Revision of the Structure and Total Synthesis of Topsentin C

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Abstract

An efficient synthetic approach to access (indol-3-yl)ethane-1,2-diamines with a protecting group at the indole N atom from readily available 3-(2-nitrovinyl)indoles is reported. This approach includes solvent-free conjugate addition of O-pivaloylhydroxylamines to 1-Boc-3-(2-nitrovinyl)indoles followed by mild reduction of the adducts. The obtained (indol-3-yl)ethane-1,2-diamines are convenient synthetic precursors for several classes of marine alkaloids. The first total synthesis of racemic topsentin C, a secondary metabolite from Hexadella sp., based on this approach is reported. The initially proposed structure for topsentin C has been revised.

Key words bisindole alkaloid, topsentin, hamacanthin, spongotine, diamine, hydroxylamine

Secondary metabolites from marine invertebrates continue to be an attractive research topic because new structures and compounds with useful biological activity can be discovered.1 A whole series of alkaloids containing the (indol-3-yl)ethane-1,2-diamine moiety in their structures and their aromatized derivatives were isolated from deep-water sponges in the last 30 years.2 In particular, spongotines (1) and topsentins (2) contain two indoles connected through imidazoline or imidazole linker. Two indole substituents in the structures of hamacanthins (3) and dragmacidins (4) are bonded to dihydropyrazinone and piperazine rings, respectively (Figure 1). The (indol-3-yl)ethane-1,2-diamine moiety in several alkaloids of the examined group contains one or two methyl groups; for example, dragmacidins A and B (4) and topsentin C. The latter compound was isolated from Hexadella sp., and its structure was assigned to imidazoline derivative 5a (Figure 2).3 Furthermore, the alkaloids could contain one or more Br atoms, which in general is characteristic of marine secondary metabolites.4 Notably, the 1,2-diaminoethyl group in the indole 3-position, in contrast to 2-aminoethyl, is uncharacteristic for terrestrial indole alkaloids.

Figure 1 Several marine alkaloids containing an (indol-3-yl)ethanedi-amine fragment and their aromatized derivatives

Total syntheses of many of the natural products from this group have been reported;2,5,6 however, no synthesis of topsentin C has been reported. Compounds exhibiting anti-
bacterial, cytotoxic, antiviral, and fungicidal properties were discovered among these alkaloids and their synthetic analogues.2,7

![Proposed structure of topsentin C](image)

(Indol-3-yl)ethane-1,2-diamines could be convenient synthetic precursors of topsentins, spongotines, and hamacanthins.5a–c Furthermore, these diamines are of independent interest because their simple derivatives were recently shown to be capable of preventing the development of resistance to fluoroquinolone antibiotics in *Staphylococcus aureus*.8

Only two synthetic approaches to (indol-3-yl)ethane-1,2-diamines have been published and neither of them allowed the corresponding N3-methyl derivatives to be produced.5a–c It was also reported that diamines of this type with an unsubstituted indole N atom are relatively stable only as the salts.5a We propose a convenient preparative synthetic approach to (indol-3-yl)ethane-1,2-diamines (6) with a protected indole N atom that is based on mild reduction of 7, the addition product of O-pivaloylhydroxylamines (8) and 3-nitrovinylindoles (9) (Scheme 1). The proposed method has been used for the total synthesis of topsentin C, the previously proposed structure of which has been revised by us.

![Our Synthetic approach to (indol-3-yl)ethanediamine 6](image)

Starting nitrovinylindoles 9, with tert-butoxycarbonyl-protected indole N atoms, were synthesized from the corresponding indoles by formylation using N,N-dimethylformamide (DMF) and SOCl2, followed by condensation of the obtained aldehydes with nitromethane and addition of the protecting group in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) (Scheme 2). We also prepared 1-ace-

![Attempts to convert nitrovinylindole 9b into the corresponding indolic diamines by using aliphatic amines or O-benzylhydroxylamine](image)
with O-benzylhydroxylamine was reduced as expected by H₂ over Pd/C with hydrogenolysis of the C–Br bond to form diamine 6a (Scheme 3).

Indolic adduct 11 decomposed upon heating with Zn in HOAc, and reduction with Zn under milder conditions was not complete. The yield of diamine 6b was <15% even when the amount of Zn and the reaction time were increased; the main product was 12 (Scheme 3).

O-Acylhydroxylamines have highly labile N–O bonds and have recently been used in synthetic procedures based on sigmatropic shifts with cleavage of N–O bonds in addition to amination reaction. Conjugate addition of O-acylhydroxylamines to electron-deficient alkenes has not yet been described, in contrast to O-alkyhydroxylamines. We decided to study the possibility of adding O-pivaloylhydroxylamine and its N-methyl derivative to nitrovinylindoles 9 followed by reduction of the resulting adducts. Derivatives of sterically hindered pivalic acid were chosen because they isomerize rather slowly into the corresponding hydroxamic acids, in contrast to the simpler O-acylhydroxylamines.

Hydrochlorides of O-pivaloylhydroxylamine and N-methyl-O-pivaloylhydroxylamine were synthesized by using the previously reported methods. The corresponding free bases were isolated immediately before performing the next step.

As it turned out, the reaction of nitrovinylindoles 9a with O-pivaloylhydroxylamine (8a, 1.5 equiv) in CH₂Cl₂ was complete in 96 hours and gave target adduct 7a. We also found that the solvent-free reaction was much faster. The reagents could be mixed and left overnight in a closed vessel. The nitrovinylindoles dissolved gradually, then crystals of the product formed. The solvent-free reaction was clearly advantageous from a green chemistry point of view. In this manner, we obtained the series of adducts 7a–h in high yields (Table 1).

The next step was the reduction of adducts 7. We decided to use Zn and acid, anticipating that their hydroxylamine N–O bond would undergo reductive cleavage at room or reduced temperature. Thus, the reduction of 7a using Zn (10 equiv) and HOAc in MeOH afforded target diamine 6a in 34% yield (Table 2, entry 1).

### Table 1 Synthesis of Adducts 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>7a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Boc</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>7b</td>
<td>Br</td>
<td>H</td>
<td>H</td>
<td>Boc</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>9a</td>
<td>7c</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Boc</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>9b</td>
<td>7d</td>
<td>Br</td>
<td>H</td>
<td>Me</td>
<td>Boc</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>9c</td>
<td>7e</td>
<td>H</td>
<td>Br</td>
<td>Me</td>
<td>Boc</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>9d</td>
<td>7f</td>
<td>OMe</td>
<td>H</td>
<td>Me</td>
<td>Boc</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>9e</td>
<td>7g</td>
<td>H</td>
<td>Cl</td>
<td>Me</td>
<td>Boc</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>9f</td>
<td>7h</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Ac</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>9g</td>
<td>–[a]</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>0</td>
</tr>
</tbody>
</table>

[a] Nitrovinylindole 9g, with a methyl on the indole N atom, did not react.

### Table 2 Reduction of Adducts 7a,c

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Equiv. Zn</th>
<th>Acid (equiv)</th>
<th>Solvent</th>
<th>t (h)</th>
<th>T (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>10</td>
<td>AcOH (150)</td>
<td>MeOH</td>
<td>2</td>
<td>0–20</td>
<td>34</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>10</td>
<td>AcOH (150)</td>
<td>MeOH</td>
<td>6</td>
<td>0–20</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>10</td>
<td>AcOH (150)</td>
<td>MeOH/H₂O/EtOAc</td>
<td>2</td>
<td>0–20</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>20</td>
<td>AcOH (150)</td>
<td>MeOH/H₂O/EtOAc</td>
<td>2</td>
<td>0–20</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>15</td>
<td>HCl (30)</td>
<td>MeOH/EtOAc</td>
<td>2</td>
<td>–10 to 5</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>15</td>
<td>HBr (30)</td>
<td>MeOH/EtOAc</td>
<td>2</td>
<td>–10 to 5</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>15</td>
<td>NH₄Br (15)</td>
<td>EtOH/H₂O/EtOAc</td>
<td>2</td>
<td>20</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>15</td>
<td>HBr (30)</td>
<td>MeOH/EtOAc</td>
<td>2</td>
<td>–10 to 5</td>
<td>68</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>20</td>
<td>HBr (40)</td>
<td>MeOH/EtOAc</td>
<td>6</td>
<td>–10 to 5</td>
<td>93</td>
</tr>
</tbody>
</table>
The reaction proceeded rather quickly. However, it was accompanied by the formation of several unidentified side products. Increasing the reaction time did not lead to an increase in the yield of 6a. We found that the yield could be increased by adding H₂O and EtOAc to the reaction mixture (keeping the solution homogeneous) and by doubling the amount of Zn (cf. Table 2, entries 3 and 4). Replacing HOAc with concentrated HCl at reduced temperature led to a further increase in the yield (entry 5). Finally, the use of HBr (40%) allowed target diamine 6a to be obtained with a very good yield (entry 6). It was also possible to conduct the reduction of adduct 7a in the presence of NH₂Br (entry 7). The reduction of adduct 7c, with a methyl group on the hydroxylamine N atom, was more difficult. However, increasing the reaction time and amount of Zn provided a high yield of diamine 6c (entry 9). The developed method was extended to adducts 7b and 7d–f (Table 3). Boc derivatives gave the corresponding diamines 6b and 6d–g in good and high yields, whereas diamine 6h, with an acetyl on the indole N atom, was unstable and decomposed even in solution.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>PG</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>7a</td>
<td>6a</td>
<td>H</td>
<td>H</td>
<td>Boc</td>
<td>84</td>
</tr>
<tr>
<td>2a</td>
<td>7b</td>
<td>6b</td>
<td>Br</td>
<td>H</td>
<td>Boc</td>
<td>95</td>
</tr>
<tr>
<td>3a</td>
<td>7c</td>
<td>6c</td>
<td>H</td>
<td>Me</td>
<td>Boc</td>
<td>93</td>
</tr>
<tr>
<td>4a</td>
<td>7d</td>
<td>6d</td>
<td>H</td>
<td>Br</td>
<td>Me</td>
<td>86</td>
</tr>
<tr>
<td>5a</td>
<td>7e</td>
<td>6e</td>
<td>H</td>
<td>Br</td>
<td>Me</td>
<td>92</td>
</tr>
<tr>
<td>6a</td>
<td>7f</td>
<td>6f</td>
<td>OMe</td>
<td>H</td>
<td>Boc</td>
<td>75</td>
</tr>
<tr>
<td>7a</td>
<td>7g</td>
<td>6g</td>
<td>H</td>
<td>Cl</td>
<td>Me</td>
<td>90</td>
</tr>
<tr>
<td>8a</td>
<td>7h</td>
<td>6h</td>
<td>H</td>
<td>Me</td>
<td>Ac</td>
<td>–¹</td>
</tr>
</tbody>
</table>

* Reaction conditions: Zn (15 equiv), HBr (30 equiv), 2 h.
* Reaction conditions: Zn (20 equiv), HBr (40 equiv), 6 h.
* Decomposition of the product occurred.

Having established a convenient preparative method for N¹-methyl(indol-3-yl)ethane-1,2-diamines, we focused on the total synthesis of the proposed structure for topsentin C (5a), which is related to spongotines 1 and other previously isolated topsentins. The imidazoline fragment of 5a and its analogue 5b, without a Br atom, was constructed by using the previously reported synthetic method for imidazolines that involved condensation of the vicinal diamines with aldehydes (including α-keto aldehydes) followed by oxidation of the resulting cyclic aminal.5c,18 The required indolglyoxals 14a and 14b were prepared from corresponding 3-acetylindoles 15a and 15b through iodination followed by Kornblum oxidation (Scheme 4).19

The aforementioned syntheses of indolglyoxals 14a and 14b, condensations with diamines 6c and 6e, and subsequent oxidations to imidazolines 16a and 16b were carried out in one pot. This made the developed procedure attractive for preparative reactions. The protecting group could be removed to afford 5a and 5b. As it turned out, the spectral characteristics of 5a synthesized by us and the characteristics of topsentin C that was isolated from the natural source, differed dramatically. Therefore, the initially proposed structure of topsentin C had to be revised. Thus, the synthesized 5a was a methylated spongotine C derivative that has not yet been observed in nature. The developed method enables analogues of spongotines and topsentins to be synthesized to study their biological properties, which are known to change abruptly if even a single methyl is added to the molecule.17

We assumed that natural topsentin C was structurally related to hamacanthins A (3) but not spongotines (1), and was the 1-methyl derivative of hamacanthin A 17a (Figure 3),20 which should have a set of NMR signals similar to that of 5a.
We synthesized bis(indolyl)dihydropyrazinones 17a and 17b through cyclization of diamines 6e and 6c with indoleglyoxylic acid chlorides 18a and 18b to confirm this hypothesis (Scheme 5).

Acid chlorides 18a and 18b were obtained through acylation of the corresponding indoles by using oxalyl chloride according to published methods.6k The reaction first gave a mixture of amides 19 and 20, which were further cyclized without isolation (Scheme 6). As noted earlier during the development of synthetic methods for hamacanthins, these amides can undergo reversible transformations under the cyclization conditions via intermediate 21, and can form a mixture of isomeric bis(indolyl)dihydropyrazinones.6b In this case, the cyclization was unidirectional because of the methyl group, so that 22a and 22b were isolated only.21 These compounds were converted into target 17a and 17b by removing the protecting group. The structure of compound 17a was established by X-ray crystallographic analysis (Figure 4).

The spectral characteristics of bis(indolyl)dihydropyrazinone 17a were consistent with those of natural topsentin C,3,22 in contrast to imidazoline 5a (Table 4). This data con-

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**Scheme 5** Synthesis of topsentin C and its analogue

**Scheme 6** Mechanism of dihydropyrazinone ring formation

---

**Table 4** $^1$H NMR Data for Natural Topsentin C and for Compounds 17a and 5a

<table>
<thead>
<tr>
<th>$^1$H</th>
<th>17a</th>
<th>Topsentin C</th>
<th>5a</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)CH$_3$</td>
<td>3.04 (s)</td>
<td>3.05 (s)</td>
<td>2.82 (s)</td>
</tr>
<tr>
<td>CHCH$_2$H$_5$</td>
<td>4.26 (dd, $J = 16.5, 5.5$)</td>
<td>4.27 (dd, $J = 16.5, 5.3$)</td>
<td>3.91 (dd, $J = 15.3, 10.3$)</td>
</tr>
<tr>
<td>CHCH$_2$H$_5$</td>
<td>4.41 (dd, $J = 16.5, 5.2$)</td>
<td>4.41 (dd, $J = 16.5, 5.2$)</td>
<td>4.31 (dd, $J = 15.3, 11.3$)</td>
</tr>
<tr>
<td>CHCH$_2$H$_5$</td>
<td>5.15 (dd, $J = 5.5, 5.2$)</td>
<td>5.16 (dd, $J = 5.3, 5.2, &lt;1$)</td>
<td>4.89 (dd, $J = 11.3, 10.3$)</td>
</tr>
</tbody>
</table>

Indolic H

1' | 10.70 (br s) | 10.71 (br s) | 11.37 (br s) |
2' | 8.62 (d, $J = 2.75$) | 8.62 (d, $J = 2.7$) | 8.68 (s) |
4' | 8.37 (d, $J = 8.6$) | 8.37 (d, $J = 8.7$) | 8.32 (d, $J = 8.5$) |
5' | 7.17–7.23 (m)$^b$ | 7.20 (dd, $J = 8.7, 1.8$) | 7.41 (dd, $J = 8.5, 1.7$) |
7' | 7.66 (d, $J = 1.8$) | 7.66 (d, $J = 1.8$) | 7.76 (d, $J = 1.6$) |
1'' | 10.34 (br s) | 10.34 (br s) | 10.42 (br s) |
2'' | 7.17–7.23 (m)$^b$ | 7.22 (dd, $J = 2.5, <1$) | 7.45 (d, $J = 2.1$) |
4'' | 7.69 (d, $J = 8.6$) | 7.69 (d, $J = 8.5$) | 7.63 (d, $J = 8.5$) |
5'' | 7.17–7.23 (m)$^b$ | 7.20 (dd, $J = 8.5, 1.7$) | 7.17 (dd, $J = 8.5, 1.7$) |
7'' | 7.63 (d, $J = 1.7$) | 7.63 (d, $J = 1.7$) | 7.65 (d, $J = 1.6$) |

---

$^a$ Recorded in acetone-$d_6$; shift in ppm, coupling in Hz.

$^b$ Double resonance experiments and COSY gave the same interpretation of these signals as shown for natural topsentin C (see the Supporting Information).
firmed our hypothesis regarding the structure of the natural topsentin C.

Thus, we have developed a convenient preparative synthetic method to prepare (indol-3-yl)ethane-1,2-diamines and found that the natural topsentin C has the structure 17a. The total synthesis of racemic 17a was carried out in seven steps from 6-bromoindole 9c in 55% overall yield.

Starting reagents were either purchased from commercial sources and used without additional purification or were prepared according to reported procedures. 1H and 13C NMR spectra were acquired with 400, 500, or 600 MHz spectrometers at r.t. and referenced to the residual signals of the solvent (for 1H and 13C). The solvents for NMR samples were DMSO-d_6, CDCl_3, and acetone-d_6. Chemical shifts are reported in parts per million (δ, ppm). Coupling constants are reported in Hertz (J, Hz). The peak patterns are indicated as: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; dd, doublet of doublets; br s, broad singlet. Signal assignment was based on COSY, HSQC, HMBC and NOESY experiments. Infrared spectra were measured with an Infralum FT-801 FT/IR instrument. The wavelengths are reported in reciprocal centimeters (ν_max, cm⁻¹). Mass spectra were recorded with LCMS-8040 triple quadrupole liquid chromatograph mass-spectrometer from Shimadzu (ESI) and Kratos MS-30 mass spectrometer (EI, 70 eV). Elemental analysis was performed with an Euro Vector EA-3000 elemental analyzer. The X-ray data collection of 17a was performed with a Bruker APEX-II CCD diffractometer at 120 K. Details of the X-ray structure determination are given in the Supporting Information.

**tert-Butyl 5-Bromo-3-[(E)-2-nitrovinyl]-1H-indole-1-carboxylate (9b): Typical Procedure**

5-Bromoindole (1.35 g, 6.9 mmol) was formylated as described for 1H-indole-3-carbaldehyde to produce 6-bromo-1H-indole-3-carbaldehyde (1.50 g, 97%) with the exception that the obtained product was not purified by refluxing in EIOH.

5-Bromo-1H-indole-3-carbaldehyde (1.50 g, 6.7 mmol) and NH_2OAc (0.52 g, 6.7 mmol) were heated at reflux in CH_3NO_2 (18 mL, 335 mmol) for 45 min, cooled to r.t., and treated with H_2O (70 mL). The product was extracted with EtOAc (70 mL), washed with H_2O (5 × 50 mL) and NaCl solution (20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to afford 5-bromo-3-[(E)-2-nitrovinyl]-1H-indole (1.72 g, 96%, brownish crystals), which was dried in vacuo and used without further purification.

A suspension of 5-bromo-3-[(E)-2-nitrovinyl]-1H-indole (1.72 g, 6.4 mmol) and DMAP (0.08 g, 0.64 mmol) in anhydrous THF (7 mL) was treated with a solution of Boc_2O (2.1 g, 9.7 mmol) in anhydrous THF (7 mL) dropwise at 0–5 °C over a period of 15 min, stirred at r.t. for 3 h, and concentrated in vacuo. The residue was dissolved in CH_3Cl_2 (50 mL), washed with citric acid solution (10%, 20 mL), H_2O (20 mL), and conc NaCl solution (15 mL), and dried over anhydrous Na_2SO_4. The CH_3Cl_2 was evaporated in vacuo and the residue was purified by chromatography on a column of silica gel (EtOAc-hexane, 6:1) to provide tert-butyl 5-bromo-3-[(E)-2-nitrovinyl]-1H-indole-1-carboxylate.

Yield: 2.11 g (83% from 5-bromoindole); pale-yellow solid; mp 156–157 °C (MeOH); R_f 0.55 (EtOAc-hexane, 1:8).
**tert-Butyl 6-Chloro-3-[1-(Benzyloxy)amino]-2-nitrovinyl]-1H-indole-1-carboxylate (9c)**

Yield: 1.71 g (77% from 6-chloroindole); mp 130–132 °C (MeOH); Rf = 0.62 (EtOAc–hexane, 1:8).

MS (EI, 70 eV): m/z (%) = 319 (8), 318 (41) [M]+, 263 (17), 262 (81) [M – CH₂], 219 (23), 218 (28) [M – CH₃ – CO₂], 186 (31), 175 (69), 156 (29), 57 (100).

Anal. Calc'd for C₁₆H₁₈N₂O₅: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.28; H, 5.70; N, 8.80.

**tert-Butyl 6-Chloro-3-[1-(Pivaloyloxy)amino]-2-nitrovinyl]-1H-indole-1-carboxylate (9e)**

Yield: 1.17 g (77% from 6-chloroindole); mp 130–132 °C (MeOH); Rf = 0.62 (EtOAc–hexane, 1:8).

IR (film): 3131, 2983, 2294 w, 1741 s (CO), 1634, 1508, 1431, 1340, 1299, 1240, 1154, 1103, 968, 845, 810, 762, 732, 660, 594 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 8.54 (s, 1 H), 8.32 (d, J = 13.7 Hz, 1 H, CH=CHNO₂), 8.17 (d, J = 13.7 Hz, 1 H, CH=CHNO₂), 8.08 (d, J = 1.7 Hz, 1 H, CH=CHNO₂), 8.04 (d, J = 8.6 Hz, 1 H), 7.36 (dd, J = 8.6, 1.7 Hz, 1 H), 1.15 (s, 9 H, C(CH₃)₃).

13C NMR (100 MHz, DMSO-d₆): δ = 132.80, 129.90, 127.84, 115.87, 114.10, 112.13, 103.33, 85.04, 55.73, 27.56 (3C).
**tert-Butyl 3-[[Pivaloyloxy]amino]-2-nitroethyl]-5-bromo-1H-indole-1-carboxylate (7b)**

Yield: 1.62 g (96%); white solid; mp 108–109 °C (hexane); \( R_f = 0.39 \) (EtOAc–hexane, 1:8).

**IR** (film): 3260, 2974, 2935, 1728 s (CO), 1557, 1453, 1378, 1276, 1157, 1092, 1057, 872, 805, 778, 664, 620 cm\(^{-1}\).

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \( \delta = 8.19 \) (d, \( J = 8.1 \) Hz, 1 H), 7.89 (d, \( J = 3.5 \) Hz, 1 H, NH), 7.70 (d, \( J = 7.7 \) Hz, 1 H), 7.67 (s, 1 H), 7.39 (dd, \( J = 8.1, 7.3 \) Hz, 1 H, CH-CH\(_{\text{H}}\)), 5.01 (dd, \( J = 12.9, 8.0 \) Hz, 1 H, CHCH\(_{\text{H}}\)), 4.75 (dd, \( J = 12.9, 4.5 \) Hz, 1 H, CHCH\(_{\text{H}}\)), 1.68 (s, 9 H, OC(CH\(_3\))\(_3\)), 1.24 (s, 9 H, C(CH\(_3\))\(_3\)).

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \( \delta = 178.21, 149.15, 135.48, 127.82, 125.36, 124.60, 123.23, 118.99, 115.61, 113.38, 84.51, 78.04, 56.25, 38.44, 28.15 (3C), 26.90 (3C).

**MS (ESI):** \( m/z = 406 \) [M + H\(^+\)], 345 [M – CH\(_2\)NO\(_2\) + H\(^+\)], 304 [M – (CH\(_3\))\(_2\)CO\(_2\)H + H\(^+\)].

Anal. Calcld for C\(_{20}\)H\(_{28}\)BrN\(_3\)O\(_6\): C, 50.70; H, 5.66; N, 8.43. Found: C, 50.90; H, 5.81; N, 8.25.

**tert-Butyl 3-[[Pivaloyloxy]methyl]amino]-2-nitroethyl]-6-bromo-1H-indole-1-carboxylate (7e)**

Yield: 1.70 g (98%); light-beige solid; mp 115–116 °C (hexane); \( R_f = 0.39 \) (EtOAc–hexane, 1:8).

**IR** (film): 2976, 2933, 1762 s (CO), 1727 s (CO), 1561, 1433, 1370, 1255, 1152, 1097, 865, 818, 772, 679, 590 cm\(^{-1}\).

\( \text{[M + H]} + = 522/520 \) [M + Na\(^+\)], 451/449 [M – CH\(_3\)NO\(_2\) + H\(^+\)], 380/378 [M – (CH\(_3\))\(_2\)CO\(_2\)H + H\(^+\)].

Anal. Calcld for C\(_{20}\)H\(_{26}\)BrN\(_3\)O\(_6\): C, 50.61; H, 5.66; N, 8.43. Found: C, 50.73; H, 5.72; N, 8.42.

**tert-Butyl 3-[[Pivaloyloxy]methyl]amino]-2-nitroethyl]-5-methoxy-1H-indole-1-carboxylate (7f)**

Yield: 1.43 g (91%); yellow solid; mp 96 °C (hexane); \( R_f = 0.39 \) (EtOAc–hexane, 1:8).

**IR** (film): 2971, 2935, 1755 s (CO), 1731 s (CO), 1557, 1480, 1382, 1286, 1157, 1098, 1070, 849, 807, 767, 677, 626 cm\(^{-1}\).

**\(^1\)H NMR** (600 MHz, CDCl\(_3\)): \( \delta = 8.04 \) (br s, 1 H), 7.64 (d, \( J = 7.3 \) Hz, 1 H), 7.28 (d, \( J = 1.7 \) Hz, 1 H), 5.07 (dd, \( J = 7.3, 1.7 \) Hz, 1 H), 5.02 (dd, \( J = 4.5, 5.0 \) Hz, 1 H, CHCH\(_{\text{H}}\)), 4.98 (dd, \( J = 12.4, 7.4 \) Hz, 1 H, CHCH\(_{\text{H}}\)), 4.63 (dd, \( J = 12.7, 5.8 \) Hz, 1 H, CHCH\(_{\text{H}}\)), 2.66 (s, 3 H, NCH\(_3\)), 1.69 (s, 9 H, OC(CH\(_3\))\(_3\)), 1.26 (s, 9 H, C(O)C(CH\(_3\))\(_3\)).

**\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)): \( \delta = 175.89, 156.27, 149.14, 130.00, 129.53, 125.39, 116.13, 114.07, 113.70, 102.11, 84.21, 77.00, 62.13, 55.78, 43.71, 38.66, 28.12 (3C), 27.06 (3C).

**MS (ESI):** \( m/z = 450 \) [M + H\(^+\)], 348 [M – (CH\(_3\))\(_2\)CO\(_2\)H + H\(^+\)].

Anal. Calcld for C\(_{20}\)H\(_{26}\)NO\(_6\): C, 58.78; H, 6.95; N, 9.35. Found: C, 58.89; H, 7.00; N, 9.23.

**tert-Butyl 3-[[Pivaloyloxy]methyl]amino]-2-nitroethyl]-6-chloro-1H-indole-1-carboxylate (7g)**

Yield: 1.54 g (97%); light-brown solid; mp 108–109 °C (hexane); \( R_f = 0.39 \) (EtOAc–hexane, 1:8).

**IR** (film): 2976, 2906, 1754 s (CO), 1744 s (CO), 1562, 1439, 1368, 1256, 1157, 1090, 866, 817, 761, 661, 600 cm\(^{-1}\).

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)): \( \delta = 8.31 \) (s, 1 H), 7.75 (d, \( J = 8.5 \) Hz, 1 H), 7.65 (s, 1 H), 7.27 (dd, \( J = 8.5, 1.7 \) Hz, 1 H), 4.92–5.02 (m, 2 H, CHCH\(_{\text{H}}\) + CHCH\(_{\text{H}}\)), 4.63 (dd, \( J = 12.1, 5.3 \) Hz, 1 H, CHCH\(_{\text{H}}\)), 2.66 (s, 3 H, NCH\(_3\)), 1.68 (s, 9 H, OC(CH\(_3\))\(_3\)), 1.25 (s, 9 H, C(O)C(CH\(_3\))\(_3\)).
Catalytic Hydrogenation of Adduct 11

To a solution of adduct 11 (0.54 g, 1.1 mmol) in MeOH (10 mL) was added AcOH (9.5 mL, 1.16 mol) and 5% Pd on charcoal (0.05 g) and the mixture was purged with hydrogen. The mixture was vigorously stirred under a hydrogen atmosphere (1 atm) for 18 h, filtered, and the mixture was vigorously stirred further for 12 h, filtered, and concentrated in vacuo. The residue was dissolved in CH2Cl2 (50 mL), treated with cold NaOH solution (10%, 40 mL), and dried over anhydrous Na2SO4. The solvent was removed in vacuo and the residue was dissolved in CH2Cl2 (100 mL), treated with cold NaOH solution (10%, 90 mL) and concd NaCl solutions (20 mL), and dried over anhydrous Na2SO4. The solvent was removed in vacuo to afford target diamine 6a.

Synthesis of (3-(3-Indolyl)ethane-1,2-diamines 6; General Procedure B

To a solution of adduct 11 (0.54 g, 1.1 mmol) in MeOH (10 mL) was added AcOH (9.5 mL, 1.16 mol) and Zn dust (1.43 g, 22 mmol). The resulting mixture was vigorously stirred at r.t. for 2 h, and then another portion of Zn dust (1.44 g, 22 mmol) was added. The reaction mixture was stirred further at 0–5 °C for 5 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was stirred further at 0–5 °C for 5 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was stirred further at 0–5 °C for 5 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was stirred further at 0–5 °C for 5 h, and filtered.

Reduction of Adduct 11 with Zn Dust

To a solution of adduct 11 (0.54 g, 1.1 mmol) in MeOH (10 mL) was added AcOH (9.5 mL, 1.16 mol) and Zn dust (1.43 g, 22 mmol). The resulting mixture was vigorously stirred at r.t. for 2 h, and then another portion of Zn dust (1.44 g, 22 mmol) was added. The reaction mixture was stirred further at 0–5 °C for 5 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was stirred further at 0–5 °C for 5 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was stirred further at 0–5 °C for 5 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was stirred further at 0–5 °C for 5 h, and filtered.
1-[5-Bromo-(1-tert-Butoxycarbonyl)-1H-indol-3-yl]ethane-1,2-diamine (6b)  
Obtained by following General Procedure A.  
Yield: 0.59 g (93%); pale-yellow viscous oil;  
\[ R_f = 0.46 \text{(CHCl}_3–\text{MeOH–} \text{H}_2\text{O)} \].

MS (ESI):  \[ m/z = 276 \text{ [M + H]}^+ \].

1H NMR (400 MHz, CDCl\(_3\)):  \[ \delta = 8.37 \text{ (br s, 1 H, 7-H)}, 7.55 \text{ (s, 1 H, 2-H)}, 7.70 \text{ (d, } J = 8.4 \text{ Hz, 1 H, 4-H)}, 7.50 \text{ (s, 1 H, 1-H, 5-H)}, 7.33 \text{ (dd, } J = 8.4, 1.7 \text{ Hz, 1 H, 6-H)}, 7.34 \text{ (dd, } J = 6.5, 5.5 \text{ Hz, 1 H, CHCH}_2\text{H}_3\text{)}, 3.82 \text{ (dd, } J = 6.5, 4.5 \text{ Hz, 1 H, CHCH}_2\text{H}_3\text{)}, 3.10 \text{ (dd, } J = 12.7, 5.4 \text{ Hz, 1 H, CHCH}_2\text{H}_3\text{)}, 2.98 \text{ (dd, } J = 12.7, 6.4 \text{ Hz, 1 H, CHCH}_2\text{H}_3\text{)}, 2.43 \text{ (s, 3 H, NCH}_3\text{)}, 1.68 \text{ (s, 9 H, OC(CH}_3\text{)}_3\text{)}. \]

13C NMR (100 MHz, CDCl\(_3\)):  \[ \delta = 149.23, 136.56, 128.20, 125.69, 124.42, 122.24, 121.75, 119.58, 118.25, 84.23, 59.65, 46.11, 34.43, 28.12 (3C). \]

MS (ESI):  \[ m/z = 370/368 \text{ [M + H]}^+ \].

Anal. Calcd for C\(_{16}\)H\(_{23}\)N\(_3\)O\(_2\): C, 66.91; H, 8.02; N, 14.52. Found: C, 63.81; H, 7.96; N, 13.10.

1-[5-Methoxy-(1-tert-Butoxycarbonyl)-1H-indol-3-yl]-N\(_1\)-methylthiolane-1,2-diamine (6e)  
Obtained by following General Procedure B.  
Yield: 0.74 g (92%); pale-yellow viscous oil;  
\[ R_f = 0.34 \text{(CHCl}_3–\text{MeOH–} \text{H}_2\text{O)} \].

MS (ESI):  \[ m/z = 318 \text{ [M + H]}^+ \].

Anal. Calcd for C\(_{17}\)H\(_{25}\)N\(_3\)O\(_3\): C, 64.61; H, 7.96; N, 14.52. Found: C, 63.81; H, 7.96; N, 13.10.
tert-Butyl 6-Bromo-3-[(6-bromo-1H-indol-3-yl)-1-methyl-6-oxo-1,2,3,6-tetrahydroprazin-2-yl]-1H-indole-1-carboxylate (22a)

A solution of diamine 6e (0.26 g, 0.70 mmol) in EtOH (2.6 mL) at 0–5 °C was treated portionwise with acetyl chloride 18a (0.20 g, 0.7 mmol) over a period of 10 min and stirred for 15 min at r.t. Anhydrous Ac2O (57.4 mg, 0.57 mmol) and AcOEt (0.26 mL) were then added and the reaction mixture was heated at reflux for 1.5 h. After cooling, the mixture was diluted with EtOAc (25 mL), washed with saturated NaHCO3 (20 mL) and concd NaCl (10 mL) solutions, and dried over anhydrous Na2SO4. The solvent was removed in vacuo and the residue was purified by chromatography on a column with silica gel (toluene–EtOAc, 3:1) to provide the title compound.

Yield: 0.302 g (72%); pale-yellow amorphous solid; Rf = 0.49 (toluene–EtOAc, 2:1).

IR (film): 3151 br, 2976, 2932, 1740 s (CO), 1650, 1491, 1436, 1369, 1252, 1154, 1088, 809, 731, 589 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 8.89 (br s, 1 H, NH), 8.47 (d, J = 2.6 Hz, 1 H), 8.35 (br s, 1 H), 8.27 (d, J = 8.8 Hz, 1 H), 7.54 (d, J = 1.8 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.42 (br s, 1 H), 7.40 (d, J = 8.4, 1.8 Hz, 1 H), 7.28 (d, J = 8.8, 1.8 Hz, 1 H), 7.46 (d, J = 5.9, 5.5 Hz, 1 H, CH(CH3)2), 4.38 (d, J = 16.5, 5.9 Hz, 1 H, CH(CH3)2), 3.10 (s, 3 H, NCH3), 1.60 (s, 9 H, OC(CH3)3).

13C NMR (125 MHz, CDCl3): δ = 157.84, 157.21, 148.91, 136.90, 136.52, 131.99, 127.18, 126.25, 125.22, 124.65, 124.54, 124.10, 119.98, 118.94, 118.79, 117.00, 116.40, 114.11, 112.13, 84.90, 53.31, 51.87, 33.00, 28.00 (3C).

MS (ESI): m/z = 602/601 (M + H)+.

Anal. Calc’d for C26H26N4O3: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.41; H, 5.84; N, 12.55.

tert-Butyl 3-[5-(1H-indol-3-yl)-1-methyl-6-oxo-1,2,3,6-tetrahydroprazin-2-yl]-1H-indole-1-carboxylate (22b)

The compound was prepared as described for 22a.

Yield: 0.214 g (69%); light-brown amorphous solid; Rf = 0.45 (toluene–EtOAc, 2:1).

IR (film): 3270 br, 2976, 2931, 1736 s (CO), 1650, 1590, 1453, 1371, 1310, 1256, 1155, 1088, 852, 746, 591 cm⁻¹.

1H NMR (400 MHz, CDCl3): δ = 8.88 (br s, 1 H, NH), 8.54 (d, J = 2.6 Hz, 1 H), 8.43 (d, J = 8.7 Hz, 1 H), 8.14 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 7.7 Hz, 1 H), 7.45 (s, 1 H), 7.33–7.42 (m, 2 H), 7.25–7.31 (m, 1 H), 7.17–7.25 (m, 2 H), 4.98 (d, J = 5.9, 5.4 Hz, 1 H, CH(CH3)2), 4.46 (d, J = 16.5, 5.9 Hz, 1 H, CH(CH3)2), 3.13 (s, 3 H, NCH3), 1.60 (s, 9 H, OC(CH3)3).

13C NMR (100 MHz, CDCl3): δ = 158.07, 157.29, 149.36, 136.09, 135.87, 132.13, 128.44, 126.23, 124.93, 124.18, 122.94 (2C), 122.70, 121.57, 118.93, 117.00, 115.67, 111.94, 111.19, 84.20, 53.45, 51.63, 32.96, 28.06 (3C).

MS (ESI): m/z = 443 [M + H]+.
Removal of the Boc Protecting Group; General Procedure

A suspension of the substrate (0.43 mmol) in CH2Cl2 (2 mL) at 0–5 °C was treated with TFA (0.4 mL, 5.2 mmol) in four portions, stirred at the same temperature for 20 min, left overnight, and evaporated in vacuo. The residue was dissolved in EtOAc (40 mL), washed with saturated NaHCO3 (2 × 20 mL) and conc NaCl (20 mL) solutions, and dried over anhydrous Na2SO4. The solvent was removed in vacuo and the residue was puriﬁed by chromatography on a column with silica gel.

(6-Bromo-1H-indol-3-yl)[5-(6-bromo-1H-indol-3-yl)-1-methyl-4,5-dihydro-1H-imidazol-2-yl]methylene (5a)

Yield: 0.210 g (98%); light-beige solid; mp 247–249 °C (dec.) (EtOAc); \( R_f \) = 0.36 (CHCl3–MeOH, 20:1).

IR (film): 3426, 3119, 3012, 2850, 1637, 1569, 1513, 1450, 1265, 1172, 1100, 1011, 851, 744 cm–1.

1H NMR (400 MHz, DMSO-d6): \( \delta = 12.30 \) (br s, 1 H, 1′-NH), 11.20 (br s, 1 H, 1′′-NH), 8.68 (s, 1 H, 2′-H), 8.32 (d, \( J = 8.5 \) Hz, 1 H, 4′-H), 7.76 (d, \( J = 1.6 \) Hz, 1 H, 7′-H), 7.65 (d, \( J = 1.6 \) Hz, 1 H, 7′-H), 7.63 (d, \( J = 8.5 \) Hz, 1 H, 4′-H), 7.45 (d, \( J = 2.1 \) Hz, 1 H, 2′-H), 7.41 (dd, \( J = 8.5 \), 1.7 Hz, 1 H, 5′-H), 7.17 (dd, \( J = 8.5 \), 1.7 Hz, 1 H, 5′-H), 4.90 (dd, \( J = 11.3 \), 10.3 Hz, 1 H, CHCHaHb), 4.31 (dd, \( J = 15.3 \), 11.3 Hz, 1 H, CHCHaHb), 3.91 (dd, \( J = 15.3 \), 10.3 Hz, 1 H, CHCHbHc), 2.82 (s, 3 H, NCH3).

13C NMR (100 MHz, DMSO-d6): \( \delta = 183.28, 163.42, 139.61, 139.36, 138.78, 126.40, 126.31, 125.93, 125.78, 124.34, 123.13, 121.83, 117.27, 117.62, 116.13, 115.88, 115.83, 62.40, 61.88, 32.51.

MS (ESI): \( m/z = 502/501/500 \) [M + H]+.


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Supporting Information

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References


