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Asymmetric total synthesis of reported structure of eudistomidin B, an indole alkaloid isolated from a marine tunicate

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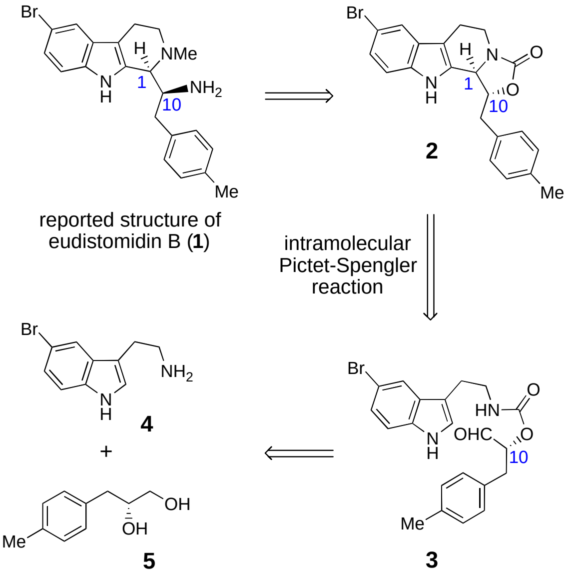
ABSTRACT

Eudistomidin B, isolated from a marine tunicate, was originally assigned a tetrahydro-β-carboline structure with a 2-*p*-tolylethanamine residue. Asymmetric total synthesis of the reported structure of natural product, which features an intramolecular diastereoselective Pictet-Spengler cyclization, suggests that the reported structure of the natural product needs to be revised.

In connection with our chemical and pharmacological studies on the β-carboline class of indole alkaloids,[1] we are interested in the marine indole alkaloid eudistomidin B (**1**),[2] which was isolated from the Okinawan tunicate *Eudistoma glaucus* and has unique biological activities, including potent cytotoxicity to murine leukemia L1210 and L5178Y cells and the ability to activate rabbit heart muscle actomyosin ATPase. This natural product has a novel structure composed of a brominated tetrahydro-β-carboline and a unique 2-*p*-tolylethanamine residue, which are joined together at the C-1 position of the former skeleton and the α position of the tolylethanamine residue, generating consecutive chiral centers at C-1 and C-10 positions. The intriguing chemical structures and interesting biological activities prompted us to embark on the asymmetric total synthesis of eudistomidin B (**1**).

Our retrosynthesis, which is shown in Scheme 1, was based on the intramolecular Pictet-Spengler cyclization strategy that was successfully used in our synthesis of subincanadines.[3] Stereoselective construction of the tetrahydro-β-carboline skeleton in **2** was expected to be accomplished by the intramolecular Pictet-Spengler reaction using aldehyde **3** that tethered 5-bromotryptamine (**4**) and optically active aldehyde prepared from diol **5**. Transformation of the secondary hydroxyl group at C-10 in **2** into the amino function, accompanied by inversion of the stereochemistry, would furnish target molecule **1**.



Scheme 1. Retrosynthetic analysis.

The synthesis began with the preparation of optically active diol **5** (Scheme 2) from *p*-tolualdehyde via a seven-step operation that included the proline-catalyzed asymmetric aminoxylation[4] of aldehyde **6**. Reductive cleavage of the N–O bond in **7** using PtO_2 under H_2 atmosphere gave diol **5** (mp 65–67 °C, $[\alpha]_D^{23}$ +17.4 (*c* 1.0, $CHCl_3$)) in 82% yield, which showed 99% ee as determined by chiral HPLC column chromatography. After selective protection of the

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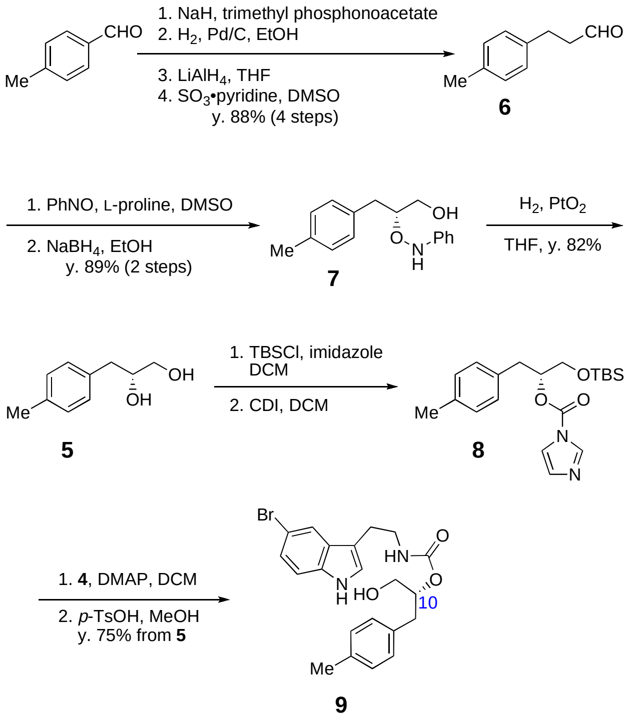


Scheme 2.

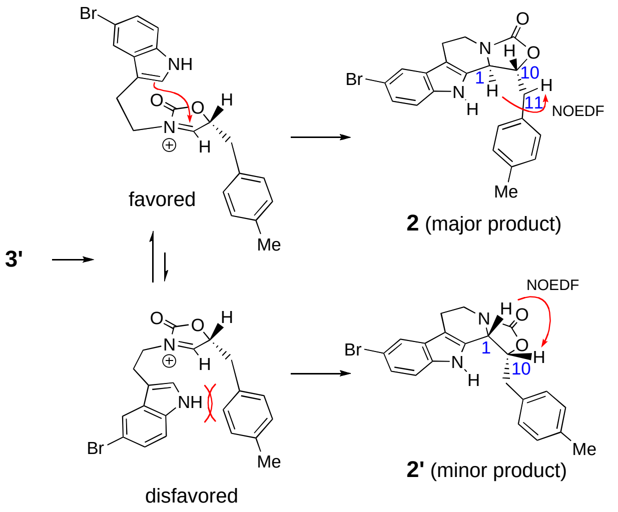
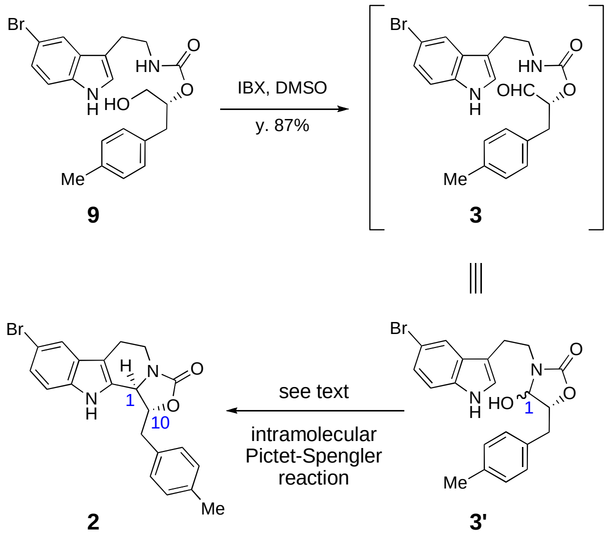


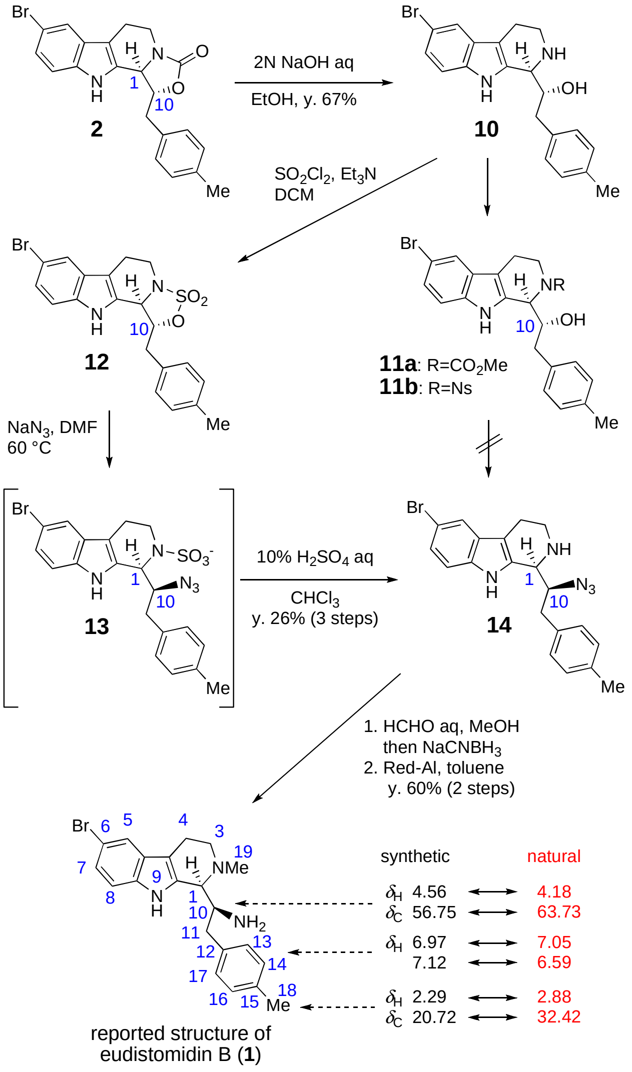
Figure 1.

primary alcohol in diol **5** with a TBS group, the remaining hydroxyl group was condensed with 1,1′-carbonyldiimidazole (CDI) to give carbamate **8**, which was then treated with 5-bromotryptamine (**4**)[5] in DCM in the presence of DMAP, followed by PTS in MeOH, to afford carbamate **9** in 75% overall yield from **5**.

Next, the primary alcohol in **9** was oxidized with IBX to give aldehyde **3** in 87% yield (Scheme 3). Compound 3 was found to exist in hemiaminal form **3′** in solution, as demonstrated by the chemical shift appearing at δ 82 (C-1) in the ^{13}C NMR spectrum. Treatment of **3** with TFA in DCM at 0 °C gave the cyclization products in 98% yield with a diastereomeric ratio of 4:1, which could be separated by column chromatography. The stereochemistries of major product **2**[6] as well as minor product **2′** were determined by *NOE* experiments (Fig. 1): irradiation of the proton at C-1 caused a significant signal enhancement of the proton on the methylene group (C-11) of the side chain in **2** and of the proton at C-10 in minor product **2′**, respectively, demonstrating the trans relationship of the two protons at C-1 and C-10 in the major product **2**. Diastereoselectivity of the intramolecular Pictet-Spengler reaction of **3**



Scheme 3.



Scheme 4.

Table 1
^{1}H and ^{13}C NMR data for synthetic and natural[2] eudistomidin B in $CDCl_3 + CF_3CO_2D$ (10:1)

Position	δ_H (500 MHz)		δ_C (125 MHz)	
	Synthetic	Natural	Synthetic	Natural
1	5.28 (s)	5.19 (d, 8.9)	62.77	63.59
3	3.88 (m)	3.28 (dd, 12.2, 5.3)	50.36	45.80
	3.77 (br dd, 14.0, 4.0)	2.86 (m)		
4	3.21 (2H, overlapped)	2.82 (m)	15.29	15.00
		2.38 (dd, 15.6, 4.2)		
4a			107.27	105.53
4b			126.74	122.40
5	7.71 (d, 1.7)	7.52 (d, 1.6)	121.40	121.05
6			114.51	113.61
7	7.46 (dd, 8.7, 1.7)	7.39 (dd, 8.7, 1.6)	127.96	126.91
8	7.34 (d, 8.7)	7.42 (d, 8.7)	113.67	113.87
8a			136.05	135.49
9		11.08 (s)		
9a			121.24	137.57
10	4.56 (br d, 9.8)	4.18 (m)	56.75	63.73
11	3.21 (overlapped)	3.23 (dd, 14.7, 3.1)	34.32	33.27
	3.09 (m)	3.03 (dd, 14.7, 9.7)		
12			128.69	134.10
13, 17	6.97 (2H, d, 7.9)	7.05 (2H, d, 7.5)	128.58	128.87
14, 16	7.12 (2H, d, 7.9)	6.59 (2H, d, 7.5)	130.49	128.52
15			139.47	134.10
18	2.29 (3H, s)	2.88 (3H, s)	20.72	32.42
19	3.15 (3H, s)	2.92 (3H, s)	42.54	39.75

could be improved to 16:1 by using TMSCl as acid. The high diastereoselectivity of the cyclization could be due to the plausible acyliminium intermediate, in which the indole nucleus would attack from the less hindered side (anti from the side chain), as depicted in Figure 1.

To accomplish the total synthesis, we next investigated the introduction of an amino function to the C-10 position, which is accompanied by the inversion of stereochemistry. The carbonyl group in **2** was removed by alkaline hydrolysis and the resulting secondary amine in **10** was protected as carbamate or sulfonamide (Scheme 4). All attempts to conduct the nucleophilic substitution of the free alcohol in **11a** or **11b** under Mitsunobu conditions or of the C-10-*O*-mesyl derivatives prepared from **11a** or **11b** with sodium azide gave unsuccessful results. Then, we modified the cyclic sulfamate strategy developed by White and Garst[7] and applied it to the synthesis. Treatment of amino alcohol **10** with 1.2 equiv of sulfuryl chloride in DCM at −78 °C in the presence of Et_3N for 2 h gave unstable cyclic sulfamate **12**. To this mixture was added 10 equiv of sodium azide in DMF. The reaction mixture was heated at 60 °C to facilitate nucleophilic ring opening with the azide group at C-10. After cooling to room temperature, the reaction mixture was treated with 10% aqueous sulfuric acid to hydrolyze resulting sulfamidic acid intermediate **13** to give azidoamine derivative **14** in 26% overall yield. By careful treatment and column chromatography, unstable cyclic sulfamate **12**[8] could be isolated in low yield (9–15%) and then transformed to **14** with the same procedure as above-mentioned in 64% yield. Finally, reductive methylation of the secondary amine in **14** and successive reduction of the azide function with Red-Al furnished the target molecule in 60% yield (2 steps).

The structure of synthetic compound 1[9] ($[\alpha]_D^{25}$ free base: +42.0 (*c* 0.57, $CHCl_3$), TFA salt: +63.4 (*c* 0.78, $CHCl_3$)) was confirmed by detailed spectroscopic analyses, including 2D-NMR (COSY, HMQC, and HMBC) spectroscopy. However, significant differences were noted between our NMR data (see Table 1) and those reported for the natural product ($[\alpha]_D^{22}$ −76.4 (*c* 0.3, $CHCl_3$)). In particular, the chemical shifts at H-10, 13, 14, and 18 in the ^{1}H NMR spectra and at C-10 and 18 in the ^{13}C NMR spectra showed marked differences, as depicted in Scheme 4. Hence, we concluded that natural eudistomidin B does not have structure 1, and inconsistencies in the data reported for the natural product hindered us from proposing a credible alternative structure.

Acknowledgment

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5. 5-Bromotryptamine was prepared from 5-bromoindole via a three-step operation: (i) $POCl_3$, DMF, 40 °C, y. 94%; (ii) NH_4OAc, $MeNO_2$, reflux, y. 74%; (iii) $NaBH_4$, BF_3–Et_2O, THF, reflux, y. 77%.
6. Compound **2**: mp 219–221 °C (from EtOAc); $[\alpha]_D^{25}$ +1.7 (*c* 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 1.9 Hz, H-5), 7.38 (2H, d, *J* = 8.0 Hz, H-14, H-16), 7.31 (2H, d, *J* = 8.0 Hz, H-13, H-17), 7.17 (1H, dd, *J* = 8.8, 1.9 Hz, H-7), 6.70 (1H, d, *J* = 8.8 Hz, H-8), 5.52 (1H, br s, N_9-H), 4.80 (1H, d, *J* = 8.1, 1.8, 1.8 Hz, H-1), 4.46 (1H, ddd, *J* = 11.0, 8.1, 4.5 Hz, H-10), 4.26 (1H, dd, *J* = 13.5, 5.2 Hz, H-3), 3.61 (1H, dd, *J* = 13.0, 4.5 Hz, H-11), 3.09 (1H, ddd, *J* = 13.5, 11.5, 5.0 Hz, H-3), 2.98 (1H, dd, *J* = 13.0, 11.0 Hz, H-11), 2.78 (1H, dddd, *J* = 15.4, 11.5, 6.1, 2.2 Hz, H-4), 2.69 (1H, br dd, *J* = 15.4, 5.0 Hz, H-4), 2.53 (3H, s, H_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (C-19), 138.1 (C-15), 134.5 (C-8a), 131.6 (C-12), 130.5 (C-9a), 130.3 (C-14, C-16), 130.1 (C-13, C-17), 128.0 (C-4b), 125.2 (C-7), 121.2 (C-5), 112.9 (C-6), 112.1 (C-8), 108.5 (C-4a), 80.8 (C-10), 56.6 (C-1), 40.0 (C-11), 38.7 (C-3), 21.1 (C-18), 20.7 (C-4); UV (MeOH) λ_{max} nm 300 (sh), 291, 229; IR (ATR) ν_{max} cm^{-1} 3230, 2363, 1715, 1417, 1233, 789; EIMS *m*/*z* (%) 412 (100, M^++2), 410 (99, M^+), 306 (98), 304 (92); HREIMS *m*/*z* 410.0629 (M^+, calcd for $C_{21}H_{19}N_2O_2{}^{79}Br$, 410.0629).
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8. Compound **12**: $[\alpha]_D^{25}$ +35.2 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 1.8 Hz, H-5), 7.39 (2H, d, *J* = 8.0 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 7.18 (1H, dd, *J* = 8.6, 1.8 Hz, H-7), 6.63 (1H, d, *J* = 8.6 Hz, H-8), 5.45 (1H, br s, N_9-H), 4.91 (1H, d, *J* = 7.8 Hz, H-1), 4.74 (1H, ddd, *J* = 10.9, 7.8, 4.6 Hz), 3.64 (2H, overlapped), 3.48 (1H, ddd, *J* = 12.8, 7.9, 4.7 Hz), 3.16 (1H, dd, *J* = 13.1, 10.9 Hz), 2.97 (1H, m), 2.74 (1H, m), 2.55 (3H, s, H_3-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.7, 134.3, 133.9, 129.41, 129.36, 128.7, 124.6, 120.8, 112.5, 112.3, 110.0, 67.2, 54.3, 41.6, 37.1, 22.5, 21.1 (C-18); UV (MeOH) λ_{max} nm 299 (sh), 291 (sh), 282, 229; IR (ATR) ν_{max} cm^{-1} 3384, 2920, 2850, 1715, 1518, 1441, 1317, 1312, 1176; EIMS *m*/*z* (%) 448 (32, M^++2), 446 (30, M^+), 368 (9), 366 (10), 250 (96), 248 (100); HREIMS *m*/*z* 446.0300 (M^+, calcd for $C_{20}H_{19}N_2O_3S^{79}Br$, 446.0299).
9. Synthetic **1**: as free base $[\alpha]_D^{25}$ +42.0 (*c* 0.57, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.42 (1H, br s, N_9-H), 7.62 (1H, d, *J* = 1.7 Hz, H-5), 7.19 (1H, dd, *J* = 8.5, 1.7 Hz, H-7), 7.18 (1H, d, *J* = 8.5 Hz, H-8), 7.13 (2H, d, *J* = 8.1 Hz, H-14, H-16), 7.12 (2H, d, *J* = 8.1 Hz, H-13, H-17), 3.41 (1H, dd, *J* = 13.7, 2.7 Hz, H-11), 3.38 (1H, br d, *J* = 8.9 Hz, H-1), 3.22 (1H, ddd, *J* = 13.7, 8.5, 5.1 Hz, H-3), 3.10 (2H, overlapped, H-3, H-10), 2.83 (1H, m, H-4), 2.60 (1H, br d, *J* = 15.3 Hz, H-4), 2.49 (1H, dd, *J* = 13.7, 9.5 Hz, H-11), 2.47 (3H, s, H_3-19), 2.34 (3H, s, H_3-18); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.93, 135.80, 135.27, 134.20, 129.37, 129.31, 128.92, 123.87 (C-7), 120.63 (C-5), 112.31 (C-8), 112.16, 107.44, 63.46 (C-1), 55.98 (C-10), 47.88 (br, C-3), 41.51 (C-11), 39.81 (br, C-19), 21.01 (C-18), 16.36 (C-4); UV (MeOH) λ_{max} nm 300 (sh), 291, 230; IR (ATR) ν_{max} cm^{-1} 2920, 2844, 1576, 1440, 1305, 1020; EIMS *m*/*z* (%) 399 (1, M^++2), 397 (1, M^+), 265 (97), 263 (100); HREIMS *m*/*z* 397.1153 (M^+, calcd for $C_{21}H_{24}N_3{}^{79}Br$, 397.1153). As TFA salt $[\alpha]_D^{25}$ +63.4 (*c* 0.78, $CHCl_3$); ^{1}H and ^{13}C NMR data, see Table 1; UV (MeOH) λ_{max} nm 301 (sh), 292, 229; IR (ATR) ν_{max} cm^{-1} 2925, 2855, 1668, 1444, 1139, 797.