A Short Synthesis of (−)-Dendrobine

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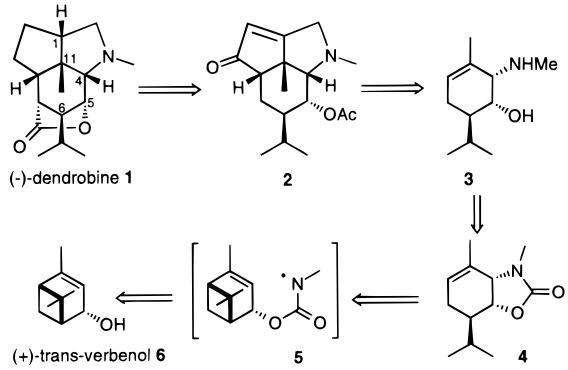
(−)-Dendrobine (**1**), the major alkaloid constituent of the Chinese ornamental orchid *Dendrobium nobile*,[1] exhibits interesting antipyretic and hypotensive activities.[2] Since the elucidation of its structure in 1964,[3] dendrobine (**1**) has attracted much attention as a challenging synthetic target. The first total syntheses of **1** were completed in the 1970's,[4] but efficient and stereoselective routes to this molecule were only reported in the 1990's,[5] all involving new synthetic methods, culminating in two formal[5b,d] and one total[5e] enantioselective syntheses.

Our synthetic strategy to (−)-dendrobine (**1**) is based on the early introduction of the three stereogenic centers at C(4), C(5), and C(6), thus resolving all the stereochemical problems for the final compound (Scheme 1). The amino alcohol **3** would therefore constitute an attractive intermediate, since the amino group at C(4) could serve as a template for the stereoselective construction of the azatricyclo[6.2.1.$0^{4,11}$]undecane ring system by a Pauson−Khand reaction (**3** → **2**),[6,7] whereas the hydroxy group at C(5) would control the stereochemistry of the bridged lactone, after introduction of a carboxylate equivalent at C(7) (**2** → **1**). As part as our general interest in new radical processes, we have recently developped nitrogen-centered radical cyclizations,[8] providing a novel access to various heterocycles.[9,10] As an application of this new methodology, we presumed that key intermediate **3** would be obtained from (+)-*trans*-verbenol (**6**), after a radical cascade involving cyclization−fragmentation of a carbamyl radical **5**, to give oxazolidinone **4** with the desired stereochemistry.

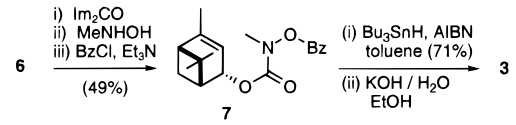
The *O*-benzoyl-*N*-hydroxyurethane **7** was chosen as a suitable precursor for the crucial carbamyl radical cyclization, since the addition of a tributylstannyl radical to the oxygen of the benzoate would induce cleavage of the weak N−O bond, and formation of the desired radical **5**. Conversion of (+)-*trans*-verbenol (**6**),[11] into **7** was accomplished by carbonyl imidazolide formation, treatment with *N*-methyl hydroxylamine, and subsequent benzoylation to afford **7** in 49% overall yield without isolation of the intermediates (Scheme 2). As expected, slow addition of Bu_3SnH and AIBN to a refluxing solution of **7** in toluene produced the desired oxazolidinone **4** in 71% yield. Hydrolysis of **4** afforded the amino alcohol **3** in 68% yield.[12] This represents an interesting example of a successful cyclization of a carbamyl radical,[9a−b] and opens the way to the synthesis of cyclic cis vicinal amino alcohols.[13]

Next, we investigated the construction of the tricyclic core of dendrobine, involving the formation of the central C(1)−C(11) bond. After unsuccessful attempts to form the hydroindole skeleton via cyclization of a carbamoylmethyl radical onto the C(11)−C(8) bond within **3**,[14] we turned to a different strategy, involving Pauson−Khand reaction[6] of the *N*-propargyl derivative **8**, readily obtained from **3** by treatment with propargyl bromide, and subsequent acetylation of the hydroxy group (88% yield). Treatment of the alkyne−$Co(CO)_6$ complex derived from **8** with *N*-methylmorpholine oxide hydrate[15] in the usual solvents (CH_2Cl_2 or THF/CH_2Cl_2) resulted in a slow conversion into the desired

Scheme 1. Retrosynthetic Analysis of (−)-Dendrobine



Scheme 2. Synthesis of the Intermediate Amino Alcohol **3**



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(1) (a) Suzuki, H.; Keimatsu, I.; Ito, K. *J. Pharm. Soc. Jpn.* **1932**, *52*, 1049−1060. (b) Suzuki, H.; Keimatsu, I.; Ito, K. *J. Pharm. Soc. Jpn.* **1934**, *54*, 802−812.

(2) Porter, L. *Chem. Rev.* **1967**, *67*, 441−464.

(3) (a) Inubushi, Y.; Sazaki, Y.; Tsuda, Y.; Yasui, B.; Konika, T.; Matsumoto, J. Katarao, E.; Nakano, J. *Tetrahedron* **1964**, *20*, 2007−2023. (b) Inubushi, Y.; Sazaki, Y.; Tsuda, Y.; Nakano, J. *Tetrahedron Lett.* **1965**, *20*, 1519−1523.

(4) (a) Yamada, K.; Suzuki, M.; Hayakawa, Y.; Aoki, K.; Nakamura, H.; Nagase, H.; Hirata, Y. *J. Am. Chem. Soc.* **1972**, *94*, 8278−8280. (b) Inubushi, Y.; Kikushi, T.; Ibuka, T.; Tanaka, T.; Saji, I.; Tokane, K. *Chem. Pharm. Bull.* **1974**, *22*, 349−369. (c) Kende, A. S.; Bentley, T. J.; Mader, R. A.; Ridge, D. *J. Am. Chem. Soc.* **1974**, *96*, 4332−4334. (d) Roush, W. R. *J. Am. Chem. Soc.* **1980**, *102*, 1390−1404.

(5) (a) Martin, S. F.; Li, W. *J. Org. Chem.* **1991**, *56*, 642−650. (b) Trost, B. M.; Tasker, A. S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670−672. (c) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089−4095. (d) Mori, M.; Uesaka, N.; Shibasaki, M.; Saitoh, F.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633−5642. (e) Sha, C.-K.; Chiu, R.-T.; Yang, C.-F.; Yao, N.-T.; Tseng, W.-H.; Liao, F.-L.; Wang, S.-L. *J. Am. Chem. Soc.* **1997**, *119*, 4130−4135.

(6) For a previous approach to the dendrobine skeleton using the Pauson−Khand reaction, see: Takano, S.; Inomata, K.; Ogasawara, K. *Chem. Lett.* **1992**, 443−446.

(7) For recent reviews of the Pauson−Khand reaction, see: (a) Schore, N. E. *Org. React.* **1991**, *40*, 1−90. (b) Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds; Pergamon: Oxford, 1991; Vol. 5, pp 1037−1064. (c) Geis, O.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **1998**, *37*, 911−914.

(8) For reviews of cyclizations of nitrogen-centered radicals, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594. (b) Zard, S. Z. *Synlett* **1996**, 1148−1158.

(9) (a) Callier, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 6109−6112. (b) Boivin, J.; Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Schiano, A.-M.; Zard, S. Z. *Tetrahedron* **1995**, *51*, 6517−6528. (c) Callier-Dublanchet, A.-C.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1995**, *36*, 8791−8794.

(10) We have recently completed a short synthesis of (±)-γ-lycorane involving a cascade process starting with a nitrogen-centered radical: Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *39*, 2125−2126.

(11) Whitham, G. H. *J. Chem. Soc.* **1961**, 2232−2236.

(12) This two-step process was best carried out in one pot, without isolation of **4**, allowing a simple purification of **3** and separation of tin residues by an acid−base extraction (68% yield from **7**).

(13) The introduction of a cis vicinal amino alcohol functionality is generally more challenging than for the trans isomer. See: (a) Knapp, S. *Chem. Soc. Rev.* **1999**, *28*, 61−72. Interesting compounds in this class include the aminocyclitols (e.g., (+)-valienamine), the aminocyclopentitols (e.g., (+)-mannostatin), or the conduramines: (b) Balci, M.; Sutbeyaz, Y.; Secen, H. *Tetrahedron* **1993**, *49*, 8039−8058. (c) Posternak, T. *The Cyclitols* Holden-Day Inc.: San Francisco, 1965. (d) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444−458.

(14) Our initial plan featured a 5-exo-trig radical cyclization of a dichloroacetamide, induced by the Ni/AcOH combination, recently developed in our laboratory: Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029−1040 and references cited therein. In model studies, the cyclization worked well in the absence of the methyl group on C(11); however, when the methyl group was present, a rare 1,4-allylic hydrogen abstraction on C(4) took place. These unwanted, but nevertheless interesting, reactions will be detailed in the full paper.

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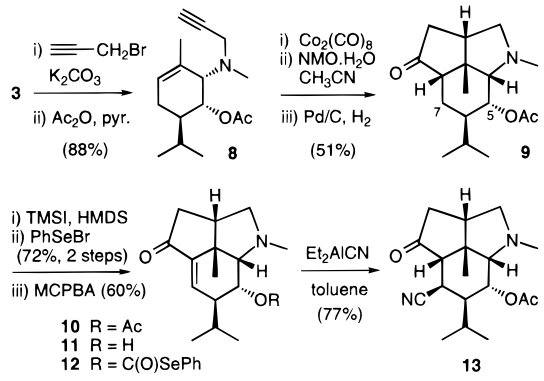
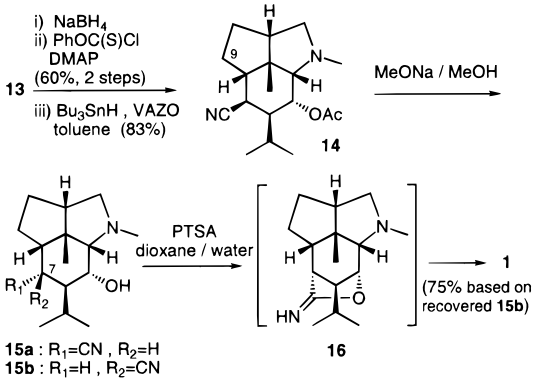
Scheme 3. Synthesis of the Cyanoketone **13**



cyclopentenone **2**, along with an unexpected ring-opened product.[16] This problem was overcome by using acetonitrile as the solvent,[17] and **2** was then exclusively obtained (Scheme 3). This somewhat unstable cyclopentenone **2** was directly hydrogenated (Pd/C, H_2) to afford the tricyclic ketone **9** as a single diastereoisomer (51% from **8**).

Having achieved the construction of the azatricyclo[6.2.1.$0^{4,11}$]-undecane ring system of dendrobine, we then proceeded to construct the final bridged lactone ring, which required functionalization at C(7). Treatment of **9** with iodotrimethylsilane and HMDS in CH_2Cl_2 at −20 °C[18] afforded exclusively the more substituted enol silyl ether.[19] Reaction with phenylselenenyl bromide gave the α-seleno ketone (72% yield from **9**), which was directly oxidized to **10** (60% yield). Direct construction of the lactone ring from the hydroxy group at C(5) was first envisioned. Thus, a nucleophilic alkoxycarbonyl radical derived from selenocarbonate **12** would have readily cyclized onto the electron-deficient double bond.[20] Unfortunately, all attempts to form **12** from **11** remained unsuccessful.[21] On the other hand, treatment of **10** with diethylaluminum cyanide in toluene at 70 °C afforded the cyanoketone **13** as a single diastereoisomer in 77% yield. Delivery of the nitrile took place from the least hindered β-face with the cyano group ending up in an axial disposition.

Scheme 4. Synthesis of (−)-Dendrobine **1**



Epimerisation at C(7) was delayed to the last step of the synthesis to avoid problems associated with the presence of the ketone at C(9).[22] Reduction of ketone **13** with sodium borohydride, followed by treatment with phenyl chlorothionoformate provided the corresponding thiocarbonate in 60% overall yield. Subsequent Barton−McCombie deoxygenation[23] afforded **14** in 83% yield (Scheme 4). As expected, exposure of **14** to sodium methoxide in methanol at 100 °C for 24 h (sealed tube) caused partial epimerisation at C(7) and hydrolysis of the acetate group to give a 1:1 mixture of the two epimeric hydroxy nitriles **15a** and **15b**. Finally, the mixture of epimers was directly treated with *p*-toluenesulfonic acid in aqueous 1,4-dioxane at reflux to furnish (−)-dendrobine (**1**), along with unreacted hydroxy nitrile **15b**. It is noteworthy that **15b** was fully recovered from this last reaction, in accord with a prior cyclization of hydroxy-nitrile **15a** to iminolactone **16**,[24] which then undergoes hydrolysis to (−)-dendrobine (**1**) (75% from **14** based on recovered **15b**).[25]

In summary, a concise, enantioselective synthesis of (−)-dendrobine (**1**) has been achieved in 13 steps, starting from (+)-trans-verbenol (**6**). A cascade involving a carbamyl radical, allowed the efficient formation of amino alcohol **3** from **6**, with the creation of the three principal stereogenic centers. The application of the Pauson−Khand reaction (**8** → **2**) to construct the crucial quaternary center at C(11) and the curious solvent effect, which remains to be clarified, are other interesting features of this synthesis.

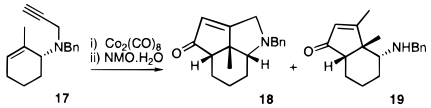
Acknowledgment. This paper is dedicated with respect and admiration to Professor K. U. Ingold, on the occasion of his 70th birthday. We wish to thank the Ministry of Education for a Ph.D. grant to one of us (J.C.) and Michel Levart for numerous GC−MS spectra which speeded up our work considerably.

Supporting Information Available: Experimental procedures as well as a compilation of spectral and analytical data of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA990707P

(15) For acceleration of Pauson−Khand cycloadditions with tertiary amine *N*-oxides, see: (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289−5292. (b) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, H. L.; Yoo, S.-E. *Synlett* **1991**, 204−206.

(16) Model studies on *N*-propargyl derivative **17** were undertaken to confirm these intriguing results: under the same conditions, Pauson−Khand reaction of **17** afforded a mixture of expected tricyclic cyclopentenone **18**, along with the bicyclic product **19**. In the case of **8**, a similar ring-opened product was formed, but its structure has not been established unambiguously. The course of the reaction is quite dependent on the solvent, since formation of ring-opened products can be suppressed by using more coordinating solvents, such as acetonitrile. The mechanism for the formation of **19** is still not clear, but



solvent	18	19
CH_2Cl_2	34%	14%
CH_2Cl_2 / THF	52%	10%
CH_3CN	63%	—

one can speculate that the presence of the basic β-nitrogen within an intermediate complex may induce a β-elimination to give **19** after protonation. Analogous observations have been made with zirconium-mediated [2 + 2 + 1] cycloadditions of related benzylamines: ref 5d and Barluenga, J.; Sanz, R.; Fananas, F. *Chem.—Eur. J.* **1997**, *3*, 1324−1336. We are not aware of any previous report of such ring-opened products in the Pauson−Khand reaction of propargylic amines, but similar observations were made when allyl propargyl ethers were subjected to Pauson−Khand conditions in the absence of oxygen. In our case, the influence of oxygen was not significant. See ref 15b and Smit, W. A.; Simonyan, S. O.; Tarasov, V. A.; Michaelian, G. S.; Gybin, A. S.; Ibragimov, I. I.; Caple, R.; Froen, D.; Kreager, A. *Synthesis* **1989**, 472−476.

(17) For a study of the influence of coordinating solvents on the Pauson−Khand reaction, see: Krafft, M. E.; Scott, I. L.; Romero, R. H.; Feibelmann, S.; Van Pelt, C. E. *J. Am. Chem. Soc.* **1997**, *119*, 7199−7207.

(18) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730−732.

(19) Interestingly, treatment of ketone **9** with TMSOTf and Et_3N in refluxing CH_2Cl_2 afforded a 78:22 mixture of regioisomers in favor of the less substituted isomer. Moreover, model studies have disclosed the importance of the methyl group at C(11) in the regiochemistry of the enol silyl ether formation.

(20) For related cyclizations of alcoxycarbonyl radicals, see: (a) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187−6189. (b) Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696−4705.

(21) Surprisingly, upon treatment with phosgene, **11** underwent N-demethylation, and subsequent formation of a tetracyclic oxazolidinone. On the other hand, the carbonyl imidazolide derived from **11** failed to undergo substitution by benzeneselenol, probably because of steric hindrance.

(22) It is noteworthy that removal of the acetate group from ketone **9** or cyanoketone **13** induced cyclization of the hydroxy group onto the carbonyl function at C(9) to give the corresponding lactol, which could be isolated as its TMS ether.

(23) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585.

(24) Compound **16** can be obtained by treatment of **15a** with anhydrous *p*-toluenesulfonic acid in refluxing toluene. For previous isolation of a similar iminolactone, see ref 4b.

(25) In principle, it may be possible to convert cyanoketone **13** directly into iminoether **16** (or even to dendrobine) by treatment with hydrazine under Wolff−Kishner conditions. Epimerisation of a similar nitrile under these conditions has already been observed; see ref 4b; unfortunately, preliminary trials have so far proved unsuccessful.