# The First Total Synthesis of (–)-Benzomalvin A *via* Intramolecular Aza-Wittig Reactions

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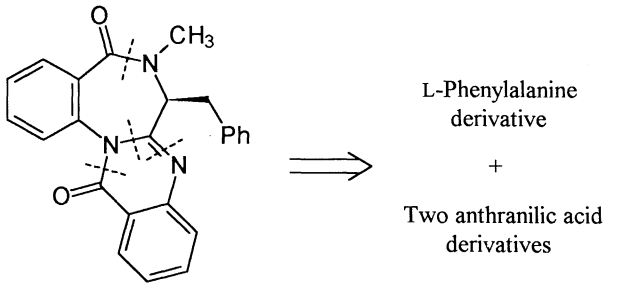
The first total synthesis of (–)-benzomalvin A **1**, which possesses quinazolin-4(3*H*)-one moiety and 1,4-benzodiazepin-5-one moiety, was described. Both of 6- and 7-membered ring skeletons were efficiently constructed by intramolecular aza-Wittig reactions as the key reactions.

Recently much of our efforts have been directed towards efficient synthesis of quinazolin-4(3*H*)-ones,[1] 1,4-benzodiazepines[2,3] and pyrazino[2,3-*e*][1,4]diazepines[4] by utilizing intramolecular aza-Wittig reaction.[5-8] We wish to report here on the successful synthesis of (–)-benzomalvin A **1** by intramolecular aza-Wittig methodology.

In the course of screening microbial broths for neurokinin receptor antagonists, (–)-benzomalvin A **1**, (+)-benzomalvin B and (+)-benzomalvin C containing both quinazolin-4(3*H*)-one skeleton and 1,4-benzodiazepin-5-one skeleton have been recently isolated from the culture broth of a fungus identified as a *Penicillium* sp. (–)-Benzomalvin A **1** showed inhibitory activity against substance P at the guinea pig, rat and human neurokinin NK1 receptors, respectively. Pharmacological activity of (–)-benzomalvin A **1** was stronger than those of (+)-benzomalvin B and (+)-benzomalvin C, respectively.[9]

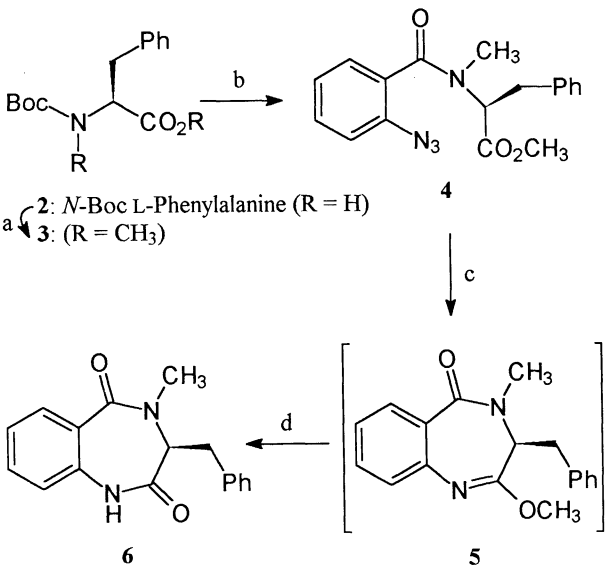
According to retrosynthetic analysis of (–)-benzomalvin A **1** cleaved as dotted lines in Fig. 1, this molecule can be regarded as composed of two anthranilic acid moieties and L-phenylalanine derivative.




(–)-Benzomalvin A **1**

**Figure 1.**

We prepared, at first, the corresponding 7-membered compound, (3*S*)-3-benzyl-4-methyl-1,4-benzodiazepin-2,5(1*H*, 4*H*)-dione **6** as follows (Scheme 1). *N*-Boc-L-phenylalanine as a starting material was converted to **3** by exhaustive methylation by MeI (16 equiv.) and NaH (2.1 equiv.) in THF : DMF (10 : 1) at reflux for 24 h.[10] After deprotection of *tert*-butoxycarbonyl function of **3** by 15% HCl in methanol at 50 °C for 1 h, treatment of the mixture of this amino acid derivative and *o*-azidobenzoyl chloride (1.0 equiv.) with triethyl amine (2.1 equiv.) in THF at from 0 °C for 15 min to room temperature for 16 h furnished the

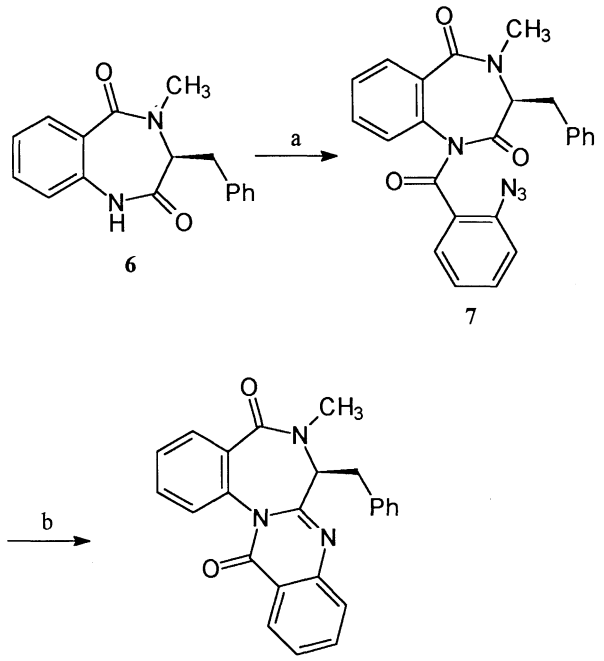



**Scheme 1.** *Reagents and conditions*: a) NaH (2.1 equiv.), $CH_3I$ (16 equiv.), THF : DMF = 10 : 1, reflux, 24 h; b) 15% HCl in $CH_3OH$, 50 °C, 1 h, then *o*-azidobenzoyl chloride (1.0 equiv.), $Et_3N$ (2.1 equiv.), THF, 0 °C, 15 min → room temp., 16 h; c) $Bu_3P$ (1.1 equiv.), toluene, room temp., 2.5 h, then reflux, 10 h; d) THF : HCl = 40 : 1, 50 °C, 2.5 h, overall yield 58% from **2**.

desired azide derivative **4**. The reaction of **4** with tributylphosphine proceeded to form the corresponding iminophosphorane intermediate ($N_3$ → $N{=}PBu_3$) *via* Staudinger reaction at room temperature for 2.5 h. Subsequently a desired 7 membered compound, (3*S*)-3-benzyl-2-methoxy-4-methyl-1,4-benzodiazepin-5(4*H*)-one **5** was produced on heating in toluene *via* intramolecular aza-Wittig reaction. Without purification, **5** was converted to amide derivative **6** by hydrolysis in THF : HCl (40 : 1) at 50 °C for 2.5 h.

Quinazolinone annelation of **6** was carried out as follows (Scheme 2). Lithiated **6** with KHMDS (1.0 equiv.) was treated with *o*-azidobenzoyl chloride at –78 °C in THF to afford imide derivative **7**, the precursor of (–)-benzomalvin A. As the final drive to (–)-benzomalvin A **1**, **7** was treated with triphenylphosphine to generate the corresponding iminophosphorane which reacted the imide carbonyl function to afford (–)-benzomalvin A **1** under the mild conditions in 80% overall yield from **6**.

Specific behavior of (–)-benzomalvin A **1** and comparison of the spectral and physical data ($^1H$ NMR, $^{13}C$ NMR and MS) with those reported for natural product gave satisfying matching results.[9] However, the optical rotation value of the synthetic (–)-




**(–)-Benzomalvin A**

**Scheme 2**. *Reagents and conditions* : a) KHMDS (1.0 equiv.), THF, –78 °C, 1 h then *o*-azidobenzoyl chloride (1.0 equiv.), THF, –78 °C, 30 min then room temp., 1 h, 82 %; b) $Ph_3P$ (1.1 equiv.), toluene, room temp., overnight then reflux 8 h, 98 %.

benzomalvin A was not reached the reported one of natural (–)-benzomalvin A (–69° *vs.* –109° in c 1.0 $CH_3OH$, respectively). Thus, the optical purity of the synthetic (–)-benzomalvin A was 85% ee based on HPLC analysis using specially modified cellulose as a stationary phase.[11,12] In addition, as the optical purity of **6** was 90% ee, the methylation process caused a little racemization. In summary, we reported an efficient total synthesis of (–)-benzomalvin A utilizing intramolecular aza-Wittig reactions as the key reactions. Investigation on a specific conformational dynamic behavior of (–)-benzomalvin A and development of least racemic process for the methylation is under way in our laboratory.

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