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A Total Synthesis of AI-77-B

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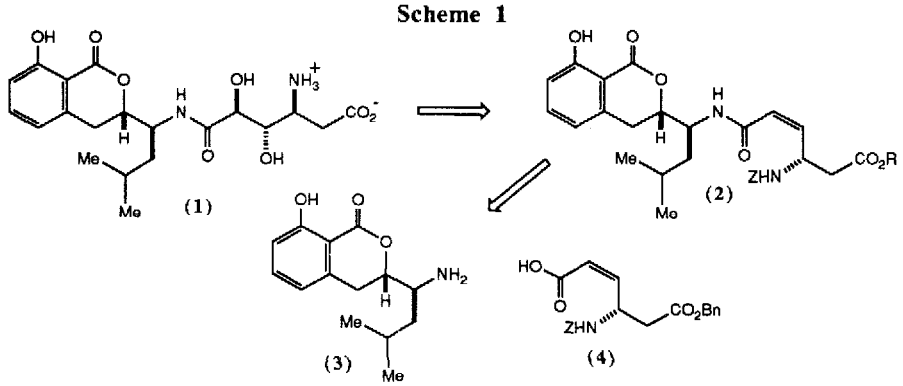
Key Words: Natural Product; AI-77-B; Gastroprotective; Total synthesis; Enantioselective.

Abstract: *A short total synthesis of AI-77-B (1) is reported, which produces the natural enantiomer using S-leucine and S-aspartic acid as the optically active starting materials.*

A number of 3,4-dihydroisocoumarin derivatives bearing hydroxylated amino acid side chains have been isolated from natural sources, and most of these compounds possess potentially useful biological activity.[1] The most intensively studied compound in this class, AI-77-B (**1**), was isolated from *Bacillus pumilus* AI-77 and shown to possess potent gastroprotective activity without being anticholinergic, antihistaminergic, or central suppressive.[1a,2] Total syntheses of AI-77-B have been reported,[3] and a number of alternative preparations of the hydroxylated amino acid portion are available.[3,4] In this Letter we report a short, practical total synthesis of the natural enantiomer of AI-77-B.

The synthetic plan which was followed is outlined in Scheme 1. This plan was adopted in an attempt to provide a relatively short route to AI-77-B using the minimum of protecting groups, and which in principle could be used to provide related compounds.

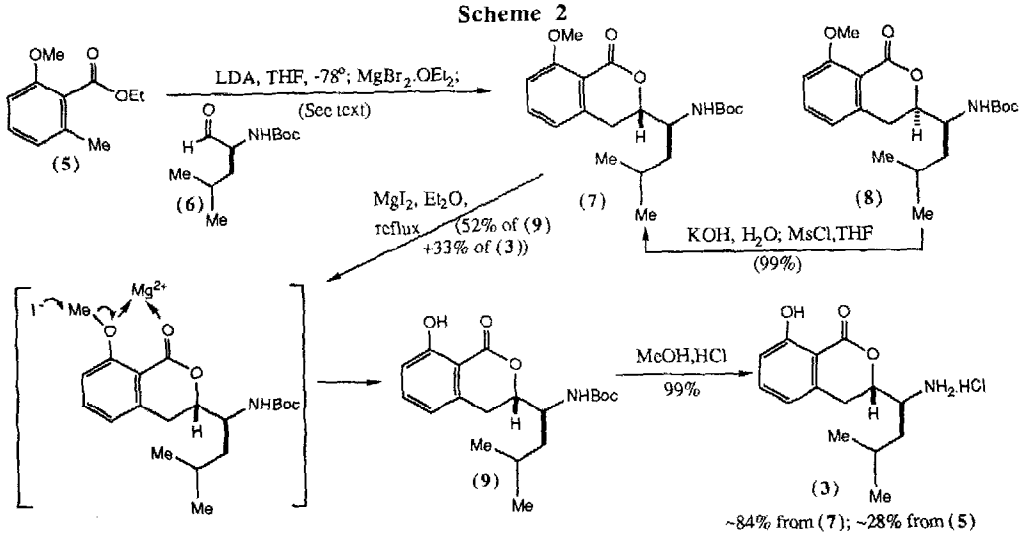
Scheme 1



By analogy with a previous synthesis of mellein[5] it was anticipated that the 'aromatic unit' (3) could be prepared by the addition of the anion derived from (5) to N-(t-butoxycarbonyl)leucinal (6), an approach which was used in the first total synthesis of AI-77-B.[3a] In our hands the addition of the lithium anion of (5) to (6) was found to to be difficult to reproduce, and yields were always low. After considerable experimentation we found that the 'magnesium' anion of (5) (Scheme 2) provided a reproducible yield of the desired lactone, and that a further quantity of this material could be obtained by inverting[6] the undesired diastereoisomer (Scheme

2) and by cyclisation of any un-lactonised product (the ratio of (7):(8) was *ca.* 2.2:1, and the total yield of (7) after the above processing was routinely *ca.* 33%). Although far from ideal, this protocol did allow the preparation of gram quantities of the lactone (7) from readily available starting materials. O-Demethylation was achieved by treatment of (7) with magnesium iodide (generated *in situ*) to give (9) along with some fully deprotected amine hydrochloride (3) after processing. Magnesium iodide was chosen for this demethylation in the expectation that the combination of a strongly chelating cation and nucleophilic anion would allow for selective methyl cleavage *via* the intermediate illustrated in Scheme 2.[7] Conversion of (9) into (3) then provided a total overall yield of 84% [from (7)] of the desired hydrochloride.

Scheme 2

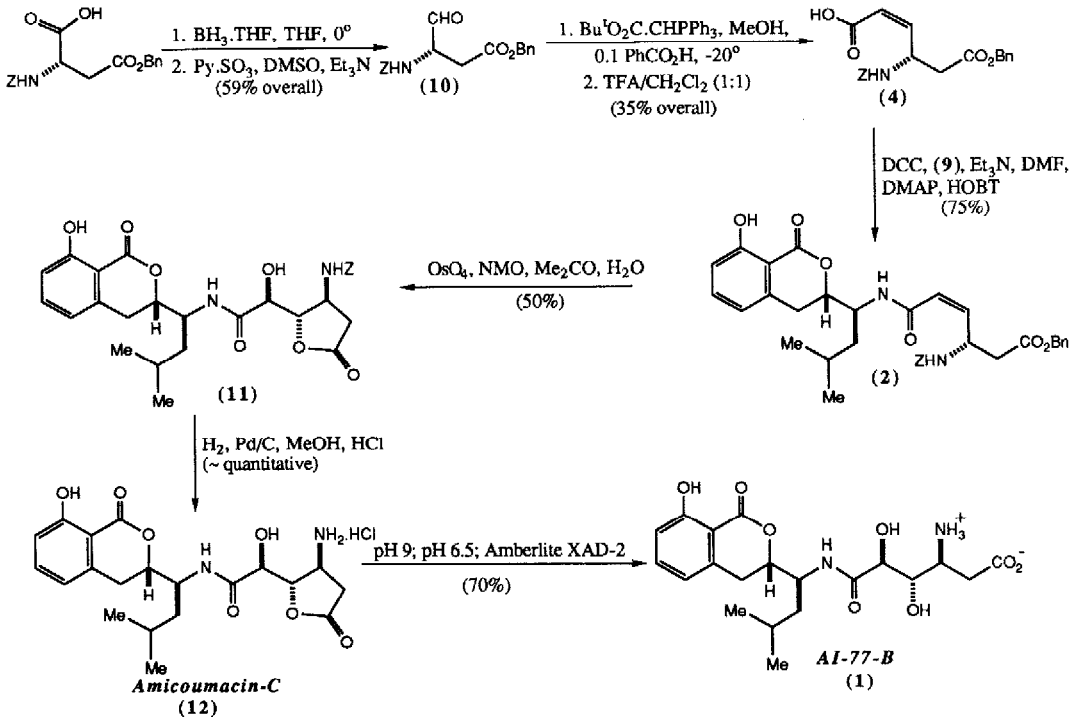


The precursor for the hydroxylated amino acid unit (4) was prepared from the aldehyde (10), itself easily prepared from commercially available β-benzyl-N-benzyloxycarbonyl-L-aspartate (Scheme 3). We were unable to achieve better than 1:1 *cis:trans* olefin in the Wittig coupling of aldehyde (10) with t-butyl triphenylphosphoranylidene)acetate. Nevertheless the combined yield is high, and on a large scale the desired *cis*-isomer can be made to crystallise directly from the reaction mixture thereby making this approach highly attractive for practical synthesis (the yield of pure, recrystallised olefin is *ca.* 37%). Olefinic acid (4) was then coupled with the 'aromatic unit' in good yield [up to 15% of the *trans*-(2) was isolated from this reaction depending on conditions and reagents].

The final asymmetric centres were then introduced by dihydroxylation using catalytic osmium tetroxide. It was hoped that some diastereoselectivity might be observed in the osmylation of (2), but in practice the diastereoselectivity was very low. Attempts to achieve 'double asymmetric induction' (and thereby improve the diastereoselectivity) using Sharpless' enantioselective catalysts were also unsuccessful.[8] Nevertheless, when run on a 400mg scale the dihydroxylation provided a 50% yield of the desired γ-lactone (11), the diol resulting from attack on the 'undesired' face of the alkene did not close to a γ-lactone under the reaction conditions, making isolation and identification of both products straightforward. Catalytic hydrogenolysis of (11) in the presence of HCl gave a quantitative yield of (12), a compound isolated from the fermentation of *Bacillus pumilus* BN-103 and known as amicoumacin-C.[1c] Synthetic amicoumacin-C was then converted into AI-77-B to provide material with tlc, optical rotation,high resolution FAB mass spectrum, ir spectrum, and

^{1}Hnmr spectrum identical to those of an authentic sample. Analogous hydrogenolysis of the diol obtained from (2) gave a compound isomeric with AI-77-B at the hydroxyl-bearing carbons.

Scheme 3



In conclusion we have prepared the natural enantiomers of AI-77-B, amicoumacin-C, and an analogue of AI-77-B with opposite absolute configuration at the hydroxyl-bearing carbons, by a route which has the potential for further refinement and analogue synthesis.

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