Aziridination of α,β-unsaturated esters bearing allylic hydroxy groups with 3-acetoxyaminoquinazolinones: evidence for a mechanism comprising Michael addition–S_N2 nucleophilic displacement of acetoxy for aziridination of α,β-unsaturated esters

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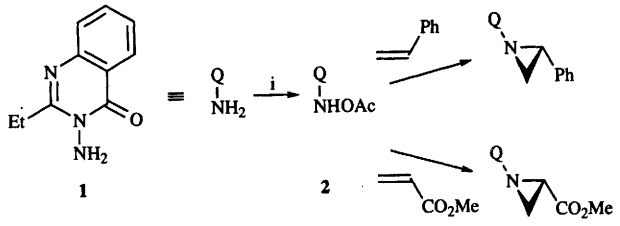
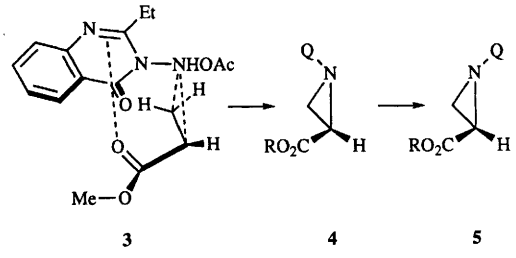
Aziridinations of the allylic alcohol-bearing α,β-unsaturated esters 6 and 7 and their corresponding acetates 8 and 9 have been carried out under standard conditions using 3-acetoxyaminoquinazolinone 2. Whereas the preferred sense of diastereoselectivity in aziridination of allyl alcohol 6 is inverted by comparison with its acetate 8, the preferred sense of diastereoselectivity is retained in aziridination of allylic alcohol 7 by comparison with its acetate 9. A mechanism is proposed for aziridinations of α,β-unsaturated esters in which Michael addition of the N-acetoxy nitrogen to the β-position of the ester runs ahead of S_N2-type nucleophilic displacement of the acetoxy group from nitrogen.

3-Acetoxyaminoquinazolinones *e.g.* **2** (QNHOAc) are aziridinating agents for both electrophilic and nucleophilic alkenes (Scheme 1).[1] Inversion at the exocyclic nitrogen in QNHOAc **2**



Scheme 1 *Reagents and conditions:* i, $Pb(OAc)_4$, CH_2Cl_2, −20 °C

is slow on the NMR time scale but fast on the time scale for aziridination of alkenes.[2] The transition state geometry for aziridination of methyl acrylate with QNHOAc **2** is believed to resemble **3** (Scheme 2) with the quinazolinone and ester group



Scheme 2

cis in the kinetically-formed product **4** but *trans* in the thermodynamically more stable isolated product **5** as a result of inversion at the aziridine ring nitrogen.[1]

The attractive interaction between the ester group and the quinazolinone ring which gives rise to less stable aziridine *cis*-invertomer **4** is assumed to be between the ester carbonyl oxygen and the quinazolinone carbonyl carbon (dotted line in **3**) with the ester in the s-*cis* conformation. Interestingly, attempted aziridination using QNHOAc **2** of α,β-unsaturated lactones, whose α,β-unsaturated carbonyl unit must exist in the s-*trans* conformation, gave no aziridine products at all.[1] It appears therefore that the existence of the secondary interaction, *i.e.* one not leading to bonding in the product, between the two carbonyl groups in the transition state, is vital

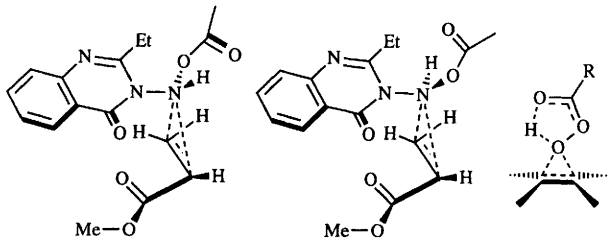
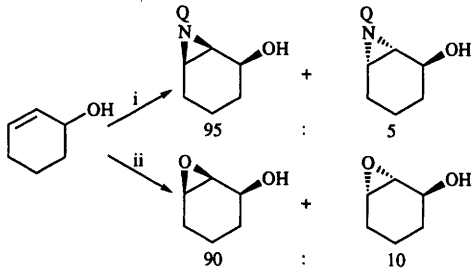


Fig. 1

to ensure primary interaction leading to formation of the aziridine ring.

Although inversion at the exocyclic nitrogen is fast on the time-scale of aziridination using QNHOAc **2**, there are still two positions in the transition state which can be taken up by the H and by OAc of the NHOAc group. These positions can be loosely described as the OAc group being *syn* or *anti* to the quinazolinone carbonyl group (Fig. 1) although the precise orientations of H and OAc are unknown.

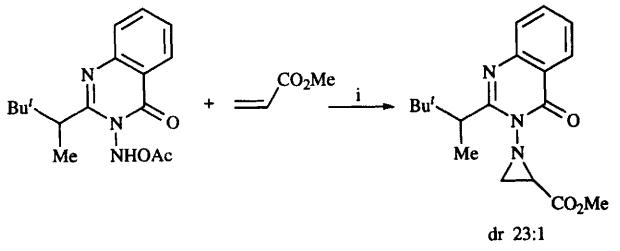
In the transition state for these aziridinations, elimination of the elements of acetic acid and formation of the 3-membered ring are analogous to the well-known Bartlett mechanism of epoxidation using peroxyacids (Fig. 1). We have shown elsewhere[3] that for cyclohexenols, epoxidation using peroxyacids and aziridination using QNHOAc **2** give quantitatively similar *syn*-stereoselectivity (Scheme 3). In both cases, the origin of this



Scheme 3 *Reagents:* i, QNHOAc **2**; ii, RCO_3H

stereoselectivity is ascribed to hydrogen bonding between the allylic hydroxy group and the acetoxy oxygen and hence *syn*-delivery of the oxygen/(Q)-nitrogen of the 3-membered ring.

Using 3-acetoxyaminoquinazolinones with chiral 2-substituents, high or even complete diastereoselectivity is possible in aziridination of prochiral alkenes, particularly in the presence of trifluoroacetic acid (Scheme 4).[4]



Scheme 4 *Reagents and conditions:* i, TFA, CH_2Cl_2, −60 °C

One of the goals in this work is to bring about complete (reagent-controlled) diastereoselectivity in aziridination of a range of prochiral alkenes by the use of enantiopure 3-acetoxyaminoquinazolinones bearing chiral 2-substituents (Scheme 4). A complete description of the transition state for the aziridination would allow *rational design* of the substituents comprising this chiral centre for maximisation of this diastereoselectivity. Ring-opening of the resulting enantiopure aziridines followed by removal of the quinazolinone ring by reductive cleavage of the N–N bond could provide a range of chirons including amino acids.[5]

Clearly, for a complete description of the transition state, the preference, if any, for a *syn*- or *anti*-disposition of the OAc group according to Fig. 1 is required. Thus a preference for an *anti*-configuration would mean that the acetoxy group may be close enough to the quinazolinone chiral 2-substituent to affect the site preferences of its three component atoms/groups. To examine whether such a preference exists, we prepared and carried out aziridinations of α,β-unsaturated esters **6** and **7** bearing an allylic alcohol function in the γ position and on the α-substituent, respectively.[6] If there is a requirement in the aziridination transition state for an *anti*-relationship between the acetoxy group and the quinazolinone carbonyl then only with the γ-hydroxycrotonate **6** is hydrogen bonding possible [Fig. 2(*a*)] always assuming that the secondary interaction between the ester and quinazolinone is conserved [dotted line in Fig. 2(*a*)]. Conversely if a *syn*-relationship is required, then hydrogen bonding is possible only with the α-hydroxymethylacrylate **7** [Fig. 2(*b*)].†

We also prepared the two acetates **8** and **9** from the alcohols **6** and **7** respectively and carried out aziridinations on them using QNHOAc **2**. In these aziridinations, two and one new chiral centres are created from compounds **6** (and **8**) and **7** (and **9**) respectively and so the formation of diastereoisomers is anticipated. Although three new chiral centres are present in aziridines derived from alcohol **6** and its acetate **8**, the configurations of the two centres on the aziridine ring are always related since aziridinations of configured alkenes using QNHOAc **2** are stereospecific with retention of the alkene configuration in the aziridine product.

Whilst hydrogen bonding is conceivable in the transition state for aziridination of either compound **6** or **7** [or both: Figs. 2(*a*) and 2(*b*)] it would be absent in aziridination of the respective acetates **8** and **9**. It was thought that a comparison of the diastereoselectivities obtained in aziridinations of compounds **6**–**9** might provide evidence for the presence of hydrogen bonding in the transition states for aziridinations of alcohols **6** and/or **7**: the presence of such hydrogen bonding *either* for the case of **6** or **7** (but not both) might indicate the

† In these transition states in Fig. 2, we assume that hydrogen bonding is to the N-bound oxygen of the ester but hydrogen bonding to the ester carbonyl oxygen has not been excluded.

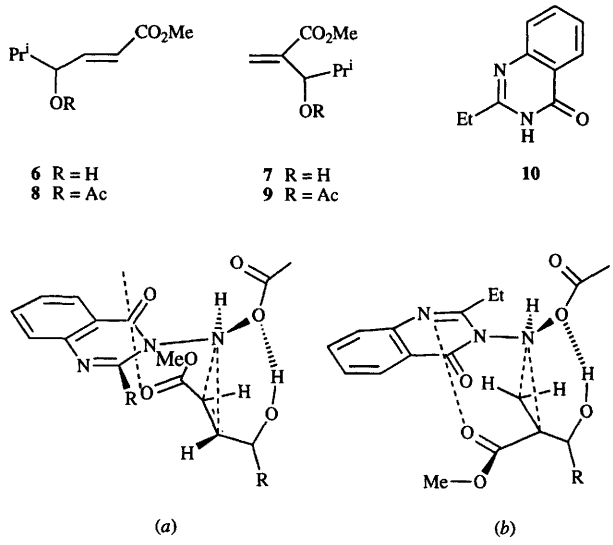
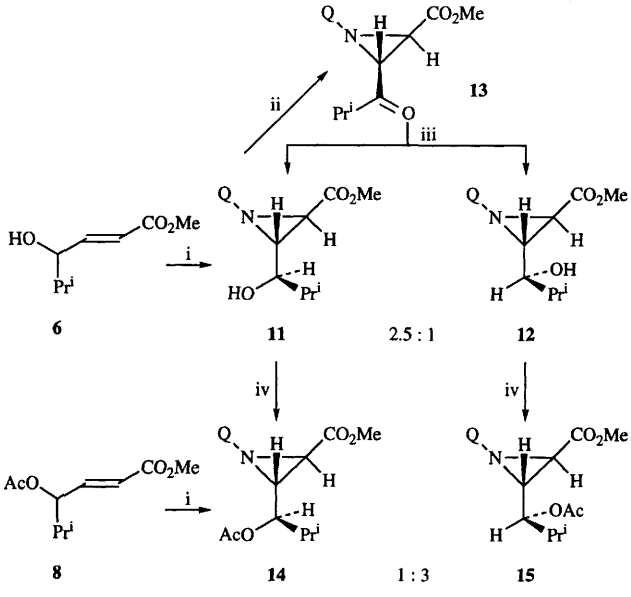


Fig. 2

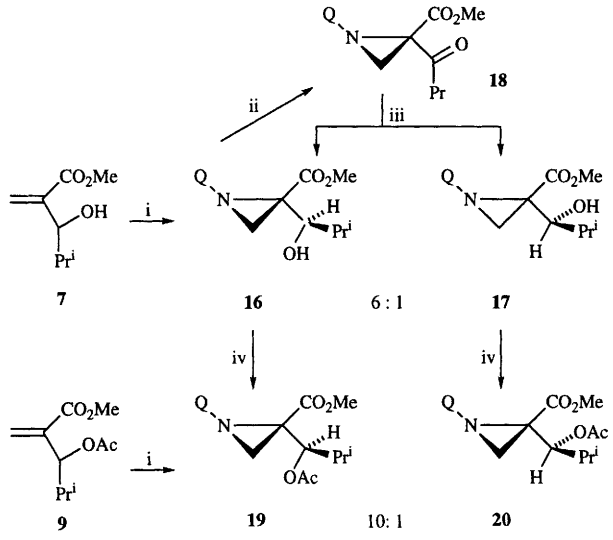
presence of a (stereoelectronic) preference for the location of the N-acetoxy group in the *absence* of such hydrogen bonding *i.e.* it might be applicable to aziridinations of any alkene and not just those bearing allylic hydroxy groups.

Aziridinations of alcohols **6** and **7** and their corresponding acetates **8** and **9** were carried out using solutions of QNHOAc **2**, prepared under standard conditions at −20 °C in dichloromethane (see Experimental), adding the allylic alcohol or allylic acetate and allowing the solution to warm to ambient temperature. The ratios of aziridine diastereoisomers obtained were measured by integration of appropriate signals in the NMR spectra of the crude reaction mixtures and are summarised in Schemes 5 and 6. The only by-product in these



Scheme 5 *Reagents and conditions:* i, QNHOAc **2**, CH_2Cl_2, −20 °C ⟶ RT; ii, DMSO, $(CF_3CO)_2O$; iii, $NaBH_4$; iv, Ac_2O, pyridine

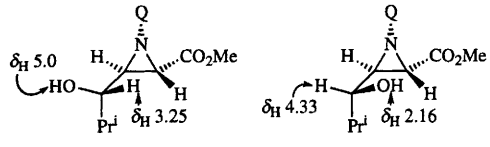
aziridinations is the quinazolin-4(3*H*)-one **10** (QH) which is the major decomposition product of QNHOAc **2** in the absence of any alkene or in the presence of an insufficiently reactive alkene. Assignments of signals in the NMR spectra of the crude products were facilitated by separation of pure diastereoisomers of all compounds in Schemes 5 and 6, except for the minor acetates **14** and **20**, either by crystallisation of the crude reaction product or by chromatography. Fortunately, all of the diastereoisomers in Schemes 5 and 6, except for aziridine ketones **13** and **18**, exist as single *N*-invertomers in solution and



Scheme 6 *Reagents and conditions:* i, QNHOAc **2**, CH_2Cl_2, −20 °C ⟶ RT; ii, DMSO, $(CF_3CO)_2O$; iii, $NaBH_4$; iv, Ac_2O, pyridine

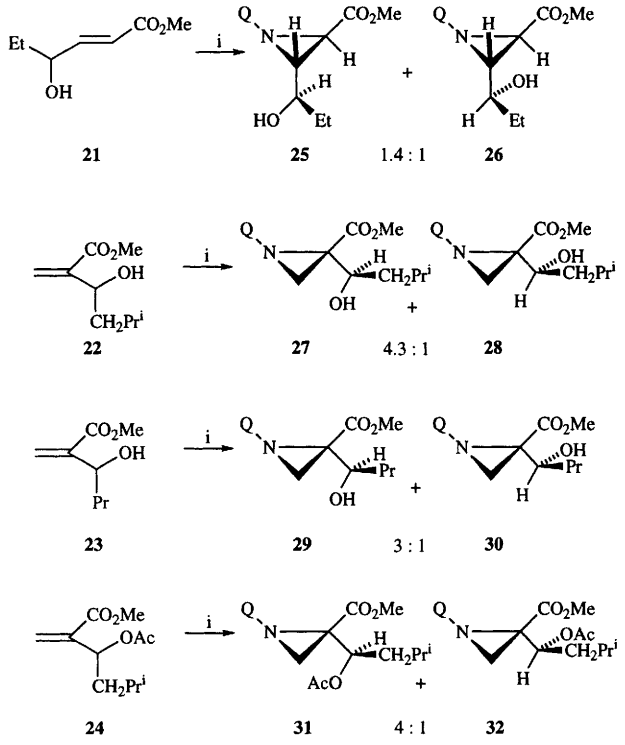
this facilitates measurement of the diastereoisomer ratios in the crude reaction mixtures by NMR spectroscopy. Acetylation of the pure aziridine alcohols (or mixture of aziridine alcohols) also served to interrelate these alcohols and acetates in Schemes 5 and 6. That the alcohols **11** and **12** were, as expected, epimeric at the hydroxy-substituted carbon was confirmed by oxidation (Swern) of the pure alcohol **11** to the ketone **13** and then reduction ($NaBH_4$) of **13** to give a mixture of alcohols **11** and **12**. An analogous procedure established the epimeric relationship between alcohols **16** and **17**.

The stereostructures of all aziridines in Schemes 5 and 6 were proved by X-ray crystal structure determinations on the major aziridine alcohols **11** and **16**[6] and by the chemical correlations referred to above. In addition, for all aziridines in Schemes 5 and 6 (except ketones **13** and **18**) there was a correlation in their NMR spectra between the chemical shift positions of the methine proton on the hydroxy-bearing carbon (for the aziridine alcohols) or on the acetoxy-bearing carbon (for the aziridine acetates) and their relative configurations. Thus these methine protons in alcohols **11** and **12** resonate at δ 3.25 and 4.35 and in acetates **14** and **15** at δ 4.82 and 5.37 respectively. For the alcohols **16** and **17**, the corresponding chemical shifts of the methine protons are δ 4.6 and 3.15 and for acetates **19** and **20** δ 5.95 and 5.31 respectively. The ordering of these chemical shift positions is consistent with the presence in solution for *e.g.* alcohols **11** and **12** of predominant conformations **11′** and **12′** in which the isopropyl group occupies the least sterically hindered position and consequently the methine proton is *endo* and shielded by the aziridine ring (in **11′**) or *exo* and unshielded (in **12′**). For the alcohols in Schemes 5 and 6 there is also a similar correlation between hydroxy-bearing carbon configuration and chemical shift position for the hydroxy protons (see **11′** and **12′**).



11′ **12′**

We have also carried out aziridinations using QNHOAc **2** of the allylic hydroxy-substituted α,β-unsaturated esters **21**–**23** and of the acetate **24** (Scheme 7). The ratios of the corresponding aziridines formed are given in Scheme 7 and the assignments of relative configuration to the major and minor aziridine alcohol diastereoisomers in each case were made from



Scheme 7 *Reagents and conditions:* i, QNHOAc **2** CH_2Cl_2, −20 °C ⟶ RT

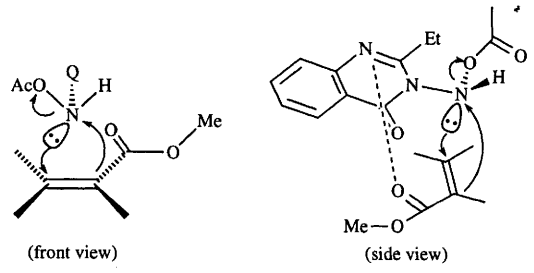


Fig. 3

the chemical shift of the methine proton at the hydroxy-bearing carbon and using its correlation with relative configuration established for aziridine alcohols in Schemes 5 and 6. In aziridination of acetate **24**, only diastereoisomer **31** was isolated (21%) after chromatography; its relative configuration was established by acetylation of aziridine alcohol **29**.

Discussion

There is a striking difference in the preferred sense of diastereoselectivity in aziridination of the alcohols by comparison with their acetates between Scheme 5 and Scheme 6. Thus whereas the preferred sense of diastereoselectivity is *inverted* in aziridines from alcohol **6** by comparison with those from its acetate **8** (2.5 : 1 ⟶ 1 : 3), it is *retained* in aziridines from alcohol **7** by comparison with those from its acetate **9** (6 : 1 ⟶ 10 : 1). A comparison of the ratios of diastereoisomers in Schemes 5, 6 and 7 shows that a reduction in the bulk of the alkyl group at the hydroxy-bearing carbon leads to a reduction in diastereoselectivity in formation of the aziridines. Retention of the preferred sense of diastereoselectivity is also observed for aziridination of allylic alcohol **22** by comparison with its acetate **24**.

To rationalise these changes in the preferred sense of diastereoselectivity we make the following proposals for the mechanism of aziridination of α,β-unsaturated esters by QNHOAc **2**; the reaction, shown diagrammatically in Fig. 3, comprises a Michael addition by the NHOAc nitrogen to the β-carbon of the ester and a nucleophilic displacement of

the NHOAc acetoxy which is S_N2-like. The Michael addition component of this mechanism accounts for the requirement for an s-*cis* conformation of the α,β-unsaturated ester referred to earlier: secondary interaction between the ester carbonyl oxygen and the quinazolinone carbonyl carbon activates the α,β-unsaturated ester toward this Michael addition but this secondary interaction is only feasible when the ester is in the s-*cis* conformation. There are now a number of examples of bimolecular nucleophilic substitution at nitrogen which proceed with *inversion of* configuration *i.e.* in an S_N2-mode.[7] Although the aziridination in Fig. 3 is considered to proceed *via* a single transition state, Michael addition is assumed to be running slightly ahead of the displacement of acetoxy.

Applying this mechanism to aziridination of alcohols **6** and **7**, it is clear that hydrogen bonding in the transition state is possible with the γ-hydroxycrotonate **6** [Fig. 4(*a*)] but not for α-hydroxymethylacrylate **7** [Fig. 4(*b*)]. In aziridination of the corresponding acetates **8** and **9** the corresponding transition states for formation of the major diastereoisomers are believed to be as depicted in Fig. 4(*c*) and (*d*). Formation of the major aziridine diastereoisomer **11** [Fig. 4(*a*)] is the result of a preference of the isopropyl group for the less-hindered 'outside' position when the hydroxy group is hydrogen bonded as shown. In aziridination of the allylic acetate **8** [Fig. 4(*c*)], however, the acetoxy group will take up a position *anti* to the σ bond which is being formed to maximise σ*–π* interaction and thus lower the LUMO energy level of the alkene (Felkin Ahn).‡[8] Again the isopropyl group takes up an outside position preferentially and thus the preferred sense of diastereoselectivity in Fig. 4(*c*) is opposite to that obtained in Fig. 4(*a*).

To account for the preferred sense of diastereoselectivity in aziridination of alcohol **7** which is the same as its acetate **9**, similar transition states are proposed [Fig. 4(*b*) and (*d*)] but with OAc replacing OH. In these cases, the isopropyl group is not only in the sterically least hindered position but also can interact with the HOMO of the alkene, raising its level by σ–π interaction (nucleophilic displacement of the acetoxy group from nitrogen is construed as overlap of the HOMO of the alkene with the LUMO of the N–OAc bond). With the isopropyl group in this position, the preferred sense of diastereoselectivity arises from the placement of the hydroxy or acetoxy group 'inside' as in Fig. 4(*b*) and (*d*) rather than 'outside' as in Fig. 5(*a*).

The high preference of the hydroxy/acetoxy group for the 'inside' position is intriguing. Stabilisation of the 'outside'-positioned hydroxy by hydrogen bonding as in Fig. 5(*b*) would not be expected: in addition to the normal ester resonance which reduces the basicity of the methoxy oxygen of the ester, activation towards Michael addition by the secondary interaction referred to earlier will further diminish the basicity of this oxygen. This preference for the 'inside' position by the hydroxy/acetoxy is analogous to the same preference of an alkoxy group in a variety of electrophilic reactions on double bonds.[9] It is possible that, when it does not enter into hydrogen bonding, the hydroxy group resembles the alkoxy group and exhibits a similar preference for the 'inside' position in the electrophilic component of this aziridination (displacement of the acetoxy group by the alkene). It is also possible that, for compounds like the α,β-unsaturated ester **7**, there is a conformational preference for an inside location of the hydroxy group and aziridination takes place largely from this more abundant conformation. The work of Gung *et al.*[10] has shown that such a conformational preference exists in γ-hydroxycrotonates (like **6**) with the C–O bond of the alcohol eclipsing the double bond of the alkene (such a preference must be overridden in aziridination of compound **6** when the hydroxy group is involved in hydrogen bonding).

‡ In frontier orbital terms, the Michael addition is a HOMO(QNHOCAc)–LUMO(alkene) interaction.

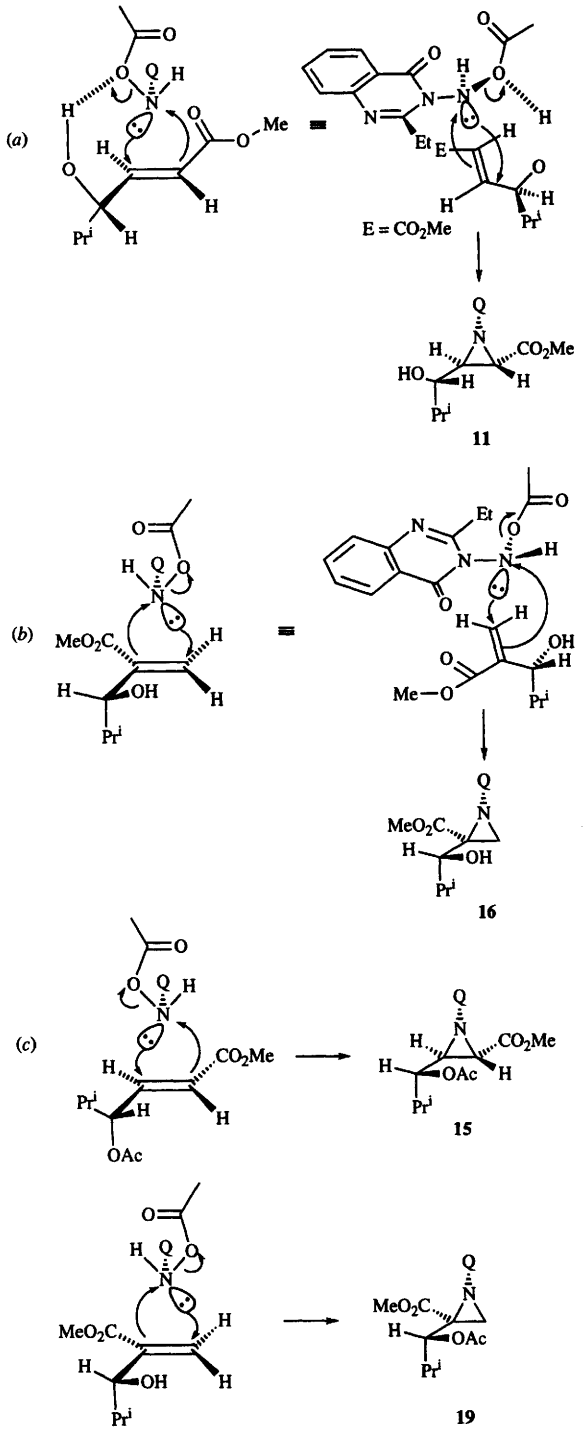


Fig. 4

Of relevance to the work described in this paper is the high diastereoselectivity obtained in aziridination of enantiopure α,β-unsaturated esters *e.g.* **33** by oxidative addition of *N*-aminophthalimide **34** using lead tetraacetate (Scheme 8).[11] The preferred sense of this diastereoselectivity can now be accounted for with the transition state model **35**§ analogous to that previously used for 3-acetoxyaminoquinazolinone-mediated aziridinations of γ-acetoxy-α,β-unsaturated esters [Fig. 4(*c*)]. In this transition state, the CH_2O acetal oxygen at the chiral centre occupies the activating *anti*-position to the

§ In this work (ref. 11) the reactive intermediate was formulated as phthalimidonitrene but in view of our subsequent work (R. S. Atkinson, D. W. Jones and B. J. Kelly, *J. Chem. Soc., Perkin Trans 1*, 1991, 1344) there is little doubt that it is in fact *N*-acetoxyaminophthalimide analogous to QNHOAc **2**.

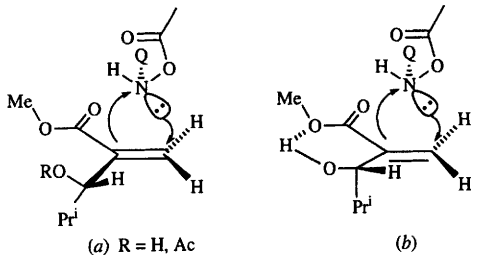
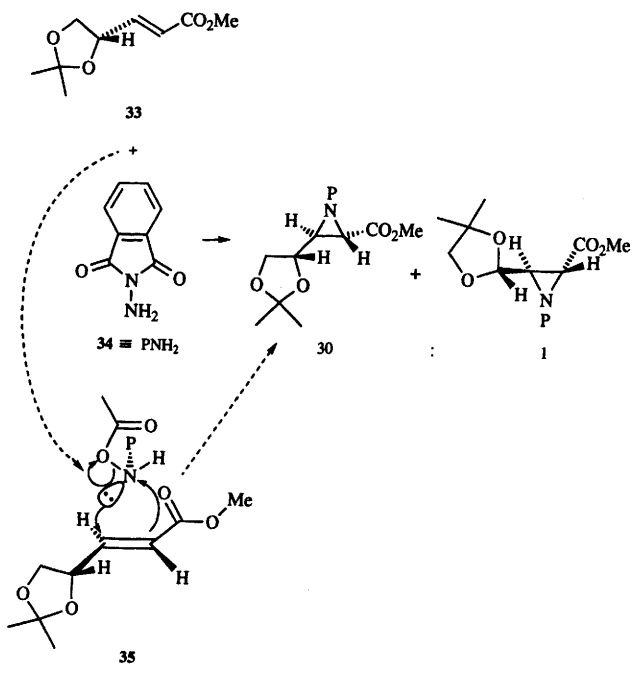


Fig. 5



Scheme 8

incoming nucleophile and the hydrogen at this chiral centre is in the less sterically hindered 'inside' position.

The conclusion from this study, therefore, is that in aziridination of α,β-unsaturated esters using QNHOAc **2** there is a stereoelectronic requirement for an *anti*-relationship between the N-acetoxy group and the quinazolinone carbonyl group with a transition state resembling that in Fig. 1 (*anti*). Although the evidence for this transition state has been adduced from a study of allyl hydroxy-bearing α,β-unsaturated esters it is likely that it applies to others lacking the hydrogen bonding hydroxy group [*cf.* the aziridination of compound **7**: Fig. 4(*b*)].

One of the major differences between epoxidation of alkenes using peroxyacids and aziridination using 3-acetoxyaminoquinazolinones is the lack of reactivity of α,β-unsaturated esters towards peroxyacids. The transition states and mechanisms shown in Fig. 4 account for this difference in reactivity: secondary interaction between the ester and the quinazolinone ring activates the β-position towards Michael addition, an activation not possible using peroxyacids.

Experimental

For instrumentation and general experimental details see refs. 2, 5 and 12. Unless otherwise indicated, ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ using tetramethylsilane as internal standard and ^{13}C spectra at 75 MHz in the same solvent. Assignments of ^{13}C resonances were assisted by the use of DEPT. IR Spectra were recorded using Nujol mulls unless otherwise indicated. Mass spectra were obtained using a Kratos Concept mass spectrometer: except for the molecular ion M^+, only peaks > 20% of the base peaks are given. High resolution masses were obtained by peak-matching using perfluorokerosene. Dichloromethane was dried before use by distillation from calcium hydride. Dimethyl sulfoxide was dried over Linde 4 Å molecular sieves. Oxalyl chloride was used as a solution (2.0 M) in dichloromethane supplied by Aldrich. Light petroleum refers to the fraction bp 40–60 °C. Ether refers to diethyl ether. Drying of organic solutions was carried out using magnesium sulfate.

(*E*)-Methyl 4-hydroxy-5-methylhex-2-enoate **6** and (*E*)-methyl 4-hydroxyhex-2-enoate **21** were prepared by literature methods.[13] For the (previously unreported) NMR spectrum of **6**: δ_H($CDCl_3$, 90 MHz) 7.0 (dd, *J* 15 and 6, C*H*=CHCO$_2$Me), 6.1 (dd, *J* 15 and 1, CH=C*H*CO$_2$Me), 4.1 (2 × d, *J* 6 and ≃6, C*H*OH), 3.7 (s, CO_2Me), 2.6 (s, OH), 1.8 (m, C*H*Me$_2$) and 1.0 (d, *J* 6, CH*Me*)$_2$. Methyl (*E*)-5-methyl-4-acetoxyhex-2-enoate **8** was prepared from the corresponding alcohol (2 g) using pyridine (2 cm^3) and acetic anhydride (5 cm^3). After 4 h, the mixture was poured into ice–water (20 cm^3), stirred for 20 min then extracted with dichloromethane (2 × 25 cm^3). The organic layers were separated, washed with aqueous sodium hydrogen carbonate (30 cm^3) then water (30 cm^3), dried and the solvent evaporated under reduced pressure. Distillation of the residue gave the acetate **8**, bp 86–87 °C (3 mmHg) (lit.,[14] bp not given); δ_H($CDCl_3$, 90 MHz) 6.85 (dd, *J* 15 and 6, C*H*=CHCO$_2$Me), 6.0 (d, *J* 15, C*H*CO$_2$Me), 5.3 (2 × d, *J* 6 and *ca.* 6, C*H*OAc), 3.8 (s, CO_2Me), 2.2 (s, OCOCH_3), 2.0 (m, C*H*Me$_2$) and 0.95 (d, *J* 6, CH*Me*$_2$). Methyl 3-hydroxy-4-methylpent-1-ene-2-carboxylate **7** was prepared by the literature method[15] and purified by chromatography over silica using light petroleum–ethyl acetate (4:1) as eluent (R_f 0.45) (33% yield). For the (previously unreported) NMR spectrum of **7**; δ_H($CDCl_3$, 90 MHz) 6.2 (s, CO_2Me), 5.8 (*H*CH=C), 4.1 (d, *J* 9, C*H*OH), 3.7 (s, CO_2Me), 2.8 [br s, OH (D_2O exch.)], 2.0 (m, C*H*Me$_2$) and 1.0 (2 × d, *J* 6 and *ca.* 6, CH*Me*$_2$). Methyl 3-hydroxy-5-methylhex-1-ene-2-carboxylate **22** and methyl 3-hydroxyhex-1-ene-2-carboxylate **23** were prepared by the literature method[15] and the products used without further purification. Methyl 3-acetoxy-5-methylhex-1-ene-2-carboxylate **24** was prepared from the corresponding alcohol **20** (2.2 g) using pyridine (6 cm^3) and acetic anhydride (6 cm^3) by the method given above. After work-up the acetate was purified by distillation, bp 126–127 °C (0.5 mmHg) (66%); δ_H($CDCl_3$, 90 MHz) 6.23 (s, *H*CH=C), 5.67 (s, HC*H*=C), 5.51 (br m, C*H*OAc), 3.63 (s, CO_2CH_3), 2.01 (s, OCOCH_3 superimposed on m, C*H*Me$_2$), 1.59 (br m, CH_2CHMe$_2$) and 0.96 (2 × d, *J* 6, CH*Me*$_2$).

General procedure for aziridinations using QNHOAc 2

To a well-stirred solution of dry dichloromethane (2 cm^3) at −12 °C was added powdered lead tetraacetate (LTA) (1.23 g, 2.8 mmol) in one portion. After the LTA had dissolved, the mixture was cooled to −20 °C before dropwise addition over *ca.* 6 min of 3-amino-2-ethylquinazolin-4(3*H*)-one **1** (0.5 g, 2.65 mmol) in dry dichloromethane (5 cm^3). The resulting slurry was stirred at −20 °C for a further 5 min before addition of the alkene (1.4 mol equiv.) in one portion. After 2 min at −20 °C the solution was allowed to warm to room temperature, stirring throughout. Lead diacetate was separated, the dichloromethane solution washed with saturated aqueous sodium hydrogen carbonate (15 cm^3) then water (15 cm^3), dried and the solvent removed under reduced pressure.

Aziridination of alcohol 6

A solution of QNHOAc **2** was prepared by the procedure given above and α,β-unsaturated ester **6** (0.58 g, 3.70 mmol) added. After reaction and work up, the crude product [containing a 2.5:1 ratio of diastereoisomers **11** and **12** from integration comparison of peaks in the NMR at δ_H 3.75 and 3.86 (see below)] was triturated with cold dry ether (1 cm^3) to give an off-white solid. The solid material was filtered and found to be a mixture (3:1) of the major aziridine diastereoisomer **11** with quinazolin-4(3*H*)-one **10** respectively, from comparison of the signals at δ_H 3.3 **11** and 10.9 **10**. Crystallisation from ethanol

gave only rel-(1′S,2S,3S)-*methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-3-(1-*hydroxy*-2-*methylpropyl*)*aziridine*-2-*carboxylate* **11** (major diastereoisomer) as a colourless solid (0.36 g, 39%), mp 101–103 °C (Found: C, 62.5; H, 6.65; N, 12.2. $C_{18}H_{23}N_3O_4$ requires C, 62.6; H, 6.7; N, 12.15%); ν_{max}/cm^{-1} 3410m, 1740s, 1660s and 1600s; δ_H 8.2 [dd, *J* 8.1 and 1, 5-H(Q)], 7.7 [ddd, *J* 8.1, 7 and 1, 7-H(Q)], 7.6 [d, *J* 8.1, 8-H(Q)], 7.4 [ddd, *J* 8.1, 7 and 1, 6-H(Q)], 5.0 (s, OH, D_2O exch.), 3.75 (dd, *J* 8.8 and 5, azir. 3-H), 3.69 (s, CO_2CH_3), 3.3 (d, *J* 5, azir. 2-H), 3.25 (dd, *J* 8.8 and 2.9, C*H*OH), 3.05 [dq, (ABX_3) J_{AB} 16.5 and J_{AX} 7.3, CH_3CHH], 2.7 [dq, (ABX_3) J_{AB} 16.5 and J_{AX} 7.3, CH_3CHH], 1.75 (m, 8 lines visible, *J* 6.7, C*H*Me_2), 1.4 (t, *J* 7.3, CH_2CH_3), 1.05 (d, *J* 6.8, CH_3CHCH_3) and 1.03 (d, *J* 6.8, CH_3CHCH_3); *m*/*z* (%) 345 (M^+, 30), 302 (35), 272 (41), 200 (39), 175 (32), 174 (100), 173 (52), 131 (59) and 130 (43). An X-ray crystal structure determination was obtained for this diastereoisomer[6] from a crystal grown in ethanol which confirmed its 2*S*, 3*S*, CHOH-(*S*) relative configuration.

The ether filtrate after trituration above was concentrated under reduced pressure and the resulting oil was chromatographed over silica using light petroleum–ethyl acetate (4:1) as eluent. More of the major aziridine diastereoisomer **11** above (R_f 0.29) was eluted (0.069 g, 8%) followed by rel-(1′R,2S,3S)-*methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-3-(1-*hydroxy*-2-*methylpropyl*)*aziridine*-2-*carboxylate* **12** (minor diastereoisomer) which was isolated as a colourless solid (R_f 0.19) (0.126 g, 14%), mp 140–141 °C (from ethanol) (Found: C, 67.5; H, 6.7; N, 12.15. $C_{18}H_{23}N_3O_4$ requires C, 67.6; H, 6.7; N, 12.15%); ν_{max}/cm^{-1} 3530s br, 1745s, 1670s and 1600s; δ_H 8.2 [dd, *J* 8 and 1.1, 5-H(Q)], 7.7 [ddd, *J* 8, 7 and 1.1, 7-H(Q)], 7.6 [d, *J* 8, 8-H(Q)], 7.43 [ddd, *J* 8, 7 and 1.1, 6-H(Q)], 4.33 (m, C*H*OH, D_2O shake gives a dd, *J ca.* 5 and 1), 3.86 (br d, azir. 3-H), 3.69 (s, CO_2CH_3), 3.58 (d, *J* 5.2, azir. 2-H), 3.05 [dq, (ABX_3) J_{AB} 16.5 and J_{AX} 7.5, CH_3CHH], 2.75 [dq, (ABX_3) J_{AB} 16.5 and J_{AX} 7.5, CH_3CHH], 2.16 [s, CHO*H* (D_2O exch.)], 1.9 (m, C*H*Me_2), 1.05 (d, *J* 6.8, CH_3CHCH_3) and 1.03 (d, *J* 6.8, CH_3CHCH_3); δ_C 160.00 (CO_2CH_3), 160.05 [C=O(Q)], 155.89 [N=C(Q)], 145.92 [*C*N=C(Q)], 133.59, 126.53, 126.17, 126.09 [4 × CH(Q)], 120.93 [*C*C=O(Q)], 70.62 (CHOH), 53.73 (azir. C-2), 52.80 (CO_2CH_3), 43.51 (azir. C-3), 31.63 (*C*HMe_2), 26.72 (CH_3CH_2) and 16.46, 17.55 and 10.49 (CH_3CHCH_3 and CH_3CH_2); *m*/*z* (%) 345 (M^+, 31), 302 (37), 272 (40), 200 (38), 175 (32), 174 (100), 173 (56), 131 (58) and 130 (43).

Swern oxidation of aziridine 11

A 3-necked flask containing a PTFE-coated stirring bar was flame dried and kept under an atmosphere of dry nitrogen. Oxalyl chloride (0.61 cm^3, 1.16 mmol) was added, the flask cooled to −60 °C and then a solution of DMSO (0.21 cm^3, 2.93 mmol) in dry dichloromethane (1 cm^3) added dropwise with stirring. After 10 min, aziridine **11** (0.46 g, 1.33 mmol) as a solution in dry dichloromethane (5 cm^3) was added dropwise over 5 min keeping the temperature of the stirred solution at *ca.* −60 °C throughout. After a further 20 min triethylamine (0.93 cm^3, 6.696 mmol) was added in one portion, the cooling bath removed and the solution allowed to reach ambient temperature whereupon the reaction was quenched with water (10 cm^3). The organic layer was then separated, washed successively with aqueous hydrochloric acid (1%, 5 cm^3), saturated aqueous sodium carbonate (5 cm^3), saturated brine (5 cm^3) and then dried. After evaporation of the bulk of the solvent under reduced pressure, the crude product was triturated with cold dry ether (4 cm^3) to give *methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-3-(2-*methylpropanoyl*)*aziridine*-2-*carboxylate* **13** as colourless crystals (0.42 g, 92%), mp 111–112 °C (from ethanol) (Found: M^+, 343.153. $C_{18}H_{21}N_3O_4$ requires *M*, 343.153); ν_{max}/cm^{-1} 1750m, 1710w, 1680s and 1600s; δ_H(1.7:1 mixture of *N*-invertomers) major *N*-invertomer: 8.05 [dd, *J* 7.9 and 0.8, 5-H(Q)], 7.65–7.35 [m, 6-H(Q), 7-H(Q), 8-H(Q)], 4.14 (d, *J* 4.5, azir. 3-H), 3.9 (s, CO_2CH_3), 3.65 (d, *J* 4.5, azir. 2-H), 3.2 (m, C*H*Me_2), 2.95 (m, CH_3CH_2), 1.41 (t, *J* 6.1, CH_3CH_2Q), 1.15 (d, *J* 6.5, CH_3CHCH_3) and 1.13 (d, *J* 6.5, CH_3CHCH_3); minor *N*-invertomer (observable peaks): 8.18 [dd, *J* 7.7 and 1.2, 5-H(Q)], 4.53 (d, *J* 4.8, azir. 2-H), 3.67 (s, CO_2CH_3), 3.64 (d, *J* 4.8, azir. 3-H), 1.25 (d, *J* 6, CH_3CHCH_3) and 1.23 (d, *J* 6, CH_3CHCH_3); *m*/*z* (%) 343 (M^+, 26), 285 (12), 284 (67), 200 (36), 175 (24), 174 (100), 173 (61), 149 (22), 131 (99), 130 (66), 119 (21), 103 (22), 76 (23) and 71 (24).

Reduction of ketone 13 with sodium borohydride

To the above aziridine ketone **13** (0.41 g, 1.19 mmol) dissolved in dry methanol (15 cm^3) was added sodium borohydride (0.07 g, 1.8 mmol) in small portions over 20 min. The reaction's progress was monitored by TLC [light petroleum–ethyl acetate (4:1)] and after 30 min, when no starting material remained, the crude reaction mixture was poured into water (60 cm^3). Excess methanol was removed by evaporation under reduced pressure and the residual aqueous solution extracted with dichloromethane (30 cm^3), the dichloromethane solution washed with water (15 cm^3) and dried. After concentration under reduced pressure the clear waxy oil obtained (0.238 g, 58%) was found to contain a 2.1:1 mixture of aziridine alcohol diastereoisomers **11** and **12** from NMR spectral comparison with the mixture obtained from aziridination of allylic alcohol **6** (see above) and from integration of the signals at δ 3.33 and 3.58 for aziridine 2-H in **11** and **12**, respectively.

Aziridination of acetate 8

The aziridination procedure above was followed using **1** (0.4 g), LTA (0.985 g) and acetate **8** (0.593 g, 1.4 mol equiv.) in dichloromethane (5 cm^3). The crude product, which contained a 3:1 mixture of aziridine diastereoisomers **15** and **14** [from integration comparison of the signals at δ_H 3.89 and 4.2 in its NMR spectrum (see below)] was triturated with cold dry ether (1 cm^3) to give an off-white solid which was separated and proved to be quinazolin-4(3*H*)-one **10** (0.066 g). The ether filtrate was evaporated under reduced pressure and the residue chromatographed over silica using light petroleum–ethyl acetate (2:1) as eluent. The two aziridine diastereoisomers methyl 1-(2-ethyl-4-oxoquinazolin-3-yl)-3-(1-acetoxy-2-methylpropyl)aziridine-2-carboxylate **15** and **14** (R_f 0.38) (0.28 g, 34%) were co-eluted in a 3.4:1 ratio from comparison of the same signals referred to above in the NMR spectrum of the mixture; ν_{max}/cm^{-1} 1745s, 1670s, 1600s and 1560w; δ_H major diastereoisomer **15**: 8.21 [dd, *J* 8.1 and 1.1, 5-H(Q)], 7.65–7.4 [m, 6-H(Q), 7-H(Q), 8-H(Q)], 5.37 (dd, *J* 4.9 and 3.4, C*H*OAc), 3.89 (br m, azir. 3-H), 3.67 (s, CO_2CH_3), 3.64 (d, *J* 4.9, azir. 2-H), 3.05–2.75 (m, CH_3CH_2), 2.12 (s, CHOCOCH_3), 1.95 (m, C*H*Me_2), 1.4 (t, *J* 7.3, CH_3CH_2), 0.94 (d, *J* 6, CH_3CHCH_3) and 0.91 (d, *J* 6, CH_3CHCH_3); minor aziridine diastereoisomer **14** (observable peaks): 8.2 [dd, *J* 8 and 1, 5-H(Q)], 4.82 (dd, *J* 7.2 and 4.8, C*H*OAc), 4.2 (dd, *J* 7.2 and 4.8, azir. 3-H), 3.63 (s, CO_2CH_3), 3.25 (d, *J* 4.8, azir. 2-H), 2.06 (s, CHOCOCH_3), 1.41 (t, *J* 7.3, CH_3CH_2) and 1.05 (2 × d, *J* 7 and 7, CH_3CHCH_3); *m*/*z* (%) 387 (M^+, 5), 328 (33), 272 (44), 268 (100), 175 (26), 176 (48), 173 (33), 131 (52) and 130 (37).

Acetylation of aziridines 11 and 12

The crude aziridination product of allylic alcohol **6** containing **11** and **12** (ratio 2.6:1) was acetylated as described above using pyridine (10 cm^3) and acetic anhydride (5 cm^3). After work-up, the product, containing a *ca.* 3:1 ratio of diastereoisomers **14** and **15** (from integration comparison of the peaks at δ_H 4.2 and 3.89 in its NMR spectrum) was triturated with cold dry ether (1 cm^3) to give an off-white solid (0.51 g) which was separated and found to be a 3:1 mixture of the aziridine acetate diastereoisomer **14** and quinazolin-4(3*H*)-one **10** from comparison of peaks at δ_H 3.25 and 10.9. This solid was then crystallised from ethanol to give the *aziridine diastereoisomer* **14** (0.39 g, 38%) as colourless crystals, mp 115–116 °C (Found: C, 61.9; H, 6.55; N, 10.8. $C_{20}H_{25}N_3O_5$ requires C, 62.0; H, 6.5; N, 10.9%);

ν_{max}/cm^{-1} 1745s, 1670s, 1600s and 1560w; δ_H 8.2 [d, J 1.8, 5-H(Q)], 7.65 [m, 7-H(Q), 8-H(Q)], 7.41 [ddd, J 8, 6.9 and 1.1, 6-H(Q)], 4.82 (dd, J 7.2 and 5.7, C*H*OAc), 4.2 (dd, J 7.2 and 5, azir. 3-H), 3.63 (s, CO_2CH_3), 3.25 (d, J 5, azir. 2-H), 3.1 [dq, (ABX_3) J_{AB} 16.7 and J_{AX} 7.4, CH_3CHH], 2.76 [dq, (ABX_3) J_{AB} 16.7 and J_{AX} 7.4, CH_3CHH], 2.2 (m, C*H*Me$_2$ and s, CHOCO-C*H*$_3$), 1.41 (t, J 7.3, C*H*$_3$CH$_2$) and 1.05 (2 × d, J 6.6 and 6.6, C*H*$_3$CHC*H*$_3$); m/z (%) 387 (M^+, 5), 328 (33), 272 (44), 268 (100), 175 (26), 174 (48), 173 (33), 131 (52) and 130 (37).

The ether filtrate was evaporated under reduced pressure and the residue chromatographed over silica using light petroleum–ethyl acetate (2:1) as eluent to give a mixture of the same aziridine diastereoisomers **14** and **15** (ratio now 1:1.5) (R_f 0.37) (0.21 g, 21%, overall yield 59%). The major component of this mixture **15** corresponded to the minor diastereoisomer in the crude reaction mixture from acetylation of the aziridine alcohols above with δ_H 5.36 (dd, J 4.9 and 3.7, C*H*OAc), 3.86 (br m, azir. 3-H), 3.64 (s, CO_2CH_3) and 3.63 (d, J 4.9, azir. 2-H) and was identical to the major diastereoisomer isolated from aziridination of acetate **8** (see above).

Aziridination of alcohol 7

A solution of QNHOAc **2** was prepared by the general procedure given above from **1** (2 g, 0.011 mol) and LTA (4.93 g, 0.011 mol) in dichloromethane (40 cm^3) and allylic alcohol **7** (2.34 g, 0.015 mol) was added. After reaction and work-up, the crude product [containing a 6.1:1 ratio of aziridine diastereoisomers **16** and **17**, respectively, from integration of peaks at δ 3.4 and 3.25 in its NMR spectrum (see below)] was triturated with cold dry ether (2 cm^3) to give an off-white solid (1.21 g) which was separated. NMR Analysis showed this solid was a mixture of aziridine **16** and quinazolin-4(3*H*)-one **10** (ratio 3.5:1) from comparison of peaks at δ_H 3.19 and 10.9 respectively. Flash chromatography over silica using ethyl acetate–light petroleum (1:1) as eluent gave *methyl* 1-(*2-ethyl-4-oxoquinazolin-3-yl*)-2-(*1-hydroxy-2-methylpropyl*)*aziridine-2-carboxylate* **16** (major diastereoisomer) (R_f 0.48) as a colourless solid (0.86 g, 23%), mp 121–122 °C (from ethanol) (Found: C, 62.35; H, 6.75; N, 12.05. $C_{18}H_{23}N_3O_4$ requires C, 62.6; H, 6.7; N, 12.15%); ν_{max}/cm^{-1} 3750w br, 1727s, 1670s and 1595s; δ_H 8.1 [dd, J 8.2 and 1.2, 5-H(Q)], 7.7 [m, H-7(Q), H-8(Q)], 7.4 [ddd, J 8.2, 8 and 1.5, H-6(Q)], 4.6 (d, J 3.4, C*H*OH), 3.55 (s, CO_2CH_3), 3.4 (d, J 1.2, azir. 3α-H), 3.19 (d, J 1.2, azir. β-H), 3.0 (q, J 7.3, C*H*$_2$CH$_3$), 2.74 (s, CHO*H*, D_2O exch.), 2.1 (m, C*H*Me$_2$), 1.4 (t, J 7.3, CH$_2$C*H*$_3$), 1.1 (d, J *ca.* 7, C*H*$_3$CHCH$_3$) and 0.9 (d, J *ca.* 7, CH$_3$CHC*H*$_3$); m/z (%) 345 (M^+, 4), 302 (44), 273 (22), 270 (100), 214 (69), 200 (45), 189 (38), 175 (28), 174 (88), 173 (83), 158 (49), 131 (95), 130 (67), 119 (29), 103 (22) and 76 (27). An X-ray crystal structure determination of this diastereoisomer[6] on a crystal grown in ethanol confirmed its 2*S*, CHOH-(*S*) relative configuration. The ether filtrate from the trituration above was evaporated under reduced pressure and the residue was chromatographed over silica using ethyl acetate–light petroleum (1:1) as eluent to give more of the major aziridine diastereoisomer **16** (R_f 0.48) (0.155 g, 4%; overall yield 27%).

The minor aziridine diastereoisomer **17** was not eluted from the column; however, signals in the ^{1}H NMR spectrum of the crude reaction product were attributable to it at δ_H 3.54 (s, CO_2CH_3), 3.25 (s, azir. 3-H), 2.45 (br m, C*H*Me$_2$) and 1.1 (d, J 6.3, C*H*$_3$CHCH$_3$). These assignments were confirmed when a pure sample of the aziridine **17** became available from reduction of the aziridine ketone **18** (see below).

Aziridination of acetate 9

A solution of QNHOAc **2** was prepared by the general procedure given above from **1** (0.5 g) and LTA (1.25 g) in dichloromethane (7 cm^3) and allylic acetate **9** (0.741 g) added. After work-up, the crude product [containing a 10:1 ratio of diastereoisomers **19**:**20** from integration comparison of the peaks at δ_H 5.95 and 5.31 in its NMR spectrum (see below)] was chromatographed over silica using light petroleum–ethyl acetate (4:1) as eluent to give *methyl* 1-(*2-ethyl-4-oxoquinazolin-3-yl*)-2-(*1-hydroxy-2-methylpropyl*)*aziridine-2-carboxylate* **19** (major diastereoisomer) (R_f 0.26) as a colourless solid (0.21 g, 21%), mp 124–125 °C (from ethanol) (Found: C, 61.7; H, 6.5; N, 10.75. $C_{20}H_{25}N_3O_5$ requires C, 62.0; H, 6.5; N, 10.85%); ν_{max}/cm^{-1} 1745s, 1675s and 1600s; δ_H 8.1 [dd, J 8 and 1.4, 5-H(Q)], 7.6 [m, 7-H(Q), 8-H(Q)], 7.4 (ddd, J 8, *ca.* 8 and 1.3, 6-H(Q)], 5.95 (d, J 3.1, C*H*OAc), 3.7 (d, J 2.4, azir. 3α-H), 3.55 (s, CO_2CH_3), 3.15 (d, J 2.4, azir. 3β-H), 3.05 [dq, (ABX_3) J_{AB} 14.9 and J_{AX} 7.4, CH_3CHHQ], 2.85 [dq, (ABX_3) J_{AB} 14.9 and J_{AX} 7.3, CH_3CHHQ], 2.3 (d × heptet, J 6.9 and 3.1, C*H*Me$_2$), 2.09 (s, CHOCO*Me*), 1.35 (t, J *ca.* 7, C*H*$_3$CH$_2$Q), 1.0 (d, J 6.9, C*H*$_3$CHCH$_3$) and 0.85 (d, J 6.9, CH$_3$CHC*H*$_3$); δ_C 169.91, 165.72 (CO_2CH_3, CHO*C*OCH$_3$), 159.69 [C=O(Q)], 156.65 [N=C(Q)], 145.59 [*C*N=C(Q)], 133.42, 126.52, 125.94, 125.91 [4 × CH(Q)], 120.81 [*C*C=O(Q)], 70.45 (CHOAc), 52.81 (CO_2CH_3), 52.36 (azir. C-2), 46.56 (azir. C-3), 29.75 (*C*HMe$_2$), 26.98 (CH$_3$*C*H$_2$Q), 20.49, 19.66 and 15.81 (*C*H$_3$CH*C*H$_3$, CHOCO*C*H$_3$) and 10.64 (*C*H$_3$CH$_2$Q); m/z (%) 387 (M^+, 4), 270 (21), 200 (20), 174 (100), 173 (36), 131 (35) and 130 (24).

The minor aziridine diastereoisomer **20** was not eluted from the column but its characteristic signals could be identified in the ^{1}H NMR spectrum of the crude reaction mixture at δ_H 5.31 (d, J 6.8, C*H*OCOCH$_3$), 3.56 (s, CO_2CH_3), 3.19 (d, J 1.1, azir. 3α-H), 2.84 (d, J 1.1, azir. 3β-H), 2.06 (s, CHOCOC*H*$_3$) and 1.44 (t, J 7.3, C*H*$_3$CH$_2$Q). These assignments were confirmed when the same signals were observed in the crude reaction product from acetylation of a mixture containing a less disparate ratio of aziridine alcohols **16** and **17** (see below).

Acetylation of aziridine alcohols 16 and 17

The crude reaction product (containing a 6:1 ratio of **16**:**17**) from aziridination of allylic alcohol **7** with QNHOAc **2** was acetylated using the procedure given earlier. After work-up, the crude product, containing a 5.4:1 ratio of diastereoisomers **16**:**17** from comparison of the peaks in its NMR spectrum at δ 5.31 and 3.70 respectively, was chromatographed over silica using light petroleum–ethyl acetate (2:1) as eluent to give the major aziridine diastereoisomer **19** (R_f 0.44) as colourless crystals (0.311 g, 30%) mp 124–125 °C (from ethanol). This major aziridine diastereoisomer was identical by NMR comparison with the major aziridine diastereoisomer **19** isolated from aziridination of the allylic acetate **9** described above.

Swern oxidation of aziridine alcohol 16

Oxidation of **16** was carried out using the procedure described above using oxalyl chloride (0.974 cm^3, 1.94 mmol), DMSO (0.28 cm^3, 3.89 mmol), aziridine **16** (0.6 g, 1.74 mmol) and triethylamine (1.22 cm^3, 8.74 mmol) in dry dichloromethane (6.2 cm^3). After work-up the crude product was triturated with cold dry ether (2 cm^3) to give a white solid which was separated and then crystallised from ethanol to give *methyl* 1-(*2-ethyl-4-oxoquinazolin-3-yl*)-2-(*2-methylpropanoyl*)*aziridine-2-carboxylate* **18** (0.334 g, 56%), mp 100–101 °C (Found: C, 67.85; H, 6.2; N, 12.15. $C_{18}H_{21}N_3O_4$ requires C, 67.95; H, 6.15; N, 12.25%); ν_{max}/cm^{-1} 1725s, 1710w, 1675s and 1600s; δ_H(3.4:1 mixture of *N*-invertomers), major *N*-invertomer: 8.15 [dd, J 8.1 and 1, 5-H(Q)], 7.69 [m, 7-H(Q), 8-H(Q)], 7.43 [m, 6-H(Q)], 3.9 (heptet, J 6.8, C*H*Me$_2$), 3.65 (s, CO_2CH_3), 3.2 (d, J 1, azir. 3α-H), 3.07 (d, J 1, azir. 3β-H), 3.0 (q, J 7.3, CH$_3$C*H*$_2$Q), 1.4 (t, J 7.3, C*H*$_3$CH$_2$Q), 1.3 (d, J 6.8, C*H*$_3$CHCH$_3$) and 1.2 d, J 6.8, CH$_3$CHCH$_3$); minor invertomer (observable peaks): 8.06 [dd, J 8 and 0.9, 5-H(Q)], 3.96 (s, CO_2CH_3), 3.45 (s, azir. 3β-H), 3.43 (heptet, J 6.8, C*H*Me$_2$), 3.17 (s, azir. 3α-H), 2.97 (q, J 7.4, CH$_3$C*H*$_2$Q), 1.43 (t, J 7.4, C*H*$_3$CH$_2$Q), 1.14 (d, J 6.5, C*H*$_3$CHCH$_3$) and 1.07 (d, J 6.5, CH$_3$CHC*H*$_3$); m/z (%) 343 (M^+, 51), 214 (23), 174 (46), 173 (27), 131 (100) and 130 (38).

Reduction of ketone 18 with sodium borohydride

Reduction was carried out using the procedure described earlier using sodium borohydride (0.038 g, 1.0 mmol), dry methanol (8 cm^3) and aziridine ketone **18** (0.3 g, 0.875 mmol). The crude product obtained after work up (containing a 1:1.1 ratio of diastereoisomers **16** and **17** from comparison of the peaks in its NMR spectrum at δ_H 3.4 and 3.25 respectively) was chromatographed over silica using light petroleum–ethyl acetate (2:1) as eluent to give the aziridine diastereoisomer **16** as a white solid (R_f 0.68) (0.145 g, 48%) mp 121–122 °C (from ethanol) identical with the major diastereoisomer from aziridination of allylic alcohol **7** (see above).

Further elution gave the *aziridine alcohol* **17** (minor diastereoisomer from aziridination of allylic alcohol **7**) (R_f 0.59) as colourless crystals (0.14 g, 45%), mp 114–115 °C (from ethanol) (Found: C, 62.35; H, 6.75; N, 12.05. $C_{18}H_{23}N_3O_4$ requires C, 62.6; H, 6.7; N, 12.15%); ν_{max}/cm^{-1} 3475s br, 1725s, 1665s and 1610w; δ_H 8.1 [d, *J ca.* 8.2, 5-H(Q)], 7.65 [m, 7-H(Q), 8-H(Q)], 7.4 [ddd, *J* 8.2, *ca.* 8 and 1.5, 6-H(Q)], 4.8 (d, *J* 2.8, CHO*H*, D_2O exch.), 3.6 (s, CO_2CH_3), 3.25 (s, azir. 3α-H), 3.15 (dd, *J ca.* 9 and 2.8, C*H*OH, D_2O exch. to d, *J ca.* 9), 3.05 (m, CH_3CH_2Q), 2.9 (s, azir. 3β-H), 2.45 (m, C*H*Me_2), 1.45 (t, *J* 7.3, CH_3CH_2Q), 1.15 (d, *J* 6.8, CH_3CHCH_3) and 0.9 (d, *J* 6.8, CH_3CHCH_3); *m/z* (%) (M^+, 29), 302 (62), 273 (36), 270 (100), 214 (66), 200 (35), 189 (47), 175 (26), 174 (95), 173 (72), 158 (30), 131 (81), 130 (53), 119 (21), 83 (11) and 76 (25).

Aziridination of allylic alcohol 21

A solution of QNHOAc **2** was prepared from **1** (0.563 g) and LTA (1.39 g), in dichloromethane (6 cm^3) as directed above and allylic alcohol **21** (0.6 g) added. After reaction and work-up, the crude product [containing a 1.4:1 ratio of aziridine diastereoisomers **25**:**26** from integration comparison of the signals in the NMR spectrum at δ_H 3.75 and 3.96 (see below)] was triturated with cold dry ether (2 cm^3) to give a mixture of the major aziridine diastereoisomer **25** and the quinazolin-4(3*H*)-one **10** in a 4:1 ratio as an off-white solid (0.29 g). Crystallisation from ethanol gave *methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-3-(1-*hydroxypropyl*)*aziridine*-2-*carboxylate* **25** (major diastereoisomer) (0.261 g, 27%) as colourless crystals, mp 116–118 °C (Found: C, 61.55; H, 6.4; N, 12.55. $C_{17}H_{21}N_3O_4$ requires C, 61.6; H, 6.4; N, 12.7%); ν_{max}/cm^{-1} 3475s br, 1745s, 1660s and 1575w; δ_H 8.2 [dd, *J* 8 and 1, 5-H(Q)], 7.67 [ddd, *J* 8, 6.9 and 1, 7-H(Q)], 7.62 [d, *J* 8, 8-H(Q)], 7.44 [ddd, *J* 8, 6.9 and *ca.* 1, 6-H(Q)], 4.7 (d, *J* 1.9, CHO*H*, D_2O exch.), 3.75 (dd, *J* 8 and 5.1, azir. 3-H), 3.65 (s, CO_2CH_3), 3.5 (m, C*H*OH), 3.3 (d, *J* 5.1, azir. 2-H), 2.9 [dq, (ABX_3) J_{AB} 16.5 and J_{AX} 7.3, CH_3CH*H*], 2.6 [dq, (ABX_3) J_{AB} 16.5 and J_{AX} 7.3, CH_3CH*H*], 1.7 (struct. m, CH_3CH_2CHOH), 1.4 (t, *J* 7.3, CH_3CH_2) and 1.05 (t, *J* 7.5, CH_3CH_2CHOH); *m/z* (%) 331 (M^+, 43), 272 (81), 200 (47), 175 (28), 174 (100), 173 (51), 131 (51) and 130 (33).

The ether filtrate after trituration above was evaporated under reduced pressure to give an oily residue which was chromatographed over silica using ether acetate–light petroleum (1:1) as eluent to recover more of the major aziridine diastereoisomer **25** (R_f 0.35) (0.04 g, 4%, overall yield 31%). The minor aziridine diastereoisomer **26** was not eluted but was identified in the oily residue above from signals in its NMR spectrum at δ_H 5.24 (m, C*H*OH), 3.96 (br m, azir. 3-H), 3.46 (d, *J* 5, azir. 2-H).

Aziridination of allylic alcohol 22

A solution of QNHOAc **2** was prepared as described above from **1** (0.5 g) and LTA (1.23 g) in dry dichloromethane (6 cm^3) and allylic alcohol **22** (0.64 g) added. The crude product after the usual work up [containing a 4.3:1 ratio of aziridine diastereoisomers **27**:**28** respectively, from integration of peaks at δ 3.15 and 2.95 in its NMR spectrum (see below)] was triturated with cold dry ether (1 cm^3) to give a colourless solid which was separated and identified as the quinazolin-4(3*H*)-one **10**. The ether solution was evaporated under reduced pressure and the residual oil set aside for 3 days which resulted in its solidification. The white solid isolated by trituration with cold light petroleum (1 cm^3) was found to be the *methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-2-(1-*hydroxy*-3-*methylbutyl*)*aziridine*-2-*carboxylate* **27** (major diastereoisomer) (0.21 g, 22%) giving colourless crystals, mp 74–75 °C (from ethanol) (Found: M^+, 359.185. $C_{19}H_{25}N_3O_4$ requires *M*, 359.185); ν_{max}/cm^{-1} 3500s br, 1740s, 1675s and 1600s; δ_H 8.1 [dd, *J ca.* 8 and 1, 5-H(Q)], 7.65 [m, 7-H(Q), 8-H(Q)], 7.4 [ddd, *J* 8, 6.7 and 1, 6-H(Q)], 4.75 (t, *J* 6.8, C*H*OH), 3.55 (s, CO_2CH_3), 3.15 (s, azir. 3α-H), 3.0 (m, CH_3CH_2Q and azir. 3β-H), 2.92 (s, CHO*H*, D_2O exch.), 2.0 (heptet, *J* 6.8, C*H*Me_2), 1.45 (t, *J* 7.3, CH_3CH_2Q overlapping m, Pr^iCH_2), 1.05 (d, *J* 6.7, CH_3CHCH_3) and 0.95 (d, *J* 6.7, CH_3CHCH_3); *m/z* (%) 359 (M^+, 11), 200 (22), 189 (29), 175 (33), 174 (100), 73 (55), 131 (97), 130 (70), 103 (23) and 76 (26).

The light petroleum extract from the trituration above was evaporated under reduced pressure and the residue chromatographed over silica using light petroleum–ethyl acetate (2:1) as eluent. This gave the *aziridine* **28** (minor diastereoisomer) (R_f 0.17) as a clear oil (0.12 g, 13%) (Found: M, 359.185. $C_{19}H_{25}N_3O_4$ requires *M*, 359.185); ν_{max}/cm^{-1} 3500m, 1725s, 1675s and 1610w; δ_H 8.1 [d, *J ca.* 8.1, 5-H(Q)], 7.65 [m, 7-H(Q), H-8(Q)], 7.4 [ddd, *J ca.* 8.1, 6.3 and 1, 6-H(Q)], 4.15 (dd, *J* 10.1 and 3, C*H*OH), 3.55 (s, CO_2CH_3), 3.15 (d, *J* 1, azir. 3α-H), 3.05 (q, *J* 7.3, CH_3CH_2Q), 2.95 (d, *J* 1, azir. 3β-H), 1.95 (m, C*H*Me_2), 1.75 (ddd, *J* 14, 10.1 and *ca.* 4, Pr^iCH*H*), 1.6 (ddd, *J ca.* 15, *ca.* 10 and 3, Pr^iCH*H*), 1.45 (t, *J* 7.3, CH_3CH_2Q) and 1.00 (2 × d, *J* 7.1 and *ca.* 7.1, CH_3CHCH_3); δ_C 167.18 (CO_2CH_3), 155.99 [C=O(Q)], 155.43 [N=C(Q)], 145.72 [*C*N=C(Q)], 134.46, 126.67, 126.44, 125.77 [4 × CH(Q)], 120.36 [*C*C=O(Q)], 70.44 (CHOH), 53.46 (azir. C-2), 52.69 (CO_2CH_3), 44.46 (azir. C-3), 41.71 (Pr^iCH_2), 26.92 (CH_3CH_2Q), 24.46 (*C*HMe_2), 23.63, 21.45 (CH_3CHCH_3) and 10.53 (CH_3CH_2Q); *m/z* (%) 359 (M^+, 23), 302 (25), 270 (44), 214 (21), 200 (27), 189 (33), 175 (37), 174 (10), 173 (52), 131 (79) and 130 (54).

Aziridination of allylic alcohol 23

A solution of QNHOAc **2** was prepared as above using **1** (0.5 g) and LTA (1.232 g) in dry dichloromethane (6 cm^3) and allylic alcohol **23** (0.58 g) was added. After reaction and work-up, the crude product [containing a 3:1 ratio of aziridines **29**:**30** respectively, from integration comparison of signals at δ_H 3.2 and 3.15 in its NMR spectrum (see below)] was triturated with cold dry ether (1 cm^3) to free a colourless solid which was filtered off and found to be a 5:1 mixture of the major aziridine diastereoisomer **29** and quinazolin-4(3*H*)-one **10**. Crystallisation of the solid from ethanol gave *methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-2-(1-*hydroxybutyl*)*aziridine*-2-*carboxylate* **29** (major diastereoisomer) (0.255 g, 28%) as colourless crystals, mp 97–99 °C (Found: C, 62.25; H, 6.7; N, 12.0. $C_{18}H_{23}N_3O_4$ requires C, 62.6; H, 6.7; N, 12.15%); ν_{max}/cm^{-1} 3500s br, 1725s, 1675s and 1610s; δ_H 8.1 [dd, *J* 8 and *ca.* 1, 5-H(Q)], 7.65 [m br, 7-H(Q), 8-H(Q)], 7.4 [ddd, *J ca.* 8, 6.7 and 1, 6-H(Q)], 4.65 [m, C*H*(Pr)OH], 3.6 (s, CO_2CH_3), 3.2 (d, *J* 1, azir. 3α-H), 3.05 (d, *J* 1, azir. 3β-H), 3.0 (m, CH_3CH_2Q and CHO*H*), 1.75–1.4 (br m, $CH_3CH_2CH_2CHOH$), 1.45 (t, *J* 7.2, CH_3CH_2Q) and 1.00 (t, *J* 6.4, $CH_3CH_2CH_2$); δ_C 166.79 (CO_2CH_3), 159.97 [C=O(Q)], 155.24 [N=C(Q)], 145.79 [*C*N=C(Q)], 133.60, 126.62, 126.29, 125.75 [4 × CH(Q)], 120.40 [*C*C=O(Q)], 66.97 (CHOH), 53.24 (azir. C-2), 52.79 (CO_2CH_3), 43.07, 34.87, 26.91, 18.80 (CH_3CH_2Q, $CH_3CH_2CH_2$ and azir. C-3), 13.87 (CH_3CH_2Q) and 10.48 ($CH_3CH_2CH_2$); *m/z* (%) 345 (M^+, 15), 270 (27), 214 (25), 200 (20), 189 (40), 175 (27), 174 (100), 173 (73), 131 (72), 130 (51), 119 (30), 113 (21) and 76 (28).

Attempted isolation of the minor aziridine diastereoisomer **30** by flash chromatography of the ether-soluble material after trituration above, was unsuccessful. Signals in the NMR spectrum of crude aziridination product above were assigned to

this minor diastereoisomer **30** at δ_H 4.15 (dd, *J* 9.2 and 3.5, C*H*OH), 3.54 (s, CO_2CH_3), 3.15 (s, azir. 3α-H) and 3.07 (s, azir. 3β-H).

Aziridination of allylic acetate 24

The allylic acetate **24** (1.585 g) was added to a solution of QNHOAc **2** prepared from **1** (1 g) and LTA (2.46 g) in dry dichloromethane (16 cm^3) as described above. After reaction and work-up the crude product was chromatographed over silica using light petroleum–ethyl acetate (4:1) as eluent to give a clear oil (R_f 0.16) which, when triturated with cold dry diethyl ether (1 cm^3), gave a white solid. Crystallisation of this solid from ethanol gave *methyl* 1-(2-*ethyl*-4-*oxoquinazolin*-3-*yl*)-2-(1-*acetoxy*-3-*methylbutyl*)*aziridine*-2-*carboxylate* **31** (major diastereoisomer) (0.45 g, 21%) as a colourless solid, mp 89–91 °C (Found: C, 62.8; H, 6.8; N, 10.45. $C_{21}H_{27}N_3O_5$ requires C, 62.8; H, 6.8; N, 10.45%); ν_{max}/cm^{-1} 1740s, 1680s and 1600s; δ_H 8.05 [d, *J ca.* 8, 5-H(Q)], 7.44 [br m, 7-H(Q), 8-H(Q)], 7.27 [br m, 6-H(Q)], 5.7 (br d, *J* 9.1, C*H*OAc), 3.49 (s, CO_2CH_3), 3.22 (s, azir. 3α-H), 3.0 (br m, azir. 3β-H and CH_3CH_2Q), 1.99 (s, $CHOCOCH_3$), 1.67 (br m, CH_2CHMe_2), 1.31 (br t, *J* 6.9, CH_3CH_2Q) and 0.89 (br m, CH_3CHCH_3); δ_C 169.81, 165.88 (CO_2CH_3, $CHCOCH_3$), 159.55 [C=O(Q)], 155.87 [N=C(Q)], 145.66 [*C*N=C(Q)], 133.75, 126.58, 125.95, 125.85 [4 × CH(Q)], 120.76 [*C*C=O(Q)], 66.28 (*C*HOCOCH$_3$), 52.67 (CO_2CH_3), 52.20 (azir. C-2), 42.33 (azir. C-3 and CO_2CH_3), 39.63 (CH_3Pr^i), 26.93 (CH_3CH_2Q), 24.51 ($CHMe_2$), 23.32 ($CHOCOCH_3$), 21.16, 20.71 (CH_3CHCH_3) and 10.56 (CH_3-CH_2Q); *m*/*z* (%) 401 (M^+, 3), 175 (21), 174 (100), 173 (28), 131 (30) and 130 (26).

The minor aziridine diastereoisomer **32** was not eluted from the column; its presence in the crude reaction product [from the signal in its NMR spectrum at δ_H 3.12 (see below)] could not be confirmed because of signals from impurities but the ratio of **31**:**32** is >4:1.

Acetylation of aziridine alcohols 27 and 28

A mixture of aziridine alcohols **27** and **28** (4.3:1 respectively) obtained as described above from **1** (1 g), LTA (2.4 g) and allylic alcohol **22** (1.274 g) in dichloromethane (11 cm^3) was acetylated using the procedure given earlier for preparation of **8**. After work-up, the crude product (containing a 4.6:1 ratio of diastereoisomers **31**:**32** respectively, from comparison of the peaks in its NMR spectrum at δ 3.22 and 3.12) was chromatographed over silica using light petroleum–ethyl acetate (4:1) to give the major aziridine diastereoisomer (R_f 0.19) as colourless crystals (0.86 g, 41%), mp 89–91 °C (from ethanol) identical with the major aziridine diastereoisomer **31** from aziridination of allylic acetate **24** above.

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