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First total synthesis of eudistalbin A

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Abstract

Eudistalbin A was isolated from marine *tunicate eudistoma album* and possess cytotoxic activity ($ED_{50} < 3.2$ μg/mL) *in vitro* against the growth of KB human buccal carinoma cells. The synthetic eudistalbin A showed potent inhibitory activity against the breast carcinoma cell line MDA-231 with an IC_{50} value of 2.1 μmol/L using the metabolic assay MTT. All structures of new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS and optical rotation.

Keywords: β-Carboline; Eudistalbin A; Pictet–Spengler reaction; Henry reaction; Total synthesis

Alkaloids with a β-carboline nucleus, containing planar tricyclic system, have been reported to be biologically active by inhibiting topoisomerases [1,2], CDK (cyclin-dependent kinases) [3,4], NF-kappaB signaling [5] and DNA synthesis [6], and by intercalating into DNA [7]. Marine tunicates are a typical class of β-carboline alkaloids including eudistalbin A, eudistomidin C and eudistomin T (Fig. 1). They have been the source of secondary metabolites possessing interesting antiviral, antibacterial and other biological activities. Eudistomin T and 6-methyl eudistomidin C have been successfully synthesized [8,9].

Eudistalbin A was isolated from EtOH extract of the marine *tunicate eudistoma album* and possess cytotoxic activity *in vitro* against the growth of KB human buccal carinoma cells ($ED_{50} < 3.2$ μg/mL) [10]. We report here the total synthesis and configuration confirmation of eudistalbin A with modified methods based on literatures [9,11–13].

Structural analysis of eudistalbin A, eudistomidin C and eudistomin T reveals that they may be biosynthetically derived *in vivo* from tryptophan residue, often ring-A functionalized, condensed with a second amino acid such as a leucine, cysteine and phenylalanine. Subsequent metabolic processes, including oxidation, dehydrogenation and decarboxylation, may then be envisioned to give rise to the corresponding three marine alkaloids structures as described in Scheme 1 [14].

According to the biomimetic synthesis, we choose BOC-L-leucine **1** as one of starting materials in the synthesis of eudistalbin A. The total synthetic route was shown in Scheme 2.

Firstly, Boc-L-leucine **1** was converted to the intermediate **2** using *N*,*O*-dimethylhydroxylamine and carbonyldiimidazole (CDI) in the presence of *N*,*N*-diisopropylethylamine (DIEA) in anhydrous THF and DMF with the yield of 89%. Compound **2** was reduced by $LiAlH_4$ to compound **3** in 86% yield [15].

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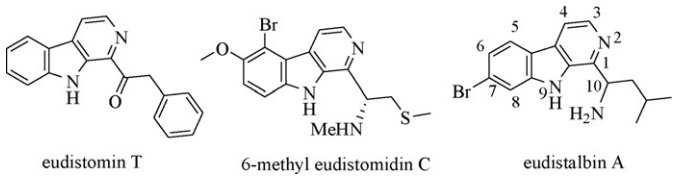
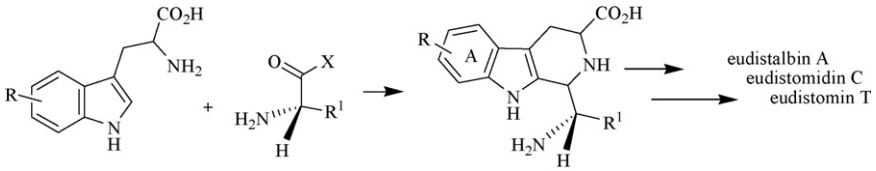


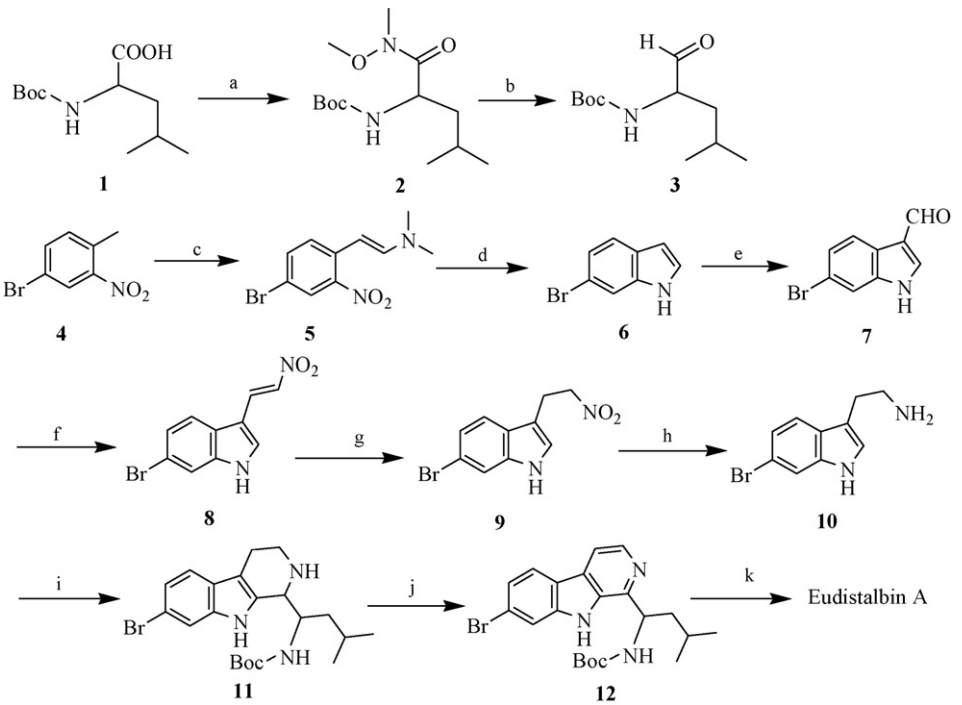
Fig. 1. The structure of compounds.



Scheme 1. The route of biomimetic synthesis of eudistalbin A, eudistomidin C and eudistomin T.

Secondly, 4-bromo-2-nitrotoluene **4** was treated with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) and pyrrolidine at 110 °C to give the crude intermediate **5**, which was subjected to reductive cyclization with zinc in acetic acid and afforded 6-bromoindole **6** in 55% yield. 6-Bromoindole-3-carboxaldehyde **7** was obtained from **6** by Vilsmeier–Hacck reaction in the presence of phosphorus oxychloride ($POCl_3$) in DMF with yield of 98%. Compound **7** was condensed with nitromethane (CH_3NO_2) based on the classical Henry reaction to form compound **8** in 92% yield. Reduction of compound **8** by $NaBH_4$ at room temperature gave compound **9** in 98% yield. Subsequently, compound **9** was refluxed in THF with $LiAlH_4$ to give 6-bromotryptamine **10** with 95% yield.

Pictet–Spengler condensation was performed by the addition of two mole equivalents of trifluoroacetic acid (TFA) to a cooled equimolar solution of compound **3** and 6-bromotryptamine **10** in CH_2Cl_2 at −78 °C, followed by neutralization with triethylamine, to give 1,2,3,4-tetrahydro-β-carboline **11** in 76% yield.



Scheme 2. Reagents and conditions: (a) *N*,*O*-dimethylhydroxylamine hydrochloride, CDI/DIEA/THF/DMF, rt., 89%; (b) $LiAlH_4/Et_2O$, 0–5 °C, 86%; (c) DMF-DMA/pyrrolidine/DMF, rt.; (d) Zn, HOAc, 55%(from **4**); (e) $POCl_3$/DMF/NaOH, 98%; (f) CH_3NO_2/CH_3COONH_4/ benzene, reflux, 92%; (g) $NaBH_4$/THF/CH_3OH, rt., 98%; (h) $LiAlH_4$/THF, reflux, 95%; (i) **3**, TFA/CH_2Cl_2, −78 °C, 76%; (j) DDQ/THF, 40 °C, 90%; (k) TFA/CH_2Cl_2, rt., 98%.

The key step was the dehydrogenation of compound **11**. As discussed earlier in other syntheses of β-carboline alkaloids, several methods may be used, such as the use of Pd/C [11], elemental sulfur [12], $Pb(OAc)_4$ [13] and DDQ [9]. As a result, refluxing of compound **11** with Pd/C in xylene, elemental sulfur in xylene or with $Pb(OAc)_4$ in glacial acetic acid did not lead to any dehydrogenation. When using elemental sulfur or Pd/C without solvent at high temperature of 200 °C for a few minutes gave low yields of dehydrogenation products of compound **11**. ^{1}H NMR analysis showed that loss of the Boc group occurred. Ultimately, the best method proved to be the dehydrogenation with DDQ [9]. Compound **11** was transformed into the intermediate **12** through DDQ oxidation in THF at 40 °C with the yield of 90%. In succession, removal of BOC group from **12** using TFA as catalyst afforded the target eudistalbin A in 98% yield. The structures of new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS or optical rotation [16].

The optical rotation of synthetic eudistalbin A (found: $[\alpha]_D^{20}$ −10.5 (*c* 0.1, MeOH); $[\alpha]_D^{20}$ −16.0 (*c* 0.5, DMSO)) was identical with those of natural eudistalbin A ($[\alpha]_D^{20}$ −10.0 (*c* 0.1, MeOH)) [10]. The synthetic eudistalbin A showed potent inhibitory activity against the breast carcinoma cell line MDA-231 with an IC_{50} value of 2.1 μmol/L using the metabolic assay MTT.

In conclusion, an efficient synthetic method for eudistalbin A was developed. It is highly expected that this methodology not only can be used in the synthesis of other β-carbolines possessing an amino acid side chain, but also be useful in the synthesis of other complex natural products. Further application of this strategy is underway in our laboratory.

Acknowledgment

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[16] Spectral data. Compound **11** $[\alpha]_D^{20}$ −8.1 (*c* 0.2, MeOH); HRMS: *m/z* calcd. for $C_{21}H_{31}N_3O_2Br^+$, 436.1600; found: 436.1592; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.75 (brs, 1H), 7.41 (s, 1H), 7.28 (d, 1H, *J* = 7.8 Hz), 7.13 (d, 1H, *J* = 7.8 Hz), 4.94 (m, 1H), 4.26 (m, 1H), 4.13 (s, 1H), 3.39 (m, 1H), 3.00 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 1.71 (m, 1H), 1.56 (m, 1H), 1.48 (s, 1H), 1.34 (m, 1H), 1.17 (s, 9H), 0.99 (d, 3H, *J* = 6.4 Hz), 0.96 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 137.3, 134.6, 126.6, 122.4, 119.1, 114.8, 114.2, 110.5, 79.9, 57.8, 49.5, 44.1, 41.3, 28.3, 25.3, 23.4, 22.3, 22.0. Compound **12** $[\alpha]_D^{20}$ −9.0 (*c* 0.2, MeOH); HRMS: *m/z* calcd. for $C_{21}H_{27}N_3O_2Br^+$, 432.1287; found: 432.1283; ^{1}H NMR (600 MHz, $CDCl_3$): δ 10.28 (brs, 1H), 8.36 (d, 1H, *J* = 5.0 Hz), 7.79 (d, 1H, *J* = 8.7 Hz), 7.71 (d, 1H, *J* = 5.0 Hz), 7.33 (m, 1H), 7.27 (d, 1H, *J* = 8.7 Hz), 5.40 (m, 1H), 2.05 (m, 1H), 1.98 (m, 1H), 1.79 (m, 1H), 1.44 (s, 9H), 0.99 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.3, 145.4, 141.3, 138.3, 134.3, 128.7, 123.1, 122.6, 122.1, 120.6, 114.8, 113.9, 80.7, 49.9, 41.7, 28.6, 25.2, 23.4, 22.2. Eudistalbin A: $[\alpha]_D^{20}$ −10.5 (*c* 0.1, MeOH); $[\alpha]_D^{20}$ −16.0 (*c* 0.5, DMSO); HRMS: *m/z* calcd. for $C_{16}H_{19}N_3Br^+$, 332.0762; found: 332.0773; ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.31 (d, 1H, *J* = 5.0 Hz), 8.17 (d, 1H, *J* = 8.2 Hz), 8.01 (d, 1H, *J* = 5.0 Hz), 7.85 (s, 1H), 7.36 (d, 1H, *J* = 8.2 Hz), 4.63 (t, 1H, *J* = 6.9 Hz), 1.79 (m, 1H), 1.74 (m, 1H), 1.52 (m, 1H), 0.88 (d, 3H, *J* = 6.9 Hz), 0.83 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 148.2, 141.9, 138.4, 133.9, 128.2, 123.9, 122.7, 121.3, 120.5, 115.3, 114.1, 52.3, 45.6, 24.9, 23.4, 22.6.