Synthesis of tetrahydroquinolines, hexahydrobenzoindolizines and an aryl phosphonate linker for the generation of catalytic antibodies

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Syntheses of 6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline-3-methanol 10 and 1,2,3,5,6,10b-hexahydrobenzo[*g*]indolizine-6-methanol 34 are described. The aryl phosphonic acid 14, which can be used as a linker to a protein, is synthesised and coupled to the above alcohols. These haptens, when linked to a protein, are intended to generate antibodies able to catalyse cationic cyclisation reactions.

Cationic cyclisations are a fundamental type of reaction implicated in the biosynthesis of the vast number of isoprenoid natural products.[1] This class of reaction is catalysed by terpene cyclase enzymes, which operate on a very limited number of substrates. Nevertheless, they are the key steps in the formation of thousands of terpene natural products, ranging from simple monoterpenes, like camphor, to more complex biologically important compounds like Taxol™ and steroids like cholesterol. The feature of the majority of these cyclisation reactions is the ionisation of an allylic pyrophosphate to generate a transient allylic cation, which is then attacked by an electron-rich double bond. This generates a further cationic centre, which can be attacked by other double bonds or can trigger rearrangement reactions involving alkyl or hydride migrations. The cascade of reactions terminates when the reactive cationic species is quenched by loss of a proton or nucleophilic attack by water or pyrophosphate.

Catalysis of a cationic cyclisation requires control of the initial generation and stabilisation of the carbocation. Antibodies could, in principle, be excellent catalysts for the ionisation and control of the cyclisation process, in that they have been shown to be capable of catalysing complex reactions in which it was necessary to simultaneously stabilise point charges, overcome entropic barriers and provide a chiral binding pocket for stereoselectivity.[2] In essence, the problem reduces to that of generation of the carbocation in an environment that fosters and controls the cyclisation reaction.

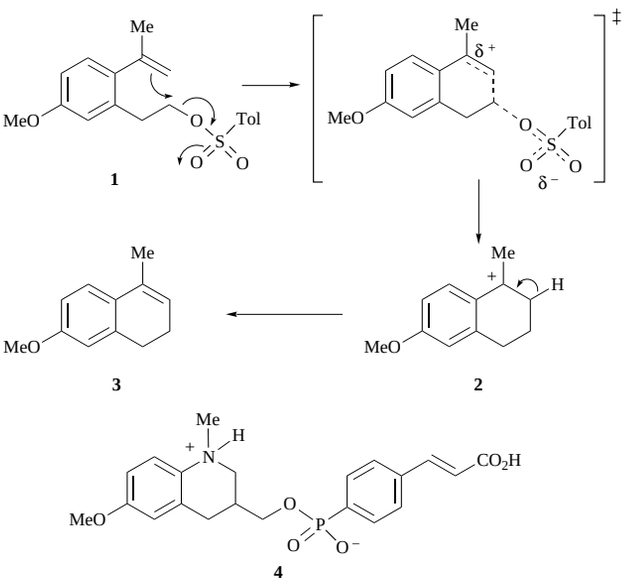
We are interested in generating antibodies designed to catalyse cationic cyclisations and are encouraged by recent reports of catalytic antibodies exhibiting this reactivity.[3] In principle, such antibodies could be used to assemble novel carbon skeletons.

Our strategy is to use a transition state analogue (TSA) which mimics the initial cation formed and the leaving group as it departs. The developing positive and negative charges are mimicked by a positively charged nitrogen atom and a phosphonate respectively. This strategy has evolved from a previous study in our laboratory on a more complex cyclisation in which the cation mimicked was that formed after two cyclisation reactions.[4] In this paper we describe the synthesis of substrates and TSAs for two potential cationic cyclisations using this principle.

Results and discussion

Synthesis of the first transition state analogue

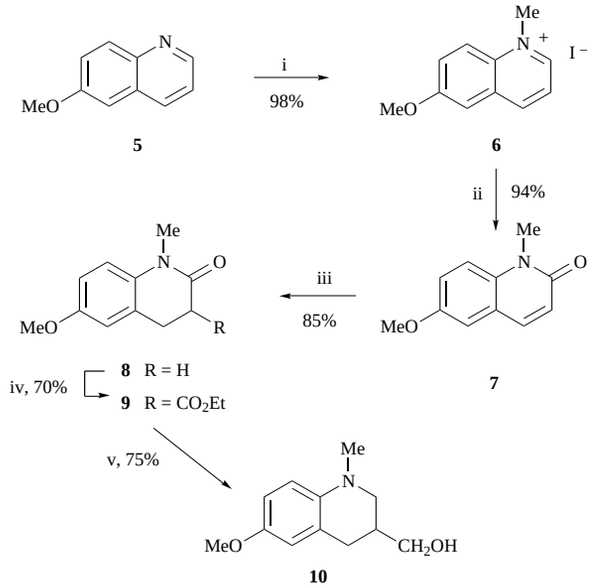
The first cationic cyclisation which we hope to catalyse using antibodies is shown in Scheme 1. In this reaction the leaving group is an arenesulfonate ion and the cation **2** formed upon cyclisation is benzylic and additionally stabilised by an electron-donating *p*-methoxy group. Loss of a proton from cation **2** would give alkene **3** as the product. The TSA chosen for this reaction, **4**, has a protonated amine at the position of the positive charge in the intermediate benzylic cation **2**. The arenesulfonate leaving group is mimicked by an arylphosphonate ion, which also provides the point of attachment of the carboxylic acid side-chain to be used to link the TSA to a protein. This point of attachment will ensure that the sulfonate leaving group is able to leave the antibody combining site when ionisation of the substrate **1** occurs. The phosphonate group is separated from the bicyclic skeleton by an extra methylene group so as to mimic the lengthening of the carbon to the oxygen bond which occurs during the reaction.



Scheme 1 (Tol = *p*-tolyl)

The strategy for the synthesis of the tetrahydroisoquinoline moiety **10** of TSA **4** involved dihydroisoquinolone **8** as a key intermediate, which was metallated and reacted with an electrophile to introduce the required side-chain (Scheme 2). The synthesis began with 6-methoxyquinoline **5**, which was methylated with methyl iodide in acetone.[5] The resultant quinolinium salt **6** was then oxidised with $K_3Fe(CN)_6$[6] to give the α,β-unsaturated lactam **7** which was subsequently hydrogenated at 40 atmospheres pressure over 10% palladium-on-carbon to give the dihydroquinolone **8** in good yield over the three steps.

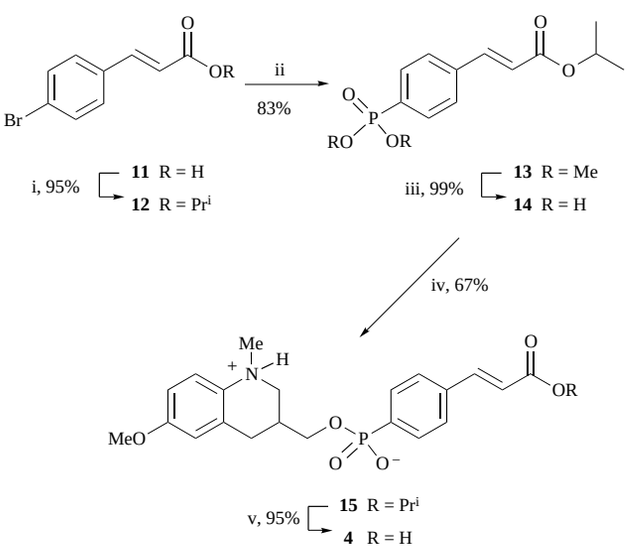
Lithiation of the lactam **8** with lithium diisopropylamide (LDA) in the presence of ethyl cyanoformate, afforded the ester **9** in 70% yield (97% based on unrecovered starting material)



Scheme 2 *Reagents and conditions:* i, MeI, acetone, reflux; ii, $K_3Fe(CN)_6$, KOH, H_2O, 0 °C; iii, H_2 (40 atm), Pd/C, EtOH, 48 h; iv, LDA, $CNCO_2Et$, THF, −78 °C; v, $LiAlH_4$, THF, reflux

and reduction with $LiAlH_4$ gave the desired amino alcohol **10** in 75% yield.

The phosphonic acid **14**, which was to be used as the linker to the protein, was synthesised starting from bromocinnamic acid **11** (Scheme 3). After protection of the acid as its isopropyl ester,



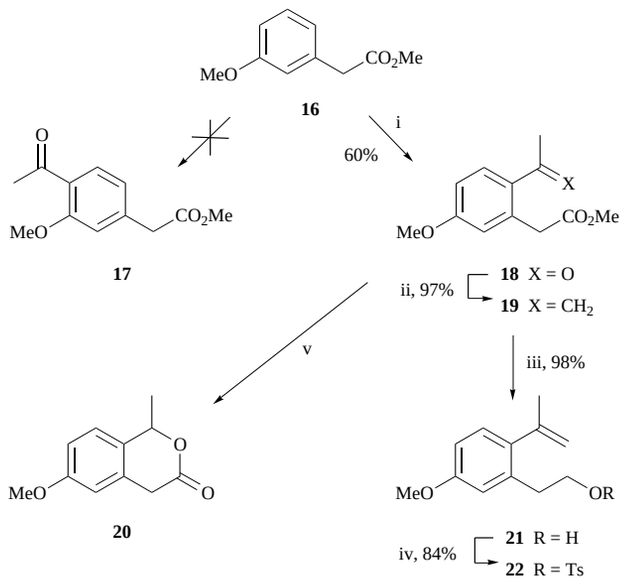
Scheme 3 *Reagents and conditions:* i, Pr^iOH, H_2SO_4, reflux; ii, $(Ph_3P)_4Pd$, $HPO(OMe)_2$, Et_3N, PhMe, 90 °C; iii, TMSCl, NaI, CH_3CN; iv, **10**, DCC, DMAP, THF, reflux; v, KOH, MeOH

palladium-catalysed coupling of the bromide **12** with dimethyl phosphite[7] gave the phosphonate ester **13** in good yield. Cleavage of the methyl esters using trimethylsilyl iodide[8] then gave the phosphonic acid **14**.

Finally the amino alcohol **10** was coupled to the phosphonic acid **14** using dicyclohexylcarbodiimide and 4-dimethylaminopyridine[9] to afford the ester **15** in 67% yield. Hydrolysis of the ester under alkaline conditions gave the hapten **4** in 95% yield.

Synthesis of the first substrate

The substrate **22**, required for the first proposed antibody-catalysed reaction, was synthesised starting from methyl 3-methoxyphenylacetate **16** (Scheme 4). Friedel-Crafts's acetylation[10] of **16** gave a single ketone **18**. The position of the



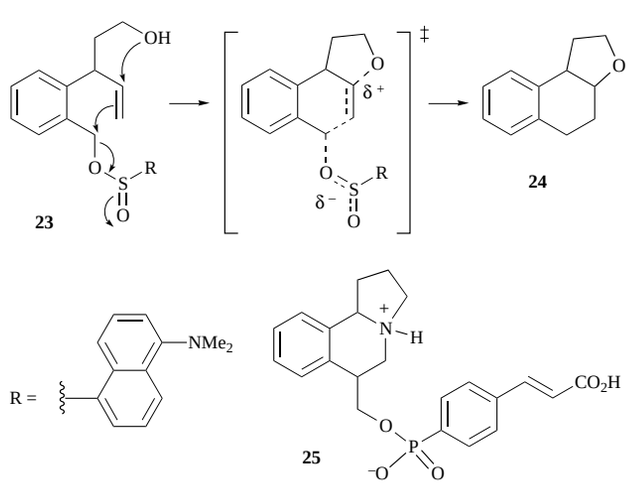
Scheme 4 *Reagents and conditions:* i, AcCl, $AlCl_3$; ii, Tebbe reagent, THF, 0 °C; iii, $LiAlH_4$, Et_2O, 0 °C; iv, TsCl, pyridine, 0 °C; v, $NaBH_4$, MeOH, 0 °C (Ts = tosyl)

acetylation was confirmed by reduction with sodium borohydride to give the lactone **20**. This lactone could not be formed from the alternative acetylation product **17**.

A Wittig reaction of the ketone **18** with methylenetriphenylphosphorane did not give any of the desired product, perhaps because the ketone is rather deactivated. However, methylenation using the Tebbe reagent[11] gave the olefin **19** in 97% yield. Finally, reduction of the ester group with $LiAlH_4$ gave the alcohol **21**, which was transformed into the toluene-*p*-sulfonate **22** in 84% yield.[12]

Synthesis of the second transition state analogue

One risk of the foregoing strategy for the generation of antibodies to catalyse a cationic cyclisation is that an anionic centre on the antibody, induced by the cationic site in the TSA, may trap the cationic intermediate formed during the desired cyclisation reaction. This is an inherent problem in cationic cyclisations. The second reaction that we aimed to catalyse, shown in Scheme 5, sought to overcome this problem by having an alco-

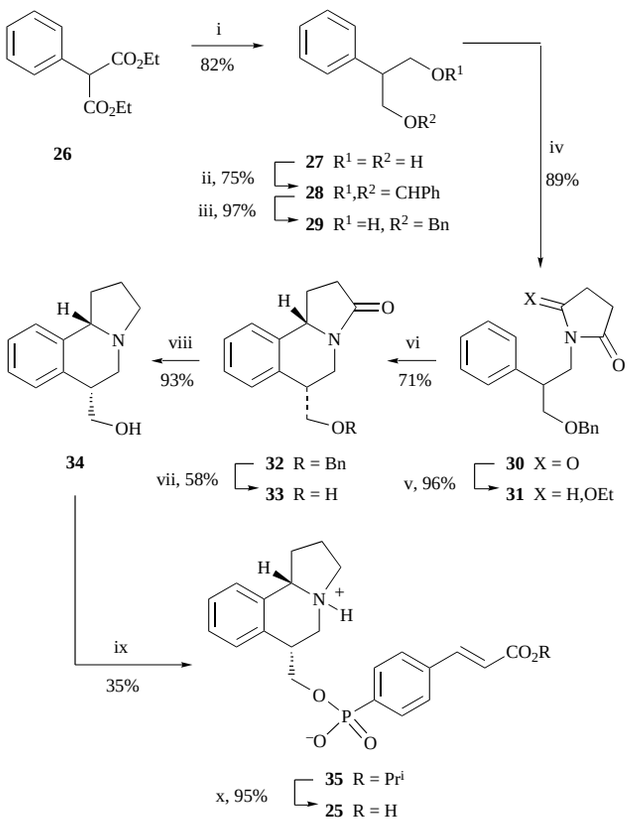


Scheme 5

hol group in the substrate to act as an intramolecular nucleophile. Trapping of the developing cation by this −OH group would lead to the cyclic ether **24** as the product. The leaving group in the substrate **23** is in a benzylic position and previous work has shown that benzylic sulfonates are too unstable under

aqueous conditions.[13] Success of the cyclisation is more likely if we use a sulfinate which has more suitable reactivity. The 5-dimethylaminonaphthalene-1-sulfinate (dansinate) leaving group (as in **23**) is particularly suitable because of the large change in fluorescence between an ester (such as **23**) and the sulfinate anion.[13]

The TSA chosen for this reaction was the aminophosphonate **25**. Our synthetic strategy to **25** (Scheme 6) aims to make the



Scheme 6 *Reagents and conditions:* i, $LiAlH_4$, Et_2O, 0 °C; ii, PhCHO, $ZnCl_2$, $CHCl_3$; iii, Bu^i_2AlH, PhMe; iv, succinimide, DEAD, Ph_3P, THF; v, $NaBH_4$, EtOH, HCl, 0 °C; vi, HCO_2H; vii, H_2 (1 atm), Pd/C, EtOH; diastereoisomers separated; viii, $LiAlH_4$, THF, reflux; ix, **14**, $SOCl_2$, DMF; x, KOH, MeOH

tricyclic skeleton by an acid-catalysed cationic cyclisation of ethoxylactam **31** (*via* the corresponding acyliminium ion[14]). The synthesis starts with the diol **27**, which was made by reduction of the diester **26** with $LiAlH_4$ in diethyl ether.[15] The diol **27** was monoprotected selectively[16] by treatment with benzaldehyde in the presence of $ZnCl_2$[17] to give the acetal **28**, and then cleavage with DIBAL in toluene to give the monobenzyl ether **29** in high yield. Mitsunobu reaction[18] of the alcohol group of **29** yielded the succinimide **30** in 89% yield. The ethoxylactam **31** was prepared in high yield by reduction of the succinimide with $NaBH_4$ in the presence of ethanol and hydrochloric acid.[14]

The acid-catalysed cyclisation of the ethoxylactam **31** proceeded well in formic acid at room temperature, giving a mixture of diastereoisomers in a ratio of 8.4 to 1. The relative stereochemistry of the major diastereoisomer was elucidated as **32** by ^{1}H NMR experiments (COSY and NOE). This major product is presumably formed *via* the chair-shaped transition state **36** in which the CH_2OBn group is pseudoaxial. The chair transition state **37** leading to the minor diastereoisomer is probably higher in energy because of an $A_{1,3}$ interaction between the CH_2OBn group and the benzene ring.

The mixture of diastereoisomers **32** was deprotected by hydrogenolysis to give the free alcohols **33** in an unchanged ratio of 8.4:1. The two diastereoisomers were separated at this stage and the relative stereochemistry of the major one was

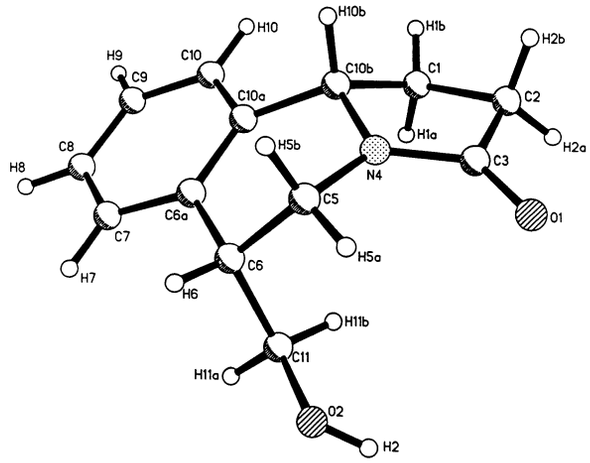
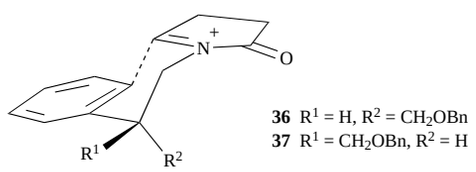


Fig. 1 X-Ray crystal structure of lactam **33**



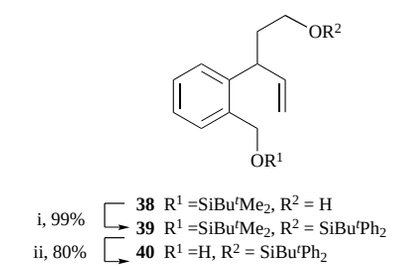
Possible transition states during acid-catalysed cyclisation of **31**

unequivocally confirmed as **33** by X-ray crystallography (Fig. 1).[19] The molecules of **33** pair up in the crystal with the oxygen atoms close enough to indicate an intermolecular hydrogen bond between the −OH of one molecule and the C=O of the other. Finally, the major diastereoisomer of lactam **33** was reduced with $LiAlH_4$ in THF to give the amine **34** in 93% yield.

For the coupling of phosphonic acid **14** to the amino alcohol **34**, the previous conditions gave only a low yield of coupled product (22%). Several different conditions were tried but the best yield obtained was 35%, using thionyl chloride to activate the phosphonic acid.[20] Finally the isopropyl ester of the coupled product **35** was hydrolysed under alkaline conditions to give the hapten **25** in 95% yield.

Synthesis of the second substrate

The synthesis of the second substrate requires a monoprotected diol such as **40** (Scheme 7). This was readily made by trans-



Scheme 7 *Reagents:* i, Bu^tPh_2SiCl, imidazole, DMF; ii, PPTS, EtOH

position of the protecting group from the alternative monoprotected diol **38** (the synthesis of **38** has been described previously[4]). Transformation of alcohols such as **38** into their dansinate esters (*e.g.* **23**) has also been described.[13] It was not performed in the present work because sulfinate esters, being more labile than their parent alcohols, are best prepared shortly before they are to be used.

Conclusions

In this paper, efficient syntheses of two novel heterocyclic compounds, a tetrahydroquinoline-3-methanol **10** and a hexa-

hydrobenzoindolizine-6-methanol **34**, have been described. In addition the synthesis of an arylphosphonic acid which can be used as a linker to a protein has been described. Antibodies specific for the haptens **4** and **25** will be generated to test if they catalyse the desired cationic cyclisation reactions. In addition, the combination of positively and negatively charged groups that should be induced in the antibody combining site by these haptens may well lead to the catalysis of alternative reactions such as β-elimination reactions or intramolecular aldol condensations.

Experimental

General directions

General directions are as in ref. 4. IR Spectra were determined using a 1710 Fourier Transform spectrometer as NaCl plates or KBr discs; proton NMR spectra were recorded on either a Bruker AM200, AM400 or DPX500 spectrometer, operating at 200, 400 and 500 MHz respectively, with tetramethylsilane (TMS) as internal standard; *J* values are given in Hz. Where indicated, the number of protons attached to each carbon in the ^{13}C NMR spectrum was determined using the APT (attached proton test) *J*-modulated spin-echo pulse sequence.

6-Methoxy-1-methyl-2(1*H*)-quinolone 7

A stirred suspension of the quinolinium iodide **6**[5] (3.17 g, 10.5 mmol) in water (50 cm^3) was cooled to 0 °C and a solution of $K_3Fe(CN)_6$ (20.8 g, 63.1 mmol) in water (63 cm^3) was added dropwise over 1 h. Then a solution of KOH (7.07 g, 126.2 mmol) in water (10.5 cm^3) was added dropwise over 30 min. Toluene was then added (50 cm^3) and the mixture was heated at 35 °C for 15 min. The organic layer was separated and the aqueous layer was extracted with diethyl ether (100 cm^3) and dichloromethane (2 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with acetone–dichloromethane (1:4), to yield the *quinolone* **7** (1.86 g, 94%) as needles, mp 72–73 °C (Found: C, 69.8; H, 5.8; N, 7.3%. MH^+, 190.0859. $C_{11}H_{11}NO_2$ requires C, 69.8; H, 5.85; N, 7.4%; *M*H, 190.0868); λ_{max}(EtOH)/nm 350, 272, 233 and 211; ν_{max}/cm^{-1} 1646 (C=O); δ_H(200 MHz, $CDCl_3$) 7.76 (1 H, d, *J* 9.4, 4-H), 7.46 (1 H, d, *J* 8.9, 8-H), 7.36 (1 H, dd, *J* 2.8 and 8.9, 7-H), 7.16 (1 H, d, *J* 2.8, 5-H), 6.87 (1 H, d, *J* 9.4, 3-H), 4.03 (3 H, s, MeO) and 3.86 (3 H, s, MeN); δ_C(50 MHz, $CDCl_3$) 161.8 (C), 154.6 (C), 138.3 (CH), 134.6 (C), 122.3 (CH), 121.3 (C), 119.0 (CH), 115.3 (CH), 110.5 (CH), 56.6 (MeO) and 29.4 (MeN); *m/z* (FAB + ve) 190 (MH^+).

6-Methoxy-1-methyl-3,4-dihydro-2(1*H*)-quinolone 8

A suspension of the lactam **7** (1.35 g, 7.13 mmol) and 10% palladium-on-carbon (130 mg) in absolute ethanol (28 cm^3) was shaken under 40 atmospheres pressure of hydrogen at room temperature for 48 h. The mixture was filtered through Celite and the residue was washed with ethanol. The filtrate and washings were evaporated under reduced pressure and the residue was purified by flash column chromatography, eluting with acetone–light petroleum (bp 40–60 °C) (1:4), to yield *dihydroquinolone* **8** (1.15 g, 85%) as needles, mp 62–63 °C (from ethanol) (Found: C, 69.0; H, 6.9; N, 7.3%; MH^+, 192.1028. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%; *M*H, 192.1024); λ_{max}(EtOH)/nm 258 and 211; ν_{max}/cm^{-1} 1665 (C=O); δ_H(400 MHz, $CDCl_3$) 6.85 (1 H, d, *J* 8.7, 8-H), 6.69 (2 H, m, 5- and 7-H), 3.74 (3 H, s, MeO), 3.28 (3 H, s, MeN), 2.82 (2 H, t, *J* 7.3, CH_2) and 2.57 (2 H, t, *J* 7.3, CH_2); δ_C(100 MHz, APT, $CDCl_3$) 169.8 (C), 155.2 (C), 134.2 (C), 127.6 (C), 115.4 (CH), 113.8 (CH), 111.7 (CH), 55.4 (MeO), 31.6 (CH_2), 29.5 (MeN) and 25.6 (CH_2); *m/z* (FAB + ve) 192 (MH^+).

3-Ethoxycarbonyl-6-methoxy-1-methyl-3,4-dihydro-2(1*H*)-quinolone 9

A stirred solution of the quinolone **8** (209 mg, 1.09 mmol) in dry THF (4.4 cm^3) and ethyl cyanoformate (160 mm^3, 1.64 mmol) under argon was cooled to −78 °C and a freshly prepared solution of lithium diisopropylamide[21] in THF (0.3 mol dm^{-3}; 8 cm^3, 2.4 mmol) was added over 1.5 h. Water was then added and the mixture was warmed to room temperature and extracted with diethyl ether. The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with diethyl ether–light petroleum (bp 40–60 °C) (1:1 and then 3:1), to give recovered starting material (59 mg, 28%) and *ester* **9** (201 mg, 70%) as an oil (Found: MH^+, 264.1250. $C_{14}H_{17}NO_4$ requires *M*H, 264.1236); ν_{max}/cm^{-1} 1732 (C=O) and 1667 (C=O); δ_H(400 MHz, $CDCl_3$) 6.90 (1 H, d, *J* 8.8, 8-H), 6.77 (1 H, dd, *J* 8.8 and 2.8, 7-H), 6.73 (1 H, d, *J* 2.8, 5-H), 4.18 (2 H, m, C*H*$_2$Me), 3.76 (3 H, s, MeO), 3.58 (1 H, dd, *J* 9.3 and 5.8, CH_2C*H*), 3.28 (1 H, dd, *J* 9.3 and 15.5, CH*H*CH), 3.35 (3 H, s, MeN), 3.02 (1 H, dd, *J* 15.5 and 5.8, C*H*HCH) and 1.20 (3 H, t, *J* 7.1, CH_2*Me*); δ_C(100 MHz, APT, $CDCl_3$) 169.5 (C), 166.2 (C), 155.6 (C), 133.5 (C), 125.5 (C), 115.8 (CH), 114.1 (CH), 112.4 (CH), 61.6 (CH_2), 55.6 (MeO), 48.1 (MeN), 30.1 (CH), 29.0 (CH_2) and 14.1 (Me); *m/z* (FAB + ve) 264 (MH^+).

3-Hydroxymethyl-6-methoxy-1-methyl-1,2,3,4-tetrahydroquinoline 10

A solution of the quinolone **9** (192 mg, 0.73 mmol) in dry THF (6 cm^3) was added to a stirred suspension of lithium aluminium hydride (56 mg, 1.46 mmol) in dry THF (1 cm^3) under argon at 0 °C. The mixture was heated at reflux for 1 h and then poured into a mixture of diethyl ether and ice. The organic layer was separated and the aqueous layer extracted with diethyl ether (4 × 20 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with diethyl ether to give the *alcohol* **10** (113 mg, 75%) as an oil (Found: M^+, 207.1246. $C_{12}H_{17}NO_2$ requires *M*, 207.1259); ν_{max}/cm^{-1} 3368 (O−H); δ_H(400 MHz, $CDCl_3$) 6.68 (1 H, dd, *J* 3.0 and 8.8, 7-H), 6.61 (1 H, d, *J* 3.0, 5-H), 6.58 (1 H, d, *J* 8.8, 8-H), 3.73 (3 H, s, MeO), 3.69 (1 H, dd, *J* 10.6 and 5.7, C*H*HOH), 3.60 (1 H, dd, *J* 10.6 and 7.4, CH*H*OH), 3.23 (1 H, ddd, *J* 10.9, 3.7 and 1.4, NC*H*H), 2.93 (1 H, dd, *J* 10.9 and 8.0, NC*H*H), 2.83 (3 H, s, MeN), 2.77 (1 H, dd, *J* 16.2 and 5.6, ArC*H*H), 2.55 (dd, 1 H, *J* 16.2 and 8.5, ArCH*H*), 2.29–2.20 (1 H, m, CH) and 1.77 (1 H, br s, OH); δ_C(100 MHz, APT, $CDCl_3$) 151.5 (C), 141.3 (C), 123.5 (C), 115.2 (CH), 112.5 (CH), 112.2 (CH), 65.6 (CH_2), 55.7 (MeO), 54.0 (CH_2), 39.9 (MeN), 35.4 (CH) and 30.4 (CH_2); *m/z* (FAB + ve) 207 (MH^+).

Isopropyl 4-bromocinnamate 12

A suspension of 4-bromocinnamic acid **11** (1.03 g, 4.52 mmol) in propan-2-ol (6 cm^3) and conc. H_2SO_4 (0.25 cm^3) was heated at reflux for 24 h, then cooled and poured onto ice. The mixture was extracted with diethyl ether and the extracts dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (2:3), and the resulting oil was crystallised from ethanol to give the *ester* **12** (1.16 g, 95%) as prisms, mp 61–62 °C (Found: C, 53.4; H, 4.8; Br, 29.6%; MH^+, 269.0201. $C_{12}H_{13}BrO_2$ requires C, 53.55; H, 4.9; Br, 29.7%; *M*H, 269.0178); λ_{max}(EtOH)/nm 283, 218 and 203; ν_{max}/cm^{-1} 1707 (C=O) and 1638 (C=C); δ_H(200 MHz, $CDCl_3$) 7.58 and 6.38 (each 1 H, d, *J* 16, CH=CH), 7.50 and 7.36 (each 2 H, d, *J* 8.5, ArH), 5.12 (1 H, septet, *J* 6.3, C*H*Me$_2$) and 1.30 (6 H, d, *J* 6.3, 2 × Me); δ_C(50 MHz, $CDCl_3$) 166.2 (C), 142.7 (CH), 133.5 (C), 132.1 (CH), 129.4 (CH), 124.3 (C), 119.5 (CH), 68.0 (CH) and 21.9 (Me); *m/z* (FAB + ve) 271 and 269 (MH^+).

Dimethyl 4-[(*E*)-2-(isopropoxycarbonyl)ethenyl]phenylphosphonate 13

A solution of the bromide **12** (1.0 g, 3.72 mmol) in dry toluene

(10 cm^3) was added to a stirred mixture of $Pd(Ph_3P)_4$ (215 mg, 0.186 mmol), dimethyl phosphite (375 mm^3, 4.09 mmol) and freshly distilled triethylamine (572 mm^3, 4.09 mmol) under argon at room temperature. The mixture was heated at 90 °C for 6 h, then cooled to room temperature, diluted with diethyl ether, filtered through Celite and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–dichloromethane (1:1), to yield the *phosphonate* **13** (917 mg, 83%) as an oil (Found: MH^+, 299.1067. $C_{14}H_{19}O_5P$ requires *M*H, 299.1048); ν_{max}/cm^{-1} 1712 (C=O) and 1639 (C=C); δ_H(200 MHz, $CDCl_3$) 7.79 (2 H, dd, J_{HP} 12.9 and J_{HH} 8.2, ArH), 7.64 and 6.47 (each 1 H, d, *J* 16, CH=CH), 7.43 (2 H, d, *J* 8.2, ArH), 5.12 (1 H, septet, *J* 6.2, C*H*Me_2), 3.78 and 3.72 (each 3 H, s, MeO) and 1.29 (6 H, d, *J* 6.2, 2 × Me); δ_C(100 MHz, APT, $CDCl_3$) 165.9 (C), 142.7 (CH), 138.5 (C), 132.4 (CH, J_{CP} 10), 128.5 (C, J_{CP} 190), 127.8 (CH, J_{CP} 15), 121.5 (CH), 68.1 (CH), 52.8 (MeO), 52.7 (MeO) and 21.9 (Me); *m/z* (FAB + ve) 299 (MH^+) and 257 ($M^+ - CHMe_2$).

4-[(*E*)-2-(Isopropoxycarbonyl)ethenyl]phenylphosphonic acid 14

A suspension of phosphonate **13** (631 mg, 2.12 mmol) and anhydrous sodium iodide (1.26 g, 8.47 mmol) in dry acetonitrile (20 cm^3) under argon at room temperature was stirred with chlorotrimethylsilane (1.2 cm^3, 8.47 mmol) for 1 h. The solvent was evaporated under reduced pressure, water was added (20 cm^3) and the aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was recrystallised from ethyl acetate to give *phosphonic acid* **14** (570 mg, 99%) as an amorphous solid, mp 175–176 °C (Found: C, 53.4; H, 5.6; P, 11.5%; MH^+, 271.0721. $C_{12}H_{15}O_5P$ requires C, 53.3; H, 5.6; P, 11.5%; *M*H, 271.0735); ν_{max}/cm^{-1} 3422 (O–H), 1716 (C=O) and 1637 (C=C); δ_H(400 MHz, CD_3OD) 7.82 (2 H, dd, J_{HH} 8.3 and J_{HP} 13.0, ArH), 7.72–7.66 (3 H, m, CH=C and 2 × ArH), 6.60 (1 H, d, *J* 16.1, C=CH), 5.09 (1 H, septet, *J* 6.3, C*H*Me_2) and 1.30 (6 H, d, *J* 6.3, 2 × Me); δ_C(100 MHz, APT, CD_3OD) 168.1 (C), 145.4 (CH), 141.2 (C, J_{CP} 176), 136.9 (C), 132.4 (CH, J_{CP} 9), 128.5 (CH, J_{CP} 14), 120.3 (CH), 69.3 (CH) and 22.1 (Me); *m/z* (FAB + ve) 271 (MH^+).

(6-Methoxy-1-methyl-1,2,3,4-tetrahydroquinolin-1-ium-3-yl)-methyl 4-[(*E*)-2-(isopropoxycarbonyl)ethenyl]phenylphosphonate 15

A solution of 1,3-dicyclohexylcarbodiimide (DCC) (85 mg, 0.41 mmol) in dry THF (1 cm^3) was added to a stirred suspension of alcohol **10** (106 mg, 0.75 mmol), 4-dimethylaminopyridine (36 mg, 0.75 mmol) and phosphonic acid **14** (101 mg, 0.37 mmol) in dry THF (3 cm^3) under argon. The resultant suspension was heated at reflux for 3 h. After cooling to room temperature the dicyclohexylurea was removed by filtration, water was added (10 cm^3) and the aqueous layer was extracted with chloroform (4 × 25 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with dichloromethane–methanol (95:5 then 85:15), to yield the *phosphonate ester* **15** (114 mg, 67%) as an amorphous solid (Found: MH^+, 460.1896. $C_{24}H_{31}NO_6P$ requires *M*H, 460.1889); ν_{max}/cm^{-1} 3420 (O–H) and 1712 (C=O); δ_H(400 MHz, CD_3OD) 7.80 (2 H, dd, *J* 11.8 and 8, ArH), 7.60 (1 H, d, *J* 16.1, C*H*=C), 7.52 (2 H, dd, *J* 8 and 3, ArH), 6.59–6.42 (4 H, m, 3 × ArH and C=C*H*), 5.08 (1 H, septet, *J* 6.3, C*H*Me_2), 3.73–3.54 (2 H, m, CH_2O), 3.64 (3 H, s, MeO), 3.06 (1 H, d *J* 9.9, NHC*H*H), 2.72–2.59 (2 H, m, ArC*H*H and NHC*H*H), 2.67 (3 H, s, MeN), 2.36 (1 H, dd, *J* 16.2 and 9.1, ArC*H*H), 2.18 (1 H, m, C*H*CH_2) and 1.25 (6 H, d, *J* 6.3, CHMe_2); δ_C(100 MHz, APT, CD_3OD) 167.8 (C), 153.1 (C), 145.0 (CH), 142.3 (C), 138.3 (C, J_{CP} 182), 137.3 (C), 133.4 (CH, J_{CP} 9), 128.5 (CH, J_{CP} 14), 124.6 (C), 120.6 (CH), 116.0 (CH), 113.9 (CH), 113.2 (CH), 69.3 (CH), 67.7 (CH_2), 56.0 (MeO), 54.9 (CH_2), 40.4 (MeN), 35.3 (CH), 31.2 (CH_2) and 22.2 (CH_3); *m/z* (FAB + ve) 460 (MH^+).

(6-Methoxy-1-methyl-1,2,3,4-tetrahydroquinolin-1-ium-3-yl)-methyl 4-[(*E*)-2-carboxyethenyl]phenylphosphonate 4

A solution of the ester **15** (110 mg, 0.24 mmol) was stirred with a solution of potassium hydroxide in methanol (2.7 mol dm^{-3}; 4 cm^3) under argon at room temperature for 24 h and then evaporated under reduced pressure. The residue was dissolved in water (10 cm^3) and Dowex-50W X8-400 (NH_4^+) ion exchange resin was added until the pH dropped to between 9–10. The ion exchange resin was filtered off and the filtrate was lyophilised to give the *acid* **4** (95 mg, 95%) as an amorphous solid (Found: MH^+, 418.1445. $C_{21}H_{25}NO_6P$ requires *M*H, 418.1419); ν_{max}/cm^{-1} 2928 (N^+–H) and 1636 (C=O); δ_H(500 MHz, CD_3OD) 7.78 (2 H, dd, *J* 11.8 and 8.0, ArH), 7.55 (2 H, dd, *J* 8.1 and 2.8, ArH), 7.45 (1 H, d, *J* 16.0, C*H*=C), 6.61–6.50 (4 H, m, 3 × ArH and C=C*H*), 3.78–3.75 (1 H, m, C*H*HO), 3.74–3.48 (1 H, m, C*H*HO), 3.34 (3 H, s, MeO), 3.15 (1 H, dd, *J* 11.0 and 2.7, NHC*H*H), 2.78 (1 H, dd, *J* 10.6 and 9.0, NHC*H*H), 2.72 (3 H, s, MeN), 2.71 (1 H, dd, *J* 16.5 and 5.3, ArC*H*H), 2.46 (1 H, dd, *J* 16.5 and 9.2, ArC*H*H) and 2.34 (1 H, m, C*H*CH_2); δ_C(100 MHz, APT, CD_3OD) 171.6 (C), 153.3 (C), 144.6 (CH), 142.4 (C), 138.3 (C, J_{CP} 176), 137.9 (C), 133.1 (CH, J_{CP} 9), 128.4 (CH, J_{CP} 14), 124.9 (C), 122.6 (CH), 116.1 (CH), 114.0 (CH), 113.4 (CH), 67.7 (CH_2), 56.1 (MeO), 55.0 (CH_2), 40.4 (MeN), 35.5 (CH) and 31.0 (CH_2); *m/z* (FAB + ve) 418 (MH^+).

Methyl 2-acetyl-5-methoxyphenylacetate 18

A solution of methyl 3-methoxyphenylacetate **16** (651 mg, 3.61 mmol) in acetyl chloride (0.26 cm^3, 3.61 mmol) was added dropwise to a stirred suspension of $AlCl_3$ (1.06 g, 7.95 mmol) in dry dichloromethane (3 cm^3) under argon at 0 °C. The resultant suspension was stirred for 1 h at 0 °C and 30 min at room temperature, then poured into 10% hydrochloric acid (20 cm^3) and extracted with dichloromethane (3 × 50 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was crystallised from diethyl ether to give *ketone* **18** (476 mg, 60%) as needles, mp 86–87 °C (Found: C, 64.75; H, 6.4%; M^+, 222.0892. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%; *M*, 222.0892); ν_{max}/cm^{-1} 1736 (C=O) and 1665 (C=O); δ_H(400 MHz, $CDCl_3$) 7.84 (1 H, d, *J* 8.7, 3-H), 6.85 (1 H, dd, *J* 8.7 and 2.4, 4-H), 6.74 (1 H, d, *J* 2.4, 6-H), 3.91 (2 H, s, CH_2), 3.84 and 3.69 (each 3 H, s, MeO) and 2.53 (3 H, s, MeCO); δ_C(100 MHz, APT, $CDCl_3$) 199.0 (C), 171.7 (C), 162.2 (C), 137.6 (C), 133.0 (CH), 129.3 (C), 118.7 (CH), 111.7 (CH), 55.4 (MeO), 51.8 (MeO), 41.0 (CH_2) and 28.3 (Me); *m/z* (EI) 222 (M^+).

Methyl 5-methoxy-2-(1-methylethenyl)phenylacetate 19

A solution of Tebbe's reagent in toluene (*ca.* 0.5 mol dm^{-3}; 22.5 cm^3, 11.2 mmol) was added slowly to a stirred solution of the ketone **18** (2.27 g, 10.2 mmol) in dry THF (35 cm^3) under argon at 0 °C. The mixture was stirred at room temperature for 2 h and then was diluted with diethyl ether (125 cm^3). Aqueous sodium hydroxide (0.1 mol dm^{-3}; 10–20 drops) was added very slowly and then the mixture was dried ($MgSO_4$), filtered through Celite and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:9), to yield *alkene* **19** (2.18 g, 97%) as an oil (Found: M^+, 220.1098. $C_{13}H_{16}O_3$ requires *M*, 220.1099); ν_{max}/cm^{-1} 1738 (C=O) and 1608 (C=C); δ_H(400 MHz, $CDCl_3$) 7.08 (1 H, d, *J* 8.3, 3-H), 6.79 (2 H, m, ArH), 5.20 and 4.80 (each 1 H, m, C=C*H*H), 3.79 (3 H, s, MeO), 3.67 (5 H, s, CH_2 and MeO) and 2.00 (3 H, d, *J* 2.9, Me); δ_C(100 MHz, APT, $CDCl_3$) 172.3 (C), 158.3 (C), 144.3 (C), 136.6 (C), 132.0 (C), 129.1 (CH), 115.6 (CH_2), 115.5 (CH), 112.6 (CH), 55.2 (MeO), 52.0 (MeO), 38.7 (CH_2) and 25.1 (Me); *m/z* (EI) 220 (M^+) and 205 ($M^+ - Me$).

2-[5-Methoxy-2-(1-methylethenyl)phenyl]ethanol 21

A solution of the ester **19** (758 mg, 3.45 mmol) in dry diethyl ether (30 cm^3) was added *via* cannula to a stirred suspension of

lithium aluminium hydride (261 mg, 6.9 mmol) in dry diethyl ether (1 cm^3) under argon at 0 °C. The suspension was stirred at 0 °C for 1 h and then was poured into a mixture of ice and diethyl ether. The mixture was acidified with 10% hydrochloric acid and extracted with diethyl ether (3 × 30 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (2:3), to yield the *alcohol* **21** (649 mg, 98%) as an oil (Found: M^+, 192.1150. $C_{12}H_{16}O_2$ requires *M*, 192.1150); ν_{max}/cm^{-1} 3348 (O–H) and 1606 (C=C); δ_H(400 MHz, $CDCl_3$) 7.06 (1 H, d, *J* 8.1, 3-H), 6.79 (1 H, d, *J* 2.6, 6-H), 6.74 (1 H, dd, *J* 8.1 and 2.6, 4-H), 5.18 and 4.83 (each 1 H, br s, C=C*H*H), 3.78 (5 H, br s, CH_2OH and MeO), 2.89 (2 H, t, *J* 8.1, ArCH_2), 2.31 (1 H, br s, OH) and 2.03 (3 H, s, Me); δ_C(100 MHz, APT, $CDCl_3$) 158.2 (C), 144.9 (C), 136.6 (C), 136.1 (C), 129.2 (CH), 115.2 (CH_2), 115.0 (CH), 111.3 (CH), 63.4 (CH_2), 55.0 (MeO), 36.3 (CH_2) and 25.3 (Me); *m/z* (EI) 192 (M^+).

2-[5-Methoxy-2-(1-methylethenyl)phenyl]ethyl toluene-*p*-sulfonate 22

A solution of alcohol **21** (1.03 g, 5.35 mmol) in dry pyridine (15 cm^3) was stirred with tosyl chloride (2.04 g, 10.7 mmol) at 0 °C under argon for 6 h and then was kept in the freezer overnight. The mixture was poured into ice–water and extracted with diethyl ether (2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:3), to yield *toluene*-p-*sulfonate* **22** (1.77 g, 84%) as an oil (Found: M^+, 346.1234. $C_{19}H_{22}O_4S$ requires *M*, 346.1239); ν_{max}/cm^{-1} 1607 (C=C); δ_H(400 MHz, $CDCl_3$) 7.67 and 7.27 (each 2 H, d, *J* 8.3, Ts, ArH), 6.99 (1 H, d, *J* 8.4, 3-H), 6.72 (1 H, dd, *J* 8.4 and 2.6, 4-H), 6.61 (2 H, d, *J* 2.6, 6-H), 5.09 and 4.65 (each 1 H, br s, C=C*H*H), 4.14 (2 H, t, *J* 7.3, CH_2O), 3.74 (3 H, s, MeO), 2.95 (2 H, t, *J* 7.3, CH_2CH_2O), 2.42 (3 H, s, Ar*Me*) and 1.91 (3 H, d, *J* 0.8, C=CMe); δ_C(100 MHz, APT, $CDCl_3$) 158.3 (C), 144.6 (C), 144.4 (C), 136.6 (C), 133.8 (C), 132.8 (C), 129.7 (CH), 129.3 (CH), 127.8 (CH), 115.5 (CH_2), 115.0 (CH), 112.2 (CH), 70.5 (CH_2), 55.1 (MeO), 32.6 (CH_2), 25.3 (Me) and 21.6 (Me); *m/z* (EI) 346 (M^+).

2,5-Diphenyl-1,3-dioxane 28

Freshly distilled benzaldehyde (3.7 cm^3, 37 mmol) was added to a stirred suspension of the diol **27**[15] (3.51 g, 23.1 mmol) and anhydrous $ZnCl_2$ (4.09 g, 30 mmol) in chloroform (115 cm^3). The mixture was stirred overnight at room temperature, then diluted with water and extracted with dichloromethane (3 × 100 cm^3). The combined organic layers were washed with dilute aqueous sodium thiosulfate, dried (Na_2SO_4) and evaporated under reduced pressure to give the *cyclic acetal* **28** (4.16 g, 75%) as needles, mp 96–97 °C [from dichloromethane–light petroleum (bp 40–60 °C) (2:98)] (Found: C, 80.2; H, 6.8%; MH^+, 241.1241. $C_{16}H_{16}O_2$ requires C, 80.0; H, 6.7%; *M*H, 241.1228); λ_{max}(EtOH)/nm 209; δ_H(200 MHz, $CDCl_3$) 7.68–7.57 (2 H, m, ArH), 7.49–7.25 (8 H, m, ArH), 5.63 (1 H, s, OCHO), 4.46–4.37 (2 H, m, 2 × C*H*H) and 4.09 (2 H, t, *J* 10.2, 2 × C*H*H) and 3.50–3.34 (1 H, m, PhC*H*); δ_C(50 MHz, $CDCl_3$) 138.2 (C), 137.6 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 127.4 (CH), 126.1 (CH), 101.5 (CH), 72.3 (CH) and 41.1 (CH_2); *m/z* (FAB + ve) 241 (MH^+).

3-Benzyloxy-2-phenylpropan-1-ol 29

A solution of diisobutylaluminium hydride in toluene (1.5 mol dm^{-3}; 18.3 cm^3, 27.5 mmol) was added to a stirred solution of the acetal **28** (2.2 g, 9.17 mmol) in dry toluene (8 cm^3) under argon at room temperature. The mixture was stirred for 3 h and then quenched with MeOH at 0 °C. Water was added and the mixture was acidified to pH 4. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:3), to yield recovered starting material (70 mg, 3%) and *alcohol* **29** (2.09 g, 94%) as an oil (Found: MH^+, 243.1378. $C_{16}H_{18}O_2$ requires *M*H, 243.1385); ν_{max}/cm^{-1} 3410 (O–H); δ_H(200 MHz, $CDCl_3$) 7.42–7.20 (10 H, m, ArH), 4.57 (2 H, s, CH_2Ph), 4.09–3.75 (4 H, m, 2 × CH_2), 3.30–3.17 (1 H, m, C*H*Ph) and 2.45 (1 H, br s, OH); δ_C(100 MHz, APT, $CDCl_3$) 139.6 (C), 137.8 (C), 128.6 (CH), 128.4 (CH), 128.0 (CH), 127.7 (CH), 127.6 (CH), 127.0 (CH), 73.6 (CH_2), 73.4 (CH_2), 66.4 (CH_2) and 47.8 (CH); *m/z* (FAB + ve) 243 (MH^+).

N-(3-Benzyloxy-2-phenylpropyl)succinimide 30

A solution of the alcohol **29** (2.09 g, 8.63 mmol), succinimide (1.11 g, 11.2 mmol) and diethyl azodicarboxylate (1.5 cm^3, 9.5 mmol) in dry THF (35 cm^3) under argon at 0 °C was treated with a solution of triphenylphosphine (2.5 g, 9.5 mmol) in dry THF (9.5 cm^3) and then stirred at room temperature for 6 h. Water was added (10 cm^3) and the mixture was extracted with dichloromethane (3 × 25 cm^3). The combined extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (2:3), to give recovered starting alcohol **29** (198 mg, 9%) and *succinimide* **30** (2.4 g, 86%) as an oil. Recrystallisation from ethanol gave **30** as needles, mp 69–70 °C (Found: C, 74.3; H, 6.6; N, 4.2%; MH^+, 324.1618. $C_{20}H_{21}NO_3$ requires C, 74.3; H, 6.5; N, 4.3%; *M*H, 324.1600); ν_{max}/cm^{-1} 1698 (C=O); δ_H(200 MHz, $CDCl_3$) 7.37–7.21 (10 H, m, ArH), 4.46 and 4.40 (each 1 H, d, *J* 15.5, OC*H*HPh), 3.97–3.51 (5 H, m, CH_2CHCH_2) and 2.38 (4 H, s, CH_2CH_2); δ_C(100 MHz, APT, $CDCl_3$) 177.3 (C), 139.2 (C), 138.1 (C), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.7 (CH), 127.2 (CH), 73.5 (CH_2), 73.2 (CH_2), 42.9 (CH), 42.3 (CH_2) and 27.9 (CH_2); *m/z* (FAB + ve) 324 (MH^+).

1-(3-Benzyloxy-2-phenylpropyl)-5-ethoxy-2-pyrrolidone 31

A stirred solution of succinimide **30** (568 mg, 1.76 mmol) in absolute ethanol (35 cm^3) was stirred with sodium borohydride (475 mg, 12.3 mmol) under argon for 5 h, during which time a solution of conc. hydrochloric acid in absolute ethanol (1.85 mol dm^{-3}; 3 drops) was added every 15 min. The mixture was then acidified to pH 3 with more ethanolic hydrochloric acid. The resultant mixture was poured into dilute aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to yield *ethoxylactam* **31** (593 mg, 96%) as an oil, which NMR spectroscopy showed to be a mixture of diastereoisomers (*ca.* 1.3:1) (Found: MH^+, 354.2072. $C_{22}H_{27}NO_3$ requires *M*H, 354.2069); ν_{max}/cm^{-1} 1698 (C=O); δ_H(400 MHz, $CDCl_3$) 7.33–7.19 (10 H, m, ArH), 4.75 (0.5 H, t, *J* 4.3 and 3.2, C*H*OEt), 4.50 and 4.47 (each 1 H, d, *J* 16.9, OC*H*HPh), 4.29 (0.5 H, t, *J* 5.3 and 2.3, C*H*OEt), 4.01 (0.5 H, dd, *J* 13.6 and 6.4, C*H*HOBn), 3.90 (0.5 H, dd, *J* 13.8 and 8.1, C*H*HOBn), 3.70–3.62 (2 H, m, OCH_2Me), 3.49–3.17 (4 H, m, CH_2C*H*PhCH*H*OBn), 2.41 and 2.22–2.07 (each 1 H, m, CH_2C=O), 1.86–1.75 (2 H, m, CH_2CHOEt) and 1.18 and 1.13 (each 1.5 H, t, *J* 7.0, Me); δ_C(100 MHz, APT, $CDCl_3$) (major diastereoisomer) 175.1 (C), 141.0 (C), 138.3 (C), 128.5 (CH), 128.2 (CH), 127.5 (CH), 127.5 (CH), 127.0 (CH), 89.2 (CH), 73.0 (CH_2), 72.6 (CH_2), 61.4 (CH_2), 44.4 (CH), 43.6 (CH_2), 28.7 (CH_2), 24.7 (CH_2) and 15.2 (Me); (minor diastereoisomer) 175.1 (C), 140.1 (C), 138.2 (C), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 126.9 (CH), 89.1 (CH), 73.1 (CH_2), 72.7 (CH_2), 61.6 (CH_2), 44.0 (CH), 42.3 (CH_2), 28.7 (CH_2), 24.8 (CH_2) and 15.3 (Me); *m/z* (FAB + ve) 354 (MH^+).

6-Benzyloxymethyl-1,5,6,10b-tetrahydrobenzo[*g*]indolizin-3(2*H*)-one 32

A solution of the ethoxylactam **31** (94 mg, 0.27 mmol) in formic acid (6 cm^3) was stirred at room temperature for 22 h and then evaporated under reduced pressure. The residue was dissolved in dichloromethane and washed with dilute aqueous sodium hydrogen carbonate. The organic layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (3:1), to give the *tricyclic lactam* **32** (58 mg, 71%) as an oil (Found: MH^+, 308.1669. $C_{20}H_{21}NO_2$ requires *M*H, 308.1650), which NMR spectroscopy showed to be a mixture of diastereoisomers (8.4:1); ν_{max}/cm^{-1} 1716 and 1682 (C=O); *m/z* (FAB + ve) 308 (MH^+). The two isomers were separated by PLC, eluting with dichloromethane–acetone (9:1), for NMR analysis.

For the major (6*R**,10b*S**)-isomer: δ_H(400 MHz, $CDCl_3$) 7.37–7.09 (9 H, m, ArH), 4.76 (1 H, t, *J* 8.2, 10b-H), 4.58 and 4.47 (each 1 H, d, *J* 11.7, PhC*H*H), 4.57 (1 H, d, *J* 13.1, 5-H_β), 3.49 (1 H, ddd, *J* 9.4, 4.3 and 4.0, 6-H), 3.35 (1 H, t, *J* 9.4, C*H*HOBn), 3.11 (1 H, t, *J* 9.4 and 4.3, CH*H*OBn), 3.05 (1 H, dd, *J* 13.1 and 4.0, 5-H_α), 2.70–2.54 (2 H, m, 1-H_α and 2-H_β), 2.46 (1 H, m, 2-H_α) and 1.75 (1 H, m, 1-H_β); δ_C(100 MHz, APT, $CDCl_3$) 173.6 (C), 138.2 (C), 137.9 (C), 133.7 (C), 130.1 (CH), 128.3 (CH), 127.8 (CH), 127.5 (CH), 127.3 (CH), 126.8 (CH), 124.8 (CH), 73.5 (CH_2), 73.3 (CH_2), 56.8 (CH), 39.4 (CH), 38.1 (CH_2), 31.8 (CH_2) and 27.9 (CH_2).

For the minor (6*S**,10b*S**)-isomer: δ_H(400 MHz, $CDCl_3$) 7.35–7.11 (9 H, m, ArH), 4.76 (1 H, t, *J* 8.0, 10b-H), 4.56 and 4.52 (each 1 H, d, *J* 12.5, PhC*H*H), 4.43 (1 H, dd, *J* 13.1 and 6.2, 5-H_β), 3.81 (1 H, dd, *J* 9.5 and 4.8, C*H*HOBn), 3.68 (1 H, dd, *J* 9.5 and 6.7, CH*H*OBn), 3.25 (1 H, m, 6-H), 3.06 (1 H, dd, *J* 13.1 and 9.7, 5-H_α), 2.70–2.51 (2 H, m, 1-H_α and 2-H_β), 2.44 (1 H, m, 2-H_α) and 1.92–1.82 (1 H, m, 1-H_β); δ_C(100 MHz, APT, $CDCl_3$) 173.2 (C), 138.1 (C), 138.0 (C), 134.7 (C), 128.4 (CH), 127.7 (2 × CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 124.8 (CH), 73.2 (CH_2), 71.3 (CH_2), 56.7 (CH), 40.2 (CH_2), 37.6 (CH), 31.6 (CH_2) and 27.5 (CH_2).

6-Hydroxymethyl-1,5,6,10b-tetrahydrobenzo[*g*]indolizin-3(2*H*)-one 33

The mixture of diastereoisomeric benzyl ethers **32** (85 mg, 0.28 mmol) and 10% palladium-on-carbon (85 mg) were stirred in absolute ethanol (2 cm^3) under an atmosphere of hydrogen for 8 h. The mixture was then filtered through Celite, washing with more absolute ethanol. The filtrate and washings were evaporated under reduced pressure and the residue was purified by flash column chromatography, eluting with dichloromethane–tetrahydrofuran (4:1), to give a mixture of the *diastereoisomeric alcohols* **33** (35 mg, 58%) as a solid. Recrystallisation from ethanol gave the (6*R**,10b*S**)-isomer as prisms, mp 157–158 °C (Found: C, 71.7; H, 7.0; N, 6.35%; MH^+, 218.1181. $C_{13}H_{15}NO_2$ requires C, 71.9; H, 6.95; N, 6.45%; *M*H, 218.1181); ν_{max}/cm^{-1} 3324 (O–H) and 1672 (C=O); δ_H(400 MHz, $CDCl_3$) 7.28–7.10 (4 H, m, ArH), 4.86 (1 H, t, *J* 7.8, 10b-H), 4.50 (1 H, d, *J* 13.3, 5-H_β), 3.67–3.60 and 3.37–3.31 (each 1 H, m, CH_2OH), 3.13–3.00 (3 H, m, 5-H_α, 6-H and OH), 2.76–2.60 (2 H, m, 2-H_β and 1-H_α), 2.52–2.45 (1 H, m, 2-H_α) and 1.91–1.81 (1 H, m, 1-H_β); δ_C(100 MHz, APT, $CDCl_3$) 174.8 (C), 137.8 (C), 133.9 (C), 129.8 (CH), 127.5 (CH), 126.9 (CH), 125.2 (CH), 64.9 (CH), 57.1 (CH_2), 41.2 (CH), 37.6 (CH_2), 31.4 (CH_2) and 27.8 (CH_2); *m/z* (CI) 435 (2M + H^+), 235 (M + NH_4^+) and 218 (MH^+).

For NMR analysis the minor (6*S**,10b*S**)-isomer was obtained pure from the mother liquors by PLC eluting with dichloromethane–methanol (19:1); δ_H(400 MHz, $CDCl_3$) 7.36 and 7.12 (each 1 H, dd, *J* 8.8 and 3.6, 7- and 10-H), 7.23 (2 H, m, 8- and 9-H), 4.77 (1 H, t, *J* 8.0, 10b-H), 4.29 (1 H, dd, *J* 11.3 and 10.5, 5-H_α), 3.98 (1 H, dd, *J* 11.2 and 3.7, C*H*HOH), 3.90 (1 H, dd, *J* 11.3 and 5.8, CH*H*OH), 3.12 (2 H, m, 6-H and 5-H_β), 2.88 (1 H, br s, OH), 2.70–2.62 (1 H, m, 1-H_α), 2.59–2.50 (1 H, m, 2-H_α), 2.45–2.38 (1 H, m, 2-H_β) and 1.91–1.81 (1 H, m, 1-H_β); δ_C(100 MHz, APT, $CDCl_3$) 173.5 (C), 138.3 (C), 134.2 (C), 127.3 (CH), 127.0 (CH), 126.9 (CH), 124.9 (CH), 63.6 (CH_2), 56.7 (CH), 39.8 (CH_2), 39.5 (CH), 31.5 (CH_2) and 27.4 (CH_2).

1,2,3,5,6,10b-Hexahydrobenzo[*g*]indolizine-6-methanol 34

A solution of the (6*R**,10b*S**)-alcohol **33** (210 mg, 0.97 mmol) in dry THF (18 cm^3) was added to a stirred suspension of lithium aluminium hydride (75 mg, 1.94 mmol) in dry THF (2 cm^3) under argon at 0 °C. The mixture was heated at reflux for 1 h, then cooled and poured into a mixture of diethyl ether and ice. The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with dichloromethane–methanol (17:3) to yield the *amine* **34** (183 mg, 93%) as an oil (Found: MH^+, 204.1388. $C_{13}H_{17}NO$ requires *M*H, 204.1388); ν_{max}/cm^{-1} 3354 (O–H); δ_H(400 MHz, $CDCl_3$) 7.26–7.08 (4 H, m, ArH), 4.09 (1 H, dd, *J* 2.7 and 9.9, C*H*HOH), 3.38 (1 H, dt, *J* 2.0 and 3.2 and 9.9, CH*H*OH), 3.35 (1 H, d, *J* 11.1, 5-H_β), 3.22–3.17 (2 H, m), 2.99 (1 H, br s, 6-H), 2.83 (1 H, d, *J* 11.1, 5-H_α), 2.43–2.34 (2 H, m), 1.96–1.87 (2 H, m) and 1.77–1.69 (1 H, m); δ_C(100 MHz, APT, $CDCl_3$) 138.5 (C), 135.2 (C), 128.0 (CH), 126.9 (CH), 126.5 (CH), 124.9 (CH), 70.4 (CH_2), 64.8 (CH), 54.1 (CH_2), 53.0 (CH_2), 40.0 (CH), 29.0 (CH_2) and 21.5 (CH_2); *m/z* (CI) 204 (MH^+).

(1,2,3,5,6,10b-Hexahydrobenzo[*g*]indolizin-4-ium-6-yl)methyl 4-[(*E*)-2-(isopropoxycarbonyl)ethenyl]phenylphosphonate 35

To a stirred suspension of the phosphonic acid **14** (55 mg, 0.20 mmol) in dry DMF (1 cm^3) at −15 °C under argon was added thionyl chloride (20 mm^3, 0.24 mmol). The resultant mixture was stirred at 0 °C for 1 h and then a solution of the alcohol **34** (82 mg, 0.40 mmol) in dry DMF (1 cm^3) was added and the mixture was stirred at room temperature for a further 24 h. Water was added (1 cm^3) and the mixture was extracted with diethyl ether (6 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by PLC, eluting with propan-1-ol–water–ammonia (18:1:1), to yield the *phosphonate ester* **35** (32 mg, 35%) as an amorphous solid (Found: MH^+, 456.1933. $C_{25}H_{30}NO_5P$ requires *M*H, 456.1939); ν_{max}/cm^{-1} 3139–3030 (N–H) and 1703 (C=O); δ_H(500 MHz, CD_3OD) 7.71 (2 H, dd, *J* 11.9 and 8.0, ArH), 7.66 (1 H, d, *J* 16.0, C*H*=C), 7.59 (2 H, dd, *J* 8.0 and 2.8, ArH), 7.30–7.21 (4 H, m, ArH), 6.54 (1 H, d, *J* 16.0, C=C*H*), 5.09 (1 H, septet, *J* 6.3, C*H*Me_2), 4.49 (1 H, dd, *J* 7.3 and 8.4), 4.25 (1 H, m), 4.03 (1 H, m), 3.60–3.43 (5 H, m), 2.71 (1 H, m), 2.22 (2 H, m), 2.05 (1 H, quintet, *J* 11.1) and 1.31 (6 H, d, *J* 6.3, CHMe_2); δ_C(100 MHz, APT, CD_3OD) 168.0 (C), 145.1 (CH), 138.9 (C, *J* 176), 137.7 (C), 133.7 (C), 133.1 (CH, *J* 9), 132.7 (C), 129.0 (CH, *J* 14), 128.8 (CH), 128.7 (CH), 127.9 (CH), 127.6 (CH), 120.8 (CH), 69.5 (CH), 66.4 (CH_2), 65.0 (CH), 55.9 (CH_2), 50.9 (CH_2), 36.4 (CH), 30.8 (CH_2), 22.1 (CH_2) and 22.1 (Me); *m/z* (FAB + ve) 456 (MH^+).

(1,2,3,5,6,10b-Hexahydrobenzo[*g*]indolizin-4-ium-6-yl)methyl 4-[(*E*)-2-carboxyethenyl]phenylphosphonate 25

A solution of the ester **32** (21 mg, 46.2 μmol) in methanolic potassium hydroxide (2.7 mol dm^{-3}; 1 cm^3) was stirred under argon at room temperature for 24 h and then evaporated under reduced pressure. The residue was dissolved in water (10 cm^3) and Dowex-50WX8-400 (NH_4^+) ion exchange resin was added until the pH dropped to between 9 and 10. The resin was filtered off and the filtrate was lyophilised to yield the *acid* **25** (18 mg, 95%) as an amorphous solid (Found: MH^+, 414.1481. $C_{22}H_{24}NO_5P$ requires *M*H, 414.1470); ν_{max}/cm^{-1} 3422–3144 (O–H) and 1700 (C=O); δ_H(500 MHz, CD_3OD) 7.70 (2 H, dd, *J* 11.8 and 8.1, ArH), 7.55 (2 H, dd, *J* 2.9 and 8.1, ArH), 7.51 (1 H, d, *J* 16.0, CH=C), 7.32–7.21 (4 H, m, ArH), 6.55 (1 H, d, *J*

16.0, C=CH), 4.47 (1 H, m), 4.26 (1 H, m), 4.00 (1 H, m), 3.49–3.41 (5 H, m), 2.69 (1 H, m), 2.20 (2 H, m) and 2.03 (1 H, quintet, *J* 10.8); δ_C(100 MHz, APT, CD_3OD) 173.4 (C), 145.4 (CH), 141.9 (CH), 138.8 (C), 136.8 (C, *J* 178), 134.0 (C), 133.0 (CH, *J* 9), 129.3 (CH), 128.6 (CH), 128.3 (CH, *J* 14), 128.0 (CH), 127.6 (CH), 125.5 (CH), 66.4 (CH_2), 64.9 (CH), 55.9 (CH_2), 50.9 (CH_2), 38.5 (CH), 30.8 (CH_2) and 22.2 (CH_2); *m/z* (FAB + ve) 414 (MH^+).

3-[2-(*tert*-Butyldimethylsilyloxymethyl)phenyl]-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene 39

A suspension of alcohol **38**[4] (518 mg, 1.69 mmol) and imidazole (288 mg, 4.23 mmol) in dry DMF (4.2 cm^3) under argon at room temperature was stirred with chloro(*tert*-butyl)diphenylsilane (660 mm^3, 2.54 mmol) for 24 h, then diluted with water (25 cm^3) and extracted with diethyl ether (10 cm^3). The organic layer was washed with water (3 × 25 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:19), to yield the *silyl ether* **39** (908 mg, 99%) as an oil; ν_{max}/cm^{-1} 1632 (C=C); δ_H(400 MHz, $CDCl_3$) 7.67–7.59 (4 H, m, ArH), 7.48–7.13 (10 H, m, 2 × Ph), 5.90–5.81 (1 H, m, C*H*=CH_2), 4.02 (2 H, m, CH=C*H*$_2$), 4.84 and 4.81 (each 1 H, d, *J* 18.3, ArC*H*H), 3.79 (1 H, q, *J* 7.4, ArC*H*), 3.64 (2 H, m, CH_2CH_2O), 1.97 (2 H, q, *J* 6.7, CH_2CH_2O), 1.05 and 0.93 (each 9 H, s, Bu^t) and 0.07 and 0.05 (each 3 H, s, $SiMe_2$); δ_C(100 MHz, APT, $CDCl_3$) 141.3 (CH), 140.5 (C), 138.8 (C), 135.6 (CH), 135.5 (CH), 133.8 (C), 129.6 (CH), 129.5 (CH), 127.6 (CH), 127.1 (CH), 126.6 (CH), 126.3 (CH), 126.0 (CH), 114.4 (CH_2), 62.6 (CH_2), 61.6 (CH_2), 39.7 (CH), 37.6 (CH_2), 26.9 [C(*C*H_3)$_3$], 26.0 [C(*C*H_3)$_3$], 19.2 [*C*(CH_3)$_3$], 18.4 [*C*(CH_3)$_3$] and −5.3 ($SiCH_3$).

3-(2-Hydroxymethylphenyl)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene 40

A suspension of the alcohol **39** (841 mg, 1.55 mmol) in absolute ethanol (8 cm^3) was stirred with pyridinium toluene-*p*-sulfonate (117 mg, 0.46 mmol) for 48 h at room temperature.[22] The solvent was evaporated under reduced pressure, water was added (10 cm^3) and the aqueous layer was extracted with ethyl acetate (3 × 30 cm^3). The combined organic layers were washed with brine and then with water, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (bp 40–60 °C) (1:9), to yield the *alcohol* **40** (530 mg, 80%) as an oil (Found: MH^+, 431.2402. $C_{28}H_{34}O_2Si$ requires *M*H, 431.2406); ν_{max}/cm^{-1} 3417 (O–H) and 1635 (C=C); δ_H(400 MHz, $CDCl_3$) 7.69–7.57 (4 H, m, ArH), 7.44–7.19 (10 H, m, 2 × Ph), 6.03–5.86 (1 H, m, C*H*=CH_2), 5.05–4.92 (2 H, m, CH=C*H*$_2$), 4.86–4.64 (2 H, m, ArC*H*$_2$O), 4.02 (1 H, q, *J* 7.2, ArC*H*), 3.73–3.52 (2 H, m, CH_2CH_2O), 2.28 (1 H, dd, *J* 8.7 and 6.1, OH), 1.98–1.67 (2 H, m, CH_2CH_2O) and 1.06 (9 H, s, Bu^t); δ_C(100 MHz, APT, $CDCl_3$) 142.1 (CH), 141.8 (C), 138.7 (C), 135.6 (CH), 135.5 (CH), 133.5 (C), 133.4 (C), 129.7 (CH), 129.6 (CH), 129.2 (CH), 128.3 (CH), 127.6 (2 × CH), 127.2 (CH), 126.4 (CH), 114.4 (CH_2), 63.3 (CH_2), 61.6 (CH_2), 39.9 (CH), 38.0 (CH_2), 26.8 [C(*C*H_3)$_3$] and 19.1 [*C*(CH_3)$_3$]; *m/z* (FAB + ve) 431 (MH^+) and 413 ($MH^+ - H_2O$).

Crystal structure determination for 1

$C_{13}H_{15}NO_2$, *M* = 217.26, monoclinic, space group $P2_1/c$ (no. 14), *a* = 9.173(2), *b* = 15.831(3), *c* = 7.883(2) Å, *β* = 105.36(3)°, *V* = 1103.9(4) $Å^3$, *T* = 293(2) K, D_c = 1.307 Mg m^{-3}, *Z* = 4, *F*(000) = 464, molybdenum K*α* radiation, *λ* = 0710 73 Å, *μ*(Mo-K*α*) = 0.088 mm^{-1}. Crystal dimensions 0.30 × 0.32 × *0.33 mm*.

2349 Refelections were recorded on a Rigaku AFC7R diffractometer in the range 2.57 < *θ* < 27.50°, and averaged to give 2189 reflections (R_{int} = 0.0351). The structure was solved by direct methods (SHELXS-86:TREF) and refined by full-matrix least-squares based on F^2 (SHELXL-93). H-atoms were placed in idealised positions and allowed to ride on the relevant heavy atom with independent isotropic vibrational parameters. The structure refinement converged to R_1 = 0.0513 and wR_2 = 0.1146 for reflections with $I > 2\sigma(I)$ and R_1 = 0.0982 and wR_2 = 0.1403 for all data.

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