5H_{13}O_2Si$ ($M^+-{}^t$Bu) 133.0685, found 133.0685.

4.3. Ethyl 5-(*tert*-Butyldimethylsilyloxy)-2-methyl-2-pentenoate

To a stirred −78 °C solution of dimethylsulfoxide (3.18 mL, 47.3 mmol) in CH_2Cl_2 (70 mL) under N_2 atmosphere was added oxalyl chloride (2.07 mL, 23.7 mmol). The resultant mixture was stirred for 15 min and to a solution of 1-(*tert*-butyldimethylsilyloxy)-propan-3-ol (3.00 g, 15.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 20 min at −78 °C, triethylamine (9.92 mL, 71.1 mmol) was added at −78 °C, and the resulting mixture was allowed to warm into room temperature. After 30 min, the reaction mixture was quenched with 10% aqueous HCl and the resulting mixture was extracted with CH_2Cl_2 (20 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Concentration afforded the crude aldehyde, which was used in the next step without further purification. To a suspension of NaH (0.825 g, 18.9 mmol, 55% in dispersion oil) in THF (85 mL) was added ethyl 2-diphenylphosphonopropionate (6.85 g, 20.5 mmol) at 0 °C under N_2 atmosphere and the mixture was stirred at the same temperature for 30 min. A solution of the crude aldehyde in THF (10 mL) was added to the Wittig mixture at −78 °C. After stirring for 15 min at −78 °C, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with hexane (20 mL×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=99:1) to afford ethyl 5-(*tert*-butyldimethylsilyloxy)-2-methyl-2-pentenoate (3.70 g, two steps 86%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.01 (tq, *J*=1.4, 7.2 Hz, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 3.68 (t, *J*=6.5 Hz, 2H), 2.68 (dtq, *J*=1.4, 6.5, 7.2 Hz, 2H), 1.91 (dt, *J*=1.4, 1.4 Hz, 3H), 1.30 (t, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.0, 139.3, 128.4, 62.5, 60.0, 33.2, 25.9, 20.7, 18.3, 14.2, −5.4; IR (neat): 2929, 2858, 1717, 1463, 1255, 1213, 1102, 837, 776; HRMS *m*/*z* (EI) calcd for $C_{10}H_{19}O_3Si$ ($M^+-{}^t$Bu) 215.1103, found 215.1116.

4.4. 5-(*tert*-Butyldimethylsilyloxy)-2-methyl-2-penten-1-ol (4)

To a solution of ethyl 5-(*tert*-butyldimethylsilyloxy)-2-methyl-2-pentenoate (2.18 g, 8.00 mmol) in THF (45 mL) was added diisobutylaluminum hydride (0.95 M in *n*-hexane solution) (23.9 mL, 22.7 mmol) at −78 °C under N_2 atmosphere. The mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with 10% aqueous HCl and the resulting mixture was extracted with diethyl ether (10 mL×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=97:3) to afford 5-(*tert*-butyldimethylsilyloxy)-2-methyl-2-penten-1-ol (0.939 g, 51%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.30 (t, *J*=7.9 Hz, 1H), 4.05 (d, *J*=5.8 Hz, 2H), 3.62 (t, *J*=5.8 Hz, 2H), 2.34–2.27 (m, 3H), 1.82 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.9, 124.6, 62.5, 61.5, 31.1, 25.9, 22.2, 18.5, −5.5; IR (neat): 3600–3050, 2929, 2858, 1472, 1255, 1104; HRMS *m*/*z* (EI) calcd for $C_8H_{17}O_2Si$ ($M^+-{}^t$Bu) 173.0998, found 173.0982.

4.5. (2*R*,3*S*)-5-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-2-methylpenten-1-ol (5)

To a stirred −20 °C solution of $Ti(O^iPr)_4$ (4.06 g, 14.3 mmol) and MS4A (6.49 g) in CH_2Cl_2 (30 mL) were added D-(−)-diethyl tartrate (2.94 g, 14.3 mmol) and a solution of 5-(*tert*-butyldimethylsilyloxy)-2-methyl-2-penten-1-ol **4** (2.99 g, 13.0 mmol) in CH_2Cl_2 (10 mL). The resultant mixture was stirred for 15 min and to a solution of 5.33 M solution of ^{t}BuOOH in toluene (5.35 mL, 28.5 mmol) was added dropwise at same temperature. The reaction flask was then placed into a −20 °C freezer and allowed to remain at that temperature for 5 days. To the reaction mixture was added 10% aqueous tartaric acid at −20 °C with stirring for 30 min at 0 °C. The reaction mixture was filtered through a pad of Celite. The aqueous layers were extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, concentrated in vacuo. To a solution of the crude epoxy alcohol in diethyl ether (15 mL) was added 1 N aqueous NaOH (15 mL) and the resulting mixture was stirred for 30 min at 0 °C. The aqueous layer was extracted with diethyl ether (5 mL×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=97:3) to afford (2*R*,3*S*)-5-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-2-methylpenten-1-ol (2.88 g, 90%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.87 (ddd, *J*=3.8, 4.5, 10.3 Hz, 1H), 3.76 (dt, *J*=2.8, 11.0 Hz, 1H), 3.68 (d, *J*=11.7 Hz, 1H), 3.53 (d, *J*=11.7 Hz, 1H), 2.81 (dd, *J*=4.1, 9.6 Hz, 1H), 2.05 (dq, *J*=3.4, 14.4 Hz, 1H), 1.79–1.66 (m, 1H), 1.44 (s, 3H), 0.92 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 64.5, 62.4, 60.6, 60.6, 31.2, 26.0, 20.4, 18.5, −5.5or −5.6; IR (neat): 3600–3050, 2955, 2929, 2858, 1472, 1257, 1095; $[\alpha]_D^{20}$ −13.2° (*c* 0.93, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_8H_{15}O_2Si$ ($M^+-{}^t$Bu−H_2O) 171.0841, found 171.0832.

4.6. Ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-4,5-epoxy-4-methyl-2-heptenoate (6)

To a stirred −78 °C solution of dimethylsulfoxide (2.22 mL, 33.0 mmol) in CH_2Cl_2 (45 mL) under N_2 atmosphere was added oxalyl chloride (1.44 mL, 16.5 mmol). The resultant mixture was stirred for 20 min and a solution of (2*R*,3*S*)-5-(*tert*-butyldimethylsilyloxy)-2,3-epoxy-2-methylpenten-1-ol **5** (2.70 g, 11.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 20 min at −78 °C, triethylamine (6.88 mL, 49.3 mmol) was added at −78 °C, and the resulting mixture was allowed to warm into room temperature. After 15 min, the reaction mixture was quenched with 10% aqueous HCl and the resulting mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Concentration afforded the crude aldehyde, which was used in the next step without further purification. To a suspension of NaH (0.669 g, 15.3 mmol, 55% in dispersion oil) in THF (100 mL) was added ethyl diethylphosphonoacetate (3.27 mL, 16.5 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at the same temperature for 30 min. A solution of the crude aldehyde in THF (10 mL) was added to the Wittig mixture at −78 °C. After stirring for 20 min at −78 °C, the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with hexane (20 mL×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=49:1) to afford ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-4,5-epoxy-4-methyl-2-heptenoate (3.18 g, two steps 92%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.88 (d, *J*=15.8 Hz, 1H), 6.00 (d, *J*=15.5 Hz, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 3.74 (t, *J*=6.2 Hz, 2H), 3.14 (t, *J*=6.2 Hz, 1H), 1.71 (dt, *J*=6.2, 6.2 Hz, 2H), 1.48 (s, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.9, 145.6, 123.5, 64.5, 60.5, 60.2, 59.6, 31.6, 25.9, 21.4, 18.3, 14.2, −5.4; IR (neat): 2930, 2858, 1723, 1472, 1366, 1303, 1257, 1175, 1097;

$[\alpha]_D^{20}$ −26.4° (*c* 0.95, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{12}H_{21}O_4Si$ ($M^+-{}^tBu$) 257.1209, found 257.1200.

4.7. Ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methyl-2-heptenoate (7)

To a mixture of $Pd_2(dba)_3CHCl_3$ (0.247 g, 0.239 mmol) in dioxane (40 ml) was added *n*-Bu_3P (59.3 μL, 0.239 mmol). To the solution was added formic acid (1.80 mL, 47.7 mmol) and Et_3N (2.49 mL, 18.0 mmol) in dioxane (10 mL) at room temperature, and the mixture was stirred for 5 min. A solution of ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-4,5-epoxy-4-methyl-2-heptenoate **6** (3.00 g, 9.54 mmol) in dioxane (10 mL) was added to the solution, and the mixture was stirred for 3 h. The reaction mixture was diluted with diethyl ether and filtered through a silica gel pad and followed by Florisil sequentially with diethyl ether. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex/AcOEt=19:1) to afford ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methyl-2-heptenoate (2.72 g, 90%) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 6.95 (dd, *J*=8.3, 15.8 Hz, 1H), 5.89 (dd, *J*=1.0, 15.8 Hz, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 3.95–3.80 (m, 3H), 2.50–2.39 (m, 1H), 1.76–1.70 (m, 2H), 1.30 (t, *J*=7.2 Hz, 3H), 1.11 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 166.5, 150.7, 121.6, 75.0, 62.8, 60.1, 42.6, 35.3, 25.8, 18.0, 15.2, 14.2, −5.7; IR (neat): 3600–3050, 2957, 2930, 2884, 2858, 1721, 1472, 1369, 1257, 1093; $[\alpha]_D^{20}$ 12.2° (*c* 0.96, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{14}H_{27}O_3Si$ (M^+−OEt) 271.1729, found 271.1720.

4.8. Ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-4-methyl-2-heptenoate

To a solution of ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-methyl-2-heptenoate **7** (2.51 g, 7.93 mmol), and ethyldiisopropylamine (2.08 mL, 11.9 mmol) in CH_2Cl_2 (40 mL) was added chloromethyl methyl ether (0.78 mL, 10.3 mmol) at 0 °C under an argon atmosphere and the mixture was stirred at room temperature. After stirring for 6 h at 0 °C, ethyldiisopropylamine (1.38 mL, 7.92 mmol) and chloromethyl methyl ether (0.60 mL, 7.90 mmol) were added to the reaction mixture and stirred for 16.5 h at the room temperature. The reaction mixture was quenched with H_2O, and the resulting mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with 10% aqueous HCl, 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=49:1) to afford ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethoxy-4-methyl-2-heptenoate (2.55 g, 89%) as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 6.95 (dd, *J*=7.6, 15.8 Hz, 1H), 5.84 (d, *J*=15.8 Hz, 1H), 4.66 (q, *J*=6.9 Hz, 2H), 4.19 (q, *J*=7.2 Hz, 2H), 3.75–3.65 (m, 3H), 3.38 (s, 3H), 2.68–2.62 (m, 1H), 1.68–1.60 (m, 2H), 1.29 (t, *J*=7.6 Hz, 3H), 1.11 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 166.5, 150.6, 121.5, 96.5, 77.9, 60.2, 59.5, 55.7, 40.2, 34.6, 25.9, 18.2, 14.5, 14.2, −5.4; IR (neat): 2930, 2857, 1722, 1256, 1098, 1038; $[\alpha]_D^{20}$ 9.2° (*c* 1.19, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{14}H_{27}O_5Si$ ($M^+-{}^tBu$) 303.1628, found 303.1613.

4.9. (4*R*,5*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methoxymethyloxy-4-methyl-2-hepten-1-ol

To a solution of ethyl (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethoxy-4-methyl-2-heptenoate (2.50 g, 6.93 mmol) in THF (40 mL) was added diisobutylaluminum hydride (1.02 M *n*-hexane solution) (23.8 mL, 24.3 mmol) at −78 °C under N_2 atmosphere. The mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with 10% aqueous HCl and the resulting mixture was extracted with ethyl acetate (10 mL×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=17:3) to afford (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-4-methyl-2-hepten-1-ol (2.20 g, 99%) as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 5.68–5.66 (m, 2H), 4.66 (d, *J*=1.0 Hz, 2H), 4.12 (d, *J*=3.1 Hz, 2H), 3.72–3.62 (m, 3H), 3.39 (s, 3H), 2.52–2.46 (m, 1H), 1.67–1.62 (m, 2H), 1.06 (d, *J*=6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 134.5, 129.5, 96.4, 78.6, 63.7, 59.8, 55.7, 39.8, 34.4, 25.9, 18.2, 15.2, −5.4; IR (neat): 3600–3050, 2930, 1255, 1097, 1039; $[\alpha]_D^{20}$ 1.2° (*c* 0.94, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{15}H_{31}O_3Si$ (M^+−OMe) 287.2042, found 287.2048.

4.10. (4*R*,5*S*)-7-(*tert*-Butyldimethylsilyloxy)-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene

To a solution of (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethoxy-4-methyl-2-hepten-1-ol (2.05 g, 6.44 mmol) in CH_2Cl_2 (65 mL) were added *p*-toluene sulfonic acid monohydrate (56.3 mg, 0.33 mmol) and 3,4-dihydro-2*H*-pyran (0.70 mL, 7.66 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with CH_2Cl_2 (5 mL×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=19:1) to afford (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-4-methyl-1-tetrahydropyrayloxy-2-heptene (2.54 g, 98%) as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 5.66–5.60 (m, 2H), 4.66 (s, 2H), 4.63–4.61 (m, 1H), 4.23–4.18 (m, 1H), 3.98–3.83 (m, 2H), 3.72–3.63 (m, 3H), 3.54–3.46 (m, 1H), 3.38 (s, 3H), 2.54–2.47 (m, 1H), 1.85–1.52 (m, 8H), 1.05 (dd, *J*=1.0, 6.9 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); IR (neat): 2931, 1471, 1097, 1039; $[\alpha]_D^{20}$ 2.6° (*c* 0.97, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{15}H_{27}O_5$ (M^+−TBS) 287.1858, found 287.1860.

4.11. (4*R*,5*S*)-7-Hydroxy-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene (8)

To a solution of (4*R*,5*S*)-7-(*tert*-butyldimethylsilyloxy)-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene (2.49 g, 6.18 mmol) in THF (12 mL) was added TBAF (1.0 M THF solution) (7.42 mL, 7.42 mmol) at 0 °C under an argon atmosphere. The resulting mixture was allowed to warm into room temperature for 17.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with ethyl acetate (5 mL×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=17:3) to afford (4*R*,5*S*)-7-hydroxy-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene (1.64 g, 92%) as yellow oil. ^1H NMR (300 MHz, $CDCl_3$) *δ*: 5.65–5.63 (m, 2H), 4.72–4.61 (m, 3H), 4.23–4.18 (m, 1H), 3.98–3.93 (m, 1H), 3.92–3.82 (m, 1H), 3.80–3.66 (m, 3H), 3.54–3.47 (m, 1H), 3.42 (s, 3H), 2.53–2.46 (m, 1H), 1.85–1.50 (m, 8H), 1.04 (dd, *J*=1.4, 6.9 Hz, 3H); IR (neat): 3600–3050, 2945, 1454, 1036; $[\alpha]_D^{20}$ −74.6° (*c* 1.06, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{13}H_{23}O_3$ (M^+−MOM) 227.1647, found 227.1629.

4.12. (4*R*,5*S*)-7-Azido-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene

To a solution of (4*R*,5*S*)-7-hydroxy-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene **8** (1.50 g, 5.20 mmol)

in CH_2Cl_2 (26 mL) were added triethylamine (0.75 mL, 5.41 mmol) and methanesulfonyl chloride (0.45 mL, 5.81 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with water and the resulting mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$. Concentration afforded the crude product, which was used in the next step without further purification. To a solution of the crude (4*R*,5*S*)-7-methanesulfonyloxy-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene in DMF (26 mL) were added NaN_3 (1.01 g, 15.5 mmol) and NH_4Cl (0.83 g, 15.5 mmol) at room temperature under an argon atmosphere and the mixture was stirred over night at 55 °C. The reaction mixture was quenched with water and the resulting mixture was extracted with diethyl ether (10 mL×3). The combined organic layers were washed with water (10 mL×3) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (eluent; Hex/AcOEt=19:1) to afford (4*R*,5*S*)-7-azido-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene (1.23 g, two steps 75%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.65–5.62 (m, 2H), 4.69–4.61 (m, 3H), 4.24–4.19 (m, 1H), 3.99–3.84 (m, 2H), 3.61–3.41 (m, 3H), 3.39 (s, 3H), 3.37–3.32 (m, 1H), 2.55–2.49 (m, 1H), 1.88–1.53 (m, 8H), 1.05 (dd, *J*=0.7, 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 134.8, 127.3, 97.8, 96.4, 78.6, 67.7 or 67.6, 62.2, 55.8, 48.3, 39.7 or 39.6, 30.6, 30.2, 25.4, 19.5, 14.5 or 14.3; IR (neat): 2942, 2096, 1455, 1263, 1037; $[\alpha]_D^{20}$ −34.6° (*c* 0.97, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{13}H_{22}NO_3$ (M^+−OMOM−N_2) 240.1600, found 240.1584.

4.13. (4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptenylamide

To a solution of (4*R*,5*S*)-7-azido-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptene (1.13 g, 3.61 mmol) in THF (36 mL) was added $LiAlH_4$ (0.27 g, 7.11 mmol) at 0 °C under an argon atmosphere for 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4 and was filtered through a pad of Celite. Concentration afforded the crude product, which was used in the next step without further purification. To a solution of the crude (4*R*,5*S*)-5-methoxymethoxy-4-methyl-1-tetrahydropyranyloxy-2-heptenylamine in CH_2Cl_2 (7 mL) were added di-*tert*-butyl dicarbonate (1.24 mL, 5.40 mmol) and triethylamine (0.76 mL, 5.45 mmol) at room temperature under an argon atmosphere, and the mixture was stirred over night at the same temperature. The reaction mixture was diluted with ethyl acetate and quenched with 10% aqueous HCl. The aqueous phase was extracted with ethyl acetate (5 mL×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=19:1) to afford (4*R*,5*S*)-*N*-(*tert*-butoxycarbonyl)-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptenylamide (1.35 g, two steps 96%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.63–5.61 (m, 2H), 4.82 (br s, 0.75H), 4.69–4.61 (m, 3H), 4.23–4.17 (m, 1H), 3.98–3.83 (m, 2H), 3.54–3.49 (m, 2H), 3.39 (s, 3H), 3.28–3.15 (m, 2H), 2.51–2.05 (m, 1H), 1.88–1.52 (m, 8H), 1.44 (s, 9H), 1.03 (dd, *J*=1.0, 6.9 Hz, 3H); IR (neat): 3353, 2938, 1715, 1038; $[\alpha]_D^{20}$ −39.7° (*c* 1.05, $CHCl_3$); MS (EI), *m*/*z* 387 (M^+).

4.14. (4*R*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-1-hydroxy-5-methoxymethyloxy-4-methyl-2-heptenylamide (9)

To a solution of (4*R*,5*S*)-*N*-(*tert*-butoxycarbonyl)-5-methoxymethyloxy-4-methyl-1-tetrahydropyranyloxy-2-heptenylamide (1.02 g, 2.63 mmol) in methanol (26 mL) was added *p*-toluene sulfonic acid monohydrate (22.7 mg, 0.13 mmol) at 0 °C under an argon atmosphere. The resulting mixture was allowed to warm into room temperature. After stirring for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with ethyl acetate (5 mL×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 (4*R*,5*S*)-*N*-(*tert*-butoxycarbonyl)-1-hydroxy-5-methoxymethyloxy-4-methyl-2-heptenylamide (0.78 g, 98%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.68–5.63 (m, 2H), 4.86 (br s, 1H), 4.69–4.62 (m, *J*=6.9, 8.9 Hz, 2H), 4.11–4.10 (m, 2H), 3.52 (dt, *J*=4.1, 8.3 Hz, 1H), 3.39 (s, 3H), 3.25–3.16 (m, 2H), 2.51–2.45 (m, 1H), 1.89 (br s, 1H), 1.71–1.54 (m, 2H), 1.44 (s, 9H), 1.04 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.0, 133.9, 129.9, 96.5, 79.6, 79.1, 63.6, 55.9, 39.8, 37.5, 31.1, 28.4, 14.8; IR (neat): 3600–3050, 2932, 1696, 1037; $[\alpha]_D^{20}$ −16.1° (*c* 1.02, $CHCl_3$); HRMS *m*/*z* (EI) calcd for $C_{11}H_{19}NO_4$ (M^+−O^{t}Bu−H) 229.1314, found 229.1322.

4.15. (2*R*,3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-vinyl-piperidine (10)

To a solution of (4*R*,5*S*)-*N*-(*tert*-butoxycarbonyl)-1-hydroxy-5-methoxymethyloxy-4-methyl-2-heptenylamide **9** (702 mg, 2.31 mmol) in THF (23 ml) was added bis(acetonitrile)palladium (II) dichloride (59.9 mg, 0.231 mmol) at 0 °C under an argon atmosphere, and the mixture was stirred for 4.5 h at room temperature. The reaction mixture was filtered through a pad of silica gel and followed by a pad of Florisil sequentially with diethyl ether. Concentration afforded the crude product was purified by silica gel column chromatography (eluent; Hex/AcOEt=9:1) to afford (2*R*,3*R*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-vinyl-piperidine (544 mg, 82%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.77 (ddd, *J*=3.8, 10.7, 17.2 Hz, 1H), 5.20 (ddd, *J*=1.0, 2.4, 10.7 Hz, 1H), 5.07 (ddd, *J*=1.0, 2.1, 17.2 Hz, 1H), 4.65 (s, 2H), 4.08 (dd, *J*=4.8, 13.8 Hz, 1H), 3.83 (dt, *J*=4.8, 11.4 Hz, 1H), 3.36 (s, 3H), 2.91 (dt, *J*=3.8, 13.4 Hz, 1H), 2.20 (t, *J*=6.5 Hz, 1H), 1.79–1.58 (m, 3H), 1.46 (s, 9H), 1.04 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8, 136.4, 115.7, 94.6, 79.6, 72.4, 58.8, 55.3, 38.5, 36.1, 28.3, 26.0, 11.5; IR (neat): 2929, 1696, 1042; $[\alpha]_D^{20}$ −17.4° (*c* 1.07, $CHCl_3$); MS (EI), *m*/*z* 285 (M^+); HRMS *m*/*z* (EI) calcd for $C_{15}H_{27}NO_4$ 285.1940, found 285.1916.

4.16. (2*R*,3*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-(4-phenyl-1,3-butadienyl)-piperidine (11)

A gas of O_3 was bubbled into a solution of (2*R*,3*R*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-vinyl-piperidine **10** (202 mg, 0.708 mmol) in CH_2Cl_2/MeOH (5 mL, 1:4) at −78 °C until the solution was turned to blue. Then an argon gas bubbled through the solution until its color was clear. Dimethyl sulfide (0.16 mL, 2.19 mmol) was added to the reaction mixture. The resulting mixture was allowed to warm into room temperature. After stirring for 15 min, the reaction mixture was quenched with water, and the resulting mixture was extracted with hexane (5 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$. Concentration afforded the crude aldehyde, which was used in the next step without further purification. To a suspension of diethyl (*E*)-cinnamylphosphonate (198 mg, 0.779 mmol) in THF (3 mL) was added *n*-BuLi (0.55 mL, 0.913 mmol) at −78 °C under an argon atmosphere and the mixture was stirred at the same temperature for 40 min. A solution of the crude aldehyde in THF (4 mL) was added to the Wittig mixture at −78 °C. After stirring for 10 min at −78 °C, the reaction mixture was stirred over night at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl

and the resulting mixture was extracted with diethyl ether (5 ml×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=19:1) to afford (2*R*,3*R*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-(4-phenyl-1,3-butadienyl)-piperidine (212 mg, two steps 78%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.20 (m, 5H), 6.78 (dd, *J*=10.3, 15.5 Hz, 1H), 6.51 (d, *J*=15.8 Hz, 1H), 6.21 (ddd, *J*=1.7, 10.3, 15.5 Hz, 1H), 5.77 (dd, *J*=4.5, 15.5 Hz, 1H), 4.67–4.65 (m, 2H), 4.16–4.09 (m, 1H), 3.86 (dt, *J*=4.8, 11.4 Hz, 1H), 3.37 (s, 3H), 2.94 (dt, *J*=3.8, 13.1 Hz, 1H), 2.26–2.18 (m, 1H), 1.76–1.64 (m, 3H), 1.48 (s, 9H), 1.05 (d, *J*=6.9 Hz, 3H); IR (neat): 2931, 1693, 1456, 1365, 1259, 1151, 1106; HRMS *m*/*z* (EI) calcd for $C_{23}H_{33}NO_4$ (M^+) 387.2410, found 387.2395.

4.17. Dienomycin C ((+)-1) and dienomycin C ((+)-1) hydrochloride salt

A solution of (2*R*,3*R*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-(4-phenyl-1,3-butadienyl)-piperidine **11** (82.3 mg, 0.212 mmol) in methanol (2 mL) was added a catalytic amount of concd HCl at room temperature under an argon atmosphere and the mixture was stirred at 40 °C for 26 h. Concentration afforded the crude product was purified by silica gel column chromatography (eluent; Hex/AcOEt=9:1→AcOEt/MeOH=9:1) to afford dienomycin C ((+)-**1**) (33.1 mg) as the hydrochloride salt, white solid. The solid was recrystallized (mp 208–211 °C). The dienomycin C as the hydrochloride salt were diluted with benzene and 1 N aqueous NaOH added. The aqueous layer was extracted with benzene. The combined organic layers were concentrated in vacuo to afford dienomycin C ((+)-**1**) (30.3 mg, 58%) as white solid. The analytical sample of dienomycin C ((+)-**1**) was recrystallized (16.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40–7.19 (m, 5H), 6.76 (dd, *J*=10.3, 15.8 Hz, 1H), 6.52 (d, *J*=15.8 Hz, 1H), 6.36 (dd, *J*=10.7, 15.1 Hz, 1H), 5.72 (dd, *J*=8.6, 15.1 Hz, 1H), 3.94 (q, *J*=2.8 Hz, 1H), 3.26 (dd, *J*=8.9, 9.6 Hz, 1H), 3.12 (dq, *J*=4.1, 11.7 Hz, 1H), 2.88 (dt, *J*=3.4, 11.0 Hz, 1H), 1.85–1.75 (m, 2H), 1.60–1.54 (m, 1H), 0.93 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.2, 135.7, 132.5, 132.1, 128.6, 128.5, 127.5, 126.3, 69.0, 59.2, 40.3, 40.0, 33.4, 15.0; IR (neat): 3600–3050, 2930, 1448; MS (EI), *m*/*z* 243 (M^+); HRMS *m*/*z* (EI) calcd for $C_{16}H_{21}NO$ (M^+) 243.1623, found 243.1627; $[\alpha]_D^{20}$ 45.4° (*c* 0.88, methanol, as hydrochloride salt) (lit.[1] +65°);[8] $[\alpha]_D^{25}$ 45.1° (*c* 0.81, methanol, as free base).

4.18. (2*S*,3*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,3-epoxy-2-methylpenten-1-ol (12)[9]

According to the Sharpless asymmetric epoxidation by using L-(+)-diethyl tartrate, (+)-**12** was prepared from **4** in 83% yield. $[\alpha]_D^{20}$ 14.6° (*c* 1.11, $CHCl_3$).

4.19. (4*S*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-1-hydroxy-5-methoxymethyloxy-4-methyl-2-heptenylamide (13)

According to the same producere,[9] the enantiomer **13** was prepared in 78% yield; $[\alpha]_D^{20}$ 17.1° (*c* 1.06, $CHCl_3$).

4.20. (2*S*,3*S*,4*R*)-*N*-(*tert*-Butoxycarbonyl)-4-methoxymethyloxy-3-methyl-2-vinyl-piperidine (14)

According to the same producere,[9] the enantiomer **14** was prepared in 75% yield; $[\alpha]_D^{20}$ 18.7° (*c* 0.98, $CHCl_3$).

4.21. Dienomycin C ((−)-1) and dienomycin C ((−)-1) hydrochloride salt

According to the same producere,[9] (−)-dienomycin C was prepared in 43% yield; $[\alpha]_D^{20}$ −44.4° (*c* 0.97, methanol, as hydrochloride salt).

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Supplementary data

Experimental procedures, products characterization and copies of NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.08.048. These data include MOL files and InChiKeys of the most important compounds described in this article.

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9. The all experimental procedures of the synthesis of (−)-**1** was involved in the Supplementary data.
10. The reaction mechanism was shown in Ref. 5b.
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