N-Alkenyl Nitrone Dipolar Cycloaddition Routes to Piperidines and Indolizidines. Part 6.† Allylic Stereocontrol in the Intramolecular Cyclisation of Monosubstituted Nitrones

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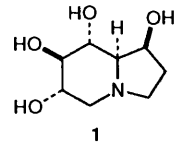
The intramolecular, thermal dipolar cycloadditions of the (*Z*)-*N*-alk-4-enyl nitrones **18–21**, **34** and **35** bearing a single, allylic substituent were investigated. Certain alkoxy substituted nitrones **18–21** showed a remarkable preference for the formation of axially substituted isoxazolidines **22a–24a**, whereas the propyl and trifluoromethyl substituted nitrones **35** and **34** gave the equatorially substituted cycloadducts **37** and **36a** respectively, consistent with the involvement of 'chair-like' transition states **38**.

The piperidine and indolizidine ring systems are common structural features of many naturally occurring, biologically active alkaloids. In recent years a considerable research effort has been directed towards the isolation, biological evaluation and total synthesis of polyhydroxylated indolizidines and piperidines, such as castanospermine **1**[2] and deoxynojirimycin **2**.[3] The ability of this class of molecules to modulate the *in vivo*



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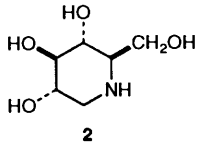

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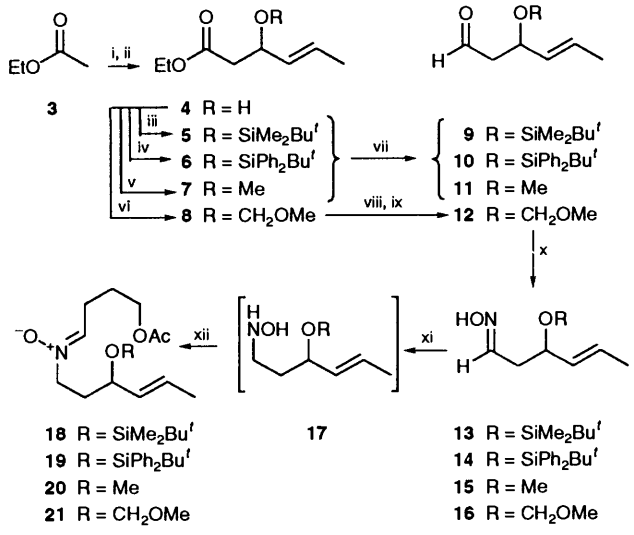
oligosaccharide chemistry of mammals, insects and plants gives rise to an extraordinarily wide range of potential uses, spanning for example the fields of diabetes therapy, immunoregulation, plant growth regulation, pest control and antiviral therapy.[4] Special interest has been generated by those polyhydroxylated indolizidines and piperidines which inhibit the *in vitro* replication and cytotoxicity of the Human Immunodeficiency Virus (HIV).[5]

We have previously developed a nitrone-based stereoselective synthetic route to all-*cis* 2,3,6-substituted piperidines, which has led to total syntheses of carpamic acid,[6] several dendrobatid 8-methyl indolizidines[7–9] and, most recently, the B/C indolizidine ring fragment of gephyrotoxin.[1,10] The key to this approach has been the application of a thermal, intramolecular cycloaddition of a (*Z*)-*N*-alk-4-enyl nitrone to construct the piperidine ring. The stereocontrol in this reaction arises from a presumed 'chair-like' folding of the six-membered cyclic transition state, in which a carbon substituent adjacent to the nitrogen atom adopts a pseudo-equatorial orientation.[11] The starting nitrones can be prepared as single enantiomers, leading to the synthesis of single enantiomers of the natural products.[8] A similar approach has been used by another group in a synthesis of pumiliotoxin C.[12]

We wished to investigate the extension of this methodology to the synthesis of polyhydroxylated alkaloids. We chose to examine the cyclisation of nitrones bearing a single allylic oxygen substituent to explore whether the products could be predicted by the chair-like transition state, to determine the stereoselectivity of the cyclisation, and to test the compatibility of various oxygen protecting groups with this strategy.



Scheme 1 *Reagents and conditions:* i, LDA, THF, −70 °C; ii, (*E*)-MeCH=CHCHO, −70 °C; iii, imidazole, Me_2Bu^tSiCl, CH_2Cl_2, room temp.; iv, imidazole, Ph_2Bu^tSiCl, DMF, 60 °C; v, MeI, Ag_2O, DMF, room temp.; vi, $MeOCH_2Cl$, Pr^i_2NEt, toluene, reflux; vii, DIBAL-H, toluene, −85 °C; viii, $LiAlH_4$, Et_2O, 0 °C; ix, Swern oxidation with pH 5 buffered work-up; x, NH_2OH·HCl, NaOAc, EtOH–H_2O, room temp.; xi, $NaCNBH_3$, HCl, pH 3–4, MeOH, 0 °C ⟶ room temp.; xii, $AcO[CH_2]_3CHO$, $MgSO_4$, CH_2Cl_2, 0 °C

Results and Discussion

The synthesis of the singly substituted nitrones **18–21** was carried out as described in Scheme 1.

The carbon skeleton was conveniently constructed by an aldol reaction of the lithium enolate of ethyl acetate with crotonaldehyde, which proceeded smoothly to give the β-hydroxy ester **4** in 92% yield (Scheme 1).[13] The aldol product **4** was found to be unstable in strongly basic media, undergoing β-elimination to give ethyl sorbate. The choice of protecting groups for the alcohol was therefore restricted to those which could be introduced under neutral or mildly basic conditions. Within this limitation, a range of protecting groups of varied steric bulk was selected. Thus the alcohol **4** was converted into the silyl ethers **5** and **6** in 99 and 94% yields respectively, and

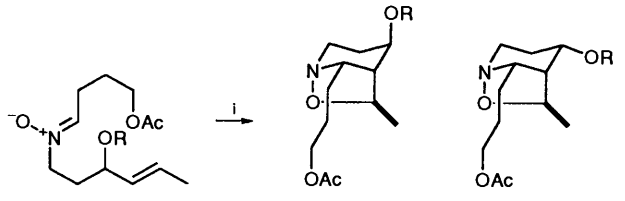
† Part 5: ref. 1.

into the methoxymethyl ether **8** in 88%. Methylation of the alcohol **4** was more problematic as even the mild reagent combination of silver(I) oxide and methyl iodide led to some elimination, resulting in only 34% recovery of the pure methyl ether **7** after chromatography.

The esters **5**, **6** and **7** were reduced cleanly by diisobutylaluminium hydride at low temperature. The resultant aldehydes were condensed with hydroxylamine to yield the corresponding oximes **13**, **14** and **15** (76–86% over two steps). Unfortunately, β-elimination of the alkoxide was encountered again when the methoxymethyl protected ester **8** was treated with diisobutylaluminium hydride, accompanied by significant over-reduction. This was circumvented by clean reduction of the ester **8** to the alcohol with lithium aluminium hydride followed by reoxidation to the aldehyde **12**. Several reagents were examined to effect this transformation, all of which suffered from elimination by-products. The optimum conditions consisted of a Swern oxidation which was quenched at −40 °C with citric acid and buffered at pH 5 during the subsequent work-up. The aldehyde **12** from this reaction was condensed with hydroxylamine to give the oxime **16** in moderate yield (52% over two steps).

The oximes were reduced with sodium cyanoborohydride at pH 3–4 to furnish the intermediate hydroxylamines **17**. To avoid potential intramolecular cyclisations of the hydroxylamines **17**,[11,14] these compounds were condensed immediately with 4-acetoxybutanal[15] to give the nitrones **18–21** (49–70%).

With the nitrones in hand, the stereochemical course of the intramolecular dipolar cycloaddition was investigated (Scheme 2). Dilute (0.01–0.02 mmol dm^{-3}) toluene solutions of the nitrones were heated to reflux for 18 h using a Dean–Stark

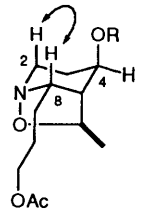


18 R = $SiMe_2Bu^t$ **22a** R = $SiMe_2Bu^t$ **22b** R = $SiMe_2Bu^t$
19 R = $SiPh_2Bu^t$ **23a** R = $SiPh_2Bu^t$ **23b** R = $SiPh_2Bu^t$
20 R = Me **24a** R = Me **24b** R = Me
21 R = CH_2OMe **25a** R = CH_2OMe **25b** R = CH_2OMe

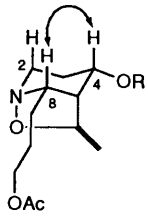
Scheme 2 *Reagents and conditions:* i, toluene, reflux. Note that, for convenience, structures **22a–25a** are drawn as arising from opposite enantiomers of the respective racemic precursors **18–21** compared with structures **22b–25b**. This convention is maintained throughout.

apparatus to remove adventitious moisture. This procedure has been found to maximise the recovery of cycloadducts from the reaction. The results are summarised in Table 1.

The cyclisation of the *tert*-butyldimethylsiloxy substituted nitrone **18** exhibited an unexpected preference for formation of the axially substituted isoxazolidine **22a**. A similar selectivity in favour of the axial product **24a** was observed with the methoxy substituted nitrone **20**. In the remaining examples the cyclisations showed little preference for axial over equatorial.



22a R = $SiMe_2Bu^t$



22b R = $SiMe_2Bu^t$

Table 1 Yields and relative proportion of adducts arising from cycloaddition of nitrones **18–21**

Cycloadducts	R	Yield (%)	a:b
22	$SiMe_2Bu^t$	86	2.1:1[a]
23	$SiPh_2Bu^t$	85	1.2:1[b]
24	Me	68	1.8:1[a]
25	$-CH_2OMe$	97	1.1:1[b,c]

[a] After chromatographic separation of the cycloadducts. [b] From NMR analysis of the unseparated cycloadducts. [c] After hydrolysis of the acetate ester and chromatographic separation.

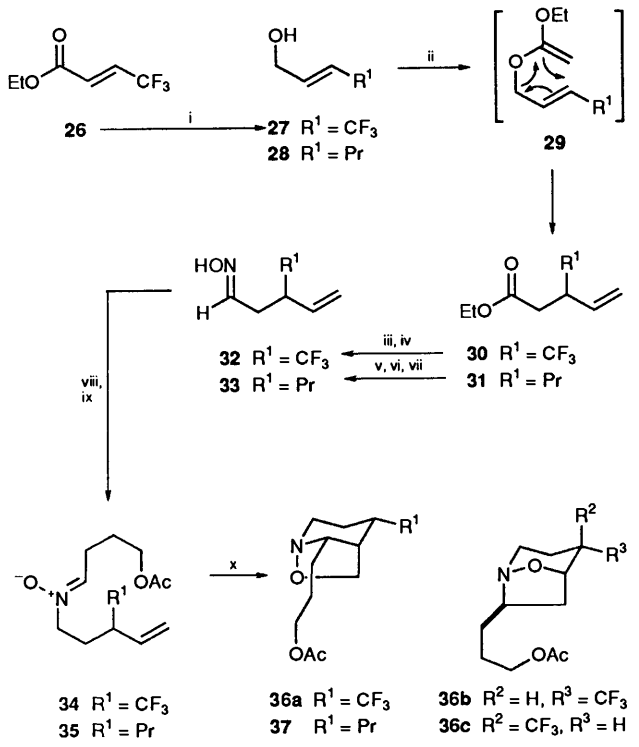
These results were in marked contrast to the very high selectivity for equatorial substitution observed in our earlier work on nitrones bearing carbon substituents adjacent to nitrogen.[1,7–10]

It is appropriate to comment on the assignment of the stereochemistry of the cycloadducts **22–25**. This was achieved by high field ^1H nuclear magnetic resonance (NMR), facilitated by the rigid bicyclic framework of the isoxazolidines and by the good separations in chemical shift of key protons in these molecules. For example, in the equatorially substituted cycloadduct **22b**, proton 4-H δ 3.80 (1 H, ddd, *J* 9.6, 6.9 and 3.0) exhibited a *trans* diaxial coupling to 3-H. Complementing this feature was the observation of a transannular nuclear Overhauser enhancement (NOE) between 4-H and its co-axial neighbour 8-H. The corresponding axially substituted cycloadduct **22a** showed neither the large coupling to 4-H, δ 3.99 (1 H, dd, *J* 4.8 and 3.5) nor any NOE from other axial protons.

All spectroscopic data were consistent with the six-membered ring of the isoxazolidines adopting a 'chair-like' conformation. For example, the 2-H_β showed a large *trans* + diaxial coupling in all the cycloadducts prepared. In the cycloadduct **22a** this was supported by an NOE observed between the two axial protons 2-H_β and 8-H. Other researchers have also reported 'chair-like' conformations to be dominant in the cyclisation of related *C*-alkenyl nitrones,[16] although a recent synthesis of the histrionicotoxin framework by Parsons *et al.* involved intramolecular cyclisation which was best rationalised through a 'boat-like' transition state.[17] That the six-membered ring of the products **22–25** is locked in a rigid chair conformation does not seem in doubt. For this reason, and also from the results of some semi-empirical calculations of minimised conformations for the transition states for the reaction using the Spartan® computational package, we have no reason to believe that boat transition states intervene at a lower energy than the corresponding chair conformations.

The cyclisation of the *tert*-butyldimethylsiloxy substituted nitrone **18** was investigated further. Altering the temperature of the reaction by changing the solvent to benzene or xylene affected the rate of cyclisation but did not greatly change the ratio of the two products, although the reaction became marginally more selective at the lower temperature (**22a**:**22b**, 2.8:1). When the pure minor isoxazolidine **22b** was heated in refluxing xylene, no equilibration to the axially substituted product was observed, indicating that the cycloaddition was not reversible under the conditions of the reaction, and implying that the observed selectivity was kinetic in origin.

To discern a clear picture of the stereoelectronic factors involved in the cyclisations, the synthesis of two direct carbon-substituted analogues of the nitrones **18–21** was undertaken (Scheme 3). Nitrones bearing a relatively electron-rich alkyl substituent (**35**, R^1 = Pr) and a corresponding electron-deficient carbon substituent (**34**, R^1 = CF_3) were selected. The carbon frameworks of these nitrones were readily constructed through a Johnson–Claisen rearrangement of the ketene acetals **29** derived *in situ* from the allylic alcohols **27** and **28**.[18] The



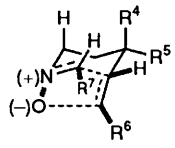
Scheme 3 *Reagents and conditions:* i, $LiAlH_4$, $AlCl_3$, Et_2O, 0 °C; ii, $MeC(OEt)_3$, $EtCO_2H$ (cat.), heat; iii, DIBAL-H, CH_2Cl_2, −78 °C; iv, NH_2OH·HCl, pyridine, MeOH, room temp.; v, $LiAlH_4$, Et_2O, room temp.; vi, PCC, CH_2Cl_2, room temp.; vii, NH_2OH·HCl, NaOAc, EtOH–H_2O, room temp.; viii, $NaCNBH_3$, HCl, pH 3–4, MeOH, 0 °C; ix, $AcO[CH_2]_3CHO$, $MgSO_4$, CH_2Cl_2, 0 °C; x, toluene, reflux

precursor alcohol **27** was prepared from the commercially available ester **26**.[19] Heating the alcohols **27** and **28** with triethyl orthoformate and a catalytic quantity of acid afforded the esters **30** (78%) and **31** (43%). In the case of the trifluoromethyl substituted alcohol **27**, forcing conditions (200 °C, sealed tube) were necessary to achieve the [3.3] sigmatropic rearrangement.

The trifluoromethyl substituted ester **30** was converted into the aldoxime **32** by diisobutylaluminium hydride reduction and condensation of the intermediate aldehyde with hydroxylamine (85% over two steps). A similar transformation of the propyl substituted ester **31** was achieved by complete reduction to the alcohol, followed by reoxidation and subsequent oxime formation (26% over three steps). The nitrones **34** and **35** were prepared from the aldoximes in the manner previously described.

Heating the nitrone **35** in refluxing toluene gave a single cycloaddition product in moderate yield (40%). Analysis of this product using proton–carbon and proton–proton correlation NMR spectroscopy showed it to be the equatorially substituted isoxazolidine **37**, a result in keeping with our previous observations on carbon-substituted nitrones. In contrast, the cycloaddition of the trifluoromethyl substituted nitrone **34** produced essentially the equatorial adduct **36a** (32%) together with small amounts (10.5%) of the regioisomeric products **36b** and **36c** as determined by gas chromatographic analysis of the reaction mixture. The materials were subsequently separated by silica gel and HPLC chromatography and identified unambiguously by a combination of homonuclear proton NMR decoupling and NOE experiments. The minor products **36b** and **36c** were identified as regioisomeric cycloaddition products where the carbon atom of the nitrone had become directly bonded to the terminal carbon of the olefin. The regiochemical outcome of the nitrone–olefin cycloaddition correlates, in part, with the magnitudes of the atomic orbital coefficients of the highest occupied molecular orbital (HOMO) of the olefin and the lowest unoccupied molecular orbital (LUMO) of the nitrone.[20] In the intramolecular cycloaddition of the *N*-pentenyl nitrones in this study the preference for six- over seven-membered ring formation in the leading C–C bond-forming step is the dominant factor controlling the regiochemistry, but other subtle substituent effects have also been observed to exert control over the regiochemistry of the cycloaddition.[11] The methyl substituted alkenes have approximately equal orbital coefficients, and in this case the regioselectivity is entropic and steric in origin. The regioisomer where C–C bond formation leads to a developing six-membered ring is favoured entropically over that leading to a seven-membered ring. Additionally, formation of the latter isomer involves an eclipsing interaction of the nitrone (*Z*)-substituent with the terminal methyl substituent of the alkene. This is avoided in the isomer arising from a developing six-membered ring in the initial C–C bond formation. When the alkene is unsubstituted this steric factor is removed. The alkene is also more polarised with the larger coefficient on the terminal atom. The frontier orbital therefore directs formation of the entropically less favourable isomer, and a mixture is observed.

To discuss the stereoselectivities observed in the above cyclisations it is helpful to draw on the theoretical models that Houk and co-workers have developed to describe the intermolecular reactions of allylic systems, including the additions of nitrile oxides to double bonds.[21] These have been extended recently to include higher level calculations including transition structures.[22] Notable features are that (i) it is sterically favourable for nitrone reactants to approach the dipolarophile double bond *anti* to the largest allylic substituent; (ii) for electrophilic attack on the olefin, electron withdrawing allylic substituents favour the 'inside' orientation with respect to the double bond, to minimise unfavourable overlap with the HOMO of the olefin. Other groups investigating the intramolecular dipolar cycloadditions of *C*-alkenyl nitrones have observed stereochemical outcomes consistent with these principles.[23] These authors have noted the importance of allylic 1,3-strain[24] at either the nitrone or alkene double bond in determining stereoselectivity.[23] Such allylic 1,3-strain is minimal for the (*E*)-alkenes employed in this study and is not considered to be a critical element of the stereocontrol in these cycloadditions. On the other hand recent studies by Kibayashi and co-workers[25] have illustrated the importance of the 'inside alkoxy effect' in determining the diastereoselectivity of certain intermolecular nitrone cycloadditions to alkenes bearing allylic alkoxy substituents. The regio- and stereo-selectivity of allylic alcohol dipolarophile cycloadditions to nitrones can also be controlled by metal ion chelation.[26]



38a	**38b**
R^4 = alkoxy, alkyl	R^4 = H
R^5 = H	R^5 = alkoxy, alkyl
R^6 = Me or H	R^6 = Me or H
R^7 = $[CH_2]_3OAc$	R^7 = $[CH_2]_3OAc$

For the formation of the isoxazolidines **22**–**25**, **36a** and **37**, the chair-like transition states **38** can be used to rationalise the observed product ratios, and we do not consider that the evidence in favour of boat-like transition states is convincing. It is noteworthy that the constraints of intramolecular cyclisation in these examples necessitate that the carbon tether between the reacting π-systems occupies the 'inside' position at the allylic double bond. Steric factors are expected to favour the formation

of the equatorially substituted products *via* the transition state **38b**, corresponding to the *anti* transition state proposed by Houk. This minimises the developing 1,3-diaxial repulsions at the allylic centre and also minimises repulsions between the axial substituent and the approaching dipole. For the cyclisation of the propyl substituted nitrone **35** these considerations are reinforced by an interaction between the *anti* C–C σ bonding orbital and the alkene HOMO which raises the HOMO. A single cycloadduct **37** was observed as a consequence, although the presence of small quantities of minor by-products cannot be excluded from consideration.

In the cycloaddition of nitrones and electron-rich alkenes the dominant frontier orbital interaction is between the HOMO of the alkene and the LUMO of the dipole. An equatorially disposed electron withdrawing group (R) *anti* to the approaching dipole, as in transition state **38b**, will allow an overlap of the C–R σ* orbital with the alkene HOMO, which lowers the HOMO and raises the energy of the transition state. The 'outside', axial transition state **38a** then becomes competitive in energy. Thus, when the allylic substituent is an alkoxy group, steric and electronic factors are in competition, and dominance of the latter can lead to a remarkable preference for the axial product with certain alkoxy substituents. A boat-like transition state would avoid the unfavourable interaction between an electronegative C–R σ* orbital and the alkene HOMO, and also the unfavourable axial position of the substituent. However, we do not consider that such gains would outweigh the considerable disadvantage (*ca.* 25 kJ mol^{-1}) of a boat, and the final product is indisputably chair-like.

Some correlation of product ratios with protecting group size was observed in the cyclisation of the nitrones **18–21**, although this is not strong. An upper limit to the ratio of axial to equatorial products seems to have been reached with **23a** (R = Bu^tMe_2Si). This may reflect the inherent anisotropy of the oxygen substituent, which can adopt a conformation that directs the protecting group away from the forming six-membered ring. This minimises the direct steric effect of the protecting group on the cyclisation, although there are unfavourable entropy changes associated with such a conformational restriction that will vary between substituents.[27] It is generally observed that hetero-substituents show a reduced preference for equatorial substitution in simple cyclohexanes compared with corresponding carbon substituents,[28a,b] and there is recent evidence to support the larger steric bulk of Bu^tMe_2SiO compared with Bu^tPh_2SiO as cyclohexyl substituents.[28c]

A critical difference was observed between the oxygen substituted nitrones and the trifluoromethyl substituted example **34**. In this case the electronic factors (*i.e.* a relatively weak polarisation of the CF_3–C σ bond) favouring transition state **38a** are outweighed by the size of the substituent (*A* values:[28] OMe, *ca.* 3.1 kJ mol^{-1} and CF_3, *ca.* 10 kJ mol^{-1}). The relative importance of steric and electronic effects of the trifluoromethyl group is not widely appreciated. A trifluoromethyl substituent shows good σ-delocalisation of charge on to the fluorine atoms, but the C–CF_3 σ* orbital is a relatively poor electron acceptor. Whether this is due to negative hyperconjugation from the lone pair electrons on the fluorine atoms or electrostatic effects remains a subject of debate.[29] Thus the transition state leading to the axial product is much more disfavoured than that leading to the equatorial product, which would involve only a very weak contribution from the unfavourable π–σ* interaction. However, in the formation of the regioisomeric cycloadducts **36b, c** one of the developing transannular 1,3-diaxial interactions is removed. It is then possible to observe, with a trifluoromethyl substituent, the product **36c** resulting from reaction through the electronically preferred transition state. We expect that a careful search of the by-products of the reaction leading to compound **37** would also reveal evidence for the analogous regioisomer. Such products have been detected in small quantities for nitrones bearing two alkoxy substituents (allylic and homoallylic).[30]

In summary, we have demonstrated that an allylic substituent at the alkene can exert strong stereocontrol over the cycloaddition of monosubstituted (*Z*)-*N*-alk-4-enyl nitrones. When the allylic substituent is electron withdrawing and can polarise the σ-bond to carbon (*e.g.* alkoxy, but not trifluoromethyl) a clear preference for the axial product can be observed. However, competition between steric and electronic contributions may result in low selectivities. Conversely, electron donating substituents afford a high degree of steric control because steric and electronic factors can act in concert.

Experimental

NMR spectra were recorded using Bruker AC200, WM250, AC250, AM360 and WM400 instruments (*J* values are given in Hz). Low and high resolution electron impact mass spectra were determined on AEI MS902 and MS30 instruments respectively. Chemical ionisation spectra were recorded by Dr. J. Ballantine and co-workers at the SERC Mass Spectrometry Service, Swansea. IR spectra were recorded on a Perkin-Elmer 1310 spectrophotometer, calibrated relative to polystyrene or a Perkin-Elmer 1600 FT instrument. Microanalyses were performed by Mr. D. Flory and staff at the Department of Chemistry, Cambridge. Melting points were determined on a Büchi 510 apparatus. Flash column chromatography was carried out on Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was carried out on Merck Kieselgel 60 GF254 plates, coated to a thickness of 0.25 mm. Gas chromatography (GC) was carried out using a Carlo Erba 4130 instrument [S.G.E. BP5 (5% phenylmethylsiloxane as stationary phase) 25 m column, diameter 0.33 mm, carrier gas flow rate 2.0 cm^3 min^{-1}]. THF refers to tetrahydrofuran distilled from potassium in a recycling still. Dimethyl sulfoxide (DMSO) was dried by distillation from calcium hydride and stored over 4 Å molecular sieves. Ether refers to diethyl ether. Triethylamine was dried by distillation from calcium hydride, and stored over calcium hydride or potassium hydroxide.

Ethyl (4E)-3-*Hydroxyhex*-4-*enoate* **4**.—A solution of butyl lithium in hexane (1.6 mol dm^{-3}; 62.5 cm^3, 100 mmol) was added dropwise at 10 °C to a stirred solution of dry diisopropylamine (14 cm^3, 100 mmol) in dry tetrahydrofuran (120 cm^3) under nitrogen. After being stirred for 30 min at 0 °C, the reaction mixture was cooled to −70 °C, and dry ethyl acetate (9.8 cm^3, 100 mmol) was added dropwise. The resulting solution was stirred for 1 h at −70 °C, becoming very pale yellow. Dry crotonaldehyde (8.3 cm^3, 100 mmol) was added dropwise to it, and the reaction mixture was stirred at −70 °C for 1 h. The reaction was quenched at −70 °C by addition of glacial acetic acid (8.6 cm^3, 150 mmol) and the resulting gel was diluted with saturated aqueous sodium hydrogen carbonate (100 cm^3) and warmed to room temperature. The resulting suspension was filtered through Celite, and the filtrate was washed with ether (100 cm^3). The aqueous and organic phases were separated, and the aqueous layer was saturated with sodium chloride, prior to extraction with ether (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$), and solvent was removed by evaporation to give a yellow liquid. Flash column chromatography on silica gel, eluting with 10% ethyl acetate–dichloromethane, gave the *title compound* **4** (14.5 g, 92%) as a mobile yellow liquid (Found: C, 60.4; H, 8.9. $C_8H_{14}O_3$ requires C, 60.7; H, 8.9%); R_f 0.33 (10% EtOAc–CH_2Cl_2); $\nu_{max}(CCl_4)$/cm^{-1} 3620w (free OH), 3550br (H-bonded OH), 1720s (C=O) and 970s (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 5.69

(1 H, dqd, *J* 15.3, 6.4 and 1.0, CH=C*H*Me), 5.46 (1 H, ddq, *J* 15.3, 6.5 and 1.5, C*H*=CHMe), 4.43 (1 H, dt, *J* 6.0 and 6.0, C*H*OH), 4.12 (2 H, q, *J* 7.1, CH_3CH_2O), 3.07–2.77 (1 H, br, exchanges in D_2O, OH), 2.47 (2 H, d, *J* 6.0, CH_2CHOH), 1.65 (3 H, dd, *J* 6.4 and 1.0, CH=CH*Me*) and 1.22 (3 H, t, *J* 7.1, CH_3CH_2O); δ_C(100 MHz; $CDCl_3$) 172.3 (s), 131.8 (d), 127.3 (d), 66.8 (d), 60.6 (t), 41.5 (t), 17.5 (q) and 14.1 (q); *m/z* (EI) 158 (M^+, 12%), 143 (15), 113 (14), 112 (14), 88 (13), 84 (12), 71 (100), 70 (52), 69 (40), 61 (13), 60 (30), 55 (12) and 53 (10) (Found: M^+, 158.0938. $C_8H_{14}O_3$ requires *M*, 158.0943).

Ethyl (4E)-3-(tert-*Butyldimethylsiloxy*)*hex*-4-*enoate* **5**.—A solution of imidazole (8.3 g, 122 mmol) in dry dichloromethane (70 cm^3) was added at room temperature to a stirred solution of freshly distilled *tert*-butyldimethylsilyl chloride (6.6 g, 44 mmol) in dry dichloromethane (30 cm^3). To the resulting white suspension was added a solution of the β-hydroxy ester **4** (5.7 g, 36 mmol) in dry dichloromethane (40 cm^3). The suspension was stirred at room temperature under nitrogen for 4 h, then quenched by addition of saturated aqueous sodium hydrogen carbonate (100 cm^3). The two phases were separated, and the aqueous layer was saturated with sodium chloride prior to extraction with dichloromethane (2 × 40 cm^3). The combined organic layers were dried ($MgSO_4$), and solvent was removed by evaporation to give a pale yellow liquid. Flash column chromatography on silica gel, eluting with dichloromethane, gave the *title compound* **5** (9.72 g, 99%) as a clear, colourless liquid (Found: C, 61.8; H, 10.2. $C_{14}H_{28}O_3Si$ requires C, 61.7; H, 10.4%); R_f 0.42 (9:1, hexane–Et_2O); $\nu_{max}(CCl_4)/cm^{-1}$ 3030w (sp^2 C–H), 1735s (C=O), 1670w (C=C) and 955s (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 5.61 (1 H, dqd, *J* 15.3, 6.6 and 0.6, CH=C*H*Me), 5.41 (1 H, ddq, *J* 15.2, 6.9 and 1.4, C*H*=CHMe), 4.52–4.46 (1 H, m, C*H*OSi), 4.09 (2 H, qd, *J* 7.2 and 2.2, CH_3CH_2O), 2.49 [1 H, dd, *J* 14.3 and 8.0, C(O)CH*H*′], 2.37 [1 H, dd, *J* 14.3 and 5.3, C(O)CH*H*′], 1.64 (3 H, ddd, *J* 6.6, 1.4 and 0.8, CH=CH*Me*), 1.23 (3 H, t, *J* 7.2, CH_3CH_2O), 0.83 (9 H, s, SiBu^t), 0.01 (3 H, s, SiMe) and 0.00 (3 H, s, SiMe); δ_C(100 MHz; $CDCl_3$) 171.3 (s), 133.4 (d), 126.0 (d), 70.7 (d), 60.2 (t), 44.1 (t), 25.7 (q), 18.0 (d), 17.5 (q), 14.2 (q), −4.3 (q) and −5.1 (q); *m/z* (EI) 257 [$(M - Me)^+$, 65%], 227 (60), 215 (98), 187 (25), 145 (50), 117 (20), 103 (45), 75 (100) and 73 (40) [Found: $(M - Me)^+$, 257.1573. $C_{13}H_{25}O_3Si$ requires *M*, 257.1573].

Ethyl (4E)-3-(tert-*Butyldiphenylsiloxy*)*hex*-4-*enoate* **6**.—A solution of the alcohol **4** (6.1 g, 39 mmol) in dry dimethylformamide (30 cm^3) was added at room temperature to a stirred solution of *tert*-butyldiphenylsilyl chloride (12.7 g, 46 mmol) and imidazole (6.3 g, 93 mmol) in dry dimethylformamide (100 cm^3) under nitrogen. The solution was stirred at 60 °C under nitrogen for 2.5 h, then poured into saturated aqueous brine (500 cm^3). The aqueous solution was extracted with dichloromethane (6 × 200 cm^3). The combined organic layers were dried ($MgSO_4$) and the solvent was removed by evaporation to give a yellow oil. Flash column chromatography on silica gel, eluting with 1:1 hexane–dichloromethane, gave the *title compound* **6** (14.4 g, 94%) as a viscous, straw-coloured oil (Found: C, 72.4; H, 8.0. $C_{24}H_{32}O_3Si$ requires C, 72.7; H, 8.1%); R_f 0.4 (1:1, hexane–CH_2Cl_2); $\nu_{max}(CCl_4)/cm^{-1}$ 3075s (sp^2 C–H), 1740s (C=O), 1670m (C=C) and 955s (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 7.70–7.60 (4 H, m, 4 of $SiPh_2$), 7.40–7.30 (6 H, m, 6 of $SiPh_2$), 5.40 (1 H, ddq, *J* 15.7, 7.5 and 1.1, C*H*=CHMe), 5.21 (1 H, dq, *J* 15.7 and 5.2, CH=C*H*Me), 4.55 (1 H, ddd, *J* 7.7, 7.2 and 6.0, CHOSi), 4.07 (1 H, qd, *J* 7.1 and 3.5, $CH_3CHH'O$), 4.05 (1 H, qd, *J* 7.1 and 3.5, $CH_3CHH'O$), 2.58 (1 H, dd, *J* 14.3 and 7.2, O=CCH*H*′), 2.42 (1 H, dd, *J* 14.3 and 6.0, O=CH*H*′), 1.45 (3 H, dd, *J* 5.2 and 1.1, CH=CH*Me*), 1.19 (3 H, t, *J* 7.1, CH_3CH_2O) and 1.03 (9 H, s, SiBu^t); δ_C(100 MHz; $CDCl_3$) 171.0 (s), 136.0 (d), 135.9 (d), 134.1 (s), 134.0 (s), 132.4 (d), 129.5 (d), 129.4 (d), 127.4 (d), 127.3 (d), 127.1 (d), 71.5 (q), 60.2 (t), 43.7 (t), 26.9 (q), 19.2 (s), 17.4 (q) and 14.1 (q); *m/z* (CI) 397 [$(M + H)^+$, 22%], 339 (34), 319 (22), 158 (33) and 141 (100) [Found: $(M + H)^+$, 397.2200. $C_{24}H_{33}O_3Si$ requires *M*, 397.2199].

Ethyl (4E)-3-*Methoxyhex*-4-*enoate* **7**.—Solid silver(I) oxide (10.0 g, 71 mmol) was added to a solution of β-hydroxy ester **4** (8.00 g, 35 mmol) and methyl iodide (20 cm^3, 320 mmol) in dry dimethylformamide (40 cm^3). The black suspension was stirred at room temperature for 48 h. The mixture was filtered through Celite, washing with ethyl acetate (200 cm^3). The filtrate was washed with water (200 cm^3) and the aqueous layer was extracted with ethyl acetate (100 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed by evaporation. Flash column chromatography on silica gel, eluting with 5% ethyl acetate–hexane, gave the *methyl ether* **7** (2.03 g, 34%) as a straw-coloured liquid. Also isolated was a mixture of the methyl ether **7** and ethyl hexa-2,4-dienoate (1.65 g, methyl ether **7**:ethyl hexa-2,4-dienoate, 4:1 by NMR analysis); R_f 0.7 (20% EtOAc–hexane); $\nu_{max}(CCl_4)/cm^{-1}$ 3000 (sp^2 C–H), 2825w (OCH_3), 1750s (C=O), 1675w (C=C) and 950m (*trans*-substituted C=C); δ_H(360 MHz; $CDCl_3$) 5.72 (1 H, dq, *J* 12.6 and 6.0, CH=C*H*CH$_3$), 5.32 (1 H, ddq, *J* 12.6, 8.1 and 1.6, C*H*=CHCH$_3$), 4.14 (2 H, q, *J* 7.2, OCH_2CH_3), 3.97 (1 H, ddd, *J* 8.1, 8.1 and 5.6, CH_AH_BCHOMe), 3.25 (3 H, s, OCH_3), 2.58 (1 H, dd, *J* 15.0 and 8.1, CH_AH_BCHOMe), 2.42 (1 H, dd, *J* 15.0 and 5.6, CH_AH_BCHOMe), 1.72 (3 H, dd, *J* 6.0 and 1.6, CH=CHC*H*$_3$) and 1.25 (3 H, t, *J* 7.2, OCH_2CH_3); δ_C(90 MHz; $CDCl_3$) 171.6 (s), 130.1 (d), 129.8 (d), 78.8 (d), 60.4 (t), 56.1 (q), 41.3 (t), 17.7 (q) and 14.2 (q); *m/z* (CI) 190 [$(M + NH_4)^+$, 75%], 173 [$(M + H)^+$, 52], 158 (30), 141 (100) and 85 (65) [Found: $(M + H)^+$, 173.1178. $C_9H_{17}O_3$ requires *M*, 173.1178].

Ethyl (4E)-3-(*Methoxymethoxy*)*hex*-4-*enoate* **8**.—Methoxymethyl chloride (6.8 cm^3, 89 mmol) was added dropwise at 0 °C to a stirred solution of the β-hydroxy ester **4** (11.66 g, 74 mmol) and dry diisopropylethylamine (15.5 cm^3, 89 mmol) in dry chloroform (60 cm^3) under nitrogen. The solution was stirred at 0 °C until the white fumes formed during the addition had subsided, and was then heated at reflux for 17.5 h. Analysis by TLC indicated the presence of starting material. Further methoxymethyl chloride (2.81 cm^3, 36 mmol) and diisopropylethylamine (6.5 cm^3, 36 mmol) were added, and the solution was refluxed for a further 4 h. The solution was cooled to room temperature and poured into ice-cold ether (400 cm^3). The quaternary amine salt was allowed to crystallize out over 4 days. The salt was filtered off and the filtrate was evaporated. Flash column chromatography on silica gel, eluting with 1:1 light petroleum (40–60 °C)–dichloromethane, gave the *title compound* **8** as a mobile, yellow liquid (13.12 g, 88%) (Found: C, 59.7; H, 9.1. $C_{10}H_{18}O_4$ requires C, 59.4; H, 9.0%); R_f 0.5 (1:1, hexane–Et_2O); $\nu_{max}(CCl_4)/cm^{-1}$ 1740s (C=O) and 1670 (C=C); δ_H(250 MHz; $CDCl_3$) 5.72 (1 H, dq, *J* 15.0 and 6.5, CH=C*H*Me), 5.30 (1 H, ddq, *J* 15, 8.3 and 1.6, C*H*=CHMe), 4.67 (1 H, d, *J* 6.8, OC*H*H′O), 4.47 (1 H, d, *J* 6.8, OCH*H*′O), 4.44–4.38 (1 H, m, C*H*OCH$_2$OMe), 4.12 (2 H, q, *J* 7.2, OCH_2CH_3), 3.31 (3 H, s, OMe), 2.59 (1 H, dd, *J* 15 and 8.4, EtO_2CCHH'), 2.44 (1 H, dd, *J* 15 and 5.4, EtO_2CCHH'), 1.68 (3 H, dd, *J* 6.5 and 1.6, CH=C*H*Me) and 1.23 (3 H, t, *J* 7.2, OCH_2CH_3); δ_C(100 MHz; $CDCl_3$) 170.9 (s), 130.3 (d), 129.4 (d), 93.3 (t), 73.2 (d), 60.4 (t), 55.3 (q), 41.3 (t), 17.6 (q) and 14.2 (q); *m/z* (EI) 171 [$(M - OMe)^+$, 35%], 170 (40), 157 (90), 141 (50), 127 (30), 115 (45), 99 (32), 85 (27), 72 (38), 69 (76) and 59 (100).

(4E)-3-(tert-*Butyldimethylsiloxy*)*hex*-4-*enal* **9**.—A solution of diisobutylaluminium hydride in toluene (1.5 mol dm^{-3}; 35 cm^3, 52 mmol) was added dropwise at −85 °C to a stirred solution of the protected ester **5** (8.13 g, 29.8 mmol) in dry tetrahydrofuran (150 cm^3) under nitrogen. The solution was stirred at −90 °C for 2.5 h, then quenched by dropwise addition of saturated aqueous ammonium chloride (15 cm^3) ($T \leqslant -75$ °C). The reaction mixture was allowed to warm to room temperature, and saturated aqueous Rochelle salt (potassium sodium tartrate) solution (50 cm^3) was added. The solution was poured into brine (100 cm^3) and then ethyl acetate (150 cm^3) was added. Agitation of the mixture led to formation of a gel. Further Rochelle salt solution (50 cm^3) and ethyl acetate (50 cm^3) were added to the gel, which was left overnight to break down. The resulting two liquid phases were separated, and the aqueous layer was saturated with sodium chloride prior to extraction with ethyl acetate (3 × 150 cm^3). The combined organic layers were dried ($MgSO_4$) and then the solvent was removed by evaporation to give a yellow liquid. Flash column chromatography on silica gel, eluting with 9:1 hexane–ether ⟶ 100% ether, gave the *title compound* **9** as a colourless liquid (6.11 g, 90%); R_f 0.33 (9:1, hexane–Et_2O); $\nu_{max}(CCl_4)/cm^{-1}$ 3035w (sp^2 C–H), 2710m (O=C–H), 1725s (C=O), 1670w (C=C) and 960s (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 9.74 (1 H, t, *J* 2.5, CHO), 5.65 (1 H, dqd, *J* 15.3, 6.2 and 0.7, CH=C*H*Me), 5.38 (1 H, ddq, *J* 15.3, 6.5 and 1.4, C*H*=CHMe), 4.57 (1 H, dt, *J* 6.0 and 6.0, CHOSi), 2.58 (1 H, ddd, *J* 16.0, 7.0 and 2.9, C*H*H'C=O), 2.46 (1 H, ddd, *J* 16.0, 5.0 and 2.2, CH*H'*C=O), 1.66 (3 H, dd, *J* 6.2 and 0.7, CH=CH*Me*), 0.84 (9 H, s, SiBu^t), 0.03 (3 H, s, SiMe) and 0.01 (3 H, s, SiMe); δ_C(100 MHz; $CDCl_3$) 202.1 (d), 133.1 (d), 126.3 (d), 69.4 (d), 51.6 (t), 25.7 (q), 18.0 (s), 17.5 (q), −4.2 (q) and −5.0 (q); *m*/*z* (EI) 213 [(M − Me)$^+$, 60%)] 185 (75), 171 (86), 130 (45), 127 (30) and 101 (100) [Found: (M − Me)$^+$, 213.1318. $C_{11}H_{21}O_2Si$ requires *M*, 213.1311].

(4E)-3-(tert-*Butyldiphenylsiloxy*)*hex*-4-*enal* **10**.—A similar procedure to that described for compound **9** was followed. *Aldehyde* **10** was obtained as a white solid (4.07 g, 76%), m.p. 55–57 °C (Found: C, 74.65; H, 7.9. $C_{22}H_{28}O_2Si$ requires C, 74.95; H, 8.0%); R_f 0.2 (1:1, hexane–CH_2Cl_2); $\nu_{max}(CCl_4)/cm^{-1}$ 3040s (sp^2 C–H), 3030s (sp^2 C–H), 2720w (O=C–H), 1725s (C=O), 1670w (C=C) and 965m (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 9.71 (1 H, t, *J* 2.6, O=CH), 7.70–7.60 (4 H, m, 4 of $SiPh_2$), 7.40–7.30 (6 H, m, 6 of $SiPh_2$), 5.50–5.30 (2 H, m, CH=C*H*Me), 4.65–4.55 (1 H, m, CHOSi), 2.55–2.45 (2 H, m, O=CCH_2), 1.53 (3 H, dd, *J* 5.9 and 0.7, CH=CH*Me*) and 1.05 (9 H, s, SiBu^t); δ_C(100 MHz; $CDCl_3$) 201.9 (d), 135.9 (d), 135.8 (d), 133.7 (s), 132.2 (d), 129.8 (d), 129.6 (d), 127.6 (d), 127.4 (d), 127.2 (d), 70.3 (d), 51.3 (t), 26.9 (q), 19.2 (s) and 17.4 (q); *m*/*z* (CI) 370 [(M + NH_4)$^+$, 9%], 295 (9) and 97 (100) [Found: (M + NH_4)$^+$, 370.2202. $C_{22}H_{32}NO_2Si$ requires *M*, 370.2202].

(4E)-3-(tert-*Butyldimethylsiloxy*)*hex*-4-*enal Oxime* **13**.—A solution of anhydrous sodium acetate (5.82 g, 71 mmol) and hydroxylamine hydrochloride (4.93 g, 71 mmol) in water (80 cm^3) was added to a solution of the aldehyde **9** (5.42 g, 23.7 mmol) in ethanol (80 cm^3). The resulting emulsion was stirred at room temperature under nitrogen for 4 h. Ethanol was removed by evaporation, and the aqueous residue was saturated with sodium chloride prior to extraction with dichloromethane (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$) and then solvent was removed by evaporation to give a clear colourless liquid. Filtration through a short silica column, eluting with 5 ⟶ 10% ethyl acetate–dichloromethane gave the *title compound* **13** (5.42 g, 95%) as a clear colourless liquid (Found: C, 59.5; H, 10.2; N, 5.7. $C_{12}H_{25}NO_2Si$ requires C, 59.2; H, 10.4; N, 5.8%); R_f 0.3 (CH_2Cl_2); $\nu_{max}(CCl_4)/cm^{-1}$ 3600s (free OH), 3250br (H-bonded OH), 3100s (H-bonded OH) and 1665m (C=C); δ_H(250 MHz; $CDCl_3$) 2 geometrical isomers in 1:1 ratio; 9.50–8.50 (1 H, br s, OH), 7.41 (0.5 H, t, *J* 6.4, *H*C=NOH), 6.81 (0.5 H, t, *J* 5.0, *H*C=NOH), 5.68–5.50 (1 H, m, CH=C*H*Me), 5.46–5.36 (1 H, m, C*H*=CHMe), 4.33–4.18 (1 H, 2 × dt, *J* 6.1 and 6.1, CHOSi), 2.55 and 2.35 (2 H, 2 × t, *J* 6.0, CH_2C=N), 1.66 (3 H, d, *J* 6.2, CH=CH*Me*), 0.86 (9 H, s, SiBu^t) and 0.04–0.00 (6 H, 4 × s, $SiMe_2$); δ_C(100 MHz; $CDCl_3$) 2 geometrical isomers in 1:1 ratio; 149.8 (d), 149.6 (d), 133.5 (d), 133.4 (d), 126.2 (d), 126.0 (d), 71.7 (d), 70.4 (d), 38.2 (t), 33.7 (t), 25.8 (q), 18.1 (s), 17.5 (q), −4.4 (q) and −4.9 (q); *m*/*z* (CI) 244 [(M + H)$^+$, 18%], 185 (100), 168 (15), 145 (45), 127 (32), 112 (95), 92 (15) and 75 (60) [Found: (M + H)$^+$, 244.1733. $C_{12}H_{26}NO_2Si$ requires *M*, 244.1733].

(4E)-3-(tert-*Butyldiphenylsiloxy*)*hex*-4-*enal Oxime* **14**.—A similar procedure to that described for compound **13** was followed. *Oxime* **14** was obtained as a colourless glass (8.16 g, 100%) (Found: C, 71.85; H, 8.1; N, 4.1. $C_{22}H_{29}NO_2Si$ requires C, 71.9; H, 7.95; N, 3.8%); R_f 0.7 (30% Et_2O–CH_2Cl_2); $\nu_{max}(CCl_4)/cm^{-1}$ 3605s (free OH), 3300br (H-bonded OH), 3070s (sp^2 C–H), 3060s (sp^2 C–H), 1670w (C=C) and 965s (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 2 geometrical isomers in 1:1 ratio; 7.7–7.6 (4 H, m, 4 of $SiPh_2$) 7.4–7.3 (6.5 H, m, 6 of $SiPh_2$ and N=CH), 6.80 (0.5 H, t, *J* 4.0, N=CH), 5.48–5.20 (2 H, m, C*H*=C*H*Me), 4.35–4.25 (1 H, m, CHOSi), 2.71–2.52 (2 H, m, N=CCH_2), 1.55–1.52 (3 H, m, CH=CH*Me*) and 1.06–1.05 (9 H, 2 × s, SiBu^t); δ_C(100 MHz; $CDCl_3$) 2 geometrical isomers in 1:1 ratio; 149.6 (d), 149.4 (d), 136.0 (d), 135.9 (d), 135.9 (d), 133.9 (s), 132.6 (d), 132.4 (d), 129.7 (d), 129.5 (d), 127.6 (d), 127.4 (d), 127.2 (d), 126.9 (d), 72.3 (d), 71.3 (d), 37.9 (q), 33.3 (t), 27.0 (t), 19.3 (s) and 17.5 (q); *m*/*z* (FAB; NOBA matrix) 368 [(M + H)$^+$, 40%], 310 (79), 199 (79) and 135 (100).

(4E)-3-*Methoxyhex*-4-*enal Oxime* **15**.—A solution of diisobutylaluminium hydride in toluene (1.5 mol dm^{-3}; 5 cm^3, 7.5 mmol) was added dropwise at −78 °C to a stirred solution of the ethyl ester **7** (1.00 g, 5.81 mmol) in dry toluene (30 cm^3) under nitrogen. The solution was stirred at −78 °C for 45 min and then quenched by the addition of methanol (2 cm^3). After 5 min, the mixture was diluted with aqueous tartaric acid (1 mol dm^{-3}; 50 cm^3) and warmed to room temperature. The mixture was further diluted with ethyl acetate (20 cm^3) and stirred at room temperature for 20 min. The two phases were separated and the aqueous phase was extracted with ethyl acetate (30 cm^3). The combined organic layers were added immediately to an aqueous solution (20 cm^3) of hydroxylamine hydrochloride (1.40 g, 20 mmol) and sodium acetate (1.60 g, 20 mmol). Ethanol (30 cm^3) was added and the emulsion was stirred at room temperature for 30 min, then at 0 °C for 18 h. The mixture was diluted with brine (50 cm^3) and the two phases were separated. The aqueous phase was extracted with ethyl acetate (50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and the solvent was removed by evaporation. Flash column chromatography on silica gel, eluting with 20% ethyl acetate–hexane, gave the *oxime* **15** (0.717 g, 86%) as a straw-coloured liquid; R_f 0.3 (20% EtOAc–hexane); $\nu_{max}(CCl_4)/cm^{-1}$ 3600m (free OH), 3250br (H-bonded OH), 2825w (OCH_3), 1680w (C=C) and 970s (*trans*-substituted C=C); δ_H(360 MHz; $CDCl_3$) 1:1 mixture of *cis* and *trans* oximes 7.44 (0.5 H, t, *J* 9.1, HON=C*H*CH_2), 6.82 (0.5 H, t, *J* 7.6, HON=C*H*CH_2), 5.76–5.65 (1 H, m, CH=C*H*CH_3), 5.38–5.27 (1 H, m, C*H*=CHCH_3), 3.78–3.62 (1 H, m, CH_2C*H*OMe), 3.27 (1.5 H, s, OCH_3), 3.25 (1.5 H, s, OCH_3), 2.66–2.50 (1 H, m, CH_AH_BCHOMe), 2.48–2.36 (1 H, m, CH_AH_BCHOMe) and 1.73 (3 H, br m, *J* 9.3, C=CHCH_3); *m*/*z* (CI) 287 [(M_2 + H)$^+$; 10%], 161 [(M + NH_4)$^+$, 55], 144

[$(M + H)^+$, 100], 128 (55) and 85 (78) [Found: $(M + H)^+$, 144.1025. $C_7H_{14}NO_2$ requires *M*, 144.1025].

(4E)-3-(*Methoxymethoxy*)*hex*-4-*enal Oxime* **16**.—A solution of lithium aluminium hydride in ether (1.0 mol dm^{-3}; 15 cm^3, 15 mmol) was added dropwise at 0 °C to a stirred solution of the ester **8** (6.96 g, 34.4 mmol) in dry ether (100 cm^3) under nitrogen. After 1 h, analysis by TLC indicated the presence of starting material. Further lithium aluminium hydride solution (5 cm^3, 5 mmol) was added, and the reaction mixture was stirred for 1 h. The reaction was quenched by the cautious addition of aqueous sodium hydroxide (20%; 10 cm^3), followed by water (50 cm^3). The resulting gel was stirred for 1 h, warmed to room temperature, and then filtered through Celite. The two phases were separated, and the aqueous layer was saturated with sodium chloride prior to extraction with ether (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent was removed by evaporation. Filtration through silica, eluting with ether, gave (4E)-3-(*methoxymethoxy*)*hex*-4-*en*-1-*ol* (5.25 g, 95%) as a pale yellow liquid; R_f 0.45 (Et_2O); $\nu_{max}(CCl_4)/cm^{-1}$ 3650m (free OH), 3560br (H-bonded OH) and 1675m (C=C); δ_H(250 MHz; $CDCl_3$) 5.67 (1 H, dq, *J* 15.3 and 6.5, CH=C*H*Me), 5.31 (1 H, ddq, *J* 15.3, 8.2 and 1.6, C*H*=CHMe), 4.70 (1 H, d, *J* 6.6, OC*H*'HOMe), 4.48 (1 H, d, *J* 6.6, OCH'*H*OMe), 4.17 (1 H, dt, *J* 6 and 8, C*H*OCH$_2$OMe), 3.80–3.68 (2 H, m, CH_2OH), 3.36 (3 H, s, OMe), 2.35 (1 H, br s, OH), 1.83–1.72 (2 H, m, CH_2CH$_2$OH) and 1.69 (3 H, dd, *J* 6.5 and 1.6, CH=CH*Me*); δ_C(100 MHz; $CDCl_3$) 130.5 (d), 129.5 (d), 93.4 (t), 75.8 (d), 60.2 (t), 55.5 (q), 38.0 (t) and 17.6 (q); *m*/*z* (EI) 145 [$(M - Me)^+$, 22%)] 143 [$(M - OH)^+$, 5], 129 (30), 128 (90), 115 (100), 99 (20), 98 (15), 65 (15), 81 (20), 73 (15), 72 (17), 69 (42) and 55 (25).

A solution of dry dimethyl sulfoxide (8.8 cm^3, 124 mmol) in dry dichloromethane (10 cm^3) was added dropwise at −70 °C to a stirred solution of oxalyl chloride (5.4 cm^3, 62 mmol) in dry dichloromethane (150 cm^3) under nitrogen. A solution of (4*E*)-3-(methoxymethoxy)hex-4-en-1-ol (6.60 g, 41 mmol) in dry dichloromethane was added dropwise at −70 °C. The resulting white suspension was stirred at −70 °C for 30 min, followed by dropwise addition of dry triethylamine (34.3 cm^3, 246 mmol) at −70 °C over 45 min. The reaction was warmed to −40 °C for 20 min. Solid, powdered citric acid (12 g, 61 mmol) was added, and the mixture was warmed to room temperature. Water (100 cm^3) was added and the two phases were separated. The aqueous layer was extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and then the solvent was removed by evaporation to give a brown slurry. The residues were filtered through a pad of silica gel, eluting with ether. The filtrate was concentrated to give the crude aldehyde **12** as a brown oil. The crude aldehyde **12** was redissolved in ethanol (20 cm^3) and a solution of hydroxylamine hydrochloride (8.6 g, 124 mmol) and sodium acetate (10.2 g, 124 mmol) in water (50 cm^3) was added. The resulting emulsion was stirred at room temperature for 4 h. Most of the ethanol was removed by evaporation, and the aqueous residue was extracted with dichloromethane (4 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent was removed by evaporation. Flash column chromatography on silica gel, eluting with 5% ⟶ 10% ⟶ 20% ethyl acetate–dichloromethane, yielded *oxime* **16** (2.77 g, 52%) (Found: C, 55.6; H, 8.8; N, 7.8. $C_8H_{15}NO_3$ requires C, 55.5; H, 8.7; N, 8.1%); R_f 0.44 (10% EtOAc–CH_2Cl_2); $\nu_{max}(CCl_4)/cm^{-1}$ 3620s (free OH), 3340br (H-bonded OH) and 1675w (C=C); δ_H(250 MHz; $CDCl_3$) 2 geometrical isomers in a 1:1 ratio; 7.43 and 6.81 (1 H, 2 × t, *J* 6.3 and 5.2, *H*C=NOH), 5.75–5.64 (1 H, m, CH=C*H*Me), 5.36–5.24 (1 H, m, C*H*=CHMe), 4.71–4.46 (2 H, 8 signals, OCH_2OMe), 4.19–4.08 (1 H, m, C*H*OCH$_2$OMe), 3.34 and 3.32 (3 H, 2 × s, OMe), 2.66–2.58 and 2.47–2.39 (2 H, 2 × m, CH_2CH=NOH) and 1.70–1.67 (3 H, 4 signals, CH=CH*Me*); δ_C(100 MHz; $CDCl_3$) 2 geometrical isomers in a 1:1 ratio, 149.2 (d), 149.1 (d), 130.4 (d), 130.3 (d), 129.8 (d), 129.7 (d), 93.2 (t), 93.1 (t), 74.3 (d), 73.6 (d), 55.4 (q), 35.7 (t), 31.2 (t) and 17.7 (q); *m*/*z* (EI) 156 [$(M - OH)^+$, 25%], 142 (28), 129 (35), 128 (62), 115 (100), 112 (40), 94 (30), 85 (20), 69 (42), 68 (21) and 67 (42).

(Z)-N-[3-(tert-*butyldimethylsiloxy*)*hex*-4-*enyl*]-4-*acetoxybutylideneamine* N-*oxide* **18**.—Sodium cyanoborohydride (1.7 g, 27 mmol) was added at −5 °C to a stirred solution of the oxime **13** (2.53 g, 10.4 mmol) and a few drops of Methyl Orange indicator in dry methanol (50 cm^3) under nitrogen. A solution of hydrochloric acid in methanol (6 mol dm^{-3}) was added dropwise to keep the solution just pink (pH 3). The endpoint of the reaction was reached after 10 min. The solution was made alkaline with aqueous sodium hydroxide (20%) and then poured into ice–brine (200 cm^3). The aqueous suspension was extracted at 0 °C with dichloromethane (200 cm^3). The organic extract was washed with saturated brine (20 cm^3) and dried ($MgSO_4$), before immediate addition to a solution of 4-acetoxybutanal[15] (1.8 g, 13.8 mmol) in dichloromethane (10 cm^3) with a little solid magnesium sulfate. The resulting suspension was stirred at 0 °C under nitrogen for 2 h. The mixture was filtered, and solvent was removed by evaporation to give the crude nitrone as an almost colourless, somewhat viscous liquid. Flash column chromatography on silica gel, eluting with ethyl acetate, gave the *nitrone* **18** (2.23 g, 60%) as a viscous, colourless oil (Found: C, 60.5; H, 9.6; N, 3.7. $C_{18}H_{35}NO_4Si$ requires C, 60.5; H, 9.9; N, 3.9%); R_f 0.1 (Et_2O); $\nu_{max}(CCl_4)/cm^{-1}$ 3070w (sp^2 C–H), 3020m (C=C–H), 1730s (C=O) and 1665m (C=C); δ_H(250 MHz; $CDCl_3$) 6.64 (1 H, t, *J* 5.8, CH=N^+), 5.53 (1 H, dq, *J* 15.3 and 6.6, CH=C*H*Me), 5.32 (1 H, dd, *J* 15.3 and 6.6, C*H*=CHMe), 4.15–3.95 (3 H, m, CH_2OAc and CHOSi), 3.74 (2 H, t, *J* 7.2, CH_2N^+), 2.47 (2 H, dt, *J* 7.0 and 7.0, CH_2CH=CN^+), 2.15–1.72 [7 H, methylene envelope; including 1.96 (3 H, s, O=CMe)], 1.58 (3 H, d, *J* 6.2, CH=CH*Me*), 0.80 (9 H, s, SiBu^t), −0.05 (3 H, s, SiMe) and −0.07 (3 H, s, SiMe); δ_C(100 MHz; $CDCl_3$) 170.9 (s), 137.5 (d), 133.4 (d), 126.2 (d), 70.9 (d), 63.6 (t), 61.7 (t), 35.8 (t), 25.8 (q), 24.7 (t), 23.5 (t), 20.8 (q), 18.1 (s), 17.5 (q), −4.1 (q) and −4.9 (q).

(Z)-N-[3-(tert-*Butyldiphenylsiloxy*)*hex*-4-*enyl*]-4-*acetoxybutylideneamine* N-*oxide* **19**.—A similar procedure to that described for compound **18** was followed. *Nitrone* **19** was obtained as a colourless oil (3.99 g, 70%); R_f 0.11 (10% Et_2O–CH_2Cl_2); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (sp^2 C–H), 1740s (C=O) and 960w (*trans*-substituted C=C); δ_H(250 MHz; $CDCl_3$) 7.70–7.50 (4 H, m, 4 of $SiPh_2$), 7.40–7.20 (6 H, m, 6 of $SiPh_2$), 6.47 (1 H, t, *J* 4.9, N^+=CH), 5.40–5.20 (2 H, m, C*H*=C*H*Me), 4.17 (1 H, dt, *J* 7.0 and 7.0, CHOSi), 4.08 (2 H, t, *J* 6.1, CH_2OAc), 3.76 (2 H, t, *J* 7.6, N^+CH_2), 2.50–2.40 (2 H, m, N^+=CHCH_2), 2.06 (3 H, s, O=CMe), 2.09 (2 H, dt, *J* 5.7 and 5.7, $N^+CH_2CH_2$), 1.77 (2 H, tt, *J* 6.1 and 6.1, CH_2CH$_2$OAc), 1.49 (3 H, d, *J* 5.7, CH=CH*Me*) and 1.05 (9 H, s, SiBu^t); δ_C(100 MHz; $CDCl_3$) 171.0 (s), 137.5 (d), 135.9 (d), 135.8 (d), 135.6 (d), 134.1 (s), 133.8 (s), 132.6 (d), 129.7 (d), 128.6 (d), 127.7 (d), 127.6 (d), 127.1 (d), 71.9 (d), 63.7 (t), 61.5 (t), 35.6 (d), 27.0 (q), 24.5 (t), 23.4 (t), 20.9 (q), 19.3 (q) and 17.4 (s); *m*/*z* (CI) 482 [$(M + H)^+$, 100%] 466 (24) and 424 (30) [Found: $(M + H)^+$, 482.2645. $C_{28}H_{40}NO_4Si$ requires *M*, 482.2726].

(Z)-N-(3-*Methoxyhex*-4-*enyl*)-4-*acetoxybutylideneamine* N-*Oxide* **20**.—A similar procedure to that described for compound **18** was followed. *Nitrone* **20** was obtained as a straw-coloured oil (0.443 g, 49%); R_f 0.3 (10% EtOH–EtOAc); δ_H(360 MHz; $CDCl_3$) 6.73 (1 H, t, *J* 6, $^+$N=C*H*CH$_2$), 5.67 (1 H, dq, *J* 15.4 and 6.6, CH=C*H*CH$_3$), 5.29 (1 H, ddq, *J* 15.4, 6.3 and 1.6,

C*H*=CHCH$_3$), 4.13 (2 H, t, *J* 7.5, CH$_2$C*H*$_2$OAc), 4.09–3.79 (2 H, m, $^+$NC*H*$_2$CH$_2$), 3.57–3.51 (1 H, m, CH$_2$C*H*OMe), 3.22 (3 H, s, OCH$_3$), 2.56 (2 H, td, *J* 7.5 and 6, $^+$N=CHC*H*$_2$CH$_2$), 2.21–2.16 (1 H, m, $^+$NCH$_2$CH$_A$*H*$_B$CHOMe), 2.05 (3 H, s, OCOCH$_3$), 2.03–1.95 (1 H, m, $^+$NCH$_2$C*H*$_A$H$_B$CHOMe), 1.88 (2 H, tt, *J* 7.5 and 6.6, CH$_2$C*H*$_2$CH$_2$OAc) and 1.72 (3 H, dd, *J* 6.6 and 1.6, CH=CHC*H*$_3$); δ_C(90 MHz; CDCl$_3$) 171.0 (s), 138.0 (d), 130.4 (d), 129.8 (d), 79.1 (d), 63.7 (t), 61.8 (t), 55.9 (q), 33.2 (t), 24.7 (t), 23.5 (t), 20.9 (q) and 17.7 (q); *m*/*z* (CI) 258 [(M + H)$^+$, 100%], 242 (10) and 163 (20) [Found: (M + H)$^+$, 258.1705. C$_{13}$H$_{24}$NO$_4$ requires *M*, 258.1705].

(Z)-[3-(*Methoxymethoxy*)*hex*-4-*enyl*]-4-*acetoxybutylidene-amine* N-*Oxide* **21**.—A similar procedure to that described for compound **18** was followed. *Nitrone* **21** was obtained as a clear colourless oil (1.71 g, 68%) (Found: C, 58.5; H, 8.6; N, 4.6. C$_{14}$H$_{25}$NO$_5$ requires C, 58.5; H, 8.8; N, 4.9%); R_f 0.32 (5% MeOH–EtOAc); ν_{max}(CCl$_4$)/cm^{-1} 1745s (C=O) and 1675w (C=C); δ_H(250 MHz; CDCl$_3$) 6.72 (1 H, t, *J* 5.8, CH=N$^+$), 5.66 (1 H, dq, *J* 15.3 and 6.5, CH=C*H*Me), 5.27 (1 H, ddq, *J* 15.3, 8 and 1.4, C*H*=CHMe), 4.65 (1 H, d, *J* 6.6, OC*H*H′OMe), 4.46 (1 H, d, *J* 6.6, OCH*H*′OMe), 4.07 (2 H, t, *J* 6.4, C*H*$_2$OAc), 4.02–3.96 (1 H, m, C*H*OCH$_2$OMe), 3.84 (2 H, t, *J* 7.3, CH$_2$N$^+$), 3.32 (3 H, s, OMe), 2.57–2.49 (2 H, m, CH$_2$), 2.20–2.06 (2 H, m, CH$_2$), 2.02 (3 H, s, OCMe), 1.90–1.79 (2 H, m, CH$_2$), and 1.68 (3 H, dd, *J* 6.5 and 1.4, CH=CH*Me*); δ_C(100 MHz; CDCl$_3$) 171.0 (s), 137.8 (d), 130.1 (d), 129.9 (d), 93.5 (t), 74.2 (d), 63.6 (t), 61.6 (t), 55.5 (q), 33.3 (t), 24.6 (t), 23.4 (t), 20.9 (q) and 17.6 (q); *m*/*z* (EI) 287 (M$^+$, 30%), 242 (41), 226 (80), 166 (38), 165 (42), 157 (47), 152 (62), 146 (50), 126 (71), 97 (75) and 81 (100) (Found: M$^+$, 287.1743. C$_{14}$H$_{25}$NO$_5$ requires *M*, 287.1733).

(4′S*,5′R*,6′S*,8′R*)- **22a** *and* (4′S*,5′S*,6′R*,8′S*)-3-{4′-(tert-*Butyldimethylsiloxy*)-6′-*methyl*-7′-*oxa*-1′-*azabicyclo*-[3.2.1]*octan*-8′-*yl*)*propyl Acetate* **22b**.—A solution of the nitrone **18** (1.57 g, 4.39 mmol) in dry toluene (250 cm^3) was heated at reflux under nitrogen for 18 h in a Dean–Stark apparatus for the azeotropic removal of water. The solution was cooled and toluene was removed by evaporation. Flash column chromatography on silica gel, eluting with 1:1 hexane–ether gave the *axially substituted cycloadduct* **22a** (0.905 g, 58%) as the less polar product, and the *equatorially substituted cycloadduct* **22b** (0.431 g, 28%) as the more polar product.

Data for **22a**: (Found: C, 60.2; H, 9.7; N, 3.65. C$_{18}$H$_{35}$NO$_4$Si requires C, 60.5; H, 9.9; N, 3.9%); R_f 0.5 (Et$_2$O); ν_{max}(CCl$_4$)/cm^{-1} 1735s (C=O); δ_H(250 MHz; CDCl$_3$) 4.10–4.03 (3 H, m, C*H*$_2$OAc and NOC*H*Me), 3.99 (1 H, dd, *J* 4.8 and 3.5, CHOSi), 3.54 (1 H, dd, *J* 8.0 and 5.5, NC*H*CH), 3.21 (1 H, dd, *J* 14.0 and 7.0, NC*H*$_\alpha$H$_\beta$CH$_2$), 2.96 (1 H, ddd, *J* 14.0, 12.0 and 5.8, NCH$_\alpha$*H*$_\beta$CH$_2$), 2.16 (1 H, d, *J* 4.8, NCHC*H*), 2.01 (3 H, s, O=CMe), 1.99–1.61 (4 H, m, 2 × CH$_2$), 1.39–1.29 (2 H, m, CH$_2$), 1.24 (3 H, d, *J* 6.6, NOCH*Me*), 0.86 (9 H, s, SiBu^t) and 0.03 (6 H, s, SiMe$_2$); δ_C(100 MHz; CDCl$_3$) 171.1 (s), 78.7 (d), 69.0 (d), 64.2 (t), 64.0 (q), 55.0 (d), 54.0 (t), 29.0 (t), 27.3 (t), 26.6 (t), 25.7 (q), 21.6 (q), 21.0 (d), 17.9 (s) and −4.86 (q); *m*/*z* (EI) 357 (M$^+$, 35%), 340 (30), 314 (80), 300 (55), 298 (30), 256 (25), 171 (38), 122 (20), 117 (35), 98 (65), 95 (25), 82 (40), 81 (70), 75 (100), 73 (75), 71 (28) and 55 (29) (Found: M$^+$, 357.2338. C$_{18}$H$_{35}$NO$_4$Si requires *M*, 357.2335).

Data for **22b**: R_f 0.4 (Et$_2$O); ν_{max}(CCl$_4$)/cm^{-1} 1735s (C=O); δ_H(250 MHz; CDCl$_3$) 4.38 (1 H, q, *J* 6.6, NOC*H*Me), 4.12–4.00 (2 H, m, C*H*$_2$OAc), 3.80 (1 H, ddd, *J* 9.6, 6.9 and 3.0, CHOSi), 3.27 (1 H, dd, *J* 14.2 and 6.4, NC*H*$_\alpha$H$_\beta$CH$_2$), 2.65 (1 H, ddd, *J* 14.2, 11.7 and 6.5, NCH$_\alpha$*H*$_\beta$CH$_2$), 2.59–2.54 (1 H, m, NC*H*CH), 2.12 (1 H, d, *J* 3.0, NCHC*H*), 2.02 (3 H, s, O=CMe), 2.01–1.25 (6 H, methylene envelope), 1.22 (3 H, d, *J* 6.6, NOCH*Me*), 0.85 (9 H, s, SiBu^t), 0.03 (3 H, s, SiMe) and 0.02 (3 H, s, SiMe); δ_C(100 MHz; CDCl$_3$) 171.1 (s), 76.3 (d), 70.2 (d), 69.7 (q), 64.2 (q), 55.9 (t), 55.4 (d), 29.6 (t), 29.1 (t), 26.7 (t), 26.1 (t), 25.7 (q), 21.6 (q), 21.0 (d), 17.9 (s), −4.4 (q) and −4.6 (q); *m*/*z* (EI) 357 (M$^+$, 60%), 342 (28), 340 (56), 314 (75), 312 (30), 300 (58), 117 (20), 98 (33), 82 (28), 81 (38), 75 (100) and 73 (47) (Found: M$^+$, 357.2353. C$_{18}$H$_{35}$NO$_4$Si requires *M*, 357.2335).

(4′S*,5′R*,6′S*,8′R*)- **23a** *and* (4′S*,5′S*,6′R*,8′S*)-3-{4′-(tert-*Butyldiphenylsiloxy*)-6′-*methyl*-7′-*oxa*-1′-*azabicylo*-[3.2.1]*octan*-8′-*yl*}*propyl Acetate* **23b**.—A similar procedure to that described for compounds **22a** and **22b** was followed. Isoxazolidines **23a** and **23b** were obtained as an inseparable mixture of oils (0.785 g, 80%). The ratio of **23a** to **23b** was determined as 1.2:1 from ^{1}H NMR data. Data for mixture of **23a** and **23b**: R_f 0.11 (10% Et$_2$O–CH$_2$Cl$_2$); ν_{max}(CCl$_4$)/cm^{-1} 1740s (C=O); δ_H(250 MHz; CDCl$_3$) 7.67–7.60 (8 H, m, 8 of 4 × Ph), 7.34–4.47 (12 H, m, 12 of 4 × Ph), 4.57 (1 H, q, *J* 6.5, NOC*H*Me **23b**), 4.13–3.89 (7 H, m, 2 × C*H*$_2$OAc, NOC*H*Me **23a** and CHOSi **23a**), 3.83 (1 H, ddd, *J* 9.4, 6.4 and 2.7, CHOSi **23b**), 3.72 (1 H, dd, *J* 8.0 and 5.5, NC*H*CH **23a**), 3.23 (2 H, apparent dd, $J_{apparent}$ 14.1 and 7.0, 2 × NC*H*$_\alpha$H$_\beta$), 3.08 (1 H, ddd, *J* 14.0, 12.1 and 5.8, NCH$_\alpha$*H*$_\beta$ **23a**), 2.54 (1 H, dd, *J* 8.0 and 5.5, NCH$_\alpha$*H*$_\beta$ **23b**), 2.36 (1 H, dd, *J* 8.0 and 5.5, NC*H*CH **23b**), 2.07–2.05 (2 H, m, 2 × NCHC*H*), 2.05 and 2.00 (6 H, 2 × s, 2 × O=CMe), 1.98–1.28 (12 H, m, methylene envelope), 1.25 and 1.09 (6 H, 2 × d, *J* 6.7 and 6.5, 2 × NOCH*Me*), 1.08 and 1.05 (18 H, 2 × s, 2 × SiBu^t); δ_C(100 MHz; CDCl$_3$) 171.1 (s), 135.7 (d), 135.6 (d), 134.1 (d), 133.9 (s), 133.8 (s), 133.6 (s), 129.91 (d), 129.86 (d), 129.8 (d), 127.74 (d), 127.67 (d), 78.6 (d), 76.4 (d), 71.0 (d), 70.0 (d), 69.4 (d), 64.3 (d), 64.3 (t), 64.1 (t), 55.9 (t), 54.5 (d), 54.4 (d), 54.1 (t), 29.3 (t), 29.0 (t), 28.7 (t), 26.95 (q), 26.88 (q), 26.7 (t), 26.3 (t), 21.6 (q), 21.5 (q), 21.02 (d), 20.97 (d), 19.14 (s) and 19.08 (s); *m*/*z* (CI) 482 [(M + H)$^+$, 100%], 424 (20), 226 (5), 196 (4), 182 (2), 166 (3), 140 (1), 122 (3) and 98 (6) [Found: (M + H)$^+$, 482.2750. C$_{28}$H$_{40}$NO$_4$Si requires *M*, 482.2726].

(4′S*,5′R*,6′S*,8′R*)- **24a** *and* (4′S*,5′S*,6′R*,8′S*)-3-(4′-*Methoxy*-6′-*methyl*-7′-*oxa*-1′-*azabicyclo*[3.2.1]*octan*-8′-*yl*)-*propyl Acetate* **24b**.—A similar procedure to that described for compounds **22a** and **22b** was followed. Repeated flash column chromatography on silica gel, eluting with ethyl acetate, gave the *axially substituted cycloadduct* **24a** (0.171 g, 41%) as a straw-coloured oil, and the *equatorially substituted cycloadduct* **24b** (0.094 g, 22%) as a colourless liquid.

Data for **24a**: (Found: C, 60.9; H, 9.0; N, 5.5. C$_{13}$H$_{23}$NO$_4$ requires C, 60.7; H, 9.0; N, 5.4%); R_f 0.6 (EtOAc); ν_{max}(CCl$_4$)/cm^{-1} 2825w (OCH$_3$) and 1740s (C=O); δ_H(360 MHz; CDCl$_3$) 4.17–4.03 (3 H, m, C*H*$_2$OAc and C*H*CH$_3$), 3.53 (1 H, dd, *J* 4.5 and 4.5, C*H*OCH$_3$), 3.42–3.37 (1 H, m, NC*H*CH), 3.33 (3 H, s, OCH$_3$), 3.23 (1 H, dd, *J* 14.2 and 7.2, NC*H*$_\alpha$H$_\beta$CH$_2$), 2.95 (1 H, ddd, *J* 14.2, 12.1 and 6.0, NCH$_\alpha$*H*$_\beta$CH$_2$), 2.44 (1 H, d, *J* 4.5, NCHC*H*), 2.05 (3 H, s, COCH$_3$), 1.93–1.82 (2 H, m, 1 of CH$_2$CH$_2$ and NCH$_2$C*H*$_\alpha$H$_\beta$), 1.75–1.66 (2 H, m, 2 of CH$_2$CH$_2$), 1.56 (1 H, dd, *J* 15.3 and 6.0, NCH$_2$CH$_\alpha$*H*$_\beta$), 1.41–1.36 (1 H, m, 1 of CH$_2$CH$_2$) and 1.29 (3 H, d, *J* 6.5, CHC*H*$_3$); δ_C(90 MHz; CDCl$_3$) 171.2 (s), 78.8 (d), 77.8 (d), 64.4 (t), 64.3 (d), 56.1 (q), 54.1 (t), 51.4 (d), 29.1 (t), 26.7 (t), 23.2 (t), 21.7 (q) and 21.0 (q); *m*/*z* (CI) 258 [(M + H)$^+$, 100%], 198 (12) and 82 (18) [Found: (M + H)$^+$, 258.1705. C$_{13}$H$_{24}$NO$_4$ requires *M*, 258.1705].

Data for **24b**: (Found: C, 60.5; H, 8.9; N, 5.6. C$_{13}$H$_{23}$NO$_4$ requires C, 60.7; H, 9.0; N, 5.4%); R_f 0.5 (EtOAc); ν_{max}(CCl$_4$)/cm^{-1} 2825w (OCH$_3$) and 1745s (C=O); δ_H(360 MHz; CDCl$_3$) 4.38 (1 H, q, *J* 6.7, C*H*CH$_3$), 4.15–4.05 (2 H, m, C*H*$_2$OAc), 3.35–3.25 (2 H, m, NC*H*$_\alpha$H$_\beta$CH$_2$ and C*H*OCH$_3$), 3.34 (3 H, s, OCH$_3$), 2.76 (1 H, ddd, *J* 13, 13 and 6.5, NCH$_\alpha$*H*$_\beta$CH$_2$), 2.72–2.64 (1 H, m, NC*H*CH), 2.47 (1 H, br s,

NCHC*H*), 2.05 (3 H, s, $COCH_3$), 1.96–1.80 (2 H, m, methylene envelope), 1.78–1.40 (4 H, m, methylene envelope) and 1.29 (3 H, d, *J* 6.7, $OCHCH_3$); δ_C(90 MHz; $CDCl_3$) 171.5 (s), 78.7 (d), 76.5 (d), 69.8 (d), 64.3 (t), 55.9 (t), 55.2 (q), 51.0 (d), 29.2 (t), 26.7 (t), 26.1 (t), 21.6 (q) and 21.0 (q); *m/z* (CI) 258 [$(M + H)^+$, 100%], 226 (25), 198 (20), 156 (10) and 82 (19) [Found: $(M + H)^+$, 258.1705. $C_{13}H_{24}NO_4$ requires *M*, 258.1705].

4'S*,5'R*,6'S*,8'R*)- **25a** *and* (4'S*,5'S*,6'R*,8'S*)-3-{4'-(*Methoxymethoxy*)-6'-*methyl*-7'-*oxa*-1'-*azabicyclo*[3.2.1]*octan*-8'-*yl*}*propyl Acetate* **25b**.—A similar procedure to that described for compounds **22a** and **22b** was followed. Isoxazolidines **25a** and **25b** were obtained as an inseparable mixture of oils (1.64 g, 97%). The ratio of **25a** to **25b** was determined as *ca.* 1:1 from ^1H NMR data. Data for a mixture of **25a** and **25b**: (Found: C, 58.5; H, 8.8; N, 4.65. $C_{14}H_{25}NO_5$ requires C, 58.5; H, 8.8; N, 4.9%); R_f 0.44 (5% MeOH–EtOAc); $\nu_{max}(CCl_4)/cm^{-1}$ 1740s (C=O); δ_H(250 MHz; $CDCl_3$) 4.70–4.60 (4 H, m, 2 × OCH_2OMe), 4.38 (1 H, q, *J* 6.6, NOC*H*Me **25b**), 4.15–3.98 (5 H, m, NOC*H*Me **25a** and 2 × CH_2OAc), 3.88 (1 H, t, *J* 4.3, $CHOCH_2OMe$ **25a**), 3.77 (1 H, ddd, *J* 9.7, 6.5 and 2.9, $CHOCH_2OMe$ **25b**), 3.46 (1 H, t, *J* 3.0, NC*H*CH **25a**), 3.36 and 3.35 (6 H, 2 × s, 2 × OMe), 3.34–3.22 (2 H, m, 2 × $NCH_\alpha H_\beta CH_2$), 2.95 (1 H, ddd, *J* 14.2, 12.0 and 5.9, $NCH_\alpha H_\beta CH_2$ **25a**), 2.70 (1 H, ddd, *J* 14.4, 12.0 and 6.1, $NCH_\alpha H_\beta CH_2$ **25b**), 2.63–2.58 (1 H, m, NC*H*CH **25b**), 2.41 (1 H, d, *J* 2.4, NCHC*H*), 2.38 (1 H, *J* 4.7, NCHC*H*), 2.03 and 2.02 (6 H, 2 × s, 2 × CO*Me*), 2.00–1.30 (12 H, methylene envelope) and 1.26 (6 H, apparent d, *J* 6.6, 2 × NOCH*Me*); δ_C(100 MHz; $CDCl_3$) 171.2, 95.2, 94.7, 78.8, 75.4, 74.1, 69.9, 64.7, 64.3, 64.1, 55.8, 55.5, 55.4, 54.2, 52.5, 29.1, 29.0, 26.8, 26.7, 26.5, 24.2, 21.6, 21.5 and 21.0; *m/z* (EI) 287 (M^+, 50%), 244 (30), 228 (48), 226 (40), 165 (21), 126 (50), 99 (22), 98 (35), 97 (82), 96 (30), 95 (75), 82 (40), 81 (100), 71 (35) and 55 (30) (Found: M^+, 287.1748. $C_{14}H_{25}NO_5$ requires *M*, 287.1733).

4,4,4-*Trifluorobut*-2-*en*-1-*ol*[19] **27**.—Aluminium chloride (5.69 g, 0.043 mol) was added slowly to dry ether (100 cm^3) at 0 °C under nitrogen. After stirring for 15 min, lithium aluminium hydride (4.91 g, 0.129 mol) was added slowly, keeping the temperature below 5 °C. A solution of ethyl 4,4,4-trifluorobut-2-enoate (10.76 g, 0.064 mol) in dry ether (20 cm^3) was added dropwise to the mixture over 40 min ($T \leqslant 5$ °C). After a further 40 min of stirring at 0 °C under nitrogen, the reaction mixture was quenched with saturated aqueous sodium sulfate, resulting in the formation of a dark grey precipitate. The ether was decanted off and the precipitate was washed repeatedly with ether (10 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent removed by evaporation to leave a residue (*ca.* 20 cm^3) which was purified by distillation to give the alcohol **27** (6.23 g, 78%) as a colourless oil, b.p. 122–123 °C/760 mmHg; ν_{max}(neat)/cm^{-1} 3334s (OH), 2927s (sp^3 C–H) and 1688m (C=C); δ_H(250 MHz; $CDCl_3$) 6.46 (1 H, dtq, *J* 15.7, 4.0 and $^4J_{HF}$ 2.1, F_3CCH=C*H*), 5.90 (1 H, dqt, *J* 15.7, 2.3 and $^3J_{HF}$ 6.5, F_3CCH=CH), 4.28–4.22 (2 H, m, CH_2) and 2.73 (1 H, br s, OH); δ_C(63 MHz; $CDCl_3$) 139.0 (CH, q, $^3J_{CF}$ 0.6), 123.2 (C, q, $^1J_{CF}$ 266), 117.7 (CH, q, $^2J_{CF}$ 42) and 60.8 (CH_2, s); δ_F(235 MHz; $CDCl_3$) −64.8 to −64.7 (m, CF_3); *m/z* (EI) 126 (M^+, 20.4%), 125 [$(M^+ - H)^+$, 56], 106 (68), 77 (99) and 57 (100) (Found: M^+, 126.0298. $C_4H_5F_3O$ requires *M*, 126.0292).

3-*Trifluoromethylpent*-4-*enoate* **30**.—4,4,4-Trifluorobut-2-en-1-ol **27** (4.26 g, 0.034 mol), triethyl orthoacetate (35 cm^3, 0.19 mol) and propionic acid (30 drops, catalytic) were placed in a glass tube inside a sealed autoclave. The mixture was heated at 200 °C for 16 h causing the internal pressure to rise to 22 atm. The reaction mixture was cooled to room temperature and the excess of triethyl orthoacetate was hydrolysed by pouring the reaction mixture into ice cold aqueous HCl (0.05 mol dm^{-3}; 200 cm^3). The aqueous phase was then extracted with ether (4 × 30 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent removed by evaporation to leave a residue which was purified using flash column chromatography on silica gel, eluting with 2.5% ether–hexane. Fractions containing **30** were combined and concentrated under reduced pressure to give a residue which was further purified by distillation to give the *ester* **30** (2.61 g, 39%) as a colourless oil, b.p. 144–147 °C/760 mmHg (Found: C, 49.15; H, 5.5. $C_8H_{11}F_3O_2$ requires C, 49.0; H, 5.65%); R_f 0.46 (20% Et_2O–hexane); ν_{max}(neat)/cm^{-1} 2985m (sp^3 C–H), 1741s (C=O) and 1648w (C=C); δ_H(250 MHz; $CDCl_3$) 5.68 (1 H, ddd, *J* 17.2, 10.0 and 8.2, C*H*=CH_2), 5.35–5.28 (2 H, m, CH=C*H*$_2$), 4.12 (2 H, q, *J* 7.0, CH_2O), 3.43–3.23 (1 H, m, F_3CCH), 2.73 (1 H, dd, J_{AB} 15.9 and 4.5, O=CC*H*H'), 2.47 (1 H, dd, J_{AB} 15.9 and 9.8, O=CCH*H'*) and 1.22 (3 H, t, *J* 7.1, CH_3); δ_C(63 MHz; $CDCl_3$) 170.0 (C, s), 130.1 (CH, s), 126.2 (C, q, $^1J_{CF}$ 280), 121.5 (CH_2, s), 61.0 (CH_2, s), 44.5 (CH, q, $^2J_{CF}$ 28), 33.3 (CH_2, q, $^3J_{CF}$ 2.2) and 14.1 (CH_3, s); δ_F(235 MHz; $CDCl_3$) −72.2 (d, $^3J_{HF}$ 8.8, CF_3); *m/z* (CI) 214 [$(M + NH_4)^+$, 86%)], 196 (100), 176 (23), 125 (37), 100 (93), 77 (34) and 69 (91) [Found: $(M + NH_4)^+$, 214.1055. $C_8H_{15}F_3NO_2$ requires *M*, 214.1055].

Ethyl 3-*Propylpent*-4-*enoate* **31**.—A mixture of alcohol **28** (7.04 g, 70.3 mmol), triethyl orthoacetate (90 cm^3, 491 mmol) and propionic acid (20 drops, catalytic) was heated at 125 °C under nitrogen in a Dean–Stark apparatus to remove ethanol by distillation. After 2 h, the temperature of the mixture was increased to 150 °C and heating was continued for a further 2 h. The reaction mixture was cooled and excess of triethyl orthoacetate was removed by evaporation at reduced pressure to give a yellow oil. The oil was filtered through silica gel, eluting with 5% ethyl acetate–hexane, to give *ester* **31** (9.48 g, 78%) contaminated with triethyl orthoacetate, R_f 0.7 (10% EtOAc–hexane); $\nu_{max}(CCl_4)/cm^{-1}$ 3080w (sp^2 C–H), 1740s (C=O), 995w and 915m (C=CH_2); δ_H(250 MHz; $CDCl_3$) 5.59 (1 H, ddd, *J* 18.5, 10.2 and 8.4, C*H*=CH_2), 5.03–4.94 (2 H, m, CH=C*H*$_2$), 4.09 (2 H, q, *J* 7.1, OCH_2CH_3), 2.52–2.49 (1 H, m, C*H*CH=CH_2), 2.37–2.19 (2 H, m, O=CCH_2), 1.36–1.09 (7 H, m, OCH_2CH_3 and $CH_2CH_2CH_3$) and 0.86 (3 H, m, $CH_2CH_2CH_3$); δ_C(100 MHz; $CDCl_3$) 172.5 (s), 141.1 (d), 114.8 (t), 57.3 (t), 40.2 (t), 40.1 (t), 36.6 (t), 20.0 (t), 15.2 (q) and 13.9 (q); *m/z* (CI) 171 [$(M + H)^+$, 12%], 123 (79), 94 (38), 78 (33), 58 (50) and 44 (100) [Found: $(M + H)^+$, 171.1385. $C_{10}H_{19}O_2$ requires *M*, 172.1385].

3-*Trifluoromethylpent*-4-*enal Oxime* **32**.—A solution of diisobutylaluminium hydride in dichloromethane (1.0 mol dm^{-3}; 30 cm^3, 30 mmol) was added dropwise over 1 h to a solution of ester **30** (2.11 g, 11 mmol) in dry dichloromethane (100 cm^3) at −74 °C under nitrogen. After stirring for an additional 1 h, the reaction was quenched by the dropwise addition of methanol (10 cm^3) whilst the reaction mixture was maintained at −74 °C. The reaction mixture was warmed to −30 °C and then added to ice cold aqueous HCl (0.6 mol dm^{-3}; 250 cm^3). The organic phase was separated and the aqueous phase was extracted with dichloromethane (3 × 20 cm^3). The organic layers were combined. TLC showed clean, complete formation of the aldehyde (R_f 0.53 in 50% Et_2O–hexane). Hydroxylamine hydrochloride (2.25 g, 0.035 mol), methanol (20 cm^3) and pyridine (20 cm^3) were added to the solution containing the aldehyde, and the mixture was stirred for 40 min at room temperature. The reaction mixture was washed with aqueous HCl (1.8 mol dm^{-3}; 110 cm^3) and the aqueous phase was back-extracted with dichloromethane (2 × 50 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent

removed by evaporation to leave a residue which was purified using flash column chromatography on silica gel, eluting with 30% ether–hexane, to give the *oxime* **32** (1.52 g, 85%) as a colourless oil; R_f 0.63 (50% Et_2O–hexane) and 0.52 (50% Et_2O–hexane); ν_{max}(neat)/cm^{-1} 3270s (OH), 2924s (sp^3 C–H) and 1646w (C=C); δ_H(250 MHz; $CDCl_3$) 2 geometrical isomers in a 1.3:1 ratio; 9.84 (0.57 H, br s, NOH), 9.38 (0.43 H, br s, NOH), 7.37 (0.43 H, t, *J* 6.2, CH=N), 6.72 (0.57 H, t, *J* 5.2, CH=N), 5.77–5.59 (1 H, m, C*H*=CH_2), 5.38–5.28 (2 H, m, CH=CH_2), 3.12–2.89 (1 H, m, F_3CCH) and 2.86–2.38 (2 H, m, CH_2CH=N); δ_C(63 MHz; $CDCl_3$) 148.2 (CH, s), 148.0 (CH, s), 130.2 (CH, q, $^3J_{CF}$ 2.39), 126.2 (C, q, $^1J_{CF}$ 280), 126.1 (C, q, $^1J_{CF}$ 280), 122.1 (CH_2, s), 121.8 (CH_2, s), 46.3 (CH, q, $^2J_{CF}$ 27.2), 45.4 (CH, q, $^2J_{CF}$ 27.4), 28.1 (CH_2, s) and 23.6 (CH_2, s); δ_F(235 MHz; $CDCl_3$) −71.7 (1.71 F, d, $^3J_{HF}$ 8.6, CF_3) and −71.9 (1.29 F, d, $^3J_{HF}$ 8.5, CF_3); *m*/*z* (EI) 167 (M^+, 43%), 150 (96), 98 (79), 77 (100) and 57 (61) (Found: M^+, 167.0550. $C_6H_8F_3NO$ requires *M*, 167.0558).

3-*Propylpent*-4-*enal Oxime* **33**.—A solution of the ester **31** (7.28 g, 42.7 mmol) was added dropwise at room temperature to a stirred suspension of lithium aluminium hydride (3.2 g, 84 mmol) in dry ether (90 cm^3) under nitrogen. The suspension was stirred for 18 h at room temperature. The reaction mixture was then cooled to 0 °C and dry acetone (35 cm^3) was added cautiously over 45 min, causing vigorous effervescence. After stirring for a further 30 min, water (35 cm^3) was added and the mixture was stirred at room temperature for 1 h. Saturated aqueous tartaric acid (100 cm^3) was added and then the mixture was stirred until all precipitants had dissolved. The solution was poured into ethyl acetate (200 cm^3) and diluted with saturated aqueous tartaric acid (40 cm^3). The two phases were separated and the aqueous layer was extracted with ethyl acetate (3 × 200 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent was removed by evaporation. Flash column chromatography on silica gel, eluting with ethyl acetate, yielded 3-propylpent-4-en-1-ol (4.67 g).

A solution of 3-propylpent-4-en-1-ol (2.65 g, 20.7 mmol) in dry dichloromethane (20 cm^3) was added at room temperature to a stirred suspension of pyridinium chlorochromate (11.01 g, 51.7 mmol) in dry dichloromethane (130 cm^3). After stirring for 2.5 h, ether (180 cm^3) was added to it and the supernatant was decanted. The solid residues were washed with ether (3 × 15 cm^3) and the combined ethereal solutions were filtered twice through short columns of Florisil, eluting with fresh ether. The solvent was removed by evaporation to give a yellow oil. Flash column chromatography on silica gel, eluting with 1:1 hexane–ethyl acetate, yielded the aldehyde (1.50 g) as a pale yellow oil. A solution of the aldehyde (0.83 g, 6.6 mmol) in ethanol (20 cm^3) was added at room temperature to a stirred solution of hydroxylamine hydrochloride (1.35 g, 19.4 mmol) and sodium acetate (2.65 g, 19.5 mmol) in water (20 cm^3). The resulting solution was stirred at room temperature for 17 h. The reaction mixture was diluted with water (65 cm^3) and the ethanol was removed by evaporation. The aqueous residue was saturated with sodium chloride prior to extraction with ether (3 × 200 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and then the solvent was removed by evaporation. Filtration through silica gel, eluting with ether, yielded *oxime* **33** (0.49 g, 26% from **31**); R_f 0.4 (1:1, EtOAc–hexane); ν_{max}(CCl_4)/cm^{-1} 3260br (H-bonded OH), 3080w (sp^2 C–H), 1640w (C=C), 995m and 915s (C=CH_2); δ_H(250 MHz; $CDCl_3$) 2 geometrical isomers in a 1:1 ratio; 8.71 (1 H, br s, OH), 7.37 and 6.71 (1 H, 2 × t, *J* 6.3 and 5.1, C*H*=NOH), 5.65–5.42 (1 H, m, C*H*=CH_2), 5.03–4.91 (2 H, m, CH=CH_2), 2.54–2.44 (0.5 H, m, C*H*CH_2CH=NOH), 2.36–2.13 (2.5 H, m, CH_2CH=NOH and C*H*CH_2CH=NOH), 1.35–1.26 (4 H, m, $CH_2CH_2CH_3$) and 0.89 (3 H, apparent t, $J_{apparent}$ 4.8, $CH_2CH_2CH_3$); δ_C(100 MHz; $CDCl_3$) 2 geometrical isomers in a 1:1 ratio; 151.4 (d), 151.2 (d), 141.5 (d), 141.3 (d), 115.3 (t), 115.1 (t), 41.7 (d), 41.0 (d), 36.9 (t), 36.6 (t), 34.6 (t), 29.9 (t), 20.1 (t), 20.0 (t) and 14.0 (q); *m*/*z* (CI) 142 [(M + H)$^+$, 10%], 126 (100), 98 (11), 82 (10), 58 (21) and 44 (21) [Found: (M + H)$^+$, 142.1232. $C_8H_{16}NO$ requires *M*, 142.1232].

(Z)-N-(3-*Trifluoromethylpent*-4-*enyl*)-4-*acetoxybutylidene-amine* N-*Oxide* **34**.—A similar procedure to that described for compound **18** was followed. *Nitrone* **34** was obtained as a colourless oil (1.79 g, 75%) (Found: C, 49.8; H, 6.3; N, 4.8. $C_{12}H_{18}F_3NO_3$ requires C, 51.2; H, 6.45; N, 5.0%); R_f 0.17 (5% MeOH–CH_2Cl_2); ν_{max}(neat)/cm^{-1} 2958m (sp^3 C–H) and 1735s (C=O); δ_H(200 MHz; $CDCl_3$) 6.62 (1 H, t, *J* 6.3, CH=N), 5.60–5.43 (1 H, m, H_2C=C*H*), 5.28–5.14 (2 H, m, H_2C=CH), 3.94 (2 H, t, *J* 6.6, CH_2O), 3.78–3.54 (2 H, m, NCH_2), 2.83–2.59 (1 H, m, CF_3CH), 2.46–2.18 (4 H, m, CF_3CHCH_2 and N=CHCH_2), 1.89 (3 H, s, CH_3) and 1.81–1.65 (2 H, m, OCH_2CH_2); δ_C(50 MHz; $CDCl_3$) 170.6 (C, s), 138.6 (CH, s), 130.1 (CH, s), 126.0 (C, q, *J* 279), 122.1 (CH_2, s), 63.5 (CH_2, s), 61.3 (CH_2, s), 45.5 (CH, q, *J* 27), 24.9 (CH_2, s), 24.2 (CH_2, s), 23.1 (CH_2, s) and 20.5 (CH_3, s); *m*/*z* (CI) 282 [(M + H)$^+$, 100%], 266 (7), 222 (11), 170 (44) and 154 (8) [Found: (M + H)$^+$, 282.1317. $C_{12}H_{19}F_3NO_3$ requires *M*, 282.1317].

(Z)-N-(3-*Propylpent*-4-*enyl*)-4-*acetoxybutylideneamine* N-*Oxide* **35**.—A similar procedure to that described for compound **18** was followed. *Nitrone* **35** was obtained as a colourless oil (0.102 g, 28%); ν_{max}(CCl_4)/cm^{-1} 1740s (C=O); R_f 0.28, 10% MeOH–EtOAc; δ_H(250 MHz; $CDCl_3$) 6.67 (1 H, t, *J* 5.8, CH=N$^+$), 5.40 (1 H, ddd, *J* 17.0, 10.0 and 9.1, C*H*=CH_2), 4.98–4.84 (2 H, m, CH=CH_2), 4.00 (2 H, t, *J* 6.4, CH_2OAc), 3.70–3.61 (2 H, m, CH_2N^+), 2.51–2.43 (2 H, m, CH_2CH=N$^+$), 2.33–2.17 (1 H, m, C*H*CH=CH_2), 2.05–1.01 [11 H, methylene envelope including 1.96 (3 H, s, O=CMe)] and 0.90–0.70 (3 H, m, $CH_2CH_2CH_3$); *m*/*z* (CI) 256 [(M + H)$^+$, 100%)] 240 (22), 183 (28), 164 (85) and 142 (43) [Found: (M + H)$^+$, 256.1913. $C_{14}H_{26}NO_3$ requires *M*, 256.1913].

(4′S*,5′S*,8′S*)-3-(4′-*Trifluoromethyl*-7′-*oxa*-1′-*azabicyclo*-[3.2.1]*octan*-8′-*yl*)*propyl Acetate* **36a**, (4′R*,5′S*,7′R*)-**36b** *and* (4′S*,5′S*,7′R*)-3-(4′-*Trifluoromethyl*-8′-*oxa*-1′-*azabicyclo*-[3.2.1]*octan*-7′-*yl*)*propyl Acetate* **36c**.—A similar procedure to that described for compounds **22a** and **22b** was followed. Purification by flash column chromatography and HPLC gave isoxazolidines **36a** (0.162 g, 32%), **36b** (0.051 g, 10%) and **36c** (0.053 g, 11%). Data for **36a**: (Found: C, 51.3; H, 6.5; N, 5.0. $C_{12}H_{18}F_3NO_3$ requires C, 51.2; H, 6.45; N, 5.0%); R_f 0.53 (80% EtOAc–hexane); ν_{max}($CHCl_3$)/cm^{-1} 2960s (sp^3 C–H) and 1741s (C=O); δ_H(400 MHz; $CDCl_3$), 4.22 (1 H, d, *J* 7.9, C$H_\alpha H_\beta$O), 4.12–4.01 (2 H, m, CH_2OAc), 3.74 (1 H, dd, *J* 7.9 and 5.0, CH$_\alpha H_\beta$O), 3.40 (1 H, dd, *J* 14.4 and 6.2, CH$_\alpha H_\beta$N), 2.89 (1 H, dd, *J* 8.8 and 5.4, NCH), 2.81 (1 H, ddd, *J* 14.4, 12.1 and 5.4, C$H_\alpha H_\beta$N), 2.65 (1 H, d, *J* 5.0, OCH_2CH), 2.50–2.39 (1 H, m, $CHCF_3$), 2.02 (3 H, s, CH_3) and 2.01–1.31 (6 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 171.1 (C, s), 126.1 (C, q, $^1J_{CF}$ 282), 70.9 (CH, s), 68.9 (CH_2, s), 64.0 (CH_2, s), 55.4 (CH_2, s), 43.4 (CH, q, $^2J_{CF}$ 35), 41.0 (CH, s), 28.0 (CH_2, s), 25.6 (CH_2, s), 20.9 (CH_3, s) and 18.2 (CH_2, s); δ_F(235 MHz; $CDCl_3$) −71.9 (d, $^3J_{HF}$ 8.8, CF_3); *m*/*z* (CI) 282 [(M + H)$^+$, 100%], 264 (6), 238 (3), 222 (13) and 192 (2) [Found: (M + H)$^+$, 282.1317. $C_{12}H_{19}F_3NO_3$ requires *M*, 282.1317].

Data for **36b**: (Found: C, 51.5; H, 6.5; N, 5.05. $C_{12}H_{18}F_3NO_3$ requires C, 51.2; H, 6.45; N, 5.0%); R_f 0.38 (70% EtOAc–hexane); ν_{max}(CCl_4)/cm^{-1} 2956s (sp^3 C–H) and 1741s (C=O); δ_H(360 MHz; $CDCl_3$) 4.54 (1 H, d, *J* 7.0, CHO), 4.13–4.02 (2 H, m, CH_2OAc), 3.43 (1 H, ddd, *J* 14.4, 12.5 and 4.7, CH$_\alpha$CH_βN), 3.16–3.09 (1 H, m, CHN), 2.88 (1 H, dd, *J* 14.4 and 5.3, C$H_\alpha H_\beta$N), 2.82–2.69 (1 H, m, $CHCF_3$), 2.57 (1 H, dd, *J* 13.0

and 8.2, $OCHCH_{\alpha}H_{\beta}$), 2.04 (3 H, s, CH_3), 1.90–1.57 (6 H, m, methylene envelope) and 1.47–1.44 (1 H, m, methylene); δ_C(100 MHz; $CDCl_3$) 171.2 (C, s), 125.4 (C, q, $^1J_{CF}$ 278), 74.0 (CH, s), 64.2 (CH_2, s), 63.9 (CH, s), 53.7 (CH_2, s), 42.7 (CH, q, $^2J_{CF}$ 26.3), 37.5 (CH_2, s), 33.6 (CH_2, s), 26.3 (CH_2, s), 21.0 (CH_3, s) and 15.6 (CH_2, s); δ_F(235 MHz; $CDCl_3$) −71.4 (d, $^3J_{HF}$ 9.0, CF_3); *m/z* (EI) 281 (M^+, 7%), 238 (100), 222 (61), 208 (5), 194 (4), 180 (14), 167 (3), 154 (5) and 91 (9) (Found: M^+, 281.1239. $C_{12}H_{18}F_3NO_3$ requires *M*, 281.1239).

Data for **36c**: R_f 0.38 (70% EtOAc–hexane); $\nu_{max}(CHCl_3)$/cm^{-1} 2956s (sp^3 C–H) and 1744s (C=O); δ_H(400 MHz; $CDCl_3$) 4.55 (1 H, d, *J* 6.8, CHO), 4.10 (2 H, t, *J* 6.2, CH_2OAc), 3.53–3.45 (1 H, m, CHN), 3.42–3.34 (1 H, m, $NCH_{\alpha}H_{\beta}$), 3.08–3.03 (1 H, m, $NCH_{\alpha}H_{\beta}$), 2.85–2.77 (1 H, m, $CHCF_3$), 2.42 (1 H, ddd, *J* 12.7, 9.9 and 8.0, $OCHCH_{\alpha}H_{\beta}$), 2.05 (3 H, s, CH_3), 1.86 (1 H, dd, *J* 12.7 and 7.1, $OCHCH_{\alpha}H_{\beta}$) and 1.79–1.58 (6 H, m, methylene envelope); δ_C(100 MHz; $CDCl_3$) 171.1 (C, s), 125.4 (C, q, $^1J_{CF}$ 282), 73.5 (CH, s), 64.5 (CH_2, s), 63.7 (CH, s), 47.6 (CH_2, s), 42.7 (CH, q, $^2J_{CF}$ 26.3), 36.0 (CH_2, s), 27.1 (CH_2, s), 25.4 (CH_2, s), 20.9 (CH_3, s) and 16.8 (CH_2, s); δ_F(235 MHz; $CDCl_3$) −71.4 (d, $^3J_{HF}$ 9.0, CF_3); *m/z* (CI) 282 [$(M + H)^+$, 100%], 264 (3), 238 (2), 222 (6) and 71 (7) [Found: $(M + H)^+$, 282.1317. $C_{12}H_{19}F_3NO_3$ requires *M*, 282.1317].

(4′R*,5′R*,6′S*,8′R*)-3-(4′-*Propyl*-7′-*oxa*-1′-*azabicyclo*-[3.2.1]*octan*-8′-*yl*)*propyl Acetate* **37**.—A similar procedure to that described for compounds **22a** and **22b** was followed. *Isoxazolidine* **37** was obtained as a colourless oil (0.36 g, 40%); R_f 0.5 (EtOAc); $\nu_{max}(CCl_4)$/cm^{-1} 2900s (sp^3 C–H) and 1730s (C=O); δ_H(250 MHz; $CDCl_3$) 4.08–4.02 (2 H, m, CH_2OAc), 3.91 (1 H, d, *J* 7.1, NOCHH′), 3.64 (1 H, dd, *J* 7.1 and 5.2, NOCHH′), 3.27 (1 H, dd, *J* 14.1 and 5.8, $NCH_{\alpha}H_{\beta}CH_2$), 2.83 (1 H, dd, *J* 8.5 and 5.7, NCHCH), 2.72 (1 H, ddd, *J* 14.1, 11.4 and 5.8, $NCH_{\alpha}CH_{\beta}CH_2$), 2.24–2.21 (1 H, m, NCHCH), 2.01 (3 H, s, O=CMe), 1.98–1.07 (11 H, methylene envelope and NCHCHCH) and 0.86 (3 H, t, *J* 7.0, $CH_2CH_2CH_3$); δ_C(100 MHz; $CDCl_3$) 171.2 (s), 71.5 (d), 68.5 (t), 64.3 (t), 56.7 (t), 46.7 (d), 39.0 (d), 37.3 (t), 28.2 (t), 25.8 (t), 25.7 (t), 21.0 (q), 19.5 (t) and 14.2 (q); *m/z* (CI) 256 [$(M + H)^+$, 100%], 212 (1) and 196 (3) [Found: $(M + H)^+$, 256.1913. $C_{14}H_{26}NO_3$ requires *M*, 256.1913].

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