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Formal Synthesis of Cephalotaxine

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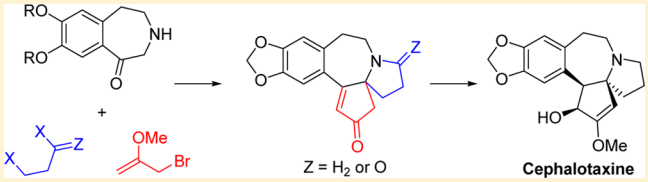
Supporting Information

ABSTRACT: A formal synthesis of cephalotaxine, the parent member of the *Cephalotaxus* alkaloids, was achieved. It features a practical four-step assembly of the benzazepine-bearing pentacyclic ring system through two alkylation reactions, acidic hydrolysis, and aldolization.



Cephalotaxine (CET, **1**), the major alkaloid isolated from *Cephalotaxus species*,[1] possesses a unique benzazepine moiety that fused with two five-membered rings (Figure 1).

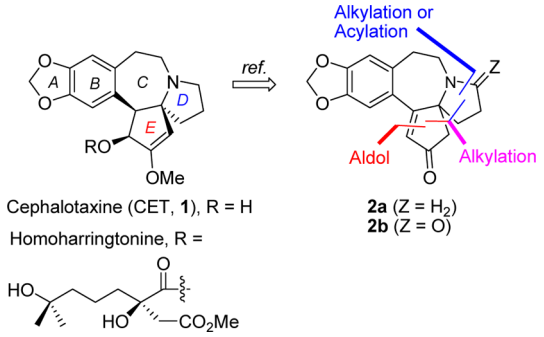
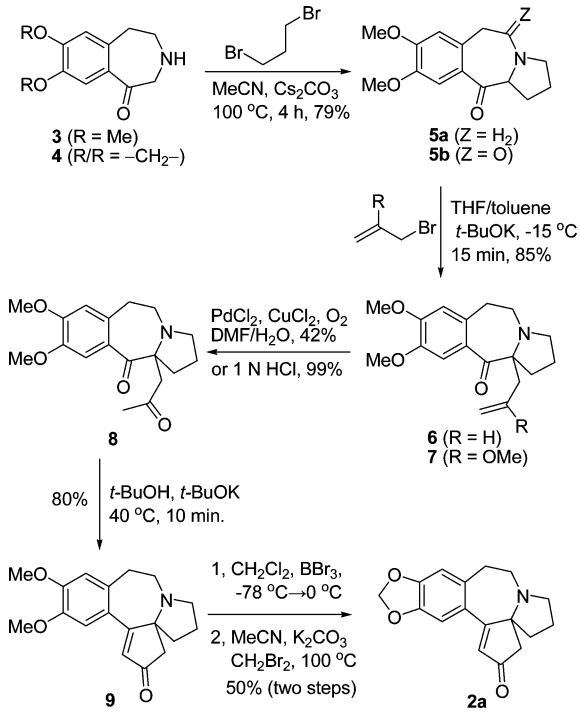


Figure 1. Cephalotaxine and homoharringtonine and key reactions for the synthesis of **2**.

Several naturally occurring ester derivatives of CET such as harringtonine, homoharringtonine, isoharringtonine, and deoxyharringtonine exhibited intriguing antitumor properties, especially in mice leukemia systems.[1] Notably, homoharringtonine (Figure 1), with significant efficacy in clinical trials to cure chronic myeloid leukemia,[2] was the subject of an application for a new drug authorization in the US and Europe in 2011. The unique structure of CET and the important biological activities of its derivatives[1] rendered this group of alkaloids attractive synthetic targets.[1e,3] Nonetheless, development of a more practical and efficient synthetic approach to CET is still urgent in view of the potential pharmaceutical needs. We[4] describe herein a rapid construction of the pentacyclic ABCDE-ring skeleton **2a** (**2b**) employing conventional alkylation and aldol condensation as key steps (Figure 1). Our synthesis focused on the efficient construction of the D- and E-ring of **2**.

As outlined in Scheme 1, the synthesis commenced from a known benzazepine **3**,[5,6] which was prepared according to Zhao's procedure.[6b,c] We took advantage of the potential of this

Scheme 1. Synthesis of Pentacycle 2a from 3



benzazepine subunit and envisioned that a suitable electrophile should be easily fused to **3** to form a pyrrolidine. The BCD-ring pyrrolobenzazepines are classic intermediates in the total synthesis of CET.[7] Treatment of **3** with 1,3-dibromopropane in MeCN in the presence of Cs_2CO_3 at reflux for 4 h afforded the *N*- and *C*-alkylated annulation product **5a** in one step (79%). Amino ketone **5a** is a pyrrolobenzazepine that can be formally regarded as the reduction product of amido ketone **5b**.

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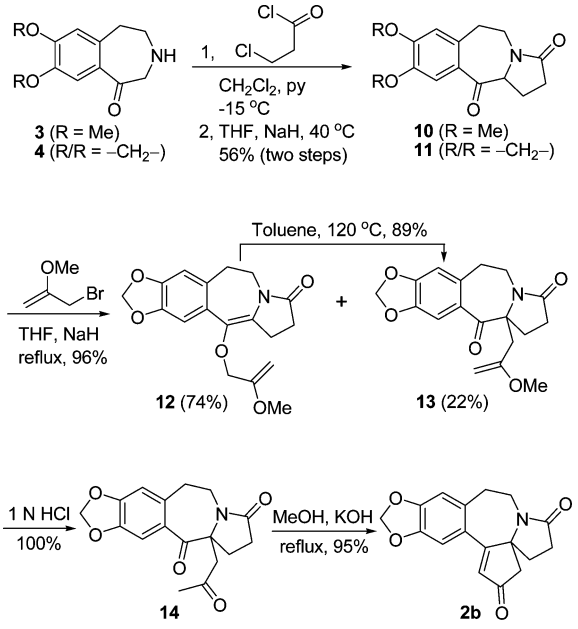
Compound **5b** was a key intermediate in Hanaoka's procedure.[7g] Further alkylation of **5a** with allyl bromide yielded **6** (THF/toluene, *t*-BuOK, 85%). Thus, the successive alkylation reactions (**3** → **5a** → **6**) provided the requisite skeleton of CET in high yield. However, subsequent Wacker oxidation of olefin **6** only gave diketone **8** in 42% yields. To find a more efficient E-ring building block, we attempted to use 2-methoxyallyl bromide as acetonyl alkylating agent[8] to react with **5a** under the same conditions as those used for **6**, which was followed by acidic hydrolysis of the newly formed enol methyl ether **7** to furnish diketone **8** in 84% overall yield. Elaboration of **8** to the core ring skeleton (**9**) of CET was accomplished by standard aldol condensation (*t*-BuOH, *t*-BuOK, 40 °C, 10 min, 80%). The two methoxy groups of **9** were transformed into a methylenedioxy group by usual method[9] to afford pentacycle **2a** in 50% yield. The synthetic **2a** exhibits spectroscopic properties identical to those reported by Li.[4d,10] Thus, we have accomplished a formal synthesis of CET via a facile construction of **2a** from **3** using conventional reations.

In a parallel study, we also attempted to employ **4**[6] as starting materials (Scheme 1). However, treatment of **4** using the above conditions led to none of the desired product, presumably a result of the instability of the methylenedioxy analogue of **5a**.[11] To overcome this difficulty, 3-chloropropanoyl chloride was used to react with **3**/**4** (Scheme 2) to give the corresponding

Scheme 2. Modified Synthetic Route of 2b from 4



acylated products, which were directly subjected to an intramolecular alkylation to give the stabilized amido ketone **10** and **11** in 56% yield, respectively. This also constituted a formal synthesis of CET since the conversion of **11** to CET has been demonstrated by Hanaoka and co-workers.[7h] An improvement over the use of allyl bromide for the synthesis of diketone **14**[7h] is shown in Scheme 2. Following the same procedure as in Scheme 1, we treated **11** with 2-methoxyallyl bromide to afford the enol ether **12** (74%) as a major product along with the C-allyl derivative **13** (22%). Claisen rearrangement was applied to convert **12** to **13** (89%), which was exposed to 1 N HCl in methanol to give rise to diketone **14** in quantitative yield. At last, compound **14** was transformed into amido pentacycle **2b** through intramolecular aldolization in 95% yield.[7h] This modified route was superior to previous procedures[7h] by virtue of the readily available pyrrolobenzazepine **11** and diketone **14**, and afforded **2b** in 47% overall yield from **4** in four steps.

In summary, application of conventional alkylation, acidic hydrolysis, and aldol condensation provided a rapid entry to the synthetically challenging pentacyclic ring system **2b** (**2a**) of cephalotaxine. Using 3-chloropropanoyl chloride and 2-methoxyallyl bromide as building blocks to construct the five-membered D- and E-ring of cephalotaxine, respectively, we can easily obtain **2b** on 10 g scale. This practical and efficient route should be of great potential for preparation of the natural and synthetic ester derivatives of cephalotaxine. Studies along this line and development of an asymmetric variant of this route to construct optically active **2b** are in progress.

EXPERIMENTAL SECTION

8,9-Dimethoxy-2,3,5,6-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11(11a*H*)-one (5a). To a solution of **3** (110 mg, 0.5 mmol) in 15 mL of MeCN were added 1,3-dibromopropane (201 mg, 1 mmol) and Cs_2CO_3 (489 mg, 1.5 mmol). After the reaction was stirred at reflux for 4 h, the mixture was filtered, and the filtrate was evaporated under reduced pressure to give a residue, which was purified by flash column chromatography eluting with petroleum ether/EtOAc (1:1) to give amino ketone **5a** (103 mg, 0.395 mmol, 79% yield) as a yellowish oil: R_f = 0.2 (petroleum ether/EtOAc = 1:1); IR (film) ν_{max} 2934, 2791, 1665, 1597, 1510, 1263, 1143, 1021, 1003 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34 (1H, s), 6.69 (1H, s), 3.93 (3H, s), 3.90 (3H, s), 3.54 (1H, dd, J = 10 Hz, 3 Hz), 3.25−3.20 (1H, m), 3.15−3.07 (2H, m), 2.85−2.78 (2H, m), 2.58 (1H, q, J = 17 Hz, 9 Hz), 2.46−2.40 (1H, m), 2.22−2.13 (1H, m), 1.80−1.73 (2H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 152.2, 147.9, 133.5, 130.4, 112.1, 111.5, 68.2, 56.03, 55.98, 55.6, 51.90, 34.1, 28.1, 23.9 ppm; HRMS (ESI) m/z $[M + H]^+$ found for 262.1439, calcd for $C_{15}H_{20}NO_3$ 262.1438.

11a-Allyl-8,9-dimethoxy-2,3,5,6-tetrahydro-1*H*-benzo[*d*]-pyrrolo[1,2-*a*]azepin-11(11a*H*)-one (6). To a mixture of **5a** (130 mg, 0.5 mmol) and allyl bromide (73 mg, 0.6 mmol) in dry THF/toluene (1: 1, 10 mL) was slowly added a solution of *t*-BuOK (68 mg, 0.6 mmol) in 2 mL of THF under nitrogen atmosphere at −15 °C. After being stirred at that temperature for 15 min, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (3:1) to give the compound **6** (128 mg, 0.425 mmol, 85% yield) as an oil: R_f = 0.3 (petroleum ether/EtOAc = 1:1); IR (film) ν_{max} 2935, 2816, 1660, 1597, 1511, 1452, 1347, 1265, 1215, 1043 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (1H, s), 6.65 (1H, s), 5.86−5.79 (1H, m), 5.05−4.97 (2H, m), 3.92 (3H, s), 3.88 (3H, s), 3.31−3.26 (1H, m), 3.17−3.11 (1H, m), 3.07−2.96 (3H, m), 2.91−2.86 (1H, m), 2.57−2.45 (2H, m), 2.36−2.30 (1H, m), 1.97−1.92 (1H, m), 1.82−1.75 (2H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.8, 151.3, 147.5, 134.3, 132.6, 131.5, 118.0, 112.1, 111.5, 74.2, 60.00, 55.96, 53.7, 48.2, 39.4, 34.9, 33.5, 21.9 ppm; HRMS (ESI) m/z $[M + H]^+$ found for 302.1741, calc for $C_{18}H_{24}NO_3$ 302.1751.

8,9-Dimethoxy-11a-(2-methoxyallyl)-2,3,5,6-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11(11a*H*)-one (7). Treatment of **5a** (130 mg, 0.5 mmol) with 2-methoxyallyl bromide (140 mg, 0.6 mmol, 65% purity)[8] under the same conditions as those for **6** provided compound **7** (141 mg, 0.425 mmol, 85% yield) as an oil: R_f = 0.3 (petroleum ether/EtOAc = 1:1); IR (film) ν_{max} 2958, 2834, 1668, 1599, 1513, 1289, 1267, 1217, 1140, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (1H, s), 6.62 (1H, s), 3.90 (2H, d, J = 14.5 Hz), 3.91

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(3H, s), 3.88 (3H, s), 3.45 (3H, s), 3.36−3.32 (1H, m), 3.12−3.06 (1H, m), 3.02−2.71 (4H, m), 2.725 (1H, d, J = 14.5 Hz), 2.49 (1H, d, J = 14 Hz), 2.34−2.28 (1H, m), 2.10−2.04 (1H, m), 1.82−1.75 (2H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 161.2, 151.1, 147.4, 132.3, 131.7, 112.5, 111.3, 84.0, 73.7, 55.9 (2C), 54.5, 53.4, 48.4, 40.3, 34.9, 33.2, 21.7 ppm; HRMS (ESI) m/z [M + Na]$^+$ found for 354.1680, calcd for $C_{19}H_{25}NNaO_4$ 354.1676.

8,9-Dimethoxy-11a-(2-oxopropyl)-2,3,5,6-tetrahydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]azepin-11(11a*H*)-one (8). **(1) Wacker Oxidation Conditions.** To a mixture of $PdCl_2$ (18 mg, 0.1 mmol), $CuCl_2$ (67 mg, 0.5 mmol), and NaCl (94 mg, 1 mmol) in 5 mL of water was added a solution of **6** (150 mg, 0.5 mmol) in 3 mL of DMF under oxygen. The resulting mixture was vigorously stirred at 40 °C for 2 h and then cooled to room temperature, adjusted to pH 9−10 with solid $NaHCO_3$, and extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1:1) to give the compound **8** (66 mg, 0.21 mmol, 42% yield) as a yellowish gum. **(2) Acidic Hydrolysis Conditions.** To a solution of **7** (165 mg, 0.5 mmol) in 5 mL of methanol was added 1 mL of 1 N HCl. After being stirred at room temperature for 10 min, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (5 × 15 mL). The combined organic layers were washed with water and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1:1) to give the compound **8** (157 mg, 0.495 mmol, 99% yield) as a yellowish gum: R_f = 0.3 (pure EtOAc); IR (film) ν_{max} 2937, 2831, 1736, 1710, 1676, 1602, 1514, 1462, 1357, 1262, 1219, 1137 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (1H, s), 6.64 (1H, s), 3.90 (3H, s), 3.87 (3H, s), 3.23−3.19 (1H, m), 3.13−3.04 (2H, m), 3.03−2.97 (1H, m), 2.945 (1H, d, J = 15.5 Hz), 2.92−2.89 (1H, m), 2.81 (1H, q, J = 17 Hz, 8 Hz), 2.73 (1H, d, J = 15.5 Hz), 2.52−2.45 (1H, m), 2.08 (3H, s), 1.98−1.93 (1H, m), 1.86−1.80 (2H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3, 206.2, 151.0, 147.5, 131.7, 131.0, 112.0, 111.3, 73.5, 60.0, 55.9, 53.0, 49.1, 48.2, 35.2, 33.1, 31.6, 22.4 ppm; HRMS (ESI) m/z [M + Na]$^+$ found for 340.1526, calcd for $C_{18}H_{23}NNaO_4$ 340.1520.

8,9-Dimethoxy-2,3,5,6-tetrahydro-1*H*-benzo[*d*]cyclopenta-[*b*]pyrrolo[1,2-*a*]azepin-12(13*H*)-one (9). To a solution of **8** (121 mg, 0.382 mmol) in 10 mL of dry *t*-BuOH was added *t*-BuOK (51 mg, 0.45 mmol). After the mixture was stirred at 40 °C for 10 min, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The mixture was diluted with 20 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1: 2) to give enone **9** (92 mg, 0.306 mmol, 80% yield) as a yellowish gum: R_f = 0.2 (pure EtOAc); IR (film) ν_{max} 2930, 2843, 1687, 1598, 1514, 1461, 1365, 1250, 1222, 1026 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (1H, s), 6.69 (1H, s), 6.12 (1H, s), 3.90 (3H, s), 3.88 (3H, s), 3.56−3.49 (1H, m), 3.38−3.32 (1H, m), 3.15−3.11 (1H, m), 2.98−2.95 (3H, m), 2.64 (2H, s), 1.94−1.76 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 181.3, 150.0, 147.2, 130.9, 130.5, 125.5, 112.8, 112.4, 74.8, 56.0, 55.9, 54.6, 48.9, 44.1, 39.7, 32.3, 24.8 ppm; HRMS (ESI) m/z [M + H]$^+$ found for 300.1593, calcd for $C_{18}H_{22}NO_3$ 300.1594.

2,3,5,6-Tetrahydro-1*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*d*]-cyclopenta[*b*]pyrrolo[1,2-*a*]azepin-13(14*H*)-one (2a). To a solution of **9** (60 mg, 0.20 mmol) in 5 mL of CH_2Cl_2 was added a 1 M BBr_3 solution in CH_2Cl_2 (1.0 mL, 1.0 mmol) at −78 °C under nitrogen atmosphere, and the solution was allowed to warm to room temperature for 1.5 h. MeOH (2 mL) was added at 0 °C, and then the low-boiling material was evaporated. The residue was dissolved in 1 N HCl (3 mL), and the aqueous layer was washed with chloroform. The aqueous solution was heated for 20 min at 95 °C and then neutralized with saturated $NaHCO_3$ at 0 °C. The aqueous layer was extracted with CH_2Cl_2, and the organic layer was dried over Na_2SO_4 and concentrated. To the residue in 5 mL of MeCN were added K_2CO_3 (138 mg, 1 mmol) and CH_2Br_2 (174 mg, 1 mmol). The mixture was stirred at 100 °C for 3 h and then filtered. The filtrate was evaporated to give a residue, which was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1: 1) to give **2a** (28 mg, 0.10 mmol, 50% yield) as a yellowish gum: R_f = 0.2 (petroleum ether/EtOAc = 1:4); IR (film) ν_{max} 2922, 1688, 1617, 1583, 1486, 1040 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (1H, s), 6.67 (1H, s), 6.08 (1H, s), 5.99 (1H, s), 5.97 (1H, s), 3.48−3.41 (1H, m), 3.35−3.28 (1H, m), 3.11−3.07 (1H, m), 2.94−2.91 (3H, m), 2.62 (2H, s), 1.93−1.72 (4H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 181.4, 149.0, 146.2, 132.0, 131.4, 126.6, 110.0, 109.3, 101.5, 74.6, 54.3, 49.1, 44.0, 39.5, 32.7, 24.7 ppm; HRMS (ESI) m/z [M + H]$^+$ found for 284.1287, calcd for $C_{17}H_{18}NO_3$ 284.1281.

8,9-Dimethoxy-5,6-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]-azepine-3,11(2*H*,11a*H*)-dione (10). To a solution of **3** (4.4 g, 20 mmol) in dry CH_2Cl_2/pyridine (4: 1, 100 mL) was added a solution of 3-chloropropanoyl (3.8 g, 30 mmol) in 20 mL of dry CH_2Cl_2 drop by drop at −20 °C. After being stirred at that temperature for 5 min, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4, and evaporated to give a residue, which was dissolved in 60 mL of dry THF. To the solution was added NaH (1 g, 25 mmol). After being stirred at 40 °C for 1 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and brine and dried over Na_2SO_4. After the solvent was evaporated, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1:1) to give **10** (3.08 g, 11.2 mmol, 56% yield) as a gum: R_f = 0.2 (petroleum ether/EtOAc = 1:3); IR (film) ν_{max} 2937, 1683, 1599, 1516, 1461, 1360, 1268, 1225, 1139 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (1H, s), 6.70 (1H, s), 4.40 (1H, d, J = 6.5 Hz), 3.94 (3H, s), 3.89 (3H, s), 3.93−3.86 (1H, m), 3.45 (1H, dd, J = 12.5 Hz, 2.5 Hz), 3.26−3.19 (1H, m), 2.98−2.94 (1H, m), 2.78−2.75 (1H, m), 2.37−2.30 (3H, m) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 175.1, 153.2, 148.3, 133.7, 129.0, 112.2, 111.7, 64.6, 56.1, 56.0, 41.5, 32.7, 30.0, 23.1 ppm; HRMS (ESI) m/z [M + Na]$^+$ found for 298.1051, calcd for $C_{15}H_{17}NO_4$ 298.1050.

10,10a-Dihydro-5*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*d*]-pyrrolo[1,2-*a*]azepine-8,11(6*H*,9*H*)-dione (11). The reaction was carried out as those for **10** to give **11** (56% yield) as white crystals: mp 154−156 °C;[12] R_f = 0.1 (petroleum ether/EtOAc = 1: 2); IR (film) ν_{max} 1677, 1615, 1483, 1249, 1037 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, s), 6.67 (1H, s), 6.02 (2H, s), 4.35 (1H, d, J = 7.5 Hz), 3.91 (1H, t, J = 10.5 Hz), 3.39 (1H, d, J = 11.5 Hz), 3.20−3.10 (1H, m), 2.91 (1H, d, J = 14.5 Hz), 2.66 (1H, d, J = 6 Hz), 2.45−2.29 (3H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 175.2, 151.9, 147.4, 135.1, 131.0, 109.6, 108.7, 101.9, 64.6, 41.3, 32.6, 29.9, 23.6 ppm; HRMS (ESI) m/z [M + H]$^+$ found for 260.0917, calcd for $C_{14}H_{14}NO_4$ 260.0917.

11-((2-Methoxyallyl)oxy)-9,10-dihydro-5*H*-[1,3]dioxolo-[4′,5′:4,5]benzo[1,2-*d*]pyrrolo[1,2-*a*]azepin-8(6*H*)-one (12) and 10a-(2-Methoxyallyl)-10,10a-dihydro-5*H*-[1,3]dioxolo-[4′,5′:4,5]benzo[1,2-*d*]pyrrolo[1,2-*a*]azepine-8,11(6*H*,9*H*)-dione (13). To a stirred mixture of NaH (0.80 g, 20 mmol, 60% in mineral oil) in 60 mL of dry THF was added slowly a solution of compound **11** (2.59 g, 10 mmol) in 50 mL of dry THF under argon. After the mixture was refluxed for 30 min, 2-methoxyallyl bromide (4.65 g, 20 mmol, 65% purity) was added, and heating was continued until all of the ketone **11** had reacted (several hours, monitored by TLC). Thirty milliliters of saturated $NaHCO_3$ was added to terminate the reaction. The mixture was extracted with EtOAc (3 × 100 mL). The combined extracts were washed with water and saturated brine, dried over anhydrous Na_2SO_4, and concentrated at 45 °C under vacuum to give a residue, which was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (2: 1) to give compound **12** (2.43 g, 7.4 mmol, 74% yield) as a yellow solid and **13** (0.72 g, 2.2 mmol, 22% yield) as a white solid. Compound **12**: mp

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132−134 °C; R_f = 0.6 (petroleum ether/EtOAc = 1:2); IR (film) ν_{max} 1718, 1655, 1502, 1481, 1369, 1270, 1239, 1192 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 (1H, s), 6.61 (1H, s), 5.95 (2H, s), 4.15 (1H, d, J = 2 Hz), 4.11 (1H, d, J = 2 Hz), 4.01 (2H, s), 3.65−3.90 (2H, br), 3.60 (3H, s), 2.98−2.95 (2H, m), 2.83 (2H, br), 2.52 (2H, t, J = 8 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.3, 146.7, 146.1, 132.4, 132.3, 130.7, 126.3, 109.3, 105.5, 100.9, 84.4, 71.1, 54.8, 44.1, 34.2, 28.3, 21.5 ppm; HRMS (ESI) m/z $[M + H]^+$ found for 330.1338, calcd for $C_{18}H_{20}NO_5$ 330.1336. Compound **13**: mp 170−172 °C; R_f = 0.4 (petroleum ether/EtOAc = 1:2); IR (film) ν_{max} 1686, 1631, 1500, 1485, 1400, 1374, 1287, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (1H, s), 6.63 (1H, s), 5.99 (2H, s), 4.20−4.13 (1H, m), 4.10 (2H, s), 3.51 (3H, s), 3.43−3.39 (1H, m), 305−2.98 (1H, m), 2.87 (1H, d, J = 14.5 Hz), 2.83−2.79 (1H, m), 2.76 (1H, d, J = 14.5 Hz), 2.48−2.42 (1H, m), 2.29−2.22 (1H, m), 2.17−2.11(1H, m), 2.03−1.99 (1H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.1, 175.8, 158.7, 150.8, 146.7, 132.0, 131.6, 108.8, 108.2, 101.6, 85.7, 72.8, 54.8, 39.0, 37.6, 30.8, 29.7, 29.3 ppm; HRMS (ESI) m/z $[M + H]^+$ found for 330.1336, calc for $C_{18}H_{20}NO_5$ 330.1336. A solution of compound **12** (2.43 g, 7.39 mmol) in 50 mL of toluene was heated for 5 h at 120 °C. There obtained compound **13** (2.16 g, 6.57 mmol) in 89% yield.

10a-(2-Oxopropyl)-10,10a-dihydro-5*H*-[1,3]dioxolo-[4′,5′:4,5]benzo[1,2-*d*]pyrrolo[1,2-*a*]azepine-8,11(6*H*,9*H*)-dione (14). To a solution of compound **13** (2.16 g, 6.57 mmol) in 60 mL of methanol was added 15 mL of 1 N HCl. After being stirred at room temperature for 30 min, the mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layer was washed with water and saturated brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1: 2) to give compound **14** (2.07 g, 6.57 mmol, 100% yield) as a white solid: mp 175−178 °C; R_f = 0.3 (petroleum ether/EtOAc = 1: 4); IR (film) ν_{max} 1705, 1679, 1614, 1500, 1482, 1462, 1438, 1398, 1372, 1283, 1242 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, s), 6.63 (1H, s), 6.00 (2H, s), 4.33−4.27 (1H, m), 3.26 (1H, d, J = 17 Hz), 3.09−3.02 (2H, m), 3.00 (1H, d, J = 17 Hz), 2.88−2.83 (1H,m), 2.50−2.41 (1H, m), 2.37−2.30 (1H, m), 2.25 (3H, s), 2.23−2.15 (2H, m) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 204.5, 175.4, 150.9, 146.9, 131.9, 131.6, 109.3, 108.3, 101.7, 71.2, 44.9, 38.0, 31.6, 31.5, 30.5, 29.2 ppm; HRMS (ESI) m/z $[M + H]^+$ found for 316.1177, calcd for $C_{17}H_{18}O_5N$ 316.1179.

5,6-Dihydro-1*H*-[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*d*]-cyclopenta[*b*]pyrrolo[1,2-*a*]azepine-3,13(2*H*,14*H*)-dione (2b). To a solution of compound **14** (2.07 g, 6.57 mmol) in 50 mL of methanol was added 10% KOH solution (20 mL, 35 mmol). The reaction mixture was heated at reflux for 2 h, cooled to room temperature, and extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layer was washed with water and saturated brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (1: 2) to give compound **2b** (1.85 g, 6.24 mmol, 95% yield) as a colorless crystal: mp 268−270 °C; R_f = 0.2 (petroleum ether/EtOAc = 1:4); IR (film) ν_{max} 1713, 1679, 1623, 1481, 1406, 1229, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.70 (1H, s), 6.69 (1H, s), 6.21 (1H, s), 6.01 (1H, s), 6.00 (1H, s), 4.09−4.04 (1H, m), 3.39−3.32 (1H, m), 3.13−3.07 (1H, m), 2.99 (1H, dt, J = 17 Hz, 4 Hz), 2.80 (1H, d, J = 17 Hz), 2.64 (1H, d, J = 17.5 Hz), 2.60−2.52 (1H, m), 2.32−2.25 (1H, m), 2.09−2.03 (1H, m), 1.97−1.93 (1H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 177.5, 173.5, 149.3, 146.2, 132.1, 130.6, 123.7, 110.5, 108.6, 101.5, 71.5, 47.6, 35.8, 33.8, 33.4, 30.0 ppm; HRMS (ESI) m/z $[M + H]^+$ found for 298.1071, calcd for $C_{17}H_{16}O_4N$ 298.1074.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for compounds **5a**, **6**−**9**, **2a**, **10**−**14** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

This paper is dedicated to Prof. Wei-Dong Li (Nankai University).

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(12) Hanaoka reported that the mp of **11** was 172−175 °C; see ref 7h.

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