Efficient Synthesis of Bromocyclopenta[*b*]indoles via a Bromination – Reduction Sequence

Nicolas Lachance* and Wing Yan Chan

Merck Frosst Centre for Therapeutic Research, P.O. Box 1005,
Pointe Claire-Dorval, Québec, Canada, H9R 4P8

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Substituted cyclopenta[*b*]indoles are selectively brominated in good yields with excess pyridine – Br_2 charge-transfer complex ($PyBr_2$) in a one-pot reaction to provide 5 and/or 7-bromoindoles. The mechanism involves the formation of an adduct (addition of bromine on the central double bond) which is subsequently reduced *in situ* with Zn and AcOH. A variety of functional groups in the cyclopentyl and the benzenoid rings are tolerated.

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Introduction.

Indoles are of interest in the pharmaceutical industry as this important core is present in many biologically active compounds such as Indomethacin, Maxalt, Accoleit and Ramatroban [1]. As part of our medicinal chemistry program, we became interested in the synthesis of substituted cyclopenta[*b*]indoles (Figure 1) and we envisioned that bromoindoles could serve as versatile synthetic intermediates in their preparation [2]. Although indoles, such as tetrahydrocarbazoles, with halogen on the benzenoid moiety can be obtained *via de novo* indole synthesis, all our attempts to prepare 3,5-dibromo or 3,5-disubstituted cyclopenta[*b*]indoles under literature procedures failed in our laboratory [3]. To solve this problem, we were interested in a direct bromination of the indole core. Several groups have investigated bromination chemistry of indoles [4], however, few examples are reported with annulated systems [4c,5]. We wish to report herein our results in developing a one-pot bromination – reduction sequence resulting in good yields of halogenated indoles.

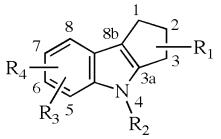


Figure 1. The numbering system used in this article for cyclopenta-[*b*]indoles based on IUPAC nomenclature.

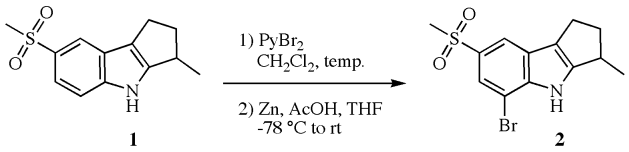
Results and Discussion.

Most of the starting indoles required for our studies were readily prepared by exposing various aryl hydrazines and cyclopentanone to Fischer indole reaction conditions [6]. Under these conditions, α-monosubstituted cyclopentanones gave low yields of the corresponding indoles. For these substrates, an alternative preparation involving the reaction of *ortho* iodoanilines and ketones was undertaken [7]. After their condensation [8], the corresponding enamine intermediate was submitted to Heck reaction conditions as described by Chen *et al.* to generate the cyclic indole core [9]. A Nazarov cyclization was also utilized to prepare a gem dimethyl cyclopenta[*b*]indole [10].

We began by investigating the reaction of indole **1** under standard bromination conditions such as Br_2, NBS and pyridinium perbromide [4c,d]. With these reagents, only decomposition of the indole starting material **1** was observed and this led us to examine the use of the pyridine – Br_2 charge-transfer complex ($PyBr_2$) [11]. Thus, treatment of **1** with an excess of $PyBr_2$ (prepared *in situ* by the addition of Br_2 to pyridine in CH_2Cl_2 at -78 °C) at -20 °C resulted in complete consumption of the starting material within half an hour as judged by tlc. Addition of a suspension of Zn in AcOH and THF to the solution at -78 °C and subsequent warming of the reaction mixture to room temperature provided bromoindole **2** in only 5% yield along with recovered starting material **1** (80%) (Table 1, entry 1). Increasing the

Table 1

Effect of Time, Temperature and Concentration of $PyBr_2$ on the Bromination of Cyclopenta[*b*]indole **1**



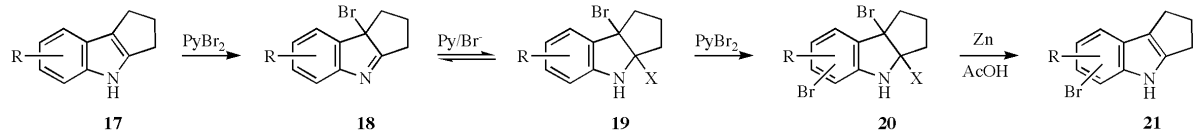
Entry	$PyBr_2$ [a] (equiv)	Time (min)	Temp. (°C)	Conversion [b] (%)	Yield [c] (%)
1	2.2	30	-20	20	5
2	2.2	15	0	45	8
3	3.3	30	-20	25	18
4	3.3	60	-20	50	37
5	3.3	30	-10	60	38
6	5	30	-20	40	31
7	10	30	-20	– [d]	59
8	10	60	-20	70	54
9	15	30	-20	65	49

[a] $PyBr_2$ was prepared *in situ* at -78 °C; [b] Established by the amount of starting material recovered after the reduction with Zn/AcOH (5 to 15 equiv); [c] Isolated yield after the reduction step; [d] Not measured.

number of equivalents of $PyBr_2$ led to an increase in the formation of the desired bromoindole **2**. The optimal bromination conditions for this substrate involved the use of 10 equiv of $PyBr_2$ at -20 °C to provide 59% yield of the bromination product (Table 1, entry 7). During the course of our optimization studies, we observed that the reaction temperature was an important element in the success of the bromination – reduction sequence. Low temperatures, such as -20 °C for the bromination of **1** and -78 °C for the subsequent reduction with Zn, led to less degradation material and higher yields of product **2** (Table 1).

Having established an efficient halogenation of indole **1**, we next investigated the scope of this method. In general, a variety of indoles were successfully brominated as illustrated in Table 2. One exception however was indole **7** where the starting material was recovered unchanged after the treatment with Zn. As outlined in Scheme 1, our proposed mechanism for the indole bromination reaction involves the formation of an indolenine **18**, which has been previously reported by Dmitrienko *et al.* [4c], and indolines **19** and **20** as intermediates. These indolines were observed during the course of the bromination with the substrate **5**.

Scheme 1



X = Py or Br

Proposed Mechanism for the Bromination of Cyclopenta[*b*]indoles

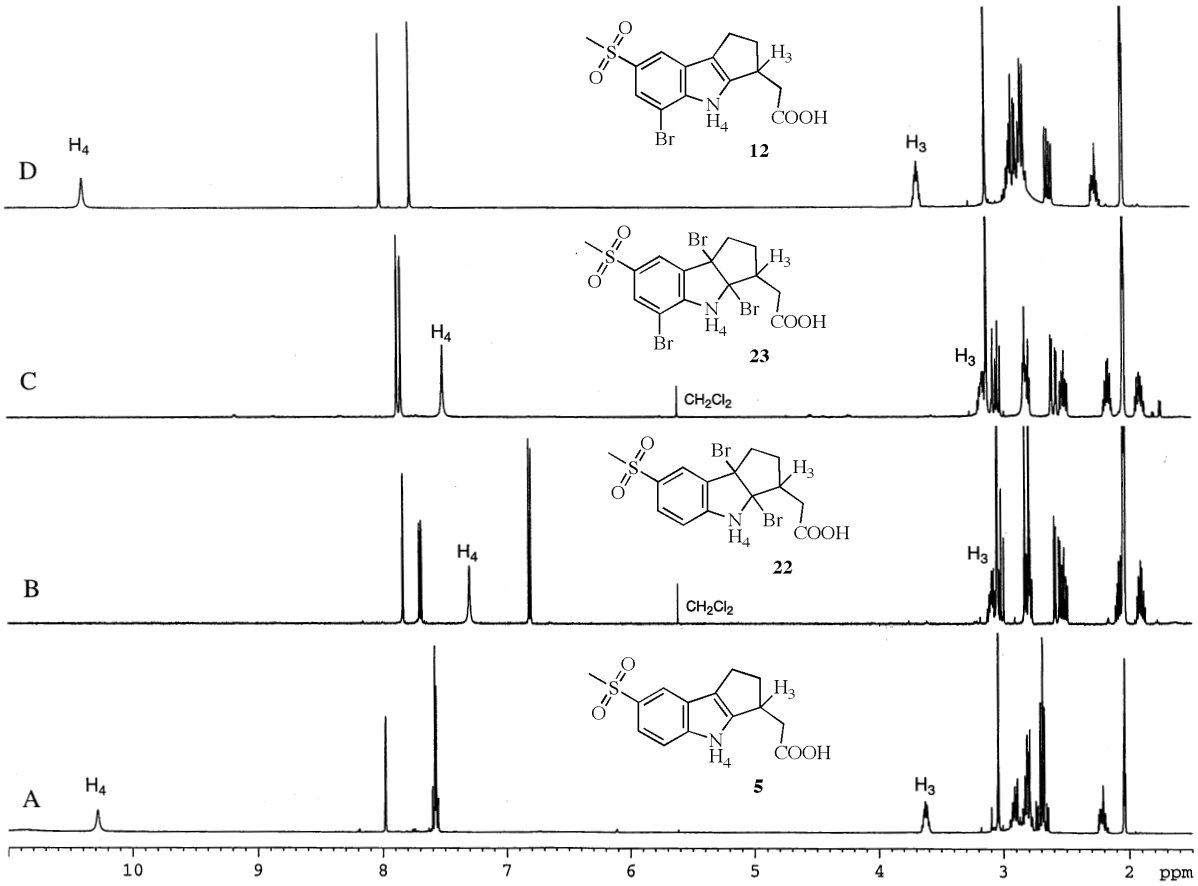
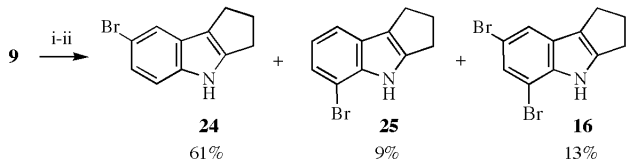


Figure 2. Crude ^1H nmr (500 MHz, acetone-d_6) of the bromination reaction of cyclopenta[*b*]indole 5 followed by the reduction of the intermediates **22** and **23** formed: (A) cyclopenta[*b*]indole **5**, (B) indoline **22** after the addition of 1 equiv of $PyBr_2$ at -20 °C, (C) indoline **23** after the addition of excess $PyBr_2$ at 0 °C, (D) bromocyclopenta[*b*]indole **12** after the addition of Zn and AcOH.

Scheme 2



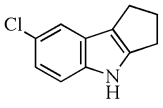
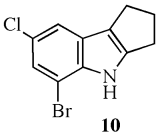
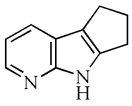
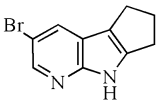
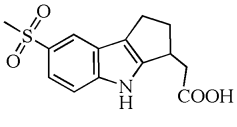
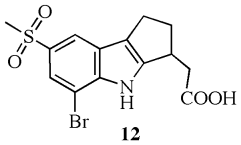
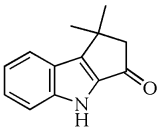
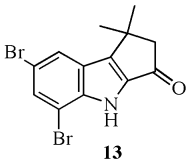
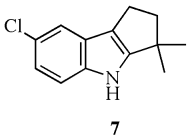
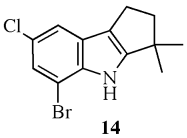
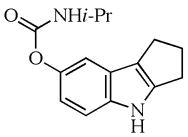
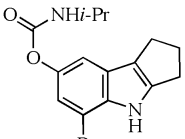
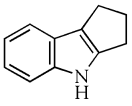
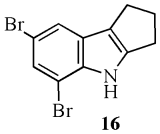
Reagents and conditions: (i) $PyBr_2$ (2.5 equiv), CH_2Cl_2, -20 °C, 30 min; (ii) Zn/AcOH (5 equiv), THF, -78 °C to rt. Yield estimated by ^1H nmr.

Regioselectivity of the Bromination of Cyclopenta[*b*]indole **9**

Treatment of indole **5** with 1 equiv of $PyBr_2$ led to the formation of the bromoindoline **22** which has been isolated and characterized (Figure 2, Spectrum B) [12,13]. Further treatment of **22** with an excess of $PyBr_2$ delivered the bromoindoline **23** (Figure 2, Spectrum C) [12,14]. The fact that indole **7** did not provide any of the expected bromination product **14** suggests that the halogenation on the benzenoid unit requires the indoline intermediate. For substrate **7**, we propose that the formation of the indoline **19** from the intermediate **18** was not possible due to the steric hindrance of the gem dimethyl substituents that halt the progress of the reaction. However, indole **6**, which

Table 2

Synthesis of Bromocyclopenta[*b*]indoles via a Bromination – Reduction Sequence

Entry	Substrate	Rxn cond [a]	Product	Yield [b] (%)
1	 **3**	A	 **10**	95
2	 **4**	A	 **11**	97
3	 **5**	B	 **12**	96
4	 **6**	C	 **13**	92
5	 **7**	C	 **14**	0 [c]
6	 **8**	A	 **15**	96
7	 **9**	A	 **16**	97

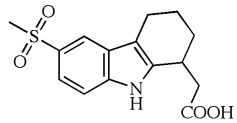
[a] Reactions were performed with $PyBr_2$ (5 to 10 equiv) for 30 min followed by treatment with Zn/AcOH (5 to 10 equiv) at -78 °C; A = bromination performed at -20 °C; B = 0 °C; C = rt, 30 to 60 min; [b] Isolated yield; [c] Most of the starting indole **7** was recovered.

possess these substituents at the 1 position of the indole core, gave good yield of dibromo **13** [15]. Due to the steric hindrance of the substitution pattern present in **6**, the bromination may proceed directly through the benzenoid ring.

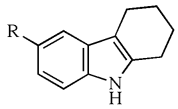
The regioselectivity of the indole bromination was explored with substrate **9**. Reducing the number of equiv of $PyBr_2$ to 2.5 resulted in the formation of mono 7-bromoindole **24** in 61% yield based on ^1H nmr experiments (Scheme 2). In this example, bromination of the benzenoid unit occurs first at the 7 position. The substitution pattern of **16** was confirmed by comparing its ^1H nmr spectrum to that of an authentic sample synthesized from bromocyclopenta[*b*]indole **25** under the current bromination conditions.

The influence of an *N*-substituent on the current bromination reaction was investigated by substituting the nitrogen with a methyl or a tosyl group. Exposure of these analogs to our standard reaction conditions only led to recovery of starting material or decomposition. Performing the reaction at different temperature did not improve the reaction, underlining the importance of the free nitrogen on the indole to the success of this reaction.

We next investigated the standard bromination conditions on tetrahydrocarbazoles **26**, **27** and **28**. Monitoring by tlc the consumption of **26** with $PyBr_2$ and running ^1H nmr experiments on the crude material, showed the formation of anticipated bromo intermediates. The reduction with Zn of these intermediates only led to recovery of starting material. The reaction was also performed with **27** and **28** without success. Surprisingly, the bromination – reduction sequence developed in our current study, while successful with cyclopenta[*b*]indoles, is completely inoperative with the related cyclohexyl analogs. This reactivity difference may be a result of the corresponding strain of the indole 3a – 8b double bond as an important factor for the formation of the indoline intermediates **19** and **20**.



26



27 R = H
28 R = Cl

Conclusion.

In summary, an efficient procedure has been outlined for the preparation of 5 and/or 7-bromocyclopenta[*b*]indoles by use of a bromination – reduction sequence. This reaction has significant advantages over other reported methods to prepare these versatile synthetic intermediates and should provide broad applicability for the synthesis of functionalized cyclopenta[*b*]indoles [2].

EXPERIMENTAL

Melting points are uncorrected. nmr spectra were recorded in acetone-d_6 solution at room temperature, unless otherwise stated, with solvent as the internal standard for ^1H (500 MHz) and for ^{13}C (125 MHz). tlc analyses were performed on Merck Kieselgel 60 F_{254} plates. All reactions with air-sensitive compounds were carried out under a nitrogen atmosphere. 4-(Methylsulfonyl)aniline hydrochloride and ethyl (2-oxocyclopentyl)acetate were obtained from Acros Chemicals. 2,2-Dimethylcyclopentanone, **3**, **27** and **28** were purchased from Aldrich and 1-(phenylsulfonyl)-1*H*-indole from Lancaster. Column chromatography was conducted with silica gel 230-400 mesh. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY. Hrms were performed by Biomedical Mass Spectrometry Unit, McGill University, Montreal, Qc, Canada.

3-Methyl-7-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]-indole (**1**).

To a suspension of 4-(methylsulfonyl)aniline hydrochloride (4.97 g, 23.9 mmol) in EtOH (100 mL) was added a solution of *t*-BuOK in THF (1.0 *M*, 26.0 mL). The slurry was stirred at rt for 15 min, and a suspension of I_2 (6.10 g, 24.0 mmol) and Ag_2SO_4 (8.37 g, 26.8 mmol) in EtOH (800 mL) was added in one portion. The resulting mixture was heated to 50 °C for 3 h. The hot mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by recrystallization from EtOH to afford 2-iodo-4-(methylsulfonyl)aniline as a pale yellow solid (4.96 g, 70%): mp 201-202 °C; ^1H nmr: δ 8.08 (1 H, d, *J* = 2.0 Hz), 7.63 (1 H, dd, *J* = 8.5, 2.0 Hz), 6.93 (1 H, d, *J* = 8.5 Hz), 5.78 (2 H, br s), 3.03 (3 H, s); ^{13}C nmr δ 153.6, 139.3, 130.6, 129.7, 114.0, 81.0, 44.8. Hrms Calcd for $C_7H_9INO_2S$: $[M + H]^+$ = 297.9399. Found: 297.9400.

Anal. Calcd. for $C_7H_8INO_2S$: C, 28.30; H, 2.71; N, 4.71. Found: C, 28.44; H, 2.86; N, 4.84.

The previous *o*-iodoaniline (4.01 g, 13.5 mmol) was mixed with 2-methylcyclopentanone (1.50 mL, 14.0 mmol), *p*-TsOH•H_2O (26 mg, 0.14 mmol), and $(EtO)_4Si$ (4.00 mL, 17.9 mmol) in DMF (4 mL), and heated to 130 °C for 6 h. After cooling to 120 °C, to the mixture was successively added DMF (10 mL), $Pd(OAc)_2$ (120 mg, 0.54 mmol) and Hünig's base (7.00 mL, 40.5 mmol), and then the mixture was stirred at 125 °C for 3 h. The mixture was diluted with EtOAc, washed with HCl (1 *N*) and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (toluene/EtOAc = 4/1) to afford **1** as a yellow solid (1.43 g, 42%): mp 153-154 °C (hexane-EtOAc); ^1H nmr: δ 10.57 (1 H, br s), 7.96 (1 H, d, *J* = 1.4 Hz), 7.56 (1 H, dd, *J* = 8.6, 1.4 Hz), 7.49 (1 H, d, *J* = 8.6 Hz), 3.35 (1 H, m), 3.04 (3 H, s), 2.91-2.73 (3 H, m), 2.08 (1H, m), 1.29 (3 H, d, *J* = 6.8 Hz); ^{13}C nmr δ 152.4, 144.3, 132.7, 125.0, 119.7, 119.3 (2), 112.8, 45.2, 38.7, 34.3, 24.0, 20.2. Hrms Calcd for $C_{13}H_{16}NO_2S$: $[M + H]^+$ = 250.0902. Found: 250.0901.

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.41; H, 5.99; N, 5.71.

[7-(Methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic Acid (**5**).

Following the preparation of **1**, the reaction of ethyl (2-oxocyclopentyl)acetate (12.9 g, 76.0 mmol) and 2-iodo-4-(methylsulfonyl)aniline (19.4 g, 65.4 mmol) afforded ethyl [7-(methyl-

sulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetate. After hydrolysis with THF (80 mL), MeOH (40 mL) and NaOH (2 *N*, 40.0 mL) at rt for 1.5 h, the mixture was acidified with HCl (1 *N*) and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was triturated (hexane/EtOAc) to afford **5** as a pale brown solid (9.13 g, 48%): mp 222-223 °C; ^{1}H nmr: δ 10.86 (1 H, br s), 10.28 (1 H, br s), 7.98 (1 H, s), 7.58 (2 H, m), 3.63 (1 H, m), 3.04 (3 H, s), 2.91 (1 H, m), 2.85-2.77 (2 H, m), 2.74-2.65 (2 H, m), 2.21 (1 H, m); ^{13}C nmr δ 174.2, 149.9, 144.2, 132.7, 124.6, 120.6, 119.6, 119.5, 113.2, 45.2, 39.5, 36.4, 36.2, 23.7. Hrms Calcd for $C_{14}H_{16}NO_4S$: $[M + H]^+$ = 294.0800. Found: 294.0801.

Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77. Found: C, 57.21; H, 5.10; N, 4.78.

1,1-Dimethyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (**6**).

To a solution of 1-(phenylsulfonyl)-1*H*-indole (5.15 g, 20.0 mmol) in THF (200 mL) at -78 °C was added dropwise a solution of *t*-BuLi (1.7 *M* in pentane, 15.5 mL). The resulting solution was stirred at -78 °C for 1 h and a solution of freshly distilled 3-methylbut-2-enal (2.50 mL, 25.9 mmol) in THF (50 mL) was added dropwise over 30 min. The mixture was stirred at -78 °C for 45 min. After warming to rt, the mixture was acidified with aqueous NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give crude 3-methyl-1-[1-(phenylsulfonyl)-1*H*-indol-2-yl]but-2-en-1-ol as an orange oil, which was used for the next step without further purification. To a solution of the crude alcohol in CH_2Cl_2 (200 mL) at rt was added 4-methylmorpholine *N*-oxide (3.51 g, 30.0 mmol) and 4 Å molecular sieves (5.89 g). After 20 min, tetrapropylammonium perruthenate (360 mg, 1.00 mmol) was added and the mixture was stirred overnight at rt. The reaction mixture was purified by column chromatography on silica gel (CH_2Cl_2). Unreacted alcohol recovered was resubmitted to the same reaction conditions to afford, after recrystallization (hexane/CH_2Cl_2) of the combined fractions, 3-methyl-1-[1-(phenylsulfonyl)-1*H*-indol-2-yl]but-2-en-1-one [16] as a white solid (2.80 g, 33%): mp 120-121 °C; ^{13}C nmr: δ 184.2, 157.8, 142.6, 139.4, 139.0, 134.9, 129.9, 129.7, 128.2, 127.8, 125.1, 124.2, 123.6, 116.5, 116.3, 27.8, 21.0. Hrms Calcd for $C_{19}H_{18}NO_3S$: $[M + H]^+$ = 340.1007. Found: 340.1009.

To a solution of the previous ketone (2.50 g, 7.40 mmol) in toluene (90 mL) at rt was added dropwise BF_3•OEt_2 (2.93 mL, 23.3 mmol). The resulting mixture was heated to 120 °C overnight. The mixture was diluted with EtOAc, washed with brine, dried (Na_2SO_4), and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (toluene/EtOAc = 4/1) to afford 1,1-dimethyl-4-(phenylsulfonyl)-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one as a brown solid (2.00 g, 80%): mp 199-200 °C (hexane-EtOAc); ^{1}H nmr: δ 8.34 (1 H, d, *J* = 8.0 Hz), 8.17 (2 H, d, *J* = 7.6 Hz), 7.87 (1 H, d, *J* = 7.9 Hz), 7.70 (1 H, t, *J* = 7.5 Hz), 7.61 (3 H, m), 7.41 (1 H, t, *J* = 7.6 Hz), 2.82 (2 H, s), 1.50 (6 H, s); ^{13}C nmr: δ 189.0, 161.6, 144.1, 139.5, 137.0, 135.3, 130.3, 129.8, 128.2, 125.0, 124.6, 123.2, 116.4, 58.2, 35.5, 28.3. Hrms Calcd for $C_{19}H_{17}KNO_3S$: $[M + K]^+$ = 378.0566. Found: 378.0565.

Anal. Calcd. for $C_{19}H_{17}NO_3S$: C, 67.24; H, 5.05; N, 4.13. Found: C, 67.44; H, 4.84; N, 4.42.

A mixture of the previous cyclic ketone (2.38 g, 7.10 mmol) and NaOMe (prepared from Na (1.83 g, 80.0 mmol)) in MeOH (100 mL)) was heated to 80 °C for 15 min. The mixture was poured into HCl (1 *N*) and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (toluene/EtOAc = 4/1) to afford **6** [10b] as a brown solid (1.25 g, 88%): mp 163-164 °C (hexane-EtOAc); ^{13}C nmr: δ 192.6, 153.8, 144.8, 138.1, 127.2, 123.0, 122.5, 121.0, 114.5, 58.2, 36.1, 29.3.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.17; H, 6.31; N, 7.12.

7-Chloro-3,3-dimethyl-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**7**).

A mixture of 4-chlorophenylhydrazine hydrochloride (3.42 g, 19.1 mmol) and 2,2-dimethylcyclopentanone (2.40 mL, 19.1 mmol) in AcOH (40 mL) was heated to 125 °C overnight. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (hexane/EtOAc = 9/1) and by recrystallization from hexane to afford **7** as a white solid (1.09 g, 26%): mp 115-116 °C; ^{1}H nmr: δ 10.15 (1 H, br s), 7.33 (1 H, d, *J* = 2.0 Hz), 7.27 (1 H, d, *J* = 8.5 Hz), 6.97 (1 H, dd, *J* = 8.5, 2.0 Hz), 2.75 (2 H, m), 2.32 (2 H, m), 1.32 (6 H, s); ^{13}C nmr: δ 154.4, 140.4, 126.8, 124.8, 120.5, 118.3, 116.3, 113.5, 46.4, 40.1, 27.9, 23.2. Hrms Calcd for $C_{13}H_{15}ClN$: $[M + H]^+$ = 220.0893. Found: 220.0894.

Anal. Calcd for $C_{13}H_{14}ClN$: C, 71.07; H, 6.42; N, 6.38. Found: C, 71.18; H, 6.17; N, 6.53.

1,2,3,4-Tetrahydrocyclopenta[*b*]indol-7-yl isopropylcarbamate (**8**).

Following the preparation of **7**, the reaction of 4-methoxyphenylhydrazine hydrochloride (5.04 g, 28.9 mmol) and cyclopentanone (5.10 mL, 57.7 mmol) in EtOH (175 mL) heated to 100 °C for 30 min afforded, after recrystallization from hexane-CH_2Cl_2, 7-methoxy-1,2,3,4-tetrahydrocyclopenta[*b*]-indole [6d] as a pale brown solid (3.98 g, 73%): mp 126-127 °C (hexane-CH_2Cl_2); ^{13}C nmr: δ 154.7, 145.6, 137.4, 126.0, 119.1, 112.7, 110.2, 101.3, 55.8, 29.2, 26.2, 24.9.

To a solution of the previous methoxyindole (1.01g, 5.37 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added dropwise a solution of BBr_3 in CH_2Cl_2 (1.0 *M*, 6.00 mL). The resulting mixture was warmed to rt for 30 min. The mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give crude 1,2,3,4-tetrahydrocyclopenta[*b*]indol-7-ol as a brown oil, which was used for the next step without further purification. To a solution of the crude phenol in THF (10 mL) at rt was added Et_3N (375 µL, 2.69 mmol) and isopropyl isocyanate (3.20 mL, 32.6 mmol) and the reaction mixture was stirred overnight at rt. The mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel (hexane/EtOAc = 3/1) and by recrystallization from hexane-EtOAc to afford **8** as a white solid (1.06 g, 76%): mp 188-189 °C; ^{1}H nmr: δ 9.89 (1 H, br s), 7.21 (1H, d, *J* = 8.6 Hz), 7.02 (1 H, d, *J* = 1.7 Hz), 6.71 (1 H, dd, *J* = 8.6, 1.7 Hz), 6.43 (1 H, br d, *J* = 6.3 Hz), 3.80 (1 H,

m), 2.82 (2 H, m), 2.73 (2H, m), 2.47 (2H, m), 1.20 (6H, d, *J* = 6.5 Hz); ^{13}C nmr: δ 155.5, 146.3, 145.6, 139.7, 125.5, 119.3, 115.1, 112.0, 111.3, 43.8, 29.2, 26.2, 24.8, 22.9. Hrms Calcd for $C_{15}H_{19}N_2O_2$: $[M + H]^+$ = 259.1447. Found: 259.1447.

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.75; H, 6.90; N, 10.75.

1,2,3,4-Tetrahydrocyclopenta[*b*]indole (**9**).

Following the preparation of **7**, the reaction of phenylhydrazine hydrochloride (20.1 g, 139 mmol) and cyclopentanone (12.2 mL, 138 mmol) heated to 125 °C for 1.5 h afforded **9** [6d] as a white solid (9.64 g, 44%): ^{13}C nmr: δ 144.8, 142.4, 125.7, 120.6, 119.5, 119.2, 118.8, 112.2, 29.3, 26.2, 24.9.

Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 84.21; H, 6.90; N, 8.96.

General Procedure for the Synthesis of Bromocyclopenta[*b*]-indole (**2**, **10-16, 24-25**).

To a solution of cyclopenta[*b*]indole (0.41 mmol) in CH_2Cl_2 (1.6 mL) at -78 °C was added sequentially pyridine (330 μL, 4.10 mmol) and a solution of Br_2 in CH_2Cl_2 (1.0 *M*, 4.10 mL). The mixture was stirred at -20 °C for 30 min and cooled to -78 °C. A suspension of Zn (290 mg, 4.50 mmol) and AcOH (120 μL, 2.10 mmol) in THF (2 mL) was added portionwise and the resulting mixture was warmed to rt over 30 min and kept at rt for another 30 min. The mixture was poured into HCl (1 *N*) or 10% aqueous AcOH and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography on silica gel eluting with the suitable toluene/EtOAc mixture to give the corresponding bromoindole.

5-Bromo-3-methyl-7-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**2**).

Following the general procedure, the reaction of **1** (101 mg, 0.41 mmol), pyridine (330 μL, 4.08 mmol) and Br_2 (1.0 *M*, 4.10 mL) afforded **2** as a white solid (79 mg, 59%): mp 216-217 °C (hexane-EtOAc); ^{1}H nmr: δ 10.76 (1 H, br s), 7.98 (1 H, s), 7.74 (1 H, d, *J* = 1.6 Hz), 3.37 (1 H, m), 3.12 (3 H, s), 2.93-2.75 (3 H, m), 2.08 (1H, m), 1.33 (3 H, d, *J* = 6.9 Hz); ^{13}C nmr: δ 153.5, 142.1, 134.2, 126.1, 121.5, 121.3, 118.8, 105.0, 45.1, 38.6, 34.3, 24.0, 20.1. Hrms Calcd for $C_{13}H_{14}KBrNO_2S$: $[M + K]^+$ = 365.9566. Found: 365.9567.

Anal. Calcd. for $C_{13}H_{14}BrNO_2S$: C, 47.57; H, 4.30; N, 4.27. Found: C, 47.73; H, 4.21; N, 4.24.

5-Bromo-7-chloro-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**10**).

Following the general procedure, the reaction of **3** (255 mg, 1.33 mmol), pyridine (540 μL, 6.68 mmol) and Br_2 (1.0 *M*, 6.60 mL) afforded **10** as a white solid (342 mg, 95%): mp 109-110 °C (hexane); ^{1}H nmr: δ 10.28 (1 H, br s), 7.36 (1 H, d, *J* = 1.7 Hz), 7.20 (1 H, d, *J* = 1.7 Hz), 2.87 (2 H, m), 2.77 (2 H, m), 2.50 (2 H, m); ^{13}C nmr: δ 148.5, 138.9, 127.4, 125.1, 122.5, 121.0, 118.2, 105.3, 29.1, 26.2, 24.7. Hrms Calcd for $C_{11}H_{10}BrClN$: $[M + H]^+$ = 269.9685. Found: 269.9684.

Anal. Calcd for $C_{11}H_9BrClN$: C, 48.83; H, 3.35; N, 5.18. Found: C, 49.12; H, 3.19; N, 5.32.

3-Bromo-5,6,7,8-tetrahydrocyclopenta[4,5]pyrrolo[2,3-*b*]pyridine (**11**).

Following the general procedure, the reaction of **4** [6a] (253 mg, 1.58 mmol), pyridine (640 μL, 7.91 mmol) and Br_2 (1.0 *M*, 7.90 mL) afforded **11** as a white solid (366 mg, 97%): mp 214-215 °C (hexane-CH_2Cl_2); ^{1}H nmr: δ 10.62 (1 H, br s), 8.09 (1 H, d, *J* = 1.4 Hz), 7.87 (1 H, d, *J* = 1.4 Hz), 2.91 (2 H, m), 2.78 (2 H, m), 2.47 (2 H, m); ^{13}C nmr: δ 152.4, 147.6, 141.5, 128.1, 120.0, 116.9, 111.6, 28.2, 26.6, 25.0. Hrms Calcd for $C_{10}H_{10}BrN_2$: $[M + H]^+$ = 237.0027. Found: 237.0027.

Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.66; H, 3.83; N, 11.82. Found: C, 50.86; H, 3.63; N, 11.83.

[5-Bromo-7-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]-indol-3-yl]acetic acid (**12**).

Following the general procedure, the reaction of **5** (242 mg, 0.82 mmol), pyridine (400 μL, 4.95 mmol) and Br_2 (1.0 *M*, 4.10 mL) stirred at 0 °C afforded **12** as a pale brown solid (296 mg, 96%): mp 278-279 °C; ^{1}H nmr: δ 11.05 (1 H, br s), 10.37 (1 H, br s), 8.00 (1 H, s), 7.76 (1 H, d, *J* = 1.2 Hz), 3.67 (1 H, m), 3.13 (3 H, s), 2.96-2.80 (4 H, m), 2.62 (1 H, dd, *J* = 16.5, 8.2 Hz), 2.27 (1 H, m); ^{13}C nmr (dmso-d_6): δ 173.3, 150.2, 140.7, 132.5, 124.5, 120.4, 120.3, 117.7, 104.3, 44.3, 38.5, 35.4, 35.2, 23.1. Hrms Calcd for $C_{14}H_{14}KBrNO_4S$: $[M + K]^+$ = 409.9464. Found: 409.9466.

Anal. Calcd. for $C_{14}H_{14}BrNO_4S$: C, 45.17; H, 3.79; N, 3.76. Found: C, 45.41; H, 3.70; N, 3.82.

5,7-Dibromo-1,1-dimethyl-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (**13**).

Following the general procedure, the reaction of **6** (201 mg, 1.01 mmol), pyridine (810 μL, 10.0 mmol) and Br_2 (1.0 *M*, 10.0 mL) stirred at rt for 60 min afforded **13** as a white solid (330 mg, 92%): mp 186-187 °C; ^{1}H nmr: δ 10.97 (1 H, br s), 8.05 (1 H, s), 7.71 (1 H, s), 2.79 (2 H, s), 1.57 (6 H, s); ^{13}C nmr: δ 192.6, 153.3, 141.8, 140.0, 131.4, 125.4, 124.2, 113.4, 107.7, 58.1, 36.4, 29.0. Hrms Calcd for $C_{13}H_{12}Br_2NO$: $[M + H]^+$ = 355.9286. Found: 355.9285.

Anal. Calcd. for $C_{13}H_{11}Br_2NO$: C, 43.73; H, 3.11; N, 3.92. Found: C, 43.70; H, 3.14; N, 4.06.

5-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indol-7-yl isopropylcarbamate (**15**).

Following the general procedure, the reaction of **8** (102 mg, 0.39 mmol), pyridine (170 μL, 2.10 mmol) and Br_2 (1.0 *M*, 2.0 mL) afforded **15** as a white solid (128 mg, 96%): mp 168-169 °C; ^{1}H nmr: δ 10.06 (1 H, br s), 7.05 (1H, d, *J* = 1.6 Hz), 6.98 (1 H, d, *J* = 1.6 Hz), 6.56 (1 H, br d, *J* = 6.7 Hz), 3.79 (1 H, m), 2.84 (2 H, m), 2.74 (2H, m), 2.48 (2H, m), 1.20 (6H, d, *J* = 6.6 Hz); ^{13}C nmr: δ 155.1, 147.7, 145.7, 137.7, 126.3, 120.8, 117.9, 111.0, 103.5, 43.9, 29.1, 26.2, 24.8, 22.9. Hrms Calcd for $C_{15}H_{17}BrKN_2O_2$: $[M + K]^+$ = 375.0110. Found: 375.0109.

Anal. Calcd. for $C_{15}H_{17}BrN_2O_2$: C, 53.43; H, 5.08; N, 8.31. Found: C, 53.54; H, 5.16; N, 8.32.

5,7-Dibromo-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**16**).

Following the general procedure, the reaction of **9** (206 mg, 1.31 mmol), pyridine (1.06 mL, 13.1 mmol) and Br_2 (1.0 *M*, 13.0 mL) afforded **16** as a white solid (401 mg, 97%): mp 123-124 °C; ^{1}H nmr: δ 10.30 (1 H, br s), 7.51 (1 H, d, *J* = 1.4 Hz), 7.32 (1 H, d, *J* = 1.4 Hz), 2.87 (2 H, m), 2.76 (2 H, m), 2.50 (2 H, m); ^{13}C nmr: δ 148.3, 139.1, 128.1, 124.9, 120.8, 120.5, 112.1, 105.3, 29.1, 26.2, 24.7. Hrms Calcd for $C_{11}H_{10}Br_2N$: $[M + H]^+$ = 313.9180. Found: 313.9179.

Anal. Calcd for $C_{11}H_9Br_2N$: C, 41.94; H, 2.88; N, 4.45. Found: C, 42.25; H, 2.78; N, 4.50.

7-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**24**).

Following the general procedure, the reaction of **9** (203 mg, 1.29 mmol), pyridine (260 µL, 3.21 mmol) and Br_2 (1.0 *M*, 3.20 mL) afforded **24** [6c] as a yellow solid (141 mg, 46%; (61%) estimated by ^{1}H nmr of the crude material); hrms Calcd for $C_{11}H_{11}BrN$: $[M + H]^+$ = 236.0075. Found: 236.0074.

Anal. Calcd. for $C_{11}H_{10}BrN$: C, 55.96; H, 4.27; N, 5.93. Found: C, 55.96; H, 4.01; N, 5.99.

5-Bromo-1,2,3,4-tetrahydrocyclopenta[*b*]indole (**25**).

Following the preparation of **7**, the reaction of 2-bromophenylhydrazine hydrochloride (10.6 g, 47.6 mmol) and cyclopentanone (4.20 mL, 47.5 mmol) heated to 125 °C for 20 min afforded **25** as an off-white solid (1.53 g, 14%). Compound **25** was a minor product in the synthesis of **24** ((9%) estimated by ^{1}H nmr of the crude material **24**; difficult to isolate from compound **16**): mp 83-84 °C (hexane); ^{1}H nmr: δ 10.05 (1 H, br s), 7.34 (1 H, d, *J* = 7.8 Hz), 7.18 (1 H, d, *J* = 7.7 Hz), 6.91 (1 H, dd, *J* = 7.8, 7.7 Hz), 2.86 (2 H, m), 2.77 (2 H, m), 2.50 (2 H, m); ^{13}C nmr: δ 146.3, 140.2, 127.2, 123.2, 120.9, 120.6, 118.2, 104.8, 29.1, 26.2, 24.9. Hrms Calcd for $C_{11}H_{11}BrN$: $[M + H]^+$ = 236.0075. Found: 236.0074.

Anal. Calcd for $C_{11}H_{10}BrN$: C, 55.96; H, 4.27; N, 5.93. Found: C, 56.07; H, 4.00; N, 6.03.

[6-(Methylsulfonyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]acetic Acid (**26**).

Following the preparation of **1** and **5**, the reaction of ethyl (2-oxocyclohexyl)acetate (3.50 g, 19.0 mmol) and 2-iodo-4-(methylsulfonyl)aniline (4.75 g, 16.0 mmol) followed by hydrolysis of the ester afforded **26** as a pale yellow solid (803 mg, 16%): mp 229-230 °C ^{1}H nmr: δ 10.89 (1 H, br s), 10.30 (1 H, br s), 8.00 (1 H, d, *J* = 1.7 Hz), 7.58 (1 H, m), 7.54 (1H, m), 3.40 (1 H, m), 3.04 (3 H, s), 2.89 (1 H, m), 2.74 (2 H, m), 2.58 (1 H, m), 2.13 (1 H, m), 1.97 (1 H, m), 1.83 (1 H, m), 1.73 (1 H, m); ^{13}C nmr (dmso-d_6): δ 173.2, 139.5, 138.0, 130.6, 126.4, 118.9, 117.7, 111.3, 110.6, 44.7, 38.7, 30.2, 28.6, 20.7, 20.5. Hrms Calcd for $C_{15}H_{17}KNO_4S$: $[M + K]^+$ = 346.0515. Found: 346.0515.

Anal. Calcd for $C_{15}H_{17}NO_4S$: C, 58.61; H, 5.57; N, 4.56. Found: C, 58.64; H, 5.46; N, 4.57.

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* Corresponding author. Tel: 514 428 8696; Fax: 514 428 4900; E-mail: nicolas_lachance@merck.com

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[12] Removal of traces of chlorinated solvent led to a fast decomposition of indoline intermediates **22** and **23**.

[13] The incorporation of two bromine atoms is supported by mass spectrum analysis (APCI, negative mode) giving rise to signals at 454, 452 and 450 corresponding to $C_{14}H_{14}Br_2NO_4S$: $[M-H]^-$.

[14] The incorporation of three bromine atoms is supported by mass spectrum analysis (APCI, negative mode) giving rise to signals at 534, 532, 530 and 528 corresponding to $C_{14}H_{13}Br_3NO_4S$: $[M-H]^-$.

[15] The regioselectivity of the bromination of **6** was confirmed by NOE experiments on **13**.

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