Hydrocyanation of some α,β-unsaturated ketones, and the synthesis of some unusual isoxazoles

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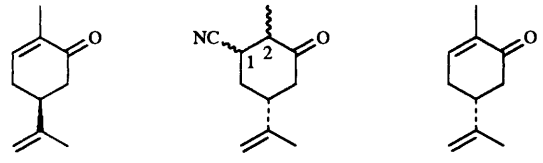
β-Cyano-α-methylcycloalkanones are regiospecifically nitrosated at the α-position by pentyl nitrite in methanolic sodium methoxide to give fused isoxazolo-lactams *via* a pathway probably involving sequential cycloalkanone cleavage, isoxazole formation and lactamisation. The chemistry of some new compounds derived from the hydrocyanation products of (−)-carvone is described.

The reaction of (+)-carvone **1** with potassium cyanide–acetic acid was first described in 1906 by Lapworth[1] who, by using cold aqueous ethanol as solvent, obtained a carbonitrile (*ent*-**2a**), mp 93.5–94.5 °C, $[\alpha]_D$ +13.5. Lapworth and Steele[2] later prepared an isomer, mp 84 °C, $[\alpha]_D$ −42.1, by reaction of **1** with potassium cyanide in a hot mixture of ethanol, ethyl acetate and water. Almost 50 years later Djerassi *et al.*,[3] using



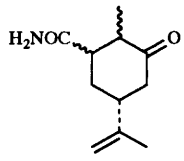
(+)-**1** **2** (−)-**3**

a β-CN, β-Me
b α-CN, β-Me
c β-CN, α-Me
d α-CN, α-Me

(−)-carvone **3**, showed by chemical correlations and by ORD methods that the first carbonitrile was the kinetically-controlled product of configuration **2a** and that the second isomer was the all-equatorial **2b**. The latter workers also isolated and identified a third isomer **2c**, and demonstrated the presence of a fourth isomer **2d** in the reaction mixture by chromatography.

We have repeated Lapworth's[1] work using (−)-carvone **3**, and have confirmed the relative configuration of **2a** by NMR spin-decoupling experiments. In particular, the 1α-H signal was a closely-spaced multiplet at δ 3.37, $W_{\frac{1}{2}}$ 14 Hz, confirming the axial configuration of the cyano group, and the 5β-H was identified as a triplet of triplets at δ 2.81, *J* 13 and 4 Hz. While our work was in progress, Bousquet *et al.*[4] carried out a similar NMR study on the nitrile **2a** and reached the same conclusion regarding its configuration.

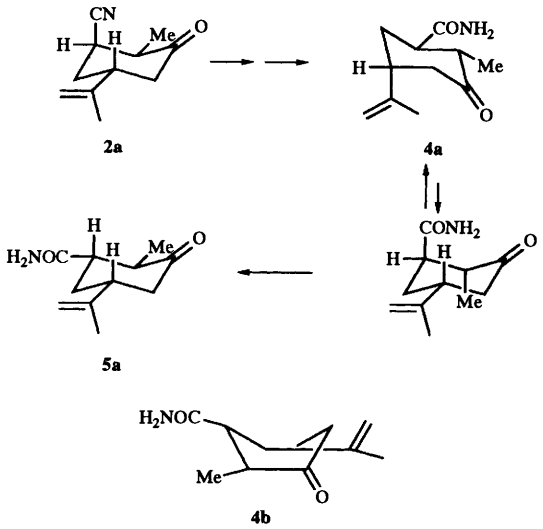
On repeating the preparation of **2b** using Lapworth and Steele's method[2] we found that if the reaction was allowed to continue for an extended period a complex mixture of products was obtained from which **2b** was not isolated, and which consisted principally of a compound having mp 125–126 °C and $[\alpha]_D$ +23.7. Its spectroscopic characteristics and elemental analysis suggested that this material was the amide **4**, whose configuration corresponded to that of the minor nitrile **2c**. The ^{1}H NMR spectrum of the amide showed its solution conformation to be **4a**. In particular, irradiation of the 2-methyl doublet collapsed the multiplet due to 2-H to a doublet of *J* 10.3 Hz, and the 5-H signal was a broad quintet, $W_{\frac{1}{2}}$ 13 Hz, consistent only with an axial isopropenyl group. Boat conformers do not predominate in cyclohexanones unless they relieve undesirable interactions which exist in the available chair forms. Consideration of possible boat forms of **4** suggested that the most plausible of these conformers is **4b** where all three substituents are equatorial. However, **4b** suffers



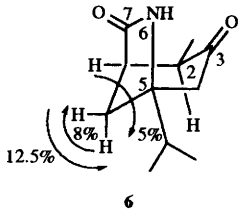
4 β-$CONH_2$, α-Me
5 α-$CONH_2$, β-Me

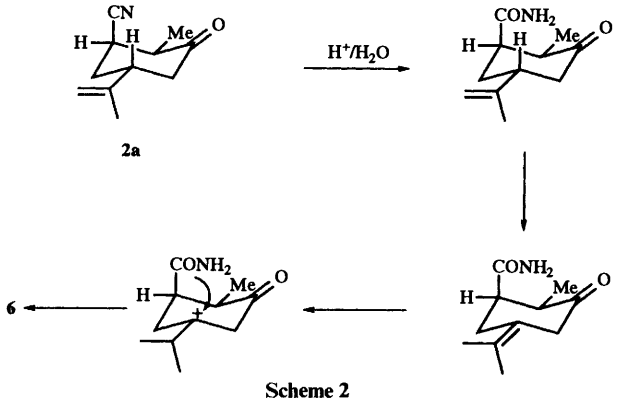
eclipsing interactions not present in the chair form **4a**, and the ^{1}H NMR signal for 5-H cannot be reconciled with its equatorial isopropenyl group. The amide **4** must clearly arise *via* hydrolysis of an intermediate nitrile. It is unlikely to be derived from nitrile **2c** since this is formed only in minor amounts[3] and the amide **4** is obtained in high yield, nor is it likely to be formed *via* hydrolysis of the all-equatorial nitrile **2b**. We regard this amide **4** as being probably derived from the major nitrile **2a** with inversion of its configuration at C-2, the large, probably solvated amide group being responsible for the molecule assuming the conformation **4a** shown. Associated with **4** were lesser amounts of the isomeric amide **5**, mp 152–153 °C, into which **4** could be converted by treatment with potassium hydroxide in methanol at reflux, and whose ^{1}H NMR spectrum was indicative of the conformation **5a**. In particular, the equatorial nature of the methyl and carboxamide groups of **5** was easily deduced, and the orientation of the isopropenyl group, which cannot be epimerised, follows from the structure of the precursor **4**. Consideration of possible boat forms of **5** suggested that the resulting eclipsing interactions would disfavour any of these with respect to the chair **5a**. The transformation of **4** into **5** thus involves inversion of configuration at both C-1 and C-2 of **4** (Scheme 1).

Lapworth[1] had hydrolysed the nitrile **2a** using cold 60% hydrobromic acid, and had obtained an amide, mp 228–230 °C. We repeated this experiment, expecting to observe amides analogous to **4** and **5**, but obtained instead a lactam, mp 224–226 °C and $[\alpha]_D$ +83.6. Lapworth had not reported any optical activity for his 'amide'. We have characterised our lactam as the bicyclic structure **6**, largely on the basis of the NOE enhancements shown and other NMR evidence (Experimental section). A mechanism for the formation of **6** is suggested in Scheme 2, the formation of lactam **6** from **2a** which bears an



Scheme 1

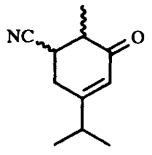




Scheme 2

axial nitrile function being consistent with both stereostructures.

When the nitrile **2a** was treated with methanesulfonic acid rather than with aqueous hydrobromic acid, the carbonitrile function was largely preserved but the double bond of the isopropenyl substituent was isomerised into conjugation with the carbonyl group. A mixture was formed from which the isomeric enones **7** and **8** were isolated, compound **8** having



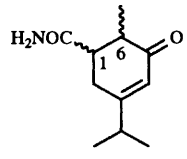
7 α-CN, β-Me
8 β-CN, β-Me

(NMR) the relative configuration of the starting nitrile **2a**. The formation of the diastereoisomer **7** requires inversion at C-1 of **2a**, and the equatorial methyl and nitrile groups were demonstrated by spin-decoupling ($J_{1,2}$ 12 Hz).

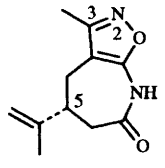
When the amides **4** or **5** were treated with hydrobromic acid or with methanesulfonic acid, mixtures of α,β-unsaturated amides were obtained. HPLC analysis showed that four compounds were present in each instance, but that each starting material had been converted into one major product. These were, with some difficulty, obtained in substantially pure form, and it was found that the unsaturated amide **9**, derived from **4**, had mp 135 °C and $[\alpha]_D$ −78.6 (90% pure by NMR). The less pure product **10**, derived from **5**, had mp 126 °C and $[\alpha]_D$ +54.7. The unsaturated amides **9** and **10** are clearly, from their NMR spectra and optical properties, largely enantiomers of each other, and this result is possible since the third chiral centre disappears as a consequence of isomerisation of the double bond.

Lapworth and Weschler[5] described the reaction of *ent*-**2a** with pentyl nitrite in the presence of sodium ethoxide. In a later paper[6] these workers identified the product of this reaction as being the isoxazoloazepine of general structure **11**. We have prepared this compound from (−)-carvone **3** and fully characterised it by spectroscopy, confirming the gross structure originally assigned in 1907.

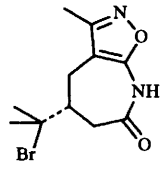
Lapworth and Weschler[5] treated the azepine *ent*-**11** with 60% aqueous hydrobromic acid and obtained an isomeric compound which they were unable to identify. They stated that this material exhibited a high optical rotation. In our hands, reaction of **11** with hydrobromic acid under identical conditions gave a bromine-containing substance. This, which was probably the tertiary bromide **12**, was not particularly stable, but gave the isomeric azepine **13** when it was refluxed with pyridine. The structure of **13** was confirmed by X-ray crystallography.[7] We have found that the conversion of **11** into **13** can be carried out more conveniently by reaction of **11** with cold methanesulfonic acid.



9 β-$CONH_2$, α-Me
10 α-$CONH_2$, β-Me



11



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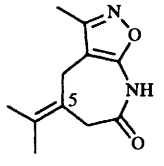

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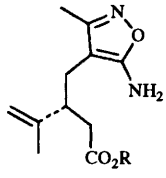
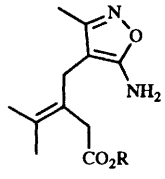


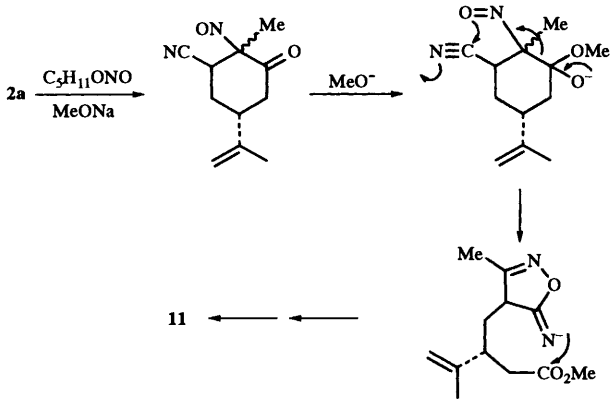
14 R = H
16 R = Me



15 R = H
17 R = Me

Hydrolysis of the lactams **11** and **13** with aqueous alkali gave the amino acids **14** and **15**, respectively. Both of these amino acids were conveniently converted into the corresponding methyl esters **16** and **17** by refluxing them in acetone solution with iodomethane and anhydrous potassium carbonate.

The reaction of pentyl nitrite with the enolate of the ketonitrile **2a** to give the isoxazoloazepine **11** is strongly exothermic, and is probably complete more rapidly than is implied in Lapworth and Weschler's paper.[5] As we suggest in Scheme 3, the overall transformation can be represented as a series of reactions in which the free amino ester **16** is not necessarily actually present. However, we have shown that in the presence of 9% sodium methoxide, the conditions used earlier for the preparation of **11**, the methyl ester **16**, which is stable towards



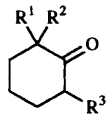
Scheme 3

methanol alone, is rapidly and quantitatively converted into the azepine **11**. Indeed, during an attempt to determine the rate of this cyclisation by following the loss of the CO_2Me signal using NMR we found that the reaction was complete before the first measurement could be made.

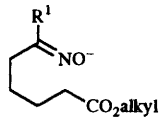
The regiospecificity of nitrosation of **2a** indicated in Scheme 3 is in accord with Lapworth's observation[8] that the nitrosation of α-alkyl substituted cyclic ketones **18** with nitrite esters in the presence of an alkoxide and the corresponding alkanol leads to oximo esters **19** *via* cleavage of the intermediate nitroso ketones **20** by alkoxide ion, and not to salts of the alternative nitroso ketones **21**.

We also found that the (optically inactive) ester **17** is rapidly cyclised to the corresponding azepine **13** by methanolic sodium methoxide.

Lapworth and Weschler[5] subjected the enantiomer of lactam **11** to reaction with mineral acids under a variety of conditions. In our hands, the lactam **11** gave the optically active 'lactonic base' **22** when treated with concentrated hydrochloric acid for an extended period. Its spectroscopic data (Experimental section) are in agreement with this structure which was further confirmed by X-ray crystallography.[7] The racemate of **22** is



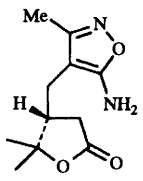
18 R^1 = alkyl, $R^2 = R^3 = H$
20 R^1 = alkyl, R^2 = NO, R^3 = H
21 R^1 = alkyl, R^2 = H, R^3 = NO



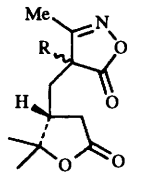
19 R^1 = alkyl

similarly formed when the optically inactive isomeric lactam **13** is the starting material. The racemic form of **22** is obtained as its relatively insoluble hydrochloride as a minor product when **11** is treated with hydrochloric acid, most likely because of partial isomerisation of **11** to **13** during the reaction period. Methanesulfonic acid can also be used to convert **13** into *rac*-**22**. The formation of the lactonic base **22** can be easily rationalised.

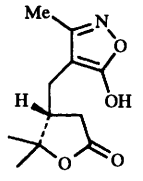
Treatment of (−)-**22** with hot dilute sulfuric acid yields the 'lactonic acid' **23**: the racemate of this compound is obtained when *rac*-**22** is the starting material. In their earlier paper[5] Lapworth and Weschler gave mp 70–72 °C for (+)-**23**, but later[6] stated that their product was hydrated and that it had the enolic structure **24** on the grounds that it readily brominated to give **25**. Our sample of (−)-**23** had mp 108–109 °C, analysed well for $C_{11}H_{15}NO_4$, and had an IR spectrum (Nujol) in agreement with the keto form **23**, but its NMR spectra (^1H and ^{13}C) were both consistent with the enol tautomer **24**. The



(−)-**22**



(−)-**23** R = H
25 R = Br



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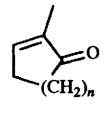
compound gave a strong ferric reaction in aqueous methanol, and is probably enolised in hydroxylic solvents.

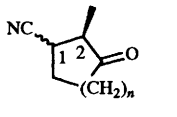
It is interesting that both the racemic 'lactonic base' **22**, mp 153–154 °C and the racemic 'lactonic acid' **23**, mp 142 °C have higher melting points than do the corresponding optically active isomers, mp 118–119 and 108–109 °C, respectively.

Having satisfied ourselves regarding the details of Lapworth's original work on compounds derived from carvone **3**, we considered that the generality of the reaction leading from α-alkylated cycloalkanones to isoxazolo-lactams such as **11** was worthy of further investigation. In particular, we were interested in finding out if cycloalkanones of ring sizes greater or lesser than six-membered would give analogous products. In the event, we have demonstrated that both cyclopentanones and cycloheptanones of appropriate structure can indeed be converted into novel bicyclic products of this type wherein isoxazole and lactam rings are mutually fused.

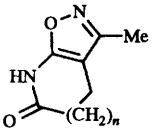
2-Methylcyclopentenone **26** was hydrocyanated to give a mixture of epimeric keto nitriles **27**. This mixture had previously been described,[9] but we have been able to separate by column chromatography, and identify, the *cis*-isomer **27a**. In its NMR spectrum, spin-decoupling of the 2-methyl doublet revealed the 2-H signal as a double doublet, J 11.5 and 1.3 Hz. The very minor *trans*-isomer **27b**, isolated in 90% purity,



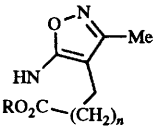
26 $n = 1$
31 $n = 2$



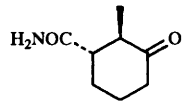
27a $n = 1$, β-CN
27b $n = 1$, α-CN
32a $n = 2$, α-CN
32b $n = 2$, β-CN



28 $n = 1$
33 $n = 2$



29 $n = 1$, R = H
30 $n = 1$, R = Me
34 $n = 2$, R = H
35 $n = 2$, R = Me



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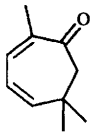
showed $J_{1,2}$ 5.5 Hz. When these compounds (mainly the *cis*-isomer) were treated with pentyl nitrite in methanolic sodium methoxide, the lactam **28**, mp 209–210 °C (decomp.) was formed, and had spectroscopic features in full accord with its structure. Hydrolysis of **28** using sodium hydroxide gave the corresponding amino acid **29**, mp 161 °C, which was converted into its methyl ester **30** using potassium carbonate and iodomethane in acetone. This ester was easily cyclised to the lactam **28** by treatment with sodium methoxide in cold methanol.

2-Methylcyclohexenone **31**[10] was hydrocyanated to a mixture of isomeric keto nitriles **32** by Lapworth's method.[1]

This mixture has also been previously described,[9] and the solid isomer, mp 55 °C (lit.,[9] 57–58 °C), which can be separated from it can now be identified as the *trans*-form **32a**. In its NMR spectrum there were overlapping multiplets in the range δ 2.45–2.66 for the 1-H and 2-H signals. These were simplified by decoupling of the 2-methyl group which collapsed the 2-H signal to a doublet, J 11.5 Hz. The 1-H signal could then be clearly seen as a partially overlapping double triplet, J 11.5 and 4 Hz. These data are consistent only with the diequatorial substituted structure **32a**. Reaction of the mixed isomers **32** with pentyl nitrite and sodium methoxide in the usual way gave the expected lactam **33**, whose spectra revealed the expected features. This compound could be hydrolysed to give the corresponding amino acid **34** which could not be isolated in pure form but whose methyl ester **35** readily cyclised to the lactam **33** with methoxide.

From the non-volatile portion of the reaction mixture obtained by the hydrocyanation of 2-methylcyclohexenone **31** we were able to isolate the *trans*-amide **36**. Its ^{1}H NMR spectrum showed a multiplet at δ 2.76 due to 2-H. Irradiation of the 2-methyl doublet at δ 1.06 collapsed this to a doublet of J 12 Hz, indicating the *trans*-diaxial arrangement of the 1- and 2-H atoms.



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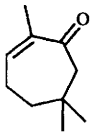

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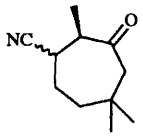
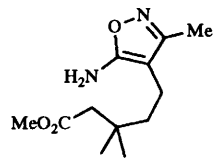


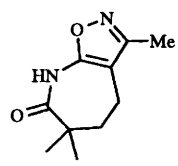
39a α-CN
39b β-CN

Eucarvone **37** was successfully reduced to the dihydro derivative **38** by hydrogenation using Wilkinson's catalyst in benzene solution. The selective reduction of an isolated double bond in the presence of one which is conjugated to a carbonyl function by use of this catalyst has been described for the case of carvone **1**,[11] but the regiospecific reduction of a dienone system such as that found in **37** appears to be novel. Eucarvone **37** has also been reduced to its dihydro-derivative **38** using Raney nickel as catalyst.[12] Hydrocyanation of dihydroeucarvone **38** gave a 3:1 mixture (NMR) of the derived keto nitriles **39**, which was separated by careful chromatography into the (major) *trans*-form **39a**, mp 72–73 °C, and the *cis*-form **39b**, mp 45 °C. The stereostructures of **39a** and **39b** were derived by analysis of their NMR spectra. A study of Dreiding models of the two nitriles **39** showed that the *trans*-form **39a** has, despite its conformational mobility, a much larger average dihedral angle between its 1-H and 2-H than does the *cis*-isomer **39b**. In particular, in their most stable conformations with the nitrile and 2-methyl groups pseudoequatorial, this angle is *ca.* 180° for the *trans*-isomer and *ca.* 45° for the *cis*-isomer. In the light of this and their respective 1-H/2-H coupling constants of 10 and 5 Hz, we have assigned the configurations shown. When this mixture was treated with pentyl nitrite in the presence of sodium methoxide at 0 °C the product was the amino ester **40** rather than the expected lactam **41**. This was not entirely unexpected given the mild conditions which were used. However, treatment of **40** with sodium methoxide in refluxing methanol gave the eight-membered lactam **41** in good overall yield.

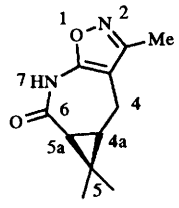
The nitrosation reaction described above is capable of wider application. Thus, the tricyclic lactam **42** could be formed from the cyanocaranone **43**,[13] although some side-reactions also occurred. Hydrobromination of the cyanodihydrocarvone **2a** using hydrogen bromide in anhydrous acetic acid took place rapidly without configurational change to give the bromide **44**. The relative configuration of **44** could not be unambiguously



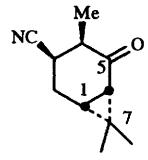
40



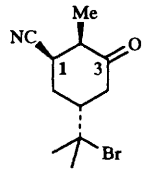
41



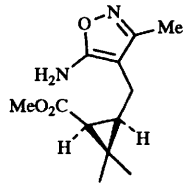
42



43



44



45

assigned by NMR, but X-ray analysis[14] of the derived cyanocaranone **43** established its structure. Cyclisation of **44** to give **43** was accomplished by treating an ethereal solution of the bromide with a slight excess of sodium methoxide in methanol. Reaction of **43** with pentyl nitrite in the presence of the same base led to the methyl ester **45** rather than directly to the lactam **42**. However, the ester **45** was converted into **42** when it was refluxed gently with sodium methoxide in methanol.

Experimental

General experimental conditions

^{1}H NMR spectra were measured for solutions in $CDCl_3$ unless otherwise stated, with tetramethylsilane as internal standard. 300 MHz spectra were obtained using a Bruker MSL-300 spectrometer, and 360 MHz spectra were obtained using a Bruker WM-360 instrument. ^{13}C NMR spectra were recorded at 90.56 MHz in the solvents stated. J values are given in Hz. IR spectra were measured using a Perkin-Elmer 883 spectrometer. Optical rotations, recorded in units of 10^{-1} deg cm^2 g^{-1}, were measured at the stated temperatures and in the stated solvents using a Perkin-Elmer 141 polarimeter. Mass spectra were measured using Fisons VG Platform II or Varian CH 5D spectrometers. All solvents were purified by distillation. Column chromatography was carried out over Merck Kieselgel 60 70–230 mesh silica gel, and TLC was carried out using Merck Kieselgel-60 F_{254} plates. HPLC analysis was carried out using a Spheri-5 RP-18 5 micron Brownlee column and guard which were fitted to a Waters 994 programmable photodiode array detector. The solvent system used was 80:20 methanol–distilled water. The (−)-carvone used in this work had $[\alpha]_D$ −55.4 (c 3.3 in $CHCl_3$).

(−)-(1*R*,2*R*,5*R*)-2-Methyl-5-(1′-methylvinyl)-3-oxocyclohexanecarbonitrile 2a

Reaction of (−)-carvone **3** with hydrogen cyanide according to Lapworth's method[1] gave the title carbonitrile, mp 93–94 °C, $[\alpha]_D^{18}$ −4.0 (c 1.04 in $CHCl_3$) (lit.,[1] 93.5–94.5 °C); ν_{max}(Nujol)/cm^{-1} 3415, 3085, 2238 (CN), 1715 (CO), 1675, 1645 and 900 (C=CH$_2$); δ_H(360 MHz) 1.27 (3 H, d, J 7, 2-Me), 1.78 (3 H, s, MeC=C), 1.99 (1 H, ddd, J 15, 13 and 4.5, 6α-H), 2.31 (2

H, m, 6β-H and either 4α- or 4β-H), 2.60 (1 H, m, 2-H), 2.64 (1 H, m, 4α- or 4β-H), 2.81 (1 H, ttt, *J* 13 and 4, 5-H), 3.37 (1 H, m, *J* 5.5 and 4.5, 1-H), and 4.82 and 4.87 (2 H, 2 s, CH_2=C). Irradiation at δ 2.60 collapsed the doublet at 1.27 (2-Me) to a singlet. Irradiation at δ 1.99 (6α-H) collapsed the triple triplet at 2.81 (5-H) to a broad doublet, the broad doublet at 2.31 to a multiplet, and simplified the multiplet at 3.37 (1-H). Irradiation of the multiplet at δ 3.37 collapsed the multiplet at 1.99 to a double doublet; δ_C 12.55 (2-Me), 20.48 (MeC=C), 32.78 (6-CH_2), 35.63 (1-CH), 42.25 (5-CH), 44.96 (2-CH), 45.88 (4-CH_2), 111.12 (CH_2=), 118.68 (*C*=CH_2), 145.47 (CN) and 206.89 (CO); *m/z* (EI, 5% and greater) 177 (M^+; 36), 162 (32), 134 (30), 133 (12), 110 (22), 109 (21), 96 (12), 95 (76), 83 (12), 82 (48), 81 (19), 69 (25), 68 (100), 67 (98), 66 (14), 55 (12) and 53 (27).

(−)-(1*R*,2*R*,5*R*)-2-Methyl-5-(1′-methylvinyl)-3-oxocyclohexanecarboxamide 4

A hot solution of (−)-carvone **3** (60 g) in ethyl acetate (30 cm^3) was rapidly added to a stirred refluxing solution of potassium cyanide (30 g) in a mixture of water (80 cm^3) and ethanol (80 cm^3). Reflux was continued for a further 20 min and the solution was then set aside for 60 h (*cf.* ref. 2). Work-up gave a thick syrup which contained (TLC) unchanged carvone and four other compounds. The syrup was dissolved in the minimum quantity of hot 40% ethyl acetate in hexane and the solution chilled to give the *amide* **4** (20.5 g), mp 125–126 °C after recrystallisation from ethyl acetate–hexane, $[\alpha]_D^{20}$ +23.7 (*c* 10.6 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3420, 3340, 3300, 3200, 1700, 1675, 1630, 910 and 895; δ_H(300 MHz) 1.04 (3 H, d, *J* 6.6, 2-Me), 1.77 (3 H, s, MeC=C), 2.06 (1 H, ddt, $J_{6\alpha,6\beta}$ 9.45, $J_{6\alpha,1} = J_{6\alpha,5}$ 4.5, $J_{6\alpha,4\alpha}$ 1.65, 6α-H), 2.17 (1 H, ddd, $J_{6\beta,6\alpha}$ 9.45, $J_{6\beta,1}$ 10.3, $J_{6\beta,5}$ 4.3, 6β-H), 2.27 (1 H, dt, $J_{1,6\beta} = J_{1,2}$ 10.3, $J_{1,6\alpha}$ 4.5, 1-H) 2.56 (1 H, ddd, $J_{4\beta,4\alpha}$ 15.0, $J_{4\beta,5}$ 6.0, $J_{4\beta,2}$ 1.0, 4β-H), 2.60 (1 H, ddd, $J_{4\alpha,4\beta}$ 15.0, $J_{4\alpha,5}$ 3.84, $J_{4\alpha,6\alpha}$ 1.65, 4α-H), 2.66 (1 H, ddq, $J_{2,1}$ 10.3, J_{2,CH_3} 6.6, $J_{2,4\beta}$ 1.0, 2-H), 2.83 (1 H, br q, $W_{\frac{1}{2}}$ 13, 5-H), 4.66 (1 H, m, CH_a=C), 4.88 (1 H, m, CH_b=C) and 5.60 and 5.80 (each 1 H, 2 br s, NH_2). Irradiation of the doublet at δ 1.04 collapsed the multiplet at 2.66 to a doublet of *J* 10.3; δ_c 12.87 (2-Me), 22.15 (Me), 31.1 (6-CH_2), 40.93 (5-CH), 44.1 (4-CH_2), 46.2 (2-CH), 47.44 (1-CH_2), 112.9 (CH_2=), 146.1 (C=), 175.9 ($CONH_2$) and 211.5 (CO); *m/z* (10% and greater apart from M^+) 195 (M^+, 4), 152 (12), 151 (100), 109 (74), 86 (58), 69 (16), 68 (27), 55 (21) and 53 (10) (Found: C, 67.5; H, 8.5; N, 7.01. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.8; N, 7.17%).

Distillation of the mother liquors after removal of the amide yielded (−)-carvone **3** (5.2 g) and a thick glass, bp 174–190 °C at 0.13 mmHg, which, refluxed with ether gave a further crop of the amide **4** (15.8 g), mp 125–126 °C after recrystallisation from ethyl acetate–hexane. The mother liquors from this crystallisation gave a second amide **5** (0.7 g) which, after several recrystallisations from benzene, had mp 152–153 °C and which is further described below. IR spectroscopy indicated that no nitriles were present in the mother liquors.

(+)-(1*S*,2*R*,5*R*)-2-Methyl-5-(1′-methylvinyl)-3-oxocyclohexanecarboxamide 5

The amide **4** (0.5 g) was refluxed overnight with 5% potassium hydroxide in methanol (10 cm^3). Removal of methanol followed by addition of water gave the *amide* **5** (0.5 g), mp 152–153 °C from hot water, $[\alpha]_D^{18}$ +14.7 (*c* 0.54 in $CHCl_3$), ν_{max}(Nujol)/cm^{-1} 3400, 3320, 3300, 3200, 1720, 1660, 1630, 910 and 895; δ_H(300 MHz) 1.02 (3 H, d, *J* 6.4, 2-Me), 1.74 (3 H, s, MeC=C), 1.98 (2 H, m, 6α- and 6β-H), 2.18 (1 H, td, *J* 11.6 and 4.0, 1-H), 2.40 (3 H, m, 4α-, 4β- and 5-H), 2.71 (1 H, dq, *J* 11.6 and 6.4, 2-H), 4.74 (1 H, br s, CH_a=), 4.77 (1 H, m, CH_b=), 5.68 (1 H, br s, NH_a) and 5.95 (1 H, br s, NH_b); δ_C 12.11 (Me), 20.04 (Me), 34.6 (CH_2), 45.22 (CH), 45.97 (CH), 46.34 (CH_2), 51.95 (CH), 110.6 (CH_2=), 146.4 (C=), 175.4 ($CONH_2$) and 211.1 (CO); *m/z* (10% and greater) 195 (M^+; 28), 178 (10), 152 (15), 151 (98), 124 (12), 123 (20), 113 (22), 112 (15), 110 (15), 109 (100), 107 (12), 97 (10), 95 (17), 87 (18), 86 (45), 85 (15), 81 (28), 79 (10), 72 (37), 69 (49), 68 (46), 55 (61) and 53 (27) (Found: C, 67.9; H, 8.7; N, 6.92. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.78; N, 7.17%). No acidic compounds were formed in this reaction.

(+)-(1*S*,2*S*,5*R*)-5-Isopropyl-2-methyl-6-azabicyclo[3.2.1]-octane-3,7-dione 6

The nitrile **2a** (1 g) was dissolved in 60% hydrobromic acid (3.5 cm^3) and the mixture was set aside for 48 h.[1] Work-up afforded the bicyclic *lactam* **6** (0.2 g), mp 224–226 °C from ethyl acetate, $[\alpha]_D$ +83.6 (*c* 0.6 in MeOH) (lit.,[1] mp 228–230 °C, no $[\alpha]_D$ quoted); ν_{max}(Nujol)/cm^{-1} 3155, 3075, 1717, 1702, 1667, 1132, 1047, 895 and 775; δ_H(360 MHz) 1.00 (6 H, d, *J* 6.5 Me_2CH), 1.26 (3 H, d, *J* 6.5, MeCH), 1.85 (1 H, heptet, *J* 6.5, C*H*Me_2), 1.97 (1 H, d, *J* 11, 8α-H), 2.27 (1 H, dd, *J* 11.0 and 5.0, 8β-H), 2.52 (2 H, collapsed Abq, 4α- and 4β-H), 2.54 (1 H, m, 2-H), 2.67 (1 H, dd, *J* 5.0 and 3.6, 1-H) and 6.1 (1 H, br s, NH). Irradiation of the doublet at δ 1.26 collapsed the multiplet at 2.54 to a doublet of *J* 3.6 Hz. Irradiation of the heptet at δ 1.85 collapsed the doublet at 1.00 to a singlet. Irradiation of the multiplet at δ 2.67 collapsed the double doublet at 2.27 to a doublet. Irradiation of the doublet at δ 1.00 collapsed the heptet at 1.85 to a singlet; δ_C 12.6, 16.8, 17.1, 30.9, 34.2, 40.2 (CH_2), 46.5, 47.6 (CH_2), 48.8, 64.2 (quaternary C), 176.7 (CONH) and 209.1 (CO); *m/z* (EI, 5% and greater) 195 (M^+; 15), 152 (25), 136 (12), 124 (100), 110 (25), 96 (12), 81 (22), 69 (34) and 55 (42); *m/z* (CI; NH_3) 213 ($M^+ + NH_4$; 42) and 196 ($M^+ + 1$; 100) (Found; C, 67.5; H, 9.0; N, 7.3. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.78; N, 7.17%).

Reaction of the nitrile 2a with methanesulfonic acid: (−)-(1*S*,6*R*)-3-isopropyl-6-methyl-5-oxocyclohex-3-enecarbonitrile 7 and (−)-(1*R*,6*R*)-3-isopropyl-6-methyl-5-oxocyclohex-3-enecarbonitrile 8

The nitrile **2a** (5 g) and anhydrous methanesulfonic acid (20 cm^3) were stirred together at 0 °C until a clear solution was formed after which the mixture was set aside for 24 h. After this time, it was diluted with water (50 cm^3) and extracted with dichloromethane (3 × 20 cm^3). The combined extracts were washed with aqueous sodium hydrogen carbonate, dried and evaporated to give a thick oil (3.8 g) which partially solidified with time. Trituration with a little ethyl acetate gave a solid (0.5 g), mp 129–130 °C after recrystallisation from ethyl acetate, $[\alpha]_D^{18}$ −63.8 (*c* 0.58 in $CHCl_3$). The residue obtained by evaporation of the ethyl acetate mother liquors was chromatographed on silica gel using 35% ethyl acetate in hexane as eluent. The early fractions yielded the trans-*nitrile* **7** (0.75 g), mp 87–88 °C, $[\alpha]_D^{18}$ −146.4 (*c* 0.7 in $CHCl_3$): ν_{max}(Nujol)/cm^{-1} 2244, 1679, 1633, 1315, 1252, 1230, 1183, 1123, 1098, 1071, 1010, 990, 934, 909, 722, 679 and 666; δ_H(360 MHz) 1.13 and 1.14 (6 H, 2 d, *J* 7.0, CH*Me*$_2$), 1.37 (3 H, d, *J* 7.0, 6-Me), 2.45 (1 H, heptet, *J* 7.0, C*H*Me_2), 2.53 (1 H, m, 6-H, 2.72 (2 H, m, 2-H_2), 2.85 (1 H, m, 1-H) and 5.90 (1 H, m, 4-H). Irradiation of the doublet at δ 1.37 collapsed the multiplet at 2.53 to a clean doublet of *J* 12; δ_C 13.38, 20.15, 20.6, 30.72 (CH_2), 33.14, 35.27, 42.86, 119.78 (CN), 123.35 (C-4), 166.7 (C-5) and 196.63 (CO); *m/z* (5% and greater) 177 (M^+; 22), 111 (8), 110 (100), 109 (5), 95 (65), 82 (5), 68 (28), 53 (8) and 50 (5) (Found: C, 74.8; H, 8.4; N, 8.03. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%). Later fractions from the column afforded the cis-*nitrile* **8** (0.45 g), mp 41–42 °C from pentane–ethyl acetate, $[\alpha]_D^{18}$ −31.1° (*c* 0.37 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 2240, 1670, 1630, 1195 and 900; δ_H(360 MHz) 1.16 (6 H, d, *J* 7.0, CH*Me*$_2$), 1.34 (3 H, d, *J* 7.0, 6-Me), 2.49 (1 H, heptet, *J* 7.0, C*H*Me_2), 2.62 (1 H, dq, *J* 7.0 and 4.5, 6-H), 2.69 (2 H, d, *J* 4.5, 2-H_2), 3.34 (1 H, q, *J* 4.5, 1-H) and 6.0 (1 H, s, 4-H). Irradiation

of the doublet at δ 1.34 collapsed the double quartet at 2.62 to a doublet; irradiation of the doublet at δ 2.69 collapsed the quartet at 3.34 to a doublet, and irradiation of the quartet at δ 3.34 collapsed the doublet at 2.69 to a singlet and the double quartet at 2.62 to a quartet (Found: C, 74.3; H, 8.65; N, 7.8. $C_{11}H_{15}NO$ requires C, 74.54; H, 8.53; N, 7.90%]. Final elution of the column using methanol afforded a sticky yellow substance (0.5 g) whose IR spectrum suggested the presence of amides. It was not further investigated.

Reaction of the amides 4 and 5 with acids

(a) The amide **4** (0.5 g) was added to 60% hydrobromic acid (2.5 cm^3) at 0 °C and the mixture was stirred at room temperature until dissolution had taken place. After storage overnight the mixture was added to ice, neutralised with aqueous sodium hydrogen carbonate and extracted several times with dichloromethane. Evaporation of the combined extracts gave a solid (0.35 g), mp 120 °C, which was relatively soluble in water. Recrystallisation from ethyl acetate–hexane raised the mp to 130 °C when the material had $[\alpha]_D^{20}$ −59.8 (*c* 0.82 in $CHCl_3$); λ_{max}(EtOH)/nm 239 (log ε 4.02) and 313 (1.72); ν_{max}(Nujol)/cm^{-1} 3387, 3217, 1670, 1638, 1618, 1278, 960 and 880. Its ^1H NMR spectrum was complex, and at least 22 signals were present in the ^{13}C NMR spectrum. HPLC analysis showed that four compounds were present in a mixture, their ratios being 12.6, 14.4, 70.3 and 2.6% in order of elution. If the amide **4** (0.5 g) was treated with methanesulfonic acid (2.5 cm^3) in exactly the same manner as described above for its reaction with hydrobromic acid, a similar mixture of products was obtained from which the major isomer (corresponding to the main product of the first reaction) could be purified by repeated recrystallisations from ethyl acetate–hexane. It, (−)-(1*R*,6*S*)-isopropyl-6-methyl-5-oxocyclohex-3-enecarboxamide **9**, had mp 135 °C, $[\alpha]_D^{20}$ −78.6 (*c* 0.28 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3390, 3218, 1666, 1642 and 1622; δ_H(360 MHz) 1.08 (3 H, d, *J* 6.5, CHMeCH_3), 1.10 (3 H, d, *J* 6.5, CHMeCH_3), 1.16 (3 H, d, J 6.5, 6-Me), 2.42 (1 H, m, partially overlapping, C*H*Me_2), 2.42–2.49 (1 H, m, partially overlapping, 2α-H), 2.54 (1 H, m, 1-H), 2.62 (1 H, dq, *J* 11 and 6.5, 6-H), 2.75 (1, ddd, *J* 17, 11 and 2.5, 2β-H), 5.68 and 5.78 (each 1 H, br s, NH_2) and 5.88 (1 H, d, *J* 2.5, 4-H). Irradiation of the d at δ 1.16 collapsed the dq at δ 2.62 to a doublet of *J* 11 Hz. Irradiation of the dq at δ 2.62 collapsed the d at δ 1.16 to a singlet (Found: C, 67.4; H, 8.9; N, 7.1. $C_{11}H_{17}NO_2$ requires C, 67.66; H, 8.78; N, 7.17%).

(b) The amide **5** (0.4 g) was treated with 60% aqueous hydrobromic acid in the same way as described above for compound **4**. Work-up gave crude (+)-(1*S*,2*S*)-3-isopropyl-6-methyl-5-oxocyclohex-3-enecarboxamide **10** (0.3 g), mp 120–122 °C raised to 129–130 °C after recrystallisation from ethyl acetate and then having $[\alpha]_D^{20}$ +57.4 (*c* 0.75 in $CHCl_3$). Its IR and NMR spectra were virtually identical with those of the crude product obtained in the same way from compound **4**.

(−)-(5*R*)-3-Methyl-5-(1′-methylvinyl)-7-oxo-4,5,6,7-tetrahydro-8*H*-isoxazolo[5,4-*b*]azepine 11[5]

A stirred solution of sodium ethoxide (11.5% in ethanol; 100 cm^3) was cooled to −10 °C and the carbonitrile **2a** (30 g) was slowly added to it. After dissolution was complete pentyl nitrite (22 g) was added to the mixture during 1 h, the temperature of the mixture being kept < 0 °C; the reaction was strongly exothermic. After a further 1 h at 0 °C the mixture was left overnight at room temperature and then diluted with water, filtered and saturated with carbon dioxide. The precipitated lactam **11** (22 g) had mp 134–135 °C (ethyl acetate–hexane); $[\alpha]_D^{18}$ −143 (*c* 1.06 in $CHCl_3$) (lit.,[5] for the enantiomer mp 138–139 °C, $[\alpha]_D$ +121); λ_{max}(EtOH)/nm 251 (log ε 4.08); ν_{max}(Nujol)/cm^{-1} 3520, 3420, 3180, 3100, 1693, 1661s and 1534; δ_H(300 MHz) 1.83 (3 H, s, CH_3C=C), 2.19 (3 H, s, 3-CH_3), 2.56 (2 H, m, 6-H_2), 2.76 (3 H, m, 4-H_2 and 5-H), 4.80 and 4.85 (2 H, 2 s, CH_2=C) and 8.26 (1 H, br s, NH); δ_C 10.37, 20.41, 27.31 (CH_2), 37.98, 42.16 (CH_2), 96.66 (quaternary), 111.19 (CH_2), 146.38 (quaternary), 156.29 (quaternary), 161.38 (quaternary) and 171.23 ($CONH_2$); *m/z* (EI; 10% and greater) 206 (M^+, 22) 123 (10), 111 (100), 95 (40), 68 (45), 58 (28), 55 (22) and 53 (11) (Found: C, 63.8; H, 6.6; N, 13.5. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.58%).

5-Isopropylidene-3-methyl-7-oxo-4,5,6,7-tetrahydro-8*H*-isoxazolo[5,4-*b*]azepine 13

(a) The azepine **11** was treated with 60% aqueous hydrobromic acid according to Lapworth and Weschler[5] to yield a crude product which contained bromine and which had a tendency to decompose. This was refluxed with pyridine to give a low yield of the azepine **13** which is fully described below.

(b) The azepine **11** (2 g) was stirred at room temperature with methanesulfonic acid (12 cm^3) during 40 min. After this time, the reaction mixture was poured onto ice to give the *lactam* **13** (1.6 g), mp 185–186 °C from aqueous ethanol, $[\alpha]_D$ 0 (*c* 1.2 in MeOH) (lit.,[5] mp 180 °C, $[\alpha]_D$ > 200); ν_{max}(Nujol)/cm^{-1} 3180, 3100, 3000, 1680 and 1650; δ_H(300 MHz) 1.76 and 1.83 (6 H, 2 s, Me_2C=C), 2.20 (3 H, s, 3-CH_3), 3.20 (2 H, s, 6-H_2), 3.28 (2 H, s, 4-H_2) and 8.60 (1 H, br s, NH); δ_C 10.46, 20.82, 20.87, 26.61 (CH_2), 40.86 (CH_2), 97.77 (quaternary), 118.10 (quaternary), 132.26 (quaternary), 156.94 (quaternary), 161.03 (quaternary) and 169.95 ($CONH_2$) (Found: C, 64.2; H 6.8; N, 13.5. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.58%).

(+)-3-(5′-Amino-3′-methylisoxazol-4′-ylmethyl)-4-methylpent-4-enoic acid 14

The lactam **11** (1.5 g) in aqueous sodium hydroxide (10%; 12 cm^3) was refluxed for 5 h after which the reaction mixture was cooled and saturated with carbon dioxide to liberate unchanged lactam. The lactam was filtered off and the filtrate was acidified with concentrated hydrochloric acid to give the amino acid **14** (1.5 g), mp 151–152 °C from aqueous ethanol, $[\alpha]_D^{18}$ +45.1 (*c* 0.74 in EtOH) (lit.,[5] mp 155 °C and $[\alpha]_D$ −41.2 for the enantiomer); λ_{max}(EtOH)/nm 254 (log ε 3.94); ν_{max}(Nujol)/cm^{-1} 3407, 3328, 1692, 1652, 1599 and 1505; δ_H(300 MHz in [$^2H_6$]-DMSO) 1.69 (3 H, s, CH_3C=C), 1.97 (3 H, s, 3-CH_3), 2.29 (4 H, m, CH_2 groups), 2.53 (1 H, partly obscured m, CHC=C), 4.70 and 4.71 (each 1 H, 2 s, CH_2=C), 6.31 (2 H, s, exch. D_2O, NH_2) and 11.98 (1 H, br s, exch. D_2O, CO_2H); δ_C([$^2H_6$]DMSO) 10.15, 19.7, 25.4 (CH_2), 37.5 (CH_2), 43.2 (CH), 87.3 (quaternary), 111.0 (CH_2), 146.9 (quaternary), 159.8 (quaternary), 167.1 (quaternary) and 173.6 (CO_2H) (Found: C, 58.7; H, 7.1; N, 12.4. $C_{11}H_{16}N_2O_3$ requires C, 58.91; H, 7.19; N, 12.49%).

3-(5′-Amino-3′-methylisoxazol-4′-ylmethyl)-4-methylpent-3-enoic acid 15

The lactam **13** (1.0 g) was hydrolysed in the same way as described for compound **11** above to yield the *amino acid* **15** (0.97 g), mp 170–171 °C from MeOH–H_2O, $[\alpha]_D$ 0; ν_{max}-(Nujol)/cm^{-1} 3390, 3310, 3220, 3180, 2630, 1690, 1658, 1610, 1510 and 1280; δ_H([$^2H_6$]DMSO) 1.63 (3 H, s, MeC=C), 1.79 (3 H, s, MeC=C), 1.89 (3 H, s, Ar*Me*), 2.82 (2 H, s, C=C-CH_2), 2.97 (2 H, s, C=CCH_2), 6.17 (2 H, s, NH_2) and 11.96 (1 H, s, CO_2H) (Found: C, 58.67; H, 6.9; N, 12.41 $C_{11}H_{16}N_2O_3$ requires C, 58.91; H, 7.19; N, 12.4%).

(+)-Methyl 3-(5′-amino-3′-methylisoxazol-4′-ylmethyl)-4-methylpent-4-enoate 16

A mixture of the amino-acid **14** (0.5 g), anhydrous potassium carbonate (0.3 g), iodomethane (0.5 cm^3) and acetone (5.0 cm^3) was stirred and refluxed for 1.5 h to give the ester **16** (0.4 g), mp 95–96 °C from ethyl acetate–hexane (lit.,[5] 99–100 °C), $[\alpha]_D^{18}$ +24.1 (*c* 1.6 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3360, 3180, 1710,

1655, 1610, 1500, 1155 and 900; δ_H(300 MHz) 1.74 (3 H, s, CH_3C=C), 2.07 (3 H, s, 3'-CH_3), 2.32 (2 H, m, CH_2CO_2Me), 2.43 (2 H, m, 2 H), 2.70 (1 H, quintet, J 6.5 Hz, 3-H), 3.60 (3 H, s, OMe), 4.71 (2 H, br s, NH_2) and 4.72 and 4.80 (each 1 H, 2 s, CH_2=C); δ_C 10.45, 20.60, 25.37 (CH_2), 37.37 (CH_2), 43.04, 51.73, 90.21 (quaternary), 111.96 (CH_2), 146.37 (quaternary), 161.19 (quaternary), 165.88 (quaternary) and 173.63 (CO_2Me); m/z (5% and greater) 238 (M^+; 5), 112 (8), 111 (100), 83 (5), 68 (6), 58 (18) and 56 (10) (Found; C, 60.2; H, 7.3; N, 11.7. $C_{12}H_{18}N_2O_3$ requires C, 60.48; H, 7.61; N, 11.76%).

Methyl 3-(5'-amino-3'-methylisoxazol-4'-ylmethyl)-4-methylpent-3-enoate 17

This ester was prepared from the acid **15** (0.3 g) exactly as described for the preceding example. It (0.25 g) had mp 82 °C (hexane–ethyl acetate), $[\alpha]_D$ 0; ν_{max}(Nujol)/cm^{-1} 3420, 3380, 3300, 3150, 2700, 1740, 1655, 1625 and 1515; δ_H(300 MHz) 1.75 (3 H, s, *Me*C=C), 1.84 (3 H, s, *Me*C=C), 2.06 (3 H, s, 3'-*Me*), 2.98 (2 H, s, CH_2), 3.06 (2 H, s, CH_2), 3.63 (3 H, s, O*Me*) and 4.60 (2 H, br s, NH_2) (Found; C, 60.3; H, 7.3; N, 11.5. $C_{12}H_{18}N_2O_3$ requires C, 60.48; H, 7.61; N, 11.6%).

Cyclisation of the methyl ester 16

The ester **16** (50 mg) was dissolved in 9% sodium methoxide in methanol. After 1.5 h water (2 cm^3) was added to the solution which was then saturated with carbon dioxide to give the lactam **11** (15 mg), mp 134–135 °C without recrystallisation. The ester **16** was recovered unchanged after storage for 24 h in methanol alone.

Cyclisation of the methyl ester 17

This compound (18 mg) was set aside overnight with 9% sodium methoxide in methanol (1 cm^3). Work-up as described above for the previous example gave the lactam **13** (14 mg), mp and mixed mp 186 °C.

(±)- and (−)-3-(5'-Amino-3'-methylisoxazol-4'-ylmethyl)-4,4-dimethylbutanolide 22

These compounds were obtained *via* a modification of Lapworth and Weschler's method.[6] The (−)-lactam **11** (5 g) was slowly added to stirred, concentrated hydrochloric acid (25 cm^3), and stirring was continued until a clear solution was obtained. This was set aside for 3 days after which it was diluted with water (25 cm^3). A highly crystalline hydrochloride (1.33 g) was formed, mp *ca.* 200 °C with blackening. Treatment of this with saturated aqueous sodium hydrogen carbonate solution gave principally (±)-**22** (0.96 g), mp 146–147 °C (lit.,[6] 157–158 °C) (see below). The mother liquors remaining after removal of the hydrochloride were neutralised with 2 mol dm^{-3} aqueous sodium hydroxide to give the (−)-butanolide **22** (3.25 g), mp 118–119 °C from ethyl acetate–hexane, $[\alpha]_D^{18}$ −14.5 (c 1.0 in $CHCl_3$) (lit.,[6] mp 122–123 °C and $[\alpha]_D$ +6.55 for the enantiomer); ν_{max}(Nujol)/cm^{-1} 3373, 3316, 3290, 3249, 3203, 1762, 1740, 1652, 1620, 1510, 1288, 1186, 1127 and 939; δ_H(300 MHz) 1.36 and 1.45 (each 3 H, 2 s, Me_2C), 2.12, (3 H, s, 3-Me), 2.14–2.60 (5 H, series of ms, 2 CH_2 and CH) and 4.44 (2 H, br s, exch. D_2O, NH_2); δ_C 10.59, 21.83 (CH_2), 21.84, 27.42, 34.95 (CH_2), 45.31, 86.08 (quaternary), 89.42 (quaternary), 160.46 (quaternary), 165.25 (quaternary) and 175.11 (CO) (Found: C, 58.95; H, 7.3; N, 12.4. $C_{11}H_{16}N_2O_3$ requires C, 58.95; H, 7.19; N, 12.49%). In an alternative preparation of the (±)-butanolide **22**, the optically inactive lactam **13** (0.5 g) was treated with concentrated hydrochloric acid (2.5 cm^3) as described above. After 48 h, water (3 cm^3) was added when the hydrochloride (0.46 g) was deposited. This and its acidic mother liquors were neutralised using 2 mol dm^{-3} aqueous sodium hydroxide to give racemic **22** (0.48 g), mp 153–154 °C, $[\alpha]_D^{18}$ 0 (c 0.92 in MeOH) (lit.,[6] mp 157–158 °C); ν_{max}(Nujol)/cm^{-1} 3400, 3320, 3275w, 3230w, 3175, 1760, 1745w, 1665, 1620 and 1510 cm^{-1}. Its ^{1}H and ^{13}C NMR spectra were identical with those of the (−)-form (Found: C, 59.1; H, 7.0; N, 12.6. $C_{11}H_{16}N_2O_3$ requires C, 58.95; H, 7.19; N, 12.49%).

(−)- and (±)-3-(4',5'-Dihydro-3'-methyl-5'-oxoisoxazol-4'-yl)-methyl-4,4-dimethylbutanolide 23

The (−)-butanolide **22** (1 g) was heated with 1 mol dm^{-3} aqueous sulfuric acid (20 cm^3) on a water-bath during 2 h. The reaction mixture was then cooled and extracted with dichloromethane to give a brown syrup (1 g), TLC analysis of which showed the presence of some unchanged **22**. The syrup was extracted with saturated aqueous sodium hydrogen carbonate and the extract was then acidified to give **23** (0.61 g) as a syrup which slowly solidified. Recrystallisation from ethyl acetate gave **23**, mp 108–109 °C, $[\alpha]_D^{18}$ −36.9 (c 0.75 in $CHCl_3$) (lit.,[6] mp 70–72 °C, $[\alpha]_D$ +37.6 for the enantiomer); ν_{max}(Nujol)/cm^{-1} 2710, 1780, 1760, 1750, 1690, 1600 and 1565; δ_H(300 MHz) 1.36 and 1.47 (each 3 H, 2 s, Me_2C), 2.18, (3 H, s, 3-Me), 2.13–2.23 (1 H, obs m, CH_2CHCH_2), 2.30–2.43 (2 H, m, $CHCH_2CH$) and 2.55–2.64 (2 H, m, CH_2CO); δ_C 10.74, 21.91, 21.93 (CH_2), 27.38, 34.90 (CH_2), 44.07, 86.56 (quaternary), 97.61 (quaternary), 161.43 (quaternary), 173.22 (CO) and 175.62 (CO) (Found: C, 58.85; H, 6.8; N, 6.15. $C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.7; N, 6.22%). The racemic form of **23** (0.4 g) was obtained similarly from the (±)-butanolide **22** (1.0 g) and 1 mol dm^{-3} sulfuric acid (20 cm^3). It had mp 142 °C from ethyl acetate and $[\alpha]_D$ 0 (c 0.5 in MeOH). Its spectra were identical with those of the (−)-form described above (Found: C, 58.8; H, 6.6; N, 6.1. $C_{11}H_{15}NO_4$ requires C, 58.65; H, 6.71; N, 6.22%).

***cis*- and *trans*-2-Methyl-3-oxocyclopentanecarbonitriles 27**

2-Methylcyclopent-2-enone **26** (5 g), acetone cyanohydrin (5.75 g), methanol (15.3 cm^3) and water (6 cm^3) containing sodium carbonate (0.383 g) were heated together at reflux during 3 h. The cooled reaction mixture was poured into water (75 cm^3) and extracted with ether (3 × 70 cm^3). The combined extracts were washed with water, dried and evaporated to give a mixture of the nitriles **27a** and **27b** as a pale yellow oil (5.34 g). Cooling using solid CO_2 followed by trituration with light petroleum (bp 40–60 °C) gave a small quantity (118 mg) of colourless crystals, mp 46–46.5 °C. These were recrystallised from pentane to give the pure *cis*-nitrile **27a** as colourless crystals, mp 55 °C (lit.,[9] 57–58 °C); δ_H(360 MHz) 1.28 (3 H, d, J 7, 2-Me), 2.07–2.3 (2 H, m, 5-H_2) and 2.35–2.55 (3 H, m, 4-H_2 and 2-H). Irradiation of the doublet at δ 1.28 collapsed a multiplet at δ 2.44 (2-H) to a double doublet (J 11.5 and 1.3); m/z (5% and greater) 123 (25; M^+), 95 (5), 94 (11), 80 (6), 69 (23), 68 (41), 67 (7), 57 (32), 55 (100), 53 (7) and 52 (7) (Found: C, 68.1; H, 7.24; N, 11.3. C_7H_9NO requires C, 68.27; H, 7.37; N, 11.37%). ^{1}H NMR spectroscopy confirmed that most of the crude product obtained as described above was the *cis*-isomer **27a**, and this crystallised slowly with time. Chromatography of a portion (0.5 g) of the crude product on silica gel, eluting with ether, gave a partial separation of the *cis*- and *trans*-isomers. Later fractions gave a substantially pure sample of the minor *trans*-isomer **27b** as a colourless oil which had δ_H(360 MHz) 1.30 (3 H, d, J 7, 2-Me), a series of overlapping multiplets in the range δ 2.14–2.54 and a multiplet (1 H, H-1) at 3.39. Irradiation of the 2-methyl doublet at δ 1.30 collapsed the half-hidden multiplet at 2.44 to a doublet of J 5.5.

3-Methyl-4,5,6,7-tetrahydroisoxazolo[5,4-*b*]pyridin-6-one 28 (with Mr Julien Webb)

A mixture of the carbonitriles **27a** and **27b** (0.63 g) was dissolved in 9% sodium methoxide in methanol (3 cm^3) at 0 °C, and pentyl nitrite (1.1 cm^3) was carefully added to the stirred

solution. On addition of the first drop of the nitrite ester, the temperature rose to 30 °C and white fumes were produced. After again cooling the mixture to 0 °C the remainder of the nitrite was added without difficulty. Stirring was continued at 0 °C for 30 min, and then at room temperature for 2 h after which the dark reaction mixture was left in the refrigerator overnight. Solvents were removed under reduced pressure and water (2 cm^3) was added to the residue to give a very dark but clear solution. This was filtered through charcoal and then carefully neutralised using concentrated hydrochloric acid. The solid product (0.45 g), mp 182–185 °C, was collected, washed with water and recrystallised (charcoal) from hot water to yield the *azine* **28** as pale yellow *needles*, mp 209–210 °C with pre-blackening; ν_{max}(Nujol)/cm^{-1} 3591w, 3103, 1696, 1668, 1543 and 1358; δ_H(300 MHz) 2.21 (3 H, s, Me), 2.67 [4 H, m, $(CH_2)_2$] and 8.63 (1 H, s, N*H*); δ_C([$^2H_6$]DMSO) 9.65, 14.02 (CH_2), 30.51 (CH_2), 90.64, 157.91, 162.03 and 170.15; *m/z* 153 (9), 152 (M^+; 100), 151 (10), 149 (14), 111 (10), 110 (60), 109 (9), 108 (10), 107 (6), 86 (20), 84 (35), 83 (13), 82 (13), 81 (22), 80 (11), 71 (10), 68 (31), 67 (22), 58 (12), 56 (29), 55 (13), 54 (10) and 52 (13) (Found: C, 55.23; H, 5.6; N, 18.7. $C_7H_8N_2O_2$ requires C, 55.25; H, 5.30; N, 18.41%).

3-(5-Amino-3-methylisoxazol-4-yl)propanoic acid 29 and its methyl ester 30

The lactam **28** (0.55 g) was refluxed with aqueous sodium hydroxide (10%; 5 cm^3) during 4.5 h. Work-up gave the *acid* **29** (0.5 g), mp 161 °C from aqueous ethanol; ν_{max}(Nujol)/cm^{-1} 3385, 3256, 2598, 2480, 1970, 1682, 1657, 1626, 1507, 1439, 1271, 1200, 1010 and 892; δ_H(300 MHz) 2.21 (3 H, s, Me), 2.29–2.50 (4 H, m, CH_2 groups), 6.28 (2 H, s, NH_2) and 12.11 (1 H, br s, CO_2H); δ_C 10.01, 16.40 (CH_2), 33.60 (CH_2), 88.05 (quaternary), 159.79 (quaternary), 166.75 (quaternary) and 174.22 (*C*O_2H), *m/z* 170 (M^+; 48), 112 (8), 111 (100), 82 (12), 81 (11), 68 (22), 67 (10), 59 (62), 55 (36), 54 (10), 53 (6) and 55 (5) (Found: C, 49.4; H, 5.9; N, 16.5. $C_7H_{10}N_2O_3$ requires C, 49.40; H, 5.90; N, 16.48%). The *methyl ester* **30**, prepared in the manner described above, had mp 63 °C from light petroleum; ν_{max}(Nujol)/cm^{-1} 3350, 3149, 2098 and 1734; δ_H(300 MHz) 2.13 (3 H, s, 3-Me), 2.49 (4 H, br s, CH_2 groups), 3.67 (3 H, s, OMe) and 4.70 (2 H, br s, NH_2); *m/z* 184 (M^+; 40), 152 (6), 126 (7), 112 (8), 111 (100), 110 (7), 98 (13), 83 (9), 82 (9), 69 (17), 67 (6), 58 (42), 55 (26) and 54 (8) (Found: C, 52.2; H, 6.8; N, 15.1. $C_8H_{12}N_2O_3$ requires C, 52.16; H, 6.57; N, 15.21%).

trans- and *cis*-2-Methyl-3-oxocyclohexanecarbonitriles 32a and 32b

Glacial acetic acid (3.8 g) was added with stirring to an ice-cold mixture of 2-methylcyclohexenone (6.85 g) in ethanol (35 cm^3) and water (20 cm^3) containing potassium cyanide (5.7 g). The brown solution was then stirred at room temperature overnight, diluted with water (10 cm^3) and extracted with dichloromethane. The carbonitriles were distilled to give a syrup (3.1 g), bp 84–86 °C at 0.8–1.0 mm Hg (lit.,[9] bp 120 °C at 3.5 mmHg), which slowly became semi-solid. Filtration gave the *trans*-nitrile **32a** (0.13 g), mp 55 °C from pentane–ethyl acetate (lit.,[9] mp 57–58 °C); ν_{max}(Nujol)/cm^{-1} 3406, 2242, 1711, 1020 and 968 cm^{-1}, δ_H(360 MHz) 1.28 (3 H, d, *J* 7, 2-Me), 1.69 (1 H, m, CH), 2.0–2.4 (4 H, series of ms, two CH_2 groups) and 2.45–2.66 (3 H, series of ms, 2-H, 1-H and CH). Irradiation of the methyl protons collapsed the multiplet at δ 2.5 to a doublet of *J* 11.5 and a partially obscured double triplet, *J* 11.5 and 4; *m/z* (10% and greater) 137 (M^+; 33), 109 (16), 108 (13), 94 (24), 81 (11), 69 (27) and 55 (100).

3-Methyl-5,6,7,8-tetrahydro-4*H*-isoxazolo[5,4-*b*]azepin-7-one 33

The syrupy mixture of isomeric nitriles **32a** and **32b** (1.1 g) in 9% methanolic sodium methoxide (6 cm^3) was cooled to −5 °C and pentyl nitrite (1 g) in methanol (2 cm^3) was added to the stirred solution during 15 min. The mixture was kept at room temperature overnight, diluted with water (10 cm^3), filtered, and the filtrate was saturated with carbon dioxide to give the *lactam* **33** (0.7 g), mp 220 °C from aqueous ethanol; ν_{max}(Nujol)/cm^{-1} 3120, 1685, 1650 and 1535; δ_H(360 MHz) 2.05 (2 H, m, 5-H_2), 2.19 (3 H, s, 3-Me), 2.49 (2 H, t, *J* 7.0, 6-H_2), 2.70 (2 H, m, 4-H_2) and 8.62 (1 H, br s, NH); δ_C([$^2H_6$]DMSO) 9.96, 19.09 (CH_2), 21.46 (CH_2), 37.03 (CH_2), 97.47 (quaternary), 157.70 (quaternary), 160.95 (quaternary) and 172.04 (CO); *m/z* (10% and greater) 166 (M^+; 50), 111 (100), 68 (11), 58 (35) and 56 (33) (Found: C, 57.5; H, 6.2; N, 16.67. $C_8H_{10}N_2O_2$ requires C, 57.82; H, 6.07, N, 16.86%].

Hydrolysis of the lactam 33 and preparation of the methyl ester 35

The lactam **33** (1.0 g) was refluxed with 10% aqueous sodium hydroxide (7 cm^3) during 4.5 h after which careful neutralisation of the alkaline reaction mixture with concentrated hydrochloric acid gave the *acid* **34** (1.05 g), mp 122 °C after recrystallisation from water; ν_{max}(Nujol)/cm^{-1} 3447, 3326, 3278, 3194, 1708, 1653, 1613 and 1500 (Found: C, 52.0; H, 6.5; N, 15.45. $C_8H_{12}N_2O_3$ requires C, 52.16; H, 6.37; N, 15.21%). This compound (0.8 g), in a mixture of acetone (18 cm^3) and methanol (18 cm^3) was refluxed for 12 h with iodomethane (2.4 cm^3) and anhydrous potassium carbonate (1.0 g). The mixture was extracted with ether and the extract washed with aqueous potassium carbonate and worked up to give a syrup (0.5 g) which slowly solidified to afford the *ester* **35**, mp 75–76 °C raised to 78 °C after recrystallisation from ethyl acetate-hexane; ν_{max}(Nujol)/cm^{-1} 3351, 3324, 3279, 3176, 1708 (C=O, lower than expected, H-bonding to NH_2), 1655, 1617, 1503, 1408, 1343, 1268, 1167, 1104, 1056, 1031 and 1008; δ_H(300 MHz) 1.72 (2 H, quintet, *J* 6.0, CH_2), 2.08 (3 H, s, MeC=N), 2.21 (2 H, t, *J* 6.0, CH_2), 2.30 (2 H, t, *J* 6.0, CH_2), 3.65 (3 H, s, CO_2Me) and 4.66 (2 H, br s, NH_2); δ_C 10.28 (Me), 20.15 (CH_2), 24.61 (CH_2), 32.55 (CH_2), 51.64 (CO_2CH_3), 90.84, 160.84, 165.66 and 174.31 (*C*O_2Me) (Found: C, 54.3; H, 7.12; N, 13.99. $C_9H_{14}N_2O_3$ requires C, 54.53; H, 7.12; N, 14.13%).

Cyclisation of the ester 35

The ester **35** (48 mg), in sodium methoxide solution (9% in methanol; 0.3 cm^3) was set aside overnight. Water (1 cm^3) was added to the solution which was then saturated with carbon dioxide to give the lactam **33** (30 mg), mp and mixed mp 216 °C.

trans-2-Methyl-3-oxocyclohexanecarboxamide 36

The residue remaining after distillation of the nitriles **32a** and **32b** (0.5 g) was triturated with a little ethyl acetate to give the *amide* **36** (0.1 g), mp 181 °C from ethyl acetate–hexane; ν_{max}(Nujol)/cm^{-1} 3380, 3180, 1690, 1665, 1630 and 1625; δ_H(360 MHz) 1.06 (3 H, d, *J* 6.5, 2-Me, 1.72 (1 H, m, 5β-H), 2.05 (2 H, m, CH groups), 2.20 (2 H, m, 1-H and CH), 2.44 (2 H, m, 4-H_2), 2.76 (1 H, m, 2-H) and 5.52 and 5.62 (each 1 H, 2 s, NH_2). Irradiation of the doublet at δ 1.06 collapsed the multiplet at 2.76 to a doublet of *J* 12; δ_C([$^2H_6$]DMSO) 12.22, 25.71 (CH_2), 28.90 (CH_2), 40.7 (CH_2), 45.62, 51.76, 174.69 (*C*ONH_2) and 211.68 (CO); *m/z* (5% and greater) 155 (M^+; 36), 127 (9), 126 (11), 113 (10), 112 (51), 111 (100), 99 (7), 98 (12), 87 (9), 86 (22), 83 (9), 72 (36), 69 (19), 60 (30), 57 (11) and 55 (53) (Found: C, 61.8; H, 8.4; N, 9.0. $C_8H_{13}NO_2$ requires C, 61.91; H, 8.44; N, 9.03%).

Dihydroeucarvone 38

Eucarvone (10 g) dissolved in a mixture of benzene (125 cm^3) and methanol (125 cm^3) was hydrogenated with Wilkinson's catalyst (250 mg) at 1 atm until 1 equiv. of hydrogen had been taken up.

The solvents were evaporated at reduced pressure and hexane (100 cm^3) was added to the mixture which was then filtered through Celite and evaporated to give dihydroeucarvone **38** (9.8 g); ν_{max}(film)/cm^{-1} 1697 and 1660; δ_H($CDCl_3$; 60 MHz) 1.00 (6 H, s, CMe_2), 1.50 (2 H, m, CH_2), 1.76 (2 H, br s, CH_2), 2.30 (2 H, m, CH_2), 2.43 (3 H, s, MeC=C) and 6.58 (1 H, t, *J* 6, HC=C).

2,5,5-Trimethyl-3-oxocycloheptanecarbonitriles 39

A mixture of dihydroeucarvone **38** (*ca.* 80% purity; 4 g), acetone cyanohydrin (4.4 g), methanol (12 cm^3) and anhydrous potassium carbonate (0.25 g) was stirred and refluxed for 5 h. The reaction mixture was then cooled and diluted with ether (30 cm^3). The black solution was washed with water (×3), dried and distilled at 0.4 mmHg after removal of solvents. A mixture of the isomeric nitriles **39** (2.9 g) was collected at 96–100 °C/0.4 mmHg as a colourless *oil* which became semi-solid on storage. This was stirred with 15% ethyl acetate in hexane (*ca.* 2 cm^3) to give the trans-*nitrile* **39a** (0.38 g), mp 72–73 °C after recrystallisation from pentane containing a few drops of ethyl acetate; ν_{max}(Nujol)/cm^{-1} 3374, 2239 and 1695; δ_H(360 MHz) 0.96 and 1.04 (each 3 H, 2 s, *gem*-dimethyl groups), 1.30 (3 H, d, *J* 6.5, 2-Me), 1.50, 1.80 and 2.09 (1 H, m, 2 H, m and 1 H, m, 6-H_2 and 7-H_2), 2.35 (1 H, d, *J* 11.5, 4-H_a), 2.50 (1 H, d, *J* 11.5, 4-H_b), 2.61 (1 H, dt, *J* 10 and 2, 1-H) and 2.68 (1 H, dq, *J* 10 and 6.5, 2-H). Irradiation of the doublet at δ 1.30 collapsed the dq at 2.68 to a doublet; δ_C 17.35, 27.04 (CH_2), 27.60, 30.96, 32.81, 35.24, 41.83 (CH_2), 50.30, 53.13 (CH_2), 121.28 (CN) and 209.70 (CO); *m*/*z* 179 (M^+; 6), 164 (6), 84 (6), 83 (100), 72 (6), 69 (32), 56 (21), 55 (20) and 53 (6) (Found: C, 73.88; H, 9.26; N, 7.70. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.81%). A further quantity (0.1 g) of the *trans*-nitrile **39a**, mp 69–70 °C was obtained when the mother liquors from the crystallisation described above were cooled to −5 °C and then filtered. The residue from the mother liquors was chromatographed on silica gel using 20% ethyl acetate in hexane as eluent. Early fractions gave a further quantity of the nitrile **39a** (0.48 g); later fractions gave an oil (0.4 g) which was again chromatographed. The oily product solidified and was recrystallised from pentane containing a little ethyl acetate to yield the cis-*nitrile* **39b** (0.3 g), mp 45 °C; ν_{max}(Nujol)/cm^{-1} 3366, 2240 and 1690; δ_H(360 MHz) 0.95 and 1.06 (each 3 H, 2 s, *gem*-dimethyl groups), 1.35 (3 H, d, *J* 6, 2-Me), 1.63 (1 H, m), 1.88 (2 H, m) and 2.05 (1 H, m) (6-H_2 and 7-H_2), 2.36 (1 H, dd, *J* 12.5 and 1, 4-H_a), 2.58 (1 H, dq, *J* 6 and 5, 2-H), 2.77 (1 H, d, *J* 12.5, 4-H_b) and 3.17 (1 H, ddd, *J* 6, 5 and 2, 1-H). Irradiation of the doublet at δ 1.35 collapsed the m at δ 2.58 to a doublet, (*J* 5 Hz). Irradiation of the multiplet at δ 2.58 collapsed the doublet at 1.35 to a singlet; δ_C 16.06, 25.85 (CH_2), 27.01, 31.52, 32.57 (CMe_2), 33.44, 40.00 (CH_2), 48.03, 54.49 (CH_2), 119.58 (CN) and 210.28 (CO); *m*/*z* 179 (M^+, 6), 164 (7), 84 (6), 83 (100), 70 (7), 69 (28), 68 (10), 57 (9) and 56 (8) (Found: C, 73.55; H, 9.3; N, 7.6. $C_{11}H_{17}NO$ requires C, 73.70; H, 9.56; N, 7.81%).

Methyl 3,3-dimethyl-5-(5′-amino-3′-methylisoxazol-4′-yl)-pentanoate 40

The mixture of isomeric nitriles **39** (0.85 g) was added carefully to a stirred solution of sodium methoxide (9%; 2.6 cm^3) in methanol kept at 0 °C after which a solution of pentyl nitrite (0.72 g) in methanol (2 cm^3) was added to the mixture the temperature being kept < 0 °C. The mixture was stirred at 0 °C during a further 30 min and then left in the refrigerator overnight. It was then diluted with water to give an opalescent mixture which was extracted with ether to give the *ester* **40** (1 g), mp 80 °C after recrystallisation from hexane–ethyl acetate; ν_{max}(Nujol)/cm^{-1} 3374, 3203, 1708, 1660, 1625 and 1504; δ_H(360 MHz) 1.03 (6 H, s, CMe_2), 1.40 (2 H, m, 4-CH_2), 2.12 (3 H, s, MeC=N), 2.19 (2 H, m, 5-CH_2), 2.34 (2 H, s, CH_2CO_2Me), 3.69 (3 H, s, CO_2CH_3) and 4.65 (2 H, br s, NH_2); δ_C 10.24 (Me), 16.27 (CH_2), 28.23 (Me), 33.25 (CMe_2), 40.29 (CH_2), 44.17 (CH_2), 51.45 (CO_2CH_3), 91.88 (quaternary), 160.63 (quaternary), 165.21 (quaternary) and 173.13 (CO); *m*/*z* (EI) 240 (M^+; 19), 209 (4), 125 (17), 111 (100), 98 (4), 85 (6), 83 (12), 73 (5), 68 (9), 60 (5), 58 (23) and 55 (14) (Found: C, 60.0; H, 8.2; N, 11.5. $C_{12}H_{20}N_2O_3$ requires C, 59.98; H, 8.39; N, 11.66%).

3,6,6-Trimethyl-4,5,6,7,8,9-hexahydroisoxazolo[5,4-*b*]azocin-8-one 41

A solution of the ester **40** (120 mg) in 9% sodium methoxide in methanol (2 cm^3) was gently refluxed for 1 h. The methanol was removed under reduced pressure and the residue was dissolved in water (3 cm^3). Neutralisation with concentrated hydrochloric acid gave the *lactam* **41** (100 mg), mp 217–218 °C from aqueous ethanol; ν_{max}(Nujol)/cm^{-1} 3177, 3096, 1685, 1651, 1520, 1419, 1353 and 1341; δ_H(360 MHz) 1.13 (6 H, s, *gem*-dimethyl groups), 1.78 (2 H, br s, 5-H_2), 2.20 (3 H, s, 3-Me), 2.37 (2 H, s, 7-H_2), 2.49 (2 H, m, 4-H_2) and 7.42 (1 H, br s, N*H*); δ_C 10.24, 17.13 (CH_2), 29.06, 32.43, 34.74 (CH_2), 43.94 (CH_2), 103.05 (quaternary), 157.3 (C-3), 161.34 (quaternary) and 170.65 (CO); *m*/*z* (5% and greater) 209 (M + 1; 5), 208 (34), 180 (20), 165 (7), 139 (62), 137 (8), 136 (9), 125 (10), 124 (100), 123 (7), 122 (32), 111 (30), 109 (6), 98 (5), 96 (12), 95 (47), 83 (42), 82 (11), 81 (39), 80 (6), 79 (9), 77 (5), 69 (20), 68 (12), 67 (14), 66 (6), 58 (22), 57 (12), 56 (33), 55 (12), 54 (13), 52 (9) and 51 (5) (Found: C, 63.3; H, 7.9; N, 13.2. $C_{11}H_{16}N_2O_2$ requires C, 63.44; H, 7.74; N, 13.45%).

(−)-(1*R*,2*R*,5*R*)-5-(1′-Bromo-1′-methylethyl)-2-methyl-3-oxocyclohexanecarbonitrile 44

The nitrile **2a** (10 g) was shaken with cold, anhydrous hydrogen bromide in acetic acid (45%; 10 cm^3) until it dissolved. The mixture solidified after *ca.* 5 min. After a further 20 min, ice–water was added to the mixture which was then filtered in order to collect the solid hydrobromide. After recrystallisation from ethyl acetate–hexane the product (12.92 g) had mp 82–83 °C (lit.,[15] mp 82–83 °C), $[\alpha]_D^{20}$ −37.9 (*c* 1.2 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3440, 2240 and 1720; δ_H(360 MHz) 1.26 (3 H, d, *J* 7, 2-*Me*), 1.78 (3 H, s, *Me*), 1.86 (3 H, s, *Me*), 2.05 (1 H, dm, *J* 11.5, 6-H), 2.10 (1 H, dd, *J* 11.5 and 4.0, 6β-H), 2.40–2.50 (2 H, complex m, 4α-H or 4β-H and 5-H), 2.60 (1 H, quintet, *J* *ca.* 6.5, 2-H), 2.78 (1 H, dm, *J* 13.5, 4β-H or 4α-H) and 3.36 (1 H, dt, *J* 6.0 and 4.0, H-1); δ_C 12.39, 30.9 (CH_2), 32.5, 33.0, 34.8, 43.9 (CH_2), 44.9, 47.7, 69.6 (quaternary), 118.7 (CN) and 206.4 (C=O).

(−)-(1*S*,3*R*,4*R*,6*S*]-4,7,7-Trimethyl-5-oxobicyclo[4.1.0]-heptane-3-carbonitrile 43

A cold, stirred solution of the bromide **44** (5 g) in dry ether (125 cm^3) was slowly treated with sodium methoxide in methanol (9%; 35 cm^3, 1.3 equiv.), with continued stirring for 1 h after addition of the base. The mixture was filtered to remove precipitated sodium bromide (1.85 g; 92%), and the filtrate was washed with water to give a syrup (2.9 g) which slowly solidified. Crystallisation of this from ethyl acetate–hexane gave the keto nitrile **43**, mp 55 °C, $[\alpha]_D^{22}$ −330 (*c* 2.2 in $CHCl_3$) (lit.,[13] mp 54–55 °C; $[\alpha]_D$ +298 for the enantiomer in EtOH); ν_{max}(Nujol)/cm^{-1} 3364, 2241 and 1687; δ_H(300 MHz) 1.12 (3 H, s, *Me*), 1.15 (3 H, s, *Me*), 1.18 (3 H, d, *J* 6.8, 4-*Me*), 1.60 (1 H, d, *J* 7.7, 6-H), 1.68 (1 H, m, 1-H), 1.80 (1 H, m, 2α-H or 2β-H), 2.14 (1 H, m, 4-H), 2.42 (1 H, m, 2β-H or 2α-H) and 3.05 (1 H, m, 3-H); δ_C 13.46, 16.33, 22.97 (CH_2), 28.16 (overlapping signals, one quaternary), 28.73, 34.33, 36.9, 44.8, 119.9 (CN) and 205.87 (C=O); *m*/*z* 177 (M^+; 3), 111 (30), 109 (6), 95 (31), 83 (6), 82 (49), 81 (10), 79 (13), 77 (12), 68 (14),

67 (100), 65 (16), 55 (15), 54 (13) and 53 (27) (Found: C, 74.28, H, 8.63; N, 7.77. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.53; N, 7.90%).

Nitrosation of 43: (−)-(1*S*,3*R*) methyl 3-[4′-(5′-amino 3′-methylisoxazol-4-yl)methyl]-2,2-dimethylcyclopropane-carboxylate 45

The cyanocaranone **43** (3 g) was stirred with cold (−5 °C) sodium methoxide in methanol (9%; 7 cm^3), and pentyl nitrite (2.5 g) was added to the solution during 15 min, the reaction temperature being kept < 0 °C. Stirring was continued during a further 1 h, after which the dark mixture was stored in a freezer overnight. After this it was diluted with water to give a deeply wine-coloured solution which was extracted with ether. The combined extracts were washed with water, dried and evaporated to yield a pale yellow syrup, bp 148–150 °C/0.6 mmHg. TLC (ethyl acetate–hexane, 1 : 1) showed the presence of major (R_F 0.53) and minor (R_F 0.7) products. Column chromatography using the same solvent system afforded the pure major product (0.73 g) as a syrup which slowly solidified. Recrystallisation of the product from light petroleum (bp 30–40 °C) gave the *ester* **45**, mp 52–53 °C, $[\alpha]_D^{20}$ −19.9 (*c* 2.2 in $CHCl_3$), ν_{max}/cm^{-1} 3407, 3321, 3193, 1710, 1650 and 1505; δ_H(300 MHz) 1.18 (3 H, s, *Me*), 1.26 (3 H, s, *Me*), 1.26 (1 H, obs. m, 3-H), 1.43 (1 H, d, *J* 8.5, 1-H), 2.15 (3 H, s, 3′-*Me*), 2.45–2.76 (2 H, ABm, CH_2), 3.62 (3 H, s, OMe) and 4.50 (2 H, br s, NH_2) (Found: C, 60.5; H, 7.8; N, 11.6. $C_{12}H_{18}N_2O_3$ requires C, 60.48; H, 7.61; N, 11.76%).

Cyclisation of the ester 45: (+)-(4a*R*,5a*S*)-3,5,5-trimethyl-4,4a,5,5a,6,7-hexahydrocyclopropa[*e*]isoxazolo[5,4-b]azepin-6-one 42

The ester **45** (0.75 g) was gently refluxed with sodium methoxide in methanol (9%, 5 cm^3) during 1 h to give a black, but clear, alkaline solution. This was diluted with water (10 cm^3), acidified with hydrochloric acid and extracted with ethyl acetate. Work-up of the extract afforded a black tar which upon trituration with ether yielded the *lactam* **42** (0.15 g), mp 134–136 °C from ethyl acetate–hexane, $[\alpha]_D^{20}$ +230.5 (*c* 0.6 in $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3517, 3197, 3100, 1652 and 1532; δ_H(300 MHz) 1.13 (3 H, s, *Me*), 1.25 (3 H, s, *Me*), 1.53 (1 H, m, 4a-H), 1.73 (1 H, d, $J_{4a,5a}$ 8, 5a-H), 2.16 (3 H, s, 3-*Me*), 2.60 (1 H, dd, *J* 16.8 and 4.7, 4β-H), 2.85 (1 H, dd, *J* 16.8 and 8.2, 4α-H) and 9.0 (1 H, br s, N*H*); δ_C 10.25, 16.09, 16.21 (CH_2), 24.23 (quaternary), 28.59, 29.76, 30.56, 104.79 (quaternary), 108.77 (quaternary), 110.11 (quaternary) and 156.55 (*C*ONH); *m*/*z* 206 (M^+, 19), 150 (12), 137 (11), 136 (6), 124 (18), 122 (13), 123 (6), 120 (9), 111 (19), 110 (11), 109 (100), 108 (22), 107 (6), 106 (10), 97(6), 96 (60), 95 (15), 94 (21), 93 (13), 91 (13), 84 (7), 83 (25), 82 (16), 81 (44), 80 (18), 79 (34), 78 (8), 77 (25), 70 (7), 69 (7), 68 (21), 67 (44), 66 (16), 65 (13), 58 (23), 57 (67), 55 (25), 54 (13) and 53 (38) (Found: C, 63.9; H, 7.1; N, 13.7. $C_{11}H_{14}N_2O_2$ requires C, 64.06; H, 6.84; N, 13.58%).

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