Facile Total Synthesis of (±)-Nimbiol

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A facile total synthesis of (±)-nimbiol **1** has been achieved. In order to decrease the dioxo byproduct **2a**, an improved oxidation system of CrO_3/H_2O/HOAc/NaOAc was used.

Keywords: Abietane; Nimbiol; Diterpene; Steric hindrance.

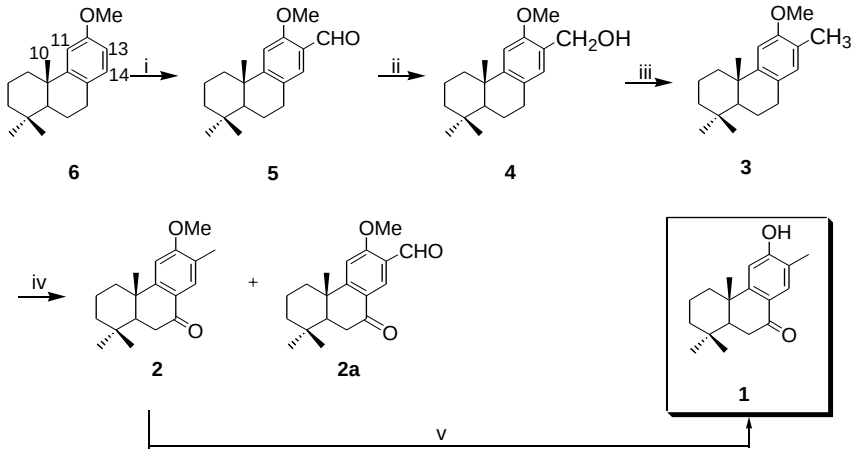
INTRODUCTION

(±)-Nimbiol **1** is a member of the aromatic tricyclic diterpenes[1] and was isolated first from the trunk bark of *Melia azadirachta Linn*, which is used as an antiseptic agent and a medicine for curing a variety of skin diseases in rural India.[2] It is different from the other abietic diterpenes in that the substituent at C-13 is a methyl group, not an isopropyl group.[3,4] As (±)-nimbiol bears a unique structure and modest biological activities, it arouses the interest of chemists. Using podocarpic acid as starting material, Bible and Wenkert gave a partial synthesis to nimbiol.[5,6] Fetizon and Delobelle gave an approach to (±)-nimbiol, but their route had a fatal defect in that the A/B ring configuration contained two ismoers.[7] Very recently, Karpha described a total synthesis of (±)-nimbiol to solve the A/B fusion configuration problem but it involved too many steps.[8] Meyer synthesized (±)-nimbiol through a A→AB→ABC strategy by 14 steps in low yield.[9] As an extension of our previous work,[10,11] herein we report an efficient total synthesis of (±)-nimbiol. The salient feature of our approach lies in that the A/B ring was all *trans* fusion. At the same time, if chiral starting material **6** was used, (+)-nimbiol can be obtained correspondingly.

RESULTS AND DISCUSSION

As shown in Scheme I, based on the synthetic works published before,[10] through the synthetic route of AC→ABC, the tricyclic compound **6** was obtained.[10a,10b] Through the lit-

Scheme I



i: BuLi, THF, and then DMF, -78 °C; ii: $NaBH_4$, MeOH, r.t. 1 h; iii: (a) MsCl, TEA, CH_2Cl_2, -20 °C; (b) $LiAlH_4$, THF, reflux, 6 h; iv: CrO_3/H_2O/HOAc/NaOAc, r.t. 1.5 h; v: NaSEt, DMF, 130 °C

erature, if the chiral (S)-α-cyclocitral was used as starting material, (5S,10S)-12-Methoxy-podocarpane-8,11,13-triene **6** can be obtained.[11]

In order to introduce a functionality at C-13, compound **6** was treated with BuLi and subsequent DMF at -78 °C to afford the formylated product **5**. After purification and careful characterization of the resulting product, only the C-13 formylated product was found; no C-11 formylated product was observed. This result can be explained by steric hindrance. As shown in Fig. 1 (The geometry was optimized by semi-empirical quantum chemistry AM1 method in HyperChem 6.0), the methyl group at C-10 held back the approach of the DMF molecule at very low temperatures.

Therefore, the DMF molecule was more favorable to approach C-13 and led to compound **5**. And this result is consistent with the X-ray.[12]

After reduction of compound **5** by $NaBH_4$, the corresponding alcohol **4** was obtained. This alcohol was protected by methyl sulphonyl chloride in CH_2Cl_2 and triethylamine at -20 °C. Compound **3** was readily available after the subsequent reduction of the above sulfonate by $LiAlH_4$.

To obtain the C-7 oxo compound **2** in high yield, Jones' oxidation system was used, but the ratio of dioxo **2a** and compound **2** is 1:4. This is mainly because the oxidizing ability of Jones' reagent was in harmony with the acidity of the system. To decrease oxidizing ability of the Jones' reagent, anhydrous sodium acetate and water was added carefully to buffer the above system. Finally, the oxidation system of CrO_3/H_2O/HOAc/NaOAc (90 mg/0.2 mL/1 mL/80 mg) was used. Through this ameliorated system, the ratio of target compound **2** and dioxo compound **2a** decreased to 8:1.

With the compound **2** in hand, (±)-nimbiol **1** was afforded after a very effective demethylation method by sodium ethylthiolate[13] was employed.

In summary, we have developed a simple and efficient route to (±)-nimbiol in high yield. In addition, the formylating reaction gave excellent regioselectivity at low temperature and this result can be explained by a geometric model. Significantly, we found a mild oxidation system, which can be used to achieve target compound **2** in a high ratio.

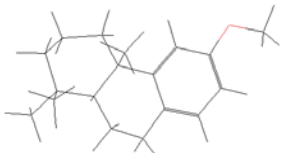


Fig. 1

EXPERIMENTAL

Melting points were measured on a Kofler apparatus and were uncorrected. The ^{1}H-NMR and ^{13}C-NMR data were recorded in $CDCl_3$ solution with a Bruker AM-400 MHz spectrometer. The chemical shifts are referenced on TMS in *ppm* on the 'δ' scale if not noted otherwise. Mass spectra were reported on a HP-5988 mass spectrometer (EI).

(±)-12-Methoxy-13-formylpodocarpane-8,11,13-trene (5)

At argon, to a solution of **6** (820 mg, 3.2 mmol) in anhydrous THF (10 mL) was added BuLi in hexane (1.6 N, 2.2 mL) at -20 °C dropwise. The mixture was stirred for 1 h at this temperature and another 3 h at room temperature, and then the temperature of the reaction system was cooled to -78 °C. Then anhydrous DMF (1.2 mL) was added to the above solution. The reaction mixture was stirred at this temperature for 2 h and then quenched with water and then extracted with ether (3 × 50 mL). The combined organic layer was washed with saturated NH_4Cl, brine, and dried over anhydrous $MgSO_4$. The solvent was distilled in a vacuum, and the residue was purified through chromatography to afford **5** (820 mg, 89%) as yellow oil. ^{1}H-NMR: 0.93 (s, 3H), 0.95 (s, 3H), 1.20 (s, 3H), 1.26-1.65 (m, 6H), 1.70-1.94 (m, 3H), 2.80-2.94 (m, 2H), 3.88 (s, 3H), 6.88 (s, 1H), 7.49 (s, 1H), 10.36 (s, 1H). ^{13}C-NMR: 18.74, 19.04, 21.52, 24.27, 27.52, 29.04, 33.07, 38.68, 41.34, 49.07, 49.70, 55.53, 107.23, 111.52, 128.78, 135.87, 158.81, 159.85, 189.30. MS (EI): 286 (M^+, 100), 271 (70), 243 (6), 229 (25), 203 (70), 201 (56), 189 (69), 149 (36) and 115 (28). Found: C, 79.66; H, 9.17. $C_{19}H_{26}O_2$ requires C, 79.68; H, 9.15.

(±)-12-Methoxy-13-hydroxymethylpodocarpane-8,11,13-trene (4)

To a solution of **5** (600 mg, 2.1 mmol) in methanol (15 mL) was added $NaBH_4$ (100 mg) and $CeCl_3 \cdot 7H_2O$ (10 mg) and the reaction mixture was stirred for 1 h at room temperature. Then cold water was added; the mixture was extracted with ether (3 × 50 mL), and the combined organic layer was washed with brine, and then dried with Na_2SO_4. Evaporation of the solvent and then purification of the residue by column chromatography gave the alcohol (570 mg, 95%). ^{1}H-NMR: 0.96 (s, 3H), 0.98 (s, 3H), 1.24 (s, 3H), 1.22-1.67 (m, 6H), 1.66-1.88 (m, 2H), 2.28 (m, 1H), 2.75-2.92 (m, 2H), 3.85 (s, 3H), 4.63 (s, 2H), 6.79 (s, 1H), 6.95 (s, 1H). ^{13}C-NMR: 19.13, 20.95, 21.45, 24.56, 29.39, 34.42, 37.87, 38.77, 41.46, 49.17, 50.25, 55.10, 61.56, 106.03, 109.89, 129.07, 135.31, 150.33,

155.28. MS (EI): 288 (M^+, 38), 273 (37), 243 (9), 203 (20), 191 (36), 187 (38), 177 (37) and 151 (100). Found: C, 79.13; H, 9.71. $C_{19}H_{28}O_2$ requires C, 79.12; H, 9.78.

(±)-Nimbiol methyl ether (2)

To a solution of the above alcohol (570 mg, 1.97 mmol) in CH_2Cl_2 (20 mL) was added triethylamine (0.5 mL) and methyl sulphonyl chloride (0.5 mL) at -20 °C. The mixture was stirred for 3 h at this temperature, and then quenched with water, extracted with ether, and the combined organic layer was washed with brine and then dried with Na_2SO_4. Evaporation of the solvent gave the sulfonate. This sulfonate was dissolved in anhydrous THF (10 mL) directly. $LiAlH_4$ (40 mg) was added to the above solution, and the mixture was refluxed for 6 h. The reaction mixture was quenched with a few drops of saturated Na_2SO_4 and extracted with ether (3 × 50 mL); the combined organic layer was washed with brine and then dried with Na_2SO_4. The solvent was evaporated to afford crude **3** as yellow oil (530 mg, 98%). This compound was not purified further for the next step. To a solution of **3** (200 mg, 0.74 mmol) in acetic acid (3 mL) was added the mixture of CrO_3/H_2O/HOAc/NaOAc (90 mg/0.2 mL/1 mL/80 mg) at room temperature. The mixture was stirred for 1.5 h, and then diluted with water. After extraction with dichloromethane, the combined organic layer was washed with saturated sodium bicarbonate, brine and then dried with Na_2SO_4. The solvent was evaporated and the residue was purified by flash column chromatography affording (±)-nimbiol methyl ether **2** (165 mg, 80%) and **2a** (30 mg, 10%).

2: White needle crystals, Mp: 142-143 °C (lit[3], 142-143 °C), ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (s, 3H), 1.00 (s, 3H), 1.25 (s, 3H), 1.27-1.53 (m, 1H), 1.52-1.88 (m, 5H), 2.19 (s, 3H), 2.31 (d, J = 12 Hz, 1H), 2.58-2.70 (m, 2H), 3.90 (s, 3H), 6.74 (s, 1H), 7.81 (s, 1H). ^{13}C-NMR: 15.57, 18.88, 21.32, 23.24, 32.55, 33.27, 35.94, 37.99, 38.30, 41.33, 49.72, 55.34, 104.01, 123.84, 124.86, 129.66, 156.78, 162.48, 198.37. MS (EI): 286 (M^+, 25), 271 (12), 203 (24), 189 (33), 175 (26) and 153 (100). Found: C, 79.66; H, 9.17. $C_{19}H_{26}O_2$ requires C, 79.68; H, 9.15.

2a: White solid, Mp: 157-158 °C, ^{1}H-NMR (400 MHz, $CDCl_3$): 0.96 (s, 3H), 1.02 (s, 3H), 1.27 (s, 3H), 1.55-1.89 (6H), 2.33 (d, J = 12 Hz, 1H), 2.58-2.76 (s, 2H), 4.01 (s, 3H), 6.92 (s, 1H), 8.50 (s, 1H), 10.37 (s, 1H). ^{13}C-NMR: 18.77, 21.40, 23.12, 29.69, 32.51, 33.46, 35.89, 37.88, 41.17, 48.89, 55.90, 106.07, 128.06, 130.24, 156.15, 158.30, 164.19, 188.75, 197.24. MS (EI): 300 (M^+, 51), 285 (28), 243 (20), 203 (74), 189 (26), 149 (10) and 115 (44). Found: C, 76.01; H, 8.08. $C_{19}H_{24}O_3$ requires C, 75.97; H, 8.07.

Nimbiol (1)

To a solution of ethylthiol (0.4 mL, 5.5 mmol) in anhydrous DMF was added NaH (132 mg, 5.5 mmol) and the mixture was stirred for 30 minutes. Then a solution of nimbiol methyl ether **2** (89 mg, 0.3 mmol) in DMF (5 mL) was added, and the mixture was heated to 130 °C for 4 h. After cooling, the mixture was quenched with diluted HCl and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified through column chromatography to give nimbiol **1** (82 mg, 96%). Mp: 248-249 (lit[3], 250-251 °C), ^{1}H-NMR (400 MHz, DMSO-d_6): 0.87 (s, 3H), 0.93 (s, 3H), 1.13 (s, 3H), 2.08 (s, 3H), 6.67 (s, 1H), 7.57 (s, 1H), 10.23 (s, 1H). ^{13}C-NMR: 15.36, 18.45, 21.10, 23.03, 32.28, 32.84, 35.43, 37.45, 38.08, 41.81, 49.13, 108.89, 122.26, 122.42, 129.40, 156.16, 160.94, 196.37. MS (EI): 272 (M^+, 48), 257 (47), 189 (62), 175 (64), 149 (47) and 121 (50). Found: C, 79.35; H, 8.82. $C_{18}H_{24}O_2$ requires C, 79.37; H, 8.88.

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