Studies into the synthesis of a sub-unit of the neurotoxic alkaloid methyllycaconitine

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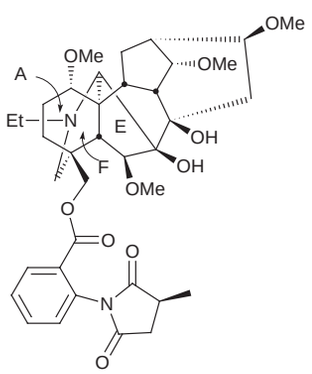
A potentially toxophoric subunit of methyllycaconitine has been synthesised from penta-1,4-dien-3-ol as the mixture of diastereomers **2a** and **2b**, in 14 steps and 5% overall yield.

Methyllycaconitine (MLA) **1**, a norditerpenoid alkaloid, is a characteristic extractive of *Delphinium* (*Ranunculaceae*) and *Aconitum* species[1,2] and is highly toxic to both mammals and



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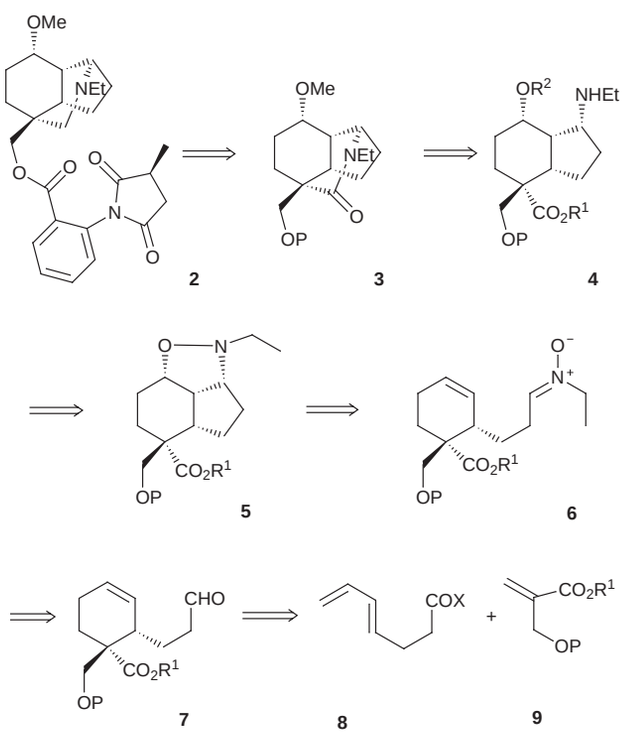
insects. *Delphinium* spp. are responsible for more cattle deaths in North America than any other plant.[3,4] Crude preparations have been used by various civilisations for the treatment of head and body lice. The earliest such application, involving a pounded extract of *D. staphysagria* seeds, was reported by Pliny the Elder in AD77, and a similar preparation was still used by the British Army in 1815.[5]

The toxicity of MLA arises from its action at the neuromuscular junction where it inhibits neurotransmission and induces paralysis.[6] It is the most potent nonproteinaceous competitive antagonist at neuronal vertebrate and invertebrate α-bungarotoxin binding sites[7] which, in the mammalian brain, correspond to the pentameric ligand-gated cation channels, the nicotinic acetylcholine receptors (nAChRs).[8] It is this activity and the high affinity for the α7 subtype[9] that has led to extensive use of MLA as a ligand for distinguishing nAChR subtypes; it has comparable potency to α-bungarotoxin but is more selective.[10] As these receptors may be implicated in Alzheimer's disease,[8,11] this aspect of the selectivity of MLA has become very important.

Because of MLA's high toxicity to animals it would be banned as an agrochemical; however if the inhibitory action is localised in a toxophoric section, a smaller subunit could find practical application if it were possible to find an analogue that would bind to insect, but not to mammalian, nAChRs. To this end, a number of MLA analogues have been prepared,[12,13] derived mainly from natural products, either directly, or *via* semisynthesis. These have been used in structure–activity relationship investigations and it has been shown that the methyl group on the succinimido ring[12] and the ethyl group of the tertiary amine[13] are important. It has been postulated that the portion of MLA from the *N*-ethyl group through carbons 19, 4, 18 and the ester functionality at C-18 bear a formal resemblance to the acylated homocholine motif.[14] This led us to investigate the synthesis of the AEF tricyclic fragment **2** which incorporates all of the desired features and hence should have significant biological activity. The retrosynthetic analysis is shown in Scheme 1.

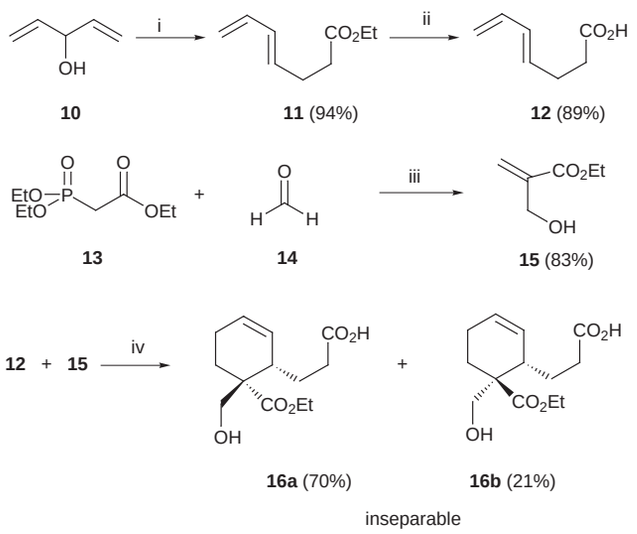


2 **3** **4** **5** **6** **7** **8** **9**

Scheme 1 P = protecting group

The key compound is the isoxazolidine **5**. This compound contains all the stereocentres required for the synthesis of **2** and it was envisaged that reductive N–O scission and further manipulation would give the target molecule. The stereocentres are set up in two key reactions—the intramolecular 1,3-dipolar addition of the nitrone functionality to the alkene in **6** and the Diels–Alder reaction of **8** and **9**.

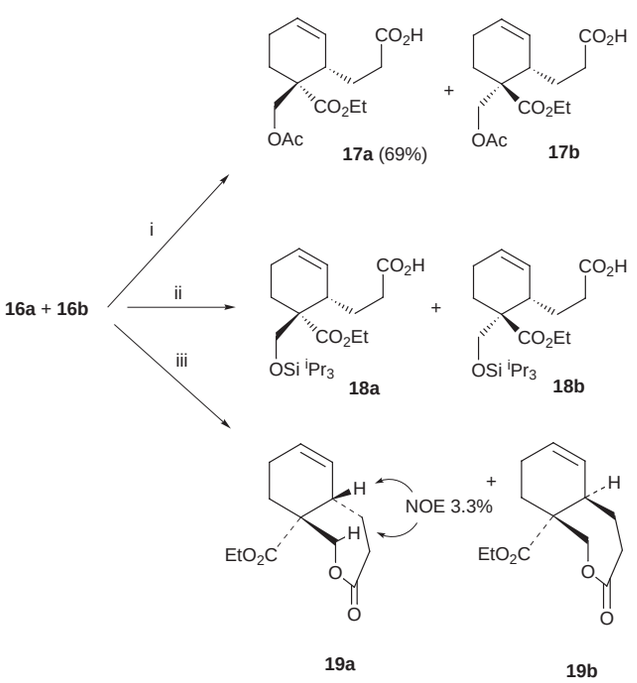
The first part of the forward synthesis is shown in Scheme 2. Penta-1,4-dien-3-ol **10** was heated with triethyl orthoacetate and catalytic propanoic acid, and the resulting ester **11** was subjected to alkaline hydrolysis to afford the (*E*)-hepta-4,6-dienoic acid **12**.[15] The methacrylate **15** was prepared in 83%



Scheme 2 *Reagents and conditions*: i, $MeC(OEt)_3$, EtCOOH, 140 °C, 3 h; ii, KOH, MeOH; iii, aq. K_2CO_3; iv, $NaHCO_3$, LiCl, H_2O, 60 °C, 120 h.

yield by reaction of triethyl phosphonoacetate **13** with formaldehyde **14** in the presence of potassium carbonate.[16] Diels–Alder reaction of the sodium salt of the acid **12** with the methacrylate **15** in aqueous 5 M lithium chloride[17] yielded the cyclohexene acid **16** in 91% yield, but with a low *endo* **16a**:*exo* **16b** ratio. Unfortunately the *endo*:*exo* ratio could not be improved beyond 3.3:1. Much experimentation was required to discover the most suitable substituents, dienophile and reaction conditions to minimise polymerisation and raise the *endo*:*exo* ratio to this modest level. Furthermore, separation of the two products could not be achieved directly. To circumvent stereochemical problems, experiments with diethyl methylenemalonate as dienophile were also tried but proved unsatisfactory, providing only moderate yields of adduct.

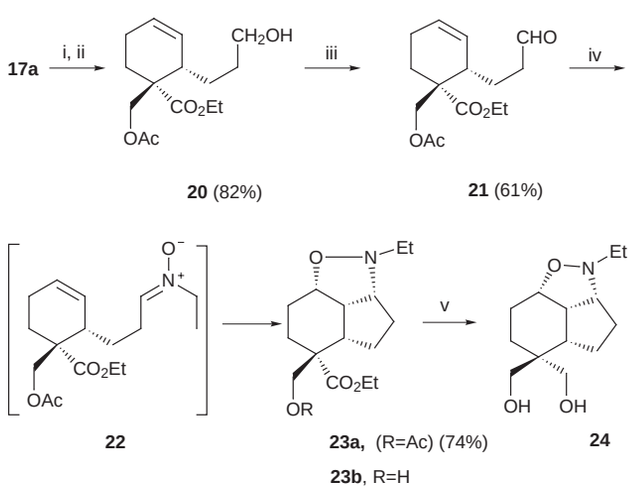
To separate the stereoisomers **16** both the acetates **17a**,**b** and the triisopropylsilyl (TIPS) ethers **18a**,**b** were prepared by standard methods (Scheme 3); the latter pair could readily be separated by chromatography. The stereochemical identity of the adducts was determined by lactonisation of the mixture



Scheme 3 *Reagents*: i, Ac_2O, pyridine; ii, TIPSCl, imidazole; iii, DCC, DMAP.

of hydroxy acids **16a**,**b** with dicyclohexylcarbodiimide. The lactones **19a** and **19b** were readily separated, and NMR measurements on the major crystalline lactone **19a** showed an NOE effect of 3.3% between the ring junction proton and the *axial* oxymethylene proton (see cipher **19a**). Molecular modelling studies using MACROMODEL V4.0 indicated that only the *endo*-adduct could adopt a conformation in which these protons were close. Since the major lactone was derived from the major alcohol **16a** the stereochemistries of the latter and of acetates **17** and silyl ethers **18** were as indicated. This was confirmed by the success of the subsequent synthetic chemistry and by an X-ray analysis of an intermediate later in the sequence (see below).

Thus the *endo*-acid **17a** could be obtained as a single diastereoisomer in a satisfactory overall yield of 69%, and was taken on through the synthesis. Reduction of **17a** was achieved through a two step procedure, first forming a mixed anhydride with diisopropylamine and isobutyl chloroformate, followed by *in situ* reduction with sodium borohydride[18] to give the alcohol **20** in 82% yield. Oxidation with tetrapropylammonium perruthenate (TPAP) and NMO[19] gave the aldehyde **21** in 61% yield, which was converted to the isoxazolidine **23** *via* the nitrone **22** in a one-pot process in 74% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: i, $(^iPr)_2NEt$, $^tBuOCOCl$, DME; ii, $NaBH_4$, DME–H_2O (4:1); iii, TPAP, NMO, DCM; iv, EtNHOH·TFA, PhH, reflux; v, $LiAlH_4$, dioxan, reflux 4 h.

The strategy then required reductive cleavage of the N–O bond. In earlier work with a similar substrate,[20] we had found nickel chloride–sodium borohydride to be highly effective under mild conditions. However the isoxazolidine **23a** was unchanged by prolonged treatment with this reagent. A range of alternative methods were investigated (listed in the Experimental section) but without avail. Only deacetylation to the alcohol **23b** was observed in several instances and reduction with lithium aluminium hydride at 100 °C over 4 h yielded only the diol **24** with the N–O bond still intact.

Thus we decided to deploy a two-step procedure whereby the isoxazolidine was first cleaved oxidatively[21] to the nitrone **26** (Scheme 5). Treatment of the isoxazolidine with stoichiometric MCPBA at 0 °C gave the *N*-oxide **25**, which spontaneously ring opened with elimination to afford the desired nitrone in 85% yield. At this point single crystal X-ray analysis of the nitrone (Fig. 1) showed that the desired stereochemistry had been set-up by the Diels–Alder and 1,3-dipolar addition steps and stereochemical integrity of the C–N bond had been retained in the oxidative cleavage step.

Reduction of the nitrone **26** was effected cleanly by catalytic hydrogenation using Adam's catalyst in ethyl acetate–acetic acid (10:1). The product amine **27** could not be chromatographed on silica and the only method of purification available

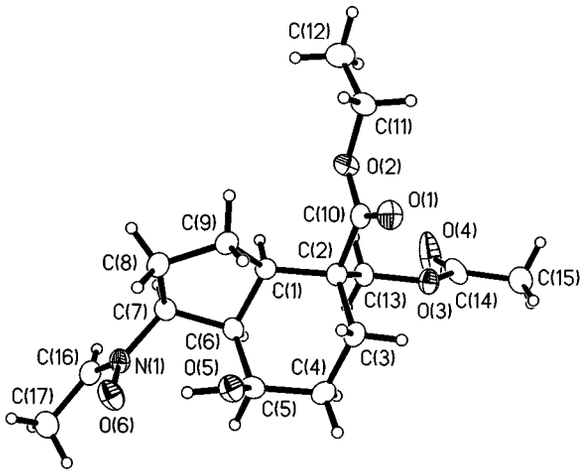
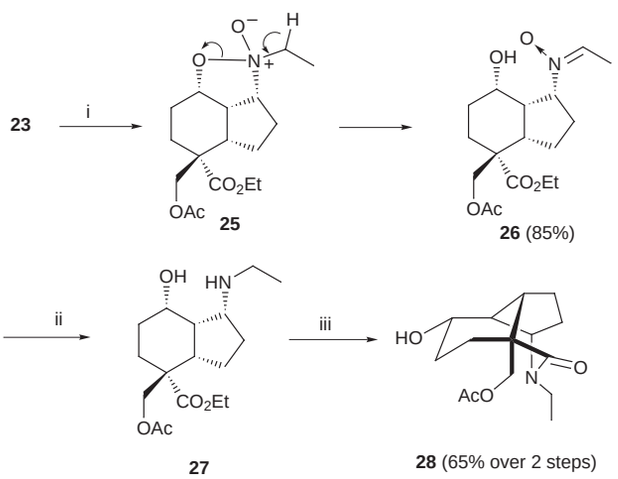


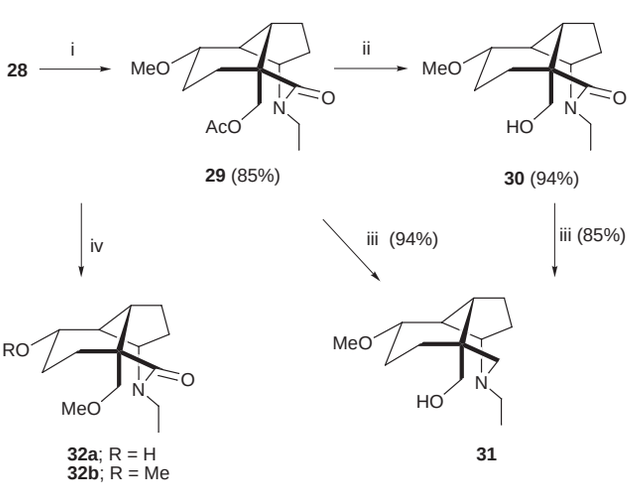
Fig. 1 X-Ray crystallographic structure of the nitrone **26**.



Scheme 5 *Reagents and conditions*: i, MCPBA, DCM, 0 °C; ii, PtO_2, H_2 (1 atm), EtOH, EtOAc; iii, xylene, reflux, 24 h.

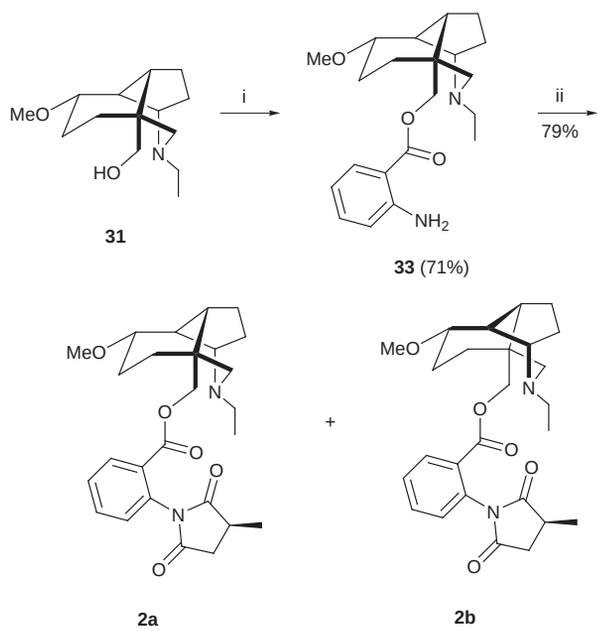
was to extract the crude product into aqueous acid, extract with ethyl acetate to remove impurities, basify and re-extract to obtain the product. The amide **28**, containing the desired tricyclic system, was produced by refluxing the crude amine **27** in xylene for 24 h in an overall yield of 65% for the two steps.

The alcohol function in amide **28** was methylated by refluxing the compound in methyl iodide in the presence of silver(I) oxide, to give the required ether **29** in 85% yield (Scheme 6). Performing the *O*-methylation step before the reduction of the amide eliminated problems of formation of quaternary ammonium salts. Methylation of the hydroxy group using sodium hydride and methyl iodide was also investigated, but resulted in saponification of the acetate and preferential methylation of the primary alcohol, eventually yielding a mixture of the ethers **32a** and **32b**. The acetate **29** was then treated with potassium carbonate in methanol to afford the alcohol **30**. This product was heated to reflux in the presence of four equivalents of $LiAlH_4$ in dioxane for 12 hours and the desired amine **31** obtained in 85% yield. These two steps could be combined by reducing acetate **29** directly to the desired alcohol **31**, with lithium aluminium hydride in a satisfying 94% yield.



Scheme 6 *Reagents and conditions*: i, MeI, Ag_2O, reflux, 24 h; ii, K_2CO_3, MeOH; iii, $LiAlH_4$, dioxane, reflux, 12 h; iv, NaH, MeI.

With the alcohol **31** in hand, we were now able to attempt the final stage of the synthesis—the esterification of the alcohol functionality with 2-(methylsuccinimido)benzoic acid (Scheme 7). Examination of the literature revealed a successful two step

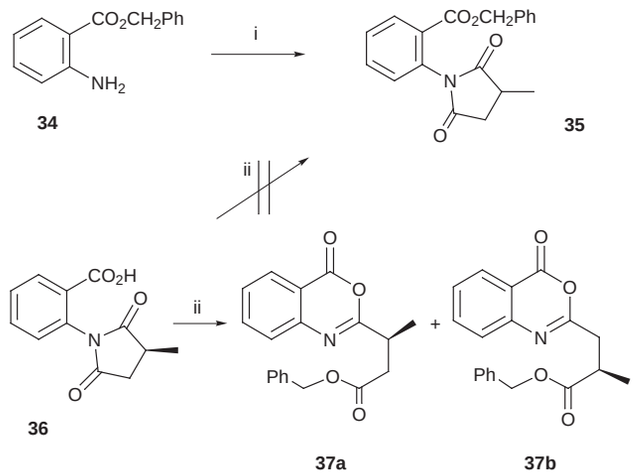


Scheme 7 *Reagents and conditions*: i, isatoic anhydride, DMAP, DMF, 110 °C, 24 h; ii, xylene, reflux, 24 h.

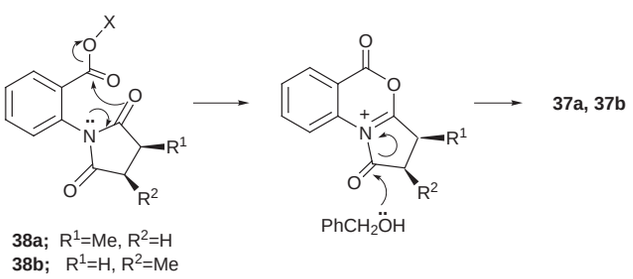
protocol for the attachment of the methylsuccinimidobenzoate moiety.[22] Reaction of **31** with isatoic anhydride in DMF in the presence of DMAP at 110 °C for 24 h gave the anthranilate **33** in 71% yield. The anthranilate **33** was heated to reflux in xylene with (*S*)-(−)-methylsuccinic anhydride[23] for 24 h to afford the desired AEF tricycle in 79% yield (14 steps, 5% overall) as a mixture of diastereomers **2a**,**b**.

As a side issue we examined briefly a possible alternative and more convergent protocol using less drastic methods, (Scheme 8), which might have had value with less resilient reactants. Thus using benzyl alcohol as a model we first prepared benzyl anthranilate **34** and generated from it the imide **35** by reaction with methylsuccinic anhydride. We then attempted to form the same imide by esterifying **36**, made by literature methods,[22] with benzyl alcohol and dicyclohexylcarbodiimide. However the product proved to be a mixture of isomers, which we propose to be the 1,3-oxazinones **37a** and **37b**; the structural assignments are supported by comparison with literature NMR data for 4*H*-1,3-benzoxazin-4-ones.[24] These heterocycles were presumably formed as summarised in cipher **38** (Scheme 9). Hence this apparently attractive synthetic short cut is ineffective.

At this stage we had hoped to be able to separate the diastereometric mixture of **2a** and **2b** that we had obtained. Regrettably, this was not achieved in the present study. The differences in the NMR spectra of the two diastereomers were very slight (only the C-methyls showed any chemical shift difference in the ^{13}C NMR spectrum), suggesting that the physical properties were likely to be very similar. For this reason we



Scheme 8 *Reagents*: i, methylsuccinic anhydride. 1,1′-carbonyldiimidazole, CH_2Cl_2; ii, DCC, $PhCH_2OH$.



Scheme 9

made a series of derivatives of the racemic alcohol **31** using chiral acids in the hope that we would be able to resolve the enantiomers. The derivatives successfully synthesised were the mandelate, the *N*-tosylphenylalanine derivative and the camphorsulfonate. With these derivatives, again very little difference in the ^{13}C NMR spectra was observed and again no separation was achieved. Since the separation of this diastereoisomeric mixture clearly required a substantial investment of work, it was decided to proceed with biological evaluation of the mixture, and return to the problem of separation if the *in vivo* effects were sufficiently interesting to justify the costs. Preliminary results† do indicate that the product has significant activity in a bind site assay, being able to displace approximately 35% bungarotoxin from binding at 1 ppm. Wider biological testing is in progress and results will be reported elsewhere.

A preliminary account of this synthetic work has been published.[25]

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained in chloroform, using a Perkin-Elmer 1600 series FTIR or a Perkin-Elmer 1720-X FTIR instrument. ^1H NMR spectra were recorded on a Bruker AM 250 (250 MHz), a Bruker 400 (400 MHz) or a JEOL EX270 (270 MHz) instrument. ^{13}C NMR spectra were recorded on either a JEOL EX 270 (67.8 MHz) or a Bruker AM 400 (100.6 MHz) instrument. Spectra were recorded as solutions in deuteriochloroform unless otherwise stated. The chemical shifts are reported relative to chloroform (7.27 ppm and 77.0 ppm) and the multiplicity of a signal is designated one of the following abbreviations: s, singlet; d, doublet; t, triplet, q quartet; sept., septet; br, broad; m, multiplet. All observed coupling constants, *J*, are reported in Hertz. Multiplicities in the ^{13}C spectra were obtained using a DEPT sequence. Mass spectra were recorded on a VG Autospec or a AEI MS902 or a VG 7070F instrument using electron impact ionisation at 70 eV. Column chromatography was performed using Merck silica gel 60. Solvents and reagents were purified by literature procedures.[20b] Organic extracts were dried over anhydrous magnesium sulfate. All reactions were performed under an atmosphere of nitrogen unless otherwise stated. Ether refers to diethyl ether, and light petroleum to the fraction boiling at 40–60 °C.

3-(2-Ethoxycarbonyl-2-hydroxymethylcyclohex-5-enyl)propanoic acid 16

To a solution of (*E*)-hepta-4,6-dienoic acid **12** (9.86 g, 78 mmol) in water (30 ml) at 25 °C was added sodium bicarbonate (6.57 g, 78 mmol) portionwise over 30 min. After gas evolution had subsided, ethyl 2-(hydroxymethyl)acrylate **15** (20.34 g, 156 mmol) and lithium chloride (6.14 g, 143 mmol) were added. The mixture was warmed to 60 °C and stirred for 120 h. The mixture was allowed to cool to room temperature, extracted with ether (3 × 40) to remove unreacted acrylate, acidified to pH 3 with 2 M aqueous hydrochloric acid and extracted into ether (3 × 40 ml). The extracts were washed with brine, dried and concentrated. The product was subjected to column chromatography (dichloromethane–ethyl acetate, 7 : 3) to yield the *title compound* **16** as a colourless oil (18.16 g, 91%), but as an inseparable mixture of *endo* **16a** and *exo* **16b** products.

exo-product **16b**: δ_H (270 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7, OCH_2CH_3), 1.40–1.70 (2H, m, 3-H), 1.80–1.95 (2H, m, 3′-H), 1.95–2.15 (3H, m, 1′-H, 4′-H), 2.20–2.50 (2H, m, 2-H), 3.59 (1H, d, *J* 11, CH_aOH), 3.78 (1H, d, *J* 11, CH_bOH), 4.11 (2H, q, *J* 7, OCH_2CH_3), 5.44–5.54 (2H, m, 5′-H, 6′-H); δ_C (67.8 MHz, $CDCl_3$) 14.04 (OCH_2CH_3), 20.94 (C-3′), 22.19 (C-4′), 27.82 (C-3), 31.84 (C-2), 37.63 (C-1′), 49.65 (C-2′), 61.19 (OCH_2CH_3), 65.10 (CH_2OH), 127.10 and 127.28 (C-5′, C-6′), 176.84 and 177.97 (C=O).

endo product **16a**: see below for data for pure compound.

3-[(1*S**,2*R**)-2-Acetoxymethyl-2-ethoxycarbonylcyclohex-5-enyl]propanoic acid 17a

To a solution of 3-(2-ethoxycarbonyl-2-hydroxymethylcyclohex-5-enyl)propanoic acid (18.05 g, 0.070 mmol) in acetic anhydride (22.8 g) at 0 °C was added pyridine (6.85 g). The mixture was allowed to warm to 25 °C and stirred for 16 h. The solvent was removed *in vacuo* and to the residue was added water (25 ml). The mixture was stirred for 10 min and diluted with ethyl acetate. The organic phase was separated, washed with water, aqueous copper sulfate solution and brine, then dried and concentrated. The product was subjected to column chromatography (ethyl acetate–dichloromethane, 3 : 17) to yield the *title compound* **17a** (14.52 g, 69%) as a white solid, mp 80–82 °C (Found: C, 60.09; H, 7.62%; M^+, 298.1417. $C_{15}H_{22}O_6$ requires: C, 60.39; H, 7.43%; M^+, 298.1416); ν_{max}/cm^{-1} 3027 (OH), 1741 (C=O); δ_H (270 MHz, $CDCl_3$), 1.23 (3H, t, *J* 7, OCH_2CH_3), 1.26–1.80 (2H, m, 3-H), 1.85–2.20 (5H, m, 1′-H, 3′-H_2, 4′-H_2), 1.98 (3H, s, $C(O)CH_3$), 2.31–2.60 (2H, m, 2-H_2), 4.07–4.26 (4H, m, OCH_2CH_3, 2′-CH_2), 5.57–5.70 (2H, m, 5′-H, 6′-H) ppm; δ_C (67.8 MHz, $CDCl_3$) 14.00 (OCH_2CH_3), 20.07 (C-3′), 20.60 ($C(O)CH_3$), 21.82 (C-4′), 27.93 (C-3), 31.41 (C-2), 37.40 (C-1′), 48.12 (C-2′), 60.03 (2′-CH_2), 66.31 (OCH_2CH_3), 126.38, 127.39 (C-5′, C-6′), 170.16, 174.18 and 179.14 (C=O); *m/z* 298 (M^+, 0.3%), 253 ($M^+ - OEt$, 7%), 252 (3), 220 (7), 192 (67), 105 (100).

3-[(1*S**,2*R**)-2-Ethoxycarbonyl-2-hydroxymethylcyclohex-5-enyl]propanoic acid 16a

To a stirred solution of acetate **17a** (100 mg, 0.336 mmol) in ethanol (5 ml) at room temperature was added potassium car-

† We thank Dr T. Lewis, Zeneca Agrochemicals, for this information.

bonate (300 mg, 2.17 mmol) in one portion. The solution was stirred for 45 min and filtered. The solvent was removed *in vacuo* and the residue taken up in water. The aqueous solution was extracted with ethyl acetate (2 × 5 ml) and the organic fractions discarded. The aqueous layer was acidified to pH 3 and extracted with ethyl acetate (2 × 5 ml). The combined organic fractions were washed with brine, dried and concentrated *in vacuo* to give the *title compound* **16a** as a pale yellow oil (73 mg, 85%); δ_H (270 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7, OCH_2CH_3), 1.40–1.70 (2H, m, 3-H), 1.80–1.95 (2H, m, 3′-H_2), 1.95–2.15 (3H, m, 1′H, 4′-H), 2.20–2.50 (2H, m, 2-H_2), 3.69 (1H, d, *J* 11, CH_aOH), 3.71 (1H, d, *J* 11, CH_bOH), 4.12 (2H, q, *J* 7, OCH_2CH_3), 5.54–5.64 (2H, m, 5′-H, 6′-H); δ_C (67.8 MHz, $CDCl_3$) 14.04 (OCH_2CH_3), 20.94 (C-3′), 21.94 (C-4′), 27.82 (C-3), 31.57 (C-2), 36.93 (C-1′), 50.17 (C-2′), 60.70 (OCH_2CH_3), 65.10 (2′-CH_2), 126.86, 126.95 (C-5′, C-6′), 175.78 and 178.72 (C=O).

3-[2-Ethoxycarbonyl-2-(triisopropylsilyloxymethyl)cyclohex-5-enyl]propanoic acid 18

To a solution of the hydroxy acid **16** (2.50 g, 9.8 mmol) in dichloromethane (20 ml) at 25 °C was added imidazole (1.61 g, 24 mmol) portionwise over 5 min and triisopropylsilyl chloride (2.27 g, 12 mmol) portionwise over 5 min. A white precipitate of imidazole hydrochloride was observed. The mixture was stirred for 3 h, washed with 2 M aqueous hydrochloric acid and brine. The organic phase was dried and concentrated. The product was subjected to column chromatography (light petroleum–ethyl acetate, 3:1) to yield *3-[(1S*,2R*)-2-ethoxycarbonyl-2-(triisopropylsilyloxymethyl)cyclohex-5-enyl]propanoic acid* **18a** as a colourless oil (1.96 g, 47%) and *3-[(1R*,2R*)-2-ethoxycarbonyl-2-(triisopropylsilyloxymethyl)cyclohex-5-enyl]propanoic acid* **18b** as a colourless oil (0.90 g, 22%).

Acid **18a**: (Found: C, 63.98; H, 10.02%; M^+, 412.265. $C_{22}H_{40}SiO_5$ requires: C, 64.04; H, 9.78%; *M*, 412.265); ν_{max}(liquid film)/cm^{-1} 3479 (OH), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05 (18H, d, *J* 7.4, 3 × SiCH(CH_3)$_2$), 1.22–1.33 (3H, sept., *J* 7.4, 3 × SiCH(CH_3)$_2$), 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.52–1.62 (1H, m, 3-H_a), 1.68–1.77 (1H, m, 3-H_b), 1.85–2.10 (4H, m, 3′-H_2, 4′-H_2), 2.11–2.30 (1H, m, 1′-H), 2.32–2.38 (1H, m, 2-H_a), 2.43–2.51 (1H, m, 2-H_b), 3.69 (1H, d, *J* 11.2, 2′-CH_a), 3.76 (1H, d, *J* 11.2, 2′-CH_b), 4.17 (2H, q, *J* 7.1, OCH_2CH_3), 5.61–5.70 (2H, m, 5′-H, 6′-H) ppm; δ_C (100.6 MHz, $CDCl_3$) 11.9 (3 × SiCH(CH_3)$_2$), 14.2 (OCH_2CH_3), 17.8 (3 × SiCH(CH_3)$_2$), 21.7, 22.2 (C-3′, C-4′), 28.3 (C-3), 33.6 (C-2), 37.3 (C-1′), 50.3 (C-2′), 60.6 (OCH_2CH_3), 65.4 (2-CH_2), 126.8, 127.4 (C-5′, C-6′), 173.4, 175.4 (2 × CO) ppm; *m*/*z* 412 (M^+, 4%), 369 (100).

Acid **18b**: (Found: C, 63.77; H, 9.90%; M^+, 4.12.265. $C_{22}H_{40}SiO_5$ requires: C, 64.04; H, 9.78%; *M*, 4.12.265); ν_{max}(liquid film)/cm^{-1} 3500 (OH), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05 (18H, d, *J* 7.4, 3 × SiCH(CH_3)$_2$), 1.24 (3H, sept., *J* 7.4, 3 × SiCH(CH_3)$_2$), 1.25 (3H, dd, *J* 7.1, 7.1, OCH_2CH_3), 1.31 (1H, m, 3-H_a), 1.76 (2H, m, 3-H_b, 3′-H_a), 1.87 (1H, m, 3′-H_b), 2.01–2.09 (2H, m, 4′-H_2), 2.35 (1H, m, 2-H_a), 2.43 (1H, m, 2-H_b), 2.67–2.73 (1H, m, 1′-H), 3.50–3.60 (1H, m, 2′-CH_a), 3.84 (1H, d, *J* 11.6, 2′-CH_b), 4.17 (1H, q, *J* 7.1, OCH_2CH_3), 4.18 (1H, q, *J* 7.1, OCH_2CH_3), 5.58 (1H, m, 5′-H), 5.68 (1H, m, 6′-H) ppm; δ_C (100.6 MHz, $CDCl_3$) 11.8 (3 × SiCH(CH_3)$_2$), 14.0 (OCH_2CH_3), 17.9 (3 × SiCH(CH_3)$_2$), 22.3 (C-4′), 25.9, 26.3 (C-3, C-3′), 33.7 (C-2), 38.0 (C-1′), 50.0 (C-2′), 6.07 (OCH_2CH_3), 62.3 (2-CH_2), 126.7, 127.6 (C-5′, C-6′), 173.4, 176.6 (2 × CO) ppm; *m*/*z* 412 (M^+, 5%), 369 (100).

1-Ethoxycarbonyl-4-oxo-3-oxabicyclo[5.4.0]undec-8-ene 19

To a solution of the hydroxy acid **16** (0.20 g, 0.80 mmol) in dichloromethane (40 ml) at 25 °C was added *N*,*N*-dimethylaminopyridine (0.01 g, 0.01 mmol) and dicyclohexylcarbodiimide (0.18 g, 0.90 mmol) portionwise over 5 min. The mixture was stirred for 18 h, after which time a precipitate of dicyclohexylurea had formed. The mixture was filtered and the filtrate was washed with water, 5% aqueous acetic acid and water. The organic phase was dried and concentrated. The product was subjected to column chromatography (light petroleum–ethyl acetate, 4:1) to yield *(1R,7S)-1-ethoxycarbonyl-4-oxo-3-oxabicyclo[5.4.0]undec-8-ene* **19a** as a white crystalline solid (0.11 g, 59%) and *(1R,7R)-1-ethoxycarbonyl-4-oxo-3-oxabicyclo[5.4.0]undec-8-ene* **19b** as a colourless oil (0.04 g, 22%).

Lactone **19a**: (Found: C, 65.29; H, 7.97%; M^+, 238.121. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61%; *M*, 238.121); ν_{max}($CHCl_3$ solution)/cm^{-1} 1732 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, dd, *J* 7.1, 7.1, OCH_2CH_3), 1.46–1.55 (1H, m, 11-H_a), 1.73–1.81 (1H, m, 6-H_a), 1.98–2.12 (3H, m, 10-H_2, 11-H_b), 2.29–2.33 (1H, m, 7-H), 2.36–2.47 (1H, m, 6-H_b), 2.58–2.71 (2H, m, 5-H_2), 4.09 (1H, q, *J* 7.1, OCH_aCH_3), 4.10 (1H, q, *J* 7.1, OCH_bCH_3), 4.14 (1H, d, *J* 12.3, 2-H_a), 4.21 (1H, d, *J* 12.3, 2-H_b), 5.44 (1H, br m, 8-H), 5.53 (1H, m, 9-H) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.0 (OCH_2CH_3), 23.4 (C-10), 26.3 (C-6), 30.4 (C-11), 34.0 (C-5), 46.6 (C-7), 49.5 (C-1), 60.8 (OCH_2CH_3), 74.6 (C-2), 125.6, 130.1 (C-8, C-9), 171.1, 174.5 (2 × CO) ppm; *m*/*z* 238 (M^+, 8%), 178 (9), 174 (44), 147 (31).

Lactone **19b**: (Found: C, 64.95; H, 7.85%; M^+, 238.120. $C_{13}H_{18}O_4$ requires: C, 65.53; H, 7.61%; *M*, 238.121); ν_{max}(liquid film)/cm^{-1} 1736 (C=O), 1654 (C=C); δ_H (400 MHz, $CDCl_3$) 1.19 (3H, dd, *J* 7.1, 7.1, OCH_2CH_3), 1.62–1.73 (2H, m, 6-H_a, 11-H_a), 1.82–2.12 (4H, m, 6-H_b, 10-H_2, 11-H_b), 2.41 (1H, br m, 5-H_a), 2.56 (1H, ddd, *J* 14.6, 11.9, 2.7, 5-H_b), 2.97 (1H, br m, 7-H), 4.11 (1H, q, *J* 7.1, OCH_aCH_3), 4.12 (1H, q, *J* 7.1, OCH_bCH_3), 4.22 (2H, s, 2-H_2), 5.39 (1H, br m, 8-H), 5.75 (1H, br m, 9-H) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.5 (OCH_2CH_3), 21.9 (C-10), 26.0 (C-6), 29.7 (C-11), 30.0 (C-5), 37.3 (C-7), 48.0 (C-1), 61.3 (OCH_2CH_3), 69.0 (C-2), 127.7 (C-9), 129.6 (C-8), 173.5, 175.4 (2 × CO) ppm; *m*/*z* 238 (M^+, 7%), 193 (13), 192 (67), 165 (54).

3-[(1S*,2R*)-2-Acetoxymethyl-2-ethoxycarbonylcyclohex-5-enyl]propan-1-ol 20

To a solution of the acid **17a** (11.60 g, 39.26 mmol) in dimethoxyethane (140 ml) at 25 °C was added diisopropylethylamine (4.99 g, 39.26 mmol) followed by isobutyl chloroformate (5.35 g, 39.26 mmol) which was added cautiously over 15 min. The mixture was stirred for 80 min after which time a precipitate of diisopropylethylamine hydrochloride had formed. The mixture was filtered and the residue was washed with dimethoxyethane. To the filtrate at 25 °C was added a solution of sodium borohydride (4.47 g, 116.22 mmol) in water (30 ml) cautiously over 15 min and the mixture was stirred for 20 min. Vigorous gas evolution was observed which subsided quickly. The mixture was quenched with water and extracted into ether. The extracts were washed with brine, dried and concentrated. The product was subjected to column chromatography (light petroleum–ethyl acetate, 4:1) to yield the *title compound* **20** as a colourless oil (9.01 g, 82%) (Found: C, 63.25; H, 9.01. $C_{15}H_{24}O_5$ requires: C, 63.36; H, 8.51%; Found: $M^+ - OEt$, 239.128. $C_{13}H_{19}O_4$ requires: 239.128); ν_{max}(liquid film)/cm^{-1} 3436 (OH), 1742 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, dd, *J* 7.1, 7.1, OCH_2CH_3), 1.25–1.30 (2H, m, 1′-H_2), 1.42–1.50 (1H, m, 2′-H_a), 1.61–1.68 (1H, m, 2′-H_b), 1.96 (3H, s, C(O)CH_3), 1.80–2.08 (5H, m, 2-H, 5-H_2, 6-H_2), 2.21 (1H, br s, OH), 3.53 (2H, t, *J* 6.6, 3′-H_2), 4.09–4.19 (2H, m, 1-CH_a, OCH_aCH_3), 4.12 (1H, q, *J* 7.1, OCH_bCH_3), 4.22 (1H, d, *J* 10.8, 1-CH_b), 5.53–5.66 (2H, m, 3-H, 4-H) ppm; δ_C (67.8 MHz, $CDCl_3$) 14.24 (OCH_2CH_3), 20.32 (C-6), 20.78 (C(O)CH_3), 22.02 (C-5), 29.51 (C-1′), 30.25 (C-2′), 38.29 (C-2), 48.54 (C-1), 60.62 (OCH_2CH_3), 62.78 (C-3′), 66.62 (1-CH_2), 126.49, 127.75 (C-3, C-4) 170.84, 174.71 (2 × CO) ppm; *m*/*z* 239 ($M^+ - OEt$, 6%), 196 (8), 178 (100).

3-[(1S*,2R*)-2-Acetoxymethyl-2-ethoxycarbonylcyclohex-5-enyl]propanol 21

To a solution of the alcohol **20** (4.99 g, 17.39 mmol) and

N-methylmorpholine *N*-oxide (3.09 g, 26.46 mmol) in dichloromethane (70 ml) at 25 °C were added crushed 4 Å molecular sieves (11.1 g). To the suspension was added tetrapropylammonium perruthenate (0.302 g, 0.756 mmol) cautiously over 5 min. The mixture was stirred for 45 min, filtered through silica and concentrated. The product was subjected to column chromatography (ethyl acetate–light petroleum, 1:3) to yield the *title compound* **21** as a pale yellow oil (3.02 g, 61%) (Found: $M^+ + H$, 283.149. $C_{15}H_{23}O_5$ requires: 283.155); ν_{max}(liquid film)/cm^{-1} 1724 (C=O), 1652 (C=C); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, OCH_2CH_3), 1.50–1.60 (1H, m, 1′-H_a), 1.65–1.74 (1H, m, 1′-H_b), 1.85–2.18 (5H, m, 2-H, 5-H_2, 6-H_2), 2.39–2.47 (1H, m, 2′H_a), 2.55 (1H, dddd, *J* 17.2, 9.2, 6.0, 1.5, 2′-H_b), 4.13–4.25 (2H, m, OCH_2CH_3), 4.20 (1H, d, *J* 10.8, 1-CH_a), 4.27 (1H, d, *J* 10.8, 1-CH_b), 5.60–5.67 (1H, m, CH), 5.67–5.73 (1H, m, CH), 9.74 (1H, t, *J* 1.5, 3′-H) ppm; δ_C (100.6 MHz, $CDCl_3$) 14.3 (OCH_2CH_3), 20.3, 22.0 (C-5, C-6), 20.7 (C(O)CH_3), 25.5 (C-1′), 37.7 (C-2), 41.4 (C-2′), 48.4 (C-1), 60.81 (1-CH_2), 66.5 (OCH_2CH_3), 126.6, 127.7 (C-3, C-4), 170.8, 174.3 (2 × CO), 201.8 (C-3′) ppm; *m*/*z* (FAB + ve) 283 ($M^+ + H$, 6%).

(1*R**,4*S**,7*R**,8*S**,11*S**)-7-Acetoxymethyl-7-ethoxycarbonyl-2-ethyl-2-aza-3-oxatricyclo[6.2.1.0^{4,11}]undecane 23a

A solution of the aldehyde **21** (1.34 g, 4.73 mmol), *N*-ethylhydroxylamine trifluoroacetic acid (1.65 g, 9.44 mmol) and triethylamine (0.96 g, 9.49 mmol) in benzene (140 ml) was heated to reflux for 3 h. The solution was diluted with ether, filtered and concentrated. The product was subjected to column chromatography (ether–light petroleum, 3:1) to yield the *title compound* **23a** as a white solid (1.14 g, 74%), mp 62–64 °C (Found: C, 62.73; H, 8.37; N, 4.31%; M^+, 325.188. $C_{17}H_{27}NO_5$ requires: C, 62.77; H, 8.63; N, 4.32%; *M*, 325.189); ν_{max}(solution, $CHCl_3$)/cm^{-1} 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.08 (3H, dd, *J* 7.1, 7.1, NCH_2CH_3), 1.23 (3H, dd, *J* 7.1, 7.1, OCH_2CH_3), 1.26–1.34 (1H, m, 9-H_a), 1.47–1.86 (4H, m, 9-H_b, 8-H, 6-H_a, 5-H_a), 1.92–2.08 (3H, m, 10-H_a, 6-H_b, 5-H_b), 2.03 (3H, s, C(O)CH_3), 1.96 (1H, m, 10-H_b), 2.65 (1H, dq, *J* 12.0, 7.1, NCH_aCH$_3$), 2.79 (1H, m, 11-H), 2.90 (1H, dq, *J* 12.0, 7.1, NCH_bCH$_3$), 3.57 (1H, dd, *J* 6.7, 6.7, 1-H), 4.17–4.22 (1H, m, 4-H), 4.13 (1H, q, *J* 7.1, OCH_aCH$_3$), 4.17 (1H, q, *J* 7.1, OCH_bCH$_3$), 4.23 (1H, d, *J* 11.0, 12-CH_a), 4.39 (1H, d, *J* 11.0, 12-CH_b) ppm; δ_C (100.6 MHz, $CDCl_3$) 13.1 (NCH_2CH_3), 14.2 (OCH_2CH_3), 16.4 (C-6), 20.8 (C(O)CH_3), 20.8 (C-5), 27.6 (C-9), 34.2 (C-5), 41.6 (C-7), 46.1 (C-11), 47.2 (C-7), 51.5 (NCH_2CH_3), 60.8 (OCH_2CH_3), 65.7 (7-CH_2), 71.3 (C-4), 72.3 (C-1), 170.9, 174.6 (2 × CO) ppm; *m*/*z* 325 (M^+, 100%), 310 (58), 280 (24), 252 (14), 84 (25).

(1*R**,4*S**,8*S**,11*S**)-2-Ethyl-7,7-bis(hydroxymethyl)-2-aza-3-oxatricyclo[6.2.1.0^{4,11}]undecane 24

In an attempted N–O bond reduction, to a suspension of lithium aluminium hydride (0.03 g, 0.9 mol) in ether (2 ml) at 25 °C was added the isoxazolidine **23** (0.03 g, 0.09 mmol) in ether (2 ml) dropwise over 10 min.[37,38] The mixture was heated to reflux for 2 h, 2 M aqueous sodium hydroxide was added and the liquid phase was decanted off. The ether layer was separated, dried and concentrated to yield the *title compound* **24** as a colourless solid (0.02 g, 96%) (Found: M^+, 241.169. $C_{13}H_{23}NO_3$ requires: 241.168); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, dd, *J* 7.1, 7.1, NCH_2CH_3), 1.19–1.23 (1H, m, 6-H_a), 1.40–1.60 (4H, m, 5-H_a, 6-H_b, 9-H_a, 10-H_a), 1.71–2.03 (4H, m, 5-H_b, 7-H, 9-H_b, 10-H_b), 2.65–2.71 (1H, m, NCH_aCH$_3$), 2.81 (1H, m, 11-H), 2.89–2.96 (1H, m, NCH_bCH$_3$), 3.47 (3H, m, 4-H, 8-CH_2), 3.71 (2H, s, 8-CH_2), 4.21 (1H, br m, 1-H) ppm; *m*/*z* 241 (M^+, 100%), 226 (73), 210 (23).

(1*S**,2*S**,5*R**,6*S**,9*R**)-*N*-(5-Acetoxymethyl-5-ethoxycarbonyl-2-hydroxybicyclo[4.3.0]nonan-9-yl)ethylideneamine-*N*-oxide 26

To a stirred solution of isoxazolidine **23** (4.51 g, 13.87 mmol) in dichloromethane (200 ml) at 0 °C was added MCPBA (2.40 g, 14.1 mmol). The solution was stirred at this temperature for 30 min and quenched with saturated bicarbonate solution (200 ml). The organic layer was separated and the aqueous layer was further extracted with dichloromethane (2 × 200 ml). The combined organic extracts were washed with brine, dried and concentrated. Column chromatography ethyl acetate–methanol (5:1) and recrystallisation from ethyl acetate–methanol (5:1) gave the *title compound* **26** as a white solid (4.04 g, 85%), mp 143–145 °C and recovered starting material (0.40 g, 9%) (Found: C, 59.4; H, 8.2; N, 3.95%; MH^+, 342.1916. $C_{17}H_{27}NO_6$ requires: C, 59.8; H, 8.0; N, 4.1; MH^+, 342.1916). ν_{max}/cm^{-1} ($CHCl_3$) 3275 (OH), 1738 (C=O), 1602 (nitrone); δ_H ($CDCl_3$) 1.19 (3H, t, *J* 7, OCH_2CH_3), 1.34–1.61 (3H, m, 3-H_a, 4-H_a, 7-H_a), 1.72–2.37 (6H, m, 1-H, 3-H_b, 4-H_b, 6-H, 7-H_b, 8-H_a), 1.95 (3H, s, CO*Me*), 2.01 (3H, d, *J* 6, N=CHCH_3), 2.56–2.70 (1H, m, 8-Hb), 3.86 (1H, s, 2-H), 4.01–4.21 (3H, m, CH_aOAc, OCH_2CH_3), 4.4 (2H, m, CH_bOAc, 9-H), 6.22 (1H, s, OH), 6.96 (1H, q, *J* 6, N=*CH*); δ_C ($CDCl_3$, 270 MHz) 13.0 (q, NCNCH_3), 14.2 (q, OCH_2CH_3), 16.2 (t, C-7), 20.7 (q, COCH_3), 25.2 (t, C-4), 25.8 (t, C-8), 26.6 (t, C-3), 41.1 (d, C-6), 47.2 (d, C-1), 47.4 (s, C-5), 60.7 (t, OCH_2CH$_3$), 64.3 (d, C-2), 66.1 (t, CH_2OAc), 76.8 (d, C-9), 137.3 (N=*C*H), 170.7 (s, C=O), 174.1 (s, C=O); *m*/*z* (FAB) 342 (MH^+, 18%), 324 (9), 149 (11), 147 (27), 136 (18), 131 (22), 91 (17), 73 (100).

(1*S**,2*S**,5*R**,6*S**,9*R**)-Ethyl 5-acetoxymethyl-9-ethylamino-2-hydroxybicyclo[4.3.0]nonane-5-carboxylate 27

To a solution of nitrone **26** (1.34 g, 3.93 mmol) in ethanol (54 ml) was added acetic acid (5.4 ml) and PtO_2 (125 mg). The solution was placed under an atmosphere of hydrogen and shaken until no further uptake of hydrogen was observed. The reaction mixture was diluted with water (150 ml), extracted with ethyl acetate (2 × 50 ml) (to remove the acetic acid), basified with potassium carbonate, extracted with dichloromethane (3 × 50 ml), dried and concentrated to afford the *title compound* **27** as a pale yellow oil (1.20 g, 93%) (Found: C, 62.18; H, 9.02; N, 4.40%; MH^+, 328.2138. $C_{17}H_{29}NO_5$ requires: C, 62.36; H, 8.93; N, 4.28%; MH^+, 328.2124); ν_{max}/cm^{-1} ($CHCl_3$) 3310 (OH, NH), 1730 and 1719 (C=O); δ_H ($CDCl_3$, 270 MHz) 1.05 (3H, t, *J* 7, NCH_2CH_3), 1.18 (3H, t, *J* 7, OCH_2CH_3), 1.3–1.6 (4H, m, 3-H_a, 4-H_a, 7-H_a, 8-H_a), 1.6–2.0 (5H, m, 1-H, 3-H, 4-H_b, 6-H, 8-H_b), 1.95 (3H, s, CO*Me*), 2.2 (1H, m, 7-H_b), 2.5–2.7 (2H, m, NCH_2), 3.3 (1H, m, 9-H), 3.5 (2H, br, OH, NH), 3.95 (1H, br m, 2-H), 4.0–4.2 (3H, m, OCH_2CH_3, CH_aOAc), 4.37 (1H, d, *J* 11, CH_bOAc); δ_C ($CDCl_3$, 67.8 MHz) 14.16 (q, OCH_2CH_3), 14.84 (q, NCH_2CH_3), 16.4 (t, C-7), 20.7 (q, COCH_3), 25.8 (t, C-4), 26.5 (t, C-3), 30.8 (t, C-8), 41.8, 42.4 (d, C-6, C-1), 43.4 (NCH_2), 47.3 (s, C-5), 60.5 (t, OCH_2CH$_3$), 61.0 (d, C-9), 64.6 (d, C-2), 66.0 (t, CH_2OAc), 170.8 (s, C=O), 174.5 (s, C=O); *m*/*z* (EI) 327 (M^+, 0.8%), 310 (3), 298 (5), 281 (4), 266 (5), 178 (12), 177 (20), 91 (12), 85 (18), 84 (100).

(1*R**,4*R**,7*S**,8*S**,9*S**)-1-Acetoxymethyl-3-aza-3-ethyl-9-hydroxy-2-oxotricyclo[5.4.0.0^{4,8}]undecane 28

The amine **27** (1.20 g, 3.67 mmol) was dissolved in xylene (50 ml) and heated to reflux for 24 h. The solvent was removed *in vacuo* and the residue taken up in dichloromethane and decolourising charcoal added. The suspension was stirred for 10 min, filtered and concentrated. Column chromatography (ethyl acetate) afforded the *title compound* **28** (715 mg, 70%) as a white solid, mp 109–111 °C (Found: C, 64.10; H, 8.38; N, 4.74%; MH^+, 281.1623. $C_{15}H_{23}NO_4$ requires: C, 64.04; H, 8.24; N, 4.98; MH^+, 281.1627); ν_{max}/cm^{-1} ($CHCl_3$) 3390 (OH), 1730 and 1719 (C=O), 1643 (amide); δ_H ($CDCl_3$) 1.11 (3H, t, *J* 7, NCH_2CH_3), 1.5–1.9 (8H, m, 5-H_2, 6-H_2, 10-H_2, 11-H_2), 2.00 (3H, s, CO*Me*), 2.05 (1H, m, 8-H), 2.14 (1H, m, 7-H), 2.73 (1H, dq, *J* 14.7, NCH_aCH$_3$), 3.75 (1H, s, 4-H), 3.86 (1H, dq, *J* 14.7, NCH_bCH$_3$), 4.07 (1H, m, 9-H), 4.23 (1H, d, *J* 11.6, C*H*HOAc),

4.30 (1H, d, *J* 11.6, CH*H*OAc); δ_C ($CDCl_3$, 67.8 MHz) 13.55 (q, NCH_2CH_3), 21.4 (q, $COCH_3$), 23.92 (t, C-10), 29.27 (t, C-5), 32.72, 32.98 (t, C-6, C-11), 39.88 (d, C-7), 40.77 (t, NCH_2), 47.23 (s, C-1), 57.99 (d, C-4), 66.25 (t, CH_2OAc), 69.83 (d, C-9), 170.46 (s, C=O), 171.25 (s, C=O); *m*/*z* (EI) 281 (M^+, 37%), 238 (100), 222 (17), 91 (13).

(1*R,4*R**,7*S**,8*S**,9*S**)-3-Aza-3-ethyl-9-hydroxy-1-methoxymethyl-2-oxotricyclo[5.4.0.0^{4,8}]undecane 32a and (1*R**,4*R**,7*S**,8*S**,9*S**)-3-aza-3-ethyl-9-methoxy-1-methoxymethyl-2-oxotricyclo[5.4.0.0^{4,8}]undecane 32b**

To a suspension of sodium hydride (1 mg, 0.43 mmol) in THF (2 ml) was added lactam **28** (11 mg, 0.039 mmol) and methyl iodide (24 mg, 0.172 mmol). The solution was heated to reflux for 8 h and the methyl iodide removed by distillation. The residue was taken up in water (5 ml) and extracted with ether (3 × 5 ml). The combined organic fractions were dried and concentrated *in vacuo*. The crude products were purified by column chromatography (ethyl acetate followed by 9 : 1 ethyl acetate–methanol) to afford **32a** (2 mg, 20%) and **32b** (3 mg, 30%) as colourless oils.

Ether 32a. (Found: M^+, 253.1668. $C_{14}H_{23}NO_3$ requires: M^+, 253.1678); δ_H ($CDCl_3$) 1.1 (3H, t, *J* 7, NCH_2CH_3), 1.5–1.9 (8H, m, 5-H_2, 6-H_2, 10-H_2, 11-H_2), 2.0 (1H, m, 8-H), 2.25 (1H, m, 7-H), 2.7 (1H, m, NCH_aCH_3), 3.25 (3H, s, OMe), 3.5 (2H, AB quartet, CH_2OMe), 3.7 (1H, br s, 4-H), 3.85 (1H, m, NCH_bCH_3), 4.05 (1H, m, 9-H); *m*/*z* (EI) 253 (M^+, 16%), 239 (15), 238 (100), 194 (10).

Ether 32b. (Found: M^+, 267.1830. $C_{15}H_{25}NO_3$ requires: M^+, 267.1834); δ_H ($CDCl_3$) 1.15 (3H, t, *J* 7, NCH_2CH_3), 1.5–2.0 (8H, m, 5-H_2, 6-H_2, 10-H_2, 11-H_2), 2.18 (1H, m, 8-H), 2.30 (1H, m, 7-H), 2.75 (1H, m, NCH_aCH_3), 3.35 (3H, s, OMe), 3.40 (3H, s, OMe), 3.55–3.65 (3H, m, 9-H, CH_2OMe), 3.7 (1H, br s, 4-H), 3.9 (1H, m, NCH_bCH_3).

(1*R,4*R**,7*S**,8*S**,9*S**)-1-Acetoxymethyl-3-aza-3-ethyl-9-methoxy-2-oxotricyclo[5.4.0.0^{4,8}]undecane 29**

To a stirred solution of lactam **28** (1.37 g, 4.88 mmol) in methyl iodide (20 ml) was added silver(I) oxide (1.5 g, 6.48 mmol). The suspension was heated to reflux for 16 h and the methyl iodide evaporated. The residue was taken up in dichloromethane–water (20 ml each) and the organic layer separated. The organic layer was washed with brine, dried and concentrated. Column chromatography (ethyl acetate–dichloromethane, 1 : 1) afforded the *title compound* **29** as a white solid (1.23 g, 85%), mp 49–51 °C (Found: C, 65.20; H, 8.68; N, 4.78%; M^+, 295.1787. $C_{16}H_{25}NO_4$ requires C, 65.06; H, 8.53; N, 4.74%; M^+, 295.1783); ν_{max}/cm^{-1} ($CHCl_3$) 1737 (C=O), 1642 (amide); δ_H ($CDCl_3$) 1.08 (3H, t, *J* 7, NCH_2CH_3), 1.44–1.94 (8H, m, 5-H_2, 6-H_2, 10-H_2, 11-H_2), 1.99 (3H, s, CO*Me*), 2.13 (2H, br m, 7-H, 8-H), 2.72 (1H, dq, *J* 14, 7, NCH_aCH_3), 3.33 (3H, s, O*Me*), 3.56 (1H, br m, 9-H), 3.66 (1H, br m, 4-H), 3.83 (1H, dq, *J* 14, 7, NCH_bCH_3), 4.24 (1H, d, *J* 11, CH_aOAc), 4.31 (1H, d, *J* 11, CH_bOAc); δ_C ($CDCl_3$, 67.8 MHz) 12.94 (q, NCH_2CH_3), 20.92 (q, $COCH_3$), 23.45 (t, C-5), 25.23 (t, C-10), 32.26, 32.29 (t, C-6, C-11), 39.44 (d, C-7), 40.34 (t, NCH_2), 44.17 (d, C-8), 46.97 (s, C-1), 56.19 (q, O*Me*), 57.83 (d, C-4), 65.86 (t, CH_2OAc), 77.85 (d, C-9), 169.85 (s, C=O), 170.71 (s, C=O); *m*/*z* (EI) 295 (M^+, 51%), 252 (100), 236 (20), 205 (30), 170 (12), 131 (21), 112 (18), 91 (33).

(1*R,4*R**,7*S**,8*S**,9*S**)-3-Aza-3-ethyl-1-hydroxymethyl-9-methoxy-2-oxotricyclo[5.4.0.0^{4,8}]undecane 30**

To a stirred solution of acetate **29** (424 mg, 1.44 mmol) in methanol (30 ml) at room temperature was added potassium carbonate (1.2 g, 8.68 mmol) and the solution stirred for 40 min. The solution was filtered, neutralized with acetic acid and the solvent removed *in vacuo*. The organic layer was washed with brine, dried and concentrated *in vacuo*. The solid product was recrystallised from ether to afford the *title compound* **30** as a white solid (343 mg, 94%), mp 81–83 °C (Found: C, 66.15; H, 9.44; N, 5.47%; M^+, 254.1743. $C_{16}H_{25}NO_4$ requires: C, 66.37; H, 9.15, N, 5.53%; M^+, 254.1756); ν_{max}/cm^{-1} ($CHCl_3$) 3205 (OH), 1614, 1592; δ_H ($CDCl_3$) 1.15 (3H, t, *J* 7, NCH_2CH_3), 1.14–1.26 (1H, m, 6-H_a), 1.36–1.52 (1H, m, 10-H_a), 1.61–1.95 (5H, m, 5-H_2, 7-H, 11-H_2), 1.99–2.07 (1H, m, 10-H_b), 2.14–2.19 (1H, m, 8-H), 2.40–2.47 (1H, m, 6-H_b), 2.70–2.84 (1H, m, NCH_aCH_3), 3.20 (1H, d, *J* 10, CH_aOH), 3.40 (3H, s, O*Me*), 3.60–3.68 (1H, m, 9-H), 3.73 (1H, br m, 4-H), 3.80–3.98 (1H, m, NCH_bCH_3), 4.08 (1H, d, *J* 10, CH_bOH); δ_C ($CDCl_3$, 67.8 MHz) 12.83 (q, NCH_2CH_3), 23.45 (t, C-5), 25.09 (t, C-10), 31.39 (C-6), 32.19 (t, C-11), 40.06 (t, NCH_2), 41.64 (d, C-7), 44.42 (d, C-8), 46.26 (s, C-1), 56.12 (q, O*Me*), 57.70 (d, C-4), 66.72 (t, CH_2OH), 77.99 (d, C-9), 173.84 (s, C=O); *m*/*z* (CI, CH_4) 254 (M^+, 100%), 252 (14), 223 (11), 222 (14).

(1*R,4*R**,7*S**,8*S**,9*S**)-3-Aza-3-ethyl-1-hydroxymethyl-9-methoxytricyclo[5.4.0.0^{4,8}]undecane 31**

Lithium aluminium hydride (130 mg, 3.4 mmol) was added to a stirred solution of lactam **29** (248 mg, 0.84 mmol) in dioxane (10 ml). The mixture was heated to reflux for 22 h. The dioxane was removed *in vacuo* to yield a pale yellow solid. Column chromatography (9 : 1 : 0.1 chloroform–methanol–33% ammonia solution) gave the *title compound* **31** as a white solid (189 mg, 94%), mp 69 °C (Found: C, 70.00; H, 10.76; N, 5.89%; M^+, 239.1878. $C_{14}H_{25}NO_2$ requires: C, 70.25; H, 10.53; N, 5.85%; M^+, 239.1885); ν_{max}/cm^{-1} ($CHCl_3$) 3355 (OH), 2821 (C–H), 1461 (C–H), 1351 (C–N), 1106 (C–O), 966; δ_H ($CDCl_3$) 0.94 (3H, t, *J* 7, NCH_2CH_3), 1.07–1.25 (2H, m, 5-H_a, 6-H_a), 1.34–1.87 (8H, m, 2-H_a, 5-H_b, 6-H_b, 7-H, 8-H, 10-H_a, 11-H_2), 2.03–2.33 (2H, m, NCH_2CH_3), 2.44 (1H, d, *J* 11, 2-H_b), 2.58–2.78 (1H, m, 10-H_b), 3.20 (1H, d, *J* 11, 12-H_a), 3.22 (1H, m, 4-H), 3.26 (1H, d, *J* 11, 12-H_b), 3.33 (3H, s, O*Me*), 3.56 (1H, br m, 9-H); δ_C ($CDCl_3$, 67.8 MHz) 13.16 (q, NCH_2CH_3), 21.49 (t, C-6), 23.85 (t, C-5), 26.45 (t, C-10), 33.01 (t, C-11), 36.70 (s, C-1), 40.97 (d, C-7), 44.62 (d, C-8), 48.97 (t, NCH_2), 53.10 (t, C-2), 56.10 (q, O*Me*), 60.00 (d, C-4), 69.17 (t, CH_2OH), 79.71 (d, C-9); *m*/*z* (EI) 240 (MH^+, 2%), 239 (M^+, 8), 224 (14), 222 (31), 208 (100), 180 (10), 41 (15).

(1*R,4*R**,7*S**,8*S**,9*S**)-1-(2′-Aminobenzoylmethyl)-3-aza-3-ethyl-9-methoxytricyclo[5.4.0.0^{4,8}]undecane 33**

To a solution of amine **31** (216 mg, 0.86 mmol) in DMF (2 ml) was added DMAP (20 mg) and isatoic anhydride (173 mg, 1.01 mmol). The resultant solution was stirred at 110 °C for 20 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (chloroform), to afford the *title compound* **33** as a white solid (230 mg, 71%), mp 106–108 °C (Found: C, 70.10; H, 8.66, N, 7.72%; *M*$^+$, 358.2241. $C_{21}H_{30}N_2O_3$ requires: C, 70.36; H, 8.44; N, 7.81%; *M*$^+$, 358.2256); ν_{max}/cm^{-1} ($CHCl_3$) 3506 and 3380 (NH_2), 2821 (C–H), 1739, 1729, 1682 (C=O), 1615, 1590, 1582, 1487, 1301, 1105 (C–O); δ_H ($CDCl_3$) 0.94 (3H, t, *J* 7, NCH_2CH_3), 1.15–1.29 (1H, m, 6-H_a), 1.40–2.01 (9H, m, 2-H_a, 5-H_2, 6-H_b, 7-H, 8-H, 10-H_a, 11-H_2), 2.01–2.31 (2H, m, NCH_2CH_3), 2.56 (1H, d, *J* 11, 2-H_b), 2.57–2.72 (1H, m, 10-H_b), 3.27 (1H, t, *J* 4, 4-H), 3.33 (3H, s, O*Me*), 3.54 (1H, m, 9-H), 3.87 (2H, br s, 12-H_2), 5.69 (2H, br s, NH_2), 6.54–6.59 (2H, m, ArH), 7.18 (1H, t, *J* 7, ArH), 7.51 (1H, d, *J* 8, ArH); δ_C ($CDCl_3$, 67.8 MHz) 13.05 (q, NCH_2CH_3), 21.46 (t, C-6), 24.05 (t, C-5), 26.35 (t, C-10), 33.61 (t, C-11), 35.78 (s, C-1), 41.51 (d, C-7), 44.46 (d, C-8), 48.81 (t, NCH_2), 53.07 (t, C-2), 56.01 (q, O*Me*), 59.57 (d, C-4), 69.90 (t, C-12), 79.41 (d, C-9), 110.64 (s, Ar), 116.08 (d, Ar), 116.60 (Ar), 130.87 (Ar), 133.96 (Ar), 150.49 (s, Ar), 167.96 (s, C=O); *m*/*z* (EI) 358 (11%), 328 (23), 327 (100), 238 (10), 120 (22), 119 (18).

(1*R,4*R**,7*S**,8*S**,9*S**)-3-Aza-3-ethyl-9-methoxy-1-[2′-(2″-methylsuccinimido)benzyloxymethyl]tricyclo[5.4.0.0^{4,8}]undecane 2**

To a stirred solution of anthranilate **33** (134 mg, 0.37 mmol) in xylene (8 ml) was added methylsuccinic acid (127 mg, 1.12 mmol) and DMAP (40 mg). The solution was heated to reflux for 48 h and the solvent removed *in vacuo*. The residue was purified by column chromatography (chloroform–methanol 9:1), to afford the *title compound* as a 1:1 mixture of diastereoisomers **2a** and **2b**, as a pale yellow oil (135 mg, 79%) (Found: MH$^+$, 455.2562. $C_{26}H_{34}N_2O_5$ requires: MH$^+$, 455.2546); ν_{max}/cm^{-1} ($CHCl_3$) 2821, 1778, 1713, 1604; δ_H ($CDCl_3$) 0.95 (3H, t, *J* 7, NCH_2CH_3), 1.15–1.28 (1H, m, 6-H$_a$), 1.41 (3H, br s, 2″-Me), 1.48–1.92 (9H, m, 2-H$_a$, 5-H$_2$, 6-H$_b$, 7-H, 8-H, 10-H$_a$, 11-H$_2$), 2.07–2.31 (2H, m, NCH_2CH_3), 2.48–2.71 (2H, m, 10-H$_b$, 2″-H), 2.53 (1H, d, *J* 11, 2-H$_b$), 2.90–3.10 (2H, br m, 3″-H), 3.27 (1H, t, *J* 4, 4-H), 3.34 (3H, s, O*Me*), 3.50–3.60 (1H, m, 9-H), 3.85 (2H, br s, 12-H$_2$), 7.26 (1H, d, *J* 7, ArH), 7.54 (1H, t, *J* 7, ArH), 7.66 (1H, t, *J* 7, ArH), 8.11 (1H, d, *J* 8, ArH); δ_C ($CDCl_3$, 67.8 MHz) 13.08 (q, NCH_2CH_3), 16.28 and 16.52 (q, 2″-Me), 21.51 (t, C-6), 24.12 (t, C-5), 26.35 (t, C-10), 33.57 (t, C-11), 35.19 and 35.37 (d, C-2″), 35.83 (s, C-1), 36.97 (t, C-3″), 41.49 (d, C-7), 44.48 (d, C-8), 48.86 (t, NCH_2), 53.01 (t, C-2), 56.12 (q, O*Me*), 59.59 (d, C-4), 70.87 and 70.96 (t, C-12), 79.35 (d, C-9), 127.24 (s, Ar), 129.38 (d, Ar), 129.90 (d, Ar), 131.39 (d, Ar), 132.87 (s, Ar), 133.44 (d, Ar), 164.13 (s, C=O), 175.88 and 176.05 (s, C=O), 179.93 (s, C=O), *m*/*z* (FAB) 455 (MH$^+$, 40%), 454 (11), 453 (22), 423 (26), 216 (17), 109 (25), 105 (20), 95 (44), 55 (100).

(*RS*)-Benzyl 2-(2-methylsuccinimido)benzoate 35

Benzyl anthranilate (0.9 g, 3.96 mmol), (*RS*)-2-methylsuccinic anhydride (0.5 g, 5.3 mmol) and 1,1′-carbonyldiimidazole (0.9 g, 5.84 mmol) were dissolved in dichloromethane (20 ml) and the mixture was stirred at ambient temperature overnight. The mixture was then diluted with dichloromethane (30 ml) and partitioned with dilute aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (2 × 30 ml), and the combined extracts were washed with brine, dried and evaporated. The residue was chromatographed on silica, eluting with dichloromethane to yield the *title ester* **35** as a pale orange oil (0.69 g, 54%) (Found: M$^+$, 323.113. $C_{19}H_{17}NO_4$ requires: M$^+$, 323.116); ν_{max}/cm^{-1} 1779 and 1732 (br); δ_H (270 MHz, $CDCl_3$) 1.42 (3H, d, *J* 6.8), 2.44, 2.75, 3.05 (each 1H, br m), 5.37 (2H, s, OCH_2), 7.33 (1H, d, *J* 7.8, 3-H), 7.56 (1H, br dd, *J* approx. 7.6, 7.6, 5-H), 7.73 (1H, br ddd, *J* 1.6, approx. 7.6, 7.6, 4-H) and 8.27 (1H, vbr s, 6-H).

Reaction of 2-(2-methylsuccinimido)benzoic acid with benzyl alcohol

To 2-(2-methylsuccinimido)benzoic acid (mp 171–173 °C; *m*/*z* 233.069, $C_{12}H_{11}NO_4$ requires: M$^+$, 233.069; prepared by the method used for 2-succinimidobenzoic acid;[22] 100 mg, 0.44 mmol) in acetonitrile (2 ml) was added dicyclohexylcarbodiimide (88 mg, 0.44 mmol), dimethylaminopyridine (6 mg) and benzyl alcohol (12 mg, 0.11 mmol). The mixture was stirred overnight when it was filtered and the filtrate was evaporated to dryness. The residue was dissolved in dichloromethane, washed with aq. sodium bicarbonate and brine, dried and evaporated. The product was chromatographed on silica eluting with dichloromethane to afford a mixture of the 4*H*-1,3-benzoxazin-4-ones **37a** and **37b**, which were not separated (Found: M$^+$, 323.113. $C_{19}H_{17}NO_4$ requires: M$^+$, 323.116); ν_{max}/cm^{-1} 1758 (br); δ_H (270 MHz, $CDCl_3$) (major isomer) 1.26 (3H, d, *J* 6.9), 2.5–3.3 (3H, m), 5.03 (2H, s), 7.2 (5H, br s), 7.25–7.4 (2H, m), 7.68 (1H, m) and 8.08 (1H, m); (minor isomer) 1.33 (3H, d, *J* 6.3), 2.5–3.3 (3H, m), 5.06 (2H, s), 7.2 (5H, br s), 7.25–7.4 (2H, m), 7.68 (1H, m) and 8.08 (1H, m); δ_C (100.6 MHz, $CDCl_3$) (selected data) 17.0 and 18.0 (2 × Me), 35.7 and 36.4 (2 × CH), 37.6 and 37.9 (2 × CH_2), 66.4 and 66.5 (2 × CH_2), 116.7 and 116.8 (2 × C-4a), 146.0 and 146.2 (2 × C-8a), 159.5 (2 × CO), 160.6 and 164.4 (2 × CN), 171.3 and 174.7 (2 × CO_2H).

X-Ray data for compound 26

Experimental.‡ A colourless block was mounted on a glass fibre and transferred to the diffractometer.

Crystal data. $C_{17}H_{27}NO_6$, $M = 341.40$. Monoclinic, $a = 10.878(2)$, $b = 9.579(2)$, $c = 16.477(3)$ Å, $\beta = 91.349(13)°$, $V = 1716.5(5)$ Å^3 [from 2θ values of 33 reflections measured at $\pm\omega$ ($26 \leqslant 2\theta \leqslant 34°$, $\lambda = 0.71073$ Å, $T = 150(2)$ K)], space group $P2_1/c$ (No. 14), $Z = 4$, $D_x = 1.321$ g cm^{-3}, colourless block $0.55 \times 0.54 \times 0.52$ mm, μ(Mo-Kα) = 0.099 mm^{-1}.

Data collection and processing. Stoe Stadi-4 four-circle diffractometer, ω/θ scans with ω scan width $(1.1 + 0.35 \tan\theta)°$, graphite-monochromated Mo-Kα X-radiation; 4372 reflections measured ($5 \leqslant 2\theta \leqslant 50°$, $\pm h$, $\pm k$, $\pm l$), 3028 unique [merging $R = 0.020$], giving 2531 with $F \geqslant 4\sigma(F)$ and 3028 which were retained in all calculations. No crystal decay was observed and no corrections were applied for absorption.

Structure solution and refinement. Automatic direct methods[26] (all non-H atoms). Full-matrix least-squares refinement[27] with all non-H atoms anisotropic; methyl and hydroxy hydrogen atoms were located from a ΔF synthesis, all others were placed geometrically; methyl and hydroxy H atoms were refined as part of rigid groups while others were allowed to ride on their parent atoms, with $U_{iso}(H) = xU_{eq}(C)$ [$x = 1.5$ for methyl and hydroxy hydrogens and 1.2 for others]. The weighting scheme $w^{-1} = [\sigma^2(F_o^2) + (0.027P)^2 + 1.10P]$, $P = \frac{1}{3}[\mathrm{MAX}(F_o^2,0) + 2F_c^2]$, gave satisfactory agreement analyses. Final R_1 [$F \geqslant 4\sigma(F)$] = 0.0386, wR_2 [all data] = 0.0928, $S[F^2] = 1.12$ for 223 refined parameters. An extinction correction[27] refined to 0.0041(7) and the final ΔF synthesis showed no peaks above ±0.22 e Å^{-3}. Fig. 1 was produced using SHELXTL/PC.[28]

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‡ Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 1*, available *via* the RSC web page (http:www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/278.

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