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Total Synthesis of the Tetracyclic Indole Alkaloid Ht-13-B

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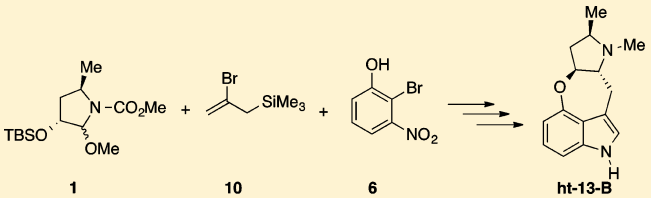
Supporting Information

ABSTRACT: An expedient synthesis corroborating the proposed structure of the tetracyclic indole alkaloid ht-13-B is presented. Key synthetic steps include acyliminium ion allylation, a Mitsunobu reaction, a palladium-catalyzed Stille–Kelly cross coupling reaction, and a carbon monoxide-mediated palladium-catalyzed reductive *N*-heterocyclization. The chiral centers are ultimately derived from commercially available *trans*-4-hydroxy-L-proline.



Two unique tetracyclic indole alkaloids were isolated in the year 2000 from *Streptomyces* sp. (PA-48561) by Kamiguchi and Yasui.[1] The alkaloids were named ht-13-A and ht-13-B, and their structures were elucidated by ^{1}H and ^{13}C NMR, UV, IR, and LRMS analyses (Figure 1). The indoles

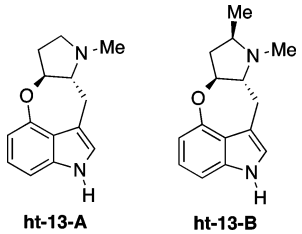


Figure 1. Indole alkaloids ht-13-A and ht-13-B.

showed an affinity for serotonin receptors. To the best of our knowledge, ht-13-A and ht-13-B are the only two examples of naturally occurring 3,4-oxepino-fused indoles. Herein is reported the first total synthesis of ht-13-B in seven steps starting from two previously reported intermediates.

3,4-Fused indoles are usually prepared by the installation of additional ring(s) onto a preformed indole framework. Pertinent to the synthesis of ht-13-B, 3,4-oxepine-fused indoles have been prepared by intramolecular C–O coupling reactions at the 4-position of the indole skeleton via enolate *O*-arylation of a benzyne intermediate,[2] copper-catalyzed *O*-arylation of an alcohol,[3] and nucleophilic aromatic substitution of a 4-nitro group.[4]

A handful of examples have been reported wherein both the 3,4-fused ring and the pyrrole ring were sequentially assembled onto a functionalized benzene ring. This includes an intramolecular variation of the Larock indole synthesis[5,6] and an intramolecular Fischer indole synthesis.[7] In addition, interesting rhodium(III)-catalyzed intramolecular amidoarylation and hydroarylation have recently been described by three different research groups.[8] We have previously reported a sequential intramolecular Heck reaction and palladium-catalyzed *N*-heterocyclization sequence to afford 3,4-fused indoles, including a 3,4-oxepine-fused ring system (Scheme 1).[9]

The sequence depicted in Scheme 1 forms the basis for the initial retrosynthetic analysis of ht-13-B (Figure 2). Hydride reduction of an *N*-alkoxycarbonyl protecting group should furnish ht-13-B. The carbamate would serve both as a protecting group limiting undesired coordination to palladium in earlier steps and as a source of the *N*-methyl group found in ht-13-B. In line with Scheme 1, the pyrrole ring of the indole would be formed via a palladium-catalyzed *N*-heterocyclization in the presence of carbon monoxide.[10] The pyrrolidine and benzene rings may be connected utilizing a Mitsunobu reaction of 2-bromo-3-nitrophenol with the allyl-substituted *N*-protected pyrrolidine **4** (R = *t*-Bu). Finally, compound **4** was thought to be derived from diastereoselective allylation of the known pyrrolidine **1** via an acyliminium ion type intermediate.

Pyrrolidine **1** was prepared from commercially available *trans*-4-hydroxy-L-proline following the procedure by Tanaka and Sawanishi (Scheme 2).[11] Introduction of the allyl side chain was achieved using allyl trimethylsilane in the presence of titanium tetrachloride to afford **2**.[12] The Boc-protecting group was unexpectedly removed during the course of the reaction prior to purification.[13] In addition, the product mixture proved to be sensitive to purification by chromatography on silica gel. Compound **2** was obtained as a mixture of two inseparable diastereomers in an approximate 5:1 ratio. The stereochemistry of either isomer could not be confirmed at this point in the synthesis. However, the major isomer was expected, based on ample literature precedence, to have a cis relationship between the allyl and the *tert*-(butyldimethylsilyl)oxy (OTBS) groups.[11,12,14]

The pyrolidine nitrogen in compound **2** was reprotected to give **3**. We were unable to separate the isomers, and interpretation of the NMR spectra after chromatography was complicated not only by the presence of two diastereomers but also by the fact that each of the diastereomers exists as a

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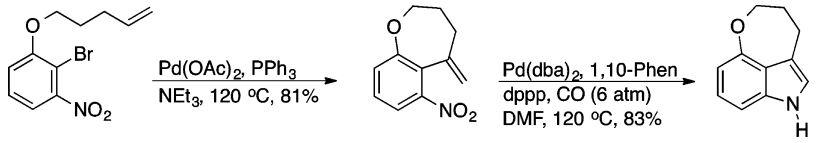
Scheme 1. Synthesis of a 3,4-Fused Oxepinoindole



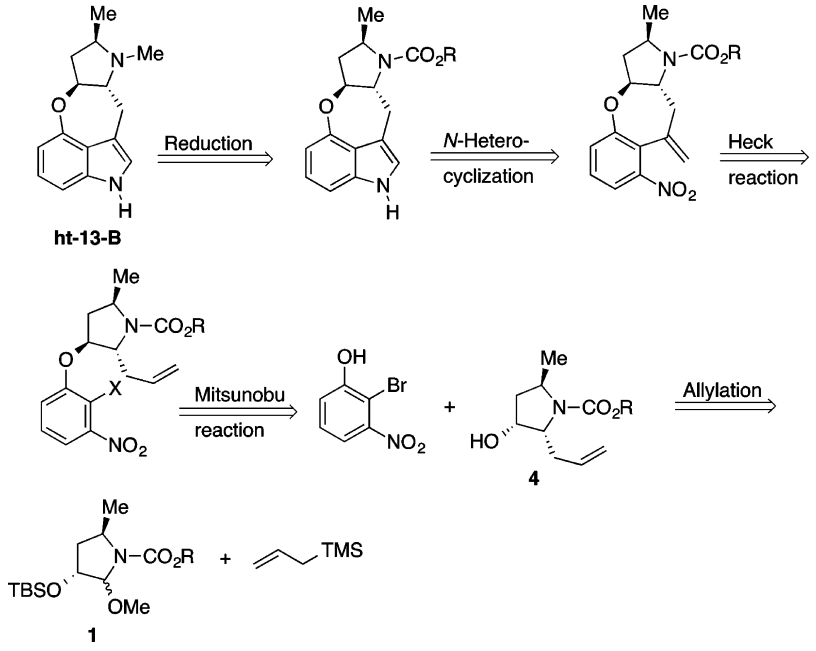
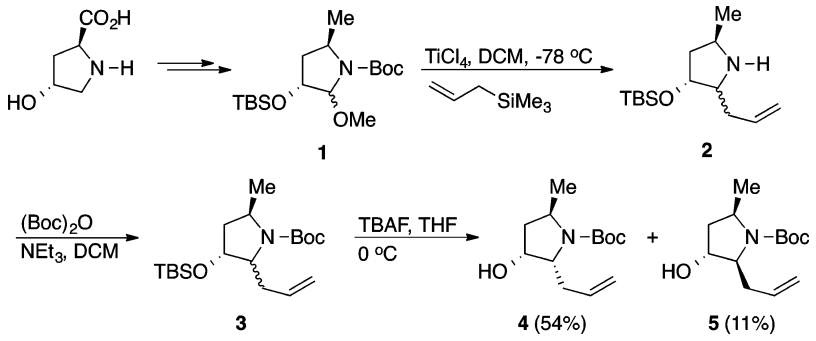


Figure 2. Initial retrosynthetic analysis of ht-13-B.

Scheme 2. Synthesis of Mitsunobu Precursor 4



mixture of amide bond rotamers. Removal of the *t*-butyldimethylsilyl group using tetrabutylammonium fluoride (TBAF) afforded the diastereomeric compounds **4** and **5**. Gratifyingly, the diastereomers were readily separated by chromatography on silica gel at this point in the synthesis. Executing the sequence from **1** to **4** and **5** without purification of the intermediates gave a significantly better overall yield. The yields of **4** and **5** in Scheme 2 represent the three-step yield from **1**.

A Mitsunobu reaction of major isomer **4** with 2-bromo-3-nitrophenol (**6**)[15] using triphenylphosphine and diisopropylazodicarboxylate (DIAD) gave expected product **7** in 70% isolated yield (Scheme 3). The inverted trans stereochemistry between the aryl ether and OTBS group was established by NOE NMR experiments. This in turn confirms the cis stereochemistry of major product **2** from the initial allylation reaction.

Intramolecular Heck reaction[16] of **7** gave only 8-endo trig cyclization products **8** in low isolated yields.[17,18] The expected 7-exo trig cyclization to afford **9** was not observed by ^{1}H NMR of the crude reaction mixture. Several additional catalyst systems were examined, all affording 8-endo product **8** in similar or lower isolated yields. Although the tricyclic compound cannot be used in the synthesis of ht-13-B, the trans stereochemistry of the pyrrolidine−oxepine ring fusion was confirmed by single crystal X-ray analysis of **8** (see Supporting Information).

Considering the exclusive formation of 8-endo cyclization product **8** from the Heck reaction of **7**, a different approach was needed for the preparation of key intermediate **9**. Palladium(0)-catalyzed intramolecular coupling reactions of substrates containing two separate electrophilic sites (e.g., a halide or triflate) are able to undergo oxidative addition. One such coupling is the Stille−Kelly reaction.[19,20] In this reaction, one

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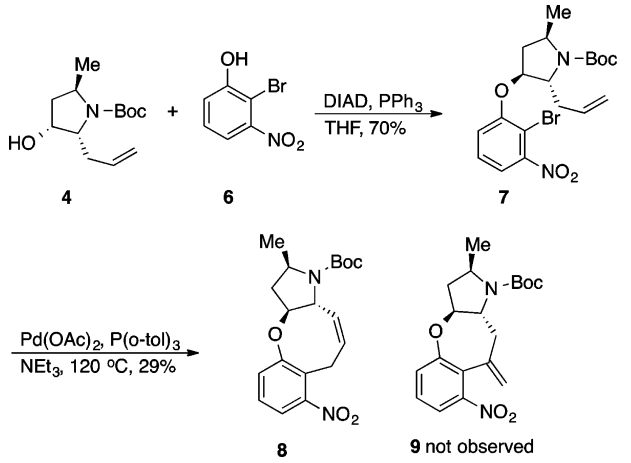
Scheme 3. Mitsunobu and Intramolecular Heck Reactions



electrophilic site undergoes intermolecular palladium-catalyzed trialkylstannylation using hexaalkylditin followed by an intramolecular Kosugi–Migita–Stille reaction. This one-pot coupling reaction has mostly been used for aryl–aryl couplings,[20c,21] although coupling reactions of a few aryl electrophiles with vinyl triflates,[20a,b,22] and a vinyl bromide with a vinyl triflate,[20d] have been reported. No aryl electrophile–vinyl bromide couplings have been reported to the best of our knowledge. In contrast to the Heck reaction, the ring size of the product depends on the position of the two electrophilic sites; thus, a halide on the internal alkene carbon of the allyl group of the pyrrolidine ring should give rise to a seven-membered ring with an exocyclic alkene (Figure 3).

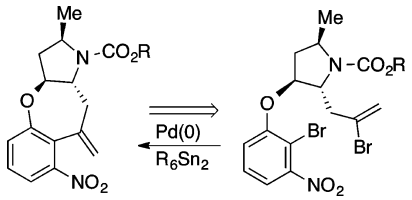


Figure 3. Modified oxepine cyclization precursor.

The new cyclization precursor was prepared in a fashion similar to compound 7. Treatment of **1** with an excess of 2-bromo-2-propen-1-yltrimethylsilane (**10**)[23] afforded allylation product **11**, again with the loss of the Boc-protecting group (Scheme 4).[24] In addition to **11**, bicyclic compound **12** was also isolated as a mixture of diastereomers. Related bicyclic compounds have been reported from gold-catalyzed cyclizations between an N-Boc group and an alkyne[25] or an allene.[26] Compound **11** was isolated as a 9:1 mixture of isomers after chromatography. The relative cis stereochemistry between the allyl and the OTBS groups of the major isomer of **11** was elucidated by double pulsed field gradient spin echo nuclear Overhauser effect (DPFGSE-NOE) NMR experiments. It should be noted that the mixture of isomers could not be separated at any point in the synthesis prior to the final product.

Other Lewis acids have been employed in reactions of related acyliminium ion intermediates with nucleophiles. For example, no loss of the Boc-group was observed using BF_3–OEt_2.[14,27] Thus, the reaction of **1** with **10** in the presence of BF_3–OEt_2 as the Lewis acid and the influence of the reaction temperature was briefly investigated (Table 1). Under an identical temperature profile as that used for the reaction in the presence of $TiCl_4$, an inferior yield of an inseparable mixture of isomeric **11** mixed with unknown side products was obtained. Treatment of **1** with **10** at −78 °C did not go to completion even after extended reaction times. In addition to a significant amount of starting material, a low yield of the allylated pyrrolidine **13** having an intact Boc-group was isolated. Finally, all of the starting material was consumed at a higher reaction temperature (−30 °C), but the yield of **13** was still unsatisfactory. As was the case employing $TiCl_4$, a significant amount of bicyclic product **12** was also isolated. It was concluded that BF_3–OEt_2 did not significantly improve the outcome of the reaction.

Purified amine **11** was reprotected as a methyl carbamate using methyl chloroformate to afford **14** (Scheme 4). A significantly higher overall yield of **14** from **1** was obtained without purification of crude **11** (55% vs 23%). Removal of the TBS group with TBAF to give **15** followed by a Mitsunobu reaction with 2-bromo-3-nitrophenol (**6**) gave anticipated compound **16**. Stille–Kelly reaction of **16** with hexamethylditin in the presence of a catalyst system consisting of bis(dibenzylidenacetone)-palladium(0)-triphenylphosphine produced desired tricyclic compound **17**. Although the starting material was completely consumed, no other products were isolated. A few additional catalyst systems were examined to improve the yield of the reaction. However, inferior results were obtained in all cases. As an alternative to coupling of tin reagents, a boron variant wherein one of the halides is transformed to borate followed by intramolecular Suzuki coupling has been reported, for example, using bis(pinacolato)-diborane.[21,28] All attempted couplings of **16** using the latter strategy were unsuccessful, resulting only in complete loss of starting material and the formation of intractable products.

The structure and relative stereochemistry of indole precursor **17** were confirmed by extensive NMR experiments and single crystal X-ray analysis (see Supporting Information). Palladium-catalyzed reductive *N*-heterocyclization of **17** in the presence of carbon monoxide gave expected tetracyclic indole **18**, the immediate precursor to the alkaloid ht-13-B, as a single isomer. Finally, the *N*-methoxycarbonyl protecting group of **18** was reduced to a methyl group using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene at 110 °C to afford ht-13-B in high isolated yield.[29] Reduction of **18** using a large excess of lithium aluminum hydride (LAH) in refluxing tetrahydrofuran (THF) was also attempted; however, this only resulted in complete recovery of the starting material. The structure of the final product was elucidated by extensive NMR experiments and single crystal X-ray analysis (see Supporting Information). The NMR, IR, HRMS, melting point,[30] and optical rotation were compared with literature data, which all corroborated the originally proposed structure. The overall yield of ht-13-B in seven steps starting from **1** was 8%.

■ EXPERIMENTAL SECTION

General Procedures. All NMR spectra were recorded in $CDCl_3$ at 600 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR, ^{1}H-broadband decoupled) at ambient temperature unless otherwise stated. Chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^{1}H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. HRMS data were obtained via electrospray ionization (ESI) with an ion trap mass analyzer.

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Scheme 4. Synthesis of Ht-13-B

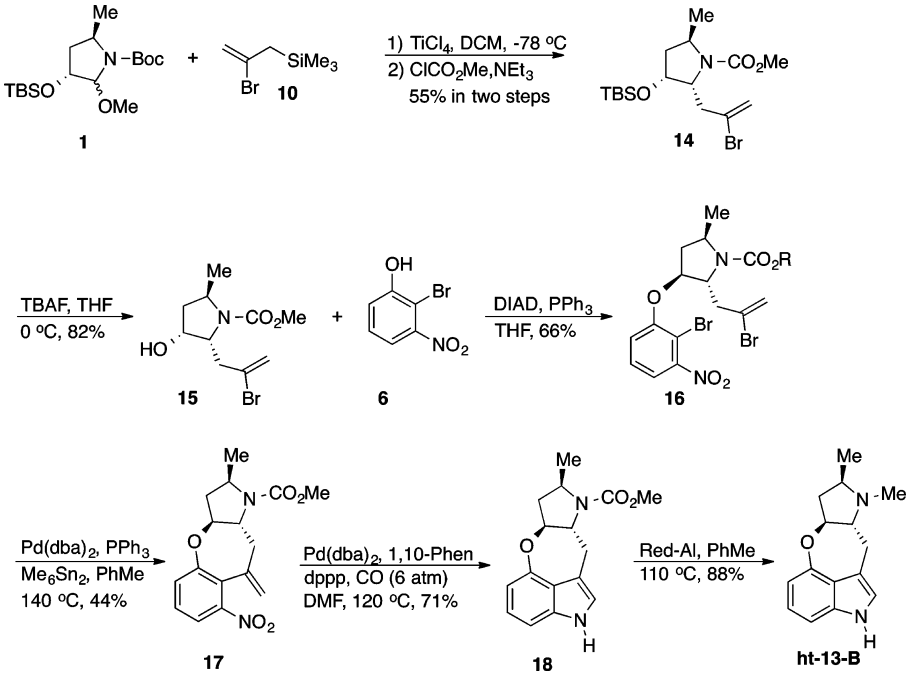
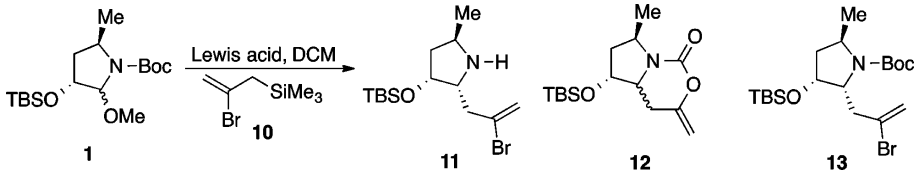


Table 1. Allylation of 1 Using 2-Bromo-2-propen-1-yltrimethylsilane (11)



Lewis acid	temperature	products (% isolated yield)		
$TiCl_4$	−78 °C to RT	**11** (56%)	**12** (30%)	
BF_3OEt_2	−78 °C to RT	**11** (<41%)[a]	**12** (trace)	
BF_3OEt_2	−78 °C	**1** (47%)		**13** (19%)
BF_3OEt_2	−78 to −30 °C		**12** (23%)	**13** (43%)

[a]Mixture of isomers plus unknown products.

THF was purified and dried via two consecutive columns composed of activated alumina and Q5 catalyst on a Glass Contours solvent purification system. Dichloromethane and toluene were purified and dried via two consecutive columns composed of activated alumina on a Glass Contours solvent purification system. Hexanes and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures are referenced the first time they are used in the Experimental Section; all other reagents were obtained from commercial sources and used as received. All reactions were performed under a nitrogen atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure.

3(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-5(*R*)-methyl-2-(2-propen-1-yl)pyrrolidine (2). A solution of **1**[11] (762 mg, 2.20 mmol) and allyltrimethylsilane (1.40 mL, 8.81 mmol) in CH_2Cl_2 (10 mL) was cooled to −78 °C and stirred for 15 min. $TiCl_4$ (490 μL, 4.46 mmol) dissolved in CH_2Cl_2 (5 mL) was slowly added via an addition funnel. The cold bath was removed after 5 min, and the mixture was stirred at ambient temperature for an additional 2 h. The reaction mixture was poured into a slurry of $Na_2CO_3{\cdot}10H_2O$ (6 g) in CH_2Cl_2 (7 mL). After being stirred for 15 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed to afford the crude mixture of isomeric **2** (511 mg). The product decomposed upon purification, and **2** was thus used as such to prepare **3**.

Spectral data from the 5:1 mixture of isomers of **2**. Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.09 (d, *J* = 17.4 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.20 (br s, 1H), 3.58 (dt, *J* = 14.4, 7.2 Hz, 1H), 3.13 (dt, *J* = 7.1, 3.4 Hz, 1H), 2.33 (pent, *J* = 6.6 Hz, 1H), 2.26 (pent, *J* = 7.2 Hz, 1H), 1.92 (dd, *J* = 12.6, 6.6 Hz, 1H), 1.49 (ddd, *J* = 13.2, 9.0, 4.8 Hz, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 136.0, 116.5, 73.9, 62.9, 51.3, 43.8, 33.7, 25.8, 22.1, 18.0, −4.4, −5.0.

Partial spectral data for the minor isomer of **2**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (pent, *J* = 4.2 Hz, 1H), 3.37 (ddd, *J* = 15.0, 12.6, 6.0 Hz, 2H), 2.95 (dt, *J* = 7.6, 5.3 Hz, 1H), 2.14 (pent, *J* = 7.4 Hz, 1H), 1.75 (ddd, *J* = 13.2, 6.6, 3.6 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 135.7, 116.9, 67.0, 52.3, 43.5, 38.3, 21.3, 18.0, −4.5, −4.7.

1-(*tert*-Butoxycarbonyl)-3(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5(*R*)-methyl-2-(2-propen-1-yl)-pyrrolidine (3). To a suspension of **2** (511 mg, 2.00 mmol) and CH_2Cl_2 (5 mL) was added triethylamine (0.84 mL, 6.03 mmol). The solution was cooled to −20 °C followed by addition of di-*t*-butyl dicarbonate (475 mg, 2.18 mmol), and the reaction mixture was stirred for 20 h slowly reaching ambient temperature. The reaction mixture was washed with H_3PO_4 (aqueous, 1 M, 2 × 5 mL) and saturated $NaHCO_3$ (aqueous, 2 × 5 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvents were removed giving crude **3** (627 mg). The material was used as such to

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prepare **4** and **5**. In a separate experiment on an 8.21 mmol scale of **2**, the crude product was purified by chromatography (hexanes/EtOAc, 1:1), affording a mixture of isomers used for characterization.

Spectral data from the mixture for the major isomer/rotamer of **3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.86 (pent, J = 8.0 Hz, 1H), 5.02 (d, J = 18.6 Hz, 1H), 4.95 (d, J = 9.6 Hz, 1H), 4.45−4.43 (m, 1H), 4.03−3.76 (m, 2H), 2.61−2.49 (m, 1H), 2.26−2.24 (m, 1H), 1.93−2.08 (m, 1H), 1.69−1.65 (m, 1H), 1.47 (s, 9H), 1.19 (d, J = 6.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H).

Partial spectral data for minor isomer/rotamer of **3**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (pent, J = 8.6 Hz, 1H), 1.45 (s, 9H), 1.15 (d, J = 6.0 Hz, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H).

Spectral data for the mixture of both isomers of **3**: ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 146.7, 136.7, 136.5, 135.1, 116.9, 116.3, 85.1, 79.2, 78.9, 78.9, 70.8, 70.2, 67.2, 60.4, 60.1, 52.4, 51.7, 50.6, 50.4, 40.0, 39.0, 33.7, 32.3, 28.6, 28.5, 27.4, 25.8, 25.7, 22.3, 21.2, 18.1, 17.9, −4.9; IR (ATR) 2957, 2930, 1693, 1383; HRMS (ESI) calcd for $C_{19}H_{37}NNaO_3Si$ $[M + Na]^+$ 378.2440, found 378.2440.

1-(*t*-Butoxycarbonyl)-3(*R*)-hydroxy-5(*R*)-methyl-2(*R*)-(2-propen-1-yl)pyrrolidine (4) and 1-(*t*-Butoxycarbonyl)-3(*R*)-hydroxy-5(*R*)-methyl-2(*S*)-(2-propen-1-yl)pyrrolidine (5). To a 0 °C cold solution of **3** (626 mg, 1.76 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (1 M in THF, 3.8 mL). The reaction mixture was stirred for 26 h slowly allowing for the cold bath to reach ambient temperature. The reaction mixture was poured into H_2O (50 mL) and extracted with EtOAc (4 × 25 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 7:3) gave **4** (286 mg, 1.18 mmol, 54%) followed by **5** (56 mg, 0.23 mmol, 11%).[31]

Spectral data of **4** as a mixture of rotamers at ambient temperature: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.95−5.88 (m, 1H), 5.10 (d, J = 17.4 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 4.54 (s, 1H), 3.89 (br s, 2H), 2.91 (br s, 1H), 2.55 (s, 1H), 2.37 (s, 1H), 2.08−2.04 (m, 1H), 1.82−1.78 (m, 1H), 1.47 (s, 9H), 1.19 (br s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.0, 136.3, 116.5, 79.3, 70.4, 70.1, 59.5, 50.5, 39.2, 38.2, 33.6, 32.3, 28.4, 21.8, 20.7; IR (ATR) 3436, 1663, 1366, 1172, 1063 cm^{-1}; $[\alpha]_D^{25}$ − 39.6 (c 1.02, $CHCl_3$); HRMS (ESI) calcd for $C_{13}H_{24}NO_3$ $[M + H]^+$ 242.1756, found 242.1751.

Partial spectral data for **4** as a mixture of rotamers at 60 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.91 (ddt, J = 17.4, 10.2, 7.2 Hz, 1H), 5.11 (dq, J = 17.4, 1.8 Hz, 1H), 5.02 (d with further fine splitting, J = 10.2 Hz, 1H), 4.51 (dt, J = 16.8, 7.2 Hz, 1H), 3.93 (br s, 1H), 3.87 (pent, J = 6.6 Hz, 1H), 2.54 (pent, J = 7.2 Hz, 1 Hz, 0.5H), 2.45 (br s, 1H), 2.21 (br s, 1H), 2.04 (ddt, J = 12.0, 10.8, 9.0 Hz, 1H), 1.79 (ddd, J = 12.0, 6.6, 1.8 Hz, 1H), 1.47 (s, 9H), 1.19 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.1, 136.5, 129.9, 116.5, 79.3, 70.6, 59.7, 50.7, 39.2, 33.0, 28.5, 28.4, 21.3.

Spectral data for **5** as a mixture of rotamers at ambient temperature: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77−5.84 (m, 1H), 5.09−5.06 (m, 2H), 4.11 (s, 1H), 4.00 (br s, 1H), 3.78 (s, 1H), 2.42 (br s, 1H), 2.06−2.09 (m, 3H), 1.74−1.79 (m, 1H), 1.47 (s, 9H), 1.27 (br s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 134.8, 117.2, 79.3, 73.2, 66.8, 52.1, 40.6, 38.6, 28.5, 21.9; IR (ATR) 3405, 1664, 1390, 1169, 1096 cm^{-1}; $[\alpha]_D^{25}$ − 8.1 ± 0.7 (c 5.75, MeOH); HRMS (ESI) calcd for $C_{13}H_{24}NO_3$ $[M + H]^+$ 242.1756, found 242.1751.

Partial spectral data for **5** as a mixture of rotamers at 60 °C: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81 (ddt, J = 16.8, 10.2, 6.9 Hz, 1H), 5.09−5.05 (m, 2H), 4.11 (t, J = 1.2 Hz, 1H), 4.00 (q, J = 6.6 Hz, 1H), 3.76 (br s, 1H), 2.44−2.42 (m, 1H), 2.09 (dt with further fine splitting, J = 15.0, 7.8 Hz, 1H), 2.05 (dddd, J = 13.7, 7.4, 2.7, 1.3 Hz, 1H), 1.76 (ddd, J = 13.8, 8.4, 4.8 Hz, 1H), 1.73 (br s, 1H), 1.47 (s, 9H), 1.26 (d, J = 6.6 Hz, 3H); Ambient temperature: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.1, 134.9, 117.1, 79.3, 73.7, 67.0, 52.3, 40.8, 38.6, 28.6, 22.1.

2(*R*)-(2-Propen-1-yl)-1-(*t*-butoxycarbonyl)-3(*S*)-(2-bromo-3-nitrophenoxy-5(*R*)-methylpyrrolidine (7). To a solution of **4** (423 mg, 1.75 mmol) in THF (5 mL) were added triphenylphosphine (690 mg, 2.63 mmol) and **6** (574 mg, 2.63 mmol). The solution was cooled to 0 °C in an ice bath, and diisopropylazodicarboxylate (520 μL, 2.62 mmol) was added dropwise. The mixture was stirred at ambient temperature for 2 h. The solvent was removed, and the resulting mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated $NaHCO_3$ (sat. aqueous, 25 mL) and HCl (10% aqueous, 25 mL). The organic phase was dried ($MgSO_4$) and filtered, and the solvent was removed. Purification by chromatography (hexanes/EtOAc, 7:3) gave **7** (542 mg, 1.23 mmol, 70%) as a pale yellow oil.

Spectral data for **7** as a mixture of rotamers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, J = 7.8 Hz, 0.5H), 7.35 (t, J = 7.2 Hz, 0.5H), 7.30 (d, J = 9.0 Hz, 0.5H), 7.29 (d, J = 8.4 Hz, 0.5H), 7.05 (d, J=8.4 Hz, 1H), 5.90−5.80 (m, 1H), 5.19 (d, J = 16.8 Hz, 1H), 5.18 (d, J = 10.8 Hz, 1H), 4.70 (s, 0.5H), 4.69 (s, 0.5H), 3.96−4.14 (m, 2H), 2.77 (d, J = 13.2 Hz, 0.5H), 2.62 (d, J = 9.6 Hz, 0.5H), 2.52−2.44 (m, 1H), 2.20−2.14 (m, 1H), 2.04−1.96 (m, 1H), 1.48 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 155.2, 153.8, 153.3, 152.2, 152.2, 134.3, 134.0, 128.4, 128.3, 118.7, 118.6, 116.6, 116.5, 116.1, 116.0, 105.5, 105.3, 82.4, 81.1, 79.6, 79.6, 62.9, 62.7, 60.3, 53.2, 53.1, 37.4, 36.4, 36.1, 35.5, 28.4, 21.7, 20.5; IR (ATR) 2976, 1682, 1534, 1387, 1269 cm^{-1}; $[\alpha]_D^{25}$ 0.12 ± 0.01 (c 1.0, MeOH); HRMS (ESI) calcd for $C_{19}H_{26}BrN_2O_5$ $[M + H]^+$ 441.1026, found 441.1023.

Tricyclic Compounds (8). A solution of **7** (200 mg, 0.45 mmol), $Pd(OAc)_2$ (7.4 mg, 0.03 mmol), and tri(*o*-tolyl)phosphine (39 mg, 0.13 mmol) in triethylamine (7 mL) in a Teflon screw-capped ACE-Glass pressure tube was stirred at 120 °C for 31 h. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 9:1) to give (47 mg, 0.13 mmol, 29%) as a white solid.[32]

Spectral data for **8** as a 1:1 mixture of rotamers: mp 125−127 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.2, 2.4 Hz, 1H), 7.28−7.24 (m, 2H), 6.08 (br s, 1H), 5.83 (br s, 0.5H), 5.73 (br s, 0.5H), 4.90 (br s, 1H), 3.80 (ddt, J = 16.8, 10.2, 7.2 Hz, 3H), 3.29 (dd, J = 12.6, 7.2 Hz, 1H), 2.57 (br s, 1H), 1.93 (dt, J = 12.6, 10.8 Hz, 1H), 1.48 (s, 9H), 1.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.8, 153.9, 149.9, 136.2, 134.3, 133.2, 128.4, 128.2, 127.7, 127.3, 126.8, 125.9, 120.6, 120.5, 87.3, 86.8, 80.0, 61.8, 56.4, 52.2, 51.6, 40.3, 37.4, 28.4, 26.4, 21.8, 20.1; IR (ATR) 1691,1528, 1154, 1031, 712 cm^{-1}; $[\alpha]_D^{25}$ 159.0 ± 0.6 (c 1.0, MeOH); HRMS (ESI) calcd for $C_{19}H_{25}N_2O_5$ $[M + H]^+$ 361.1758, found 361.1758.

2(*R*)-(2-Bromo-2-propen-1-yl)-3(*R*)-[(*tert*-butyldimethylsilyl)-oxy]-5(*R*)-methylpyrrolidine (11) and 5(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-(4a)-hexahydro-3-methylene-7(*R*)-methyl-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (12). A solution of **1** (123 mg, 0.36 mmol) and 2-bromo-2-propen-1-yl trimethylsilane (250 μL, 1.43 mmol) in CH_2Cl_2 (4 μL) was cooled to −78 °C and stirred for 15 min. A solution of $TiCl_4$ (74 μL, 0.67 mmol) in CH_2Cl_2 (1.5 mL) was added slowly. The cold bath was removed after 5 min, and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3 \cdot 10H_2O$ (1.2 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed. Purification by chromatography (hexanes/EtOAc, 1:1) gave, in order of elution, **12** (32 mg, 0.11 mmol, 30%, *dr* = 1.8:1) as a pale brown oil and **11** (67 mg, 0.20 mmol, 56%, *dr* approximately 9:1)[33] as a brown oil.

Spectral data for the major isomer of **11**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (d, J = 1.2 Hz, 1H), 5.49 (d, J = 1.6 Hz, 1H), 4.58 (br s, 1H), 4.30 (br dt, 1H), 3.66 (dpent, J = 8.6, 6.7 Hz, 1H), 3.58 (dt, J = 6.7, 3.9 Hz, 1H), 2.69 (d, J = 6.7 Hz, 2H), 1.96 (ddd, J = 13.3, 7.0, 2.0 Hz, 1H), 1.60 (ddd, J = 13.3, 9.0, 4.3 Hz, 1H), 1.26 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3, 118.8, 73.4, 61.0, 51.7, 43.4, 40.9, 25.8, 21.4, 18.0, −4.4, −4.9; IR (ATR) 2956, 1701, 1125, 1051, 833, 773 cm^{-1}; $[\alpha]_D^{25}$ −12 ± 2 (c 0.1, $CHCl_3$); HRMS (ESI) calcd for $C_{14}H_{29}BrNOSi$ $[M + H]^+$ 334.1202, found 334.1197.

Spectral data from a 1:1 mixture of diastereomeric **12**: ^{1}H (600 MHz, $CDCl_3$) NMR δ 4.65−4.63 (br m, 2H), 4.24 (t, J = 1.8 Hz, 1H), 4.22 (t, J = 1.8 Hz, 1H), 4.17 (t, J = 3.0 Hz, 1H), 4.10 (dp, J = 6.8, 4.0 Hz, 1H), 4.06 (br dp, J = 5.2, 4.4 Hz, 1H), 3.96 (ddd, J = 14.4, 7.8, 6.6 Hz, 1H), 3.59 (ddd, J = 12.0, 4.2, 3.6 Hz, 1H), 3.27 (ddd, J = 11.4, 7.8, 3.0 Hz, 1H), 2.81 (dd, J = 13.8, 3.0 Hz, 1H), 2.51 (ddt, J = 13.5, 11.8, 1.8 Hz, 1H), 2.37 (dd, J = 13.2, 4.2 Hz, 1H), 2.16 (ddt, J = 13.8, 12.0, 1.8 Hz, 1H), 2.07 (dd, J = 13.2, 6.6 Hz, 1H), 1.95 (ddd, J = 19.2, 10.2,

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8.4 Hz, 1H), 1.84 (dd, J = 12.6, 6.0 Hz, 1H), 1.57 (ddd, J = 13.8, 10.2, 3.6 Hz, 1H), 1.35 (d, J = 6.0 Hz, 3H), 1.28 (d, J = 6.6 Hz, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 152.3, 150.4, 149.0, 92.9, 92.8, 74.4, 71.3, 60.6, 60.0, 53.2, 51.9, 41.8, 39.6, 31.7, 26.5, 25.6, 25.5, 20.8, 19.9, 17.9, 17.8, −4.6, −4.7, −4.9, −5.1; IR (ATR) 2930, 1721, 1251, 1057, 832 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{28}NO_3Si$ $[M + H]^+$ 298.1838, found 298.1829.

2(*R*)-(2-Bromo-2-propen-1-yl)-3(*R*)-[(*tert*-butyldimethylsilyl)-oxy]-1-(*t*-butoxycarbonyl)-5(*R*)-methyl-pyrrolidine (13) and (12). A solution of **1** (100 mg, 0.29 mmol) and 2-bromoallyltrimethylsilane (200 μL, 1.16 mmol) in CH_2Cl_2 (2 mL) was cooled to −78 °C and stirred for 15 min. $BF_3{\cdot}Et_2O$ (82 μL, 0.66 mmol) was added slowly. The mixture was stirred at −78 °C for 1 h and then slowly warmed to −30 °C in 1 h and stirred for additional 1.5 h. Then, the mixture was quenched by pouring it into $NaHCO_3$ (sat. aqueous, 10 mL) at −30 °C. The mixture was warmed to ambient temperature and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. The resulting residue was purified by chromatography (hexanes/EtOAc, 60:1) to afford, in order of elution, **13** (54 mg, 0.12 mmol, 43%, *dr* = 8:1) as a colorless oil and **12** (20 mg, 0.07 mmol, 23%, *dr* = 1.1:1) as a brown oil.

Spectral data for major isomer/rotamer of **13**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 °C) δ 5.59 (d, J = 1.0 1H), 5.39 (s, 1H), 4.46 (dt, J = 10.8, 6.8 Hz, 1H), 4.17−4.08 (m, 1H), 3.84 (pent, J = 6.6 Hz, 1H), 2.86 (dd, J = 15.1, 6.4 Hz, 1H), 2.67−2.53 (m, 1H), 2.10−2.0 (m, 1H), 1.66 (dd, J=11.0, 6.6 Hz, 1H), 1.45 (s, 9H), 1.19 (d, J=6.3 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

Partial spectral data for minor isomer/rotamer of **13**: ^{1}H NMR (400 MHz, $CDCl_3$, 65 °C) δ 5.58 (s, 1H), 5.46 (d, J = 0.9 Hz, 1H), 4.31 (pent, J = 4.7 Hz, 1H), 3.41 (dd, J = 11.2, 4.8 Hz, 1H), 2.7 (br d, 1H), 1.44 (s, 9H).

Spectral data for mixture of both isomers of **13**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 153.9, 132.0, 131.8, 118.9, 118.4, 118.2, 79.8, 79.3, 78.9, 70.6, 70.0, 66.2, 58.5, 58.3, 52.5, 51.7, 50.4, 50.1, 40.8, 39.5, 39.4, 38.6, 28.5, 25.8, 25.7, 25.6, 22.1, 21.0, 18.2, 17.9, 17.8, −4.7, −4.8, −4.8, −4.9, −4.9; IR (ATR) 2957,1694, 1384, 1068, 774 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{37}BrNO_3Si$ $[M + H]^+$ 434.1726, found 434.1722.

2(*R*)-(2-Bromo-2-propen-1-yl)-3(*R*)-[(*tert*-butyldimethylsilyl)-oxy]-1-(methoxycarbonyl)-5(*R*)-methylpyrrolidine (14). To a suspension of **11** (61 mg, 0.18 mmol) and CH_2Cl_2 (1.0 mL) was added triethylamine (73 μL, 0.52 mmol), followed by dropwise addition of methyl chloroformate (30 μL, 0.39 mmol). The reaction mixture was stirred at ambient temperature for 20 h then poured into brine (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were combined, dried ($MgSO_4$), and filtered. The solvents were removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 40:1) to give **14** (29 mg, 0.074 mmol, 41%, *dr* approximately 9:1) as a colorless oil.

Spectral data for **14** from the mixture of isomers. Major isomer: ^{1}H NMR (600 MHz, $CDCl_3$, 65 °C) δ 5.55 (s, 1H), 5.39 (s, 1H), 4.48 (dt, J = 11.4, 7.2 Hz, 1H), 4.19 (q, J = 6.0 Hz, 1H), 3.91 (pent, J = 6.6 Hz, 1H), 3.63 (s, 3H), 2.87 (dd, J = 15.0, 5.4 Hz, 1H), 2.53 (br s, 1H), 2.11−2.02 (q, J = 9.6 Hz, 1H), 1.70 (dd, J = 12.6, 6.6 Hz, 1H), 1.22 (d, J = 6.1 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H).

Partial spectral data for the minor isomer: ^{1}H NMR (600 MHz, $CDCl_3$, 65 °C) δ 4.35 (pent, J = 4.8 Hz, 1H), 4.00 (m, 1H), 3.67 (s, 3H).

From the mixture of isomers/rotamers at ambient temperature: ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.3, 132.2, 118.5, 117.8, 70.1, 59.0, 58.2, 52.0, 51.4, 50.3, 41.3, 39.6, 39.4, 38.5, 25.8, 25.7, 21.9, 21.0, 18.1, −4.9, −4.9; IR (ATR) 2955,1702, 1371, 1079, 774 cm^{-1}; $[\alpha]_D^{25}$ 2.4 ± 0.1 (c 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{30}BrNNaO_3Si$ $[M + Na]^+$ 414.1076, found 414.1072.

Alternative Synthesis of 14. A solution of **1** (687 mg, 1.99 mmol) and 2-bromoallyltrimethylsilane (1.37 mL, 7.97 mmol) in CH_2Cl_2 (22 mL) was cooled to −78 °C and stirred for 15 min. $TiCl_4$ (410 μL, 3.74 mmol) in CH_2Cl_2 (8 mL) was added slowly. The cold bath was removed after 5 min, and the mixture was stirred at ambient temperature for an additional 1 h. $Na_2CO_3{\cdot}10H_2O$ (6.68 g) was added slowly. After stirring for 30 min, the mixture was dried ($MgSO_4$) and filtered, and the solvent was removed to give a light yellow residue (802 mg). The residue was dissolved in CH_2Cl_2 (6 mL), and triethylamine (960 μL, 6.92 mmol) was added followed by dropwise addition of methyl chloroformate (400 μL, 5.16 mmol). The reaction mixture was stirred at ambient temperature for 18 h. Brine (50 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. The resulting residue was purified by chromatography (hexanes/EtOAc, 40:1) to give **14** (426 mg, 1.09 mmol, 55%, *dr* approximately 9:1) as a colorless oil.

2(*R*)-(2-Bromo-2-propen-1-yl)-3(*R*)-hydroxy-1-(methoxycarbonyl)-5(*R*)-methylpyrrolidine (15). To a solution of **14** (191 mg, 0.49 mmol) in THF (4 mL) was added tetrabutylammonium fluoride (1 M in THF, 0.93 mL). The reaction mixture was stirred at ambient temperature for 2 h. The resulting mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 3:1) gave **15** (112 mg, 0.40 mmol, 82%)[34] as a white solid.

Spectral data for **15** as a mixture of rotamers: mp 65−66 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.69 (s, 0.4H), 5.62 (s, 0.6H), 5.46 (s, 1H), 4.57 (m, 1H), 4.18 (td, J = 6.0, 4.2 Hz, 1H), 3.94 (s, 1H), 3.66 (s, 3H), 2.98 (s, 0.4H), 2.87 (dd, J = 14.4, 7.2 Hz, 1H), 2.57 (s, 0.6H), 2.00−2.35 (br m, 2H), 1.84 (dd, J = 11.4, 5.4), 1.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) major rotamer δ 155.2, 131.6, 118.0, 69.1, 57.8, 51.4, 50.3, 40.9, 37.4, 20.4; Partial ^{13}C NMR (150 MHz, $CDCl_3$) spectral data for minor rotamer δ 131.1, 118.6, 58.8, 51.9, 50.7, 39.0, 38.7, 21.3; IR (ATR) 3359, 2965, 1668, 1376, 1068, 734 cm^{-1}; $[\alpha]_D^{25}$ −11.6 ± 0.1 (c 1, $CHCl_3$); HRMS (ESI) calcd for $C_{10}H_{16}BrNNaO_3$ $[M + Na]^+$ 300.0211, found 300.0200.

3(*S*)-(2-Bromo-3-nitrophenoxy)-2(*R*)-(2-bromo-propen-1-yl)-1-(methoxycarbonyl)-5(*R*)-methylpyrrolidine (16). To a solution of **15** (607 mg, 2.18 mmol) in THF (32 mL) were added triphenylphosphine (1.95 g, 7.45 mmol) and **6** (713 mg, 3.27 mmol). The solution was cooled to 0 °C, and diisopropylazodicarboxylate (1.74 mL, 8.84 mmol) was added dropwise. The mixture was stirred at ambient temperature for 19 h; brine (50 mL) was added, and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvent was removed at reduced pressure. Purification by chromatography (CH_2Cl_2/hexanes, 1:1, then CH_2Cl_2) gave **16** (693 mg, 1.45 mmol, 66%) as a pale yellow oil.

Spectral data for **16** as a mixture of rotamers: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (t, J = 8.2 Hz, 0.5H), 7.37 (t, J = 8.1 Hz, 0.5H), 7.32 (d, J = 7.0 Hz, 0.5H), 7.31 (d, J = 7.9 Hz, 0.5H), 7.11 (d, J = 8.2 Hz, 0.5H), 7.10 (d, J = 8.2 Hz, 0.5H), 5.73 (s, 0.5H), 5.71 (s, 0.5H), 5.61 (s, 1H), 4.88 (d, J = 4.7 Hz, 0.5H), 4.83 (d, J = 4.6 Hz, 0.5H), 4.40 (dd, J = 10.0, 2.3 Hz, 0.5H), 4.31 (dd, J = 9.9, 2.8 Hz, 0.5H), 4.16 (pd, J = 6.3, 2.3 Hz, 0.5H), 4.08 (d, J = 6.4 Hz, 0.5H), 3.72 (s, 1.5H), 3.71 (s, 1.5H), 3.19 (dd, J = 14.5, 2.8 Hz, 0.5H), 2.94 (dd, J = 14.3, 3.0 Hz, 0.5H), 2.56−2.39 (m, 2H), 2.08 (d, J = 14.2 Hz, 0.5H), 2.06 (d, J = 14.5 Hz, 0.5H), 1.54 (d, J = 6.4 Hz, 1.5H), 1.48 (d, J = 6.5 Hz, 1.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 154.9, 154.8, 154.8, 154.3, 152.0, 152.0, 129.2, 129.2, 128.5, 128.5, 120.4, 120.4, 116.9, 116.8, 116.3, 116.3, 105.4, 105.3, 81.4, 80.4, 62.6, 61.5, 53.5, 53.0, 52.2, 52.1, 44.1, 42.4, 36.2, 35.3, 21.5, 20.4; IR (ATR) 2954, 1686, 1533, 1357, 1268, 732 cm^{-1}; $[\alpha]_D^{25}$ −1.4 ± 0.1 (c 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{18}Br_2N_2NaO_5$ $[M + Na]^+$ 498.9480, found 498.9462.

Tricyclic Compound 17. A solution of **16** (100 mg, 0.21 mmol), $Pd(dba)_2$ (30 mg, 0.05 mmol), triphenylphosphine (55 mg, 0.21 mmol), and hexamethylditin (105 mg, 0.32 mmol) in toluene (2 mL) was stirred at 140 °C for 3 h. The mixture was cooled to ambient temperature, diluted with EtOAc (4 mL), and washed with NH_4OH (10% aqueous, 4 × 2 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 10:1) to give **17** (29 mg, 0.09 mmol, 44%)[35] as a brown solid.

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Spectral data for **17** as a mixture of rotamers:[36] mp 139−142 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 65 °C) δ 7.35 (br s, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.08 (br s, 1H), 5.26 (br s, 1H), 4.94 (s, 1H), 3.91 (br m, 2H), 3.70 (s, 3H), 2.53 (dt, J = 12.6, 7.2 Hz, 1H), 2.31 (br s, 1H), 1.74 (dd, J = 15.6, 9.6 Hz, 1H), 1.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.0, 155.2, 155.1, 154.7, 151.7, 139.3, 138.7, 129.3, 128.8, 128.3, 124.0, 121.9, 120.7, 119.7, 118.9, 116.1, 85.3, 78.6, 62.1, 57.5, 52.7, 52.0, 51.3, 43.5, 42.4, 39.5, 38.3, 37.7, 21.6, 20.1; IR (ATR) 2955, 1695, 1527, 1251, 1071, 733 cm^{-1}; $[\alpha]_D^{25}$ −240.9 ± 0.3 (c 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{18}N_2NaO_5$ $[M + Na]^+$ 341.1113, found 341.1111.

(6a*R*,8*R*,9a*S*)-7-Methoxycarbonyl-6,6a,7,8,9,9a-hexahydro-8-methyl-*H*-pyrrolo[2′,3′:6,7]oxepino[4,3,2-*cd*]indole (18). A solution of **17** (119 mg, 0.37 mmol), $Pd(dba)_2$ (12.9 mg, 0.02 mmol),1,3-bis(diphenylphosphino)propane (9.23 mg, 0.02 mmol), and 1,10-phenanthroline (8.12 mg, 0.05 mmol) in anhydrous DMF (1.2 mL) in a Teflon screw-capped ACE-Glass pressure tube was saturated with carbon monoxide (4 cycles to 6 atm of CO). The reaction mixture was stirred under CO (6 atm) at 120 °C for 37 h. The mixture was cooled to ambient temperature, diluted with EtOAc (10 mL), and washed with brine (2 × 10 mL). The organic phase was dried ($MgSO_4$) and filtered. The solvent was removed, and the resulting residue was purified by chromatography (hexanes/EtOAc, 4:1) to afford **18** (76 mg, 0.27 mmol, 71%) as a white solid.

Spectral data for **18** from a mixture of rotamers: mp 190−193 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.99 (dd, J = 7.8, 0.6 Hz, 1H), 6.97 (br s, 1H), 6.65 (d, J = 7.8 Hz, 1H), 4.44 (apparent dt, J = 7.8, 1.8 Hz, 1H), 4.35 (br s, 0.5H), 4.02 (br pent, J = 4.6 Hz, 1H), 3.95 (dpent, J = 9.6, 6.6 Hz, 1H), partially overlapping 3.9 (br s, 0.5H), 3.75 (s, 3H), 2.64 (br s, 1H), 2.54 (br s, 1H), 2.01 (dt, J = 12.6, 9.6 Hz, 1H), 1.53 (br s, 1.5H), 1.43 (br s, 1.5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 155.2, 151.5, 138.6, 122.6, 120.8, 116.8, 109.7, 105.6, 104.3, 84.4, 63.4, 52.3, 51.9, 39.7, 31.4, 30.1, 21.5, 20.0; IR (ATR) 3323, 2925, 1676, 1074, 733 cm^{-1}; $[\alpha]_D^{25}$ −286.5 ± 0.4 (c 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{16}H_{19}N_2O_3$ $[M + H]^+$ 287.1396, found 287.1391.

6,6a(*R*),7,8,9,9a(*S*)-Hexahydro-7,8(*R*)-dimethyl-*H*-pyrrolo-[2′,3′:6,7]oxepino[4,3,2-*cd*]indole (ht-13-B). To a solution of **18** (116 mg, 0.41 mmol) in anhydrous toluene (40 mL) was added sodium bis(2-methoxyethoxy)aluminumhydride (in toluene ∼3.5M, 2.56 mL, 8.96 mmol) dropwise. The mixture was stirred at 110 °C for 5 h and then allowed to cool to ambient temperature. Brine (80 mL) was added, and the mixture was extracted with EtOAc (3 × 80 mL). The organic phases were combined, dried ($MgSO_4$), and filtered. The solvent was removed, and the resulting residue was purified by chromatography (EtOAc) to give ht-13-B (88 mg, 0.36 mmol, 88%) as a white solid.

Spectral data for synthetic ht-13-B: mp 180−182 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 7.07 (t, J = 7.8 Hz, 1H), 6.98 (s, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 7.8 Hz 1H), 4.45 (ddd, J = 10.2, 6.0, 4.2 Hz, 1H), 3.45 (dpent, J = 6.6, 2.4 Hz, 1H), 3.37 (dd, J = 15.0, 4.2 Hz, 1H), 3.17 (ddd, J = 12.0, 6.0, 4.2 Hz, 1H), 2.73 (ddd, J = 14.4, 10.2, 7.8 Hz, 1H), 2.65 (ddd, J = 14.4, 12.0, 1.8 Hz, 1H), 2.45 (s, 3H), 1.87 (ddd, J = 13.8, 3.6, 2.4 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.0, 138.8, 122.7, 120.3, 117.0, 110.7, 106.0, 104.0, 86.1, 67.3, 57.9, 38.6, 35.0, 29.0, 14.2; IR (ATR) 3400, 3154, 2925, 1244, 1067, 733 cm^{-1}; $[\alpha]_D^{25}$ −202.1 ± 0.1 (c 1.0, $CHCl_3$); HRMS (ESI) calcd for $C_{15}H_{19}N_2O$ $[M + H]^+$ 243.1497, found 243.1492.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra and single crystal X-ray information files. 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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(30) Mp 180−182 °C; lit. mp (ref 1) 182−184 °C.
(31) Overall yield starting from **1**.
(32) A small amount of a second unidentified product was observed in the NMR spectra, but the products could not be separated by chromatography.
(33) The diastereomeric ratio varied from 2:1 to 1:1 between different runs.
(34) We were unable to determine *dr* due to broad unresolved NMR resonances.
(35) Integration of the two resolved methyl doublets at *d* 1.32 and 1.27 in the ^{1}H NMR spectrum at 65 °C suggest a *dr* of 15:1.
(36) Most of the ^{1}H NMR signals were unresolved even at 65 °C.

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