Stereocontrolled Synthesis of (2S,3S,8S,9S,4E,6E)-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic Acid (Adda),[1] the Amino Acid Characteristic of Microcystins and Nodularin

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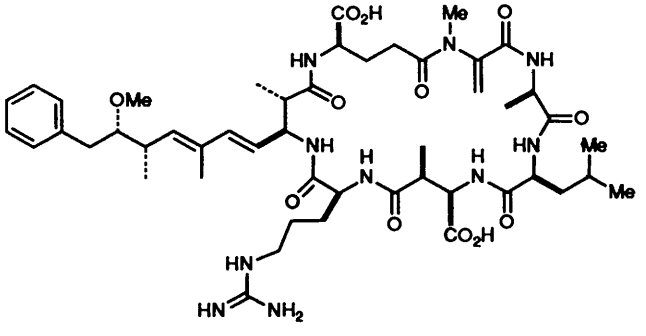
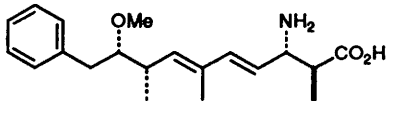
(4*R*,5*S*)-4-Methyl-5-phenyloxazolindin-2-one has been used as a chiral template to construct the 8*S* and 9*S* chiral centres of (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (Adda), the 2*S* and 3*S* centres being derived from D-aspartic acid.

A number of potent hepatotoxins produced by cyanobacteria have been reported in the literature in recent years. Examples include the heptapeptide microcystin-LR[1,2] **1** from *Microcystis aeruginosa* and the pentapeptide nodularin[1] from *Nodularia spumigena*. Both closely related peptides contain the unique C_{20} amino acid (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid,[1] or Adda **2**.



1, Microcystin-LR

It has been suggested that the hepatotoxicity of these cyclic peptides may be due to the presence of the Adda moiety.[1,3] Here we report an efficient, stereocontrolled total synthesis of t-Boc-Adda (Boc = butoxycarbonyl), which will allow for its production in multigram quantities, for hepatoxicity studies and for the synthesis of its parent peptides. Although parts of the synthesis are similar to that previously reported by Rinehart,[1b] the chiral centres at positions 8 and 9 are prepared in a stereocontrolled manner and thus do not require the use of HPLC to separate unwanted diastereoisomers.



2, Adda

For controlling the chirality at positions 8 and 9 of Adda, we used Evans'[4] chiral oxazolidine template methodology as shown in Scheme 1. Thus, straightforward *N*-acylation of oxazolidone **3** with propionyl chloride furnished the propionyloxazolidine **4**. Enolisation of **4** with dibutylboron trifluoromethanesulfonate and trialkylamine followed by aldol condensation with phenylacetaldehyde provided the alcohol **5** having both 2'-methyl and 3'-hydroxy chiral centres of the desired configuration. *O*-Methylation of **5** using trimethyloxonium tetrafluoroborate in the presence of bis(dimethylamino)naphthalene (proton sponge) produced the methyl ether **6**, which was cleaved using lithium borohydride to yield the alcohol **7**. The recovered oxazolidone **3** was isolated and recycled.

Rinehart and co-workers obtained an optical rotation of $[\alpha]_D$ 10.5‡ for their sample of alcohol **7**, which was synthesized from (2*S*,3*S*)-methyl 3-hydroxy-2-methylpropanoate[1a] and shown to have an enantiomeric excess of 80% by ^{1}H NMR (chiral shift reagent).§ Thus, a specific rotation of $[\alpha]_D$ 13.1 would correspond to 100% optical purity. The specific rotation of our alcohol **7** $[\alpha]_D$ 13.2, suggesting an ee of 100%. To provide further evidence that the optical purity of alcohol **7** was close to 100%, a 400 MHz ^{1}H NMR spectrum was run under Rinehart's conditions.§ As expected, the chiral shift reagent revealed no methoxy resonances corresponding to the (*R*,*R*)-antipode.

Oxidation of the alcohol **7** with pyridine–sulfur trioxide–DMSO gave the aldehyde **8**, which then underwent a Wittig reaction with 1-ethoxycarbonylethylidene(triphenyl)-phosphorane (the reagents were stirred in DMF for six days at room temp.). The resultant *E*/*Z* mixture of unsaturated esters **9–10**, obtained in a 4.5:1 (*cis*/*trans*) ratio, was reduced using diisobutylaluminium hydride (DIBAL-H) to afford the alcohols **11–12**. The dominant regioisomer was shown to have the *E* configuration (*trans*) by dynamic nuclear Overhauser enhancement (DNOE) experiments.¶ This mixture of alcohols was most conveniently carried on and separated at a later stage.

To determine whether racemisation of the 4*S* chiral centre of the esters **9**, **10** had occurred during the Wittig reaction with 1-ethoxycarbonylethylidene(triphenyl)phosphorane, a portion of this mixture was ozonised at −78 °C and then reduced with sodium borohydride (−78 to 23 °C) to give the alcohol **7a**. A comparison of the specific optical rotation of alcohol **7a** (11.1) with that of **7** (13.2) indicated that some racemisation had occurred. This was supported by a 400 MHz ^{1}H NMR spectrum of **7a**, which indicated the presence of 15% of the (2*R*,3*S*)-diastereoisomer.

If the first Wittig reaction to produce the esters **9–10** was carried out in refluxing benzene,[3] a similar diastereoisomeric

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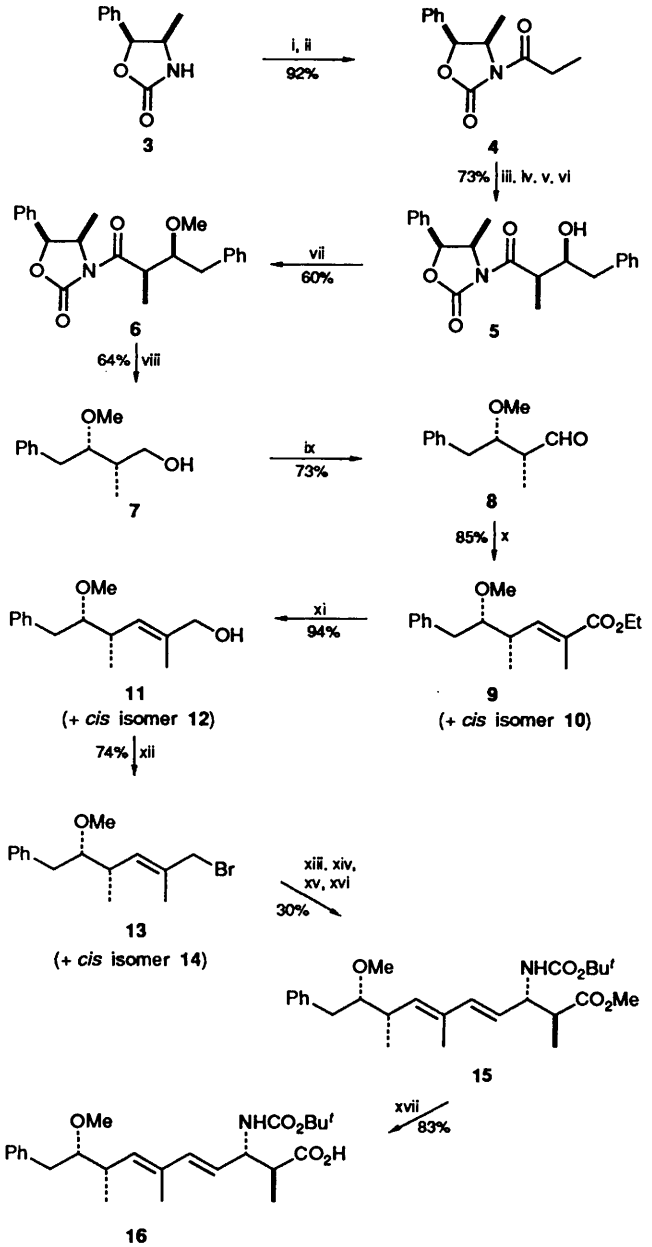
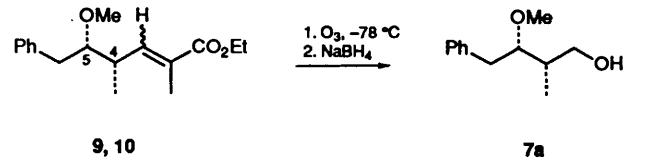
‡ $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}.

§ Personal communication. K. L. Rinehart's preparation of (2*S*,3*S*)-3-methoxy-2-methyl-4-phenylbutanol also produced *ca.* 10% of the (2*R*,3*R*)-antipode. This was revealed in the 300 MHz ^{1}H NMR spectrum upon addition of the chiral shift reagent (*R*)-trifluoroanthrylethanol as a 6% solution in benzene, which resulted in the separation of the methoxy resonances of the two enantiomers.

¶ The olefinic proton appearing at 5.34 of the mixture **11**, **12** was irradiated, resulting in 6% enhancement of the hydroxymethylene peak occuring at 4.0 of the major isomer.



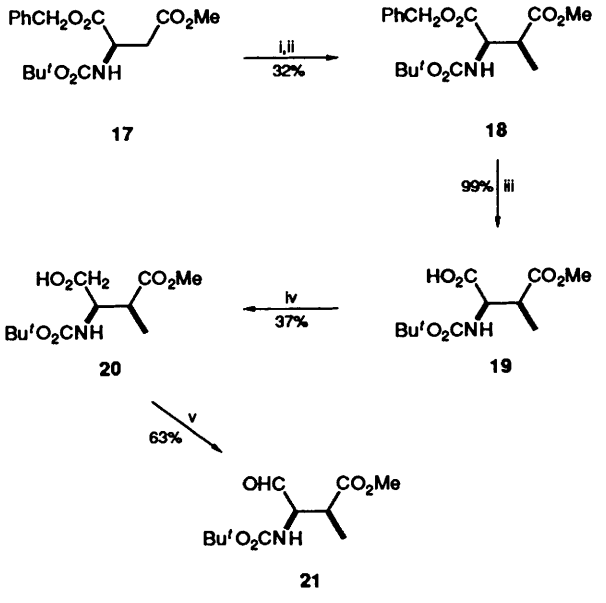
Scheme 1 *Reagents and conditions:* i, 1.6 mol dm^{-3} BuLi in hexanes, THF, −78 °C, 30 min; ii. EtCOCl, −78 °C to room temp., 2 h; iii, $Bu_2BOSO_2CF_3$ (1.1 equiv.), DCM, 0 °C; iv, $(Pr^i)_2EtN$ (1.2 equiv.), 0 °C, 30 min; v, $PhCH_2CHO$ (1.1 equiv.), −78 °C, 30 min, then room temp. for 1.5 h; vi, 30% H_2O_2 in methanol, 0 °C, 1 h; vii, $Me_3O^+BF_4^-$, proton sponge (1.16 equiv.), DCM, room temp., 7 days; viii; $LiBH_4$ (1 equiv.), room temp., 16 h; ix, $Py.SO_3$ (3.0 equiv.), DMSO, 30 min; x, $Ph_3P{=}C(Me)CO_2Et$ (1.05 equiv.), DMF, room temp., 6 d or PhH, reflux, 4 h; xi, DIBAL-H (11.0 equiv.), −78 °C for 2 h, then room temp. overnight; xii, PPh_3 (2 equiv.), CBr_4 (2 equiv.), Et_2O, room temp., 7 h; xiii, PPh_3, benzene, reflux, 6 h; xiv, 1.6 mol dm^{-3} BuLi in hexanes, THF, 0 °C, 10 min; xv, 21 (0.9 equiv.), THF, 0 °C, 3 h; xvi, aq. NH_4Cl; xvii, 1 mol dm^{-3} NaOH (2 equiv.), MeOH, room temp., 4 days.



mixture consisting of 88% of the (4*S*,5*S*) *cis* and *trans* esters **9**, **10** and 12% of the (4*R*,5*S*) *cis* and *trans* esters was obtained.

These amounts of racemisation were, however, less than that obtained by other workers in their synthesis of Adda,[1b] since the Wittig reaction when carried out in refluxing toluene gave a diastereoisomeric mixture consisting of 65% of the (4*S*,5*S*)-esters and 35% of the 4*R*,5*S*-esters.

Next, the aldehyde **21** was synthesized as shown in Scheme 2. Dianion alkylation of methyl ester **17** to give the desired *erythro* diastereoisomer **18** proved to be somewhat troublesome. If alkylation of the dianion derived from **17** was carried out at −78 °C, the product ratio consisted of 96% unwanted *threo* diastereoisomer along with only 4% of the desired *erythro* isomer **18**. However, by forming the dianion of **17** at −78 °C and then allowing it to react with methyl iodide at −7 °C gave a product ratio of 43% *erythro* **18** and 57% *threo*. Next, hydrogenolysis of **18** furnished the acid **19**, which was then reduced by borane in THF (with careful monitoring of the reaction by TLC) to give the stable alcohol **20**. Mild oxidation of this alcohol was conveniently accomplished in DMSO with pyridine–sulfur trioxide in the presence of triethylamine to yield the desired aldehyde **21**.



Scheme 2 *Reagents and conditions:* i, LHMDS (2.0 equiv), THF, −78 °C, 30 min; ii, MeI (1.2 equiv.), −7 °C, 1 h; iii, H_2/Pd, MeOH, 2 h; iv, BH_3·THF (3.0 equiv), 0 °C, 1 h; v, pyridine–SO_3 (3.0 equiv.), DMSO, Et_3N (3.0 equiv.), room temp., 30 min.

The mixture of alcohols **11**, **12** (Scheme 1) was converted into the bromides **13**, **14** and thence to the corresponding triphenylphosphine salts. The ylide derived from the triphenylphosphine salt of **13**, **14** was reacted with the protected aldehyde **21**, to give a mixture of the four possible geometric isomers. The mixture was readily separated by PTLC to give the desired isomer **15**, care being taken to avoid possible photochemical isomerization. Hydrolysis of the isomer **15** with dilute methanolic sodium hydroxide gave t-Boc-Adda **16**. The 400 MHz ^1H NMR spectrum indicated the presence of 6% of 2*S*,3*R*,8*S*,9*S*-Adda, probably due to partial racemisation of the 3*S*-centre during the second Wittig reaction leading to compound **15**. The overall yield for the 11-step synthesis of Adda was 2.1%.

Experimental

Microanalysis were performed by Desert Analytics of Tucson, Arizona. IR spectra were measured with a Perkin-Elmer 1310 spectrophotometer. ^1H NMR spectra were recorded at either 90 MHz on a JOEL FX 90Q instrument or at 400 MHz on a Varian

XL 400 instrument with tetramethylsilane as an internal standard; J values are given in Hz. ^{13}C NMR spectra were determined on a Varian XL 400 instrument with tetramethylsilane as an internal standard. Electron impact mass spectra (EIMS) were measured on a LKB 9000 instrument and chemical ionisation mass spectra (CIMS) were measured on a Ribermag R10-10C instrument. High resolution mass spectra (HRMS) were carried out on a VG 7070E-HF instrument at the University of Minnesota. Optical rotations were measured on an Autopol III 589-10 polarimeter using sucrose as a calibration standard; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Column chromatography was performed on silica gel 130–270 mesh, 60 A (Aldrich No. 28,860-8) with a medium-pressure apparatus.

(4R,5S)-4-*Methyl*-5-*phenyl*-1-*propionyloxazolidin*-2-*one* **4**.—(+)-(4*R*,5*R*)-4-Methyl-5-phenyloxazolidin-2-one (26.55 g, 0.15 mol) in dry tetrahydrofuran (270 cm^3) under argon at −78 °C was added dropwise a solution of butyllithium in hexanes (1.6 mol dm^{-3}; 93.8 cm^3, 0.15 mol) and the mixture stirred at − 78 °C for 30 min. Propionyl chloride (13.1 cm^3, 0.15 mol) was added dropwise and the mixture allowed to warm to room temperature over 2 h. It was then poured onto ice and extracted with ether (× 2). The combined organic extracts were washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give crude material (37.2 g). Flash column chromatography of this (20% ethyl acetate in hexanes) gave pure oxazolidinone **4** (32.0 g, 92%) as a colourless oil: $[\alpha]_D^{20}$ +133.1 (*c* 1.00, EtOH); ν_{max}(neat)/cm^{-1} 2985, 1780, 1700; δ_H($CDCl_3$) 0.90 (3 H, d, *J* 6.5, 4-Me), 1.18 (3 H, t, *J* 7.5, CH_2CH_3), 2.96 (2 H, q, *J* 7.5, $COCH_2$), 4.76 (1 H, qu, *J* 7.0, NCH), 5.67 (1 H, d, *J* 7.5, OCH) and 7.37 (5 H, m, Ph); *m*/*z* (EIMS) 233 (M^+ peak), 176, 163, 116 and 107 (Found: C, 66.8; H, 6.5; N, 6.1. Calc. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00%).

(2′R,3′S,4R,5S)-3-[3′-*Hydroxy*-2′-*methyl*-4′-*phenylbutanoyl*]-4-*methyl*-5-*phenyloxazolidin*-2-*one* **5**.—A solution of compound **4** (1.0 g, 4.3 mmol) in dichloromethane (10 cm^3) was treated with a solution in dichloromethane of dibutylboron triflate (1 mol dm^{-3}; 1.30 g, 4.74 mmol, 4.74 cm^3, 1.1 equiv.) under argon at 0 °C. Diisopropylethylamine (0.67 g, 5.16 mmol, 0.90 cm^3, 1.2 equiv.) was added and the resulting solution stirred at 0 °C for 30 min. It was then cooled to −78 °C and treated with phenylacetaldehyde (90.57 g, 4.74 mmol, 0.56 cm^3, 1.1 equiv.) whilst being stirred at −78 °C for 30 min. Subsequently the mixture was stirred at room temperature (22 °C) for 1.5 h, before being quenched with pH 7 buffer. Oxidation with 30% hydrogen peroxide in methanol at 0 °C for 1 h gave crude product as a yellow oil. Flash column chromatography of this (40% ethyl acetate in hexanes) gave the pure alcohol **5** (1:1 g, 73%) as a yellow oil which crystallized with time: m.p. 98–99 °C; $[\alpha]_D^{22}$ −24.9° (*c* 1.00, EtOH); ν_{max}(neat)/cm^{-1} 3540, 3005, 1780 and 1685; δ_H($CDCl_3$) 0.89 (3 H, d, *J* 6.5, 4-Me) 1.34 (3 H, d, *J* 7.0, $COCHCH_3$), 2.74 (1 H, s, OH), 2.82 (3 H, d, *J* 7.0, $PhCH_2$), 3.84 (1 H, dq, *J* 7.0, 3.5, CHCHOH), 4.22 (1 H, seven lines, *J* 3.2, CHOH), 5.65 (1 H, d, *J* 7.0, CHOCO) and 7.28 (5 H, m, Ph); *m*/*z* (EIMS) 354 (M + H), 355 (M–H_2O), 262 (M–91), 178, 134, 91, 77 and 65 (Found: C, 71.3; H, 6.5; N, 4.0. Calc. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96%).

(2′R,3′S,4R,5S)-3-(3′-*Methoxy*-2′-*methyl*-4′-*phenylbutanoyl*)-4-*methyl*-5-*phenyl*-2-*oxazolidin*-2-*one* **6**.—A mixture of compound **5** (1.0 g, 2.83 mmol), trimethyloxonium tetrafluoroborate (0.42 g, 2.83 mmol) and 1,8-bis(dimethylamino)naphthalene (0.71 g, 3.30 mmol, 1.1 equiv.) in dichloromethane (5 cm^3) was stirred at 22 °C for 5 days. The resulting solution was quenched with ice–water and extracted with dichloromethane (× 3). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), filtered and evaporated to give the crude oxazolidinone **6** as a dark oil. Flash column chromatography of this (40% ethyl acetate in hexanes) gave the pure oxazolidinone **6** (0.62 g, 60%) as a pale yellow oil; $[\alpha]_D^{21}$ −21.5 (*c* 0.158, EtOH); ν_{max}/cm^{-1} 2980, 2925, 1780 and 1700; δ_H($CDCl_3$) 0.87 (3 H, d, *J* 6.6, $NCHCH_3$), 1.28 (3 H, d, *J* 6.6, $COCHCH_3$), 2.85 (2 H, d, *J* 6.2, CHPh), 3.26 (3 H, s, OMe), 3.71 (1 H, q, *J* 5.3, CHCHOMe), 3.96 (1 H, qu, *J* 6.7, CHOMe), 4.65 (1 H, qu, *J* 7.0, NCHMe), 5.59 (1 H, d, *J* 7.1, OCHPh) and 7.37 (5 H, m, Ph); *m*/*z* (EIMS) 368 (M + H), 335 (M–MeOH), 276, 232, 160, 99 and 91 (Found: C, 71.8; H, 6.8; N, 3.6. Calc. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81%).

(2S,3S)-3-*Methoxy*-2-*methyl*-4-*phenylbutanol* **7**.—To a suspension of lithium borohydride (0.18 g, 8.17 mmol) in dry tetrahydrofuran (6 cm^3) under argon at 0–5 °C, was added dropwise a solution of compound **6** (3.0 g, 8.17 mmol) in dry tetrahydrofuran (6 cm^3) and the mixture stirred at 20 °C for 16 h. It was then cooled in ice and slowly diluted with water (20 cm^3). Subsequently, the mixture was poured onto ice-cold saturated aqueous ammonium chloride (50 cm^3) and the product extracted with ether. The extract was washed with brine and water, dried ($MgSO_4$), filtered and evaporated under reduced pressure to leave the crude alcohol **7** as a yellow oil. Flash column chromatography (40% ethyl acetate in hexanes) of this yielded the pure alcohol **7** (0.81 g, 51%) as a yellow oil: $[\alpha]_D^{20}$ +13.3 (*c* 0.395; EtOH); ν_{max}/cm^{-1} 3420, 2920 and 1490; δ_H($CDCl_3$) 0.97 (3 H, d, *J* 7.1, $CHCH_3$), 1.91 (1 H, m, CHMe), 2.45 (1 H, br s, OH), 2.81 (2 H, d of q, *J* 9.9, 7.1), 3.30 (3 H, s, OMe), 3.58 (3 H, m, CH_2OH, CHOMe) and 7.24 (5 H, s, Ph); *m*/*z* (C.I.M.S-NH_4) 212 (M + NH_4) and 195 (100, M + H) (Found: C, 73.9; H, 9.4. Calc. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%).

(2S,3S)-3-*Methoxy*-2-*methyl*-4-*phenylbutanal* **8**.—A solution of compound **7** (5.50 g, 28.0 mmol) in dimethyl sulfoxide (140 cm^3) was treated with triethylamine (8.69 g, 86.0 mmol) and the resulting solution cooled in an ice-bath. Pyridine–sulfur trioxide (13.7 g, 86.0 mmol) was added portionwise and the resulting mixture stirred at 22 °C for 30 min. It was then poured into ice-cold 10% aqueous citric acid (200 cm^3) and the product extracted with diethyl ether. The combined organic extracts were washed with 10% aqueous citric acid, water, saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the aldehyde **8** (3.86 g, 71%) as a light brown oil which was not purified further. It was essentially pure as judged by ^1H NMR; ν_{max}/cm^{-1} 2935, 1710 and 1455; δ($CDCl_3$) 1.17 (3 H, d, *J* 7.0, $CHCH_3$), 2.38 (1 H, 8 lines, *J* 3.6, CHCHO), 2.85 (2 H, d of q, *J* 6.6, 14, CH_2Ph), 3.30 (3 H, s, OMe), 3.88 (1 H, d of t, *J* 3.1, 7.0, CHOMe), 7.24 (5 H, m, Ph) and 9.68 (1 H, s, CHO); *m*/*z* (CIMS) 210 (M + NH_4), 193 (M + H) and 175 (100).

(4S,5S)-*Ethyl*-5-*methoxy*-2,4-*dimethyl*-6-*phenylhex*-2-*enoate* **9**, **10** (88% *trans*).—A mixture of compound **8** (1.0 g, 5.2 mmol) and 1-ethoxycarbonylethylidene(triphenyl)phosphorane (1.98 g, 5.47 mmol, 1.05 equiv.) were heated under reflux in dry benzene (20 cm^3) for 4 h. The mixture was poured into water (20 cm^3) and extracted with diethyl ether (3 × 15 cm^3). The combined ethereal extracts were washed with water and brine, dried ($MgSO_4$) and evaporated to give crude compounds **9**, **10**. Flash column chromatography (40% ethyl acetate in hexanes) of these gave pure compounds **9**, **10** (1.22 g, 85%) as a pale yellow oil: $[\alpha]_D^{21}$ −13.6 (*c* 0.34, $CHCl_3$); ν_{max}/cm^{-1} 2980, 2925 and 1710; δ_H($CDCl_3$) 1.08 (3 H, d, *J* 7.0, $CHCH_3$), 1.30 (3 H, t, *J* 7.0, CH_2CH_3), 1.74 (3 H, d, *J* 1.3, allylic Me), 2.73 and 2.80 (2 H, 2 d, *J* 3.5 and 1.3 respectively, CH_2Ph), 3.26 (3 H, s, OMe), 4.20 (2 H, q, *J* 7.1, CH_2CH_3), 6.68 (1 H, d of q, *J* 10.2, 1.4, allylic H)

and 7.23 (5 H, m, Ph); *m/z* (CIMS) 294 (100, M + NH_4 peak), 277 (M + H peak) and 245 (M-OMe peak) (Found: C, 73.6; H, 8.7. Calc. for $C_{17}H_{24}O_3$: C, 73.88; H. 8.75%).

Ozonolysis of Compounds **9** and **10**.—A solution of compounds **9**, **10** (100 mg, 0.36 mmol) in methanol (20 cm^3) at −78 °C was ozonised until its colour was a persistent greyish blue (5 min). Sodium borohydride (100 mg, 2.63 mmol) was added to the reaction mixture which was then allowed to warm up from −78 °C to room temperature over a period of 2 h. It was then added cautiously to ice-cold 5% hydrochloric acid and the product extracted out with ether. The extract was washed with brine, 10% aqueous sodium carbonate and brine, dried ($MgSO_4$), filtered and evaporated to leave a yellow oil. This was purified on a preparative silica gel TLC plate, eluting with 40% ethyl acetate in hexanes to give the alcohol **7a** (34 mg, 48%) as a pale yellow oil: $[\alpha]_D^{20}$ +11.8 (*c* 0.288; EtOH). Its spectra compared well with those of a previously prepared specimen.

(2R,3S)-1-*Benzyl* 4-*Methyl* N-tert-*Butoxycarbonyl*-3-*methyl-aspartate* **18**.—A stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (6.14 cm^3, 29.4 mmol) in dry THF (40 cm^3) was cooled to 0 °C and treated with a solution of BuLi in hexanes (1.6 mol dm^{-3}; 19.3 cm^3, 30.9 mmol). The resulting mixture was stirred for 10 min at 0–5 °C and then cooled to −78 °C. A solution of the ester **17** (4.5 g, 13.4 mmol) in dry THF (10 cm^3) was added dropwise over 20 min and the mixture then stirred at −78 °C for 1 h. It was then warmed to −7 °C and methyl iodide (1.02 cm^3, 16.4 mmol) added. After the resulting solution had been stirred at −9 to −6 °C for 1 h it was poured onto saturated aqueous ammonium chloride–ice and extracted with diethyl ether. The combined ethereal extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated to leave crude compound **18** as an orange oil. Flash column chromatography of this eluting with hexane–EtOAc (8.5:1.5 to 7.5:2.5) gave the desired *erythro* isomer **18** (1.75 g, 37%) as a colourless oil: $[\alpha]_D^{22}$ +10.7; ν_{max}(neat)/cm^{-1} 3440, 3000, 1740 and 1500; δ_H($CDCl_3$) 1.24 (3 H, d, *J* 7.5, CHCH_3), 1.45 (9 H, s, Bu^t), 3.10–3.32 (1 H, m, C*H*Me), 3.57 (3 H, s, OCH_3), 4.56 (1 H, dd, 3 and 9.5, C*H*NH), 5.16 (2 H, s, CH_2Ph), 5.42 (1 H, d, *J* 9.5, N*H*) and 7.34 (5 H, s Ph) (Found: C, 61.7; H, 7.35; N. 3.9. Calc. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99%).

(2R,3S)-4-*Methyl* N-tert-*Butoxycarbonyl*-3-*methylaspartate* **19**.—A solution of compound **18** (2.0 g, 5.70 mmol) in methanol (60 cm^3) and 5% palladium on carbon (0.45 g) was stirred under a hydrogen atmosphere for 2 h. The catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure at 40 °C to leave the acid **19** (3.72 g, 98%) as a colourless oil which was not purified further. It was essentially pure as judged by ^{1}H NMR; $[\alpha]_D^{21}$ −9.1 (*c* 0.37, EtOH); ν_{max}(neat)/cm^{-1} 3400, 2980 and 1740; δ_H($CDCl_3$) 1.29 (3 H, d, *J* 7.5, CHCH_3), 1.45 (9 H, s, Bu^t), 3.15–3.35 (1 H, m, NHC*H*), 3.72 (3 H, s, OMe), 4.54 (1 H, dd, *J* 3, 9.5, NHCHC*H*), 5.54 (1 H, d, *J* 9.5, N*H*), 8.84 (1 H, br s, CO_2H); *m/z* (EIMS) 216 (M–CO_2H), 174, 160, 116, 101 and 88.

(2S,3R)-*Methyl* 3-tert-*Butoxycarbonyl*)*amino*-4-*hydroxy*-2-*methylbutyrate* **20**.—To a solution of borane in THF (1 mol dm^{-3}; 11.5 cm^3, 11.5 mmol) at 0 °C was slowly added the carboxylic acid **19** (1.0 g, 3.83 mmol) in dry THF (4 cm^3). The reaction mixture was stirred at 0 °C for 1 h and then added slowly to aqueous sodium hydrogen carbonate (0.1 mol dm^{-3})–ice. The product was extracted with dichloromethane and the combined extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure to leave crude compound **20** as a yellow oil. Flash column chromatography (40% ethyl acetate in hexanes) of this gave the pure alcohol **20** (0.34 g, 37%) as a colourless oil: $[\alpha]_D^{22}$ +10.5; ν_{max}(neat)/cm^{-1} 3400, 2920 and 1610; δ_H($CDCl_3$) 1.25 (3 H, d, *J* 7.5), 1.45 (9 H, s, Bu^t), 2.23 (1 H, br s, O*H*), 2.75–2.95 (1 H, m, C*H*CO_2Me), 3.65 (2 H, m, CH_2OH), 3.70 (3 H, s, OCH_3), 3.75 (1 H, m, C*H*$NHCO_2$) and 5.30 (1 H, br s, NH); *m/z* (CIMS) 265 (M + NH_4), 248 (M + H), 233, 209, 192, 177 and 148 (Found: C, 53.55; H, 8.6; N, 5.9. Calc. for $C_{11}H_{21}NO_5$: C, 53,42; H, 8.56; N, 5.66%).

(2R,3S)-2-tert-*Butoxycarbonyl*)*amino*-3-*methoxycarbonyl*-3-*methylbutanal* **21**.—To the alcohol **20** (116 mg, 0.470 mmol) in dry DMSO (1 cm^3) at room temp. under an argon atmosphere was added triethylamine (0.20 cm^3, 1.45 mmol) followed by a solution of sulfur trioxide–pyridine (224 mg, 1.41 mmol) in dry DMSO (1 cm^3) and the resulting mixture stirred at room temp. for 30 min. The mixture was then extracted with dichloromethane and the extract washed with water, aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give **21** (73 mg, 63%) as a yellow oil which was not purified further. It was essentially pure as judged by ^{1}H NMR; δ_H($CDCl_3$) 1.27 (3 H, d, *J* 7.5, CHCH_3), 1.45 (9 H, s, Bu^t), 2.78–3.02 (1 H, m, C*H*CO_2Me), 3.72 (3 H, s, OMe), 4.15–4.38 (1 H, m, C*H*NH), 5.52 (1 H, br s, N*H*) and 9.55 (1 H, s, CHO).

(4S,5S)-5-*Methoxy*-2,4-*dimethyl*-6-*phenylhex*-2-*en*-1-*ol* **11**, **12** (88% *trans*).—A solution of compounds **9**, **10** (500 mg, 1.81 mmol) in dry hexanes (3 cm^3) was cooled to −78 °C and treated with a large excess of a solution of diisobutylaluminium hydride in hexanes (1.0 mol dm^{-3}; 24 cm^3, 24 mmol). The resulting reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to room temperature overnight. The reaction mixture was cooled to 0–5 °C in an ice-bath and ammonium chloride added dropwise until effervescence had ceased. Water was added and the gelatious mixture transferred to a separating funnel where it was extracted with ethyl acetate. The combined extracts were washed with brine (×2), dried ($MgSO_4$), filtered and evaporated to leave the alcohols **11**, **12** (0.40 g, 95%) as a yellow oil: $[\alpha]_D^{23}$ −3.74 (*c* 0.427, EtOH); ν/cm^{-1} 3400, 2930 and 1495; δ_H($CDCl_3$) 1.01 (3 H, d, *J* 6.6, CHCH_3), 1.57 (3 H, s, allylic Me), 1.83 (2 H, br s, OH + H_2O), 2.40–2.65 (1 H, m, C*H*CH_3), 2.72 and 2.78 (2 H, d and br s, *J* 3.6, CH_2Ph), 3.23 (3 H, s, OMe), 3.97 (2 H, br s, CH_2OH), 5.32 (1 H, br d, *J* 9.7, allylic H) and 7.24 (5 H, s, Ph); *m/z* (CIMS) 252 (M + NH_4) (Found: C, 76.6; H, 9.2. Calc. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%).

(4S,5S)-1-*Bromo*-5-*methoxy*-2,4-*dimethyl*-6-*phenylhex*-2-*ene* **13**, **14** (88% *trans*).—To a stirred solution of the alcohol (1.0 g, 4.27 mmol) in dry ether (20 cm^3), under an argon atmosphere, was added carbon tetrabromide (2.82 g, 8.54 mmol) followed by a solution of triphenylphosphine (2.22 g, 8.54 mmol) in dry ether (30 cm^3). The mixture was stirred at room temp. for 7 h. The triphenylphosphine oxide was filtered off and washed with ether and the filtrate evaporated to dryness under reduced pressure. Flash column chromatography (40% ethyl acetate in hexanes) of the residue gave the desired bromide (0.810 g, 64%) as a yellow oil: $[\alpha]_D^{22}$ +2.2 (*c* 0.59, EtOH); ν_{max}(neat)/cm^{-1} 2920, 1600 and 1495; δ_H($CDCl_3$) 1.03 (3 H, d, *J* 6.6, CHCH_3), 1.66 (3 H, d, *J* 1.4, allylic Me), 2.30–2.65 (1 H, m, C*H*CH_3), 2.72 and 2.79 (2 H, 2 d, *J* 4.4, 2.6, CH_2Ph), 3.26 (3 H, s, OMe), 3.97 (2 H, s, CH_2Br), 5.53 (1 H, br d, *J* 11.5, allylic H) and 7.24 (5 H, s, Ph).

(2S,3S,8S,9S)-*Methyl*-3-tert-*Butoxycarbonylamino*-9-*methoxy*-2,6,8-*trimethyl*-10-*phenyldeca*-4,6-*dienoate* **15**.—To a solution of **13**, **14** (520 mg, 1.70 mmol) in benzene (50 cm^3) was added a solution of triphenylphosphine (460 mg, 1.70 mmol) in benzene (20 cm^3) and the mixture heated under reflux for 6 h. It was then evaporated under reduced pressure to give the corresponding phosphonium salt (860 mg). To this salt (860 mg,

1.54 mmol) in dry THF (10 cm^3) at −78 °C was added a solution of butyllithium in hexanes (1.6 mol dm^{-3}; 1.0 cm^3, 1.6 mmol) and the mixture stirred at 0 °C for 10 min. The aldehyde (370 mg, 1.49 mmol) in dry THF (10 cm^3) was added and the mixture was stirred at 0 °C for 3 h. It was then poured into ammonium chloride–ice and extracted with diethyl ether. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated under reduced pressure to give crude **15**. Preparative TLC, eluting with 25% ethyl acetate in hexanes gave the pure title compound **15** (220 mg, 33%) as a colourless oil: $[\alpha]_D^{22}$ −7.9 (*c* 0.1, $CHCl_3$); $\delta_H(CDCl_3)$ 1.03 (3 H, d, *J* 6.8, MeOCHCHCH_3), 1.23 (3 H, d, *J* 6.8, MeO_2CCHCH_3), 1.46 (9 H, s, Bu^t), 2.55–2.85 (4 H, m, PhCH_2, MeOCHC*H*, MeO_2CCH), 3.15–3.22 (1 H, m, C*H*OMe), 3.24 (3 H, s, OMe), 3.68 (3 H, s, CO_2CH_3), 4.38 (1 H, br s, NHC*H*), 5.3 (1 H, s, N*H*), 5.36–5.53 (2 H, m, MeC=C*H*, CCH=C*H*), 6.19 (1 H, d, *J* 16, CC*H*=CH) and 7.15–7.23 (5 H, m, Ph) (Found: C, 70.05; H, 8.9; N, 2.9. Calc. for $C_{26}H_{39}NO_5$: C, 70.08; H, 8.82; N, 3.14%).

t-Boc-Adda **16**.—A solution of compound **15** (150 mg, 0.336 mmol) in methanol (6 cm^3) under argon at room temp. was treated with a solution of sodium hydroxide (27 mg, 0.669 mmol) in water (0.75 cm^3). The resulting pale yellow solution was stirred at room temp. for 96 h and then poured onto dil. HCl–ice (60 cm^3) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and evaporated under reduced pressure to leave the required acid (120 mg, 83%) as a yellow oil: $[\alpha]_D^{22}$ −15.1 (*c* 0.1, $CHCl_3$); $\delta_H(CDCl_3)$ 1.03 (3 H, d, *J* 6.8, MeOCHCHCH_3), 1.27 (3 H, d, *J* 6.8, HO_2CCHCH_3), 1.46 (9 H, s, Bu^t), 2.56–2.64 (1 H, m, MeOCHC*H*), 2.64–2.73 (1 H, m, C*H*CO_2H), 2.75–2.84 (2 H, m, CH_2Ph), 3.18–3.23 (1 H, m, C*H*OMe), 3.24 (3 H, s, OMe), 4.40 (1 H, br s, NHC*H*), 5.25 (1 H, br s, NH), 5.40 (1 H, d, *J* 11.0, MeCH=C*H*), 5.48 (1 H, dd, *J* 6.0, 16.0, CH=C*H*), 6.22 (1 H, d, *J* 16.0, CC*H*=CH) and 7.25 (5 H, m, Ph); *m/z* (CIMS) 449 (m + NH_4) and 432 (M + H); (Found: M, 431.2636. Calc. for $C_{25}H_{37}NO_5$: 431.2671.)

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