JOC The Journal of Organic Chemistry

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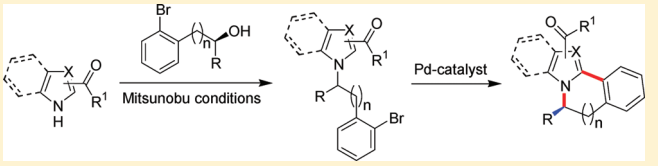
Synthesis of Fused Imidazoles, Pyrroles, and Indoles with a Defined Stereocenter α to Nitrogen Utilizing Mitsunobu Alkylation Followed by Palladium-Catalyzed Cyclization

Joydev K. Laha and Gregory D. Cuny*

Laboratory for Drug Discovery in Neurodegeneration, Harvard NeuroDiscovery Center, Brigham & Women's Hospital and Harvard Medical School, 65 Landsdowne Street, Cambridge, Massachusetts 02139, United States

Supporting Information

ABSTRACT: Nitrogen-containing fused heterocycles comprise many compounds that demonstrate interesting biological activities. A new synthetic approach involving Mitsunobu alkylation of imidazoles, pyrroles, and indoles followed by palladium-catalyzed cyclization has been developed providing access to fused heterocycles with a defined stereochemistry α to nitrogen. While ethyl imidazole or indole carboxylates are good substrates for Mitsunobu alkylation with optically pure secondary benzylic alcohols, the corresponding pyrroles are poor substrates presumably due to the increased pK_a of the NH. The presence of a synthetically versatile trichloroacetyl functional group on the pyrroles significantly reduces the pK_a and thereby facilitates Mitsunobu alkylation. Subsequent cyclization of the alkylated products mediated by palladium in the presence or absence of a ligand gave fused heterocycles in good to excellent yields.



Etomidate (**1a**) is a $GABA_A$ agonist with fast-acting sedative–hypnotic properties, while providing hemodynamic stability (Figure 1).[1] However, it also binds with high affinity to 11β-hydroxylase, potently suppressing the synthesis of steroids by the adrenal glands.[2] The stereocenter α to nitrogen in this class of molecules has an important influence on both of these pharmacological activities. For example, the anesthetic potency of etomidate's (*R*)-enantiomer is 1 order of magnitude higher than the (*S*)-enantiomer,[1d] while the adrenal inhibitory potency of the (*R*)-enantiomer of metomidate, the methyl ester derivative of **1a**, is 1 order of magnitude lower than the (*S*)-enantiomer.[2] The prolonged adrenocortical steroid synthesis suppression caused by etomidate has limited its clinical utility. In the course of conducting a structure–activity relationship (SAR) study to identify compounds with the desired pharmacological activities for general anesthesia, we discovered that a pyrrole analogue of etomidate, (*R*)-ethyl 1-(1-phenylethyl)-1*H*-pyrrole-2-carboxylate, termed carboetomidate (**1b**), specifically designed not to bind with high affinity to 11β-hydroxylase was a potent hypnotic with hemodynamic stability but lacked adrenocortical steroid synthesis suppression.[3] As part of continued SAR studies for etomidate, derivatives were contemplated in which the pendent phenyl and imidazole or pyrrole were connected through a C–C bond into a fused ring (e.g., **2**). However, synthesis of heterocycles such as **2** with a defined stereocenter α to nitrogen had limited literature precedence. Interestingly, similar compounds that lack a substituent α to nitrogen have been described as useful pharmaceutical agents and are also present in several natural products, including a subset of lamellarin alkaloids (e.g., lamellarin G, **3**). Hence, devising a synthetic strategy for the construction of

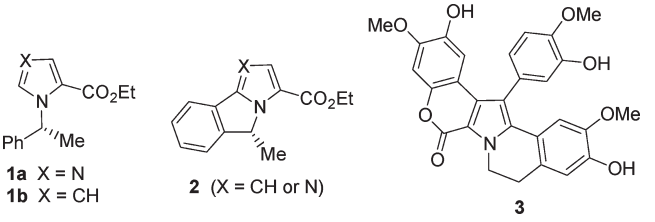


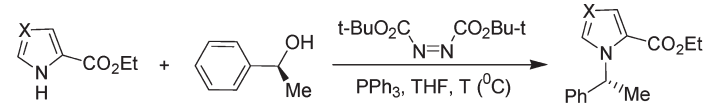
Figure 1. Structures of etomidate (**1a**), carboetomidate (**1b**), stereodefined fused heterocycle **2**, and lamellarin G (**3**).

fused heterocycles with a defined stereochemistry α to nitrogen appeared warranted.

A number of methods for the synthesis of fused heterocycles lacking a stereocenter α to nitrogen have been reported, including intramolecular cyclization of *N*-alkylated heterocycles[4−10] and a tandem process involving intermolecular *ortho*-alkylation of an aromatic C–H bond followed by intramolecular arylation.[11] Cyclization has been achieved by photostimulation,[4] tin hydride mediated reactions,[5] copper catalysis,[6] palladium-catalyzed reactions involving C–H bond activation of either aryl or heteroaryl components,[7−9] and palladium-catalyzed decarboxylative cross-couplings.[10] Several of these methods also involve the preparation of *N*-alkylated heterocycles using base-mediated anion generation of a nitrogen heterocycle followed by alkylation with an alkyl halide.[7−9] While *N*-alkylation of nitrogen heterocycles using primary alkyl halides is efficient, poor yields are often

Received: June 13, 2011
Published: September 13, 2011

Scheme 1. Synthesis of Etomidate (1a) and Carboetomidate (1b)



4a X = N
4b X = CH

5

	T (^{0}C)	Yield (%)
1a X = N	-40	70
1b X = CH	-40	0
	rt	17

obtained with secondary alkyl halides that can readily undergo elimination under basic reaction conditions. Moreover, formation of a stereogenic center α to nitrogen by alkylation with secondary alkyl halides has been rarely documented.[12] Herein, we report the use of Mitsunobu alkylation of imidazoles, pyrroles, and indoles followed by palladium-catalyzed cyclization to provide access to fused heterocycles with defined stereochemistry α to nitrogen.

The Mitsunobu reaction has been useful for alkylating nitrogen heterocycles using primary alcohols as the coupling partner provided the NH of the heterocycle has a pK_a < 11. However, sterically hindered secondary alcohols have often been poor substrates for the Mitsunobu reaction.[13] For example, the reaction of 4,5-dicyanoimidazole with the optically pure secondary benzylic alcohol (*S*)-1-phenylpropanol was reported to give the corresponding *N*-alkylated product in only 40% ee at room temperature or at −25 °C.[14] Racemization has been minimized by conducting the reaction at lower temperatures. For example, the reaction of methyl 1*H*-imidazole-5-carboxylate and (*S*)-1-phenylethanol in the presence of di-*tert*-butyl azodicarboxylate (DtBAD) and PPh_3 at −40 °C gave enantiomerically pure *N*-alkylated product metomidate in 67% yield.[2b] Using similar conditions, we were able to synthesize **1a** by coupling ethyl 1*H*-imidazole-5-carboxylate (**4a**) and (*S*)-1-phenylethanol (**5**) in 70% yield (Scheme 1). However, attempts to synthesize carboetomidate (**1b**) using this protocol were less successful. For example, the reaction of ethyl pyrrole-2-carboxylate (**4b**) and **5** at −40 °C did not produce **1b**. Conducting the reaction at room temperature did give the desired product **1b** in >99%ee, as determined by chiral HPLC, but in only 17% yield with a significant amount of **4b** remaining even after 72 h. Presumably the lower yield with the pyrrole derivative was due to the increased pK_a of the NH proton for the pyrrole compared to the imidazole. At this stage, an alternate pyrrole substrate was sought that would have a lower pK_a and that could be conveniently converted to **1b**. Since *N*-alkylation of pyrroles with a primary alcohol has been achieved successfully under Mitsunobu condition in the presence of an electron-withdrawing group this strategy was investigated with secondary alcohols.[15]

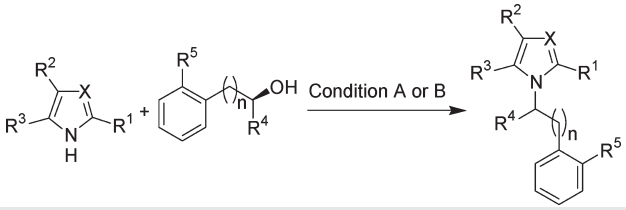
A survey of various substituted pyrrole derivatives was undertaken in order to identify a functional group that would facilitate the Mitsunobu coupling with **5**. Pyrrole did not undergo alkylation, while only a trace amount of the corresponding *N*-alkylated product was observed with pyrrole-2-carboxamide (Table 1, entries 1 and 2). A complex mixture of products was obtained with pyrrole-2-carboxaldehyde (entry 3). Addition of a bromine to the pyrrole ester, for example, with ethyl 4-bromopyrrole-2-carboxylate[16] or ethyl 5-bromopyrrole-2-carboxylate,[17] did not significantly improve the yield of the alkylated products **1c** and **1d** (entries 4 and 5). Similar reactivity was observed in the case of pyrrole-2-carbonitrile with the formation of **1e** in 20% yield (entry 6). However, a significant increase in yield of the alkylated product was obtained for pyrrole derivatives containing a trihaloacetyl group. For example, 2-(trifluoroacetyl)- or 2-(tricholoroacetyl)pyrrole reacted with **5** in the presence of DtBAD and PPh_3 at room temperature to give the alkylated products **1f** and **1g** in 51% and 55% yields, respectively, and >99% ee as determined with **1g** by chiral HPLC (entries 7 and 8). Presumably the increased yields for these two substrates reflect the lower pK_a values for the pyrrole NH caused by the strong electron-withdrawing nature of the trihaloacetyl group. Moreover, tricholoroacetyl also provides a convenient synthetic handle for conversion to other functionalities.[18] For example, treatment of **1g** with NaOEt in ethanol at room temperature for 1 h gave **1b** in 90% yield. Overall, 2-(tricholoroacetyl)pyrrole was converted to **1b** in two steps and in ∼50% yield, which was a significant improvement over the direct alkylation process.

The Mitsunobu alkylation was further extended to the preparation of substrates containing a bromine atom in the heterocycle or the alkylating component required for the synthesis of fused heterocycles. Following a similar protocol as described for the preparation of **1a** (conditions A), reaction of **4a** or ethyl imidazole-2-carboxylate and (*S*)-(−)-2-bromo-α-methylbenzyl alcohol gave 64% yield of **1h**[19] (entry 9) in >99% ee as determined by chiral HPLC and **1i** in 76% yield (entry 10). 2-(Tricholoroacetyl)pyrrole was alkylated with (*S*)-(−)-2-bromo-α-methylbenzyl alcohol or an alcohol without a methyl substituent, such as 2-bromobenzyl alcohol under conditions B, to give **1j-TCA** and **1k-TCA** in 62% and 51% yields, respectively (entries 11 and 12). Comparable reactivity of ethyl 3-indole carboxylate and 3-(tricholoroacetyl)indole[20] with (*S*)-(−)-2-bromo-α-methylbenzyl alcohol was observed, which led to the formation of **1l** and **1l-TCA** in 55% and 74% yields, respectively (entries 13 and 14). Finally, the homologous primary alcohols 2-bromophenethyl alcohol and 3-(2-bromophenyl)propan-1-ol[21] were allowed to react with **4a** under conditions B to give **1m** and **1n** in 65% and 67% yields, respectively (entries 15 and 16).

With the establishment of Mitsunobu alkylation as a viable route for introducing stereocenters α to nitrogen in imidazoles, pyrroles, and indoles, the palladium-catalyzed cyclizations of these substrates were studied. Heating a mixture of **1h**, K_2CO_3, and 10 mol % of $Pd(OAc)_2$ at 120 °C for 24 h (conditions C) gave **2a** in 93% yield (entry 1, Table 2). Under similar conditions, only a moderate yield (45%) of **2b** was obtained from **1i** (entry 2). Compound **1j**, obtained in 88% yield from **1j-TCA** by treatment with NaOEt in ethanol at room temperature for 3 h, under conditions C gave pyrrole-fused heterocycle **2c** in 82% yield (entry 3). Indole **1l** underwent regioselective cyclization at the 2-positon to give **2d** under conditions C, albeit in poor yield (<15%). However, other ligands such as SPhos (conditions D) and triphenylphosphine (conditions E) resulted in improved

dx.doi.org/10.1021/jo201237h |*J. Org. Chem.* 2011, 76, 8477–8482

Table 1. Mitsunobu Alkylation of Imidazoles, Pyrroles, and Indoles



entry	X	R^1	R^2	R^3	R^4	R^5	n	conditions[a]	product	% yield[b]
1	CH	H	H	H	Me	H	0	B		0
2	CH	CONHMe	H	H	Me	H	0	B		trace
3	CH	CHO	H	H	Me	H	0	B	*c*	0
4	CH	CO_2Et	Br	H	Me	H	0	B	**1c**	24
5	CH	CO_2Et	H	Br	Me	H	0	B	**1d**	25
6	CH	CN	H	H	Me	H	0	B	**1e**	20
7	CH	$COCF_3$	H	H	Me	H	0	B	**1f**	51
8	CH	$COCCl_3$	H	H	Me	H	0	B	**1g**	55
9	N	H	CO_2Et	H	Me	Br	0	A	**1h**	64
10	N	CO_2Et	H	H	Me	Br	0	A	**1i**	76
11	CH	$COCCl_3$	H	H	Me	Br	0	B	**1j-TCA**	62
12	CH	$COCCl_3$	H	H	H	Br	0	B	**1k-TCA**	51
13[e]	CCO_2Et	H	CHCH=CHCH		Me	Br	0	B	**1l**	55
14	$CCOCCl_3$	H	CHCH=CHCH		Me	Br	0	B	**1l-TCA**[d]	74
15	N	H	CO_2Et	H	H	Br	1	B	**1m**	65
16	N	H	CO_2Et	H	H	Br	2	B	**1n**	67

[a] Conditions A: alcohol (1.1 equiv), PPh_3 (1.3 equiv), DtBAD (1.35 equiv), THF, −40 °C, 3 h. Conditions B: alcohol (1.1 equiv), PPh_3 (1.3 equiv), DtBAD (1.35 equiv), THF, rt, 24 h. [b] Isolated yield. [c] Complex mixture. [d] Compound **1l** could also be obtained from **1l-TCA** in 87% yield by treatment with NaOEt in ethanol at room temperature for 3 h. [e] While the alkylation of ethyl indole-2-carboxylate gave 43% yield of the corresponding alkylated product, subsequent cyclization was not successful.

yields (48−52%, entry 4). In all cases, no product corresponding to cyclization at the 7-position was observed. The outcome of the cyclization of **1o**, which contains a secondary carboxylamide, was also of interest (entry 5). Compound **1o**, obtained in 98% yield from **1j-TCA** by treatment with 2 M $MeNH_2$ in THF, underwent cyclization regioselectively at the 5-positon under Pd-mediated conditions to give **2e** in 20% yield using condition C. Other ligands such as SPhos (conditions D) and Xantphos (conditions F) resulted in improved yields (70−80%). Interestingly, only C−C bond rather than C−N bond formation was observed in these cases. Cyclization of **1p** (obtained in 99% yield from **1k-TCA** by treatment with 2 M $MeNH_2$ in THF), which lacks the substituent α to nitrogen using conditions D, gave the pyrrolo-[2,1-*c*][1,4]benzodiazepine derivative **2f** in 57% yield (entry 6), which has not previously been prepared by a metal-mediated process.[22] However, the reasons for the different regioselectivities of substrates **1o** and **1p** are not readily apparent. The cyclization efficiency was also examined with a substrate containing a bromine atom on the heterocycle **1d** using conditions C−E (entry 7). However, **2c** was only generated in poor yields (10−20%) under these conditions. Finally, compounds **1m** and **1n** underwent Pd-mediated cyclizations using conditions C to generate the imidazole fused heterocycles **2g** and **2h** in 75% and 50% yields, respectively (entries 8 and 9).

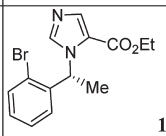
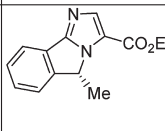
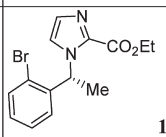
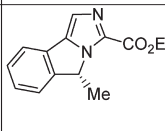
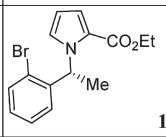
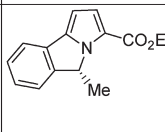
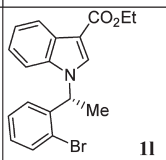
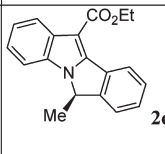
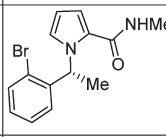
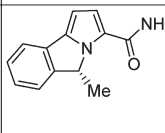
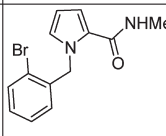
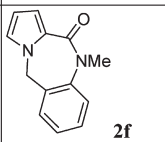
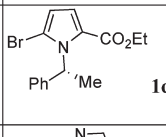
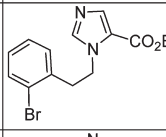
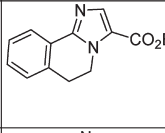
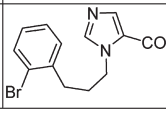
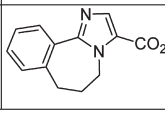
In conclusion, utilization of Mitsunobu alkylation of imidazoles, pyrroles, and indoles with optically pure secondary benzylic alcohols has been demonstrated. In addition, trichloroacetyl-substituted pyrroles offered better substrates for Mitsunobu alkylations and provides a convenient means for subsequent introduction of other functionality, as demonstrated by an improved synthesis of the potent hemodynamically stable sedative−hypnotic carboetomidate. Finally, palladium-mediated cyclizations of alkylated imidazoles, pyrroles, and indoles afforded fused derivatives with defined stereocenters α to the nitrogen were illustrated. These compounds will be useful in the continuing SAR studies of carboetomidate and in broader screening campaigns for identifying other biological activities.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. Ethyl 4-bromopyrrole carboxylate,[16] ethyl 5-bromopyrrole carboxylate,[17] 3-(trichloroacetyl)indole,[20] and 3-(2-bromophenyl)propan-1-ol[21] were prepared following literature procedures. All palladium reactions were conducted under an argon atmosphere. The ^1H NMR spectra were obtained using a 400 or 500 MHz spectrometer. All ^1H NMR spectra conducted in $CDCl_3$ and are reported in δ (ppm) and are reference to tetramethylsilane (TMS). Coupling constants (*J* values) are reported in hertz. All ^{13}C NMR spectra were recorded in $CDCl_3$. Note that for some compounds one or two signals did not resolve in the ^{13}C NMR spectra. Column chromatography was performed utilizing a CombiFlash Sg 100c separation system with disposable silica gel columns. High-resolution mass spectra were obtained by using a IonSpec 4.7 T FTMS. All melting points were taken in glass capillary tubes and are uncorrected. The enantiomeric purities (% ee) of **1b** and **1h** were determined by HPLC analysis using a Daicel Chiralpak AD column (250 × 4.6 mm) eluting with hexanes/*i*-PrOH (99:1 for **1b** and eluting time 12.59 min; 90:10 for **1h** and eluting time 8.50 min).

dx.doi.org/10.1021/jo201237h |*J. Org. Chem.* 2011, 76, 8477–8482

Table 2. Synthesis of Fused Imidazole, Pyrrole, and Indole Heterocycles

Entry	Substrate	Condition[a]	Product	(%)[b]
1	 **1h**	C	 **2a**	93
2	 **1i**	C	 **2b**	45
3	 **1j**[c]	C	 **2c**	82
4	 **1l**	C D E	 **2d**[d]	15 48 52
5	 **1o**	C D F	 **2e**	20 70 80
6	 **1p**	D	 **2f**	57
7	 **1d**	C D E	**2c**	10 15 20
8	 **1m**	C	 **2g**	75
9	 **1n**	C	 **2h**	50

[a] Conditions C: $Pd(OAc)_2$, K_2CO_3, DMF, 120 °C, 24 h. ConditionsD: $Pd_2(dba)_3$, Sphos, Cs_2CO_3, dioxane, 100 °C, 24 h. Conditions E: $Pd(PPh_3)_4$, Cs_2CO_3, dioxane, 100 °C, 24 h. Conditions F; $Pd(OAc)_2$, Xantphos, Cs_2CO_3, dioxane, 100 °C, 24 h. [b] Yield of fused heterocycles. [c] Attempted cyclization of **1j-TCA** under conditions E only gave extensive decomposition. [d] Ca. 90% pure.

General Procedure for Mitsunobu Alkylation. A solution of alcohol (1.10 mmol) in anhydrous THF (2 mL) was added dropwise to a stirred solution of heterocyclic substrate (1.00 mmol) and triphenylphosphine (340 mg, 1.30 mmol) in anhydrous THF (3 mL) under an argon atmosphere at −40 °C (condition A) or room temperature (condition B). Then a solution of di-*tert*-butyl azodicarboxylate (304 mg, 1.35 mmol) in anhydrous THF (2 mL) was added, and the reaction mixture was allowed to stir at the same temperature for 2 h (condition A) or overnight (condition B). The reaction mixture was concentrated under reduced pressure. The residue was mixed with diethyl ether (5 mL) and stirred for 2 h. The residue was collected and washed with diethyl ether (3 × 2 mL). The filtrate was evaporated under reduced pressure to yield a residue, which was purified by flash chromatography on silica gel (hexanes/ethyl acetate) to give the title compounds.

*(R)-Ethyl 1-(1-phenylethyl)-1H-imidazole-5-carboxylate (**1a**)*:[1] viscous liquid; 70% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3H), 1.85 (d, J = 7.0 Hz, 2H), 4.21−4.31 (m, 2H), 6.36 (q, J = 7.0 Hz, 1H), 7.17−7.19 (m, 2H), 7.26−7.30 (m, 1H), 7.32−7.37 (m, 2H), 7.71 (s, 1H), 7.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.1, 55.2, 55.3, 60.3, 122.5, 126.1, 127.8, 128.7, 137.9, 138.0, 139.6, 141.0, 160.1; HRMS obsd 245.1293, calcd 245.1285 (for $C_{14}H_{16}N_2O_2$, M + H).

*(R)-Ethyl 4-bromo-1-(1-phenylethyl)-1H-pyrrole-2-carboxylate (**1c**)*: viscous liquid; 24% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 1.77 (d, J = 7.0 Hz, 3H), 4.17−4.28 (m, 2H), 6.58 (q, J = 7.0 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 7.15−7.18 (m, 2H), 7.24−7.27 (m, 1H), 7.30−7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 22.0, 55.8, 60.2, 95.9, 119.8, 123.0, 124.9, 126.3, 127.7, 128.7, 142.0, 160.3; HRMS obsd 321.0360, calcd 321.0364 for $C_{15}H_{16}NO_2Br$.

*(R)-Ethyl 5-bromo-1-(1-phenylethyl)-1H-pyrrole-2-carboxylate (**1d**)*: viscous liquid; 25% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3H), 2.00 (d, J = 7. 0 Hz, 3H), 4.22 (q, J = 7.5 Hz, 2H), 6.22 (d, J = 4.0 Hz, 1H), 6.80 (q, J = 7.0 Hz, 1H), 7.02 (d, J = 4. 0 Hz, 1H), 7.08−7.15 (m, 2H), 7.21−7.25 (m, 1H), 7.28−7.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 18.2, 55.0, 60.2, 110.2, 113.0, 119.2, 124.3, 126.3, 126.8, 128.2, 141.1, 160.4; HRMS obsd 321.0365, calcd 321.0364 for $C_{15}H_{16}NO_2Br$.

*(R)-1-(1-Phenylethyl)-1H-pyrrole-2-carbonitrile (**1e**)*: viscous liquid; 20% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (d, J = 7.5 Hz, 3H), 5.58 (q, J = 7.5 Hz, 1H), 6.20−6.22 (m, 1H), 6.81 (dd, J = 4.0, 1.5, Hz, 1H), 6.94−6.96 (m, 1H), 7.16−7.19 (m, 2H), 7.27−7.32 (m, 1H), 7.33−7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 57.7, 103.9, 109.6, 113.9, 120.3, 123.8, 126.2, 128.2, 128.9, 140.9; HRMS obsd 196.1002, calcd 196.1000 for $C_{13}H_{12}N_2$.

*(R)-2,2,2-Trifluoro-1-(1-phenylethyl-1H-pyrrole-2-yl)ethan-1-one (**1f**)*: viscous liquid; 51% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (d, J = 7. 0 Hz, 3H), 6.31−6.33 (m, 1H), 6.53 (q, J = 7.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 7.27−7.29 (m, 3H), 7.31−7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 56.8, 110.6, 112.7, 115.7, 118.5, 124.4, 125.0 (q, J = 175 Hz), 126.4, 127.8, 128.8, 131.0, 141.6, 169.6 (q, J = 20 Hz); HRMS obsd 267.0870, calcd 267.0871 for $C_{14}H_{12}NOF_3$.

*(R)-2,2,2-Trichloro-1-(1-phenylethyl-1H-pyrrole-2-yl)ethan-1-one (**1g**)*: viscous liquid (>99% ee); 55% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.82 (d, J = 7. 0 Hz, 3H), 6.28 (dd, J = 4.0, 2.5 Hz, 1H), 6.53 (q, J = 7.0 Hz, 1H), 7.15 (d, J = 7.5 Hz, 2H), 7.17−7.19 (m, 1H), 7.24−7.28 (m, 1H), 7.31−7.34 (m, 2H), 7.61 (dd, J = 4.0, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 56.9, 96.7, 109.4, 121.8, 125.0, 126.5, 127.8, 128.8, 130.0, 142.1, 172.8. Anal. Calcd for $C_{14}H_{12}NOCl_3$: C, 53.11; H, 3.82; N, 4.42. Found: C, 53.50; H, 3.87; N, 4.37.

*(R)-Ethyl 1-(1-(2-bromo)-phenylethyl)-1H-imidazole-5-carboxylate (**1h**)*:[19] viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J = 7.5 Hz, 3H), 1.87 (d, J = 7.0 Hz, 2H), 4.18−4.33 (m, 2H), 6.52 (q, J = 7.0 Hz, 1H), 6.82 (dd, J = 7.5, 1.5 Hz, 1H), 7.16 (dt, J = 7.5, 1.5 Hz, 1H), 7.60 (dd, J = 7.5, 1.5 Hz, 1H), 7.67 (d, J = 1.5 Hz, 1H), 7.81 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.6, 55.7, 55.8, 60.4, 123.4, 126.0, 128.0, 129.3, 133.3, 138.1, 139.6, 140.4, 159.8; HRMS obsd 323.0389, calcd 323.0389 (for $C_{14}H_{16}N_2O_2Br$, M + H).

*(R)-Ethyl 1-(1-(2-bromo)phenylethyl)-1H-imidazole-2-carboxylate (**1i**)*: viscous liquid; 37% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.0 Hz, 3H), 1.84 (d, J = 7.5 Hz, 3H), 4.32−4.40 (m, 1H), 6.71 (q, J = 7.0 Hz, 1H), 7.09 (d, J = 1.0 Hz, 1H), 7.18 (dd, J = 7.5, 1.5 Hz, 1H), 7.19 (d, J = 1.0 Hz, 1H), 7.26−7.29 (m, 1H), 7.59 (dd, J = 7.5, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 21.1, 56.5, 61.5,

dx.doi.org/10.1021/jo201237h |*J. Org. Chem.* 2011, 76, 8477–8482

122.3, 124.0, 126.5, 128.1, 129.6, 129.7, 133.6, 136.9, 140.6, 159.0; HRMS obsd 323.0389, calcd 323.0394 for $C_{14}H_{16}N_2O_2Br$ (M + H).

*(R)-2,2,2-Trichloro-1-(1-(2-bromo)phenylethyl-1H-pyrrol-2-yl)ethan-1-one (**1j-TCA**):* viscous liquid; 62% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (d, J = 7.0 Hz, 3H), 6.27 (dd, J = 4.5, 1.5 Hz, 1H), 6.57 (q, J = 7.0 Hz, 1H), 6.85 (dd, J = 7.0, 1.5 Hz, 1H), 7.07−7.09 (m, 1H), 7.13 (dt, J = 7.0, 1.5 Hz, 1H), 7.23 (dt, J = 7.0, 1.5 Hz, 1H), 7.56 (dd, J = 7.5, 1.5 Hz, 1H), 7.60 (dd, J = 4.5, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 57.4, 109.3, 122.0, 124.0, 124.9, 126.5, 127.9, 129.3, 129.8, 133.5, 141.3, 172.5; HRMS obsd 392.9092, calcd 392.9090 for $C_{14}H_{11}NOCl_3Br$.

*(R)-2,2,2-Trichloro-1-(2-bromobenzyl-1H-pyrrol-2-yl)ethan-1-one (**1k-TCA**):* white solid; 51% yield; mp 96−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (s, 2H), 6.34 (dd, J = 4.0, 2.5 Hz, 1H), 6.53 (dd, J = 8.0, 1.5 Hz, 1H), 7.03 (dd, J = 2.5, 1.5 Hz, 1H), 7.15 (dt, J = 8.0, 2.0 Hz, 1H), 7.21 (dt, J = 8.0, 2.0 Hz, 1H), 7.59 (dd, J = 8.0, 1.5 Hz, 1H), 7.64 (dd, J = 4.0, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.9, 96.2, 109.8, 121.7, 122.4, 124.7, 127.3, 128.0, 129.2, 132.9, 133.3, 136.9, 172.8; HRMS obsd 378.8936, calcd 378.8933 for $C_{13}H_9NOCl_3Br$.

*(R)-Ethyl 1-(1-(2-bromo)phenylethyl)-1H-indole-3-carboxylate (**1l**):* white solid; 55% yield; mp 94−96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, J = 7.5 Hz, 3H), 1.93 (d, J = 7.5 Hz, 3H), 4.39−4.46 (m, 2H), 6.03 (q, J = 7.0 Hz, 1H), 6.80 (dd, J = 7.5, 1.5 Hz, 1H), 7.10−7.17 (m, 4H), 7.19−7.24 (m, 1H), 7.60 (dd, J = 7.5, 1.5 Hz, 1H), 8.13 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 20.5, 55.2, 59.8, 107.9, 110.7, 121.7, 122.1, 122.3, 122.9, 126.5, 128.3, 129.4, 131.3, 133.1, 137.5, 138.0, 141.5, 165.0; HRMS obsd 372.0593, calcd 372.0602 ($C_{19}H_{19}NO_2Br$, M + H).

*(R)-2,2,2-Trichloro-1-(1-(2-bromo)phenylethyl-1H-indol-3-yl)-ethan-1-one (**1l-TCA**):* viscous liquid; 74% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.98 (d, J = 7.0 Hz, 3H), 6.10 (q, J = 7.0 Hz, 1H), 6.82 (dd, J = 7.0, 2.0 Hz, 1H), 7.14−7.23 (m, 4H), 7.32−7.36 (m, 1H), 7.62−7.64 (m, 1H), 8.42 (d, J = 8.0 z, 1H), 8.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 55.7, 55.8, 96.9, 105.8, 111.0, 122.4, 122.7, 123.9, 124.2, 126.2, 128.5, 129.7, 133.3, 134.3, 136.4, 139.9, 176.8; HRMS obsd 442.9245, calcd 442.9246 for $C_{18}H_{13}NOCl_3Br$.

*Ethyl 1-(2-bromophenethyl)-1H-imidazole-5-carboxylate (**1m**):* viscous liquid; 65% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, J = 7.0 Hz, 3H), 3.23 (t, J = 7.0 Hz, 2H), 4.36 (q, J = 7.0 Hz, 2H), 4.55 (t, J = 7.0 Hz, 2H), 6.98 (dd, J = 8.0, 2.0 Hz, 1H), 7.11 (dt, J = 7.0, 1.5 Hz, 1H), 7.18 (dt, J = 7.0, 1.5 Hz, 1H), 7.25 (s, 1H), 7.56 (dd, J = 7.0, 1.5 Hz, 1H), 7.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 37.5, 46.3, 60.4, 122.3, 124.3, 131.0, 132.8, 132.9, 136.7, 137.7, 137.8, 141.9, 160.2; HRMS obsd 323.0389, calcd 323.0392 for $C_{14}H_{16}N_2O_2Br$, M + H.

*Ethyl 1-(2-bromophenyl-1-propanol)-1H-imidazole-5-carboxylate (**1n**):* viscous liquid; 67% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3H), 2.09−2.16 (m, 2H), 2.74 (t, J = 8.5 Hz, 2H), 4.32 (q, J = 7.0 Hz, 2H), 4.38 (t, J = 7.0 Hz, 2H), 7.08 (dt, J = 7.0, 1.5 Hz, 1H), 7.19 (dd, J = 7.0, 2.0 Hz, 1H), 7.22−7.25 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 7.75 (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 31.3, 33.3, 46.7, 60.6, 122.8, 124.5, 127.7, 128.1, 130.3, 133.1, 138.2, 140.1, 142.1, 160.4; HRMS obsd 337.0546, calcd 337.0546 for ($C_{15}H_{18}N_2O_2Br$, M + H).

General Procedure for Conversion of Trichloroacetyl to Ethyl Ester. The substrate (0.2 mmol) dissolved in 1 mL of EtOH was treated with 21% NaOEt in EtOH (0.1 mL) at room temperature for 1−3 h. The reaction mixture was then concentrated followed by column chromatography purification on silica gel (hexanes/ethyl acetate) to give the title compound.

*(R)-Ethyl 1-(2-bromophenylethyl)-1H-pyrrol-2-carboxylate (**1j**):* viscous liquid; 88% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.5 Hz, 3H), 1.79 (d, J = 7.5 Hz, 3H), 4.13−4.24(m, 2H), 6.20 (dd, J = 4.0, 3.0 Hz, 1H), 6.61 (q, J = 7.0 Hz, 1H), 6.71 (dd, J = 8.0, 1.5 Hz, 1H), 7.01−7.03 (m, 1H), 7.05 (dd, J = 4.0, 2.0 Hz, 1H), 7.11 (dt, J = 8.0, 1.5 Hz, 1H), 7.19−7.23 (m, 1H), 7.55 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.8, 56.4, 59.9, 108.3, 119.0, 123.0, 123.4, 125.5, 126.3, 128.0, 133.3, 142.8, 160.9; HRMS obsd 322.0437, calcd 322.0441 for $C_{15}H_{17}NO_2Br$, M + H.

General Procedure for Conversion of Trichloroacetyl to Amide. The substrate (0.2 mmol) was treated with 2 M $MeNH_2$ in THF (0.5 mL) at room temperature for 3−5 h. The reaction mixture was then concentrated followed by column chromatography purification on silica gel (hexanes/ethyl acetate) to give the title compound.

*(R)-1-(2-Bromophenylethyl)-1H-pyrrol-N-methyl-2-carboxamide (**1o**):* viscous liquid; 98% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81 (d, J = 7.0 Hz, 3H), 2.86 (d, J = 5.5 Hz, 3H), 5.78 (br, 1H), 6.13−6.15 (m, 1H), 6.54 (dd, J = 4.0, 1.5 Hz, 1H), 6.78 (q, J = 7.0 Hz, 1H), 6.85−6.86 (m, 1H), 6.89 (dd, J = 8.0, 1.5 Hz, 1H), 7.10 (dt, J = 7.0, 1.5 Hz, 1H), 7.23 (dt, J = 7.0, 1.5 Hz, 1H), 7.55 (dd, J = 8.0, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 26.2, 55.8, 107.5, 111.9, 123.5, 123.7, 126.3, 126.6, 127.7, 128.8, 133.3, 142.6, 162.4; HRMS obsd 307.0440, calcd 307.0444 for $C_{14}H_{16}N_2OBr$, M + H.

*(R)-1-(2-Bromobenzyl)-1H-pyrrol-N-methyl-2-carboxamide (**1p**):* white solid; 99% yield; mp 96−98 °C; IR (KBr, cm^{-1}) 1028, 1260, 1542, 1647, 3020, 3469; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.90 (d, J = 5.0 Hz, 3H), 5.68 (s, 2H), 5.87 (br, 1H), 6.17 (dd, J = 4.0, 2.5 Hz, 1H), 6.58 (dd, J = 4.0, 1.5 Hz, 1H), 6.62 (dd, J = 8.0, 1.0 Hz, 1H), 6.77 (dd, J = 2.5, 1.5 Hz, 1H), 7.10 (dt, J = 8.0, 2.0 Hz, 1H), 7.18 (dt, J = 8.0, 2.0 Hz, 1H), 7.54 (dd, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.2, 52.2, 108.2, 111.9, 122.3, 126.0, 127.3, 127.8, 128.1, 128.8, 132.6, 138.5, 162.5. Anal. Calcd for $C_{13}H_{13}N_2OBr$: C, 53.26; H, 4.47; N, 9.56. Found: C, 53.14; H, 4.53; N, 9.59.

General Procedure for Palladium-Catalyzed Cyclizations. To a solution of substrate (0.1 mmol) in DMF or dioxane (1 mL) were added $Pd(OAc)_2$ (0.01 mmol) or $Pd_2(dba)_3$ (0.005 mmol), no ligand (conditions C) or a ligand (0.01−0.02 mmol) [Sphos (conditions D), PPh_3 (conditions E), or Xantphos (condition F)], and anhydrous K_2CO_3 or Cs_2CO_3 (0.5 mmol). The reaction mixture was heated at 100 or 120 °C for 24 h in a screw-capped vial and then concentrated under reduced pressure. Excess ethyl acetate was added to the solid black residue. The organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, and then filtered. The filtrate was concentrated followed by column chromatography purification on silica gel (hexanes/ethyl acetate) to give the title compounds.

*Ethyl 5-methylimidazo[2,1-a]isoindole-3-carboxylate (**2a**):* white solid; 93% yield; mp 75−77 °C; IR (KBr, cm^{-1}) 2925, 1695, 1243; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41 (t, J = 7.0 Hz, 3H), 1.77 (d, J = 7.0 Hz, 3H), 4.39 (q, J = 7.0 Hz, 2H), 5.38 (q, J = 7.0 Hz, 1H), 7.41−7.48 (m, 3H), 7.86−7.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.8, 58.5, 60.7, 120.8, 122.1, 122.9, 128.2, 128.6, 128.8, 145.0, 148.9, 155.9, 160.2; HRMS obsd 243.1129, calcd 243.1128 for $C_{14}H_{15}N_2O_2$, M + H.

*Ethyl 5-methylimidazo[5,1-a]isoindole-3-carboxylate (**2b**):* white solid; 45% yield; mp 100−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (t, J = 7.0 Hz, 3H), 1.79 (d, J = 7.0 Hz, 3H), 4.43−4.48 (m, 2H), 5.57 (q, J = 7.0 Hz, 1H), 7.33−7.36 (m, 2H), 7.39−7.42 (m, 2H), 7.59−7.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 20.3, 60.0, 61.6, 120.6, 120.7, 123.2, 127.8, 128.5, 128.6, 141.8, 147.7, 159.0; HRMS obsd 243.1128, calcd 243.1133 for $C_{14}H_{15}N_2O_2$ (M + H).

*Ethyl 5-methylpyrrolo[2,1-a]isoindole-3-carboxylate (**2c**):* viscous liquid; 82% yield; IR (KBr, cm^{-1}) 748, 1110, 1141, 1254, 1446, 1695, 2978; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 7.0 Hz, 3H), 1.75 (d, J = 7.0 Hz, 3H), 4.38 (q, J = 7.0 Hz, 2H), 5.51 (q, J = 7.0 Hz, 1H), 6.35 (d, J = 4.0 Hz, 1H), 7.11 (d, J = 4.0 Hz, 1H), 7.27−7.31 (m, 1H), 7.35−7.41 (m, 2H), 7.56 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 20.9, 60.0, 60.1, 99.7, 119.7, 120.5, 121.2, 122.6, 126.7, 128.1, 131.4, 142.7, 147.6, 161.0; HRMS obsd 242.1181, calcd 242.1175 for $C_{15}H_{16}NO_2$, M + H.

*Ethyl 5-methylindolo[2,1-a]isoindole 3-carboxylate (**2d**):* viscous liquid; 52% yield (ca. 90% pure); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (t, J = 7.0 Hz, 3H), 1.80 (d, J = 7.0 Hz, 3H), 4.52 (q, J = 7.0 Hz, 2H), 5.36 (q, J = 7.0 Hz, 1H), 7.26−7.30 (m, 2H), 7.42−7.52 (m, 4H), 8.27−8.30

dx.doi.org/10.1021/jo201237h |*J. Org. Chem.* 2011, 76, 8477–8482

(m, 1H), 8.77 (d, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ, 14.9, 21.4, 57.0, 60.0, 99.5, 109.9, 121.8, 122.3, 123.2, 125.9, 128.7, 129.5, 130.5, 131.0, 132.7, 133.1, 145.8, 148.8, 165.9; HRMS obsd 292.1332, calcd 292.1333 for $C_{19}H_{18}NO_2$, M + H.

5-Methylpyrrolo[2,1-a]isoindole N-methyl-3-carboxamide (**2e**): white solid; 80% yield; mp 140−142 °C; IR (KBr, cm^{-1}) 750, 1538, 1563, 1629, 3303; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.71 (d, J = 7.0 Hz, 3H), 2.98 (d, J = 5.0 Hz, 3H), 5.60 (q, J = 7.0 Hz, 1H), 5.82 (br, 1H), 6.28 (d, J = 4.0 Hz, 1H), 6.65 (d, J = 4.0 Hz, 1H), 7.25 (dt, J = 7.0, 1.5 Hz, 1H), 7.33 (t, J = 7.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 26.1, 59.9, 98.8, 114.6, 119.3, 122.6, 123.4, 126.3, 127.8, 131.3, 141.0, 147.4, 161.8; HRMS obsd 227.1178, calcd 227.1181 for $C_{14}H_{15}N_2O$, M + H.

5H-Pyrrolo[2,1-c]-2-oxo-N-methyl[1,4]benzodiazepine (**2f**): white solid; 57% yield; mp 136−138 °C; IR (KBr, cm^{-1}):1358, 1602, 1622, 3008, 3692; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (s, 3H), 5.16 (s, 2H), 6.04 (dd, J = 4.0, 2.5 Hz, 1H), 6.65−6.67 (m, 1H), 7.04 (dd, J = 4.0, 1.5 Hz, 1H), 7.20 (dt, J = 7.5, 1.5 Hz, 1H), 7.39−7.41 (m, 2H), 7.43−7.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 51.0, 108.8, 117.0, 122.2, 123.2, 125.4, 126.2, 128.1, 129.3, 131.4, 142.7, 162.0; HRMS obsd 213.1022, calcd 213.1025 for ($C_{13}H_{13}N_2O$, M + H).

Ethyl 5,6-dihydroimidazo[2.1-a]isoquinoline-3-carboxylate (**2g**): viscous liquid; 75% yield; IR (KBr, cm^{-1}) 719, 1072, 1109, 1182, 1253, 1710, 2981; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (t, J = 7.0 Hz, 3H), 3.17 (t, J = 7.0 Hz, 2H), 4.36 (q, J = 7.0 Hz, 2H), 4.62 (t, J = 7.0 Hz, 2H), 7.26−7.28 (m, 1H), 7.35−7.38 (m, 2H), 7.82 (s, 1H), 8.06−8.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.3, 42.3, 60.6, 122.6, 124.8, 126.4, 127.7, 127.8, 129.9, 133.3, 137.8, 148.3, 160.7; HRMS obsd 243.1128, calcd 243.1129 for $C_{14}H_{15}N_2O_2$, M + H.

6,7-Dihydroimidazo[2,1-a][2]benzazepine (**2h**): viscous liquid; 50% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (t, J = 7.0 Hz, 3H), 2.35−2.40 (m, 2H), 2.70 (t, J = 7.5 Hz, 2H), 4.34−4.38 (m, 4H), 7.28−7.32 (m, 1H), 7.39−7.42 (m, 2H), 7.77−7.80 (m, 1H), 7.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 30.7, 32.0, 42.8, 60.5, 123.2, 127.3, 129.1, 129.5, 130.2, 130.6, 137.2, 139.0, 153.7, 160.9; HRMS obsd 257.1284, calcd 257.1290 for $C_{15}H_{17}N_2O_2$, M + H.

■ ASSOCIATED CONTENT

Supporting Information. Spectral data for all compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: gcuny@rics.bwh.harvard.edu.

■ ACKNOWLEDGMENT

We thank the Harvard NeuroDiscovery Center and Partners Healthcare for financial support.

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