Synthesis of the A/E/F sections of conaconitine, napelline and related diterpenoid alkaloids of the aconitine group

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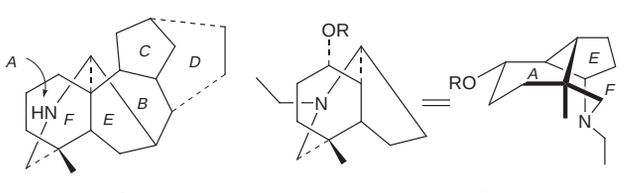
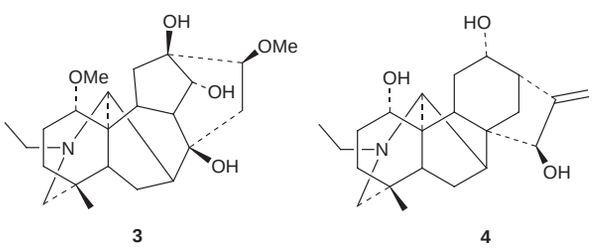
The tricyclic amines (±)-**2**; R = H and R = Me with five stereogenic centres, representing the A/E/F ring system of the title alkaloids, have been synthesised from penta-1,4-dien-3-ol in eight (overall yield 20%) and nine steps (overall yield 16%) respectively.

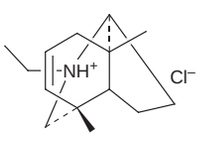
The diterpenoid and norditerpenoid alkaloids[1] comprise one of the most interesting groups of natural products. Crude preparations from plants of the genera *Aconitum*, *Delphinium* and a few others have long had a broad range of applications[2] ranging from covert human poisons *e.g.* arrowhead dips and (reputedly) agents for euthanasia, to traditional medical uses in neuralgia, gout, hypertension, rheumatism *etc.*, and they have even been included as ingredients in intoxicating liquors. The alkaloid constituents contain structurally complex pentacyclic and hexacyclic systems which can be divided into four groups, aconitines, lycoctonines, atisines and veatchines. A commonly observed sub-unit is the A/E/F tricycle section as in *e.g.* the aconitine skeleton **1**, almost invariably functionalised by oxygenation. In connection with an interest in compounds containing sub-structures of aconitine and methyllycaconitine which might display useful physiological activity, we selected several target molecules comprising the nitrogen-containing A/E/F unit with simple oxygenation patterns. In this paper we focus on the target system **2**, with a 1-hydroxy or methoxy group, as found in conaconitine **3**[3] (aconitine group), napelline **4**[4] (veatchine group), karakolline, karasamine, liangshanine *etc.*[1] The only reported synthesis[5] of an A/E/F fragment is that of compound **5**, related to cardiopetaline. This tricycle was constructed using an intramolecular Diels–Alder reaction and an imino-ene reaction to form the rings, in 11 steps and 2% overall yield. A number of bicyclic analogues of methyllycaconitine have been synthesised.[6]



1 **2**



3 **4**



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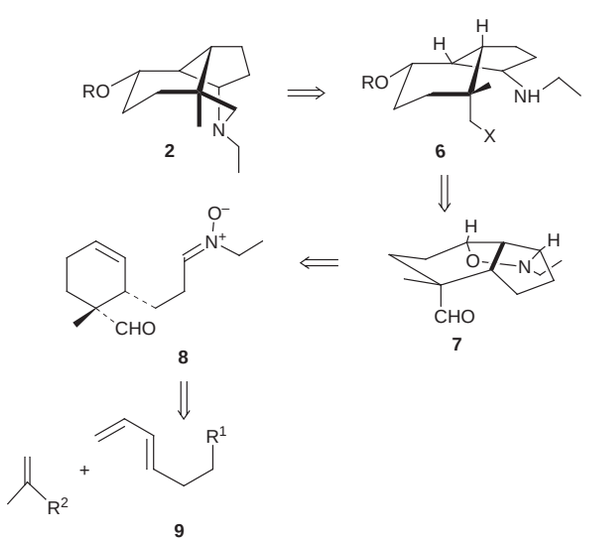
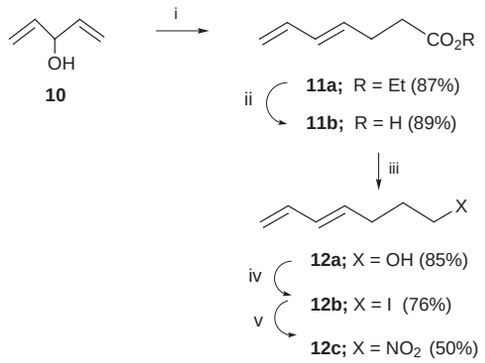
In this paper we report the syntheses of the tricylic amines **2** (R = H) and **2** (R = Me) in a short sequence showing high regio- and stereo-specificity, and which offers the potential for enantioselectivity. The retrosynthetic analysis (Scheme 1) involved an initial C–N bond disconnection from **2** to a *cis*-fused 6,5-bicarbocycle **6**, in which the N and ether O were envisaged as relating to the oxazolidine **7**. Heterocycle **7** could then be viewed as the product of intramolecular 1,3-dipolar cycloaddition of the nitrone **8**, derivable in turn from a Diels–Alder reaction.



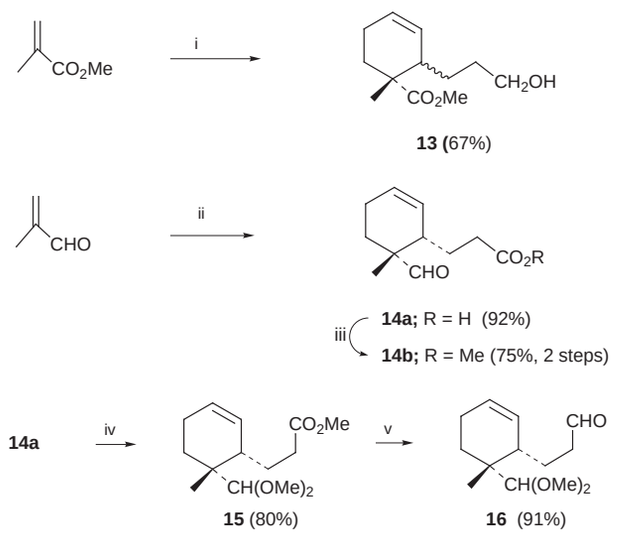
Scheme 1 Retrosynthetic plan.

The starting point for such a route required a suitably functionalised (*E*)-heptadiene **9**. The orthoester Claisen extension and rearrangement of penta-1,4-dienol **10** on heating with triethyl orthoacetate provided a very effective route[7] to ethyl (*E*)-hepta-4,6-dienoate **11a**, and hence to the corresponding acid **11b** (Scheme 2). In order to explore a range of Diels–Alder variations we also prepared (*E*)-heptadienol **12a**, and converted it into the iodide **12b** and the nitro compound **12c**. Diels–Alder reactions of dienes **11a**, **11b** and **12a–c** with methyl methacrylate and methacrolein were then explored using either neat reagents or as solutions in organic solvents, with quinol as additive, at various temperatures. The effects of aluminium trichloride catalyst were also investigated. Although a fully com-



Scheme 2 *Reagents and conditions*: i, $CH_3C(OEt)_3$, $EtCO_2H$, 142 °C, 3.5 h; ii, KOH, MeOH; iii, $LiAlH_4$; iv, Ph_3P, I_2, imidazole; v, $AgNO_2$.

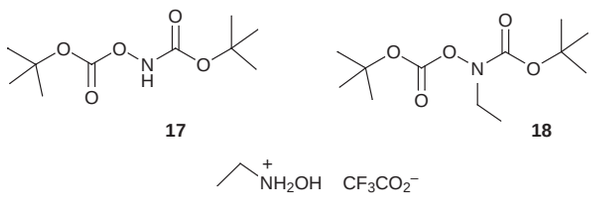
prehensive and systematic series of trials was not attempted, the results from a range of reaction conditions were disappointing; reasonable yields could be obtained, and polymerisation of the dienophile avoided, but the *endo*:*exo* ratios were unsatisfactory. For example the dienol **12a** reacted with methyl methacrylate at 220 °C over 6.5 h in the presence of quinol to afford the adduct **13** in 67% yield, but in an essentially non-stereospecific manner (Scheme 3). We then resorted to the use of water as solvent for



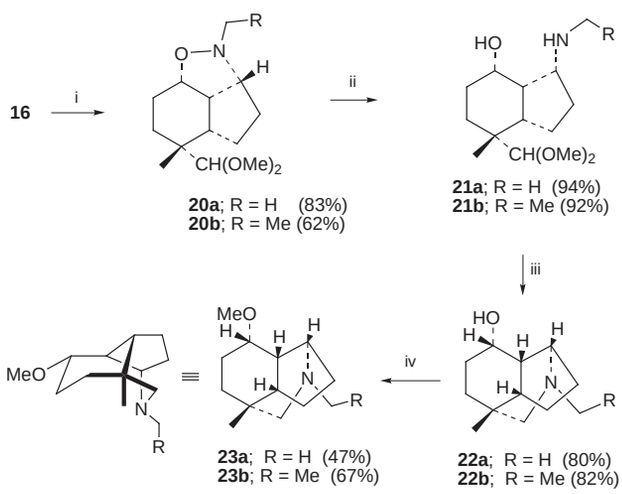
Scheme 3 *Reagents and conditions*: i, **12a**, quinol, 220 °C, 6.5 h; ii, **11b**, aq. $NaHCO_3$, 45 °C, 24 h; iii, CH_2N_2; iv, $HC(OMe)_3$, MeOH, PTSA; v, DIBAL-H, toluene, −80 °C.

this reaction, following the work of Grieco and co-workers.[8] Using reported literature conditions, an aqueous solution of the sodium salt of acid **11b** (4 equiv.) was treated with methacrolein (1 equiv.). The crude organic acid products containing adduct **14a** were methylated with diazomethane. Chromatography of the esters afforded the desired *endo*-cyclohexene **14b** with spectroscopic data in accord with the literature report.[8] The drawback of this approach was the use of excess diene, the less accessible component. However, on running the reaction in deuteriated water with varying ratios of diene:dienophile concentrations and NMR monitoring it was ascertained that there were no problems in using excess methacrolein. Thus reaction of the sodium salt of acid **11b** (1 equiv.) with methacrolein (4 equiv.) in water at 45 °C for 24 h gave the *endo*-cyclohexene acid **14a** as the major stereoisomer (15:1 *endo*:*exo*), in 92% yield.

Simultaneous acetalisation and esterification of acid **14a** was carried out by refluxing with trimethyl orthoformate and methanol, with toluene-*p*-sulfonic acid catalyst, providing the ester **15** which was reduced by diisobutylaluminium hydride directly to the aldehyde **16**. For the planned nitrone cycloaddition both methyl- and ethyl-hydroxylamines were required; the latter was synthesised by ethylation of the bis-*N,O*-Boc hydroxylamine **17**, to afford the *N*-ethyl compound **18**.[9] Deprotection of the latter product provided ethylhydroxylammonium trifluoroacetate **19**, used directly in subsequent reactions.



The aldehyde **16** reacted with both methyl- and ethylhydroxylamines in refluxing benzene to yield the isoxazolidines **20a** and **20b** respectively (Scheme 4). Efficient cleavage of the



Scheme 4 *Reagents and conditions*: i, MeNHOH·HCl or EtNHOH·TFA, Et_3N, benzene, reflux, 3.5 h; ii, $NiCl_2 \cdot 6\ H_2O$, $NaBH_4$, MeOH; iii, *a*, 5 M HCl; *b*, buffer pH 5.5; *c*, $NaCNBH_3$; iv, NaH, THF, MeI.

N–O bond was achieved using nickel chloride–sodium borohydride. The heterocyclic ring was then closed by a one-pot reductive amination procedure,[10] in which the amines **21a** and **21b** were treated with 5 M hydrochloric acid to hydrolyse the acetal, the resulting solution was buffered to pH 5.5, and reduction of the resulting cyclic imine intermediate was effected with sodium cyanoborohydride, to afford the tricycles **22a** and **22b** in excellent yield. Finally *O*-methylation was achieved by treatment of the corresponding alkoxide with methyl iodide, to afford the target compounds **23a** and **23b**. Molecular models indicate that competing *N*-alkylation in this step is inhibited by steric compression of the resulting quaternary ammonium salts, and in agreement the yields of *O*-methyl ether were significantly greater for the *N*-ethyl compound than for the *N*-methyl relative.

The *endo*-stereochemistry of the adduct **14a** is demonstrated by the subsequent successful reductive amination, and the remaining stereochemistry in the final product is controlled by the nitrone cycloaddition. As an additional check, single crystal X-ray analysis of the oxazolidine **20a** was carried out, and confirmed the assignments given here (see Fig. 1).

A related alternative strategy was also investigated, using a nitrile oxide cycloaddition. Thus the aldehyde **16** was converted into the oxime **24** (Scheme 5). Treatment of this oxime with chloramine-T in refluxing methanol gave the isoxazole **25** (39%) which could be reduced to the hydroxy amine **26** by nickel chloride–sodium borohydride (45%). In view of the modest yield obtained in the first attempts at these reactions, and the

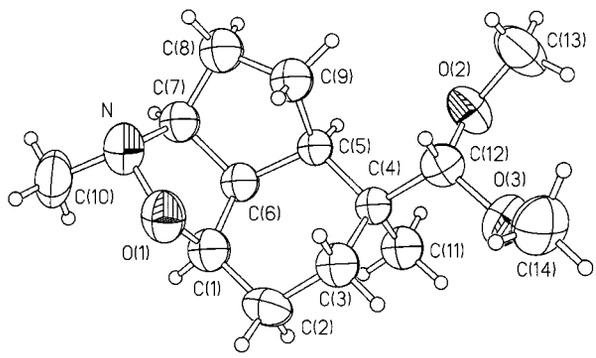
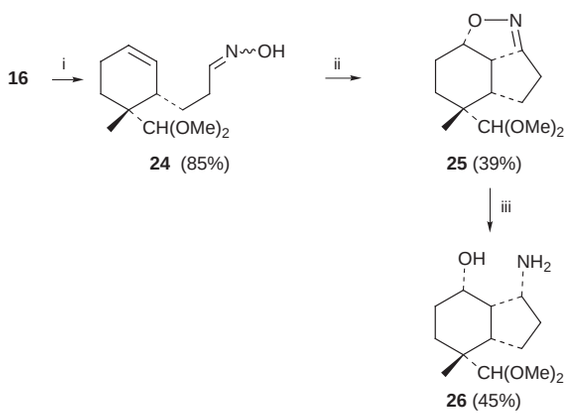


Fig. 1



Scheme 5 *Reagents and conditions*: i, $NH_2OH{\cdot}HCl$, pyridine; ii, MeOH, chloramine-T, reflux, 4.5 h; iii, $NiCl_2$, $NaBH_4$, MeOH.

success of the nitrone cycloaddition route, this pathway was explored no further.

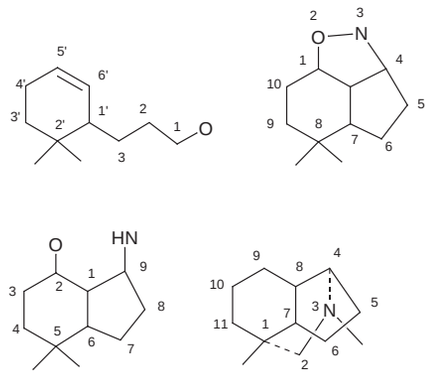
Thus the synthesis of the desired tricyclic amines **2** (R = H) and **2** (R = Me) containing five stereogenic centres, and modelling the A/E/F ring system of the title alkaloids, has been effected in eight and nine steps respectively from the commercially available penta-1,4-dien-3-ol, with overall yields 20 and 16%. Future work will focus on the extension of this route to provide homochiral products through an enantioselective cycloaddition process, and the introduction of further oxygenation.

Experimental

Unless otherwise stated the following generalisations apply. All melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were obtained using a Perkin-Elmer 1600 series FTIR or a Perkin-Elmer 1720-X FTIR instrument as thin films (liquids) or chloroform solutions (solids). ^{1}H NMR spectra were recorded on either a Bruker AM 250 (250 MHz) or a Bruker 400 (400 MHz) instrument. The spectra were recorded as dilute solutions in deuteriochloroform: the multiplicity of a signal is designated as: s, singlet; d, doublet; t, triplet; q, quartet; sept., septet; br, broad; m, multiplet. Observed coupling constants, *J*, are reported in Hertz. ^{13}C NMR spectra were recorded on either a JEOL EX 270 (67.8 MHz) or a Bruker AM400 (100.6 MHz) instrument, as dilute solutions in deuteriochloroform. Multiplicities 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 and the following solvent systems were used: A, petroleum ether (bp 40–60 °C)–diethyl ether; B, petroleum ether (bp 40–60 °C)–ethyl acetate. Routinely, dry organic solvents were stored under nitrogen. Benzene, toluene and diethyl ether were dried over sodium wire. Other organic solvents were dried by distillation from the following: THF (sodium, benzophenone), dichloromethane (calcium hydride), dimethoxyethane (sodium). Organic extracts were dried over anhydrous magnesium sulfate and the solvent was removed on a Buchi rotary evaporator. Sodium hydride was handled as a 60% suspension in mineral oil and was washed with petroleum ether (bp 40–60 °C) prior to use.

The numberings used in systematic nomenclature and in NMR assignments are shown below.



(*E*,*E*)-Ethyl hepta-4,6-dienoate 11a

A solution of penta-1,4-dien-3-ol **10** (5.00 g, 59.4 mmol) and propionic acid (0.4 g, 5.4 mmol) in triethyl orthoacetate (70 ml) was heated to reflux[7a] for 1 h. The mixture was cooled and ethanol was removed by distillation [bp 68 °C (760 mmHg)]. The mixture was heated to reflux for 2 h, cooled and ethanol was again removed by distillation. 2,6-Di-*tert*-butyl-4-methylphenol (0.2 g, 0.9 mmol) was added and triethyl orthoacetate was removed *in vacuo* [bp 45–50 °C (18 mmHg)]. The product was subjected to column chromatography (solvent A, 4 : 1) to yield the title compound as a colourless oil (7.97 g, 87%) (Found: M^+, 154.097. $C_9H_{14}O_2$ requires: 154.099); ν_{max}(liquid film)/cm^{-1} 1737 (C=O), 1654, 1604 (C=C); δ_H(250 MHz, $CDCl_3$) 1.25 (3H, t, *J* 7.1, OCH_2CH_3), 2.41 (4H, m, 2-H_2, 3-H_2), 4.14 (2H, q, *J* 7.1, OCH_2CH_3), 4.99 (1H, dd, *J* 10.2, 1.5, 7-H_a), 5.11 (1H, dd, *J* 16.8, 1.5, 7-H_b), 5.63–5.75 (1H, m, 4-H), 6.09 (1H, dd, *J* 15.0, 10.2, 5-H), 6.30 (1H, ddd, *J* 16.8, 10.2, 10.2, 6-H); δ_C(67.8 MHz, $CDCl_3$) 14.1 (OCH_2CH_3), 27.7 (CH_2), 33.7 (CH_2), 60.2 (OCH_2CH_3), 115.0 (C-7), 131.8 (CH), 132.5 (CH), 136.7 (CH), 172.7 (CO); *m*/*z* 154 (43%), 109 (29), 81 (100), 67 (90).

(*E*,*E*)-Hepta-4,6-dienoic acid 11b

A solution of (*E*,*E*)-ethyl hepta-4,6-dienoate **11a** (3.00 g, 19.5 mmol) and potassium hydroxide (5.0 g, 89 mmol) in dry methanol (25 ml) was heated to reflux for 1.5 h.[7b] Methanol was removed *in vacuo* and the residue partitioned between diethyl ether and water. The aqueous layer was separated, acidified to pH 3 with 2 M aqueous hydrochloric acid and extracted into diethyl ether. The extracts were washed with brine, dried and concentrated to yield the title compound as a yellow oil (2.18 g, 89%) (Found: C, 66.66, H, 8.39%; M^+, 126.065. $C_7H_{10}O_2$ requires: C, 66.65, H, 7.99%; *M*, 126.068); ν_{max}(liquid film)/cm^{-1} 1711 (C=O), 1654, 1604 (C=C); δ_H(250 MHz, $CDCl_3$) 2.39–2.52 (4H, m, 2-H_2, 3-H_2), 5.01 (1H, d, *J* 10.2, 7-H_a), 5.14 (1H, d, *J* 16.8, 7-H_b), 5.71 (1H, dt, *J* 15.1, 6.6, 4-H), 6.11 (1H, dd, *J* 15.1, 10.2, 5-H), 6.31 (1H, ddd, *J* 16.8, 10.2, 10.2, 6-H), 11.54 (1H, s, CO_2H); δ_C(67.8 MHz, $CDCl_3$) 27.1 (CH_2), 33.3 (CH_2), 115.5 (C-7), 131.9 (2 × CH), 136.6 (CH), 179.2 (CO); *m*/*z* 126 (63%), 81 (100), 67 (81).

(*E*,*E*)-Hepta-4,6-dienol 12a

To a suspension of lithium aluminium hydride (4.9 g, 130 mmol) in diethyl ether (75 ml) at 0 °C was added (*E*,*E*)-ethyl hepta-4,6-dienoate **11a** (5.0 g, 32 mmol) dropwise over 10 min.[7a]

The mixture was allowed to warm to 25 °C and stirred for 1 h. The excess lithium aluminium hydride was cautiously quenched sequentially with ethyl acetate, methanol and water. 1 M Aqueous hydrochloric acid was added to break up any solid material and the mixture was extracted into diethyl ether. The extracts were washed with sodium bicarbonate solution, dried and concentrated. The product was subjected to column chromatography (solvent A, 1:2) to yield the title compound as a colourless oil (3.10 g, 85%) (Found: M^+, 112.084. $C_7H_{12}O$ requires: 112.089); ν_{max}(liquid film)/cm^{-1} 3339 (OH), 1652, 1603 (C=C); δ_H(250 MHz, $CDCl_3$) 1.61–1.72 (2H, m, 2-H_2), 2.12–2.21 (2H, m, 3-H_2), 3.64 (2H, t, *J* 6.5, 1-H_2), 4.96 (1H, d, *J* 10.2, 7-H_a), 5.09 (1H, d, *J* 16.9, 7-H_b), 5.70 (1H, dt, *J* 14.9, 7.4, 4-H), 6.07 (1H, dd, *J* 14.9, 10.2, 5-H), 6.30 (1H, ddd, *J* 16.9, 10.2, 10.2, 6-H); δ_C(67.8 MHz, $CDCl_3$) 28.7 (C-2), 31.9 (C-3), 60.0 (C-1), 115.0 (C-7), 131.3 (C-4), 134.3 (C-5), 137.0 (C-6); *m*/*z* 112 (16%), 94 (15).

(*E*,*E*)-1-Iodohepta-4,6-diene 12b

To a solution of triphenylphosphine (2.8 g, 11 mmol) and imidazole (0.73 g, 11 mmol) in acetonitrile (40 ml) at 25 °C under argon was added iodine (2.7 g, 11 mmol). The solution turned yellow and a white precipitate was observed. (*E*,*E*)-Hepta-4,6-dienol **12a** (1.0 g, 9 mmol) in acetonitrile (10 ml) was added dropwise over 5 min. The mixture was stirred for 4 h, diluted wth ethyl acetate and washed with aqueous sodium thiosulfate and aqueous copper sulfate. The organic phase was dried and concentrated. The product was subjected to column chromatography (solvent A, 4:1) to yield the title compound as a yellow oil (1.5 g, 76%) (Found: M^+, 221.992. $C_7H_{11}I$ requires: 221.991); δ_H(250 MHz, $CDCl_3$) 1.79–1.90 (2H, m, 2-H_2), 2.09–2.18 (2H, m, 3-H_2), 3.12 (2H, t, *J* 6.9, 1-H_2), 4.93 (1H, d, *J* 10.2, 7-H_a), 5.06 (1H, d, *J* 17.0, 7-H_b), 5.56 (1H, dt, *J* 15.0, 7.0, 4-H), 6.04 (1H, dd, *J* 15.0, 10.2, 5-H), 6.23 (1H, ddd, *J* 17.0, 10.2, 10.2, 6-H); δ_C(67.8 MHz, $CDCl_3$) 6.7 (C-1), 33.0 (CH_2), 33.4 (CH_2), 115.9 (C-7), 132.6 (CH), 132.7 (CH), 137.2 (CH); *m*/*z* 222 (95%), 95 (70), 67 (100).

(*E*,*E*)-1-Nitrohepta-4,6-diene 12c

To a suspension of silver nitrite (4.0 g, 26 mmol) in diethyl ether (20 ml) at 0 °C in the dark was added (*E*,*E*)-1-iodohepta-4,6-diene **12b** (4.5 g, 20 mmol) in diethyl ether (30 ml) dropwise over 30 min. The mixture was stirred for 24 h at 0 °C, then at 25 °C for 20 h. The mixture was filtered and the residue was washed with diethyl ether. The filtrate was concentrated and the product was subjected to column chromatography (solvent A, 5:1) to yield the *title compound* as a yellow oil (1.4 g, 50%) along with starting material (0.75 g, 17%) (Found: M^+, 141.082. $C_7H_{11}NO_2$ requires: 141.079); ν_{max}(liquid film)/cm^{-1} 1554 (NO); δ_H(250 MHz, $CDCl_3$) 2.10–2.22 (4H, m, 2-H_2, 3-H_2), 4.39 (2H, t, *J* 6.7, 1-H_2), 5.03 (1H, d, *J* 10.2, 7-H_a), 5.15 (1H, d, *J* 16.7, 7-H_b), 5.63 (1H, dt, *J* 15.0, 6.7, 4-H), 6.10 (1H, dd, *J* 15.0, 10.2, 5-H), 6.30 (1H, ddd, *J* 16.7, 10.2, 10.2, 6-H); δ_C(67.8 MHz, $CDCl_3$) 26.7 (CH_2), 28.9 (CH_2), 74.7 (C-1), 116.2 (C-7), 131.4 (CH), 132.9 (CH), 136.4 (CH); *m*/*z* 141 (3%), 95(21), 79 (100).

3-(2-Methoxycarbonyl-2-methylcyclohex-5-enyl)-1-hydroxypropane 13

A mixture of (*E*,*E*)-ethyl hepta-4,6-dienol **12a** (0.10 g, 0.9 mmol), methyl methacrylate (0.05 g, 0.5 mmol) and quinol[11] (1 mg, 9×10^{-3} mmol) was heated to 220 °C in a closed system for 6.5 h. After cooling, the mixture was subjected to column chromatography (solvent A, 1:1) to yield the *title compound* as a mixture of diastereoisomers, as a colourless oil (0.06 g, 67%) (Found: $(M - HCO_2Me)^+$, 152.120. $C_{10}H_{16}O$ requires: 152.120); δ_H(250 MHz, $CDCl_3$) 0.78, 0.92 (3H, 2 × s, 2′-H_3), 1.08–1.63 (4H, m, 2 × CH_2), 1.74 (2.5H, m, 0.5 × 1′-H, CH_2), 2.11 (2H, m, CH_2), 2.40 (0.5H, m, 0.5 × 1′-H), 3.28–3.38 (2H, m, 1-H_2), 3.39, 3.40 (3H, 2 × s, OCH_3), 5.21–5.48 (2H, m, 5-H, 6-H); δ_C(67.8 MHz, $CDCl_3$) 15.1, 15.7 (2-CH_3), 22.1, 22.3 (CH_2), 25.6, 27.1 (CH_2), 29.7, 30.0 (CH_2), 30.4, 32.1 (CH_2), 39.5, 42.2 (C-1′), 44.4, 44.6 (C-2′), 51.4, 51.8 (OCH_3), 62.4, 62.7 (C-1), 125.2, 125.5 (CH), 128.0, 128.7 (CH), 178.0, 178.9 (CO); *m*/*z* 152 (22%), 135 (49), 107 (69).

3-[(1*S*,2*R*)-2-Formyl-2-methylcyclohex-5-enyl]propionic acid 14a

To a solution of (*E*,*E*)-hepta-4,6-dienoic acid **11b** (2.80 g, 22 mmol) in water (10 ml) at 25 °C was added sodium bicarbonate (1.86 g, 22 mmol) portionwise over 5 min, and, after gas evolution had subsided, freshly distilled methacrolein (6.22 g, 89 mmol) was added. The mixture was warmed to 45 °C and stirred for 24 h. The mixture was acidified to pH 3 with 2 M aqueous hydrochloric acid and extracted into diethyl ether. The extracts were washed with brine, dried and concentrated. The product was subjected to column chromatography (solvent A, 2:1) to yield the title compound as a low melting solid (4.30 g, 92%); mp 25–28°C (Found: C, 67.48, H, 8.49%; M^+, 196.104. $C_{11}H_{16}O_3$ requires: C, 67.32, H, 8.22%; *M*, 196.110); ν_{max}(liquid film)/cm^{-1} 3181 (OH), 1717 (C=O); δ_H(250 MHz, $CDCl_3$) 1.12 (3H, s, 2′-CH_3), 1.50–1.60 (2H, m, 3-H_a, 3′-H_a), 1.82–1.92 (2H, m, 3-H_b, 3′-H_b), 2.02–2.27 (3H, br m, 1′-H, 4′-H_2), 2.39 (1H, ddd, *J* 16.3, 8.6, 7.7, 2-H_a), 2.53 (1H, ddd, *J* 16.3, 8.8, 5.5, 2-H_b), 5.69–5.80 (2H, m, 5′-H, 6′-H), 9.66 (1H, s, 2′-CH); δ_C(67.8 MHz, $CDCl_3$) 19.9 (2′-CH_3), 22.1 (C-4′), 26.6, 26.8 (C-3, C-3′), 31.7 (C-2), 36.8 (C-1′), 47.4 (C-2′), 126.7, 127.6 (C-5′, C-6′), 179.2 (C-1), 206.4 (CHO); *m*/*z* 196 (2%), 178 (25), 167 (10), 150 (21), 126 (17).

Methyl 3-[(1*S*,2*R*)-2-formyl-2-methylcyclohex-5-enyl]-propionate 14b

To a solution of (*E*,*E*)-hepta-4,6-dienoic acid **11b** (1.0 g, 7.9 mmol) in water (4 ml) was added sodium bicarbonate (0.63 g, 7.5 mmol) and freshly distilled methacrolein (0.14 g, 2.0 mmol) at 25 °C.[8a] The mixture was stirred for 24 h and the mixture was acidified to pH 3 with 2 M aqueous hydrochloric acid and extracted into diethyl ether. The extracts were washed with brine, dried and concentrated.

To a solution of diazomethane (1.01 g, 24 mmol) in diethyl ether (60 ml) at 25 °C, formed by the standard procedure from Diazald, was added the crude reaction mixture (1.70 g) dropwise over 10 min. The mixture was left for 1 h without stirring and quenched with acetic acid. The mixture was basified to pH 9 with aqueous sodium bicarbonate and extracted into diethyl ether. The extracts were dried and concentrated. The product was subjected to column chromatography (solvent A, 4:1) to yield methyl 3-[(1*S*,2*R*)-2-formyl-2-methylcyclohex-5-enyl]-propionate[8a] (0.47 g, 75%) and methyl hepta-4,6-dienoate (0.04 g, 5%).

Methyl 3-[(1*S*,2*R*)-2-formyl-2-methylcyclohex-5-enyl]propionate; ν_{max}(liquid film)/cm^{-1} 1738 (C=O), 1653 (C=C); δ_H(270 MHz, $CDCl_3$) 1.04 (3H, s, 2′-CH_3), 1.06–1.11 (1H, m, 4′-H_a), 1.42–1.53 (2H, m, 3-H_a, 3′-H_a), 1.72–1.86 (2H, m, 3-H_b, 3′-H_b), 1.99–2.08 (2H, m, 1′-H, 4′-H_b), 2.20–2.47 (2H, m, 2-H_2), 3.60 (3H, s, OCH_3), 5.55–5.72 (2H, m, 5′-H, 6′-H), 9.59 (1H, s, 2′-CH); δ_C(67.8 MHz, $CDCl_3$) 20.0 (2′-CH_3), 22.2 (C-4′), 27.0, 27.1 (C-3, C-3′), 32.0 (C-2), 40.9 (C-1′), 47.5 (C-2′), 51.5 (OCH_3), 127.0, 127.4 (C-5′, C-6′), 173.5 (C-1), 206.2 (CHO).

Methyl 3-[(1*S*,2*R*)-2-dimethoxymethyl-2-methylcyclohex-5-enyl]propionate 15

To a solution of 3-[(1*S*,2*R*)-2-formyl-2-methylcyclohex-5-enyl]-propionic acid **14a** (1.50 g, 7.63 mmol) and toluene-*p*-sulfonic acid (0.01 g, 0.05 mmol) in methanol (8 ml) heated to reflux was added trimethyl orthoformate (0.88 g, 8.3 mmol) over 5 min. The mixture was heated to reflux for 1 h and, after cooling, was

quenched with sodium (0.25 g, 11 mmol) in methanol (2 ml). The mixture was washed with water, dried and concentrated. The product was subjected to column chromatography (solvent B, 4:1) to yield the *title compound* as a pale orange oil (1.58 g, 80%) (Found: C, 65.95, H, 9.85. $C_{14}H_{24}O_4$ requires: C, 65.60, H, 9.44%; Found: $(M - OMe)^+$, 225.148. $C_{13}H_{21}O_3$ requires: 225.149); ν_{max}(liquid film)/cm^{-1} 1741 (C=O), 1653 (C=C); δ_H(250 MHz, $CDCl_3$) 0.92 (3H, s, 2′-CH_3), 1.36–1.51 (3H, m, 3-H_a, 3′-H_2), 1.81–1.88 (1H, m, 1′-H), 1.89–1.97 (1H, m, 3-H_b), 2.00–2.03 (2H, m, 4′-H_2), 2.28 (1H, ddd, *J* 15.6, 10.1, 5.3, 2-H_a), 2.46 (1H, ddd, *J* 15.6, 10.4, 5.3, 2-H_b), 3.47 (3H, s, CH(OC*H*$_3$)$_2$), 3.56 (3H, s, CH(OC*H*$_3$)$_2$), 3.67 (3H, s, OCH_3), 3.99 (1H, s, *CH*$(OCH_3)_2$), 5.59–5.67 (2H, m, 5′-H, 6′-H); δ_C(67.8 MHz, $CDCl_3$) 16.9 (2′-CH_3), 22.2 (C-4′), 25.6 (C-3′), 27.1 (C-3), 32.2 (C-2), 40.6 (C-2′), 41.0 (C-1′), 51.4, 56.8 (CH(O*C*H$_3$)$_2$), 60.1 (OCH_3), 111.8 (*C*H$(OCH_3)_2$), 126.4, 128.6 (C-5′, C-6′), 174.4 (C-1); *m*/*z* 225 (3%), 192 (13), 85 (40), 75 (100).

3-[(1*S*,2*R*)-Dimethoxymethyl-2-methylcyclohex-5-enyl]propanal 16

To a solution of methyl 3-[(1*S*,2*R*)-2-dimethoxymethyl-2-methylcyclohexen-5-yl]propionate **15** (1.50 g, 5.8 mmol) in toluene (30 ml) at −78 °C was added 1.5 M diisobutylaluminium hydride in toluene (4.70 ml, 7.05 mmol) dropwise over 5 min. After 1.5 h the solution was diluted with diethyl ether and 2 M aqueous hydrochloric acid was added. The aqueous layer was separated and extracted with diethyl ether. The combined extracts were dried and concentrated. The product was subjected to column chromatography (solvent A, 5:2) to yield the *title compound* as a colourless solid (1.21 g, 91%); mp 18–20 °C (Found: C, 68.52, H, 10.26. $C_{13}H_{22}O_3$ requires: C, 68.99, H, 9.80%; Found: $(M - OMe)^+$, 195. $C_{12}H_{19}O_2$ requires: 195); ν_{max}(liquid film)/cm^{-1} 1724 (C=O), 1652 (C=C); δ_H(250 MHz, $CDCl_3$) 0.93 (3H, s, 2′-CH_3), 1.37–1.56 (3H, m, 3-H_a, 3′-H_2), 1.85 (1H, br m, 1′-H), 1.91–1.99 (1H, m, 3-H_b), 2.03 (2H, m, 4′-H_2), 2.42 (1H, dddd, *J* 17.1, 9.6, 5.8, 1.7, 2-H_a), 2.58 (1H, dddd, *J* 17.1, 10.0, 5.6, 1.7, 2-H_b), 3.47 (3H, s, CH(OC*H*$_3$)$_2$), 3.57 (3H, s, CH(OC*H*$_3$)$_2$), 4.00 (1H, s, C*H*$(OCH_3)_2$), 5.58–5.68 (2H, m, 5′-H, 6′-H), 9.79 (1H, t, *J* 1.7, 1-H); δ_C(67.8 MHz, $CDCl_3$) 16.9 (2′-CH_3), 21.9 (C-4′), 23.6 (C-3′), 25.1 (C-3), 40.3 (C-2′), 40.6 (C-1′), 41.7 (C-2), 56.4, 59.6 (CH(O*C*H$_3$)$_2$), 111.6 (*C*H$(OCH_3)_2$), 126.1, 128.3 (C-5′, C-6′), 202.3 (C-1); *m*/*z* (FAB +ve) 195 (15%), 163 (14).

N,*O*-Bis-*tert*-butoxycarbonylhydroxylamine 17

To a solution of *N*-hydroxylamine hydrochloride (10.4 g, 0.15 mol) and sodium carbonate (19.9 g, 0.19 mol) in water (75 ml) at 35 °C was added di-*tert*-butyldicarbonate (68.8 g, 0.32 mol) portionwise over 2.5 h. After 45 min, the solution was cooled to 25 °C and stirred for 16 h. The mixture was extracted into toluene and the extracts were dried and concentrated. The product was recrystallised from hexane to yield the title compound as white cubes (29.6 g, 85%); mp 67–71 °C (hexane) [lit.,[9] mp 70–72 °C (hexane)] (Found: C, 51.26, H, 8.50, N, 6.14. $C_{10}H_{19}NO_5$ requires: C, 51.49, H, 8.21, N, 6.00%); ν_{max}(KBr disc)/cm^{-1} 3273 (NH), 1796 (OC=O), 1740 (NC=O); δ_H(400 MHz, $CDCl_3$) 1.50 (9H, s, 3 × CH_3), 1.52 (9H, s, 3 × CH_3), 7.51 (1H, br s, NH); δ_C(100.6 MHz, $CDCl_3$) 27.7 (C(*C*H$_3$)$_3$), 28.0 (C(*C*H$_3$)$_3$), 83.0, 85.2 (2 × C), 153.6, 155.8 (2 × CO).

N,*O*-Bis-*tert*-butoxycarbonyl-*N*-ethylhydroxylamine 18

To a solution of *N*,*O*-bis-*tert*-butoxycarbonylhydroxylamine **17** (15.0 g, 64 mmol) in *N*,*N*-dimethylformamide (80 ml) at 25 °C was added potassium carbonate (11.1 g, 80 mmol). To the suspension at 30 °C was added ethyl iodide (11.1 g, 71 mmol) dropwise over 45 min. After 2.5 h, the solution was cooled to 25 °C and diluted with water and toluene. The toluene layer was separated, washed with water, dried and concentrated to yield the *title compound*[9] as a yellow oil (16.5 g, 99%); ν_{max}(liquid film)/cm^{-1} 1785 (OC=O), 1717 (NC=O); δ_H(400 MHz, $CDCl_3$) 1.19 (3H, t, *J* 7.1, NCH_2CH_3), 1.49 (9H, s, C(*CH*$_3$)$_3$), 1.57 (9H, s, C(*CH*$_3$)$_3$), 3.61 (2H, br q, N*CH*$_2$CH$_3$); δ_C(100.6 MHz, $CDCl_3$) 11.8 (NCH_2CH_3), 27.4, 27.9 (2 × C(*CH*$_3$)$_3$), 44.9 (N*CH*$_2$CH$_3$), 81.9, 82.3 (2 × *C*(CH$_3$)$_3$), 153.6, 155.8 (2 × CO).

N-Ethylhydroxylammonium trifluoroacetate 19

To a solution of *N*,*O*-bis-*tert*-butoxycarbonyl-*N*-ethylhydroxylamine **18** (12.0 g, 46 mmol) in dichloromethane (60 ml) at 25 °C was added trifluoroacetic acid (15.7 g, 140 mmol) dropwise over 10 min. The mixture was stirred for 1.5 h and the solvent and excess trifluoroacetic acid were removed *in vacuo* to yield the *title compound* as a crystalline solid (7.33 g, 91%), mp 89 °C; δ_H(400 MHz, $CDCl_3$) 1.38 (3H, t, *J* 7.1, NCH_2CH_3), 3.40 (2H, t, *J* 7.1, N*CH*$_2$CH$_3$).

(1β,4β,7β,11β)-3-Methyl-8α-dimethoxymethyl-8β-methyl-3-aza-2-oxatricyclo[5.3.1.0^{4,11}]undecane 20a †

A solution of 3-[(1*S*,2*R*)-dimethoxymethyl-2-methylcyclohex-5-enyl]propanal **16** (0.20 g, 0.88 mmol), *N*-methylhydroxylamine hydrochloride (0.16 g, 1.9 mmol) and triethylamine (0.14 g, 1.9 mmol) in benzene (5 ml) was heated to reflux for 3.5 h. The solution was diluted with diethyl ether, filtered and concentrated. The product was subjected to column chromatography (solvent A, 2:3) to yield the *title compound* as white needles (0.19 g, 83%); mp 75–81 °C (Found: C, 66.05; H, 10.20; N, 5.40%; M^+, 255.183. $C_{14}H_{25}NO_3$ requires: C, 65.85; H, 9.87; N, 5.49%; *M*, 255.183); ν_{max}(solution, $CHCl_3$)/cm^{-1} 2974, 2973 (CH_2, CH); δ_H(270 MHz, $CDCl_3$) 0.93 (3H, s, 8-CH_3), 1.16–1.21 (1H, m, 9-H_a), 1.37–1.52 (4H, m, 5-H_a, 6-H_2, 9-H_b), 1.61 (1H, br m, 7-H), 1.80–1.85 (2H, m, 10-H_2), 1.97 (1H, m, 5-H_b), 2.64 (3H, s, NCH_3), 2.80 (1H, m, 11-H), 3.42 (1H, br m, 4-H), 3.42 (3H, s, CH(OC*H*$_3$)$_2$), 3.52 (3H, s, CH(OC*H*$_3$)$_2$), 3.81 (1H, s, C*H*$(OCH_3)_2$), 4.22 (1H, br m, 1-H); δ_C(100.6 MHz, d_6-DMSO, 80 °C) 17.2 (8-CH_3), 20.3 (C-10), 21.4 (C-9), 25.7 (C-6), 33.3 (C-5), 40.2 (C-8), 43.8 (C-7), 44.0 (NCH_3), 45.8 (C-11), 56.1, 58.2 (CH(*OC*H$_3$)$_2$), 70.4 (C-1), 71.8 (C-4), 112.2 (*C*H$(OCH_3)_2$); *m*/*z* 255 (16%), 240 (69), 224 (12), 75 (100).

(1β,4β,7β,11β)-3-Ethyl-8α-dimethoxymethyl-8β-methyl-3-aza-2-oxatricyclo[5.3.1.0^{4,11}]undecane 20b †

A solution of 3-[(1*S*,2*R*)-2-dimethoxymethyl-2-methylcyclohex-5-enyl]propanal **16** (0.12 g, 0.54 mmol), *N*-ethylhydroxylamine trifluoroacetic acid (0.20 g, 1.1 mmol) and triethylamine (0.12 g, 1.1 mmol) in benzene (5 ml) was heated to reflux for 4 h. The solution was diluted with diethyl ether, filtered and concentrated. The product was subjected to column chromatography (solvent A, 2:3) to yield the *title compound* as a colourless oil which solidified on standing (0.09 g, 62%); mp 65–69 °C (Found: C, 66.99; H, 10.49; N, 5.22. $C_{15}H_{27}NO_3$ requires: C, 66.88; H, 10.10; N, 5.20%; Found: MH^+, 269.197. $C_{15}H_{28}NO_3$ requires: 269.199); ν_{max}(solution, $CHCl_3$)/cm^{-1} 2943 (CH_2, CH); δ_H(400 MHz, $CDCl_3$) 0.93 (3H, s, 8-CH_3), 1.08 (3H, dd, *J* 7.1, 7.1, NCH_2CH_3), 1.17–1.25 (1H, m, 9-H_a), 1.38–1.56 (4H, m, 5-H_a, 6-H_2, 9-H_b), 1.56–1.63 (1H, m, 7-H), 1.76–1.84 (2H, m, 10-H_2), 1.96 (1H, m, 5-H_b), 2.76 (1H, m, 11-H), 2.60–2.67 (1H, m, N*CH*$_a$CH$_3$), 2.85–2.94 (1H, m, N*CH*$_b$CH$_3$), 3.42–3.51 (1H, m, 4-H), 3.43 (3H, s, CH(OC*H*$_3$)$_2$), 3.52 (3H, s, CH(OC*H*$_3$)$_2$), 3.82 (1H, s, *CH*$(OCH_3)_2$), 4.11 (1H, br m, 1-H); δ_C(100.6 MHz, $CDCl_3$) 13.1 (NCH_2CH_3), 17.0 (8-CH_3), 21.0 (C-10), 22.0 (C-9), 26.4 (C-6), 34.9 (C-5), 40.2 (C-8), 44.4 (C-7), 46.2 (C-11), 51.4

† The correct IUPAC names for compounds **20a** and **20b** are 1β,4β,8β,11β-2-methyl-7α-dimethoxymethyl-7β-methyl-2-aza-3-oxatricyclo[6.2.1.0^{4,11}]undecane and 1β,4β,8β,11β-2-ethyl-7α-dimethoxymethyl-7β-methyl-2-axa-3-oxatricyclo[6.2.1.o^{4,11}]undecane respectively.

(NCH_3), 56.9, 60.2 ($CH(OCH_3)_2$), 71.5, 71.7 (C-1, C-4), 113.4 ($CH(OCH_3)_2$); *m*/*z* 269 (12%), 238 (9), 222 (5), 75 (100).

(1β,2α,6β,9α)-9-Methylamino-5α-dimethoxymethyl-5β-methylbicyclo[4.3.0]nonan-2-ol 21a

To a stirred solution of 1β,4β,7β,11β-3-methyl-8α-dimethoxymethyl-8β-methyl-3-aza-2-oxatricyclo[5.3.1.$0^{4,11}$]undecane **20a** (0.50 g, 2.0 mmol) in methanol (40 ml) at 25 °C was added nickel chloride hexahydrate (0.93 g, 3.9 mmol). Sodium borohydride (0.46 g, 11.8 mmol) was added portionwise over 5 min, the mixture turned black and evolution of gas was observed. The mixture was stirred for 2 h, the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 ml) and conc. aqueous ammonia (50 ml). The mixture was stirred for 1.5 h and the two layers were separated. The aqueous layer was extracted with dichloromethane and the combined organic phases were dried and concentrated to yield the *title compound* as unstable orange crystals (0.48 g, 94%) (Found: $(M - Me)^+$, 242.175. $C_{13}H_{24}NO_3$ requires: 242.176); ν_{max}(solution, $CHCl_3$)/cm^{-1} 3343 (NH, OH); δ_H(400 MHz, $CDCl_3$) 0.97 (3H, s, 5-CH_3), 1.21–1.25 (1H, m, 4-H_a), 1.38–1.54 (2H, m, 7-H_a, 8-H_a), 1.62–1.83 (4H, m, 3-H_2, 4-H_b, 6-H), 1.93–2.09 (3H, m, 1-H, 7-H_b, 8-H_b), 2.46 (3H, s, NCH_3), 3.22 (9-H), 3.45 (3H, s, $CH(OCH_3)_2$), 3.56 (3H, s, $CH(OCH_3)_2$), 3.87 (1H, s, $CH(OCH_3)_2$), 4.01 (1H, br m, 2-H); δ_C(67.8 MHz, $CDCl_3$) 17.6 (5-CH_3), 23.0 (C-4), 25.5 (C-7), 26.8 (C-3), 32.4 (NCH_3), 36.4 (C-8), 40.6 (C-5), 42.6 (C-1), 45.6 (C-6), 57.0, 60.6 ($CH(OCH_3)_2$), 63.1 (C-9), 66.0 (C-2), 113.8 ($CH(OCH_3)_2$); *m*/*z* 242 (20%), 225 (2), 210 (14), 194 (16).

(1β,2α,6β,9α)-9-Ethylamino-5α-dimethoxymethyl-5β-methylbicyclo[4.3.0]nonan-2-ol 21b

To a solution of 1β,4β,7β,11β-3-ethyl-8α-dimethoxymethyl-8β-methyl-3-aza-2-oxatricyclo[5.3.1.$0^{4,11}$]undecane **20b** (0.50 g, 1.9 mmol) in methanol (40 ml) at 25 °C was added nickel chloride hexahydrate (0.88 g, 3.7 mmol). Sodium borohydride (0.42 g, 11 mmol) was added portionwise over 5 min, the mixture turned black and evolution of gas was observed. The mixture was stirred for 2 h, the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (50 ml) and conc. aqueous ammonia (50 ml). The mixture was stirred for a further 1.5 h and the two layers were separated. The aqueous layer was extracted into dichloromethane and the combined extracts were dried and concentrated to yield the *title compound* as a brown oil which solidified on standing (0.46 g, 92%); mp 88–94 °C (Found: M^+, 271.211. $C_{15}H_{29}NO_3$ requires: 271.215); ν_{max}(solution, $CHCl_3$)/cm^{-1} 3318 (br OH, NH); δ_H(400 MHz, $CDCl_3$) 0.97 (3H, s, 5-CH_3), 1.11 (3H, dd, *J* 7.1, 7.1, NCH_2CH_3), 1.18–1.64 (1H, m, 4-H_a), 1.38–1.52 (2H, m, 7-H_a, 8-H_a), 1.64–1.81 (4H, m, 3-H_2, 4-H_b, 6-H), 1.94–2.06 (3H, m, 1-H, 7-H_b, 8-H_b), 2.65 (1H, dq, *J* 14.7, 7.1, NCH_aCH_3), 2.66 (1H, dq, *J* 14.7, 7.1, NCH_bCH_3), 3.32 (1H, ddd, *J* 10.1, 7.1, 6.8, 9-H), 3.45 (3H, s, $CH(OCH_3)_2$), 3.56 (3H, s, $CH(OCH_3)_2$), 3.87 (1H, s, $CH(OCH_3)_2$), 3.99 (1H, br m, 2-H); δ_C(100.6 MHz, $CDCl_3$) 15.0 (NCH_2CH_3), 17.0 (5-CH_3), 22.2 (C-4), 24.7 (C-7), 26.2 (C-3), 31.9 (C-8), 39.8 (C-5), 42.0 (C-1), 43.2 (NCH_2CH_3), 44.8 (C-6), 56.2, 59.6 ($CH(OCH_3)_2$), 60.3 (C-9), 65.2 (C-2), 113.0 ($CH(OCH_3)_2$); *m*/*z* 271 (0.5%), 256 (25), 224 (9), 208 (16), 75 (100).

(1β,4β,7β,8β,9α)-1,3-Dimethyl-3-azatricyclo[5.4.0.$0^{4,8}$]undecan-9-ol 22a

1β,2α,6β,9α-9-Methylamino-5α-dimethoxymethyl-5β-methylbicyclo[4.3.0]nonan-2-ol **21a** (0.19 g, 0.70 mmol) was treated with 5 M hydrochloric acid (1.8 ml) and the mixture was stirred at 25 °C for 1.5 h. 25% w/v Aqueous sodium hydroxide (2 ml) was added and the mixture was buffered to pH 5.5 with a freshly prepared citrate–phosphate buffer (10 ml). The mixture was stirred for 3 h after which time 1 M sodium cyanoborohydride in tetrahydrofuran (1.4 ml, 1.4 mmol) was added dropwise over 5 min.[32] The mixture was stirred for a further 1.5 h, basified to pH 12 with 2 M aqueous sodium hydroxide, and the product was extracted into dichloromethane. The extracts were dried and concentrated to yield the *title compound* as a yellow solid (0.11 g, 80%); mp 82–86 °C (decomp.) (Found: M^+, 195.161. $C_{12}H_{21}NO$ requires: 195.162); ν_{max}(solution, $CHCl_3$)/cm^{-1} 2792 (NCH); δ_H(400 MHz, $CDCl_3$) 0.68 (3H, s, 1-CH_3), 1.16–1.23 (1H, m, 5-H_a), 1.29 (1H, dddd, *J* 13.6, 13.6, 5.2, 2.6, 11-H_a), 1.48–1.57 (4H, m, 6-H_2, 7-H, 11-H_b), 1.68–1.84 (3H, m, 5-H_b, 8-H, 10-H_a), 1.87 (1H, dd, *J* 11.4, 2.6, 2-H_a), 2.03 (3H, s, NCH_3), 2.22 (1H, d, *J* 11.4, 2-H_b), 2.39–2.50 (1H, m, 10-H_b), 3.16 (1H, dd, *J* 4.5, 4.5, 4-H), 3.96 (1H, dd, *J* 10.5, 6.2, 9-H); δ_C(100.6 MHz, $CDCl_3$) 20.3 (C-5), 24.4 (C-6), 25.9 (1-CH_3), 31.1 (C-10), 32.1 (C-1), 38.6 (C-11), 42.4 (NCH_3), 45.0 (C-7), 47.9 (C-8), 59.8 (C-2), 60.9 (C-4), 70.5 (C-9); *m*/*z* 195 (30%), 178 (85), 166 (100), 136 (17).

(1β,4β,7β,8β,9α)-3-Ethyl-1-methyl-3-azatricyclo[5.4.0.$0^{4,8}$]-undecan-9-ol 22b

1β,2α,6β,9α-9-Ethylamino-5α-dimethoxymethyl-5β-methylbicyclo[4.3.0]nonan-2-ol **21b** (0.35 g, 1.3 mmol) was treated with 5 M aqueous hydrochloric acid (3.5 ml) and the mixture was stirred at 25 °C for 1.75 h. 25% w/v Aqueous sodium hydroxide (4 ml) was added and the mixture was buffered to pH 5.5 with a freshly prepared citrate–phosphate buffer[33] (20 ml). After 3.5 h 1 M sodium cyanoborohydride in THF (2.58 ml, 2.58 mmol) was added dropwise over 5 min. The mixture was stirred for a further 1.5 h, basified to pH 12 with 2 M aqueous sodium hydroxide, and the product extracted into dichloromethane. The extracts were dried and concentrated to yield the *title compound* as a yellow solid (0.21 g, 82%); mp 58–65 °C (decomp.) (Found: M^+, 209.178. $C_{13}H_{23}NO$ requires: 209.178); ν_{max}(solution, $CHCl_3$)/m^{-1} 2796 (NCH); δ_H(400 MHz, $CDCl_3$) 0.69 (3H, s, 1-CH_3), 0.99 (3H, dd, *J* 7.1, 7.1, NCH_2CH_3), 1.21–1.36 (2H, m, 5-H_a, 11-H_a), 1.49–1.59 (4H, m, 6-H_2, 7-H, 11-H_b), 1.66–1.81 (2H, m, 5-H_b, 10-H_a), 1.85 (1H, m, 8-H), 1.90 (1H, dd, *J* 11.5, 2.3, 2-H_a), 2.23 (1H, m, NCH_aCH_3), 2.32 (1H, m, NCH_bCH_3), 2.38–2.49 (1H, m, 10-H_b), 2.42 (1H, d, *J* 11.5, 2-H_b), 3.36 (1H, dd, *J* 4.5, 4.5, 4-H), 3.96 (1H, ddd, *J* 10.5, 6.3, 6.3, 9-H); δ_C(100.6 MHz, $CDCl_3$) 12.7 (NCH_2CH_3), 21.2 (C-5), 24.2 (C-6), 25.8 (1-CH_3), 30.9 (C-10), 32.1 (C-1), 38.2 (C-11), 45.2 (C-7), 47.6 (C-8), 49.0 (NCH_2CH_3), 57.3 (C-2), 59.1 (C-4), 70.0 (C-9); *m*/*z* 209 (31%), 194 (51), 180 (100), 164 (10), 122 (29).

(1β,4β,7β,8β,9α)-9-Methoxy-1,3-dimethyl-3-azatricyclo-[5.4.0.$0^{4,8}$]undecane 23a

To a suspension of sodium hydride (0.10 g, 2.6 mmol) in tetrahydrofuran (6 ml) at 25 °C was added (1β,4β,7β,8β,9α)-1,3-dimethyl-3-azatricyclo[5.4.0.$0^{4,8}$]undecan-9-ol **22a** (0.05 g, 0.26 mmol). The mixture was heated to reflux for 30 min and methyl iodide (1.46 g, 10.2 mmol) was added cautiously. The mixture was heated to reflux for a further 5.5 h. After cooling to 25 °C, the mixture was partitioned between water and diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The combined extracts were dried and concentrated to yield the *title compound* as a yellow oil (25 mg, 47%) (Found: M^+, 209.174. $C_{13}H_{23}NO$ requires: 209.178); ν_{max}(liquid film)/cm^{-1} 2785 (NCH); δ_H(400 MHz, $CDCl_3$) 0.72 (3H, s, 1-CH_3), 1.17–1.42 (2H, m, 5-H_a, 11-H_a), 1.51, 1.65 (4H, m, 6-H_2, 7-H, 11-H_b), 1.73–1.84 (2H, m, 5-H_b, 10-H_a), 1.89–1.93 (2H, m, 8-H, 2-H_a), 2.08 (3H, s, NCH_3), 2.29 (1H, d, *J* 11.3, 2-H_b), 2.61 (1H, m, 10-H_b), 3.16 (1H, dd, *J* 4.3, 4.3, 4-H), 3.40 (3H, s, OCH_3), 3.58 (1H, ddd, *J* 11.0, 5.7, 5.7, 9-H); δ_C(100.6 MHz, $CDCl_3$) 20.5 (C-5), 24.2 (C-6), 25.8 (1-CH_3), 27.0 (C-10), 32.3 (C-1), 38.8 (C-11), 42.5 (NCH_3), 44.9, 45.2 (C-7, C-8), 56.1 (OCH_3), 59.7 (C-2), 60.8 (C-4), 79.9 (C-9); *m*/*z* 209 (15%), 180 (36), 178 (100), 136 (11).

(1β,4β,7β,8β,9α)-3-Ethyl-9-methoxy-1-methyl-3-azatricyclo-[5.4.0.0^{4,8}]undecane 23b

To a suspension of sodium hydride (0.20 g, 5.1 mmol) in tetrahydrofuran (12 ml) at 25 °C was added (1β,4β,7β,8β,9α)-3-ethyl-1-methyl-3-azatricyclo[5.4.0.0^{4,8}]undecan-9-ol **22b** (0.10 g, 0.48 mmol). The mixture was heated to reflux for 30 min and methyl iodide (1.46 g, 10.2 mmol) was added cautiously. The mixture was heated to reflux for a further 5.5 h. After cooling to 25 °C, the mixture was partitioned between water and diethyl ether. The aqueous layer was separated and extracted with diethyl ether. The combined ether extracts were dried and concentrated to yield the *title compound* as an orange oil (0.072 g, 67%) (Found: $(M - OCH_3)^+$, 192.174. $C_{13}H_{22}N$ requires: 192.175); ν_{max}(liquid film)/cm^{-1} 2813 (NCH); δ_H(400 MHz, $CDCl_3$) 0.71 (3H, s, 1-CH_3), 0.99 (3H, dd, *J* 7.1, 7.1, NCH_2CH_3), 1.17–1.34 (2H, m, 5-H_a, 11-H_a), 1.49–1.63 (4H, m, 6-H_2, 7-H, 11-H_b), 1.68–1.79 (2H, m, 5-H_b, 10-H_a), 1.82–1.89 (1H, m, 8-H), 1.84 (1H, dd, *J* 11.9, 2.8, 2-H_a), 2.12 (1H, dq, *J* 11.9, 7.1, NCH_aCH_3), 2.30 (1H, dq, *J* 11.9, 7.1, NCH_bCH_3), 2.39 (1H, d, *J* 11.2, 2-H_b), 2.68–2.75 (1H, m, 10-H_b), 3.25 (1H, dd, *J* 4.4, 4.4, 4-H), 3.38 (3H, s, OCH_3), 3.57 (1H, m, 9-H); δ_C(100.6 MHz, $CDCl_3$) 13.2 (NCH_2CH_3), 21.6 (C-5), 24.4 (C-6), 26.0 (1-CH_3), 27.2 (C-10), 32.3 (C-1), 39.0 (C-11), 45.0 (C-7), 46.1 (C-8), 49.0 (NCH_2CH_3), 56.1 (C-2), 57.2 (C-4), 59.5 (OCH_3), 80.2 (C-9); *m*/*z* 192 (5%), 165 (6), 123 (15).

3-[(1α,2β)-2-Dimethoxymethyl-2-methylcyclohex-5-enyl]propanal oxime 24

To a solution of 3-[(1*S*,2*R*)-2-dimethoxymethyl-2-methylcyclohex-5-enyl]propanal **16** (400 mg, 1.76 mmol) in pyridine (6 ml) at 25 °C was added *N*-hydroxylamine hydrochloride (488 mg, 7.04 mmol). After 2.5 h the mixture was concentrated *in vacuo* and the residue was partitioned between diethyl ether and water. The ether layer was separated and washed with aqueous sodium hydroxide, dried and concentrated. The product was subjected to column chromatography (solvent A, 4:1) to yield the *title compound* as a colourless oil (353 mg, 85%); (Found: $(M - OMe - H_2O)^+$, 192.138. $C_{12}H_{18}NO$ requires: 192.139); ν_{max}(liquid film)/cm^{-1} 3338 (OH), 1652 (C=C). δ_H(250 MHz, $CDCl_3$) 0.89, 0.90 (3H, 2 × s, 2′-CH_3), 1.07–1.50 (2H, m, CH_2), 1.66–1.90 (2H, m, CH_2), 1.96–2.22 (3H, m, CH, CH_2), 2.26–2.45 (2H, m, 1′-H, CH_2), 3.43, 3.44 (3H, 2 × s, $CH(OCH_3)_2$), 3.53, 3.54 (3H, 2 × s, $CH(OCH_3)_2$), 3.94, 3.95 (1H, 2 × s, $CH(OCH_3)_2$), 5.58–5.74 (2H, m, 5′-H, 6′-H), 6.79 (0.4H, br s, 0.4 × OH), 7.41 (0.6H, t, *J* 6.0, 0.6 × OH); δ_C(67.8 MHz, $CDCl_3$) 17.0, 17.1 (2′-CH_3), 22.1 (C-4′), 25.6, 25.7 (CH_2), 27.5, 27.8 (CH_2), 28.4 (CH_2), 36.8 (C-4), 40.5, 41.0 (C-1′), 41.2 (C-2′), 56.7 ($CH(OCH_3)_2$), 59.9 ($CH(OCH_3)_2$), 111.9 ($CH(OCH_3)_2$), 126.0, 128.8, 128.9 (2 × CH), 151.9 (C-1); *m*/*z* 192 (6%), 160 (6), 93 (14), 75 (100).

(1β,7β,11β)-8α-Dimethoxymethyl-8β-methyl-3-aza-2-oxatricyclo-[5.3.1.0^{4,11}]undec-3-ene 25‡

To a solution of 3-[(1*S*,2*R*)-dimethoxymethyl-2-methylcyclohex-5-enyl)propanal oxime **24** (346 mg, 1.43 mmol) in methanol (12 ml) at 25 °C was added chloramine-T (359 mg, 1.58 mmol). The mixture was refluxed for 4.5 h then concentrated *in vacuo*. The residue was partitioned between diethyl ether and water. The ether layer was separated and washed with aqueous sodium hydroxide, dried and concentrated. The product was subjected to column chromatography (solvent A, 2:3) to yield the *title compound* as a yellow oil (132 mg, 39%); (Found: $(M - MeOH)^+$, 207.127. $C_{12}H_{17}NO_2$ requires: 207.126); δ_H(250 MHz, $CDCl_3$) 0.83 (3H, s, 8-CH_3), 1.12–1.22 (1H, m, CH), 1.27–1.39 (1H, m, CH), 1.57–1.81 (3H, m, CH, CH_2), 1.91–2.03 (1H, m, CH), 2.08–2.34 (2H, m, CH_2), 2.46 (1H, dd, *J* 6.4, 6.8, CH), 3.38 (3H, s, $CH(OCH_3)_2$), 3.46 (3H, s, $CH(OCH_3)_2$), 3.68 (1H, t, *J* 11.1, 11-H), 3.79 (1H, s, $CH(OCH_3)_2$), 4.66 (1H, ddd, *J* 11.1, 7.4, 3.5, 1-H); δ_C(67.8 MHz, $CDCl_3$) 19.6 (8-CH_3), 23.2 (CH_2), 23.3 (CH_2), 24.1 (CH_2), 27.4 (CH_2), 36.1 (C-7), 37.8 (C-8), 50.5 (C-1), 57.0 ($CH(OCH_3)_2$), 59.8 ($CH(OCH_3)_2$), 77.0 (C-11), 111.5 ($CH(OCH_3)_2$), 167.3 (C-4); *m*/*z* 196 (2%), 178 (25), 167 (10), 150 (21), 126 (17), 75 (100).

(1β,2α,6β,9α)-9-Amino-3α-dimethoxymethyl-3β-methylbicyclo-[5.4.0]nonan-2-ol 26

To a solution of (1β,7β,11β)-8α-dimethoxymethyl-8β-methyl-3-aza-2-oxatricyclo[5.3.1.0^{4,11}]undec-3-ene **25** (120 mg, 0.50 mmol) in methanol (10 ml) at 25 °C was added nickel chloride hexahydrate (238 mg, 1.0 mmol). The mixture was cooled to 0 °C and sodium borohydride (95 mg, 2.5 mmol) was added portionwise, the mixture turned black and evolution of gas was observed. The mixture was stirred at 0 °C for 3 h, the solvent was removed *in vacuo* and the residue was dissolved in dichloromethane (12 ml) and conc. aqueous ammonia (12 ml). The mixture was stirred for a further 2 h and the two layers were separated. The aqueous layer was extracted with dichloromethane and the combined dichloromethane extracts were dried and concentrated to yield the *title compound* as unstable orange crystals (54 mg, 45%) (Found: $(M - Me)^+$, 228.160. $C_{12}H_{22}NO_3$ requires: 228.160); ν_{max}(solution, $CHCl_3$)/cm^{-1} 3372 (OH, NH); δ_H(250 MHz, $CDCl_3$) 0.93 (3H, s, 5-CH_3), 1.20 (1H, m, 4-H_a), 1.34–1.50 (2H, m, 7-H_a, 8-H_a), 1.63–1.76 (4H, m, 3-H_2, 4-H_b, 6-H), 1.85–2.05 (3H, m, 1-H, 7-H_b, 8-H_b), 3.41 (3H, s, $CH(OCH_3)_2$), 3.52 (3H, s, $CH(OCH_3)_2$), 3.58–3.62 (1H, m, 9-H), 3.84 (1H, s, $CH(OCH_3)_2$), 4.01 (1H, br m, 1-H); *m*/*z* 228 (3%), 212 (5), 211 (12), 75 (100).

X-Ray study of compound 20a

Crystal data. Data were collected from a single crystal (colourless plate, 0.37 × 0.21 × 0.06 mm) of the tricycle **20a**, using an Enraf-Nonius CAD4 diffractometer and Ni-filtered Cu-Kα radiation. *Crystal data*: monoclinic, space group $P2_1/c$, $a = 9.397(1)$, $b = 12.089(1)$, $c = 13.052(2)$ Å, $\beta = 105.40(1)°$, $U = 1429.5(3)$ Å^3, $Z = 4$, $D_x = 1.19$ g cm^{-3}, $\bar{\lambda} = 1.54178$ Å, $\mu = 6.6$ cm^{-1}. 2172 Reflections (1464 unique, 688 observed with $I > 2\sigma(I)$) were measured by $2\theta/\omega$ scan, $\theta \leq 50°$, 27.4% loss of standard reflection intensities was noted during the data collection.

Solution and refinement. The structure was solved by direct methods using SHELXS-86[12a] and refined by full-matrix least-squares methods (9 outer non-H atoms anisotropic, the rest isotropic, all H atoms 'riding') with SHELXL-93[12b] programs; an empirical extinction correction was applied.[13] The refinement converged at $R = 0.055$; residual features in the difference Fourier map ranged from 0.22 to −0.19 e Å^{-3}.

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 207/259.

‡ The correct IUPAC name for this compound is (4β,8β,11β)-7α-dimethoxymethyl-7β-methyl-2-aza-3-oxatricyclo[6.2.1.0^{4,11}]undec-1-ene.

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