Effective formal synthesis of benzomalvin A

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Abstract A short and effective strategy for the construction of the tetracyclic core structure of the biologically active compound benzomalvin A from cheap commercially available (S)-phenylalanine and isatoic anhydride is described. This three-pot methodology was successfully implemented to synthesize N-demethylbenzomalvin A on a multi-gram scale with 54% overall yield.

Keywords Natural products · Alkaloids · Benzodiazepine-fused quinazolinones

Introduction

Biologically active alkaloids are usually isolated from natural resources in tiny quantities after tedious, highly expensive work that involves the consumption of large amounts of the natural resources. The synthesis of these biologically active alkaloids in the laboratory from simple and cheap starting materials is a very attractive approach that could help to save our limited natural resources. Benzomalvins A–C (**1–3**; see Scheme 1) are a class of benzodiazepine-fused quinazolinones that are isolated from a fungus identified as *Penicillium sp.* [1, 2]. Benzomalvin A showed potent inhibitory activity against substance P at the guinea pig, rat, and human neurokinin receptor [1].
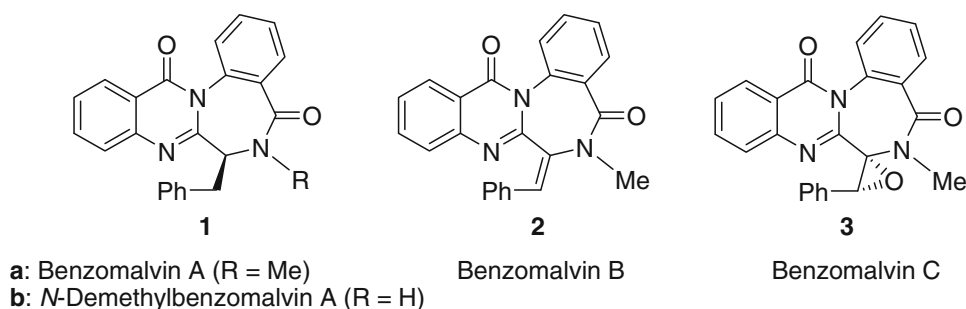
The synthesis of enantiomerically pure benzomalvin A (**1**) was achieved with a very low yield (4% overall yield) [2]. Furthermore, benzomalvins were prepared by Eguchi using

expensive and explosive starting materials (Bu$_3$P, 2-N$_3$-PhCOCl) [3, 4]. The synthesis of a racemic mixture of benzomalvin A was reported by Liu et al. [5] with a 16% overall yield using microwave-assisted reactions. A modified Eguchi protocol using polymer-supported triphenylphosphine was implemented by Thomas et al. [6] to produce a diverse multi-arrayed library of benzodiazepine-quinazolinone alkaloids. Ellman's solid-phase method for fluorous synthesis was adopted by Zhang et al. [7] to devise a new protocol for the synthesis of quinazolinobenzodiazepinedione alkaloids. Recently, N-demethylbenzomalvin A (**1b**) and other quinazolinobenzodiazepinedione alkaloids were prepared by the dehydrocyclization of anthranilate-containing tripeptides using scandium triflate and microwaves [8]. Furthermore, Zhichkin et al. [9] synthesized several quinazolinobenzodiazepinedione alkaloids in enantiopure form via a reductive cyclization of 2-nitrobenzamides with yields of 20–65%.
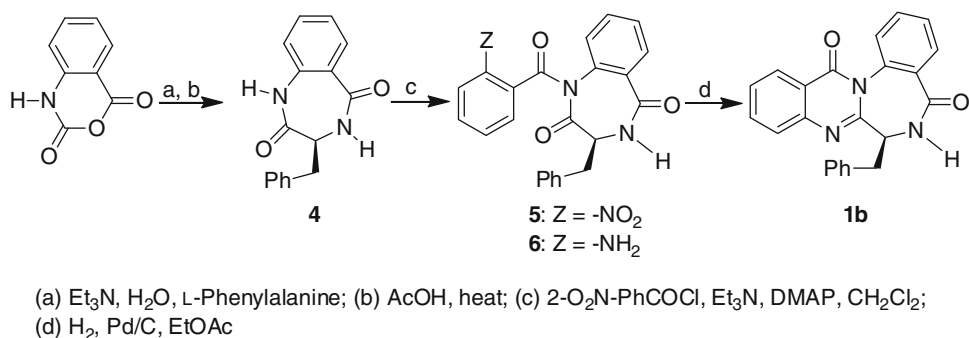
Although the documented protocols provided different routes to quinazolinobenzodiazepinediones including benzomalvins, they do have some drawbacks. All of these aforementioned protocols require several steps and cannot be conducted at a multi-gram scale. Moreover, they suffer from the high cost and poor availability of reagents such as 2-azidobenzoyl chloride and transition metals, the pollution caused by the phosphine oxide by-product, the harsh reaction conditions required, and their low atom economy. These facts, coupled with our desire to develop an efficacious methodology for biologically active alkaloids, and in continuation of our work on heterocycles [10–13], prompted us to devise an efficient and simple method of synthesis for N-demethylbenzomalvin A (**1b**). The synthetic pathway described here is short, amenable to large-scale preparation, and can be extended to synthesize a wide range of N-substituted benzomalvin A derivatives for further biological evaluation.

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Scheme 1

1
a: Benzomalvin A (R = Me)
b: *N*-Demethylbenzomalvin A (R = H)

2
Benzomalvin B

3
Benzomalvin C

Scheme 2

(a) Et$_3$N, H$_2$O, L-Phenylalanine; (b) AcOH, heat; (c) 2-O$_2$N-PhCOCl, Et$_3$N, DMAP, CH$_2$Cl$_2$;
(d) H$_2$, Pd/C, EtOAc

Results and discussion

From a retrosynthetic perspective, benzomalvin A (**1a**) could be derived synthetically using two consecutive acylation–cyclization reactions. Thus, our study commenced with the acylation of L-phenylalanine with isatoic anhydride in aqueous solution containing triethylamine, followed by intramolecular cyclization via heating in acetic acid to furnish the bicyclic product **4** in excellent yield (Scheme 2) [2]. The ^{1}H NMR spectrum of **4** displayed the characteristic signals of the suggested structure. The signals from a doublet of doublets at 3.06 and 3.45 ppm were assigned to methylene benzylic protons. A doublet of triplets attributed to the methine proton was observed at 4.08 ppm.

Benzoylation of 1,4-benzodiazepin-2,5-dione **4** with freshly prepared 2-nitrobenzoyl chloride in the presence of a catalytic amount of dimethylaminopyridine (DMAP) and Et$_3$N in dry CH$_2$Cl$_2$ furnished the intermediate **5**. Monitoring the reaction mixture by TLC indicated that the conversion of **4** to the nitro derivative **5** was complete and clean. However, aqueous work-up resulted in partial hydrolysis of the product **5** to the starting materials 2-nitrobenzoic acid and the bicycle **4**. Similarly, hydrolysis of the nitro derivative **5** was observed when the solvent was evaporated and the residue was loaded onto a silica gel column for purification. Therefore, the reduction of the nitro group to the corresponding aniline derivative **6** was investigated with crude **5** obtained after filtering the residue dissolved in ethyl acetate through a pad of silica gel,

followed by evaporation of the solvent. The reduction of the nitro compound **5** was conducted under mild conditions (H$_2$/Pd/C). Fortunately, the reduction process was accompanied by the simultaneous N-heterocyclization of the generated aniline derivative **6** to give *N*-demethylbenzomalvin A (**1b**) in good yield (60%). Careful monitoring of the progress of the reaction by TLC did not show a spot corresponding to the expected reduction product **6**. It is worth mentioning that it was found to be essential to pass the crude nitro derivative **5** dissolved in ethyl acetate through a pad of silica gel in order for the reduction to occur effectively. Without this process, the starting nitro derivative **5** remains intact after hydrogenation for 24 h, probably due to the poisoning of the catalyst with sulfur originating from the SOCl$_2$ used to prepare *o*-nitrobenzoyl chloride. The structure of **1b** was confirmed by various spectroscopic techniques, including ^{1}H NMR, ^{13}C NMR, and mass spectral data and the results were in complete agreement with reported data [8]. The ^{1}H NMR spectrum of **1b** displayed two doublets of doublets, assigned to the benzylic protons at 3.29 and 3.76 ppm. Furthermore, the signal from a doublet of triplets at 4.48 ppm was attributed to the methine proton. The ^{13}C NMR spectrum of **1b** displayed 21 signals. The benzylic and methine carbons were observed at 35.3 and 55.6 ppm, respectively. Moreover, the APT experiment indicated the presence of eight quaternary carbons.

In conclusion, the work presented here provides an efficient and inexpensive procedure for the synthesis of *N*-demethylbenzomalvin A from commercially available

starting materials. This experimentally simple and environmentally friendly approach is now implemented in our labs to prepare a wide range of benzomalvin A derivatives for biological evaluation.

Experimental

Melting points were measured using an electrothermal digital melting point apparatus. IR spectra were recorded using a Nicolet Impact 410 FT-IR spectrophotometer. Both ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C). The chemical shifts are given on the δ scale (ppm) relative to TMS (used as the internal standard). Mass spectra (MS) were obtained on an API 3000 LC/MS/MS spectrometer manufactured by Applied Biosystems MDS Sciex with an APCI/ESI ion source type used in positive-ion detection mode. Elemental analysis (C, N, H) was performed on a CE-440 elemental analyzer, and the results were found to be in good agreement with calculated values.

(S)-3-Benzyl-3,4-dihydro-1H-benzo[e][1, 4]diazepine-2,5-dione (4, $C_{16}H_{14}O_2N_2$)

Triethylamine (4.04 g, 0.04 mol) was added to a mixture of 3.02 g isatoic anhydride (0.02 mol) and 3.30 g L-phenylalanine (0.02 mol) in 40 cm^3 water. The mixture was stirred at room temperature for 12 h, and the homogeneous solution was then concentrated under vacuum to give an oily material. The oily residue was dissolved in 50 cm^3 glacial acetic acid. The resulting solution was then heated under reflux for 6 h. The solution was concentrated and the resulting solid was crystallized from 30% ethyl acetate in *n*-hexane to give 4.75 g (89%) pure 4; m.p.: 243–244 °C (238–242 °C in [2]).

N-Demethylbenzomalvin A ($1b$, $C_{23}H_{17}O_3N_2$)

A solution of 3.71 g *o*-nitrobenzoyl chloride (0.02 mol) in 30 cm^3 CH$_2$Cl$_2$ was added drop-wise to a solution of 5.32 g benzodiazepindione 4 (0.02 mol) in 250 cm^3 dry CH$_2$Cl$_2$ containing 2.63 g triethylamine (0.026 mol) and a catalytic amount of DMAP. The system was stirred at room temperature for 3 h, and the reaction mixture was then concentrated, dissolved in ethyl acetate, and passed through a short pad of silica gel to furnish the nitro derivative 5 after drying. The crude residue 5 was dissolved in 300 cm^3 ethyl acetate, and 1.00 g 3% Pd/C was added. The resulting mixture was stirred under a balloon of hydrogen gas. After reduction was complete (4 h), as revealed by TLC monitoring, the reaction mixture was filtered over a pad of Celite. The filtrate was concentrated and the residue was purified by silica gel column chromatography using 25–45% ethyl acetate in *n*-hexane to furnish 4.42 g (60%) $1b$; m.p.: 139–140 °C (140–142 °C in [8]).

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