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Note

Total synthesis of (±)-Nimbonone

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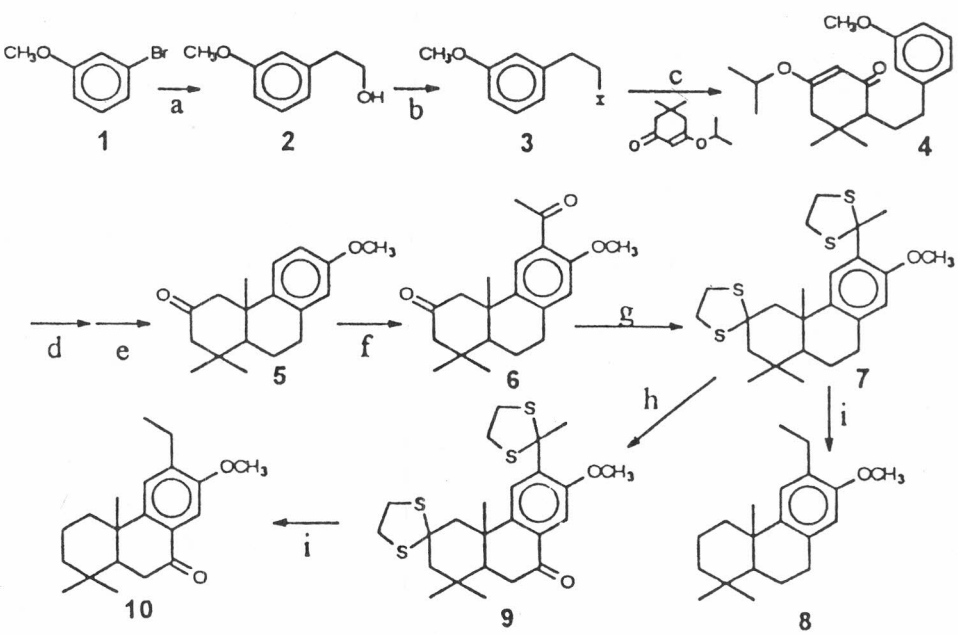
A first expeditious total synthesis of (±)-Nimbonone **10**, a novel naturally occurring diterpenoid isolated from the Neem tree, is described. In order to induce the ethyl substituent, Friedel-Crafts acetylation and then decarbonylation have been employed as the key steps.

Although a large number of aromatic tricyclic diterpenes have been isolated[1], there are few of them having ethyl substituent. The syntheses of this group of diterpenes have seldom been reported. (±)-Nimbonone **10** is one of this group of diterpenes which was recently isolated from Neem tree by Iffat Ara *et al.*[2] In our earlier study[3], we chose (±)-Nimbonone as the target molecule, and attempted to get the ethyl substituent by Friedel-Crafts acetylation and decarbonylation. Now, we report herein the first synthesis of (±)-Nimbonone **10** using a novel strategy. Meanwhile, another aromatic tricyclic diterpene having ethyl substituent, (±)-12-ethyl-13-methoxy-8,11,13-podocarpatriene **8** has also been synthesized (cf. **Scheme I**).

As shown in Scheme I, *m*-Bromoanisol **1** on reaction with *n*-BuLi at low temperature followed by treatment with ethylene oxide gave 2-(3-methoxy)phenylethanol **2** which was converted to iodide **3** by Corey's method[4]. 5,5-Dimethyl-3-isopropoxy-2-cyclohexanone was deprotonated (LDA, THF, –78°C) and alkylated with iodide **3** to give 3-isopropoxy-5,5-dimethyl-6-(3-methoxyphe-



a. n-BuLi, ethylene oxide; b. I_2, Ph_3P, imidazole; c. LDA; d. MeLi; e. 85%H_3PO_4; f. CH_3COCl, $AlCl_3$; g. $(HSCH_2)_2$, 8%$FeCl_3 \cdot SiO_2$; h. CrO_3 / HOAc; i. Raney Ni

Scheme I

nyl)ethyl-2-cyclohexenone **4**. The enone **4** on treatment with excess methyllithium followed by reaction with 85% H_3PO_4 underwent cyclization to give the ring-C aromatic tricyclic compound **5** (*trans*- and *cis*-isomers). Compound **5** on reaction with $AlCl_3$ and CH_3COCl at 0°C afforded (±)-12-acetyl-13-methoxy-8, 11, 13-podocarpatrien-2-one **6** which was treated with ethanethiol and 8% $FeCl_3.SiO_2$ in CH_2Cl_2 to yield (±)-12-ethyl-13-methoxy-8,11,13-podocarpatrien-2,15-dione diethylthioacetal **7**. Compound **7** on reaction with Raney Ni gave (±)-12-ethyl-13-methoxy-8,11,13-podocarpatriene **8**. Also, **7** on CrO_3 oxidation in aq. acetic acid followed by treatment with Raney Ni furnished (±)-Nimbonone **10**. The overall yield was 10%.

Experimental Section

General. All compounds described are racemic. IR spectra (KBr) were recorded on a Nicolet 170 SXFT-IR spectrometer, ^{1}H NMR spectra on a Bruker Am 400 spectrometer using TMS as internal standard and mass spectra on a ZAB-HS spectrometer. Microanalyses were performed on a MOD-1106 elemental analyzer. Standard flash column techniques were employed to purify the crude reaction mixture using 200-300 mesh silica gel under positive nitrogen pressure.

2-(3-Methoxy)phenylethanol 2. To a stirred, cooled (–78°C) solution of *m*-bromoanisole (18.4 g, 98 mmoles) in dry THF (100 mL) was added dropwise *n*-butyllithium (45 mL. 1.8 *M* in Et_2O) at –78°C. The mixture was stirred further for 40 min, and then ethylene oxide (8.6 g, 195 mmoles) in dry Et_2O (20 mL) was added to it. Stirring was continued at –78°C for another 1 hr and then stirred overnight at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and the product obtained was extracted with ether and dried. The alcohol **2** (13 g, 86 mmoles) was obtained in 87% yield as a red oil. Anal. Calcd for C_7H_7OBr: C, 55.26; H, 4.60. Found: C, 55.01; H, 4.39%; IR (KBr): 3262 (OH) cm^{-1}; MS: m/z 152 (M^+), 135, 122, 121, 105, 91, 75; ^{1}H NMR ($CDCl_3$): δ 7.17 (1H, d, *J*=7.9 Hz, ArH), 6.76 (3H, m, ArH), 2.71 (2H, t, *J*=6.7 Hz, Ar-CH_2–), 3.68 (3H, s, OCH_3), 3.70 (2H, t, *J*=6.7 Hz, –CH_2OH).

3-Isopropoxy-5,5-dimethyl-6-(3-methoxyphenyl)-ethyl-2-cyclohexenone 4. To a stirred, cooled (0°C) solution of **2** (13 g, 86 mmoles), recrystallized Ph_3P (32.2 g, 110 mmoles) and imidazole (7.8 g, 115 mmoles) in 60 mL CH_3CN and dry ether (100 mL), was added slowly iodine (30 g, 118 mmoles). The resulting brown mixture was stirred for 1 hr and 600 mL of ether was used to dilute the mixture. It was washed sequentially with saturated aqueous $Na_2S_2O_3$, saturated aqueous $CuSO_4$ and water, and dried. The organic layer was concentrated and the residue filtered through silica gel using petrol ether as eluent. The pure iodide **3** was obtained quantitatively, which was used directly in the next reaction without identification.

To a cooled (–78°C), stirred solution of LDA (80 mL, 1 *M*) was added a solution of 5,5-dimethyl-3-isopropoxy-2-cyclohexenone (14.5 g, 79 mmoles) in dry THF (30 mL). The mixture was stirred for 40 min at –78°C and then a solution of iodide **3** (18 g, 69 mmoles) in dry THF (30 mL) was added dropwise. The mixture was allowed to warm up to room temperature and stored for 24 hr. It was then treated with saturated aqueous NH_4Cl. The mixture was extracted with ether and dried. Careful chromatography using petrol ether-ethyl acetate (4:1, v/v) as eluent gave the enone **4** (13 g, 41 mmoles) as a red oil in 61% yield. Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.95; H, 8.86. Found: C, 75.64; H, 8.57%; IR (KBr): 1652 (C=O) cm^{-1}; MS: m/z 316 (M^+), 301, 273, 257, 182, 167, 125, 107, 91, 69; ^{1}H NMR ($CDCl_3$): δ 7.18 (1H, d, *J*=7.9 Hz, ArH), 6.76 (3H, m, ArH), 5.27 (1H, s, C=CH), 4.43 (1H, sept, *J*=6.1 Hz, $OCHMe_2$), 3.77 (3H, s, OCH_3), 1.28 [6H, d, *J*=6.1 Hz, $OCH(CH_3)_2$], 1.06 (3H, s, CH_3), 0.95 (3H, s, CH_3).

(±)-13-Methoxy-8,11,13-podocarpatrien-2-one 5. To a stirred solution of the enone **4** (2 g, 6.33 mmoles) in dry THF (20 mL) was added MeLi (15 mL, 1.2 *M* in Et_2O). The mixture was stirred at room temperature for 2 hr and then quenched with water. A usual work-up gave an unstable crude product which was subjected to cyclization directly with 85% H_3PO_4 as reported in the literature[5].

In a 50 mL round-bottomed flask equipped with a condenser and a nitrogen inlet, the above crude product and 30 mL 85% H_3PO_4 were charged. The mixture was stirred at 115°C for 6 hr, cooled and the dark mixture poured into 20 mL water. The product was extracted with ether and dried. After removal of the solvent, the residue was purified through column chromatography using petrol ether-ethyl acetate (4.1) as eluent. The mixture of

inseperable epimers **5** (1.03 g, 3.79 mmoles) was obtained as a white foam in 60% yield. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.41; H, 8.82. Found: C, 79.05; H, 8.58%; IR (KBr): 1708 (C=O) cm^{-1}; MS: m/z 272 (M^+), 257, 215, 173, 115, 83; ^1H NMR ($CDCl_3$): δ 7.29 (1H, d, *J*=7.8 Hz, ArH), 7.13 (1H, d, *J*=7.8 Hz, ArH), 6.54 (1H, s, ArH), 3.81 (3H, s, OCH_3), 1.19 (3H, s, 10-CH_3), 1.15, 0.96 (2×3H, 2s, 2×CH_3).

(±)-12-Acetyl-13-methoxy-8, 11, 13-podocarpatrien-2-one 6. To a solution of compound **5** (183 mg, 0.673 mmoles) in CH_2Cl_2 (5 mL) was added aluminium chloride (524 mg) at 0°C. Acetyl chloride (0.36 mL) was then added slowly to the mixture at 0°C with stirring. The mixture was stirred at room temperature overnight. Ice-water (20 mL) was added and the mixture extracted with ether. The ethereal extract was washed successively with 10% aqueous $NaHCO_3$ and brine, then dried and evaporated. Chromatography using petrol ether-ethyl acetate (2:1) as eluent gave the compound **6** (190 mg, 0.605 mmoles) as a yellow foam in 90% yield. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.43; H, 8.82. Found: C, 76.07; H, 7.96%; IR (KBr): 1710 (C=O), 1668 (C=O) cm^{-1}; MS: m/z 314 (M^+), 299, 257, 243, 215, 150, 83; ^1H NMR ($CDCl_3$): δ 7.55 (1H, s, ArH), 6.58 (1H, s, ArH), 3.71 (3H, s, OCH_3), 2.54 (3H, s, CH_3), 1.34 (3H, s, 10-CH_3), 1.20, 1.02 (2×3H, 2s, 2×CH_3).

(±)-12-Ethyl-13-methoxy-8, 11, 13-podocarpatriene-2,15-dione diethylthioacetal 7. To a stirred solution of compound **6** (190 mg, 0.605 mmoles) in 10 mL anhydrous CH_2Cl_2 was added $HSCH_2CH_2SH$ (241 mg, 2.56 mmoles) and 8% $FeCl_3.SiO_2$ (300 mg). The mixture was stirred for 30 min and then filtered through silica gel using ether as eluent to get rid of SiO_2. The mixture was washed with 10% NaOH, water and brine, then dried and evaporated. Chromatography using petrol ether-ethyl acetate (10:1) as eluent gave the compound **7** (208 mg, 0.446 mmoles) as a yellow foam in 78% yield; IR (KBr): 1275 (SCH_2) cm^{-1}; MS: m/z 466 (M^+), 451, 433, 417, 383, 375, 331, 297, 233, 149, 119, 81; ^1H NMR ($CDCl_3$): δ 7.76 (1H, s, ArH), 6.59 (1H, s, ArH), 3.89 (3H, s, OCH_3), 1.46 (3H, s, CH_3), 1.27 (3H, s, 10-CH_3), 1.20, 1.02 (2×3H, 2s, 2×CH_3).

(±)-12-Ethyl-13-methoxy-8, 11, 13-podocarpatriene 8. To a stirred solution of compound **7** (80 mg, 0.172 mmoles) in ethanol (10 mL) was added freshly activated Raney Ni (500 mg). The solution was refluxed for 18 hr, filtered through silica gel using ethanol as eluent to remove the solid residue, and then evaporated. Chromatography using petrol ether-ethyl acetate (10:1) as eluent gave the compound **8** (37.4 mg, 0.131 mmoles) as a yellow oil in 68% yield. Anal. Calcd for $C_{20}H_{30}O$: C, 83.92; H, 10.49. Found: C, 83.66; H, 10.11%; IR (KBr): 1063 (OCH_3) cm^{-1}; MS: m/z 286 (M^+), 271, 215, 189, 128, 69; ^1H NMR ($CDCl_3$): δ 7.06 (1H, s, ArH), 6.54 (1H, s, ArH), 3.82 (3H, s, OCH_3), 1.31 (3H, t, CH_3), 1.22 (3H, s, 10-CH_3), 0.98, 0.84 (2×3H, 2s, 2×CH_3).

(±)-Nimbononyl-2,15-dione diethylthioacetal 9. The compound **7** (120 mg, 0.257 mmoles) was dissolved in glacial acetic acid (0.5 mL) and CrO_3 (100 mg) in 88% aqueous acetic acid (5 mL) was added to it. The mixture was stirred at room temperature for 24 hr, diluted to 10 mL with water and extracted with ether. The ethereal extract was washed with saturated $NaHCO_3$ and then with water, dried and evaporated. Chromatography using petrol ether-ethyl acetate (8:1) as eluent gave the compound **9** (89 mg, 0.185 mmoles) as a yellow oil in 72% yield; IR (KBr): 1674 (C=O), 1262 (SCH_2) cm^{-1}; MS: 480 (M^+), 465, 451, 404, 373, 359, 314, 243, 215, 201; ^1H NMR ($CDCl_3$): δ 7.59 (1H, s, ArH), 6.66 (1H, s, ArH), 3.89 (3H, s, OCH_3), 1.21 (3H, s, 10-CH_3), 1.16, 1.00 (2×3H, 2s, 2×CH_3).

(±)-Nimbonone 10. To a stirred solution of compound **9** (89 mg, 0.185 mmoles) in ethanol (10 mL) was added freshly activated Raney Ni (500 mg). The solution was refluxed for 18 hr, filtered through silica gel using ethanol as eluate to remove the solid residue, and then evaporated. Chromatography using petrol ether-ethyl acetate (5:1) as eluent gave the compound **10** (36 mg, 0.122 mmoles) as a yellow oil in 66% yield. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.98; H, 9.33. Found: C, 79.62; H, 9.01%; IR (KBr): 1674 (C=O) cm^{-1}; MS: m/z 300 (M^+), 285, 258, 227, 196, 152, 135, 105, 91, 69; ^1H NMR ($CDCl_3$): δ 7.52 (1H, s, ArH), 6.83 (1H, s, ArH), 3.89 (3H, s, OCH_3), 2.78 (2H, m, Ar-CH_2), 1.26 (3H, t, *J*=6.2 Hz, CH_2-CH_3), 1.02 (3H, s, 10-CH_3), 0.92, 0.87 (2×3H, 2s, 2×CH_3), 2.41 (2H, m, $COCH_2$).

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