The Enantioselective Total Synthesis of a β-Carboline Alkaloid, (*S*)-(−)-Dichotomine C

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The first enantioselective synthesis of a β-carboline alkaloid, dichotomine C, possessing antiallergic effects, was achieved by constructing a β-carboline framework based on the microwave-assisted thermal electrocyclic reaction of a 1-azahexatriene system, followed by the Sharpless asymmetric dihydroxylation.

Key words (*S*)-(−)-dichotomine C; first synthesis; enantioselective synthesis; aza-electrocyclic reaction; microwave

Six new β-carboline alkaloids, dichotomines A, B, C and D, and dichotomides I and II, possessing antiallergic effects, were isolated from *Stellaria dichotoma* by Yoshikawa and coworkers in 2004 (Fig. 1).[1] The structures of the new compounds were determined by spectroscopic and chemical analyses. The absolute configuration of the C14-position in dichotomines A—D were determined to be the *S*-form using the modified Mosher's method. Furthermore, examination of the antiallergic effects of the isolated compounds on the release of the β-hexosaminidase in RBL-2H3 cells indicated that dichotomine C had inhibitory activity.

In the course of our studies, we developed a synthesis of biologically active condensed heterocyclic compounds, including natural products, based on a thermal electrocyclic reaction[2—4] of either hexatriene[5—7] or azahexatriene[5,6,8] systems incorporating a principal aromatic or heteroaromatic moiety. Here, we describe the first total synthesis of dichotomine C (**1**) by applying pyrido-annelation and the Sharpless asymmetric dihydroxylation. In a retro-synthetic analysis (Chart 1), we speculated that dichotomine C (**1**) could be derived from 1-chloro-β-carboline **3** through asymmetric dihydroxylation of 1-ethenyl-β-carboline **2**. We also speculated that alkyl β-carboline-3-carboxylate **4** could be obtained by a thermal electrocyclic reaction of 3-alkenylindole-2-carbaldehyde oxime **5** as an application of the synthesis of the β-carboline framework using the 1-azahexatriene system.

The required β-carboline **4** was prepared in three steps starting from *N*-methoxymethyl(MOM)-3-iodoindole-2-carbaldehyde[9] (**6**) (Chart 2). The Heck reaction[10] between the aldehyde **6** and methyl acrylate in the presence of $Pd(OAc)_2$ in dimethylformamide gave the 3-alkenylindole-2-carbaldehyde **7** (85%). Subsequent treatment of the alkenylindole **7** with hydroxylamine produced the oxime **5** (75%) as the 1-azahexatriene system, which was subjected to a microwave-assisted thermal electrocyclic reaction in 1,2-dichlorobenzene to yield methyl β-carboline-3-carboxylate **4** (94%).

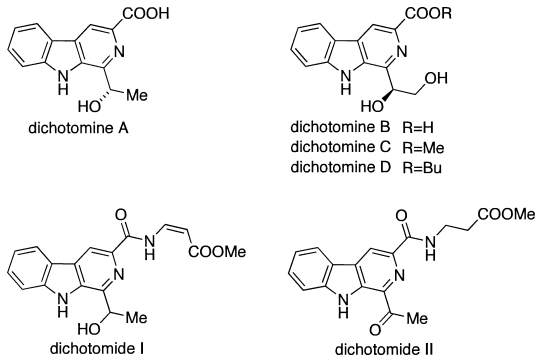

Fig. 1

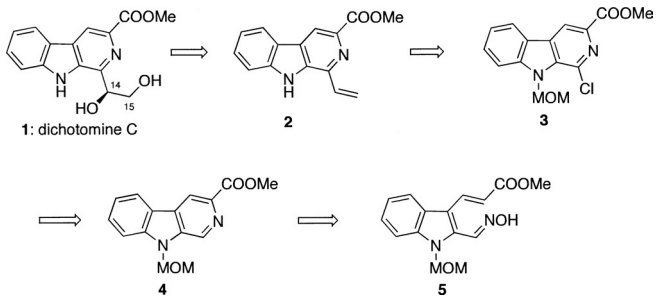

Chart 1

Table 1. Physical and Spectroscopic Data of Dichotomine C (**1**)[15]

	Natural product (**1**)[a]	Synthetic dichotomine C[b] (+)-**1** from AD-mix-α	Synthetic dichotomine C[b] (−)-**1** from AD-mix-β
^{1}H-NMR (pyridine-d_5)	3.97 (3H, s)	3.96 (3H, s)	3.96 (3H, s)
	4.61 (2H, m)	4.55—4.72 (2H, m)	4.54—4.71 (2H, m)
	5.94 (1H, m)	5.90—5.96 (1H, m)	5.91—5.94 (1H, m)
	7.39 (1H, m)	7.36—7.43 (1H, m)	7.37—7.42 (1H, m)
	7.60 (1H, m)	7.56—7.63 (1H, m)	7.56—7.63 (1H, m)
	7.75 (1H, d, J=7.3 Hz)	7.74 (1H, d, J=7.3 Hz)	7.72 (1H, d, J=7.3 Hz)
	8.34 (1H, d, J=7.3 Hz)	8.35 (1H, d, J=7.3 Hz)	8.35 (1H, d, J=7.3 Hz)
	9.09 (1H, s)	9.10 (1H, s)	9.12 (1H, s)
	12.60 (1H, br s)	12.64 (1H, br s)	12.62 (1H, br s)
MS m/z	286	286	286
mp °C	—	200—202	196—198
IR (cm^{-1})	3300, 1723	3267, 1720	3345, 1716
$[\alpha]_D^{27}$	−16.6° (c=0.50, MeOH)	+11.9° (c=0.50, MeOH)	−17.9° (c=0.02, MeOH)

a) 500 MHz, *b*) 300 MHz.

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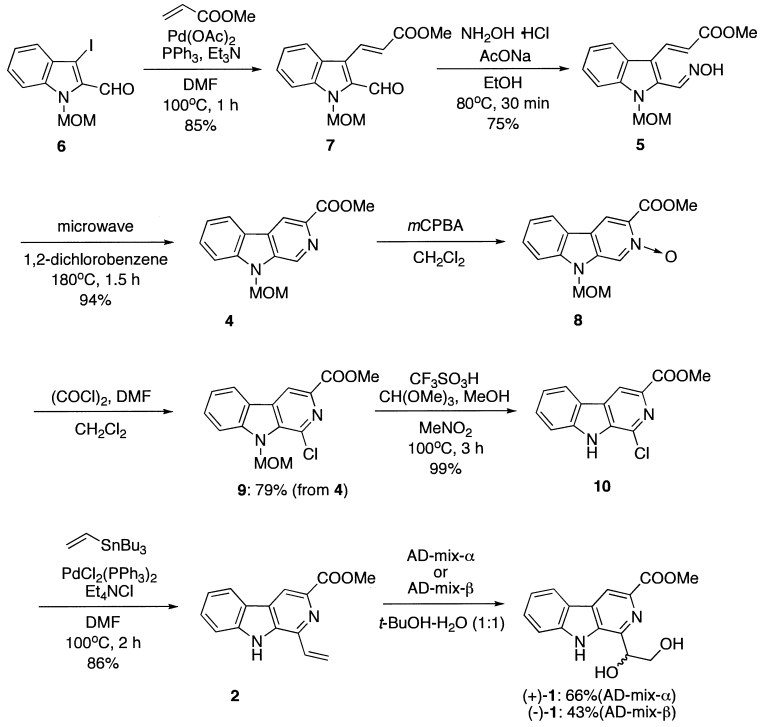

Chart 2

The key compound **2** was synthesized from the *N*-MOM-β-carboline **4** in four steps. Namely, treatment of **4** with *m*-chloroperbenzoic acid (*m*CPBA) followed by chlorination with oxalyl chloride[11] in CH_2Cl_2 yielded the *N*-MOM-1-chloro-β-carboline **9** (79% from **4**). Cleavage of the MOM group of **9** with trifluoromethanesulfonic acid in the presence of methanol and trimethyl orthformate in nitromethane[12] afforded the 1-chloro-β-carboline **10** (99%). The key compound **2** was synthesized in 86% yield from **10** and vinyl tributyltin in the presence of $PdCl_2(PPh_3)_2$ in dimethylformamide by the Stille reaction. Finally, asymmetric dihydroxylation of the 1-ethenyl-β-carboline **2** with AD-mix-α and -β was examined. Contrary to the Sharpless rule,[13] (−)-dichotomine C (−)-(**1**) (43%, $[\alpha]_D^{27}$ −17.9°, c=0.02 in MeOH, 99.8%ee[14]) and its enantiomer (+)-(**1**) (66%, $[\alpha]_D^{27}$ +11.9°, c=0.5 in MeOH, 80%ee[14]) were obtained by AD-mix-β and AD-mix-α, respectively. The physical and spectroscopic data of synthetic dichotomine C (**1**) were identical to those of natural dichotomine C (**1**), as shown in Table 1.

In conclusion, an enantioselective total synthesis of the 1,3-disubstituted β-carboline alkaloid (*S*)-(−)-dichotomine C (**1**) and its enantiomer (+)-(**1**) was achieved in an eight-step sequence (17% overall yield from **6** to (−)-**1**) by a microwave-assisted thermal electrocyclic reaction of the 1-azahexatriene system involving the indole 2,3-bond, followed by the Sharpless dihydroxylation. Further studies in this series are in progress.

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14) The enantiomeric excess of the synthetic (*S*)-(−)-dichotomine C (**1**) and its enantiomer (+)-(**1**) were determined by the ^{1}H-NMR ratio of their (*R*)-MαNP esters, which was synthesized by esterification of the C15-primary hydroxy group in dichotomine C (**1**) with pivaloyl chloride, followed by treatment of the C14-secondary hydroxy group with (*R*)-2-methoxy-2-(1-naphthyl)propionic acid (MαNP acid) in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine.
15) Although DMSO-d_6 as the measurement solvent for the ^{1}H-NMR spectrum of natural (−)-dichotomine C (**1**) was described in ref. 1, the ^{1}H-NMR spectrum data of synthetic (−)-**1** by DMSO-d_6 were not identical with those of natural (−)-**1**: ^{1}H-NMR (300 MHz, DMSO-d_6) δ: 3.77—3.87 (2H, m), 3.89 (3H, s), 4.83 (1H, t, J=5.9 Hz), 5.04—5.12 (1H, m), 5.91 (1H, d, J=4.4 Hz), 7.27 (1H, t, J=7.3 Hz), 7.56 (1H, t, J=7.3 Hz), 7.72—7.76 (1H, m), 8.35 (1H, d, J=7.3 Hz), 8.82 (1H, s), 11.61 (1H, s). The ^{1}H-NMR spectrum of synthetic (−)-**1** was measured again in pyridine d_6 by the corrected information from Professor M. Yoshikawa.