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An Alternative Synthesis of Dolby−Weinreb Enamine en Route to Cephalotaxine

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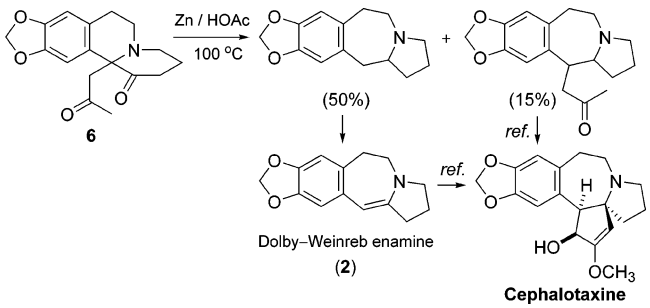
Received January 24, 2005



A novel alternative synthesis of the Dolby−Weinreb enamine (**2**) was achieved from readily available amino dione **6** by a mild transannular Clemmensen−Clemo−Prelog−Leonard reductive rearrangement, which thus constitutes a formal total synthesis of cephalotaxine.

Dolby−Weinreb enamine (**2**), a benzazepine heterocycle, has been a key advanced intermediate in the classical Weinreb synthesis[1] of cephalotaxine (CET, **1**), which is the core structure of the structurally unique antileukemia *Cephalotaxus* alkaloid ester derivatives.[2] Enamine **2** was also synthesized by other groups[3] following the pioneering works by Dolby and Weinreb in this field, via different annulation approaches, as outlined in Figure 1, respectively.

We have recently disclosed[4a] two novel approaches for the total synthesis of CET, among which a mild transannular reductive rearrangement (Clemmensen−Clemo−Prelog−Leonard rearrangement)[4a] of cyclic α-amino ketone **3** was employed as one of the key steps (**3** → **4**) for the construction of the substituted benzazepine ring system (*ABCD*)[5,6] of CET (cf. Figure 2).

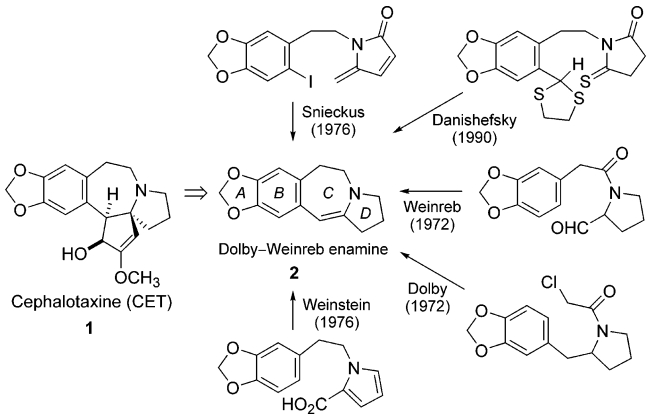


FIGURE 1. Syntheses of Dolby−Weinreb enamine (**2**) en route to CET.

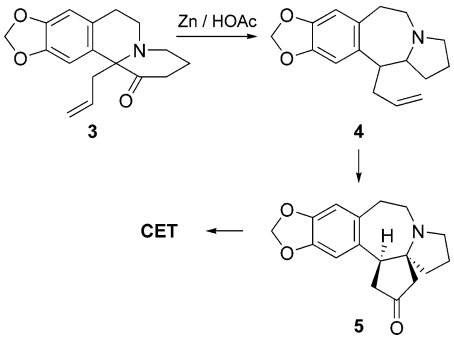


FIGURE 2. Previous synthesis of the benzazepine ring system (*ABCD*) of CET (ref 4a).

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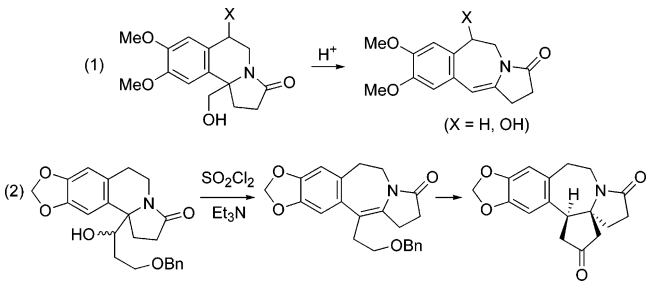
(1) (a) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503. (b) Weinreb, S. M.; Semmelhack, M. F. *Acc. Chem. Res.* **1975**, *8*, 158.

(2) For general reviews, see: (a) Huang, L.; Xue, Z. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1984; Vol. 23, pp 157−226. (b) Jalil Miah, M. A.; Hudlicky, T.; Reed, J. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 199−269.

(3) Cf.: (a) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691. (b) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875. (c) Tse, I.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1976**, 505. (d) Fang, F. G.; Maier, M. E.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 831.

(4) (a) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931 and references therein. For other recent synthesis of CET, see also: (b) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (c) Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922. (d) Li, W.-D. Z.; Ma, B.-C. *J. Org. Chem.* **2005**, http://dx.doi.org/10.1021/jo048046o.

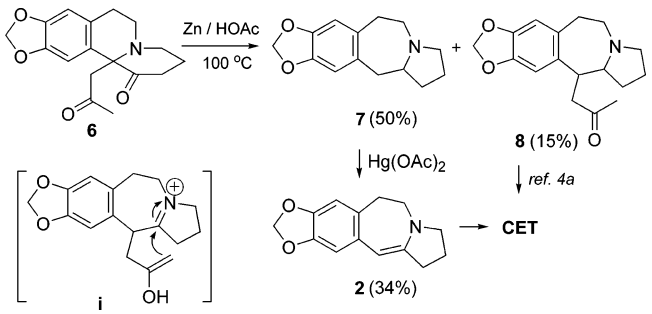
(5) For other related rearrangement approaches for the *ABCD* benzazepine ring system of CET, cf.: (a) p 239 of ref 2b (eq 1 below; Hudlicky, T.; Hiranuma, H.; Hiranuma, S. Unpublished results, 1983). (b) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885 (eq 2 below):



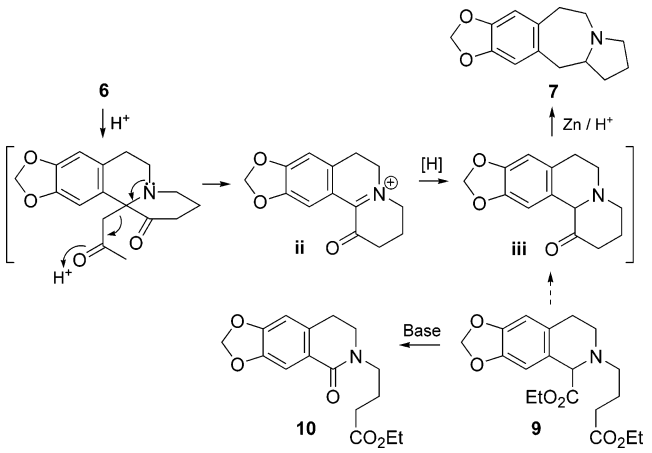
(6) For reviews on benzazepine alkaloid synthesis, see: (a) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 931. (b) Liang, X.-T. *J. Chin. Chem. Soc.* (*Taipei*) **1995**, *42*, 601. For a recent example of this approach, see: (c) Liu, Y.-X.; Liang, X.-T. *Chin. Chem. Lett.* **2001**, *12*, 7.

10.1021/jo050143+ CCC: $30.25
Published on Web 04/16/2005

SCHEME 1. Reductive Rearrangement of Amino Dione 6



SCHEME 2. A Possible Mechanistic Pathway for the Conversion of 6 → 7



With readily available allyl-substituted cyclic α-amino ketone **3** in hand, we obtained[4a] the corresponding amino dione **6** by Wacker oxidation, which was subjected to the reductive rearrangement in hoping to effect a tandem rearrangement−intramolecular Mannich-type cyclization to pentacycle **5** via a hypothetic intermediate **i** (cf. arrows in Scheme 1). To our surprise, reduction of amino dione **6** with zinc powder in hot glacial acetic acid produced the Dolby benzazepine **7** (hydrochloride salt, mp 262−264 °C, lit.[3a] mp 265−266 °C) as the major product (50%) and a minor product of known[4a] amino ketone **8** (15%). The identity of structures **7** and **8** was fully confirmed spectroscopically by comparison with reported data.[1,3,4a] Oxidative dehydrogenation[1,3] of **7** with $Hg(OAc)_2$ in warm aqueous acetic acid afforded the labile title enamine **2** (34%, mp 81−82 °C, lit.[3a] mp 82−83 °C).

An apparent mechanistic pathway to benzazepine **7** was depicted in Scheme 2, in which an acid-catalyzed retro-Mannich−reductive rearrangement pathway (**6** → **ii** → **iii**) predominated and ultimately led to **7**. The minor reductive rearrangement product **8** was formed through the normal transannular reductive rearrangement of the cyclic α-amino ketone unit possibly via the reduction of intermediate **i**. In fact, our previous efforts for preparing the cyclic α-amino ketone **iii**, which in principle would be an ideal cyclic α-amino ketone substrate for effecting the designated Clemmensen−Clemo−Prelog−Leonard reductive rearrangement to benzazepine **7**, from a diester precursor **9**[4a] by Dieckmann condensation (KO^{t}Bu, toluene, reflux), resulted in the formation of an autoxidative decarboxylation[7] product **10**[8] instead. Although the expected Mannich-type cyclization was not observed, the alternative synthesis of reductive rearrangement products **7** and **8** constitutes a formal synthesis of CET.

In short, an alternative synthesis of the Dolby−Weinreb enamine (**2**), a classical intermediate en route to CET synthesis, was achieved from readily available cyclic amino dione **6** by a mild Clemmensen−Clemo−Prelog−Leonard reductive rearrangement. This facile transannular rearrangement would find further useful applications in the synthesis of polycyclic *N*-heterocycles.[9]

Experimental Section[10]

Preparation of 8,9-Methylenedioxy-2,3,5,6,11,11a-hexhydro-1*H*-pyrrolo[2,1-*b*][3]benzazepine 7 (Dolby Benzazepine). Amino dione **6** (99.0 mg, 0.33 mmol) was dissolved in 5 mL of glacial acetic acid and treated with Zn dust (296 mg) in one portion. The mixture was then brought to 100 °C and vigorously stirred for 3 h under N_2. The acetic acid was evaporated in vacuo, and the residue was poured into 5 mL of saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (10 mL × 3). The resulting organic extracts were combined, washed with water and brine, and dried. Evaporation of the solvent in vacuo followed by chromatographic purification on silica gel gave the Dolby amine **7** as a colorless hygroscopic gum (38 mg, 50%) and amino ketone **8** (15 mg, 15%) as a colorless film. The corresponding hydrochloride salt of cyclic amine **7** was obtained by titration with concentrated HCl in chloroform to give a colorless solid, mp 262−264 °C (lit.[3a] mp 265−266 °C). **7**: IR (KBr) ν 2923, 1505, 1484, 1243, 1039, 936, 863 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (br s, 2H), 1.71 (br s, 2H), 1.80−1.95 (m, 1H), 2.18−2.25 (m, 1H), 2.26−2.60 (m, 1H), 2.61−2.65 (m, 2H), 2.90−3.12 (m, 4H), 5.89 (s, 2H), 6.55 (s, 1H), 6.68 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.0, 25.3, 29.4, 31.5, 52.8, 56.8, 63.6, 100.9, 105.2, 108.7, 127.7, 136.7, 146.1 (2C) ppm; EIMS (*m/z*, %) 231 (M^+, 50), 230 (100), 202 (44), 189 (13), 175 (39); HRMS (ESI) *m/z* obsd 232.1334 ([M + H]$^+$, calcd for $C_{14}H_{18}NO_2$ 232.1332).

Preparation of 8,9-Methylenedioxy-2,3,5,6-tetrahydro-1*H*-pyrrolo[2,1-*b*][3]benzazepine 2 (Dolby−Weinreb Enamine).[3a] A solution of the Dolby benzazepine **7** (60.0 mg, 0.26 mmol) in 2% aqueous acetic acid (3 mL) was treated with $Hg(OAc)_2$ (700 mg, 2.20 mmol) at room temperature. The reaction mixture was brought to 100 °C and stirred for 2 h under N_2. The reaction mixture was filtered; the filtrate was basicified with 50% aqueous sodium hydroxide to pH 11 and extracted with EtOAc (10 mL × 3). The combined organic phases were washed with brine, dried, and concentrated to give a pale yellowish gum (20 mg, 34%). The gum solidified when kept in the cold, mp 81−82 °C (lit.[3a] mp 82−83 °C). **2**: IR (KBr) ν_{max} 2903, 1641, 1603, 1498, 1481, 1418, 1345, 1269, 1034, 928, 863 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−2.05 (m, 2H), 2.11−2.28 (m, 2H), 2.31 (t, J = 6.9 Hz, 1H), 2.59−3.02 (m, 3H), 3.44−3.57 (m, 2H), 5.19 (br s, 1H), 5.92 (s, 2H), 6.54 (br s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 28.4, 33.2, 46.4, 47.1, 101.6, 107.1, 108.3(2C), 146.9 (2C), 166.2, 177.0 ppm; EIMS (*m/z*) 229 (M^+, 71), 228 (M

(7) Cf.: (a) Vaccher, C.; Berthelot, P.; Debaert, M.; Barbry, D. *J. Heterocycl. Chem.* **1984**, *21*, 1201. (b) Kawase, M. *Chem. Pharm. Bull.* **1997**, *45*, 1248.

(8) Spectral data for **10**: IR (KBr) ν_{max} 2930, 1730, 1645, 1611, 1480 1268, 1035 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 3H), 1.88−1.95 (m, 2 H), 2.35 (t, J = 7.3 Hz, 2 H), 2.85 (t, J = 6.6 Hz, 2 H), 3.49 (t, J = 6.6 Hz, 2 H), 3.54 (t, J = 7.2 Hz, 2 H), 4.08 (q, J = 7.2 Hz, 2 H), 5.95 (s, 2 H), 6.57 (s, 1 H), 7.48 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 23.0, 28.2, 31.6, 46.1, 46.6, 60.4, 101.4, 106.8, 108.1, 123.6, 133.4, 146.8, 150.3, 164.1, 173.2 ppm; EIMS *m/z* [M^+] 305 (64), 260 (33), 218 (81), 204 (100), 162 (28), 134 (19); HRMS (EI) *m/z* observed 306.1332 ([M + H]$^+$, calcd 306.1336 for $C_{17}H_{18}NO_3$).

(9) Studies along this line are ongoing in our laboratory.

(10) For General Experimental Procedures, cf.: Supporting Information of ref 4a.

− 1, 100), 214 (30), 149 (81); HRMS (ESI) *m/z* obsd 230.1178 ($[M + H]^+$, calcd for $C_{14}H_{16}NO_2$ 230.1176).

Acknowledgment. We thank the National Natural Science Foundation (Distinguished Youth Fund 29925204 and QT 20021001), Fok Ying Tung Education Foundation (Fund 71012), and Ministry of National Education (Funds 99114 and 2000-66) of China for financial support. The Cheung Kong Scholars program and the Outstanding Scholars program of Nankai University are gratefully acknowledged.

Supporting Information Available: ^1H NMR, ^{13}C NMR, IR, and HRMS spectrum of compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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