Total Synthesis of AI-77-B

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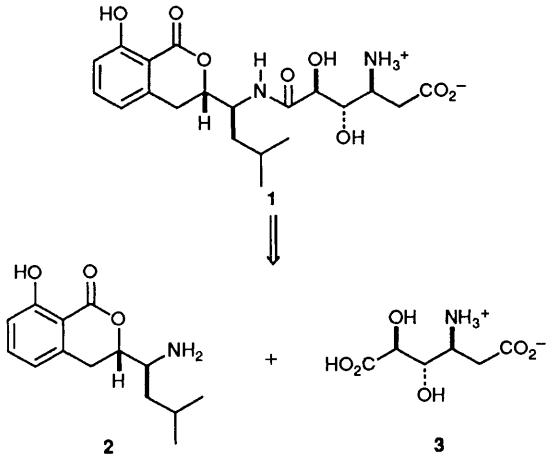
Stereoselective hydroxylation of the β-lactam ester **8** is a key step in a total synthesis of AI-77-B **1**.

The AI-77s are a small family of 3,4-dihydroisocoumarin derivatives isolated from a culture broth of *Bacillus pumilus* AI-77.[1] AI-77-B **1** exhibits biological activity against stress ulcers in rats, yet is non-central suppressive, non-anticholinergic and non-antihistaminergic.[2] Aspects of the chemistry and synthesis of AI-77-B have been studied,[3–5] the first total synthesis having been described in 1989.[6]

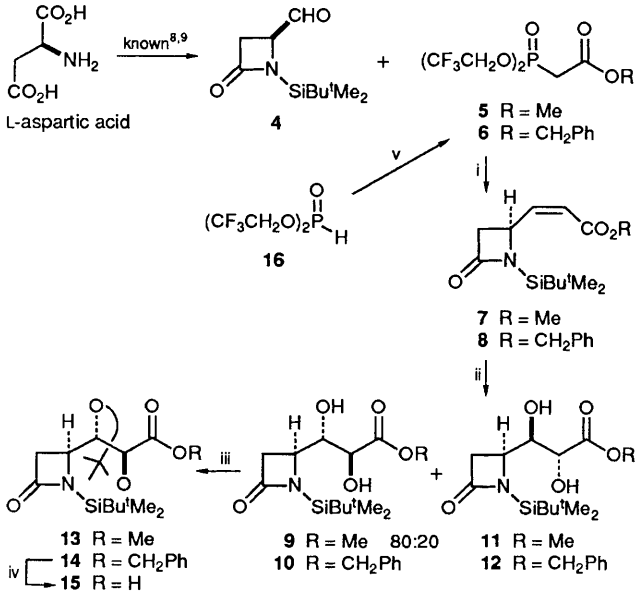
AI-77-B is a dipeptide derived from the 3,4-dihydroisocoumarin **2** and the amino acid **3**. Since the latter is a β-amino acid, it was decided to investigate its synthesis from a homochiral β-lactam, introducing the hydroxy substituents by *cis*-hydroxylation. β-Lactams have recently been used in other β-amino acid syntheses.[7] We now report a total synthesis of AI-77-B using this approach.

The β-lactam aldehyde **4** is available in five steps from aspartic acid,[8,9] and was condensed with methyl bis(2,2,2-trifluoroethyl)phosphonoacetate **5**[10] to give the (*Z*)-α,β-unsaturated ester **7**. Oxidation using a catalytic amount of osmium tetroxide and *N*-methylmorpholine-*N*-oxide was found to be moderately stereoselective, and gave a mixture of diols **9** and **11**, ratio *ca.* 80 : 20. The major diol was shown to be

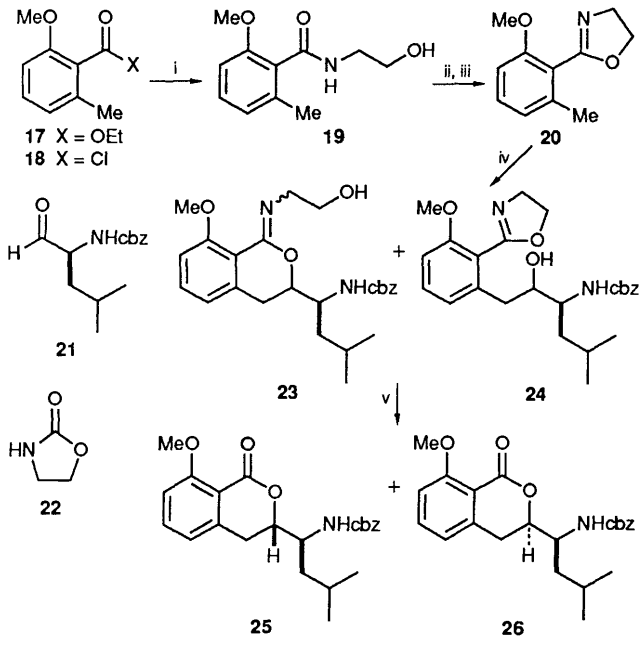


1

2 **3**



Scheme 1 *Reagents and conditions*: i, 18-c-6, K_2CO_3, toluene, −22 to −0°C, 1 h (**7** 70%; **8** 76%, *Z* : *E* = 85 : 15); ii, OsO_4(0.1 equiv.), *N*-methylmorpholine-*N*-oxide, acetone–H_2O, 3 d, (75%); iii, 2,2-dimethoxypropane, toluene-*p*-sulphonic acid (cat.) (**13** 58%; **14** 75%); iv, H_2 (1 atm.), 10% Pd/C, EtOH (97%); v, NaH, benzene, 0.5 h, room temp. then $BrCH_2CO_2CH_2Ph$, tetrahydrofuran (THF), 48 h (45%)



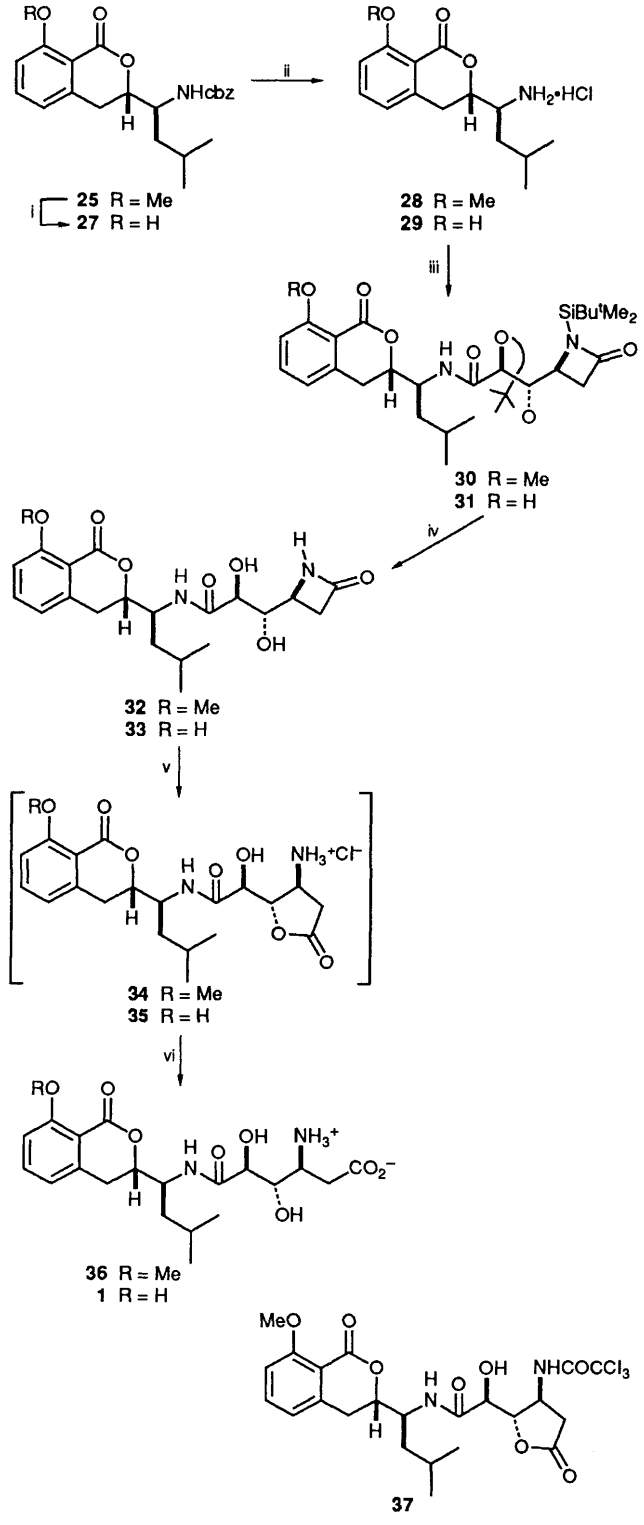
Scheme 2 *Reagents and conditions*: i, **18** + **22**, 70 °C, 2 h, then NaOH, aq. EtOH, reflux, 2 h; ii, thionyl chloride, reflux 2 h; iii, NaOH, aq. EtOH, reflux 2 h (65% of **20** from **18**); iv, n-butyl-lithium, THF, −78 °C, 30 min, add to **21**-MgCl (from **21** + *tert*-BuMgCl, THF, −78 °C); v, silica, CH_2Cl_2, room temp., 18 h (45% of **25** and **26** from **21**)

the required (2′*S*,3′*S*,4*S*)-diastereoisomer **9** by X-ray diffraction,† and corresponds to hydroxylation having taken place on the *re*-face. The minor product was, therefore, assigned the (2′*R*,3′*R*,4*S*)-stereochemistry **11**. Diol protection gave the acetonide **13**, but attempts to hydrolyse the methyl ester gave only low yields of complex mixtures of products. To prepare the free acid, it was decided to prepare the corresponding benzyl ester which would be removable by hydrogenolysis.

Benzyl bis(2,2,2-trifluoroethyl)phosphonoacetate **6** was prepared by alkylation of bis(2,2,2-trifluoroethyl) phosphite **16**,[11] and was condensed with aldehyde **4** to give the (*Z*)-ester **8** together with a small amount, 11%, of its (*E*)-isomer. Oxidation with osmium tetroxide proceeded as before to give a mixture of diols identified as the (2′*S*,3′*S*,4*S*)- and (2′*R*,3′*R*,4*S*)-isomers **10** and **12**, ratio 80:20, determined by comparison of their ^{1}H NMR spectra with those of the corresponding methyl esters. Diol protection and hydrogenolysis gave the required acid **15**.

In our hands, the chelation controlled addition of ethyl 2-methoxy-6-methylbenzoate **17**[12] to cbz-protected leucinal **21**[13] (cbz = benzyloxycarbonyl) was unreliable as a route to the protected amino-lactone **25**.[6] Instead the acid chloride **18** was converted into the hydroxyamide **19** using oxazolone **22**,[14] and the hydroxyamide cyclized to provide the oxazoline **20**. This was deprotonated using n-butyl-lithium, and the lithiated oxazoline added at −78 °C to cbz-protected leucinal **21**, which had previously been treated with 1 equiv. of *tert*-butylmagnesium chloride, to give a mixture of products identified as the aldol adducts **23** and **24**. This mixture was not separated, rather it was treated with silica in dichloromethane, which effected hydrolysis, and gave a separable mixture of the cbz-protected amino-lactones **25** and **26**, ratio 85:15 (45% from aldehyde **21**). The optical purity of lactone **25** was shown to correspond to an e.e. of at least 90% by examination of its ^{1}H NMR spectrum in the presence of the chiral shift reagent, 1-(9-anthryl)-2,2,2-trifluoroethanol.

† Details of the X-ray determination will be given in a full paper.



Scheme 3 *Reagents and conditions*: i, boron tribromide (2 equiv.), −78 °C, 3 min (72%); ii, H_2, Pd/C, HCl (*ca.* 2 equiv.), Et_2O, EtOH, 5 h (95%); iii, dicyclohexylcarbodiimide (DCC), 4-dimethylaminopyridine, **15**, CH_2Cl_2, 0 °C, 30 min then room temp., 18 h (**30** 65%, **31** 55%); iv, 1:1 aqueous HCl (3 mol dm^{-3})–THF, 0 °C, 30 min then room temp., 6 h (80%); v, NaOH (pH 12), 1:1 H_2O:EtOH, room temp., 18 h, cool to 0 °C, add 3 mol dm^{-3} HCl in MeOH to adjust pH to 1.3, 0 °C. 2 h; vi, NaOH (pH 9), 1:1 H_2O:EtOH, room temp., 18 h, adjust pH to 6.5 (aq. HCl)

Hydrogenolysis of **25** under acidic conditions gave amine hydrochloride **28**, which was coupled with acid **15** to give the protected dipeptide **30**. Deprotection under acidic conditions gave the dihydroxy-dipeptide **32**.

It was decided to investigate hydrolysis of the β-lactam under *basic* conditions by analogy with the conditions used for conversion of the *N*-acylated γ-lactone **37**, available from natural AI-77-B, into AI-77-B methyl ether **36**.[3] Thus, treatment of the β-lactam diol **32** with sodium hydroxide at pH 12 gave a polar intermediate which on acidification to pH 1.3 gave a less polar compound tentatively identified as the bis-lactone **34** by analogy with the literature.[3]‡ Further treatment with sodium hydroxide at pH 9, followed by careful acidification to pH 6.5, then gave AI-77-B methyl ether **36** identified by comparison of its spectroscopic data with those published,[3] and by comparison with authentic AI-77-B.§

Demethylation of the phenolic methyl ether **25** using boron tribromide, followed by hydrogenolysis of the cbz-protecting group under acidic conditions gave the phenolic amine hydrochloride **29**. This was coupled with acid **15** and the dipeptide **31** converted into AI-77-B **1** following the sequence developed using the methyl ether.‡ The synthetic AI-77-B **1** was identified by direct comparison of its spectroscopic and physical data with those of an authentic sample of natural material.§

This synthesis describes an approach to AI-77-B **1** which is suitable for the synthesis of analogues for biological evaluation. Of interest is the preparation of the benzyl phosphonate **6** which should be useful for (*Z*)-alkene synthesis, the use of the oxazoline **22** for the aldol condensation, the selective removal of the phenolic methyl ether from lactone **28** in the presence of the cbz-protected amine, and the stereoselective hydroxylation of esters **7** and **8**. Generally the oxidation of chiral allylic amine derivatives using osmium tetroxide is not usefully stereoselective.[16] The stereoselectivity of the hydroxylation of esters **7** and **8** may be due to the (*Z*)-geometry of the double bond,[17] or to the presence of the bulky *N*-substituent on the β-lactam.

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‡ The IR spectrum of our γ-lactone hydrochloride **35** was identical to that of amicoumacin C, which was identified as **35**, reproduced in the literature.[15] However, its NMR spectrum was slightly different from that reported for the γ-lactone hydrochloride obtained from AI-77-B[3] although identical to that of a sample prepared from authentic AI-77-B following the published procedure in our laboratory: δ_H(CD_3OD, 500 MHz) 0.92 and 0.98 (each 3 H, d, *J* 6 Hz, CH_3), 1.43 (1 H, m, 4′-H), 1.69 (1 H, m, 3′-H), 1.80 (1 H, m, 4′-H), 2.56 (1 H, dd, *J* 18 2 Hz, 11′-H), 2.96–3.09 [2 H, m, C(4)-H_2], 3.22 (1 H, dd, *J* 18, 9 Hz, 11′-H), 4.16–4.23 (2 H, m, 5′-H and 10′-H), 4.46 (1 H, d, *J* 4 Hz, 8′-H), 4.69–4.76 (1 H, m, 3-H), 4.87 (1 H, t, *J* 4 Hz, 9′-H), 6.82 and 6.86 (each 1 H, d, *J* 7 Hz, 5-H and 7-H) and 7.47 (1 H, t, *J* 7 Hz, 6-H). (For the numbering scheme used, see ref. 1.) The spectrum reported in the literature[3] may correspond to the free amine, not the hydrochloride. Full details will be reported in a full paper.

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