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Total Synthesis of Marine Sponge Bis(indole) Alkaloids of the Topsentin Class

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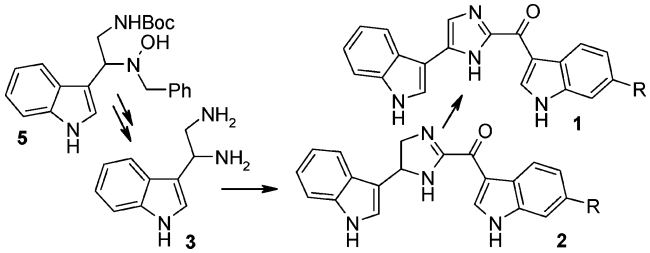
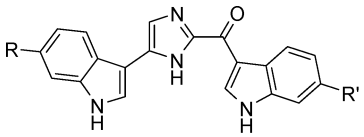


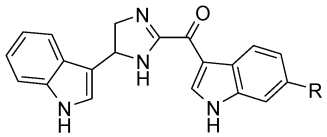
The synthesis of four natural bis(indole) alkaloids of topsentin class **1** and **2** is described. Their bis(indole) α-carbonylimidazoline and subsequently bis(indole) α-carbonylimidazole moieties have been built *via* the condensation between indolic α-ketothioimidate salts **4** and 1-(indol-3′-yl)-1,2-diaminoethane **3**. This compound results from the *β*-amino indolic hydroxylamine **5** by a two-step sequence. This is the first total synthesis of compounds **1d**, **2a**, and **2b**.

In the search of novel bioactive natural substances, biologists turned their attention to the studies of marine organisms.[1] Among them, sponges appear to be one of the richest phyla in toxicogenic species because of their ability to produce a wide variety of metabolites[2] that, in several cases, are responsible of the observed toxicity. To this aim, bioactive crude extracts of sponges were selected, and bioassay-guided fractionation led to the isolation of bis(indole) alkaloids such as nortopsentins, topsentins, dragmacidins, and hamacanthins.[3]

Topsentins **1** and 4,5-dihydrotopsentins **2** were found in several marine sponges, including Mediterranean *Topsentia genitrix* and Carribbean or Korean *Spongosorites* sp. (Figure 1).[3,4] These metabolites have received considerable attention because of their potent properties such as antitumor, antiviral, and antiinflammatory activities.[5] This wide range of bioactivity[6] and their novel structural features have made them attractive targets for both biomedical and synthetic purposes.



1a: R= R'= H: topsentin A or deoxytopsentin
1b: R= H, R'= OH: topsentin B1 or topsentin
1c: R= Br, R'= OH: topsentin B2 or bromotopsentin
1d: R= H, R'= Br: isobromodeoxytopsentin
1e: R= H, R'= OMe: *O*-methyltopsentin



2a: R= H: topsentin D
2b: R= Br : (+)-spongotine B

FIGURE 1. Structures of several topsentins **1** and 4,5-dihydrotopsentins **2**.

The synthesis of a few of them has been described, mainly natural topsentins **1a**,**b**,[7a−e] and synthetic *O*-methyltopsentin **1e**,[7f] containing the α-carbonylimidazole moiety. Surprisingly, the synthesis of natural 4,5-dihydrotopsentins **2**, containing the α-carbonylimidazoline unit, is not described. In this paper, we report a common convergent approach to these moieties through the synthesis of natural topsentin D **2a**, spongotine B **2b**, topsentin A **1a**, isobromodeoxytopsentin **1d**, and synthetic *O*-methyltopsentin **1e** from the same starting building block, *β*-amino indolic *N*-hydroxylamine **5**.[8,9] Indeed, this precursor contains the 1-(indol-3′-yl)-1,2-diaminoethane unit **3**, the key

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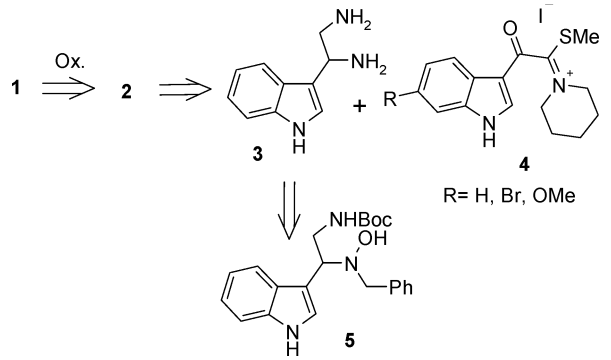


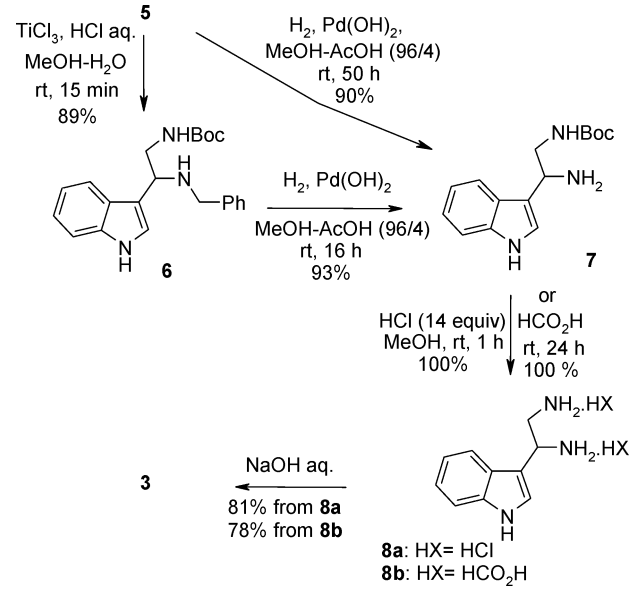
FIGURE 2. Retrosynthetic analysis of topsentins **1** and 4,5-dihydrotopsentins **2**.

substructure of the indolic alkaloid targets. Our strategy is based on (i) the easy and efficient transformation of this precursor **5** into the key intermediate indolic 1,2-diamine **3**, (ii) its condensation with 3-indolyl α-ketothioimidate salts **4** to give the 4,5-dihydrotopsentin family compounds **2**, including **2a** and **2b**, and (iii) the oxidation of the obtained imidazoline spacer into the corresponding imidazole core providing topsentins **1a**, **1d**, and **1e** (Figure 2). To the best of our knowledge, this is the first total synthesis of natural topsentin **1d** and 4,5-dihydrotopsentins **2a** and **2b**.

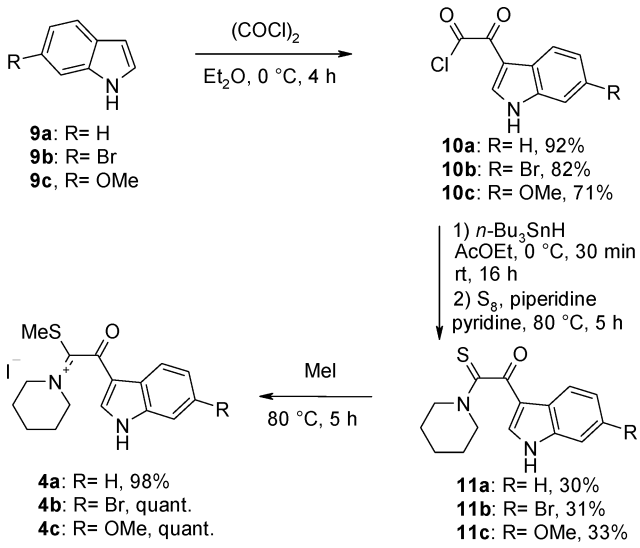
The *β*-amino indolic *N*-hydroxylamine **5**[8,9] was transformed by a three-step sequence into 1-(indol-3′-yl)-1,2-diaminoethane **3**. The first step consists of the reduction of the *N*-hydroxylamine into the corresponding amine by cleavage of the N−O bond. One of the known methods uses $TiCl_3$ in acidic medium.[10] This procedure is highly efficient and the reaction is fast (0.25−0.5 h). Treatment of *β*-amino *N*-hydroxylamine **5** by $TiCl_3$ (2 equiv) in a methanol−aqueous HCl mixture led to indolic diprotected diamine **6** in a nearly quantitative yield. In the next step, hydrogenation of the benzyl group with Pearlman's catalyst ($Pd(OH)_2$) afforded the corresponding indolic monoprotected diamine **7** in 93% yield. During this work, we found that this compound could be obtained in one step directly from indolic *N*-hydroxylamine **5**, by catalytic hydrogenation with $Pd(OH)_2$ in a MeOH−AcOH mixture (96/4) at room temperature for 50 h (Scheme 1).

Removal of the Boc group with 8% solution of HCl in methanol[11] or in pure formic acid afforded quantitatively the expected indolic 1,2-diamine salts **8a** and **8b,** respectively. These compounds are easily isolated by evaporation of excess reactants and solvent (HCl/MeOH or HCO_2H) under vacuum and purified by a simple wash with CH_2Cl_2. These compounds are stable and could be stored at 0 °C over long periods without any degradation. Basic treatment of these salts **8a** or **8b** with an aqueous 20% NaOH solution led to the expected free indolic 1,2-diamine **3** with 81% and 78% yields, respectively. However, this compound is unstable and should be immediately engaged

SCHEME 1. Synthesis of Diamine 3



SCHEME 2. Synthesis of α-Ketothioimidate Salts 4a−c



in the subsequent reaction. We therefore decided to use the salt **8a** as starting material in the following work.

With salt **8a** in hands, we found that 3-indolyl α-ketothioimidate salts **4a−c** would be the appropriate partners. Indeed, aliphatic thioimidate salts are known for their great ability to react with aliphatic 1,2-diamines in order to incorporate an imidazoline moiety as an amide bond replacement in peptides.[12] The salts **4a−c** have been synthesized from the commercially available indoles **9a−c** in four steps as depicted in Scheme 2. The known 3-indolyl-α-oxoacetyl chloride derivatives **10a−c** were prepared by reaction of the corresponding indoles **9a−c** with oxalyl chloride in ether.[13] Treatment with Bu_3SnH in ethyl acetate[14] gave the intermediate aldehydes which were im-

(9) The *β*-amino indolic *N*-hydroxylamine **5** has been prepared in a two-step sequence from *N*-(*tert*-butoxycarbonyl)-aminoacetaldehyde in 84% overall yield. This aldehyde is commercially available. However, for a recent and efficient synthesis of this compound, see: Myers, M. C.; Pokorski, J. K.; Apella, D. H. *Org. Lett*. **2004**, *6*, 4699.

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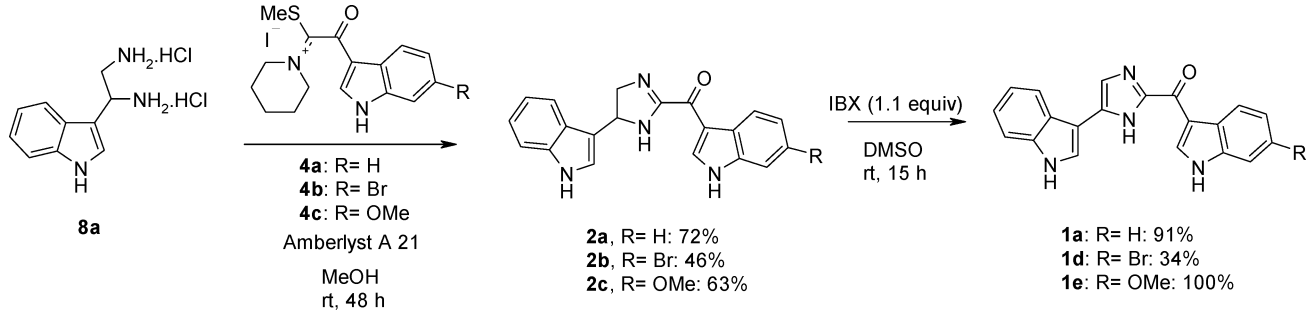
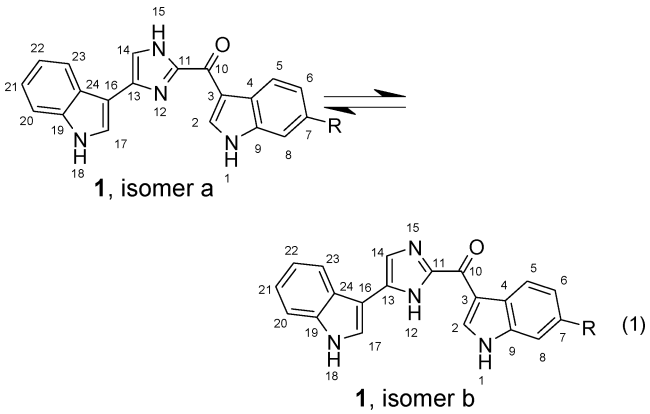
SCHEME 3. Synthesis of Topsentins 1 and 4,5-Dihydrotopsentins 2



mediately reacted with solid sulfur and piperidine in pyridine[15] to afford the expected 3-indolyl-α-ketothioamides **11a**−**c**. Finally, these compounds were converted to the corresponding *S*-methylthioimidate salts **4a**−**c** in excellent yields by treatment with an excess of methyl iodide at reflux. Because of their relative instability (slow decomposition), these intermediates were rapidly used.

Salts **4a**−**c** were then condensed with 1-(indol-3′-yl)-1,2-diaminoethane **3**, prepared *in situ* from **8a** by treatment with Amberlyst A21 in MeOH, to give the racemic bis(indole) ketoimidazolines **2a**−**c**, including natural topsentin D **2a** and spongotine B **2b**. Finally, oxidation of compounds **2a**−**c** with *o*-iodoxybenzoic acid (IBX, 1.1 equiv) in dry DMSO[16] afforded the expected topsentin A **1a**, isobromodeoxytopsentin **1d** (with a nonoptimized yield), and *O*-methyltopsentin **1e** (Scheme 3).

For these synthetic compounds **1**, mixtures of slowly interconverting tautomers (ratios: 55/45) were observed by ^{1}H and ^{13}C NMR in neutral solution (CD_3COCD_3) as previously described for **1a**[4a,b] and **1e**[7f] (eq 1). ^{1}H NMR spectra show a splitting of all signals, which could be suppressed by addition of 1% of CF_3COOD into the deuterated solvent. ^{1}H NMR chemical shifts and coupling constants of synthetic topsentins correspond to those previously described in the literature for topsentins.[4a,b,7f]



In summary, we have accomplished the total syntheses of topsentin D **2a** and spongotine B **2b** in 65% and 41% overall yield in three steps, respectively, and of isobromodeoxytopsentin **1d**, topsentin A **1a**, and *O*-methyltopsentin **1e**, respectively, with 14%, 59%, and 57% overall yields in four steps from indolic *N*-hydroxylamine **5**.[9] These syntheses involved the construction of the α-ketoimidazoline and α-ketoimidazole units *via* condensation of 3-indolyl α-ketothioimidate salts **4a**−**c** with 1-(indol-3′-yl)-1,2-diaminoethane **3**. This approach constitutes the first method for the synthesis of bis(indol-3′-yl)-α-ketoimidazolines **2** and a new way for the preparation of bis(indol-3′-yl)-α-ketoimidazole derivatives **1**.

Experimental Section

1-[*N*-(Benzyl)-amino]-2-[*N*′-(*tert*-butoxycarbonyl)amino]-1-(indol-3′-yl)ethane (6). To a stirred solution of 0.42 g (1.10 mmol) of indolic *N*-hydroxylamine **5** in 6 mL of methanol was added 2.07 mL (2.50 g, 2.40 mmol) of a 15% aqueous solution of $TiCl_3$. The resulting mixture was stirred at rt during 2 h. A large excess of an aqueous solution of 20% NaOH, saturated with NaCl, was added. Methanol was removed under vacuum, and the crude mixture was extracted three times by EtOAc. The combined organic layers were washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (eluent: EtOAc). The protected diamine **6** was obtained (0.36 g, 0.98 mmol) as a white solid. Yield: 89%. Mp: 45−48 °C. IR (neat): 3416, 3310, 3059, 2978, 2880, 1696, 1502, 1453, 1393, 1341, 1250, 1104, 1031 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.42 (s, 9H), 1.81 (bs, 1H), 3.38−3.60 (m, 2H), 3.72 (AB, J_{AB} = 13.4 Hz, $\delta_A - \delta_B$ = 18.0 Hz, 2H), 4.11 (t, J = 5.8 Hz, 1H), 4.99 (bs, 1H), 6.95−7.40 (m, 9H), 7.66 (d, J = 7.5 Hz, 1H), 8.76 (s, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 28.3, 45.4, 51.3, 54.6, 79.2, 111.4, 115.6, 119.3, 122.0, 122.3, 126.2, 126.8, 128.1, 128.3, 136.6, 140.4, 156.3. LRMS (DCI, NH_3 + isobutane): m/z = 366 [(M + H)$^+$], 259, 235, 203, 108. Anal. calcd for $C_{22}H_{27}N_3O_2$: C, 72.33; H, 7.40; N, 11.51. Found: C, 72.71; H, 7.48; N, 11.41.

1-Amino-2-[*N*′-(*tert*-butoxycarbonyl)amino]-1-(indol-3′-yl)ethane (7). Route A: From Indolic *N*-Hydroxylamine (5). To a stirred solution of 2.0 g (5.25 mmol) of indolic *N*-hydroxylamine **5** in 93 mL of methanol and 3.5 mL of acetic acid was added 0.8 g of Pearlman's catalyst ($Pd(OH)_2$). Argon was replaced by hydrogen. The resulting mixture was then stirred at rt for 40 h. It was then filtered through celite. The resulting filtrate was treated by an aqueous 6 N solution of NaOH. Methanol was evaporated under vacuum. The resulting aqueous mixture was extracted three times with EtOAc. Combined organics layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (eluent: EtOAc). Product **7** was obtained as a white solid (1.31 g, 4.75 mmol, 90%). **Route B: From Indolic Diamine (6).** To a stirred solution of 0.43 g (1.20 mmol) of indolic diamine **6** in 24 mL of methanol and 1 mL of acetic acid was added 0.17 g of Pearlman's catalyst ($Pd(OH)_2$). Argon was replaced by hydrogen. The resulting mixture was then stirred at rt during 40 h. It was then filtered through celite. The resulting filtrate was treated by an aqueous 6 N solution of NaOH. Methanol was evaporated under vacuum. The resulting aqueous mixture was extracted five times

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with EtOAc. Combined organics layers were washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography (eluant: EtOAc). Product **7** was obtained as a white solid (0.30 g, 1.1 mmol, 92%). Mp: 145−146 °C. IR (neat): 3404, 3339, 3308, 3053, 2977, 2930, 1703, 1693, 1682, 1537, 1531, 1519, 1514, 1504, 1455, 1393, 1367, 1337, 1251, 1170 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.44 (s, 9H), 1.76 (br s, 2H), 3.39 (ddd, J = 6.5, 7.0 and 13.0 Hz, 1H), 3.57 (ddd, J = 5.5, 6.5 and 13.0 Hz, 1H), 4.41 (dd, J = 5.5 and 7.0 Hz, 1H), 4.90 (br s, 1H), 7.12 (ddd, J = 1.0, 7.5 and 7.5 Hz, 1H), 7.13 (s, 1H), 7.20 (ddd, J = 1.0, 7.5 and 7.5 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 8.30 (bs, 1H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 28.4, 47.5, 48.7, 79.3, 111.3, 118.6, 119.3, 119.6, 121.0, 122.3, 125.9, 136.6, 156.2. LRMS (DCI, NH_3 + isobutane): m/z = 276 [$(M + H)^+$]. Anal. calcd for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.22; H, 7.69; N, 15.19.

1,2-Diamino-1-(indol-3′-yl)ethane Dihydrochloride (8a). A cold solution of hydrochloric acid was prepared at 0 °C by adding 4.69 mL (5.2 g, 66.5 mmol) of freshly distilled acetyl chloride to 15 mL of dry methanol. The solution was stirred for 15 min at 0 °C. A solution of protected diamine **7** (1.31 g, 4.75 mmol) in 20 mL of methanol was then added into the acidic solution at 0 °C. The resulting mixture was stirred for an additional 1 h. Methanol was then slowly evaporated under vacuum, without heating. The indolic 1,2-diamine salt **8a** was obtained as a brown solid (1.28 g, 4.75 mmol). Yield: 100%. Mp: 170 °C (decomposition). IR (KBr): 3350, 2953, 2672, 1588, 1484, 1459, 1434, 1339, 1099, 1012 cm^{-1}. ^1H NMR (CD_3OD, 300 MHz): δ = 3.65−3.85 (m, 2H), 5.09 (dd, J = 6.3 and 8.7 Hz, 1H), 7.18 (dt, J = 1.3 and 7.0 Hz, 1H), 7.24 (dt, J = 1.3 and 7.0 Hz, 1H), 7.45−7.51 (m, 1H), 7.69 (s, 1H), 7.77−7.83 (m, 1H). ^{13}C NMR (CD_3OD, 75.5 MHz): δ = 42.4, 47.1, 107.0, 113.1, 119.0, 121.3, 123.8, 126.7, 126.7, 138.3. LRMS (ESI): m/z = 176 for $C_{10}H_{14}N_3$ [$(M + H)^+$], 159 for $C_{10}H_{11}N_2$ [$(M - NH_2)^+$]. HRMS (ESI): Calcd for $C_{10}H_{14}N_3$: 176.1182. Found: 176.1184 [$(M + H)^+$]. Calcd for $C_{10}H_{11}N_2$: 159.0917. Found: 159.0917 [$(M - NH_2)^+$].

Indol-3′-yl-[5′′-(indol-3′′-yl)-4,5-dihydroimidazol-2-yl]ketone (topsentin D) (2a). To a stirred solution of indolic diamine dihydrochloride **8a** (50 mg, 0.20 mmol) and thioimidate iodide **4a** (83 mg, 0.20 mmol) in distilled methanol (1 mL) was added Amberlyst A21 (200 mg). The resulting mixture was stirred for 60 h at rt. Methanol was then removed under vacuum. To the residue were added water and ethyl acetate. The aqueous layer was extracted three times with EtOAc. The combined organic layers were then washed with brine and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel (eluent: EtOAc). The α-ketoimidazoline **2a** (topsentin D) was obtained as a white solid (48 mg, 0.15 mmol). Yield: 72%. IR (KBr): 2919, 2851, 1705, 1617, 1582, 1435, 1421, 1374, 1239, 1128 cm^{-1}. ^1H NMR (CD_3OD, 300 MHz): δ = 3.98 (dd, J = 8.6 and 12 Hz, 1H), 4.31 (t, J = 12 Hz, 1H), 5.56 (dd, J = 8.6 and 12 Hz, 1H), 7.04 (dt, J = 1.0 and 7.9 Hz, 1H), 7.14 (dt, J = 1 and 7.2 Hz, 1H), 7.25−7.31 (m, 2H), 7.31 (s, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.46−7.52 (m, 1H), 7.63 (d, J = 7.9 Hz, 1H), 8.27−8.33 (m, 1H), 8.47 (s, 1H). ^{13}C NMR (CD_3OD, 75.5 MHz): δ = 56.6, 59.1, 112.8, 113.3, 115.8, 117.1, 119.7, 120.3, 122.9, 123.0, 123.8, 124.1, 125.2, 126.7, 127.3, 138.6, 138.9, 139.4, 164.4, 180.3. LRMS (ESI): m/z = 329 [$(M + H)^+$]. HRMS (ESI) calcd for $C_{20}H_{17}N_4O$: 329.1402. Found: 329.1396 [$(M + H)^+$].

Topsentin A (1a). IBX (0.17 mmol, 47 mg) was added to a solution of the topsentin D **2a** (50 mg, 0.15 mmol) in 0.6 mL of DMSO. The resulting mixture was stirred at rt during 15 h and monitored by TLC until completion. It was then quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (0.38 mL) and an equal volume of EtOAc. The mixture was treated by a saturated aqueous solution of $NaHCO_3$. Aqueous layer was then extracted three times by EtOAc. Combined organic layers were successively washed with an aqueous saturated solution of $NaHCO_3$ and brine and then dried over anhydrous $MgSO_4$. After the removal of the solvent, the residue was purified by column chromatography on silica gel (eluent: EtOAc/pentane, 1:1). Topsentin A **1a** was obtained as a yellow solid (45 mg, 0.14 mmol). Yield: 91%. Mp: 140 °C (dec). IR (neat): 3392, 2927, 1693, 1589, 1518, 1454, 1428, 1260, 1240, 1111, 852, 749 cm^{-1}. ^1H NMR (CD_3COCD_3, 500 MHz): Isomer **a**: δ = 7.12−7.24 (m, 2H), 7.24−7.29 (m, 2H,), 7.47 (d, J = 8.0 Hz), 7.54−7.60 (m, 1H), 7.72 (s, 1H), 7.85 (d, J = 2.0 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 8.48−8.56 (m, 1H), 9.65 (d, J = 3.0 Hz, 1H), 10.38 (s, 1H), 11.16 (s, 1H), 12.07 (s, 1H). Isomer **b**: δ = 7.12−7.24 (m, 2H), 7.24−7.29 (m, 2H), 7.52 (d, J = 8.0 Hz, 1H), 7.54−7.60 (m, 1H), 7.63 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 2.5 Hz, 1H), 8.50−8.56 (m, 1H), 9.42 (d, J = 2.5 Hz, 1H), 10.63 (s, 1H), 11.10 (s, 1H), 12.14 (s, 1H). ^1H NMR (CD_3COCD_3 + TFA-*d* + D_2O, 500 MHz): δ = 7.22 (t, J = 7.0 and 8.0 Hz, 1H), 7.25 (t, J = 7.0 and 8.0 Hz, 1H), 7.28−7.34 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.58−7.63 (m, 1H), 7.97 (d, J = 8.0 Hz, 1H), 8.01 (s, 1H), 8.16 (s, 1H), 8.34−8.38 (m, 1H), 8.90 (s, 1H). DEPT ^{13}C NMR (CD_3COCD_3, 75.5 MHz): Isomers **a** and **b**: δ = 106.6, 111.9, 112.3, 112.70, 112.75, 112.78, 115.0, 115.3, 115.4, 120.3, 120.4, 121.0, 121.2, 122.4, 122.7, 122.8, 123.0, 123.0, 123.2, 123.8, 123.9, 124.3, 126.0, 126.4, 127.1, 128.1, 131.0, 137.3, 137.4, 137.6, 137.8, 137.9, 138.1, 140.2, 146.6, 177.1. DEPT ^{13}C NMR (CD_3COCD_3, TFA-*d*, D_2O, 75.5 MHz): δ = 103.1, 113.1, 113.5, 114.9, 116.4, 119.7, 121.6, 122.5, 123.6, 123.9, 125.2, 125.4, 126.3, 127.0, 132.3, 137.6, 138.0, 138.3, 141.6, 171.9. LRMS (ESI): m/z = 327 [$(M + H)^+$]. HRMS (ESI) calcd for $C_{20}H_{15}N_4O$: 327.1246. Found: 327.1243 [$(M + H)^+$].

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Supporting Information Available: Experimental procedures and characterization data for compounds **1d**, **1e**, **2b, 2c, 4a, 4b, 4c, 11a, 11b, 11c**, and ^1H and ^{13}C or ^{13}C DEPT NMR spectra for compounds **1a**, **1d**, **1e**, **2a**, **2b**, **2c**, **4a**, **4b**, **4c**, and **8a** This material is available free of charge via the Internet at http://pubs.acs.org.

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