Nitration of α,β-unsaturated esters. Evidence for positive charge build-up adjacent to carbonyl carbon

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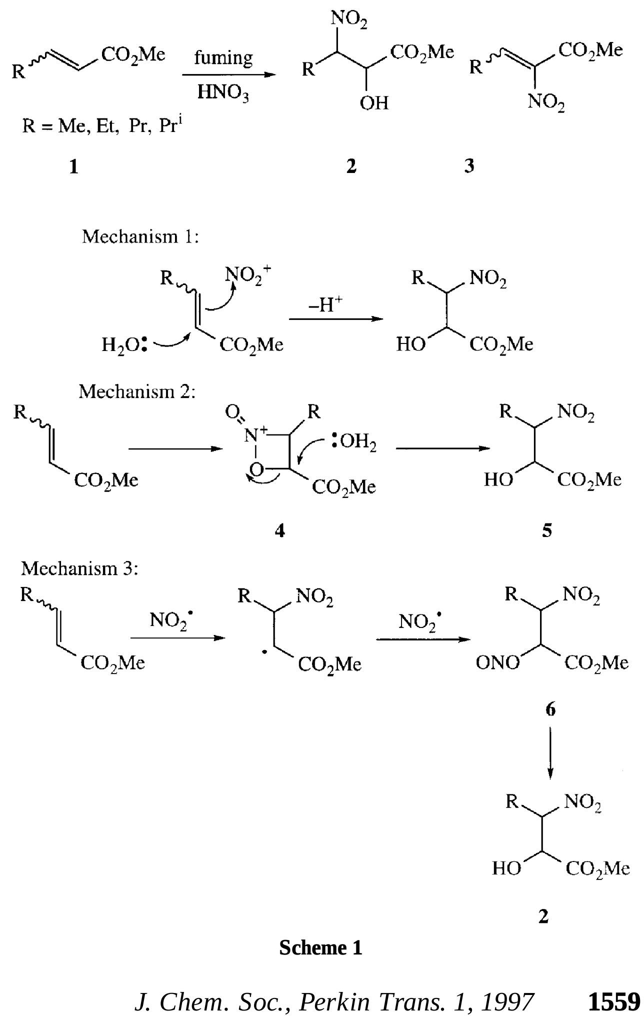
Reactive intermediates formed in the nitration of certain α,β-unsaturated esters with nitronium tetrafluoroborate exhibit behaviour expected of highly reactive α-carbonyl cations. Three diagnostic reaction types have been observed which indicate the presence of these destabilised cations: (i) trapping in a Ritter reaction, (ii) cyclopropane formation from propyl cations, (iii) Wagner–Meerwein migration of alkyl groups. Semi-empirical calculations of the relative gas-phase stabilities of the proposed intermediate cations are useful in rationalising the observed chemistry.

Introduction

The stabilisation of negative charge by an adjacent electron-withdrawing carbonyl group, 'enolate stabilisation', underpins modern synthetic chemistry. As positive charge is highly destabilised by an adjacent electron-withdrawing group, the cationic equivalent of an enolate anion is seldom described. However, recent reviews[1–6] attest to the formation of such 'destabilised' cations adjacent to carbonyl and other electron-withdrawing groups. Observations made in the literature and in our own research on the regiochemistry of nitration of alkenes prompted us to investigate this area to assess the relative accessibility of such 'cations' both by experiment and using semi-empirical computational methods. Throughout this paper, it is recognised that naked cations are unlikely to exist in solution in the solvent used (acetonitrile). Hence the term 'carbocation' will be used in the sense in which organic chemists normally use it when speaking of reactions in solution, as a species which may be heavily solvated, but which nevertheless bears significant positive charge density on the carbon and is capable of demonstrating this fact through its chemical behaviour.

Shin *et al.* isolated[7,8] α-hydroxy-β-nitro esters **2** and α-nitro-α,β-unsaturated esters **3** from nitration of α,β-unsaturated esters **1** with fuming nitric acid (Scheme 1). Although the authors chose not to comment on the mechanism of the formation of these compounds, the unusual regiochemistry of **2** would be consistent with the intermediacy of an α-carbonyl cation. However, the nitration of alkenes with nitric acid can occur by a variety of mechanisms,[9] and hence a number of alternative mechanisms may also be proposed for the α,β-unsaturated esters. Below we consider three: mechanism 1 features a concerted addition of the nitronium ion and water to the double bond. The mechanism would not require extensive build up of positive charge α to the ester, but it would require the organisation of three species in the transition state. A second possible mechanism could involve a [2 + 2] cycloaddition[10] of the nitronium ion to the alkene to give cyclic structure **4**. Ring opening by water would lead to the isolated nitro alcohol **5**.[11] A third explanation might be that the nitric acid acts as a source of $NO_2^{\bullet}$ and this adds to the alkene[12] forming a nitroalkyl radical. This could then be trapped by $ONO^{\bullet}$ to form the nitro nitrite **6**, as for the reactions of alkenes with N_2O_4. Hydrolysis would then afford the nitro alcohol **2**.

The wish to distinguish between these and other possible mechanisms prompted the current study of the nitration of α,β-unsaturated esters; in particular we were keen to look for any evidence for the involvement of α-carbonyl cations. We chose



Scheme 1

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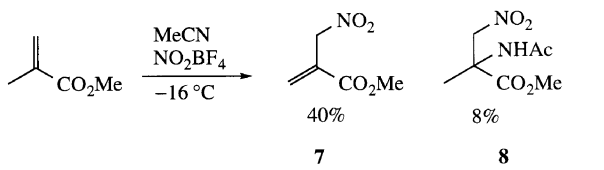
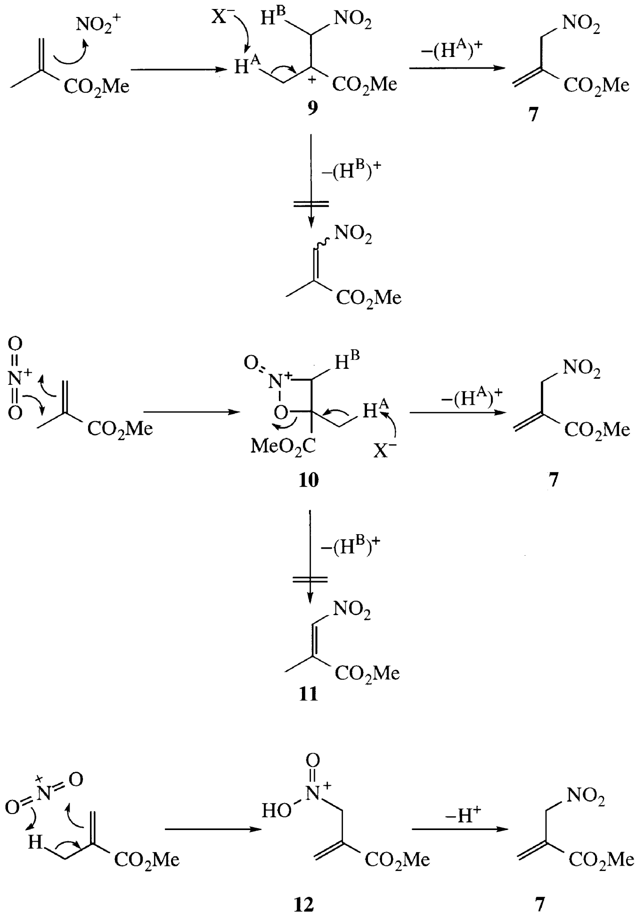
the nitration of α,β-unsaturated esters in dry acetonitrile with nitronium tetrafluoroborate for these studies.[13]

Discussion

Nitration of methyl methacrylate afforded two products, the allylic nitro compound **7** and the nitroacetamide **8**. Three possible mechanisms can be proposed for the formation of **7** (Scheme 2). The first of these is a mechanism where addition of





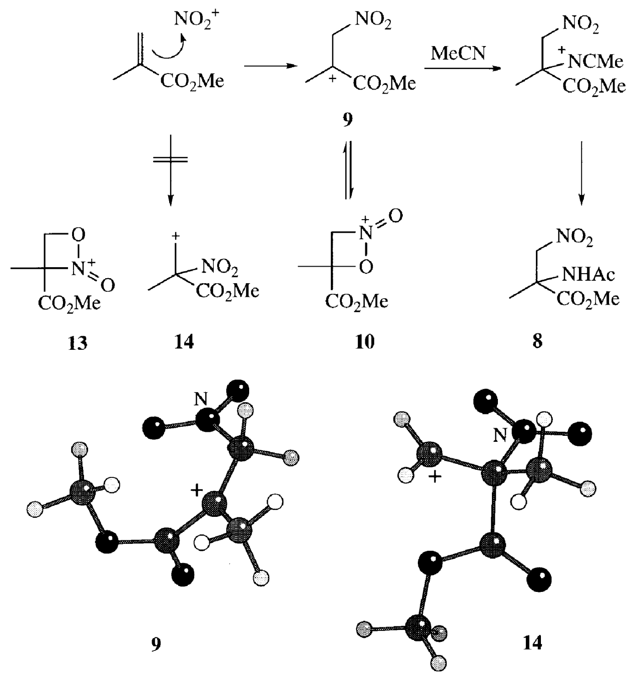
Scheme 2

the nitronium ion occurs to give the α-carbonyl cation **9**; deprotonation of H^A would give the allylic nitro compound **7**. On this mechanism one might expect to isolate product(s) resulting from loss of H^B; none was observed.

A second possible mechanism features the [2 + 2] cycloaddition[10] described above. Deprotonation would then occur from the exocyclic site H^A rather than from the endocyclic site H^B, accounting for the formation of **7** rather than **11**.

A third mechanism would also account for the exclusive formation of the allylic nitro compound **7** rather than the conjugated nitro compound **11**. It involves an ene reaction, with the nitronium ion acting as the enophile.[10] Deprotonation of **12** would afford the observed product **7**.

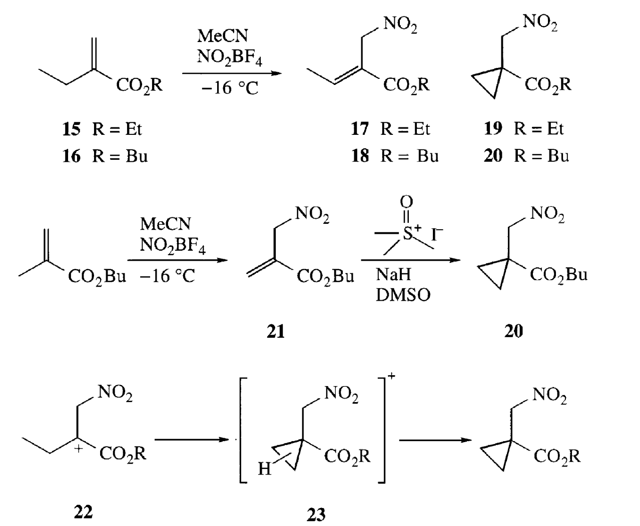
As for the formation of compound **8**, the regiochemistry suggested that an α-carbonyl cation **9** might be an intermediate in its formation, which was then trapped by acetonitrile. To obtain further understanding of the relative stabilities of the possible intermediate cations in this reaction, calculations have been carried out using AM1. These showed that the tertiary α-carbonyl cation **9** was of considerably lower energy ($\Delta E = 21$ kcal mol^{-1}; 1 cal = 4.184 J) than the alternative primary carbocation **14**, mirroring the regiochemical findings of the experiment (Scheme 3). Interestingly, however, the four-membered



Scheme 3

ring system **10** is *ca.* 1 kcal mol^{-1} lower in energy than **9**. Hence this may be in equilibrium with **9**. Further, the four-membered ring system **13** is apparently lower in energy than any of **9**, **10** or **14**. This implies that there are significant kinetic barriers to the formation of **13**.

Following this finding, a number of analogues of methyl methacrylate were prepared and subjected to nitration. These compounds were uniformly prepared from the corresponding malonates. The first pair were ethyl substituted acrylates **15** and **16** (Scheme 4). Nitration of these compounds provided allylic



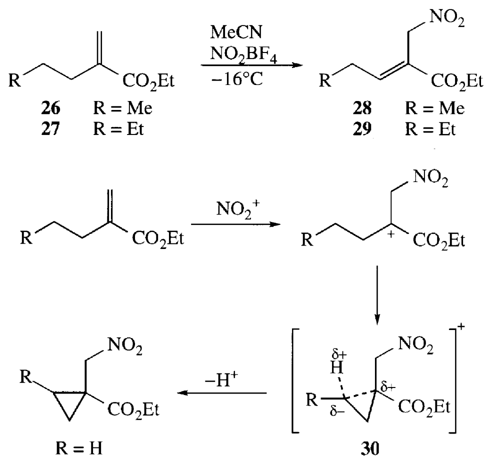
Scheme 4

nitro compounds, **17** and **18** respectively and cyclopropanes, **19** and **20** respectively. The identity of cyclopropane **20** was confirmed by an independent synthesis. Nitration of butyl methacrylate afforded the allylic nitro compound **21**. This was cyclopropanated using the Corey ylide method[14] to give the cyclopropane **20**. The formation of the cyclopropanes provided excellent evidence for the high level of positive charge developed on the α-carbon. It is proposed that the α-carbonyl cations **22** cyclised *via* the protonated cyclopropanes **23**.

The formation of cyclopropanes from propyl cations appears to have been first reported by Skell and Starer,[15] and Silver[16] in consecutive publications. Both publications were concerned with the constituents of the hydrocarbon fractions obtained from the deamination of aminopropane using aqueous nitrous acid solution. The authors proposed that the propyl cation cyclised *via* protonated cyclopropane to form the observed product, cyclopropane.

More recently, high level *ab initio* studies have been carried out[17,18] on the $C_3H_7^+$ and $C_4H_9^+$ potential energy surfaces and these calculations suggested that protonated cyclopropanes are minima on these surfaces, which supports Skell's proposal. Protonated cyclopropanes have been reviewed.[19–21] ‡

Inspired by these cyclopropanation reactions, it was felt that nitration of suitably substituted acrylates with longer alkyl chains might lead to the formation of substituted cyclopropanes. To test this hypothesis, the esters **26** and **27** were prepared (Scheme 5). However, on nitration, only the allylic nitro

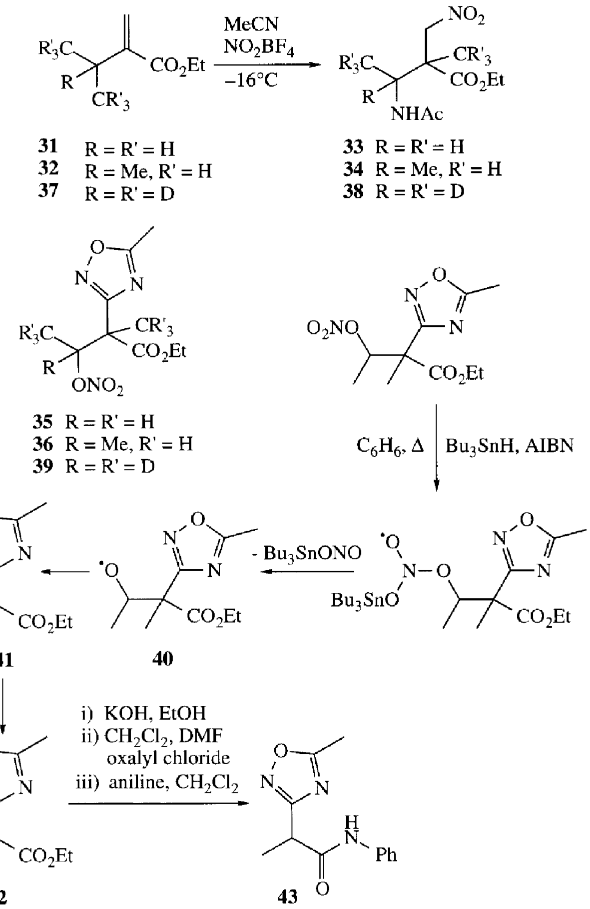


Scheme 5

compounds **28** and **29** were isolated, with no trace of the corresponding cyclopropanes.

There are two possible explanations as to why no cyclopropanation was seen in these reactions. The first considers steric interactions in the transition state **30** for the formation of the protonated cyclopropane. When R is methyl or ethyl, there may be steric interactions between R and either the ester or the nitromethyl group, preventing the cyclisation. With R = H, the interactions would be much less serious allowing the cyclisation to occur. The second explanation considers electronic distribution in the transition state. There may be negative charge build up on the γ-carbon and this will be destabilised by an inductive effect where R is methyl or ethyl.

The formation of cyclopropanes indicates the intermediacy of propyl cations. However a more commonly reported reaction for carbocations is the Wagner–Meerwein rearrangement. To see if Wagner–Meerwein rearrangements could be observed in these nitration reactions, more highly substituted acrylates were prepared. On nitration of the acrylate esters **31** and **32**, the predicted Wagner–Meerwein migration did occur. The products isolated were the 1,3-nitroacetamides **33** and **34** and rather surprisingly, the oxadiazoles **35** and **36** respectively (Scheme 6).

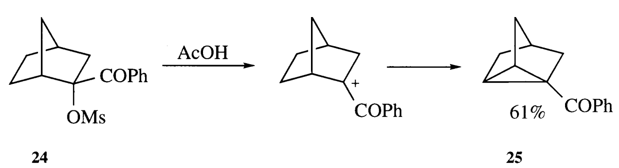


Scheme 6

The structure of the oxadiazole **35** was determined by analysis of the physical data. Combustion analysis suggested the molecular formula $C_{10}H_{15}N_3O_6$ and this was confirmed by the presence of $(M + H)^+$ in the FAB spectrum. The ester group was clearly present from both NMR and IR spectra. The presence of the nitrate functional group was determined by absorbances at 1634 and 1280 cm^{-1} in the IR spectrum, by the loss of ONO_2 in the EI spectrum and by the loss of NO_2 and ONO_2 in the FAB mass spectrum. The oxadiazole ring was more difficult to assign, but showed a characteristic IR absorbance at 1588 cm^{-1}. The UV spectrum showed no absorbance above 205 nm; weak UV absorbances are characteristic of 1,2,4-oxadiazoles. The EI mass spectrum showed a peak at *m/z* 138 (59%), due to a molecular fragment $(C_6H_6N_2O_2)^{+\bullet}$. Although the mechanism of the formation of this ion may be quite complex, it is likely that this fragment is formed by loss of the elements of OEt and $MeCHONO_2$ from the parent ion. This suggested oxadiazole **35** as a likely product structure and also suggested that a methyl migration had occurred.

It was thought that the mass spectrum of the heptadeuteriated analogue of the oxadiazole could confirm that the migration had occurred, thus providing important evidence for the structure of this product. Accordingly, the acrylate ester **37** was prepared, starting from 2-bromo[$^2H_7$]propane. As expected, nitration afforded the deuteriated nitroacetamide **38** and oxadiazole **39**. The EI mass spectrum of this oxadiazole showed a peak at *m/z* 141 (66%), analogous to the fragment discussed

‡ Reference should be made at this stage to another published example of cyclopropane formation from an α-carbonyl cation. This occurred[22] on solvolysis of the norbornyl methyl sulfonate **24**. Presumably the cyclopropane **25** was formed from the α-carbonyl cation which cyclised *via* a protonated cyclopropane. Products resulting from Wagner–Meerwein rearrangements were also isolated.



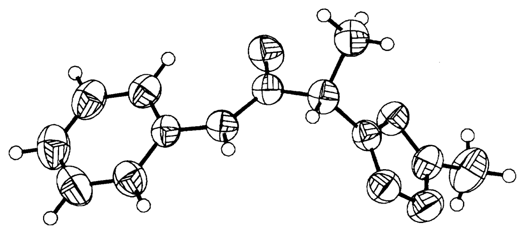
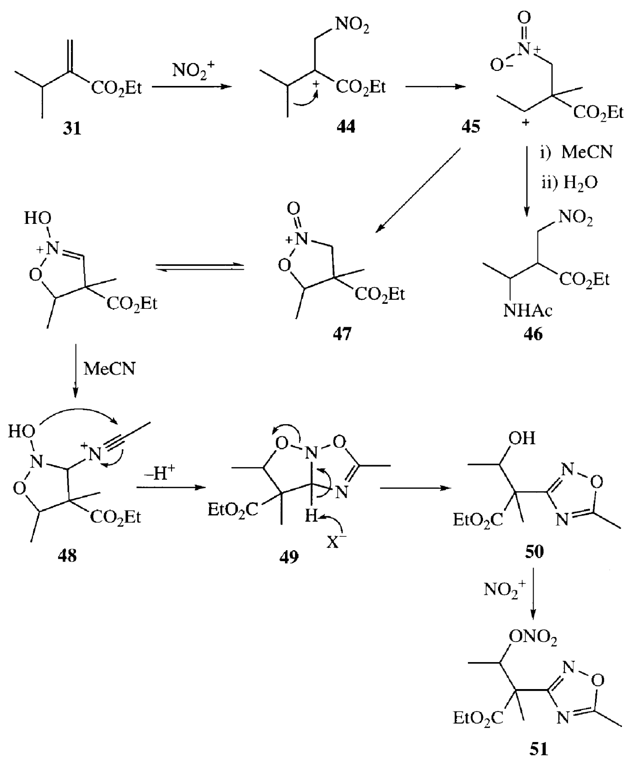


Fig. 1 X-Ray crystal structure of **43**

above, which backed up the suggestion that the methyl migration had occurred in the formation of the compound.

To confirm the structure of the oxadiazole **35**, an X-ray crystal structure determination of a derived compound was sought. Compound **35** existed as a 3:1 mixture of diastereomers and so to simplify this situation, it was reacted with tributyltin hydride in benzene with a small amount of AIBN initiator. The tributyltin radicals were predicted to attack the nitrate ester,[23] and form the alkoxyl radical **40** with loss of tributyltin nitrite. Fragmentation, with loss of acetaldehyde would afford the stabilised radical **41**, which should abstract hydrogen from tributyltin hydride to form the ester **42**. The ester **42** was indeed formed and was then converted *via* its acid and acid chloride into the anilide **43**. This was a white crystalline solid and an X-ray crystal structure was determined (Fig. 1).[13] §

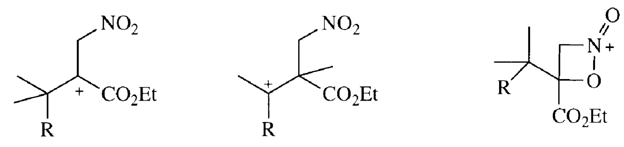
With this confirmation of structure in hand, it remained to explain the formation of nitroacetamide **33** and oxadiazole **35**. Nitration of the double bond in **31** occurs to form the α-carbonyl cation **44** (Scheme 7). Methyl migration then occurs to form the



Scheme 7

more stable secondary cation **45**. This is trapped by acetonitrile in a Ritter reaction to give **46**. Alternatively, the cation is trapped by the intramolecular nitro group, forming the cyclic structure **47**. Tautomerism of this intermediate, followed by attack of acetonitrile gives the nitrilium species **48**. 5-*endo-dig* Cyclisation

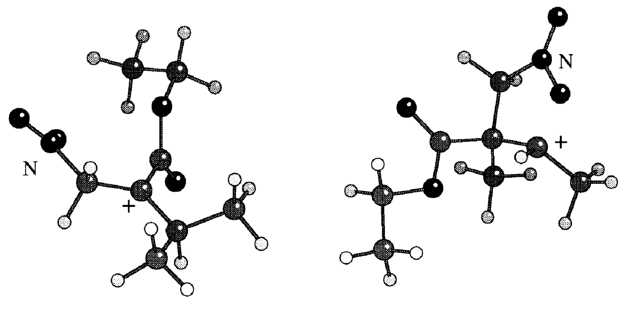
§ Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/101.



R = H, **44** R = Me, **52**

R = H, **45** R = Me, **53**

R = H, **54** R = Me, **55**



44 **45**

Fig. 2

followed by deprotonation would then form the bicyclic compound **49**, which on aromatisation would give the oxadiazole **50**. Subsequent nitration of the alcohol affords the nitrate ester **51**.

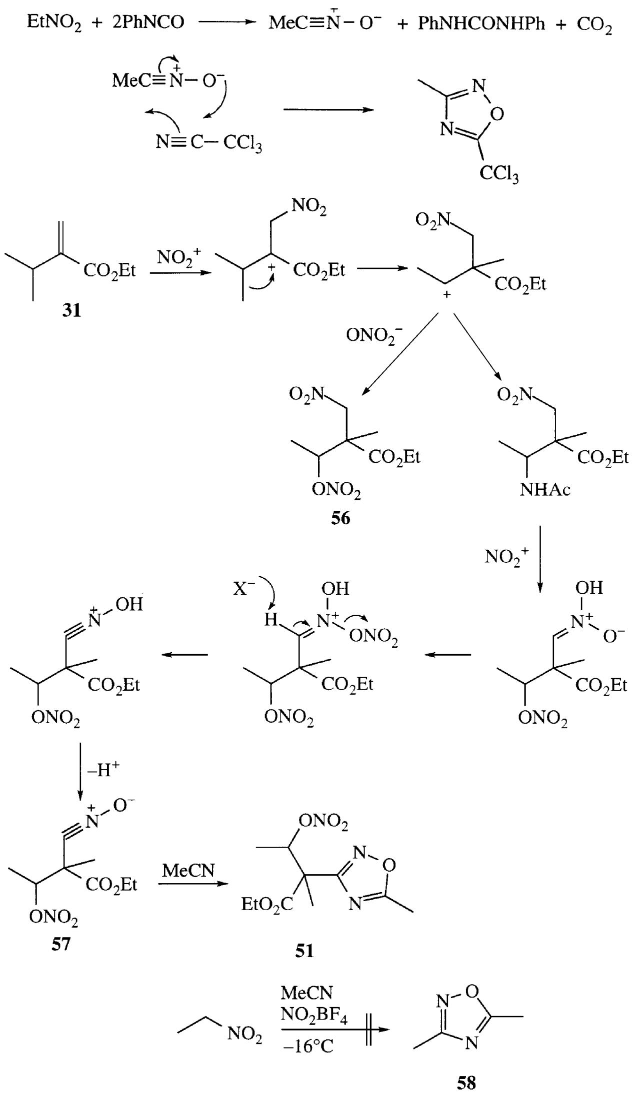
AM1 calculations were performed on **44** and **45** (Fig. 2). The results showed the secondary cation **45** to be 35 kcal mol^{-1} more stable than the tertiary α-carbonyl cation **44**, confirming that the methyl migration was favourable. (Furthermore, AM1 calculations found that the minimised structure of the tertiary cation **53** was 36 kcal mol^{-1} more stable than that of the tertiary α-carbonyl cation **52** again in line with the observed migration seen in the reaction of ester **32**. In both **45** and **53**, considerable bonding is seen between the nitro oxygen and the carbocation; these carbocations are substantially distorted from planarity as a result; the nitro oxygen–carbocation distance is 1.51 Å in **45** and 1.54 Å in **53**. Cations **44** and **52** appear to be between 1 and 2 kcal mol^{-1} more stable than their four-membered ring counterparts **54** and **55**).

The chemistry of 1,2,4-oxadiazoles has been reviewed by Eloy.[24] He reported that these heterocycles may be prepared by reaction of a nitrile, a nitro compound, phenyl isocyanate and catalytic triethylamine. For a previous report of this synthesis see Mukaiyama and Hoshino.[25] This reaction involves a dehydration of the nitro compound to a nitrile oxide by phenyl isocyanate followed by a cycloaddition reaction (Scheme 8). (The reaction only worked for nitriles which were activated by electron-withdrawing groups.) Anneser *et al.*[26] have also reported that the cycloaddition of nitriles to nitrile oxides requires an activated nitrile. A similar mechanism might apply in this case. [We are grateful to Drs M. J. E. Hewlins (Cardiff) and W. J. Kerr (Strathclyde) for independently making this suggestion.] The Scheme shows that **31** may react to afford a nitronitrate **56**. Further reaction with the nitronium ion acting as dehydrating agent could form nitrile oxide **57**. The cycloaddition then occurs with acetonitrile to give the oxadiazole **51**.

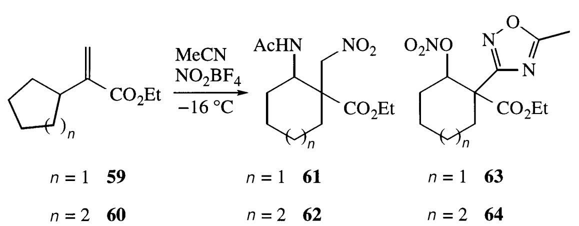
To investigate this pathway, nitroethane was reacted with nitronium tetrafluoroborate in acetonitrile. No trace of the oxadiazole **58** was seen under these conditions, suggesting that this type of reaction is not related to our oxadiazole formation.

Finally, the cyclic substrates **59** and **60** were prepared to test the generality of the Wagner–Meerwein migrations (Scheme 9). Nitration of these compounds afforded the ring expanded nitroacetamides **61** and **62** and the oxadiazoles **63** and **64**.

In conclusion, these studies show three strands of evidence for the build-up of considerable positive charge on the carbon adjacent to the carbonyl group in the nitration of α,β-unsaturated esters, namely (i) the Ritter reaction seen in the



Scheme 8



Scheme 9

formation of **8**, (ii) the formation of cyclopropanes **19** and **20** and (iii) the Wagner–Meerwein rearrangements of intermediates derived from **31**, **32**, **37**, **59** and **60**. The mechanisms proposed in Scheme 1 avoid mandatory accumulation of positive charge α to a carbonyl group, but the results presented here clearly demonstrate that a *tertiary* carbon adjacent to an ester carbonyl may indeed bear significant positive charge and such cases are likely to be widely encountered in synthetic chemistry.

Compound **7** and related allylic nitro compounds may arise by an ene reaction; the ene reaction could feature considerable positive charge adjacent to the carbonyl group. However, intermediates such as **10** appear from our AM1 calculations to be comparable in energy to **9** and so may feature in our reactions.

Experimental

General information

Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Microanalyses were determined using a Perkin-Elmer 240B elemental analyser. IR spectra were measured using a Perkin-Elmer 1600 series FTIR spectrometer. UV spectra were recorded on a Philips PU8720 instrument. ^{1}H NMR spectra were recorded at 250 MHz with a digital resolution of 0.25 Hz per point on a Bruker WM250, at 270 MHz with a digital resolution of 0.33 per Hz point or at 400 MHz with a digital resolution of 0.31 Hz per point on a Bruker AM400 machine. ^{13}C NMR spectra were recorded at 67.8 MHz on a JEOL EX270 or at 100 MHz on a Bruker AM400 machine. These were run as decoupled spectra and assigned using DEPT and correlation spectroscopy. All NMR experiments were carried out in deuteriochloroform with tetramethylsilane as internal reference. Coupling constants (J) are reported in hertz (Hz). In several cases, where mixtures of diastereomers were obtained, the overlapping signals have been reported as multiplets, unless the coupling constant of each isomer could be ascertained. In cases where one isomer was formed in excess, wherever possible the minor isomer has been marked (*). The following abbreviations have been used to assign the multiplicity of the signals observed in the ^{1}H NMR spectra; s singlet, d doublet, t triplet, q quartet, m m, br broad. Mass spectra [electron impact (EI) and fast atom bombardment (FAB)] were recorded on VG AE1 MS902, VG Micromass 70E or VG Autospec spectrometers. Some of the high resolution FAB spectra were recorded at the EPSRC Mass Spectrometry Service, Swansea on a VG Autospec. FAB mass spectra were recorded for positive ions in a *m*-nitrobenzyl alcohol matrix. The X-ray crystal structure was recorded at the EPSRC X-ray crystallography service, Cardiff.

Where necessary, solvents were dried and/or distilled before use. THF was dried over sodium wire and distilled freshly from potassium–benzophenone. Acetonitrile was dried over 4 Å molecular sieves and distilled from calcium hydride. Dichloromethane was distilled from calcium hydride. DMSO was dried over 4 Å sieves and vacuum distilled. Benzene was dried over sodium wire. All light petroleum (petrol) was of boiling range 40–60 °C and was distilled before use. Hexane was a mixture of isomeric hexanes and was distilled before use. Flash column chromatography was performed using Sorbsil C60 (May & Baker), Kieselgel 60 (Art 9385) or Kieselgel HF254 silica gels.

AM1 calculations were performed on a Silicon Graphics Indy R5000, using the Spartan calculational package available from Wavefunction Inc.

Nitration of methyl methacrylate in acetonitrile

Nitronium tetrafluoroborate (458 mg, 3.44 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with argon. The stirred solution was cooled in a salt–ice bath at −16 °C and methyl methacrylate (688 mg, 6.88 mmol) was added rapidly. The reaction was stirred for 2 h, water (50 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were dried over sodium sulfate and evaporated to give a pale yellow oil (369 mg).

Column chromatography (50% ethyl acetate–petrol) led to the isolation of methyl 2-methylene-3-nitropropanoate[27,28] **7** as a colourless oil (200 mg, 1.38 mmol, 40%) (Found: C, 41.3; H, 5.1; N, 9.9. $C_5H_7NO_4$ requires C, 41.4; H, 4.8; N, 9.7%) [Found: $M^+ - OMe$ (EI), 114.0193. $C_5H_7NO_4$ requires $M^+ - OMe$, 114.0191]; ν_{max}(film)/cm^{-1} 3014, 2958 (CH), 1724 (C=O), 1644 (C=C), 1560 (N=O), 1348 (N=O), 899 (=CH_2); δ_H(250 MHz, $CDCl_3$) 3.82 (3 H, s, CO_2Me), 5.20 (2 H, d, J 0.9, CH_2), 6.06 (1 H, br s, =CH), 6.64 (1 H, br s, =CH); δ_C(67.8 MHz, $CDCl_3$) 52.2 (OMe), 74.9 (CH_2NO_2), 130.2 (=C), 133.9 (CH_2), 164.7 (C=O); *m/z* (EI) 114 ($M^+ - OMe$, 29%), 99 ($M^+ - NO_2$, 55), 59 (CO_2Me^+, 100); and *methyl 2-acetamido-2-methyl-3-nitropropanoate* **8** as a white solid which was recrystallised from diethyl ether (56 mg, 0.28 mmol, 8%); mp 84–87 °C [Found: $(M + H)^+$ (FAB) 205.0819. $C_7H_{12}N_2O_5$ requires $(M + H)^+$, 205.0824]; ν_{max}($CHCl_3$)/cm^{-1} 3411 (N–H), 1748 (C=O), 1681 (C=O), 1558 (N=O), 1357 (N=O); δ_H(250 MHz, $CDCl_3$) 1.66 (3 H, s, Me), 2.02 (3 H, s, Me), 3.85 (3 H, s, Me), 4.95 (1 H, d, *J* 13.4, CH_2NO_2), 5.43 (1 H, d, *J* 13.4, CH_2NO_2), 6.66 (1 H, br s, NH); δ_C(67.8 MHz, $CDCl_3$) 20.9 (Me), 23.4 (Me), 53.5 (Me), 58.2 (C), 76.9 (CH_2), 170.2 (C=O), 171.6 (C=O); *m/z* (FAB) 205 [$(M + H)^+$, 33%], 158 ($M^+ - NO_2$, 7), 43 (Ac^+, 85).

Synthesis of ethyl 2-methylenebutanoate 15 [29]

Potassium hydroxide (4.48 g, 80.0 mmol) in dry ethanol (70 ml) was added dropwise over 2 h to a stirred solution of diethyl 2-ethylpropanedioate (15.0 g, 80.0 mmol) in dry ethanol (25 ml). The solution was stirred at room temperature for 24 h and the alcohol evaporated off. The high viscosity residue was dissolved in water (30 ml) and extracted with dichloromethane (2 × 20 ml). The aqueous layer was cooled in ice and concentrated hydrochloric acid (6.6 ml) was added dropwise. The reaction mixture was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give ethyl hydrogen 2-ethylpropanedioate as a colourless oil (9.34 g, 58.4 mmol, 73%). Piperidine (600 mg, 7.06 mmol) and paraformaldehyde (1.74 g, 58.0 mmol) were added to a solution of the ethyl hydrogen 2-ethylpropanedioate in pyridine (15 ml). The solution was heated under reflux until the end of evolution of carbon dioxide.

After cooling, the reaction was poured onto water (50 ml) and extracted with pentane (3 × 50 ml). The pentane phases were washed successively with water (20 ml), 2 M hydrochloric acid (20 ml), water, saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give ethyl 2-methylenebutanoate **15** as a colourless oil (4.45 g, 39.0 mmol, 49%, 67% from half ester) [Found: M^+ (EI), 128.0810. $C_7H_{12}O_2$ requires *M*, 128.0837]; ν_{max}(film)/cm^{-1} 2973, 2878 (CH), 1719 (C=O), 1631 (C=C), 1176 (C–O), 818 (=CH_2); δ_H(250 MHz, $CDCl_3$) 1.08 (3 H, t, *J* 7.4, Me), 1.30 (3 H, t, *J* 7.0, Me), 2.33 (2 H, qdd, *J* 7.4, 1.5, 0.4, CH_2), 4.21 (2 H, q, *J* 7.0, OCH_2), 5.51 (1 H, m, =CH), 6.13 (1 H, m, =CH); δ_C(67.8 MHz, $CDCl_3$) 12.6 (Me), 14.2 (Me), 24.8 (CH_2), 60.5 (OCH_2), 123.2 (=CH_2), 142.5 (=C), 167.2 (C=O); *m/z* (EI) 128 (M^+, 14%), 113 ($M^+ - Me$, 27), 100 ($M^+ - C_2H_4$, 34), 55 ($M^+ - CO_2Et$, 100).

Nitration of ethyl 2-methylenebutanoate 15

Nitronium tetrafluoroborate (687 mg, 5.16 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and ethyl 2-methylenebutanoate (1.32 g, 10.3 mmol) was added rapidly. The reaction was stirred for 2 h, water (30 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a pale yellow oil (954 mg). Column chromatography (6–10–100% ethyl acetate–petrol) led to the isolation of a mixture of isomers (348 mg, 4.02 mmol, 39%). HPLC [(3% ethyl acetate–hexane) (3 ml min^{-1}), Waters Porasil 125 Å 15–20 µm, 9 × 300 mm] led to the isolation of *ethyl* 2-*nitromethylbut*-2-*enoate* **17** as a colourless oil (Found: C, 48.5; H, 6.6; N, 7.8. $C_7H_{11}NO_4$ requires C, 48.5; H, 6.4; N, 8.1%) [Found: $M^+ - NO_2$ (EI), 127.0746. $C_7H_{11}NO_4$ requires $M - NO_2$, 127.0759]; ν_{max}-($CHCl_3$)/cm^{-1} 2990, 2928, 2853 (CH), 1712 (C=O), 1658 (C=C), 1564 (N=O), 1347 (N=O), 1145 (C–O); δ_H(400 MHz, $CDCl_3$) 1.30 (3 H, t, *J* 7.1, Me), 1.97 (3 H, d, *J* 7.3, Me), 4.25 (2 H, q, *J* 7.1, OCH_2), 5.26 (2 H, s, CH_2NO_2), 7.39 (1 H, q, *J* 7.3, =CH); δ_C(67.8 MHz, $CDCl_3$) 14.1 (Me), 15.0 (Me), 61.5 (CH_2), 70.0 (CH_2), 123.7 (=C), 147.1 (=CH), 165.2 (C=O); *m/z* (EI) 127 ($M^+ - NO_2$, 100%), 99 ($C_4H_5NO_2^+$, 92), 81 ($C_5H_5O^+$, 60); and *ethyl* 1-*nitromethylcyclopropanecarboxylate* **19** as a colourless oil (Found: C, 48.6; H, 6.7; N, 8.0. $C_7H_{11}NO_4$ requires C, 48.5; H, 6.4; N, 8.1%) [Found: $M^+ - NO_2$ (EI), 127.0763. $C_7H_{11}NO_4$ requires $M - NO_2$, 127.0759]; ν_{max}($CHCl_3$)/cm^{-1} 2945, 2837 (CH), 1727 (C=O), 1564 (N=O), 1345 (N=O), 1160 (C–O); δ_H(250 MHz, $CDCl_3$) 1.06 (2 H, dd, *J* 7.6, 4.8, CH_2), 1.24 (3 H, t, *J* 7.1, Me), 1.57 (2 H, dd, *J* 7.6, 4.8, CH_2), 4.17 (2 H, q, *J* 7.1, OCH_2), 4.53 (2 H, s, CH_2NO_2); δ_C(100 MHz, $CDCl_3$) 14.1 (Me), 15.5 (2 CH_2), 21.6 (C), 61.7 (CH_2), 78.2 (CH_2), 171.9 (C=O); *m/z* (EI) 128 ($M^+ - NO_2 + H$, 16%), 127 ($M^+ - NO_2$, 6), 99 ($M^+ - CO_2Et$, 100).

Synthesis of butyl 2-methylenebutanoate 16 [30]

Potassium hydroxide (4.00 g, 71.4 mmol) in dry ethanol (70 ml) was added dropwise over 2 h to a stirred solution of diethyl 2-ethylpropanedioate (13.4 g, 71.4 mmol) in dry butan-1-ol (25 ml). The solution was stirred at room temperature for 30 h and the alcohol evaporated off. The high viscosity residue was dissolved in water (30 ml) and extracted with dichloromethane (2 × 20 ml). The aqueous layer was cooled in ice and concentrated hydrochloric acid (5.95 ml) was added dropwise. The reaction mixture was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give butyl hydrogen 2-ethylpropanedioate as a colourless oil (11.8 g, 62.7 mmol).

Piperidine (600 mg, 7 mmol) and paraformaldehyde (1.89 g, 63 mmol) were added to a solution of butyl hydrogen 2-ethylpropanedioate in pyridine (15 ml). The solution was heated under reflux until the end of evolution of carbon dioxide.

After cooling, the reaction was poured onto water (50 ml) and extracted with pentane (3 × 50 ml). The pentane phases were washed successively with water (20 ml), 2 M hydrochloric acid (20 ml), water (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a pale yellow oil. Column chromatography (8% diethyl ether–pentane) led to the isolation of butyl 2-methylenebutanoate **16** as a colourless oil (1.90 g, 13.4 mmol, 19%) [Found: M^+ (EI), 156.1141. $C_9H_{16}O_2$ requires *M*, 156.1150] (Found: C, 69.3; H, 10.7. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%); ν_{max}(film)/cm^{-1} 2963, 2875 (CH), 1720 (C=O), 1632 (C=C), 1168 (C–O), 817 (=CH); δ_H(250 MHz, $CDCl_3$) 0.96 (3 H, t, *J* 7, Me), 1.09 (3 H, t, *J* 7, Me), 1.41 (2 H, m, CH_2), 1.67 (2 H, m, CH_2), 2.34 (2 H, m, CH_2), 4.17 (2 H, t, *J* 7, OCH_2), 5.52 (1 H, dd, *J* 3.1, 1.2, =CH), 6.14 (1 H, dd, *J* 2.3, 1.3, =CH); δ_C(67.8 MHz, $CDCl_3$) 12.4 (Me), 13.4 (Me), 19.0 (CH_2), 24.6 (CH_2), 30.5 (CH_2), 64.0 (OCH_2), 122.8 (=CH_2), 142.3 (=C), 166.9 (C=O); *m/z* (EI) 156 (M^+, 1%), 127 ($M^+ - Et$, 2), 101 (CO_2Bu^+, 100), 83 ($M^+ - OBu$, 82), 55 ($M^+ - CO_2Bu$, 75).

Nitration of butyl 2-methylenebutanoate 16

Nitronium tetrafluoroborate (367 mg, 2.75 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and butyl 2-methylenebutanoate (850 mg, 5.51 mmol) was added rapidly. The reaction was stirred for 2 h, water (50 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a pale orange oil (795 mg). Column chromatography (8–100% ethyl acetate, hexane) led to the separation of a mixture of isomers (200 mg, 0.99 mmol, 36%). HPLC [(4% ethyl acetate–hexane) (3 ml min^{-1}), Waters Porasil 125 Å, 15–20 µm, 9 × 300 mm] led to the isolation of *butyl* 2-*nitromethylbut*-2-*enoate* **18** as a colourless oil (NMR yield 28%) [Found: $(M + H)^+$ (FAB), 202.1065. $C_9H_{15}NO_4$ requires $(M + H)^+$, 202.1079] (Found: C, 54.0; H, 7.7; N, 7.0. $C_9H_{15}NO_4$ requires C, 53.7; H, 7.1; N, 7.0%); ν_{max}($CHCl_3$)/cm^{-1} 2934 (CH), 1710 (C=O), 1658 (C=C), 1561 (N=O), 1348 (N=O), 1146 (C–O); δ_H(250 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 7.3, Me), 1.39 (2 H, tq, *J* 7.3, 7.3, CH_2), 1.65 (2 H, m, CH_2), 1.97 (3 H, d, *J* 7.3, Me), 4.19 (2 H, t, *J* 7.3, OCH_2), 5.26 (2 H, s, CH_2NO_2), 7.37 (1 H, q, *J* 7.3, =CH); δ_C(67.8 MHz, $CDCl_3$) 13.6 (Me), 14.9 (Me), 19.1 (CH_2), 30.5 (CH_2), 65.3 (CH_2), 69.9 (CH_2), 123.8 (C), 147.0 (CH), 165.2

(C=O); *m/z* (FAB) 403 [(2 M + H)$^+$, 4%], 202 [(M + H)$^+$, 100], 155 (M$^+$ − NO_2, 23), 154 (M$^+$ − HNO_2, 23), 128 (M$^+$ − OBu, 48); and *butyl 1-nitromethylcyclopropanecarboxylate* **20** as a colourless oil (NMR yield 22%) [Found: (M + H)$^+$ (FAB), 202.1072. $C_9H_{15}NO_4$ requires (M + H)$^+$, 202.1079] (Found: C, 53.6; H, 7.7; N, 6.8. $C_9H_{15}O_4N$ requires C, 53.7; H, 7.5; N, 7.0%); ν_{max}($CHCl_3$)/cm^{-1} 2934 (CH), 1725 (C=O), 1562 (N=O), 1347 (N=O), 1169 (C−O); δ_H(250 MHz, $CDCl_3$) 0.92 (3 H, t, *J* 7.2, Me), 1.07 (2 H, dd, *J* 6.1, 4.8, CH_2), 1.34 (2 H, m, CH_2), 1.60 (4 H, m, CH_2), 4.11 (2 H, t, *J* 6.6, OCH_2), 4.52 (2 H, s, CH_2NO_2); δ_C(67.8 MHz, $CDCl_3$) 13.6 (Me), 15.5 (2 CH_2), 19.0 (CH_2), 21.6 (C), 30.5 (CH_2), 65.5 (CH_2), 78.1 (CH_2NO_2), 171.9 (C=O); *m/z* (FAB) 403 [(2 M + H)$^+$, 4%], 202 [(M + H)$^+$, 100], 155 (M$^+$ − NO_2, 23), 128 (M$^+$ − OBu, 60).

Nitration of butyl methacrylate

Nitronium tetrafluoroborate (541 mg, 4.07 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and butyl methacrylate (578 mg, 648 µl, 4.07 mmol) was added rapidly. The reaction was stirred for 2 h, water (50 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a pale yellow oil (615 mg). Column chromatography (10% ethyl acetate–hexane) led to the isolation of butyl 2-methylene-3-nitropropanoate[27] **21** as a colourless oil (260 mg, 1.39 mmol, 34%) (Found: C, 51.4; H, 7.3; N, 7.3. $C_8H_{13}NO_4$ requires C, 51.3; H, 7.0; N, 7.5%); ν_{max}($CHCl_3$)/cm^{-1} 2962, 2875 (CH), 1722 (C=O), 1645 (C=C), 1562 (N=O), 1341 (N=O); δ_H(250 MHz, $CDCl_3$) 0.94 (3 H, t, *J* 7, Me), 1.67 (2 H, m, CH_2), 3.81 (2 H, m, CH_2), 4.22 (2 H, t, *J* 7, OCH_2), 5.17 (2 H, s, CH_2NO_2), 6.00 (1 H, s, =CH), 6.63 (1 H, s, =CH); δ_C(67.8 MHz, $CDCl_3$) 13.4 (Me), 18.9 (CH_2), 30.3 (CH_2), 65.4 (CH_2), 75.2 (CH_2NO_2), 130.7 (=C), 133.5 (=CH_2), 164.3 (C=O); *m/z* (FAB) 46 (NO_2^+, 73%).

Cyclopropanation of butyl 2-methylene-3-nitropropanoate 21

Sodium hydride (47.2 mg of 60% dispersion, 1.18 mmol) was washed with tetrahydrofuran (2 × 3 ml) and then DMSO (5 ml) was added. Trimethylsulfoxonium iodide (259 mg, 1.18 mmol) was added in one portion. After stirring for 45 min, butyl 2-methylene-3-nitropropanoate (200 mg, 1.07 mmol) in DMSO (1 ml) was added rapidly. After stirring for 1.5 h, the reaction was quenched with 3% cold hydrochloric acid (10 ml). The reaction was extracted with diethyl ether (3 × 30 ml). The combined ether extracts were dried over sodium sulfate and evaporated to give a brown oil. Column chromatography (10% ethyl acetate–hexane) led to the isolation of butyl 1-nitromethylcyclopropanecarboxylate contaminated with iodine. The mixture was taken up in dichloromethane (5 ml) and washed with aqueous sodium thiosulfate (5 ml). This led to the isolation of *butyl 1-nitromethylcyclopropanecarboxylate* **20** as a colourless oil (22 mg, 0.11 mmol, 10%). This compound was identical to the compound produced from the nitration of butyl 2-methylenepropanoate by TLC, ^{1}H NMR and IR spectroscopy.

Synthesis of ethyl 2-methylenepentanoate 26

Potassium hydroxide (4.48 g, 80.0 mmol) in dry ethanol (70 ml) was added dropwise over 2 h to a stirred solution of diethyl 2-propylpropanedioate (16.1 g, 80 mmol) in dry ethanol (25 ml). The solution was stirred at room temperature for 24 h and the alcohol evaporated off. The high viscosity residue was dissolved in water (30 ml) and extracted with dichloromethane (2 × 20 ml). The aqueous layer was cooled in ice and concentrated hydrochloric acid (6.6 ml) was added dropwise. The reaction mixture was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give ethyl hydrogen 2-propylpropanedioate as a colourless oil (9.74 g, 56.0 mmol, 70%).

Piperidine (600 mg, 7.06 mmol) and paraformaldehyde (1.68 g, 56.0 mmol) were added to a solution of ethyl hydrogen 2-propylpropanedioate in pyridine (15 ml). The solution was heated under reflux until the end of evolution of carbon dioxide.

After cooling, the reaction was poured onto water (50 ml) and extracted with pentane (3 × 50 ml). The pentane phases were washed successively with water, 2 M hydrochloric acid (20 ml), water (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a colourless oil. Kugelrohr distillation led to the isolation of ethyl 2-methylenepentanoate **26** as a colourless oil (4.80 g, 37.5 mmol, 47%, 67% from half ester); bp 25 °C/0.2 mmHg (lit.,[31] 48 °C/8 mmHg) [Found: M$^+$ (EI), 142.0996. $C_8H_{14}O_2$ requires *M*, 142.0994] (Found: C, 67.8; H, 10.3. $C_8H_{14}O_2$ requires C, 67.6; H, 9.9%); ν_{max}(film)/cm^{-1} 2961, 2874 (CH), 1718 (C=O), 1631 (C=C), 1160 (C−O), 818 (=CH); δ_H(250 MHz, $CDCl_3$) 0.93 (3 H, t, *J* 7.3, Me), 1.30 (3 H, t, *J* 7.1, Me), 1.50 (2 H, m, CH_2), 2.28 (2 H, t, *J* 7.3, CH_2), 4.21 (2 H, q, *J* 7.1, OCH_2), 5.51 (1 H, bd, *J* 1.4, =CH), 6.14 (1 H, d, *J* 1.4, =CH); δ_C(67.8 MHz, $CDCl_3$) 13.5 (Me), 14.1 (Me), 21.5 (CH_2), 33.8 (CH_2), 60.4 (OCH_2), 124.1 (=CH_2), 140.8 (=C), 167.2 (C=O); *m/z* (EI) 142 (M$^+$, 11%), 114 (M$^+$ − C_2H_4, 36), 97 (M$^+$ − OEt, 75), 69 (M$^+$ − CO_2Et, 100).

Synthesis of ethyl 2-methylenehexanoate 27[31]

Potassium hydroxide (2.98 g, 53.2 mmol) in dry ethanol (32 ml) was added dropwise over 30 min to a solution of diethyl 2-butylpropanedioate (11.5 g, 11.6 ml, 53.0 mmol) in dry ethanol (32 ml). The solution was stirred at room temperature for 12 h and the alcohol evaporated off. The high viscosity residue was dissolved in water (10 ml) and then concentrated hydrochloric acid (4.4 ml) was added dropwise. The reaction mixture was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give ethyl hydrogen 2-butylpropanedioate as a colourless oil.

Piperidine (430 mg, 5.06 mmol) and paraformaldehyde (1.25 g, 42.5 mmol) were added to a solution of ethyl hydrogen 2-butylpropanedioate in pyridine (15 ml). The solution was heated under reflux until the end of evolution of carbon dioxide.

After cooling, the reaction was poured onto water (50 ml) and extracted with pentane (4 × 30 ml). The pentane phases were washed successively with water, hydrochloric acid (2 M), water, saturated aqueous sodium hydrogen carbonate and brine. The combined organic extracts were dried over sodium sulfate and evaporated to give a colourless oil. Column chromatography (2% ethyl acetate–petrol) led to the isolation of ethyl 2-methylenehexanoate **27** as a colourless oil (5.84 g, 38.0 mmol, 72%) [Found: M$^+$ (EI), 156.1130. $C_9H_{16}O_2$ requires *M*, 156.1150] (Found: C, 69.1; H, 10.6. $C_9H_{16}O_2$ requires C, 69.2; H, 10.3%); ν_{max}(film)/cm^{-1} 2958, 2873 (CH), 1719 (C=O), 1631 (C=C), 1158 (C−O), 818 (=CH); δ_H(250 MHz, $CDCl_3$) 0.91 (3 H, t, *J* 7.0, Me), 1.30 (3 H, t, *J* 7.1, Me), 1.43 (4 H, m, CH_2), 2.30 (2 H, t, *J* 6.8, CH_2), 4.20 (2 H, q, *J* 7.1, OCH_2), 5.50 (1 H, d, *J* 1.2, =CH), 6.12 (1 H, s, =CH); δ_C(67.8 MHz, $CDCl_3$) 13.5 (Me), 13.8 (Me), 22.0 (CH_2), 30.4 (CH_2), 31.3 (CH_2), 60.1 (OCH_2), 123.6 (=CH_2), 140.9 (=C), 166.8 (C=O); *m/z* (EI) 156 (M$^+$, 37%), 128 (M$^+$ − C_2H_4, 31), 111 (M$^+$ − OEt, 63).

Nitration of ethyl 2-methylenepentanoate 26

Nitronium tetrafluoroborate (532 mg, 4.00 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and ethyl 2-methylenepentanoate (1.14 g, 8.03 mmol) was added rapidly. The reaction was stirred for 3 h, water (30 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a pale yellow oil (992 mg). Column chromatography (10% ethyl acetate–hexane) led to the isolation of *ethyl 2-*

nitromethylpent-2-*enoate* **28** as a colourless oil (171 mg, 0.91 mmol, 23%, NMR yield 21.4%) (Found: C, 51.4; H, 7.1; N, 7.6. $C_8H_{13}NO_4$ requires C, 51.3; H, 7.0; N, 7.5%) [Found: $M^+ - NO_2$ (EI), 141.0898. $C_8H_{13}NO_4$ requires $M - NO_2$, 141.0916]; $\nu_{max}(CHCl_3)/cm^{-1}$ 2938, 2853 (CH), 1712 (C=O), 1653 (C=C), 1564 (N=O), 1353 (N=O), 1152 (C–O); δ_H(400 MHz, $CDCl_3$) 1.13 (3 H, t, *J* 7.5, CH_3), 1.31 (3 H, t, *J* 7.3, CH_3), 2.32 (2 H, dq, *J* 7.5, 7.5, CH_2), 4.25 (2 H, q, *J* 7.1, OCH_2), 5.24 (2 H, s, CH_2NO_2), 7.27 (1 H, t, *J* 7.8, =CH); δ_C(67.8 MHz, $CDCl_3$) 12.7 (Me), 14.1 (Me), 25.6 (CH_2), 61.4 (CH_2), 70.1 (CH_2), 122.1 (=C), 153.3 (=CH), 165.3 (C=O); *m/z* (EI) 141 ($M^+ - NO_2$, 35%), 113 ($M^+ - NO_2 - C_2H_4$, 100), 95 ($M^+ - OEt - HNO_2$, 81), 67 ($M^+ - HNO_2 - CO_2Et$, 100); *m/z* (FAB) 188 [$(M + H)^+$, 11%], 141 ($M^+ - NO_2$, 12).

Nitration of ethyl 2-methylenehexanoate 27

Nitronium tetrafluoroborate (516 mg, 3.88 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and ethyl 2-methylenehexanoate (1.10 g, 7.05 mmol) was added rapidly. The reaction was stirred for 3 h, water (30 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a pale yellow oil (1.30 g). Column chromatography (10% ethyl acetate–hexane) led to the isolation of *ethyl* 2-*nitromethylhex*-2-*enoate* **29** as a colourless oil (94.1 mg, 0.47 mmol, 12%) (Found: C, 53.8; H, 7.8; N, 6.9. $C_9H_{15}NO_4$ requires C, 53.7; H, 7.5; N, 7.0%) [Found: $M^+ - OEt$ (EI), 156.0723. $C_9H_{15}NO_4$ requires $M - OEt$, 156.0661]; $\nu_{max}(CHCl_3)/cm^{-1}$ 2935, 2874 (CH), 1713 (C=O), 1652 (C=C), 1565 (N=O), 1353 (N=O), 1151 (C–O); δ_H(250 MHz, $CDCl_3$) 0.97 (3 H, t, *J* 7.4, Me), 1.31 (3 H, t, *J* 7.0, Me), 1.55 (2 H, m, CH_2), 2.27 (2 H, m, CH_2), 4.25 (2 H, q, *J* 7.0, OCH_2), 5.25 (2 H, s, CH_2NO_2), 7.28 (1 H, t, *J* 7.6, =CH); δ_C(67.8 MHz, $CDCl_3$) 13.6 (Me), 14.0 (Me), 21.5 (CH_2), 31.0 (CH_2), 61.3 (CH_2), 70.2 (CH_2NO_2), 122.7 (C), 151.8 (CH), 165.2 (C=O); *m/z* (EI) 156 ($M^+ - OEt$, 16%), 155 ($M^+ - NO_2$, 28), 127 ($M^+ - NO_2 - C_2H_4$, 27), 109 ($C_7H_{11}N^+$, 79).

Synthesis of diethyl 2-isopropylpropanedioate [32]

Sodium (960 mg, 41.7 mmol) was added to dry ethanol (20 ml) in a flask flushed with nitrogen. When the sodium had dissolved, the stirred solution was brought to 55 °C and diethyl propanedioate (6.50 g, 6.16 ml, 40.7 mmol) was added over 30 s. After stirring for 1 h, 2-bromopropane (3.61 ml, 5 g, 40.65 mmol) was added over 1 min. The solution was stirred at 55 °C for 44 h and the alcohol evaporated off. The residue was taken up in water (30 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a pale yellow liquid (6.79 g). Column chromatography of a 500 mg aliquot (10% ethyl acetate–hexane) led to the isolation of diethyl 2-isopropylpropanedioate as a colourless oil (320 mg, 1.58 mmol, 52%) (Found: C, 59.7; H, 9.3. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%) [Found: $M^+ - C_3H_6$ (EI), 160.0733. $C_{10}H_{18}O_4$ requires $M^+ - C_3H_6$, 160.0736]; $\nu_{max}(film)/cm^{-1}$ 2939, 2876 (CH), 1735 (C=O); δ_H(250 MHz, $CDCl_3$) 1.00 (6 H, d, *J* 6.7, Me), 1.27 (6 H, t, *J* 7.2, Me), 2.38 (1 H, m, CH), 3.10 (1 H, d, *J* 8.6, CH), 4.19 (4 H, *J* 7.2, OCH_2); δ_C(67.8 MHz, $CDCl_3$) 13.7 (2 Me), 20.0 (2 Me), 28.3 (CH), 58.7 (CH), 60.6 (2 CH_2), 168.4 (2 C=O); *m/z* (EI) 160 ($M^+ - C_3H_6$, 100%), 157 ($M^+ - OEt$, 76).

Synthesis of ethyl 2-methylene-3-methylbutanoate 31 [31]

Potassium hydroxide (2.98 g, 53.2 mmol) in dry ethanol (32 ml) was added dropwise over 30 min to a solution of diethyl 2-isopropylpropanedioate (10.8 g, 10.9 ml, 53.5 mmol) in dry ethanol (32 ml). The solution was stirred at room temperature for 12 h and the alcohol evaporated off. The high viscosity residue was dissolved in water (30 ml) and concentrated hydrochloric acid (4.4 ml) was added dropwise. The reaction mixture was extracted with diethyl ether (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated.

Piperidine (430 mg, 5.06 mmol) and paraformaldehyde (1.25 g, 42.5 mmol) were added to a solution of ethyl hydrogen 2-isopropylpropanedioate in pyridine (9 ml). The solution was heated under reflux until the end of evolution of carbon dioxide.

After cooling, the reaction was poured onto water (50 ml) and extracted with pentane (3 × 50 ml). The pentane phases were washed successively with water, 2 M hydrochloric acid (20 ml), water (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a colourless oil. Column chromatography (2% ethyl acetate–petrol) led to the isolation of ethyl 2-methylene-3-methylbutanoate **31** (3.19 g, 22.5 mmol, 42%) [Found: M^+ (EI), 142.0968. $C_8H_{14}O_2$ requires *M*, 142.0994] (Found: C, 67.3; H, 10.2. $C_8H_{14}O_2$ requires C, 67.6; H, 9.9%); $\nu_{max}(film)/cm^{-1}$ 2965, 2874 (CH), 1719 (C=O), 1626 (C=C), 1183 (C–O); δ_H(250 MHz, $CDCl_3$) 1.08 (6 H, d, *J* 6.8, Me), 1.31 (3 H, t, *J* 7.1, Me), 2.82 (1 H, br qq, *J* 6.8, 6.8, CH), 4.21 (2 H, q, *J* 7.1, OCH_2), 5.50 (1 H, dd, *J* 1.1, 1.1, =CH), 6.12 (1 H, br s, =CH); δ_C(67.8 MHz, $CDCl_3$) 13.9 (Me), 21.4 (2 Me), 29.0 (CH), 60.0 (OCH_2), 121.0 ($=CH_2$), 147.1 (=C), 166.9 (C=O); *m/z* (EI) 142 (M^+, 8%), 127 ($M^+ - Me$, 6), 114 ($M^+ - C_2H_4$, 24), 97 ($M^+ - OEt$, 47), 69 ($M^+ - CO_2Et$, 100).

Nitration of ethyl 2-methylene-3-methylbutanoate 31

Nitronium tetrafluoroborate (504 mg, 3.79 mmol) was added to dry acetonitrile (20 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and ethyl 2-methylene-3-methylbutanoate (1.07 g, 7.57 mmol) was added rapidly. The reaction was stirred for 2 h, water (50 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a pale yellow oil (852 mg). Column chromatography (8–70–100% ethyl acetate–pentane) led to the isolation of 3-*ethoxycarbonyl*-3-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)*butan*-2-*yl nitrate* **35** as a 2 : 3 mixture of diastereomers, as a colourless oil (176 mg, 0.64 mmol, 17.0%) [Found: $(M + H)^+$ (EI), 274.0987. $C_{10}H_{15}N_3O_6$ requires $(M + H)^+$, 274.1039] (Found: C, 44.3; H, 5.8; N, 15.3. $C_{10}H_{15}N_3O_6$ requires C, 44.0; H, 5.5; N, 15.4%); $\nu_{max}(film)/cm^{-1}$ 2989, 2907 (CH), 1743 (C=O), 1634 (ON=O), 1588 (C=N), 1280 (ON=O); δ_H(250 MHz, $CDCl_3$) 1.22 (t, *J* 7.1, Me), 1.24 (t, *J* 7.1, Me)*, 1.36 (d, *J* 6.5, Me), 1.41 (d, *J* 6.5, Me)*, 1.70 (s, Me)*, 1.71 (s, Me), 2.59 (s, Me)*, 2.61 (s, Me), 4.20 (2 H in 2 diastereomers, m, OCH_2), 5.96 (q, *J* 6.5, CH)*, 6.04 (q, *J* 6.5, CH); δ_C(67.8 MHz, $CDCl_3$) 12.4 (Me), 13.9 (Me), 13.9 (Me)*, 14.6 (Me), 15.6 (Me), 16.7 (Me)*, 50.6 (C), 50.8 (C)*, 62.4 (CH_2), 62.4 (CH_2)*, 80.2 ($CHONO_2$)*, 80.4 ($CHONO_2$), 169.3 (=C), 169.7 (=C)*, 169.8 (=C), 176.9 (=C)*, 177.2 (=C); *m/z* (EI) 274 [$(M + H)^+$, 2%], 211 ($M^+ - ONO_2$, 5), 183 ($M^+ - ONO_2 - C_2H_4$, 9), 155 ($C_7H_{11}N_2O_2^+$, 21), 138 ($C_6H_6N_2O_2^+$, 59), 43 ($C_2H_3O^+$, 100); *m/z* (FAB) 547 [$(2M + H)^+$, 3%], 274 [$(M + H)^+$, 100], 227 ($M^+ - NO_2$, 9), 211 ($M^+ - ONO_2$, 16), 138 ($C_6H_6N_2O_2^+$, 51); and *ethyl* 2-*nitromethyl*-2-*methyl*-3-*acetamidobutanoate* **33** as a 1 : 4 mixture of diastereomers, as a white solid (343 mg, 1.39 mmol, 37%); mp 92–95 °C [Found: $(M + H)^+$ (FAB), 247.1292. $C_{10}H_{18}N_2O_5$ requires $(M + H)^+$, 247.1294]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3434 (N–H), 2991 (CH), 2942 (CH), 1737 (C=O), 1674 (C=O), 1558 (N=O), 1373 (N=O); δ_H(250 MHz, $CDCl_3$) 1.08 (d, *J* 6.9, Me), 1.12 (d, *J* 6.9, Me)*, 1.23 (s, Me), 1.27 (t, *J* 7.1, Me), 1.30 (t, *J* 7.1, Me)*, 1.97 (s, Me)*, 1.99 (s, Me), 4.21 (2 H in 2 diastereomers, q, *J* 7.1, OCH_2), 4.30 (d, *J* 13.5, CH_2NO_2), 4.35 (1 H in 2 diastereomers, m, CH), 4.91 (d, *J* 13.5, CH_2NO_2)*, 4.96 (d, *J* 13.5, CH_2NO_2), 6.29 (br d, *J* 8.5, NH)*, 6.43 (br d, *J* 8.5, NH); δ_C(67.8 MHz, $CDCl_3$) 14.2 (Me), 14.3 (Me), 16.7 (Me), 16.9 (Me)*, 18.0 (Me)*, 23.5 (Me), 23.6 (Me)*, 48.3 (CH), 49.7 (CH)*, 49.9 (C)*, 51.2 (C), 62.2 (CH_2), 62.3 (CH_2)*, 81.3 (CH_2NO_2), 81.4

(CH_2NO_2)*, 170.0 (C=O)*, 170.6 (C=O), 172.6 (C=O), 172.9 (C=O)*; *m/z* (EI) 247 [$(M + H)^+$, 2%], 189 ($C_8H_{15}NO_4^+$, 7), 86 ($C_4H_8NO^+$, 100); *m/z* (FAB) 493 [$(2\ M + H)^+$, 11%], 247 [$(M + H)^+$, 100], 200 ($M^+ - NO_2$, 10).

Synthesis of diethyl 2-([$^2H_7$]isopropyl)propanedioate [33]

Sodium (980 mg, 42.6 mmol) was added to dry ethanol (20 ml) in a flask flushed with nitrogen. When the sodium had dissolved, the solution was brought to 52 °C and diethyl propanedioate (6.50 g, 6.16 ml, 40.7 mmol) was added over 5 min. After stirring for 1 h, 2-bromo[$^2H_7$]propane (3.61 ml, 5.00 g, 40.7 mmol) was added over 1 min. The solution was stirred at 52 °C for 44 h and the alcohol distilled off. The residue was taken up in water (40 ml) and extracted with dichloromethane (3 × 40 ml). The combined organic extracts were washed with water, dried over sodium sulfate and evaporated to give an orange liquid (8.44 g). Column chromatography (10% ethyl acetate–hexane) led to the isolation of diethyl 2-([$^2H_7$]isopropyl)propanedioate as a colourless oil (6.33 g, 30.3 mmol, 75%); ν_{max}(film)/cm^{-1} 2983, 2939 (CH), 2222 (C–D), 1733 (C=O); δ_H(250 MHz, $CDCl_3$) 1.27 (6 H, t, *J* 7.1, Me), 3.10 (1 H, s, CH), 4.19 (4 H, q, *J* 7.1, OCH_2); δ_C(100 MHz, $CDCl_3$) 13.9 (2 Me), 19.1 (m, CD_3), 27.8 (m, CD), 58.7 (CH), 60.9 (2 OCH_2), 168.7 (2 C=O); *m/z* (FAB) 210 [$(M + H)^+$, 15%], 164 ($M^+ - OEt$, 12), 136 ($M^+ - CO_2Et$, 47).

Synthesis of ethyl 2-methylene-3-[$^2H_3$]methyl[$^2H_4$]butanoate 37

Potassium hydroxide (1.67 g, 29.8 mmol) in dry ethanol was added over 5 min to a stirred solution of diethyl 2-([$^2H_7$]isopropyl)propanedioate in dry ethanol (15 ml). After stirring for 2.5 days, the ethanol was evaporated off. The viscous residue was taken up in water (25 ml) and extracted with dichloromethane (2 × 25 ml). To the aqueous layer was added concentrated hydrochloric acid (1.6 ml) and the reaction stirred for 15 min. The reaction was extracted with dichloromethane (3 × 25 ml), dried over sodium sulfate and evaporated to give ethyl hydrogen 2-([$^2H_7$]isopropyl)propanedioate as a colourless oil (4.67 g, 25.8 mmol, 87%).

Ethyl hydrogen 2-([$^2H_7$]isopropyl)propanedioate (4.67 g, 25.8 mmol) was dissolved in pyridine (15 ml) and then piperidine (336 mg, 3.95 mmol) and paraformaldehyde (774 mg, 25.8 mmol) were added. The suspension was refluxed until the end of evolution of carbon dioxide (*ca.* 3 h). After cooling, water (30 ml) was added and the reaction extracted with pentane (3 × 30 ml). The combined organic extracts were washed with water (20 ml), 2 M hydrochloric acid (20 ml), water (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml), brine (20 ml), dried over sodium sulfate and evaporated to give a colourless oil (3 g). Column chromatography (3% diethyl ether–pentane) led to the isolation of *ethyl* 2-*methylene*-3-[$^2H_3$]*methyl*[$^2H_4$]*butanoate* **37** as a colourless oil (2.60 g, 12.4 mmol, 48% from half ester, 41.6% overall) [Found: M^+ (EI), 149.1421. $C_8H_7D_7O_2$ requires *M*, 149.1424]; ν_{max}(film)/cm^{-1} 2982, 2937 (CH), 2221 (C–D), 1717 (C=O), 759 (C=CH_2); δ_H(250 MHz, $CDCl_3$) 1.31 (3 H, t, *J* 7.1, Me), 4.21 (2 H, q, *J* 7.1, OCH_2), 5.49 (1 H, d, *J* 1.1, =CH_2), 6.11 (1 H, d, *J* 1.1, CH_2); δ_C(100 MHz, $CDCl_3$) 14.1 (Me), 20.6 (m, 2 CD_3), 28.5 (m, CD), 60.3 (CH_2), 122.8 (=CH_2), 147.3 (=C), 167.3 (C=O); *m/z* (EI) M^+, 149 (M^+, 35%), 121 ($M^+ - C_2H_4$, 26), 104 ($M^+ - OEt$, 67), 76 ($M^+ - CO_2Et$, 100).

Nitration of ethyl 2-methylene-3-[$^2H_3$]methyl[$^2H_4$]butanoate 37

Nitronium tetrafluoroborate (615 mg, 4.62 mmol) was added to dry acetonitrile (20 ml) in a flask flushed with nitrogen. The stirred solution was cooled in a bath at −16 °C, ethyl 2-methylene-3-[$^2H_3$]methyl[$^2H_4$]butanoate (689 mg, 4.62 mmol) was added in one portion. After stirring for 4 h, water (30 ml) was added and the reaction extracted with dichloromethane (3 × 30 ml). The combined organic extracts were washed with water, dried over sodium sulfate and evaporated to give a yellow oil (700 mg). Column chromatography (8–70% ethyl acetate–hexane) led to the isolation of 3-*ethoxycarbonyl*-3-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)[$^2H_7$]*butan*-2-*yl nitrate* **39** as a 3 : 4 mixture of diastereomers, as a colourless oil (228 mg, 0.80 mmol, 17.3%) [Found: $(M + H)^+$ (FAB), 281.1476. $C_{10}H_8D_7N_3O_6$ requires $(M + H)^+$, 281.1478]; ν_{max}($CHCl_3$)/cm^{-1} 2915 (CH), 2247 (C–D), 1738 (C=O), 1644 (ON=O), 1587 (C=N), 1298 (ON=O); λ_{max}/nm 217.7 (ε/dm^3 mol^{-1} cm^{-1} 290); δ_H(400 MHz, $CDCl_3$) 1.23 (t, *J* 7.1, Me), 1.25 (t, *J* 7.1, Me)*, 2.59 (s, Me), 2.60 (s, Me), 4.21 (2 H in 2 diastereomers, m, OCH_2); δ_C(100 MHz, $CDCl_3$) 12.2 (Me), 13.7 (Me), 13.7 (Me)*, 15.0 (m, CD_3), 62.2 (OCH_2), 62.2 (CH_2)*, 79.5 (m, CD), 169.1 (=C)*, 169.5 (=C), 169.6 (=C), 176.8 (=C)*, 177.0 (=C); *m/z* (FAB) 281 [$(M + H)^+$, 15%], 219 ($M^+ - ONO_2 + H$, 4); *m/z* (EI) 235 ($M^+ - OEt$, 2%), 141 ($C_6H_3D_3O_2N_2^+$, 66); and two separable diastereomers of ethyl 2-nitromethyl-2-[$^2H_3$]methyl-3-acetamido[$^2H_4$]butanoate **38**. Diastereomer 1 was a white solid (45.1 mg, 0.18 mmol, 3.8%) [Found: $(M + H)^+$ (EI), 254.1749. $C_{10}H_{12}D_7N_2O_5$ requires $(M + H)^+$, 254.1733]; ν_{max}($CHCl_3$)/cm^{-1} 3436 (N–H), 1722 (C=O), 1682 (C=O), 1561 (N=O), 1373 (N=O); δ_H(400 MHz, $CDCl_3$) 1.30 (3 H, t, *J* 7.1, Me), 1.95 (3 H, s, Me), 4.21 (2 H, q, *J* 7.1, OCH_2), 4.55 (1 H, d, *J* 14.5, CH_2), 4.85 (1 H, d, *J* 14.5, CH_2), 5.67 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 14.1 (Me), 24.2 (Me), 24.8 (m, CD_3), 49.5 (m, CD), 53.5 (C), 61.6 (OCH_2), 73.4 (CH_2NO_2), 170.2 (C=O), 171.1 (C=O); *m/z* (EI) 254 [$(M + H)^+$, 5%], 223 ($M^+ - NO$, 10). Diastereomer 2 was a white solid (151 mg, 0.60 mmol, 13%) [Found: $(M + H)^+$ (FAB), 254.1747. $C_{10}H_{12}D_7N_2O_5$ requires $(M + H)^+$, 254.1733]; ν_{max}($CHCl_3$)/cm^{-1} 3435 (N–H), 2992 (CH), 2360, 2238 (C–D), 1735, 1675 (C=O), 1557 (N=O), 1376 (N=O); δ_H(400 MHz, $CDCl_3$) 1.31 (3 H, t, *J* 7.1, Me), 2.02 (3 H, s, Me), 4.25 (2 H, q, *J* 7.1, OCH_2), 4.35 (1 H, d, *J* 13.5, CH_2), 4.99 (1 H, d, *J* 13.5, CH_2), 6.37 (1 H, br s, NH); δ_C(100 MHz, $CDCl_3$) 13.02 (m, CD_3), 13.92 (Me), 15.46 (m, CD_3), 23.17 (Me), 47.43 (m, CD), 50.48 (C), 61.83 (CH_2), 80.94 (CH_2), 170.14 (C=O), 172.20 (C=O); *m/z* (FAB) 254 [$(M + H)^+$, 100%].

Synthesis of ethyl 2-(5-methyl-1,2,4-oxadiazol-3-yl)propanoate 42

To a solution of the nitrate ester **35** (300 mg, 1.10 mmol) in dry benzene (60 ml), was added tributyltin hydride (294 µl, 320 mg, 1.10 mmol) and AIBN (60.0 mg, 0.36 mmol, 0.3 equiv.). The solution was refluxed for 3.5 h and the solvent was evaporated to give a pale yellow oil. Column chromatography (10% ethyl acetate–hexane) led to the isolation of *ethyl* 2-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)*propanoate* **42** as a colourless oil (124 mg, 0.67 mmol, 61%); ν_{max}($CHCl_3$)/cm^{-1} 2988, 2943 (CH), 1742 (C=O), 1589 (C=N); δ_H(400 MHz, $CDCl_3$) 1.26 (3 H, t, *J* 7.1, Me), 1.59 (3 H, d, *J* 7.2, Me), 2.59 (3 H, s, Me), 3.95 (1 H, q, *J* 7.2, CH), 4.19 (2 H, m, OCH_2); δ_C(67.8 MHz, $CDCl_3$) 12.3 (Me), 14.0 (Me), 15.0 (Me), 37.9 (CH), 61.5 (CH_2), 169.2 (=C), 170.8 (=C), 176.7 (=C).

2-(5-Methyl-1,2,4-oxadiazol-3-yl)propanoic acid

Potassium hydroxide (33.6 mg, 0.6 mmol) was added to a stirred solution of ethyl 2-(5-methyl-1,2,4-oxadiazol-3-yl)propanoate **42** (99.3 mg, 0.54 mmol) in ethanol (6 ml). After stirring for 20 h, the ethanol was evaporated. The residue taken up in water and extracted with dichloromethane (1 × 20 ml). The aqueous layer was acidified with concentrated hydrochloric acid and then extracted with dichloromethane (2 × 20 ml). The combined organic layers were dried over sodium sulfate and evaporated to give 2-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)*propanoic acid* as a pale yellow oil (35.5 mg, 0.23 mmol, 42%); δ_H(250 MHz, $CDCl_3$) 1.59 (3 H, d, *J* 7.3, Me), 2.59 (3 H, s, Me), 3.99 (1 H, q, *J* 7.3, CH), 9.29 (1 H, br s, CO_2H); δ_C(67.8 MHz, $CDCl_3$) 12.3 (Me), 29.7 (Me), 37.6 (CH), 168.6 (=C), 175.8 (=C), 177.1 (=C).

Synthesis of 2-(5-methyl-1,2,4-oxadiazol-3-yl)propananilide 43

2-(5-methyl-1,2,4-oxadiazol-3-yl)propanoic acid (54 mg, 0.346 mmol) was dissolved in dichloromethane (10 ml) and oxalyl

Table 1 Crystal data and structure refinement for **43**

Empirical formula	$C_{12}H_{13}N_3O_2$
Formula weight	231.10
Temperature	293(2) K
Wavelength	0.710 69 Å
Crystal system	Monoclinic
Space group	*P*2(1)/a
Unit cell dimension	*a* 9.2294(11) Å
	b 11.7100(11) Å
	c 11.1879(9) Å
	β 95.034(13)°
Volume	1204.5(2) $Å^3$
Z	4
Density (calculated)	1.275 Mg m^{-3}
Absorption coefficient	0.090 mm^{-1}
F(000)	488
Crystal size	0.27 × 0.19 × 0.16 mm
θ Range for data collected	1.83 to 24.97°
Index ranges	$-7 \le h \le 10$, $-12 \le k \le 13$, $-12 \le l \le 11$
Reflections collected	4821
Independent reflections	1771 (R_{int} = 0.0571)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1771/0/156
Goodness of fit on F^2	0.891
Final *R* indices [$I > 2\sigma(I)$]	*R*1 0.0489, *wR*2 0.1109
R indices (all data)	*R*1 0.0743, *wR*2 0.1164
Largest diff. peak and hole	0.188 and −0.195 e $Å^{-3}$

chloride (220 mg, 1.73 mmol, 151 µl) was added. After stirring for 1 h, the solvent was evaporated. The residue was taken up in dichloromethane (10 ml) and aniline (50.0 mg, 0.54 mmol, 49 µl) was added. After stirring for 1.5 h, 2 M hydrochloric acid was added and the reaction extracted with dichloromethane (3 × 10 ml). Column chromatography (50% ethyl acetate–hexane) led to the isolation of 2-(5-methyl-1,2,4-oxadiazol-3-yl)propananilide **43** as a white solid (35.7 mg, 0.15 mmol, 43%); mp 105–107 °C (Found: C, 62.4; H, 5.9; N, 18.2. $C_{12}H_{13}N_3O_2$ requires C, 62.3; H, 5.7; N, 18.2%) [Found: M^+ (EI), 231.1005. $C_{12}N_{13}N_3O_2$ requires *M*, 231.1008]; ν_{max}($CHCl_3$)/cm^{-1} 3684, 3620, 3338 (N–H), 3028 (CH), 1693 (C=O), 1601, 1589, 1549 (Ar C=C); δ_H(250 MHz, $CDCl_3$) 1.69 (3 H, d, *J* 7.2, Me), 2.64 (3 H, s, Me), 3.98 (1 H, q, *J* 7.2, CH), 7.10 (1 H, dd, *J* 7.6, 7.6, ArH), 7.32 (2 H, dd, *J* 7.6, 7.6, ArH), 7.52 (2 H, d, *J* 7.6, ArH), 8.33 (1 H, br s, NH); δ_C(67.8 MHz, $CDCl_3$) 12.4 (Me), 15.8 (Me), 39.9 (CH), 119.9 (CH), 124.5 (CH), 129.0 (CH), 137.6 (C), 167.6 (=C), 169.6 (=C), 177.1 (=C); *m/z* (EI) 231 (M^+, 50%), 112 ($C_5H_8N_2O^+$, 63), 93 ($PhNH_2^+$, 100). Crystallisation from dichloromethane–ethyl acetate by slow evaporation led to the isolation of white needles which allowed an X-ray crystal structure to be determined, see Table 1.§

Ethyl 2-methylene-3,3-dimethylbutanoate 32

Potassium hydroxide (1.29 g, 23.15 mmol) in dry ethanol (25 ml) was added dropwise over 2 h to a stirred solution of diethyl 2-*tert*-butylpropanedioate (5.00 g, 23.2 mmol) in dry ethanol (25 ml). The solution was stirred at room temperature for 5 days and then the alcohol was evaporated off. The high viscosity residue was dissolved in water (30 ml) and extracted with dichloromethane (3 × 20 ml). The aqueous layer was cooled in ice and concentrated hydrochloric acid (2.2 ml) was added dropwise. The reaction mixture was extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a colourless oil (3.0 g).

Piperidine (225 mg, 2.65 mmol) and paraformaldehyde (570 mg, 19.0 mmol) were added to a solution of the ethyl hydrogen 2-*tert*-butylpropanedioate in pyridine (7 ml). The solution was heated under reflux until the end of evolution of carbon dioxide.

After cooling, the reaction was poured onto water (30 ml) and extracted with pentane (3 × 50 ml). The pentane phases were washed successively with water, 2 M hydrochloric acid (20 ml), water (20 ml), saturated aqueous sodium hydrogen carbonate (20 ml) and brine (20 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a colourless oil. Column chromatography (15% dichloromethane–petrol) led to the separation of *ethyl* 2-*methylene*-3,3-*dimethylbutanoate* **32** as a colourless oil (300 mg, 1.92 mmol, 8.3%); ν_{max}(film)/cm^{-1} 2928 (CH), 1712 (C=O), 1115 (C–O); δ_H(250 MHz, $CDCl_3$) 1.21 (9 H, s, Bu^t), 1.31 (3 H, t, *J* 7.1, Me), 4.20 (2 H, q, *J* 7.1, OCH_2), 5.51 (1 H, s, =CH), 5.92 (1 H, s, =CH); δ_C(67.8 MHz, $CDCl_3$) 14.1 (Me), 29.3 (Bu^t), 34.8 (C), 60.1 (CH_2), 120.5 (CH_2), 150.3 (=C), 167.9 (C=O).

Nitration of 2-methylene-3,3-dimethylbutanoate 32

Nitronium tetrafluoroborate (140 mg, 1.05 mmol) was added to dry acetonitrile (12 ml) in a flame-dried flask flushed with nitrogen. The stirred solution was cooled in a salt–ice bath at −16 °C and ethyl 2-methylene-3,3-dimethylbutanoate (200 mg, 1.30 mmol) was added rapidly. The reaction was stirred for 2 h, water (30 ml) was added and the reaction mixture extracted with dichloromethane (3 × 30 ml). The combined organic layers were washed with water (30 ml), dried over sodium sulfate and evaporated to give a colourless semi-solid (190 mg). Column chromatography (30–70% ethyl acetate–hexane) led to the isolation of 2-*methyl*-3-*ethoxycarbonyl*-3-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)*butan*-2-*yl nitrate* **36** as a colourless oil (24.2 mg, 0.084 mmol, 7.9%) [Found: $(M + H)^+$ (FAB), 288.1169. $C_{11}H_{17}N_3O_6$ requires $(M + H)^+$, 288.1196]; ν_{max}/cm^{-1} 2991, 2939 (CH), 1732 (C=O), 1633 (ON=O), 1590 (C=N), 1297 (ON=O); δ_H(250 MHz, $CDCl_3$) 1.25 (3 H, t, *J* 7.1, Me), 1.79 (3 H, s, Me), 1.89 (3 H, s, Me), 2.60 (3 H, s, Me), 4.23 (2 H, m, OCH_2); δ_C(100 MHz, $CDCl_3$) 12.1 (Me), 13.6 (Me), 18.7 (Me), 22.0 (Me), 22.1 (Me), 54.7 (C), 61.8 (OCH_2), 92.8 (C), 169.5 (=C), 169.7 (=C), 175.7 (=C); *m/z* (FAB) 288 [$(M + H)^+$, 75%], 225 ($M^+ - ONO_2$, 100), 184 ($M^+ - ONO_2$ − MeCN, 49), 138 ($M^+ - HNO_3$ − MeCN − OEt, 40); and *ethyl* 2,3-*dimethyl*-2-*nitromethyl*-3-*acetamidobutanoate* **34** as a white solid (23 mg, 0.088 mmol, 8.4%); mp 78–80 °C [Found: $(M + H)^+$ (FAB), 261.1474. $C_{11}H_{20}N_2O_5$ requires $(M + H)^+$, 261.1450]; ν_{max}($CHCl_3$)/cm^{-1} 3434, 3367 (N–H), 2941, 2852 (CH), 1715 (C=O), 1682 (C=O), 1564 (N=O), 1367 (N=O); δ_H(250 MHz, $CDCl_3$) 1.33 (3 H, t, *J* 7.1, Me), 1.33 (3 H, s, Me), 1.39 (3 H, s, Me), 1.51 (3 H, s, Me), 1.96 (3 H, s, Me), 4.27 (2 H, m, OCH_2), 4.68 (1 H, d, *J* 13.8, CH_2), 5.11 (1 H, d, *J* 13.8, CH_2), 6.05 (1 H, s, NH); δ_C(100 MHz, $CDCl_3$) 13.4 (Me), 15.3 (Me), 22.5 (Me), 23.3 (Me), 24.3 (Me), 52.7 (C), 57.1 (C), 61.5 (OCH_2), 79.6 (CH_2NO_2), 169.5 (C=O), 172.6 (C=O); *m/z* (FAB) 261 [$(M + H)^+$, 72%], 154 (57), 69 (81), 55 (100).

Synthesis of diethyl 2-cyclopentylpropanedioate

Sodium (1.60 g, 69.6 mmol) was added to dry ethanol (50 ml) in a flask flushed with nitrogen. The solution was brought to reflux and diethyl propanedioate (10.7 g, 10.2 ml, 67.0 mmol) was added. After refluxing for 45 min, cyclopentyl bromide (10.0 g, 10.2 ml, 67.0 mmol) was added. After refluxing for 20 h, the ethanol was distilled off and the residue taken up in water (30 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a colourless liquid (15.0 g). Distillation gave diethyl 2-cyclopentylpropanedioate as a colourless liquid (12.6 g, 55.3 mmol, 79%); bp 102–105 °C/2 mmHg (lit.,[34] 115–117 °C/2 mmHg) (Found: C, 63.1; H, 8.9. $C_{12}H_{20}O_4$ requires C, 63.1; H, 8.8%) [Found: M^+ − OEt (EI), 183.1015. $C_{12}H_{20}O_4$ requires *M* − OEt, 183.1021]; ν_{max}(film)/cm^{-1} 2958, 2871 (CH), 1753 and 1734 (C=O), 1147 (C–O); δ_H(270 MHz, $CDCl_3$) 1.27 (8 H, m, CH_2 and Me), 1.57 (4 H, m, CH_2), 1.84 (2 H, m, CH_2), 2.48 (1 H, m, CH), 3.17 (1 H, d, *J* 10.3, CH), 4.19 (4 H, q, *J* 7.2, OCH_2); δ_C(67.8 MHz, $CDCl_3$) 13.5 (2 Me), 24.2 (2 CH_2), 30.2 (2 CH_2), 39.1 (CH), 56.8 (CH), 60.4 (2 OCH_2), 168.3 (2 C=O); *m/z* (EI) 183 (M^+ − OEt, 25%), 160 ($M^+ - C_5H_8$, 100), 133 ($C_5H_9O_4^+$, 31).

Synthesis of diethyl 2-cyclohexylpropanedioate

Sodium (1.54 g, 66.9 mmol) was added to dry ethanol (50 ml) in a flask flushed with nitrogen. The solution was brought to reflux and diethyl propanedioate (10.7 g, 10.17 ml, 67.0 mmol) was added. After refluxing for 30 min, cyclohexyl bromide (10.9 g, 18.3 ml, 67.0 mmol) was added. After refluxing for 20 h, the ethanol was distilled off, the residue taken up in water (30 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give a yellow liquid (13.3 g). Distillation gave diethyl 2-cyclohexylpropanedioate as a colourless liquid (6.50 g, 26.8 mmol, 40%); bp 94–96 °C/0.6 mmHg (lit.,[35] 122–123 °C/4 mmHg) [Found: $M^+ - OEt$ (EI), 197.1193. $C_{13}H_{22}O_4$ requires $M - OEt$, 197.1178]; ν_{max}(film)/cm^{-1} 2981, 2929, 2854 (CH), 1732 (C=O); δ_H(250 MHz, $CDCl_3$) 1.08 (4 H, m, CH_2), 1.27 (6 H, t, *J* 7.2, Me), 1.27 (2 H, m, CH_2), 1.69 (6 H, m, CH_2), 2.07 (1 H, m, CH), 3.13 (1 H, d, *J* 9.2, CH), 4.18 (4 H, q, *J* 7.2, OCH_2); δ_C(67.8 MHz, $CDCl_3$) 13.7 (2 Me), 25.6 (2 CH_2), 25.7 (CH_2), 30.3 (2 CH_2), 37.5 (CH), 57.9 (CH), 60.5 (2 OCH_2), 168.9 (2 C=O); *m/z* (EI) 197 ($M^+ - OEt$, 16%), 160 ($M^+ - C_6H_{10}$, 100), 115 ($C_5H_7O_3{}^+$, 35).

Synthesis of ethyl 2-cyclopentylprop-2-enoate 59

Potassium hydroxide (2.88 g, 51.3 mmol) in dry ethanol (30 ml) was added to a stirred solution of diethyl 2-cyclopentylpropanedioate (11.7 g, 51.3 mmol) in dry ethanol (15 ml) over 10 min. After stirring for 24 h, the ethanol was evaporated off and the viscous residue taken up in water (50 ml) and then extracted with dichloromethane (2 × 20 ml). The aqueous layer was acidified with concentrated hydrochloric acid (2.9 ml) and extracted with dichloromethane (3 × 20 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give ethyl hydrogen 2-cyclopentylpropanedioate as a colourless oil (8.79 g, 43.9 mmol, 86%).

Ethyl hydrogen 2-cyclopentylpropanedioate (8.79 g, 43.9 mmol) was dissolved in pyridine (32 ml) and piperidine (60.0 mg, 0.71 mmol) and paraformaldehyde (1.32 g, 44.0 mmol) were added. The suspension was refluxed until the end of evolution of carbon dioxide. After cooling, water (40 ml) was added and the reaction extracted with pentane (3 × 75 ml). The combined pentane extracts were washed with water (30 ml), 2 M hydrochloric acid (30 ml), water (30 ml), saturated aqueous sodium hydrogen carbonate (30 ml) and brine (30 ml) then dried over sodium sulfate and evaporated to give a colourless liquid.

Column chromatography (10% diethyl ether–pentane), followed by Kugelrohr distillation led to the isolation of ethyl 2-cyclopentylprop-2-enoate **59** as a colourless liquid (4.80 g, 28.3 mmol, 55% overall, 64% from half ester); bp 135 °C/12 mmHg (lit.,[36] 50–51 °C/0.5 mmHg) [Found: M^+ (EI), 168.1148; $C_{10}H_{16}O_2$ requires *M*, 168.1150]; ν_{max}(film)/cm^{-1} 2955, 2871 (CH), 1717 (C=O), 1628 (C=C); δ_H(250 MHz, $CDCl_3$) 1.30 (3 H, t, *J* 7.1, Me), 1.40 (2 H, m, CH_2), 1.63 (4 H, m, CH_2), 1.92 (2 H, m, CH_2), 2.86 (1 H, m, CH), 4.21 (2 H, q, *J* 7.1, OCH_2), 5.52 (1 H, dd, *J* 1.1, 1.1, CH_2), 6.10 (1 H, dd, *J* 1.1, 1.1, CH_2); δ_C(67.8 MHz, $CDCl_3$) 13.9 (2 Me), 24.7 (2 CH_2), 31.6 (2 CH_2), 41.2 (CH), 60.1 (OCH_2), 121.1 (=CH_2), 144.6 (=C), 167.2 (2 C=O); *m/z* (EI) 168 (M^+, 32%), 140 ($M^+ - C_2H_4$, 28), 123 ($M^+ - OEt$, 46), 95 ($C_7H_{11}{}^+$, 100).

Synthesis of ethyl 2-cyclohexylprop-2-enoate 60[37]

Potassium hydroxide (1.39 g, 24.8 mmol) in dry ethanol (10 ml) was added to a stirred solution of diethyl 2-cyclohexylpropanedioate (6.00 g, 24.8 mmol) in dry ethanol (22 ml) over 15 min. After stirring for 24 h, the ethanol was evaporated off, the viscous residue taken up in water (30 ml) and extracted with dichloromethane (2 × 20 ml). The aqueous layer was acidified with concentrated hydrochloric acid (1.5 ml) and extracted with dichloromethane (3 × 30 ml). The combined organic extracts were dried over sodium sulfate and evaporated to give ethyl hydrogen 2-cyclohexylpropanedioate as a colourless oil (4.79 g, 22.4 mmol, 90%).

Ethyl hydrogen 2-cyclohexylpropanedioate (4.79 g, 22.4 mmol) was dissolved in pyridine (25 ml) and piperidine (35.0 mg, 0.42 mmol) and paraformaldehyde (890 mg, 22.4 mmol) were added. The suspension was refluxed until the end of evolution of carbon dioxide. After cooling, water (30 ml) was added and the reaction extracted with pentane (3 × 30 ml). The combined pentane extracts were washed with water (30 ml), dilute hydrochloric acid (30 ml), water (30 ml), saturated aqueous sodium hydrogen carbonate (30 ml) and brine (30 ml) then dried over sodium sulfate and evaporated to give a colourless liquid (2.98 g).

Column chromatography (4% diethyl ether–pentane) led to the isolation of ethyl 2-cyclohexylprop-2-enoate **60** as a colourless liquid (2.90 g, 15.9 mmol, 64% overall, 72% from half ester) [Found: M^+ (EI), 182.1305. $C_{11}H_{18}O_2$ requires *M*, 182.1307]; ν_{max}(film)/cm^{-1} 2926, 2980, 2852 (CH), 1716 (C=O), 1627 (C=C); δ_H(400 MHz, $CDCl_3$) 1.13 (2 H, m, CH_2), 1.33 (2 H, m, CH_2), 1.76 (6 H, m, CH_2), 2.44 (1 H, m, CH), 4.20 (2 H, q, *J* 7.1, OCH_2), 5.46 (1 H, dd, *J* 1.0, 1.0, =CH_2), 6.09 (1 H, d, *J* 1.0, =CH_2); δ_C(67.8 MHz, $CDCl_3$) 14.0 (Me), 26.1 (CH_2), 26.5 (2 CH_2), 32.4 (2 CH_2), 38.9 (CH), 60.3 (OCH_2), 121.5 (=CH_2), 146.4 (=C), 167.2 (C=O); *m/z* (EI) 182 (M^+, 57%), 153 ($M^+ - Et$, 23), 137 ($M^+ - OEt$, 52), 67 ($C_5H_7{}^+$, 100).

Nitration of ethyl 2-cyclopentylprop-2-enoate 59

Nitronium tetrafluoroborate (995 mg, 7.48 mmol) was added to dry acetonitrile (30 ml) in a flask flushed with nitrogen. The stirred solution was cooled in an ice bath at −16 °C and ethyl 2-cyclopentylprop-2-enoate (1.26 g, 7.48 mmol) was added in one portion. The reaction was stirred for 4 h, water (30 ml) was added and the reaction was extracted with dichloromethane (3 × 30 ml). The combined organic extracts were washed with water, dried over sodium sulfate and evaporated to give a yellow oil (1.76 g). Column chromatography (10–30–50–70–100% ethyl actate–hexane) led to the recovery of ethyl 2-cyclopentylprop-2-enoate **59** as a colourless oil (180 mg, 1.07 mmol; 14.5%); and to the isolation of 2-*ethoxycarbonyl*-2-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)*cyclohexyl nitrate* **63** as a 1:4 mixture of diastereomers, as a colourless oil (234 mg, 0.78 mmol, 10.5%, 16% based on recovered starting material) [Found: $(M + H)^+$ (FAB), 300.1159. $C_{12}H_{17}N_3O_6$ requires $(M + H)^+$, 300.1196]; λ_{max}(EtOH)/nm 212 (ε/dm^3 mol^{-1} cm^{-1} 1760); ν_{max}(film)/cm^{-1} 2944, 2869 (CH), 1738 (C=O), 1633 (ON=O), 1588 (C=N), 1281 (ON=O); δ_H(400 MHz, $CDCl_3$) 1.19 (t, *J* 7.1, Me)*, 1.25 (t, *J* 7.2, Me), 1.45 (m, CH_2), 1.65 (m, CH_2), 2.02 (m, CH_2), 2.22 (m, CH_2), 2.47 (m, CH_2), 2.62 (s, Me), 2.66 (s, Me)*, 4.15 (m, OCH_2)*, 4.26 (m, OCH_2), 5.97 (m, $CHONO_2$), 6.10 (m, $CHONO_2$)*; δ_C(100 MHz, $CDCl_3$) 12.1 (Me), 13.7 (Me)*, 13.7 (Me), 19.7 (CH_2)*, 20.4 (CH_2), 20.7 (CH_2)*, 21.5 (CH_2), 25.9 (CH_2)*, 26.3 (CH_2), 27.9 (CH_2)*, 28.8 (CH_2), 50.4 (C)*, 50.8 (C), 61.9 (OCH_2)*, 62.1 (OCH_2), 79.8 (CH)*, 80.0 (CH), 168.4 (=C)*, 168.9 (=C), 168.9 (=C)*, 169.2 (=C), 176.7 (=C), 177.1 (=C)*; *m/z* (FAB) 300 [$(M + H)^+$, 100%], 253 ($M^+ - NO_2$, 9), 237 ($M^+ - ONO_2$, 5), 226 ($M^+ - NO_2 - C_2H_4 + H$, 17); and two separable diastereomers of *ethyl* 2-*acetamido*-1-*nitromethylcyclohexanecarboxylate* **61**. Diastereomer 1 was a white crystalline solid (127 mg, 0.47 mmol, 6.3%, 9.7% based on recovered starting material); mp 130–132 °C [Found: $(M + H)^+$ (FAB), 273.1418. $C_{12}H_{20}N_2O_5$ requires $(M + H)^+$, 273.1450]; ν_{max}($CHCl_3$)/cm^{-1} 3429 (N–H), 2945, 2862 (CH), 1726, 1667 (C=O), 1563, 1372 (N=O); δ_H(400 MHz, $CDCl_3$) 1.32 (3 H, t, *J* 7.1, Me), 1.35 (3 H, m, CH_2), 1.67 (4 H, m, CH_2), 1.95 (3 H, s, Me), 2.23 (1 H, m, CH_2), 4.04 (1 H, m, CH), 4.28 (2 H, q, *J* 7.1, OCH_2), 4.50 (1 H, d, *J* 12.6, CH_2), 4.66 (1 H, d, *J* 12.6, CH_2), 6.60 (1 H, br d, *J* 9.0, NH); δ_C(100 MHz, $CDCl_3$) 13.8 (Me), 21.7 (CH_2), 23.0 (Me), 24.5 (CH_2), 30.0 (CH_2), 32.4 (CH_2), 50.4 (C), 52.3 (CH), 61.7 (CH_2), 82.1 (CH_2), 169.7 (C=O), 172.1 (C=O); *m/z* (FAB) 273 [$(M + H)^+$, 100%]; *m/z* (EI) 226 ($M^+ - NO_2$, 50%), 184 ($M^+ - NO_2 - Ac + H$, 65), 138 ($C_8H_{12}NO$, 100); and diastereomer 2 was a white crystalline solid (96 mg, 0.35 mmol, 4.7%, 7.2% based on recovered starting material); mp 158–159 °C [Found: $(M + H)^+$, 273.1463. $C_{12}H_{21}N_2O_5$ requires $(M + H)^+$, 273.1450]; ν_{max}($CHCl_3$)/cm^{-1} 1733, 1680 (C=O), 1557, 1376 (ON=O); δ_H(250 MHz, $CDCl_3$) 1.22 (3 H, t, J 7.1, Me), 1.50 (6 H, m, CH_2), 1.73 (2 H, m, CH_2), 1.95 (3 H, s, Me), 4.14 (2 H, m, OCH_2), 4.45 (1 H, m, CH), 4.53 (1 H, d, J 13.8, CH_2), 4.85 (1 H, d, J 13.8, CH_2), 6.73 (1 H, br d, J 9.4, NH); δ_C(100 MHz, $CDCl_3$) 13.9 (Me), 20.9 (CH_2), 21.9 (CH_2), 23.1 (Me), 28.0 (CH_2), 28.3 (CH_2), 49.1 (C), 50.1 (CH), 61.7 (CH_2), 77.4 (CH_2), 170.2 (C=O), 172.0 (C=O); m/z (FAB) 273 [$(M + H)^+$, 100%], 226 ($M^+ - NO_2$, 13); m/z (EI) 226 ($M^+ - NO_2$, 50%), 184 ($M^+ - NO_2 - Ac + H$, 55), 138 ($C_8H_{12}NO$, 100).

Nitration of ethyl 2-cyclohexylprop-2-enoate 60

Nitronium tetrafluoroborate (565 mg, 4.65 mmol) was added to dry acetonitrile (20 ml) in a flask flushed with nitrogen. The stirred solution was cooled in an ice bath at −16 °C and ethyl 2-cyclohexylprop-2-enoate (774 mg, 4.25 mmol) was added in one portion. The reaction was stirred for 4 h, water (30 ml) was added and the reaction was extracted with dichloromethane (3 × 30 ml). The combined organic extracts were washed with water, dried over sodium sulfate and evaporated to give a yellow oil (1.04 g). Column chromatography (10–30–50–70–100% ethyl acetate–hexane) led to the recovery of ethyl 2-cyclohexylprop-2-enoate **60** as a colourless oil (233 mg, 1.38 mmol, 18.5%) and to the isolation of 2-*ethoxycarbonyl*-2-(5-*methyl*-1,2,4-*oxadiazol*-3-*yl*)*cycloheptyl nitrate* **64** as a 3 : 4 mixture of two diastereomers, as a colourless oil (227 mg, 0.73 mmol, 15.6%, 40% based on recovered starting material) (Found: C, 50.1; H, 6.5; N, 13.3. $C_{13}H_{19}N_3O_6$ requires C, 49.8; H, 6.1; N, 13.4%) [Found: $M^+ - NO_2$ (EI), 251.1420. $C_{13}H_{19}O_6N_3$ requires $M - NO_2$, 251.1396]; λ_{max}(EtOH)/nm 214 (ε/dm^3 mol^{-1} cm^{-1} 1005); ν_{max}(film)/cm^{-1} 2937 and 2867 (CH), 1738 (C=O), 1632 (ON=O), 1588 (C=N), 1279 (ON=O); δ_H(400 MHz, $CDCl_3$) 1.12 (t, J 7.1, Me), 1.14 (t, J 7.2, Me), 1.58 (m, CH_2), 1.90 (m, CH_2), 2.22 (m, CH_2), 2.49 (s, Me), 2.50 (s, Me), 4.14 (2 H in 2 diastereomers, m, OCH_2), 5.86 (1 H in 2 diastereomers, dd, J 10.0, 8.5, $CHONO_2$); δ_C(100 MHz, $CDCl_3$) 12.11 (Me), 13.7 (Me), 22.3 (CH_2), 22.8 (CH_2), 23.0 (CH_2), 23.1 (CH_2), 27.4 (CH_2), 28.0 (CH_2), 28.6 (CH_2), 28.9 (CH_2), 32.1 (2 CH_2), 54.4 (C), 54.7 (C), 62.0 (CH_2), 62.1 (CH_2), 83.6 (CH), 84.2 (CH), 169.3 (2=C), 170.2 (2=C), 176.4 (=C), 176.7 (=C); m/z (EI) 267 ($M^+ - NO_2$, 12%), 251 ($M^+ - ONO_2$, 3), 151 ($C_9H_{11}O_2$, 83); and two separable diastereomers of *ethyl* 2-*acetamido*-1-*nitromethylcycloheptanecarboxylate* **62**. Diastereomer 1 was a white crystalline solid (16.9 mg, 0.06 mmol, 1.3%, 3.2% based on recovered starting material); mp 120–121.5 °C (Found: C, 54.8; H, 8.1; N, 9.7. $C_{13}H_{22}O_5N_2$ requires C, 54.6; H, 7.7; N, 9.8%) [Found: $(M + H)^+$ (EI), 287.1641. $C_{13}H_{22}N_2O_5$ requires $(M + H)^+$, 287.1607]; ν_{max}($CHCl_3$)/cm^{-1} 3438 (N–H), 2933, 2859 (CH), 1726 (C=O), 1679 (C=O), 1558 (N=O), 1373 (N=O); δ_H(250 MHz, $CDCl_3$) 1.30 (3 H, t, J 7.1, Me), 1.38 (1 H, m, CH_2), 1.78 (8 H, m, CH_2), 2.00 (3 H, s, Me), 2.21 (1 H, m, CH_2), 4.22 (2 H, q, J 7.1, OCH_2), 4.53 (1 H, d, J 13.1, CH_2), 4.67 (1 H, m, CH), 4.83 (1 H, d, J 13.1, CH_2), 5.81 (1 H, br d, J 11.1, NH); δ_C(67.8 MHz, $CDCl_3$) 13.7 (Me), 22.7 (CH_2), 22.9 (Me), 23.9 (CH_2), 27.6 (CH_2), 31.1 (CH_2), 31.2 (CH_2), 51.8 (C), 52.9 (CH), 61.5 (CH_2), 79.0 (CH_2), 169.7 (C=O), 172.7 (C=O); m/z (EI) 287 [$(M + H)^+$, 1], 240 ($M^+ - NO_2$, 21), 198 ($M^+ - NO_2 - Ac + H$, 77), 152 ($M^+ - OEt - NO_2 - Ac$, 95), 43 (Ac^+, 100); and diastereomer 2 was a white crystalline solid (167 mg, 0.58 mmol, 12.6%, 31.8% based on recovered starting material); mp 128–131 °C; δ_H(400 MHz, $CDCl_3$) 1.27 (1 H, m, CH_2), 1.33 (3 H, t, J 7.1, Me), 1.61 (7 H, m, CH_2), 1.98 (1 H, m, CH_2), 1.93 (3 H, s, Me), 2.05 (1 H, m, CH_2), 4.15 (1 H, t, J 9.1, CH), 4.30 (2 H, q, J 7.1, OCH_2), 4.52 (1 H, d, J 12.9, CH_2), 4.69 (1 H, d, J 12.9, CH_2), 6.41 (1 H, br d, J 9.1, NH); δ_C(67.8 MHz, $CDCl_3$) 14.0 (Me), 22.3 (CH_2), 23.3 (Me), 25.1 (CH_2), 27.0 (CH_2), 32.4 (CH_2), 33.1 (CH_2), 53.0 (C), 54.2 (CH), 61.9 (CH_2), 82.0 (CH_2), 169.4 (C=O), 172.8 (C=O).

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