First Total Synthesis of (±)-Celaphanol A

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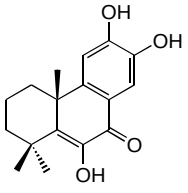
The first total synthesis of (±)-Celaphanol A was accomplished starting from α-cyclocitral and 3,4-dimethoxy benzyl chloride in six steps. The intramolecular cyclization with $BF_3{\cdot}Et_2O$ and enolization in *t*-BuOK/*t*-BuOH were the key steps. The process of intramolecular cyclization afforded an all-*cis* isomer intermediate for synthesis of aromatic tricyclic diterpenes.

INTRODUCTION

Celaphanol A (Fig. 1) is a diterpene isolated from the stems of *Celastrus stephanotifolius*,[1] which has been the subject of continued and growing interest, due to the range of biological activities shown by many members of this family.[2] Some have been used in traditional medicine[3] or as a stimulant[4] from ancient times. In order to study further relationships between the structure and biological activity of the diterpene compound and as an extension of diterpenoid synthesis in our laboratory,[5,6] the synthesis of the title compound was achieved through the AC-ABC ring construction synthetic strategy. We present here the first total synthesis of (±)-Celaphanol A by a simple convergent route.

RESULTS AND DISCUSSION

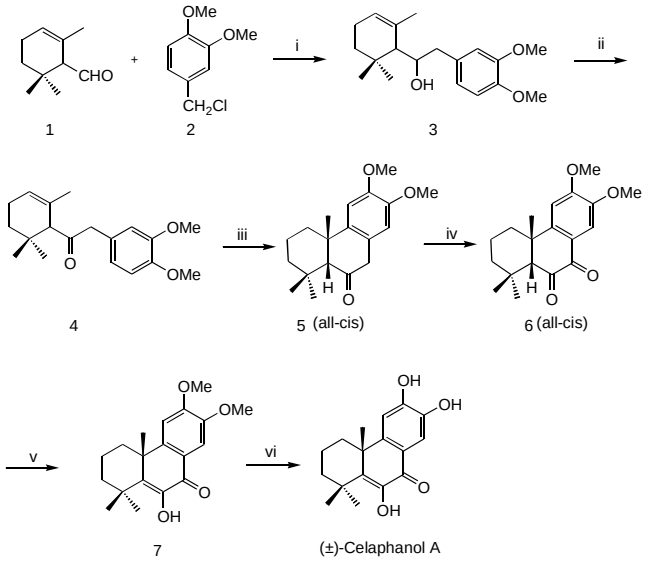
As shown in Scheme I, α-cyclocitral (**1**) and 3,4-dimethoxy benzyl chloride (**2**) were used as the starting materials. The latter was prepared from readily available vanillin in three steps. The condensation of **1** and the Grignard reagent of **2** in dry diethyl ether in a stream of argon afforded the desired alcohol (**3**), which was then oxidized with pyridinium chlorochromate in CH_2Cl_2 to yield ketone (**4**). The intramolecular cyclization of **4** with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at room temperature afforded all-*cis* isomer (**5**) in over 93% yield and no *trans*-isomer was detected from its ^1H NMR spectrum. The *cis*-configuration of A/B ring junction in **5** was characterized specifically by an upfield signal of the $C_{4\alpha}$ methyl group at 0.37 ppm. According to the literature,[7] when A/B ring is a *cis* junction, the $C_{4\alpha}$ methyl group remains within the sphere of magnetic influence of aromatic ring C, the chemical shift of the $C_{4\alpha}$ methyl group appears at about 0.40 ppm. When A/B ring is a *trans* junction, the $C_{4\alpha}$ methyl group is deshielded by aromatic ring C, the chemical shift of



Celaphanol A

Fig. 1.

Scheme I



Reagents and conditions: (i) Mg, Et_2O, reflux, 2 h; (ii) PCC, CH_2Cl_2, r.t., 2.5 h; (iii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, r.t.; (iv) CrO_3/HOAc, r.t., 0.5 h; (v) *t*-BuOK/*t*-BuOH, r.t., 2 h; (vi) BBr_3, CH_2Cl_2, 0 °C, 0.5 h.

$C_{4\alpha}$ methyl group will appear at about 1.00 ppm.

Oxidation of compound **5** with CrO_3/HOAc afforded diketone (**6**) in good yield. Treatment of **6** with *t*-BuOK/*t*-BuOH afforded compound (**7**) in 80% yield. Finally, demethylation of **7** with BBr_3 in CH_2Cl_2 furnished the target molecule (±)-Celaphanol A in 85% yield.

In conclusion, in the present work, a simple convergent synthetic route has been developed for the newly discovered diterpenoid.

EXPERIMENTAL SECTION

Melting points were measured on a Kofler apparatus and are not corrected. IR spectra were recorded on a Nicolet NEXUS 670 FT-IR spectrometer. Mass spectra were recorded on a ZAB-HS spectrometer. Elemental analyses were performed on a Carlo-Erba 1106 instrument. The ^{1}H NMR and ^{13}C NMR data were recorded in $CDCl_3$ with Bruker AM-200 and AM-400 MHz spectrometers. The chemical shifts are reported in ppm and refer $CHCl_3$ and with TMS as internal standard. Diethyl ether was freshly distilled over Na/benzophenone and CH_2Cl_2 was distilled over CaH_2 before use. Standard flash chromatography was employed to purify the crude reaction mixture using 200-300 mesh silica gel.

3,4-Dimethoxy-α-(2,4,4-trimethyl-1-cyclohexen-3-yl)-benzeneethanol (3)

To the Grignard reagent prepared from compound **2** (9.3 g, 50 mmol) and magnesium powder (1.32 g, 55 mmol) in dry ether (30 mL) under an argon atmosphere, α-cyclocitral **1** (7.0 g, 46 mmol) in ether (20 mL) was added. After refluxing for 2 h, the reaction mixture was stirred at room temperature for 4 h and then quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with ether and washed with brine and dried over Na_2SO_4 and then evaporated *in vacuo*. The residue was purified by column chromatography using hexane-ethyl acetate (6:1) as the eluent, to afford **3** (11.1 g: 79%) as an oil. IR: 2930, 3579 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 0.79 (s, 3H), 0.85 (s, 3H), 1.83 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.05 (m, 1H), 5.65 (s, 1H), 6.70-6.79 (m, 3H). MS (EI): 304, 180, 151, 41.

2-(3,4-Dimethoxyphenyl)-1-(2,4,4-trimethyl-1-cyclohexen-3-yl)ethanone (4)

Pyridinium chlorochromate (3.23 g, 15 mmol) was added at 0-5 ℃ to a stirred solution of compound **3** (3.04 g, 10 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for an additional 2.5 h and then diluted with ether. After the addition of water, the mixture was extracted with ether and washed with brine and dried over Na_2SO_4 and then evaporated *in vacuo*. The residue was purified by column chromatography using hexane-ethyl acetate (15:1) as the eluent, to afford **4** (2.57 g: 85%) as an oil. IR: 1688, 2956 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 0.95 (s, 6H), 1.38 (s, 3H), 2.92 (s, 1H), 3.70 (d, 2H), 3.84 (s, 3H), 3.86 (s, 3H), 5.57 (s, 1H), 6.73-6.85 (m, 3H). MS (EI): 302, 151, 123, 81.

(*Cis*)-4b,6,7,8,8a,10-Hexahydro-2,3-dimethoxy-4b,8,8-trimethyl-9(5H)-phenanthrenone (5)

To a solution of ketone **4** (302 mg, 1 mmol) in CH_2Cl_2 (20 mL) was added $BF_3{\cdot}Et_2O$ (0.6 mL) dropwise at room temperature. The mixture was allowed to stand for 24 h at this temperature and then quenched with aqueous sodium bicarbonate. After the usual work-up, the product was purified by column chromatography on silica gel using hexane-ethyl acetate (12:1) as the eluent, to give **5** (282 mg: 93%) as white needles. Mp: 128-130 ℃. IR: 1690, 2924 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 0.37 (s, 3H), 0.95 (s, 3H), 1.06 (s, 3H), 1.26-2.49 (m, 6H), 2.09 (s, 1H), 3.55 (dd, 2H), 3.86 (s, 3H), 3.91 (s, 3H), 6.57 (s, 1H), 6.85 (s, 1H). MS (EI): 302, 287, 217, 69.

(*Cis*)-1,2,3,4,4a,10a-Hexahydro-6,7-dimethoxy-1,1,4a-trimethyl-9,10-phenanthrenedione (6)

To a solution of **5** (302 mg, 1 mmol) in acetic acid (5 mL) was added CrO_3 (100 mg, 1 mmol) in acetic acid (5 mL). The mixture was stirred at room temperature for 0.5 h, and then was quenched with water. After extraction with ether, the combined organic layer was washed with 10% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and then evaporated *in vacuo*. The crude product was purified by column chromatography using hexane-ethyl acetate (6:1) as the eluent, to give **6** (285 mg: 90%) as yellow solid. Mp: 199-202 ℃. IR: 1655, 1711 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 0.45 (s, 3H), 0.98 (s, 3H), 1.25 (s, 3H), 1.44-2.55 (m, 6H), 2.68 (s, 1H), 3.96 (s, 3H), 4.03 (s, 3H), 6.87 (s, 1H), 7.60 (s, 1H). MS (EI): 316, 273, 206, 57.

(±)-2,3,4,4a-Tetrahydro-10-hydroxy-6,7-dimethoxy-1,1,4a-trimethyl-9(1H)-phenanthrenone (7) (Celaphanol A Dimethyl Ether)

To a solution of *t*-BuOK (4.2 g) in *t*-BuOH (30 mL), diketone **6** (190 mg, 0.6 mmol) was added slowly. The mixture was stirred at room temperature for 2 h and poured into 10% aqueous HCl, then extracted with ether. The combined organic layer was washed with 10% aqueous $NaHCO_3$ and

brine, dried over Na_2SO_4 and then evaporated to dryness. The residue was purified by flash column chromatography using hexane-ethyl acetate (10:1) as the eluent, to afford **7** (153 mg: 80%) as white needles. Mp: 119-121 ℃. IR: 1596, 1622, 3339 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ ppm 1.43 (s, 3H), 1.44 (s, 3H), 1.52 (s, 3H), 1.75-2.35 (m, 6H), 3.94 (s, 3H), 3.96 (s, 3H), 6.90 (s, 1H), 7.12 (s, 1H), 7.56 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): 17.52, 27.57, 28.02, 33.62, 34.69, 35.95, 37.63, 40.54, 56.06, 107.23, 107.28, 120.75, 141.29, 143.67, 147.99, 149.81, 153.56, 179.43. MS (EI): 316, 273, 247, 43. (Found: C, 72.21; H, 7.59. $C_{19}H_{24}O_4$ requires C, 72.13; H, 7.65%).

(±)-Celaphanol A

A solution of **7** (140 mg) and boron tribromide (0.2 mL) in CH_2Cl_2 (2 mL) was stirred at 0 ℃ for 0.5 h, diluted with ether, and then poured into ice water. The mixture was extracted with ether, washed with brine, dried over Na_2SO_4, and then evaporated to dryness. The residue was purified by flash column chromatography using hexane-ethyl acetate (4:1) as the eluent, to afford (±)-Celaphanol A (108 mg: 85%) as red solid. Mp: 186-188 ℃. IR: 1650, 1700, 3413 cm^{-1}. ^1H NMR (200 MHz, CD_3COCD_3): δ ppm 1.36 (m, 1H), 1.50 (s, 3H), 1.54 (s, 3H), 1.60 (s, 3H), 1.59 (m, 1H), 1.75 (m, 2H), 1.89 (m, 1H), 2.39 (m, 1H), 7.05 (s, 1H), 8.24 (s, 1H). ^{13}C NMR (400 MHz, CD_3COCD_3): 18.0, 27.9, 28.3, 33.9, 35.1, 36.3, 38.3, 40.8, 111.8, 112.4, 120.8, 140.6, 143.4, 144.9, 149.8, 151.8, 179.9. MS (EI): 288, 273, 245, 232, 218, 190. (Found: C, 70.92, H, 6.93. $C_{17}H_{20}O_4$ requires C, 70.81; H, 6.99%). The above data were consistent with the literature.[1]

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Key Words

(±)-Celaphanol A; Diterpene; Total synthesis.

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