



## Total synthesis of Eudistomins Y<sub>1</sub>–Y<sub>6</sub>

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### ABSTRACT

The first total synthesis of Eudistomins Y<sub>1</sub>–Y<sub>6</sub>, brominated phenolic  $\beta$ -carboline marine metabolites with a unique benzoyl moiety at C1, have been prepared in three steps, utilizing MAOS, in overall yields ranging from 6% to 25%.

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$\beta$ -Carboline alkaloids are a prevalent class of biologically active natural products **1–4** with a wide range of structural (Fig. 1) and pharmacological (cytotoxic, antiviral, antimicrobial, etc.) diversity.<sup>1–11</sup> Of these, the eudistomins represent an ever-expanding sub-class isolated from marine tunicates of the *Eudistoma* genus.<sup>12–21</sup> Since the initial discovery by Rinehart in 1987 of Eudistomins A–Q (**4**),<sup>12</sup> additional members Eudistomins R–W have been reported.<sup>12–21</sup>

In 2008, seven new  $\beta$ -carboline-based metabolites, coined Eudistomins Y<sub>1</sub>–Y<sub>7</sub> (Fig. 2) were isolated from a tunicate of the genus *Eudistoma* off the coast of Korea by Kang and co-workers.<sup>22</sup> These new metabolites differ from all previously reported Eudistomins A–W by the presence of a benzoyl group at C1. Preliminary biological evaluation demonstrated that Eudistomin Y<sub>6</sub> (**10**) had a moderate antibacterial activity against Gram-positive bacteria (*Staphylococcus epidermidis* and *Bacillus subtilis*, MICs of 12.5 and 25  $\mu$ g/mL, respectively) without cytotoxicity in an MTT assay at 100  $\mu$ M.<sup>22</sup> However, no synthetic efforts toward these novel metabolites have been reported to date.

We, and others, have developed expedited synthetic routes to access  $\beta$ -carboline alkaloids, and our laboratory has also synthesized unnatural analogs with unique and unexpected biological activities.<sup>23</sup> Based on the unique structures of Eudistomins Y<sub>1</sub>–Y<sub>7</sub> (**5–11**), the initial biological activity, and the potential for diversity-oriented synthesis once an expedient synthetic route was in place, we initiated a total synthesis campaign targeting **5–11**.

Our retrosynthetic analysis is shown in Scheme 1. We envisioned the direct precursor of Eudistomins Y<sub>1</sub>–Y<sub>7</sub> (**5–11**) to be an appropriately functionalized 1-benzyl-4,9-dihydro-3H-pyrido[3,4-b]indole **12**, that could be oxidized to deliver **5–11**.<sup>24</sup> Tricycle **12** would be accessed through a Bischler–Napieralski reaction<sup>25</sup> with intermediate **13**, which could be prepared by a coupling reaction

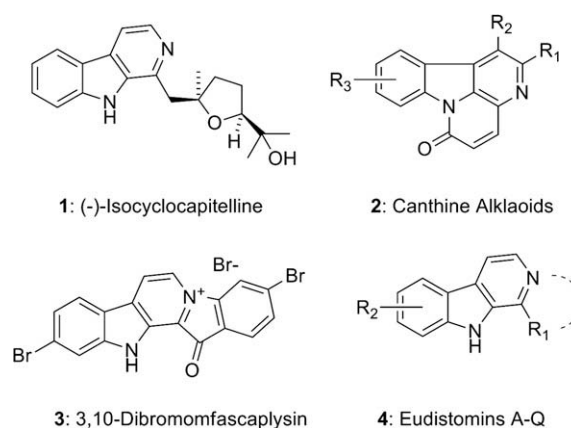
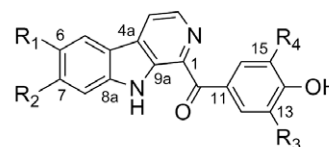


Figure 1. Representative  $\beta$ -carboline alkaloids **1–4**.

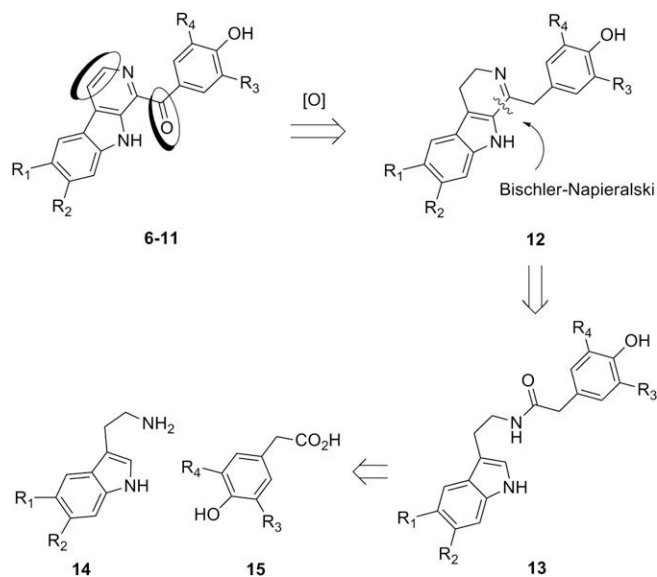


5: Eudistomin Y <sub>1</sub>	R <sub>1</sub> = H	R <sub>2</sub> = H	R <sub>3</sub> = H	R <sub>4</sub> = H
6: Eudistomin Y <sub>2</sub>	R <sub>1</sub> = Br	R <sub>2</sub> = H	R <sub>3</sub> = H	R <sub>4</sub> = H
7: Eudistomin Y <sub>3</sub>	R <sub>1</sub> = H	R <sub>2</sub> = H	R <sub>3</sub> = Br	R <sub>4</sub> = H
8: Eudistomin Y <sub>4</sub>	R <sub>1</sub> = Br	R <sub>2</sub> = H	R <sub>3</sub> = Br	R <sub>4</sub> = H
9: Eudistomin Y <sub>5</sub>	R <sub>1</sub> = H	R <sub>2</sub> = H	R <sub>3</sub> = Br	R <sub>4</sub> = Br
10: Eudistomin Y <sub>6</sub>	R <sub>1</sub> = Br	R <sub>2</sub> = H	R <sub>3</sub> = Br	R <sub>4</sub> = Br
11: Eudistomin Y <sub>7</sub>	R <sub>1</sub> = H	R <sub>2</sub> = Br	R <sub>3</sub> = Br	R <sub>4</sub> = Br

Figure 2. Structures of Eudistomins Y<sub>1</sub>–Y<sub>7</sub> (**5–11**).

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**Scheme 1.** Retrosynthetic analysis of Eudistomins Y<sub>1</sub>–Y<sub>7</sub> (6–11).

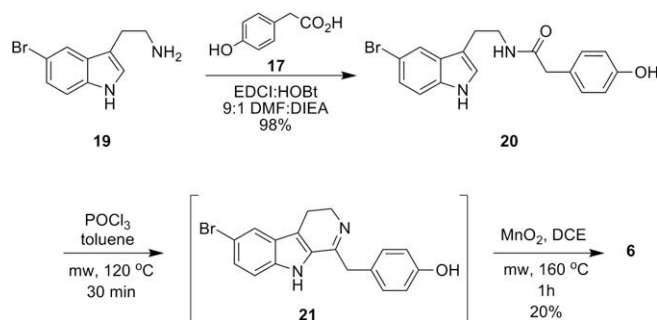
between the appropriately functionalized *p*-hydroxyphenylacetic acid **14** and (1*H*-indol-3-yl)ethanamine **15**.

Our synthetic efforts initially focused on Eudistomin Y<sub>1</sub> (**5**), the simplest member of this class (Scheme 2). A standard EDCI/HOBt coupling reaction between (1*H*-indol-3-yl)ethanamine **16** and *p*-hydroxyphenylacetic acid **17** gave **18** in 79% yield. Classical Bischler–Napieralski conditions proved sluggish, so we developed microwave-assisted conditions (POCl<sub>3</sub>, toluene, 120 °C, 30 min) which smoothly delivered **19**. Multiple oxidation conditions were also explored, including standard *hν*/O<sub>2</sub>, but good results were ultimately achieved with MnO<sub>2</sub> under another microwave-assisted protocol to produce Eudistomin Y<sub>1</sub> (**5**) in 31% yield for the two steps with crude **19**. Thus, a rapid three-step, two-pot sequence was designed and optimized to access the Eudistomin Y<sub>1</sub>–Y<sub>7</sub> (**5**–**11**) scaffold in 25% overall yield.<sup>26</sup>

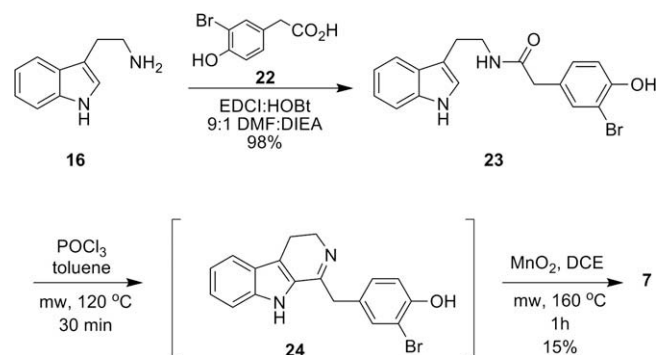
To access the brominated congeners, Eudistomins Y<sub>2</sub>–Y<sub>7</sub> (**6**–**11**), we were pleased to find that all of the requisite starting materials were readily accessible, except the 2-(6-bromo-1*H*-indol-3-yl)ethanamine required to synthesize **11**, which was readily prepared.

Similarly, Eudistomin Y<sub>2</sub> (**6**) was prepared by a standard EDCI/HOBt coupling reaction between 2-(5-bromo-1*H*-indol-3-yl)ethanamine **19** and *p*-hydroxyphenylacetic acid **17** gave **20** in 90% yield (Scheme 3). Our microwave-assisted Bischler–Napieralski conditions provided **21**, which carried forward crude into a microwave-assisted MnO<sub>2</sub> protocol to deliver Eudistomin Y<sub>2</sub> (**6**) in 20% yield for the two steps and 18% overall.

Eudistomin Y<sub>3</sub> (**7**), containing a bromine on the benzoyl moiety, was prepared by a standard EDCI/HOBt coupling reaction between



**Scheme 3.** Total synthesis of Eudistomin Y<sub>2</sub> (**6**).

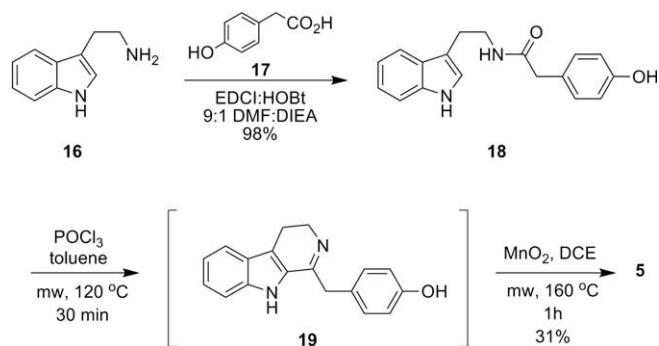


**Scheme 4.** Total synthesis of Eudistomin Y<sub>3</sub> (**7**).

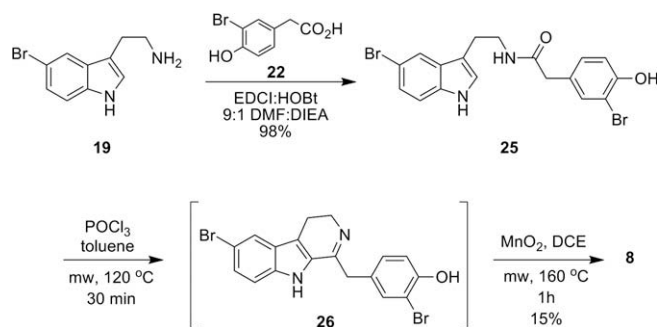
(1*H*-indol-3-yl)ethanamine **16** and 3-bromo-4-hydroxyphenylacetic acid **22** to afford **23** in 98% yield (Scheme 4). Application of a now standard microwave-assisted Bischler–Napieralski protocol provided crude **24**, followed by our microwave-assisted MnO<sub>2</sub> protocol to deliver Eudistomin Y<sub>3</sub> (**7**) in 15% yield.

Eudistomin Y<sub>4</sub> (**8**) possess bromines on both the (1*H*-indol-3-yl)ethanamine component **14** and the *p*-hydroxyphenylacetic acid **15**. Fortunately, our standard three-step, two-pot sequence proved to work with equivalent efficiency (Scheme 5). In the event, 2-(5-bromo-1*H*-indol-3-yl)ethanamine **19** was coupled to 3-bromo-4-hydroxyphenylacetic acid **22** employing EDCI/HOBt conditions to provide **25**. Two successive microwave-assisted reactions (Bischler–Napieralski and MnO<sub>2</sub> oxidation) delivered Eudistomin Y<sub>4</sub> (**8**) in 15% overall yield.

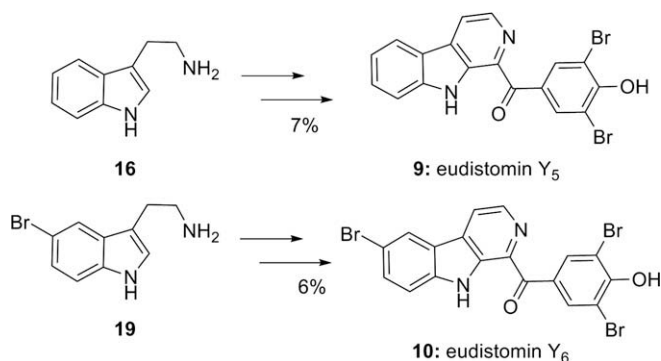
Following the protocols outlined in Schemes 1–4, Eudistomins Y<sub>5</sub> and Y<sub>6</sub> (**9** and **10**) were synthesized in three steps with overall yields of 7% and 6%, respectively (Scheme 6). While the amide coupling steps proceeded in high yields, the polybrominated sub-



**Scheme 2.** Total synthesis of Eudistomin Y<sub>1</sub> (**5**).



**Scheme 5.** Total synthesis of Eudistomin Y<sub>4</sub> (**8**).



Scheme 6. Total synthesis of Eudistomin Y<sub>5</sub> (9) and Y<sub>6</sub> (10).

strates performed poorly in the microwave-assisted Bischler–Napieralski and MnO<sub>2</sub> oxidation reactions.

In every case, the <sup>1</sup>H and <sup>13</sup>C NMR spectra of the synthetic Eudistomins Y<sub>1</sub>–Y<sub>6</sub> matched that reported for the natural products (5–10).<sup>27</sup> Attempts to prepare Eudistomin Y<sub>7</sub> failed employing this methodology, due perhaps to stereoelectronic effects and/or solubility issues of the polybrominated scaffold. Overall yields for the three-step, two-pot process were low, but not unexpected based on the electronics of the system with the carbonyl moiety at C1. For the Bischler–Napieralski and MnO<sub>2</sub> oxidation steps, thermal conditions failed entirely. Only MAOs provided the desired Eudistomin scaffold, but in modest to poor yields.

Thus, the first total synthesis of Eudistomins Y<sub>1</sub>–Y<sub>6</sub> (5–10) has been completed, requiring only three synthetic steps in a two-pot process and with overall yields ranging from 6% to 25%. We are currently evaluating 5–10 against a large panel of discrete molecular targets in radioligand binding assays,<sup>28</sup> and we are in the process of initiating a diversity-oriented synthesis campaign to synthesize libraries of unnatural analogs.<sup>29</sup> These efforts are underway and will be reported in due course.

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- Representative experimental.** Tryptamine **16** (1 g, 6.2 mmol), 4-hydroxyphenylacetic acid **17** (0.94 g, 6.2 mmol), and *N*-hydroxybenzotriazole (1.76 g, 13.0 mmol) were added to a 250 ml round-bottomed flask, and dissolved in 9:1 DMF/DIEA (50 ml). 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (3.6 g, 18.6 mmol) was then added and the reaction was allowed to stir overnight. Once complete the reaction was quenched with 1 N HCl and extracted three times with DCM (100 ml). The organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated. The crude residue was purified by column chromatography to yield coupled product **18** (1.39 g, 4.7 mmol) in 76% yield. Coupled product **18** (0.25 g, 0.850 mmol) was added to a 5 ml microwave vial and dissolved in toluene (3 ml). POCl<sub>3</sub> (0.79 ml, 8.50 mmol) was then added all at once and the reaction vessel capped, and heated to 120 °C for 30 min. Once complete the toluene was removed and the reaction quenched with satd NaHCO<sub>3</sub> and extracted three times with DCM (100 ml). The organic layer was dried with MgSO<sub>4</sub>, filtered and concentrated to obtain **21** which was used without further purification. Crude **21** (100 mg, 0.362 mmol), was added to a 20 ml MW vial and partially dissolved in DCE (10 ml). MnO<sub>2</sub> (315 mg, 3.62 mmol) was then added all at once and the reaction vessel capped and heated to 160 °C for 60 min. Once complete the reaction was vacuum filtered, concentrated, and purified by preparative HPLC to obtain **5** (32.4 mg, 0.112 mmol) in 31% yield.
- NMR (<sup>1</sup>H and <sup>13</sup>C), Hi-RES MS data for Y<sub>1</sub>–Y<sub>6</sub>.** Eudistomins Y<sub>1</sub>: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.39 (br s, 1H), 8.51 (d, *J* = 5.2 Hz, 1H), 8.41 (d, *J* = 5.2 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 8.24 (dt, *J* = 8.8, 2.8 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.92 (dt, *J* = 8.8, 2.4 Hz, 2H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 191.6, 161.9, 141.6, 137.3, 136.7, 135.6, 133.7, 130.8, 128.9, 128.2, 121.8, 120.1, 120.0, 118.2, 114.9, 112.9. HRMS (Q-TOF): *m/z* calcd for C<sub>18</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 289.0977, found: 289.0973. Eudistomins Y<sub>2</sub>: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.42 (br s, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 8.45 (d, *J* = 4.8 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 2H), 7.72 (s, 2H), 6.91 (d, *J* = 8.8 Hz, 2H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 191.1, 161.9, 140.2, 137.7, 137.1, 135.7, 133.7, 131.2, 129.7, 128.0, 124.4, 122.0, 118.7, 114.8, 112.0. HRMS (Q-TOF): *m/z* calcd for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Br [M+H]<sup>+</sup>: 367.0082, found: 367.0081. Eudistomins Y<sub>3</sub>: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 11.30 (s, 1H), 8.56 (m, 2H), 8.44 (d, *J* = 5.2 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.33 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.60 (m, 1H), 7.30 (m, 1H), 7.12 (d, 8.4 Hz, 1H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 190.2, 158.6, 141.6, 137.0, 136.7, 136.4, 135.7, 132.5, 131.0, 129.6, 128.9, 121.8, 120.1, 120.0, 118.7, 115.6, 112.9, 108.8. HRMS (Q-TOF): *m/z* calcd for C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>Br [M+H]<sup>+</sup>: 367.0082, found: 367.0082. Eudistomins Y<sub>4</sub>: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.38 (br s, 1H), 8.51 (d, *J* = 4.8 Hz, 1H), 8.42 (d, *J* = 4.8 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 6.8 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 6.92 (d, *J* = 7.2 Hz, 2H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 190.6, 160.1, 140.6, 137.6, 137.4, 136.7, 133.7, 136.3, 131.7, 130.0, 128.9, 124.7, 121.8, 120.1, 115.9, 114.9, 112.9, 108.4. HRMS (Q-TOF): *m/z* calcd for C<sub>18</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>Br<sub>2</sub> [M+H]<sup>+</sup>: 444.9817, found: 444.9817. Eudistomins Y<sub>5</sub>: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 10.15 (br s, 1H), 8.53 (m, 3H), 8.43 (m, 1H), 8.30 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.58 (t, *J* = 6.8 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 190.1, 157.8, 144.7, 138.8, 136.7, 135.9, 135.4, 135.1, 132.6, 130.9, 126.6, 121.4, 120.3, 120.1, 119.8, 113.7, 112.2, 110.7. HRMS (Q-TOF): *m/z* calcd for C<sub>18</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>NaBr<sub>2</sub> [M+Na]<sup>+</sup>: 466.9007, found: 466.9009. Eudistomins Y<sub>6</sub>: <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.62 (br s, 1H), 8.58 (d, *J* = 4.8 Hz, 1H), 8.52 (m, 3H), 7.75 (m, 2H). <sup>13</sup>C NMR (150 MHz, DMSO-*d*<sub>6</sub>) δ 189.2, 156.0, 140.8, 137.9, 136.4, 135.8, 135.2, 131.9, 130.6, 128.9, 126.6, 125.0, 122.5, 120.9, 120.0, 115.5, 112.7, 111.4. HRMS (Q-TOF): *m/z* calcd for C<sub>18</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>Br<sub>3</sub> [M+H]<sup>+</sup>: 522.8292, found: 522.8287.
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