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A novel approach to synthesis of tricyclic diterpenoid

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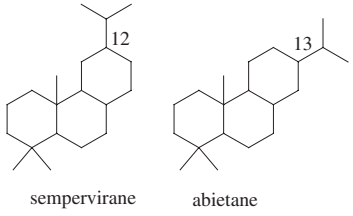
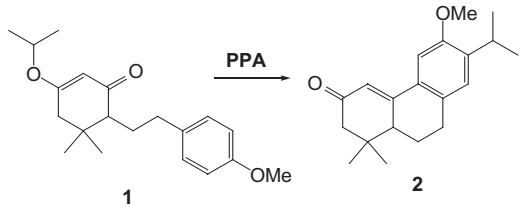
Abstract—A novel approach has been found and the first total synthesis of (±)-Salvirecognine was accomplished by using it. In which intramolecular cyclization and Friedel–Crafts alkylation took place simultaneously to afford key intermediates for synthesis of aromatic tricyclic diterpenoids.

1. Introduction

Many aromatic tricycle diterpenoids always bear an *i*-propyl group in C-12 or C-13 position, such as sempervirane or abietane (Scheme 1).[1,2] But the way of introducing *i*-propyl group to the benzene ring is always very fussy.[3] Recently we found a novel approach (Scheme 2) when we studied the total synthesis of **4**.[4] We schemed to use the route reported by our group previously[5] to synthesis **4**, but failed to cyclize **1** by using concentrate sulfate acid. When we tried to use PPA, to our surprise, the intramolecular cyclization and introduction of *i*-propyl group to the benzene ring took place simultaneously. We thought it an efficient and facile method for synthesis of aromatic tricyclic diterpenoids. So we tried several other substrates as shown in Table 1. And the first total synthesis of Salvirecognine **4** was accomplished by using the novel approach.



Scheme 1.



Scheme 2.

2. Results and discussion

As shown in Scheme 2 intramolecular cyclization and Friedel–Crafts alkylation took place simultaneously when compound **1** was treated by PPA at 125 °C. In which the *i*-propyl group was introduced to the benzene ring directly and **2** was obtained in high yield.[6] The structure of **2** was confirmed by X-ray crystallographic analysis (Fig. 1).

The possible mechanism of this novel approach is shown in Scheme 3. It may involve two Friedel–Crafts alkylations and one fragmentation. We tried several different substrates as shown in Table 1. The new method was not only applicable in the conventional [6.6.6] tricyclic compounds but also suitable in [6.5.6] tricyclic compounds.

By using the new approach as shown in Scheme 4, the first total synthesis of Salvirecognine **4**, isolated from *salvia recognit* was achieved.

Demethylation of **2** with BBr_3 in CH_2Cl_2 at 0 °C acquired **3**[7] in 85% yields. Finally, compound **3** was

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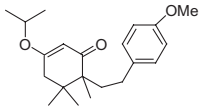
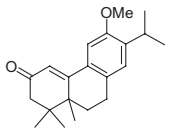
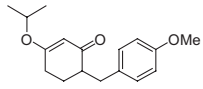
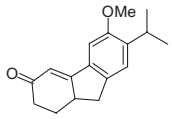
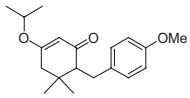
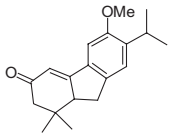
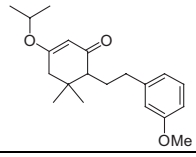
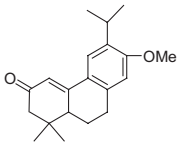
Table 1.

Entry	Substrate[a]	Time (h)	Product	Yield (%)
a		1		85
b		1		80
c		0.5		88
d		1		90

[a] All the substrates were prepared as the method of Ref. 5.

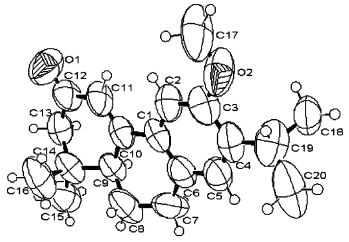
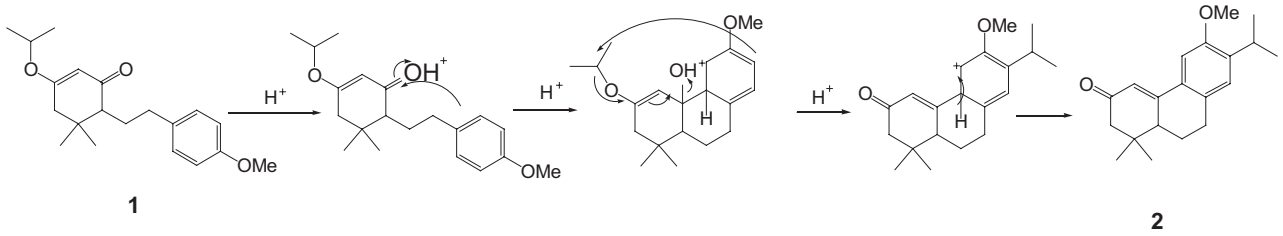


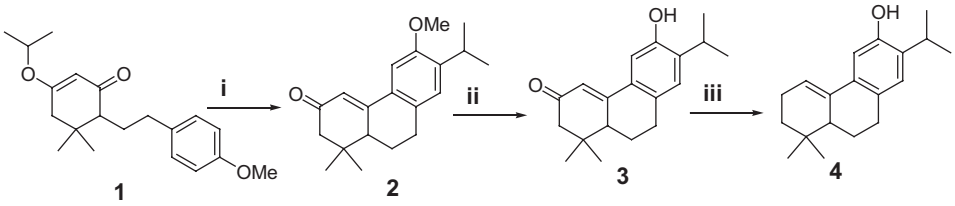
Figure 1. X-ray crystal structure of **2** (CCDC 227468).

reduced by $HAlCl_2$[8] in dry diethyl ether at 0 °C and the target molecule (±)-Salvirecognine **4** was obtained in 95% yield.

In conclusion, a novel approach has been found and the first total synthesis of Salvirecognine **4** was achieved. It is a facile and efficient method for synthesis of analogous of aromatic tricyclic diterpenoids. Further studies on the novel approach will be continued by our group.



Scheme 3.



Scheme 4. Reagents and conditions: (i) PPA, 125 °C, 90%; (ii) BBr_3, CH_2Cl_2, 85%; (iii) $AlCl_2H$, 95%.

Acknowledgements

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6. Compound **1** (0.5 g, 1.5 mmol) was added at 125 °C to a stirred PPA (prepared from 1.25 mL H_3PO_4 and 1 g P_2O_5). The mixture was stirred at 125 °C for 1 h and then poured into ice water, extracted with diethyl ether, washed with saturated aqueous Na_2CO_3 and brine, dried over Na_2SO_4 and then evaporated to dryness. The residue was purified by flash column chromatography using petroleum ether–ethyl acetate (10:1) to give the pure product **2** (0.4 g, 90%) as white needles. Mp: 140–142 °C, ^{1}H NMR (300 MHz, $CDCl_3$, δ: 0.94 (3H, s), 1.20 (9H, d, $J = 7$ Hz), 1.51–1.65 (1H, m), 2.10–2.15 (1H, m), 2.34–2.49 (2H, dd, $J = 15.9$ Hz), 2.50–2.55 (1H, m), 2.75–2.93 (2H, m), 3.30 (1H, sept, $J = 7$ Hz), 3.83 (3H, s), 6.65 (1H, br s), 7.00 (1H, s), 7.20 (1H, s). ^{13}C NMR (200 MHz, $CDCl_3$): 20.18, 22.41 (2), 23.46, 26.79, 29.04, 29.89, 36.42, 47.58, 53.31, 55.35, 105.95, 119.18, 126.89, 129.61, 133.09, 140.97, 155.51, 156.00, 199.88. HRMS(ESI) spectrum: M+H=299.2000 (calc. 299.2006). IR: 1657, 2372, 2959, 3393. X-ray crystal structure of **2** (CCDC 227468).
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