Total Syntheses of Eudistomins Y1–Y7 by an Efficient One-Pot Process of Tandem Benzylic Oxidation and Aromatization of 1-Benzyl-3,4-dihydro-β-carbolines


Keywords: Natural products / Alkaloids / Total synthesis / Nitrogen heterocycles / Aromatization

The first total synthesis of eudistomin Y7 (7) and total syntheses of eudistomins Y1–Y6 (1–6) are described. An efficient room-temperature conversion of 1-benzyl-3,4-dihydro-β-carbolines (11) into 1-benzoyl-β-carbolines (14) by a one-pot process of tandem benzylic oxidation and aromatization as the key step of these total syntheses was also studied in detail.

Introduction

Eudistomins are a sub-class of prevalent and biologically active β-carboline alkaloids, many of which have been isolated from marine tunicates of the Eudistoma genus.[1–6] Rinehart and co-workers first reported the isolation and determined the structures of eudistomins A–Q.[1] Later, Kobayashi and co-workers also reported the isolation of eudistomins A–F,[5] Kinzer and Cardellina reported the isolation of eudistomins R–T,[3] Francisco and co-workers reported the isolation of eudistomin U,[4] Quinn and co-workers reported the isolation of eudistomin V,[5] and Proksch and co-workers reported the isolation of eudistomins W and X.[6]

Eudistomins Y1–Y7 (Table 1, 1–7) are seven new members of this class of β-carboline alkaloids. These compounds were originally isolated from a tunicate of the Eudistoma genus off the coast of Korea by Kang and co-workers in 2008.[7] Recently, eudistomins Y2–Y7 (2–7) were also isolated from the Korean ascidian Synoicum sp. by Oh, Shin and co-workers in 2012.[8] Biological evaluation demonstrated that eudistomins Y1–Y7 (1–7) and their derivatives showed moderate to significant antimicrobial activity, weak cytotoxic activity, and inhibitory activities towards sortase A, isocitrate lyase, and Na+/K+-ATPase.[7,8]

Since the isolation of eudistomins Y1–Y7 (1–7) in 2008, Lindsley and co-workers have reported the first total syntheses of eudistomins Y1–Y6 (1–6).[9] However, these total syntheses suffered from low overall yields and required the use of microwave radiation. Moreover, to the best of our knowledge, the total synthesis of eudistomin Y7 (7) has not been reported to date. Considering their wide-ranging biological activities, we are interested in developing efficient and practical syntheses of eudistomins Y1–Y7 (1–7) and their derivatives. In this paper, we report the first total synthesis of eudistomin Y7 (7) and also total syntheses of eudistomins Y1–Y6 (1–6).

Results and Discussion

Our total syntheses of eudistomins Y1–Y7 (1–7) were performed according to the synthetic route shown in Scheme 1. 2-Arylacetyl chlorides were prepared prior to use by the reaction of 2-arylacetic acids 8a–d with thionyl chloride (SOCl₂) in refluxing dichloromethane. They were then exposed to tryptamine (9a) or 6-bromotryptamine (9b)
under basic conditions in a biphasic mixed solvent of dichloromethane and water (CH₂Cl₂/H₂O = 3:1), to give the desired coupling products (i.e., 10a–d) in 90, 86, 88, and 90% yields, respectively. Subsequently, compounds 10a–d were treated with phosphoryl trichloride (POCl₃) in refluxing ethyl acetate to give a tautomeric mixture of compounds 11 and 12 by a Bischler–Napieralski cyclization.⁹ Because of the imine–enamine tautomerism, the mixture of compounds 11 and 12 was hard to separate, and so it was used as such for the next step. When the tautomeric mixtures of compounds 11/12a–d were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dimethyl sulfoxide (DMSO) at room temperature under an atmosphere of air, benzylic oxidation of the imine–enamine tautomers occurred smoothly to produce 1-benzoyl-3,4-dihydro-β-carbolines 13a–d, which then rapidly turned into 1-benzoyl-β-carbolines 14a–d by oxidative aromatization. The desired compounds (i.e., 14a–d) were formed in 78, 75, 70, and 72% yields, respectively, over three steps from compounds 10a–d.

Compounds 14a–d are the precursors to eudistomins Y₁ (1), Y₃ (3), Y₅ (5), and Y₇ (7). When compounds 14a–d were treated with aqueous HBr in acetic acid at reflux (110 °C), the cleavage of the phenol methyl ethers took place to give the desired eudistomins Y₁ (1), Y₃ (3), Y₅ (5), and Y₇ (7) in 92, 92, 95, and 93% yields, respectively. When compounds 14a–c were treated with N-bromosuccinimide (NBS) in a mixed solvent of acetonitrile and acetic acid (CH₃CN/CH₃COOH = 3:1), a highly selective monobromination occurred smoothly at the C-6 position to give compounds 15a–c in almost quantitative yields. Compounds 15a–c are the precursors to eudistomins Y₂ (2), Y₄ (4), and Y₆ (6), and they were then converted into the desired eudistomins Y₂ (2), Y₄ (4), and Y₆ (6) in 93, 95, and 94% yields, respectively, after ether cleavage by treatment with aqueous HBr in acetic acid at reflux (110 °C).
6-Bromotryptamine (9b) was prepared from 6-bromo-1H-indole according to the synthetic route shown in Scheme 2. First, (E)-6-bromo-3-(2-nitrovinyl)-1H-indole (16) was prepared in 96% yield following a known procedure. Compound 16 was then treated with sodium borohydride and boric acid in a mixed solvent of 2-propanol and tetrahydrofuran to produce 6-bromo-3-(2-nitroethyl)-1H-indole (17) in 94% yield. Reduction of the nitro group of compound 17 with zinc powder in the presence of HCl gave 6-bromotryptamine 9b in 91% yield. Because the yield (86%) of the modified two-step conversion from compound 16 into compound 9b is clearly better than the yield (73%) of the known one-step procedure, it is recommended for the preparation of 6-bromotryptamine (9b).

Scheme 2. Preparation of 6-bromotryptamine (9b).

In the above-described total syntheses of eudistomins Y₁–Y₇ (1–7), the key transformation was the conversion of 1-benzyl-3,4-dihydro-β-carbolines 11 into 1-benzoyl-β-carbolines 14 by benzylic oxidation and aromatization. This key conversion can be achieved in one pot by either of two known methods. In Lindsley’s method, the one-pot conversion was carried out at 160 °C by a microwave-assisted MnO₂-oxidation protocol, but only low yields were obtained from this protocol. In Jenkins’ method, a photocatalytic protocol was used for the one-pot conversion. Although the yields of products were good, this photocatalytic protocol is not practical and convenient due to the use of a 500 W halogen lamp and the need for a short distance between the lamp and the reaction flask. In contrast, our DBU-promoted room-temperature method is much more efficient and practical than the two known protocols.

To get more insight into the above-mentioned key conversion, we prepared various 1-substituted 3,4-dihydro-β-carbolines 18, and attempted the aromatization of these compounds. When compounds 18 were treated with DBU in DMSO at room temperature or 125 °C under air, the corresponding 1-substituted-β-carbolines (i.e., 19a–i) were obtained in 72–96% yields. The results are summarized in Table 2. When R was an electron-deficient group such as benzoyl, acetyl, or an ester group, the aromatization was very fast, even at room temperature (Table 2, entries 1–4).

In contrast, when R was an alkyl or aryl group, the aromatization was sluggish at room temperature, but it occurred smoothly at 125 °C (Table 2, entries 5–9). These results imply that benzylic oxidation of 1-benzyl-3,4-dihydro-β-carbolines 11 (or 12) should occur first to form 1-benzoyl-3,4-dihydro-β-carbolines 13, and then the aromatization of 1-benzyl-3,4-dihydro-β-carbolines 13 would take place rapidly to give 1-benzoyl-β-carbolines 14. Other solvents such as ethyl acetate, tetrahydrofuran, acetonitrile, or 2-propanol were also tested, but DMSO was the most appropriate for this reaction (see also a previous report). DBU worked better than the other bases tested such as triethylamine, pyridine, 4-(dimethylamino)pyridine, sodium carbonate, potassium carbonate, potassium hydroxide, and sodium hydroxide.

Table 2. Aromatization of various 3,4-dihydro-β-carbolines 18.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Temp. °C</th>
<th>Time [h]</th>
<th>Product Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C₆H₅CO</td>
<td>30 [b]</td>
<td>0.5</td>
<td>19a</td>
</tr>
<tr>
<td>2</td>
<td>CH₃CO</td>
<td>25 [b]</td>
<td>0.5</td>
<td>19b</td>
</tr>
<tr>
<td>3</td>
<td>COOCH₃</td>
<td>25 [b]</td>
<td>3</td>
<td>19c</td>
</tr>
<tr>
<td>4</td>
<td>COOCH₂H₅</td>
<td>25 [b]</td>
<td>3</td>
<td>19d</td>
</tr>
<tr>
<td>5</td>
<td>C₆H₅</td>
<td>125</td>
<td>6</td>
<td>19e</td>
</tr>
<tr>
<td>6</td>
<td>3-(CH₃O)C₆H₅</td>
<td>125</td>
<td>6</td>
<td>19f</td>
</tr>
<tr>
<td>7</td>
<td>3,5-(CH₃O)C₆H₅</td>
<td>125</td>
<td>6</td>
<td>19g</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>125</td>
<td>10</td>
<td>19h</td>
</tr>
<tr>
<td>9</td>
<td>CH₃</td>
<td>125</td>
<td>10</td>
<td>19i</td>
</tr>
</tbody>
</table>

[a] Isolated yield. [b] Room temperature.

Conclusions

In conclusion, total syntheses of eudistomins Y₁–Y₆ (1–6) and the first total synthesis of eudistomin Y₇ (7) have been performed. Our total syntheses of eudistomins Y₁–Y₆ (1–6) are clearly more efficient and practical than the previously reported syntheses. The overall yield of eudistomin Y₁ (1) increased from 30% to 65%; the overall yield of eudistomin Y₂ (2) increased from 20% to 64%; the overall yield of eudistomin Y₃ (3) increased from 15% to 59%; the overall yield of eudistomin Y₄ (4) increased from 15% to 60%; the overall yield of eudistomin Y₅ (5) increased from 7% to 59%; and the overall yield of eudistomin Y₆ (6) increased from 6% to 57%. Eudistomin Y₇ (7) was synthesized in 60% overall yield in five steps from 6-bromo-tryptamine.

Experimental Section

General Methods: ¹H and ¹³C NMR spectra were acquired with a Bruker AM-400 spectrometer at 400 and 100 MHz, respectively.
Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded with a Nicolet Magna IR-550 instrument. Mass spectra were recorded with a HP5989A instrument. Melting points were determined with a Mel-TEMP II melting point apparatus. Column chromatography was performed on silica gel. All reagents and solvents were analytically pure. Tryptamine and 6-bromo-1H-indole were purchased from Aldrich.

**General Procedure for the Preparation of Compounds 10a–d:** Thiocyan chloride (7.140 g, 60.01 mmol) was added to a solution of compound 8 (20.00 mmol) in dichloromethane (20 mL). The mixture was stirred at reflux for 4 h. The solvent and excess thiocyan chloride were then removed by vacuum distillation. The residue was dissolved in dichloromethane (25 mL), and the resulting solution was slowly added into the cooled (0–10 °C) two-phase system of NaOH (2 m aq.; 25 mL) and a solution of compound 10 (20.00 mmol) in dichloromethane (50 mL). After the addition was finished, the reaction mixture was stirred for a further 1 h. The two phases were then separated, and the organic phase was dried with anhydrous MgSO₄. The solvent was removed by vacuum evaporation to give a solid crude product, which was purified by flash chromatography (eluent: EtOAc/hexane = 1:3) to afford pure compounds 10a–d in 90, 86, 88, and 90% yields, respectively.

**N-2-(1H-Indol-3-yl)thiophen-2-yl acetic acid (10a):** White crystals. m.p. 152.5–153.0 °C. NMR (400 MHz, [D₆]DMSO); δ = 10.82 (br. s, 1 H, NH in indole ring), 8.08 (br. s, 1 H, NHCO), 7.52 (d, J = 7.8 Hz, 1 H, 7-H in indole), 7.34 (d, J = 7.8 Hz, 1 H, 4-H in indole), 7.15 (d, J = 8.6 Hz, 2 H, both ortho-H in Ph), 7.11 (d, J = 2.1 Hz, 1 H, 2-H in indole), 7.07 (t, J = 7.8 Hz, 1 H, 6-H in indole), 6.97 (t, J = 7.8 Hz, 1 H, 5-H in indole), 6.84 (d, J = 8.6 Hz, 2 H, both meta-H in Ph), 3.72 (s, 3 H, OCH₃), 3.32 (s, 2 H, ArCH₂CONH), 3.36–3.27 (m, 2 H, CH₂NHCO), 2.81 (t, J = 7.3 Hz, 2 H, CH₂CH₂NHCO) ppm. 13C NMR (100 MHz, [D₆]DMSO); δ = 170.35 (CONH), 157.81 (Ar), 136.21 (Ar), 129.95 (Ar), 128.39 (Ar), 127.19 (Ar), 122.65 (Ar), 120.88 (Ar), 118.25 (Ar), 118.19 (Ar), 113.56 (Ar), 111.75 (Ar), 111.33 (Ar), 54.93 (OCH₃), 41.56 (CH₂NHCO), 40.06 (CH₂CH₂NHCO), 25.17 (CH₂CH₂NHCO) ppm. MS (EI): m/z (%) = 308 [M⁺] (7), 149 (6), 144 (10), 143 (100), 130 (26), 121 (9). HRMS (ESI): calced. for C₁₇H₁₈NO₂ [M⁺] 287.0708; found 287.0712.

**N-2-(1H-Indol-3-yl)thiophen-2-yl 2-(3-bromo-4-methoxyphenyl)acetamide (10b):** White crystals. m.p. 94.9–95.0 °C. 1H NMR (400 MHz, [D₆]DMSO); δ = 10.85 (br. s, 1 H, NH in indole ring), 8.73 (d, J = 7.8 Hz, 1 H, 7-H in indole), 7.36 (d, J = 7.8 Hz, 1 H, 4-H in indole), 7.32 (d, J = 1.8 Hz, 1 H, 2-H in indole), 7.20 (t, J = 7.8 Hz, 1 H, 6-H in indole), 7.11 (t, J = 7.8 Hz, 1 H, 5-H in indole), 7.01 (dd, J = 8.0, 1.6 Hz, 1 H, 6'-H in Ph), 6.85 (d, J = 1.6 Hz, 1 H, 2'-H in Ph), 6.74 (d, J = 8.0 Hz, 1 H, 5'-H in Ph), 5.49 (br. s, 1 H, NHCO), 3.86 (s, 3 H, OCH₃), 3.56–3.50 (m, 2 H, CH₂NHCO), 3.39 (s, 2 H, CH₂CONH), 2.91 (t, J = 6.5 Hz, 2 H, CH₂CONH) ppm. 13C NMR (100 MHz, [D₆]DMSO); δ = 154.00 (CONH), 142.25 (Ar), 136.20 (Ar), 129.95 (Ar), 128.39 (Ar), 127.19 (Ar), 122.65 (Ar), 120.88 (Ar), 118.25 (Ar), 118.19 (Ar), 113.56 (Ar), 111.75 (Ar), 111.33 (Ar), 54.93 (OCH₃), 41.56 (CH₂NHCO), 40.06 (CH₂CH₂NHCO), 25.17 (CH₂CH₂NHCO) ppm. MS (EI): m/z (%) = 308 [M⁺] 287.0708; found 287.0712.
(CH$_2$CONH), 25.15 (CH$_3$CH$_2$NHC0) ppm. IR (KBr film): v = 3356 (N-H), 3284 (N-H), 3082, 2940, 1649 (C=O), 1625, 1592, 1564, 1488, 1466, 1423, 1271, 1062, 1026, 748 cm$^{-1}$. HRMS (ESI): calcd. for C$_9$H$_{12}$Br$_2$N$_2$O$_3$ [M+H]$^+$ = 464.9813; found 464.9816.

N-[2-(6-Bromo-1H-indol-3-yl)ethyl]-2-[3,5-dibromo-4-methoxyphenyl]acetamide (10d): White crystals. m.p. 95.0–96.0 °C. 1H NMR (400 MHz, [D$_6$]DMSO): δ = 10.98 (br. s, 1 H, NH in indole ring), 8.18 (br. s, 1 H, HJCO), 7.51 (s, 1 H, 7-H in indole), 7.50 (s, 2 H, 2'-H and 6'-H in Ph), 7.47 (d, J = 8.4 Hz, 1 H, 4-H in indole), 7.17 (s, 1 H, 2-H in indole), 7.09 (d, J = 8.4 Hz, 1 H, 5-H in indole), 3.71s, 3 H, OCH$_3$, 3.34 (s, 2 H, CH$_2$CONH), 2.80 (s, t, J = 7.1 Hz, 2 H, CH$_2$CH$_2$NHC0) ppm. 13C NMR (100 MHz, [D$_6$]DMSO): δ = 169.11 ([CONH]), 151.85 (Ar), 137.04 (Ar), 133.27 (Ar), 126.24 (Ar), 123.79 (Ar), 121.05 (Ar), 120.02 (Ar), 116.93 (Ar), 113.88 (Ar), 113.69 (Ar), 112.15 (Ar), 60.33 (OCH$_3$), 40.46 (CH$_2$CONH), 39.96 ([CONH]= 24.87 (CH$_3$CH$_2$NHC0) ppm. IR (KBr film): v = 3294 (br. N–H), 3079, 2927, 2852, 1647 (C=O), 1637, 1569, 1471, 1449, 1419, 1261, 986, 802, 738 cm$^{-1}$. HRMS (ESI): calcd. for C$_9$H$_{12}$Br$_2$N$_2$O$_3$ [M+H]$^+$ = 542.8921; found 542.8921.

**General Procedure for the Preparation of Compounds 14a–d:** Compound 10 (5.00 mmol) was dissolved in EtOAc (60 mL), and freshly distilled POCI$_3$ (3.835 g, 25.01 mmol) was added. The mixture was stirred at room temperature for 24–48 h. When the reaction was complete (checked by TLC), the mixture was cooled down to room temperature in an ice-bath, then potassium carbonate (20% w/w aq.; 50 mL) was added. The mixture was vigorously stirred for 15 min, then the two phases were separated. The aqueous phase was re-extracted with EtOAc (30 mL). The organic extracts were combined, washed with brine (10 mL), and dried with anhydrous MgSO$_4$. The organic solution was concentrated to dryness under vacuum to give a tautomeric mixture of compounds 11 and 12, which was used as such in the next step.

The above tautomeric mixture of compounds 11 and 12 was dissolved in DMSO (15 mL), and DBU (1.525 g, 10.02 mmol) was added. The reaction mixture was then stirred at room temperature for 24–48 h. When the reaction was complete (checked by TLC), the reaction solution was poured into water (60 mL), then the mixture was extracted with EtOAc (3 × 60 mL). The organic extracts were combined, washed with brine (20 mL), and dried with anhydrous MgSO$_4$. Evaporation of the solvent gave a residue, which was purified by flash chromatography (elucent: CH$_3$Cl/CH$_2$Cl=O = 9:1) to give compounds 14a–d in 78, 75, 70, and 72% yields, respectively.

**General Procedure for the Preparation of Compounds 15a–e:** Compound 14 (1.000 mmol) was dissolved in a mixed solvent of acetonitrile (15 mL) and glacial acetic acid (5 mL), and NBS (0.196 g, 1.101 mmol) was added. The mixture was warmed and stirred at 45 °C for 30 min. Evaporation of the solvent under vacuum gave a solid residue, which was then partitioned between EtOAc (30 mL) and potassium carbonate (20% w/w aq.; 20 mL). The two phases were separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The organic extracts were combined, washed successively with sodium sulfate (saturated aq.; 10 mL) and brine (15 mL). After being dried with anhydrous MgSO$_4$, the organic solution was concentrated under vacuum. The solid crude residue was purified by flash chromatography (elucent: CHCl$_3$/EtOAc = 9:1) to give compounds 15a–e in 98, 98, and 99% yields, respectively.
Eudistomin Y1 (3): Pale yellow solid. m.p. 246 °C (dec.). Characterization data were identical with the reported data. \[9\]

Eudistomin Y4 (4): Pale yellow solid. m.p. 260 °C (dec.). Characterization data were identical with the reported data. \[9\]

Eudistomin Y5 (5): Pale yellow solid. m.p. 270 °C (dec.). Characterization data were identical with the reported data. \[9\]

Eudistomin Y6 (6): Pale yellow solid. m.p. 291 °C (dec.). Characterization data were identical with the reported data. \[9\]

Eudistomin Y7 (7): Pale yellow solid. m.p. 298 °C (dec.). \[1\] H NMR (400 MHz, [D\textsubscript{6}]DMSO): \(\delta = 11.98\) (br, s, 1 H, NH in indole ring), 8.55 (d, J = 5.0 Hz, 1 H, 3-H), 8.50 (s, 2 H, 12-H and 16-H), 8.40 (d, J = 5.0 Hz, 1 H, 4-H), 8.28 (d, J = 8.4 Hz, 1 H, 5-H), 7.94 (d, J = 1.5 Hz, 1 H, 8-H), 7.44 (dd, J = 8.4, J = 1.5 Hz, 1 H, 6-H) ppm. \[1\] H NMR (100 MHz, [D\textsubscript{6}]DMSO): \(\delta = 187.39\) (C=O), 159.46 (Ar), 158.43 (Ar), 142.24 (Ar), 137.74 (Ar), 137.36 (Ar), 135.66 (Ar), 135.40 (Ar), 130.09 (Ar), 125.93 (Ar), 121.55 (Ar), 119.29 (Ar), 118.31 (Ar), 115.40 (Ar), 112.42 (Ar) ppm IR (KBr film): \(\nu = 3395\) (N–H, O–H), 3057, 2962, 2923, 2853, 1724 (weak, C=O), 1652, 1618, 1585, 1462, 1422, 1388, 1282, 1262, 1235, 1205, 1095, 1048, 1022, 763, 624 cm\(^{-1}\). HRMS (ESI): calcd. for C\textsubscript{19}H\textsubscript{13}BrN\textsubscript{2}O\textsubscript{2} [M + H]\(^+\) 522.8292; found 522.8292.

Supporting Information (see footnote on the first page of this article): Procedure for preparation of compounds 8b and 8c Characterization data for compounds 8b, 8c, 16, and 19a-4; \[1\] H and \[1\] C NMR spectra for compounds 1–7, 8b, 8c, 9b, 10a-d, 14a-d, 15a-c, 16, 17, and 19a-4.

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Total Synthesis of Eudistomins $Y_1$–$Y_7$


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