Revision of the Structure and Total Synthesis of Topsentin C

N. E. Golantsov et al.

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. 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. 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). Furthermore, the alkaloids could contain one or more Br atoms, which in general is characteristic of marine secondary metabolites. Notably, the 1,2-diaminoethyl group in the indole 3-position, in contrast to 2-aminoethyl, is uncharacteristic for terrestrial indole alkaloids.

Total syntheses of many of the natural products from this group have been reported; 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

Figure 2 Proposed structure of tospentin C

((Indol-3-yl)ethane-1,2-diamines could be convenient synthetic precursors of tospentin, spongotines, and hama
canthins.5a–c Furthermore, these diamines are of indepen
dent interest because their simple derivatives were recently shown to be capable of preventing the development of re
sistance 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 al
low the corresponding N1-methyl derivatives to be pro
duced.5a–e 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 reduc
tion 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 tospentin C,
the previously proposed structure of which has been re
vised by us.

Scheme 1 Our Synthetic approach to (indol-3-yl)ethanediamine 6

Starting nitrovinylindoles 9, with tert-butoxycarbonyl-
protected indole N atoms, were synthesized from the corre
sponding indoles by formylation using N,N-dimethylform
amide (DMF) and SOCl2, followed by condensation of the ob
tained aldehydes with nitromethane and addition of the
protecting group in the presence of 4-(N,N-dimethylam
ino)pyridine (DMAP) (Scheme 2). We also prepared 1-acet
tyl-3-[(E)-2-nitrovinyl]-1H-indole (9f) and 1-methyl-3-
[(E)-2-nitrovinyl]-1H-indole (9g) according to described procedures.9,10

Reduction of the adducts of α,β-unsaturated nitrocom
pounds with amines, O-alkylhydroxylamines or azide anion
was proposed earlier for the synthesis of vicinal diamines.11–13 The first type of adduct was unstable, although
they could be isolated as the more stable salts.11 Adducts
with O-alkylhydroxylamines or azide anion were more sta
ble.12,13 However, catalytic hydrogenation or heating with
Zn dust in HOAc was required to cleave the hydroxylamine
N–O bond.12 Catalytic hydrogenation was also used to re
duce the azido group.13 The proposed methods turned out
to be ineffective for the synthesis of Br-containing (indol-3-
yl)ethane-1,2-diamines 6. Thus, the products 10 from the
reaction of methylamine or benzylamine with nitrovinylindi
dole 9b could not be isolated; starting 9b was recovered
and the reaction mixture formed a resin. Stable adduct 11

Scheme 2 Synthesis of 3-nitrovinylindoles 9; yields of three stages are shown

Scheme 3 Attempts to convert nitrovinylindole 9b into the corre
sponding indolic diamines by using aliphatic amines or O-benzylhydroxy
lamine
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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>
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* Nitrovinylindole 9g, with a methyl on the indole N atom, did not react.

Table 2 Reduction of Adducts 7a,c

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<th>Entry</th>
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<th>Acid (equiv)</th>
<th>Solvent</th>
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<th>T (°C)</th>
<th>Yield (%)</th>
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<td>0–20</td>
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<tr>
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<td>H</td>
<td>10</td>
<td>AcOH (150)</td>
<td>MeOH</td>
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<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>
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<td>0–20</td>
<td>48</td>
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<tr>
<td>4</td>
<td>H</td>
<td>20</td>
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<td>MeOH/H₂O/EtOAc</td>
<td>2</td>
<td>0–20</td>
<td>57</td>
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<tr>
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<td>H</td>
<td>15</td>
<td>HCl (30)</td>
<td>MeOH/EtOAc</td>
<td>2</td>
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<td>6</td>
<td>H</td>
<td>15</td>
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<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>
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<tr>
<td>8</td>
<td>Me</td>
<td>15</td>
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<td>MeOH/EtOAc</td>
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<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>
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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-alkylhydroxylamines. 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).
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 3  Synthesis of Diamines 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>R¹</th>
<th>R²</th>
<th>PG</th>
<th>Yield (%)</th>
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<td>1³</td>
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<td>H</td>
<td>H</td>
<td>Boc</td>
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<tr>
<td>2³</td>
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<tr>
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<tr>
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<td>H</td>
<td>Me</td>
<td>Ac</td>
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</table>

³ Decomposition of the product occurred.

The aforementioned syntheses of indolyglyoxals 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.

Figure 3  Revised structure of topsentin C

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 indolyglyox-
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 oxalylchloride according to published methods. 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. In this case, the cyclization was unidirectional because of the methyl group, so that 22a and 22b were isolated only. 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, in contrast to imidazoline 5a (Table 4). This data con-

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 (^3)</th>
<th>5a</th>
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<td>3.05 (s)</td>
<td>2.82 (s)</td>
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<td>CHCH(_2)</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>
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<tr>
<td>CHCH(_2)</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>
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<tr>
<td>CHCH(_2)</td>
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<td>10.71 (br s)</td>
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</tr>
<tr>
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<tr>
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<tr>
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<td>10.34 (br s)</td>
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<td>7.63 (d, (J = 1.7))</td>
<td>7.65 (d, (J = 1.6))</td>
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</tbody>
</table>

\(^a\) 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-d6, CDCl3, and acetone-d6. 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 InfraTral FT-801 FT/IR instrument. The wavelengths are reported in reciprocal centimeters (νmax, cm⁻¹). Mass spectra were recorded with LCMS-8040 triple quadrupole liquid chromatograph mass-spectrometer from Shimadzu (ESI) and Kratos MS-30 mass spectrometer with LCMS-8040 triple quadrupole liquid chromatograph mass-spectrometer. 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. The progress of the reaction was monitored by TLC and the spots were visualized under UV light (254 or 365 nm). Column chromatography was performed using silica gel (230–400 mesh). Melting points were determined with a SMP-10 apparatus and are uncorrected. Solvents were distilled and dried according to standard procedures.

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 EOH.

5-Bromo-1H-indole-3-carbaldehyde (1.50 g, 6.7 mmol) and NH4OAc (0.52 g, 6.7 mmol) were heated at reflux in CH3NO2 (18 mL, 335 mmol) for 45 min, cooled to r.t., and treated with H2O (70 mL). The product was extracted with EtOAc (70 mL), washed with H2O (5 × 50 mL) and NaCl solution (20 mL), and dried over anhydrous Na2SO4. 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 Boc2O (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 CH2Cl2 (50 mL), washed with citric acid solution (10%, 20 mL), H2O (20 mL), and conc NaCl solution (15 mL), and dried over anhydrous Na2SO4. The CH2Cl2 was evaporated in vacuo and the residue was purified by chromatography on a column of silica gel (EtOAc-hexane, 6:1) to provide tert-buty 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); Rf = 0.55 (EtOAc-hexane, 1:8).
IR (film): 3130, 2983, 2300 w, 1741 s (CO), 1639, 1509, 1452, 1368, 1344, 1240, 1153, 1107, 956, 853, 803, 764, 649, 613, 579 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 8.57 (s, 1 H), 8.33 (d, J = 13.7 Hz, 1 H, CH=CHNO₂), 8.27 (d, J = 1.9 Hz, 1 H), 8.26 (d, J = 13.7 Hz, 1 H, CH=CHNO₂), 8.02 (d, J = 8.8 Hz, 1 H), 7.56 (dd, J = 8.8, 1.9 Hz, 1 H), 1.65 (s, 9 H, C(CH₃)₃).

13C NMR (100 MHz, DMSO-d₆): δ 130.89, 128.52, 128.16, 123.08, 116.83, 116.76, 111.47, 85.53, 85.09, 27.48.

MS (EI, 70 eV): m/z (%) = 368 (14)/366 (27) [M⁺], 268 (9)/266 (27) [M – C₄H₈ – CO₂]⁺, 221 (18), 140 (21), 57 (100).

Anal. Calcd for C₁₅H₁₅ClN₂O₄: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.70; H, 4.73; N, 8.63.

tert-Butyl 6-Chloro-3-[{(E)-2-nitrovinyl]-1H-indole-1-carboxylate (9c)

Yield: 1.71 g (85% from 6-bromoindole); pale-yellow solid; mp 134–136 °C (MeOH); 1309, 1285, 1178, 1133, 1100, 874, 805, 764, 726, 591 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 8.03 (d, J = 8.9 Hz, 1 H, CH=CHNO₂), 7.58 (s, 1 H), 7.44 (dd, J = 8.9, 1.9 Hz, 1 H), 7.30–7.40 (m, 5 H, Ph), 5.84 (br s, 1 H, NH), 4.93–5.05 (m, 2 H, CH₂CH₃ – CO₂H), 4.67–4.74 (m, 2 H, CH₂Ph), 4.65 (dd, J = 11.2, 4.2 Hz, 1 H, CH₂CH₃), 1.67 (s, 9 H, O(CH₃)₃).

13C NMR (125 MHz, CDCl₃): δ 148.88, 136.92, 134.18, 130.03, 128.75, 128.48, 128.20, 127.94, 125.45, 122.16, 116.90, 116.36, 114.49, 84.78, 77.08, 76.40, 55.70, 28.09.

MS (ESI): m/z (%) = 492/490 [M + H⁺].

Addition of O-Pivaloylhydroxylamines 8a,b to Nitrovinylindoles 9a–f; General Procedure

The hydrochloride salt of the corresponding O-pivaloylhydroxylamine (6 mmol) was dissolved in CH₂Cl₂ (20 mL) and carefully shaken with saturated aqueous NaHCO₃ solution, then the organic phase was washed with concd NaCl solution and dried over anhydrous Na₂SO₄. The solvent was removed in vacuo at 30 °C and the resulting O-pivaloylhydroxylamine (ca. 5.2 mmol) was carefully mixed with nitrovinylindole (3.5 mmol) in a round-bottom vial and allowed to stand overnight at rt. The reaction mixture was triturated with hexane (7 mL) and the resulting crystals of adducts 7a–h were filtered, washed with cold hexane (2 × 4 mL), and dried in vacuo.

tert-Butyl 3-[{(Benzyloxy)amino]-2-nitroethyl]-5-bromo-1H-indole-1-carboxylate (11)

To a solution of 5-bromo-3-[(E)-2-nitrovinyl]-1H-indole (0.55 g, 1.5 mmol) in anhydrous THF (3 mL), O-benzylhydroxylamine (0.19 g, 1.6 mmol) was added. The mixture was stirred at r.t. for 1 h and allowed to stand overnight. After removing the volatile components in vacuo, the adduct 11 was obtained.

Yield: 0.74 g (ca. 100%); viscous amber oil; Rₓ = 0.53 (EtOAc–hexane, 1:8).

IR (film): 3253, 2980, 2931, 1738 s (CO), 1554, 1451, 1373, 1278, 1154, 1057, 843, 805, 750, 699, 660 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 8.03 (d, J = 8.9 Hz, 1 H, CH=CHNO₂), 7.58 (s, 1 H), 7.44 (dd, J = 8.9, 1.9 Hz, 1 H), 7.30–7.40 (m, 5 H, Ph), 5.84 (br s, 1 H, NH), 4.93–5.05 (m, 2 H, CH₂CH₃ – CO₂H), 4.67–4.74 (m, 2 H, CH₂Ph), 4.65 (dd, J = 11.2, 4.2 Hz, 1 H, CH₂CH₃), 1.67 (s, 9 H, O(CH₃)₃).

13C NMR (125 MHz, DMSO-d₆): δ 130.89, 128.52, 128.16, 123.08, 116.83, 116.76, 111.47, 85.53, 85.09, 27.48.

MS (EI, 70 eV): m/z (%) = 368/366 (11) [M⁺], 268/266 (11) [M – C₄H₈ – CO₂]⁺, 221 (18), 140 (21), 57 (100).

Anal. Calcd for C₁₅H₁₅BrN₂O₄: C, 53.89; H, 4.93; N, 8.57. Found: C, 54.01; H, 5.00; N, 8.58.
MS (ESI): \( m/z \) = 406 [M + H]\(^+\), 345 [M – CH\(_2\)NO\(_2\) + H]\(^+\), 304 [M – (CH\(_2\))\(_3\)CO\(_2\)H + H]\(^+\).
Anal. Calcld for C\(_{20}\)H\(_{27}\)N\(_3\)O\(_6\): C, 59.25; H, 6.71; N, 10.36. Found: C, 59.31; H, 6.73; N, 10.11.

tert-Butyl 3-[1-[(Pivaloyloxy)methylene]-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, 820, 787, 664 cm\(^{-1}\).

\( ^1H \) 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), 7.31 (dd, J = 7.7, 7.3 Hz, 1 H), 5.14–5.26 (m, 1 H, CH-CH\(_2\)NH), 5.01 (dd, J = 12.9, 8.0 Hz, 1 H, CHCH\(_2\)H), 4.75 (dd, J = 12.9, 4.5 Hz, 1 H, CHCH\(_2\)H), 1.68 (s, 9 H, OC(CH\(_3\))\(_3\)), 1.24 (s, 9 H, C(CH\(_3\))\(_3\)).

\( ^13C \) 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): \( m/z \) = 500/498 [M + H]\(^+\), 398/396 [M – (CH\(_2\))\(_2\)CO\(_2\)H + H]\(^+\).
Anal. Calcld for C\(_{21}\)H\(_{29}\)N\(_3\)O\(_6\): C, 56.13; H, 6.97; N, 10.02. Found: C, 56.21; H, 6.56; 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), 1651, 1433, 1370, 1255, 1152, 1097, 865, 818, 772, 679, 590 cm\(^{-1}\).

\( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.40 \) (s, 1 H), 7.70 (d, J = 8.3 Hz, 1 H, CH\(_2\)), 7.64 (d, J = 7.4 Hz, 1 H, CH\(_2\)), 7.42 (dd, J = 8.3, 1.7 Hz, 1 H, CH\(_2\)), 5.02 (dd, J = 7.4, 5.8 Hz, 1 H, CH\(_2\)), 4.98 (dd, J = 12.4, 7.4 Hz, 1 H, CH\(_2\)), 4.63 (dd, J = 12.7, 5.8 Hz, 1 H, CH\(_2\)), 2.66 (s, 3 H, NCH\(_3\)), 1.69 (s, 9 H, OC(CH\(_3\))\(_3\)), 1.26 (s, 9 H, C(CH\(_3\))\(_3\)).

\( ^13C \) NMR (100 MHz, CDCl\(_3\)): \( \delta = 175.92, 148.72, 136.02, 127.39, 126.53, 125.29, 120.84, 119.09, 118.61, 113.91, 85.13, 77.01, 70.02, 64.30, 38.64, 28.03 (3C), 27.02 (3C).

MS (ESI): \( m/z \) = 522/520 [M + Na]\(^+\).
Anal. Calcld for C\(_{21}\)H\(_{28}\)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); \( R_f = 0.33 \) (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\(^{-1}\).

\( ^1H \) NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.04 \) (br s, 1 H), 7.64 (d, J = 1.7 Hz, 1 H), 6.97 (dd, J = 9.0, 1.7 Hz, 1 H), 5.02 (dd, J = 7.4, 5.0 Hz, 1 H, CHCH\(_2\)H), 4.98 (dd, J = 12.4, 7.4 Hz, 1 H, CHCH\(_2\)H), 4.63 (dd, J = 12.4, 5.0 Hz, 1 H, CHCH\(_2\)H), 3.90 (s, 3 H, OCH\(_3\)), 2.68 (s, 3 H, NCH\(_3\)), 1.67 (s, 9 H, OC(CH\(_3\))\(_3\)), 1.25 (s, 9 H, C(CH\(_3\))\(_3\)).

\( ^1C \) 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, 70.02, 55.78, 43.71, 38.66, 28.12 (3C), 27.06 (3C).

MS (ESI): \( m/z \) = 450 [M + H]\(^+\), 348 [M – (CH\(_2\))\(_2\)CO\(_2\)H + H]\(^+\).
Anal. Calcld for C\(_{22}\)H\(_{28}\)O\(_3\)N\(_2\): C, 58.78; H, 6.95; N, 9.35. Found: C, 58.89; H, 7.00; N, 9.23.
1H NMR (600 MHz, CDCl3): δ = 8.03 (m, 1 H), 7.81 (d, J = 1.8 Hz, 1 H), 7.55 (s, 1 H), 7.41 (dd, J = 8.8, 1.8 Hz, 1 H), 7.28–7.36 (m, 5 H, Ph), 6.02 (br s, 1 H, NH), 4.64–4.70 (m, 2 H, CH2Ph), 4.19–4.24 (m, 1 H, CH(=CH2)), 3.07–3.13 (m, 2 H, CH(=CH2)), 1.67 (s, 9 H, OC(CH3)3), 1.47 (br s, 2 H, NH2).

13C NMR (150 MHz, CDCl3): δ = 149.20, 137.62, 134.28, 131.10, 128.54, 128.31, 127.85, 127.33, 124.77, 122.60, 118.24, 116.70, 115.90, 84.18, 76.73, 59.96, 43.26, 28.12 (3C).

MS (ESI): m/z = 462/460 [M + H]+.


After the chromatography, diamin e7b (5.8 mg, 15%) was also isolated. The analytical data was in accordance with the characteristics of the sample obtained from adduct 9b (see below).

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

A solution of adduct 7 (2.2 mmol) in EtOAc (8.3 mL) was added to a cooled (–10 °C) mixture of MeOH (16.5 mL) and HBr (40%, 5.5 mL, 37.8 mmol) under vigorous stirring and treated with Zn dust (2.2 g, 33 mmol). The reaction mixture was allowed to warm to 0–5 °C (1 h), stirred at that temperature for 1 h, and filtered. The precipitate was filtered off and rinsed with a small amount of MeOH. The filtrate was diluted with CH2Cl2 (100 mL), treated with crushed ice (10 g), and carefully shaken with cold NaOH solution (10%, 90 mL). The organic layer was separated and the aqueous layer was washed with CH2Cl2 (20 mL). The combined organic extracts were washed with cold NaOH solution (10%, 30 mL) and concd NaCl solutions (20 mL), and dried over anhydrous Na2SO4. The solvent was removed in vacuo to afford target diamine 6 as a yellowish oil. The product was pure enough for further syntheses. Chromatographic purification on a column with silica gel (CHCl3–MeOH–NH3(aq), 10:1:0.02) was performed, if necessary.
1-[5-Bromo-(1-tert-butoxycarbonyl)-1H-indol-3-yl]ethane-1,2-diamine (6b)

Obtained by following General Procedure A.

Yield: 0.75 g (95%); pale-yellow viscous oil; \( R_f \) = 0.46 (CHCl₃–MeOH–H₂O 10:1:0.02).

IR (film): 3325 br, 2937, 2836, 2794, 1730 s (CO), 1695, 1631, 1477, 1449, 1370, 1276, 1250, 1152, 1078, 1017, 854, 743, 676 cm⁻¹.

1³C NMR (100 MHz, CDCl₃): \( \delta = 149.37, 123.77, 119.49, 118.35, 115.31, 84.93, 59.51, 49.86, 34.43 \) ppm.

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

Anal. Calcd for C₁₅H₂₁N₃O₂: C, 65.43; H, 7.73; N, 15.15. Found: C, 65.33; H, 7.73; N, 15.15.

1-[5-Bromo-(1-tert-butoxycarbonyl)-1H-indol-3-yl]-N⁴-methylthioethane-1,2-diamine (6c)

Obtained by following General Procedure B.

Yield: 0.70 g (86%); pale-yellow viscous oil; \( R_f \) = 0.46 (CHCl₃–MeOH–H₂O 10:1:0.02).

IR (film): 3326 br, 2934, 2791, 1733 s (CO), 1602, 1449, 1373, 1275, 1256, 1156, 1055, 802, 732, 640, 611 cm⁻¹.

1³C NMR (100 MHz, CDCl₃): \( \delta = 149.19, 134.55, 131.07, 127.18, 124.42, 122.24, 120.28, 116.71, 115.77, 84.01, 59.62, 46.05, 34.42, 28.07 \ [3C].

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


1-[5-Methoxy-(1-tert-butoxycarbonyl)-1H-indol-3-yl]-N⁴-methylthioethane-1,2-diamine (6f)

Obtained by following General Procedure B.

Yield: 0.655 g (92%); pale-yellow viscous oil; \( R_f \) = 0.32 (CHCl₃–MeOH–H₂O 10:1:0.02).

IR (film): 3366 br, 2978, 2937, 2796, 1737 s (CO), 1606, 1435, 1455, 1371, 1252, 11576, 1087, 812, 767, 733, 595 cm⁻¹.

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

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**tert-Butyl 6-Bromo-3-[5-(6-bromo-1H-indol-3-yl)-1-methyl-6-oxo-1,2,3,6-tetrahydropyrazin-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 acid chlorides 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, 0.7 mmol) and AcOH (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 conc 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).

**tert-Butyl 6-Bromo-3-[5-(6-bromo-1H-indol-3-yl)-1-methyl-6-oxo-1,2,3,6-tetrahydropyrazin-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).

**tect-Butyl 6-Bromo-3-[5-(6-bromo-1H-indol-3-yl)-1-methyl-4,5-dihydro-1H-imidazol-5-yl]-1H-indole-1-carboxylate (16a)**

A solution of 3-acetyl-6-bromoindole (0.2 g, 0.84 mmol) and I2 (0.23 g, 0.92 mmol) in DMSO (1.7 mL) was heated for 2 h at 100 °C. The reaction mixture was diluted with NCS (0.11 g, 0.86 mmol) under cooling (0–5 °C), stirred for 0.5 h the reaction mixture was treated with NaHCO3 (0.08 g, 1.2 mmol) in DMSO (1.7 mL) was heated for 2 h at 100 °C. The reaction mixture was diluted with CHCl3 (50 mL), washed with saturated NaHCO3 (30 mL) and Na2SO4 (30 mL) solutions, H2O (5 × 30 mL), and conc NaCl solution (30 mL) and dried over anhydrous Na2SO4. The solvent was removed in vacuo and the solid was purified by chromatography on a column with silica gel (CHCl3–MeOH, 100:1) to provide the title compound.

Yield: 0.388 g (77%); brownish amorphous solid; Rf = 0.53 (CHCl3–MeOH, 40:1).

**tect-Butyl 6-Bromo-3-[2-(6-bromo-1H-indol-3-yl)carbonyl]-1-methyl-4,5-dihydro-1H-imidazol-5-yl]-1H-indole-1-carboxylate (16b)**

The compound was prepared as described above for 16a.

Yield: 0.290 (79%); light-brown amorphous solid; Rf = 0.46 (CHCl3–MeOH, 40:1).

**tect-Butyl 3-[5-(1H-Indol-3-yl)-1-methyl-6-oxo-1,2,3,6-tetrahydropyrazin-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).
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 concd 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); R₆ = 0.36 (CHCl₃–MeOH, 20:1).

IR (film): 3426, 3119, 3012, 2850, 1637, 1569, 1513, 1450, 1265, 1085, 988, 822, 793, 692, 600 cm⁻¹.

MS (ESI): m/z = 343 [M + H]⁺.


3,6-Di-1H-indol-3-yl-1-methyl-5,6-dihydropyrazin-2(1H)-one (17b)

Yield: 0.141 g (96%); R₆ = 0.60 (CHCl₃–MeOH, 15:1).

IR (film): 3400, 3271, 3055, 2926, 1664, 1589, 1422, 1339, 1239, 1172, 1100, 1011, 851, 744 cm⁻¹.


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Supporting Information

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References


(21) We did not observe the formation of imidazoline derivatives 16a,b in this reaction. It should also be noted that, in our experiments, compound 5a.b did not transform into the corresponding dihydropyrazinone derivatives 17.a,b upon heating in protic or aprotic solvents in the presence of acid (AcOH, PTSA, TFA, HCl).

(22) NMR 1H spectra of natural topsentin C and compound 17a are identical. There are differences in chemical shifts of several low intensity signals of tertiary carbon atoms in the 13C spectra. It is clear that due to the very small amount of isolated topsentin C, background signals or admixtures masked these low peaks in the spectrum of the natural compound.