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SmI_2-Mediated Radical Coupling Strategy to Securinega Alkaloids: Total Synthesis of (−)-14,15-Dihydrosecurinine and Formal Total Synthesis of (−)-Securinine

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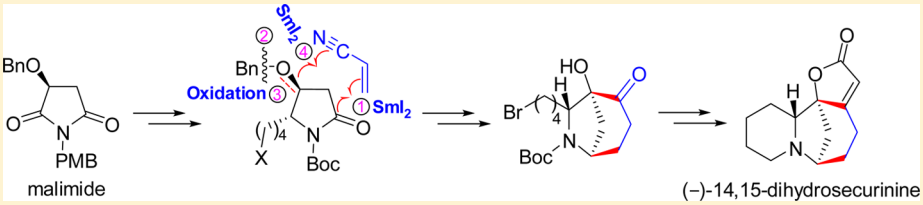
Supporting Information



ABSTRACT: The asymmetric total synthesis of (−)-14,15-dihydrosecurinine and the formal total synthesis of (−)-securinine were accomplished starting from an easily available malimide. A concise SmI_2-mediated radical coupling strategy has been developed to construct the bridged α-hydroxy 6-azabicyclo[3.2.1]octanone in four steps with high diastereoselectivity.

INTRODUCTION

The Securinega alkaloid was initially isolated in 1956 from the leaves of *Securinega suffructicosa*.[1] Since then, more than 40 Securinega alkaloids[2] have been discovered from the plants of the Euphorbiaceae family. Most of these alkaloids can be classified as securinine-type (**1**) or norsecurinine-type (**2**), both of which feature a bridged tetracyclic scaffold (Figure 1). Among the Securinega alkaloids, (−)-securinine (**5**)[3] is widespread and abundant in Euphorbiaceae and exhibits a wide range of pharmacological activities, such as a central nervous system (CNS) stimulant and antimalarial, antibacterial, and cytotoxic properties.[4] Because of its promising biological activities, (−)-securinine has received considerable attention from the synthetic community,[2,5] and several racemic[6] and asymmetric[7] total syntheses have been developed. (−)-14,15-Dihydrosecurinine (**6**) was obtained along with (−)-securinine from the roots of *Securinega suffructicosa*.[8] It is a potent CNS stimulant and an acute poison,[8] and has been used as [^{3}H]GABA[9] and AChE inhibitors.[10] Despite its interesting biological activities, the total synthesis of **6** has not been reported. Only a few semisynthetic routes from securinine via catalytic hydrogenation[11] or reduction with $NaBH_4$[12] or reductases[13] have been reported.

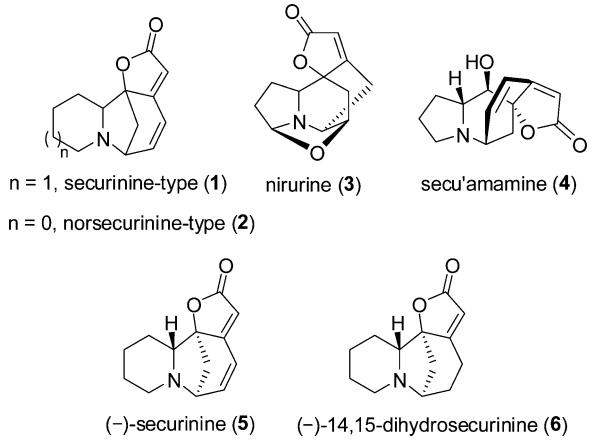


Figure 1. Skeletal frameworks and some structures of Securinega alkaloids.

Four asymmetric total syntheses of (−)-securinine (**5**) have been reported (Scheme 1).[7] Based on (+)-pipecolinic acid derivatives, Honda and co-workers accomplished the diastereoselective synthesis of (−)-securinine.[7d] The synthesis developed by Alibés and March also started from a (+)-pipecolinic acid derivative (**8**).[7c] Thadani and co-workers have recently reported an asymmetric route starting from *trans*-4-hydroxy-L-proline (**9**).[7b] Whereas all the above-mentioned work has started from chiral amino acid derivatives, Bayón and Figueredo have developed a concise enantioselective synthesis using a palladium-catalyzed enantioselective allylation reaction as the key step.[7a]

For the syntheses of securinine-type (**1**) and norsecurinine-type (**2**) alkaloids, the key is to construct ring C. To this aim, many powerful intramolecular ring-closure methods, such as

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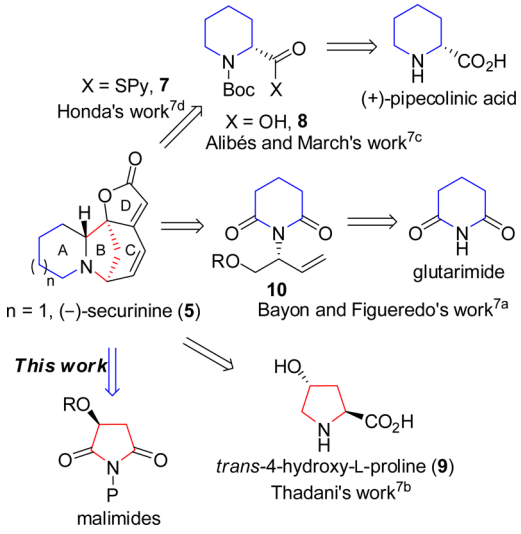
Scheme 1. Asymmetric Total Syntheses of (−)-Securinine (5)



Diels−Alder cycloaddition,[6d,14] aldol condensation,[15] ring-closing olefin metathesis,[6c,16] and Heck reactions,[7b,c] have been employed. Only one radical-based cyclization method has been applied by Weinreb's group in their total synthesis of (+)-14,15-dihydronorsecurinine, (−)-norsecurinine, and (−)-phyllanthine.[17] The C ring of these alkaloids were constructed through a SmI_2-mediated[18] intramolecular pinacol-type coupling of ketonitrile[19] **11** (Figure 2). Inspired by this

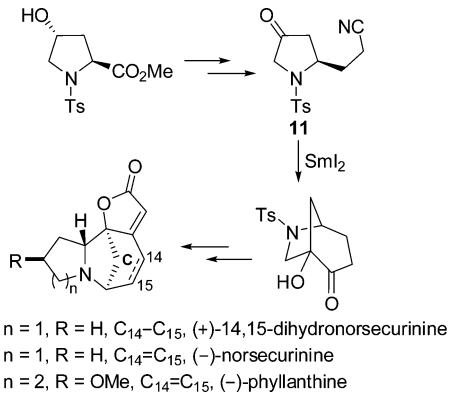
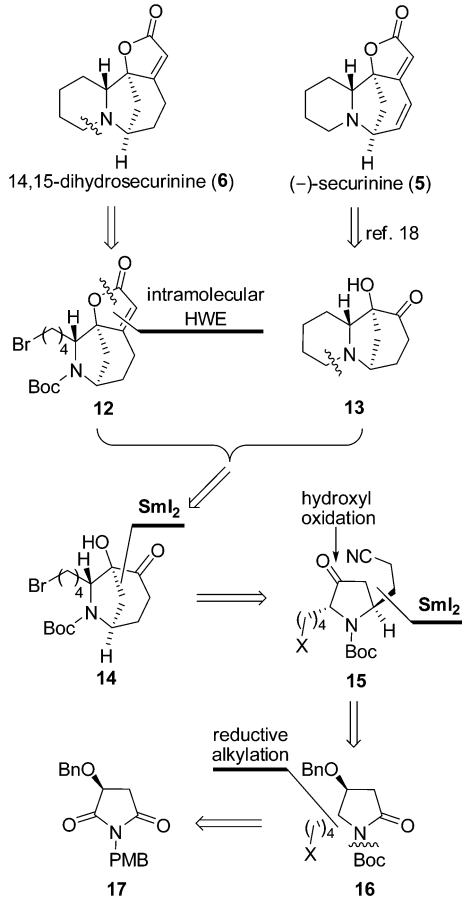


Figure 2. Weinreb's reductive coupling of ketonitrile **11**.

work, and with our continued interest in the application of SmI_2-mediated radical coupling reactions for organic synthesis,[20] we report herein the asymmetric total synthesis of (−)-14,15-dihydrosecurinine (**6**) and the formal synthesis of (−)-securinine (**5**).

In our retrosynthetic analysis of **6** (Scheme 2), ring A was envisioned to arise from an intramolecular S_N2 reaction of an amine and a tethered alkyl bromide. Intramolecular olefination reaction could be used to construct the butenolide ring D as pioneered by Weinreb[17] then by Kerr in their syntheses of Securinega alkaloids.[16a,b] Annulation of ring C could be accomplished through Weinreb's reductive coupling of ketonitrile **15**. The key intermediate **15** could be synthesized from known malimide **17** by installing the two side chains through methods developed in our laboratory.[20,21] Cyclization

Scheme 2. Retrosynthetic Analysis of 14,15-Dihydrosecurinine (6) and (−)-Securinine (5)



of **14** would allow for the access of tricyclic amine **13**, from which (−)-securinine (**5**) had been synthesized in four steps.[22]

Although Weinreb's method is used to close the ring C, our work employs a different annulation strategy and methods developed in our own laboratory for the efficient access of the key intermediate **15**. To construct the bridged tetracyclic scaffold of securinine and 14,15-dihydrosecurinine, our annulation strategy is B → A → C → D → A, whereas Weinreb used B → C → A → D in syntheses of (+)-14,15-dihydronorsecurinine, (−)-norsecurinine, and (−)-phyllanthine.[17] Importantly, for the synthesis of 14,15-dihydrosecurinine (**6**), we used six and four steps to construct rings A and C, respectively. For the same target, Weinreb's strategy required ten and seven steps to construct these two rings, respectively. As a result, we completed the total synthesis of **6** in 12 steps, whereas Weinreb employed 19 steps for (+)-14,15-dihydronorsecurinine.

RESULTS AND DISCUSSION

Our synthesis started with treating optically pure malimide **17**[23] with Grignard reagent **I**/ **II**, followed by reduction with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ to afford γ-lactams **18a**/**18b** in good yields with high regio- and diastereoselectivity (Scheme 3). The (*tert*-butyl)dimethylsilyl group was also cleaved by excess $BF_3{\cdot}Et_2O$ during the reduction step.

Attempts to remove the benzyl group of **18a** and **18b** under the catalytic transfer hydrogenation conditions (HCOOH/MeOH, 10% Pd/C, rt) or catalytic hydrogenation conditions

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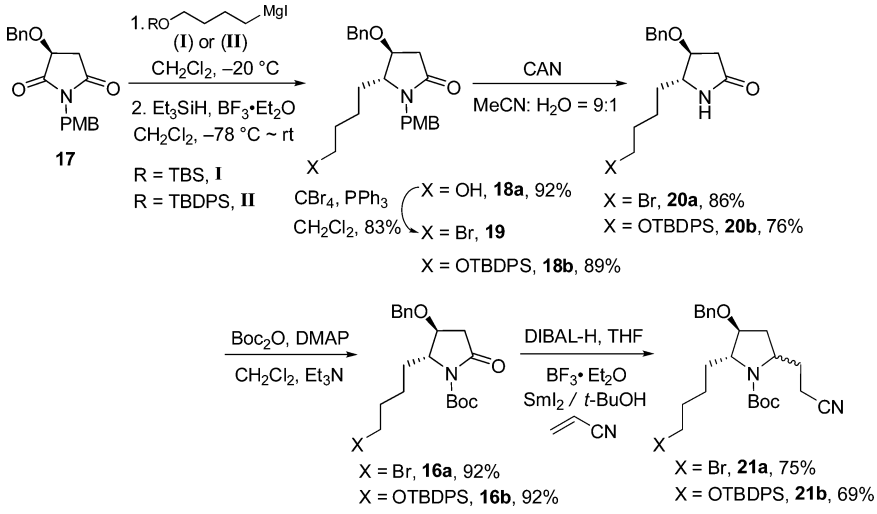
Scheme 3

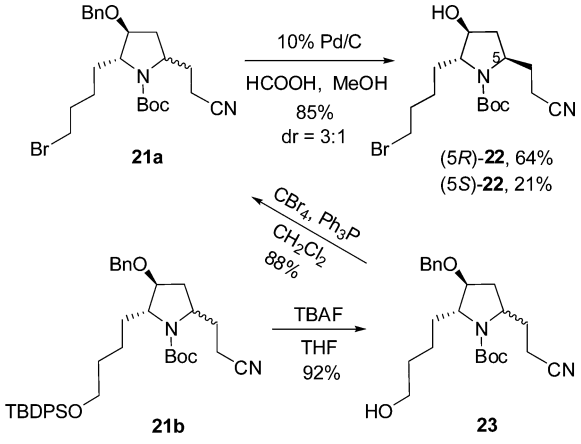


(H_2, 10% Pd/C, rt) were made. No reaction occurred for **18b** under these conditions. It seemed that the TBDPS group inhibited the hydrogenation, which was also observed over the next few steps. To avoid this unexpected effect, the hydroxyl group of **18a** was transformed to a bromo group to give lactam **19** in 83% yield with carbon tetrabromide and triphenyl phosphine. To our delight, this alkyl bromide exhibited enough chemical inertness until the closure to form ring A. The protecting group of the lactam nitrogen of **18b** and **19** was changed from the *p*-methoxyphenyl (PMB) group to the *tert*-butyloxycarbonyl (Boc) group under standard conditions to afford imides **16a** and **16b**, respectively (Scheme 3).

To introduce the cyanoethyl side chain, **16a**/**16b** was partially reduced with DIBAL-H, followed by one-pot SmI_2-mediated reductive radical coupling with acrylonitrile to afford **21a**/**21b** as an inseparable diastereomeric mixture (dr = 75:25 for **21a**, dr = 88:12 for **21b**) with the desired stereoisomer as the major product (Scheme 3). For the reaction of **16a**, SmI_2-promoted debromination started to occur if the temperature was increased above −40 °C.

The benzyl group of **21a** was removed to give pyrrolidine **22** as a separable mixture of diastereomers (75:25) in a combined yield of 85% (Scheme 4). It was important to keep the reaction time to a minimum to avoid debromination of the products. The stereochemistry of the major isomer was determined by a single-crystal X-ray diffraction to be 2*R*,5*R* (see the Supporting Information), which was desired for the synthesis of the nature products **5** and **6**.

Scheme 4



Unlike the bromide **21a**, removal of the benzyl group of silylated **21b** was found to be difficult. Catalytic hydrogenation conditions (HCOOH/MeOH, 10% Pd/C, rt or H_2, 10% Pd/C, rt) led to very low conversion, and starting material remained unchanged. Hence, the TBDPS group of **21b** was removed, and the resulting alcohol **23** was converted to the bromide **21a** (dr = 88:12) under standard conditions (Scheme 4). These results suggested that the silylated side chain of **21b** is more hindered than the brominated side chain of **21a**, and the steric hindrance of these side chains was mainly responsible for the diastereoselectivity of reductive coupling reactions of **16a** and **16b**. The more hindered **16b** led to the better 2,5-*trans*-diastereoselectivity.

With (5*R*)-**22** in hand, we proceeded to close ring C. Hence, alcohol (5*R*)-**22** was oxidized with Ley−Griffith reagent to give ketonitrile **15**,[24] which was used in the next step without purification (Scheme 5). Followed by Weinreb's method, **15** was treated with excess SmI_2 in the presence of methanol to provide the cyclized product **14** as a single diastereoisomer in 75% yield over two steps.[17] After completion of the reductive cyclization, air should be blown into the reaction flask to quench the unreacted SmI_2 before aqueous workup to avoid further reduction of the hydroxyl ketone **14** to a vicinal diol. Attempts to improve the cyclization by replacing the stoichiometric reagent SmI_2 with a catalytic amount of Cp_2TiCl_2 and a metal co-reductant failed. For example, no reaction occurred when **15** was treated with 10 mol % of Cp_2TiCl_2, Zn dust (2.0 equiv), TMSCl (3.0 equiv), and triethylamine hydrochloride (2.0 equiv).[25] Treatment of **15** with Cp_2TiCl_2 (0.5 equiv), Mg chips (5.0 equiv), and TMSCl (3.0 equiv) in THF at room temperature did lead to the formation of **14** in low yield (12%). Under these conditions, the yield of **14** could be increased to 60% if an excess of Cp_2TiCl_2 (3.0 equiv) was used.

Cleavage of the *N*-Boc group in **14**, followed by K_2CO_3-promoted cyclization, furnished the tricyclic amine **13** in 93% yield $\{[\alpha]_D^{20} = -15.2$ (*c* 1.0, $CHCl_3)\}$ (Scheme 6). The ^{13}C NMR spectrum of **13** matched well with the reported data.[22] The transformation of **13** to securinine was reported. Hence, we completed a formal total synthesis of (−)-securinine.

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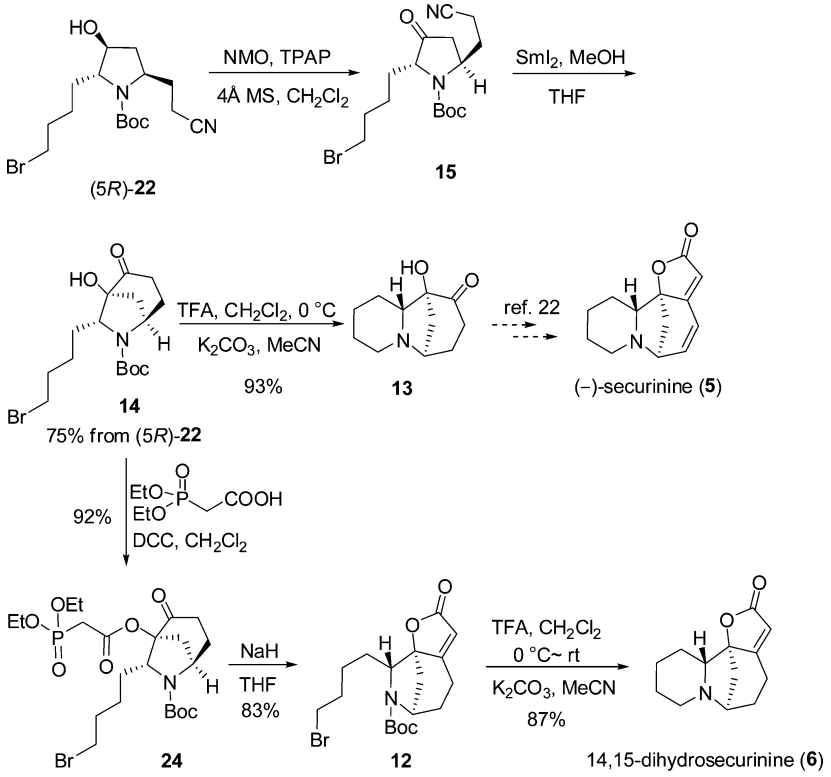
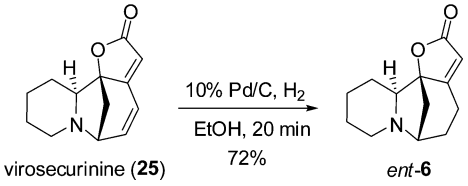
Scheme 5



Scheme 6



To access 14,15-dihydrosecurinine (**6**), **14** was subjected to a DCC-promoted esterification with diethylphosphonoacetic acid to give the phosphonate ester **24**, which was converted smoothly to butenolide **12** through an intramolecular Horner−Wadsworth−Emmons olefination reaction (Scheme 5). Cleavage of the *N*-Boc group in **12**, followed by K_2CO_3-promoted cyclization in acetonitrile for 2 days, furnished 14,15-dihydrosecurinine **6** in 87% yield {mp 56.4−58.5 °C, lit.[8,11] 58−60; $[\alpha]_D^{20}$ −1.5 (*c* 1.0, EtOH); lit.[8,11] $[\alpha]_D^{20} \approx 0$ (*c* 1, EtOH)}. The ^{13}C NMR spectrum of **6** agreed well with literature data.[12]

It was difficult to confirm the optical purity of **6** because of its small specific rotation. Hence, virosecurinine (**25**)[26] was selectively hydrogenated to afford *ent*-**6** {$[\alpha]_D^{20}$ +1.5 (*c* 1.0, EtOH)} in 72% yield (Scheme 6). Analysis of *ent*-**6** and **6** by chiral HPLC (Chiralpak AD-H+G, hexane/isopropyl alcohol = 95/5 (v/v), 220 nm) revealed that the enantiopurity of our synthetic 14,15-dihydrosecurinine (**6**) is greater than 99% ee.

CONCLUSION

In summary, we have completed the total synthesis of (−)-14,15-dihydrosecurinine (**6**) in 12 steps with an overall yield of 14.4% and the formal total synthesis of (−)-securinine (**5**) in 10 steps with an overall yield of 20.2% from a common intermediate **14**. Our divergent strategy features (1) a flexible six-step route for the construction of piperidine ring A, which is potentially applicable for the synthesis of norsecurinine-type alkaloids with a pyrrolidine ring; (2) SmI_2-mediated reductive coupling reactions for the synthesis of the bridged ring skeleton; and (3) efficient formation of the butenolide ring D through an intramolecular olefination reaction.

EXPERIMENTAL SECTION

General. Chemicals and solvents were either purchased from commercial suppliers or purified by standard techniques. Flash chromatography was carried out using silica gel 300−400 mesh. Infrared spectra were measured with a FT-IR spectrometer using film KBr pellet techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a 400/100 MHz spectrometer with tertramethylsilane (TMS) as an internal standard. HRMS spectra were recorded on an ESI-TOF mass spectrometer. The SmI_2 solution in THF (0.1 M) was prepared by mixing Sm powder and I_2 in anhydrous THF.

(4*S*,5*R*)-4-(Benzyloxy)-5-(4-hydroxybutyl)-1-(4-methoxybenzyl)-2-pyrrolidinone (18a). A solution of malimide **17**[23] (2.5 g, 7.7 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled to −20 °C under argon. To this mixture was added dropwise the Grignard reagent (0.5 M in THF, 31 mL, 15.5 mmol), which was prepared from (4-bromobutoxy)(*tert*-butyl)dimethylsilane. After being stirred at −20 °C for 2 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (15.0 mL). The aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After being filtered and concentrated under reduced pressure, the residue was passed through a short pad of silica gel eluting with ethyl acetate to afford a *N*,*O*-acetal as mixture of diastereomers.

Without further purification, the crude *N*,*O*-acetal was dissolved in dry CH_2Cl_2 (34 mL) under argon and cooled to −78 °C. Et_3SiH (10.8 mL, 68.0 mmol) and $BF_3{\cdot}Et_2O$ (2.6 mL, 20.4 mmol) were added successively. After being stirred at −78 °C for 5 h, the reaction mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 10 mL). The

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combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) to give **18a** as a colorless oil (2.71 g, yield 92%): $[\alpha]_D^{20}$ +32.1 (*c* 1.0, $CHCl_3$); IR (film) 3410, 2931, 2860, 1672, 1612, 1513, 1454, 1415, 1355, 1303, 1246, 1176, 1068, 1029, 741, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19−1.57 (m, 6H), 2.52 (dd, *J* = 2.0, 17.5 Hz, 1H), 2.72 (ddd, *J* = 0.8, 6.6, 17.5 Hz, 1H), 3.44−3.48 (m, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.79 (s, 3H), 3.87 (dt, *J* = 2.0, 6.6 Hz, 1H), 3.91 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.96 (d, *J* = 15.1 Hz, 1H), 6.81−6.87 (m, 2H), 7.15−7.35 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 30.3, 32.4, 37.4, 43.4, 55.2, 62.1, 62.9, 70.4, 75.6, 114.0, 127.5, 127.7, 128.2, 128.3, 129.1, 137.5, 158.9, 172.5; HRMS calcd for $[C_{23}H_{29}NNaO_4]^+$ (M + Na^+) 406.1989; found 406.1990.

(4*S*,5*R*)-4-(Benzyloxy)-5-(4-((*tert*-butyldiphenylsilyl)oxy)-butyl)-1-(4-methoxybenzyl)-2-pyrrolidinone (18b). **18b** was synthesized from malimide **17** by following the procedure described for the preparation of **18a**. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:4) to give **18b** (1.71 g, 89% yield) as a colorless oil: $[\alpha]_D^{20}$ +24.2 (*c* 1.0, $CHCl_3$); IR (film) 3454, 2930, 2857, 1692, 1513, 1247, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.20−1.63 (m, 6H), 2.50 (d, *J* = 17.4 Hz, 1H), 2.69 (dd, *J* = 6.5, 17.4 Hz, 1H), 3.38−3.46 (m, 1H), 3.62 (t, *J* = 6.2 Hz, 2H), 3.75 (s, 3H), 3.82−3.90 (m, 1H), 3.85 (d, *J* = 14.9 Hz, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 4.98 (d, *J* = 14.9 Hz, 1H), 6.75−6.85 (m, 2H), 7.10−7.70 (m, 17H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 21.1, 26.8, 30.3, 32.3, 37.4, 43.4, 55.2, 62.9, 63.3, 70.4, 75.8, 114.0, 127.5, 127.6, 127.7, 128.26, 128.32, 129.1, 129.6, 133.8, 135.4, 137.5, 158.9, 172.4; HRMS calcd for $[C_{39}H_{47}NNaO_4Si]^+$ (M + Na^+) 644.3167; found 644.3162.

(4*S*,5*R*)-4-(Benzyloxy)-5-(4-bromobutyl)-1-(4-methoxybenzyl)pyrrolidin-2-one (19). To a solution of **18a** (331 mg, 0.86 mmol) in CH_2Cl_2 (8.6 mL) at rt was added carbon tetrabromide (845 mg, 2.58 mmol). The resulting solution was stirred at rt for 10 min and then treated with triphenyl phosphine (676 mg, 2.58 mmol) in several portions. The resulting reaction mixture was stirred at rt for 1 h, quenched with water, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford **19** (320 mg, 83% yield) as a yellow oil: $[\alpha]_D^{20}$ +28.0 (*c* 1.0, $CHCl_3$); IR (film) 3361, 2929, 2859, 1679, 1454, 1384, 1353, 1261, 1071, 1027, 799, 740, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35−1.44 (m, 3H), 1.55−1.90 (m, 3H), 2.52 (dd, *J* = 2.1, 17.4 Hz, 1H), 2.72 (dd, *J* = 6.6, 17.4 Hz, 1H), 3.32 (t, *J* = 6.6 Hz, 2H), 3.42−3.47 (m, 1H), 3.79 (s, 3H), 3.86 (dt, *J* = 2.1, 6.6 Hz, 1H), 3.93 (d, *J* = 15.1 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.95 (d, *J* = 15.1 Hz, 1H), 6.81−6.87 (m, 2H), 7.15−7.20 (m, 2H), 7.21−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 29.7, 32.2, 33.1, 37.3, 43.5, 55.2, 62.8, 70.6, 75.6, 114.0, 127.6, 127.8, 128.2, 128.4, 129.1, 137.4, 159.0, 172.4; HRMS calcd for $[C_{23}H_{28}BrNNaO_3]^+$ (M + Na^+) 468.1145; found 468.1152.

(4*S*,5*R*)-4-(Benzyloxy)-5-(4-bromobutyl)pyrrolidin-2-one (20a). To a solution of compound **19** (153 mg, 0.34 mmol) in a mixed solvent of MeCN/H_2O (v/v = 9:1, 34 mL) was added ceric ammonium nitrate (932 mg, 1.7 mmol) at rt. After being stirred for 2 h, the reaction was quenched with water (75 mL). The resulting mixture was extracted with EtOAc (4 × 75 mL). The combined extractions were washed with a saturated aqueous solution of $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) to afford **20a** (96 mg, 86% yield) as a colorless oil: $[\alpha]_D^{20}$ +38.5 (*c* 1.0, $CHCl_3$); IR (film) 3216, 2925, 2856, 1697, 1454, 1353, 1269, 1093, 1072, 1028, 738, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42−1.58 (m, 4H), 1.86 (td, *J* = 6.7, 13.5 Hz, 2H), 2.41 (dd, *J* = 4.0, 17.3 Hz, 1H), 2.63 (dd, *J* = 7.0, 17.3 Hz, 1H), 3.39 (t, *J* = 6.7 Hz, 2H), 3.58−3.64 (m, 1H), 3.85−3.91 (m, 1H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 7.25−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.2, 32.2, 33.2, 33.7, 37.0, 60.5, 71.2, 78.8, 127.7, 127.9, 128.5, 137.4, 175.6; HRMS calcd for $[C_{15}H_{20}BrNO_2Na]^+$ (M + Na^+) 348.0570; found 348.0576.

(4*S*,5*R*)-4-(Benzyloxy)-5-(4-((*tert*-butyldiphenylsilyl)oxy)-butyl)pyrrolidin-2-one (20b). **20b** was synthesized from **18b** by following the procedure described for the synthesis of **20a**. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) to afford **20b** (610 mg, 76% yield) as a colorless oil: $[\alpha]_D^{20}$ +20.1 (*c* 1.0, $CHCl_3$); IR (film) 2930, 1700, 1111, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.40−1.58 (m, 6H), 2.38 (dd, *J* = 3.8, 17.4 Hz, 1H), 2.59 (dd, *J* = 7.0, 17.4 Hz, 1H), 3.57 (s, 1H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.83−3.86 (m, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 6.34 (s, 1H), 7.25−7.66 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 22.1, 26.9, 32.2, 34.5, 36.9, 60.6, 63.4, 71.2, 79.0, 127.6, 127.7, 127.9, 128.5, 129.6, 133.9, 135.5, 137.5, 175.2; HRMS calcd for $[C_{31}H_{39}NNaO_3Si]^+$ (M + Na^+) 524.2591; found 524.2595.

(4*S*,5*R*)-1-*tert*-Butyloxycarbonyl-4-(benzyloxy)-5-(4-bromobutyl)pyrrolidin-2-one (16a). To a solution of crude compound **20a** (337 mg, 1.04 mmol) and DMAP (6.9 mg) in anhydrous CH_2Cl_2 (11.0 mL) at 0 °C were added dropwise Et_3N (0.32 mL, 2.28 mmol) and $(Boc)_2O$ (0.52 mL at 20 °C, 2.28 mmol). After being stirred for 0.5 h at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:4) to afford **16a** (405 mg, 92% yield) as a colorless oil: $[\alpha]_D^{20}$ −26.6 (*c* 1.0, $CHCl_3$); IR (film) 2930, 2863, 1783, 1750, 1713, 1455, 1368, 1308, 1244, 1210, 1155, 1091, 1070, 1021, 847, 777, 747, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.34−1.58 (m, 3H), 1.54 (s, 9H), 1.67−1.98 (m, 3H), 2.60 (d, *J* = 18.2 Hz, 1H), 2.76 (dd, *J* = 5.7, 18.2 Hz, 1H), 3.34−3.46 (m, 2H), 3.82 (d, *J* = 5.6 Hz, 1H), 4.10−4.18 (m, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 4.56 (d, *J* = 12.1 Hz, 1H), 7.26−7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 28.0, 31.1, 32.0, 33.2, 38.3, 63.9, 70.5, 73.8, 83.1, 127.7, 128.0, 128.6, 137.2, 149.8, 171.8; HRMS calcd for $[C_{20}H_{28}BrNO_4Na]^+$ (M + Na^+) 448.1094; found 448.1091.

(4*S*,5*R*)-1-*tert*-Butyloxycarbonyl-4-(benzyloxy)-5-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)pyrrolidin-2-one (16b). **16b** was synthesized from **20b** by following the procedure described for synthesis of **16a**. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:4) to afford **16b** (1.10 g, 92% yield) as a colorless oil: $[\alpha]_D^{20}$ −20.2 (*c* 1.0, $CHCl_3$); IR (film) 2929, 1736, 1716, 1308, 1151, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.51 (s, 9H), 1.30−1.78 (m, 6H), 2.57 (d, *J* = 18.1 Hz, 1H), 2.72 (dd, *J* = 5.7, 18.1 Hz, 1H), 3.65 (t, *J* = 6.1 Hz, 2H), 3.78 (d, *J* = 6.1 Hz, 1H), 4.09−4.16 (m, 1H), 4.50 (s, 2H), 7.25−7.66 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 22.1, 26.9, 28.0, 31.9, 32.3, 38.4, 63.4, 64.2, 70.5, 74.1, 82.9, 127.58, 127.63, 127.9, 128.5, 129.6, 133.9, 135.5, 137.3, 149.8, 172.0; HRMS calcd for $[C_{36}H_{47}NO_5SiNa]^+$ (M + Na^+) 624.3116; found 624.3122.

(2*R*,3*S*)-1-*tert*-Butyloxycarbonyl-3-(benzyloxy)-2-(4-bromobutyl)-5-(2-cyanoethyl)pyrrolidine (21a). To a solution of *N*-acylcarbamate **16a** (1.0 g, 2.35 mmol) in anhydrous THF (46.0 mL) was added dropwise a solution of DIBAL-H (1.0 M in hexane, 3.5 mL, 3.5 mmol) at −78 °C. The reaction was stirred for 30 min, and MeOH (0.15 mL, 3.8 mmol) was added. The resulting reaction mixture was stirred for another 30 min at the same temperature and then treated sequentially with acrylonitrile (0.23 mL, 3.45 mmol), $BF_3{\cdot}Et_2O$ (0.58 mL, 4.6 mmol), and a freshly prepared solution of *t*-BuOH-containing SmI_2 (0.1 M in THF, 92 mL, 9.2 mmol). After being stirred at −78 °C for 10 min, the reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL). The mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (eluent: EtOAc/hexane 1:5) to afford **21a** (820 mg, 75% yield) as a mixture of epimers: IR (film) 3064, 2930, 2863, 2244, 1689, 1454,

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1391, 1365, 1256, 1172, 1121, 1095, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08−1.22 (m, 1H), 1.34−1.44 (m, 2H), 1.44−1.54 (2s br, 9H), 1.65−2.01 (m, 4H), 2.01−2.48 (m, 5H), 3.33−3.59 (m, 2H), 3.71−4.06 (m, 3H), 4.39−4.65 (m, 2H), 7.27−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.5, 23.6 23.7, 25.0, 28.4, 28.5, 29.4, 29.7, 29.8, 30.6, 32.2, 32.8, 33.6, 44.6, 44.8, 56.2, 56.6, 63.5, 63.8, 70.5, 70.8, 77.2, 79.8, 80.1, 81.1, 82.0, 119.4, 119.9, 127.5, 127.8, 128.4, 128.5, 137.8, 137.9, 153.6, 154.0; HRMS calcd for $[C_{23}H_{33}BrN_2O_3Na]^+$ (M + Na^+) 487.1567; found 487.1563.

(2*R*,3*S*)-1-*tert*-Butyloxycarbonyl-3-(benzyloxy)-2-(4-((*tert*-butyldiphenylsilyl)oxy)butyl)-5-(2-cyanoethyl)pyrrolidine (21b). **21b** was synthesized from **16b** by following the procedure described for the synthesis of **21a**. The crude product was purified by flash chromatography on a silica gel (eluent: EtOAc/hexane 1:5) to afford **21b** (0.74 g, 69% yield) as a mixture of epimers: IR (film) 3070, 2930, 2858, 2245, 1692, 1472, 1454, 1365, 1260, 1110, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02−1.07 (m, 9H), 1.09−1.41 (m, 3H), 1.41−1.54 (m, 11H), 1.54−1.84 (m, 3H), 1.84−2.22 (m, 4H), 2.22−2.46 (m, 3H), 3.64 (t, J = 6.3 Hz, 2H), 3.70−3.95 (m, 3H), 4.32−4.60 (m, 2H), 7.25−7.46 (m, 11H), 7.60−7.72 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.4, 19.2, 22.9, 26.8, 28.40, 28.44, 28.5, 29.4, 29.6, 29.8, 31.2, 32.4, 32.7, 32.8, 33.6, 56.1, 56.5, 63.6, 63.9, 70.8, 79.6, 79.8, 81.2, 82.2, 119.4, 119.9, 127.4, 127.55, 127.62, 127.7, 128.38, 128.45, 129.5, 133.9, 135.5, 137.8, 153.5, 154.0; HRMS calcd for $[C_{39}H_{52}N_2O_4NaSi]^+$ (M + Na^+) 663.3589; found 663.3588.

(2*R*,3*S*,5*R/S*)-1-*tert*-Butyloxycarbonyl-2-(4-bromobutyl)-5-(2-cyanoethyl)-3-hydroxypyrrolidine (5*R*)-22 and (5*S*)-22. HCOOH (2.4 mL) was added to a mixture of **21a** (200.0 mg, 0.43 mmol), 10% Pd/C (200 mg), and MeOH (9.2 mL). After being stirred for 6 h at room temperature, the suspension was filtered through a short pad of Celite. The filtrate was concentrated in vacuo, dissolved in ethyl acetate (15 mL), then washed with saturated aqueous solution of $NaHCO_3$ (3 × 5 mL) and brine (5 mL). The resulting organic solution was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 2:1) to afford (5*R*)-**22** (103 mg, 64% yield) as white crystals and (5*S*)-**22** (34.0 mg, 21% yield) as a yellow oil: IR (film) 3442, 2973, 2934, 2866, 2246, 1687, 1455, 1393, 1367, 1169, 1121 cm^{-1}; HRMS calcd for $[C_{16}H_{27}BrN_2O_3Na]^+$ (M + Na^+) 397.1097; found 397.1106.

(5*R*)-**22**: mp 139.3−141.3 °C, $[\alpha]_D^{20}$ −25.2 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.10−1.25 (m, 1H), 1.45−1.51 (m, 10H), 1.60−2.55 (m, 10H), 2.65 (br s, 1H, OH), 3.42 (t, J = 6.6 Hz, 2H), 3.59−3.78 (m, 1H), 3.80−3.92 (m, 1H), 4.15−4.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.3, 25.0, 28.4, 29.4, 29.9, 30.4, 31.8, 32.2, 33.4, 33.8, 35.4, 56.1, 56.5, 67.0, 67.4, 73.8, 74.7, 79.8, 80.1, 119.4, 120.0, 153.6, 154.1.

(5*S*)-**22**: $[\alpha]_D^{20}$ +12.4 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.29−1.41 (m, 1H), 1.41−1.60 (m, 3H), 1.48 (s, 9H), 1.67−1.95 (m, 5H), 2.10−2.29 (m, 2H), 2.38 (br s, 2H), 3.39−3.59 (m, 2H), 3.68−3.88 (m, 1H), 3.97−4.09 (m, 1H), 4.09−4.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 23.6, 24.8, 28.39, 28.42, 31.9, 32.1, 32.2, 33.3, 33.5, 38.4, 44.7, 55.6, 67.1, 74.0, 80.2, 119.5, 155.7.

(2*R*,3*S*)-1-*tert*-Butyloxycarbonyl-3-(benzyloxy)-5-(2-cyanoethyl)-2-(4-hydroxybutyl)pyrrolidine (23). To a solution of compound **21b** (250 mg, 0.39 mmol) in anhydrous THF (13.0 mL) at 0 °C was added dropwise tetrabutylammonium fluoride (1.0 M in THF, 3.9 mL, 3.9 mmol). After being stirred for 0.5 h at the same temperature, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexane 1:1) to afford **23** (144 mg, 92% yield) as a mixture of epimers: IR (film) 3436, 3063, 2933, 2863, 2245, 1689, 1454, 1392, 1366, 1253, 1172, 1094, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05−1.24 (m, 1H), 1.29−1.41 (m, 2H), 1.44−1.52 (m, 9H), 1.54−2.00 (m, 3H), 2.02−2.48 (m, 6H), 3.61 (t, J = 6.4 Hz, 2H), 3.72−4.16 (m, 3H), 4.32−4.71 (m, 2H), 7.24−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.4, 22.6, 22.7, 28.3, 28.40, 28.43, 29.3, 29.55, 29.64, 31.0, 32.1, 32.4, 32.56, 32.65, 33.4, 56.1, 56.5, 62.2, 62.3, 63.6, 63.8, 70.4, 70.7, 79.6, 80.0, 81.1, 82.0, 119.3, 119.8, 127.4, 127.6, 128.32, 128.35, 128.4, 137.78, 137.85, 153.6, 154.0; HRMS calcd for $[C_{23}H_{34}N_2O_4Na]^+$ (M + Na^+) 425.2411; found 425.2415.

(1*R*,5*R*,7*R*)-6-*tert*-Butyloxycarbonyl-7-(4-bromobutyl)-1-hydroxy-6-azabicyclo[3.2.1]octan-2-one (14). To a solution of (5*R*)-**22** (200 mg, 0.53 mmol) in CH_2Cl_2 (10.0 mL) were added 4 Å molecular sieves (500.0 mg), NMO (62.0 mg, 0.80 mmol), and TPAP (9.5 mg, 0.027 mmol). The resulting mixture was stirred at room temperature for 30 min before being filtered through a thin pad of silica gel (eluent: EtOAc/Hex. 1:1). The solvent was removed under reduced pressure and crude ketonitrile **15** was used in the next step without further purification.

To slurry of Sm powder (500 mg) in THF (20.0 mL) was added I_2 (747.0 mg). After being stirred for 10 min, the reaction mixture was warmed to 60 °C and stirred for an additional 3 h. The resulting SmI_2 solution was cooled to rt. A solution of **15** (195.0 mg) in THF (10.0 mL) and MeOH (0.06 mL) was added dropwise over 30 min, and the resulting reaction mixture was stirred at room temperature for 4 h. Air was blown into the reaction flask until the color of the solution turned to tawny. The reaction mixture was quenched with saturated sodium potassium tartrate solution (15 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (eluent: EtOAc/hexane 1:5) to afford α-hydroxy ketone **14** (150 mg, yield 75%) as a white solid: mp 59.0−60.6 °C; $[\alpha]_D^{20}$ −52.8 (*c* 1.0, $CHCl_3$); IR (film) 3466, 2967, 2932, 1694, 1454, 1390, 1180, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42−1.48 (m, 9H), 1.48−1.91 (m, 8H), 2.21−2.66 (m, 4H), 3.27−3.56 (m, 3H), 3.78−3.90 (ds, 1H), 4.06−4.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 and 25.8 (1C), 28.41 and 28.44 (3C), 29.5 and 30.4 (1C), 31.0 and 31.3 (1C), 32.86 and 32.96 (1C), 33.0 and 33.1 (1C), 33.6 and 33.7 (1C), 39.0 and 39.7 (1C), 52.4 and 53.0 (1C), 61.0 and 61.3 (1C), 80.0 and 80.3 (1C), 81.3 and 81.9 (1C), 154.0 and 154.1 (1C), 209.8 and 210.1 (1C); HRMS calcd for $[C_{16}H_{26}BrNO_4Na]^+$ (M + Na^+) 398.0937; found 398.0941.

Preparation of Tricyclic Amine (13). TFA (1.0 mL) was added to a solution of **14** (106 mg, 0.28 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature over 1 h. The solvent and TFA were removed in vacuo. The residue was dissolved in MeCN (12.0 mL) and treated with K_2CO_3 (309.0 mg, 2.24 mmol) at rt for 10 h under nitrogen atmosphere. The reaction mixture was filtered, and the filtrate was concentrated under vacuum to give an oily residue, which was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/ MeOH 10:1) to give **13** (51 mg, 93% yield) as a yellow oil: $[\alpha]_D^{20}$ −15.2 (*c* 1.0, $CHCl_3$); IR (film) 3477, 2932, 2852, 1713, 1449, 1408, 1350, 1203, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + D_2O) δ 1.29−1.44 (m, 2H), 1.48−1.72 (m, 5H), 1.84−1.93 (m, 1H), 2.09−2.16 (m, 1H), 2.43 (ddd, J = 2.6, 5.3, 11.2 Hz, 1H), 2.49−2.69 (m, 3H), 2.79 (ddd, J = 3.7, 9.7, 11.8 Hz, 1H), 2.92−2.99 (m, 1H), 3.31−3.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3, 24.8, 26.3, 30.1, 33.9, 40.2, 48.1, 58.5, 63.9, 83.4, 212.4; HRMS calcd for $[C_{11}H_{17}NO_2Na]^+$ (M + Na^+) 218.1151; found 218.1159.

(1*R*,5*R*,7*R*)-6-*tert*-Butyloxycarbonyl-7-(4-bromobutyl)-1-(2-(diethoxyphosphoryl)acetoxy)-6-azabicyclo[3.2.1]octan-2-one (24). Diethylphosphonoacetic acid (52 mg, 0.27 mmol) and **14** (50 mg, 0.13 mmol) were dissolved in CH_2Cl_2 (0.7 mL), and a solution of dicyclohexylcarbodiimide (55 mg, 0.27 mmol) in CH_2Cl_2 (0.5 mL) was added via cannula. The reaction was stirred at room temperature for 1 h, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate) to afford **24** (68 mg, 92% yield) as a colorless oil: $[\alpha]_D^{20}$ −36.6 (*c* 1.0, $CHCl_3$); IR (film) 2976, 2931, 2869, 1754, 1729, 1697, 1662, 1453, 1390, 1268, 1113, 1052, 1025, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 6H), 1.44−1.52 (m, 9H), 1.55−1.95 (m, 7H), 2.25−2.80 (m, 5H), 2.98−3.15 (2s br, 2H), 3.36−3.60 (m, 2H), 3.67−4.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.26 and 16.31 (2C), 23.6 and 24.1

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(1C), 25.0 and 25.3 (1C), 28.3 (3C), 29.6, 30.6, 31.4, 32.4, 32.6, 32.8, 33.4, 33.5, 33.7, 34.1, 34.8, 44.7, and 44.8 (1C), 52.9 and 53.5 (1C), 61.0, 62.6, and 62.7 (1C), 77.2, 80.2 amd 80.7 (1C), 86.8, 153.7, and 153.9 (1C), 164.0 and 164.1 and 164.2 (1C), 201.8; HRMS calcd for $[C_{22}H_{37}BrNO_8PNa]^+$ (M + Na^+) 576.1338; found 576.1341.

Preparation of 12. To a suspension of sodium hydride (60% dispersion in mineral oil, 6.3 mg, 0.17 mmol) in THF (1.8 mL) at −40 °C was added a solution of phosphonate **24** (77 mg, 0.14 mmol) in THF (1 mL). The reaction mixture was stirred for 2 h at −40 °C. Brine and Et_2O were added. The mixture was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel (eluent: EtOAc/hexane 1:2) to give **12** (46 mg, 83% yield) as a white solid: mp 99.6−100.9 °C; $[\alpha]_D^{20}$ −54.4 (*c* 1.0, $CHCl_3$); IR (film) 2969, 2932, 1766, 1694, 1646, 1390, 1160, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22−1.35 (m, 1H), 1.47−1.50 (m, 9H), 1.52−1.94 (m, 7H), 2.30−2.58 (m, 2H), 2.62−2.77 (m, 1H), 2.79−2.90 (m, 1H), 3.33−3.63 (m, 3H), 4.12−4.30 (m, 1H), 5.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2 and 22.3 (1C), 24.1 and 24.4 (1C), 28.4 (3C), 29.7 and 30.0 (1C), 31.6, 32.3, and 32.7 (1C), 37.8 and 38.5 (1C), 44.7 and 44.8 (1C), 52.7 and 53.3 (1C), 60.5 and 61.0 (1C), 80.3 and 80.6 (1C), 88.1 and 88.6 (1C), 110.47 and 110.53 (1C), 153.8 and 154.0 (1C), 171.9, 172.7, and 172.9 (1C); HRMS calcd for $[C_{18}H_{26}BrNO_4Na]^+$ (M + Na^+) 422.0937; found 422.0942.

(−)-14,15-Dihydrosecurinine (6). A solution of **12** (110 mg, 0.28 mmol) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C and treated with TFA (1.0 mL), and the reaction was allowed to warm to room temperature over 1 h. The solvent and TFA were removed in vacuo. The residue was dissolved in MeCN (5.5 mL), and K_2CO_3 (309 mg, 2.24 mmol) was added. After being stirred at rt for 24 h under nitrogen atmosphere, the reaction mixture was filtered and the filtrate was concentrated under vacuum to give an oily residue, which was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/ MeOH 40:1) to give the 14,15-dihydrosecurinine (**6**) (53 mg, 87% yield) as a pale yellow solid: mp 56.4−58.5 °C, lit.[8,11] 58−60 °C; $[\alpha]_D^{20}$ −1.5 (*c* 1.0, EtOH); lit.[8,11] $[\alpha]_D^{20} \approx 0$ (*c* 1, EtOH). IR (film) 2917, 2849, 1758, 1642, 1263, 1205, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29−1.52 (m, 6H), 1.52−1.61 (m, 1H), 1.81−1.89 (m, 1H), 1.90−1.99 (m, 1H), 2.65−2.80 (m, 3H), 2.85−3.00 (m, 3H), 3.32 (t, *J* = 4.5 Hz, 1H), 5.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.0, 23.6, 25.4, 32.3, 38.2, 48.1, 59.4, 61.3, 91.2, 109.2, 173.2, 175.6; HRMS calcd for $[C_{13}H_{18}NO_2]^+$ (M + H^+) 220.1332; found 220.1333.

(+)-14,15-Dihydrosecurinine (*ent*-6). A mixture of virosecurinine (**25**) (11 mg, 0.051 mmol) and 10% Pd/C (8.1 mg, 0.008 mmol) in ethanol (2.5 mL) was stirred under a hydrogen atmosphere at room temperature for 20 min. The reaction mixture was filtered through Celite, washed with ethanol (5 mL), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (eluent: CH_2Cl_2/ MeOH = 40:1) to give the 14,15-dihydrovirosecurinine (*ent*-**6**) (8.0 mg, 72% yield) as a pale yellow wax: $[\alpha]_D^{20}$ +1.5 (*c* 1.0, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 1.29−1.52 (m, 6H), 1.52−1.61 (m, 1H), 1.81−1.89 (m, 1H), 1.90−1.99 (m, 1H), 2.64−2.82 (m, 3H), 2.84−3.02 (m, 3H), 3.32 (t, *J* = 4.5 Hz, 1H), 5.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 23.1, 23.8, 25.6, 32.4, 38.4, 48.2, 59.5, 61.5, 91.3, 109.2, 173.3, 175.6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all new compounds and X-ray data for compound (5*R*)-**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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