EJ52-1999-595

Journal of the Chinese Chemical Society, **1999**, *46*, 595-600

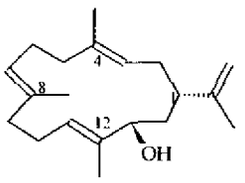
First Total Synthesis of (±)-13-Hydroxyneocembrene

Yacheng Xing* (邢雅成), Wen Cen* (岑 文), Jiong Lan (蘭 炯),
Ying Li* (李 瀛) and Yulin Li (李裕林)
National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, Peoples Republic of China

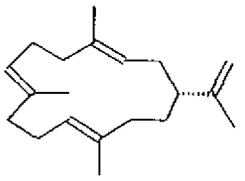
First total synthesis of (±)-13-hydroxyneocembrene (**1**), starting from 6-methyl-5-hepten-2-one (**6**) and geraniol (**7**), is described. The key steps are (i) the addition of sulfur-stabilized carbanion **12** to aldehyde **9**, (ii) the synthesis of **18** by using phase-transfer catalyzed coupling reaction, and (iii) low-valent titanium-induced intramolecular coupling of oxo aldehyde **3** to afford the target molecule after the final deprotection.

INTRODUCTION

Cembranoids, a 14-membered cyclic diterpene family, are of interest to synthetic chemists and biologists because of their unusual structure and wide range of biological activities.[1,2] (13*S*)-hydroxyneocembrene (**1**), a cembranoid which was isolated in 1988 from soft coral *Sarcophyton trocheliophorum*,[3] has been shown to be an effective inductor of the release of labeled glucose from the lecithincholesterol liposomes and has cytostatic activities.[4] It can be regarded as a hydroxy derivative of cembrene-A (**2**), which was the sex pheromone of termites.[5] The geometrical structure and absolute configuration of **1** have been defined to be 1*S*,3*E*,7*E*,11*E*,13*S*. As far as we know, the synthesis of (13*S*)-hydroxyneocembrene (**1**) has not been reported yet. We have now achieved the total synthesis of (±)-**1** and provide here the details of this accomplishment.



1



2

Our overall plan for the synthesis of (±)-hydroxyneocemberene (**1**) started from 6-methyl-5-hepten-2-one (**6**) and geraniol (**7**). The desired product can be obtained from a common precursor such as **3** by low-valent titanium-induced carbonyl coupling (Scheme I). There are previous reports to support this hypothesis. For example, McMurry found that open-chain oxo aldehydes undergo a carbonyl-coupling reaction on treatment with a solution of $TiCl_3$/Zn/Cu in dimethoxyethane (DME) to give good yields of large-ring cycloalkenes at reflux temperature[6] and large-ring cyclic 1,2-dios (pinacols) at low temperature.[7]

RESULTS AND DISCUSSION

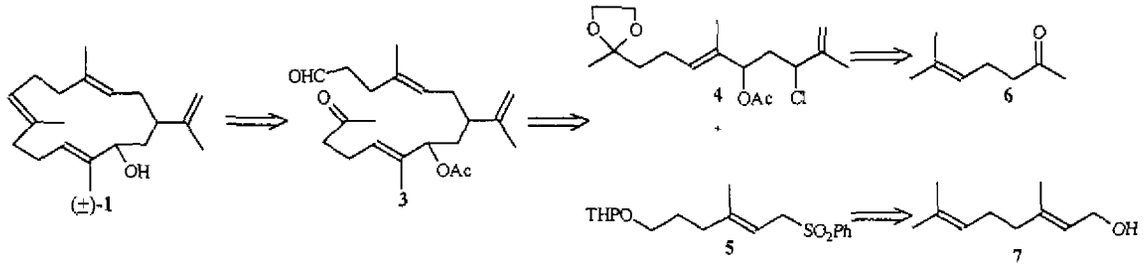
Protection of 6-methyl-5-hepten-2-one by reaction with a large excess of ethylene glycol using *p*-TsOH as a catalyst in refluxing benzene overnight yielded a 92% yield of the ethylene acetal **8**, which was oxidized by 70% *tert*-butyl hydroperoxide in the presence of selenium oxide (0.5 equiv) in dichloromethane to give aldehyde **9** in 64% yield. According to the methods described in the literature,[8] benzenesulfonyl derivative **12** was prepared, and then was lithiated with 1.5 equiv. of LDA in anhydrous THF at -78 °C under an argon atmosphere. Coupling reaction[9] of **9** with the lithium salt of **12** at the same temperature proceeded smoothly to afford **13**, of which the sulfonyl group was removed by treatment with excess of Li in ethylamine at -78 °C to give the reduced product **14** in 62% yield. Alcohol **14** reacted with Ac_2O in pyridine to give the corresponding acetate **15**, which underwent regioselective allylic chlorination with *tert*-butyl hypochlorite on silica gel to give **4**.

Another fragment, **5**, was prepared from geraniol (**7**). Geraniol was converted to geranyl phenyl sulphone **16** by using a general method.[8] Compound **16** was subjected to ozonolysis in CH_2Cl_2 at -78 °C to give the aldehyde **17**, which was converted to the corresponding alcohol by reduction with $NaBH_4$ in MeOH at 0 °C (85% yield) after protection with DHP, compound **5** was ready for coupling with compound **4**.

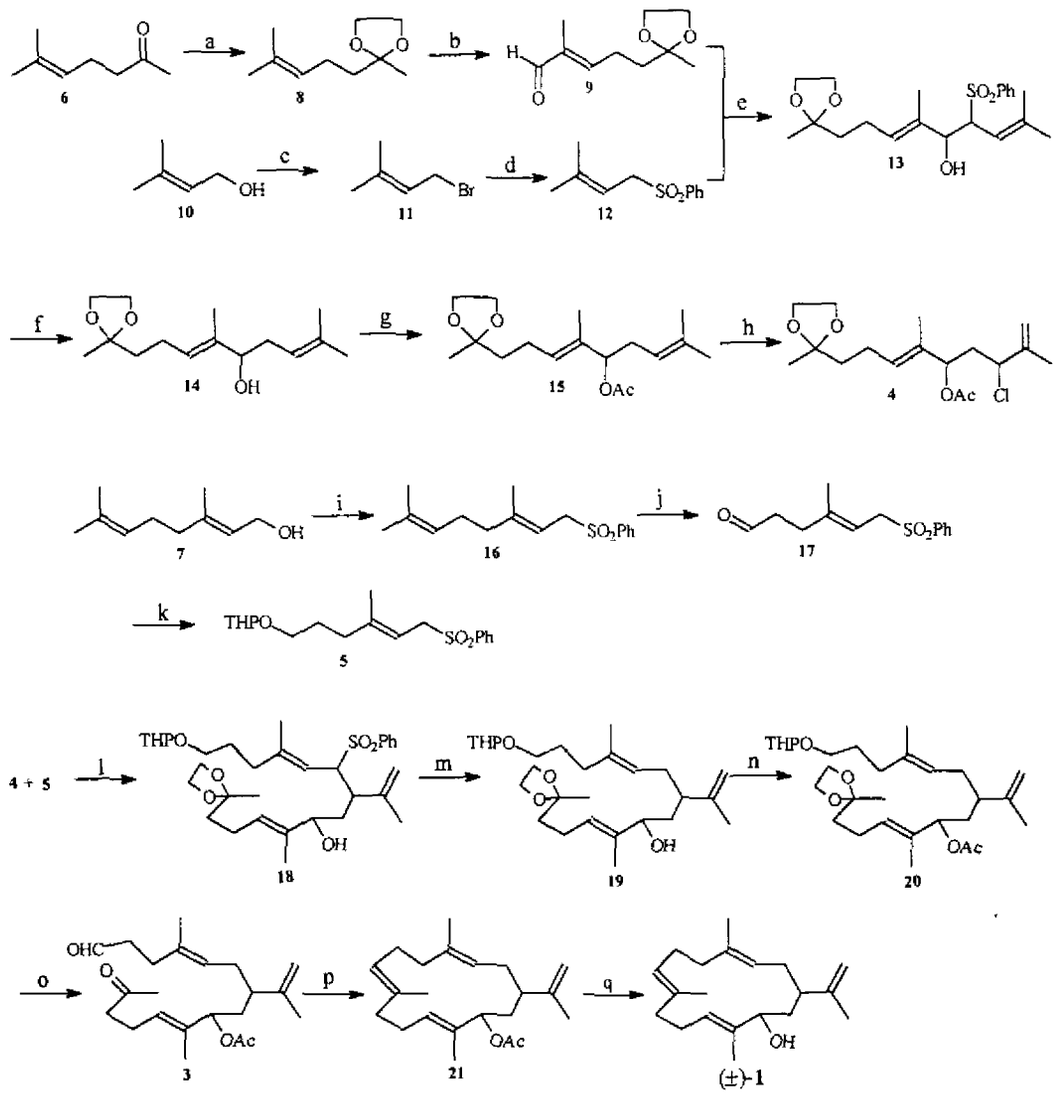
Allylic phenyl sulphone **5** was coupled with allylic chloride **4** by using $(n\text{-}C_4H_9)_4NBr$ (TBAB) as a phase-transfer catalyst in 50% NaOH to afford **18** in 50% yield[10] re-

* Present address: Department of Chemistry, Qingdao University, Qingdao, 266071

Scheme I



Scheme II



a) $HOCH_2CH_2OH$, *p*-TsOH, 92%; b) SeO_2, *t*-BuOOH, CH_2Cl_2, 0 °C~rt, 64% ; c) PBr_3, Py, 80%; d) $NaSO_2Ph$, DMF, 85%; e) $(CH_3)_2C{=}CHCH_2SO_2Ph$, LDA, THF, - 78 °C, 85%; f). Li-$EtNH_2$, THF, -78 °C, 62%; g). Ac_2O, Py, 92%; h). *t*-BuOCl, Silica gel-H, 60%; i). 1, PBr_3, Py; 2. $NaSO_2Ph$, 73%; j). O_3/CH_2Cl_2, -78 °C, then CH_3SCH_3, 80%; k). 1. $NaBH_4$ / MeOH, 0 °C, 85%; 2. DHP/*p*-TsOH, CH_2Cl_2, rt, 70%; l). 50% NaOH, TBAB, 50%; m). Li-$EtNH_2$, THF, 65%; n). Ac_2O, Py, 95%; o). 1)MeOH, *p*-TsOH, 50 °C, 82%; 2)PCC, CH_2Cl_2, 90%; p). $TiCl_4$, Zn/Cu, THF, reflux 30 h, 38%; q). K_2CO_3, MeOH, 77%.

moval of the phenylsulphone, giving alcohol **19**, and protection with Ac_2O in pyridine resulted in **20**. Compound **20** was treated with a catalytic amount of *p*-TsOH in MeOH, and then PCC in CH_2Cl_2, to give a dicarbonyl compound **3** as a colorless oil. The final crucial step of intramolecular macrocyclization was induced by low-valent titanium. A highly diluted solution of **3** (0.004 M) in dry THF was added slowly via syringe to the refluxing mixture of $TiCl_4$/Zn-Cu in THF over 30 h afforded the intramolecular cyclization compound **21**,[11] which was saponified using K_2CO_3/MeOH to give (±)-13-hydroxyneocembrene **1**.

In conclusion, we have completed the first synthesis of (±)-13-hydroxyneocembrene in 14 steps starting from 6-methyl-5-hepten-2-one and geraniol.

EXPERIMENTAL SECTION

IR spectra were obtained on a FT-170SX spectrometer. ^{1}H NMR spectra were recorded on a FT-80A or AM-400 instrument in $CDCl_3$ solution, and chemical shifts are reported in ppm units with TMS as the internal standard. Mass spectra (MS) were measured on a ZAB-HS spectrometer by direct inlet 70 eV, and signals given in *m/z* with relative intensity (%) in parenthesis. All solvents were freshly purified and dried by standard techniques prior to use. All reactions were routinely carried out under an inert atmosphere of argon and monitored by TLC unless otherwise noted. Products were purified by flash column chromatography (FCG) on silica gel (200-300 mesh), purchased from Qing Dao Marine Chemical Co. In the work up, all organic phases were washed with water and brine consecutively, then dried over anhydrous. $MgSO_4$ and filtered prior to rotary evaporation under reduced pressure.

2-Methyl-2-(4-methyl-3-pentenyl)-1,3-dioxolane (8)

A mixture of ketone **6** (10.8 g, 85.7 mmol), ethylene glycol (13.26 g, 138 mmol) and added *p*-TsOH (200 mg) in anhydrous benzene (60 mL) was refluxed for a period of 5 h with azeotropic distillation to remove water from the reaction mixture. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated to remove most of the benzene and the resulting residue was diluted with ether (200 mL), washed successively with saturated sodium bicarbonate aqueous solution, water, brine, and then dried. Evaporation of the solvent under reduced pressure gave an oily residue, which was purified by FCG on silica gel (pet. ether/Et_2O 10:1) to afford dioxolane **8** (13.4 g, 92%).

IR (film) ν 2985, 1650, 1448 cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS) δ 1.22 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.70-2.20 (m, 4H), 3.83 (s, 4H, OCH_2CH_2O), 5.00 (t, 1H, J = 6.6 Hz).

2-Methyl-2-(4-formyl-4-methyl-3-pentenyl)-1,3-dioxolane (9)

To a stirred clear mixture of selenium dioxide (1.64 g, 14.8 mmol) and 70% *tert*-butyl hydroperoxide (7.58 mL, 59.4 mmol) in CH_2Cl_2 (50 mL) was added dropwise a solution of dioxolane **8** (5.05 g, 29.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C (ice-water bath) over 30 min. The stirring was continued for 5 h at 0 °C, and the reaction mixture was allowed to warm to room temperature overnight. The mixture was diluted with ether (200 mL), washed successively with 1 N NaOH (4 × 40 mL), water, brine, and dried. Evaporation of the solvent under vacuum gave an oily crude product, which was purified by flash column chromatography (pet. ether/acetone 10:1) to afford aldehyde **9** (3.50 g, 64%) IR (film) ν 2954, 1685, 1440, 1380, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS) δ 1.28 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.70-2.50 (m, 4H), 3.89 (s, 4H, OCH_2CH_2O), 6.45 (t, 1H, J = 6.8 Hz), 9.33 (s, 1H, CHO).

2-Methyl-2-(5-hydroxyl-6-phenylsulfonyl-4,8-dimethyl-3*E*,7*E*-nonadienyl)-1,3-dioxolane (13)

A solution of freshly distilled anhydrous diisopropylamine (2.86 mL, 20.2 mmol) in THF (20 mL) was cooled to -60 °C (dry ice-acetone bath) under argon, and a *n*-hexane solution of *n*-BuLi (1.6 N, 8.4 mL, 13.45 mmol) was introduced via a dry syringe. The resulting mixture was stirred for 45 min at that temperature, and a solution of **12** (1.83 g, 8.71 mmol) in THF (10 mL) was added dropwise via syringe. The reaction mixture was stirred for an additional 2 h and cooled again to -78 °C. A solution of THF (20 mL) containing aldehyde **9** (1.61 g, 8.75 mmol) was added dropwise at -78 °C. The resulting mixture was stirred for 1.5 h at -78 °C and allowed to warm to room temperature for 1 h stirring. After quenching with saturated ammonium chloride aqueous solution, to the resulting mixture was added water (5 mL) and ether (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (3 × 40 mL). The combined organic phase was washed with water and brine. The organic phase was dried, and the solvent was evaporated in vacuum. Purification of the residue by flash column chromatography (pet. ether/acetone 8:1) gave alcohol **13** (2.92 g, 85%).

IR (film) ν 3385, 2982, 2936, 2885, 1660, 1450, 1138, 1059 cm^{-1}. ^{1}H NMR ($CDCl_3$/TMS) δ 1.23 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.70-2.50 (m, 5H), 3.88 (s, 4H, OCH_2CH_2O), 4.20-4.80 (m, 2H, CHO,

$CHSO_2$), 5.15-5.58 (m, 2H), 7.34-7.80 (m, 5H, ArH). MS *m/z* (%) 394 (M^+, 0.4), 377 (5), 189 (10), 177 (80), 153 (15), 135 (20), 81 (70), 71 (100). Anal. Calcd for $C_{21}H_{30}SO_5$: C, 63.96; H, 7.61; S, 8.12. Found: C, 63.50; H, 7.64; S, 8.01.

2-Methyl-2-(5-hydroxyl-4,8-dimethyl-3*E*,7*E*-nonadienyl)-1,3-dioxolane (14)

A solution of dry ethylamine (10 mL) in anhydrous THF (3 mL) containing 2 g lithium wire was stirred at -78 °C for 1 h, and the alcohol **13** (3.63 g, 9.2 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 0.5 h, and methanol (10 mL) was added. The solution was allowed to warm to room temperature and poured into water, and then extracted with ether. The combined organic phase was washed with water and brine, and then dried. The solution was concentrated on a rotary evaporator to give a residue, which was purified by flash column chromatography (pet. ether/acetone 18:1) to give alcohol **14** (1.45 g, 62%).

IR (film) ν 3396, 2959, 2872, 1447, 1055 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.25 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.70-2.40 (m, 7H), 3.93 (s, 4H, OCH_2CH_2O), 4.25 (m, 1H, CHO), 5.0-5.60 (m, 2H, CH=). MS *m/z* (%) 254 (M^+, 0.1), 237 (4), 177 (20), 153 (20), 135 (40), 99 (50), 81 (70), 71 (100).

2-Methyl-2-(5-acetoxy-4,8-dimethyl-3*E*,7*E*-nonadienyl)-1,3-dioxolane (15)

A mixture of alcohol **14** (1.45 g, 5.71 mmol) and Ac_2O (8 mL) in pyridine (10 mL) was stirred at room temperature for 10 h. To the reaction mixture was added water (20 mL) and then extracted with ether (4 × 15 mL). The combined organic phase was washed with water, brine, and then dried. The solvent was evaporated in vacuum, and the residue was purified by flash column chromatography (pet. ether/acetone 20:1) to give ester **15** (1.52 g, 92%).

IR (film) ν 2979, 2870, 1735, 1240, 1025 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.30 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.68-2.30 (m, 6H), 2.03 (s, 3H, CH_3CO), 3.95 (s, 4H, OCH_2CH_2O), 5.0-5.52 (m, 3H, CH=, CHO). MS *m/z* (%) 296 (M^+, 10), 281 (5), 271 (10), 175 (100), 153 (15), 135 (50), 107 (60), 71 (80). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.92; H, 9.46. Found: C, 68.48; H, 9.37.

2-Methyl-2-(5-acetoxy-7-chloro-4,8-dimethyl-3*E*,7*E*-nonadienyl)-1,3-dioxolane (4)

To a vigorous stirring mixture of **15** (1.32 g, 4.46 mmol) and silica gel (2 g) in dry *n*-hexane cooled to 0 °C was added *t*-butyl hypochlorite (0.58 g, 5.5 mmol) over 5 min. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 1 h. The mixture was filtered and the filtrate was washed with ether (10 mL). The combined organic phase was washed with 10% sodium sulfite, water, brine and then dried. The solution was concentrated on a rotary evaporator to give a residue, which was purified by flash column chromatography (pet. ether/acetone 20:1) to give ester **4** (890 mg, 60%).

IR (film) ν 2980, 2860, 1734, 1245 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.34 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 1.68-2.50 (m, 6H), 2.06 (s, 3H, CH_3CO), 3.95 (s, 4H, OCH_2CH_2O), 4.30 (m, 1H, CHCl), 4.86, 4.96 (2s, 2H, CH_2=), 5.12-5.54 (m, 2H, CH=, CHO). MS *m/z* (%) 331 (M+1, 0.3), 330 (M^+, 1.0%), 317 (10), 315 (30), 295 (25), 273 (33), 271 (100), 209 (32), 173 (65), 154 (50), 135 (50), 71 (60). Anal. Calcd for $C_{17}H_{27}O_4Cl$: C, 61.72; H, 8.17; Cl, 10.76. Found: C, 61.50; H, 8.13; Cl, 10.45.

4-Methyl-6-phenylsulfonyl-4*E*-hexenal (17)

A stirring solution of **16** (2.78 g, 10 mmol) in CH_2Cl_2 was cooled to -78 °C and subjected to ozonization. After the reaction was completed (monitored by TLC), methyl sulfide (1 mL) was added to the reaction mixture. The resulting mixture was stirred for 2 h at -20 °C and 2 h at room temperature. Evaporation of the solvent gave a residue which was purified by flash column chromatography (pet. ether/acetone 10:1) to give aldehyde **17** (2.0 g, 80%).

^1H NMR ($CDCl_3$/TMS) δ 1.38 (s, 3H, CH_3), 1.70-2.40 (m, 4H), 3.78 (d, 2H, J = 8.0 Hz, CH_2SO_2), 5.19 (t, 1H, J = 8.0 Hz, CH=), 7.48-7.90 (m, 5H, ArH), 9.76 (br., 1H, CHO).

3-Methyl-6-(2-tetrahydropyranoxy)-2-hexenyl-phenylsulfone (5)

To a stirring solution of **17** (2.0 g, 7.94 mmol) in anhydrous methanol (20 mL) was added $NaBH_4$ (0.5 g, 13.8 mmol) by portions at 0 °C. After 2 h, methanol was removed under reduced pressure and the residue was dissolved in water (10 mL), and extracted with ether (3 × 20 mL). The combined organic phase was washed with water, brine and then dried. Removal of the solvent in vacuum gave a colorless oil which was dissolved in CH_2Cl_2 (20 mL) without further purification. *p*-TsOH (20 mg) was added, followed by dropwise addition of dihydropyran (565 mg, 96.72 mmol) to the resulting solution. The mixture was stirred for 2 h at room temperature, and ether (100 mL) was added. The organic phase was washed with saturated $NaHCO_3$ aqueous solution, water, brine and then dried. The solution was concentrated on a rotary evaporator to give a residue, which was purified by flash column chromatography (pet. ether/acetone 8:1) to give product **5** (1.58 g, 60%).

IR (film) ν 2945, 2870, 1445, 1140 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.43 (s, 3H, CH_3), 1.46-2.30 (m, 10H), 3.40-4.20 (m, 6H), 4.54 (br. s, 1H, OCHO), 5.25 (t, 1H, J = 7.8 Hz), 7.48-7.90 (m, 5H, ArH).

2-Methyl-2-(4,10-dimethyl-5-hydroxy-7-isopropenyl-8-phenylsulfonyl-13-tetrahydropyranoxy)-3*E*,9*E*-tridecadienyl-1,3-dioxolane (18)

To a mixture of **4** (563 mg, 1.70 mmol) and **5** (567 mg, 1.68 mmol) in 50% NaOH aqueous (20 mL) with efficient stirring was added (n-C_4H_9)$_4$NBr (TBAB) (250 mg, 0.77 mmol). After being stirred for 24 h at room temperature, the reaction mixture was diluted with water (80 mL) and extracted with ether (4 × 20 mL). The combined organic phase was washed with water, brine and dried. Removal of the solvent in vacuum gave a colorless oil which was dissolved in MeOH and K_2CO_3 (1.0 g, 7.0 mmol) was added. The reaction mixture was stirred for 2 h at room temperature, and concentrated on a rotary evaporator to give a residue, which was purified by flash column chromatography (pet. ether/acetone 6:1) to give product **18** (495 mg, 50%).

IR (film) ν 3438, 2956, 2925, 1664, 1450, 1135 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.42 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.30-2.30 (m, 18H), 3.40-4.30 (m, 6H), 3.96 (s, 4H, OCH_2CH_2O), 4.52 (br. s, 1H, OCHO), 4.88 (s), 4.96 (s, 2H, CH_2=), 5.00-5.50 (m, 2H, CH=), 7.40-7.90 (m, 5H, ArH). MS *m/z* (%) 408 (5), 302 (10), 271 (80), 153 (60), 85 (80), 77 (100), 71 (50), 43 (26). Anal. Calcd for $C_{33}H_{50}SO_7$: C, 67.12; H, 8.47; S, 5.42. Found: C, 67.70; H, 8.50; S, 5.66.

2-Methyl-2-(4,10-dimethyl-5-hydroxyl-7-isopropenyl-13-tetrahydropyranoxy)-3*E*,9E-tridecadienyl-1,3-dioxolane (19)

A solution of dry ethylamine (5 mL) in anhydrous THF (2 mL) containing 0.5 g lithium wire was stirred at -78 °C for 1 h, and then the alcohol **18** (464 mg, 0.79 mmol) in THF (2 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 45 min, and methanol (10 mL) was added. The solution was allowed to warm to room temperature and poured into water, and then extracted with ether. The combined organic phase was washed with water and brine, and then dried. The solution was concentrated on a rotary evaporator to give a residue, which was purified by flash column chromatography (pet. ether/acetone 8:1) to give alcohol **19** (230 mg, 65%).

IR (film) ν 3505, 3438, 2955, 2925, 1668, 1054 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.28-2.50 (m, 20H), 3.50-4.30 (m, 5H), 3.94 (s, 4H, OCH_2CH_2O), 4.55 (br. s, 1H, OCHO), 4.86 (s), 4.95 (s, 2H, CH_2=), 5.00-5.50 (m, 2H, CH=). MS *m/z* (%) 450 (M^+, 1.2%), 433 (5), 271 (80), 153 (60), 85 (95), 71 (100), 43 (50).

2-Methyl-2-(5-acetoxy-4,10-dimethyl-7-isopropenyl-13-tetrahydropyranoxy)-3*E*,9*E*-tridecadienyl-1,3-dioxolane (20)

A mixture of alcohol **19** (200 mg, 0.44 mmol) and Ac_2O (4 mL) in pyridine (5 mL) was stirred at room temperature for 10 h. Water (10 mL) was added, and the mixture was extracted with ether (3 × 10 mL). The combined organic phase was washed with water, brine, and then dried. The solvent was evaporated in vacuum, and the residue was purified by flash column chromatography (pet. ether/acetone 20:1) to give ester **20** (208 mg, 95%).

IR (film) ν 2950, 2925, 1713, 1668, 1049 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.44 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.04 (s, 3H, CH_3CO), 1.40-2.30 (m, 19H), 3.50-4.50 (m, 5H, CHO, CH_2O), 3.94 (s, 4H, OCH_2CH_2O), 4.56 (br. s, 1H, OCHO), 4.80 (s), 4.84 (s, 2H, CH_2=), 5.00-5.50 (m, 2H, CH=). MS *m/z* (%) 492 (M^+, 0.3%), 460 (10), 397 (8), 289 (90), 271 (40), 153 (30), 135 (30), 93 (30), 85 (95), 71 (100), 43 (80). Anal. Calcd for $C_{29}H_{48}O_6$: C, 70.73; H, 9.76. Found: C, 70.28; H, 9.65.

9-Acetoxy-4,10-dimethyl-7-isopropenyl-14-oxo-4*E*,10*E*-pentadecadienal (3)

A solution of **20** (198 mg, 0.4 mmol) in anhydrous methanol (10 mL) containing 5 mg p-TsOH was warmed to 50 °C and stirred for 3 h. After cooling, the reaction mixture was concentrated in vacuum. The residue without further purification was dissolved in CH_2Cl_2 (5 mL) and added dropwise to a suspension of PCC (300 mg, 1.40 mmol) and 0.8 g silica gel in CH_2Cl_2 (15 mL) at room temperature with vigorous stirring. After 1 h, the reaction mixture was filtered through a short column of silica gel, the filtrate was concentrated in vacuum and purified by flash column chromatography (pet. ether/acetone 10:1) to give the corresponding aldehyde **3** (107 mg, 74%).

IR (film) ν 2950, 2925, 1713, 1668, 1049 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.54 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 2.04 (s, 3H, CH_3CO), 1.70-2.30 (m, 13H), 4.74 (m, 1H, OCHO), 4.78 (s), 4.80 (s, 2H, CH_2=), 5.00-5.50 (m, 2H, CH=), 9.65 (d, 1H, CHO). MS *m/z* (%) 362 (M^+, 10), 306 (40), 289 (40), 247 (70), 135 (80), 71 (100), 43 (80). Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.93; H, 9.39. Found: C, 72.66; H, 9.01.

13-Acetoxy-neocembrene (21)

To an anhydrous THF solution (20 mL) was added

$TiCl_4$ (0.3 mL, 2.7 mmol), dropwise via a dry syringe dropwise carefully at -78 °C with efficient stirring over 5 min. After removal of the cooling bath, Zn-Cu couple (1.0 g) was added to the resulting tetrahydrofuran suspension of $TiCl_4$·THF complex. The suspension was refluxed for 2 h, and a dilute solution of aldehyde **3** (45 mg, 0.12 mmol) in dry THF (30 mL) was added slowly via syringe over 30 h. After the addition was completed, the reaction mixture was refluxed for an additional 3 h, cooled to room temperature, and diluted with *n*-pentane (15 mL) with vigorous stirring. The resulting mixture was filtered rapidly through a short column on silica gel to give a clear filtrate which was concentrated in vacuum to yield a crude oil. Purification of the oil by flash column chromatography (pet. ether/ether 80:1) gave ester **21** (16 mg, 38%).

IR (film) ν 2952, 1735, 1664, 1243, 1022 cm^{-1}. ^1H NMR ($CDCl_3$/TMS) δ 1.56 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 2.04 (s, 3H, CH_3CO), 1.80-2.30 (m, 13H), 4.70 (m, 1H, HCO), 4.74 (s), 4.76 (s, 2H, CH=), 5.00-5.40 (m, 3H, CH=). MS *m/z* (%) 330 (M^+, 0.7%), 289 (20), 271 (100), 189 (60), 121 (80), 99 (40).

13-Hydroxyneocembrene (±-1)

A mixture of **21** (12 mg, 0.036 mmol) and K_2CO_3 powder (10 mg, 0.08 mmol) in methanol (2 mL) was stirred vigorously for 1 h at 0 °C. After removal of the solvent, the residue was purified by flash column chromatography (pet. ether/ether 50:1) to afford 13-hydroxyneocembrene **1** (8 mg, 77%).

IR (film) ν 3620, 3050, 1644, 950 cm^{-1}. ^1H *NMR* ($CDCl_3$/TMS) δ 1.56 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.85-2.50 (m, 14H), 4.40 (m, 1H,.HCO), 4.72 (s), 4.80 (s, 2H, CH_2=), 5.00-5.40 (m, 3H, CH=). MS *m/z* (%) 288 (M^+, 0.1%), 271 (5), 255 (30), 237 (20), 189 (100), 121 (60). ^{13}C NMR ($CDCl_3$/TMS) δ 14.2, 14.8, 15.6, 19.1, 23.8, 25.0, 29.6, 32.8, 37.4, 38.8, 45.3, 75.5, 110.5, 122.6, 124.7, 125.8, 133.1, 135.4, 136.2, 149.2.

ACKNOWLEDGMENT

This work was financially supported by the National Nature Science Foundation of China (Grant No. 29672015).

Received October 23, 1998.

Key Words

Total synthesis; Macrocyclization; Cemberenoid diterpene; Phase-transfer catalysis; 13-Hydroxyneocembrene.

REFERENCES

1. For a review of cembranoid synthesis, see: Tius, M. A. *Chem. Rev.* **1988**, *88*, 719.
2. Cox, N. J. G.; Mills, S. D.; Pattenden, G. *J. Chem. Soc., Perkin Trans. I* **1992** 1313, and the references cited therein.
3. Suleimenova, A. M.; Kalinovskii, A. I.; Raldugin, V. A.; Shsvtsov, S. A.; Bagaryana, I. Yu.; Gatilov, Yu. V.; Kuznetsova, T. A.; Elyalcov, G. B. *Khim. Prir. Soedin.* **1988**, *4*, 453.
4. Kuznetsova, T. A.; Popov, A. M.; Agafonova, I. G.; Suleimenova, A. M.; Elyakov, G. B. *Khim. Prir. Soedin.* **1989**, *1*, 122.
5. Moore, B. P. *Nature (London)* **1966**, *211*, 746.
6. McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655.
7. McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169.
8. Torii, S.; Uneyama, K.; Matsunami, S. *J. Org. Chem.* **1980**, *45*, 16.
9. Kato, T.; Takayanagi, H.; Vyehara, T.; Kitahara, I. Y. *Chem. Lett.* **1977**, 1009.
10. Lnoue, S.; Kaneko, T.; Takahashi, Yu.; Miyamoto, Os.; Sato, K. *J. Chem. Soc. Chem. Commun.* **1987**, 1036.
11. McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513.