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Total synthesis of Eudistomins Y_1–Y_6

J. Phillip Kennedy [a], Micah L. Breininger [b,c,d], Craig W. Lindsley [a,b,c,d,*]

[a] Department of Chemistry, Vanderbilt University & Medical Center, Nashville, TN 37232, USA
[b] Department of Pharmacology, Vanderbilt University & Medical Center, Nashville, TN 37232, USA
[c] Vanderbilt Program in Drug Discovery, Vanderbilt University & Medical Center, Nashville, TN 37232, USA
[d] Vanderbilt Specialized Chemistry Center for Accelerated Probe Development, Vanderbilt University & Medical Center, Nashville, TN 37232, USA

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ABSTRACT

The first total synthesis of Eudistomins Y_1–Y_6, brominated phenolic β-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%.

β-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.[1–11] Of these, the eudistomins represent an ever-expanding sub-class isolated from marine tunicates of the *Eudistoma* genus.[12–21] Since the initial discovery by Rinehart in 1987 of Eudistomins A–Q (**4**),[12] additional members Eudistomins R–W have been reported.[12–21]

In 2008, seven new β-carboline-based metabolites, coined Eudistomins Y_1–Y_7 (Fig. 2) were isolated from a tunicate of the genus *Eudistoma* off the coast of Korea by Kang and co-workers.[22] 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_6 (**10**) had a moderate antibacterial activity against Gram-positive bacteria (*Staphylococcus epidermis* and *Bacillus subtilis*, MICs of 12.5 and 25 μg/mL, respectively) without cytotoxicity in an MTT assay at 100 μM.[22] However, no synthetic efforts toward these novel metabolites have been reported to date.

We, and others, have developed expedited synthetic routes to access β-carboline alkaloids, and our laboratory has also synthesized unnatural analogs with unique and unexpected biological activities.[23] Based on the unique structures of Eudistomins Y_1–Y_7 (**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_1–Y_7 (**5**–**11**) to be an appropriately functionalized 1-benzyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole **12**, that could be oxidized to deliver **5**–**11**.[24] Tricycle **12** would be accessed through a Bischler–Napieralski reaction[25] with intermediate **13**, which could be prepared by a coupling reaction

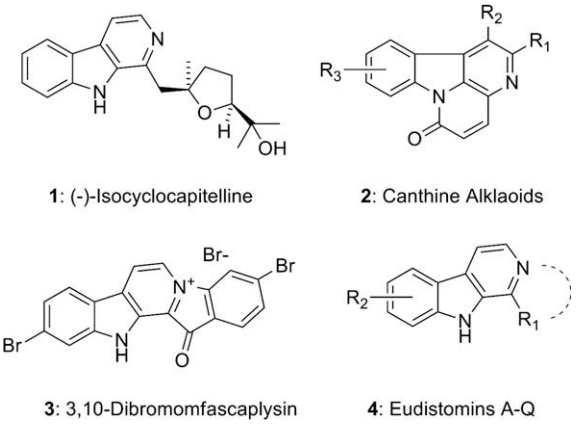
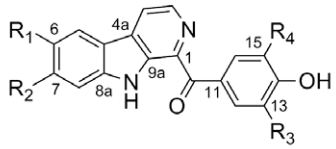


Figure 1. Representative β-carboline alkaloids **1**–**4**.



5: Eudistomin Y_1	R_1 = H	R_2 = H	R_3 = H	R_4 = H
6: Eudistomin Y_2	R_1 = Br	R_2 = H	R_3 = H	R_4 = H
7: Eudistomin Y_3	R_1 = H	R_2 = H	R_3 = Br	R_4 = H
8: Eudistomin Y_4	R_1 = Br	R_2 = H	R_3 = Br	R_4 = H
9: Eudistomin Y_5	R_1 = H	R_2 = H	R_3 = Br	R_4 = Br
10: Eudistomin Y_6	R_1 = Br	R_2 = H	R_3 = Br	R_4 = Br
11: Eudistomin Y_7	R_1 = H	R_2 = Br	R_3 = Br	R_4 = Br

Figure 2. Structures of Eudistomins Y_1–Y_7 (**5**–**11**).

* Corresponding author. Tel.: +1 615 322 8700; fax: +1 615 343 6532.
E-mail address: craig.lindsley@vanderbilt.edu (C.W. Lindsley).

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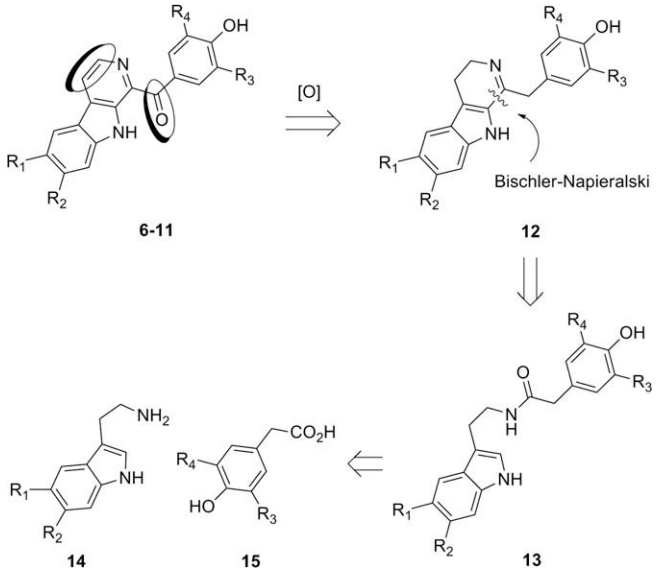


Scheme 1. Retrosynthetic analysis of Eudistomins Y_1–Y_7 (**6**–**11**).

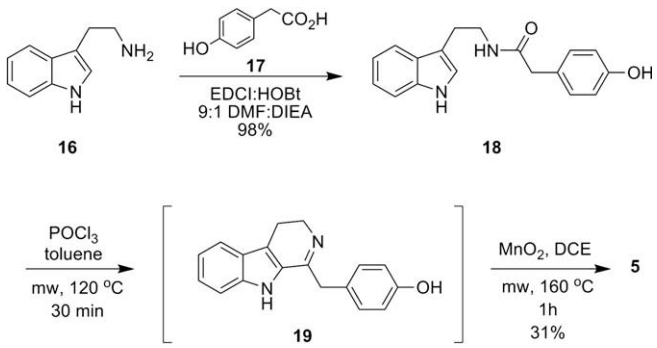
between the appropriately functionalized *p*-hydroxyphenylacetic acid **14** and (1*H*-indol-3-yl)ethanamine **15**.

Our synthetic efforts initially focused on Eudistomin Y_1 (**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 ($POCl_3$, toluene, 120 °C, 30 min) which smoothly delivered **19**. Multiple oxidation conditions were also explored, including standard hυ/O_2, but good results were ultimately achieved with MnO_2 under another microwave-assisted protocol to produce Eudistomin Y_1 (**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_1–Y_7 (**5**–**11**) scaffold in 25% overall yield.[26]

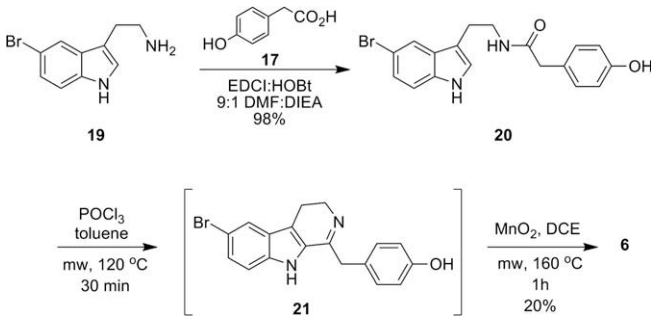
To access the brominated congeners, Eudistomins Y_2–Y_7 (**6**–**11**), we were pleased to find that all of the requisite starting materials were readily accessible, except the 2-(6-bromo-1*H*-indo-3-yl)ethanamine required to synthesize **11**, which was readily prepared.

Similarly, Eudistomin Y_2 (**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_2 protocol to deliver Eudistomin Y_2 (**6**) in 20% yield for the two steps and 18% overall.

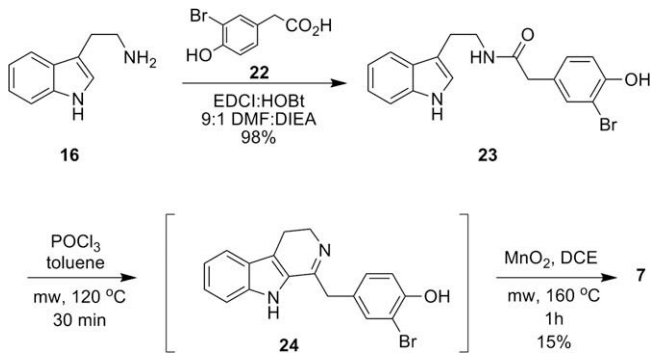
Eudistomin Y_3 (**7**), containing a bromine on the benzoyl moiety, was prepared by a standard EDCI/HOBt coupling reaction between



Scheme 2. Total synthesis of Eudistomin Y_1 (**5**).



Scheme 3. Total synthesis of Eudistomin Y_2 (**6**).

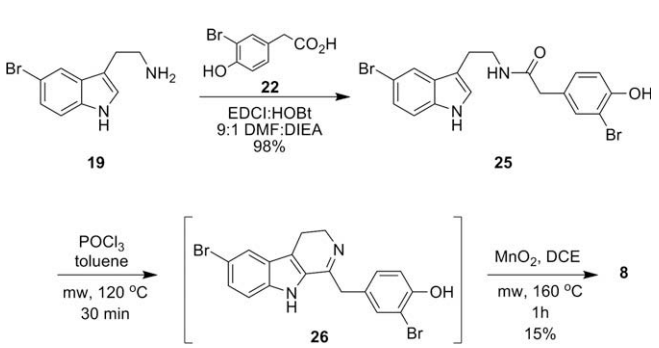


Scheme 4. Total synthesis of Eudistomin Y_3 (**7**).

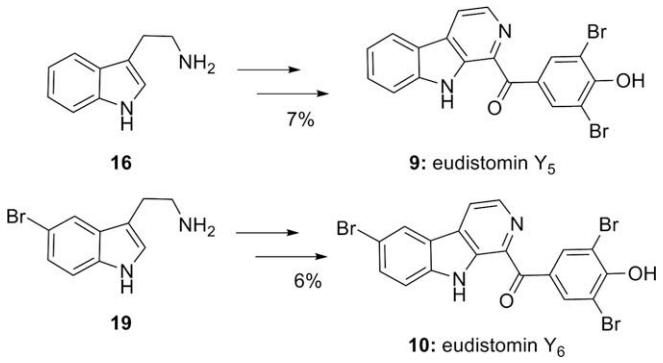
(1*H*-indol-3-yl)ethanamine **16** and 3-bromo-4-hydroxyhydroxyphenylacetic acid **22** to afford **23** in 98% yield (Scheme 4). Application of a now standard microwave-assisted Bischler–Napieralski protocol provided crude **24**, followed by our microwave-assisted MnO_2 protocol to deliver Eudistomin Y_3 (**7**) in 15% yield.

Eudistomin Y_4 (**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-hydroxyhydroxyphenylacetic acid **22** employing EDCI/HOBt conditions to provide **25**. Two successive microwave-assisted reactions (Bischler–Napieralski and MnO_2 oxidation) delivered Eudistomin Y_4 (**8**) in 15% overall yield.

Following the protocols outlined in Schemes 1–4, Eudistomins Y_5 and Y_6 (**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 5. Total synthesis of Eudistomin Y_4 (**8**).



Scheme 6. Total synthesis of Eudistomin Y_5 (**9**) and Y_6 (**10**).

strates performed poorly in the microwave-assisted Bischler–Napieralski and MnO_2 oxidation reactions.

In every case, the ^1H and ^{13}C NMR spectra of the synthetic Eudistomins Y_1–Y_6 matched that reported for the natural products (**5**–**10**).[27] Attempts to prepare Eudistomin Y_7 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_2 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_1–Y_6 (**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,[28] and we are in the process of initiating a diversity-oriented synthesis campaign to synthesize libraries of unnatural analogs.[29] These efforts are underway and will be reported in due course.

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26. *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 $MgSO_4$, 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). $POCl_3$ (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 $NaHCO_3$ and extracted three times with DCM (100 ml). The organic layer was dried with $MgSO_4$, 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_2 (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.
27. NMR (^1H and ^{13}C), Hi-RES MS data for Y_1–Y_6. Eudistomins Y_1: ^1H NMR (400 MHz, DMSO-d_6) 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). ^{13}C NMR (150 MHz, DMSO-d_6) 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 $C_{18}H_{13}N_2O_2$ [M+H$^+$]: 289.0977, found: 289.0973.
Eudistomins Y_2: ^1H NMR (400 MHz, DMSO-d_6) 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).). ^{13}C NMR (150 MHz, DMSO-d_6) 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 $C_{18}H_{12}N_2O_2Br$ [M+H$^+$]: 367.0082, found: 367.0081.
Eudistomins Y_3: ^1H NMR (400 MHz, DMSO-d_6) 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). ^{13}C NMR (150 MHz, DMSO-d_6) 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 calc for $C_{18}H_{12}N_2O_2Br$ [M+H$^+$]: 367.0082; found: 367.0082.
Eudistomins Y_4: ^1H NMR (400 MHz, DMSO-d_6) 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). ^{13}C NMR (150 MHz, DMSO-d_6) 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 $C_{18}H_{11}N_2O_2Br_2$ [M+H$^+$]: 444.9817; found: 444.9817.
Eudistomins Y_5: ^1H NMR (400 MHz, DMSO-d_6) 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). ^{13}C NMR (150 MHz, DMSO-d_6) 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 $C_{18}H_{10}N_2O_2NaBr_2$ [M+Na$^+$]: 466.9007, found: 466.9009.
Eudistomins Y_6: ^1H NMR (400 MHz, DMSO-d_6) δ 8.62 (br s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.52 (m, 3H), 7.75 (m, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) 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 $C_{18}H_{10}N_2O_2Br_3$ [M+H$^+$]: 522.8292; found: 522.8287.
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