Synthesis of C-D-ring analogues of the azasteroid A25822

Andrew J. Sutherland,[a] James K. Sutherland[a,*] and Patrick J. Crowley[b]

[a] *Chemistry Department, Victoria University of Manchester M13 9PL, UK*
[b] *Zeneca Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY, UK*

The α,β-unsaturated imines 2 and 4 were synthesised from 2,3,6-trimethylcyclohex-2-enone.

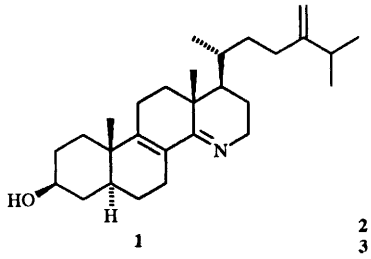
Introduction

Our previous work [1] on analogues of the antifungal azasteroids **1** [2] suggested that rings A and B might not be necessary for biological activity so we set out to prepare some analogues of the azasteroids with general structure **2**.

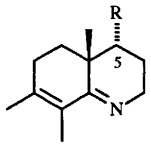
Results and discussion

The readily available enone **6** [3] was the chosen starting material. Our first objective was to synthesise the imine **3** *via* the dione **7**; however, attempts to effect Michael addition of the Li–Cu enolate of enone **6** to *trans*-but-2-enal led to 1,2 addition to the aldehyde. The trimethylsilyl enol ether of **6** reacted with $TiCl_4$ and *trans*-but-2-enal [4] in a similar way, while replacement of butenal with its dimethylacetal [5] did not give a reaction. We then examined alkylation of **6**; reaction with allyl bromide–$LiNPr^i_2$–$(Me_2N)_3PO$ (HMPA) gave the allyl enone **8** (88%). Attempts to aminate [6] the allyl double bond by direct substitution of a borane intermediate were unsuccessful, but hydroboration and oxidation gave the alcohol **9** (63%) which was mesylated (76%) and then converted into the azide **10** (71%). Reduction of **10** with H_2–Lindlar catalyst or Ph_3P [7] gave only traces of the imine **2**, but H_2–Wilkinson's catalyst formed the imine **2** (30%, improved to 70% in the presence of 2 mol dm^{-3} HCl). The crystalline imine showed a shift in its UV absorption from 234 nm to 271 nm on acidification characteristic of α,β-unsaturated imines and gave ^{1}H NMR signals at δ 3.55 (1 H, ddd, *J* 18, 10.5 and 5.6) and 3.91 (1 H, dd, *J* 18 and 5.6). Reaction of the imine **2** with $NaBH_4$ converted it into the allylamine **21** (R = H).

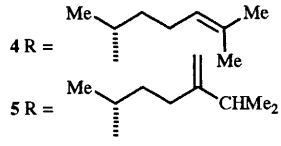
We now turned to preparing analogues with steroidal sidechains. From our previous work it was clear that a route involving Michael addition of the enolate of the ketone **6** to α,β-unsaturated aldehydes was unlikely to succeed. Alkylation of the ketone **6** with secondary allylic halides was unattractive due to difficulties in preparing and alkylating with such halides, so we decided to examine an approach using Michael addition of the enolate of **6** to α,β-unsaturated esters or nitriles despite anticipated problems with selective reduction later in the scheme. Ethyl (*E*)-4,7-dimethylocta-2,6-dienoate and a mixture of the *Z* and *E* related nitriles were prepared by Wittig condensation with 2,6-dimethylhept-5-enal, but no addition product was isolated on reaction with the enolate ($LiNPr^i_2$) of **6**, though isomerisation of the recovered ester suggested that an addition–elimination reaction was occurring. Our first attempt to prepare the more reactive ester **16** by Knovenagel condensation of 2,6-dimethylhept-5-enal with ethyl cyanoacetate gave four products (three of them inseparable); all were isomeric with the expected product **16**, but the mixture gave a ^{1}H NMR spectrum consistent with the three isomers of the cyclopentane **17** arising from an ene reaction of the ester **16**. The UV, IR and ^{1}H NMR spectra of the minor product were in accord with structure **18** derived by an intramolecular Diels–

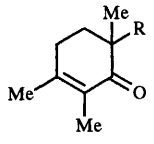


1



2 R = H
3 R = Me

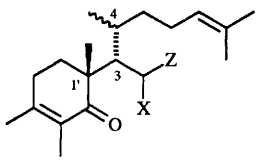




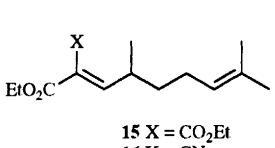
6 R=H
7 R= $CHMeCH_2CHO$
8 R= $CH_2CH{=}CH_2$
9 R= $(CH_2)_3OH$
10 R= $(CH_2)_3N_3$

Alder reaction of **16**; particularly significant was the presence of the EtO function in the absence of an ester absorption. By lowering the temperature of the reaction the required ester **16** could be obtained (68%) as a single isomer; that the nitrile was *cis* to the alkyl chain followed from ^{13}C–^1H coupling constants for the 3-H vinyl proton of 6 Hz to the *C*=O of the ester and 13.5 Hz to the *C*N. In addition a heteronuclear NOE was observed between 3-H and the *C*=O of the ester. Similar condensation of 2,6-dimethylhept-5-enal with diethyl malonate gave the ester **15** (59%). Reaction of the enolate of **6** with the esters **15** and **16** gave the adducts **11** (50%) and **12** (78%) as the expected mixtures of isomers. Deethoxycarbonylation of the nitrile **12** was achieved using Me_2SO–NaCl–water [8] to give nitrile **14** (84%); reaction of the ester **11** under similar conditions gave ester **13** (26%, improved to 68% by substitution of LiCl for NaCl). GLC of the nitrile **14** showed two peaks in a 75:25 ratio which constituted 95% of the product while the other spectroscopic evidence supported the proposed constitution, ν_{max} 2240, 1660 and 1640 cm^{-1} and ^{1}H NMR singlets at 1.10 (angular methyl), 1.75 and 1.90 (methyls on cyclohexenone ring), and 1.60, 1.62 and 1.70 (methyls on side-chain double bond). While it is by no means proven, precedent [9] suggests that the major products have the same relative stereochemistry at C-3 and C-1′, which is that indicated, and differ in the stereochemistry of the 4-methyl.

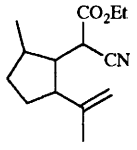
Many reducing agents were investigated in attempts to



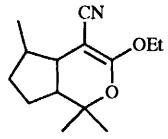
11 X = Z = CO_2Et
12 X = CN, Z = CO_2Et
13 X = CO_2Et, Z = H
14 X = CN, Z = H



15 X = CO_2Et
16 X = CN

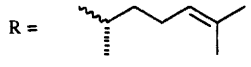


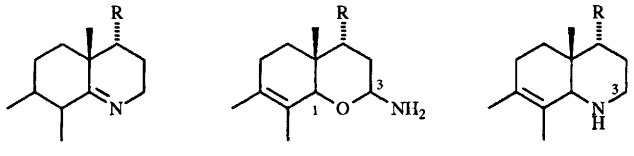
17



18

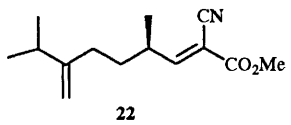
generate the imine **4** from the nitrile **14**. Few notable results were obtained; reduction with $LiAlH_4$ at −78 °C gave a tetrahydro derivative formulated as **19** (28%) due to the appearance in the ^1H NMR spectrum of additional secondary methyl signals and two one proton multiplets (δ 3.32 and 3.83) and the disappearance of the cyclohexene methyl signals. Reduction of **14** with Bu^i_2AlH (DIBAL) took a different course giving a compound formulated as the α-amino ether **20** (31%); the ^1H NMR spectrum showed additional one proton signals at δ 3.15 and 4.05 ascribed to 1-H and 3-H. Acylation with an excess of Ac_2O–pyridine gave a monoacetyl derivative which was an amide (ν_{max} 1665 cm $^{-1}$). In general cobalt compounds show greater Lewis acidity for nitrogen over oxygen and in the hope of achieving selective activation of the nitrile in compound **14** it was reduced with $NaBH_4$–$CoCl_2$·$6H_2O$. In initial experiments two inseparable isomeric compounds were formed (67%). In the ^1H NMR spectrum signals were present at δ 3.15 and 3.25 showing identical J values of 13, 4 and 1.5 Hz, consistent with the equatorial C-3 hydrogens of **21**. When the reduction was carried out using less $NaBH_4$ a product was isolated (27%) in addition to unreacted **14** and the amine **21**. This mixture of isomers gave a mass spectrum anticipated for the imines **4** and also exhibited the characteristic shift of λ_{max} from 238 nm in neutral solution to 273 nm on acidification. The ^1H NMR spectrum showed the presence of the expected olefinic methyl (× 4), angular methyl (× 1) and secondary methyl (× 1) signals; in addition to the vinylic hydrogen there were single hydrogen multiplets at δ 3.60 and 3.83 consistent with the absorptions anticipated for the C-3 methylene group of **4**.



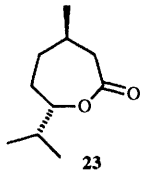


19 **20** **21**

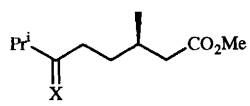
We also attempted to prepare the nitrile **22** which could be the precursor for the analogue **5** with the C_1 alkylated steroid side-chain found in the natural products. The starting material was the Baeyer–Villiger oxidation product **23**[10] of (−)-menthone which was methanolised to the ester **24** (87%) and then oxidised with Jones' reagent to the ketone **25** (89%). Wittig reaction of **25** with Ph_3PCH_2 gave the alkene **26** in poor yield (31%); this was improved to 72% using the reagents CH_2I_2–Zn–$TiCl_4$.[11] A variety of oxalylation methods failed to convert **26** into the keto ester **31** so a lengthier route to **31** was adopted. $LiAlH_4$ reduction of **26** gave alcohol **27** which was oxidised to aldehyde **28**. Condensation of **28** with $LiC(SMe)_3$[12] yielded **29** which reacted with $AgNO_3$–Ag_2O–MeOH[13] to form the ester **30**. MnO_2 oxidation of **30** gave the keto ester **31**. Reaction of **31** with KCN–AcOH gave the unstable cyanohydrin **32** but all attempts to dehydrate it to the nitrile **22** met with failure.



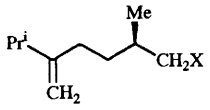
22



23



24 X = H,OH
25 X = O
26 X = CH_2



27 X = CH_2OH
28 X = CHO
29 X = $CH(OH)C(SMe)_3$
30 X = $CH(OH)CO_2Me$
31 X = $COCO_2Me$
32 X = $C(OH)CO_2Me$
CN

Experimental

All ^1H NMR spectra were measured in $CDCl_3$ at 300 MHz using a Bruker AC300 spectrometer and UV spectra in EtOH using a Shimadzu UV–VIS instrument. J Values are in Hz. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. Low resolution mass spectra were measured on a Kratos MS25 instrument in the EI and CI modes, the latter with NH_3 as carrier gas. Accurate mass measurements were determined using a Kratos MS30 instrument with a DS55 data system and IR spectra as thin films using a Perkin-Elmer 1710 FT IR spectrometer. The term 'work-up' implies washing the organic extract with brine, drying the solution with $MgSO_4$, filtration and concentration of the extract under reduced pressure. Light petroleum refers to the distillation fraction bp 40–60 °C.

6-Allyl-2,3,6-trimethylcyclohex-2-en-1-one 8

BuLi (1.5 mol dm^{-3} in cyclohexane, 3.1 cm^3) was added to Pr^i_2NH (0.65 cm^3) and HMPA (0.05 cm^3) in tetrahydrofuran (THF) at −78 °C, the temp. of the mixture was raised to 0 °C and then cooled to −78 °C. The enone **6** (0.59 g) was added, the mixture stirred for 20 min and then allyl bromide (0.62 g) was added. After 1 h at −78 °C, the mixture was allowed to rise to ambient temperature, poured into 2 mol dm^{-3} HCl, extracted with Et_2O (3 × 50 cm^3) and worked up to give the ketone **8** as an oil (0.668 g, 88%), ν_{max}/cm^{-1} 1660 and 1640; δ_H 5.72 (1 H, m), 5.05 (2 H, m), 1.90 (3 H, s), 1.76 (3 H, s) and 1.05 (3 H, s); m/z (EI) 178.

6-(3'-Hydroxypropyl)-2,3,6-trimethylcyclohex-2-en-1-one 9

The alkene **8** (0.453 g) was dissolved in THF at 0 °C and 9-borabicyclo[3.3.1]nonane (0.5 mol dm^{-3} in THF; 6.1 cm^3) added. After 15 min the temp. of the mixture was raised to 20 °C for 1 h and then cooled to 0 °C, when NaOH (1 mol dm^{-3}; 3.05 cm^3) and H_2O_2 (100 vol.; 13.05 cm^3) were added. After 30 min the mixture was extracted with Et_2O (3 × 50 cm^3). Work-up gave an oil which was chromatographed on silica gel 60 (EtOAc–light petroleum; 1:4) to give recovered starting material (0.195 g) and the *alcohol* **9** as an oil (0.25 g, 50%), ν_{max}/cm^{-1} 3440, 1660 and 1640; δ_H 3.60 (2 H, t, J 6), 1.90 (3 H, s), 1.75 (3 H, s) and 1.05 (3 H, s); m/z (EI) 196 (Found: M^+, 196.1457. $C_{12}H_{20}O_2$ requires M, 196.1462).

6-(3'-Methanesulfonyloxypropyl)-2,3,6-trimethylcyclohex-2-en-1-one

$MeSO_2Cl$ (0.36 cm^3) was added dropwise to the alcohol **9** (0.452 g) dissolved in CH_2Cl_2 (10 cm^3) and the solution cooled

to 0 °C under N_2. Et_3N (0.96 cm^3) was then added dropwise and the mixture stirred at 0 °C for 30 min. The mixture was poured into saturated aq. NH_4Cl (25 cm^3) and extracted with CH_2Cl_2 (2 × 25 cm^3). Work-up gave an oil (0.740 g, 76%) which was purified by dry column chromatography on silica gel 60H (EtOAc–light petroleum; 1:3) to give the *mesylate* as an oil (0.480 g), ν_{max}/cm^{-1} 1660 and 1640; δ_H 1.05 (3 H, s), 1.75 (3 H, s), 1.9 (3 H, s), 3.0 (3 H, s) and 4.2 (2 H, m); *m/z* (CI) 275 (Found: M^+, 274.1227. $C_{13}H_{22}SO_4$ requires *M*, 274.1239).

6-(3′-Azidopropyl)-2,3,6-trimethylcyclohex-2-en-1-one 10

NaN_3 (0.5 g) was added to the above mesylate (0.053 g) dissolved in a mixture of Me_2NCHO (5 cm^3) and water (0.5 cm^3). After it was stirred for 16 h, the mixture was poured into water (10 cm^3) and extracted with Et_2O (2 × 25 cm^3) to give an oil (0.035 g) which was purified by flash column chromatography on silica gel 60H (EtOAc–light petroleum; 1:4) to furnish the *azide* **10** as an oil (0.030 g, 71%), ν_{max}/cm^{-1} 2095, 1660 and 1640; δ_H 1.05 (3 H, s), 1.75 (3 H, s), 1.9 (3 H, s) and 3.25 (2 H, t, *J* 6); *m/z* (CI) 222 (Found: M^+, 221.1515. $C_{12}H_{19}N_3O$ requires *M*, 221.1528).

6,9,10-Trimethyl-2-azabicyclo[4.4.0]deca-1,9-diene 2

The azide **10** (0.415 g) was dissolved in MeOH (20 cm^3) and Wilkinson's catalyst (0.02 g) was added. The flask was evacuated and flushed several times with H_2 after which the solution was stirred vigorously at room temp. for 1 h. The flask was then evacuated, flushed several times with N_2 and HCl (2 mol dm^{-3}, 3 drops) added. The flask was again evacuated and flushed several times with H_2. After stirring the solution at room temperature for 30 min, the flask was evacuated and flushed with N_2 several times. The reaction mixture was poured into HCl (2 mol dm^{-3}; 50 cm^3) and Et_2O (50 cm^3). After a further extraction with HCl (50 cm^3) the combined aqueous phases were basified by the addition of solid NaOH. Extraction with Et_2O (50 cm^3) and work-up gave an oil, which was purified by flash chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 1:20 to 1:0) to furnish the *imine* **2** as a colourless oil (0.234 g, 70%). Distillation at reduced pressure gave a white solid which decomposed readily when exposed to the air and so was stored under Ar at −20 °C, mp 39–43 °C, bp 70–75 °C/0.2 mmHg; λ_{max}/nm 234, changed to 271 upon addition of acid; ν_{max}/cm^{-1} 1650 and 1620; δ_H 1.05 (3 H, s), 1.5 (6 H, m), 1.8 (6 H, s), 2.05 (1 H, m), 2.42 (1 H, m), 3.50 (1 H, ddd, *J* 5.6, 10.5, 18) and 3.92 (1 H, dd, *J* 5.6, 18); *m/z* (EI) 177, (CI) 178 (Found: M^+, 177.1513. $C_{12}H_{19}N$ requires *M*, 177.1517).

6,9,10-Trimethyl-2-azabicyclo[4.4.0]dec-9-ene

$NaBH_4$ (0.3 g) was added to a solution of imine **2** (0.141 g) in EtOH (15 cm^3) and the mixture was stirred at room temp. for 20 min, after which it was poured into water (50 cm^3) and Et_2O (50 cm^3). After further extraction with Et_2O (50 cm^3) work-up gave a colourless oil (0.121 g) which was purified by flash chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 1:2 to 1:0) to give the *amine* **21** (R = H) as a colourless oil (0.070 g, 49%), ν_{max}/cm^{-1} 3300; δ_H 0.85 (3 H, s), 1.75 (3 H, s), 2.63 (1 H, dt, *J* 5, 13) and 3.20 (1 H, dd, *J* 4, 13); *m/z* (EI) 179, (CI) 180 (Found: M^+, 178.1607. $C_{12}H_{21}N - H$ requires *M*, 178.1596).

Ethyl 2-cyano-4,8-dimethylnona-2,7-dienoate 16

Piperidine (1.69 cm^3) was dissolved in toluene (100 cm^3) and the solution (containing 4 Å molecular sieves) stirred at room temp. AcOH (0.97 cm^3) was added dropwise and the mixture stirred for 10 min. Ethyl cyanoacetate (6.05 cm^3) and 2,6-dimethylhept-5-enal (9.0 cm^3) were added and the mixture warmed to 80 °C for 1 h. The orange reaction mixture was cooled to room temp. and filtered through a pad of silica gel. The filtrate was evaporated under reduced pressure to yield the crude product as an orange oil (10.04 g) which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; 3:97) to furnish the *nitrile-ester* **16** as a pale yellow oil (9.66 g, 68%), bp 150–155 °C/0.5 mmHg; ν_{max}/cm^{-1} 2232, 1733 and 1625; δ_H 1.26 (3 H, d, *J* 7), 1.40 (3 H, t, *J* 7), 1.67 (3 H, s), 1.76 (3 H, s), 2.10 (2 H, q, *J* 7), 2.85 (1 H, m), 4.38 (2 H, q, *J* 7), 5.20 (1 H, tt, *J* 1.5 and 7) and 7.61 (1 H, d, *J* 11); $\delta_C(CD_3COCD_3)$ 14.21, 17.67, 19.35, 25.69, 26.46, 36.50, 37.49, 62.66, 109.12, 114.15, 124.29, 132.74, 161.77 and 168.70; *m/z* (EI) 235, (CI) 253 and 236 (Found: M^+, 235.1582. $C_{14}H_{21}NO_2$ requires *M*, 235.1572).

Cyclisation of the nitrile 16

The reaction was carried out as above using ethyl cyanoacetate (0.2 cm^3) and 2,6-dimethylhept-5-enal (0.28 cm^3) except that the mixture was boiled under reflux for 16 h. The orange reaction mixture was cooled to room temperature, poured into HCl (2 mol dm^{-3}; 50 cm^3) and extracted with PhMe (2 × 50 cm^3). Work-up gave an orange oil (0.266 g), which was separated by chromatography on silica gel 60 into the *orthoester* **18** (0.012 g, 3%), λ_{max}/nm 238; ν_{max}/cm^{-1} 2200 and 1630; δ_H 1.03 (3 H, d, *J* 6.75), 1.29 (3 H, t, *J* 7), 1.33 (3 H, s), 1.35 (3 H, s), 1.40 (1 H, m), 1.60 (1 H, br s), 1.75 (1 H, m), 1.97 (1 H, m), 2.11 (1 H, m), 2.27 (1 H, m), 2.40 (1 H, dd, *J* 1.5 and 6.75) and 4.11 (2 H, dq, *J* 2 and 7); *m/z* (EI) 235, (CI) 253 and 236 (Found: M^+, 235.1575. $C_{14}H_{21}NO_2$ requires *M*, 235.1572) and the three (8:1:1) isomeric cyclic *nitrile esters* **17** (0.218 g, 53%), ν_{max}/cm^{-1} 2250, 1745 and 1645; *m/z* (EI) 235, (CI) 253 (Found: M^+, 235.1580. $C_{14}H_{21}NO_2$ requires *M*, 235.1572); δ_H(isomer A) 0.98 (3 H, d, *J* 6), 1.33 (3 H, t, *J* 6.75), 1.71 (3 H, s), 3.64 (1 H, d, *J* 3), 4.26 (2 H, q, *J* 7) and 4.81 (2 H, br s); (isomer B) 1.08 (3 H, d, *J* 6), 1.30 (3 H, t, *J* 7), 1.65 (3 H, s), 3.65 (1 H, d, *J* 3), 4.14 (2 H, q, *J* 7), 4.69 (1 H, t, *J* 1.5) and 4.78 (1 H, s); (isomer C) 1.08 (3 H, d, *J* 6), 1.32 (3 H, t, *J* 6.75), 1.7 (3 H, s), 3.36 (1 H, d, *J* 3.5), 4.24 (2 H, q, *J* 7), 4.94 (1 H, s) and 5.01 (1 H, s).

Ethyl 2-ethoxycarbonyl-4,8-dimethylnona-2,7-dienoate 15

A mixture of piperidine (1.10 cm^3) and AcOH (0.63 cm^3) was dissolved in toluene (50 cm^3) containing 4 Å molecular sieves. After 10 min diethyl malonate (6.66 cm^3) and 2,6-dimethylhept-5-enal (7.0 cm^3) were added and the mixture warmed at 80 °C for 1 h. The orange reaction mixture was cooled to room temp., poured into HCl (2 mol dm^{-3}; 100 cm^3) and extracted with Et_2O (1 × 200 and 1 × 100 cm^3). Work-up gave an orange oil (11.45 g) which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 3:97 to 5:95) to furnish the *diethyl ester* **15** as an oil (7.335 g, 59%), ν_{max}/cm^{-1} 1720 and 1640; δ_H 1.05 (3 H, d, *J* 7), 1.30 (6 H, br t, *J* 7), 1.42 (2 H, t, *J* 7), 1.55 (3 H, s), 1.65 (3 H, s), 1.93 (2 H, q, *J* 7), 2.58 (1 H, br dd, *J* 7 and 11), 4.28 (4 H, dq, *J* 7), 5.05 (1 H, br t) and 6.75 (1 H, d, *J* 11); *m/z* (CI) 300 and 283 (Found: M^+, 283.1906. $C_{16}H_{26}O_4$ + H requires *M*, 283.1909).

Ethyl 2-cyano-4,8-dimethyl-3-(1′,3′,4′-trimethyl-2′-oxocyclohex-3′-enyl)non-7-enoate 12

The Li enolate of 2,3,6-trimethylcyclohex-2-en-1-one (4.95 g) was prepared as before and after 15 min at −78 °C the nitrile ester **16** (8.9 g) was added dropwise. The orange solution was stirred at −78 °C for 30 min, after which it was warmed to room temp., poured into HCl (2 mol dm^{-3}; 200 cm^3) and extracted with Et_2O (1 × 200 and 1 × 100 cm^3). Work-up gave an orange oil (12.73 g), which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 1:9 to 2:8) to give the *nitrile esters* **12** as an oil (10.59 g, 78%). The product was an inseparable mixture of isomers, ν_{max}/cm^{-1} 2260, 1745, 1665 and 1640; δ_H 1.65 (3 H, s), 1.68 (3 H, s), 1.75 (3 H, s), 1.9 (3 H, s), 2.03 (2 H, m), 4.28 (2 H, m) and 5.05 (1 H, m); *m/z* (EI) 373, (CI) 391 and 374 (Found: M^+, 373.2627. $C_{23}H_{35}NO_3$ requires *M*, 373.2617).

Ethyl 2-ethoxycarbonyl-4,8-dimethyl-3-(1′,3′,4′-trimethyl-2′-oxocyclohex-3′-enyl)non-7-enoate 11

The Li enolate of 2,3,6-trimethylcyclohex-2-en-1-one (2.87 g) was prepared as before and after 15 min at −78 °C the ester **15**

(5.86 g) was added. The orange solution was stirred at −78 °C for 30 min, after which it was warmed to room temp., poured into HCl (2 mol dm^{-3}; 200 cm^3) and extracted with Et_2O (1 × 200 and 1 × 100 cm^3). Work-up gave an oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution; 5:95) to give *diester* **11** as an oil (4.33 g, 50%), ν_{max}/cm^{-1} 1760, 1730, 1660 and 1640; δ_H 1.05 (3 H, s), 1.75 (3 H, s), 1.88 (3 H, s), 3.22 (1 H, t, *J* 5.5), 3.63 (1 H, d, *J* 5.5), 4.20 (4 H, m) and 5.05 (1 H, m); *m/z* (EI) 420, (CI) 421 (Found: M^+, 420.2877. $C_{25}H_{40}O_5$ requires *M*, 420.2876).

4,8-Dimethyl-3-(1′,3′,4′-trimethyl-2′-oxocyclohex-3′-enyl)non-7-enenitrile 14

To a solution of nitrile ester **12** (10.59 g) in Me_2SO (120 cm^3) was added NaCl (0.585 g) in water (1 cm^3) and the mixture was heated at 150 °C for 1 h. The resultant orange solution was cooled to room temp., poured into brine (200 cm^3) and extracted with Et_2O (1 × 200 and 1 × 100 cm^3). Work-up gave a yellow oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; 1:9) to give the *nitrile* **14** as an oil (7.19 g, 84%), ν_{max}/cm^{-1} 2240, 1660 and 1640; δ_H 0.93 (3 H, d, *J* 7.3), 1.00 (2 H, m), 1.10 (3 H, s), 1.60 (3 H, d), 1.70 (3 H, s), 1.75 (3 H, s), 1.90 (3 H, s) and 5.09 (1 H, m); *m/z* (EI) 301 (Found: M^+, 301.2403. $C_{20}H_{31}NO$ requires *M*, 301.2406).

Ethyl 4,8-dimethyl-3-(1′,3′,4′-trimethyl-2′-oxocyclohex-3′-enyl)-non-7-enoate 13

Diester **11** (1.925 g) was dissolved in a mixture of Me_2SO (10 cm^3) and water (0.1 cm^3) containing LiCl (0.389 g) and the mixture heated to 150 °C for 1 h. The stirred mixture was heated under reflux for 3 h. The resultant orange solution was cooled to room temp., poured into brine (100 cm^3) and extracted with EtOAc (2 × 100 cm^3). Work-up gave an oil which was purified by distillation to give the *ester* **13** (1.08 g, 68%), bp 180–185 °C/0.3 mmHg; ν_{max}/cm^{-1} 1735, 1660 and 1640; δ_H 0.83 (3 H, m), 1.22 (3 H, t, *J* 7.5), 1.58 (3 H, s), 1.67 (3 H, s), 1.71 (3 H, s), 1.88 (3 H, s), 2.53 (1 H, t, *J* 6.75), 4.12 (2 H, q, *J* 7.5) and 5.06 (1 H, m); δ_C 11.49, 14.12, 17.59, 20.20, 20.84, 21.20, 25.58, 26.37, 29.12, 30.35, 30.61, 33.07, 33.23, 42.55, 47.59, 60.10, 124.26, 129.48, 131.43, 151.42, 173.88 and 202.65; *m/z* (EI) 348, (CI) 366 and 349 (Found: M^+, 348.2670. $C_{22}H_{36}O_3$ requires *M*, 348.2664).

3-Amino-6,9,10-trimethyl-5-(6-methylhept-5-en-2-yl)-2-oxabicyclo[4.4.0]deca-9-ene 20

DIBAL (1.5 mol dm^{-3} in toluene; 0.33 cm^3) was added dropwise to the nitrile **14** (0.050 g) in THF (10 cm^3) stirred at −78 °C under N_2. After 20 min a further aliquot of Bu^i_2AlH (0.3 cm^3) was added and the mixture stirred for 1 h at −78 °C and then at room temp. for 16 h. The mixture was poured into brine (50 cm^3) and extracted with Et_2O (2 × 50 cm^3). Work-up gave an oil (0.048 g) which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 0:10 to 10:0) to give the *amine* **20** as an oil (0.015 g, 31%), ν_{max}/cm^{-1} 3385 and 3325; δ_H 1.52 (3 H, s), 1.57 (3 H, s), 1.60 (3 H, s), 1.65 (3 H, s), 3.15 (1 H, m), 4.05 (1 H, m) and 5.10 (1 H, t, *J* 5.4); *m/z* (EI) 305 and 304, (CI) 306 (Found: M^+, 305.2726. $C_{20}H_{35}NO$ requires *M*, 305.2719). Acetylation with Ac_2O–pyridine–4-(dimethylamino)pyridine gave an oily amide, ν_{max}/cm^{-1} 3295 and 1665; *m/z* (EI) 347, (CI) 365 and 348 (Found: M^+, 347.2823. $C_{22}H_{37}NO_2$ requires *M*, 347.2824).

6,9,10-Trimethyl-5-(6-methylhept-5-en-2-yl)-2-azabicyclo-[4.4.0]deca-1-ene 19

$LiAlH_4$ (1 mol dm^{-3} in THF; 1.12 cm^3) was added dropwise to the nitrile **14** (0.049 g) in THF (10 cm^3) at 0 °C under N_2. After 1 h saturated aq. potassium sodium tartrate (10 cm^3) was added dropwise and the mixture extracted with Et_2O (2 × 50 cm^3). Work-up gave an oil (0.042 g) which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 5:95 to 0:1) to give the *imine* **19** (0.018 g, 28%), ν_{max}/cm^{-1} 1650; δ_H 0.80 (3 H, d, *J* 7.3), 0.93 (3 H, d, *J* 7.3), 0.98 (3 H, d, *J* 7.3), 1.15 (3 H, s), 1.60 (3 H, s), 1.70 (3 H, s), 1.98 (2 H, q, *J* 7.3), 2.28 (1 H, m), 3.33 (1 H, m), 3.83 (1 H, m) and 5.10 (1 H, t, *J* 4); *m/z* (EI) 289, (CI) 308 and 290 (Found: M^+, 289.2763. $C_{20}H_{35}N$ requires *M*, 289.2769).

6,9,10-Trimethyl-5-(6-methylhept-5-en-2-yl)-2-azabicyclo-[4.4.0]deca-9-ene 21

Nitrile **14** (0.102 g) was dissolved in MeOH (10 cm^3) and $CoCl_2 \cdot 6H_2O$ (0.162 g) was added. After 15 min $NaBH_4$ (0.128 g) was added to the purple solution which effervesced and turned black. The mixture was stirred overnight and then similar quantities of $NaBH_4$ and $CoCl_2 \cdot 6H_2O$ were added. After 1 h the mixture was poured into water (50 cm^3) and extracted with Et_2O (2 × 50 cm^3). Work-up gave an oil (0.042 g) which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 5:95 to 0:1) to give the *amines* **21** (0.065 g, 67%), *m/z* (EI) 289 (Found: M^+, 289.2763. $C_{20}H_{35}N$ requires *M*, 289.2770); δ_H 0.80 (3 H, d, *J* 6), 0.86 (3 H, s), 1.58 (3 H, s), 1.61 (3 H, s), 1.69 (3 H, s), 1.72 (3 H, s), 2.37 (1 H, m), 2.60 (1 H, m) and 5.11 (1 H, m); in addition there were signals at 3.15 (1 H, ddd, *J* 1.5, 4 and 13) and 3.25 (1 H, ddd, *J* 1.5, 4 and 13) for the individual isomers.

6,9,10-Trimethyl-5-(6-methylhept-5-en-2-yl)-2-azabicyclo-[4.4.0]deca-1,9-diene 4

Nitrile **14** (0.075 g) was dissolved in EtOH (8 cm^3) and $CoCl_2 \cdot 6H_2O$ (0.059 g) was added at 0 °C. After 15 min $NaBH_4$ (0.025 g) was added to the purple solution which effervesced and turned black. The mixture was stirred overnight and then similar quantities of $NaBH_4$ and $CoCl_2 \cdot 6H_2O$ were added. After 15 min the mixture was poured into saturated aq. potassium sodium tartrate (50 cm^3) and extracted with Et_2O (2 × 50 cm). Work-up gave an oil (0.063 g) which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 1:3 to 0:1) to give an oil (0.019 g, 27%), λ_{max}/nm 238 (changed to 273 upon addition of dilute acid); ν_{max}/cm^{-1} 1660 and 1620; δ_H 0.80 (3 H, d, *J* 6.25), 0.95 (3 H, m), 1.10 (3 H, s), 1.60 (3 H, s), 1.70 (3 H, s), 1.80 (3 H, s), 1.90 (3 H, s), 2.33 (2 H, m), 3.60 (1 H, m), 3.88 (1 H, m) and 5.08 (1 H, m); *m/z* (EI) 287 (Found: M^+, 287.2615. $C_{20}H_{33}N$ requires *M*, 287.2613).

Methyl 6-hydroxy-4,7-dimethyl-octanoate 24

BF_3–MeOH complex (12 wt.% BF_3; 200 cm^3) was added slowly to lactone **23** (9.04 g) in MeOH (100 cm^3). After stirring for 15 h at room temp., the solution was poured into saturated aq. $NaHCO_3$ (150 cm^3). Solid $NaHCO_3$ was added to the mixture until neutral pH was reached. The solution was extracted with Et_2O (2 × 150 cm^3) and worked up to give an oil (10 g) which was purified by distillation to furnish the *hydroxy ester* **24** as an oil (9.36 g, 87%), bp 110–120 °C/0.2 mmHg; $[\alpha]_D$ −13.04 (*c* 0.034 in CH_2Cl_2); ν_{max}/cm^{-1} 3455 and 1740; δ_H 0.93 (3 H, d, *J* 6.5), 0.94 (3 H, d, *J* 6.75), 0.99 (3 H, d, *J* 6.75), 2.17 (1 H, dd, *J* 7.5 and 14.5), 2.35 (1 H, dd, *J* 6 and 14.5), 3.37 (1 H, ddd, *J* 3.25, 4.75 and 8) and 3.70 (3 H, s); δ_C 17.0, 18.9, 19.9, 30.5, 31.4, 33.0, 33.4, 41.4, 51.4, 76.9 and 173.7; *m/z* (CI) 220 (Found: M^+, 203.1648. $C_{11}H_{22}O_3$ + H requires *M*, 203.1647).

Methyl 4,7-dimethyl-6-oxo-octanoate 25

Jones' reagent was added dropwise to the hydroxy ester **24** (12.81 g) dissolved in AnalaR Me_2CO (200 cm^3) and the solution stirred at 0 °C; addition was continued until an orange colour persisted (≈15 cm^3). Pr^iOH was added dropwise until the solution turned green, whereupon the mixture was poured into water (150 cm^3) and extracted with EtOAc (2 × 150 cm^3). Work-up gave an oil which was purified by distillation to yield the *keto ester* **25** as an oil (11.64 g, 89%), bp 105–110 °C/0.65 mmHg; $[\alpha]_D$ +4.06 (neat); ν_{max}/cm^{-1} 1740 and 1710; δ_H 0.89 (3

H, d, *J* 6.5), 1.34 (6 H, d, *J* 7), 2.10 (1 H, dd, *J* 8 and 15), 2.26 (1 H, dd, *J* 6 and 15) and 3.60 (3 H, s); δ_C 18.3, 18.31, 19.6, 30.0, 30.3, 37.8, 40.8, 41.4, 51.4, 173.4 and 214.4; *m/z* (EI) 200, (CI) 218 and 201 (Found: M^+, 200.1406. $C_{11}H_{20}O_3$ requires *M*, 200.1412).

Methyl 6-isopropyl-3-methylhept-6-enoate 26

Zn powder (34.24 g) was stirred in THF (150 cm^3) at 0 °C under Ar and CH_2I_2 (23.4 cm^3) was added at such a rate so as to keep the temp. of the mixture below 15 °C. When the slurry cooled to 0 °C, $TiCl_4$ (6.7 cm^3) in CH_2Cl_2 (20 cm^3) was added dropwise, so that the temp. of the mixture remained below 15 °C. The mixture was stirred at 0 °C for 30 min then keto ester **25** (11.64 g) was added slowly. The resultant brown slurry was stirred at room temp. for 16 h, poured into water (200 cm^3) and extracted with Et_2O (2 × 200 cm^3). The combined organic phases were washed with HCl (2 mol dm^{-3}; 100 cm^3), filtered through a pad of Celite, washed with brine (2 × 100 cm^3), dried and concentrated under reduced pressure to yield an oil. Distillation gave the *ester* **26** (8.29 g, 72%), bp 90–100 °C/1.5 mmHg; $[\alpha]_D$ +4.58 (neat); ν_{max}/cm^{-1} 1740 and 1640; δ_H 0.95 (3 H, d, *J* 6.5), 1.01 (6 H, d, *J* 7), 2.14 (1 H, dd, *J* 8 and 14.5), 2.33 (1 H, dd, *J* 6 and 14.5), 3.65 (3 H, s), 4.66 (1 H, d, *J* 1) and 4.73 (1 H, s); δ_C 19.7, 21.9, 21.8, 30.3, 31.7, 33.7, 35.2, 41.6, 51.4, 106.4, 155.8 and 173.6; *m/z* (EI) 198, (CI) 216 and 199 (Found: M^+, 198.1627. $C_{12}H_{22}O_2$ requires *M*, 198.1620).

6-Isopropyl-3-methylhept-6-en-1-ol 27

$LiAlH_4$ (1 mol dm^3 in THF; 2 cm^3) was added to ester **26** (0.332 g) in THF (10 cm^3) at −78 °C under N_2. The mixture was stirred at −78 °C for 20 min and then at room temp. for 15 h after which HCl (2 mol dm^{-3}; 2 cm^3) was added dropwise. The white slurry was filtered through a pad of Celite which was washed with Et_2O (2 × 50 cm^3). The organic phase was dried and concentrated under reduced pressure to yield an oil; distillation furnished the *alcohol* **27** as an oil (0.251 g, 89%), bp 145–155 °C/0.4 mmHg; ν_{max}/cm^{-1} 3330, 3085 and 1640; δ_H 0.93 (3 H, d, *J* 6.3), 1.03 (6 H, d, *J* 6.8), 3.70 (2 H, m), 4.68 (1 H, d, *J* 1) and 4.73 (1 H, s); δ_C 19.6, 21.90, 21.93, 29.5, 31.8, 33.8, 35.7, 39.9, 61.2, 106.1 and 156.4; *m/z* (EI) 170 (Found: M^+, 170.1671. $C_{11}H_{22}O$ requires *M*, 170.1671).

6-Isopropyl-3-methylhept-6-enal 28

Pyridinium chlorochromate (0.22 g) was ground together with silica gel (0.22 g). The resulting pale orange solid was stirred in CH_2Cl_2 (10 cm^3) at room temp. under N_2 and the alcohol **27** (0.087 g) in CH_2Cl_2 (5 cm^3) was added dropwise. The resulting brown slurry was stirred at room temp. for 16 h after which Et_2O (45 cm^3) was added and a brown precipitate was formed. The slurry was filtered through a pad of silica gel and the pad washed with Et_2O (2 × 100 cm^3). Evaporation of the filtrate yielded a crude product which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; 5:95) to give the *aldehyde* **28** as an oil (0.066 g, 79%), ν_{max}/cm^{-1} 1725 and 1640; δ_H 0.98 (3 H, d, *J* 6.3), 1.03 (6 H, d, *J* 6.7), 2.44 (1 H, ddd, *J* 2, 5.5 and 16), 4.67 (1 H, d, *J* 1.5), 4.74 (1 H, s) and 9.76 (1 H, t, *J* 2); δ_C 19.9, 21.84, 21.88, 28.0, 31.7, 33.7, 35.4, 51.0, 106.6, 155.6 and 202.8; *m/z* (EI) 168, (CI) 186 and 169 (Found: M^+, 168.1512. $C_{11}H_{20}O$ requires *M*, 168.1514).

7-Isopropyl-4-methyl-1,1,1-trimethylsulfanyloct-7-en-2-ol 29

BuLi (1.6 mol dm^{-3} in THF; 13.14 cm^3) was added to $HC(SMe)_3$ (2.8 cm^3) in THF (30 cm^3) at −78 °C under Ar. After 5 min a solution of aldehyde **28** (3.21 g) in THF (20 cm^3) was added. The mixture was stirred at −78 °C for 40 min and then at −20 °C for 1 h. Water (50 cm^3) was added cautiously and the slurry extracted with Et_2O (2 × 100 cm^3). Work-up gave an oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 0:1 to 3:97) to give the *ortho esters* **29** as an oil (5.61 g, 91%). The product was an inseparable mixture of isomers, *m/z* (EI) 275, (CI) 340 (Found: M^+, 275.1505. $C_{15}H_{30}OS_3 - CH_3S$ requires *M*, 275.1503).

Methyl 2-hydroxy-7-isopropyl-4-methyloct-7-enoate 30

The ortho ester **29** (5.61 g) was dissolved in MeOH (100 cm^3) and the solution stirred at 0 °C. $AgNO_3$ (3.75 g) and silver oxide (8.11 g) were added in one portion and the resultant slurry was stirred at 0 °C for 1 h under Ar. The mixture was poured into water (100 cm^3) and extracted with Et_2O (2 × 100 cm^3). The combined extracts were washed with saturated aq. $NaHCO_3$ (100 cm^3), dilute aq. potassium sodium tartrate (100 cm^3) and worked up to give an oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 0:1 to 4:96) to yield the *hydroxy esters* **30** as a colourless oil (2.72 g, 70%), $[\alpha]_D$ +1.66 (neat); ν_{max}/cm^{-1} 3485, 1740 and 1640; δ_C 176.29 and 176.20; *m/z* (EI) 228, (CI) 246 and 229 (Found: M^+, 246.2074. $C_{13}H_{28}NO_3 + NH_4$ requires *M*, 246.2069).

Methyl 7-isopropyl-4-methyl-2-oxooct-7-enoate 31

Jones' reagent (≈4 cm^3) was added dropwise to the hydroxy esters **30** (2.72 g) dissolved in Me_2CO (50 cm^3) at 0 °C until an orange colour persisted. Pr^iOH was added until the solution turned green. The mixture was poured into water (50 cm^3) and extracted with EtOAc (2 × 50 cm^3). Work-up gave an oil which was purified by chromatography on silica gel 60 (EtOAc–light petroleum; gradient elution, 0:1 to 3:97) to give the *keto ester* **31** (1.34 g, 50%), bp 130–135 °C/0.7 mmHg; $[\alpha]_D$ +6.3 (*c* 0.039 in CH_2Cl_2); ν_{max}/cm^{-1} 1730 and 1640; δ_H 0.96 (3 H, d, *J* 6.75), 1.00 (3 H, d, *J* 6.5), 1.02 (3 H, d, *J* 6.5), 2.67 (1 H, dd, *J* 7.5 and 17), 2.85 (1 H, dd, *J* 5.5 and 17), 3.85 (3 H, s), 4.66 (1 H, d, *J* 1.3) and 4.73 (1 H, s); δ_C 19.7, 21.8, 21.9, 28.7, 31.7, 33.7, 35.3, 46.4, 52.8, 106.5, 155.6, 161.8 and 194.0; *m/z* (CI) 244 and 227 (Found: M^+, 244.1916. $C_{13}H_{26}NO_3 + NH_4$ requires *M*, 244.1913).

Methyl 2-cyano-2-hydroxy-7-isopropyl-4-methyloct-7-enoate 32

The α-keto ester **31** (0.549 g) in MeOH (2 cm^3) was added slowly to MeOH (15 cm^3) containing KCN (0.237 g) at 0 °C under N_2. Dropwise addition of AcOH (0.278 cm^3) caused an exothermic reaction and a white precipitate to be formed. The mixture was warmed to room temp. and stirred for 1 h after which it was poured into water (25 cm^3) and extracted with $CHCl_3$ (2 × 25 cm^3). Work-up in the usual way gave the *cyanohydrin* **32** as an oil (0.568 g, 92%). This product was used without any further purification because of its instability; ν_{max}/cm^{-1} 3450, 2245, 1755 and 1640; δ_H 0.97 (3 H, d, *J* 6), 1.03 (3 H, d, *J* 7.5), 1.09 (3 H, d, *J* 6), 3.95 (3 H, s), 4.68 (1 H, dd, *J* 1 and 5) and 4.75 (1 H, br s); *m/z* (EI) 253 (Found: M^+, 253.1676. $C_{14}H_{23}NO_3$ requires *M*, 253.1678).

Acknowledgements

We thank the SERC and Zeneca Agrochemicals plc for a CASE award and financial assistance.

References

1 J. Hill, J. K. Sutherland and P. Crowley, *J. Chem. Soc., Perkin Trans. 1*, 1992, 969.
2 J. W. Chamberlin, M. D. Chaney, S. Chen, P. V. Demarco, N. D. Jones and J. L. Occolowitz, *J. Antibiot.*, 1974, **27**, 992; L. D. Boek, M. M. Hoen, J. E. Westhead, R. K. Wolter and D. L. Thomas, *J. Antibiot.*, 1975, **28**, 95; K. H. Michel, R. L. Hamill, S. H. Larsen and R. H. Williams, *J. Antibiot.*, 1975, **28**, 102; R. S. Gordee and T. F. Butler, *J. Antibiot.*, 1975, **28**, 112; J. D. Bu'lock, K. Demnerova, W. J. Kilgour, F. Knauseder and A. Steinbuchel, *Biotechnol. Lett.*, 1980, **2**, 285.
3 W. G. Dauben and D. M. Michno, *J. Org. Chem.*, 1977, **42**, 682.
4 K. Narasaka, K. Soai and T. Mukaiyama, *Chem. Lett.*, 1974, 1223.
5 K. Narasaka, K. Soai, Y. Aikawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 779.

6 G. Kabalka, K. A. R. Sastry, G. W. McCollum and H. Yoshioka, *J. Org. Chem.*, 1981, **46**, 4296.
7 S. Nagarajan and B. Ganem, *J. Org. Chem.*, 1987, **52**, 5044.
8 A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 1973, 957.
9 E. J. Corey and I. N. Houpis, *J. Am. Chem. Soc.*, 1990, **112**, 8997.
10 H. Suginome and S. Yamada, *J. Org. Chem.*, 1985, **50**, 2489.
11 F. N. Tebbe, G. W. Parshall and G. S. Reddy, *J. Am. Chem. Soc.*, 1978, **100**, 3611; J. Hibino, T. Okazoe, K. Takai and H. Nozaki, *Tetrahedron Lett.*, 1985, **26**, 5579.
12 K. Beautement and J. M. Clough, *Tetrahedron Lett.*, 1987, **28**, 475.
13 D. Gravel, C. Vaziri and S. Rahal, *J. Chem. Soc., Chem. Commun.*, 1972, 1323.

Paper 5/05019G
Received 28*th July* 1995
Accepted 22*nd September* 1995