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Concerning the preparation of 6-bromotryptamine

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ABSTRACT

Most of the previous syntheses of the marine natural product 6-bromotryptamine have almost certainly led to partial debromination resulting in an impure product containing tryptamine. We show that loss of bromine occurs when lithium aluminum hydride is employed as a reducing agent in the final reaction step leading to 6-bromotryptamine. Reductive-debromination is also likely to intrude during some of the syntheses of 6-bromoindole, the typical precursor to 6-bromotryptamine. None of the seven described syntheses of 6-bromotryptamine that involve a reduction sequence from 6-bromoindole have reported elemental analyses as a measure of purity.

1. Introduction

Of more than 2000 extant brominated marine natural products [1], the 6-bromoindole and 6-bromotryptamine entities are ubiquitous in alkaloids found in marine life – dating from Tyrian Purple in 1909 [2] to myriad examples in sponges, algae, tunicates, gorgonians, bryozoa, and molluscs. Members of the flustramine [3a], aplysinopsin [3b], chartelline [3c], eudistomin [3d], topsentin [3e], tryptamine [3f], arborescidine [3g], hamacanthin [3h], securamine [3i], didemnoline [3j], dragmacidin [3k], meridianin [3l], herdmanine [3 m], opacaline [3n], purpuroine [3°], similisine [3p], tanjungide [3q], and aspidostomide [3r] families of marine alkaloids all contain the 6-bromoindole and/or the 6-bromotryptamine unit rooted in many of their metabolites.

Pursuant to a project on the synthesis of marine natural products embedded with 6-bromoindole (**1**) and/or 6-bromotryptamine (**2**), we discovered that reductive-debromination in the final step leading to 6-bromotryptamine hitherto fore has been unrecognized. We now describe our studies in this regard, and we preface our work with a comparative review of previous syntheses of **1** and **2**.

2. Results and discussion

The reductive-dehalogenation of alkyl and aryl halides by lithium aluminum hydride has been known since at least 1948 [4], and is particularly rapid in refluxing tetrahydrofuran [4d]. In 1977 we employed this reductive-debromination on 5- and 6-bromoindoles using lithium aluminum deuteride to give 5- and 6-deuterioindoles, respectively, for a (pre-2D NMR) validation of the ^{1}H and ^{13}C chemical shifts of indole [5].

Several methods are available for the synthesis of 6-bromoindole. The inaugural synthesis of 6- (and 4-) bromoindoles featured a Reissert indole synthesis [6] via the initial bromination of 2-nitrotoluene (**3**) (Scheme 1) as reported by Plieninger [7]. The 6-bromoindole (**1**) was isolated as a solid (mp 94 °C) from the mixture that also contained 4-bromoindole (oil). Pappalardo and Vitali reported a similar preparation of **1** (mp 93.5–94 °C) [8].

Higa and Scheuer described the synthesis of **1** via the nitration of 4-aminotoluene (**4**) followed by the sequence shown in Scheme 2 [9]. No reaction conditions were reported and the overall yield was 5%.

Whereas direct bromination of indole is not a feasible route to **1**, in unpublished work [5] we found that indoline (**5**) can be brominated in concentrated sulfuric acid and silver sulfate to give 6-bromoindoline (**6**) as the major product in low yield, along with some 4-bromoindoline [5]. Oxidation of 6-bromoindoline with chloranil in refluxing xylene gave **1** in good yield (Scheme 3).

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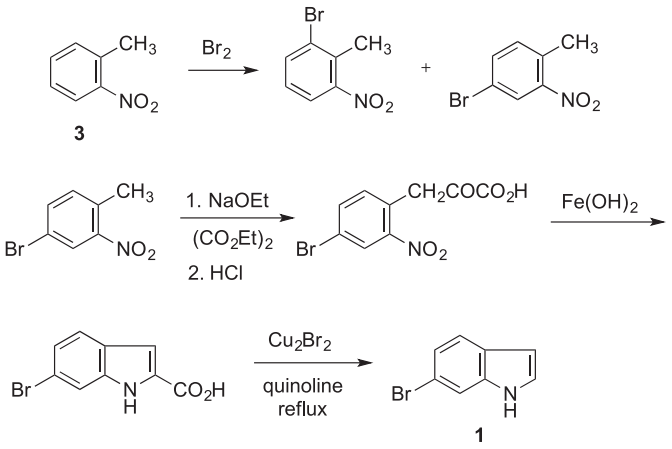
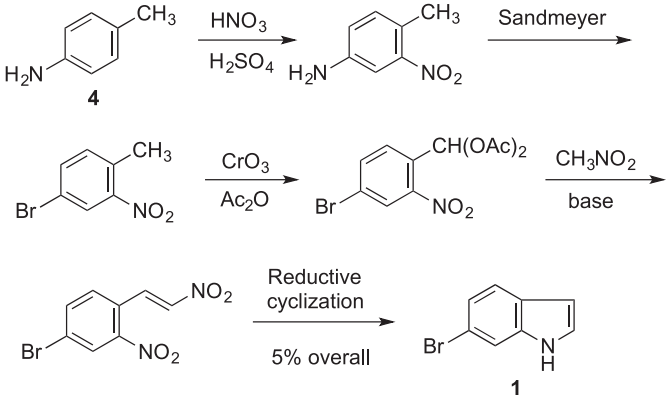
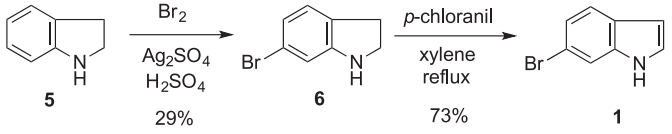


Scheme 1. Plieninger synthesis of 6-bromoindole (7).



Scheme 2. Scheuer synthesis of 6-bromoindole (9).

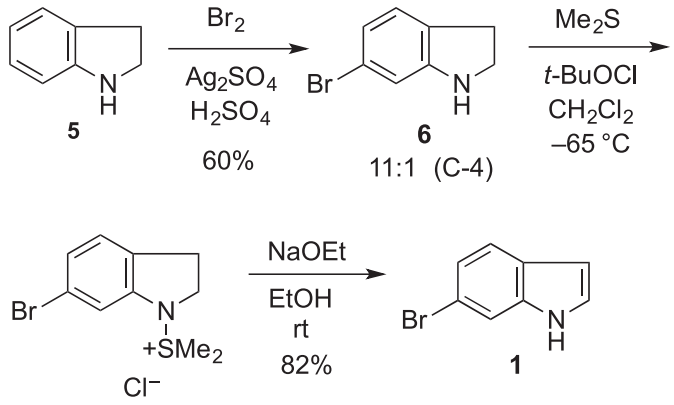


Scheme 3. Johnson synthesis of 6-bromoindole (5).

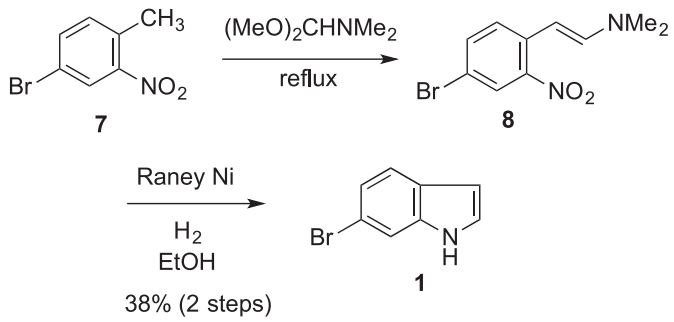
Subsequently, Kikugawa et al. reported a similar synthesis of **1** from indoline (**5**), but they employed an azasulfonium salt oxidation of the 6-bromoindoline (**6**) (Scheme 4) [10]. Whereas the mixture of C-6 and C-4 bromoindolines could not be separated, the corresponding bromoindoles could be separated by chromatography.

Sargent et al. also employed a Sandmeyer reaction to access 4-bromo-2-nitrotoluene (**7**) from 4-amino-2-nitrotoluene. The former compound was heated with *N*,*N*-dimethylformamide dimethyl acetal to afford β-dimethylamino-2-nitrostyrene (**8**), which was reduced with Raney Ni to afford **1** (Scheme 5) [11]. This sequence became known as the Leimgruber-Batcho indole synthesis [12], and has been used and modified by Rapoport [13], Rinehart [14], Carrera [15], Davidson [16], Rawal [17], and Zhang [18] to prepare 6-bromoindole (**1**) (Scheme 6).

As noted above, the key starting material in these syntheses of 6-bromoindole (**1**) is 4-bromo-2-nitrotoluene (**7**) as prepared in a Sandmeyer reaction from 4-amino-2-nitrotoluene [19], which has been known since 1884 [20]. In our hands the Sandmeyer reaction



Scheme 4. Kikugawa synthesis of 6-bromoindole [10].

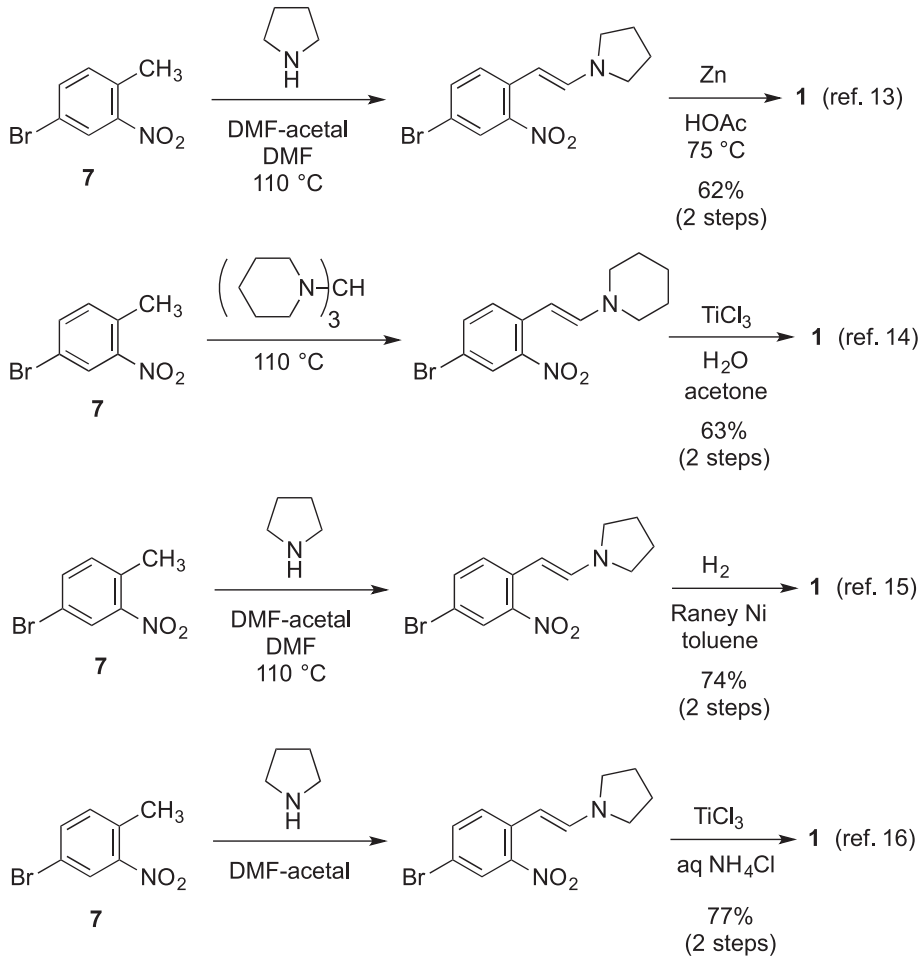


Scheme 5. Sargent synthesis of 6-bromoindole [11].

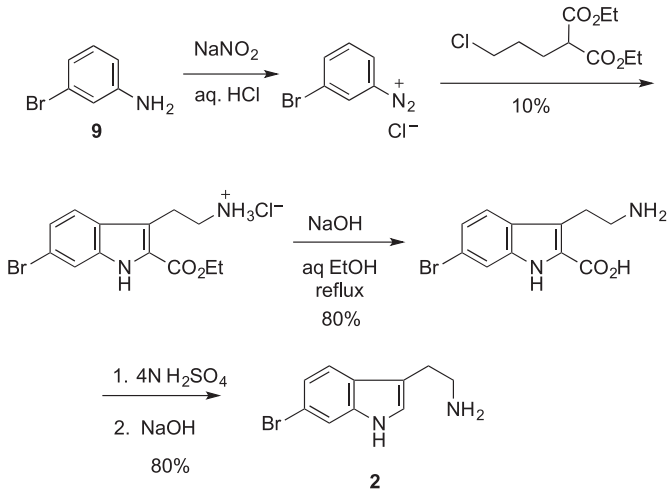
of 4-amino-2-nitrotoluene affords 4-bromo-2-nitrotoluene in 89% yield. Notably, 4-bromo-2-nitrotoluene (**7**) can also be accessed by the nitration of 4-bromotoluene [21]. For our preparation of 6-bromotryptamine (**2**) *(vide infra)* we repeated the syntheses of **1** described in Scheme 6 and we found that the reduction of the enamine intermediates was best performed with either Zn/HOAc or $TiCl_3/NH_4OAc$ (see Experimental). To verify the bromine content of our 6-bromoindole (**1**) we prepared 6-bromo-1-(phenylsulfonyl) indole in excellent yield and with the expected bromine content (cf. Experimental). This reaction was also reported by Janosik and Bergman [22], and earlier by Sasaki et al. [23], but without spectral or physical data in the latter report. We also synthesized 6-bromo-3-(2-methylaminoacetyl)indole and 2-(6-bromoindol-3-yl)-*N*-methyl-2-oxoacetamide to reconfirm the bromine level in our 6-bromoindole starting material (cf. Experimental).

Virtually all of the reported syntheses of 6-bromotryptamine (**2**) originate from 6-bromoindole (**1**). The one exception involves the Japp-Klingmann (Grandberg) variation of the Fischer indole synthesis [24] on 3-aminobromobenzene (**9**) (Scheme 7) [25]. This first synthesis of **2** provided spectral data (NMR, IR, MS), elemental analysis, and melting point (120–120.5 °C). Interestingly, this foundational synthesis of 6-bromotryptamine (**2**) preceded its isolation from the marine tunicate *Didemnum candidum* by seven years [3f].

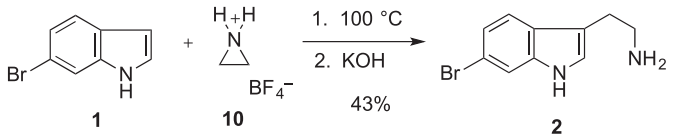
Reductive-debromination was noticed by both Rinehart [14] and Carrera [15] as a likely side reaction in their studies involving the synthesis of 6-bromotryptamine (**2**). Rinehart: "Attempted reduction of 6-bromoindole-3-glyoxylamide to 6-bromotryptamine with lithium aluminum hydride gave a mixture of largely debrominated products" [14]. Carrera: "Overreduction [of 6-bromoindole with Raney Nickel] to unsubstituted indole was observed to a small degree (≤5% as determined by NMR), but this impurity is removed



Scheme 6. Rapoport [13], Rinehart [14], Carrera [15], and Davidson [16] syntheses of 6-bromoindole



Scheme 7. Christophersen synthesis of 6-bromotryptamine [25].

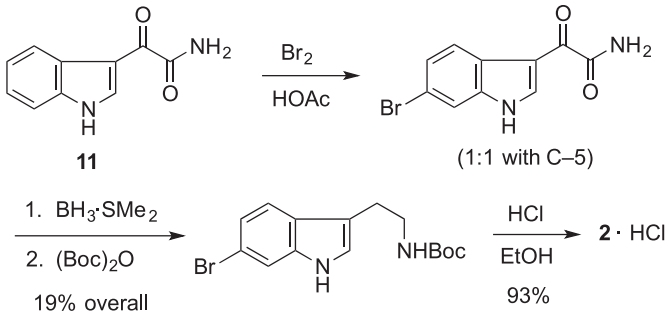


Scheme 8. Rinehart synthesis of 6-bromotryptamine [14].

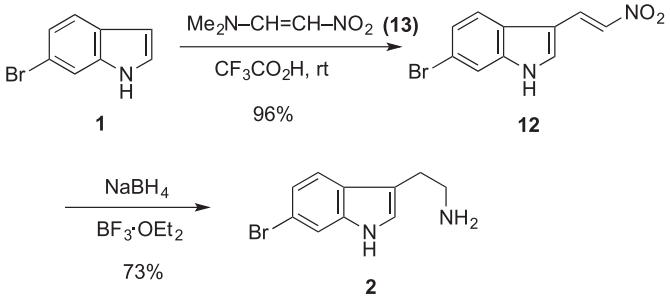
during recrystallization" [15]. In addition to his synthesis of **2** via a conventional Fischer indolization (3-bromophenylhydrazine and 4-aminobutanal diethyl acetal with zinc chloride) to give a 1.5:1 mixture of 6-bromotryptamine and 4-bromotryptamine, Rinehart employed the reaction between 6-bromoindole (**1**) and aziridinium tetrafluoroborate (**10**) to give 6-bromotryptamine (**2**) in one step (Scheme 8).

Koomen and co-workers [26] synthesized 6-bromotryptamine (**2**) from indole-3-glyoxylamide (**11**) by a sequence of C-6 bromination to give a 1:1 mixture with C-5 bromination, reduction with borane-dimethyl sulfide (avoiding lithium aluminum hydride), carbamate formation, isomer separation, and deprotection to form **2**, which was isolated as the hydrochloride (characterized by HRMS but not elemental analysis) (Scheme 9).

A popular and efficient route to 6-bromotryptamine (**2**) was pioneered by Davidson (Scheme 10) [16]. This approach involved converting 6-bromoindole (**1**) to 6-bromo-3-(2-nitrovinyl)indole (**12**) with 1-dimethylamino-2-nitroethylene (DMANE) (**13**), the Büchi reagent [27]. Reduction with sodium borohydride/boron trifluoride etherate afforded 6-bromotryptamine (**2**) in excellent overall yield. The physical state of **2** was not described nor was an elemental analysis or melting point reported (HRMS only). Rawal et al. utilized the Davidson synthesis of **2** and claimed it "to be the most efficient" [17]. The 6-bromotryptamine was also not analyzed in this report.



Scheme 9. Koomen synthesis of 6-bromotryptamine hydrochloride [26].



Scheme 10. Davidson synthesis of 6-bromotryptamine [16].

The Davidson route to 6-bromotryptamine (**2**) was adopted by Lindsley [28], Shi [29], and Andersen [30] (Scheme 11). In no case was the product analyzed for purity.

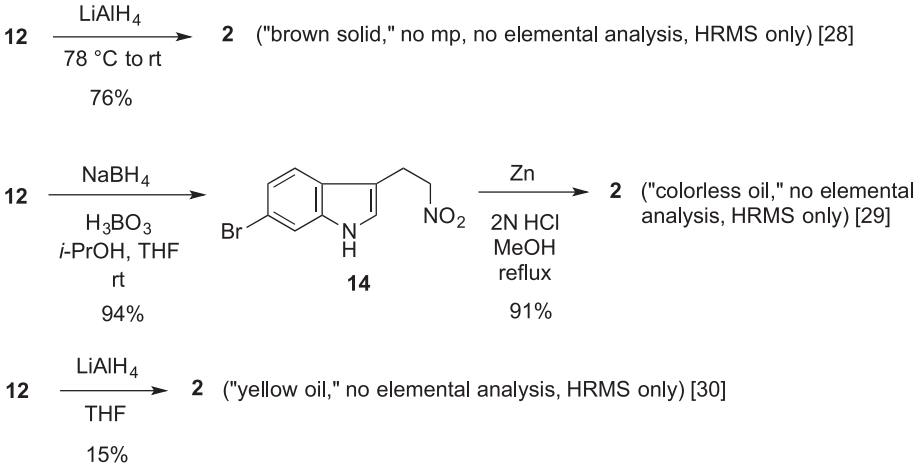
Another route to 6-bromotryptamine (**2**) involved a Henry reaction of 6-bromoindole-3-carbaldehyde (**16**) (which is also a marine natural product [31]). 6-Bromoindole-3-carbaldehyde (**16**) was first synthesized by Da Settimo et al. in 1967 [32] from the bromination of indole-3-carbaldehyde (**15**) to give in very low yield a mixture of **16** (3%) and 5-bromoindole-3-carbaldehyde (**17**) (6%). However, these workers found that treatment of 6-bromoindole (**1**) with $POCl_3$/DMF gives **16** in 92% yield (Scheme 12).

A Henry reaction of 6-bromoindole-3-carbaldehyde (**16**) to give 6-bromotryptamine (**2**) was first described by Zhang [18], followed by Kobayashi [33], and Jiang [34] (Scheme 13). In no case was an analysis of the 6-bromotryptamine product reported.

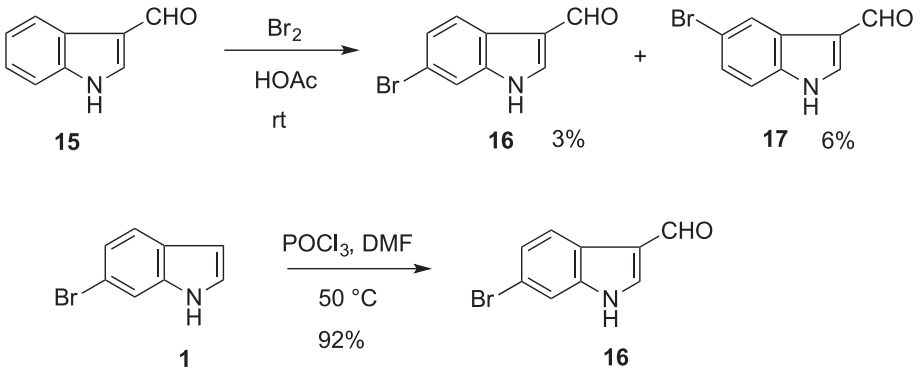
In summary, (1) the use of $LiAlH_4$ in refluxing THF in the final reduction step leading to 6-bromotryptamine (**2**) (cf. Schemes 11 and 13), (2) the description of product **2** as anything other than a colorless solid, and (3) the *complete absence* of elemental analytical data (except for HRMS in some cases) prompted our present investigation in the synthesis of 6-bromotryptamine.

We initially repeated several of the aforementioned Leimgruber-Batcho 6-bromoindole syntheses as summarized in Scheme 14. As noted earlier, we verified the bromine content in our 6-bromoindole via three derivatives *(vide supra)*. .

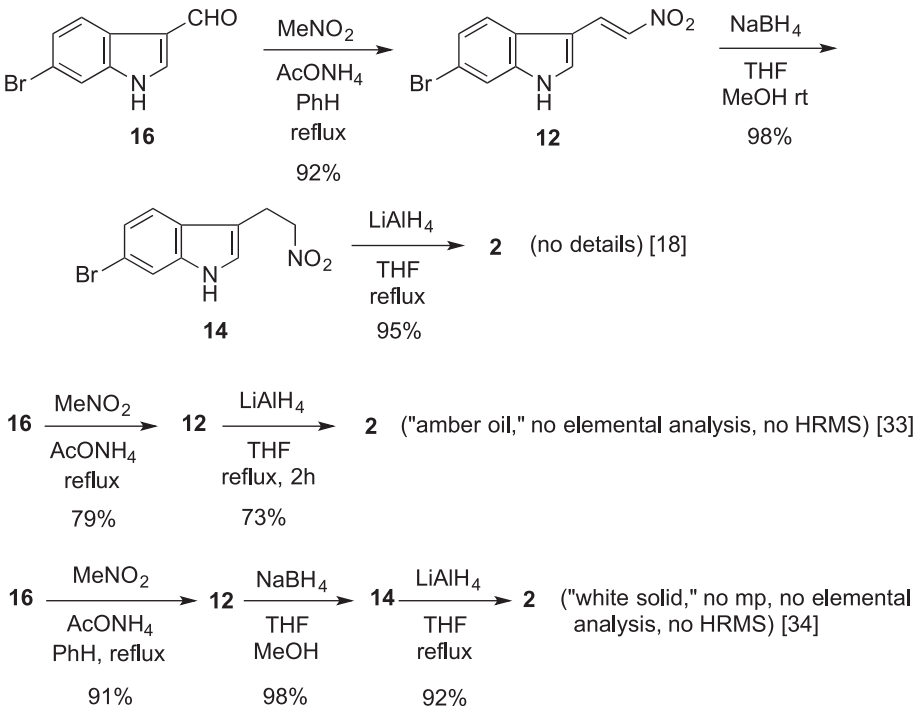
Our synthesis of 6-bromotryptamine (**2**) is depicted in Scheme 15. We used the Henry reaction with nitromethane on 6-bromoindole-3-carbaldehyde (**16**) to form **3**, and by selective



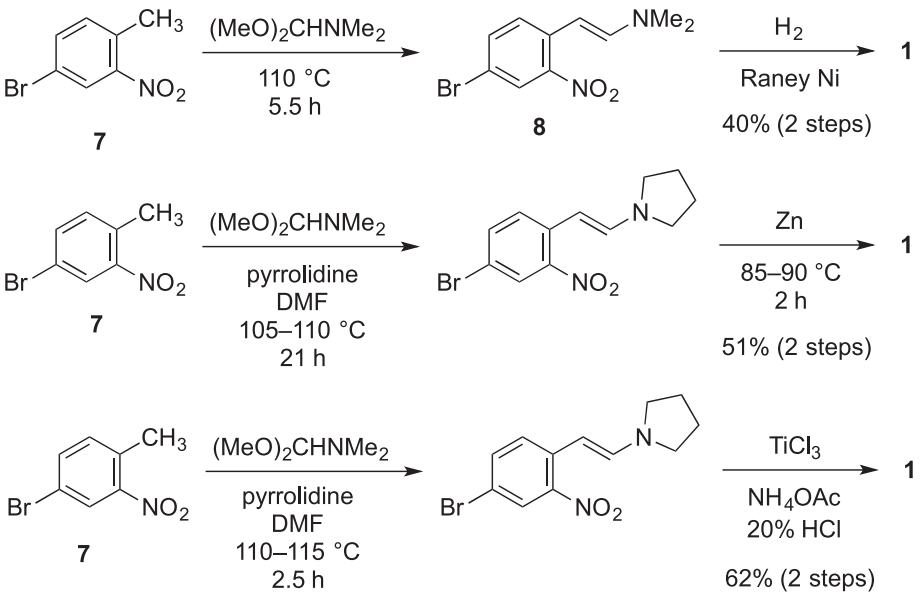
Scheme 11. Lindsley [28], Shi [29], and Andersen [30] syntheses of 6-bromotryptamine



Scheme 12. Da Settimo syntheses of 6-bromoindole-3-carbaldehyde [32].



Scheme 13. Zhang [18]. Kobayashi [33], and Jiang [34] syntheses of 6-bromotryptamine

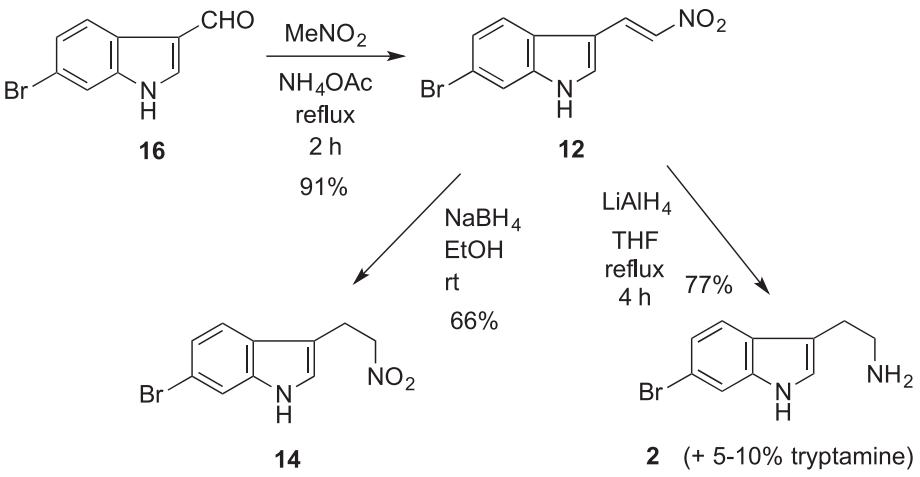


Scheme 14. Our syntheses of 6-bromoindole via a Leimgruber-Batcho reaction.

reduction of the double bond to give **14**. Direct reduction of **12** with $LiAlH_4$ gives 6-bromotryptamine (**2**) as previously reported by several groups (cf. Schemes 11 and 13). Unlike previous workers we obtained melting points and elemental analyses of **12**, **14**, and **2**. Our data clearly show that *reductive debromination is occurring in the $LiAlH_4$ step to the extent of 5–10% at a minimum, as cleared evidenced by the bromine analysis*. Proton NMR is also consistent with the presence of tryptamine (5–10%). This concurs with the qualitative observations of Rinehart and Carrera cited earlier. After recrystallization to remove tryptamine (5–10%) our 6-bromotryptamine (**2**) is a white solid having a melting point 119–119.5 °C, consistent with Grön and Christophersen, mp 120–120.5 °C [25].

3. Conclusion

Our examination of the several syntheses of 6-bromoindole (*vide supra)* indicates the most efficient and cost effective syntheses is the 4-bromo-2-nitrotoluene/Leimgruber-Batcho ($TiCl_3$ or Zn) synthesis. Based on the known propensity of $LiAlH_4$ to reductively debrominate aryl bromides in refluxing THF [4d] and the elemental analysis of our 6-bromotryptamine that shows erosion of bromine



Scheme 15. Our synthesis of 6-bromotryptamine.

using $LiAlH_4$ (Scheme 15), we urge caution in future syntheses of any bromotryptamine and their derivatives if $LiAlH_4$ is involved in their syntheses. Moreover, reductive-dehalogenation in general has been observed during catalytic hydrogenation [35], and even with sodium hydride in refluxing THF [36]. Accordingly, we recommend that elemental analyses be performed to verify the purify of both 6-bromoindole and 6-bromotryptamine, as well as derivatives if a reduction operation is involved in their syntheses. The sole reliance on high-resolution mass spectra is no evidence of purity.

4. Experimental

4.1. Indoline

To a solution of indole (1.33 g, 11.4 mmol) in glacial HOAc (20 mL) cooled to 15 °C in a H_2O ice bath was added in one portion $NaBH_3CN$ (1.89 g, 35.0 mmol). After 2 h the solution was poured into H_2O (150 mL), cooled in an ice bath, made basic by addition of NaOH pellets, and extracted with Et_2O (4 × 75 mL). The combined organic layers were washed with H_2O (2 × 100 mL), brine (2 × 100 mL), dried (Na_2SO_4), and evaporated to yield indoline (1.26 g, 93%) as a light yellow oil: ^1H NMR ($CDCl_3$) δ 7.10–7.05 (m, 1 H), 7.02–6.94 (m, 1 H), 6.70–6.63 (m, 1 H), 6.60–6.55 (m, 1 H), 3.68 (br s, 1 H), 3.44 (t, J = 8.5, 2 H), 2.95 (t, J = 8.5, 2 H); ^{13}C NMR ($CDCl_3$) δ 151.4, 129.0, 126.7, 124.3, 118.4, 109.1, 47.6, 29.6; IR (neat) cm^{-1} 3375, 3046, 3029, 2932, 2849, 1606, 1486, 1467, 1406, 1322, 1244, 1167, 1153, 1092, 1056, 1022 cm^{-1}.

4.2. 6-Bromoindoline/4-bromoindoline

Freshly distilled indoline (0.48 g, 4.0 mmol) (bp 46–47 °C/0.35 Torr) was dissolved in 97% H_2SO_4 (5 mL) and Ag_2SO_4 (0.61 g, mmol) was added in one portion. The mixture was stirred for 30 min, at which time Br_2 (0.20 mL, 8 mmol) was added via syringe. The mixture was stirred for 30 min, at which time it was poured into H_2O (30 mL) and cooled in an ice bath, made basic with an aqueous solution of NaOH (6.0 M, 45 mL), diluted with benzene (20 mL) and filtered. The phases were separated and the aqueous layer was extracted with benzene (2 × 20 mL). The combined organic layers were washed with brine (3 × 30 mL), dried (Na_2SO_4), and evaporated to yield a brown oil (0.72 g). Flash chromatography (CH_2Cl_2) gave a mixture of 6- (major) and 4-bromoindoline (minor) (0.23 g, 29%) as a light brown oil; distillation gave bp 117–118 °C (0.53 Torr); ^1H NMR ($CDCl_3$) δ 6.94–6.89 (m, 1 H), 6.79–6.74 (m, 1 H), 6.69 (s, 1 H), 3.72 (br s, 1 H), 3.53 (t, J = 8.4, 2 H), 2.93 (t, J = 8.4, 2 H); ^{13}C NMR ($CDCl_3$) δ 153.1, 128.2, 125.6, 120.9, 120.5, 112.0, 47.6, 29.1; IR (film) 3497 cm^{-1}. This product was characterized as the *N*-acetyl derivative (below).

4.3. N-acetyl-6-bromoindoline

To 0.374 g (1.89 mmol) of 6-/4-bromoindoline was added acetic anhydride (70 mL). The reaction was heated briefly to 130 °C, cooled to rt, and poured onto crushed ice (75 mL). Filtration gave 0.336 g of crude product (74%). Recrystallization from EtOH afforded needles of *N*-acetyl-6-bromoindoline, mp 134–134.5 °C; ^1H NMR ($CDCl_3$) δ 8.30 (s, 1 H), 7.22–6.90 (m, 2 H), 4.10–3.68 (m, 2 H), 3.20–2.87 (m, 2 H), 2.10 (s, 3 H); IR (nujol) 1660 cm^{-1}. *Anal.* Calcd for $C_{10}H_{10}NOBr$: C, 50.02; H, 4.20; N, 5.83. Found: C, 49.75; H, 4.09; N, 5.76.

4.4. 6-Bromoindole (**1**) by oxidation of 6- and 4-bromoindoline

To a solution of 6-/4-bromoindoline (0.44 g, 2.2 mmol) in xylenes (25 mL) was added *p*-chloranil (0.93 g, 3.8 mmol) in one portion. The dark green solution was heated to reflux for 5 h. The mixture was cooled and filtered, rinsing the filter cake with an aqueous solution of NaOH (6.0 M, 15 mL) and of H_2O (15 mL). The combined organic phases were concentrated in vacuo to 10 mL of a brown slurry. Steam distillation afforded 6-bromoindole (**1**) (0.32 g, 73%) as a white solid: mp 93–94 °C (lit [7]. mp 94 °C). The product may also be recrystallized from petroleum ether (mp 92.5–94 °C); ^1H NMR ($CDCl_3$) δ 8.10–7.92 (br s, 1 H), 7.52–7.44 (m, 2 H), 7.25–7.16 (m, 1 H), 7.14–7.06 (m, 1 H), 6.54–6.46 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 136.5, 126.7, 124.8, 123.1, 121.9, 115.4, 113.9, 102.7; IR (nujol) 3394, 1606, 1568, 1495, 1398, 1335, 1315, 1230, 1095, 1052, 893, 866, 808, 761, 731 cm^{-1}.

4.5. 4-Bromo-2-nitrotoluene (**7**)

4-Amino-2-nitrotoluene (15.24 g, 99 mmol) was slurried in H_2O (125 mL) in a 500 mL 3-necked flask equipped with a condenser, addition funnel and stopper. The suspension was heated to reflux and HBr (48%, 51.5 mL) was added dropwise. The mixture was maintained at reflux for 20 min then cooled to 0 °C. A solution of $NaNO_2$ (6.45 g, 93 mmol) in H_2O (40 mL) was added dropwise with rapid stirring while maintaining the temperature at 0 °C. The resulting diazonium solution was stirred at 0 °C for 15 min and then

added dropwise to a mechanically stirred mixture of CuBr (15.44 g, 108 mmol) in H_2O (75 mL) and HBr (48%, 33 mL) cooled to 0–5 °C with an ice bath. The thick suspension was stirred at rt for 20 min, heated on a steam bath for an additional 20 min and let stand overnight. Steam distillation afforded 4-bromo-2-nitrotoluene (17.79 g, 89%) as yellow prisms: mp 45–45.5 °C (lit [20]. mp 47 °C); ^{1}H NMR ($CDCl_3$) δ 8.10 (d, J = 2.0, 1 H), 7.62 (dd, J = 2.0, 8.2, 1 H), 7.24 (d, J = 8.2, 1 H), 2.55 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 149.5, 136.0, 134.1, 132.6, 127.5, 119.6, 20.1; IR ($CDCl_3$) 3019, 1526, 1350, 1215 cm^{-1}.

4.6. 6-Bromoindole (**1**) (raney nickel reduction)

A solution of 4-bromo-2-nitrotoluene (**7**) (0.80 g, 3.7 mmol) in *N,N*-dimethylformamide dimethyl acetal (1.40 mL, 10.5 mmol) was heated to reflux (110 °C) for 5.5 h. The bright red solution was allowed to cool to rt, diluted with benzene (50 mL) and shaken in a Parr apparatus with Raney nickel under 50 psi of H_2 for 26 h. The light yellow solution was filtered, washed with H_2O (3 × 30 mL), brine (3 × 30 mL), dried (Na_2SO_4), and evaporated to give a brown oil. Flash chromatography (hexanes/CH_2Cl_2 (1:1)) gave **1** (0.29 g, 40%) as a white powder: mp 92.5–93 °C (lit [7]. mp 94 °C). The spectroscopic data match that of authentic **1** as prepared above.

4.7. 6-Bromoindole (**1**) (zinc reduction)

To a solution of 4-bromo-2-nitrotoluene (**7**) (14.0 g, 65.0 mmol) in DMF (110 mL) was added DMF dimethyl acetal (17.3 mL, 130 mmol) and pyrrolidine (5.4 mL, 65 mmol). The solution was heated with an oil bath to 105–110 °C for 21 h. The bright red solution was allowed to cool to rt, diluted with Et_2O (400 mL) and extracted with H_2O (4 × 150 mL). The combined aqueous layers were extracted with Et_2O (100 mL). The combined organic layers were concentrated in vacuo to a red oil which crystallized on standing. The red solid was taken up in 80% HOAc (500 mL) and heated to 70 °C on an oil bath. Zinc dust (80 g, 1.2 mol) was added in four portions over 1 h and the mixture was heated to 85–90 °C for 2 h, at which time the solution was cooled and filtered. The filtrate was extracted with Et_2O (4 × 150 mL), washed with saturated aqueous $NaHCO_3$ (6 × 200 mL), brine (3 × 100 mL), dried ($MgSO_4$), and evaporated to give **xx** as a green solid. Flash chromatography (hexanes/CH_2Cl_2 (1:1)) afforded **1** as a light blue solid (8.43 g, 65%). Recrystallization from hexanes gave **1** (6.59 g, 51%) as a white solid: mp 92–93 °C (lit [7]. mp 94 °C). Concentration of the mother liquor afforded a second crop (0.60 g, 5%). The spectroscopic data match that of authentic **1** as prepared above.

4.8. 6-Bromoindole (**1**) (titanium(III) chloride reduction)

To a solution of 4-bromo-2-nitrotoluene (**7**) (2.097 g, 9.70 mmol) in DMF (25 mL) was added DMF dimethyl acetal (3.90 mL, 29.3 mmol) and pyrrolidine (0.84 mL, 10 mmol). The solution was heated with an oil bath to 110–115 °C for 135 min. The bright red solution was cooled to rt, diluted with Et_2O (100 mL) and extracted with H_2O (5 × 50 mL). The combined aqueous layers were extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (2 × 50 mL), dried ($MgSO_4$), and evaporated to a red oil which crystallized on standing. The resulting enamines were dissolved in a minimal amount of acetone and placed in a separatory funnel, shaken with an aqueous solution of NH_4OAc (4 M, 85 mL) and $TiCl_3$ (19% in 20% HCl, 40 mL) for 10 min, and extracted with Et_2O (4 × 35 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), brine (2 × 30 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (hexanes/CH_2Cl_2 (1:1)) gave **1** (1.176, 62%) as a white powder: mp 92–93 °C (lit [7]. mp 94 °C). The spectroscopic data match that of authentic **1** as prepared above.

4.9. 6-Bromo-1-(phenylsulfonyl)indole

Benzenesulfonyl chloride (2.2 g, 1.6 mL, 28 mmol) was added dropwise over 10 min to an ice cold mixture of 6-bromoindole (**1**) (1.369 g, 6.90 mmol), powdered NaOH (0.90 g, 23 mmol) and nBu$_4$NHSO$_4$ (63 mg, 0.19 mmol) in CH_2Cl_2 (35 mL). After 1 h, the mixture was removed from the ice bath and stirred for an additional 2 h. The solids were removed by filtration and the solution was evaporated to an oil which was tritrated in MeOH to give the title compound (2.20 g, 95%) in two crops: mp 98–99 °C (lit [22]. mp 100–101 °C); ^{1}H NMR ($CDCl_3$) δ 8.19 (m, 1 H), 7.88 (m, 2 H), 7.60–7.35 (m, 5 H), 6.63 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.0, 134.1, 129.5, 129.4, 126.7, 122.5, 118.3, 116.6, 109.0. The elemental analysis showed no erosion of bromine within experimental error: *Anal.* Calcd for $C_{14}H_{10}NO_2SBr$: C, 50.01; H, 3.00; N, 4.17; S, 9.52; Br, 23.77. Found: C, 50.09; H, 3.08; N, 4.11; S, 9.62; Br, 23.86.

4.10. 6-Bromo-3-(2-methylaminoacetyl)indole

To a stirred solution of $AlCl_3$ (5.35 g, 40.2 mmol) in CH_2Cl_2 (50 mL) was added $ClCH_2COCl$ (1.56 mL, 20.0 mmol) and the mixture was stirred for 15 min. A solution of 6-bromoindole (1.30 g, 6.63 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the mixture was stirred for 1 h, then quenched with crushed ice. The resulting precipitate was collected, washed with H_2O, and recrystallized from MeCN to give 0.89 g (44%) of 6-bromo-3-(2-chloroacetyl)indole as an off-white solid: mp 297.5–298 °C: IR (KBr) 1650, 1753, 1513,1479, 1440, 1417, 1330 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 12.22 (br s, 1H), 8.45 (s, 1H), 8.08 (d, J = 8.4 Hz, 1 H), 7.69 (d, J = 1.5 Hz, 1 H), 7.36 (dd, J = 8.7, 1.5 Hz, 1 H), 4.88 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 186.3, 137.5, 135.6, 125.1, 124.4, 122.8, 115.8, 115.1, 113.5, 46.4. This product was used as described below.

Methylamine (8.0 M) in EtOH (50 mL) was added to 6-bromo-3-(2-chloroacetyl)indole (3.81 g, 19.6 mmol). The solution was stirred for 4 h. The white precipitate was removed by filtration, washed with H_2O and dried (50 °C, 1 Torr) to give the title compound (2.05 g, 56%) as a white solid, mp 206–207 °C; IR (KBr) 3314, 3069, 2938, 2878, 2793, 1643, 1606, 1570, 1520, 1445, 1424, 1329, 1246, 1141, 1100, 1049, 925, 884, 809 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.39 (s, 1 H), 8.11 (m, 1 H), 7.66 (s, 1 H), 7.31 (m, 1 H), 3.82 (s, 2 H), 2.33 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 193.9, 137.4, 134.3, 124.6, 124.4, 122.9, 115.4, 114.8, 114.7, 57.3, 36.0; MS *m/e* 266/268 (M+), 237/239, 222/224 (100). The elemental analysis showed no erosion of bromine within experimental error: *Anal.* Calcd for $C_{11}H_{11}N_2OBr$: C, 49.46; H, 4.15; N, 10.49; Br, 29.91. Found: C, 49.32; H, 4.06; N, 10.41; Br, 30.03.

4.11. 2-(6-Bromoindol-3-yl)-N-methyl-2-oxoacetamide

To a solution of oxalyl chloride (0.44 mL, 0.71 g, 5.6 mmol) in Et_2O (25 mL) at 0 °C was added 6-bromoindole (1.00 g, 5.1 mmol) in Et_2O (40 mL). The solution was allowed to warm to rt and stirred for 4 h. To this mixture was added a solution of 40% aqueous methylamine in EtOH (30 mL) and the mixture was stirred at rt overnight. The resulting precipitate was collected to give 1.08 g of the title compound as a solid. The filtrate gave an additional 0.21 g for a total of 1.29 g (90%). Recrystallization from EtOH gave mp 247 °C. The elemental analysis showed no erosion of bromine within experimental error: *Anal.* Calcd for $C_{11}H_9N_2O_2Br$: C, 47.00; H, 3.23; N, 9.97; Br, 28.42. Found: C, 46.89; H, 3.24; N, 9.98; Br, 28.35.

4.12. 6-Bromoindole-3-carbaldehyde (**16**)

Phosphorus oxychloride (3.3 mL, 36 mmol) was added slowly via syringe to ice-cold dry DMF (10 mL). The solution, under N_2, was stirred for 10 min at 0–5 °C. A solution of 6-bromoindole (**1**) (4.95 g, 25 mmol) in DMF (10 mL) was added dropwise via syringe over 2 min and the solution was stirred at rt for 1 h, heated to 40 °C for 1.5 h, and poured into ice. A solution of NaOH (30 mL, 6 M) was then added dropwise and the yellow mixture was heated to 98 °C for 2 min, cooled to rt, and the precipitate that formed was collected by filtration, washed with H_2O, and dried (50 °C, 1 Torr) to give **16** (5.60 g, 100%) as a yellow solid. Recrystallization from 95% EtOH gave mp 202.5–204 °C (lit [32]. mp 203–204 °C); IR (KBr) 3420 (broad), 3156, 3035, 2910, 2791, 1635, 1573, 1523 1448, 1425, 1385, 1243, 1128, 1049, 896, 842, 806, 746, 672 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.25 (br s, 1 H), 9.92 (s, 1 H), 8.13 (s, 1 H), 8.01 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 1.8 Hz, 1 H), 7.35 (dd, J = 8.4, 1.8 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 185.2, 139.2, 137.9, 125.1, 123.2, 122.5, 118.0, 115.9, 115.2; MS *m/e* 225/223 (M+) (100), 196/194, 169/167, 143.

4.13. 6-Bromo-3-(2-nitrovinyl)indole (**12**)

A solution of **16** (0.935 g, 4.17 mmol) and NH_4OAc (0.250 g, 3.25 mmol) in nitromethane (15 mL) was refluxed for 2 h, cooled to rt, allowed to stand for 16 h. The resulting precipitate was collected by filtration, washed with H_2O and dried (50 °C, 1 Torr) to give **12** (0.820 g, 73%) as an orange solid, mp 113–114 °C. A second crop was obtained by concentration of the mother liquor (0.207 g, 18%). The analytical sample was crystallized from EtOH–H_2O: mp 113.5–114.5 °C (dec.); IR (KBr) 3240 (broad), 1610, 1568, 1520, 1476, 1293, 1221, 1130, 1053, 963, 894, 806 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.28 (br s, 1 H), 8.39 (d, J = 13.8 Hz, 1 H), 8.26 (s, 1 H), 8.03 (d, J = 13.5 Hz, 1 H), 7.97 (d, J = 8.7 Hz, 1 H), 7.72 (m, 1 H), 7.34 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 138.5, 139.7, 134.0, 131.9, 124.5, 123.7, 122.2, 115.9, 115.4, 108.2; MS *m/e* 268/266 (M+), 221/219, 141, 114 (100). The elemental analysis showed no erosion of bromine within experimental error: *Anal.* Calcd for $C_{10}H_7N_2O_2Br$: C, 44.97; H, 2.64; N, 10.49; Br, 29.92. Found: C, 45.07; H, 2.68; N, 10.39; Br, 30.01.

4.14. 6-Bromotryptamine (**2**)

To an ice cold slurry of $LiAlH_4$ (2.33 g, 62 mmol) in THF (50 mL) was added a solution of **12** in THF (50 mL) over 15 min. The mixture was heated to reflux for 4 h and was allowed to stand for 18 h. The solution was cooled to 0–5 °C in an ice bath and the excess $LiAlH_4$ was decomposed by successive additions of H_2O (2.3 mL), aqueous NaOH (6.0 M, 2.3 mL), and H_2O (7.0 mL) dropwise by syringe. The resulting precipitate was removed by filtration and extracted with Et_2O (2 × 100 mL). The layers were separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with H_2O (2 × 100 mL), brine (3 × 100 mL), dried (Na_2SO_4) and evaporated to a colorless oil that solidified on standing. The oil was purified by extraction with hot heptane to give a mixture of **2** and tryptamine (2.04 g, 77%) (10:1 by NMR): ^1H NMR ($CDCl_3$) δ 8.15 (br s, 1 H), 7.51 (d, J = 1.8 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 1 H), 7.26 (s, 1 H), 7.21 (dd, J = 8.7, 1.8 Hz, 1 H), 3.02–2.90 (m, 4 H), 1.35 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 137.2, 126.4, 122.7, 122.4, 120.0, 115.4, 114.0, 113.7, 42.2, 29.2. Recrystallization from EtOAc-heptane gave a colorless solid mp 119–119.5 °C (lit [25]. mp 120–120.5 °C). *The elemental analysis showed obvious loss of bromine*: *Anal.* Calcd for $C_{10}H_{11}N_2Br$: C, 50.23; H, 4.64; N, 11.72; Br, 33.42. Found: C, 51.70; H, 4.81; N, 11.94; Br, 31.39.

4.15. 6-Bromo-3-(2-nitroethyl)indole (**14**)

To a slurry of **12** (2.58 g, 9.67 mmol) in EtOH (200 mL) heated to 45 °C by an oil bath was added $NaBH_4$ (7.5 g, 0.20 mol) over 2 h. The mixture was cooled to rt over 1 h, the excess $NaBH_4$ was quenched with glacial HOAc, and the solution was concentrated in vacuo. The resulting solid was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), brine (3 × 50 mL), dried ($MgSO_4$), and passed through a plug of silica gel to remove a baseline impurity. The solution was evaporated to give **14** as an oil (1.72 g, 66%) that solidified on standing. Recrystallization from Et_2O/petroleum ether gave the analytical sample as clear yellow prisms: mp 64.5–65.5 °C (lit [29]. mp 57–57.5 °C); IR (KBr) 3123, 2930, 1614, 1544, 1472, 1457, 1445, 1425, 1383, 1331, 1296, 1222, 1132, 1106, 1086, 896, 806, 774 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.12 (br s, 1 H), 7.46 (d, J = 1.5 Hz, 1 H), 7.39 (d, J = 8.7 Hz, 1 H), 7.22 (dd, J = 8.7, 1.5 Hz, 1 H), 6.96 (m, 1 H), 4.62 (t, J = 7.2 Hz, 2 H), 3.42 (t, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 136.9, 125.5, 123.2, 123.0, 119.3, 115.9, 114.3, 110.1, 75.6, 23.3; MS *m/e* 268/270 (M+), 221/223, 210/208, 195, 143 (100%), 115. The elemental analysis showed no erosion of bromine within experimental error: *Anal.* Calcd for $C_{10}H_9N_2O_2Br$: C, 44.63; H, 3.37; N, 10.41; Br, 29.69. Found: C, 44.83; H, 3.40; N, 10.44; Br, 29.65.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] (a) G.W. Gribble, Prog. Chem. Org. Nat. Prod. 91 (2010) 1–619;
(b) G.W. Gribble, Arkivoc Vi, 2018, pp. 372–410.
[2] J.T. Baker, Endeavour 33 (1974) 11–12.
[3] (a) J.S. Carlé, C. Christophersen, J. Am. Chem. Soc. 101 (1979) 4012–4013;
(b) P. Djura, D.J. Faulkner, J. Org. Chem. 45 (1980) 735–737;
(c) L. Chevolot, A.-M. Chevolot, M. Gajhede, C. Larsen, U. Anthoni, C. Christophersen, J. Am. Chem. Soc. 107 (1985) 4542–4543;
(d) K.L. Rinehart Jr., J. Kobayashi, G.C. Harbour, J. Gilmore, M. Mascal, T.G. Holt, L.S. Shield, F. Lafargue, J. Am. Chem. Soc. 109 (1987) 3378–3387;
(e) K. Bartik, J.-C. Braekman, D. Daloze, C. Stoller, J. Huysecom, G. Vandevyver, R. Ottinger, Can. J. Chem. 65 (1987) 2118–2121;
(f) E. Fahy, B.C.M. Potts, D.J. Faulkner, K. Smith, J. Nat. Prod. 54 (1991) 564–569;
(g) M. Chbani, M. Païs, J.-M. Delauneux, C. Debius, J. Nat. Prod. 56 (1993) 99–104;
(h) S.P. Gunasekera, P.J. McCarthy, M. Kelly-Borges, J. Nat. Prod. 57 (1994) 1437–1441;
(i) L. Rahbaek, U. Anthoni, C. Christophersen, P.H. Nielsen, B.O. Petersen, J. Org. Chem. 61 (1996) 887–889;
(j) H.C. Vervoort, S.E. Richards-Gross, W. Fenical, A.Y. Lee, J. Clardy, J. Org. Chem. 62 (1997) 1486–1490;
(k) R.J. Capon, F. Rooney, L.M. Murray, E. Collins, A.T.R. Sim, J.A.P. Rostas, M.S. Butler, A.R. Carroll, J. Nat. Prod. 61 (1998) 660–662;
(l) L.H. Franco, E. Bal de Kier Joffé, L. Puricelli, M. Tatian, A.M. Seldes, J.A. Palermo, J. Nat. Prod. 61 (1998) 1130–1132;
(m) J.L. Li, S.C. Han, E.S. Yoo, S. Shin, J. Hong, Z. Cui, H. Li, J.H. Jung, J. Nat. Prod. 74 (2011) 1792–1797;
(n) S.T.S. Chan, A.N. Pearce, M.J. Page, M. Kaiser, B.R. Cop, J. Nat. Prod. 74 (2011) 1972–1979;
(o) S. Shen, D. Liu, C. Wei, P. Proksch, W. Lin, Bioorg. Med. Chem. 20 (2012) 6924–6928;
(p) W.-S. Sun, S. Su, R.-X. Zhu, G.-Z. Tu, W. Cheng, H. Liang, X.-Y. Guo, Y.-Y. Zhao, Q.-Y. Zhang, Tetrahedron Lett. 54 (2013) 3617–3620;
(q) C. Muria, L. Coello, R. Fernández, M.J. Martin, F. Reyes, A. Francesch, S. Munt, C. Cuevas, Mar. Drugs 12 (2014) 1116–1130;

(r) C.L.P. Patiño, C. Muniain, M.E. Knott, L. Puricelli, J.A. Palermo, J. Nat. Prod. 77 (2014) 1170–1178.
[4] (a) J.E. Johnson, R.H. Blizzard, H.W. Carhart, J. Am. Chem. Soc. 70 (1948) 3664–3665;
(b) G.J. Karabatsos, R.L. Shone, S.E. Scheppele, Tetrahedron Lett. (1964) 2113–2116;
(c) G.J. Karabatsos, R.L. Shone, J. Org. Chem. 33 (1968) 619–621;
(d) H.C. Brown, S. Krishnamurthy, J. Org. Chem. 34 (1969) 3918–3923.
[5] (a) J.L. Johnson, G.W. Gribble, unpublished;.
(b) J.L. Johnson, PhD thesis, Dartmouth College, 1977.
[6] G.W. Gribble, Indole Ring Synthesis: from Natural Products to Drug Discovery, " John Wiley & Sons, 2016 (Chapter 40).
[7] H. Plieninger, T. Suehiro, K. Suhr, M. Decker, Chem. Ber. 88 (1955) 370–376.
[8] G. Pappalardo, T. Vitali, Gazz. Chim. Ital. 88 (1958) 1147–1169.
[9] T. Higa, P.J. Scheuer, Heterocycles 4 (1976) 231–233.
[10] (a) Y. Miyake, Y. Kikugawa, J. Heterocycl. Chem. 20 (1983) 349–352;
(b) Y. Kikugawa, M. Kawase, Chem. Lett. (1981) 445–446;
(c) M. Kawase, Y. Miyake, Y. Kikugawa, J. Chem. Soc. Perkin 1 (1984) 1401–1404;
(d) C. Berrier, J.C. Jacquesy, M.P. Jouannetaud, A. Renoux, New J. Chem. 11 (1987) 605–609.
[11] G. Dellar, P. Djura, M.V. Sargent, J. Chem. Soc. Perkin 1 (1981) 1679–1680.
[12] (a) A.D. Batcho, W. Leimgruber, Org. Synth. 63 (1985) 214–218;
(b) R.D. Clark, D.B. Repke, Heterocycles 22 (1984) 195–221;
(c) G.W. Gribble, Indole Ring Synthesis: from Natural Products to Drug Discovery, " John Wiley & Sons, 2016 (Chapter 41).
[13] M.P. Moyer, J.F. Shiurba, H. Rapoport, J. Org. Chem. 51 (1986) 5106–5110.
[14] (a) K.L. Rinehart, J. Kobayashi, G.C. Harbour, J. Gilmore, M. Mascal, T.G. Holt, L.S. Shield, F. LaFargue, J. Am. Chem. Soc. 109 (1987) 3378–3387;
(b) W.A. Ayer, P.A. Crew, Y. Ma, S. Miao, Tetrahedron 48 (1992) 2919–2924.
[15] G.M. Carrera Jr., G.S. Sheppard, Synlett (1994) 93–94.
[16] R.W. Schumacher, B.S. Davidson, Tetrahedron 55 (1999) 935–942.
[17] L.S. Santos, R.A. Pilli, V.H. Rawal, J. Org. Chem. 69 (2004) 1283–1289.
[18] P.Y. Zhang, J.L. Wang, S.B. Wan, T. Jiang, Chin. Chem. Lett. 21 (2010) 889–891.
[19] C.S. Gibson, J.D.A. Johnson, J. Chem. Soc. (1929) 1229–1262.
[20] E. Nölting, A. Collin, Chem. Ber. 17 (1884) 261–268.
[21] R.B. Moodie, K. Schofield, J.B. Weston, J. Chem. Soc. Perkin 2 (1976) 1089–1100.
[22] T. Janosik, H. Shirani, N. Wahlström, I. Malky, B. Stensland, J. Bergman, Tetrahedron 62 (2006) 1699–1707.
[23] T. Sasaki, Y. Igarashi, M. Ogawa, T. Furumai, J. Antibiot. 55 (2002) 1009–1012.
[24] G.W. Gribble, Indole Ring Synthesis: from Natural Products to Drug Discovery, " John Wiley & Sons, 2016 (Chapter 2).
[25] C. Grøn, C. Christophersen, Acta Chem. Scand. B38 (1984) 709–711.
[26] B.E.A. Burm, M.M. Meijler, J. Korver, M.J. Wanner, G.J. Koomen, Tetrahedron 54 (1998) 6135–6146.
[27] G. Büchi, C.-P. Mak, J. Org. Chem. 42 (1977) 1784–1786.
[28] J.T. Brogan, S.L. Stoops, B.C. Crews, L.J. Marnett, C.W. Lindsley, ACS Chem. Neurosci. 2 (2011) 633–639.
[29] T.H. Trieu, J. Dong, Q. Zhang, B. Zheng, T.-Z. Meng, X. Lu, X.-X. Shi, Eur. J. Org Chem. (2013) 3271–3277.
[30] E.K. Olsen, E. Hansen, L.W.K. Moodie, J. Isaksson, K. Sepcic, M. Cergolj, J. Svenson, J.H. Andersen, Org. Biomol. Chem. 14 (2016) 1629–1640.
[31] (a) S.J. Wratten, M.S. Wolfe, R.J. Andersen, D.J. Faulkner, Antimicrob. Agents Chemother. 11 (1977) 411–414;
(b) T. Rasmussen, J. Jensen, U. Anthoni, C. Christophersen, P. H Nielsen, J. Nat. Prod. 56 (1993) 1553.
[32] A. Da Settimo, M.F. Saettone, E. Nannipieri, P. Barili, Gazz. Chim. Ital. 97 (1967) 1304–1316.
[33] H. Ishiyama, K. Yoshizawa, J. Kobayashi, Tetrahedron 68 (2012) 6186–6192.
[34] H. Jin, P. Zhang, K. Bijian, S. Ren, S. Wan, M.A. Alaoui-Jamali, T. Jiang, Mar. Drugs 11 (2013) 1427–1439.
[35] (a) F. Alonso, I.P. Beletskaya, M. Yus, Chem. Rev. 102 (2002) 4009–4091;
(b) K.A. Korvinson, H.K. Akula, C.T. Malinchak, D. Sebastian, W. Wei, T.A. Khandaker, M.R. Andrzejewska, B. Zajc, M.K. Lakshman, Adv. Synth. Catal. 362 (2020) 166–176.
[36] R.B. Nelson, G.W. Gribble, J. Org. Chem. 10 (1974) 1425–1426.