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Transannular Reductive Rearrangement of α-Amino Ketones: Construction of Aza-tricyclic Frameworks of Several Alkaloids

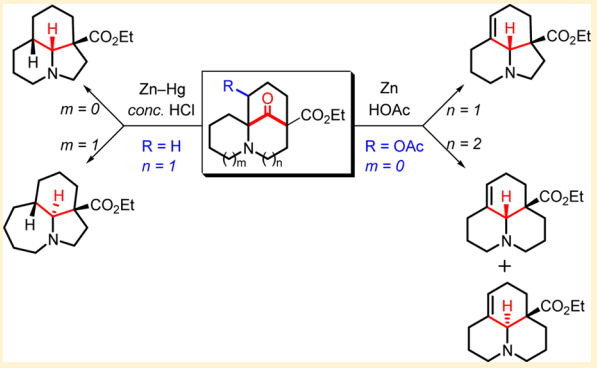
Jian Zhang,[†] Yong-Qiang Wang,[†] Xin-Wei Wang,[†] and Wei-Dong Z. Li*[,†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China

[‡]Innovative Drug Research Centre, Chongqing University, Chongqing 401331, P. R. China

Supporting Information

ABSTRACT: Transannular reductive rearrangement of bridged cyclic α-amino ketones led to the aza-tricyclic frameworks azepinoindole, hydrolulolidine, and hydrojulolidine of the typical alkaloids of *Stemona*, *Aspidosperma*, and *Lycopodium*, respectively. This facile approach demonstrates the potential applicability of the Clemmensen−Clemo−Prelog−Leonard reductive rearrangement of tricyclic α-amino ketones for the aza-heterocycle synthesis.



INTRODUCTION

During our previous studies on the total synthesis of *Cephalotaxus* alkaloids,[1] two crucial reductive rearrangement reactions (**1** → **2** and **3** → **4**; Figure 1) were designated for the construction of the benzazepine core ring system of cephalotaxine. Those facile and effective transformations were devised on the basis of an interesting Clemmensen reductive rearrangement (**5** → **7**; Figure 2) of a cyclic α-amino ketone **5**, which is in marked contrast with the complementary Wolff−

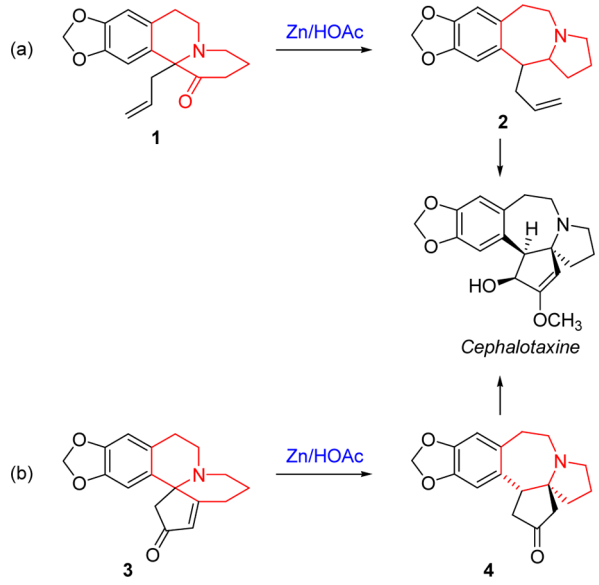


Figure 1. Previous synthesis of benzazepine core of cephalotaxine.[1a]

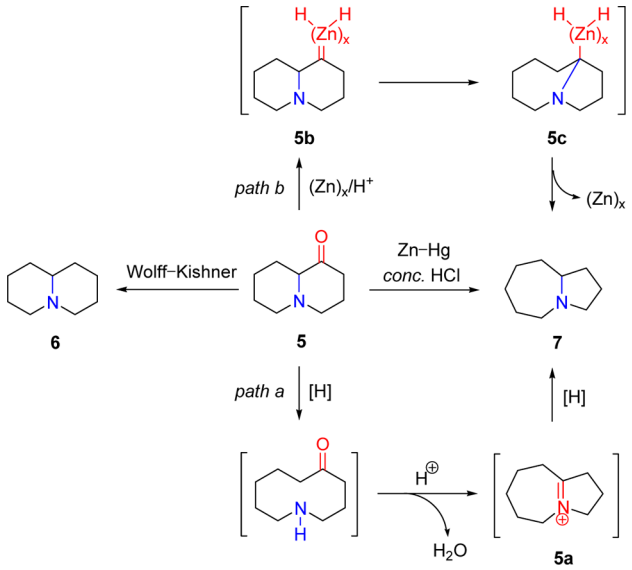


Figure 2. Clemmensen−Clemo−Prelog−Leonard reductive rearrangement.

Kishner reduction of carbonyl (**5** → **6**; Figure 2), first discovered by Clemo[2] and later verified by Prelog.[3] Subsequent systematic studies by Leonard[4] and co-workers suggested a probable mechanistic pathway involving the reductive rupture of the C−N bond, transannular formation of iminium intermediate **5a**, and subsequent reduction of **5a** as illustrated

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in Figure 2 (path a). An alternative mechanistic pathway (path b, Figure 2) via the rearrangement of the zinc carbenoid intermediate **5b** to **5c** might be suggested on the basis of recent studies on the classic Clemmensen reduction.[4l−n,o]

In seeking the general applicability of the so-named Clemmensen−Clemo−Prelog−Leonard reductive rearrangement[5] for the construction of the aza-tricyclic frameworks (i.e., azepinoindole, hydrolulolidine, and hydrojulolidine; Figure 3a−c) of some typical alkaloids of *Stemona*,[6]

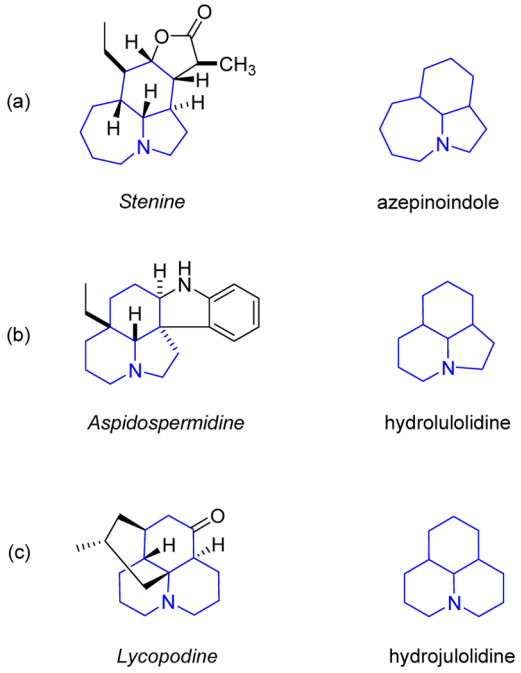

Figure 3. Typical aza-tricyclic frameworks of alkaloids.

Aspidosperma,[7] and *Lycopodium*,[8] we set out to explore a transannular reductive rearrangement approach (**9** → **10**; Figure 4) of a series of bridged cyclic α-amino ketones. This report details the experimental results of these studies.

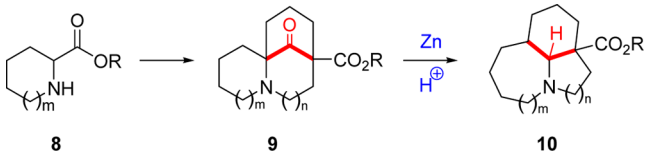

Figure 4. Transannular Clemmensen reductive rearrangement approach.

RESULTS AND DISCUSSION

As shown in Scheme 1, allylation of diester **11**[2a,9] afforded piperidine derivative **12**, which was cyclized via Dieckmann condensation to give predominately bicyclic ester **13** as the enol form. Further carbocyclization of **13** was achieved via a Mn^{III}-mediated oxidative radical process[10] to give the bridged cyclic α-amino ketone **14** in good yield. Hydrogenation of **14** afforded the desired bridged cyclic α-amino ketone **15**, which was subjected to the classic Clemmensen reduction conditions.[4] Tricyclic amine **16** was isolated as the sole reaction product in 75% yield, and its skeletal structure and stereostructure were determined by X-ray crystallography as shown (see Supporting Information for details). It is intriguing to note that the all-*trans* ring-fused azepinoindole derivative **16** is the only diastereomer produced.[11]

Encouraged by the initial case study, we next examined the reactivity of tricyclic α-amino ketone **21**, which was synthesized through an analogous reaction sequence (via **18** and **19**) as outlined in Scheme 2, from the readily available proline derivative **17**.[9b,12] When the analogous experimental protocol for the conversion of **13** → **14** was applied to the allyl ester **19**, only trace amounts of the desired bridged carbocyclization product analogous to **14** were detected. Bromination of **19** with NBS gave a mixture of diastereomeric bromide **20** in excellent yield. The bridged carbocyclization of **20** was achieved via a reductive radical pathway to afford the desired tricyclic α-amino ketone **21** in 50% yield.[13] Reductive rearrangement of **21** under the typical Clemmensen reduction conditions furnished the sole hydrolulolidine derivative **22** in 45% yield, which interestingly is an all-*cis* fused aza-tricycle whose stereostructure was established according to the studies detailed in Scheme 5 below.

As we initially planned, diester **23**[4d] was transformed smoothly into the allylated benzazepinone derivative **25** via β-ketoester **24**. However, all attempts, including the Mn^{III}-mediated oxidative cyclization and the reductive radical cyclization of the corresponding α-keto bromide, for the bridged cyclic ring closure of **25** failed. After considerable experimentation, we found that the desired tricyclic α-amino ketone derivatives **26a** and **26b** (5.5:1) could be readily prepared from β-ketoester **24** via the annulation with acrolein mediated by DBU followed by immediate acetylation. This tandem Michael−Aldolization approach[14] provides an efficient alternative synthesis for compounds bearing an acetoxy group on the bridge.

Interestingly, both diastereomers **26a** and **26b** underwent smooth transannular rearrangement under much milder reductive conditions (Zn/HOAc) even at ambient temperature (Scheme 3). The hydrojulolidine derivatives **27a** and **27b** were isolated in excellent yield in a ratio of 65:25. Notably, the olefin function was introduced in the fused tricyclic ring system. The structure of **27a** was confirmed by the X-ray crystallographic analysis of the diol derivative **28**. Diastereomeric hydrojulolidine derivative **27b** underwent facile lactonization under acidic conditions, leading to crystalline lactone **29**.

As outlined in Scheme 4, the major reductive rearrangement product **27a** was readily converted further into the hydrojulolidone **33** through a reaction sequence, which included (1) regioselective hydroxylation of olefin, (2) alcohol oxidation, (3) dehydrogenative oxidation, and (4) decarboxylation.[15] Hydrojulolidone **33** is a known advanced intermediate[14] for the synthesis of *Lycopodium* alkaloids according to the pioneering research of Wiesner[16a,b] and Snider[17e,f] in this field.[17]

The above tandem Michael−Aldol annulation method was extended to the elaboration of other reductive rearrangement precursors. As shown in Scheme 5, bicyclic amine **35**[9b,12] was annulated with acrolein smoothly and then acetylated to give the anticipated tricyclic α-amino ketone derivatives **36a** and **36b** in good yield with a ratio of 4:1. Reductive rearrangement of either **36a** or **36b** mediated by zinc dust in glacial acetic acid under a reflux furnished the sole tricyclic amine **37** in 55−58% yield. Catalytic hydrogenation of **37** produced the sole saturated tricyclic amine **22**, which is identical spectroscopically with the aforementioned Clemmensen reductive rearrangement product of **21** (Scheme 2). The all-*cis* fused stereostructure for

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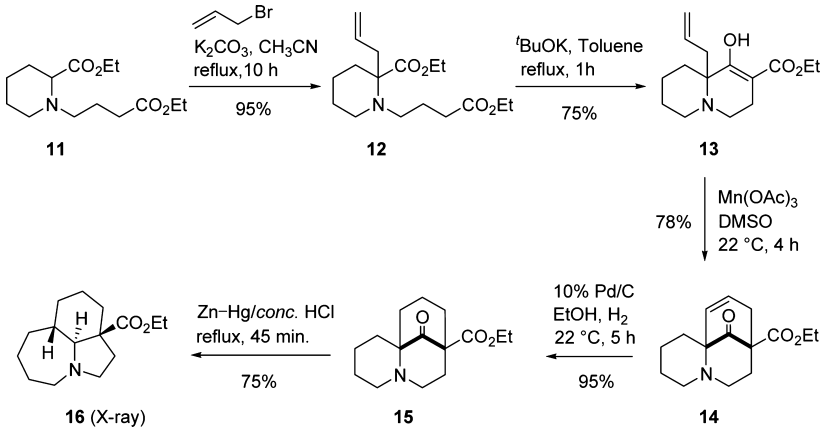
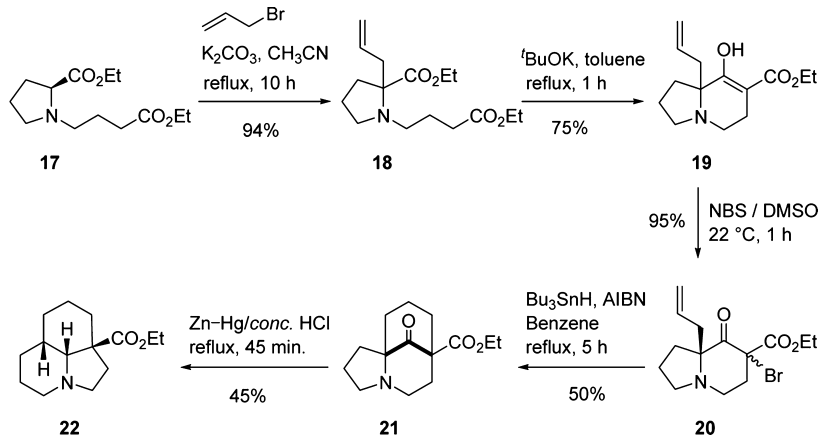
Scheme 1



Scheme 2



aza-tricycle **22** was deduced based on the fact that the dihydroxylation of **37** produced the all-*cis* fused tricyclic diol **38**, whose stereostructure was established via X-ray crystallographic analysis. It is worth noting that the attachment of an acetoxyl functional group not only facilitates the transannular reductive rearrangement but also results in the introduction of an olefin in the product ring structure for further functionalization.

CONCLUSION

We have demonstrated in this report that the bridged cyclic α-amino ketones were effective substrates for the transannular Clemmensen reductive rearrangement, leading to a potentially applicable approach for the construction of various aza-tricyclic heterocycles. Readily accessible acetoxylated bridged cyclic precursors (**26** and **36**) via tandem Michael−Aldol annulation with acrolein exhibit peculiar reactivity worthy of further study. Development of this type of transannular rearrangement and further application of this method in aza-heterocycle synthesis are underway.

EXPERIMENTAL SECTION[18]

General. Commercially available reagents were used without further purification, unless otherwise stated. ^{1}H and ^{13}C NMR spectra were taken on a 400 MHz spectrometer. Proton chemical shifts are reported in parts per million (δ) ($CDCl_3$, δ 7.27 or C_6D_6, δ 7.16), and carbon chemical shifts are reported in parts per million (δ) ($CDCl_3$, δ 77.2 or C_6D_6, δ 128.4). Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeter (cm^{-1}). HRMS were determined on a FT-ICR spectrometer. Melting points were measured on a hot stage and are uncorrected.

Ethyl 1-(4-Ethoxy-4-oxobutyl)piperidine-2-carboxylate (11).[2a,9] Anhydrous potassium carbonate (345 mg, 2.50 mmol) at room temperature was added to a mixture of ethyl 4-bromobutanoate (195 mg, 1.00 mmol) and ethyl piperidine-2-carboxylate hydrochloride (194 mg, 1.00 mmol) in anhydrous acetonitrile (10 mL). The reaction mixture was heated to reflux for 10 h. After the reaction mixture was cooled to room temperature, 5 mL of H_2O was added. The combined organics were extracted with ethyl acetate (2 × 20 mL), washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with petroleum ether/EtOAc (4:1) to give **11** as a colorless oil (260 mg, 96% yield). Compound **11**: R_f = 0.5 (2:1 petroleum ether/EtOAc); IR (film) ν_{max} 2937, 1733, 1448, 1176, 1162, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23−1.29 (m, 6H), 1.33−1.43 (m, 1H), 1.58−1.64 (m, 3H), 1.70−1.84 (m, 4H), 2.15−2.20 (m, 1H), 2.24−2.39 (m, 3H), 2.50−2.58 (m, 1H), 3.03−3.09 (m, 2H), 4.09−4.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 22.0, 22.4, 25.2, 29.5, 32.0, 50.1, 55.5, 60.0, 60.1, 65.0, 173.4, 173.7.

Ethyl 2-Allyl-1-(4-ethoxy-4-oxobutyl)piperidine-2-carboxylate (12). Anhydrous potassium carbonate (345 mg, 2.50 mmol) at room temperature was added to a mixture of compound **11** (271 mg, 1.00 mmol) and allyl bromide (0.17 mL, 2.00 mmol) in anhydrous acetonitrile (10 mL). The reaction mixture was then brought to reflux. After refluxing for 12 h, the reaction mixture was cooled to rt, and the reaction was quenched with H_2O (5 mL). The resulting mixture was extracted with ethyl acetate (2 × 20 mL), and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with

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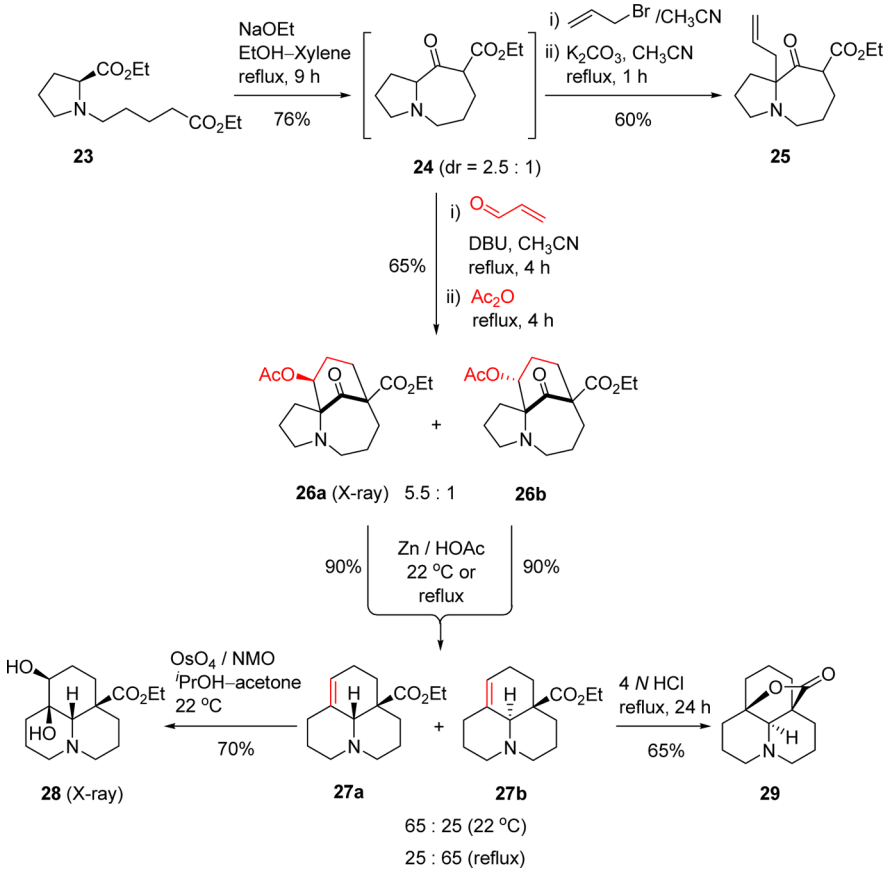
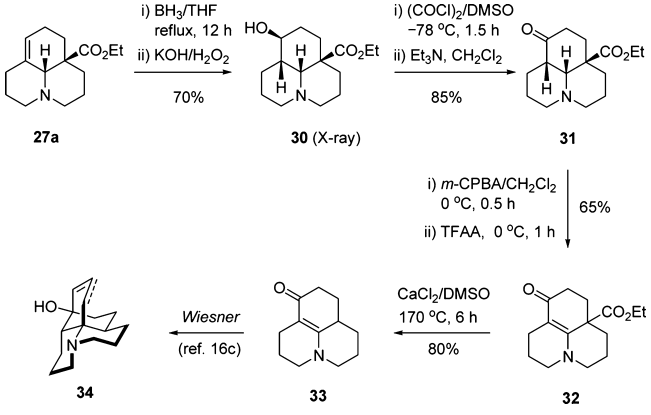
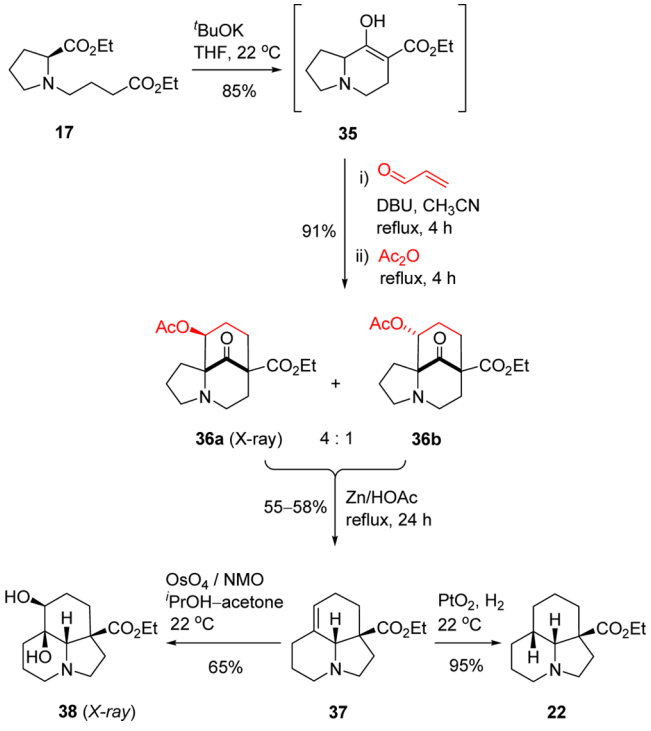
Scheme 3



Scheme 4



Scheme 5



10:1 petroleum ether/EtOAc to give compound **12** as a colorless oil (296 mg, 95% yield). Compound **12**: R_f = 0.65 (4:1 petroleum ether/EtOAc); IR (film) ν_{max} 2936, 1733, 1446, 1372, 1212, 1167, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.26 (m, 6H), 1.35–1.55 (m, 5H), 1.67–1.75 (m, 2H), 1.87–1.90 (m, 1H), 2.24–2.28 (m, 2H), 2.35–2.53 (m, 4H), 2.71–2.74 (m, 1H), 2.81–2.89 (m, 1H), 4.06–4.15 (m, 4H), 5.01–5.05 (m, 2H), 5.76–5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.4, 21.4, 24.1, 25.7, 31.9, 33.6, 40.7, 47.8, 49.9, 59.9, 60.1, 65.7, 117.5, 133.9, 173.9, 174.8; HRMS (ESI) m/z calcd for $C_{17}H_{30}NO_4$ 312.2172, found for $[M + H]^+$ 312.2169.

Ethyl 9a-Allyl-9-hydroxy-2,3,4,6,7,9a-hexahydro-1H-quinolizine-8-carboxylate (13). A solution of compound **12** (311 mg, 1.00 mmol) in toluene (2 mL) was added to a refluxing mixture of KO^{t}Bu (134 mg, 1.20 mmol) in 10 mL of dry toluene. After 45 min, the reaction mixture was cooled to rt and diluted with 20 mL of EtOAc. The mixture was washed with water and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 8:1 petroleum ether/EtOAc to give compound **13** as a colorless oil (199 mg, 75% yield). Compound **13** (predominately as the enol form): R_f = 0.20 (2:1 petroleum ether/

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EtOAc); IR (film) ν_{max} 3074, 2936, 1727, 1650, 1283, 1226, 1137, 1036; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 1.43−1.48 (m, 2H), 1.56−1.65 (m, 3H), 1.88−1.95 (m, 1H), 2.14−2.20 (m, 1H), 2.44−2.63 (m, 3H), 2.65−2.87 (m, 3H), 3.03−3.09 (m, 1H), 4.19−4.25 (m, 2H), 5.04−5.09 (m, 2H), 5.82−5.92 (m, 1H), 12.45 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.6, 21.0, 23.9, 29.6, 39.3, 44.7, 48.9, 59.9, 60.4, 95.0, 116.8, 134.2, 172.8, 174.5; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO_3$ 266.1753, found for $[M + H]^+$ 266.1751.

Ethyl 12-Oxo-1,2,3,4,6,7,8,9-octahydro-8,11a-methanopyrido[1,2-a]azocine-8-carboxylate (14). Powdered $Mn(OAc)_3{\cdot}2H_2O$ (536 mg, 2.00 mmol) at room temperature was added to a solution of compound **13** (265 mg, 1.00 mmol) in DMSO (10 mL). After the reaction mixture was stirred at room temperature for 4 h, EtOAc (40 mL) was added. The mixture was washed with water (3 × 10 mL) and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with 20:1 petroleum ether/EtOAc to give compound **14** as a colorless oil (205 mg, 78% yield). Compound **14**: R_f = 0.4 (4:1 petroleum ether/EtOAc); IR (film) ν_{max} 2940, 1736, 1721, 1639, 1256, 1143; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, 3H, J = 7.2 Hz), 1.37−1.48 (m, 3H), 1.51−1.55 (m, 2H), 1.63−1.76 (m, 3H), 1.88−2.00 (m, 2H), 2.38−2.45 (m, 1H), 2.84−2.89 (m, 1H), 2.99−3.03 (m, 1H), 3.11−3.18 (m, 1H), 4.17−4.26 (m, 3H), 6.12 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.7, 19.5, 25.7, 29.5, 36.2, 39.6, 46.9, 58.8, 61.1, 64.0, 89.9, 138.2, 171.8, 205.4; HRMS (ESI) m/z calcd for $C_{15}H_{22}NO_3$ 264.1594, found for $[M + H]^+$ 264.1600.

Ethyl 12-Oxodecahydro-8,11a-methanopyrido[1,2-a]azocine-8-carboxylate (15). A flask containing **14** (263 mg, 1.00 mmol) and 10% Pd/C (20 mg) in 5 mL of EtOH was thoroughly purged with hydrogen and was then fitted with a hydrogen balloon. After the mixture was stirred for 5 h at room temperature, it was filtered. The filtrate was concentrated under reduced pressure and to give compound **15** as a colorless oil (252 mg, 95% yield). Compound **15**: R_f = 0.20 (EtOAc); IR (film) ν_{max} 2937, 1735, 1450, 1258, 1157, 1107, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz), 1.37−1.43 (m, 2H), 1.49−1.59 (m, 4H), 1.63−1.67 (m, 1H), 1.73−1.77 (m, 1H), 1.94−1.99 (m, 1H), 2.04−2.14 (m, 2H), 2.61−2.73 (m, 5H), 2.84−2.93 (m, 1H), 3.37 (td, 1H, J = 13.0, 4.2 Hz), 4.19−4.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.6, 20.5, 25.6, 31.5, 32.5, 34.5, 35.4, 48.1, 50.2, 56.9, 61.2, 63.3, 172.2, 210.2; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO_3$ 266.1751, found for $[M + H]^+$ 266.1757.

(3^{1}S,7aS,10aS)-Ethyl Dodecahydroazepino[3,2,1-hi]indole-10a-carboxylate (16). Mossy zinc (5.20 g, 80.0 mmol) was amalgamated by being shaken with mercuric chloride (565 mg, 2.10 mmol), concentrated HCl (0.5 mL), and H_2O (8 mL) for 5 min. The resulting mixture was decanted from the amalgam and then washed once with distilled water. Compound **15** (1.06 g, 4.00 mmol) in 10 mL of concentrated HCl was added slowly to the above amalgam. The resulting mixture was heated under gentle reflux for 45 min and then cooled to room temperature, filtered, adjusted to pH 9−10 with saturated Na_2CO_3, and extracted with $CHCl_3$ (3 × 30 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 40:1 CH_2Cl_2/CH_3OH to give compound **16** as white solids (750 mg, 75% yield). Compound **16**: Mp 82−84 °C; R_f = 0.45 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2931, 1726, 1451, 1177, 1027; ^{1}H NMR (400 MHz, C_6D_6) δ 0.83−0.87 (m, 2H), 0.97 (t, 3H, J = 7.2 Hz), 1.07 (td, 1H, J = 12.0, 4.0 Hz), 1.18−1.29 (m, 1H), 1.34−1.42 (m, 1H), 1.45−1.51 (m, 2H), 1.58−1.72 (m, 6H), 1.92−1.95 (m, 1H), 2.23−2.30 (m, 2H), 2.34−2.41 (m, 2H), 2.42−2.55 (m, 1H), 2.90−2.95 (m, 1H), 3.06−3.10 (m, 1H), 3.96−4.02 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 14.3, 23.5, 26.3, 28.3, 34.1, 34.2, 34.9, 35.6, 37.3, 53.3, 53.4, 53.7, 59.7, 79.9, 174.4; HRMS (ESI) m/z calcd for $C_{15}H_{26}NO_2$ 252.1958, found for $[M + H]^+$ 252.1956. X-ray crystallographic data for **16**: $C_{15}H_{25}NO_2$, triclinic, space group $P\bar{1}$, a = 8.720(2) Å, b = 13.383(3) Å, c = 15.606(3) Å, α = 115.17(3)°, β = 96.03(3)°, γ = 98.19(3)°, Z = 5, d_{calcd} = 1.488 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0538, wR_2 = 0.1069.

(S)-Ethyl 1-(4-Ethoxy-4-oxobutyl)pyrrolidine-2-carboxylate (17).[9b,12] Compound **17** was prepared by a procedure analogous to that of compound **11** and gave a 95% yield: colorless oil; R_f = 0.3 (4:1 petroleum ether/EtOAc); IR (film) ν_{max} 2978, 1734, 1450, 1373, 1181; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.23 (m, 6H), 1.71−1.79 (m, 3H), 1.82−1.91 (m, 2H), 2.00−2.07 (m, 1H), 2.23−2.41 (m, 4H), 2.61−2.68 (m, 1H), 3.07−3.14 (m, 2H), 4.03−4.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 14.1, 23.1, 23.8, 29.1, 32.0, 53.2, 53.9, 60.0, 60.3, 65.9, 173.4, 174.1.

Ethyl 2-Allyl-1-(4-ethoxy-4-oxobutyl)pyrrolidine-2-carboxylate (18). Compound **18** was prepared by a procedure analogous to that of compound **12** and gave a 94% yield: R_f = 0.5 (3:1 petroleum ether/EtOAc); IR (film) ν_{max} 2978, 1730, 1449, 1179, 1028, 916; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.26 (m, 6H), 1.71−1.85 (m, 5H), 2.04−2.08 (m, 1H), 2.19−2.34 (m, 4H), 2.51−2.59 (m, 2H), 2.63−2.70 (m, 1H), 3.07−3.12 (m, 1H), 4.07−4.13 (m, 4H), 5.01−5.07 (m, 2H), 5.71−5.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.4, 21.7, 24.2, 31.9, 33.6, 39.2, 48.0, 51.0, 59.9, 60.1, 70.0, 117.5, 134.4, 173.7, 174.0; HRMS (ESI) m/z calcd for $C_{16}H_{28}NO_4$ 298.2013, found for $[M + H]^+$ 298.2007.

Ethyl 8a-Allyl-8-hydroxy-1,2,3,5,6,8a-hexahydroindolizine-7-carboxylate (19). Compound **19** was prepared by a procedure analogous to that of compound **13** and gave a 75% yield: R_f = 0.35 (3:1 petroleum ether/EtOAc); IR (film) ν_{max} 2936, 1651, 1611, 1222, 1038; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz), 1.64−1.73 (m, 2H), 1.87−1.93 (m, 1H), 1.98−2.04 (m, 1H), 2.09 (ddd, 1H, J = 2.4, 5.6, 15.2 Hz), 2.37−2.54 (m, 3H), 2.77 (q, 1H, J = 8.8 Hz), 2.86−2.92 (m, 2H), 2.97−3.04 (m, 1H), 4.19 (q, 2H, J = 7.2 Hz), 5.03−5.10 (m, 2H), 5.81−5.90 (m, 1H), 12.33 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 17.7, 22.6, 34.2, 41.9, 41.9, 50.6, 60.4, 64.8, 95.3, 117.0, 134.6, 172.3, 175.5; HRMS (ESI) m/z calcd for $C_{14}H_{22}NO_3$ 252.1594, found for $[M + H]^+$ 252.1594.

Ethyl 8a-Allyl-7-bromo-8-oxooctahydroindolizine-7-carboxylate (20). NBS (187 mg, 1.05 mmol) was added to a solution of compound **19** (251 mg, 1.00 mmol) in DMSO (5 mL). After the mixture was stirred at room temperature for 1 h, 20 mL of EtOAc was added. The mixture was washed with water (3 × 10 mL) and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by silica gel column chromatography eluting with 10:1 petroleum ether/EtOAc to give **20** as a yellowish oil (314 mg, 95% yield). Compound **20**: R_f = 0.4 (5:1 petroleum ether/EtOAc); IR (film) ν_{max} 1759, 1731, 1445, 1283, 1228; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, 3H, J = 7.2 Hz), 1.67−1.80 (m, 2H), 1.93−1.99 (m, 2H), 2.25−2.31 (m, 1H), 2.31−2.46 (m, 2H), 2.72−2.78 (m, 1H), 2.84−2.90 (m, 1H), 3.03−3.14 (m, 3H), 4.12−4.24 (m, 2H), 5.05−5.10 (m, 2H), 5.76−5.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 21.8, 33.2, 34.2, 38.4, 40.9, 49.6, 62.2, 66.6, 72.2, 118.6, 133.2, 165.9, 201.8; HRMS (ESI) m/z calcd for $C_{14}H_{21}BrNO_3$ 330.0699, found for $[M + H]^+$ 330.0694.

Ethyl 11-Oxooctahydro-1H-7,10a-methanopyrrolo[1,2-a]azocine-7-carboxylate (21). A solution of AIBN (10 mg) in 1 mL of anhydrous benzene was added to a solution of **20** (329 mg, 1.00 mmol) in anhydrous benzene (30 mL) under a nitrogen atmosphere. The reaction mixture was brought to reflux. A solution of n-Bu_3SnH (0.29 mL, 1.10 mmol) in 15 mL of anhydrous benzene was slowly added over 1 h via a syringe pump. After refluxing for 4 h, the reaction mixture was cooled to rt and extracted with 1 N HCl (3 × 10 mL). The combined aqueous extracts were adjusted to pH 9−10 with saturated aqueous Na_2CO_3 and extracted with $CHCl_3$ (3 × 30 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 6:1 petroleum ether/EtOAc to give compound **21** as a colorless oil (125 mg, 50% yield). Compound **21**: R_f = 0.2 (1:2 petroleum ether/EtOAc); IR (film) ν_{max} 2957, 1736, 1722, 1454, 1285, 1113, 1024; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.0 Hz), 1.36−1.41 (m, 1H), 1.49−1.59 (m, 2H), 1.67−1.75 (m, 2H), 1.94−2.02 (m, 2H), 2.17−2.37 (m, 5H), 2.48−2.54 (m, 1H), 2.68−2.73 (m, 1H), 3.11−3.16 (m, 1H), 3.20−3.24 (m, 1H), 4.22−4.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 17.5, 22.6, 31.9, 33.0, 37.8, 42.6, 49.4, 57.7, 57.5, 61.2, 71.7,

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172.7, 211.8; HRMS (ESI) m/z calcd for $C_{14}H_{22}NO_3$ 252.1594, found for $[M + H]^+$ 252.1588.

(3^{1}R,6aS,9aS)-Ethyl Decahydro-1H-pyrrolo[3,2,1-ij]-quinoline-9a-carboxylate (22). Compound **22** was prepared by a procedure analogous to that of compound **16** and gave a 45% yield: R_f = 0.55 (10:1 CH_2Cl_2/CH_3OH); IR (film) ν_{max} 2931, 1725, 1457, 1166; ^{1}H NMR (400 MHz, C_6D_6) δ 0.97 (t, 3H, J = 7.0 Hz), 1.19−1.26 (m, 2H), 1.41−1.58 (m, 3H), 1.59−1.86 (m, 6H), 1.96−2.03 (m, 2H), 2.10−2.17 (m, 2H), 2.53 (d, 1H, J = 3.2 Hz), 2.86−2.95 (m, 2H), 3.97−4.03 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 14.3, 21.4, 24.5, 25.9, 29.7, 33.0, 33.4, 35.1, 51.3, 52.9, 54.0, 60.1, 67.4, 175.8; HRMS (ESI) m/z calcd for $C_{14}H_{24}NO_2$ 238.1802, found for $[M + H]^+$ 238.1798.

(S)-Ethyl 1-(2-Ethoxy-2-oxoethyl)pyrrolidine-2-carboxylate (23).[4d] Compound **23** was prepared by a procedure analogous to that of compound **11** and gave a 95% yield as a colorless oil: R_f = 0.30 (3:1 petroleum ether/EtOAc); IR (film) ν_{max} 2979, 2943, 1735, 733; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.24 (m, 6H), 1.46−1.53 (m, 2H), 1.56−1.66 (m, 2H), 1.73−1.79 (m, 1H), 1.84−1.92 (m, 2H), 2.03−2.10 (m, 1H), 2.26−2.39 (m, 4H), 2.62−2.69 (m, 1H), 3.06−3.16 (m, 2H), 4.05−4.17 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.1, 22.8, 23.0, 28.1, 29.2, 34.0, 53.4, 54.5, 60.1, 60.4, 66.1, 173.5, 174.2.

Ethyl 9-Oxooctahydro-1H-pyrrolo[1,2-a]azepine-8-carboxylate (24). Sodium ethoxide was prepared from sodium (1.40 g, 61.00 mmol) and anhydrous EtOH (20 mL) in a 500 mL flask fitted with distillation equipment. Anhydrous xylene (200 mL) and compound **23** (15.00 g, 55.40 mmol) dissolved in 20 mL of dry xylene were successively added to the sodium ethoxide solution. The bath temperature was raised periodically, and the reaction mixture was distilled until no ethanol was detected in the distillate. The resulting residue was cooled to room temperature, and 60 mL of H_2O was added to the flask. The mixture was extracted with ethyl acetate (3 × 100 mL), and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography eluting with 2:1 petroleum ether/EtOAc to give a mixture of diastereoisomers as a yellowish oil (9.50 g, 76% yield) that could not be separated (2.5:1) chromatographically. Compound **24**: R_f = 0.50 (15:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2937, 1742, 1711, 1304, 1187, 1110; major product ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24−1.28 (m, 3H), 1.70−1.89 (m, 5H), 1.95−2.15 (m, 4H), 2.33−2.49 (m, 3H), 2.99−3.04 (m, 2H), 3.11−3.17 (m, 2H), 4.09−4.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 25.9, 28.4, 28.7, 54.6, 55.5, 56.0, 60.8, 72.4, 171.3, 209.3; HRMS (ESI) m/z calcd for $C_{12}H_{20}NO_3$ 226.1438, found for $[M + H]^+$ 226.1443.

Ethyl 9a-Allyl-9-oxooctahydro-1H-pyrrolo[1,2-a]azepine-8-carboxylate (25). Allyl bromide (2.38 mL, 27.1 mmol) was added to a solution of compound **24** (6.1 g, 27.1 mmol) in anhydrous CH_3CN (40 mL). The mixture was stirred at room temperature for 6 days. The solid residue was separated by filtration and then dissolved in 40 mL of anhydrous CH_3CN, to which anhydrous potassium carbonate (4.00 g, 29.30 mmol) was added. The resulting slurry was brought to reflux for 1.5 h. The reaction mixture was cooled to room temperature and filtered, and the filtrate was concentrated and purified by silica gel column chromatography eluting with 4:1 petroleum ether/EtOAc to give **25** as yellowish solids (4.31 g, 60% yield): R_f = 0.60 (EtOAc); IR (film) ν_{max} 2937, 2803, 1742, 1711, 1450, 1369, 1304, 1187, 1110, 1030; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.2 Hz), 1.47−1.50 (m, 1H), 1.51−1.65 (m, 1H), 1.84−1.92 (m, 4H), 1.96−2.08 (m, 2H), 2.30 (dd, 1H, J = 6.4, 6.4 Hz), 2.45 (dd, 1H, J = 8.0, 8.0 Hz), 2.74−2.81 (m, 1H), 2.92−2.97 (m, 1H), 3.13−3.17 (m, 1H), 3.24−3.28 (m, 1H), 3.89 (dd, 1H, J = 4.0, 3.6 Hz), 4.17 (q, 2H, J = 7.2 Hz), 5.03−5.11 (m, 2H), 5.88−5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.4, 23.7, 24.2, 26.4, 34.4, 37.6, 46.3, 51.1, 54.3, 60.8, 117.2, 135.2, 171.1, 210.7; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO_3$ 266.1751, found for $[M + H]^+$ 266.1756.

(8R,11S,11aR)-Ethyl 11-Acetoxy-12-oxodecahydro-8,11a-methanopyrrolo[1,2-a]azonine-8-carboxylate (26a) and (8R,11R,11aR)-Ethyl 11-Acetoxy-12-oxodecahydro-8,11a-methanopyrrolo[1,2-a]azonine-8-carboxylate (26b). DBU (0.64 mL, 4.20 mmol) under a nitrogen atmosphere was added to a solution of **24** (450 mg, 2.00 mmol) in anhydrous CH_3CN (30 mL). The reaction mixture was then brought to reflux. A solution of acrolein (134 mg, 2.40 mmol) in 2 mL of anhydrous CH_3CN was slowly added over 1 h via syringe pump. After the mixture had been refluxed for 4 h, Ac_2O (510 mg, 5.00 mmol) was added to the reaction mixture, and refluxing was continued for 4 h. Then the reaction mixture was cooled and stirred at room temperature for 5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in EtOAc (30 mL), washed with water (3 × 10 mL) and brine, and dried over anhydrous Na_2SO_4. The solvent was again evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with 2:1 petroleum ether/EtOAc to give **26a** as a yellowish solid (357 mg, 55% yield) and **26b** as a yellowish oil (65 mg, 10% yield). Compound **26a**: Mp 72 °C; R_f = 0.65 (EtOAc); IR (film) ν_{max} 2936, 1737, 1239, 1028; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, 3H, J = 7.2 Hz), 1.49 (dd, 1H, J = 13.2, 5.6 Hz), 1.58−1.76 (m, 4H), 1.84−1.96 (m, 3H), 1.99 (s, 4H), 2.28−2.44 (m, 3H), 2.54−2.70 (m, 2H), 2.86 (dd, 1H, J = 13.6, 6.0 Hz), 3.10 (t, 1H, J = 7.6 Hz), 4.04−4.16 (m, 2H), 4.89 (d, 1H, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.8, 22.3, 22.9, 25.1, 29.2, 29.3, 36.8, 54.3, 58.1, 59.7, 60.9, 73.7, 76.5, 169.9, 173.3, 207.0; HRMS (ESI) m/z calcd for $C_{17}H_{26}NO_5$ 324.1805, found for $[M + H]^+$ 324.1812. X-ray crystallographic data of **26a**: $C_{17}H_{25}NO_5$, monoclinic, space group $C2/c$, a = 30.456(6) Å, b = 8.4737(17) Å, c = 13.944(3) Å, β = 106.162(2)°, Z = 8, d_{calcd} = 1.243 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0748, wR_2 = 0.1888. Compound **26b**: R_f = 0.5 (EtOAc); IR (film) ν_{max} 2936, 2812, 1738, 1707, 1455, 1370, 1245, 1037; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.2 Hz), 1.57−1.61 (m, 1H), 1.77−1.87 (m, 3H), 1.89−1.93 (m, 2H), 1.98−2.10 (m, 3H), 2.15 (s, 3H), 2.36−2.50 (m, 3H), 2.55−2.61 (m, 1H), 2.66−2.72 (m, 1H), 3.12 (dd, 1H, J = 13.2, 6.4 Hz), 3.22−3.23 (m, 1H), 4.15−4.21 (m, 2H), 4.89 (dd, 1H, J = 11.6, 4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.3, 24.3, 24.9, 25.2, 29.6, 32.8, 36.5, 54.6, 58.9, 59.7, 61.4, 75.6, 77.3, 170.4, 173.0, 205.2; HRMS (ESI) m/z calcd for $C_{17}H_{26}NO_5$ 324.1805, found for $[M + H]^+$ 324.1799.

(4^{1}R,7aS)-Ethyl 1,2,3,4^1,5,6,7,7a,8,9-Decahydropyrido[3,2,1-ij]quinoline-7a-carboxylate (27a) and (4^{1}S,7aS)-Ethyl 1,2,3,4^1,5,6,7,7a,8,9-Decahydropyrido[3,2,1-ij]quinoline-7a-carboxylate (27b). Zn dust (650 mg, 10.00 mmol) was added to the anhydrous HOAc (10 mL) solution of **26a** or **26b** (323 mg, 1.00 mmol). After the reaction mixture was stirred at room temperature for 24 h, it was filtered, and the HOAc was evaporated under reduced pressure. The resulting residue was adjusted to pH 9−10 with saturated aqueous Na_2CO_3 and extracted with $CHCl_3$ (3 × 30 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 40:1 CH_2Cl_2/CH_3OH to give **27a** as a colorless oil (162 mg, 65% yield) and **27b** as a yellowish oil (61 mg, 25% yield). Compound **27a**: R_f = 0.40 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2935, 1728, 1244, 1164, 1110; ^{1}H NMR (400 MHz, C_6D_6) δ 0.94 (t, 3H, J = 7.2 Hz), 1.31 (s, 1H), 1.45−1.48 (m, 1H), 1.60−1.73 (m, 3H), 1.74−1.80 (m, 2H), 1.90 (t, 1H, J = 10.0 Hz), 1.97−2.25 (m, 6H), 2.56−2.58 (m, 1H), 2.75 (dt, 1H, J = 4.4, 1.6 Hz), 3.07 (s, 1H), 3.92−4.00 (m, 2H), 5.36 (d, 1H, J = 5.2 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 14.6, 22.2, 24.4, 26.6, 28.6, 35.0, 36.1, 45.7, 55.8, 58.3, 60.4, 64.1, 119.4, 138.9, 176.1; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO_2$ 250.1802, found for $[M + H]^+$ 250.1799. Compound **27b**: R_f = 0.30 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2933, 1745, 1710, 1443, 1213, 1140; ^{1}H NMR (400 MHz, C_6D_6) δ 1.00 (t, 3H, J = 7.2 Hz), 1.36−1.47 (m, 3H), 1.79−1.87 (m, 3H), 1.89−1.96 (m, 4H), 2.01−2.10 (m, 2H), 2.29−2.39 (m, 3H), 2.74−2.77 (m, 2H), 3.98−4.10 (m, 2H), 5.22 (s, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 14.3, 23.3, 23.8, 24.5, 33.0, 33.5, 36.8, 47.6, 55.9, 57.9, 60.0, 68.5, 119.3, 134.5, 173.2; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO_2$ 250.1802, found for $[M + H]^+$ 250.1802.

(4^{1}S,7aR,10S,10aR)-Ethyl 10,10a-Dihydroxydodecahydropyrido[3,2,1-ij]quinoline-7a-carboxylate (28). A catalytic

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amount of OsO_4 (dissolved in 1 mL of *i*-PrOH) at room temperature was added to an acetone (20 mL) solution of **27a** (950 mg, 3.80 mmol) and *N*-methylmorpholine *N*-oxide (NMO) (1.34 g, 11.40 mmol). After the mixture had been stirred for 24 h at room temperature, the reaction was quenched by the addition of saturated aqueous sodium sulfite solution (5 mL). The mixture was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the resulting residue was purified by silica gel column chromatography eluting with 20:1 CH_2Cl_2/MeOH to give **28** as white crystals (750 mg, 70% yield). Compound **28**: Mp 136 °C; R_f = 0.30 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 3441, 2936, 1726, 1445, 1247, 1168, 1131, 1041; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08−1.17 (m, 1H), 1.24 (t, 3H, J = 7.2 Hz), 1.41−1.55 (m, 3H), 1.64−1.79 (m, 6H), 1.92−2.07 (m, 5H), 2.28 (d, 1H, J = 12.8 Hz), 2.55 (s, 1H), 2.80 (d, 2H, J = 11.2 Hz), 4.02−4.10 (m, 2H), 4.13−4.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.4, 21.8, 25.3, 27.9, 34.9, 35.4, 44.2, 56.6, 57.5, 60.3, 67.6, 71.1, 72.6, 177.3; HRMS (ESI) m/z calcd for $C_{15}H_{26}NO_4$ 284.1856, found for $[M + H]^+$ 284.1857. X-ray crystallographic data of **28**: $C_{15}H_{25}NO_4$, triclinic, space group $P\bar{1}$, a = 8.410(5) Å, b = 8.707(6) Å, c = 10.620(7) Å, α = 101.173(6)°, β = 103.851(6)°, γ = 90.396(6)°, Z = 2, d_{calcd} = 1.272 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0462, wR_2 = 0.1094.

(4^{1}R,7aR,10aS)-Decahydro-7a,10a-(epoxymethano)pyrido-[3,2,1-ij]quinolin-11-one (29). Compound **27b** (249 mg, 1.00 mmol) was dissolved in 10 mL of HCl (4 N), and the mixture was brought to reflux for 24 h. The reaction mixture was cooled, adjusted to pH 9−10 with Na_2CO_3, and extracted with $CHCl_3$ (3 × 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 40:1 CH_2Cl_2/CH_3OH to give **29** as white crystals (145 mg, 65% yield). Compound **29**: Mp 80 °C; R_f = 0.70 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2931, 1770, 1441, 1119, 926; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20−1.29 (m, 1H), 1.36−1.51 (m, 5H), 1.60−1.75 (m, 4H), 1.80−1.96 (m, 2H), 2.04 (d, 2H, J = 4.4 Hz), 2.14−2.26 (m, 3H), 2.64 (dd, 2H, J = 11.2, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.6, 23.3, 28.4, 31.1, 32.3, 34.0, 49.6, 52.6, 52.7, 72.8, 80.5, 179.4; HRMS (ESI) m/z calcd for $C_{13}H_{20}NO_2$ 222.1489, found for $[M + H]^+$ 222.1492.

(4^{1}R,7aR,10S,10aS)-Ethyl 10-Hydroxydodecahydropyrido-[3,2,1-ij]quinoline-7a-carboxylate (30). BH_3 (1 M in THF, 3 mL, 3.00 mmol) was added to an anhydrous THF (10 mL) solution of compound **27a** (498 mg, 2.00 mmol) under a nitrogen atmosphere. The reaction mixture was brought to reflux. After refluxing for 12 h, the reaction mixture was cooled to room temperature, and KOH (4 mL, 3 M) and H_2O_2 (50%, 0.19 mL) were added to the flask. After the mixture was stirred at room temperature for 0.5 h, the organics were extracted with ethyl acetate (3 × 20 mL), and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with 30:1 CH_2Cl_2/CH_3OH to give **27** as white crystals (375 mg, 70% yield). Compound **30**: Mp 123 °C; R_f = 0.35 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 3360, 2939, 1725, 1445, 1250, 1191, 1127, 1031; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, J = 7.2 Hz), 1.29−1.38 (m, 2H), 1.39−1.48 (m, 2H), 1.53−1.60 (m, 3H), 1.67−1.70 (m, 1H), 1.78−1.93 (m, 4H), 1.96−2.06 (m, 2H), 2.10−2.17 (m, 2H), 2.58 (s, 1H), 2.75 (d, 1H, J = 10.4 Hz), 2.86 (d, 1H, J = 10.4 Hz), 4.05 (td, 1H, J = 11.2, 4.8 Hz), 4.12−4.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.6, 20.7, 25.0, 26.1, 33.5, 34.9, 41.4, 47.4, 57.1, 58.1, 60.4, 66.0, 66.5, 176.3; HRMS (ESI) m/z calcd for $C_{15}H_{26}NO_3$ 268.1907, found for $[M + H]^+$ 268.1901. X-ray crystallographic data of **30**: $C_{15}H_{25}NO_3$, monoclinic, space group $P2(1)/c$, a = 8.186(16) Å, b = 23.09(5) Å, c = 8.398(17) Å, β = 118.853(18)°, Z = 4, d_{calcd} = 1.277 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0813, wR_2 = 0.2102.

(4^{1}R,7aR,10aS)-Ethyl 10-Oxododecahydropyrido[3,2,1-ij]-quinoline-7a-carboxylate (31). DMSO (273 mg, 3.50 mmol) at −78 °C was added to an anhydrous solution of CH_2Cl_2 (5 mL) and $(COCl)_2$ (0.17 mL, 1.75 mmol) under a nitrogen atmosphere. Compound **30** (390 mg, 1.46 mmol) was added to the flask after the mixture had been stirred at −78 °C for 15 min. The reaction mixture was stirred at −78 °C for another 1.5 h before Et_3N (1.0 mL) was added. The mixture was slowly warmed to room temperature over the course of 1 h, diluted with 20 mL of CH_2Cl_2, washed with water and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 40:1 CH_2Cl_2/CH_3OH to give compound **31** as a colorless oil (320 mg, 85% yield). Compound **31**: R_f = 0.40 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2944, 1719, 1444, 1250, 1125, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14−1.21 (m, 1H), 1.30 (t, 3H, J = 7.2 Hz), 1.42 (d, 1H, J = 13.6 Hz), 1.49−1.53 (m, 1H), 1.69−1.96 (m, 4H), 1.99−2.10 (m, 3H), 2.28 (dd, 1H, J = 13.2, 2.0 Hz), 2.36−2.46 (m, 2H), 2.51−2.58 (m, 2H), 2.77−2.82 (m, 2H), 2.85 (d, 1H, J = 1.6 Hz), 4.20−4.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.5, 21.6, 23.8, 26.7, 34.3, 38.5, 46.0, 47.2, 57.1, 57.7, 60.8, 67.7, 175.8, 209.9; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO_3$ 266.1751, found for $[M + H]^+$ 266.1755.

Ethyl 10-Oxo-1,2,3,5,6,7,7a,8,9,10-decahydropyrido[3,2,1-ij]quinoline-7a-carboxylate (32). *m*-CPBA (70%, 95 mg, 0.39 mmol) at 0 °C was added to a solution of **31** (93 mg, 0.35 mmol) in 5 mL of CH_2Cl_2. The resulting mixture was stirred at 0 °C for 0.5 h and then stirred at room temperature for 3 h. After addition of 1 mL of saturated aqueous $NaHCO_3$, the reaction mixture was stirred for 5 min and extracted with $CHCl_3$. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure to give the corresponding N-oxide. The N-oxide was then taken up in 5 mL of anhydrous CH_2Cl_2 and stirred under a nitrogen atmosphere at 0 °C. Trifluoroacetic anhydride (TFAA, 0.25 mL) was added dropwise over the course of 5 min, and the resulting reaction mixture was allowed to stir for 1 h at 0 °C. The reaction mixture was concentrated in vacuo, diluted with CH_2Cl_2 (15 mL), treated with saturated aqueous Na_2CO_3 (5 mL), and stirred for 10 min. The layers were separated, and the organic layer was washed with water and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 50:1 CH_2Cl_2/CH_3OH to give **32** as a yellow oil (60 mg, 65% yield). Compound **31**: R_f = 0.40 (20:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2942, 1725, 1554, 1290, 1190; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, 3H, J = 7.2 Hz), 1.56 (td, 1H, J = 13.2, 4.4 Hz), 1.71−1.90 (m, 5H), 2.14−2.38 (m, 5H), 2.60−2.67 (m, 1H), 3.10−3.16 (m, 1H), 3.20−3.25 (m, 3H), 4.15−4.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.9, 19.9, 20.1, 32.2, 33.6, 33.7, 47.1, 50.2, 51.1, 61.4, 106.6, 157.6, 173.3, 192.7; HRMS (ESI) m/z calcd for $C_{15}H_{22}NO_3$ 264.1594, found for $[M + H]^+$ 264.1588.

2,3,5,6,7,9,10,10a-Octahydropyrido[3,2,1-ij]quinolin-8(1H)-one (33). $CaCl_2$ (152 mg, 1.36 mmol) was added to a solution of **32** (45 mg, 0.17 mmol) in 5 mL of DMSO. The mixture was heated at 170 °C for 6 h under a nitrogen atmosphere, cooled to rt, and diluted with 20 mL of CH_2Cl_2. The resulting mixture was washed with water (5 × 10 mL) and brine, dried, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography eluting with 40:1 CH_2Cl_2/CH_3OH to give **33** as a yellow oil (26 mg, 80% yield). Compound **33**: R_f = 0.35 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2934, 1603, 1543, 1315, 1190; ^{1}H NMR (400 MHz, C_6D_6) δ 0.69−0.80 (m, 1H), 1.18−1.25 (m, 3H), 1.28−1.35 (m, 1H), 1.38−1.42 (m, 1H), 1.43−1.49 (m, 2H), 1.76 (t, 1H, J = 12 Hz), 2.15−2.24 (m, 1H), 2.38−2.43 (m, 2H), 2.45−2.48 (m, 3H), 2.57 (ddd, 1H, J = 6.4, 4.0, 2.4 Hz), 2.90 (dt, 1H, J = 16, 5.6 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 20.5, 21.0, 23.2, 28.7, 29.9, 35.8, 37.4, 50.4, 50.6, 105.8, 158.4, 192.3; HRMS (ESI) m/z calcd for $C_{12}H_{18}NO$ 192.1383, found for $[M + H]^+$ 192.1380.

(7S,10S,10aR)-Ethyl 10-Acetoxy-11-oxooctahydro-1H-7,10a-methanopyrrolo[1,2-a]azocine-7-carboxylate (36a) and (7S,10R,10aR)-Ethyl 10-Acetoxy-11-oxooctahydro-1H-7,10a-methanopyrrolo[1,2-a]azocine-7-carboxylate (36b). A solution of compound **17** (6.80 g, 26.50 mmol) in dry THF (15 mL) at 0 °C was added to a stirring mixture of KO^{t}Bu (3.60 g, 31.80 mmol) in 150 mL of dry THF. After 1 h, 10 mL of water was added to quench the reaction. Then the mixture was adjusted to pH 7 with 2 M HCl and extracted with ethyl acetate (50 mL). The aqueous layer was extracted with $CHCl_3$ (5 × 50 mL), and all the combined organic extracts were

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washed with water and brine and dried over anhydrous Na_2SO_4. Then the solvent was evaporated under reduced pressure to give the crude compound **35** as a yellowish oil (4.9 g), which did not need purification. DBU (7.44 mL, 48.70 mmol) was added to the anhydrous CH_3CN (60 mL) solution of crude compound **35** (4.90 g, 23.20 mmol) under a nitrogen atmosphere. The reaction mixture was brought to reflux. A solution of acrolein (1.56 g, 27.80 mmol) in 10 mL of anhydrous CH_3CN was slowly added over the course of 1 h via syringe pump. After the mixture had been refluxed for 4 h, Ac_2O (6.80 g, 66.00 mmol) was added slowly, and the mixture continued refluxing for 1 h. The reaction mixture was cooled and stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc (60 mL), and the solution was washed with water (3 × 20 mL) and brine and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography eluting with 4:1 petroleum ether/EtOAc to give **36a** as a yellow solid (5.30 g, 65% yield) and **36b** as a yellow oil (1.32 g, 16% yield). Compound **36a**: Mp 71 °C; R_f = 0.60 (EtOAc); IR (film) ν_{max} 2951, 1784, 1455, 1371, 1235, 1117, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 1.50−1.54 (m, 1H), 1.68−1.86 (m, 4H), 2.03 (s, 3H), 2.04−2.10 (m, 1H), 2.23−2.27 (m, 1H), 2.35−2.64 (m, 4H), 2.71−2.76 (m, 1H), 3.04−3.08 (m, 1H), 3.20−3.22 (m, 1H), 4.26 (q, 2H, J = 7.2 Hz), 4.97 (q, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.0, 21.7, 22.3, 27.4, 32.1, 33.0, 49.6, 56.9, 57.4, 61.3, 73.2, 79.2, 170.1, 172.2, 207.9; HRMS (ESI) m/z calcd for $C_{16}H_{24}NO_5$ 310.1649, found for $[M + H]^+$ 310.1656. X-ray crystallographic data of **36a**: $C_{16}H_{23}NO_5$, monoclinic, space group $P2(1)/c$, a = 15.235(16) Å, b = 7.700(8) Å, c = 14.339(15) Å, β = 108.123(11)°, Z = 4, d_{calcd} = 1.285 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0491, wR_2 = 0.1167. Compound **36b**: R_f = 0.40 (EtOAc); IR (film) ν_{max} 2958, 2802, 1741, 1454, 1370, 1258, 1115, 1033; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, 3H, J = 7.2 Hz), 1.55−1.60 (m, 1H), 1.68−1.77 (m, 2H), 1.88−2.09 (m, 2H), 2.10−2.14 (m, 4H), 2.19−2.26 (m, 2H), 2.34−2.41 (m, 2H), 2.57−2.64 (m, 1H), 2.71−2.76 (m, 1H), 3.14−3.18 (m, 1H), 3.27−3.31 (m, 1H), 4.20−4.28 (m, 2H), 4.64 (dd, 1H, J = 11.2, 4.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.0, 23.3, 23.3, 29.2, 29.9, 32.4, 49.4, 56.2, 58.1, 61.4, 75.7, 78.4, 169.9, 171.8, 206.7; HRMS (ESI) m/z calcd for $C_{16}H_{24}NO_5$ 310.1649, found for $[M + H]^+$ 310.1651.

(3^{1}R,9aS)-Ethyl 2,3^1,4,5,6,8,9,9a-Octahydro-1H-pyrrolo-[3,2,1-ij]quinoline-9a-carboxylate (37). Zn dust (1.30 g, 20.00 mmol) was added to the anhydrous HOAc (30 mL) solution of **36a** or **36b** (618 mg, 2.00 mmol). The reaction mixture was brought to reflux under a nitrogen atmosphere. After refluxing for 24 h, the reaction mixture was filtered, and HOAc was evaporated under reduced pressure. The residue was adjusted to pH 9−10 with saturated Na_2CO_3 and extracted with $CHCl_3$ (3 × 30 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 40:1 CH_2Cl_2/CH_3OH to give **37** as a colorless oil (273 mg, 58% yield). Compound **37**: R_f = 0.40 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 2937, 1724, 1454, 1223, 1173, 1091, 1026; ^{1}H NMR (400 MHz, C_6D_6) δ 0.94 (t, 3H, J = 7.2 Hz), 1.43−1.50 (m, 1H), 1.61−1.75 (m, 3H), 1.84−2.02 (m, 2H), 2.08−2.27 (m, 6H), 2.84 (t, 1H, J = 7.6 Hz), 2.89 (s, 1H), 2.95 (d, 1H, J = 10.8 Hz), 3.90−4.03 (m, 2H), 5.44 (d, 1H, J = 6.0 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 14.2, 23.9, 27.5, 31.8, 33.2, 36.7, 49.9, 53.1, 53.8, 60.3, 67.1, 118.6, 136.5, 176.1; HRMS (ESI) m/z calcd for $C_{14}H_{22}NO_2$ 236.1645, found for $[M + H]^+$ 236.1650.

(3^{1}R,6aS,9aS)-Ethyl Decahydro-1H-pyrrolo[3,2,1-ij]-quinoline-9a-carboxylate (22). A flask containing **37** (50 mg, 0.21 mmol) and PtO_2 (10 mg) in 5 mL of MeOH was thoroughly purged with hydrogen and was then fitted with a hydrogen balloon. After the mixture was stirred for 72 h at room temperature, it was filtered. The filtrate was concentrated under reduced pressure and afforded **22** as a colorless oil (47 mg, 95% yield).

(3^{1}S,6aR,7S,9aS)-Ethyl 6a,7-Dihydroxydecahydro-1H-pyrrolo[3,2,1-ij]quinoline-9a-carboxylate (38). Compound **38** was prepared by a procedure analogous to that of compound **28** and gave a 65% yield: Mp 115 °C; R_f = 0.30 (10:1 CH_2Cl_2/MeOH); IR (film) ν_{max} 3354, 2937, 1725, 1448, 1214, 1027; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (td, 1H, J = 13.6, 5.6 Hz), 1.29 (t, 3H, J = 7.2 Hz), 1.52−1.76 (m, 5H), 1.88−2.05 (m, 5H), 2.15−2.22 (m, 1H), 2.34−2.39 (m, 2H), 2.97 (d, 1H, J = 10.8 Hz), 3.08 (td, 1H, J = 9.2, 3.2 Hz), 3.85 (dd, 1H, J = 11.6, 4.8 Hz), 4.18−4.25 (m, 2H), 4.85 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.8, 28.4, 32.9, 33.0, 33.4, 51.5, 51.6, 52.6, 61.5, 68.1, 70.6, 71.7, 178.6; HRMS (ESI) m/z calcd for $C_{14}H_{24}NO_4$ 270.1700, found for $[M + H]^+$ 270.1703. X-ray crystallographic data of **38**: $C_{14}H_{23}NO_4$, monoclinic, space group $P2(1)/c$, a = 9.978(6) Å, b = 8.194(5) Å, c = 17.056(10) Å, β = 95.767(7)°, Z = 4, d_{calcd} = 1.289 g/cm^3, $R_1(I > 2\sigma(I))$ = 0.0770, wR_2 = 0.1708.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental procedures, spectral data, copies of ^{1}H and ^{13}C NMR spectra for compounds **11**−**25**, **26a**, **26b**, **27a**, **27b**, **28**−**33**, **36a**, **36b**, **37**, and **38**; X-ray crystallographic data for compounds **16**, **26a**, **28**, **30**, **36a**, and **38**; and CIF files for **16**, **26a**, **28**, **30**, **36a**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wdli@cqu.edu.cn. Phone: 0086-(0)23-65678459.

Notes

The authors declare no competing financial interest.

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