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The First Total Synthesis of (-)-Benzomalvin A and Benzomalvin B via the Intramolecular Aza-Wittig Reactions

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Abstract : The first total synthesis of (-)-benzomalvin A, which possesses 4(3H)-quinazolinone and 1,4-benzodiazepin-5-one moieties, was described. Both of 6- and 7-membered ring skeletons were efficiently constructed by the intramolecular aza-Wittig reactions as the key reactions. The enantiomeric excess of synthetic (-)-benzomalvin A was more than 99.7 % based on HPLC analysis using specially modified cellulose as a stationary phase. Furthermore, investigation on a specific conformational dynamic behavior of (-)-benzomalvin A was carried out by NMR studies and X-ray crystallographic analysis, and benzomalvin B was readily synthesized from (-)-benzomalvin A by only two steps. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Over the last decade, the aza-Wittig methodology has received considerable attention because of its utility in synthesis of C=N double bond containing compounds in particular, nitrogen heterocycles.¹ We and other workers have demonstrated recently that the intramolecular aza-Wittig reaction is a powerful tool for synthesis of $5 \sim 8$ -membered heterocycles^{1a,2,3} including natural products such as DC-81,⁴ *l*-vasicinone,⁵ and (+)-fumiquinazoline G⁶ *etc*. On the other hand, the intermolecular aza-Wittig reaction followed by electrocyclization, intramolecular cycloaddition or heterocycles by Molina,⁷ Wamhoff,⁸ Quintela,⁹ Saito¹⁰ and Noguchi¹¹ *et al*. We wish to report here on the successful synthesis of (–)-benzomalvin A and benzomalvin B *via* the intramolecular aza-Wittig methodology. This paper describes detailed data and the application of the preliminary communication.¹²

RESULTS AND DISCUSSIONS

In the course of screening microbial broths for neurokinin receptor antagonists, (-)-benzomalvin A, benzomalvin B and (-)-benzomalvin C containing both 4(3H)-quinazolinone and 1,4-benzodiazepin-5-one skeletons have been recently isolated from the culture broth of a fungus identified as a *Penicillium* sp (Chart 1). (-)-Benzomalvin A showed inhibitory activity against substance P at the guinea pig, rat and human neurokinin NK1

Chart 1 Benzomalvin A, B and C.



receptors, respectively. Pharmacological activity of (–)-benzomalvin A was stronger than those of benzomalvin B and (–)-benzomalvin C, respectively.¹³ We planed the synthesis of (–)-benzomalvin A and benzomalvin B as explained in Scheme 1. Benzomalvin B may be derived from (–)-benzomalvin A synthesized from 1,4-benzodiazepine derivative having azide function 1 via the intramolecular aza-Wittig reaction. This compound consists of 2-azidobenzoyl chloride and (3S)-1,4-benzodiazepine-2,5(1H)-dione derivative 2 obtainable from L-phenylalanine derivatives 3 via the intramolecular aza-Wittig reaction and hydrolysis. Taking retrosynthetic analysis of (–)-benzomalvin A and benzomalvin B into consideration, these molecules can be regarded as composed of two molecular anthranilic acid and one L-phenylalanine or its equivalent moieties.

We prepared, at first, L-phenylalanine derivatives as follows (Scheme 2). N-Boc-L-phenylalanine **3a** as a starting material was converted into N-Boc-N-methyl-L-phenylalanine methyl ester **4** ($[\alpha]_D^{22} = -58.2^\circ$ (c 2.0

Scheme 1 Retrosynthesis of (-)-benzomalvin A and B.



CHCl₃)) by exhaustive methylation by MeI (16 equiv.) and NaH (2.1 equiv.) in THF:DMF (10:1) at reflux for 24 h.¹⁴ Furthermore, *N*-monomethylation was investigated as follows. L-Phenylalanine methyl ester hydrochloride **3b** as a starting material was subjected to formylation with excess acetic formic acid anhydride (acetic anhydride and formic acid, $-18 \,^{\circ}$ C, 30 min)¹⁵ to lead *N*-formyl-L-phenylalanine derivative **5** after dehydrochloridation by use of triethylamine. Subsequently, conversion of **5** into the corresponding *N*-methyl-L-phenylalanine methyl ester **6** was conveniently achieved by selective reduction with borane-dimethylsulfide complex (BH₃•SMe₂). Thus the formamide derivative **5** was dissolved in THF and reduced with 1.5 equiv. of BH₃•SMe₂ at room temperature for 1 h and then reflux for 2 h. The desired product was obtained in moderate yield (51 % yield, $[\alpha]_D^{24} = +23.1^{\circ}$ (c 2.0 CHCl₃)) but completely free from dimethylated product. Moreover, as an alternative method, L-phenylalanine methyl ester hydrochloride **3b** was converted into [4+2] cycloadduct, 2-azanorbornene derivative **7**. Iminium ion generated *in situ* from **3b** and aqueous formaldehyde (1.1 equiv.) in water underwent a facile cyclocondensation with cyclopentadiene at room temperature for 10 h. Subsequent, retro Diels-Alder reaction of 2-azanorbornene derivative **7** followed by trapping of the incipient iminium ion with triethylsilane (3.0 equiv.) / trifluoroacetic acid afforded *N*-methyl-L-phenylalanine methyl ester **6'** ($[\alpha]_D^{22} = +20.1^{\circ}$ (c 2.0 CHCl₃)).¹⁶ In this method, the desired product was free from dimethyl ester **6'** ($[\alpha]_D^{22} = +20.1^{\circ}$ (c 2.0 CHCl₃)).¹⁶ In this method, the desired product was free from dimethylated product, too. However, the former method was superior to the latter as to the





^a Reagents and conditions : (a) MeI (16 equiv.), NaH (2.1 equiv.), reflux, THF : DMF = 10 : 1, 24 h, 92 %; (b) Et₃N (1.1 equiv.) then Ac₂O, HCO₂H, -18 °C, 30 min, 83 %; (c) BH₃•SMe₂ (1.5 equiv.), r.t., THF, 1 h then reflux, 2 h, 51 %; (d) HCHO-H₂O (1.1 equiv.), cyclopentadiene (2.3 equiv.), r.t., 10 h, 44 %; (e) TFA : CHCl₃ = 1 : 1, Et₃SiH (3.0 equiv.), r.t., 24 h, 43 %.

yield and enantiomeric excess, and thus we adopted the former. After deprotection of tert-butoxycarbonyl function of 4 by 15% HCl in methanol at 50 °C for 1 h, treatment of the mixture of this amino acid derivative and 2azidobenzoyl chloride (1.0 equiv.), which was derived from 2-azidobenzoic acid and thionyl chloride, with triethylamine (2.1 equiv.) in THF at from 0 °C for 15 min to room temperature for 16 h furnished the desired azide derivative 8 (68 % yield, $[\alpha]_{D}^{24} = -62.4^{\circ}$ (c 1.5 CHCl₃)). Furthermore, the reaction of *N*-methyl-L-phenylalanine methyl ester 6 and 2-azidobenzoyl chloride (1.0 equiv.) with triethylamine (1.1 equiv.) in THF at from 0 °C for 15 min to room temperature for 16 h afforded the desired azide derivative 8 (94 % yield, $[\alpha]_{p}^{25} = -80.9^{\circ}$ (c 1.5 CHCl₃)). The enantiomeric excess of 8 by the former route was 91.7 % ee and that of the latter was >99.7 % ee based on HPLC analysis using specially modified cellulose as a stationary phase.¹⁷ Thus, we adopted the latter. Finally, the synthesis of (-)-benzomalvin A was carried out as follows (Scheme 4). The reaction of azide derivative 8 with tributylphosphine (1.1 equiv.) proceeded to form the corresponding iminophosphorane intermediate ($N_3 \rightarrow N_2$) N=PBu₂), which could not be isolated because of too high reactivity of the aza-Wittig cyclization at room temperature for 2.5 h. Subsequently formation of the desired 7 membered compound, (3S)-3,4-dihydro-3-phenylmethyl-2methoxy-4-methyl-1,4-benzodiazepin-5-one 9 via the intramolecular aza-Wittig reaction was completed on heating in toluene for 5 h. Without purification, 9 was converted into 1,4-benzodiazepin-2,5(1H)-dione derivative 2 by hydrolysis in TFA:H₂O:THF (1:1:12.5) at room temperature for 7 h (87 % overall yield from 8, $[\alpha]_{D}^{22} = -55.9^{\circ}$ (c 1.1 CHCl₂), >99.7 % ee). Potassiated 1,4-benzodiazepin-2,5(1H)-dione derivative 2 with KHMDS (1.0 equiv.) was treated with 2-azidobenzoyl chloride in THF at -78 °C for 30 min and at room temperature for 1 h to afford imide derivative having azide function 1, the precursor of (-)-benzomalvin A (82 % yield). As the final drive to (-)benzomalvin A, imide derivative 1 was treated with triphenylphosphine (1.1 equiv.) to generate the corresponding iminophosphorane $(N_3 \rightarrow N=PPh_3)$ which reacted the imide carbonyl function to afford (-)-benzomalvin A in toluene at room temperature for over night and at reflux for 8 h (invertomer mixture 98 % yield, vide infra). Specific behavior of (-)-benzomalvin A and comparison of the spectral and physical data (¹H NMR, ¹³C NMR, MS and $[\alpha]_D$ with those reported for natural product gave satisfying matching results.¹³ The enantiomeric excess and $\left[\alpha\right]_{D}^{21}$ of synthetic (-)-benzomalvin A were >99.7 % and -109.8° (c 1.0 MeOH) { $\left[\alpha\right]_{D}$ of natural (-)benzomalvin A was -106° (c 1.0 MeOH)}. We also studied the conformational behavior of benzomalvin A in solution. The conformation of (-)-benzomalvin A was variable with time, i.e., there were two kinds of stable

Scheme 3 Synthesis of (2-Azidobenzoyl)-L-phenylalanine Derivative 8.^a



From **4** : $[\alpha]_{D}^{24} = -62.4^{\circ}$ (c 1.5 CHCl₃), 91.7 % *ee*. From **6** : $[\alpha]_{D}^{25} = -80.9^{\circ}$ (c 1.5 CHCl₃), >99.7 % *ee*.





Scheme 4 Synthesis of (-)-Benzomalvin A.^a

a Reagents and conditions : (a) n-Bu₃P (1.1 equiv.), toluene, r.t., 2.5 h then reflux, 5 h;
(b) TFA : H₂O : THF = 1 : 1 : 12.5, r.t., 7 h, overall yield 87 % from 8; (c) (1) KHMDS (1.0 equiv.), THF, -78 °C, 1 h (2) 2-azidobenzoyl chloride (1.0 equiv.), -78 °C, 30 min then r.t., 1 h, 82 %;
(d) Ph₃P (1.1 equiv.), toluene, r.t., overnight then reflux, 8 h, 98 % (invertomer mixture).

conformers. Major one was same with natural one. Thus, we could follow the transition of (-)-benzomalvin A conformation in $CDCl_3$ by ¹H NMR. As the results, in the equilibrium of benzomalvin A, the major and minor conformers reached in ratio 76:24, which was similar with the ratio of synthetic compound (Figure 1). The conformations of major and minor isomers were characterized by NOE. Although, the NOE correlation of *N*-Me and H-7 in the major conformer was only 1 %, while that of *N*-Me and H-7 in the minor one was 13 %. Since the minor conformer suffers from steric repulsion between *N*-Me and phenyl function at 7-position, it was transformed into the major stable conformer. Furthermore, surprisingly, optical rotation of the minor benzomalvin A (>99.7 % *ee*) was shown to be +77.1° (c 1.0 MeOH). By this reason, that of the conformational mixture of benzomalvin A was -47.1° (c 1.0 MeOH) (Figure 2). Moreover, X-ray crystallographic analysis of (-)-benzomalvin A was carried out using a crystal obtained from ethyl acetate - hexane (Figure 3). The results indicated this corresponds to the minor conformer based on spatial proximity between *N*-Me and H-7, and on *Rf* value (0.29). PM3 calculation of major and minor (-)-benzomalvin A showed that the ratio was 74.6:25.4 (the difference of the heat of formations was 0.49 kcal / mol) and the energy barrier was 5.9 kcal / mol.

Next step, the synthesis of benzomalvin B was investigated as follows (Scheme 5).¹⁸ The bromination of (-)-benzomalvin A by NBS (1.1 equiv.) and AIBN (10 mol %) in carbon tetrachloride at reflux for 2 h led to



^a The ratio was determined based on ¹H NMR signals of *N*-Me at CDCl₃ at 23 °C. ^b Ratio of major conformer.

Figure 2 Conformation of (-)-Benzomalvin A.



bromo derivative 10. Because this compound was afforded as unseparable diastereomers, the mixture was reacted with DBU (2.0 equiv.) in toluene at reflux for 4 h to give benzomalvin B (overall yield 61 % from (–)-benzomalvin A). However, this methodology produced not only benzomalvin B but also (Z)-benzomalvin B, in ratio 56:44. These configuration of benzomalvin B were confirmed by NOE (Figure 3). The NOE between *N*-Me and vinylic proton of natural (E)-benzomalvin B was larger than that of (Z)-benzomalvin B (5 % vs 2 %) in accord with the given stereochemistry.

CONCLUSION

We reported an efficient total synthesis of (-)-benzomalvin A and benzomalvin B utilizing the intramolecular





aza-Wittig reactions as the key reactions. Investigation on specific conformational dynamic behavior of (-)benzomalvin A was carried out by NMR studies.

EXPERIMENTAL SECTION

General Methods. Most of the general experimental methods have been reported previously.^{4a} Optical rotations were measured with a JASCO DIP-1000 polarimeter. Flash chromatography was performed with a silica gel column (Fuji Davison BW-300 silica gel) eluted with mixed solvents [hexane (H), ethyl acetate (A)]. All reagents were of commercial quality. Solvents were dried prior to use when deemed necessary.

Synthesis of N-(2-azidobenzoyl)-N-methyl-L-phenylalanine methyl ester 8.

(From 4: see, step a of Scheme 3): A solution of *N-tert*-butoxycarbonyl-*N*-methyl-L-phenylalanine methyl ester 4 (1208 mg, 4.12 mmol) in conc. HCl (2.25 mL) and MeOH (12.75 mL) was stirred at 50 °C for 1 h. After the

Figure 4 NOE of E- and Z-Benzomalvin B.



reaction mixture was evaporated, the azeotropy was performed by dry benzene (5.0 mL \times 3). Furthermore, the reaction mixture was diluted by CH₂Cl₂ (20 mL) and dried over by MgSO₄. The solvent was removed under reduced pressure and then to the residue in THF (25 mL) was added 2-azidobenzoyl chloride, which was prepared from 2-azidobenzoic acid (672 mg, 4.12 mmol, 1.0 equiv.) and thionyl chloride (3.00 mL, 41.2 mmol, 10 equiv.) at 80 °C for 2 h, in THF (5.0 mL) and triethylamine (1.22 mL, 8.65 mmol, 2.1 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 16 h. The mixture was added water (15 mL) and extracted with ethyl acetate (20 mL \times 3). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 1:1 as the eluent) to give 2-azidobenzoyl-L-phenylalanine derivative **8** (948 mg, 2.80 mmol, 68 %).

(From 6: see, step b of Scheme 3): To a solution of N-methyl-L-phenylalanine methyl ester 6 (319 mg, 1.65 mmol) in THF (15 mL) was added 2-azidobenzoyl chloride, which was prepared from 2-azidobenzoic acid (269 mg, 1.65 mmol, 1.0 equiv.) and thionyl chloride (1.20 mL, 16.5 mmol, 10 equiv.) at 80 °C for 2 h, in THF (5.0 mL) and triethylamine (0.25 mL, 1.82 mmol, 1.1 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and at room temperature for 16 h. The mixture was added water (10 mL) and extracted with ethyl acetate (15 mL \times 3). The combined extracts were dried $(MgSO_4)$ and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 1:1 as the eluent) to give 2-azidobenzoyl-Lphenylalanine derivative 8 (526 mg, 1.55 mmol, 94 %). Light brown oil; Rf = 0.32 (A:H 1:1); $[\alpha]_{D}^{25.1} = -80.9^{\circ}$ (c 1.5 CHCl₂); IR (neat) 3583, 2951, 2130, 1741, 1643, 1453, 1293, 752, 700 cm⁻¹; ¹H NMR (CDCl₂, 200 MHz) δ 7.21-7.41 (6H, m), 6.82-7.15 (3H, m), 5.99 (0.2H, dd, J = 7.6, 1.6, Hz), 5.58 (0.8H, br), 4.41 (0.2H, dd, J = 9.0, 1.05.6, Hz), 4.26 (0.2H, dd, J=4.4, 10.6 Hz), 3.80 (2.4H, s), 3.77 (0.6H, s), 3.51 (0.8H, dd, J = 14.8, 5.4 Hz), 3.14 (0.8H, dd, J = 14.8, 11.2 Hz), 3.19 (0.6H, s), 2.66 (2.4H, s); ¹³C NMR (CDCl₂, 50 MHz) δ 171.59, 169.71, 136.71, 130.75, 129.63, 129.41 (2C), 128.82 (2C), 128.26, 127.59, 127.18, 125.35, 118.76, 62.95, 57.41, 52.59, 34.69 (for syn conformer), § 171.17, 169.84, 137.01, 130.91, 130.69, 129.19 (2C), 128.92 (2C), 128.59, 127.92, 127.39, 125.15, 118.68, 63.82, 57.27, 52.80, 35.72 (for anti conformer); MS (EI) m/z (rel. intensity) (338.36) 338 (2 %, M), 310 (9), 251 (15), 219 (26), 176 (35), 146 (100), 91 (58); Anal. Calcd. for C₁₈H₁₈N₄O₃: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.90; H, 5.21; N, 16.77.

Synthesis of (3S)-3,4-dihydro-4-methyl-3-phenylmethyl-[1,4]benzodiazepin-2,5(1H)-dione 2. To a solution of 2-azidobenzoyl-L-phenylalanine derivative 8 (493 mg, 1.46 mmol) in toluene (12 mL) was added *n*-tributylphosphine (0.395 mL, 1.60 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 2.5 h and at reflux for 5 h. After the reaction mixture was evaporated, the residue was diluted with TFA solution

(0.05 M, 29 mL; TFA:H₂O:THF 1:1:12.5). The reaction mixture was stirred at room temperature for 7 h. The mixture was neutralized with 5 % NaHCO₃ aqueous solution and extracted with ethyl acetate (15 mL \times 3). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 3:1 as the eluent) to give 1,4-benzodiazepine derivative 2 (355 mg, 1.27 mmol, 87 %).

(3S)-3,4-dihydro-2-methoxy-N-methyl-3-phenylmethyl-[1,4]benzodiazepin-5(5H)one 9. Light yellow oil; Rf = 0.49 (A:H 2:1); $[\alpha]_D^{24.3} = -149.4^{\circ}$ (c 1.0 CHCl₃); IR (neat) 2945, 1668, 1633, 1601, 1456, 1228, 763, 702 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 8.05 (1H, dd, J = 8.4, 1.8 Hz), 7.51 (1H, ddd, J = 8.4, 6.8, 1.8 Hz), 7.32-7.21 (5H, m), 6.99-6.95 (2H, m), 4.09 (1H, t, J = 8.6 Hz), 3.92 (0.9H, s), 3.79 (2.1H, s), 3.13 (0.9H, s), 2.94 (2.1H, s), 2.64 (2H, d, J = 8.6 Hz); ¹³C NMR (CDCl₃, 50 MHz) δ 167.32, 163.28, 143.49, 136.49, 132.43, 131.32, 129.26 (2C), 129.12 (2C), 129.00, 127.48, 126.59, 125.05, 64.55, 54.56, 39.15, 34.17 (Only major conformer was shown.); MS (EI) m/z (rel. intensity) (294.35) 294 (10 %, M), 203 (43), 162 (100), 130 (8); Anal. Calcd. for C₁₈H₁₈N₂O₂: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.34; H, 6.34; N, 9.24.

(3*S*)-3,4-dihydro-4-methyl-3-phenylmethyl-[1,4]benzodiazepin-2,5(1*H*)-dione 2. White solid; Rf = 0.31 (A:H 3:1); $[\alpha]_D^{21.9} = -55.9^\circ$ (c 1.1 CHCl₃); mp 67-70 °C; IR (KBr) 3221, 1689, 1633, 1483, 1454, 1251, 1045, 760, 700 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 9.33 (0.45H, s), 8.98 (0.55H, s), 8.12 (0.45H, dd, J = 7.8, 1.0 Hz), 7.96 (0.55H, dd, J = 7.8, 1.0 Hz), 7.56-7.42 (1H, m), 7.36-7.24 (5H, m), 7.09-6.94 (2H, m), 4.36 (0.55H, dd, J = 8.4, 6.6 Hz), 4.27 (0.45H, dd, J = 10.8, 6.4 Hz), 3.50 (0.55H, dd, J = 14.4, 8.4 Hz), 3.22 (0.55H, dd, J = 14.4, 6.6 Hz), 3.15 (1.65H, s), 2.92 (1.35H, s), 2.71 (0.45H, dd, J = 13.4, 11.0 Hz), 2.85 (0.45H, dd, J = 13.6, 6.4 Hz); ¹³C NMR (CDCl₃, 50 MHz) δ 172.07, 170.52, 168.89, 166.44, 136.81, 136.01, 135.92, 135.01, 133.10, 132.78, 132.20, 131.83, 129.37 (2C), 129.28 (2C), 129.22 (2C), 129.10 (2C), 127.77, 127.71, 127.33, 127.20, 125.70, 125.57, 121.05, 120.47, 68.67, 56.47, 39.77, 34.71, 32.29, 29.37; MS (EI) *m/z* (rel. intensity) (280.32) 280 (15 %, M), 189 (100), 161 (14), 148 (41); Anal. Calcd. for C₁₇H₁₈N₂O₂: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.84; H, 5.91; N, 9.81.

Synthesis of (3S)-[1-(2-azidobenzoyl)]-3,4-dihydro-4-methyl-3-phenylmethyl-[1,4]benzodiazepin-2,5(1H)dione 1. To a solution of KHMDS (0.5 M, 2.03 mL, 1.01 mmol, 1.0 equiv.) in THF (6.0 mL) was slowly added 1,4-benzodiazepin derivative 2 (284 mg, 1.01 mmol) at -78 °C. The mixture was stirred at same temperature for 1 h. To the reaction mixture was added 2-azidobenzoyl chloride, which was prepared from 2-azidobenzoic acid (165 mg, 1.01 mmol, 1.0 equiv.) and thionyl chloride (0.74 mL, 10.1 mmol, 10 equiv.) at 80 °C for 2 h, in THF (2.0 mL) at -78 °C. The mixture was stirred at same temperature for 30 min and then at room temperature for 1 h. The mixture was quenched with saturated NH_4Cl aqueous solution and extracted with ethyl acetate (12 mL × 3). The combined extracts were dried $(MgSO_A)$ and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 1:1 as the eluent) to give the precursor of (-)benzomalvin A, imide derivative 1 (355 mg, 0.83 mmol, 82 %). Light brown solid; Rf = 0.33 (A:H 1:1); $[\alpha]_{D}^{23.0}$ = -90.2° (c 0.50 CHCl₃) mp 38-42 °C; IR (neat) 3030, 2131, 1730, 1703, 1651, 1599, 1485, 1452, 1386, 1298, 1222, 1172, 754, 700 cm⁻¹; IR (KBr) 3409, 2924, 2131, 1720, 1702, 1676, 1452, 1297, 1261, 754, 700 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) & 7.93-7.89 (1H, m), 7.58-7.37 (4H, m), 7.32-7.05 (8H, m), 4.54 (0.85H, dd, J = 8.6, 6.0 Hz), 4.34 (0.15H, dd, J = 11.0, 6.0 Hz), 3.41 (0.85Hz, dd, J = 14.4, 8.6 Hz), 3.11 (0.85H, dd, J = 14.4, 6.0 Hz), 3.15 (2.55H s), 2.97 (0.45H, s), 2.68 (0.15H, dd, J = 13.8, 6.0 Hz), 2.30 (0.15H, dd, J = 13.8, 10.8 Hz); ¹³C NMR (CDCl₃, 50 MHz) δ 171.78*, 170.16, 168.79*, 168.43, 168.35, 166.57*, 137.52, 137.31*, 136.19, 135.78*, 135.50, 133.18*, 133.01, 132.78*, 132.02*, 131.92, 131.18, 130.80, 130.72, 130.56, 129.30 (2C), 129.12 (2C), 128.43, 128.12*, 127.84*, 127.52, 126.76, 125.48*, 125.39, 118.69*, 118.47, 70.88*, 58.35, 38.75*, 36.35*, 32.47, 28.58 (minor conformer was shown by * and 7 peaks of them could not be found); MS (EI) m/z (rel. intensity) (425.44) 425 (2 %, M), 397 (15), 279 (41), 236 (28), 146 (100), 90 (15); Anal. Calcd. for $C_{24}H_{19}N_5O_3$: C, 67.76; H, 4.50; N, 16.46. Found: C, 67.71; H, 4.37; N, 16.23.

Synthesis of (–)-benzomalvin A. To a solution of imide derivative 1 (159 mg, 0.374 mmol) in toluene (10 mL) was added triphenylphosphine (108 mg, 0.41 mmol, 1.1 equiv.) in toluene (2.0 mL) at room temperature. The reaction mixture was stirred at ambient temperature for over night and then at reflux for 8 h. The mixture was concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 1:1 as the eluent) to give (–)-benzomalvin A (140 mg, 0.367 mmol, invertomer mixture 98 %). White solid; Rf = 0.41 (A:H 1:1); $[\alpha]_D^{21.1} = -109.8^\circ$ (c 1.0 MeOH) {lit.,¹³ $[\alpha]_D = -106^\circ$ (c 1.0 MeOH)}; mp 98-101 °C (lit.,¹³ mp 105-115 °C); IR (KBr) 3423, 1691, 1653, 1612, 1454, 1381, 1251, 777, 698 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 8.33 (1H, dt, J = 7.8, 1.0 Hz), 7.94 (1H, ddd, J = 6.8, 2.2, 0.8 Hz), 7.84-7.81 (2H, m), 7.65-7.50 (4H, m), 7.35-7.15 (5H, m), 4.88 (1H, dd, J = 8.0, 7.0 Hz), 3.80 (1H, dd, J = 14.4, 7.8 Hz), 3.42 (1H, dd, J = 14.6, 7.0 Hz), 3.09 (3H, s); ¹³C NMR (CDCl₃, 50 MHz) δ 167.82, 161.71, 152.27, 146.38, 137.06, 135.25, 133.31, 131.83, 131.32, 130.32, 129.40 (2C), 129.34, 129.26, 129.10 (2C), 128.08 (2C), 127.95, 127.31, 122.06, 58.48, 33.25, 28.00; MS (EI) *m/z* (rel. intensity) (381.43) 381 (23 %, M), 290 (95), 249 (100), 160 (9), 130 (8), 91 (3); Anal. Calcd. for C₂₄H₁₉N₃O₂: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.64; H, 5.19; N, 10.77.

(+)-Inversion isomer. White solid; Rf = 0.29 (A:H 1:1); $[\alpha]_D^{23.2} = +77.1^{\circ}$ (c 1.0 MeOH); mp 152-154 °C; IR (KBr) 3448, 1693, 1649, 1607, 1475, 1352, 1247, 760, 698 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 8.34 (1H, ddd, J = 8.0, 1.6, 0.6 Hz), 8.05 (1H, ddd, J = 6.4, 2.6, 1.2 Hz), 7.81 (1H, ddd, J = 8.0, 7.0, 1.6 Hz), 7.71-7.58 (3H, m), 7.55 (1H, ddd, J = 7.8, 7.2, 1.4 Hz), 7.33-7.22 (4H, m), 7.01-6.96 (2H, m), 4.78 (1H, dd, J = 11.2, 6.0 Hz), 2.94 (3H, s), 2.79 (1H, dd, J = 13.8, 6.0 Hz), 2.36 (1H, dd, J = 13.8, 11.2 Hz); ¹³C NMR (CDCl₃, 50 MHz) δ 165.96, 162.04, 154.18, 146.76, 136.29, 135.45, 133.40, 132.54, 131.55, 131.07, 129.51, 129.33 (2C), 129.25 (2C), 128.54, 128.71, 128.06, 127.77, 127.68, 121.78, 70.58, 38.41, 35.97; MS (EI) *m/z* (rel. intensity) (381.43) 381 (15 %, M), 290 (89), 249 (100), 160 (10), 130 (7), 91 (4); Anal. Calcd. for C₂₄H₁₉N₃O₂: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.85; H, 4.98; N, 10.78.

Synthesis of benzomalvin B. To a solution of (-)-benzomalvin A (invertomer mixture; 139 mg, 0.36 mmol) in carbontetrachloride (8.0 mL) was added NBS (71.3 mg, 0.40 mmol, 1.1 equiv.) and AIBN (6.0 mg, 0.036 mmol, 0.1 equiv.) in turn. The mixture was stirred at reflux for 2 h. The reaction mixture was filtered and then the solvent was removed under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 1:1 as the eluent) to give bromo derivative 10 (153 mg, 0.33 mmol, invertomer and diastereomer mixture 91 %). To a solution of bromo derivative 10 (153 mg, 0.33 mmol) in toluene (5.0 mL) was added DBU (0.11 mL, 0.73 mmol, 2.0 equiv. of (-)-benzomalvin A). The mixture was stirred at reflux for 4 h. The mixture was added water (15 mL) and extracted with ethyl acetate (15 mL \times 3). The combined extracts were dried (MgSO₄) and concentrated under reduced pressure to afford a solid residue, which was purified by silica gel column chromatography (A:H 1:1 as the eluent) to give benzomalvin A).

Bromobenzomalvin A 10. Light yellow solid; Rf = 0.44 (A:H 1:1); mp 54-58 °C; IR (KBr) 3449, 2925, 1695, 1657, 1617, 1597, 1454, 1378, 728, 695 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 8.37 (0.78H, ddd, J = 8.0, 1.6, 0.6 Hz), 8.23 (0.22H, ddd, J = 8.0, 1.6, 0.6 Hz), 8.05-8.00 (0.22H, m), 7.99 (0.78H, ddd, J = 7.4, 2.0, 0.6 Hz), 7.89-7.51 (6H, m), 7.44-7.31 (5H, m), 6.05 (0.78H, d, J = 10.6 Hz), 5.77 (0.22H, d, J = 11.0 Hz), 5.52 (0.78H, d, J = 10.6 Hz), 5.23 (0.22H, d, J = 11.0 Hz), 3.31 (0.66H, s), 2.64 (2.34H, s); ¹³C NMR (CDCl₃, 125 MHz) δ 167.69*, 167.18, 161.18,

160.74*, 150.16, 149.53*, 146.13, 145.68*, 138.15*, 137.41, 135.25, 135.06*, 133.04, 132.71*, 131.68, 131.49*, 131.17, 130.49*, 130.01, 129.74 (2C), 129.72, 129.56, 129.12*, 129.03*, 128.96*, 128.30, 128.22, 128.09, 128.04, 127.99*, 127.85 (2C), 127.73*, 127.58*, 121.90, 63.24*, 61.79, 49.94*, 46.57, 28.20, 27.96* (minor diastereoisomer was shown by * and 4 peaks of them could not be found); MS (EI) m/z (rel. intensity) (460.32) 461 (2 %, M+1), 459 (2, M-1), 380 (25), 323 (10), 290 (100), 249 (86), 132 (9); Anal. Calcd. for $C_{24}H_{18}N_3O_2Br$: C, 62.62; H, 3.94; N, 9.13. Found: C, 62.84; H, 4.20; N, 8.87.

Inversion isomer. Yellow solid; Rf = 0.35 (A:H 1:1); mp 47-50 °C; IR (KBr) 3434, 2926, 1697, 1655, 1607, 1594, 1457, 1357, 729, 695 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 8.37 (0.64H, ddd, J = 7.8, 1.4, 0.6 Hz), 8.21 (0.36H, ddd, J = 7.8, 1.6, 0.6 Hz), 8.07-8.02 (0.36H, m), 7.98-7.93 (0.64H, m), 7.86-7.43 (6H, m), 7.38-7.06 (5H, m), 5.31 (0.36H, d, J = 11.4 Hz), 5.11 (0.64H, d, J = 12.0 Hz), 4.33 (0.36H, d, J = 11.4 Hz), 4.15 (0.64H, d, J = 12.0 Hz), 3.52 (1.08H, s), 2.81 (1.92H, s); ¹³C NMR (CDCl₃, 125 MHz) δ 165.36, 161.22, 151.95, 146.56, 137.07, 135.18, 132.46, 131.93, 131.81, 131.13, 129.94, 129.81, 129.06 (2C), 128.95, 128.61, 128.14 (2C), 127.97, 127.74, 121.53, 75.14, 51.70, 38.15 (for major isomer), δ 165.29, 161.42, 151.21, 146.30, 136.32, 135.37, 132.26, 131.56, 131.39, 130.68, 130.00, 129.72, 129.33 (2C), 128.92, 128.27, 128.08 (2C), 127.77, 127.56, 121.18, 74.86, 47.99, 39.15 (for minor isomer); MS (EI) *m/z* (rel. intensity) (460.32) 461 (1 %, M+1), 459 (1, M-1), 380 (16), 323 (6), 290 (100), 249 (71), 132 (5); Anal. Calcd. for C₂₄H₁₈N₃O₂Br: C, 62.62; H, 3.94; N, 9.13. Found: C, 62.83; H, 4.28; N, 8.86.

Benzomalvin B. White solid; Rf = 0.25 (A:H 1:1); mp 265-267 °C (lit., 13 mp >260 °C); IR (KBr) 3449, 3072, 2927, 1695, 1647, 1606, 1465, 1452, 1367, 1254, 775, 758, 709, 692 cm⁻¹; 1 H NMR (CDCl₃, 200 MHz) δ 8.40 (1H, ddd, J = 8.0, 1.6, 0.6 Hz), 8.02-7.97 (1H, m), 7.85 (1H, dd, J = 4.4, 1.6 Hz), 7.84-7.83 (1H, m), 7.63-7.44 (4H, m), 7.83 (5H, m), 6.92 (1H, s), 3.21 (3H, s); 13 C NMR (CDCl₃, 50 MHz) δ 166.33, 161.54, 151.61, 147.26, 135.41, 133.56, 133.24, 132.52, 132.10, 131.32, 130.61, 129.78, 129.28 (2C), 129.23 (2C), 129.12 (2C), 128.45, 128.32, 127.93, 127.83, 122.24, 36.25; MS (EI) m/z (rel. intensity) (379.41) 379 (41), 321 (100), 249 (3), 131 (89), 116 (36); Anal. Calcd. for C₂₄H₁₇N₃O₂: C, 75.98; H, 4.52; N, 11.07. Found: C, 76.01; H, 4.73; N, 10.81.

(Z)-Benzomalvin B. White solid; Rf = 0.40 (A:H 1:1); mp 251-253 °C; IR (KBr) 3448, 3065, 2927, 1694, 1665, 1606, 1470, 1453, 1373, 1266, 774, 759, 707, 694 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 8.39 (1H, ddd, J = 8.0, 1.6, 0.8 Hz), 8.02-7.97 (1H, m), 7.85 (1H, dd, J = 4.4, 1.6 Hz), 7.84-7.83 (1H, m), 7.63-7.44 (4H, m), 7.38 (5H, m), 6.92 (1H, s), 3.21 (3H, s); ¹³C NMR (CDCl₃, 50 MHz) δ 173.64, 166.60, 154.06, 147.02, 135.52, 134.60, 133.42, 132.57, 131.52, 130.55, 130.32, 130.20, 129.57 (2C), 129.45 (2C), 129.28, 129.19, 128.31, 128.08, 128.03, 127.89, 122.20, 29.81; MS (EI) *m/z* (rel. intensity) (379.41) 379 (49), 321 (100), 249 (6), 131 (81), 116 (38); Anal. Calcd. for C₂₄H₁₇N₃O₂: C, 75.98; H, 4.52; N, 11.07. Found: C, 75.84; H, 4.81; N, 10.80.

X-ray crystal structure analysis of benzomalvin A. Crystal data of benzomalvin A: $C_{24}H_{19}N_3O_2$, M = 381.43, monoclinic, P_21 (#4), a = 7.85(2) Å, b = 12.14(1) Å, c = 10.151(8) Å, b = 93.7 (1) °, V = 966(3) Å³, Z = 2.0, $D_c = 1.311$ g/cm³. A white prism from ethyl acetate / hexane (0.160 × 0.300 × 0.420 mm) was mounted on a Rigaku-AFC5S diffractmeter with graphite-monochromated Mo K α radiation ($\lambda = 0.71069$ Å). Data collection using the ω scan technique to a miximum 20 value of 55.0° gave 2499 reflections, 2335 unique ($R_{int} = 0.061$), of which 996 with $I > 2.00\sigma(I)$ reflections were used in calculations. The structure was solved by direct method and refined by full-matrix least squares technique (TEXSAN system¹⁹ as the computer program and MITHRIL²⁰ as the structure solution method). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included by calculation and were not refined. The unweighted and weighted value were 0.068 and 0.062, respectively. Atomic coordinates, bond lengths and angles, and positional parameters have been deposited.²¹ The PM3 calculations were carried out by "CAChe MOPAC Ver. 3.7" on Power Macintosh Computer.

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- 21 The authors have deposited atomic coordinates for benzomalvin A with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.