CHEMISTRY LETTERS, pp. 443-446, 1992.

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

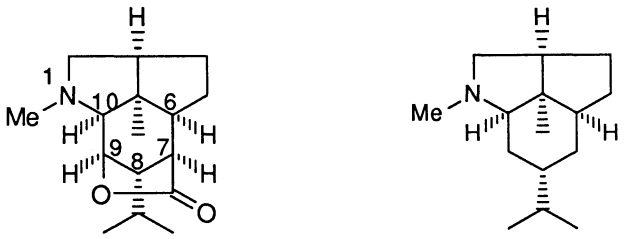
Seiichi TAKANO,* Kohei INOMATA, and Kunio OGASAWARA

Pharmaceutical Institute, Tohoku University, Aoba-ku, Sendai 980

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 activity[3] 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 derivative[5] (**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



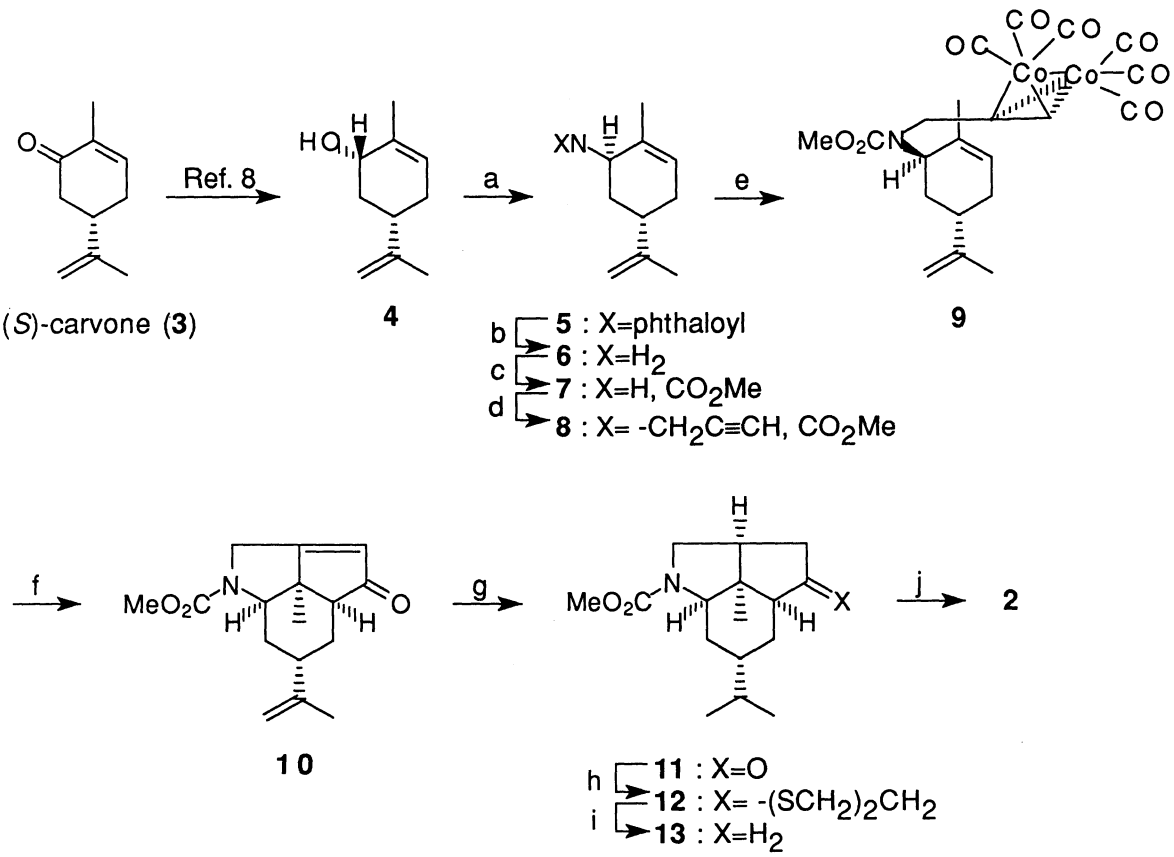
(–)-dendrobine **1** **2**

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 reduction[8] was first transformed into the phthalimide **5** [$[\alpha]_D^{28}$ +216.4° (*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 S_N2' 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° (*c* 0.91, $CHCl_3$)] in 30% overall yield *via* **6** and **7**, $[\alpha]_D^{27}$ +123.1° (*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° (*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° (*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 C_8-epimer.[10] The optical purity of **11** was determined to be 95% ee by the ^{1}H-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, Ph_3P, phthalimide, THF, 0 °C; b) hydrazine hydrate, EtOH, reflux; c) $ClCO_2Me$, Et_3N, CH_2Cl_2, room temp; d) propargyl bromide, NaH, DMF, 0 °C - room temp; e) $Co_2(CO)_8$, benzene, room temp; f) NMO, CH_2Cl_2, 0 °C - room temp; g) H_2, PtO_2, MeOH, room temp; h) propane-1,3-dithiol, *p*-TosOH (cat.), benzene, reflux; i) Raney Ni (W-2), EtOH, reflux; j) $LiAlH_4$, 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° (*c* 1.94, $CHCl_3$)] in 80% yield. Treatment of **12** with Raney nickel (W-2) in refluxing ethanol provided the carbamate **13** $[[\alpha]_D^{27}$ −72.9° (*c* 1.05, $CHCl_3$)] in 91% yield. Finally, **13** was reduced with lithium aluminum hydride to give the desired amine **2** $[[\alpha]_D^{27}$ −16.5° (*c* 0.71, $CHCl_3$)] 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.

References

1) Isolation: H. Suzuki and I. Keimatsu, *J. Pharm. Soc., Japan*, **52**, 1049 (1932).

2) Determination: Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konida, J. Matsumoto, E. Katarao, and J. Nakano, *J. Pharm. Soc., Japan*, **83**, 1184 (1963); T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, and M. Shimizu, *Chem. Pharm. Bull.*, **12**, 506 (1964); S. Yamamura and Y. Hirata, *Tetrahedron Lett.*, **1964**, 79.

3) L. Porter, *Chem. Rev.*, **67**, 441 (1967).

4) Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Saji, and K. Tokane, *J. Chem. Soc., Chem. Commun.*, **1972**, 1252; *Chem. Pharm. Bull.*, **22**, 349 (1974); K. Yamada, M. Suzuki, Y. Hayakawa, K. Aoki, H. Nakamura, H. Nagase, and Y. Hirata, *J. Am. Chem. Soc.*, **94**, 8279 (1972); A. S. Kende, T. J. Bently, R. A. Mader, and D. Ridge, *ibid.*, **96**, 4332 (1974); W. R. Roush, *ibid.*, **100**, 3599 (1978); **102**, 1390 (1980); S. F. Martin and W. Li, *J. Org. Chem.*, **54**, 265 (1989); **56**, 642 (1991).

5) An interesting approach to **2** using carvone (**3**) has been reported. Although it seemed to reach the target molecule **2**, it was accompanied by a substantial amount of an inseparable stereoisomer which made unambiguous stereochemical assignment of the products very difficult, see: K. Yamamoto, I. Kawasaki, and T. Kaneko, *Tetrahedron Lett.*, **1970**, 4859; An unfruitful non-chiral approach to **2**, see: D. N. Brattesani and C. H. Heathcock, *J. Org. Chem.*, **40**, 2165 (1975).

6) A pertinent review, see: a) N. E. Schore, *Organic Reactions*, **40**, 1 (1991). b) I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, and M. E. Foreman, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 977. c) S. W. Brown and P. L. Pauson, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1205. d) S. Shambayati, W. E. Crowe, and S. L. Schreiber, *Tetrahedron Lett.*, **31**, 5289 (1990). e) M. E. Krafft, C. A. Juliano, I. L. Scott, C. Wright, and M. D. McEachin, *J. Am. Chem. Soc.*, **113**, 1693 (1991) and references cited therein. f) N. Jeong, S. -e. Yoo, S. J. Lee, and Y. K. Chung, *Tetrahedron Lett.*, **32**, 2137 (1991).

7) S. Takano, K. Inomata, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, in press.

8) J. -L. Luche, L. Rodriguez-Hahn, and P. Crabbe, *J. Chem. Soc., Chem. Commun.*, **1978**, 601; H. Fujii, K. Oshima, and K. Utimoto, *Chem. Lett.*, **1991**, 1847.

9) O. Mitsunobu, *Synthesis*, **1981**, 1.

10) This mixture was transformed into a mixture of the target molecule **2** and its C_8-epimer, which were separated by silica gel preparative TLC: ^{1}H-NMR (500 MHz) ($CDCl_3$) spectrum of the C_8-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) ^{1}H-NMR (500 MHz) ($CDCl_3$) 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).

(Received December 10, 1991)