

A Facile Chiral Approach to the Dendrobine Skeleton by
Intramolecular Pauson-Khand Reaction

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A possible chiral synthetic route to the alkaloid (-)-dendrobine has been explored by employing intramolecular Pauson-Khand reaction as the key step. The cobalt complex generated from (S)-carvone yielded a single stereoisomer (**10**) on intramolecular Pauson-Khand reaction. The adduct **10** was transformed into decarboxy-7,9-dihydrodendrobine by a four-step reaction.

The sesquiterpene alkaloid (-)-dendrobine^{1,2)} (**1**) occurs as the major alkaloidal component of the Chinese drug "Chin-Shih-Hu" which is prepared from the ornamental orchid *Dendrobium mobile* (Orchidaceae). Due to a total of seven stereogenic centers distributed in the tetracyclic ring structure as well as its interesting physiological activity³⁾ such as antipyretic, hypotensive, and convulsant activities, there have been performed a number of synthetic investigations, culminating in five total syntheses.⁴⁾ However, none of chiral syntheses have been developed so far. In this communication we outline a simple chiral construction of the decarboxydihydro derivative⁵⁾ (**2**) as a model compound of natural (-)-dendrobine (**1**) by employing an intramolecular cyclization. This approach may be applicable to the chiral synthesis of natural (-)-dendrobine (**1**).

Our strategy involved intramolecular Pauson-Khand reaction^{6,7)} of the optically active substrate **8** prepared in a straightforward manner from (S)-carvone (**3**) in five steps. In the key reaction, the cobalt complex **9** generated from **8** was expected to undergo highly diastereoselective cyclization to furnish the tricyclic enone (**10**) owing to steric inflexibility

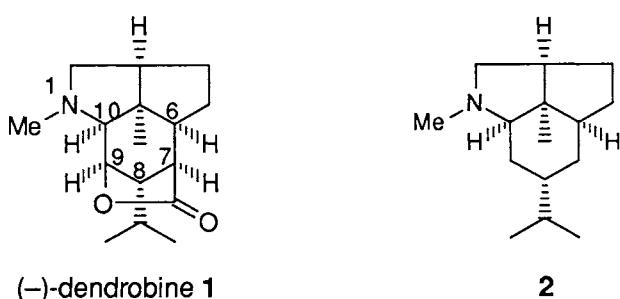
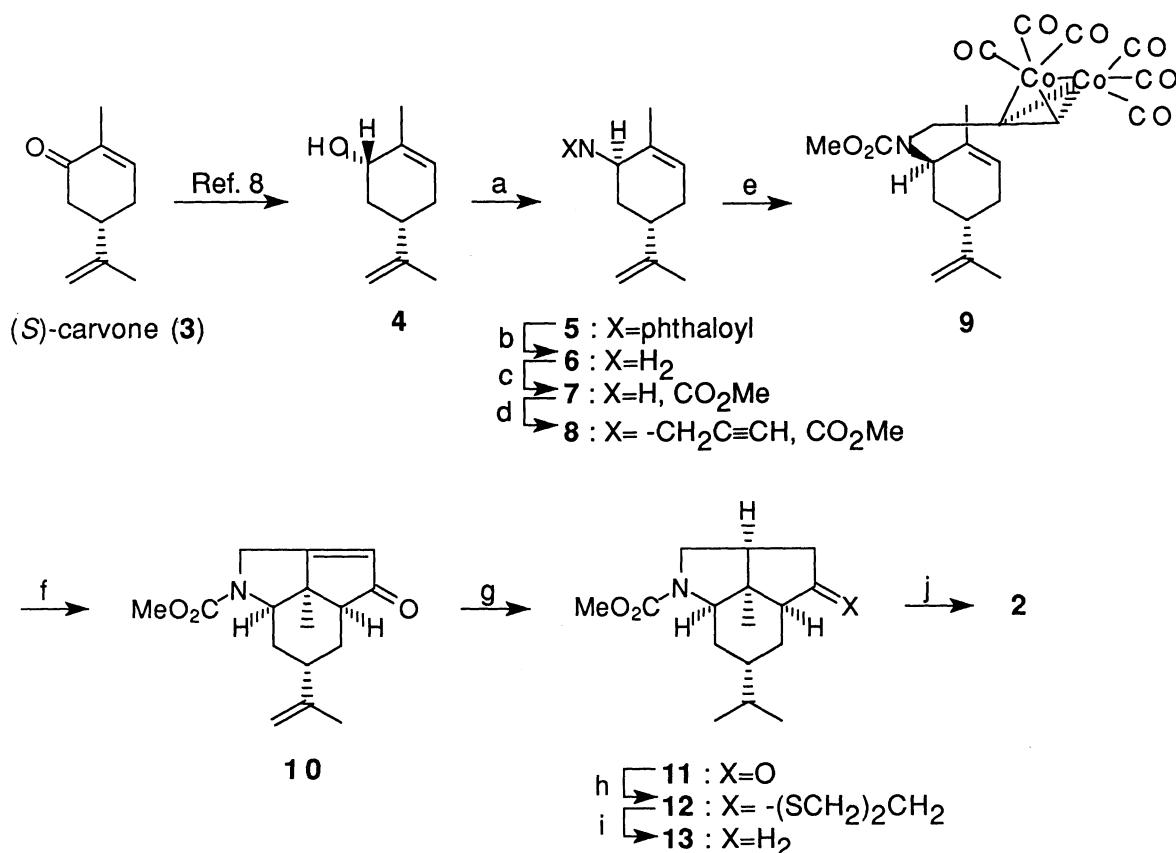


Fig. 1.

though very few precedent has reported on diastereoselection in the intramolecular Pauson-Khand reaction.

The known secondary alcohol **4** prepared from (*S*)-carvone (**3**) by stereoselective reduction⁸⁾ was first transformed into the phthalimide **5** $[\alpha]_D^{28} +216.4^\circ$ (*c* 1.24, CHCl_3) in 90% yield with inversion by the Mitsunobu conditions.⁹⁾ The HPLC analysis of the product using a chiral column (CHIRALCEL OD, 20% *i*-PrOH-hexane) revealed the optical purity of **5** to be 94.2%, indicating that partial racemization (ca. 3%) of **5** occurred probably by $\text{S}_{\text{N}}2'$ substitution during these transformations. Upon removal of the phthaloyl group, followed by sequential carbamoylation and alkylation, **5** afforded the *N,N*-disubstituted carbamate **8** $[\alpha]_D^{26} +69.9^\circ$ (*c* 0.91, CHCl_3) in 30% overall yield *via* **6** and **7**, $[\alpha]_D^{27} +123.1^\circ$ (*c* 1.02, CHCl_3). The unsatisfactory low overall yield was mostly due to high volatility of the primary amine intermediate **6**.

Treatment of **8** with dicobalt octacarbonyl afforded the complex **9** in 80% yield as a brown tar. As expected high diastereoselective cyclization occurred very facilely when **9** was subjected to the 4-methylmorpholine *N*-oxide (NMO) promoted Pauson-Khand cyclization^{6d)} (0 °C to room temperature, dichloromethane), giving the tricyclic dienone **10** $[\alpha]_D^{25} +100.5^\circ$ (*c* 1.02, CHCl_3) in 89% yield as a single product. Upon hydrogenation over Adams catalyst **10** afforded the saturated ketone **11** $[\alpha]_D^{25} +40.4^\circ$ (*c* 1.03, CHCl_3) as a single product in 72% yield. Very interestingly, when palladized carbon in place of Adams catalyst was used in hydrogenation, facile epimerization took place to generate an inseparable 1:1 mixture of **11** and its C₈-epimer.¹⁰⁾ The optical purity of **11** was determined to be 95% ee by the ¹H-NMR spectra (500 MHz) of the derived MTPA esters [(*R*)- and (*S*)-esters] of the secondary alcohol (α -H, β -OH) prepared stereoselectively from **11** with sodium borohydride.



Scheme 1.

Reagents: a) diisopropyl azodicarboxylate, Ph₃P, phthalimide, THF, 0 °C; b) hydrazine hydrate, EtOH, reflux; c) ClCO₂Me, Et₃N, CH₂Cl₂, room temp; d) propargyl bromide, NaH, DMF, 0 °C - room temp; e) Co₂(CO)₈, benzene, room temp; f) NMO, CH₂Cl₂, 0 °C - room temp; g) H₂, PtO₂, MeOH, room temp; h) propane-1,3-dithiol, *p*-TosOH (cat.), benzene, reflux; i) Raney Ni (W-2), EtOH, reflux; j) LiAlH₄, THF, reflux.

Transformation of **11** into the target molecule decarboxy-7,9-dihydrodendrobine (**2**) could be achieved in three steps in 49% overall yield. Thus, the ketone **11** was first converted into the dithiane **12** $[\alpha]_D^{27} -134.2^\circ$ (*c* 1.94, CHCl₃) in 80% yield. Treatment of **12** with Raney nickel (W-2) in refluxing ethanol provided the carbamate **13** $[\alpha]_D^{27} -72.9^\circ$ (*c* 1.05, CHCl₃) in 91% yield. Finally, **13** was reduced with lithium aluminum hydride to give the desired amine **2** $[\alpha]_D^{27} -16.5^\circ$ (*c* 0.71, CHCl₃) in 83% yield as a single product.¹¹⁾

Chiral synthesis of (-)-dendrobine (**1**) is currently under examination based on the present intramolecular Pauson-Khand approach.

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10) This mixture was transformed into a mixture of the target molecule **2** and its C₈-epimer, which were separated by silica gel preparative TLC: ¹H-NMR (500 MHz) (CDCl₃) spectrum of the C₈-epimer of **2**: δ 0.87 (dd, 6H, *J*=6.72, 15.3 Hz), 1.08 (s, 3H), 1.22-1.50 (m, 7H), 1.57-1.64 (m, 1H), 1.65-1.72 (m, 1H), 1.72-1.87 (m, 4H), 1.95 (dd, 1H, *J*=7.0, 13.8 Hz), 2.18 (s, 3H), 2.66 (d, 1H, *J*=9.8 Hz).

11) ¹H-NMR (500 MHz) (CDCl₃) δ 0.87 (dd, 6H, *J*=1.83, 6.7 Hz), 1.05 (m, 1H), 1.12 (s, 3H), 1.27 (dt, 1H, *J*=6.1, 12.8 Hz), 1.34-1.43 (m, 2H), 1.49-1.58 (m, 1H), 1.52 (dd, 1H, *J*=6.11, 12.2 Hz), 1.62 (ddd, 1H, *J*=2.5, 4.5, 12.5 Hz), 1.64-1.78 (m, 4H), 1.94 (ddd, 1H, *J*=6.71, 12.8, 19.5 Hz), 2.01 (t, 1H, *J*=8.55 Hz), 2.06 (s, 3H), 2.31 (dt, 1H, *J*=1.22, 9.15 Hz), 2.73 (d, 1H, *J*=9.76 Hz).

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