JOC The Journal of Organic Chemistry

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Preparation of 1-Substituted Tetrahydro-β-carbolines by Lithiation–Substitution

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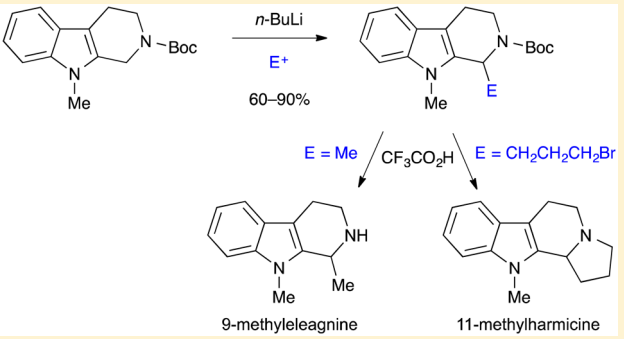
Supporting Information

ABSTRACT: A method to prepare 1-substituted *N*-Boc-tetrahydro-β-carbolines was developed by lithiation followed by electrophilic substitution. The deprotonation to give the organolithium was optimized by in situ IR spectroscopy and showed that the Boc group rotates slowly at low temperature. The chemistry was applied to the synthesis of 9-methyleleagnine (*N*-methyltetrahydroharman) and 11-methylharmicine.



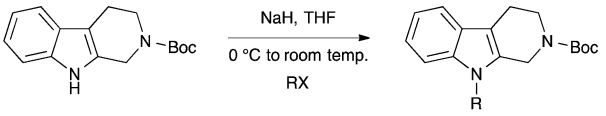
The prevalence of substituted saturated nitrogen heterocycles in natural products and medicinal drug compounds has encouraged us in our studies of the preparation of such compounds using lithiation–substitution chemistry. Lithiation can be achieved adjacent to the nitrogen atom with various *N*-substituted cyclic amines, of which the *N*-*tert*-butoxycarbonyl (Boc) group has proven to be one of the most popular.[1] We have applied this chemistry to the formation of substituted pyrrolidines,[2] piperidines,[2b,3] piperazines,[4] imidazolidines,[5] and tetrahydroisoquinolines.[6] Another important ring system found in many natural products and drug molecules is tetrahydro-β-carboline.[7] This ring system is present in alkaloids, such as eleagnine, isolated from *Chrysophyllum albidum*,[8] and harmicine, isolated from *Kopsia griffithii* (Figure 1).[9]

Figure 1. Structures of some tetrahydro-β-carboline natural products.

Tetrahydro-β-carboline can be lithiated at the 1-position when the indole nitrogen is protected as an alkyl group and the nitrogen atom in the 6-membered ring is part of a formamidine or amide.[10] However, the more common Boc group has not, as far as we are aware, been used for this chemistry. We report here the successful lithiation–substitution of this type of compound.

We prepared the Boc-protected tetrahydro-β-carboline **1** from tryptamine and paraformaldehyde in acetic acid and MeOH followed by the addition of Boc_2O using a known procedure.[11] Protection of the indole nitrogen atom was carried out to give a selection of substituted derivatives **2a–e** (Table 1). In each case, high yields of the product were obtained using NaH as the base followed by addition of the electrophile RX.

Table 1. Preparation of Substrates 2a–e



entry	RX	R	product	yield (%)
1	MOMCl	MOM	**2a**	93
2	Boc_2O	Boc	**2b**	82
3	BnBr	Bn	**2c**	94
4	TsCl	SO_2Tol	**2d**	92
5	MeI	Me	**2e**	90

Initially, we studied tetrahydro-β-carboline **2a**, and in situ IR spectroscopic monitoring indicated that lithiation was complete after ∼4 min in Et_2O/TMEDA at −50 °C (see the Supporting Information (SI)). However, the addition of iodomethane gave only byproducts rather than the desired 1-methylated product, and we found that the starting material **2a** was unstable upon standing at room temperature. Therefore, we selected to study derivatives **2b–e**.

We had similar problems upon using substrates **2c** and **2d** bearing an indole *N*-benzyl or *N*-tosyl group, respectively. Only decomposition products were obtained upon treatment of these compounds with *n*-BuLi in Et_2O/TMEDA at −50 °C. Using

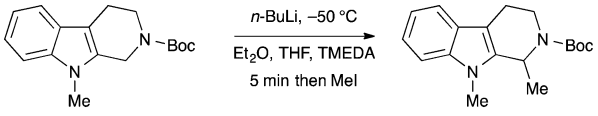
Received: April 2, 2015
Published: May 14, 2015

DOI: 10.1021/acs.joc.5b00725
J. Org. Chem. 2015, 80, 5964–5969

tetrahydro-β-carboline **2b**, the reaction with *n*-BuLi under the same conditions followed by the addition of iodomethane gave an approximately equal mixture of recovered tetrahydro-β-carboline **2b**, tetrahydro-β-carboline **1**, and its *N*-methylated analogue (**2e**); we did not observe any product from Boc migration.[12] We also attempted lithiation of tetrahydro-β-carboline **1** using two equivalents of *n*-BuLi in Et_2O/TMEDA at −50 °C followed by the addition of iodomethane; however, the only product was tetrahydro-β-carboline **2e** (isolated in 78% yield), and no products from lithiation at C-1 were obtained.

Fortunately, indole *N*-methyl analogue **2e** behaved much better in this chemistry. This compound was not very soluble in Et_2O, so THF was initially used as the cosolvent. Under these conditions, a good yield of desired product **3a** was obtained (Scheme 1).

Scheme 1. Initial Lithiation−Methylation of Tetrahydro-β-carboline 2e



The use of several solvents and an additive (TMEDA) as outlined in Scheme 1 is not ideal, so we screened a selection of solvents with and without TMEDA (Table 2). The simplest

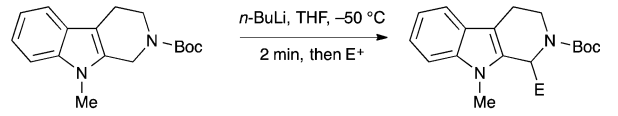
Table 2. Optimization of Lithiation of 2e

entry	solvent	temp (°C)	time (min)	yield **3a** (%)
1	THF, TMEDA	−78	10	60
2	THF	−78	10	51
3	**THF**	**−50**	**4**	**90**
4	PhMe, TMEDA	−78	10	69
5	PhMe, TMEDA	−50	4	95

conditions were to carry out the lithiation in THF at −50 °C. If the reaction was conducted at −78 °C, then the yields were generally lower (50−69% after 10 min reaction time), indicating that the rate of rotation of the Boc group was slow at this temperature. Following the reaction in THF at −50 °C by in situ IR spectroscopy showed that lithiation was complete within a few minutes (Figure 2).[13] In contrast, partial lithation followed by slow further lithiation occurs at −78 °C (see SI). Variable temperature NMR spectroscopy was carried out with tetrahydro-β-carboline **2e** (see SI). Coalescence of the signals (ratio 1.3:1) for the *N*-CH_3 group in D_8-THF occurred at 10 °C. Line shape analysis indicated that the approximate activation parameters for Boc rotation are $\Delta H^{\ddagger}$ = 59.6 kJ/mol and $\Delta S^{\ddagger}$ = −9.8 J K^{-1} mol^{-1}. The half-life for rotation can therefore be determined to be $t_{1/2}$ = ∼45 s at −50 °C and ∼85 min at −78 °C.

The optimized lithiation conditions were used to prepare a selection of 1-substituted tetrahydro-β-carboline products **3a−f** after electrophilic quenching (Scheme 2, Figure 3). Addition of

Scheme 2. Preparation of Tetrahydro-β-carbolines 3a−f



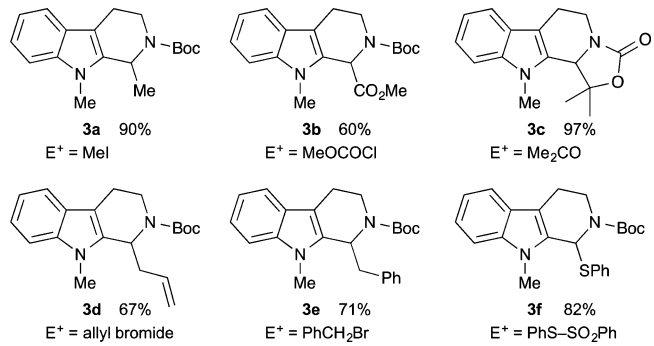


Figure 3. Structures and yields of tetrahydro-β-carboline products **3a−f**.

iodomethane gave product **3a** in 90% yield, showing that neither Et_2O nor TMEDA are required for successful reaction. The carbonyl electrophiles MeOCOCl and acetone gave products **3b** and **3c**, respectively, the latter being formed by cyclization of the intermediate alkoxide onto the Boc group. The reaction was amenable to allyl bromide or benzyl bromide as the electrophile to give products **3d** and **3e**, respectively. In addition, the electrophile PhS−SO_2Ph provided the 1-phenylthio tetrahydro-β-carboline product **3f** in good yield. However, the use of TMSCl or Bu_3SnCl gave only recovered starting material **2e**, and it is unclear why these were unsuccessful.

An attempt was made to carry out an asymmetric lithiation−substitution in the presence of the chiral ligand (−)-sparteine. To avoid competing solvation by THF, we used toluene as the

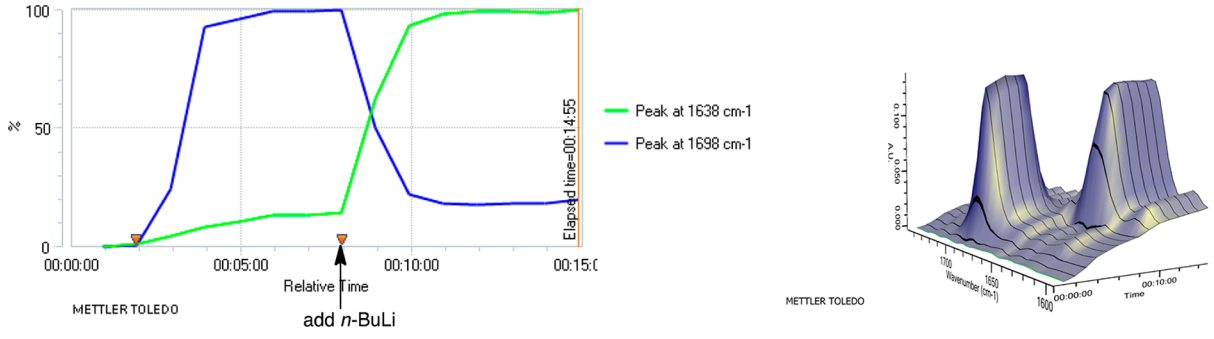


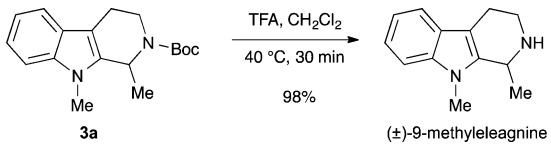
Figure 2. Monitoring the lithiation of tetrahydro-β-carboline **2e** in THF at −50 °C (blue line represents the intensity of the C═O stretching frequency of **2e** (1698 cm^{-1}) and green line of lithiated **2e** (1638 cm^{-1}) over time (in h:min:sec).

DOI: 10.1021/acs.joc.5b00725
J. Org. Chem. 2015, 80, 5964−5969

solvent. Following the lithiation by in situ IR spectroscopy showed rapid but partial (~50%) lithiation at −78 °C (corresponding to lithiation of the rotamer with the carbonyl group pointing toward the benzylic position) followed by slow further lithiation over the course of ~1 h (corresponding to slow rotation of the Boc group and subsequent lithiation) (see SI). Addition of iodomethane gave product **3a** (84% yield) but with poor enantioselectivity (56:44 er). It is possible that iodomethane quenches only slowly after warming;[14] thus, to further investigate the potential for any asymmetric induction, we added tetrahydro-*β*-carboline **2e** to a solution of premixed *n*-BuLi and chiral ligand (+)-sparteine-surrogate at −78 °C, which can be used in THF,[15] followed by trapping after only 5 min with the electrophile acetone. These conditions do not promote full lithiation due to slow rotation of the Boc group, but acetone should trap any enantioenriched organolithium at −78 °C. Product **3c** was formed in 24% yield as a racemic mixture. It is likely that the intermediate organolithium is configurationally unstable at this temperature (as found for the related tetrahydroisoquinoline),[6a] and if so, then the lack of asymmetric induction presumably arises from poor kinetic selectivity on reaction of the diastereomeric organolithium−(−)-sparteine complexes with the electrophile.[16]

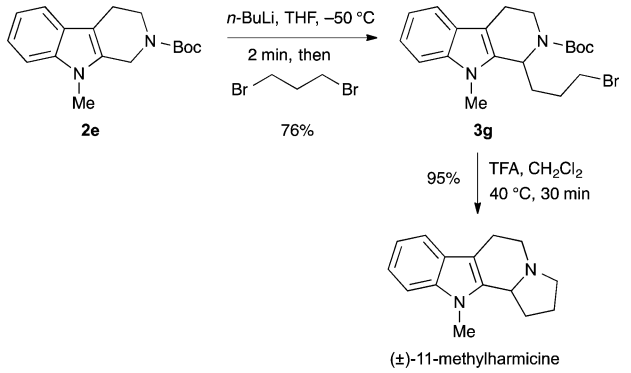
Treatment of tetrahydro-*β*-carboline product **3a** with trifluoroacetic acid (TFA) promoted deprotection of the Boc group to give 9-methyleleagnine[17] (Scheme 3). In addition, we

Scheme 3. Removal of the Boc Group from 3a



treated tetrahydro-*β*-carboline **2e** with *n*-BuLi in THF at −50 °C for 2 min followed by the addition of 1,3-dibromopropane to give product **3g** (Scheme 4). This reaction was conducted at

Scheme 4. Preparation of 11-Methylharmicine



lower concentration to help reduce any double alkylation. Product **3g** was then treated with TFA to give 11-methylharmicine.[18] These products are indole-*N*-methylated analogues of the natural products; it would be useful to be able to *N*-demethylate, although we have not attempted this transformation and related demethylations of indoles are rare in organic chemistry.[19]

We have shown that, of a range of tetrahydro-*β*-carbolines, only a simple alkyl (methyl) group on the indole nitrogen atom is suitable for Boc-directed lithiation at C-1. By using this compound, a range of different 1-substituted tetrahydro-*β*-carbolines can be prepared. The use of in situ IR spectroscopy revealed that the Boc group rotates slowly at −78 °C, and the lithiation is conducted better at −50 °C, where the Boc group is rotating more quickly. No significant asymmetric induction was obtained with this tetrahydro-*β*-carboline, (−)-sparteine or (+)-sparteine-surrogate as the chiral ligand, and iodomethane or acetone as the electrophile, although it may be possible to develop an asymmetric substitution with other chiral ligands and electrophiles. The chemistry was applied to a short synthesis of two indole-*N*-methylated natural products, eleagnine and harmicine.

EXPERIMENTAL SECTION

***tert*-Butyl-2,3,4,9-tetrahydro-1*H*-*β*-carboline-2-carboxylate (1).**[11] To a 0.25 M solution of tryptamine (10 g, 62 mmol) in a mixture of AcOH:MeOH (10:1) was added paraformaldehyde (2 g, 74 mmol). The mixture was heated to 80 °C for 1 h and then cooled to room temperature. The mixture was basified to pH 9−10 using $NH_4OH_{(aq)}$ and was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was evaporated to give the crude amine, which was added to Boc_2O (13.5 g, 62 mmol) in THF at 0 °C. The mixture was allowed to warm to room temperature over 16 h, and saturated aqueous $NaHCO_3$ was added. The mixture was extracted with Et_2O, and the combined organic extracts were washed with brine and dried ($MgSO_4$), and the solvent was evaporated. Purification by column chromatography on silica gel gave the product, which was recrystallized from MeCN to give carbamate **1** (13.8 g, 82%) as needles; mp 148−150 °C, lit.[11] 151 °C; R_f = 0.50 [petrol−EtOAc (75:25)]; FT-IR ν_{max} film 3295, 2800, 1670, 1395, 1370, 1150, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 8.60 (0.65H, br s), 8.00 (0.35H, br s), 7.51 (1H, d, J = 7.5 Hz), 7.34 (1H, d, J = 7.5 Hz), 7.23−7.09 (2H, m), 4.70 (1.3H, br s), 4.65 (0.7H, br s), 3.80 (2H, br), 2.84 (2H, br), 1.57 (9H, br s); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.6 (br), 136.3, 130.8 (br), 127.0, 121.5, 119.3, 117.9, 111.0, 108.1 (br), 80.3, 42.7, 42.0, and 41.5 (br), 28.6, 21.5 (br); HRMS (ES) $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_2$ 273.1603, found 273.1591. Data is in accordance with the literature.[11]

***tert*-Butyl-9-(methoxymethyl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline-2-carboxylate (2a).** Carbamate **1** (6.6 g, 24 mmol) in THF was added to NaH (700 mg, 60 wt % mineral oil suspension, 29 mmol) in THF (0.25 M) at 0 °C. The mixture was warmed to room temperature, and MOMCl (2.7 mL, 36 mmol) was added. After 30 min, water was added, and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (90:10), gave carbamate **2a** (7.1 g, 93%) as an oil; R_f = 0.30 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2970, 2925, 1685, 1465, 1410, 1160, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 8.0 Hz), 7.44 (1H, d, J = 8.0 Hz), 7.24 (1H, t, J = 8.0 Hz), 7.19−7.13 (1H, m), 5.38 (2H, s), 4.72 (2H, br s), 3.80 (2H, br), 3.28 (3H, s), 2.83 (2H, br), 1.55 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$, one C not observable) δ 155.2, 137.3, 132.1 (br), 127.2, 121.9, 120.0, 118.1, 109.2, 80.1, 74.1, 55.8, 42.3 (br), 40.8 (br), 28.5, 21.4 (br); HRMS (ES) $[M + Na]^+$ calcd for $C_{18}H_{24}N_2O_3Na$ 339.1685, found 339.1690.

Di-*tert*-butyl-2,3,4,9-tetrahydro-1*H*-*β*-carboline-2,9-dicarboxylate (2b). In the same manner as carbamate **2a**, carbamate **1** (272 mg, 1 mmol), NaH (60 mg, 60 wt % mineral oil suspension, 1.5 mmol), and Boc_2O (240 mg, 1.1 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **2b** (306 mg, 82%) as an amorphous solid; mp 106−108 °C; R_f = 0.45 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2975, 2930, 1725, 1695, 1375, 1360, 1140, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, d, J = 8.0 Hz), 7.43 (1H, d, J = 8.0 Hz), 7.35−7.22 (2H, m), 4.84 (2H, br s), 3.76 (2H, br), 2.76 (2H, br), 1.70 (9H, s), 1.53 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$, two C not observable) δ 155.0,

DOI: 10.1021/acs.joc.5b00725
J. Org. Chem. 2015, 80, 5964−5969

150.0, 135.9 (br), 128.9, 124.0, 122.7, 117.7, 115.4, 83.9, 80.0, 44.4 (br), 40.2 (br), 28.5, 28.3, 21.2 (br); HRMS (ES) $[M + H]^+$ calcd for $C_{21}H_{29}N_2O_4$ 373.2127, found 373.2110.

***tert*-Butyl-9-benzyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (2c).**[20] In the same manner as carbamate **2a**, carbamate **1** (272 mg, 1.0 mmol), NaH (60 mg, 60 wt % mineral oil suspension, 1.5 mmol), and BnBr (0.18 mL, 1.5 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **2c** (341 mg, 94%) as an oil; R_f = 0.55 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2980, 2930, 2850, 1695, 1410, 1365, 1235, 1160, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.56 (1H, d, J = 7.5 Hz), 7.35−7.23 (4H, m), 7.22−7.17 (2H, m), 7.09−7.02 (2H, m), 5.25 (2H, br s), 4.56 (2H, br s), 3.77 (2H, br), 2.87 (2H, br), 1.52 (5H, br s), 1.45 (4H, br s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 137.4, 137.0, 132.0 (br), 128.9, 127.5, 126.8, 126.3, 121.5, 119.4, 118.1, 109.2, 108.2 (br), 80.1, 46.8, 42.4 (br), 40.9 (br), 28.4, 21.7 (br); HRMS (ES) $[M + H]^+$ calcd for $C_{23}H_{27}N_2O_2$ 363.2073, found 363.2070. Data is in accordance with the literature.[20]

***tert*-Butyl-9-tosyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (2d).** In the same manner as carbamate **2a**, carbamate **1** (2.0 g, 7.3 mmol), NaH (360 mg, 60 wt % mineral oil suspension, 15.0 mmol), and TsCl (1.7 g, 8.8 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **2d** (2.9 g, 92%) as an amorphous solid; mp 148−150 °C; R_f = 0.25 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2980, 2935, 2845, 1695, 1425, 1370, 1170, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1H, d, J = 8.5 Hz), 7.74 (2H, br s), 7.37 (1H, d, J = 7.5 Hz), 7.34−7.16 (4H, m), 4.93 (2H, br s), 3.73 (2H, br), 2.70 (2H, br), 2.34 (3H, s), 1.53 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$, two C not observable) δ 154.7, 144.9, 136.1, 135.6, 129.9, 129.6, 126.5, 124.5, 123.5, 118.3, 114.3, 80.2, 43.4 (br), 40.3 (br), 28.5, 21.5, 21.2 (br); HRMS (ES) $[M + H]^+$ calcd for $C_{23}H_{27}N_2O_4S$ 427.1692, found 427.1678.

***tert*-Butyl-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (2e).** In the same manner as carbamate **2a**, carbamate **1** (272 mg, 1 mmol), NaH (60 mg, 60 wt % mineral oil suspension, 1.5 mmol), and MeI (0.1 mL, 1.5 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **2e** (258 mg, 90%) as an amorphous solid; mp 100−102 °C; R_f = 0.30 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2980, 2910, 1685, 1395, 1230, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 7.5 Hz), 7.35−7.29 (1H, m), 7.23 (1H, t, J = 7.5 Hz), 7.16−7.10 (1H, m), 4.68 (2H, br s), 3.80 (2H, br), 3.65 (3H, s), 2.84 (2H, br), 1.56 (9H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 137.1, 132.1 (br), 126.5, 121.2, 119.1, 118.0, 108.7, 107.4 (br), 80.1, 42.5 (br), 41.1 (br), 29.3, 28.5, 21.7 (br); HRMS (ES) $[M + H]^+$ calcd for $C_{17}H_{23}N_2O_2$ 287.1760, found 287.1762.

***tert*-Butyl-1-methyl-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (3a).** *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes) was added to carbamate **2e** (200 mg, 0.70 mmol) in THF (0.25 M) at −50 °C. After 2 min, MeI (0.07 mL, 1.05 mmol) was added, and the mixture was allowed to warm to room temperature over 16 h. Saturated aq NH_4Cl was added, and the mixture was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered, and evaporated. Purification by column chromatography on silica gel, eluting with petrol−EtOAc (90:10), gave carbamate **3a** (189 mg, 90%) as an oil; R_f = 0.40 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2980, 2930, 1685, 1410, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.57−7.49 (1H, m), 7.35−7.30 (1H, m), 7.25 (1H, t, J = 7.5 Hz), 7.19−7.11 (1H, m), 5.52 (0.6H, q, J = 6.5 Hz), 5.28 (0.4H, q, J = 6.5 Hz), 4.54 (0.4H, br dd, J = 13.0, 5.5 Hz), 4.34 (0.6H, br dd, J = 13.0, 5.5 Hz), 3.70 (3H, s), 3.36−3.15 (1H, m), 2.95−2.70 (2H, m), 1.55 (9H, br s), 1.53 (3H, d, J = 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 154.6 and 154.3, 137.3 and 137.2, 136.9 and 136.1, 126.4, 121.5 and 121.3, 119.2 and 119.1, 118.3 and 118.1, 108.9, 107.5 and 106.8 (br), 79.9, 46.6 and 45.5, 37.9 and 36.6, 29.8, 28.6, 21.6 and 21.3, 19.3 and 19.2; HRMS (ES) $[M + H]^+$ calcd for $C_{18}H_{25}N_2O_2$ 301.1916, found 301.1902.

Attempted Asymmetric Reaction. To a 0.25 M solution of *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes) and (−)-sparteine (197 mg, 0.84 mmol) in PhMe at −78 °C was added a solution of carbamate **2e** (200 mg, 0.70 mmol) in PhMe. After 1 h, MeI (0.07 mL, 1.05 mmol) was added, and the mixture was warmed to room temperature over 16 h. Purification as above gave carbamate **3a** (176 mg, 84%) as an oil; 56:44 er, as determined by chiral stationary phase HPLC (the resolution between the enantiomers of carbamate **3a** was achieved using a Beckman system fitted with a Phenomenex Lux Cellulose-2 column (250 mm × 4.60 nm i.d.) as the stationary phase with a mixture of *n*-hexane and ^{i}PrOH (99:1 v/v) as the mobile phase at a flow rate of 1 mL min^{-1} at ambient temperature and detected by UV absorbance at 254 nm). Injection volume of 20 μm of sample was prepared in a 2 g L^{-1} solution of the eluent. Under these conditions, the two components were eluted at 10.5 and 12.0 min with an analysis time of 15 min.

1-Methyl 2-*tert*-butyl-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline-1,2-dicarboxylate (3b). In the same manner as carbamate **3a**, carbamate **2e** (200 mg, 0.70 mmol), *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes), and MeOCOCl (0.08 mL, 1.05 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **3b** (145 mg, 60%) as an oil; R_f = 0.25 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2970, 2930, 1745, 1690, 1365, 1290, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.56−7.46 (1H, m), 7.37−7.31 (1H, m), 7.30−7.21 (1H, m), 7.18−7.11 (1H, m), 5.98 (0.6H, s), 5.71 (0.4H, s), 4.44−4.24 (1H, m), 3.82 (3H, br s), 3.78 (3H, br s), 3.58−3.44 (1H, m), 2.97−2.74 (2H, m), 1.54 (9H, br s); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 170.2 and 170.0, 155.5 and 154.7, 137.9 and 137.8, 129.3 and 128.5, 126.0 and 125.9, 122.2 and 122.1, 119.4 and 119.3, 118.6 and 118.4, 109.3, 109.1 and 109.0, 80.8, 54.4 and 53.0, 52.7 and 52.6, 40.5 and 39.5, 30.7, 28.4, 21.1 and 20.7; HRMS (ES) $[M + Na]^+$ calcd for $C_{19}H_{24}N_2O_4Na$ 367.1634, found 367.1648.

3,3-Dimethyl-16-methyl-4-oxa-6.16-diazatetracyclo-[7.7.0.0^{2,6}.0^{10,15}]hexadeca-1(9),10(15),11,13-tetraen-5-one (3c). In the same manner as carbamate **3a**, carbamate **2e** (200 mg, 0.70 mmol), *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes), and acetone (0.08 mL, 1.05 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (80:20), carbamate **3c** (184 mg, 97%) as an amorphous solid; mp 140−143 °C; R_f = 0.39 [petrol−EtOAc (50:50)]; FT-IR ν_{max} film 2985, 2930, 1740, 1415, 1265 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (1H, d, J = 8.0 Hz), 7.38−7.25 (2H, m), 7.22−7.15 (1H, m), 5.01 (1H, s), 4.34−4.26 (1H, m), 3.73 (3H, s), 3.06−2.94 (1H, m), 2.92−2.87 (2H, m), 1.87 (3H, s), 1.11 (3H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 137.8, 130.0, 126.4, 122.5, 119.8, 118.7, 110.9, 109.2, 82.9, 61.6, 39.7, 31.4, 27.9, 23.7, 21.7; HRMS (ES) $[M + H]^+$ calcd for $C_{16}H_{19}N_2O_2$ 271.1447, found 271.1437.

Attempted Asymmetric Reaction. To a 0.25 M solution of *n*-BuLi (0.12 mL, 0.30 mmol, 2.4 M in hexanes) and (+)-sparteine-surrogate (57 mg, 0.30 mmol) in THF (3 mL) at −78 °C was added a solution of carbamate **2e** (70 mg, 0.25 mmol) in THF (2 mL). After 5 min, acetone (0.06 mL, 0.87 mmol) was added, and the mixture was warmed to room temperature over 16 h. Purification as above gave carbamate **3c** (16 mg, 24%) as an amorphous solid; 50:50 er, as determined by chiral stationary phase HPLC (the resolution between the enantiomers of carbamate **3c** was achieved using a Beckman system fitted with a Daicel ChiralPak AD column (250 mm × 4.60 nm i.d.) as the stationary phase with a mixture of *n*-hexane and ^{i}PrOH (97:3 v/v) as the mobile phase at a flow rate of 1 mL min^{-1} at ambient temperature and detected by UV absorbance at 254 nm). Injection volume of 25 μm of sample was prepared in a 2 g L^{-1} solution of the eluent. Under these conditions, the two components were eluted at 52.6 and 58.7 min with an analysis time of 75 min.

***tert*-Butyl-1-allyl-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (3d).** In the same manner as carbamate **3a**, carbamate **2e** (200 mg, 0.70 mmol), *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes), and allyl bromide (0.09 mL, 1.05 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **3d** (153 mg, 67%) as an oil; R_f = 0.45 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2975, 2930, 1680, 1410, 1370, 1165, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.58−7.49 (1H,

DOI: 10.1021/acs.joc.5b00725
J. Org. Chem. 2015, 80, 5964−5969

m), 7.36−7.31 (1H, m), 7.29−7.22 (1H, m), 7.20−7.13 (1H, m), 6.07−5.90 (1H, m), 5.54 (0.6H, dd, J = 10.0 Hz, 4.0 Hz), 5.32 (0.4H, t, J = 6.5 Hz), 5.24−5.11 (2H, m), 4.58 (0.4H, dd, J = 13.5, 5.5 Hz), 4.35 (0.6H, dd, J = 13.5, 5.5 Hz), 3.73 (1.2H, s), 3.71 (1.8H, s), 3.37−3.17 (1H, m), 2.99−2.84 (1H, m), 2.83−2.71 (1H, m), 2.69−2.52 (2H, m), 1.55 (4H, br s), 1.54 (5H, s); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.5 and 154.6, 137.4 and 137.3, 135.8 and 135.2, 134.5, 126.6 and 126.5, 121.6 and 121.4, 119.3 and 119.2, 118.3 and 118.1, 117.6 and 117.2, 108.95 and 108.9, 108.1 and 107.5, 80.1 and 79.8, 50.4 and 49.2, 39.0 and 38.7, 38.0 and 36.6, 30.1, 28.5, 21.4 and 21.1; HRMS (ES) $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_2$ 327.2073, found 327.2075.

***tert*-Butyl-1-benzyl-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (3e).** In the same manner as carbamate **3a**, carbamate **2e** (200 mg, 0.70 mmol), *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes), and BnBr (0.12 mL, 1.05 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **3e** (187 mg, 71%) as an oil; R_f = 0.45 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2975, 2930, 1690, 1410, 1370, 1165 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.53 (1H, m), 7.43−7.21 (7H, m), 7.20−7.14 (1H, m), 5.70 (0.4H, dd, J = 8.5, 5.5 Hz), 5.45 (0.6H, dd, J = 10.0, 4.0 Hz), 4.64 (0.6H, dd, J = 13.5, 5.5 Hz), 4.32 (0.4H, dd, J = 13.5, 5.5 Hz), 3.78 (1.8H, s), 3.59 (1.2H, s), 3.43−3.30 (1H, m), 3.27−2.72 (4H, m), 1.44 (3.6H, s), 1.21 (5.4H, s); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers, one C not observable) δ 154.7 and 154.2, 138.1, 137.6 and 137.4, 135.8 and 135.2, 129.5, 128.3 and 128.1, 126.7 and 126.5, 121.7 and 121.4, 119.4 and 119.2, 118.3 and 118.1, 109.0 and 108.9, 108.2, 79.7, 52.5 and 50.7, 40.4, 38.2 and 36.5, 30.0 and 29.9, 28.5 and 28.0, 21.4 and 21.2; HRMS (ES) $[M + H]^+$ calcd for $C_{24}H_{29}N_2O_2$ 377.2229, found 377.2239.

***tert*-Butyl-9-methyl-1-(phenylthio)-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (3f).** In the same manner as carbamate **3a**, carbamate **2e** (200 mg, 0.70 mmol), *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes), and $PhSSO_2Ph$ (263 mg, 1.05 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (95:5), carbamate **3f** (226 mg, 82%) as an oil; R_f = 0.70 [petrol−EtOAc (99:1)]; FT-IR ν_{max} film 2915, 2850, 1695, 1615, 1475, 1160, 1125 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.71−7.63 (2H, m), 7.57 (0.6H, d, J = 8.0 Hz), 7.54 (0.4H, d, J = 8.0 Hz), 7.46−7.33 (4H, m), 7.32−7.26 (1H, m), 7.21−7.13 (1H, m), 6.97 (0.4H, s), 6.67 (0.6H, s), 4.60 (0.6H, dd, J = 13.0, 5.5 Hz), 4.36 (0.4H, dd, J = 13.0, 5.5 Hz), 3.97 (1.8H, s), 3.90 (1.2H, s), 3.86 (0.4H, td, J = 13.0, 5.0 Hz), 3.83 (0.6H, td, J = 13.0, 5.0 Hz), 3.04−2.77 (2H, m), 1.42 (3.6H, s), 1.18 (5.4H, s); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 153.9 and 153.1, 137.5, 135.6 and 133.9, 133.2 and 133.1, 131.5 and 131.1, 129.2 and 129.0, 128.9 and 128.2, 126.1 and 126.0, 122.5 and 122.3, 119.5, 118.7 and 118.5, 110.5 and 109.8, 109.2 and 109.2, 80.5, 61.6 and 59.6, 37.8 and 36.3, 30.0, 28.3 and 27.9, 21.4 and 21.0; HRMS (ES) $[M + Na]^+$ calcd for $C_{23}H_{26}N_2O_2SNa$ 417.1627, found 417.1613.

***tert*-Butyl-1-(3-bromopropyl)-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline-2-carboxylate (3g).** In the same manner as carbamate **3a** (but at half concentration), carbamate **2e** (200 mg, 0.70 mmol), *n*-BuLi (0.34 mL, 0.84 mmol, 2.5 M in hexanes), and 1,3-dibromopropane (0.11 mL, 1.05 mmol) gave, after flash column chromatography on silica gel eluting with petrol−EtOAc (90:10), carbamate **3g** (217 mg, 76%) as an amorphous solid; mp 74−75 °C; R_f = 0.30 [petrol−EtOAc (90:10)]; FT-IR ν_{max} film 2960, 2900, 1675, 1405, 1250, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, rotamers) δ 7.57−7.47 (1H, m), 7.36−7.30 (1H, m), 7.28−7.20 (1H, m), 7.18−7.10 (1H, m), 5.47−5.42 (0.6H, m), 5.26−5.22 (0.4H, m), 4.53 (0.4H, dd, J = 13.5, 5.5 Hz), 4.31 (0.6H, dd, J = 13.5, 5.5 Hz), 3.75−3.67 (0.8H, m), 3.72 (3H, s), 3.66−3.51 (1.2H, m), 3.31−3.08 (1H, m), 3.00−2.80 (1H, m), 2.79−2.70 (1H, m), 2.19−1.86 (4H, m), 1.54 (3.6H, s), 1.52 (5.4H, s); ^{13}C NMR (101 MHz, $CDCl_3$, rotamers) δ 155.4 and 154.6, 137.3, 135.9 and 135.2, 126.5, 121.6 and 121.4, 119.3 and 119.2, 118.2 and 118.0, 108.9, 107.8 and 107.2, 80.4 and 80.0, 49.6 and 48.5, 38.0 and 36.7, 33.8 and 33.2, 32.2 and 31.6, 30.0, 29.2 and 28.9, 28.5, 21.4 and 20.9; HRMS (ES) $[M + H]^+$ calcd for $C_{20}H_{28}N_2O_2{}^{79}Br$ 407.1334, found 407.1340.

1-Methyl-9-methyl-2,3,4,9-tetrahydro-1*H*-β-carboline (9-methyleleagnine).[17] TFA (0.25 mL, 3.3 mmol) was added to carbamate **3a** (100 mg, 0.33 mmol) in CH_2Cl_2 (0.25 M), and the mixture was heated under reflux. After 1 h, the mixture was cooled to room temperature. Water was added, and the mixture was basified to pH 9−10 with aq NaOH (2 M). The mixture was extracted with CH_2Cl_2, and the combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. Purification by column chromatography on silica gel, eluting with CH_2Cl_2−MeOH (90:10), gave 9-methyleleagnine (65 mg, 98%) as an oil; R_f = 0.55 [CH_2Cl_2−MeOH (90:10)]; FT-IR ν_{max} film 3315, 3040, 2920, 2845, 1615, 1470, 1375, 1125, 1100 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (1H, d, J = 8.0 Hz), 7.33−7.26 (1H, m), 7.26−7.20 (1H, m), 7.16−7.10 (1H, m), 4.24 (1H, q, J = 6.5 Hz), 3.63 (3H, s), 3.52 (1H, br s), 3.31−3.26 (2H, m), 2.89−2.82 (2H, m), 1.59 (3H, d, J = 6.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 136.7, 126.6, 121.5, 119.2, 118.2, 108.8, 106.9, 46.4, 38.8, 29.9, 21.7, 20.3; HRMS (ES) $[M + H]^+$ calcd for $C_{13}H_{17}N_2$ 201.1392, found 201.1384. Data is in accordance with the literature.[17]

11-Methyl-2,3,5,6,11,11b-hexahydro-1*H*-indolizino[8,7-*b*]-indole (11-methylharmicine).[18] In the same manner as 9-methyleleagnine, carbamate **3g** (60 mg, 0.15 mmol) and TFA (0.11 mL, 1.5 mmol) gave, after flash column chromatography on silica gel eluting with CH_2Cl_2−MeOH (90:10), 11-methylharmicine (33 mg, 95%) as an oil; R_f = 0.50 [CH_2Cl_2−MeOH (90:10)]; FT-IR ν_{max} film 3045, 2910, 2845, 1470, 1375, 1320, 1185, 1130 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, J = 7.5 Hz), 7.33−7.27 (1H, m), 7.23−7.19 (1H, m), 7.16−7.11 (1H, m), 4.27 (1H, t, J = 7.5 Hz), 3.69 (3H, s), 3.31−3.22 (1H, m), 3.09−2.88 (4H, m), 2.79−2.70 (1H, m), 2.51−2.40 (1H, m), 2.02−1.81 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 137.1, 126.7, 121.0, 118.9, 118.1, 108.7, 106.7, 56.3, 51.0, 46.6, 30.4, 30.2, 23.8, 18.8; HRMS (ES) $[M + H]^+$ calcd for $C_{15}H_{19}N_2$ 227.1548, found 227.1553. Data is in accordance with the literature.[18]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional information, in situ IR spectra, and NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00725.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the EPSRC, the University of Sheffield, and AstraZeneca for funding. We are grateful to Nicholas Carter for conducting the (+)-sparteine surrogate experiment and to Susan Bradshaw for help with the NMR spectroscopic studies.

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