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

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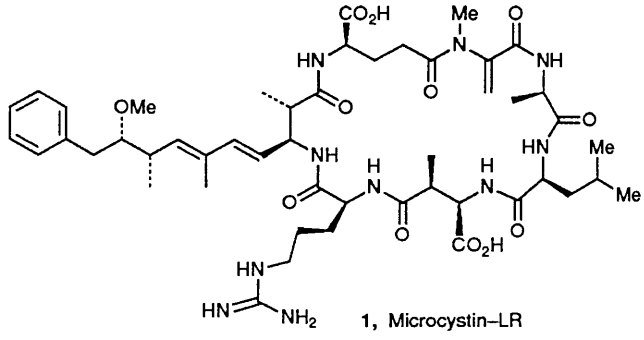
(4*R*,5*S*)-4-Methyl-5-phenyloxazolidin-2-one was used as a chiral template to construct the 8*S* and 9*S* chiral centres of (2*S*,3*S*,8*S*,9*S*)-3-amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4,6-dienoic acid (ADDA), the 2*S* and 3*S* centres were derived from D-aspartic acid.

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] (ADDA, **2**).

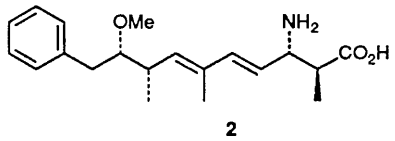
It has been suggested that the hepatotoxicity of these cyclic peptides may be due to the presence of the ADDA moiety.[1,3] In this paper we report an efficient, stereocontrolled total synthesis of Boc-ADDA (Boc = butoxycarbonyl) and ADDA itself (as its trifluoroacetate salt), which will allow for its production in multigram quantities for hepatotoxic 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.

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 the oxazolidone **3** with propionyl chloride furnished the propionyl oxazolidine **4**. Enolisation of **4** with di-n-butylboron trifluromethanesulphonate 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 1,8-bis(dimethylamino)naphthalene (proton sponge) produced the methyl ether **6**, which was cleaved using lithium borohydride to yield the enantiomerically pure alcohol **7**. The recovered oxazlidone **3** was isolated and recycled.

Oxidation of the alcohol **7** with pyridine–sulphur trioxide in dimethyl sulphoxide (DMSO) gave the aldehyde **8**, which then underwent Wittig reaction with 1-ethoxycarbonylethylidenetriphenylphosphorane. The resultant *E*/*Z* mixture of unsaturated esters **9–10**, obtained in a 4.5 : 1 (*trans* : *cis*) ratio, was reduced using diisobutylaluminium hydride (DIBAL-H) to afford 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.



1, Microcystin-LR



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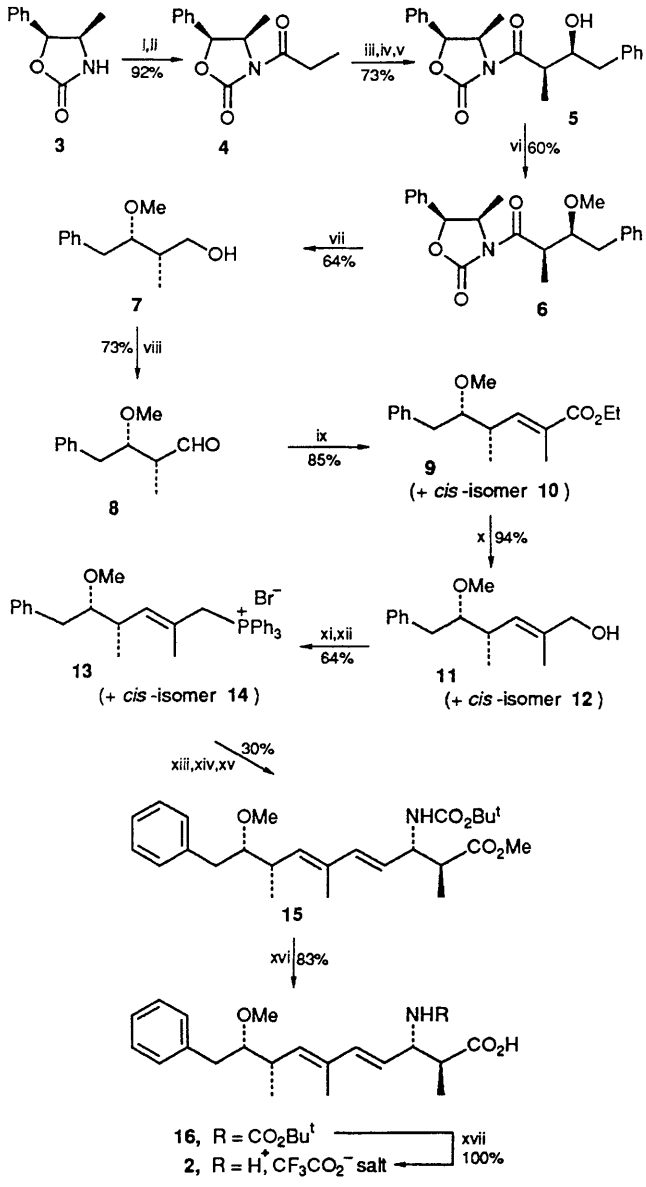
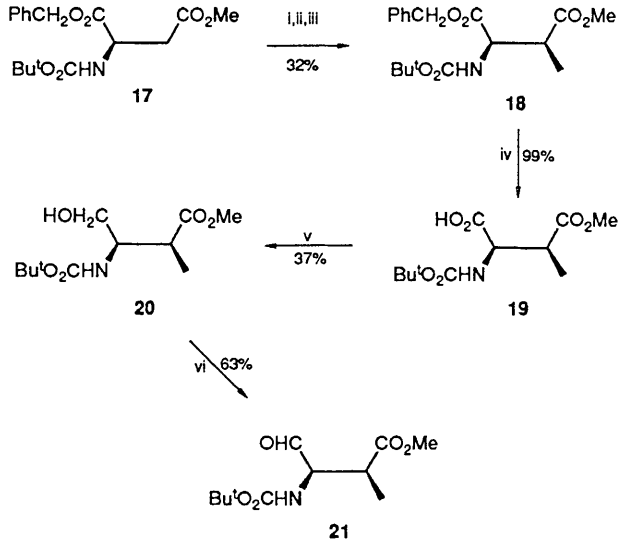
† The alkenic proton appearing at δ 5.34 of the mixture **11–12** was irradiated, resulting in 6% enhancement of the hydroxymethylene peak occurring at δ 4.0 of the major isomer.



Scheme 1. *Reagents and conditions*: i, 1.6 mol dm^{-3} Bu^nLi in hexanes, tetrahydrofuran (THF), −78 °C, 30 min; ii, EtCOCl, −78 °C to room temp. 2 h; iii, $Bu^n_2BOSO_2CF_3$ (1.1 equiv.), CH_2Cl_2, 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, $Me_3O^+BF_4^-$, proton sponge (1.16 equiv.), CH_2Cl_2, 7 days; vii, $LiBH_4$ (2 equiv.), 16 h; viii, pyridine. SO_3 (3.0 equiv.), DMSO, 30 min; ix, $Ph_3P{=}C(Me)CO_2Et$ (1.05 equiv.), dimethylformamide (DMF), 6 days; x, DIBAL-H (11.0 equiv.), −78 °C for 2 h, then room temp. overnight; xi, PPh_3 (2 equiv.), CBr_4 (2 equiv.), Et_2O, 7 h; xii, PPh_3, benzene, reflux, 6 h; xiii, 1.6 mol dm^{-3} Bu^nLi in hexanes, THF, 0 °C, 10 min; xiv, **21** (0.9 equiv.), THF, 0 °C, 3 h.; xv, aq. NH_4Cl; xvi, 1 mol dm^{-3} NaOH (2 equiv.), MeOH, 4 days; xvii, CF_3CO_2H, CH_2Cl_2, 30 min. All reactions at room temperature unless indicated otherwise.



Scheme 2. *Reagents and conditions*: i, lithium hexamethyldisilazide (2.0 equiv.), THF, −78 °C, 1 h; ii, MeI (1.2 equiv.), −7 °C, 1 h; iii aq. NH_4Cl–ice; iv, H_2/Pd, MeOH, 2 h; v, BH_3·THF (3.0 equiv.), 0 °C, 1 h; vi, pyridine–SO_3 (3.0 equiv.), DMSO, Et_3N (3.0 equiv.), room temp. 30 min

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 the alkylation of 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, a product ratio of 43% *erythro* **18** and 57% *threo* could be obtained. Next, hydrogenolysis of **18** furnished the acid **19**, which was then reduced by borane in THF (while carefully monitoring the reaction by TLC) to give the stable alcohol **20**. Mild oxidation of this alcohol was conveniently accomplished in DMSO with pyridine–sulphur trioxide in the presence of triethylamine, yielding the desired aldehyde **21**.

The mixture of alcohols **11–12** was converted to the corresponding bromides and thence to the triphenylphosphonium salts **13–14**. The ylide derived from **13–14** was treated with the protected aldehyde **21**, to give a mixture of the four possible geometric isomers. The mixture was readily separated by preparative TLC to give the desired isomer **15**, taking care to avoid possible photochemical isomerization. Hydrolysis of **15** with dilute sodium hydroxide in methanol gave Boc-ADDA **16**,‡§ which, on treatment with trifluoroacetic acid, gave ADDA **2** as its trifluoroacetate.§ The overall yield for the twelve-step synthesis of ADDA was 2.1%.

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‡ The Boc-ADDA **16** was obtained as an oil: $[\alpha]_D^{22}$ −15.1° (*c* 0.1, $CHCl_3$).

§ Structure confirmed by 400 MHz ^1H NMR spectroscopy, and electron impact, chemical ionization and high resolution electron impact mass spectrometry.