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Total Synthesis of (±)-Nimbonone and (±)-12-Ethyl-13-methoxy-8,11,13-podocarpatriene

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Abstract: A facile total synthetic route to (±)-nimbonone and (±)-12-ethyl-13-methoxy-8,11,13-podocarpatriene was developed. The Wittig reaction of α–cyclocitral with (3-methoxy-benzyl) triphenylphosphonium and intramolecular cyclization with BF_3•Et_2O in the synthetic progress were applied. In order to induce the ethyl substituent, Fiedel-Crafts acetylation and then decarbonylation had been employed.

Keywords: Total synthesis, (±)-nimbonone, diterpene.

Most diterpenoids exhibit significant bioactivities, such as antidermatophytic, antibacterial, and antioxidant. Although a large number of aromatic tricyclic diterpenoids have been isolated, there are a few of them having ethyl substituent. The synthesis of this type diterpenoids has been seldom reported. In order to further study the relationship between the structure and bioactivities of the diterpenoid, we extended the diterpene synthesis[1,2,3]. It is desirable to report herein the synthesis of (±)-nimbonone isolated from *Neem tree* by Iffat Ara *et al*[4]. Meanwhile another aromatic tricyclic diterpene having ethyl substituent, (±)-12-ethyl-13-methoxy-8,11,13-podocarpatriene has also been synthesized.

Our synthetic strategy is AC→ABC, as shown in **Scheme 1**. Condensation of **1** with **2** in THF in the presence of *n*-BuLi at low temperature afforded styrene derivative **3** in 60% yield. Partial hydrogenation of **3** in anhydrous ethanol at r.t. over 10% Pd/C gave compound **4** in 94% yield. In the intracyclization step of **4**, BF_3•Et_2O was found to be a good reagent that gave a high yield (93%) for **5**[1]. Compound **5** on reaction with $AlCl_3$ and CH_3COCl[1] at 0°C and then at room temperature in CH_2Cl_2 gave **6** in 78% yield. Compound **6** was treated with ethanethiol[5] and 8% $FeCl_3$•SiO_2 in CH_2Cl_2 to get (±)-12-ethyl-13-methoxy-8,11,13-podocarpatrien-15-one ethylthioacetal **7** in 82% yield. Compound **7** was then refluxed in ethanol in the presence of Raney Ni[5] to give another aromatic tricyclic diterpenoid **10** having ethyl substituent in 90% yield. Also, **7** was oxidized with CrO_3/Py[6] at r.t. to afford **8** in 70% yield, which was treated with Raney Ni[5] to furnish (±)-nimbonone **9** in 91% yield.

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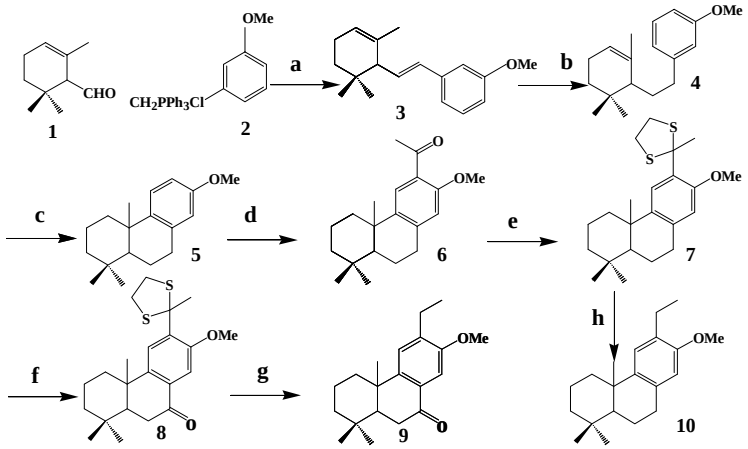
In summary, we have successfully applied the Wittig reaction, intramolecular cyclizationand Friedel-Crafts acetylation to the synthesis of (±)-nimbonone **9** and (±)-12-ethyl-13-methoxy-8,11,13-podocarpatriene **10**.

Scheme 1



Reagents and conditions: (a) *n*-BuLi, THF, -78°C, (60%); (b) 10% Pd/C, EtOH, r.t., (94%); (c) BF_3•Et_2O, CH_2Cl_2, r.t., (93%); (d) CH_3COCl, $AlCl_3$, (78%); (e) $(HSCH_2)_2$, 8% $FeCl_3$•SiO_2, CH_2Cl_2, r.t., (82%); (f) CrO_3/Py, r.t., (70%); (g) ,(h) Raney Ni, EtOH, reflux, (90%).

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References and Notes

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7. (±)-Nimbonone **9:** yellow oil. IR(KBr): 1675(C=O)cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 0.31(s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.18 (s, 3H, 10-CH_3), 1.26 (t, 3H, J=7.4Hz, CH_2CH_3), 1.6~3.1 (m, 8H, 4×CH_2), 2.71 (q, 2H, J=7.4Hz, CH_2CH_3), 3.87 (s, 3H, OCH_3), 7.12 (s, 1H, ArH), 7.48 (s, 1H, ArH); ^{13}C NMR (50MHz, $CDCl_3$, δppm): 14.0, 19.1, 22.9, 24.0, 31.9, 34.5, 35.6, 36.3, 36.9, 37.7, 42.4, 52.1, 55.4, 107.5, 125.0, 131.9, 139.7, 142.0, 155.6, 198.5; HRMS (positive-SIMS): Calcd. for: $C_{20}H_{28}O_2$: 301.2162. Found: 301.2157 (M+H).
8. Compound **10:** yellow oil. IR(KBr): 1060(OCH_3)cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$, δppm): 0.44 (s, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.20 (s, 3H, 10-CH_3), 1.29 (t, 3H, J=7.4Hz, CH_2CH_3), 2.63 (q, 2H, J=7.4Hz, CH_2CH_3), 1.7~2.9 (m, 10H, 5×CH_2), 3.82 (s, 3H, OCH_3), 6.51 (s, 1H, ArH), 7.04 (s, 1H, ArH); ^{13}C NMR (50MHz, $CDCl_3$, δppm): 14.2, 18.3, 19.4, 21.6, 23.4, 26.6, 29.7, 32.8, 34.5, 36.7, 38.2, 43.1, 50.4, 55.2, 110.3, 124.8, 129.9, 135.4, 135.5, 154.8; MS: *m/z* 286 (M^+), 271, 189, 175, 121, 91, 69. Anal. Calcd. for: $C_{20}H_{30}O$: C, 83.92; H, 10.49. Found: C, 83.71; H, 10.22.

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