PERKIN 1

Total synthesis of AI-77-B: stereoselective hydroxylation of 4-alkenylazetidinones

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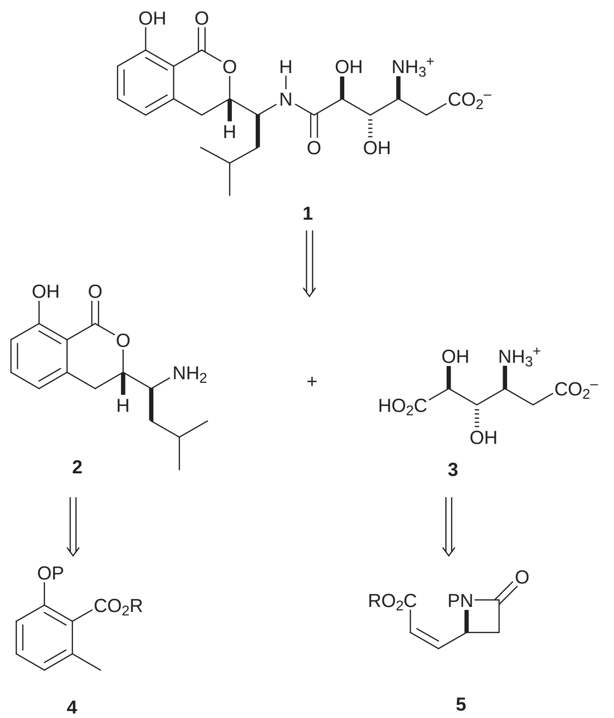
A stereoselective synthesis of the anti-ulcer compound AI-77-B **1** is described. The 4-formylazetidinone **6** was converted into the 4-(*Z*)-alkene **23** using a phosphonate condensation, and dihydroxylation using osmium tetroxide and *N*-methylmorpholine *N*-oxide gave a mixture of the diols **24** and **25** in an 80 : 20, ratio. After protection of the diol **24** as its acetonide, hydrogenolysis gave the acid **27**. The oxazoline **45** was deprotonated using butyllithium, and the lithiated oxazoline added to Cbz-protected leucinal **29**, which had previously been deprotonated by *tert*-butylmagnesium chloride, to give the lactones **30** and **31**, ratio 85 : 15, after treatment with silica in dichloromethane. Hydrogenolysis gave the aminolactone hydrochloride **52** which was condensed with the acid **27** to give the protected dipeptide **54**. Deprotection under acidic conditions gave the dihydroxyazetidinone **55**. Treatment with sodium hydroxide followed by acidification then gave the aminolactone hydrochloride **56** which on further treatment with sodium hydroxide followed by acid gave AI-77-B methyl ether **58**. Demethylation of the phenolic methyl ether **30** followed by hydrogenolysis of the Cbz-protecting group gave the aminophenol **60** which was coupled with the acid **27** and the product taken through to AI-77-B **1** following the sequence used to prepare the methyl ether **58**.

The AI-77's are a small family of 3,4-dihydroisocoumarins and derivatives isolated from a culture broth of *Bacillus pumilus* AI-77.[1] The most abundant member of the series, AI-77-B **1**, shows activity against stress ulcers in rats yet is also non-central suppressive, non-anticholinergic and non-antihistaminergic.[2] Similar compounds, the amicoumacins, have been isolated from *Bacillus pumilus* BN-103.[3] Aspects of the chemistry of the AI-77's have been studied and analogues prepared for biological evaluation.[2] The first total synthesis of AI-77-B was reported in 1989[4] and two other total syntheses and several syntheses of the dihydroxyamino acid component have been described since.[5,6] We here report full details of a total synthesis of AI-77-B **1** which features the use of the oxazoline (4,5-dihydrooxazole) **45** in the synthesis of the 3,4-dihydroisocoumarin **30** and the azetidinone **23** in the preparation of the protected hydroxyamino acid **27**.[7]

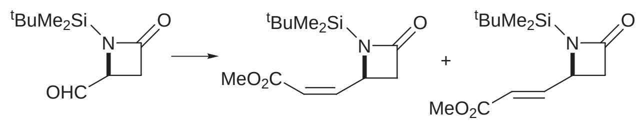
Formally AI-77-B is a dipeptide derived from the 3,4-dihydroisocoumarin **2** and the β-amino acid **3**. It was decided to investigate the synthesis of this amino acid from an azetidinone **5** which would provide simultaneous protection of the amino group and one of the carboxy functions and give scope for the stereoselective introduction of the vicinol diol moiety. At the onset of our work, it was intended to prepare the 3,4-dihydroisocoumarin by chelation controlled addition of a derivative of 2-methoxy-6-methylbenzoic acid **4** (P = Me) to a protected leucinal, as had been carried out in other syntheses of AI-77-B **1**, albeit with some difficulty.[5]



Results and discussion

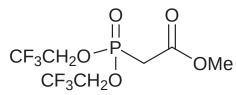
The 4-formylazetidinone **6** was prepared following the literature procedure,[8] and its conversion into the (*Z*)- and (*E*)-alkenes **7** and **8** investigated. The (*E*)-alkene **8** was the major product using (methoxycarbonylmethylene)triphenylphosphorane in methanol at 0 °C and was the exclusive product with this ylide or trimethyl phosphonoacetate and sodium hydride in tetrahydrofuran. However, the (*Z*)-alkene **7** was prepared in good yield using the bis(trifluoroethyl) phosphonate **9**[9] although better results were obtained using potassium carbonate rather than potassium hexamethyldisilazide as the base because of increased β-lactam decomposition in the presence of the stronger base. The structures of the alkenes **7** and **8** followed from their spectroscopic data and hydrogenation to the saturated ester **10**.

The stereoselectivity of hydroxylation of the (*Z*)-alkene **7** was investigated using both osmium tetroxide–*N*-methylmorpholine *N*-oxide and osmium tetroxide in the presence of quinine and quinidine ligands.[10] In all cases the preferred product was the (1′*S*,2′*S*)-diastereoisomer **11** with reasonable stereoselectivity being obtained using osmium tetroxide–*N*-methylmorpholine *N*-oxide, **11** : **12** = 82 : 18. This selectivity was enhanced, **11** : **12** = 92 : 8, when matched with the quinine ligand



6 7 8

Reagents and conditions	Isolated yields (%) 7	8
Ph_3P=$CHCO_2Me$ in MeOH, 0 °C	30	58
$(MeO)_2P(O)CH_2CO_2Me$, NaH in THF, 0 °C	—	70
9, K_2CO_3, 18-C-6, THF, 0 °C	70	—



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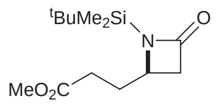

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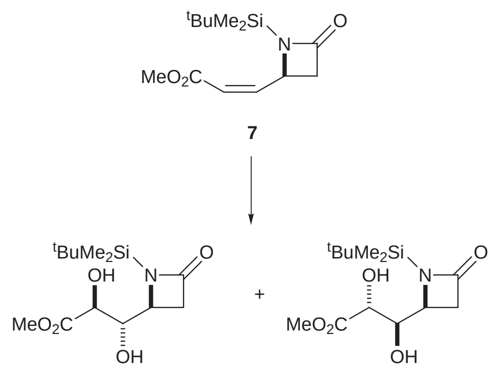


7

11 12

Reagents and conditions	Combined yields (%) of **11** and **12**	Ratio **11**:**12**
1% OsO_4, 25% dihydroquinine *p*-chloro-benzoate, *N*-methylmorpholine *N*-oxide	80	92:8
Stoichiometric OsO_4, dioxane	86	83:17
5% OsO_4, *N*-methylmorpholine *N*-oxide, acetone, water	71	82:18
1% OsO_4, 25% dihydroquinidine *p*-chloro benzoate, *N*-methylmorpholine *N*-oxide	80	75:25

and slightly reduced, but not overturned, **11**:**12** = 75:25, by the presence of the mismatched quinidine ligand.

The structures assigned to the diols **11** and **12** were supported by their spectroscopic data. The (1′*S*,2′*S*)-configuration was assigned to the major product **11** by analogy with the reported hydroxylation of the 4-alkenylazetidinone **13**,[11] which gave the diols **14** and **15**, ratio 75:25, and is consistent with the matching and mismatching observed using the quinine and quinidine ligands. The stereoselectivity is consistent with approach of the osmium tetroxide on the less hindered face of the preferred conformation of the alkene as indicated in Fig. 1. Interestingly reasonable stereoselectivity was also observed for the hydroxylation of the (*E*)-alkene **8** using osmium tetroxide–*N*-methylmorpholine *N*-oxide with the two diastereoisomeric diols **16** and **17** being obtained in a ratio of 80:20. Structure **16** was assigned to the major product in this case also by analogy with the reported stereoselectivity of hydroxylation of **13**.[11]

N-Desilylation of the diol **11** using an acidic Dowex ion exchange resin gave **18** which was converted into the NH-acetonide **19** using 2,2-dimethoxypropane and acetone in the

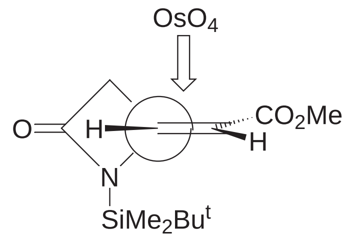
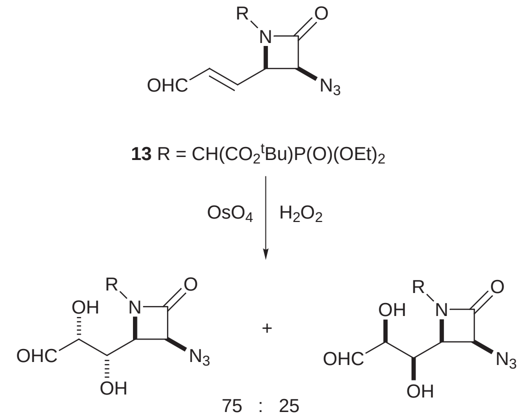
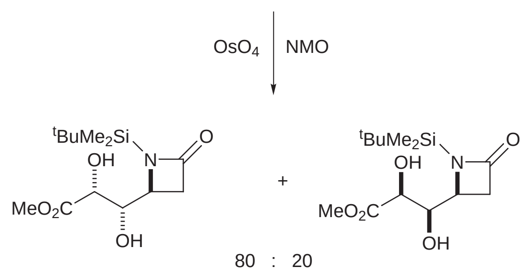


Fig. 1 Preferred approach of osmium tetroxide to the alkene **7**.



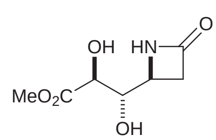
13 R = $CH(CO_2{}^tBu)P(O)(OEt)_2$

14 15



16 17

presence of a trace of toluene-*p*-sulfonic acid as catalyst, but attempts to convert this into the corresponding carboxylic acid **20** were unsuccessful. Attempts at saponification of the ester, *e.g.* by using lithium hydroxide in aqueous methanol or sodium hydroxide in aqueous methanol–tetrahydrofuran, or attempts to effect an S_N2 type of displacement of the methyl ester using lithium iodide or trimethylsilyl iodide all resulted in the formation of very polar decomposition products.



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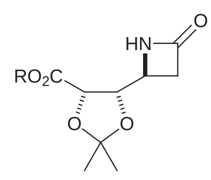
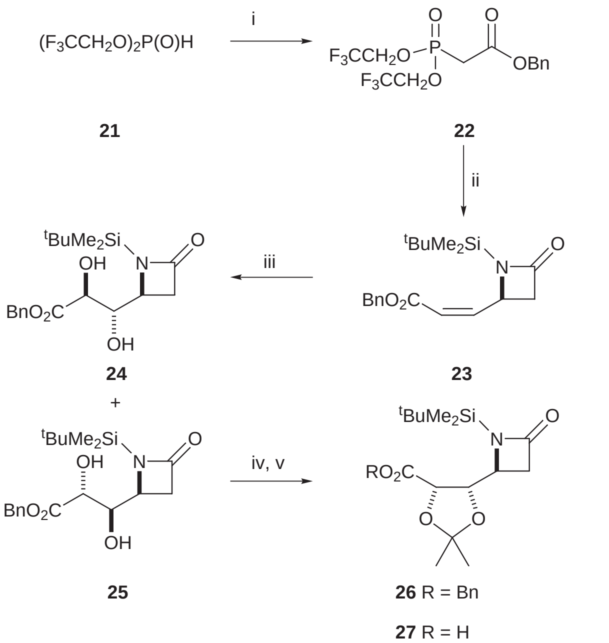


19 R = Me

20 R = H

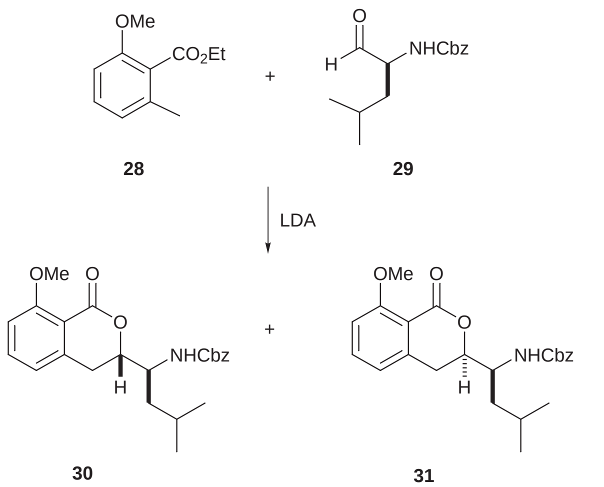
The corresponding benzyl ester was prepared to avoid this methyl ester cleavage. Bis(trifluoroethyl) phosphonate **21** was prepared from phosphonic dichloride and 2,2,2-trifluoroethanol,[12] and was alkylated using benzyl bromoacetate to give the benzyl bis(trifluoroethyl) phosphonoacetate **22**. Condensation with the aldehyde **6** was achieved using potassium carbonate in the presence of 18-crown-6 and gave the (*Z*)-benzyl ester **23** together with its (*E*)-isomer, ratio *ca.* 85:15, respectively. Hydroxylation of the (*Z*)-ester **23** using a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide



Scheme 1 *Reagents and conditions*: i, NaH, $BrCH_2CO_2Bn$ (45%); ii, **6**, K_2CO_3, 18-C-6 [76%; (*Z*) : (*E*) = 85 : 15]; iii, OsO_4 (cat.), NMO, acetone–water (75%; **24** : **25** = 80 : 20); iv, $Me_2C(OMe)_2$, TsOH (cat.) (75%); v, H_2 (1 atm), Pd/C, EtOH (97%).

gave the vicinal diols **24** and **25**, ratio 80 : 20, and protection using 2,2-dimethoxypropane followed by hydrogenolysis gave an excellent yield of the required acid **27**. In this sequence, see Scheme 1, the stereoselectivity of the phosphonate condensation was established by ^{1}H NMR, and the facial selectivity in the hydroxylation reaction was assigned by analogy with the stereoselectivity of hydroxylation of the methyl ester **7** and by comparison of the ^{1}H NMR spectra of the diols **24** and **25** with those of **11** and **12**.

In other synthetic approaches to the AI-77's, the 3,4-dihydroisocoumarin is usually obtained by chelation controlled addition of a lithiated 2-alkoxy-6-methylbenzoate to a protected leucinal.[4–6] However in our hands, deprotonation of the ethyl 2-methoxy-6-methylbenzoate **28**[13] using lithium diisopropylamide followed by addition of benzyloxycarbonyl protected leucinal **29** gave variable yields of the lactones **30** and **31**, although the stereoselectivity was good, *ca.* 92 : 8, in favour of the required stereoisomer **30**.



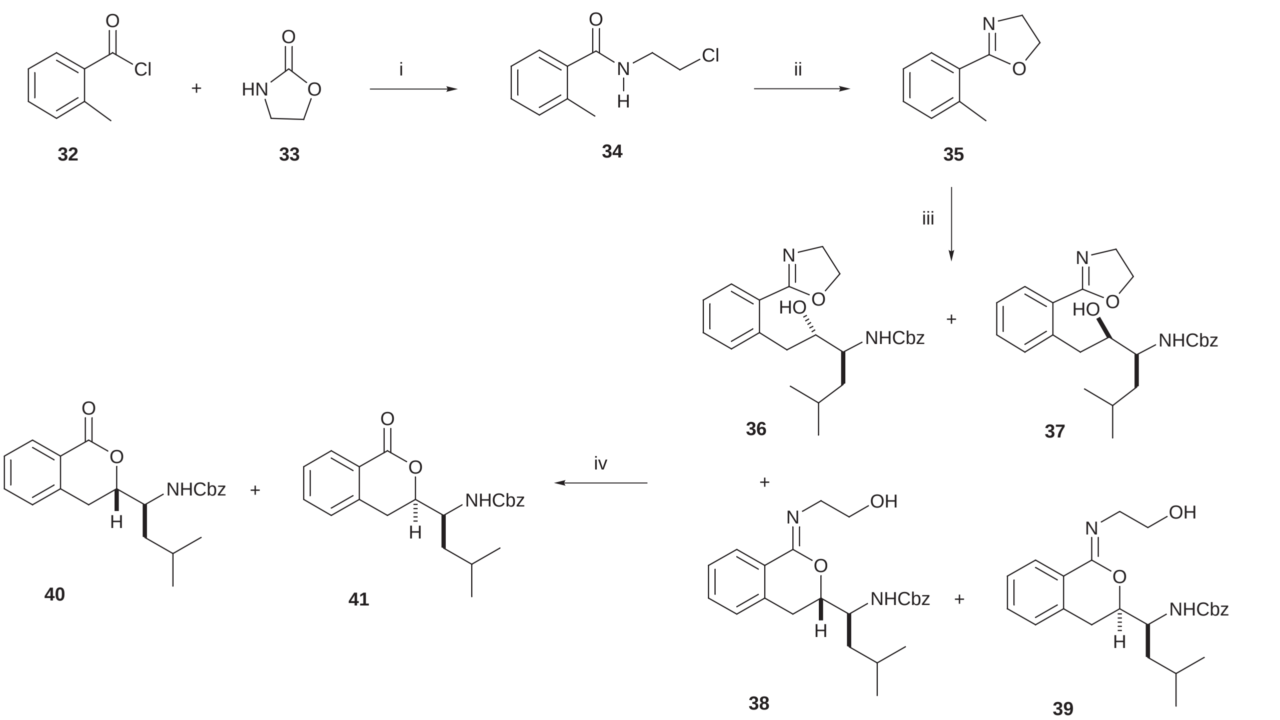
It was decided to study the addition of heterocyclic synthetic equivalents of the ester **28** to protected leucinal to see whether a more reliable procedure could be obtained. To evaluate this possibility, *o*-toluoyl chloride **32** and oxazolidin-2-one **33** were heated together to give the amide **34** which was cyclised to the oxazoline **35** by treatment with base, see Scheme 2.[14] The oxazoline was then deprotonated using butyllithium and the lithiated oxazoline added to Cbz-protected leucinal **29**[15] which had been deprotonated using *tert*-butylmagnesium chloride. On work-up of this reaction, a mixture of four products was obtained which was believed to include the oxazolines **36** and **37** together with the iminolactones **38** and **39** (combined yield 32%). Rather than attempt to separate this mixture, it was hydrolysed by aqueous hydrogen chloride to give a mixture of the lactones **40** and **41**, ratio 87 : 13, respectively, from which the major diastereoisomer **40** was isolated in a 62% yield (based on the mixture of **36**–**39**).

The structures of the lactones **40** and **41** were consistent with their spectroscopic data, and **40** was identified as the major product on the basis of chelation control of the addition to the Cbz-leucinal **29**.[4–6] Although the yields of products **36**–**39** from the reaction between the oxazoline **35** and the Cbz-protected leucinal **29** were only modest, it was decided to see whether this procedure could be applied to synthesize the required lactone **30**.

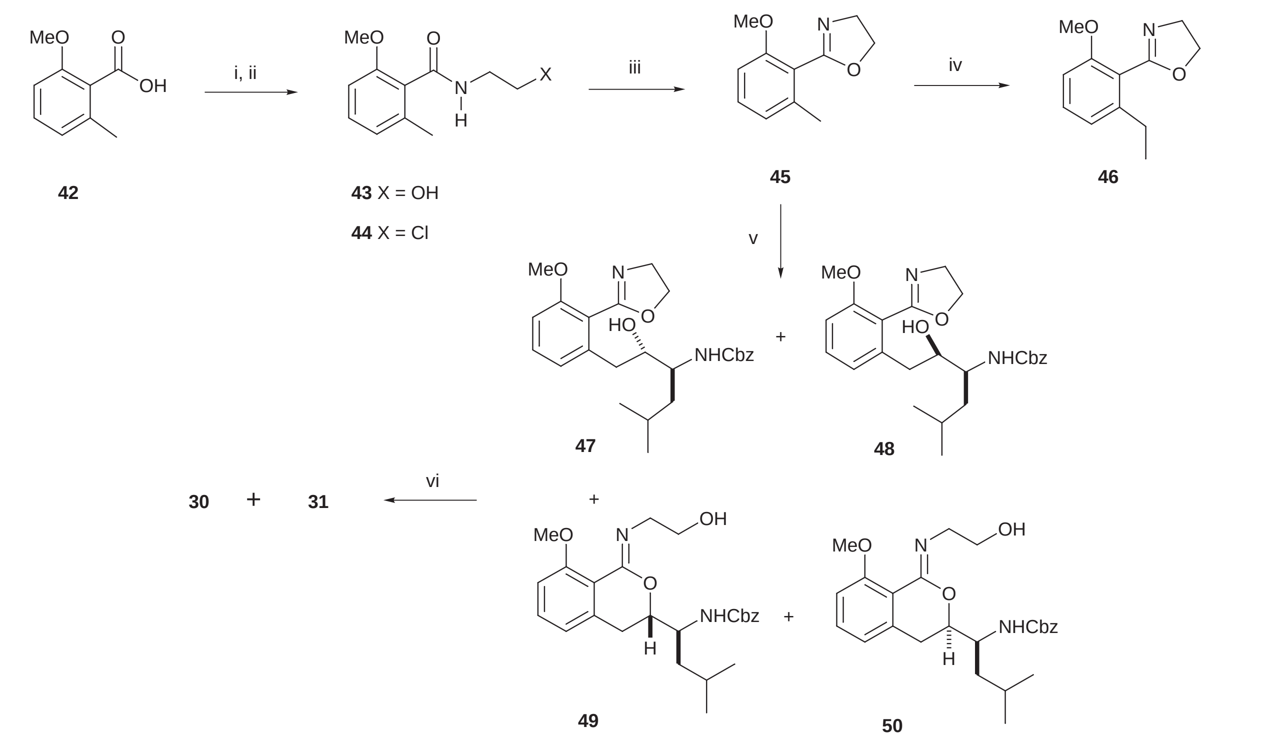
2-Methoxy-6-methylbenzoic acid **42**[13] was converted into its acid chloride which was treated with oxazolidin-2-one **33** followed by sodium hydroxide to give the *N*-hydroxyethyl amide **43** (Scheme 3). Treatment of this with thionyl chloride and then with sodium hydroxide gave the oxazoline **45**. Deprotonation of this oxazoline using butyllithium followed by the addition of an excess of methyl iodide gave an excellent yield of the methylated product **46** so confirming the conditions required for efficient oxazoline deprotonation.

Addition of the lithiated oxazoline to Cbz-leucinal **29** which had been previously deprotonated using *tert*-butylmagnesium chloride gave a mixture of products believed to include the oxazolines **47** and **48** together with the iminolactones **49** and **50**. This mixture was most conveniently converted into the required lactones by treatment with a suspension of silica gel in dichloromethane to give a mixture of the lactones **30** and **31** in a 44% yield from Cbz-leucinal **29**, ratio **30** : **31** = 87 : 13. The lactone **30** required for the synthesis of AI-77-B was isolated as a single diastereoisomer in a yield of 30% from Cbz-leucinal. Although the yields in this sequence were not significantly better than those obtained by the direct addition of the lithiated ester **28** to Cbz-leucinal **29**, in our hands it was a more reliable procedure and amenable to scaling up. The optical purity of the lactone **30** was estimated to correspond to an enantiomeric excess (ee) greater than 90% by comparison of its ^{1}H NMR spectra in the presence of the shift reagent 1-(9-anthryl)-2,2,2-trifluoroethanol **51**[16] with those of material with low ee in which peaks due to both enantiomers were clearly distinguished. At this point it was decided to develop the conditions for the final stages of a synthesis of AI-77-B by attempting a synthesis of its phenolic methyl ether.

Hydrogenolysis of the benzyloxycarbonyl protected amino-lactone **30** was carried out under acidic conditions to avoid rearrangement to the corresponding hydroxylactam, and gave the amino-lactone hydrochloride salt **52** (Scheme 4). Using dicyclohexylcarbodiimide and 4-dimethylaminopyridine, this was coupled with isobutyric acid to give the amide **53** so establishing conditions for amide formation. The hydrochloride salt **52** was then coupled with the acid **27** to give the protected dipeptide **54**. To get a consistent yield (65%) for this reaction it was necessary to use redistilled dicyclohexylcarbodiimide and recrystallized 4-dimethylaminopyridine. Other coupling procedures, *e.g.* using mixed anhyrides, were less successful in our hands. Deprotection under acidic conditions followed by a sodium bicarbonate work-up gave a product identified as the dihydroxyalkylazetidinone **55** rather than the amine corresponding to the hydrochloride salt **56** on the basis of two different NH-protons evident in its ^{1}H NMR spectrum in dimethyl sulfoxide-d_6. Treatment of the azetidinone **55** with sodium



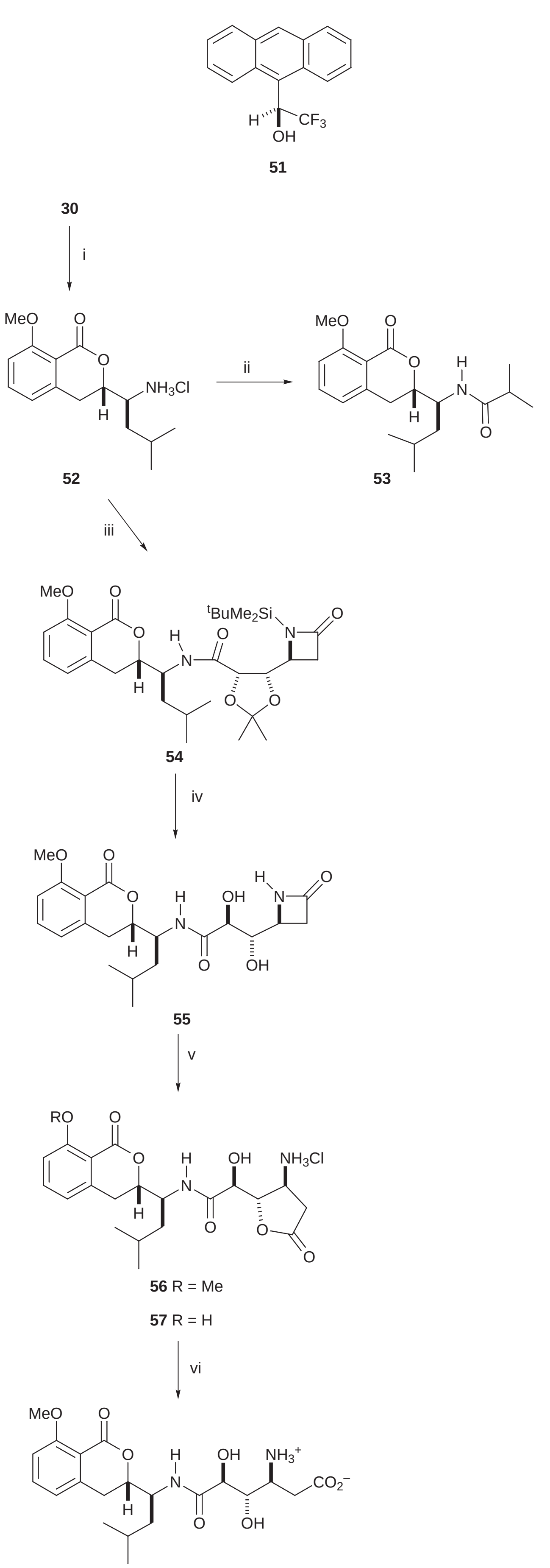
Scheme 2 *Reagents and conditions*: i, heat to 140 °C; ii, NaOH, EtOH (59% from **31**); iii, BuLi, **29**·MgCl (32%); iv, aq. HCl then sat. aq. $NaHCO_3$ (77%; **40**:**41** = 87:13; isolated yield of **40**, 62%).



Scheme 3 *Reagents and conditions*: i, thionyl chloride then **33**, 65 °C followed by NaOH, EtOH; ii, thionyl chloride, heat under reflux 1.5 h; iii, NaOH, EtOH, heat under reflux 1.5 h (65% of **45** based on acid **42**); iv, BuLi, −78 °C, 30 min, then MeI (96%); v, BuLi, **29**·MgCl; vi, silica gel, CH_2Cl_2 (44% of **30** and **31** based on **45**; **30**:**31** = 87:13; 30% of **30** isolated as a single diastereoisomer).

hydroxide followed by acidic methanol then gave the amino-lactone hydrochloride salt **56**. The structure of this bis-lactone was consistent with its spectroscopic data including an absorbance in its IR spectrum at 1788 cm^{-1} which agrees with that reported for amicoumacin C **57**.[3] Presumably in this conversion of the azetidinone **55** into the bis-lactone **56**, both the δ-lactone and the azetidinone are being cleaved by the sodium hydroxide with bis-lactonisation occurring on treatment with acid. No attempt was made to open the azetidinone selectively. It remained to hydrolyse selectively the γ-lactone ring of the bis-lactone **56** in the presence of the δ-lactone. Following the literature procedure,[2] this was achieved by treatment with sodium hydroxide at pH 9 followed by careful acidification, and gave AI-77-B methyl ether **58** in a yield of 70% based on the dihydroxyalkylazetidinone **55**. The spectroscopic data of the synthetic methyl ether **58** agreed fully with those reported for material prepared from natural AI-77-B.[2]

Cleavage of the methyl ether of the amido-lactone **30** was



Scheme 4 *Reagents and conditions*: i, H_2, Pd/C, HCl, EtOH (100%); ii, Pr^iCO_2H, DCC, DMAP, CH_2Cl_2 (70%); iii, **27**, DCC, DMAP (65%); iv, 1 : 1 aq. HCl (3 M)–THF (82%); v, NaOH, pH 12 then HCl, MeOH; vi, NaOH, pH 9 then aq. HCl, pH 6.5 (70% from **55**).

achieved by rapid treatment at low temperature with boron tribromide[17] and gave the corresponding phenol **59** (Scheme 5). Hydrogenolysis under acidic conditions gave the amine hydrochloride **60** which was coupled with the acid **27** using dicyclohexylcarbodiimide to give the amide **61**. The sequence developed for the synthesis of AI-77-B methyl ether **58** was then used to convert the azetidinone **61** through to AI-77-B **1**. Thus hydrolysis under acidic conditions gave the dihydroxyalkylazetidinone **62**. This azetidinone **62** was converted into the amino-lactone hydrochloride **57**[3] by treatment with sodium hydroxide and then with methanolic hydrogen chloride. Further treatment with sodium hydroxide followed by mild acidification finally gave synthetic AI-77-B **1**.

The structure of the synthetic AI-77-B **1** was confirmed by direct comparison of its ^{1}H and ^{13}C NMR, IR, UV and MS data with those of an authentic sample of the natural product. The only discrepancies between our data and those reported for the natural product were the coupling constants reported for the diastereotopic protons at C(5) and the proton at C(4). In our spectra of the synthetic AI-77-B and the sample of the natural product, which were the same within experimental error in both methanol-d_4 and in dimethyl sulfoxide-d_6, the higher field H(5) had the larger coupling to H(4) (*ca.* 10 Hz) whereas in the spectrum reported[1] for AI-77-B **1** in dimethyl sulfoxide-d_6, it is the lower field H(5) which has the larger coupling to H(4) (9 Hz).

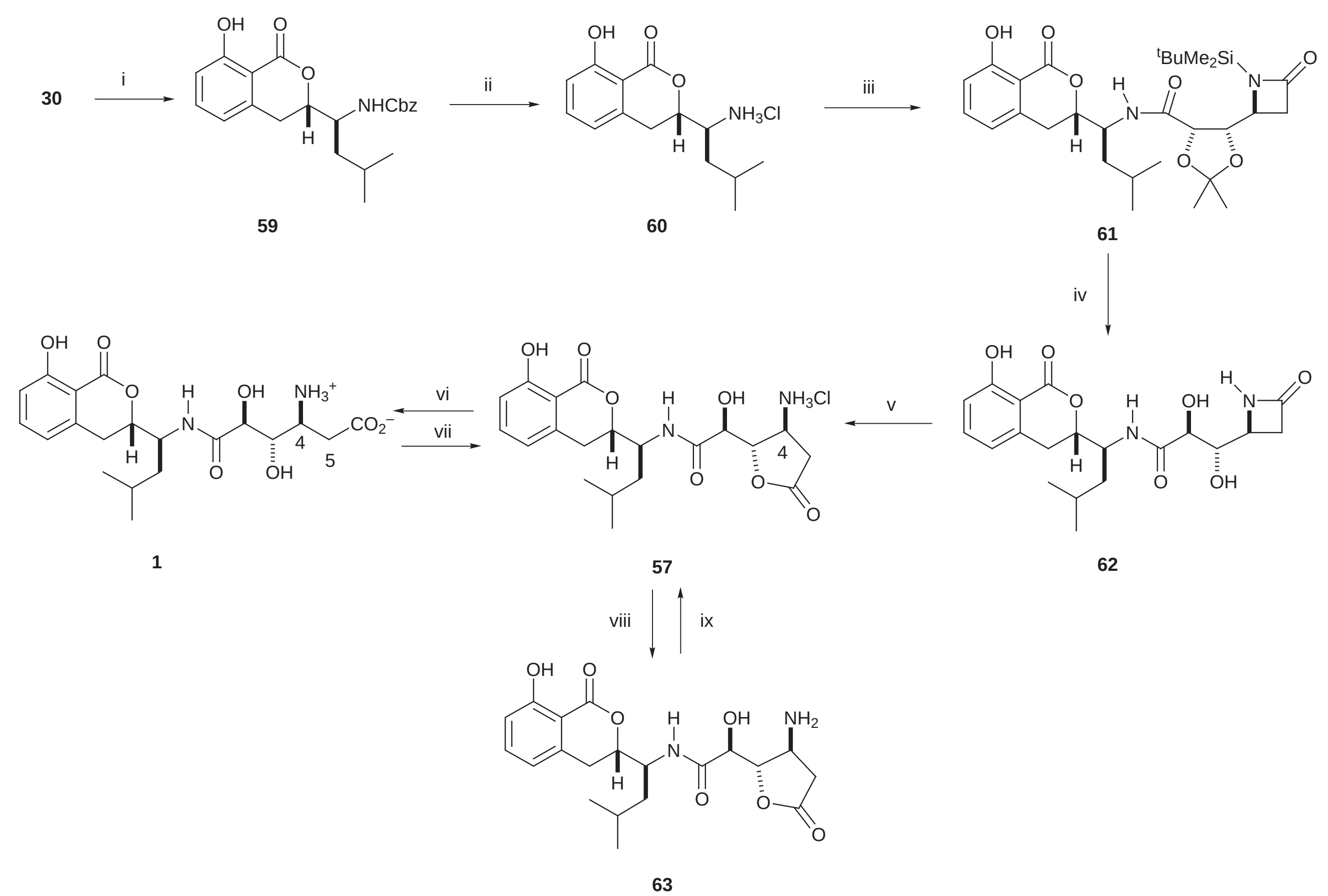
The chemical shift of H-4 of the synthetic amino-lactone hydrochloride **57**, which is itself a natural product, amicoumacin C,[3] was also different from that reported for material prepared from AI-77-B (δ 4.18 *cf.* δ 3.72).[2] However, its IR spectrum is identical to that reproduced[3] for amicoumacin C, and treatment of natural AI-77-B with acidic methanol gave amino-lactone hydrochloride **57** which was identical to that obtained from rearrangement of the dihydroxyazetidinone **62**. Treatment of this hydrochloride with sodium carbonate gave the free amino-lactone **63** which had spectra identical to those reported[2] for the amino-lactone hydrochloride **57** and which, on reprotonation with methanolic hydrogen chloride, regenerated the amino-lactone hydrochloride **57**. It would appear that the published data for the amino-lactone hydrochloride **57** may well refer to the free amino-lactone **63**.

Summary and conclusions

This work describes a stereoselective synthesis of the anti-ulcer compound AI-77-B **1**. Of interest is the stereoselectivity of the hydroxylation of the (*E*)- and (*Z*)-4-alkenylazetidinones **8** and **7/23**, and the use of the oxazolines **35** and **45** in the syntheses of the 1*H*-2-benzopyran-1-ones **30/31** and **40/41**. This work provides additional access to AI-77's and related dipeptides and may be useful for the synthesis of analogues.

Experimental

^{1}H NMR spectra were recorded on Varian Unity 500, Bruker AC 300, Varian XL 300, JEOL GX 270 and Varian Gemini 200 spectrometers in chloroform-d_1 unless otherwise stated. ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer operating at 75 MHz. *J* Values are given in Hz. IR spectra were recorded on a Perkin-Elmer 1710FT spectrometer as liquid films unless otherwise stated. Mass spectra were recorded on a Kratos MS25 mass spectrometer using electron impact (EI), chemical ionisation (CI) and fast atom bombardment (FAB) ionisation. Ultraviolet spectra were recorded on a Shimadzu UV260 spectrometer. Melting points were determined on a Kofler Block apparatus and are uncorrected. Optical rotations were recorded on an Optical Activity AA100 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Flash column chromatography was carried out using Merck silica gel 60H (40–63 μ, 230–300 mesh) or May and Baker Sorbsil C60 (40–60 μ) silica



Scheme 5 *Reagents and conditions*: i, BBr_3, CH_2Cl_2, −78 °C, 3 min (72%); ii, H_2, Pd/C, EtOH (95%); iii, **27**, DCC, DMAP, CH_2Cl_2 (54%); iv, 1 : 1 aq. HCl (3 M)–THF (74%); v, NaOH, pH 12 then HCl, MeOH; vi, NaOH, pH 9 then HCl, MeOH, pH 6.5 (72% from **62**); vii, HCl, MeOH; viii, aq. Na_2CO_3 (40%); ix, HCl, MeOH.

gel as the stationary phase. Light petroleum refers to the fraction boiling between 40 and 60 °C and was redistilled before use. All reagents and solvents were purified and/or dried by standard procedures.

(4*S*,1′*Z*)-1-*tert*-Butyldimethylsilyl-4-(2-methoxycarbonylethenyl)azetidin-2-one 7

A slurry of finely-ground potassium carbonate (643 mg, 4.66 mmol) and 18-crown-6 (2.36 g, 8.94 mmol) in dry toluene (5 cm^3) was stirred at room temperature for 24 h then cooled to −25 °C and a solution of the 4-formylazetidinone **6**[8] (500 mg, 2.35 mmol) and the bis(trifluoroethyl) phosphonate **9** (795 mg, 25 mmol) in toluene (5 cm^3) was added. The mixture was allowed to warm to 0 °C and was stirred for 1 h. Saturated aqueous ammonium chloride (10 cm^3) was added and the mixture extracted with ether. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (3 : 1) as eluent gave the *title compound* **7** (442 mg, 70%), $[a]_D^{20}$ −48 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 1750, 1720, 1645, 1465, 1438, 1410, 1285, 1252, 1200, 1180, 990, 837 and 820; δ_H 0.15 and 0.21 (each 3 H, s, $SiCH_3$), 0.96 [9 H, s, $SiC(CH_3)_3$], 2.72 (1 H, dd, *J* 15, 3, 3-H), 3.47 (1 H, dd, *J* 15, 6, 3-H′), 3.72 (3 H, s, CO_2CH_3), 5.2 (1 H, m, 4-H), 5.90 (1 H, dd, *J* 11.5, 1, 2′-H) and 6.25 (1 H, dd, *J* 11.5, 9, 1′-H); *m*/*z* (CI) 270 (M^+ + 1, 100%).

The (*Z*)-4-alkenylazetidinone **7** (269 mg, 1 mmol) was dissolved in ethyl acetate (20 cm^3), palladium (10% on charcoal; 21 mg, 0.02 mmol) was added and the mixture stirred under an atmosphere of hydrogen (14 bar) for 16 h. The catalyst was filtered off and the filtrate concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (6 : 1 to 2 : 1) as eluent gave (4*S*)-1-*tert*-butyldimethylsilyl-4-(2-methoxycarbonylethyl)azetidin-2-one **10** (270 mg, 100%), $[a]_D^{20}$ −51.8 (*c* 0.7, $CHCl_3$); ν_{max}/cm^{-1} 1740, 1322, 1302, 1255, 1192, 841 and 824; δ_H 0.25 and 0.27 (each 3 H, s, $SiCH_3$), 0.97 [9 H, s, $SiC(CH_3)_3$], 1.71 (1 H, m, 1′-H), 2.29 (3 H, m, 1′-H′, 2′-H_2), 2.59 (1 H, dd, *J* 15, 3, 3-H), 3.13 (1 H, dd, *J* 15, 6, 3-H′), 3.57 (1 H, m, 4-H), 3.70 (3 H, s, CO_2CH_3); *m*/*z* (CI) 273 (30%), 272 (M^+ + 1, 100), 230 (50) and 214 (35).

(4*S*,1′*E*)-1-*tert*-Butyldimethylsilyl-4-(2-methoxycarbonylethenyl)azetidin-2-one 8

Trimethyl phosphonoacetate (0.21 cm^3, 1.29 mmol) in tetrahydrofuran (3 cm^3) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil; 51.5 mg, 1.29 mmol) in tetrahydrofuran (5 cm^3) at 0 °C. The mixture was allowed to warm to room temperature and was stirred for 15 min. A solution of the formylazetidinone **6** (250 mg, 1.17 mmol) in tetrahydrofuran (5 cm^3) was added dropwise and the mixture stirred for a further 18 h. Saturated aqueous ammonium chloride (10 cm^3) was added and the mixture was partitioned between water and ether. The aqueous layer was extracted with ether, and the combined organic extracts were washed with water then brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (3 : 1) as eluent gave the *title compound* **8** (220 mg, 70%) as a colourless oil, $[a]_D^{20}$ −78 (*c* 0.5, $CHCl_3$) (Found: M^+, 269.1445. $C_{13}H_{23}NO_3Si$ requires *M*, 269.1447); ν_{max}/cm^{-1} 1735, 1660, 1465, 1435, 1355, 1295, 1180, 985, 841 and 770; δ_H 0.15 and 0.23 (each 3 H, s, $SiCH_3$), 0.95 [9 H, s, $SiC(CH_3)_3$], 2.83 (1 H, dd, *J* 15, 2, 3-H), 3.37 (1 H, dd, *J* 15, 5, 3-H), 3.76 (3 H, s, OCH_3), 4.12 (1 H, m, 4-H), 6.01 (1 H, d, J 16, 2′-H) and 6.90 (1 H, dd, J 16, 9, 1′-H); m/z (CI) 270 (M^+ + 1, 100%).

Hydrogenation of the (*E*)-alkene **8** gave (4*S*)-1-*tert*-butyldimethylsilyl-4-(2-methoxycarbonylethyl)azetidin-2-one **10** in quantitative yield.

(1′*S*,2′*S*,4*S*- and 1′*R*,2′*R*,4*S*)-1-*tert*-Butyldimethylsilyl-4-(1,2-dihydroxy-2-methoxycarbonylethyl)azetidin-2-ones 11 and 12

N-Methylmorpholine *N*-oxide monohydrate (818 mg, 5.97 mmol) was added to the (*Z*)-4-alkenylazetidinone **7** (1.07 g, 3.98 mmol) in acetone (85 cm^3) followed by a solution of osmium tetroxide (51 mg, 0.2 mmol) in water (34 cm^3). The reaction vessel was sealed under argon and the flask shaken for four days in the dark, the progress of the reaction being monitored by TLC. Aqueous sodium bisulfite was added and the mixture stirred overnight then filtered. The filtrate was extracted with chloroform (5 × 50 cm^3) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the *title compounds* **11** and **12** (857 mg, 71%), ratio **11**:**12** = 82:18. Repeated chromatography using chloroform–methanol (250:1→50:1) as eluent separated the diastereoisomers to give the (1′*R*,2′*R*)-isomer of the *title compound* **12** (146 mg, 12%), $[a]_D^{20}$ −45.5 (*c* 0.4, $CHCl_3$) (Found: C, 51.7; H, 8.4; N, 4.5. $C_{13}H_{25}NO_5Si$ requires C, 51.45; H, 8.3; N, 4.6%); ν_{max}/cm^{-1} 3350 and 1730; δ_H 0.27 and 0.29 (each 3 H, s, $SiCH_3$), 0.99 [9 H, s, $SiC(CH_3)_3$], 2.60 (2 H, br s, 2 × OH), 2.68 (1 H, dd, J 15, 3, 3-H), 3.12 (1 H, dd, J 15, 5, 3-H′), 3.7 (1 H, ddd, J 7, 5, 3, 4-H), 3.8 (1 H, dd, J 7.3, 1′-H), 3.86 (3 H, s, CO_2CH_3) and 4.25 (1 H, d, J 3, 2′-H); m/z (CI) 305 (25%), 304 (M^+ + 1, 100). The more polar product was the (1′*S*,2′*S*)-isomer of the *title compound* **11** (693 mg, 57%), mp 94–95 °C, $[a]_D^{20}$ −59 (*c* 0.25, $CHCl_3$); ν_{max}/cm^{-1} (KBr disc) 3540, 3500, 3380, 1740, 1705, 1650, 1465, 1440, 1345, 1255, 1215, 1195, 1100, 1055, 1005, 960, 845 and 822; δ_H 0.26 (6 H, s, 2 × $SiCH_3$), 0.98 [9 H, s, $SiC(CH_3)_3$], 2.47 (1 H, d, J 4.5, OH), 2.94 (1 H, dd, J 15, 5, 3-H), 2.95 (1 H, d, J 5, OH), 3.13 (1 H, dd, J 15, 3, 3-H′), 3.78 (1 H, m, 4-H), 3.86 (3 H, s, CO_2CH_3), 4.12 (1 H, t, J 4.5, 1′-H) and 4.20 (1 H, t, J 4.5, 2′-H); m/z (CI) 305 (24%) and 304 (M^+ + 1, 100).

Dowex was freshly acidified with aqueous hydrogen chloride (10 M) and washed with water and methanol. The acidified Dowex resin (5 g) was added to a solution of the *N*-silylazetidinone **11** (306 mg, 1.01 mmol) in methanol (25 cm^3) and the mixture stirred at room temperature until the reaction was complete as indicated by TLC. The mixture was filtered and the filtrate concentrated under reduced pressure. Chromatography of the residue using chloroform–methanol as eluent gave (1′*S*,2′*S*,4*S*)-4-(1,2-dihydroxy-2-methoxycarbonylethyl)-azetidin-2-one **18** (183 mg, 96%), $[a]_D^{20}$ −8.0 (*c* 0.2, MeOH); ν_{max}/cm^{-1} 3300 and 1730; δ_H (D_2O shake) 2.71 (1 H, dd, J 15, 2, 3-H), 2.89 (1 H, dd, J 15, 5, 3-H′), 3.64 (3 H, s, CO_2CH_3), 3.73 (1 H, td, J 5, 2, 4-H), 3.78 (1 H, m, NH), 3.87 (1 H, t, J 5, 1′-H) and 4.20 (1 H, d, J 5, 2′-H); m/z (CI) 191 (13%) and 190 (M^+ + 1, 100).

(4*S*)-1-*tert*-Butyldimethylsilyl-4-(1,2-dihydroxy-2-methoxycarbonylethyl)azetidin-2- ones 16 and 17

Following the procedure outlined for the synthesis of the diols **11** and **12**, *N*-methylmorpholine *N*-oxide (36 mg, 0.308 mmol), osmium tetroxide (5 mg, 0.02 mmol) in water (0.3 cm^3) and the (*E*)-alkene **8** (56 mg, 0.208 mmol) in acetone (2 cm^3) gave, after shaking for three days and chromatography using methanol (4%) in chloroform, the diols **16** and **17** (48 mg, 76%). Further chromatography using methanol (2%) in chloroform separated the two isomers to give the (1′*S*,2′*R*)-isomer of the *title compound* **16** (34 mg, 54%) as a white solid, mp 78–80 °C (Found: M^+ + H, 304.1569. $C_{13}H_{26}NO_5Si$ requires *M*, 304.1580); ν_{max}/cm^{-1} 3387, 1735, 1718, 1256, 1138, 841 and 826; δ_H 0.24 and 0.27 (each 3 H, s, $SiCH_3$), 0.96 [9 H, s, $SiC(CH_3)_3$], 2.59 (2 H, br s, 2 × OH), 3.03 (1 H, dd, J 16, 5, 3-H), 3.18 (1 H, dd, J 16, 3, 3-H′), 3.77 (1 H, m, 4-H), 3.85 (3 H, s, OCH_3) and 4.19 (2 H, m, 1′-H and 2′-H); m/z (CI) 306 (12%), 305 (40) and 304 (M^+ + 1, 100); and the (1′*R*,2′*S*)-isomer of the *title compound* **17** (9 mg, 14%), mp 118–120 °C (Found: M^+ + H, 304.1586. $C_{13}H_{26}NO_5Si$ requires *M*, 304.1580); ν_{max}/cm^{-1} 3338, 1756, 1708, 1279, 1252, 1199, 1123, 1065 and 843; δ_H 0.27 (6 H, s, 2 × $SiCH_3$), 1.00 [9 H, s, $SiC(CH_3)_3$], 1.67 and 2.33 (each 1 H, br s, 2 × OH), 2.80 (1 H, dd, J 15, 3, 3-H), 3.17 (1 H, dd, J 15, 5, 3-H′), 3.74 (1 H, m, 4-H), 3.87 (3 H, s, OCH_3) and 3.92 and 4.22 (each 1 H, m, 1′-H and 2′-H); m/z (CI) 305 (22%) and 304 (M^+ + 1, 100).

Benzyl [bis(2,2,2-trifluoroethyl)phosphono]acetate 22

A solution of *tert*-butyl alcohol (1.85 g, 25 mmol) in dichloromethane (5 cm^3) was added slowly to a solution of phosphorus trichloride (2.18 cm^3, 25 mmol) in dichloromethane (5 cm^3) and the mixture stirred at 0 °C for 30 min. 2,2,2-Trifluoroethanol (5.0 g, 50 mmol) in dichloromethane (5 cm^3) was added over a 10 min period and the mixture allowed to warm to room temperature and stirred for 18 h. The solvent was removed by distillation at atmospheric pressure and the product purified by distillation through a Vigreux column to give the bis(2,2,2-trifluoroethyl) phosphonate **21** (4.43 g, 72%); ν_{max}/cm^{-1} 2485, 1250, 1150 and 1080; δ_H 2.32 [1 H, s, P(O)H] and 4.42 (4 H, dq, J 11, 8, 2 × CF_3CH_2O).

Benzene (30 cm^3) was added to sodium hydride (0.79 g of 60% w/w suspension in mineral oil, 19.8 mmol) which had been washed with light petroleum (3 × 20 cm^3) followed by bis(trifluoroethyl) phosphonate (4.43 g, 18.0 mmol) in benzene (20 cm^3). The mixture was stirred for 30 min at room temperature while hydrogen gas was evolved. The reaction vessel was cooled to 5 °C and benzyl bromoacetate (4.53 g, 19.8 mmol) in tetrahydrofuran (20 cm^3) was added slowly. The mixture was allowed to warm to room temperature and stirred for 48 h before ethanol (5 cm^3), water (100 cm^3) and ether (100 cm^3) were added. The aqueous layer was extracted with ether and the ethereal extracts washed with water and brine and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate as eluent (2:1) gave the *title compound* **22** (3.18 g, 45%) (Found: M^+, 394.0412. $C_{13}H_{13}O_5PF_6$ requires *M*, 394.0405); ν_{max}/cm^{-1} 3478, 3037, 1740, 1457, 1420, 1378, 1268, 1173, 1073 and 964; δ_H 3.20 (2 H, d, J 21, PCH_2), 4.38 (4 H, dq, J 7, 6, 2 × CF_3CH_2), 5.20 (2 H, s, CH_2Ph) and 7.36 (5 H, br s, ArH); m/z (CI) 412 (M^+ + 18, 100%).

(4*S*,1′*Z*)-1-*tert*-Butyldimethylsilyl-4-(2-benzyloxycarbonylethenyl)azetidin-2-one 23

A slurry of finely-ground potassium carbonate (518 mg, 3.75 mmol) and 18-crown-6 (1.98 g, 7.50 mmol) in toluene (3 cm^3) was stirred at room temperature for 24 h. The mixture was then cooled to −25 °C and a solution of the 4-formylazetidinone **6** (399 mg, 1.87 mmol) and the benzyl phosphonate **22** in toluene (4 cm^3) was added. The mixture was allowed to warm to 0 °C and was stirred for a further 60 min. Saturated aqueous ammonium chloride (10 cm^3) was added and the mixture extracted with ether. The combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (3:1) as eluent gave the *title compound* **23** (419 mg, 65%) (Found: M^+ + H, 346.1836. $C_{19}H_{28}NO_3Si$ requires *M*, 346.1838); ν_{max}/cm^{-1} 1749, 1720, 1646, 1417, 1285, 1255, 1186, 1083, 968 and 754; δ_H 0.15 and 0.21 (each 3 H, s, $SiCH_3$), 0.94 [9 H, s, $SiC(CH_3)_3$], 2.62 (1 H, dd, J 15, 3, 3-H), 3.45 (1 H, dd, J 15, 5, 3-H′), 5.18 (2 H, s, CH_2Ph), 5.27 (1 H, m, 4-H), 5.93 (1 H, dd, J 11.5, 1, 2′-H), 6.28 (1 H, dd, J 11, 9, 1′-H), 7.8 (5 H, m, ArH); m/z 346 (M^+ + 1, 54%) and 206 (100).

(1′*S*,2′*S*,4*S*- and 1′*R*,2′*R*,4*S*)-1-*tert*-Butyldimethylsilyl-4-(1,2-dihydroxy-2-benzyloxycarbonylethyl)azetidin-2-ones 24 and 25

Following the procedure outlined for the preparation of diols **11** and **12**, *N*-methylmorpholine *N*-oxide monohydrate (176 mg, 1.52 mmol), osmium tetroxide (21 mg, 0.09 mmol) in water (5 cm^3) and the (*Z*)-alkene **23** (350 mg, 1.01 mmol) in acetone (4 cm^3) gave, after shaking in the dark for three days at room temperature and chromatography using methanol (1%) in chloroform as eluent, the (1′*R*,2′*R*)-isomer of the *title compound* **25** (58 mg, 15%); δ_H 0.20 and 0.23 (each 3 H, s, $SiCH_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 2.62 (1 H, dd, *J* 15, 3, 3-H), 2.82 (1 H, br s, OH), 3.03 (1 H, dd, *J* 15, 5, 3-H′), 3.45 (1 H, br s, OH), 3.62 (1 H, m, 4-H), 3.79 (1 H, dd, *J* 10, 2, 1′-H), 4.25 (1 H, d, *J* 2, 2′-H), 5.24 and 5.26 (each 1 H, d, *J* 10, HC*H*Ph) and 7.37 (5 H, m, ArH); followed by the more polar (1′*S*,2′*S*)-isomer of the *title compound* **24** (218 mg, 58%) (Found: $M^+ + H$, 380.1894. $C_{19}H_{30}NO_5Si$ requires *M*, 380.1893); δ_H 0.19 (6 H, s, $2 \times SiCH_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 2.86 (1 H, dd, *J* 17, 6, 3-H), 3.09 (1 H, dd, *J* 17, 3, 3-H′), 3.7 (1 H, m, 4-H), 4.09 (1 H, dd, *J* 4.5, 2, 1′-H), 4.22 (1 H, d, *J* 4.5, 2′-H), 5.25 and 5.27 (each 1 H, d, *J* 10, HC*H*Ph) and 7.38 (5 H, m, ArH); *m*/*z* (CI) 380 ($M^+ + 1$, 100%).

(1′*S*,2′*S*,4*S*)-1-*tert*-Butyldimethylsilyl-4-[1,2-(dimethylmethylenedioxy)-2-benzyloxycarbonylethyl]azetidin-2-one 26

The diol **24** (283 mg, 0.75 mmol) was added to stirred solution of dimethoxypropane (5 cm^3) in chloroform (12 cm^3), toluene-*p*-sulfonic acid (10 mg, 0.05 mmol) was added and the mixture stirred for 18 h. Saturated aqueous sodium bicarbonate was added and the aqueous layer extracted with dichloromethane. The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (5:1) as eluent gave the *title compound* **26** (252 mg, 76%), as a white solid, mp 93–95 °C (Found: C, 63.2; H, 8.1; N, 3.1; $M^+ + H$, 420.2203. $C_{22}H_{33}NO_5Si$ requires: C, 63.0; H, 7.95; N, 3.35%; $C_{22}H_{34}NO_5Si$ requires *M*, 420.2206); ν_{max}/cm^{-1} 1739, 1473, 1382, 1255, 1213, 1095, 991 and 775; δ_H 0.22 and 0.24 (3 H, s, $SiCH_3$), 0.93 [9 H, s, $SiC(CH_3)_3$], 1.37 and 1.59 (each 3 H, s, CH_3), 2.45 (1 H, dd, *J* 15, 5, 3-H), 2.89 (1 H, dd, *J* 15, 3, 3-H′), 3.71 (1 H, m, 4-H), 4.57 (1 H, dd, *J* 7, 1, 1′-H), 4.67 (1 H, d, *J* 7, 2′-H), 5.13 and 5.17 (each 1 H, d, *J* 14, HC*H*Ph) and 7.49 (5 H, m, ArH); *m*/*z* (CI) 421 (31%) and 420 ($M^+ + 1$, 100).

Palladium on activated charcoal (10% Pd; 13 mg, 0.01 mmol) was added to a solution of the benzyl ester **26** (50 mg, 0.12 mmol) in ethanol (2 cm^3) and the mixture stirred under an atmosphere of hydrogen for 18 h. Chloroform (5 cm^3) was added and the mixture filtered through Celite and concentrated under reduced pressure to give (1′*S*,2′*S*,4*S*)-1-*tert*-butyldimethylsilyl-4-[1,2-(dimethylmethylenedioxy)-2-carboxyethyl]-azetidin-2-one **27** (36.5 mg, 95%) used without further purification; ν_{max}/cm^{-1} 3939, 1724, 1640, 1464, 1382, 1316, 1256, 1212 and 1165; δ_H 0.25 and 0.27 (3 H, s, $SiCH_3$), 0.98 [9 H, s, $SiC(CH_3)_3$], 1.41 and 1.65 (each 3 H, s, CH_3), 2.88 (1 H, dd, *J* 15, 5, 3-H), 2.99 (1 H, dd, *J* 15, 2, 3-H′), 4.00 (1 H, m, 4-H), 4.24 (1 H, br s, OH) and 4.68 (2 H, m, 2′-H and 3′-H); *m*/*z* (CI) 331 (11%), 330 ($M^+ + 1$, 52), 233 (6) and 216 (8).

(3*S*- and 3*R*)-[(1*S*)-1-Benzyloxycarbonylamino-3-methylbutyl]-3,4-dihydro-1*H*-2-benzopyran-1-ones 40 and 41

Butyllithium (1.6 M in hexanes; 0.73 cm^3, 1.17 mmol) was added to a solution of the oxazoline **35**[14] (188 mg, 1.17 mmol) in tetrahydrofuran (7 cm^3) at −78 °C and this solution stirred for 30 min. Ethereal *tert*-butylmagnesium chloride (2 M; 0.59 cm^3, 1.17 mmol) was added to a solution of Cbz-leucinal **29** (291 mg, 1.17 mmol) in tetrahydrofuran (8 cm^3) at −78 °C and the solution stirred for 3 min. The solution of lithiated oxazoline was added by cannula to the solution of the deprotonated aldehyde and the mixture stirred for 1 h. Saturated aqueous ammonium chloride was added and the mixture allowed to warm to room temperature and extracted with chloroform. The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography using light petroleum–ethyl acetate (1:1) as eluent gave a mixture of the oxazolines **36** and **37** together with the imino esters **38** and **39** (155 mg).

Aqueous hydrogen chloride (3.5 M; 2 cm^3) was added dropwise to a solution of a mixture of the oxazolines **36** and **37** and the imino esters **38** and **39** (70 mg) in tetrahydrofuran (6 cm^3) and the mixture stirred for 18 h. Saturated aqueous sodium bicarbonate was added and the mixture extracted with dichloromethane. The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (4:1) as eluent gave a mixture of the diastereoisomeric lactones **40** and **41** (48 mg, 77%), ratio **40**:**41** = 7:1. Further chromatography gave the (3*S*)-isomer of the *title compound* **40** (39 mg, 62%) (Found: M^+, 367.1784. $C_{22}H_{25}NO_4$ requires *M*, 367.1783); ν_{max}/cm^{-1} 3324, 1723, 1606, 1534, 1460, 1231, 1119, 1087, 1031, 743 and 697; δ_H 0.95 and 0.97 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.46 (1 H, m, 2′-H), 1.75 (2 H, m, 2′-H′ and 3′-H), 2.84 (1 H, dd, 15, 2, 4-H), 3.18 (1 H, dd, *J* 15, 12, 4-H′), 4.08 (1 H, m, 1′-H), 4.54 (1 H, m, 3-H), 5.00 (1 H, br d, *J* 9, NH), 5.13 (2 H, s, CH_2Ph), 7.24–7.42 (7 H, m, ArH), 7.53 (1 H, t, *J* 7, ArH) and 8.07 (1 H, d, *J* 7, ArH); *m*/*z* (CI) 385 ($M^+ + 18$, 74%), 369 (72), 368 ($M^+ + 1$, 98), 334 (82), 277 (95), 260 (70) and 234 (100). The minor product was identified as the (3*R*)-isomer of the title compound **41**; δ_H (C_6D_6) 0.88 and 0.98 (each 3 H, d, *J* 7, 3′-CH_3 and 4′-H_3), 1.04 (1 H, m, 2′-H), 1.47–1.62 (2 H, m, 2′-H′ and 3′-H), 2.02 (1 H, dd, *J* 16, 3, 4-H), 2.43 (1 H, dd, *J* 15, 12, 4-H′), 3.76 (1 H, m, 3-H), 3.94 (1 H, m, 1′-H), 4.51 (1 H, br d, *J* 11, N-H), 5.12 and 5.19 (each 1 H, d, *J* 12, HC*H*Ph), 6.67 (1 H, d, *J* 7, ArH), 6.94–7.33 (7 H, m, ArH) and 8.26 (1 H, d, *J* 7, ArH).

N-(2-Hydroxyethyl)-2-methoxy-6-methylbenzamide 43

A solution of 2-methoxy-6-methylbenzoic acid **42**[13] (5.5 g, 33.1 mmol) in thionyl chloride (22 cm^3) was stirred and heated under reflux for 50 min, then allowed to cool to room temperature. The excess of thionyl chloride was removed under reduced pressure. Oxazolidin-2-one **33** (2.88 g, 33.1 mmol) was added and the mixture was stirred and heated to 65 °C for 2 h. The mixture was allowed to cool to room temperature and aqueous sodium hydroxide (10%; 35 cm^3) and ethanol (35 cm^3) were added. The mixture was heated under reflux for 2 h then allowed to cool to room temperature and acidified to pH 5 by addition of dilute aqueous hydrogen chloride. The mixture was extracted with dichloromethane, and the organic extracts washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the hydroxyethyl benzamide **43** (6.34 g). Chromatography of a sample using ethyl acetate–light petroleum (2:1) as eluent gave the *title compound* **43** as a white solid, mp 105–106 °C (Found: C, 62.9; H, 7.1; N, 6.7. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%); ν_{max}/cm^{-1} 3440, 3325, 1631, 1601, 1585, 1545, 1472, 1264, 1082 and 787; δ_H 2.25 (3 H, s, $ArCH_3$), 3.46 (2 H, m, CH_2), 3.67 (2 H, t, *J* 5, CH_2), 3.76 (3 H, s, OCH_3), 6.58 (1 H, br s, NH), 6.70 and 6.75 (each 1 H, d, *J* 7, ArH), 7.18 (1 H, t, *J* 7, ArH); *m*/*z* (CI) 210 ($M^+ + 1$, 100%) and 149 (36).

4,5-Dihydro-2-(2-methoxy-6-methylphenyl)oxazole 45

Thionyl chloride (17 cm^3) was added to the crude hydroxyethyl amide **43** (6.34 g) and the mixture stirred under reflux for 1.5 h. After cooling to room temperature, the excess of thionyl chloride was removed under reduced pressure and the residue partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The aqueous layer was extracted with dichloromethane and the combined organic phase washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the amide **44** (5.59 g). Chromatography of a sample using light petroleum–ethyl acetate (3:1) as eluent gave the chloroethyl amide **44** as a white solid, mp 120–122 °C; ν_{max}/cm^{-1} 3279, 1646, 1597, 1584, 1546, 1472, 1459, 1438, 1425, 1367, 1320, 1293, 1263, 1247 and 783; δ_H 2.32 (3 H, s, $ArCH_3$), 3.70 (4 H, m, 2 × CH_2), 3.80 (3 H, s, OCH_3), 6.40 (1 H, br s, NH), 6.74 and 6.79 (each 1 H, d, *J* 7, ArH) and 7.21 (1 H, t, *J* 7, ArH); *m*/*z* (EI) 227 (M^+, 20%), 192 (13) and 149 (100).

Aqueous sodium hydroxide (10%; 17.5 cm^3) was added to a solution of the crude 2-(chloroethyl)amide **44** (5.59 g) in ethanol (17.5 cm^3) and the mixture stirred and heated under reflux for 1.5 h. The mixture was extracted with dichloromethane, and the combined organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (1:2) as eluent gave the *title compound* **45** (4.09 g, 65%) as a white solid, mp 103–104 °C (Found: M^+, 191.0945. $C_{11}H_{13}NO_2$ requires *M*, 191.0946); λ_{max} 280.2, 228.8 nm; ν_{max}/cm^{-1} 1673, 1585, 1475, 1275, 1081 and 1049; δ_H 2.32 (3 H, s, $ArCH_3$), 3.82 (3 H, s, OCH_3), 4.10 and 4.42 (each 2 H, t, *J* 10, CH_2), 6.76 (1 H, d, *J* 7.5, ArH), 6.83 (1 H, d, *J* 6.5, ArH) and 7.26 (1 H, dd, *J* 7.5, 6.5, ArH); δ_C 19.1, 54.9, 55.6, 67.0, 108.1, 118.4, 122.0, 130.2, 138.5, 157.6 and 162.7; *m*/*z* (EI) 192 (19%), 191 (M^+, 100), 190 (32), 162 (49), 146 (33) and 133 (32).

4,5-Dihydro-2-(6-ethyl-2-methoxyphenyl)oxazole 46

Butyllithium (1.55 M in hexanes; 0.38 cm^3, 0.59 mmol) was added dropwise to the oxazoline **45** (101 mg, 0.53 mmol) in tetrahydrofuran (2 cm^3) at −78 °C. The solution was stirred for 30 min then iodomethane (0.2 cm^3) was added dropwise. Saturated aqueous ammonium chloride (3 cm^3) was added and the mixture was allowed to warm to room temperature then extracted with dichloromethane. The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **46** (105 mg, 96%); ν_{max}/cm^{-1} 1665, 1583, 1472, 1439, 1268, 1050 and 939; δ_H 1.21 (3 H, t, *J* 7, CH_2CH_3), 2.64 (2 H, q, *J* 7, CH_2CH_3), 3.81 (3 H, s, OCH_3) 4.09 and 4.42 (each 2 H, t, *J* 10, CH_2), 6.75 and 6.86 (each 1 H, d, *J* 7, ArH) and 7.29 (1 H, t, *J* 7, ArH); *m*/*z* (EI) 205 (M^+, 100%), 204 (60), 191 (23), 176 (63) and 148 (50).

(1′*S*,3*S*)-3-(1-Benzyloxycarbonylamino-3-methylbutyl)-3,4-dihydro-8-methoxy-1*H*-2-benzopyran-1-one 30

Butyllithium (2.5 M; 0.96 cm^3, 2.17 mmol) was added to a solution of the oxazoline **45** (500 mg, 2.62 mmol) in tetrahydrofuran (15 cm^3) at −78 °C and the mixture stirred for 20 min. Ethereal *tert*-butylmagnesium chloride (2 M; 1.09 cm^3, 2.18 mmol) was added to a solution of Cbz-leucinal **29** (542 mg, 2.18 mmol) in tetrahydrofuran (15 cm^3) at −78 °C and the mixture stirred for 3 min. The solution of the lithiated oxazoline was added by cannula to the solution of the deprotonated aldehyde and the mixture stirred for 5 min at −78 °C. Saturated aqueous ammonium chloride was added and the mixture allowed to warm to room temperature and extracted with chloroform. The organic extracts were washed with water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in dichloromethane (20 cm^3) and silica (5 g) was added. The slurry was stirred for 18 h then filtered and the filtrate concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave a mixture of the lactones **30** and **31** (383 mg, 44%), ratio **30**:**31** = 87:13. Further chromatography gave the (3*S*)-lactone **30**[5,6] (261 mg, 30%) as a colourless oil, $[a]_D^{20}$ −137 (*c* 1, $CHCl_3$) (Found: M^+, 397.1885. $C_{23}H_{27}NO_5$ requires *M*, 397.1889); λ_{max} 243.2, 306.0 nm; ν_{max}/cm^{-1} 3328, 1719, 1599, 1586, 1531, 1477, 1234, 1089 and 1061; δ_H (C_6D_6) 0.88 and 0.98 (each 3 H, d, *J* 7, 3′-CH_3, 4′-H_3), 1.05 (1 H, m, 2′-H), 1.55 (2 H, m, 2′-H′ and 3′-H), 2.31 (1 H, dd, *J* 16, 2, 4-H), 2.85 (1 H, dd, *J* 16, 13, 4-H′), 3.43 (3 H, s, OCH_3), 3.78 (1 H, m, 1′-H), 4.01 (1 H, m, 3-H), 4.81 (1 H, br d, *J* 10, NH), 5.13 and 5.19 (each 1 H, d, *J* 13, HC*H*Ph), 6.37 and 6.42 (each 1 H, d, *J* 7, 5-H and 7-H) and 7.03–7.3 (6 H, m, 6-H and ArH); δ_C 22.1, 23.0, 24.7, 31.8, 41.1, 51.4, 56.2, 66.9, 79.5, 110.8, 113.5, 119.5, 127.8, 128.1, 128.5, 134.7, 136.4, 142.1, 156.5, 161.2 and 162.3; *m*/*z* (CI) 398 (M^+ + 1, 0.6%), 330 (4), 328 (4), 252 (47) and 248 (66).

(1*S*,3′*S*)-[1-(3,4-Dihydro-8-methoxy-1-oxo-1*H*-2-benzopyran-3-yl)-3-methylbutyl]ammonium chloride 52

Aqueous hydrogen chloride (3 M; 2 drops) and palladium on charcoal (10% Pd, 16 mg, 0.015 mmol) were added to a suspension of lactone **30** (60 mg, 0.15 mmol) in ethanol (3 cm^3) and the reaction mixture stirred under an atmosphere of hydrogen for 6 h. The catalyst was removed by filtration through Celite and the filtrate concentrated under reduced pressure to leave the *title compound* **52** (46 mg, 100%) as an off-white solid; ν_{max}/cm^{-1} 3500, 3400, 1730, 1600, 1515, 1485, 1460, 1260, 1240 and 1060; δ_H (CD_3OD) 1.02 and 1.05 (each 3 H, d, *J* 6, 3-CH_3 and 4-H_3), 1.61–1.98 (3 H, m, 2-CH_2 and 3-H), 3.14 (2 H, m, 4′-CH_2), 3.55 (1 H, m, 1-H), 3.91 (3 H, s, OCH_3), 4.56 (1 H, m, 3′-H), 6.98 and 7.12 (each 1 H, d, *J* 7, 5′-H and 7′-H) and 7.60 (1 H, t, *J* 7, 6′-H); *m*/*z* (CI) 264 (52%), 194 (19) and 118 (100).

(1′*S*,3*S*)-3-[1-(2-Methylpropanoylamino)-3-methylbutyl]-3,4-dihydro-8-methoxy-1*H*-2-benzopyran-1-one 53

4-Dimethylaminopyridine (33 mg, 0.27 mmol) in dichloromethane (1 cm^3), isobutyric acid (0.011 cm^3, 0.12 mmol) and the amine hydrochloride **52** (38 mg, 0.12 mmol) in dichloromethane (2 cm^3) were added to a solution of *N*,*N*′-dicyclohexylcarbodiimide (27 mg, 0.13 mmol) in dichloromethane (1 cm^3) at 0 °C and the reaction mixture stirred for 10 min at 0 °C then at room temperature for 18 h. Ether (10 cm^3) was added and the mixture filtered through Celite then concentrated under reduced pressure. Chromatography of the residue using light petroleum–ethyl acetate (2:1) as eluent gave the *title compound* **53** (29.8 mg, 70%) as a colourless oil (Found: M^+, 333.1946. $C_{19}H_{27}NO_4$ requires *M*, 333.1940); ν_{max}/cm^{-1} 3315, 1720, 1645, 1598, 1536, 1236, 1097, 1058 and 1036; δ_H 0.92 and 0.94 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.17 and 1.18 (each 3 H, d, *J* 9, 2″-CH_3 and 3″-H_3), 1.4–2.0 (3 H, m, 2′-H_2 and 3′-H), 2.41 (1 H, septet, *J* 9, 2″-H), 2.79 (1 H, dd, *J* 16, 2, 4-H), 2.98 (1 H, dd, *J* 16, 12, 4-H′), 3.96 (3 H, s, OCH_3), 4.38 (2 H, m, 3-H and 1′-H), 5.72 (1 H, br d, *J* 8, NH), 6.82 and 6.91 (each 1 H, d, *J* 7, 5-H and 7-H) and 7.46 (1 H, t, *J* 6, 6-H); *m*/*z* (CI) 334 (M^+ + 1, 80%), 226 (36) and 225 (100).

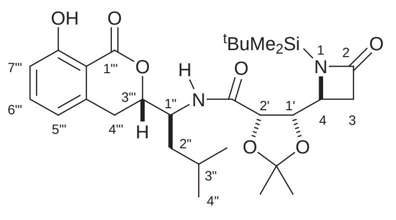
(4*S*)-1-*tert*-Butyldimethylsilyl-4-{(1*S*,2*S*)-1,2-(dimethylmethylenedioxy)-3-{1-[(3*S*)-3,4-dihydro-8-methoxy-l-oxo-1*H*-2-benzopyran-3-yl]-3-methylbutyl}amino-3-oxopropyl}azetidin-2-one 54

4-Dimethylaminopyridine (76 mg, 0.69 mmol) in dichloromethane (3 cm^3), the acid **27** (94 mg, 0.28 mmol) in dichloromethane (3 cm^3) and the amine hydrochloride **52** (94 mg, 0.32 mmol) in dichloromethane (5 cm^3) were added to a solution of *N*,*N*′-dicyclohexylcarbodiimide (70 mg, 0.34 mmol) in dichloromethane (3 cm^3) at 0 °C and the reaction mixture stirred for 10 min at 0 °C then at room temperature for 18 h. Ether (20 cm^3) was added and the mixture filtered through Celite. After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (3:2) as eluent gave the *title compound* **54**† (107 mg, 65%) as a colourless oil, $[\alpha]_D^{20}$ −135 (*c* 1, $CHCl_3$) (Found: M^+ + H, 575.3150. $C_{30}H_{47}N_2O_7Si$ requires *M*, 575.3152); ν_{max}/cm^{-1} 3410, 3325, 1740, 1680, 1630, 1600, 1585, 1515, 1475, 1280, 1255, 1215, 1090, 1060, 840 and 820; δ_H (C_6D_6) 0.14 and 0.26 (each 3 H, s, $SiCH_3$), 0.75 and 0.82 (each 3 H, d, *J* 6, 3″-CH_3 and 4″-H_3), 1.01 [9 H, s, $SiC(CH_3)_3$], 1.04 (3 H, s, CH_3), 1.20 (1 H, m), 1.26 (3 H, s, CH_3), 1.55 (2 H, m), 2.28 (1 H, dd, *J* 16, 3, 4‴-H), 2.72 (1 H, dd, *J* 16, 12, 4‴-H′), 3.03 (1 H, dd, *J* 15, 5, 3-H), 3.17 (1 H, dd, *J* 15, 3, 3-H′), 3.34 (3 H, s, OCH_3), 3.79 (1 H, m, 1″-H), 4.15 (1 H, m, 3‴-H), 4.36 (2 H, m, 1′-H, 4-H), 4.53 (1 H, dd, *J* 8, 1, 2′-H), 6.33 and 6.36 (each 1 H, d, *J* 7, 5‴-H and 7‴-H), 6.87 (1 H, d, *J* 10, NH) and 7.46 (1 H, t, *J* 6, 6‴-H); *m*/*z* (FAB) 575 (M^+ + 1, 21%) and 532 (13).

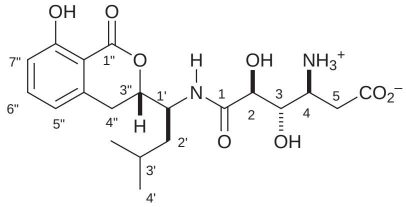
(4*S*)-4-{(1*S*,2*S*)-1,2-dihydroxy-3-{1-[(3*S*)-3,4-dihydro-8-methoxy-l-oxo-1*H*-2-benzopyran-3-yl]-3-methylbutyl}amino-3-oxopropyl}azetidin-2-one 55

Aqueous hydrogen chloride (3.5 M; 10 cm^3) was added dropwise to a solution of the acetonide **54** (55 mg, 0.096 mmol) in tetrahydrofuran (10 cm^3) at 0 °C and the mixture stirred for 30 min at 0 °C then at room temperature for 6 h. The reaction was cooled to 0 °C and saturated aqueous sodium bicarbonate (20 cm^3) was added. The mixture was extracted with chloroform and the organic extracts washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using chloroform–methanol (93 : 7) as eluent gave the *title compound* **55**† (33 mg, 82%) as a white solid, mp 105–106 °C, $[\alpha]_D^{20}$ −153 (*c* 1, $CHCl_3$) (Found: C, 59.7; H, 6.9. $C_{21}H_{28}N_2O_7$ requires C, 60.0; H, 6.7%; Found: M^+ + H, 421.1971. $C_{21}H_{29}N_2O_7$ requires *M*, 421.1975); ν_{max}/cm^{-1} 3400, 3320, 1740, 1660, 1605, 1480, 1240, 1085, 1060 and 800; δ_H (CD_3OD) 0.93 and 0.97 (each 3 H, d, *J* 6, 3″-CH_3 and 4″-H_3), 1.42 (1 H, m, 2″-H), 1.8 (2 H, m, 2″-H′ and 3″-H), 2.83–3.10 (4 H, m, 4‴-CH_2 and 3-CH_2), 3.77 (1 H, m, 4-H), 3.90 (4 H, m, OCH_3 and 1′-H), 4.10 (1 H, d, *J* 5, 2′-H), 4.13 (1 H, m, 1″-H), 5.10 (1 H, dt, *J* 10, 2, 3‴-H), 6.91 and 7.06 (each 1 H, d, *J* 7, 5‴-H and 7‴-H) and 7.46 (1 H, t, *J* 7, 6‴-H); δ_H (dimethyl sulfoxide-d_6, 55 °C) 0.87 and 0.90 (each 3 H, d, *J* 6, 3″-CH_3 and 4″-H_3), 1.35 (1 H, m, 2″-H), 1.66 (2 H, m, 2″-H′ and 3″-H), 2.73 (2 H, m, 3-CH_2), 2.79 (1 H, dd, *J* 18, 3, 4‴-H), 2.93 (1 H, dd, *J* 18, 12 4‴-H′), 3.57 (1 H, m, 4-H), 3.72 (1 H, q, *J* 5, 1′-H), 3.83 (3 H, s, OCH_3), 3.97 (1 H, t, *J* 5, 2′-H), 4.17 (1 H, m, 1″-H), 4.42 (1 H, dt, *J* 13, 2, 3‴-H), 5.02 (1 H, d, *J* 5, OH), 5.53 (1 H, d, *J* 6, OH), 6.91 and 7.05 (each 1 H, d, *J* 8, 5‴-H and 7‴-H), 7.37 (1 H, br d, *J* 10, NH) and 7.52 (2 H, m, 6‴-H and NH); *m*/*z* (FAB) 421 (M^+ + 1, 32%).

† The numbering scheme used in this paper for the azetidinone containing dipeptides is indicated in **i** and that for AI-77-B and derivatives in **ii**.



i



ii

AI-77-B methyl ether 58

Aqueous sodium hydroxide (0.05 M) was added dropwise to solution of the azetidinone **55** (15 mg, 0.036 mmol) in ethanol–water (1 : 1; 4 cm^3) until the pH of the solution reached 12. The pH was maintained at 12 by further addition of base until the starting material could no longer be detected by TLC (*ca.* 18 h). The reaction mixture was then cooled to 0 °C and acidified to pH 1.3 by addition of methanolic hydrogen chloride (3 M). The mixture was stirred at this temperature for 2 h then concentrated under reduced pressure to give the amine hydrochloride **56** (17 mg); ν_{max}/cm^{-1} 3360br, 1788, 1708, 1657, 1600, 1528, 1477, 1250 and 1069; δ_H (CD_3OD) 0.92 and 0.98 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.40 (1 H, m, 2′-H), 1.69 (2 H, m, 2′-H′ and 3′-H), 2.71 (1 H, dd, *J* 15, 12, 5-H), 3.00 (2 H, m, 4″-H_2), 3.22 (1 H, dd, *J* 16, 8, 5-H′), 3.90 (3 H, s, OCH_3), 4.0 (1 H, m), 4.19–4.36 (2 H, m), 4.51 (2 H, m), 6.94 and 7.09 (each 1 H, d, *J* 7, 5″-H and 7″-H) and 7.56 (1 H, t, *J* 7, 6″-H).

Aqueous sodium hydroxide (0.02 M) was added dropwise to a solution of the amine hydrochloride **56** (17 mg) in ethanol–water (1 : 1; 4 cm^3) until the pH reached 9. The pH was maintained at this level by further addition of base until the starting material could no longer be detected by TLC (*ca.* 18 h). The pH was then adjusted to 6.5 by dropwise addition of aqueous hydrogen chloride (0.02 M). The reaction mixture was then loaded directly onto a column of Amberlite XAD-2 resin packed with water. The column was washed with water–methanol (4 : 1) and the product isolated by eluting with water–methanol (1 : 4) to give the *title compound* **58**[17]† (11 mg, 70%) as a white solid, mp 135–138 °C; λ_{max} 241.4, 306.6 nm; ν_{max}/cm^{-1} 3279, 1721, 1657, 1599, 1585, 1477, 1243 and 1076; δ_H (CD_3OD) 0.94 and 0.99 (each 3 H, d, *J* 7, 3′-CH_3 and 4′-H_3), 1.42 (1 H, m, 2′-H), 1.63–1.87 (2 H, m, 2′-H′ and 3′-H), 2.51 (1 H, dd, *J* 16, 11, 5-H), 2.63 (1 H, dd, *J* 16, 3, 5-H′), 2.87 (1 H, dd, *J* 15, 2, 4″-H), 3.04 (1 H, dd, *J* 15, 12, 4″-H′), 3.62 (1 H, m, 4-H), 3.89 (3 H, s, OCH_3), 3.96 (1 H, m, 3-H), 4.16 (1 H, d, *J* 8, 2-H), 4.33 and 4.49 (each 1 H, m, 1′-H and 3″-H), 6.90 and 7.06 (each 1 H, d *J* 8, 5″-H and 7″-H) and 7.54 (1H, t, *J* 8, 6″-H); *m*/*z* (FAB) 440 (24%) and 439 (M^+ + 1, 100).

(1′*S*,3*S*)-3-(1-Benzyloxycarbonylamino-3-methylbutyl)-3,4-dihydro-8-hydroxy-1*H*-2-benzopyran-1-one 59

Boron tribromide (1 M in dichloromethane; 1.48 cm^3, 1.48 mmol) was added dropwise to a solution of the methyl ether **30** (280 mg, 0.705 mmol) in dichloromethane (14 cm^3) at −78 °C over 3 min. The mixture was stirred for 3 min then saturated aqueous ammonium chloride (10 cm^3) was added. After warming to room temperature, the mixture was extracted into dichloromethane and the organic extracts washed with water then brine and dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (7 : 1) as eluent gave the *title compound* **59** (194 mg, 72%) as a white solid, mp 113–114 °C, $[\alpha]_D^{20}$ −75.6 (*c* 1, $CHCl_3$) (Found: C, 69.1; H, 6.5; N, 3.7; M^+, 383.1740. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.6; N, 3.65%; *M*, 383.1733); λ_{max} 246.0, 314.4 nm; ν_{max}/cm^{-1} 3324, 3064, 1679, 1620, 1585, 1534, 1256, 1231, 1114, 1048, 737 and 698; δ_H (C_6D_6) 0.91 and 1.00 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.1 (1 H, m), 1.55 (2 H, m), 2.18 (1 H, dd, *J* 18, 3, 4-H), 2.72 (1 H, dd, *J* 18, 13, 4-H′), 3.68 (1 H, m, 3-H), 3.89 (1 H, dt, *J* 10, 3, 1′-H), 4.42 (1 H, d, *J* 10, NH), 5.17 (2 H, s, CH_2Ph), 6.20 (1 H, d, *J* 8, 7-H), 6.92 (1 H, d, *J* 8, 5-H), 7.00 (1 H, t, *J* 8, 6-H), 7.14–7.36 (5 H, m, ArH) and 11.68 (1 H, s, ArOH); *m*/*z* (CI) 401 (M^+ + 18, 4%).

Aqueous hydrogen chloride (3 M; 2 drops) and palladium on charcoal (10% Pd; 19 mg, 0.018 mmol) were added to a suspension of the protected aminolactone **59** (70 mg, 0.18 mmol) in ethanol (3 cm^3) and the reaction mixture stirred under an atmosphere of hydrogen for 3.5 h. The mixture was then filtered and concentrated under reduced pressure to leave the (1*S*,3′*S*)-

[1-(3,4-dihydro-8-hydroxy-1-oxo-1*H*-2-benzopyran-3-yl)-3-methylbutyl]ammonium chloride **60** (49 mg, 95%) as an off-white solid which was used without purification; ν_{max}/cm^{-1} 3350br, 1681, 1619, 1518, 1463, 1234, 1165 and 1113; δ_H (CD_3OD) 0.93 and 0.98 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.60 (2 H, m), 1.75 (1 H, m), 3.01–3.27 (2 H, m, 4-CH_2), 3.52 (1 H, m, 1′-H), 4.68 (1 H, m, 3-H), 6.79 and 6.82 (each 1 H, d, *J* 7, 5-H and 7-H) and 7.43 (1 H, t, *J* 7, 6-H); *m*/*z* (CI) 278 (13%), 251 (19) and 250 (100).

(4*S*)-1-*tert*-Butyldimethylsilyl-4-{(1*S*,2*S*)-1,2-(dimethylmethylenedioxy)-3-{1-[(3*S*)-3,4-dihydro-8-hydroxy-l-oxo-1*H*-2-benzopyran-3-yl]-3-methylbutyl}amino-3-oxopropyl}azetidin-2-one 61

4-Dimethylaminopyridine (60 mg, 0.49 mmol) in dichloromethane (3 cm^3), the acid **27** (72 mg, 0.23 mmol) in dichloromethane (3 cm^3) and the amine hydrochloride **60** (65 mg, 0.227 mmol) in dichloromethane (5 cm^3) were added to a solution of *N*,*N*′-dicyclohexylcarbodiimide (56 mg, 0.27 mmol) in dichloromethane (3 cm^3) at 0 °C and the mixture stirred for 10 min at 0 °C then at room temperature for 18 h. Ether (20 cm^3) was added and the mixture filtered through Celite. After concentration under reduced pressure, chromatography of the residue using light petroleum–ethyl acetate (1:1) as eluent gave the *title compound* **61**† (68 mg, 54%) as a colourless oil, $[\alpha]_D^{20}$ −75.6 (*c* 0.7, $CHCl_3$) (Found: M$^+$, 561.3011. $C_{29}H_{45}N_2O_7Si$ requires *M*, 561.2996); ν_{max}/cm^{-1} 3413, 1741, 1677, 1620, 1586, 1516, 1464, 1231, 1214 and 1069; δ_H 0.21 and 0.37 (each 3 H, s, $SiCH_3$), 0.83 and 0.90 (each 3 H, d, *J* 6, 3″-CH_3 and 4″-H_3), 1.2 (1 H, m), 1.12 [9 H, s, $SiC(CH_3)_3$], 1.14 and 1.31 (each 3 H, s, CH_3), 1.55 (2 H, m), 2.22 (1 H, dd, *J* 13, 2, 4‴-H), 2.72 (1 H, dd, *J* 13, 11, 4‴-H′), 3.07 (1 H, dd, *J* 11, 5, 3-H), 3.21 (1 H, dd, *J* 11, 2, 3-H′), 3.77 (1 H, m, 3‴-H), 4.2 (1 H, m, 1″-H), 4.40 (1 H, d, *J* 8, 2′-H), 4.43 (1 H, m, 4-H), 4.61 (1 H, dd, *J* 8, 1, 1′-H), 6.21 (1 H, d, *J* 7, 7‴-H), 6.76 (1 H, d, *J* 11, N-H), 6.89 (1 H, d, *J* 7, 5‴-H), 6.99 (1 H, t, *J* 7, 6‴-H) and 11.53 (1 H, s, ArOH); *m*/*z* (FAB) 561 (M$^+$ + 1, 65%), 545 (15), 519 (50) and 503 (80).

(4*S*)-4-{(1*S*,2*S*)-1,2-Dihydroxy-3-{1-[(3*S*)-3,4-dihydro-8-hydroxy-1-oxo-1*H*-2-benzopyran-3-yl]-3-methylbutyl}amino-3-oxopropyl}azetidin-2-one 62

Aqueous hydrogen chloride (3.5 M; 5 cm^3) was added dropwise to a stirred solution of the acetonide **61** (32 mg, 0.057 mmol) in tetrahydrofuran (5 cm^3) at 0 °C and the reaction mixture stirred for 30 min at 0 °C then at room temperature for 6 h. The reaction was cooled to 0 °C and saturated aqueous sodium bicarbonate (10 cm^3) added slowly. The mixture was extracted into chloroform, and the organic extracts washed with water and brine then dried ($MgSO_4$). After concentration under reduced pressure, chromatography of the residue using chloroform–methanol (95:5) as eluent gave the *title compound* **62** (17 mg, 74%) as a white solid, mp 99–101 °C, $[\alpha]_D^{20}$ −103.4 (*c* 1, $CHCl_3$) (Found: M$^+$ + H, 407.1826. $C_{20}H_{27}N_2O_7$ requires *M*, 407.1818); ν_{max}/cm^{-1} 3337, 1737, 1670, 1620, 1585, 1531, 1464, 1232, 1165, 1113 and 756; δ_H (CD_3OD) 0.94 and 0.98 (each 3 H, d, *J* 6, 3″-CH_3 and 4″-H_3), 1.43 (1 H, m, 2″-H), 1.77 (2 H, m, 2″-H′ and 3″-H), 2.82–3.10 (3 H, m, 4‴-H and 3-CH_2), 3.10 (1 H, dd, *J* 14, 11, 4‴-H′), 3.76 (1 H, m, 4-H), 3.88 (1 H, t, *J* 5, 1′-H), 4.10 (1 H, d, *J* 5, 2′-H), 4.33 (1 H, m, 1″-H), 4.66 (1 H, dt, *J* 11, 2, 3‴-H), 6.77 and 6.84 (each 1 H, d, *J* 8, 5‴-H and 7‴-H) and 7.44 (1 H, t, *J* 8, 6‴-H); δ_C 21.9, 23.3, 24.9, 30.5, 39.6, 40.6, 49.5, 49.7, 72.6, 72.7, 81.5, 108.2, 116.5, 118.5, 136.8, 139.5, 162.2, 169.8, 169.9 and 172.9; *m*/*z* (FAB) 405 (M$^+$ − 1, 21%).

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Aqueous sodium hydroxide (0.05 M) was added dropwise to a solution of the azetidinone **62** (20 mg, 0.05 mmol) in ethanol–water (1:1; 5 cm^3) until the pH of the mixture reached 12. The pH was maintained at this level by further addition of base until the starting material could no longer be detected by TLC (*ca.* 18 h). The mixture was then cooled to 0 °C, acidified to pH 1.3 by addition of methanolic hydrogen chloride (3 M) and stirred at this temperature for 2 h. Concentration gave the bis-lactone hydrochloride **57** (24 mg).

Aqueous sodium hydroxide (0.02 M) was added dropwise to the bis-lactone hydrochloride **57** (24 mg) in ethanol–water (1:1; 5 cm^3) until the pH reached 9. The pH was maintained at this level by further addition of base until the starting material could no longer be detected by TLC (*ca.* 18 h). The pH was then adjusted to 6.5 by dropwise addition of aqueous hydrogen chloride (0.02 M). The reaction mixture was loaded directly onto a column of Amberlite XAD-2 resin packed with water. The column was washed with water–methanol (4:1) and the product isolated by eluting with water–methanol (1:4) to give title compound **1**[1]† (15 mg, 72%) as a white solid, mp 137–138 °C (lit.,[1] mp 139.5 °C); λ_{max} 246.6, 314.6 nm; $[\alpha]_D^{20}$ −68 (*c* 0.1, MeOH) (lit.,[1] −72.2; −78); ν_{max}/cm^{-1} 3258br, 1667, 1620, 1584, 1463, 1392, 1232, 1164 and 1112; δ_H (CD_3OD) 0.91 and 0.97 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.35 (1 H, m, 2′-H), 1.74 (2 H, m, 2′-H′ and 3′-H), 2.52 (1 H, dd, *J* 16, 10, 5-H), 2.6 (1 H, dd, *J* 16, 3, 5-H′), 2.91 (1 H, dd, *J* 16, 3, 4″-H), 3.08 (1 H, dd, *J* 16, 12, 4″-H′), 3.60 (1 H, m, 4-H), 3.93 (1 H, dd, *J* 8, 4, 3-H), 4.12 (1 H, d, *J* 7, 2-H), 4.31 (1 H, dt, *J* 10, 2, 1′-H), 4.65 (1 H, dt, *J* 11, 3, 3″-H), 6.76 and 6.81 (each 1 H, d, *J* 7, 5″-H and 7″-H) and 7.5 (1 H, t, *J* 7, 6″-H); δ_H (dimethyl sulfoxide-d_6; 60 °C) 0.87 and 0.91 (each 3 H, d, *J* 6.5, 3′-CH_3 and 4′-H_3), 1.38 (1 H, m, 2′-H), 1.67 (2 H, m, 2′-H′ and 3′-H), 2.17 (1 H, dd, *J* 16, 9, 5-H), 2.35 (1 H, dd, *J* 16, 3, 5-H′), 2.90 (1 H, dd, *J* 17, 3, 4″-H), 3.05 (1 H, dd, *J* 17, 12, 4″-H′), 3.23 (1 H, m, 4-H), 3.66 (1 H, dd, *J* 7, 4, 3-H), 3.99 (1 H, d, *J* 7, 2-H), 4.21 (1 H, m, 1′-H), 4.65 (1 H, dt, *J* 12, 3, 3″-H), 6.81 (1 H, d, *J* 8, 5″-H), 6.85 (1 H, d, *J* 8, 7″-H), 7.48 (1 H, t, *J* 8, 6″-H) and 7.65 (1 H, br d, *J* 9, N-H); δ_C (dimethyl sulfoxide-d_6) 21.5, 23.3, 23.9, 29.0, 33.6, 48.0, 50.1, 71.6, 72.3, 80.9, 108.3, 115.2, 118.4, 136.2, 140.6, 160.8, 169.0 and 172.6; *m*/*z* (FAB) 425 (M$^+$ + 1, 32%), 413 (15) and 329 (35).

Natural Al-77-B **1** (2 mg, 0.005 mmol) was dissolved in methanol (2 cm^3) and methanolic hydrogen chloride was added (3 M; 1 drop). Concentration under reduced pressure gave the bis-lactone hydrochloride **57**; ν_{max}/cm^{-1} 3245, 1783, 1665, 1619, 1584, 1462, 1230, 1163 and 1110; δ_H (CD_3OD) 0.92 and 0.98 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.43 (1 H, m, 2′-H), 1.69 (1 H, m, 3′-H), 1.80 (1 H, m, 2′-H′), 2.56 (1 H, dd, *J* 18, 2, 5-H), 3.03 (2 H, m, 4″-CH_2), 3.22 (1 H, dd, *J* 18, 9, 5-H′), 4.18 (2 H, m, 1′-H and 4-H), 4.46 (1 H, d, *J* 4, 2-H), 4.72 (1 H, m, 3″-H), 4.87 (1 H, t, *J* 4, 3-H), 6.82 and 6.86 (each 1 H, d, *J* 7, 5″-H and 7″-H) and 7.47 (1 H, t, *J* 7, 6″-H); *m*/*z* (FAB) 442 (M$^+$, 20%), 439 (20), 413 (45), 407 (55), 393 (60) and 322 (75).

The bis-lactone hydrochloride **57** (5 mg, 0.012 mmol) was dissolved in saturated aqueous sodium carbonate (2 cm^3). The solution was immediately extracted with ethyl acetate and the organic extracts washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave the amino-bis-lactone **63** (2 mg, 40%); δ_H (CD_3OD) 0.91 and 0.98 (each 3 H, d, *J* 6, 3′-CH_3 and 4′-H_3), 1.33–1.91 (3 H, m, 2′-H_2 and 3′-H), 2.72 (1 H, dd, *J* 18, 3, 5-H), 2.93 (3 H, m, 4″-H_2 and 5-H), 3.66 (1 H, m, 4-H), 4.31 (1 H, m, 1′-H), 4.37 (1 H, d, *J* 3, 2-H), 4.54 (1 H, t, *J* 3, 3-H), 4.63 (1 H, m, 3″-H), 6.77 and 6.82 (each 1 H, d, *J* 7, 5″-H and 7″-H) and 7.43 (1 H, t, *J* 7, 6″-H).

On addition of methanolic hydrogen chloride (3 M; 1 drop) the hydrochloride **57** was reformed.

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