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A Novel Formal Total Synthesis of Cephalotaxine

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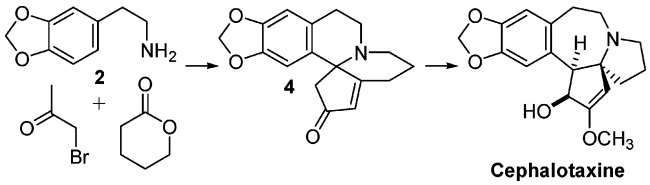

A formal total synthesis of cephalotaxine (CET), the parent structure of antileukemia *Cephalotaxus* alkaloids, was achieved through a novel synthesis of the pentacyclic amino enone **4** by a rapid annulation of readily available β-(3,4-methylenedioxy)phenethylamine (**2**), δ-valerolactone, and bromoacetone.

Cephalotaxine (**1**, CET), the parent structure of the *Cephalotaxus* alkaloids,[1] represents a unique class of benzazepine alkaloid characterized by the presence of an unusual pentacyclic ring system. The structural uniqueness of **1** and the clinically proven therapeutic potential of its ester derivatives (i.e., harringtonine and homoharringtonine) as antileukemia agents have drawn continuing interest in their chemical syntheses.[2] We recently reported[2b] a novel and efficient synthesis of CET based on a biogenesis-inspired transannular reductive rearrangement strategy. As highlighted in Figure 1, the annulation of readily available β-(3,4-methylenedioxy)-phenethylamine (**2**) with three benchtop chemicals provided a tetracyclic amino ketone **3**, which was cyclized to a spiral pentacyclic amino enone **4**; subsequent transannular reductive rearrangement of **4** furnished a pentacyclic ketone **5**, the ring skeleton of CET, which was finally converted to CET. An alternative synthetic pathway via a benzazepine intermediate **6**, derived from **3** by a transannular Clemmensen−Clemo−Prelog−Leonard reductive rearrangement,[2b] led to the discovery of an unusual oxidative Nazarov cyclization of the corresponding keto enamine **7** to a pentacyclic amino enone

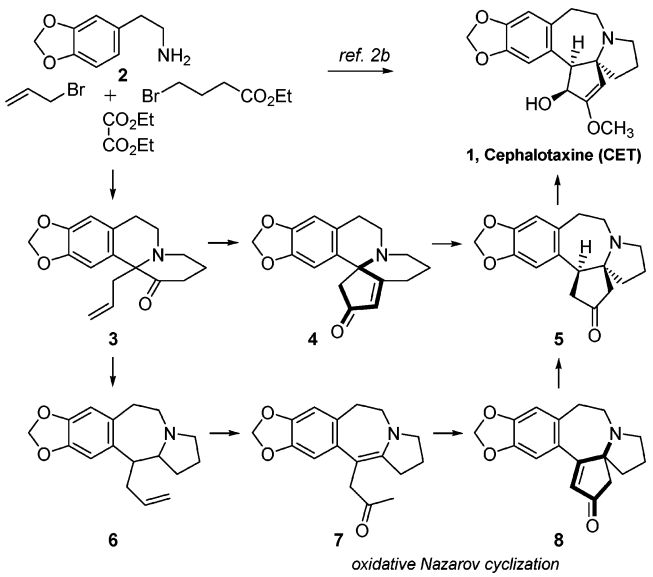

FIGURE 1. Highlights of novel CET synthesis (ref 2b).

8, which was reduced (either hydrogenative or by zinc in glacial acetic acid) to the pentacyclic ketone **5**.

In view of the ring-structure features of the pentacyclic γ-amino enones **4** and **8** (Figure 1, cf. the highlighted bonding connection), we envisioned an immediate application of this unusual oxidative cyclic enamine (Nazarov) annulation (cf. **7** → **8**)[2b] to an alternative synthesis of the key pentacyclic enone **4** from the corresponding tetracyclic keto enamine precursor **9**, a ring-structure congener of the endocyclic keto enamine **7**, via an analogous reaction pathway as depicted in Scheme 1, involving hypothetic intermediates **i** and **ii**.

A straightforward synthesis of the keto enamine **9** was outlined in Scheme 2. Bischler−Napieralski condensation of β-(3,4-methylenedioxy)phenethylamine (**2**) with δ-valerolactone mediated by phosphorus oxychloride in refluxing toluene[3] gave after basic extractive workup and acidification with 70% perchloric acid the iminium perchlorate **10** (mp 224−226 °C) in good yield. Brief treatment of perchlorate **10** with 10% aqueous NaOH at room temperature followed by extraction with methylene chloride afforded a labile enamine **11** (mp 104−106 °C), which was alkylated[4] with bromoacetone (excess, rt, 72 h) without further purification, to give after flash chromatgrophy on silica gel the desired endocyclic keto enamine **9** (20%, mp 180−182 °C) eluting with 20% ethyl acetate in hexane, and the corresponding iminium bromide **12** [50%, mp 245 °C dec] eluting with 10% methanol in chloroform. Alternatively, the above crude alkylation products (**9** and **12**) were collectively converted[5] by treatment with 70% perchloric acid in methanol into the

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(1) For 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.

(2) For recent synthesis of CET, see: (a) Planas, L.; Perard-Viret, J.; Royer, J. *J. Org. Chem.* **2004**, *69*, 3087. (b) Li, W.-D. Z.; Wang, Y.-Q. *Org. Lett.* **2003**, *5*, 2931 and references therein. (c) Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett.* **2002**, *4*, 885.

(3) Cf.: (a) Stevens, R. V.; Wentland, M. P. *J. Chem. Soc., Chem. Commun.* **1968**, 1104. (b) Szabo, L.; Kalaus, G.; Kalman, A.; Kolonits, P.; Szantay, C. *Heterocycles* **1995**, *40*, 155.

(4) Cf.: (a) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580. (b) Schut, R. N.; Ward, F. E.; Leipzig, T. J. *J. Org. Chem.* **1969**, *34*, 330. (c) Fuji, T.; Nohara, M.; Mitsukuchi, M.; Ohba, M.; Shikata, K.; Yoshifuji, S.; Ikegami, S. *Chem. Pharm. Bull.* **1975**, *23*, 144.

(5) See Experimental Section for detailed procedures.

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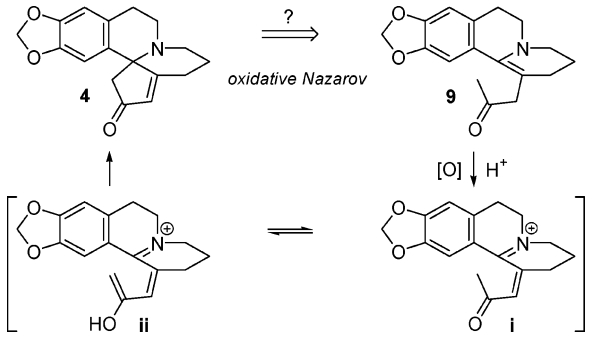
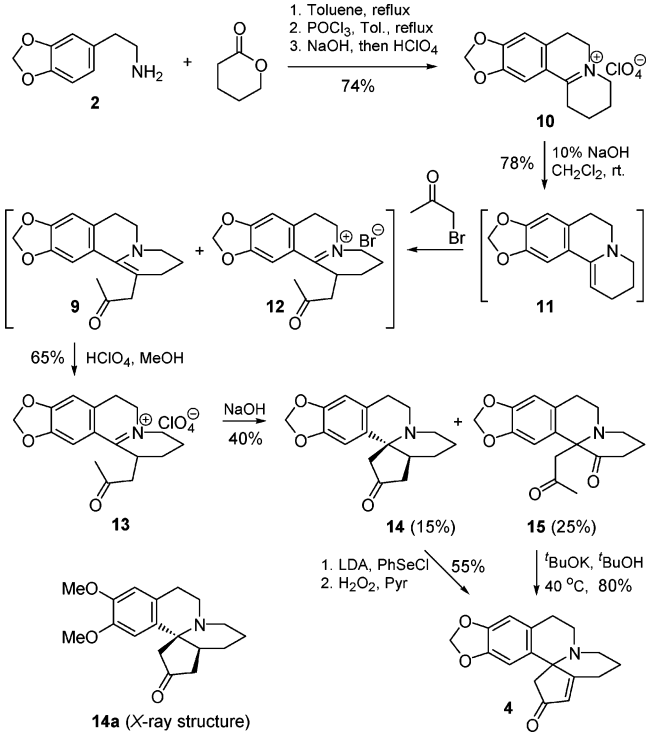
SCHEME 1. An Alternative Synthetic Plan for Pentacyclic Enone 4



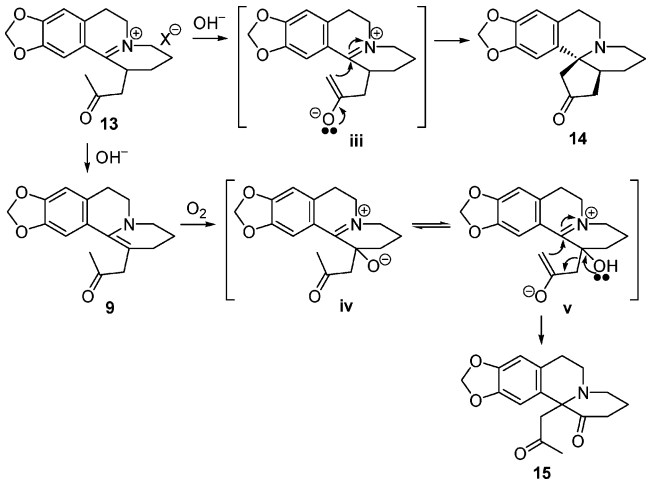
SCHEME 2. A Novel Synthesis of Pentacyclic Amino Enone 4



corresponding iminium perchlorate **13** [65%, mp 255 °C dec], which was used conveniently for further transformation due to its thermal stability. The keto enamine **9** can be readily liberated from perchlorate **13** by treatment with an equal equivalent of aqueous alkaline (NaOH) solution and subsequent extraction with chloroform.

The initial attempt to effect the anticipated cyclization of **9** to **4** under similar acidic autoxidation conditions (HOAc, air)[2b] as for the conversion of **7** → **8** was unsuccessful resulting in the recovery of starting keto enamine **9**. Further attempts under a variety of acidic conditions in the presence of various oxidants (i.e., O_2, *m*CPBA, Br_2, or NBS etc.) were also unfruitful. Surprisingly, when perchlorate **13** was exposed to an *excess* aqueous alkaline (NaOH) solution and extracted with chloroform, we obtained a saturated pentacyclic product identified as a *cis*-cyclic ketone **14** (15%, mp 171−172 °C) and a more polar product characterized as a dione **15** (25%) after flash chromatographic purification on silica gel. The pentacyclic ketone **14** is spectroscopically identical with a minor reduction product of pentacyclic enone

SCHEME 3. Possible Pathways of Transformation 13 → 14 + 15



4 (Zn, HOAc, 100 °C),[6] and its stereostructure (cis ring-fusion) was verified by the single crystal X-ray diffraction analysis of an analogously synthesized 3,4-dimethoxy congener **14a**.[7] Both amino ketones **14** and **15** were converted readily into the tetracyclic enone **4** by standard procedures as shown (Scheme 2).

As shown in Scheme 3, possible mechanistic pathways for the formation of **14** and **15** from iminium perchlorate **13** under alkaline conditions are proposed. The reliberated enamine **9** may undergo an autoxidation and further rearrangment to dione **15** by an unusual intramolecular C−C bond transposition[10] via intermediates **iv** and **v**, while a base-promoted Mannich-type cyclization of iminium perchlorate **13** via iminium enolate **iii** may account for the formation of pentacyclic ketone **14**. It is noteworthy that although both endocyclic enamines **7** and **9** are reluctant to undergo the anticipated acid-catalyzed Mannich-type annulation,[11] they are prone to *autoxidation* under acidic (for **7**)[2b] and basic conditions (for **9**), respectively. To our delight, both keto enamines **7** and **9** were transformed into the key pentacyclic enone **4** en route to CET, albeit through different pathways. The

(6) Wang, Y.-Q. Ph.D. Thesis (Novel Total Synthesis of Cephalotaxine), Lanzhou University, 2003.

(7) Spectral data for **14a**: IR (KBr) ν_{max} 2933, 1741, 1607, 1513, 1462, 1257, 1219 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.54 (m, 2H), 1.56−1.60 (m, 1H), 1.82−1.88 (m, 1H), 2.26 (d, J = 17.7 Hz, 1H), 2.30−2.38 (m, 2H), 2.62−2.66 (m, 2H), 2.86 (d, J = 17.7 Hz, 1H), 2.83−2.90 (m, 2H), 3.02−3.11 (m, 2H), 3.32−3.41 (m, 1H), 3.83 (s, 3H), 3.84 (s, 3H), 6.56 (s, 1H), 6.77 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.8, 22.0, 38.3, 38.9, 45.2, 47.4, 55.6, 56.0, 56.8, 63.0, 107.6, 111.9, 127.1, 128.4, 147.6, 147.8, 215.8 ppm; HRMS (ESI) *m/z* observed 302.1751 ([M + H]$^+$, calcd 302.1751 for $C_{18}H_{24}NO_3$). X-ray crystallographic data for **14a**: $C_{18}H_{23}NO_3$, FW 301.37, monoclinic, space group $P2_1/c$, a = 10.958(2) Å, b = 16.203(3) Å, c = 9.101(2) Å, β = 91.30(3)°, Z = 4, d_{calc} = 1.239 g/cm^3, R_1 ($I > 2\sigma(I)$) = 0.0551, wR_2 (all data) = 0.1428. See Supporting Information for detailed X-ray crystallographic data.

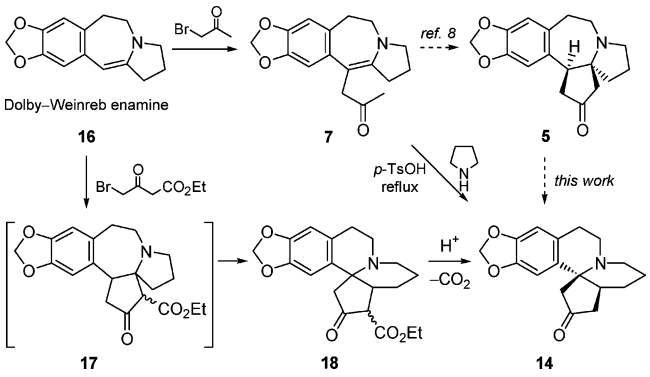
(8) Dolby, L. J.; Nelson, S. J.; Senkovich, D. *J. Org. Chem.* **1972**, *37*, 3691.

(9) Cf.: (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. (c) Weinstein, B.; Craig, A. R. *J. Org. Chem.* **1976**, *41*, 875. (d) Tse, I.; Snieckus, V. *J. Chem. Soc., Chem. Commun.* **1976**, 505. (e) Fang, F. G.; Maier, M. E.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 831.

(10) For an example, see: Noe, E.; Seraphin, D.; Zhang, Q.; Djate, F.; Henin, J.; Laronze, J.-Y.; Levy, J. *Tetrahedron Lett.* **1996**, *37*, 5701.

(11) For a review, see: Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193.

SCHEME 4. Attempted CET Synthesis by Dolby and Co-workers (Ref 8)



distinct reactivity difference between the keto enamines **7** and **9** could be a result of the subtle changes in their ring structures and the corresponding electronic properties of the tetrasubstituted enamine moiety, so that compound **7** is a more electron-rich (thus more reactive toward electrophilic autoxidation under acidic condition) β-aryl substituted enamine.

Interestingly, the pentacyclic ketone **14** had been previously obtained by Dolby and co-workers[8] in an attempted Mannich-type annulation (**7** → **5**)[2b] of the Dolby−Weinreb enamine **16**[8,9]during their earlier synthetic studies on CET, via possibly an intriguing transannular ring-skeleton isomerization (Scheme 4, cf. **16** → **17** → **18** → **14**) involving presumably the initial enamine alkylation intermediate **17**. Although the keto enamine **7** can be cyclized and isomerized to **14** in a low yield as observed by Dolby et al.,[8] the attempted transannular isomerization of our synthetic intermediate **5** under identical conditions did not produce any detectable **14** in our hands.[12] Comparably, the original Dolby conditions (*p*-TsOH, pyrrolidine, reflux) for the Mannich-type cyclization of keto enamine **7** to **14** (Scheme 4) did not effect the cyclization of our synthetic keto enamine **9** to **14** in various attempts.

In summary, we have achieved an alternative formal synthesis of CET via a facile and rapid assembly of the key pentacyclic enone **4** by a novel annulation of three readily available reagent chemicals. The CET synthesis described herein and in our previous Letter[2b] features a biomimetic transannular ring-skeletal reductive isomerization of amino enone **4** to pentacyclic ketone **5**. The intriguing reactivities of endocyclic keto enamines (**7** and **9**) were explored, i.e., the transannular isomerization reactions of **4** → **5** vs **7** → **14**. These results could be valuable for developing a practical synthesis[13] of CET and other closely related natural alkaloids.

Experimental Section.[14]

Preparation of Iminium Perchlorate 10. A mixture of β-(3,4-methylenedioxy)phenethylamine (**2**) (8.25 g, 0.05 mol) and δ-valerolactone (5.1 g, 0.051 mol) in 20 mL of toluene was brought to reflux for 8 h. The resulting mixture was cooled, and the crystalline solids were collected, washed with benzene, and recrystallized from diethyl ether to give the hydroxyamide intermediate as white solids (11.5 g, 87%). Mp 84−86 °C; IR (KBr) ν_{max} 3414, 3300, 2943, 1633, 1545, 1497, 1245, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53−1.60 (m, 2H), 1.65−1.75 (m, 2H), 2.18 (t, J = 7.2 Hz, 2H), 2.72 (t, J = 6.9 Hz, 2H), 3.45 (dd, J = 12.9 Hz, J = 6.6 Hz, 2H), 3.61(t, J = 6.0 Hz, 2H), 5.83 (br s, 1H), 5.93 (s, 2H), 6.24 (d, J = 7.8 Hz, 1H), 6.67 (br s, 1H), 6.74 (d, J = 8.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 31.9, 35.3, 36.0, 40.7, 61.9, 100.8, 108.3, 109.0, 121.6, 132.5, 146.1, 147.7, 173.2 ppm; EIMS (*m/z*) 265 (M$^+$, 2), 148 (100), 135 (17). A mixture of the above hydroxyamide (2.65 g, 10.0 mmol) and 15 mL of $POCl_3$ in 30 mL of anhydrous toluene was refluxed for 10 h under N_2 atmosphere. After evaporation of the solvent in vacuo, the residue was taken up in water (25 mL) and extracted with Et_2O (20 mL × 2). The aqueous phase was basicified with 50% aqueous NaOH to pH 10 at 0 °C and extracted with $CHCl_3$ (50 mL × 3). The combined organic layers were washed with water and brine and dried. After the solvent was evaporated in vacuo, the resulting residue was taken in 12 mL of EtOH and acidified with 70% $HClO_4$ to pH 5. The crystalline iminium perchlorate **10** was collected and washed with EtOH−Et_2O (1:1) to give a yellowish powder (2.80 g, 85%). Mp 224−226 °C (EtOH); IR (KBr) ν_{max} 1626, 1601, 1497, 1333, 1271, 813 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.82 (d, J = 4.2 Hz, 2H), 1.91 (d, J = 3.9 Hz, 2H), 3.02 (t, J = 7.5 Hz, 2H), 3.17 (br s, 2H), 3.84 (br s, 4H), 6.19 (s, 2H), 7.06 (s, 1H), 7.55 (s, 1H) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 17.4, 20.9, 25.6, 28.3, 51.6, 54.3, 103.5, 108.6, 121.1, 135.1,147.8, 153.9, 173.4 ppm; LRMS (FAB, *m/z*) 230.2, 185.2; HRMS (ESI) *m/z* obsd 230.1176 ([M − ClO_4]$^+$, calcd 230.1173 for $C_{14}H_{16}NO_2$).

Preparation of Enamine 11. A mixture of iminium perchlorate **10** (3.29 g, 10.0 mmol) in CH_2Cl_2 (15 mL) and 1.0 M aqueous NaOH (10 mL) was stirred vigorously for 10 min at room temperature. The organic phases were separated; the aqueous layer was extracted with CH_2Cl_2 (25 mL), combined with the organic layer, and dried over anhydrous K_2CO_3. Evaporation of the solvent in vacuo followed by filtration through a pad of basic alumina gave the cyclic enamine **11** as a labile brown solid (1.79 g, 78%) after concentration in vacuo at room temperature. Mp 104−106 °C; IR (KBr) ν_{max} 1643, 1608, 1478, 1269, 1037, 753 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86−1.97 (m, 2H), 2.23 (t, J = 6.0 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 2.96 (br s, 2H), 3.06 (br s, 2H), 5.18 (br s, 1H), 5.89 (s, 2H), 6.51 (s, 1H), 7.07 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.3, 22.7, 29.9, 51.5, 100.7, 101.3, 103.0, 106.7, 107.9, 124.9, 127.9, 146.4 ppm; EIMS (*m/z*) 229 (M$^+$, 62), 228 (90), 83 (100).

Preparation of Keto Enamine 9, Iminium Bromide 12, and Iminium Perchlorate 13. A solution of enamine **11** [generated from 3.29 g (10.0 mmol) of the corresponding iminium perchlorate **10** by the above procedure] in CH_2Cl_2 was combined with bromoacetone (ca. 5.0 mL) and the resulting mixture was stirred at room temperature for 72 h under N_2. After evaporation of the solvent in vacuo, the resultant residue was divided into two portions evenly. One portion of the crude residue was purified by flash column chromatography on silica gel: eluting with petroleum ether−EtOAc (1:4) gave the desired alkylated product **9** as a yellowish solid (285 mg, 10%); and subsequent eluting with $CHCl_3$−CH_3OH (10:1) yielded the iminium bromide **12** as pale yellowish solids (910 mg, 25%). Another portion of the crude residue was taken in methanol (10 mL) and acidified with 70% $HClO_4$ to pH 5. The crystalline precipitates were collected and washed with cold methanol to give iminium perchlorate **13** as a pale yellowish solid (1.15 g, 30%). **9**: mp 180−182 °C (EtOAc−petroleum ether); IR (KBr) ν_{max} 2924, 1931, 1645, 1610, 1480, 1269, 1155, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (t, J = 6.9 Hz, 2H), 2.16 (s, 3H), 2.52 (t, J = 6.9 Hz, 2H), 2.89 (t, J = 6.3 Hz, 2H), 3.55 (t, J = 6.3 Hz, 2H), 3.61 (t, J = 6.3 Hz, 2H), 4.66 (s, 2H), 5.97 (s, 2H), 6.91(s, 1H), 7.50 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 26.0, 28.2, 31.0, 46.2, 46.4, 68.2, 101.4, 106.8, 108.1, 123.4, 133.5, 146.8, 150.2, 164.1, 172.4, 201.4 ppm; EIMS (*m/z*) 285 (M$^+$, 2), 284 (M − 1, 5), 218 (44), 204 (100); HRMS (ESI) *m/z* obsd 334.7286

(12) This result would exclude the possibility that Dolby's cyclization−isomerization of **7** → **14** may proceed via compound **5** as an intermediate.

(13) The chemical yields in this work will be subjected to further optimization.

(14) For General Experimental Procedures see the Supporting Information of ref 2b.

([M + H]$^+$, calcd 334.7286 for $C_{17}H_{20}NO_6$). **12**: mp 245 °C (CH_3OH, dec); IR (KBr) ν_{max} 3369, 1706, 1651, 1602, 1503, 1412, 1276, 1033 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.56 (m, 1H), 1.81−1.92 (m, 3H), 2.06 (s, 3H), 2.77 (d, J = 18.6 Hz, 1H), 2.97−3.08 (m, 2H), 3.45−3.55 (m, 2H), 3.78−3.84 (m, 2H), 3.84−3.92 (m, 2H), 6.19 (d, J = 11.1 Hz, 2H), 7.08 (s, 1H), 7.32 (s, 1H) ppm; ^{13}C NMR (75 MHz, d_6-DMSO) δ 18.4, 23.4, 25.6, 30.7, 31.8, 47.4, 52.2, 54.8, 103.5, 109.1, 109.6, 119.8, 136.1, 147.8, 153.7, 176.3, 206.6 ppm; HRMS (ESI) obsd 286.1442 ([M − Br]$^+$, calcd 286.1438 for $C_{17}H_{20}NO_3$). **13**: mp 255 °C (CH_3OH, dec); IR (KBr) ν_{max} 1713, 1649, 1603, 1506, 1413, 1278, 1252, 1095, 1034 cm^{-1}; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.56 (m, 1H), 1.88−1.92 (m, 3H), 2.06 (s, 3H), 2.77 (d, J = 18.6 Hz, 1H), 2.94−3.07 (m, 3H), 3.78−3.82 (m, 2H), 3.82−3.91 (m, 3H), 6.18 (d, J = 11.1 Hz, 2H), 7.08 (s, 1H), 7.31 (s, 1H); ^{13}C NMR (75 MHz, d_6-DMSO) δ 18.4, 23.4, 25.6, 30.6, 31.8, 47.3, 52.2, 54.8, 103.5, 108.4, 109.1, 119.8, 136.1, 147.8, 153.7, 176.4, 206.6 ppm; HRMS (ESI) *m/z* obsd 286.1438 ([M − ClO_4]$^+$, calcd 286.1438 for $C_{17}H_{20}NO_3$).

Preparation of *cis*-Pentacyclic Ketone 14 and Amino Dione 15 from Iminium Perchlorate 13. A mixture of iminium perchlorate **13** (1.15 g, 3.0 mmol) in water (5 mL) was basicified with 50% aqueous NaOH solution to pH 10 in an open flask with vigorous stirring for 0.5 h. The resulting aqueous mixture was extracted with $CHCl_3$ (2 × 30 mL), and the combined organic phases were washed with water and brine and dried. Evaporation of the solvent followed by flash chromatograph on silica gel eluting with 10−35% ethyl acetate in petroleum ether gave pentacyclic ketone **14** as a white solid (130 mg, 15%) and more polar amino dione **15** as a colorless gum (225 mg, 25%). **14**: mp 171−172 °C (lit.[8] mp 173−174 °C, EtOAc−petroleum ether); IR (KBr) ν_{max} 2932, 1743, 1503, 1484, 1253, 1215, 1037, 937, 861 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45−1.54 (m, 1H), 1.58−1.67 (m, 1H), 1.92−2.06 (m, 2H), 2.27 (d, J = 17.7 Hz, 1H), 2.45−2.44 (m, 1H), 2.87 (d, J = 7.2 Hz, 2H), 2.81−2.93 (m, 3H), 3.05 (d, J = 17.7 Hz, 1H), 3.34−3.55 (m, 3H), 5.93 (s, 2H), 6.57 (s, 1H), 6.81 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.47, 21.9, 22.6, 38.6, 39.1, 45.1, 47.5, 56.7, 63.7, 100.8, 104.5, 109.1, 127.9, 129.3, 146.2, 146.7, 215.6 ppm; EIMS (*m/z*) 285 (M$^+$, 33), 242 (100), 228 (76), 144(2); HRMS (ESI) *m/z* obsd 286.1438 ([M + H]$^+$, calcd 286.1436 for $C_{17}H_{20}NO_3$). **15**: IR (KBr) ν_{max} 2936, 1743, 1713, 1511, 1253, 1220, 1116 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ1.62 (m, 2H), 1.94 (m, 2H), 2.07 (s, 3H), 2.23 (m, 2H), 2.38−2.45 (m, 1H), 2.61 (d, J = 12.0 Hz, 1H), 2.83−3.00 (m, 1H), 3.04 (d, J = 12.6 Hz, 1H), 3.31−3.60 (m, 1H), 3.57 (d, J = 16.2 Hz, 1H), 5.89 (s, 2H), 6.56 (s, 1H), 6.58 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.0, 30.4, 38.1, 45.6, 47.4, 53.3, 70.6, 100.9, 106.3, 109.5, 126.2, 127.1, 146.3, 146.8, 205.4, 207.1 ppm; EIMS (*m/z*) 301 (0.3), 286 (9), 273 (34), 244 (82), 230 (100); HRMS (ESI) *m/z* obsd 302.1387 ([M + H]$^+$, calcd 302.1393 for $C_{17}H_{20}NO_4$).

Preparation of Pentacyclic Amino Enone 4. (a) From amino ketone 14. To a mixture of freshly distilled diisopropylamine (0.12 mL, 0.8 mmol) and anhydrous THF (5 mL) in a flame-dried 25 mL flask was added a solution of *n*-BuLi in hexane (1.60 M, 0.41 mL, 0.65 mmol) at −15 °C. The resulting mixture was stirred for 0.5 h at −15 °C and the flask was then cooled to −78 °C, to which a solution of ketone **14** (142 mg, 0.50 mmol) in 2 mL of THF was added dropwise. After stirring for 15 min, a solution of PhSeCl (105 mg, 0.55 mmol) in 1 mL of THF was added to the above reaction mixture, then the resulting reaction mixture was stirred for 30 min at −78 °C, quenched with 0.5 N HCl (1 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water, saturated $NaHCO_3$ solution, and brine and dried over Na_2SO_4. The solvent was removed in vacuo and the residue dissolved in 3 mL of CH_2Cl_2 and 2 mL of pyridine was treated with 30% H_2O_2 (0.5 mL) dropwise. The reaction mixture was stirred for 1 h at room temperature and extracted with EtOAc (3 × 10 mL). The organic layers were washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo followed by flash chromatograph on silica gel afforded the pentacyclic enone **4** as a colorless gum (71 mg, 55%).

(b) From amino dione 15.[2b] A solution of dione **15** (150 mg, 0.5 mmol) in 3 mL of anhydrous *t*-BuOH was treated with KOBu^t (65 mg, 0.6 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 1 h, the solvent was removed in vacuo, and the residue was taken up in 50 mL of $CHCl_3$, washed with water and brine, and dried. Evaporation of the solvent in vacuo followed by flash chromatograph on silica gel furnished the enone **4** as a colorless gum (113 mg, 80%). IR (KBr) ν_{max} 2939, 1714, 1683, 1632, 1482, 1236, 1037, 858 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80−1.90 (m, 2H), 2.05−2.10 (m, 1H), 2.44−2.57 (dd, J = 17.7 Hz, J = 17.1 Hz, 2H), 2.70−2.88 (m, d, J = 17.7 Hz, 4H), 3.01−3.17 (m, 2H), 3.30−3.42 (m, 1H), 5.90 (d, J = 4.8 Hz, 2H), 6.18 (s, 1H), 6.36 (s, 1H), 6.59 (s, 1H) ppm; ^{13}CNMR (75 MHz, $CDCl_3$) δ 22.1, 26.4, 27.0, 46.5, 46.8, 54.6, 67.0, 100.8, 104.8, 109.2, 126.0, 129.0, 129.9, 146.8 (2C), 178.6, 205.6 ppm; EIMS (*m/z*) 283 (M$^+$, 29), 254 (100), 240 (13), 226 (18); HRMS (ESI) *m/z* obsd 284.1280 ([M + H]$^+$, calcd 284.1281 for $C_{17}H_{18}NO_3$).

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Note Added in Proof. A tandem radical cyclization approach to ring skeleton of cephalotaxine has recently appeared: Taniguchi, T.; Ishita, A.; Uchiyama, M.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *J. Org. Chem.* **2005**, *70*, 1922−1925.

Supporting Information Available: ^{1}H and ^{13}C NMR spectrum of compounds **9**−**11**, **13**, **14**, **14a**, **15**, **4**, and their 3,4-dimethoxy congeners; X-ray crystallographic data of compound **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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