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Synthesis of a Model Tetracyclic Core Structure of Calyciphylline B-Type Alkaloids

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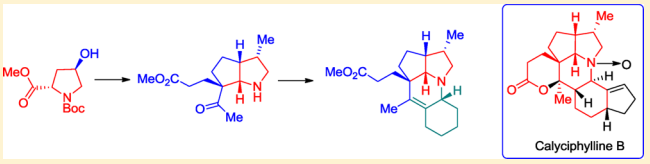
Supporting Information

ABSTRACT: Herein, we report the enantioselective synthesis of a functionalized aza-octahydropentalene and its elaboration to a model tetracyclic core structure of calyciphylline B-type alkaloids.



The *Daphniphyllum* alkaloids are a family of complex polycyclic compounds possessing unique structures harboring seven contiguous stereogenic carbons.[1] Elegant studies by Suzuki,[2a] Yamamura,[2b] and Heathcock[2c,d] have proposed a common biogenetic pathway starting with mevalonic acid, which is transformed to a squalene backbone that diverges toward a large variety of polycyclic alkaloids of the *Daphniphyllum* genus. The total synthesis of some members of *Daphniphyllum* alkaloids such as (±)-bukittinggine,[3a] (±)-methyl homodaphniphyllate,[3b] (±)-daphnilactone A,[3c] (−)-secodaphniphylline,[3d] and (+)-codaphniphylline[3e] from the Heathcock group are elegant examples of biomimetic syntheses in the field of alkaloids. Since then, significant efforts toward the synthesis of core structures of *Daphniphyllum* alkaloids have been reported.[4] However, the total synthesis of other members of the *Daphniphyllum* family such as daphmanidin E, daphenylline, and calyciphylline N were only achieved recently by Carreira,[5] Li,[6] and Smith,[7] respectively. Most recently, we have reported the total synthesis of isodaphlongamine H, the biogenetically related 5-*epi* isomer of daphlongamine H, which is the only known C6/C7 *cis*-fused member of the calyciphylline B family.[8]

In 2003, Morita and Kobayashi[9] reported the isolation and structure determination of calyciphylline B (**1**), a novel hexacyclic alkaloid isolated from *Daphniphyllum calycinum* (Figure 1). In the same year, Yue and co-workers[10] isolated deoxycalyciphylline B (**2**) and deoxyisocalyciphylline B (**3**) from the stem of *D. subverticillatum*. Soon thereafter, the corresponding methyl esters, longistylumphylline C[11] (**5**) and caldaphnidine R[12] (**6**), were also isolated, and their structures were assigned based on the X-ray structure of deoxycalyciphylline B (**2**) (Figure 1).

Yue has proposed a biosynthesis pathway for the calyciphyllines and their ester congeners that involve a pentacyclic structure (**4**), containing an aza-octahydropentalene unit and a tetrasubstituted olefin, which is believed to undergo stereospecific protiolactonization by an as yet undisclosed mechanism.[10]

Our interest in this family of *Daphniphyllum* alkaloids led to the synthesis of the core unit of daphniglaucin C from 4-(*R*)-hydroxy-L-proline.[4l] Intrigued by the proposed biogenetic precursor **4** by Yue, we set out to explore methods for the stereocontrolled synthesis of a tetracyclic compound **7** as a model for the proposed biogenetic intermediate **4** as well as longistylumphylline C (**5**) and caldaphnidine R (**6**). The retrosynthetic plan was to derive the tetracyclic compound **7** from the intramolecular cascade cyclization of an enamine as shown in Figure 2.[13]

We commenced our synthesis from the previously reported all-*syn* 3,4-disubstituted L-proline **12**, which was synthesized in eight linear steps from 4-hydroxy-L-proline (Scheme 1).[4l]

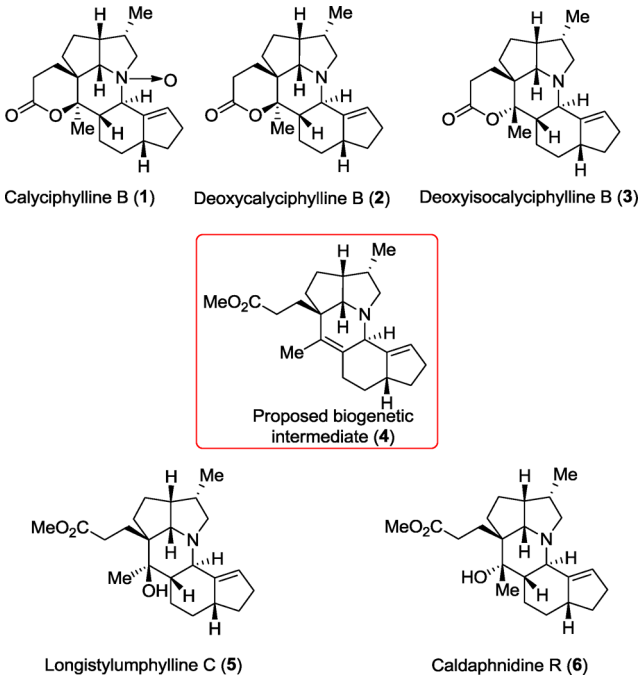


Figure 1. Calyciphylline B and related alkaloids.

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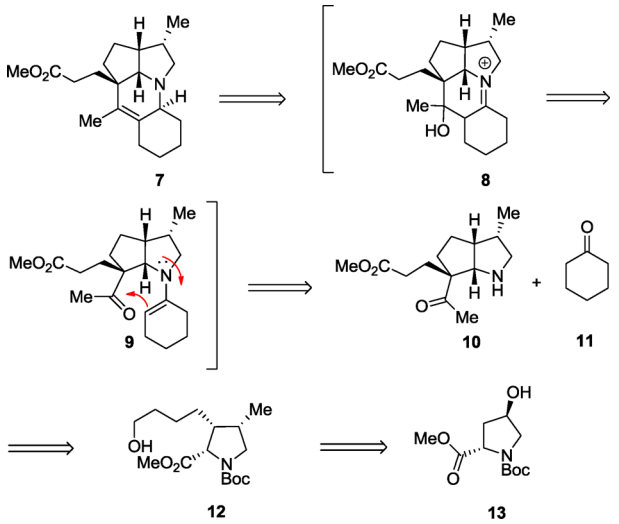
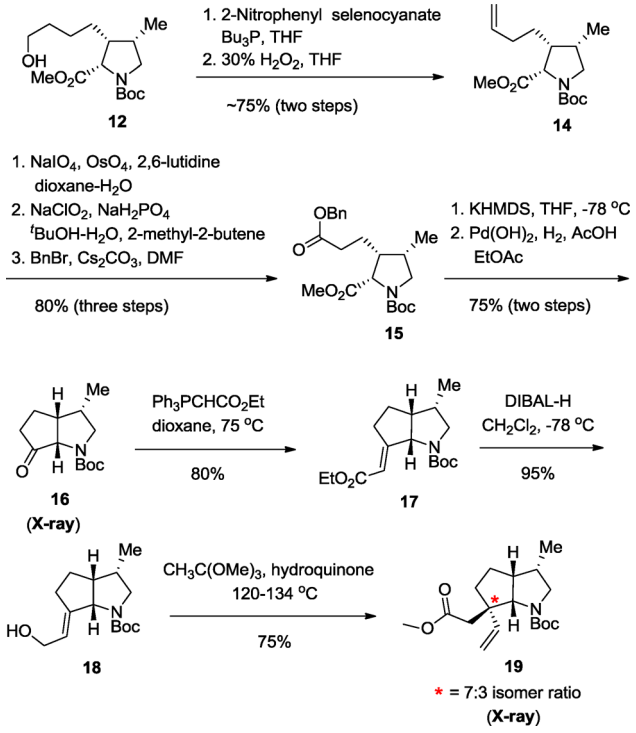


Figure 2. Retrosynthetic analysis.

Scheme 1. Synthesis of an Aza-octahydropentalene Core Structure



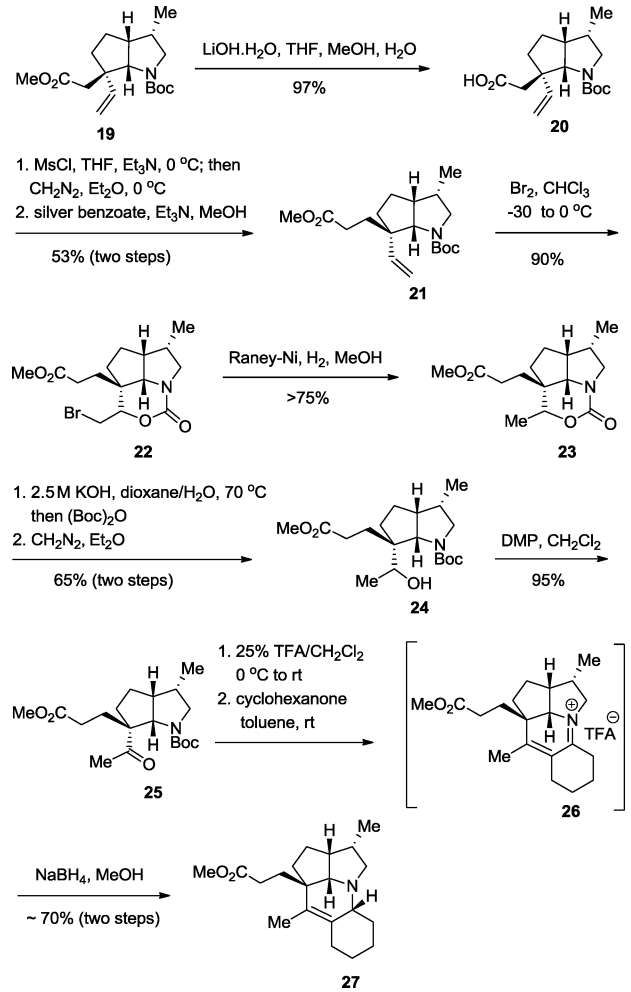
Elimination to **14** according to Grieco[14] led to the alkene **14**, which was converted to **15** in 80% yield over three consecutive steps. Treatment of **15** under Dieckmann conditions[15] using KHMDS in THF provided the corresponding β-ketoester, which was decarboxylated to the aza-bicyclic ketone **16** in 75% yield over two steps. A catalytic amount of acid was necessary to accelerate the decarboxylation process. The structure of **16** was confirmed by single-crystal X-ray analysis.[16]

Under the Wittig reaction conditions, ketone **16** underwent a two-carbon homologation to **17**, which was then converted to the allylic alcohol **18** in 76% overall yield. Various methods of sigmatropic rearrangement were attempted to obtain the desired quaternary center. Initial trials of a typical Ireland–Claisen rearrangement were unsuccessful.[17] A [2,3]-Wittig–Still[18] rearrangement with the Bu_3SnCH_2 ether of **18** afforded only 20% of the required product as a 3:1 diastereomeric mixture.[16] Ultimately, treatment of **18** under Johnson–Claisen[19] conditions with excess trimethyl orthoacetate and a catalytic amount of hydroquinone at 130 °C afforded the major isomer **19** as a 7:3 separable diastereomeric mixture in 75% yield. The structure and stereochemistry of **19** was unambiguously confirmed by X-ray analysis.

Attempted Wacker oxidation[20] of **19** provided exclusively the aldehyde instead of the expected methyl ketone.[16] Oxidation using $Hg(OAc)_2$, followed by transmetalation using $PdCl_2$,[21] led to an unknown compound. Using $Pd(OAc)_2$, benzoquinone, and $HClO_4$[22] resulted in decomposition, although a small amount of ketone product was observed when the more robust *N*-acetyl or *N*-trifluoroacetyl derivative was used.

We then focused on an Arndt–Eistert homologation (Scheme 2).[23] Thus, compound **19** was treated with LiOH in

Scheme 2. Synthesis of a Tetracyclic Core Structure



THF–MeOH–H_2O to obtain the corresponding acid **20** in excellent yield. Treatment with MsCl led to the corresponding mixed anhydride, which was treated *in situ* with an ethereal solution of diazomethane to afford the corresponding diazoketone in 76% yield.[24,25] In the presence of silver benzoate in methanol, the diazoketone was rearranged to methyl ester **21** in 70% yield.

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Treatment of **21** with Br_2 in chloroform produced the tricyclic bromocarbamate **22**, which was reduced using Raney-Ni to give **23** in 68% overall yield for the two steps. Cleavage of the carbamate and concomitant hydrolysis of the methyl ester under basic conditions, followed by protection to the *N*-Boc product and esterification with diazomethane, led to **24** in 65% overall yield. Oxidation of **24** with the Dess−Martin periodinane gave the fully functionalized aza-octahydropentalene intermediate **25** in excellent yield. Carbamate deprotection in the presence of TFA, followed by addition of cyclohexanone in toluene, led a slow iminium ion-enamine cascade reaction to give the corresponding conjugated iminium intermediate **26**, which was further treated with $NaBH_4$ to afford the tetracyclic compound **27** in 70% yield over two steps. NOESY spectroscopic analysis showed that the newly generated center possesses a β-H. Since calyciphylline B contains an α-oriented hydrogen at the same ring junction, the approach involving hydride reduction of the intermediate iminium ion represented by **26** is not suitable in this series. Nevertheless, the methodology leading to aza-octahydropentalene intermediate **25** should be useful in considering alternative approaches toward some members of the *Daphniphyllum* family of alkaloids.

In conclusion, we have developed a synthetic route to a functionalized aza-octahydropentalene motif, starting with 4-(*R*)-hydroxy-L-proline, as a potential synthetic precursor for calyciphylline B-type alkaloids. Further elaboration of the synthesis adopting an iminium ion-enamine cascade sequence led to a model aza-tetracyclic scaffold. Studies toward the convergent total synthesis of calyciphylline B-type alkaloids exploring other strategies are currently underway in our laboratories.

EXPERIMENTAL SECTION

All nonaqueous reactions were run in flame-dried glassware under a positive pressure of argon. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on commercially available precoated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium ammonium molybdate, iodine, or aqueous potassium permanganate. Flash chromatography was performed on 230−400 mesh silica gel with the indicated solvent systems. Infrared spectra were recorded on an FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer and in some cases on a 700 MHz spectrometer. Chemical shifts for ^1H NMR spectra were recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.27 ppm) and (CD_3OD, δ 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and br = broad) and coupling constant in Hz. Chemical shifts for ^{13}C NMR spectra were recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm) and (CD_3OD, δ 49.00). All spectra were obtained with complete proton decoupling. Optical rotations were determined at 589 nm at ambient temperature. Data are reported as follows: $[\alpha]_D$ concentration (c in g/100 mL), and solvent. High-resolution mass spectra were performed on an LC-MSD-TOF instrument using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Protonated molecular ions $(M + H)^+$ and (or) sodium adducts $(M + Na)^+$ were used for empirical formula confirmation.

(2*S*,3*R*,4*S*)-1-*tert*-Butyl 2-Methyl 3-(but-3-enyl)-4-methylpyrrolidine-1,2-dicarboxylate (14). Alcohol **12** (820 mg, 2.6 mmol) was dissolved in THF (26 mL), and 1-nitro-2-selenocyanatobenzene (680 mg, 2.99 mmol) was added. The solution was cooled to 0 °C, and tributylphosphine (0.75 mL, 2.99 mmol) was added dropwise. The resulting red solution was stirred for 30 min at 0 °C and then additional 3 h at room temperature when TLC analysis indicated full conversion. The product was used in the next reaction.

R_f = 0.4 (hexanes/EtOAc = 70/30), UV visible, [$KMnO_4$]. $[\alpha]_D^{20}$ = +8.3 (c = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29−8.27 (m, 1H), 7.54−7.49 (m, 2H), 7.33−7.29 (m, 1H), 4.31−4.21 (2d, J = 9.4 Hz, 1H), 3.71−3.70 (2s, 3H), 3.53−3.47 (m, 1H), 3.41−3.29 (2dd, J = 10.6, 1.8 Hz, 1H), 2.92 (t, J = 7.4 Hz, 2H), 2.50−2.44 (m, 1H), 2.34−2.27 (m, 1H), 1.83−1.76 (m, 2H), 1.56−1.49 (m, 3H), 1.49−1.39 (2s, 9H), 1.31−1.25 (m, 1H), 1.00 (d, J = 7.3 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 172.3, 154.6, 153.9, 146.9, 133.6, 133.5, 129.0, 126.5, 125.3, 79.9, 79.8, 62.2, 61.8, 53.8, 53.3, 51.5, 45.2, 44.3, 33.9, 28.6, 28.4, 28.3, 26.1, 25.9, 14.3, 14.1; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{22}H_{32}N_2NaO_6Se$ $[M + Na]^+$ 523.1378, found 523.1325.

To a stirred solution of the crude selenide in THF (24 mL) at room temperature was added H_2O_2 (2.4 mL of a 30% solution in water). The solution was stirred vigorously at room temperature for 2 h and quenched by addition of ice−water. It was then extracted with EtOAc (3 times), and the combined organic extracts were washed with brine and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc = 90/10) to give the title compound **14** (579 mg, 75% over two steps) as a colorless liquid.

R_f = 0.7 (hexanes/EtOAc = 70/30), not seen in UV, [$KMnO_4$]. $[\alpha]_D^{20}$ = +6.9 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2930, 1750, 1697, 1640, 1477, 1454, 1393, 1365, 1255,1173, 1148, 1109, 994, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.82−5.72 (m, 1H), 5.05−4.95 (m, 2H), 4.30−4.19 (2d, J = 9.4 Hz, 1H), 3.71−3.70 (2s, 3H), 3.51−3.47 (m, 1H), 3.41−3.28 (2dd, J = 10.6, 1.6 Hz, 1H), 2.52−2.44 (m, 1H), 2.32−2.25 (m, 1H), 2.13−2.07 (m, 2H), 1.57−1.48 (m, 1H), 1.44−1.39 (2s, 9H), 1.36−1.31 (m, 1H), 1.00 (d, J = 7.4 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 172.3, 154.6, 153.9, 138.0, 137.9, 115.1, 115.0, 79.8, 79.7, 62.1, 61.7, 53.3, 51.6, 51.4, 44.4, 43.5, 33.7, 32.0, 32.0, 28.4, 28.2, 25.6, 14.3, 14.1; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{16}H_{27}NNaO_4$ $[M + Na]^+$ 320.1832, found 320.1828.

(2*S*,3*R*,4*S*)-1-*tert*-Butyl 2-Methyl 3-(3-(benzyloxy)-3-oxopropyl)-4-methylpyrrolidine-1,2-dicarboxylate (15). Alkene **14** (2 g, 6.7 mmol) was dissolved in a 3:1 mixture of 1,4-dioxane:water (67 mL, 0.1 M), and $NaIO_4$ (5.8 g, 26.93 mmol) was added. The solution was cooled to 0 °C in an ice bath; then 2,6-lutidine (1.6 mL, 13.4 mmol) and catalytic amounts of OsO_4 (0.2 mL 4 wt % solution in water) were added. The resulting mixture was stirred at 0 °C for 15 min and then for another 4 h at room temperature, at which time TLC analysis indicated full conversion. The reaction mixture was quenched by addition of water and CH_2Cl_2, the biphasic mixture was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic layers were dried over Na_2SO_4, and then concentrated under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 75/25) gave the title compound (1.8 g, 90%) as a colorless liquid.

R_f = 0.3 (hexanes/EtOAc = 70/30), not seen in UV, [$KMnO_4$]. $[\alpha]_D^{20}$ = +4.3 (c = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1H), 4.33−4.23 (2d, J = 9.2 Hz, 1H), 3.71−3.70 (2s, 3H), 3.52−3.48 (2d, J = 6.8 Hz, 1H), 3.40−3.27 (2dd, J = 10.6, 1.7 Hz, 1H), 2.67−2.40 (m, 3H), 2.33−2.25 (m, 1H), 1.79−1.69 (m, 1H), 1.66−1.55 (m, 1H), 1.43−1.38 (2s, 9H), 0.99 (d, J = 7.3 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 201.3, 172.2, 172.0, 154.5, 153.9, 80.0, 80.0, 61.8, 61.4, 53.7, 53.2, 51.8, 51.6, 44.5, 43.7, 42.3, 42.2, 34.0, 28.4, 28.2, 18.9, 18.9, 14.4, 14.2; signal doubling and broadening due to Boc rotamers;

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HRMS (ESIMS): calcd for $C_{15}H_{25}NNaO_5$ $[M + Na]^+$ 322.16249, found 322.16252.

Aldehyde (1.8 g, 6.02 mmol) was dissolved in a 4:1 mixture of *tert*-butanol (196 mL) and 2-methyl-2-butene (24 mL) and cooled to 0 °C. A premixed aqueous solution of NaH_2PO_4 (2.7 g, 22.57 mmol, 15 mL) and $NaClO_2$ (2 g, 22.57 mmol, 15 mL) was added to the reaction mixture, and the biphasic mixture was stirred at 0 °C for 30 min and then at room temperature for another 2 h. The mixture was diluted with water and extracted with EtOAc (3 times). The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave the corresponding carboxylic acid (1.9 g, 99%) that was used without further purification.

$[\alpha]_D^{20}$ = +3.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.34−4.22 (2d, *J* = 9.3 Hz, 1H), 3.70−3.70 (2s, 3H), 3.52−3.47 (2d, *J* = 6.8 Hz, 1H), 3.40−3.27 (2d, *J* = 10.6 Hz, 1H), 2.52−2.35 (m, 3H), 2.32−2.25 (m, 1H), 1.80−1.68 (m, 1H), 1.65−1.56 (m, 1H), 1.43−1.38 (2s, 9H), 0.99 (d, *J* = 7.3 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 172.1, 154.0, 80.1, 80.0, 61.8, 61.3, 53.7, 53.2, 51.8, 51.6, 44.4, 43.6, 34.9, 33.9, 28.4, 28.2, 21.8, 14.3, 14.1; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{15}H_{25}NNaO_6$ $[M + Na]^+$ 338.1574, found 338.1588.

The crude carboxylic acid (1.9 g, 6.02 mmol) was dissolved in DMF (18 mL); cesium carbonate (3.9 g, 12.04 mmol) and benzyl bromide (0.9 mL, 7.24 mmol) were added sequentially. The resulting mixture was stirred for 15 h at room temperature. Water (100 mL) and 1 M aqueous HCl solution were added to adjust to pH 1−2. The mixture was extracted with EtOAc (3 times), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and purification of the residue by flash chromatography (hexanes/EtOAc = 90/10 to 70/30) gave the title compound **15** (2.2 g, 90%) as a colorless liquid.

R_f = 0.5 (hexanes/EtOAc = 70/30); [CAM]; UV visible. $[\alpha]_D^{20}$ = +10.1 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2929, 1735, 1698, 1454, 1391, 1365, 1254, 1162, 1001, 908, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.30 (m, 5H), 5.12 (s, 2H), 4.32−4.22 (2d, *J* = 9.4 Hz, 1H), 3.70−3.69 (2s, 3H), 3.50−3.46 (dd, *J* = 10.6, 6.5 Hz, 1H), 3.41−3.28 (2dd, *J* = 10.6, 1.8 Hz, 1H), 2.50−2.42 (m, 3H), 2.31−2.24 (m, 1H), 1.81−1.70 (m, 1H), 1.68−1.60 (m, 1H), 1.45−1.39 (2s, 9H), 1.00 (d, *J* = 7.3 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 172.8, 172.3, 172.1, 154.5, 153.8, 135.9, 135.8, 128.6, 128.3, 128.2, 127.6, 126.9, 79.9, 79.8, 66.3, 66.3, 61.8, 61.4, 53.7, 53.2, 51.7, 51.5, 44.4, 43.6, 34.9, 33.9, 32.7, 32.6, 28.4, 28.2, 22.0, 14.3, 14.1; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{22}H_{31}NNaO_6$ $[M + Na]^+$ 428.2044, found 428.2052.

(3*S*,3a*R*,6a*S*)-*tert*-Butyl 3-Methyl-6-oxohexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (16). In a flame-dried 500 mL flask and under an argon atmosphere benzyl ester **15** (2 g, 4.94 mmol) was dissolved in THF (500 mL) and cooled to −78 °C. A 0.5 M KHMDS solution in toluene (25 mL 12.35 mmol) was added dropwise, and the resulting yellowish solution was stirred at −78 °C for 1 h. The dry ice bath was removed, and the solution was stirred at room temperature for an additional 1 h. Saturated NH_4Cl was added, and the solution was stirred at room temperature for 15 min until disappearance of the yellow color. The phases were separated, the aqueous phase was extracted with EtOAc (3 times), and the combined organic solutions were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure gave the cyclization product as a mixture of keto and enol tautomers. The residue was dissolved in EtOAc (25 mL). AcOH (140 μL, 2.47 mmol) and $Pd(OH)_2$ 20 wt % on carbon (520 mg, 0.714 mmol) were added, and the resulting suspension was stirred under a hydrogen atmosphere for 12 h (until TLC analysis and NMR analysis of the crude reaction mixture indicated full conversion). The mixture was filtrated over a pad of silica, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc = 70/30). The decarboxylated Dieckmann cyclization product **16** was isolated as a crystalline low melting solid (886 mg, 75%) (mp 30−35 °C).

R_f = 0.3 (hexanes/EtOAc = 60/40); not seen in UV, [$KMnO_4$]. $[\alpha]_D^{20}$ = −152.9 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2967, 2929, 1752, 1690, 1476, 1454, 1389, 1364, 1309, 1255, 1163, 1108, 885, 862, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.10−3.95 (br d, 1H), 3.72 (br. s, 1H), 2.88−2.77 (m, 2H), 2.38−2.30 (m, 3H), 1.95−1.83 (m, 1H), 1.73−1.63 (m, 1H), 1.44 (s, 9H), 1.00 (d, *J* = 7.3 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.7, 212.9, 154.6, 80.0, 64.4, 52.2, 51.4, 44.3, 43.5, 37.1, 35.1, 34.5, 28.3, 19.2, 12.0; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{13}H_{21}NNaO_3$ $[M + Na]^+$ 262.1414, found 262.1414.

(3*S*,3a*R*,6a*S*,*E*)-*tert*-Butyl 6-(2-Ethoxy-2-oxoethylidene)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (17). Bicyclic ketone **16** (800 mg, 3.35 mmol) was dissolved in dry dioxane (33 mL) under an argon-atmosphere. Carbethoxymethylene-triphenylphosphorane (2.9 g, 8.38 mmol) was added, and the resulting solution was warmed to 75 °C for 22 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc = 85/15) to give the title compound **17** (828 mg, 80%) as a colorless liquid.

R_f = 0.7 (hexanes/EtOAc = 80/20); UV visible; [$KMnO_4$]. $[\alpha]_D^{20}$ = −71.5 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39−6.18 (2s, 1H), 4.67−4.48 (2d, *J* = 6.4 Hz, 1H), 4.21−4.07 (m, 2H), 3.80−3.63 (m, 1H), 3.10−2.61 (m, 4H), 2.29−2.21 (m, 1H), 1.76−1.56 (m, 2H), 1.49−1.45 (2s, 9H), 1.29−1.23 (m, 3H), 0.93 (d, *J* = 6.2 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 166.8, 164.9, 164.8, 155.0, 154.4, 116.8, 116.3, 80.0, 79.4, 66.8, 66.4, 59.6, 59.5, 52.0, 51.6, 46.9, 46.2, 34.7, 34.2, 31.5, 30.7, 28.4, 24.0, 23.6, 14.2, 12.6; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{17}H_{27}NNaO_4$ $[M + Na]^+$ 332.1832, found 332.1820.

(3*S*,3a*R*,6a*S*,*E*)-*tert*-Butyl 6-(2-Hydroxyethylidene)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (18). To a stirred solution of **17** (800 mg, 2.59 mmol) in dry dichloromethane (13 mL) at −78 °C was added 1.5 M DIBAL-H in toluene (6 mL, 9.06 mmol) dropwise. The solution was gradually warmed up to −40 °C over 2 h. The reaction was quenched by addition of aqueous saturated MeOH, and the resulting mixture was diluted with aqueous Na/K-tartrate, and then stirred vigorously for 1 h. The biphasic layer was extracted with dichloromethane (3 times), and the combined organic layers was washed with brine and dried over Na_2SO_4. Concentration under reduced pressure and purification of the residue by flash chromatography (hexanes/EtOAc = 60/40) gave the title compound **18** (622 mg, 95%) as a colorless oil.

R_f = 0.2 (hexanes/EtOAc = 70/30), not seen in UV; [CAM] [$KMnO_4$]. $[\alpha]_D^{20}$ = −40.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3424, 2960, 2929, 1666, 1476, 1454, 1391, 1364, 1253, 1164, 1110, 1073, 1004, 874, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08−5.89 (2s, 1H), 4.56−4.40 (2d, *J* = 6.3 Hz, 1H), 4.15−4.07 (m, 2H), 2.82−2.72 (m, 1H), 2.63−2.54 (m, 1H), 2.42−2.15 (m, 3H), 1.70−1.55 (m, 2H), 1.47−1.44 (2s, 9H), 0.97 (d, *J* = 6.5 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.0, 154.8, 146.1, 125.0, 124.3, 79.6, 79.1, 66.1, 65.6, 60.7, 60.6, 51.8, 51.5, 47.1, 46.7, 34.7, 34.4, 28.6, 28.5, 28.5, 27.9, 23.9, 23.5, 12.6; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{15}H_{25}NNaO_3$ $[M + Na]^+$ 290.1727, found 290.1725.

(3*S*,3a*R*,6*R*,6a*S*)-*tert*-Butyl 6-(2-Methoxy-2-oxoethyl)-3-methyl-6-vinylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (19). Allyl alcohol **18** (200 mg, 0.75 mmol) was dissolved in trimethyl orthoacetate (1.9 mL, 15 mmol), and hydroquinone (17 mg, 0.15 mmol) was added. The resulting solution was stirred at 120−125 °C for 2 h. The temperature was raised to 130−135 °C for 5 h while the residual orthoester reagent was allowed to evaporate completely. The resulting yellowish oil was heated at 130−135 °C for another 20 h to give a black tar, which was dissolved in EtOAc and concentrated under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc = 95:5) to give the title compound as an ∼7:3 mixture of diastereoisomers (182 mg, 75%). Flash chromatography (hexanes/EtOAc = 100:0 to 95:5) allowed the separation of the diastereoisomers to give the desired major isomer **19**

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in pure form as a crystalline low melting solid (colorless needles, mp 20−30 °C).

Analytical Data of the Major Diastereoisomer. R_f = 0.48 (hexanes/EtOAc = 80/20); not seen in UV; [$KMnO_4$]. $[\alpha]_D^{20}$ = −45.3 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2929, 1763, 1690, 1453, 1391, 1364, 1162, 1109, 1073, 998, 909, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dd, *J* = 17.6, 10.9, 1H), 5.04−4.96 (m, 2H), 4−19−4.12 (m, 1H), 3.81−3.58 (m, 1H), 3.62−3.59 (2s, 3H), 2.98−2.76 (2d, *J* = 14.6 Hz, 1H), 2.75−2.65 (m, 1H), 2.61−2.50 (m, 2H), 2.14−2.06 (m, 1H), 2.01−1.93 (m, 1H), 1.73−1.66 (m, 1H), 1.55−1.51 (m, 1H), 1.47−1.42 (2s, 9H), 0.94−0.91 (m, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 172.3, 154.5, 154.2, 139.9, 139.8, 113.0, 112.5, 79.7, 78.9, 71.1, 70.6, 52.0, 51.6, 51.5, 51.2, 51.2, 51.0, 48.8, 47.5, 43.6, 43.2, 35.4, 35.1, 34.5, 34.1, 28.6, 28.4, 24.3, 24.0, 12.2; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{16}H_{27}NNaO_4$ $[M + Na]^+$ 320.1832, found 320.1828.

Analytical Data of the Minor Diastereoisomer. R_f = 0.50 (hexanes/EtOAc = 80/20); not seen in UV; [$KMnO_4$]. $[\alpha]_D^{20}$ = −17.4 (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 6.15−5.95 (broad m, 1H), 5.09−5.01 (m, 2H), 4.20−4.08 (m, 1H), 3.93−3.72 (m, 1H), 3.58 (s, 3H), 2.72−2.53 (m, 3H), 2.29−2.22 (m, 1H), 2.17−2.05 (m, 1H), 1.88 (broad s, 1H), 1.64−1.52 (m, 2H), 1.48−1.45 (m, 9H), 0.96 (d, *J* = 6.9 Hz, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 172.7, 155.3, 154.9, 143.8, 143.4, 113.0, 80.0, 79.3, 71.9, 71.7, 53.5, 52.8, 52.5, 51.9, 51.1, 47.5, 46.1, 40.0, 35.6, 35.0, 34.2, 34.1, 28.4, 23.2, 12.6; signal doubling and broadening due to Boc rotamers.

2-((3*S*,3a*R*,6*R*,6a*S*)-1-(*tert*-Butoxycarbonyl)-3-methyl-6-vinyloctahydrocyclopenta[*b*]pyrrol-6-yl)acetic Acid (20). To a stirred solution of methyl ester **19** (100 mg, 0.31 mmol) in a 4:1 mixture of THF−MeOH (6.5 mL) was added an aqueous 1.0 M LiOH solution (1.5 mL, 1.5 mmol), and the resulting mixture was stirred at room temperature for 45 h. After complete consumption of the starting material, the reaction mixture was adjusted with aqueous 1 M HCl to pH 1−2. Extraction with EtOAc (3 times) and processing in the usual manner gave an oil, which was purified by flash column chromatography with 40% EtOAc in hexanes, to give compound **20** (83 mg, 97%) as a colorless solid.

R_f = 0.2 (hexanes/EtOAc = 70/30); not seen in UV; [$KMnO_4$]. $[\alpha]_D^{20}$ = −40.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3081, 2963, 2874, 1728, 1689, 1477, 1452, 1405, 1365, 1308, 1252, 1223, 1162, 1112, 1001, 944, 911, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.80−5.71 (m, 1H), 5.06−4.99 (m, 2H), 4.22−4.13 (2d, *J* = 8.2 Hz, 1H), 3.80−3.58 (2dd, *J* = 10.6, 7.4 Hz, 1H), 2.94−2.76 (d, *J* = 14.7 Hz, 1H), 2.73−2.53 (m, 3H), 2.16−2.05 (m, 1H), 2.03−1.94 (m, 1H), 1.75−1.67 (m, 1H), 1.58−1.49 (m, 2H), 1.46−1.41 (2s, 9H), 0.91 (m, 3H); signal doubling and broadening due to Boc rotamers; ^{13}C NMR (100 MHz, CDCl3): δ = 177.6, 177.2, 154.7, 154.3, 139.5, 139.5, 112.9, 112.7, 79.9, 79.2, 70.7, 70.5, 52.0, 51.5, 51.2, 51.1, 48.8, 47.4, 43.6, 43.0, 35.6, 35.3, 34.4, 34.1, 28.5, 28.4, 24.2, 24.0, 12.2; signal doubling and broadening due to Boc rotamers; HRMS (ESIMS): calcd for $C_{17}H_{27}NNaO_4$ $[M + Na]^+$ 332.1832, found 332.1829.

(3*S*,3a*R*,6*R*,6a*S*)-*tert*-Butyl 6-(3-Methoxy-3-oxopropyl)-3-methyl-6-vinylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (21). To a stirred solution of compound **20** (100 mg, 0.323 mmol) in THF (1.5 mL) at 0 °C were added Et_3N (135 μL, 1.00 mmol) and MsCl (50 μL, 0.646 mmol) successively. After 1 h, a concentrated ethereal solution of CH_2N_2 was added, and the reaction mixture was gradually warmed to room temperature over 1 h. Water was added, extracted with EtOAc, dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash column chromatography with 25% EtOAc in hexanes to give the diazoketone intermediate (81 mg, 76%) as a yellow liquid. R_f = 0.3 (30% EtOAc in hexanes), UV visible, [$KMnO_4$]. $[\alpha]_D^{20}$ = −42.1 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2961, 2873, 2097, 1727, 1684, 1637, 1477, 1452, 1401, 1362, 1322, 1255, 1161, 1110, 944, 901, 866, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.87−5.71 (m, 1H), 5.50−5.15 (2brs, 1H), 5.09−4.96 (m, 2H), 4.16 (dd, *J* = 11.6, 8.3 Hz, 1H), 3.84−3.56 (2dd, *J* = 10.9, 7.3 Hz, 1H), 2.95−2.62 (m, 2H), 2.60−2.46 (m, 2H), 2.09 (sept, *J* = 6.3 Hz, 1H), 2.01−1.89 (m, 1H), 1.82−1.69 (m, 1H), 1.60−1.50 (m, 2H), 1.49−1.40 (2s, 9H), 0.95−0.88 (2d, *J* = 5.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 193.3, 154.7, 154.2, 140.1, 113.0, 79.67, 79.0, 71.2, 70.9, 55.8, 53.2, 52.5, 52.1, 52.1, 51.6, 51.6, 48.7, 47.4, 34.8, 34.7, 34.5, 34.2, 28.6, 28.5, 28.2, 24.1, 23.9, 12.3; HRMS (ESIMS): calcd for $C_{18}H_{28}N_3O_3$ $[M + H]^+$ 334.2125, found 334.2133. Signal doubling and broadening due to Boc rotamers was observed in NMR.

To a stirred solution of the diazoketone compound (64 mg, 0.193 mmol) in dry MeOH (1 mL) at 0 °C was added a solution of AgOBz (9 mg, 0.039 mmol) and Et_3N (140 μL, 1.00 mmol) in MeOH (0.5 mL) by cannula. The reaction mixture was gradually warmed to rt over 1 h and stirred for an additional 1 h at the same temperature. Methanol was evaporated; the residue was dissolved in water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography to afford compound **21** (45 mg, 70%) as a colorless liquid.

R_f = 0.65 (20% EtOAc in hexanes), not seen in UV, [$KMnO_4$]. $[\alpha]_D^{20}$ = −17.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2961, 2883, 1742, 1692, 1475, 1438, 1404, 1376, 1365, 1225, 1164, 1111, 913, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 5.79−5.59 (m, 1H), 5.10−4.86 (m, 2H), 4.00 (2d, *J* = 8.0 Hz, 1H), 3.83−3.55 (m, 1H), 3.61 (d, *J* = 7.4 Hz, 3H), 2.67 (sept, *J* = 8.5 Hz, 1H), 2.51 (q, *J* = 11.3 Hz, 1H), 2.30−2.00 (m, 4H), 1.90−1.75 (m, 1H), 1.74−1.58 (m, 1H), 1.46 (2s, 9H), 1.35−1.25 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.4, 154.3, 140.3, 139.9, 113.4, 113.03, 79.6, 78.8, 71.8, 71.7, 53.5, 52.8, 52.2, 51.5, 51.4, 48.3, 47.1, 34.7, 34.6, 34.4, 34.2, 33.7, 33.5, 30.3, 30.0, 29.6, 28.5, 28.4, 23.7, 23.6, 12.3, 12.2; HRMS (ESIMS): calcd for $C_{19}H_{31}NNaO_4$ $[M + Na]^+$ 360.2145, found 360.2152. Signal doubling and broadening due to Boc rotamers was observed in NMR.

Methyl 3-((2a*R*,2a1*S*,3*S*,7a*S*)-7-(Bromomethyl)-3-methyl-5-oxooctahydro-1*H*-6-oxa-4a-azacyclopenta[*cd*]inden-7a-yl)-propanoate (22). To a stirred solution of compound **21** (120 mg, 0.356 mmol) in $CHCl_3$ (17 mL) at −30 °C was added bromine (43 μL, 0.534 mmol) dropwise, and the mixture was gradually warmed up to 0 °C over 2 h. After complete disappearance of starting material, the reaction mixture was quenched with $Na_2S_2O_3$ and extracted with $CHCl_3$ (3 times). The organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and finally purified by flash column chromatography with 70% EtOAc in hexanes to afford the title compound **22** (115 mg, 90%) as a colorless liquid.

R_f = 0.15 (50% EtOAc in hexanes), UV visible, [$KMnO_4$]. $[\alpha]_D^{20}$ = +20.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2959, 2887, 1735, 1694, 1420, 1438, 1320, 1279, 1245, 1181, 1141, 1107, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.48 (dd, *J* = 8.3, 2.4 Hz, 1H), 3.68 (s, 3H), 3.60−3.49 (m, 3H), 3.30 (dd, *J* = 11.3, 8.4 Hz, 1H), 3.21 (t, *J* = 10.7 Hz, 1H), 2.63 (dt, *J* = 9.6, 4.9 Hz, 1H), 2.50−2.40 (m, 1H), 2.39−2.32 (m, 2H), 1.86 (dd, *J* = 15.9, 7.8 Hz, 2H), 1.82−1.71 (m, 2H), 1.58−1.36 (m, 2H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.8, 152.2, 79.1, 69.5, 53.4, 52.1, 46.7, 46.1, 33.6, 30.0, 29.9, 28.7, 28.6, 20.9, 14.0; HRMS (ESIMS): calcd for $C_{15}H_{22}BrNNaO_4$ $[M + Na]^+$ 382.0624, found 382.0622.

Methyl 3-((2a*R*,2a1*S*,3*S*,7a*S*)-3,7-Dimethyl-5-oxooctahydro-1*H*-6-oxa-4a-azacyclopenta[*cd*]inden-7a-yl)propanoate (23). Raney-Ni (120 mg) was taken in a round-bottom flask and washed thrice with H_2O, followed by MeOH. Compound **22** (60 mg, 0.167 mmol) in MeOH (4 mL) was cannulated into the heterogeneous methanolic suspension of Raney-Ni, and a H_2 balloon was placed over the reaction. After 3 h, the reaction mixture was filtered through Celite, and the pad was washed with MeOH, filtered, concentrated under reduced pressure, and purified by flash column chromatography with EtOAc to give the title compound **23** (35 mg, 75%) as a colorless liquid.

R_f = 0.2 (70% EtOAc in hexanes), not seen in UV, [$KMnO_4$]. $[\alpha]_D^{20}$ = −9.1 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2961, 2885, 1737, 1684, 1420, 1387, 1320, 1298, 1201, 1186, 1108, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 4.37 (q, *J* = 6.4 Hz, 1H), 3.66 (s, 3H), 3.55−3.46 (m, 2H), 3.23 (t, *J* = 10.6 Hz, 1H), 2.61 (dt, *J* = 9.9, 8.4 Hz, 1H), 2.51−2.37 (m, 1H), 2.29 (t, *J* = 8.4 Hz, 2H), 1.88−1.69 (m, 4H),

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1.54−1.43 (m, 1H), 1.44−1.30 (m, 1H), 1.24 (d, J = 6.4 Hz, 3H), 1.00 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.1, 153.4, 75.4, 69.4, 53.3, 51.9, 47.3, 45.7, 33.7, 30.23, 28.6, 28.4, 20.8, 16.4, 14.2; HRMS (ESIMS): calcd for $C_{15}H_{23}NNaO_4$ $[M + Na]^+$ 304.1519, found 304.1518.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-((*S*)-1-Hydroxyethyl)-6-(3-methoxy-3-oxopropyl)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (24). To a stirred solution of compound **23** (20 mg, 0.071 mmol) in dioxane (1.2 mL) was added 2.5 M aqueous KOH (0.4 mL), and the solution was heated to 70 °C. After 3 h, the reaction mixture was cooled down to room temperature and diluted five times with 1:1 dioxane−water. Then, excess $(Boc)_2O$ (0.2 mL) was added and the reaction mixture was stirred for another 3 h, then neutralized with HCl and extracted with EtOAc (3 times). The combined extracts were dried over Na_2SO_4, concentrated under reduced pressure, and dried. The crude product was dissolved in diethyl ether and cooled down to 0 °C, and an ethereal solution of diazomethane was added. After 1 h, water was added to the reaction mixture and extracted thrice with diethyl ether. The ether layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography with 25% EtOAc−hexanes to give the title compound **24** (17 mg, 65%) as a colorless liquid

R_f = 0.25 (30% EtOAc in hexanes), not seen in UV, $[KMnO_4]$. $[\alpha]_D^{20}$ = −19.6 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3391, 2961, 2886, 1736, 1687, 1453, 1400, 1364, 1253, 1160, 1112, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.06 (d, J = 7.0 Hz, 1H), 3.83 (brs, 2H), 3.65 (s, 3H), 2.77−2.70 (m, 1H), 2.67 (t, J = 11.6 Hz, 1H), 2.62−2.50 (m, 1H), 2.32−2.21 (m, 1H), 2.16−2.06 (m, 1H), 1.97 (s, 1H), 1.67−1.49 (m, 4H), 1.46 (s, 9H), 1.34−1.25 (m, 1H), 1.14 (d, J = 6.7 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 174.6, 156.4, 80.6, 71.0, 69.2, 54.3, 53.3, 51.6, 47.2, 35.6, 31.8, 29.2, 28.4, 23.0, 18.7, 12.6; HRMS (ESIMS): calcd for $C_{19}H_{33}NNaO_5$ $[M + Na]^+$ 378.2251, found 378.2265. Signal doubling and broadening due to Boc rotamers was observed in NMR.

(3*S*,3a*R*,6*S*,6a*S*)-*tert*-Butyl 6-Acetyl-6-(3-methoxy-3-oxopropyl)-3-methylhexahydrocyclopenta[*b*]pyrrole-1(2*H*)-carboxylate (25). To a stirred solution of compound **24** (15 mg, 0.042 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added DMP (53 mg, 0.127 mmol), and the mixture was gradually warmed up to room temperature over 1 h. The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$, further stirred for 30 min at room temperature, and extracted with dichloromethane (3 times). The organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and purified by a flash column chromatography with 25% EtOAc in hexanes to afford compound **25** (14 mg, 95%) as a colorless liquid.

R_f = 0.27 (30% EtOAc in hexanes), not seen in UV, $[KMnO_4]$. $[\alpha]_D^{20}$ = +7.3 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2958, 1737, 1691, 1453, 1390, 13641160, 1111, 771, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.22 (2 brs, 1H), 3.66 (s, 3H), 3.65 (2 brs, 1H), 2.78−2.57 (m, 2H), 2.52 (t, J = 11.6 Hz, 1H), 2.25−2.00 (m, 7H), 1.92 (s, 1H), 1.75 (s, 1H), 1.57 (s, 1H), 1.42 (s, 9H), 0.94 (d, J = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 210.8, 173.4, 155.2, 80.6, 79.8, 72.8, 72.1, 63.5, 62.8, 52.2, 51.7, 48.5, 47.4, 35.0, 34.5, 33.5, 32.2, 30.7, 29.7, 28.3, 27.7, 24.7, 12.2; HRMS (ESIMS): calcd for $C_{19}H_{31}NNaO_5$ $[M + Na]^+$ 376.2094, found 376.2100. Signal doubling and broadening due to Boc rotamers was observed.

Methyl 3-((2*S*,2a*R*,2a1*S*,4a*R*)-2,5-Dimethyl-1,2,2a,2a1,3,4,4a,6,7,8,9,9a-dodecahydrobenzo[*e*]cyclopenta-[*hi*]indolizin-4a-yl)propanoate (27). To a stirred solution of compound **25** (5 mg, 0.014 mmol) in CH_2Cl_2 (0.75 mL) at 0 °C was added TFA (0.25 mL), and the solution was gradually warmed up to room temperature over 2 h. The excess TFA was removed by azeotropic removal with dry CH_2Cl_2, and the crude residue was used for the next step.

R_f = 0.5 (16% MeOH in $CHCl_3$), not seen in UV, $[KMnO_4]$. $[\alpha]_D^{20}$ = +14.2 (c = 0.5, $CHCl_3$); IR (neat): ν_{max} = 2931, 1741, 1679, 1441, 1367, 1203, 1175, 1136, 834, 800, 762, 699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ = 3.98 (d, J = 5.1 Hz, 1H), 3.67 (s, 3H), 3.00−2.91 (m, 1H), 2.75 (t, J = 11.7 Hz, 1H), 2.58−2.45 (m, 1H), 2.41−2.28 (m, 1H), 2.22 (s, 3H), 2.20−2.10 (m, 3H), 2.08−1.92 (m, 4H), 1.81−1.69 (m, 1H), 1.11 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ = 212.3, 174.4, 70.5, 65.1, 52.3, 51.2, 46.8, 36.5, 34.1, 32.0, 29.8, 26.9, 21.9, 12.7; HRMS (ESIMS): calcd for $C_{14}H_{24}NO_3$ $[M + H]^+$ 254.1751, found 254. 1755.

To a stirred solution of the preceding compound in toluene (1 mL) at room temperature was added cyclohexanone (50 μL, 0.5 mmol), and the reaction mixture was stirred for 24 h. After complete disappearance of starting material, MeOH (1 mL) was added and the solution was cooled down to 0 °C. $NaBH_4$ (60 mg, 1.5 mmol) was added to the reaction mixture and stirred for additional 1 h. The reaction mixture was quenched with aqueous saturated NH_4Cl solution, followed by addition of excess aqueous saturated $NaHCO_3$ solution, and stirred for 30 min. The biphasic layers were extracted with chloroform (3 times), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography with 7.5% MeOH in $CHCl_3$ to give the title compound **27** (3.3 mg, 70%) as an orange liquid.

R_f = 0.5 (5% MeOH in $CHCl_3$), not seen in UV, $[KMnO_4]$. $[\alpha]_D^{20}$ = −7.5 (c = 1.0, MeOH); IR (neat): ν_{max} = 2934, 2862, 2369, 2115, 1743, 1457, 1372, 1295, 1229, 1172, 1053, 763, 632 cm^{-1}; ^{1}H NMR (700 MHz, CD_3OD) δ = 3.65 (s, 3H), 2.90 (d, J = 12.5 Hz, 1H), 2.79 (d, J = 6.2 Hz, 1H), 2.71 (d, J = 15.3 Hz, 2H), 2.57 (t, J = 8.1 Hz, 1H), 2.51−2.46 (m, 1H), 2.34 (dt, J = 15.0, 7.4 Hz, 1H), 2.26−2.20 (m, 1H), 2.06−2.00 (m, 1H), 2.00−1.95 (m, 1H), 1.82−1.75 (m, 4H), 1.76−1.71 (m, 1H), 1.71−1.63 (m, 4H), 1.62 (dd, J = 4.7, 2.9 Hz, 3H), 1.44−1.36 (m, 1H), 1.27−1.19 (m, 2H), 1.00 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ = 176.2, 132.2, 129.2, 72.5, 60.1, 57.5, 52.1, 50.5, 45.8, 40.5, 34.6, 33.3, 32.7, 30.6, 28.3, 26.8, 25.3, 24.7, 16.0, 14.0; HRMS (ESIMS): calcd for $C_{20}H_{32}NO_2$ $[M + H]^+$ 318.2428, found 318.2437.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02875.

NMR spectra and X-ray crystallographic data for all the new compounds (PDF)
Crystallographic data for $C_{18}H_{29}NO_4$ (PDF)
Crystallographic data for $C_{13}H_{21}NO_3$ (PDF)
Crystallographic data for $C_{13}H_{21}NO_3$ (CIF)
Crystallographic data for $C_{18}H_{29}NO_4$ (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kang, B.; Jakubec, P.; Dixon, D. J. *Nat. Prod. Rep.* **2014**, *31*, 550−562. (b) Wu, H.; Zhang, X.; Ding, L.; Chen, S.; Yang, J.; Xu, X. *Planta Med.* **2013**, *79*, 1589−1598. (c) Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936−962.

(2) (a) Suzuki, K. T.; Okuda, S.; Niwa, H.; Toda, M.; Hirata, Y.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 799−802. (b) Niwa, H.; Hirata, Y.; Suzuki, K. T.; Yamamura, S. *Tetrahedron Lett.* **1973**, *14*, 2129−2132. (c) Heathcock, C. H. *Proc. Natl. Acad. Sci. U. S. A.* **1996**, *93*, 14323−14327. (d) Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532−1534.

DOI: 10.1021/acs.joc.5b02875
J. Org. Chem. 2016, 81, 2182−2188

(3) (a) Heathcock, C. H.; Stafford, J. A.; Clark, D. L. *J. Org. Chem.* **1992**, *57*, 2575−2585. (b) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650−5651. (c) Heathcock, C. H.; Ruggeri, R. B.; McClure, K. F. *J. Org. Chem.* **1992**, *57*, 2585−2594. (d) Heathcock, C. H.; Stafford, J. A. *J. Org. Chem.* **1992**, *57*, 2566−2574. (e) Heathcock, C. H.; Kath, J. C.; Ruggeri, R. B. *J. Org. Chem.* **1995**, *60*, 1120−1130.

(4) Recent examples of core structure synthesis: (a) Diaba, F.; Martínez-Laporta, A.; Coussanes, G.; Fernandez, I.; Bonjoch, J. *Tetrahedron* **2015**, *71*, 3642−3651 and references cited therein. (b) Stockdill, J. L.; Lopez, A. M.; Ibrahim, A. A. *Tetrahedron Lett.* **2015**, *56*, 3503−3506 and references cited therein. (c) Ma, D.; Cheng, H.; Huang, C.; Xu, L. *Tetrahedron Lett.* **2015**, *56*, 2492−2495. (d) Wang, W.; Li, G.-P.; Wang, S.-F.; Shi, Z.-F.; Cao, X.-P. *Chem. - Asian J.* **2015**, *10*, 377−382. (e) Hayakawa, I.; Niida, K.; Kigoshi, H. *Chem. Commun.* **2015**, *51*, 11568−11571. (f) Guo, J.-J.; Li, Y.; Cheng, B.; Xu, T.; Tao, C.; Yang, X.; Zhang, D.; Yan, G.; Zhai, H. *Chem. - Asian J.* **2015**, *10*, 865−868. (g) Wang, L.; Xu, C.; Chen, L.; Hao, X.; Wang, D. Z. *Org. Lett.* **2014**, *16*, 1076−1079 and references cited therein. (h) Xiong, X.; Li, Y.; Lu, Z.; Wan, M.; Deng, J.; Wu, S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294−5297. (i) Li, H.; Qiu, Y.; Zhao, C.; Yuan, Z.; Xie, X.; She, X. *Chem.—Asian J.* **2014**, *9*, 1274−1277 and references cited therein. (j) Williams, D. R.; Mondal, P. K.; Bawel, S. A.; Nag, P. P. *Org. Lett.* **2014**, *16*, 1956−1959. (k) Dorich, S.; Del Valle, J. R.; Hanessian, S. *Synlett* **2014**, *25*, 799−804. (l) Hanessian, S.; Dorich, S.; Menz, H. *Org. Lett.* **2013**, *15*, 4134−4137. (m) Yang, M.; Wang, l.; He, Z.-H.; Wang, S.-H.; Zhang, S.-Y.; Tu, Q.-Y.; Zhang, F.-M. *Org. Lett.* **2012**, *14*, 5114−5117. (n) Yao, Y.; Liang, G. *Org. Lett.* **2012**, *14*, 5499−5501. (o) Darses, B.; Michaelides, I. N.; Sladojevich, F.; Ward, J. W.; Rzepa, P. R.; Dixon, D. *Org. Lett.* **2012**, *14*, 1684−1687 and references cited therein. (p) Bélanger, G.; Boudreault, J.; Lévesque, F. *Org. Lett.* **2011**, *13*, 6204−6207. (q) Coldham, I.; Watson, L.; Adams, H.; Martin, N. G. *J. Org. Chem.* **2011**, *76*, 2360−2366 and references cited therein. (r) Ikeda, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Org. Lett.* **2009**, *11*, 1833−1836. (s) Dunn, T. B.; Ellis, J. M.; Kofink, C. C.; Manning, J. R.; Overman, L. E. *Org. Lett.* **2009**, *11*, 5658−5661. (t) Denmark, S. E.; Baiazitov, R. Y.; Nguyen, S. T. *Tetrahedron* **2009**, *65*, 6535−6548 and references cited therein. (u) Ueda, M.; Walczak, M. A. A.; Wipf, P. *Tetrahedron Lett.* **2008**, *49*, 5986−5989.

(5) Weiss, M. E.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11501−11505.

(6) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679−684.

(7) (a) Shvartsbart, A.; Smith, A. B., III *J. Am. Chem. Soc.* **2015**, *137*, 3510−3519. (b) Shvartsbart, A.; Smith, A. B., III *J. Am. Chem. Soc.* **2014**, *136*, 870−873.

(8) Chattopadhyay, A. K.; Ly, V. L.; Jakkepally, S.; Berger, G.; Hanessian, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 2577−2581.

(9) Morita, H.; Kobayashi, J. *Org. Lett.* **2003**, *5*, 2895−2898.

(10) Yang, S.-P.; Yue, J.-M. *J. Org. Chem.* **2003**, *68*, 7961−7966.

(11) Chen, X.; Zhan, Z.-J.; Yue, J.-M. *Helv. Chim. Acta* **2005**, *88*, 854−860.

(12) Zhang, C.-R.; Yang, S.-P.; Yue, J.-M. *J. Nat. Prod.* **2008**, *71*, 1663−1668.

(13) Hanessian, S.; Chattopadhyay, A. K. *Org. Lett.* **2014**, *16*, 232−235.

(14) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

(15) Schaefer, J. P.; Bloomfield, J. J. *Organic Reactions*; John Wiley and Sons: New York, 1967; Vol. *15*, p 1203.

(16) See the Supporting Information.

(17) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898.

(18) (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927−1928. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481−1487. See also: (c) Hanessian, S.; Dorich, S.; Chattopadhyay, A. K.; Büschleb, M. *J. Org. Chem.* **2013**, *78*, 8915−8921.

(19) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.-t.; Faulkner, J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743. (b) Selig, P.; Bach, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5082−5084.

(20) Tsuji, J.; Nagashima, H.; Nemoto, H. *Org. Synth., Coll.* **1990**, *7*, 137; **1984**, *62*, 9.

(21) Crimmins, M. T.; Brown, B. *J. Am. Chem. Soc.* **2004**, *126*, 10264−10266.

(22) Miller, D. G.; Wayner, D. D. M. *J. Org. Chem.* **1990**, *55*, 2924−2927.

(23) (a) Arndt, F.; Eistert, B. *Ber. Dtsch. Chem. Ges. B* **1935**, *68*, 200−208. (b) Velthuisen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10640−10641. (c) Cesar, J.; Dolenc, M. S. *Tetrahedron Lett.* **2001**, *42*, 7099−7102.

(24) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202−2211. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Fong, K. C.; He, Y.; Yoon, W. H. *Org. Lett.* **1999**, *1*, 883−886.

(25) (a) No other active esters or acid chlorides were found to be so much efficient in that process. A mixed anhydride or acid chloride formation with isobutyl- and ethylchloroformate or oxalyl chloride gave only 10% yield of diazoketone. (b) A concentrated diazomethane solution is necessary to achieve a good yield of the product.

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