Kinetic resolution of amines with enantiopure 3-*N*,*N*-diacylaminoquinazolin-4(3*H*)-ones

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The title compounds (DAQs) are chiral when the two *N*-acyl groups are different because of the absence of rotation around the *N*–*N* bond (a chiral axis). Enantiopure DAQs have been obtained by incorporation of a chiral centre in enantiopure form either into the substituent at the Q2-position or into one of the *N*-acyl groups, or into both, followed by separation of diastereoisomers. This separation is unnecessary in one case because conversion of the *N*-monoacylaminoquinazolinone (MAQ) into the DAQ is completely diastereoselective. Neither is separation of diastereoisomers necessary with 3-[*N*,*N*-di-(*S*)-2-acetoxypropanoylamino]-2-diphenylmethylquinazolin-4(3*H*)-one **37a**: this DAQ **37a** has its *N*–*N* bond rendered a chiral axis by the bias in its imide moiety wholly in favour of one *exo*/*endo* conformation.

The high *chemoselectivity* exhibited by *N*,*N*-diacetyl- or *N*,*N*-dibenzoylaminoquinazolinones in reaction with the less hindered of two secondary amines (pyrrolidine in the presence of 1 eq. of piperidine) has a *stereoselective* counterpart: reaction of the above enantiopure DAQs enantioselectively with racemic amines leading to kinetic resolution. Using 1 eq. of DAQ and 2 eq. of amine, both the derivatised and unreacted amine enantiomers are recovered with high enantiomeric excess (ee) (better than 90% ee in some cases). Some of the higher ees are found in the recovered amides where non-chemoselective attack on both *N*-acyl groups of the DAQ has occurred: from the opposite configurations of the amine component in the two amides and from the low enantiopurity of the recovered unreacted amine, reaction of each of the *N*-acyl groups with complementary enantiomers of the amine is occurring (parallel kinetic resolution).

Although higher ees are, in general, obtained using secondary amines, high ees are obtained in some cases using 1-phenylethylamine and, in particular, amino acid esters (valine and alanine).

The sense of enantioselectivity in the reactions of these DAQs with amines is controlled by the configuration of the *N*–*N* axis: replacing the Q group in an *N*-(*S*)-2-acetoxypropanoyl-*N*-acetyl-bearing DAQ by phthalimide, thus eliminating the *N*–*N* chiral axis, drastically reduces the level of kinetic resolution.

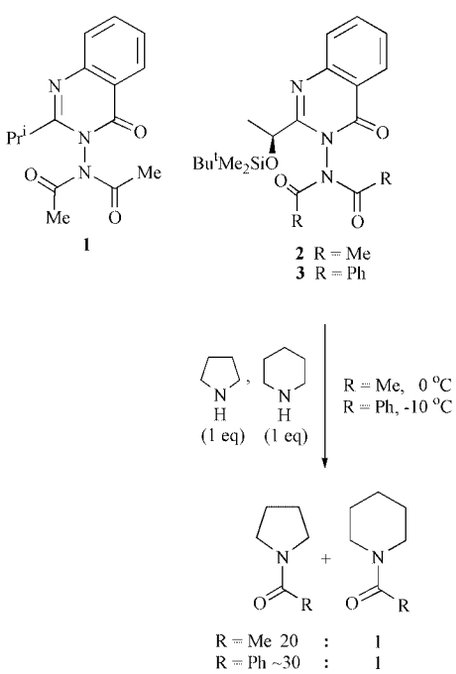
Introduction

3-*N*,*N*-Diacylaminoquinazolinones (DAQs) *e.g.* **1** are highly chemoselective acylating agents for primary amines in the presence of secondary amines and for the less sterically hindered of two secondary amines.[1]

We have improved on our previously obtained level of chemoselectivity, as measured by the preference for attack on pyrrolidine in preference to piperidine, by the use of 3-*N*,*N*-diacetylaminoquinazolinone **2**: reaction of the corresponding 3-*N*,*N*-dibenzoylaminoquinazolinone **3** at −10 °C with the same mixture of amines was even more chemoselective (Scheme 1).[2]

Of greater interest was whether this chemoselectivity had a stereoselective counterpart: would an enantiopure DAQ react selectively with one enantiomer of a racemic amine leading to kinetic resolution of that amine?[3] In DAQs having non-identical *N*-acyl groups, the *N*–*N* bond is a chiral axis, configurationally stable at room temperature, with the Q ring and the imide moiety contained in orthogonal planes. The presence of an additional chiral centre as in (racemic) DAQ **4**, allows the separation of diastereoisomers and, from the rate of conversion of one of the diastereoisomers into the other on heating in toluene, a barrier to *N*–*N* bond rotation $\Delta G^{\#}$ = 121 kJ mol^{-1} was calculated.[4]

To prepare the enantiopure DAQs required to test the stereoselectivity of their reactions with racemic amines, it was expedient to incorporate a chiral centre in enantiopure form into the DAQ and to separate the two enantiopure diastereoisomers obtained: the chiral centre could be located either in the Q2-substituent or in one of the *N*-acyl groups.



Scheme 1

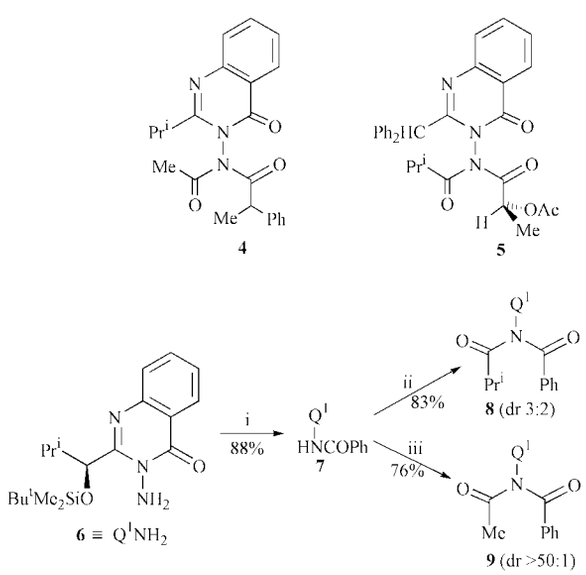
Previously we had shown that kinetic resolution of 1-phenylethylamine using the separated enantiopure diastereoisomers of DAQ **5** was feasible albeit with low enantioselectivity (55% ee and 40% ee, respectively).[4] In these resolutions, the sense of enantioselectivity was controlled by the configuration of the *N–N* bond since the two diastereoisomers of DAQ **5**, differing in configuration at this bond, reacted with different enantiomers of the amine. Subsequently, we found that acylations using DAQs were more chemoselective when applied to two *secondary* amines (*cf.* Scheme 1)[1] and so our expectation was that greater enantioselectivity would be obtained in kinetic resolutions of secondary amines using enantiopure DAQs.

In this paper we report the preparation of diastereopure and highly enantiopure DAQs **8a**, **8b**, **9**, **31a**, **31b** and **37a** and kinetic resolution experiments using 2- and 3-methylpiperidine, 1-phenylethylamine and amino acid esters with the above DAQs and with DAQs **24a–d** and **35**.

Results and discussion

3-(*N*-Acyl-*N*-benzoylamino)quinazolinones 8 and 9 (DAQ[1]s 8 and 9)

3-Aminoquinazolinone **6** (Q^1NH_2) was prepared as described previously from (L)-valine.[5] DAQ[1]s **8** and **9** were obtained by successive *N*-acylation of Q^1NH_2 **6** with benzoyl chloride and then with 2-methylpropanoyl chloride or acetyl chloride respectively (Scheme 2).



Scheme 2 *Reagents*: i, PhCOCl, pyr. CH_2Cl_2; ii, Pr^{i}COCl, pyr. CH_2Cl_2; iii, CH_3COCl, pyr. CH_2Cl_2.

Separation of DAQ[1] **8** into oily **8a** and crystalline **8b** diastereoisomers was achieved by kieselgel chromatography. An X-ray crystal structure previously determined for **8b**[3b] allowed assignment of configuration to the *N–N* axis and also revealed that the conformation of the imide moiety was the less common *exo*/*exo*† (*exo* carbonyl *cis* to Q^1). A striking feature of the crystal structure is the non-planarity of the imide with torsion angles of 24.4° and 9.7° for the N–N–C(=O) and N–C=O planes of 2-methylpropanoyl and benzoyl respectively and with the imide nitrogen pyramidalised ($\Sigma\theta$ = 352° for the sum of bond angles around nitrogen). With the benzoyl group also, the planes containing the carbonyl group and the benzene ring are inclined at an angle of 50°.

† DAQ[1]s **8b** and **9** are the only ones with *exo*/*exo* conformations for the imide moieties in their crystal structures compared with 12 structures having *exo*/*endo* imide conformations that we have obtained.

The barrier to interconversion of DAQ[1]s **8a** and **8b** was not quantified but was clearly lower than that separating the two diastereoisomers of DAQ **4** since interconversion between them took place slowly in chloroform solution at room temperature and was complete after heating at 60 °C for 2 h giving a 1 : 1 ratio of **8a** and **8b**.

By contrast, acetylation of *N*-benzoylaminoquinazolinone MAQ[1] **7** with acetyl chloride–pyridine was completely diastereoselective giving a crystalline sample of DAQ[1] **9** (76%). The X-ray crystal structure of DAQ[1] **9** (Fig. 1) was analogous

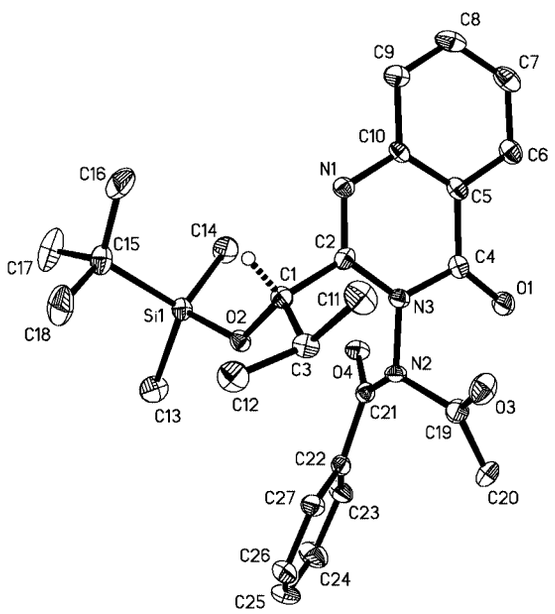


Fig. 1 Molecular structure of **9** showing the atom label scheme. Displacement parameters are shown at the 30% level. H atoms bonded to chiral centres are shown with dashed bonds, all other H atoms are omitted for clarity.

to that of DAQ[1] **8a**. However the conformation around the bond linking Q^1 to its C-2 chiral centre was different in the two structures.

Not only was DAQ[1] **9** the only diastereoisomer formed in the acetylation of MAQ[1] **7** but it also appeared to be the thermodynamically preferred since heating it at 130 °C for ~1 minute produced no additional signals from another diastereoisomer in its NMR spectrum.

The barrier to rotation around the *N–N* bond in MAQ[1] **7** is, as expected, lower than that in DAQ[1] **8a** and does not allow separation of diastereoisomers at room temperature.[6] However, the NMR spectrum of MAQ[1] **7** at room temperature shows the presence of two doublets at δ 5.08 and 6.03, both J = 7 Hz (ratio 7 : 1) presumably from Pr^{i}C*H*OSi in diastereoisomers arising from *N–N* bond rotation at a rate which is slow on the NMR timescale. When a crystalline sample of this MAQ[1] **7** was dissolved in $CDCl_3$ at −50 °C and an ^{1}H NMR spectrum measured at this temperature,‡ this Pr^{i}C*H*OSi signal appeared as two doublets (δ 4.68 and 4.43 ppm) now ratio 1 : 1.5 and, significantly, with different J values (2 and 7 Hz respectively). The disparate concentrations and J values for the species present in the spectra run at −50 °C and 27 °C and the complex changes in the spectra run at intermediate temperatures suggest the presence of a second temperature-dependent process associated with restricted rotation within the Q^1-2 substituent.

An X-ray crystal structure (Fig. 2) of MAQ **11** (Scheme 3), prepared from the corresponding 3-aminoquinazolinone **10**,

‡ It is likely that signals from the minor *N–N* bond rotamer are absent from this spectrum: enrichment of the major *N*-rotamer (second-order asymmetric transformation) and its non-interconversion with the minor *N*-rotamer at −50 °C has been demonstrated with another MAQ.[26]

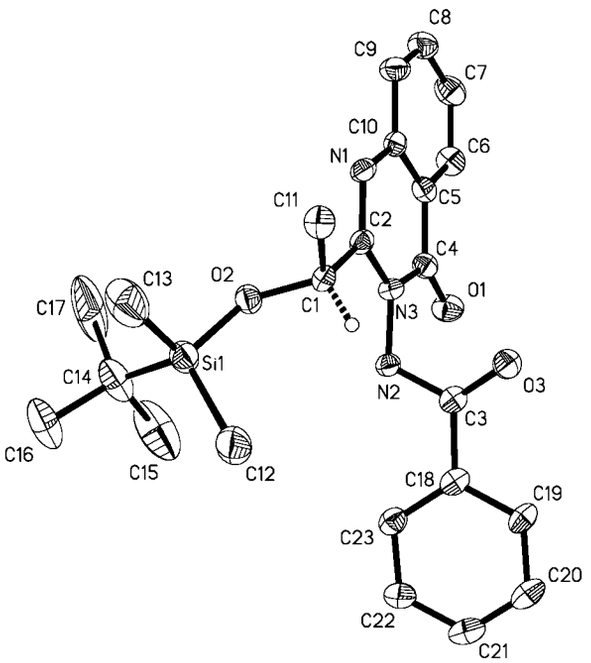
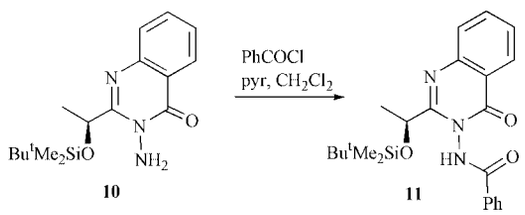


Fig. 2 Molecular structure of **11**. Details as for Fig. 1.



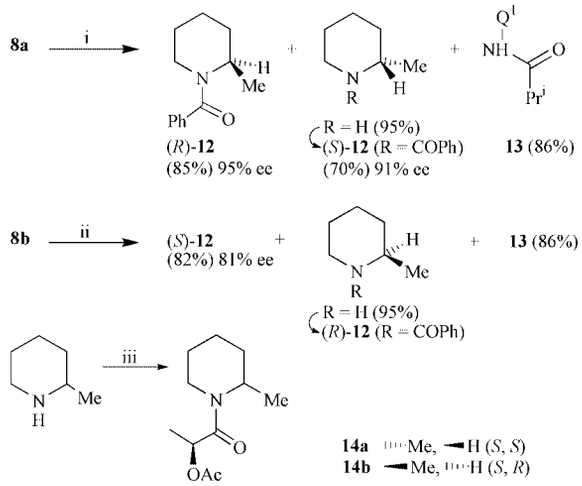
Scheme 3

shows the benzoyl group with its carbonyl *exo* as expected. Even in MAQ **11** there is a substantial deviation of the amide group from planarity (QN–CO torsion angle 14°): the benzene ring, however, is now more nearly coplanar with the carbonyl group (torsion angle, 6.6°).

Reactions of DAQ[1]s 8a, 8b and 9 with racemic amines. Reaction of oily DAQ[1] **8a** (1 eq.) with 2-methylpiperidine (2 eq.) in dichloromethane at −20 °C for 2 h and then at 5 °C for 12 h takes place highly enantioselectively. Unreacted 2-methylpiperidine was extracted with aqueous hydrochloric acid and the freed amine converted into *N*-benzoylamide **12** $[a]_D = +30$ (*c* 0.64, $CHCl_3$). The benzoylamide **12** formed in the reaction mixture was separated from the only other product MAQ[1] **13** (Scheme 4) by chromatography and had $[a]_D = -31.4$ (*c* 0.8, $CHCl_3$).

The absolute configurations and ees given in Scheme 4 are based on the specific rotation of a sample of (*S*)-*N*-benzoyl-2-methylpiperidine $[a]_D = +32.9$ (*c* 0.8, $CHCl_3$), prepared from (*S*)-2-methylpiperidine, $[a]_D = 8.9$ (*c* 2, EtOH) itself obtained from the racemic amine by resolution using (*R*)-mandelic acid.[7] The enantiopurity of this (*S*)-2-methylpiperidine was independently confirmed by its derivatisation with (*S*)-2-acetoxypropanoyl chloride and by comparison of the NMR spectrum of the product **14a** with the mixture of diastereoisomers formed from racemic 2-methylpiperidine: at 400 MHz and 50 °C, the OCOCH_3 signals from the two diastereoisomers in this mixture were completely separated.

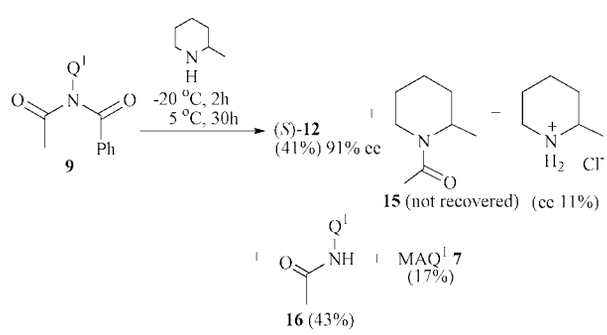
A quantitative measure of the enantioselectivity in reaction of DAQ[1] **8a** with 2-methylpiperidine was obtained from its rate of reaction with each of the separated enantiomers of this amine, $k_1(R)$ and $k_2(S)$. From the rotation values for the separated enantiomers, the faster reacting (*R*) was of 95% ee and the ratio $k_1(R) : k_2(S)$ was at least 27 : 1.



Scheme 4 *Reagents and conditions*: i, 2-Methylpiperidine (2 eq.), −20 °C, 2 h then 5 °C, 12 h; ii, 2-methylpiperidine (2 eq.), −20 °C, 2 h then 5 °C, 30 h; iii, (*S*)-$CH_3CH(OAc)COCl$, pyr. CH_2Cl_2.

Reaction of the crystalline DAQ[1] **8b** with 2-methylpiperidine was considerably slower than for its diastereoisomer above (Scheme 4). Significantly, it was the other amine enantiomer which reacted preferentially giving (*S*)-*N*-benzoylamide **12** (81% ee). Since DAQ[1]s **8a** and **8b** have the same configuration for their chiral centres but opposite configurations for their chiral *N*–*N* axes, it is the latter which control the sense of enantioselectivity.

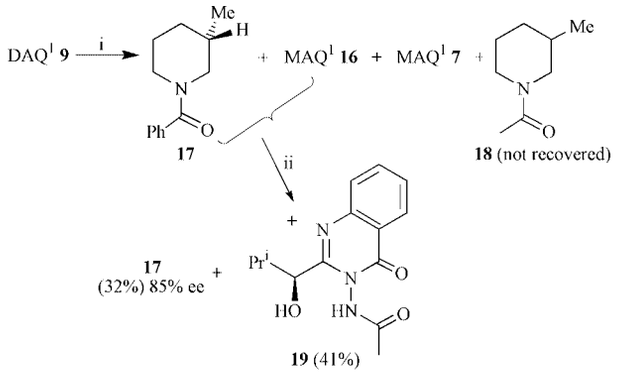
Although the oily DAQ[1] **8a** gives high enantioselectivity in its reaction with 2-methylpiperidine, its separation from DAQ[1] **8b** requires careful chromatography. By contrast, DAQ[1] **9** is formed completely diastereoselectively in good yield (see earlier). However, its reactions, unlike those of DAQ[1] **8a**, are not chemoselective: reaction with 2-methylpiperidine (Scheme 5) gave a mixture of *N*-benzoyl- and *N*-acetyl- amides



Scheme 5

12 and **15** together with their complementary MAQ[1]s **16** and **7**. From this ratio of MAQ[1]s **16** and **7**, the ratio of amides **12** : **15** formed in the crude reaction mixture was 2.5 : 1. This ratio was confirmed from the NMR spectrum of the crude reaction product at 400 MHz and −40 °C: interpretation of the spectrum at this low temperature is facilitated by separation of the broadened signals for the amides **12** and **15** into two sets of signals from the component N–CO bond rotamers.

The *N*-benzoylamide **12** (41%) isolated by chromatography was found to be the (*S*)-enantiomer of 91% ee by comparison with an authentic sample. Although the *N*-acetylamide **15** was not isolated, the unreacted 2-methylpiperidine recovered as its hydrochloride salt was found to be of low enantiopurity (11% ee) by comparison of its specific rotation with that of an enantiopure sample. It appears that the two imide carbonyl groups are reacting with complementary enantiomers of the racemic amine *i.e.* parallel kinetic resolution is occurring[8] with the two acyl groups of the imide behaving pseudoenantiotopically towards the reacting amine.

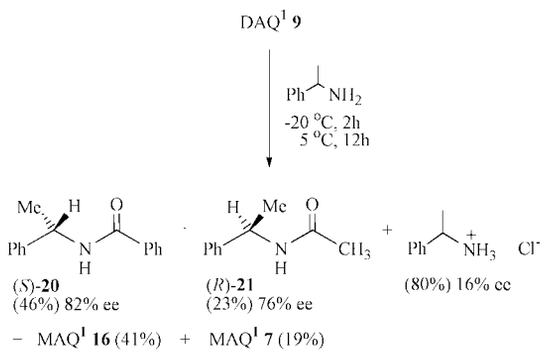


Scheme 6 *Reagents and conditions*: i, 3-Methylpiperidine (2 eq.), −20 °C, 2 h then 5 °C, 30 h; ii, TBAF, THF.

Reaction of DAQ[1] **9** with racemic 3-methylpiperidine was also studied (Scheme 6). As with 2-methylpiperidine, attack on both imide carbonyl groups occurs. Chromatography separated MAQ[1] **7** but amide **17** and MAQ[1] **16** were co-eluted. After desilylation of MAQ[1] **16** in this mixture by treating with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran, separation by flash chromatography gave *N*-benzoyl-3-methylpiperidine **17** (32%) whose (*S*)-configuration and enantiopurity (85% ee) were based on a sample prepared by benzoylation of (*R*)-3-methylpiperidine.

(*R*)-3-Methylpiperidine was obtained from the racemate by fractional crystallisation of the tartrate salts.[9] From the ratio of MAQ[1]s **16** and **7** in the crude reaction mixture, the ratio of *N*-benzoyl- to (unrecovered) *N*-acetyl-2-methylpiperidine **17** : **18** was 3 : 1.

In the reaction of DAQ[1] **9** with 1-phenylethylamine (Scheme 7) both amides **20** and **21**, resulting from attack on



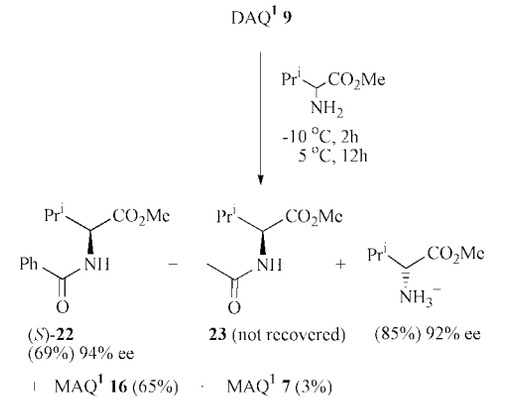
Scheme 7

imide benzoyl and acetyl groups respectively, were recovered and shown to have resulted from reactions of complementary enantiomers of the amine. As in Scheme 6, the recovered unreacted amine was of low enantiopurity (16% ee).

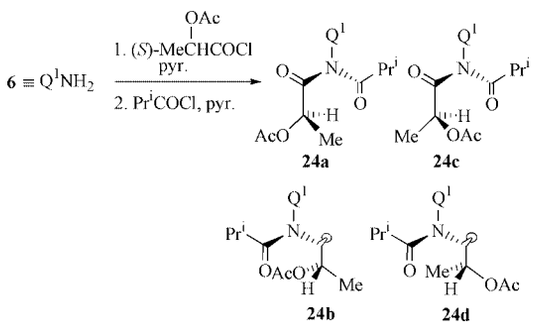
In contrast to the non-chemoselectivity in reactions of DAQ[1] **9** in Schemes 5–7, racemic valine methyl ester reacts highly chemoselectively with the benzoyl group and gave amide **22** of high enantiopurity (94% ee) by comparison with the rotation of an authentic sample (Scheme 8).

From the ratio of MAQ[1]s **16** and **7** isolated by chromatography, the chemoselectivity is 21 : 1 favouring attack on the benzoyl group.

Reaction of DAQ[1]s 24a–d with amines. In a previous paper[5] we described the preparation of DAQ[1]s **24a**–**d** by reaction of 3-aminoquinazolinone **6** (Q^1NH_2) with (*S*)-2-acetoxypropanoyl chloride followed by 2-methylpropanoyl chloride (Scheme 9). Considerable epimerisation at the (*S*)-2-acetoxypropanoyl centre occurs in the second *N*-acylation step, resulting in the formation of DAQ[1]s **24a** and **24d**, (*R*)-configured at this centre as well as **24b** and **24c**.



Scheme 8



Scheme 9

All of these four diastereoisomeric DAQ[1]s react completely chemoselectively with 1-phenylethylamine at the 2-acetoxypropanoyl group except DAQ[1] **24b** (Scheme 10).

The enantioselectivity arising from attack of the amine on the 2-acetoxypropanoyl group was quantifiable directly by NMR spectroscopy after chromatography, being equivalent to the diastereoisomer excess (de) of the amide product and measurable by comparison with spectra of authentic samples of these diastereoisomers; control experiments confirmed that no change in de occurred on chromatography.

The relative rates of reaction of DAQ[1]s **24a–d** (and other DAQs in this paper) with amines have been used to probe into the mechanism and to rationalise the stereochemistry of these acylations and will be discussed elsewhere. For the present it is noteworthy that, of these four DAQ[1]s, **24b** has the largest torsion angle between N–N–C(=O) and N–C=O bonds for the 2-methylpropanoyl (25.1°) and also the largest disparity in N–C(=O) bond lengths for 2-methylpropanoyl and 2-acetoxypropanoyl groups (1.525 Å *vs.* 1.424 Å) in the crystal structure.[5]

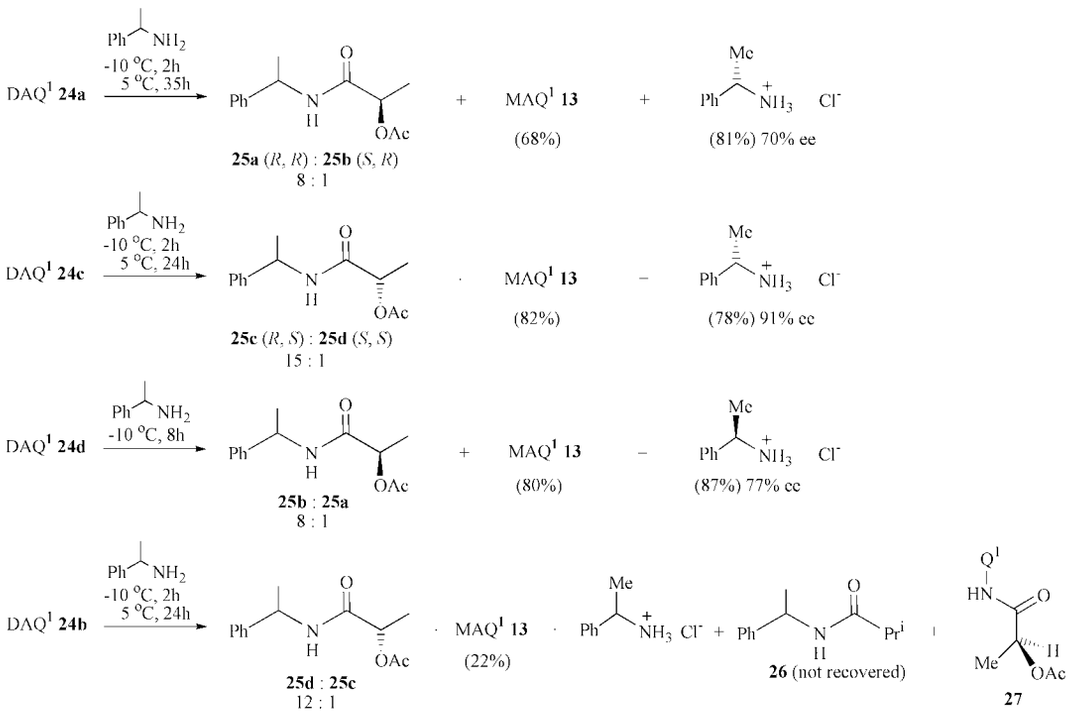
In all cases in Scheme 10, the sense of enantioselectivity is controlled by the configuration of the *N*–*N* axis. Thus DAQ[1]s **24b** and **24d** which are homochiral at their *N*–*N* axes reacted with the (*S*)-enantiomer of 1-phenylethylamine and likewise DAQ[1]s **24a** and **24c** reacted with the (*R*)-enantiomer of this amine.

2-Methylpiperidine and 2-propylpiperidine (coniine) reacted with DAQ[1] **24c**, the fastest reacting diastereoisomer of DAQ[1]s **24a–d**, highly chemo- and enantioselectively (Scheme 11).

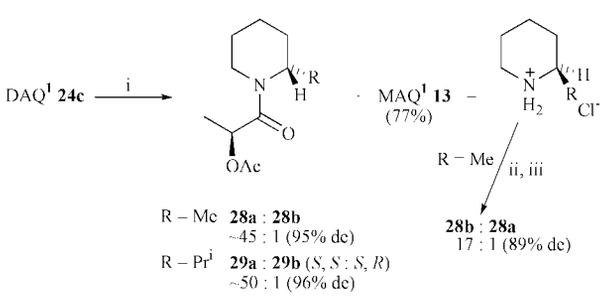
(*R*)-(−)-2-Propylpiperidine hydrochloride has $[\alpha]_D = -7.3$ (*c* 0.33, ethanol).[10] Since the recovered 2-propylpiperidine enantiomer in Scheme 11 has $[\alpha]_D = -6.7$ (*c* 0.42, ethanol) (ee 89%), the major reacting enantiomer is (*S*) and amide **29a** has the (*S*,*S*)-configuration *i.e.* 2-propyl- and 2-methylpiperidine react with DAQ[1] **24c** in the same enantiosense.

3-[*N*-2-(2*S*)-Acetoxypropanoyl-*N*-acetylamino]-2-diphenylmethylquinazolinones 31a and 31b (DAQ[2]s 31a and 31b)

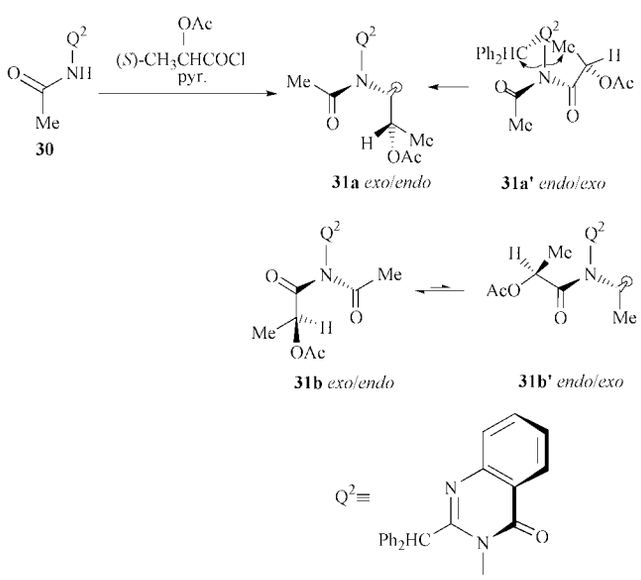
Further acylation of MAQ[2] **30** with (*S*)-2-acetoxypropanoyl chloride gave a 1 : 1 mixture of diastereoisomers **31a** and



Scheme 10



Scheme 11 *Reagents and conditions*: i, 2-Methyl- or 2-propyl-piperidine, −10 °C, 2 h then 5 °C 24 h; ii, NaOH–H_2O; iii, (*S*)-$CH_3CH(OAc)COCl$, pyr.



Scheme 12

31b (Scheme 12) which were easily separable by flash chromatography as a result of their widely differing R_f values (ΔR_f *ca.* 0.2 using light petroleum–ethyl acetate 1 : 1). Both crystal structures for these DAQ²s (Fig. 3a,b) have the same *exo*/*endo* conformation (*exo* has 2-acetoxypropanoyl carbonyl oxygen *cis* to Q²) for their imides but, as expected, opposite configurations for their *N*–*N* chiral axes.

Because there is no additional spectator chiral centre in DAQ²s **31a** and **31b** as there is in DAQ¹s **24a**–**d**, the extent of epimerisation at the 2-acetoxypropanoyl chiral centre occurring in their preparation, if any (*cf.* Scheme 9), is not apparent from the NMR spectra of the products; any such epimerisation will result in loss of their enantiopurity. In fact, the space group of DAQ² **31a** in the crystal structure (Fig. 3a) was determined to be *P*21/*n* which indicates that the molecule in this crystal is racemic. Although some epimerisation in the formation of DAQ **31a** (and probably DAQ **31b**) does occur, therefore, the extent must be very small and is not revealed in an enantiopurity assay (see below).

By analogy with the conformational equilibria present in DAQ¹s **24a**–**d**, DAQ² **31a** would be expected to have the same single *exo*/*endo* conformation for its imide in solution present in the crystal structure Fig. 3a whereas DAQ **31b** would be present as an equilibrium mixture of *exo*/*endo* and *endo*/*exo* forms. Thus, in the alternative *endo*–*exo* form of DAQ² **31a**, **31a**′, there would be an unfavourable interaction between the CH(OAc)-CH_3 and Ph_2CH groups but this would be absent in the case of the corresponding DAQ² **31b**′.

Some estimate of the likely ratio of *exo*/*endo*–*endo*/*exo* imide conformations present in **31b** can be arrived at from comparison with DAQ¹ **24c** since both have the same configurations at their chiral axes and $CH(OAc)CH_3$ chiral centres albeit with different Q2-substituents and second *N*-acyl groups. At equilibrium, the *exo*/*endo*–*endo*/*exo* ratio for DAQ¹ **24c** favours the former by 2.7 : 1 at −50 °C. Since the acetyl methyl group of DAQ² **31b** is clearly smaller than the isobutanoyl group of DAQ¹ **24c** and since the smaller this alkyl group the more likely it is to be located in the *exo*-position (*i.e.* with its carbonyl *endo*), the equilibrium position for the imide in DAQ² **31b** would be expected to favour the *exo*/*endo* conformation by a ratio considerably greater than 2.7 : 1.

The NMR spectra of DAQ²s **31a** and **31b** were broadly in line with the expectations above: the spectrum for DAQ² **31a** shows sharp signals for *e.g.* Ph_2CH and $CH(OAc)CH_3$ protons and was unchanged when run at low temperature (−50 °C). For DAQ² **31b**, both the corresponding proton signals were slightly broadened and, when the spectrum was run at 0 °C, −10 °C and

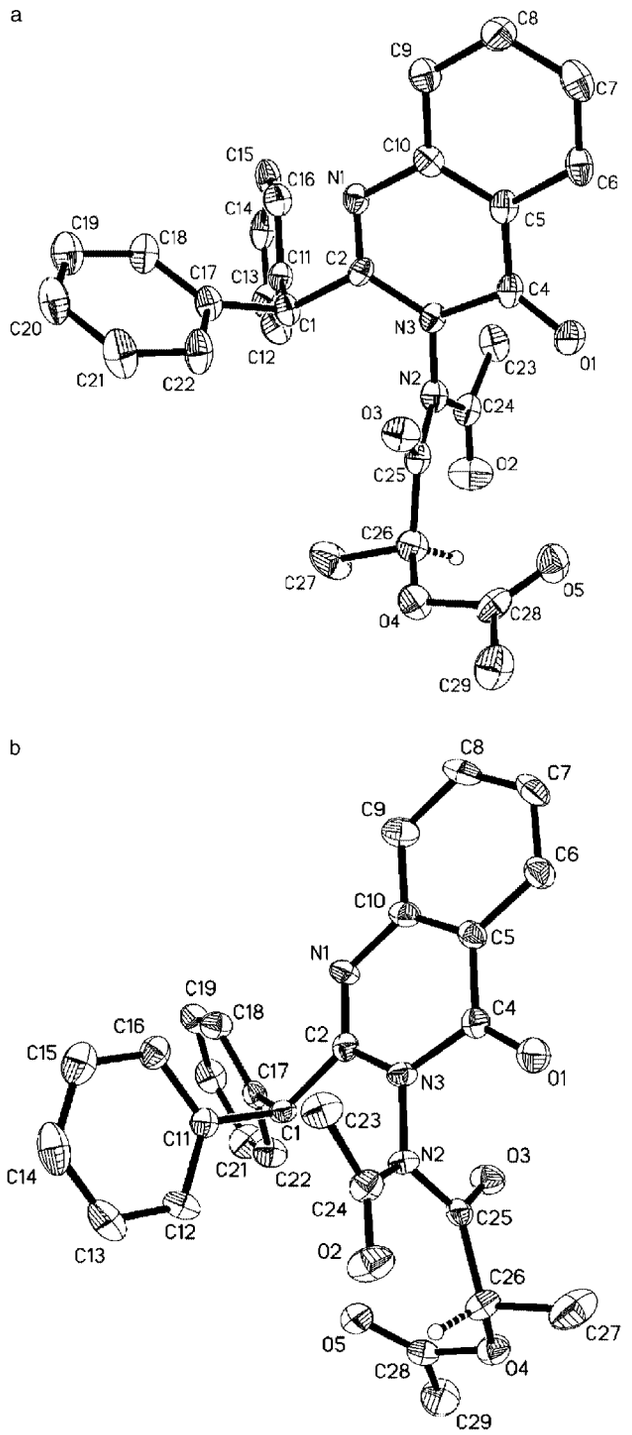
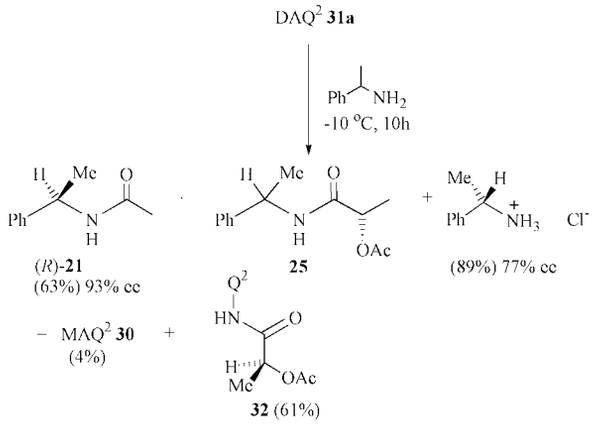


Fig. 3 a and b. The molecular structures of **31a** and **31b** respectively. Details as for Fig. 1.

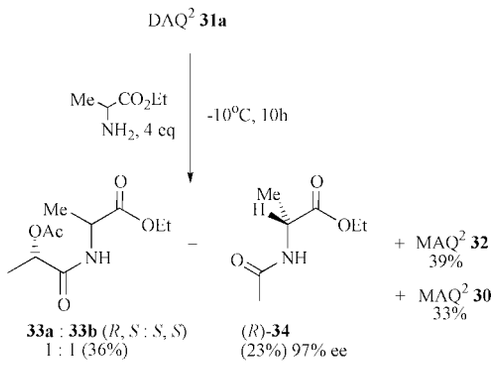
−40 °C, showed further broadening then sharpening as the temperature was lowered. At the lower temperature, however, separated signals assignable to the expected minor *endo*/*exo* conformation were not visible. That the major conformation in solution was the *exo*/*endo* **31b** was supported by the chemical shift of the C*H*(OAc)CH_3 proton at δ 6.07, consistent with its deshielding by the *endo* acetyl carbonyl oxygen.[5]

Reaction of DAQ²s 31a and 31b with amines. Reaction of DAQ² **31a** with 1-phenylethylamine was highly chemo- and stereo-selective (Scheme 13).

Reaction of DAQ² **31a** with alanine ethyl ester, however, showed little chemoselectivity and the two amides were obtained with very different stereoselectivities. Thus, using four equivalents of the amine, whereas the *N*-2-acetoxypropanoyl amide **33** was a 1 : 1 mixture of diastereoisomers, the *N*-acetyl-amide **34** was of high enantiopurity (97% ee) based on its specific rotation (Scheme 14).



Scheme 13



Scheme 14

The reaction in Scheme 14 was repeated using excess pure (L)-alanine ethyl ester and the amide isolated was shown to be diastereopure **33a** by NMR spectroscopic comparison with an authentic sample. Thus DAQ² **31a** is of high enantiopurity and little epimerisation at the 2-acetoxypropanoyl centre takes place in its formation from MAQ² **30** (*cf.* above).

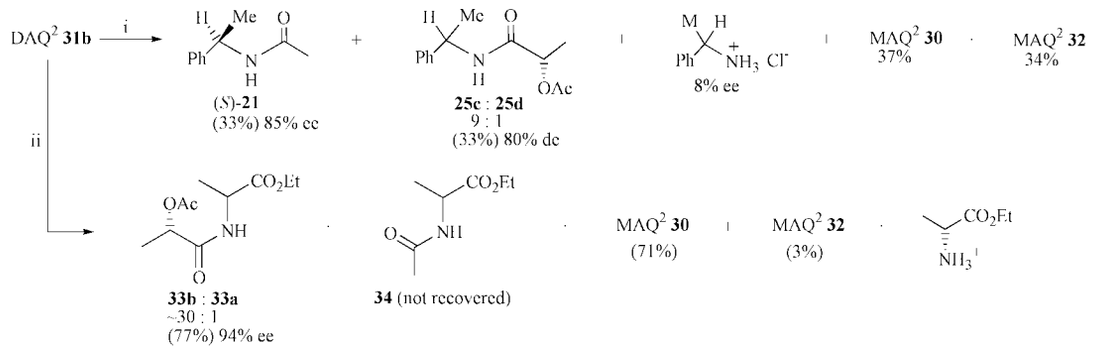
Diastereoisomeric DAQ² **31b** exhibits very different chemo- and stereo-selective behaviour to that of DAQ² **31a** with 1-phenylethylamine and alanine ethyl ester (Scheme 15). Thus the reaction with 1-phenylethylamine is now non-chemoselective but amides **21** and **25** are formed with 85% ee and 80% de respectively. Alanine ethyl ester reacted almost completely chemoselectively and the *N*-2-acetoxypropanoyl amide **33** was obtained with 94% de.

As yet, an explanation for these extraordinary differences in stereochemistry and chemo- selectivity is not available: following the reactions by NMR spectroscopy showed that DAQ² **31b** reacted at least 500 times faster with 1-phenylethylamine than DAQ² **31a**.

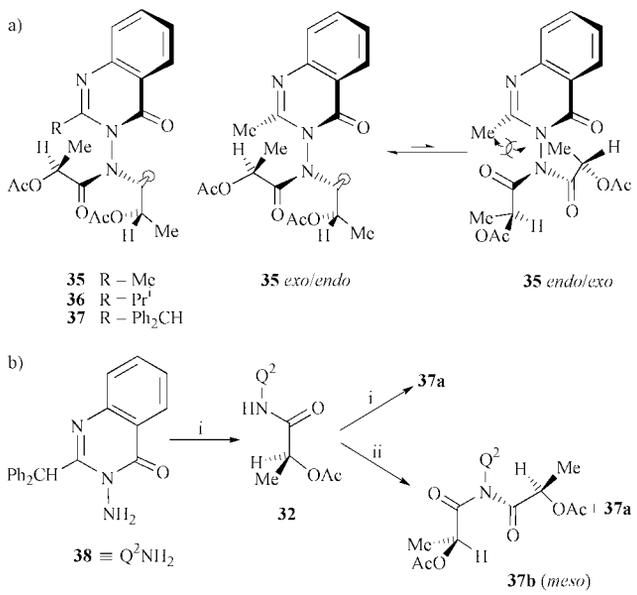
3-[*N*,*N*-Bis((*S*)-acetoxypropanoyl)amino]-2-alkylquinazolinones 35, 36 and 37 (DAQs 35, 36 and 37)

The preparation of DAQs **35** and **36** from reaction of the corresponding 3-aminoquinazolinones with excess (*S*)-2-acetoxypropanoyl chloride was also described previously (Scheme 16a). Although these DAQs had significant optical rotations, some epimerisation at both (*S*)-2-acetoxypropanoyl chiral centres, leading to partial racemisation, could not be ruled out particularly since some *meso*-isomer was isolated from the reaction mixture in the case of DAQ **35**.

In DAQ **35** also, there was a conformational bias within the imide moiety with the expected *exo*/*endo* ⇌ *endo*/*exo* equilibrium in Scheme 16a wholly on the **35** *exo*/*endo* side.



Scheme 15 *Reagents and conditions*: i, 1-Phenylethylamine −10 °C, 30 min, CH_2Cl_2; ii, alanine ethyl ester, −10 °C, 6 h, CH_2Cl_2.



Scheme 16 *Reagents*: i, (*S*)-$CH_3CH(OAc)COCl$, pyr. CH_2Cl_2; ii, *rac*-$CH_3CH(OAc)COCl$, pyr. CH_2Cl_2.

It was proposed that as for DAQ's a–d this bias arose from a high conformational preference within the 2-acetoxypropanoyl groups which led to the steric interaction shown between the methyl group in the 2-acetoxypropanoyl and that on the Q2-position thus destabilising the **35** *endo*/*exo* conformation. This conformational bias in DAQ **35** is important because the *N*–*N* bond is now clearly a chiral axis whose presence is required for high levels of enantioselectivity in reaction with racemic amines§ (see below).

DAQ² **37a** was prepared in good yield from the 3-aminoquinazolinone **38** by *N*,*N*-diacylation with (*S*)-2-acetoxypropanoyl chloride *via* the isolable MAQ² **32** (Scheme 16b). Conversion of MAQ² **32** into DAQ² **37a** was unaccountably faster than the analogous reaction forming DAQ² **35** and, importantly, no *meso* isomer **37b** was present in the crude reaction mixture. An authentic sample of *meso* DAQ² **37b** was obtained by reacting MAQ² **32** with *rac*-2-acetoxypropanoyl chloride; the ratio of **37a** : *meso* **37b** formed in this second *N*-acylation was 10 : 1 *i.e.* this reaction was highly diastereoselective. The NMR spectrum of *meso*-DAQ² **37b** showed one broad signal for the C*H*OAc proton at δ 5.45 which separated at −44 °C into two broadened signals at δ 4.9 and 5.8 (ratio 1 : 1): this *meso*-isomer **37b** would be expected to be present as a 1 : 1 mixture of the *exo*/*endo* and *endo*/*exo* conformers as is the analogous *meso*-DAQ **35**.[5]

§ If attack by the amine on both *exo* carbonyl groups of either *exo*/*endo* and *endo*/*exo* or *exo*/*exo* conformations of DAQ **35** were to occur, little enantioselectivity would be expected if the effect of the chiral centres on the latter was small as is believed to be the case.

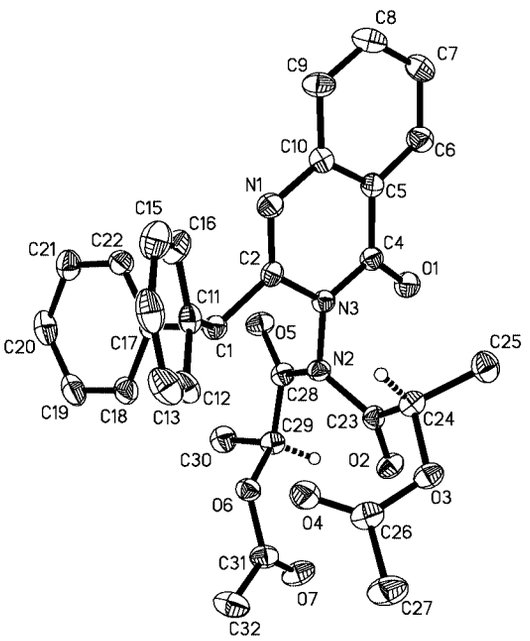


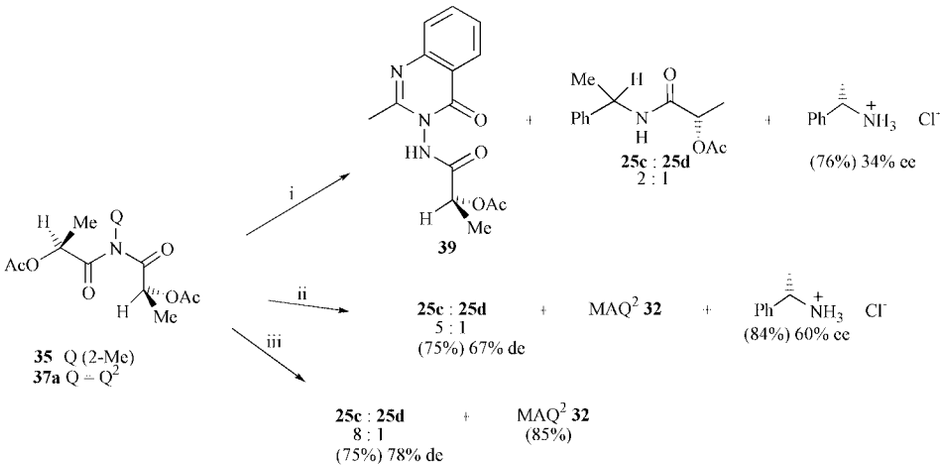
Fig. 4 The molecular structure of **37a**. Details as for Fig. 1.

In the X-ray crystal structure of DAQ² **37a** (Fig. 4) the imide is present in the usual *exo*/*endo* conformation but the torsion angle ϕ between the C=O and C–OAc bonds in the *exo*-oriented COCH(OAc)Me group (130.9°) is very different not only from the corresponding ϕ in DAQ **35** (20.8°) but also from all values for ϕ in other DAQ crystal structures containing this $COCH(OAc)CH_3$ group that we have determined.¶

The ^{1}H NMR spectrum of DAQ² **37a** also differed from those of DAQs **35** and **36** in showing broadening of the two C*H*OAc proton signals at δ 4.88 and 5.80 ppm which sharpened at −50 °C (δ 4.54 and 6.10 ppm); small additional signals also appeared at δ 4.40, 5.07 and 6.07 ppm (~20% of major signals) (the spectra of DAQs **35** and **36** were unchanged when run at −50 °C). Although the process giving rise to this signal broadening in DAQ² **37a** is not known it may arise from the abnormal ϕ value in the crystal structure above.‖ In any event, it does not appear that DAQ² **37a** is undergoing fast *exo*/*endo*–*endo*/*exo* interconversion at room temperature.

¶ For the *endo*-oriented $COCH(OAc)CH_3$ group in DAQ² **37a** ϕ is in the more normal range (37.6°).

‖ Possibly there is an equilibrium in solution between the conformation having the normal value of φ as in DAQ **37a** and that in the crystal structure.

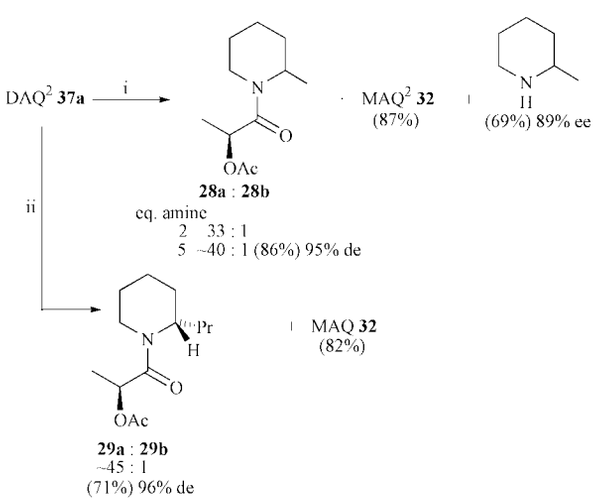


Scheme 17 *Reagents and conditions*: i, **35**, $PhCH(CH_3)NH_2$, CH_2Cl_2, −20 °C, 2 h the 0 °C, 10 h; ii, **37a** $PhCH(CH_3)NH_2$ (2 eq.), CH_2Cl_2, −20 °C, 2 h; iii, **37a**, $PhCH(CH_3)NH_2$, (5 eq.), CH_2Cl_2, −20 °C, 2 h.

Reactions of DAQs 35 and 37a with amines. The reaction products of DAQs **35** and **37a** with 1-phenylethylamine are given in Scheme 17.

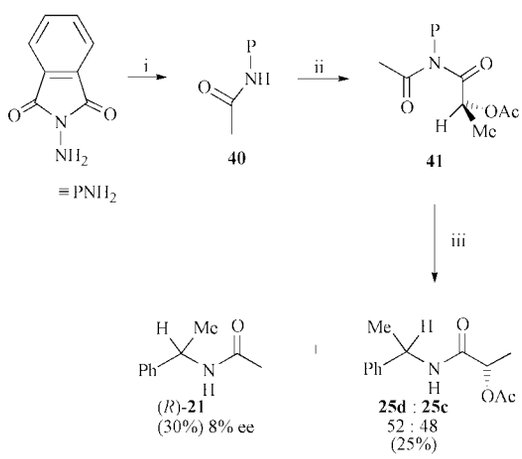
At least part of the inferior diastereopurity of the product of reaction with DAQ **35** can be ascribed to its enantioimpurity. Thus its reaction with excess (*S*)-1-phenylethylamine under the conditions in Scheme 17 gave an 8 : 1 ratio of diastereoisomers of amide **25** that must have resulted from partial epimerisation at both chiral centres in preparation of DAQ **35**. By contrast, reaction of DAQ **37a** with excess (*R*)-1-phenylethylamine using the conditions in Scheme 17 gave only **25c** the (*R*,*S*)-diastereoisomer of amide **25** confirming that DAQ **37a** is enantiopure.

Although the level of enantioselectivity in reaction of primary amines (1-phenylethylamine) with DAQ^2 **37a** is modest (even with 5 eq. of amine), with secondary amines 2-methylpiperidine and 2-propylpiperidine (coniine) the enantioselectivity is excellent (Scheme 18). Assignment of configuration to the major product **29a** was made by NMR spectroscopic comparison with the sample prepared previously (Scheme 11).



Scheme 18 *Reagents and conditions*: i, 2-Methylpiperidine, CH_2Cl_2, −20 °C, 3 h then 0 °C, 12 h; ii, 2-propylpiperidine (4 eq.), CH_2Cl_2, 5 °C, 16 h.

To assess the contribution of the 2-acetoxypropanoyl chiral centres to the stereoselectivities in reactions of DAQs containing this group, we prepared *N*-[(*S*)-2-acetoxypropanoyl]-*N*-acetylaminophthalimide (DAP) **41** and reacted it with 1-phenylethylamine (Scheme 19). At −10 °C, reaction took place on both acetyl and 2-acetoxypropanoyl groups (ratio 1.2 : 1 respectively) but the enantioselectivity/diastereoselectivity in each case was minimal.



Scheme 19 *Reagents and conditions*: i, CH_3COCl, pyr. CH_2Cl_2, RT, 24 h; ii, (*S*)-$CH_3CH(OAc)COCl$, pyr. CH_2Cl_2; iii, $PhCH(Me)NH_2$, CH_2Cl_2, 6 h, −10 °C.

Repetition of this experiment but using excess pure (*S*)-phenylethylamine gave only amide **25d** confirming that DAP **41** was enantiopure.

Conclusions

All of the DAQs examined in this work react enantioselectively with the limited range of racemic amines used. Even under the conditions of stoichiometry (1 eq. DAQ–2 eq. amine) enantioselectivities sometimes >90% are obtained in both the derivatised amine enantiomer (amide) and in the recovered enantiomer. Where reaction of the amine with the DAQ is non-chemoselective and amides derived from both the DAQ imide carbonyl groups are formed (and must be separated), each of these carbonyl groups reacts preferentially with complementary enantiomers of the amine leading to enhanced enantiopurity in the isolated amides (parallel kinetic resolution). By this means even 3-methylpiperidine was recovered with 85% ee as the *N*-benzoyl derivative by reaction with DAQ^1 **9**.

The sense of enantioselectivity in reactions of all these DAQs with amines is determined by the configuration of the *N*–*N* bond: the very low levels of enantioselectivity obtained from reaction of the *N*,*N*-diacylphthalimide **41** with 1-phenylethylamine confirms that the configuration of the chiral centre is not important for the high levels of kinetic resolution achieved.

The requirement for separation of the enantiopure diastereoisomeric DAQs used in these kinetic resolutions is obviated in the case of DAQs **9** and **37a** because their formation is completely diastereoselective.

Experimental

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-250 spectrometer at 250 MHz and 63 MHz respectively at room temperature in deuterochloroform ($CDCl_3$) unless stated otherwise. ^{1}H NMR spectra at 400 MHz and ^{13}C at 100.6 MHz were recorded on a Bruker DRX spectrometer at room temperature in deuterochloroform unless otherwise indicated. Infra-red (IR) spectra of crystalline compounds were determined using Nujol mulls and of liquids either in dichloromethane or chloroform solutions, or neat, on a Perkin–Elmer 298 spectrophotometer. Melting points (mps) were determined with a Kofler hot stage and are uncorrected. Mass spectra were determined using a Kratos Concept mass spectrometer using electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) and high resolution masses (accurate masses) were obtained by peak-matching using perfluorokerosene; except for the molecular ion M^+ or MH^+, only peaks ≥20% of the base peak are given. Some mass spectra were also determined using a Micromass Quattro lc (MQlc) spectrometer with ionisation by Electrospray and operation *via* "open Access" software with an autosampler, Elemental analysis was carried out by CHN Analysis, Wigston, Leicester. Optical rotations were determined on a Perkin–Elmer 341 polarimeter at 589 nm and are given in 10^{-1} deg cm^2 g^{-1}. Flash chromatography was carried out using silica gel C60 (35–70) (supplied by Merck & Co.) and kieselgel chromatography using kieselgel 60, 230–400 mesh. TLC was conducted on aluminium plates pre-coated with a 0.2 mm layer of silica, manufactured by Merck & Co. Purification by Chromatotron (Harrison Research California) was performed using model 7924T with circular and kieselgel 60 (PF_{254}) and also kieselgel 60 (GF_{254}) silica plates supplied by Merck & Co. Light petroleum refers to the fraction (bp 60–80 °C).

Pyridine, 2-methylpiperidine and 3-methylpiperidine were purified by distillation from calcium hydride. Ether refers to diethyl ether and was sodium dried prior to use. Tetrahydrofuran (THF) was distilled from sodium and benzophenone immediately prior to use. Routine drying of organic solutions was carried out using magnesium sulfate unless otherwise indicated. Solvent removal under reduced pressure means using a Buchi rotary evaporator and a water pump (~12 mmHg) unless otherwise indicated. *n*-Butyllithium (1.6 M) was used as received from Aldrich Chemical Co. Lead tetraacetate (LTA) (damp with acetic acid) was dried prior to use under vacuum using an oil pump (~1 mmHg) for 15 min. All reaction products were dried using an oil pump (~1 mmHg) prior to spectroscopic analysis. Yields are isolated ones unless otherwise stated.

General procedure I for the mono-*N*-acylation of 3-amino-quinazolinones

To the 3-aminoquinazolinone dissolved in dry dichloromethane (3 cm^3 g^{-1}) containing dry pyridine (1.5 mol eq.) was added the acid chloride (1.5 mol eq.) dropwise with stirring. After stirring for 12 h at room temperature, more dichloromethane was added (3 cm^3 g^{-1}) and the solution washed with saturated aqueous sodium hydrogen carbonate, then water, dried and the solvent removed under reduced pressure. The product was purified by crystallisation or chromatography as indicated.

3-Benzoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methyl-propyl]quinazolin-4(3*H*)-one 7. The general procedure **I** was followed using 3-aminoquinazolinone **6**[5] (2 g, 4.4 mmol), pyridine (0.7 cm^3, 8.8 mmol), dichloromethane (3 cm^3) and benzoyl chloride (0.97 g, 6.9 mmol). The yellow oil obtained on work-up was triturated with ethyl acetate–light petroleum and the solid obtained gave the title *3-benzoylaminoquinazolinone* **7** as colourless crystals (2.1 g, 80%), mp 147–149 °C (from light petroleum) (Found: MH^+ 452.2369. $C_{25}H_{33}N_3O_3Si$, requires MH^+ 452.2369); $[a]_D$ = +26 (*c* 1, $CHCl_3$); ν_{max}/cm^{-1} 3350 w, br, 1692s and 1609s; δ_H (mixture of *N*–*N* bond rotamers), major rotamer; −0.01 and 0.14 (6H, 2 × s, CH_3SiCH_3), 0.9 and 1.02 (6H, 2 × d, *J* 6.6, CH_3CHCH_3), 0.96 [9H, s, (CH_3)$_3$CSi], 2.13 [1H, (7 peaks), CH$_3$C*H*CH$_3$], 4.49 (1H, d, *J* 7.0, C*H*OSi), 7.4–7.61 [4H, m, 3 × C*H*(Ph) and 6-H(Q)], 7.79 [2H, m, 7 and 8-H(Q)], 8.0 [2H, m, 2 × CH(Ph)], 8.2 [1H, d, *J* 8.2, 5-H(Q)] and 9.35 (1H, s, NH); δ_H minor rotamer (observable signals), 2.42 [1H, (7 peaks), CH$_3$C*H*CH$_3$], 4.65 (1H, d, *J* 7.0, C*H*OSi) and 8.85 (1H, s, NH); from comparison of the signal at δ 4.49 and δ 4.65 the ratio of *N*–*N* bond rotamers was 7 : 1; δ_C (100.6 MHz at 50 °C) −4.7 and −4.4 (*C*H$_3$Si*C*H$_3$), 17.9 [*C*(CH$_3$)$_3$], 18.2 and 19.7 (*C*H$_3$CH*C*H$_3$), 25.8 [(*C*H$_3$)$_3$C], 33.1 [*C*H(CH$_3$)$_2$], 78.6 [br (*C*HOSi)], 120.8 [*C*CO(Q)], 126.9, 127.5, 127.8, 128.1, 129.8, 132.9 and 134.7 [5 × *C*H(Ph) and 4 × CH(Q)], 132.5 [C(Ph)], 146.6 [*C*–C=N(Q)], 160.7 [*C*N(Q)], 165.9 [*C*O(Q)] and 169.1 (Ph*C*O); *m*/*z* (%) 452 (MH^+, 100), 394 (71), 275 (19), and 187 (13).

Low temperature NMR studies were carried out on a sample of **7** crystallised from light petroleum and dissolved in $CDCl_3$ at −50 °C (see text).

3-Benzoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxyethyl]-quinazolin-4(3*H*)-one 11. The general procedure **I** above was followed using 3-aminoquinazolinone **10**[11] (3 g, 9.4 mmol), pyridine (1.1 cm^3, 13.9 mmol), dichloromethane (3 cm^3) and benzoyl chloride (1.6 g, 11.3 mmol). After work-up the yellow oil obtained was triturated with ethyl acetate–light petroleum and the solid obtained gave the title *3-benzoylaminoquinazolinone* **11** as colourless crystals (3.3 g, 82%), mp 181–182 °C (from light petroleum–ethyl acetate) (Found: C, 65.0; H, 6.9; N, 9.8. $C_{23}H_{29}N_3O_3Si$ requires C, 65.2; H, 6.9; N, 9.9%) (Found: MH^+ 424.2056. $C_{23}H_{29}N_3O_3Si$, requires MH^+ 424.2056); ν_{max}/cm^{-1} 3250w, br, 1690s and 1610s; δ_H (mixture of *N*–*N* bond rotamers), major rotamer; −0.01 and 0.1 (6H, 2 × s, CH_3Si-CH_3), 0.8 (9H, s, (CH$_3$)$_3$C), 1.44 (3H, d, *J* 6.6, CH_3CHOSi), 4.91 (1H, q, *J* 6.6, C*H*OSi), 7.3–7.5 [4H, m, 6-H(Q) and 3 × C*H*(Ph)], 7.51–7.7 [2H, structured m, 7- and 8-H(Q)], 7.85 [2H, structured m, 2 × CH(Ph)], 8.12 [1H, d, *J* 7.9, 5-H(Q)] and 9.4 (1H, s, NH); minor rotamer (observable signals), −0.09 and −0.01 (6H, 2 × s, CH_3SiCH_3), 0.79 (9H, s, (CH_3)$_3$C), 1.2 (3H, d, *J* 6.6, CH_3CHOSi), 5.0 (1H, q, *J* 6.6, C*H*OSi) and 8.9 (1H, s, NH); from comparison of the intensities of signals at δ 4.91 and 5.0 the ratio of *N*–*N* bond rotamers is 2 : 1; δ_C −4.8 and −4.3 (*C*H$_3$Si*C*H$_3$), 18.7 [(CH$_3$)$_3$*C*], 22.5 (*C*H$_3$CHOSi), 26.2 [(*C*H$_3$)$_3$C], 70.8 (*C*HOSi), 121.4 [*C*CO(Q)], 127.5, 128.2, 128.5, 129.2, 131.1, 133.1 and 135.3 [5 × CH(Ph) and 4 × CH(Q)], 31.2 [C(Ph)], 147.4 [*C*N=C(Q)], 161.4 [C=N(Q)], 166.3 and 167.7 [CO(Q) and Ph*C*O]; *m*/*z* (%) (FAB) 424 (MH^+, 100), 366 (51), 292 (22) and 145 (20).

A crystal of compound **11** suitable for X-ray structure determination (Fig. 2) was obtained from methanol.

3-(2-Methylpropanoylamino)-2-[(*S*)-1-*tert*-butyldimethylsilyl-oxy-2-methylpropyl]quinazolin-4(3*H*)-one 13. The general procedure **I** for monoacylation was followed using 3-amino-quinazolinone **6**[5] (2 g, 5.8 mmol), pyridine (0.68 g, 8.6 mmol), dichloromethane (4 cm^3) and 2-methylpropanoyl chloride (0.73 g, 6.9 mmol). The brown oil obtained on work-up was triturated with ethyl acetate–light petroleum and the solid obtained crystallised to give the title *3-(2-methylpropanoyl-amino)quinazolinone* **13** as colourless crystals (1.9 g, 79%), mp 116–118 °C (from light petroleum) (R_f 0.38, 3 : 1 light petroleum–ethyl acetate); $[a]_D$ = +27 (*c* 2.1 $CHCl_3$) (Found: MH^+ 418.2526. $C_{22}H_{36}N_3O_3Si$ requires MH^+ 418.2526); δ_H (mixture of *N*–*N* bond rotamers), major rotamer −0.02 and 0.16 (6H, 2 × s, CH_3SiCH_3), 0.94 and 1.04 (6H, 2 × d, *J* 6.6, CH_3CHCH_3), 0.97 [9H, s, (CH_3)$_3$C], 1.36 and 1.39 [6H, 2 × d, *J* 6.9, (CH_3)$_2$CHCO], 2.08 [1H, m, (7 peaks) CH$_3$C*H*CH$_3$], 2.73 [1H, h (heptet),*J* 6.9, (CH$_3$)$_2$C*H*CO], 4.45 (1H, d, *J* 7.0, C*H*OSi), 7.53 [1H, ddd, *J* 8.2, 7.0 and 1.6, 6-H(Q)], 7.75 [1H,

ddd, *J* 8.2, 7.0 and 1.6, 7-H(Q)], 7.82 [1H, dd, *J* 8.2 and 1.6, 8-H(Q)], 8.21 (1H, s, NH) and 8.31 [1H, d, *J* 8.2, 5-H(Q)]; minor rotamer (observable signals) 0.04 and 0.12 (6 H, 2 × s, CH_3SiCH_3), 2.3 [1 H, m, (7 peaks) CH_3CHCH_3] and 4.65 (1 H, d, *J* 7.0, C*H*OSi); from comparison of the signals at δ 4.45 and δ 4.65, the ratio of *N*–*N* bond rotamers was 6 : 1; δ_C −4.9 and −4.4 (*C*H_3Si*C*H_3), 18.6 [*C*$(CH_3)_3$], 19.4, 19.7, 33.2 and 34.5 (4 × *C*H_3), 26.2 [(*C*H_3)$_3$C], (*C*HOSi) missing, 121.4 [4 × *C*CO-(Q)], 127.5, 128.8 and 135.1 [4 × *C*H(Q)], 146.8 [*C*N=C(Q)], 160.4 [*C*O(Q)] and 174.1 (*C*O); *m*/*z* (%) (FAB) 418 (MH^+, 100), 360 (77), 275 (23) and 216 (31).

3-Acetylamino-2-diphenylmethylquinazolin-4(3*H*)-one 30. The general procedure **I** was followed using the 3-aminoquinazolinone **38**[4] (2 g, 6.12 mmol), pyridine (0.95 cm^3, 12 mmol), dichloromethane (4 cm^3) and acetyl chloride (0.58 g, 7.3 mmol) and the reaction mixture stirred for 24 h at room temperature. After work-up the brown oil obtained was purified by column chromatography on silica using light petroleum–ethyl acetate (1 : 1) as eluent to give the title *3-ethanoylaminoquinazolinone* **30** as colourless crystals (1.8 g, 80%) (R_f 0.34; 1 : 1 ethyl acetate–petroleum); mp 228–231 °C (from ethyl acetate) (Found: MH^+ 370.1556. $C_{23}H_{19}N_3O_2$, requires MH^+ 370.1556); δ_H 2.30 (3H, s, C*H*$_3$CO), 5.71 (1H, s, PhC*H*Ph), 7.28–7.48 [10H, m, 10 × CH(Ar)], 7.53 [1H, ddd, *J* 8.0, 6.9 and 1.1, 6-H(Q)], 7.69 [1H, d, *J* 8.0, 8-H(Q)], 7.80 [1H, ddd, *J* 8.0, 6.9 and 1.1, 7-H(Q)], 8.12 (1H, s, NH) and 8.21 [1H, dd, *J* 8.0 and 1.1, 5-H(Q)]; δ_C (d$_6$-DMSO) 20.8 (*C*H$_3$CO), 52.7 (Ph$_2$*C*H), 121.0 [*C*CO(Q)], 126.8, 127.1, 127.4, 127.5, 127.9, 128.4, 128.9, 129.4, 129.6 and 135.4 [10 × CH(Ar) and 4 × CH(Q)], 139.8 and 140.4 [2 × C(Ph)], 146.4 [*C*N=C(Q)], 159.2 and 159.3 [*C*=N(Q) and *C*O(Q)] and 169.9 (CH$_3$*C*O).

2-[(*S*)-1-*tert*-Butyldimethylsilyloxy-2-methylpropyl]-3-ethanoylaminoquinazolin-4(3*H*)-one 16. The general procedure **I** was followed using 3-aminoquinazolinone **6**[5] (1 g, 2.9 mmol), pyridine (0.34 g, 4.4 mmol), dichloromethane (2 cm^3) and acetyl chloride (0.34 g, 4.4 mmol) and the mixture was stirred for 24 h at room temperature. After work-up the brown oil obtained was purified by flash chromatography on silica using light petroleum–ethyl acetate (5 : 1) as eluent to give the *3-ethanoylaminoquinazolinone* **16** as a colourless oil (0.72 g, 64%) (R_f 0.31) (Found: MH^+ 390.2213. $C_{20}H_{31}N_3O_3Si$ requires *MH*$^+$ 390.2213); ν_{max}/cm^{-1} 3400m 1700s, 1610s, 1470s and 1075s; δ_H (mixture of *N*–*N* bond rotamers) major rotamer, −0.02 and 0.15 (6H, 2 × s, CH_3SiCH_3), 0.93 and 1.15 (6H, 2 × d, *J* 6.6, CH_3CHCH_3), 0.97 [9H, s, (*CH*$_3$)$_3$C)], 2.08 [1H, m, (7 peaks), CH_3CHCH_3], 2.3 (3H, s, C*H*$_3$CO), 4.49 (1H, d, *J* 6.9, CHOSi), 7.73 [1H, ddd, *J* 8.2, 7.0 and 1.3, 6-H(Q)], 7.76 [1H, dd, *J* 8.2 and 7.0 7-H(Q)], 7.81 [1H, dd, *J* 8.2 and 1.3, 8-H(Q)], 8.20 [1H, d, *J* 8.2, 5-H(Q)] and 8.65 (1H, s, NH); δ_H minor rotamer, (observable signals), 4.62 (1H, d, *J* 6.9, CHOSi) and 8.72 (1H, s, NH); δ_C −4.7 and −3.9 (*C*H$_3$Si*C*H$_3$), 18.4 [*C*$(CH_3)_3$], 147.3 [*C*–C=N(Q)], 157.8 [*C*N(Q)], 161.3 [*C*O(Q)] and 170.9 (CO). From comparison of the intensities of signals at δ 4.49 and δ 4.62 the ratio of rotamers was 4 : 1; δ_C −4.9 and −4.3 (*C*H$_3$Si*C*H$_3$), 18.6 [(CH$_3$)$_3$*C*], 18.7, 19.9 and 32.8 (3 × CH$_3$), 26.3 [(*C*H$_3$)$_3$C], 33.6 [(CH$_3$)$_2$*C*H], 79.0, [br (*C*HOSi)], 121.2 [*C*CO(Q)], 127.3, 127.5, 128.5 and 135.3 [4 × CH(Q)], 146.9 [*C*–C=N(Q)], 157.1 [*C*=N(Q)], 160.7 [*C*O(Q)] and 169.4 (CO); *m*/*z* (%) (FAB) 390 (MH^+, 100) 374 (20), 332 (84), 290 (21), 216 (44) and 187 (20).

General procedure II for preparation of 3-diacylaminoquinazolinones (DAQs) from 3-monoacylaminoquinazolinones (MAQs)

To a solution of the 3-acylaminoquinazolinone (1 eq.), prepared as described above, in dry dichloromethane (2 cm^3 g^{-1}) containing dry pyridine (1.5 eq.) and dry DMF (4 drops), was added the acid chloride (2–3 eq.) dropwise over 10 min and the mixture stirred and heated under reflux for 2–4 days, monitoring the disappearance of the starting 3-monoacylaminoquinazolinone by TLC. After cooling, additional dichloromethane was added, and the solution was washed with aqueous sodium hydrogen carbonate, then water, dried, and the dichloromethane removed under reduced pressure. The bulk of the residual pyridine was removed using an oil pump and the product purified by flash chromatography.

3-Diethanoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxyethyl]-quinazolinone-4(3*H*)-one 2. 3-Aminoquinazolinone **10**[11] (0.5 g, 1.24 mmol) was dissolved in acetic anhydride (1 cm^3), pyridine (1 cm^3) was added and the reaction mixture stirred at room temperature for 48 h. The solution was poured into water (1 cm^3), excess acetic anhydride decomposed by stirring for ~10 min and the product extracted into dichloromethane (2 × 20 cm^3). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (3 × 20 cm^3), then water, dried, and the solvents removed under reduced pressure. Chromatography of the oily product obtained with light petroleum–ethyl acetate (5 : 1) as eluent gave the title *DAQ* **2** (R_f 0.32) as a colourless oil (0.51, 80%) (Found: M^+ 403.2005. $C_{20}H_{29}N_3O_4Si$ requires M^+ 403.2005); δ_H −0.07 and 0.02 (6H, 2 × s, CH_3SiCH_3), 0.79 [9H, s, (*CH*$_3$)$_3$C], 1.39 (3H, d, *J* 6.6, CH_3CHO), 2.29 and 2.32 (6H, 2 × s, 2 × CH$_3$CO), 4.8 (1H, q, *J* 6.6, CHOSi), 7.4 [1H, ddd, *J* 8.2, ~7 and ~1.5, 6-H(Q)], 7.65 [1 H, dd, *J* 8.2 and ~1.5, 8-H(Q)], 7.7 [1H, ddd, *J* ~8, 7.0 and ~1.5, 7-H(Q)] and 8.15 [1H, dd, *J* ~8 and ~1.5, 5-H(Q)]; *m*/*z* (%) 403 (M^+,100), 362 (35), 346 (62), 304 (55), 262 (22), 230 (26) and 188 (21).

3-Dibenzoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxyethyl]-quinazolin-4(3*H*)-one 3. The general procedure **II** for diacylation was followed using MAQ **11** (3 g, 9.4 mmol), pyridine (1.5 g, 19 mmol), dichloromethane (5 cm^3) and benzoyl chloride (2.64 g, 19 mmol) and the reaction mixture heated under reflux for 10 h. The yellow oil obtained after work-up was purified by column chromatography on silica using light petroleum–ethyl acetate (3 : 1) as eluent and gave *DAQ* **3** (R_f 0.64) as colourless crystals (1.5 g, 41%), mp 127–129 °C (from light petroleum) (Found: C, 68.0; H, 6.3; N, 7.9. $C_{30}H_{33}N_3O_4Si$ requires C, 68.2; H, 6.3; N, 7.9%) (Found: MH^+ 528.2319. $C_{30}H_{33}N_3O_4Si$, requires *MH*$^+$ 528.2319); δ_H −0.02 and 0.01 (6H, 2 × br s, CH_3SiCH_3), 0.9 [9H, s, (*CH*$_3$)$_3$C], 1.84 (3H, br d, *J* 6.6, CH_3-CHOSi), 5.27 (1H, br q, *J* 6.6, C*H*OSi), 7.1–7.4 [7H, m, 6-H(Q) and 6 × PhCH], 7.6 [1H, ddd, *J* 8.2, 7.0 and 1.3, 7-H(Q)], 7.80–7.87 [5H, m, 8-H(Q) and 4 × CH(Ph)] and 8.4 [1H, d, *J* 8.2, 5-H(Q)]; δ_C −4.8 and −4.4 (*C*H$_3$Si*C*H$_3$), 19.0 (*C*H$_3$CHO-Si), 22.7 [(CH$_3$)$_3$*C*Si], 26.3 [(*C*H$_3$)$_3$CSi], 71.6 (*C*HOSi), 122 [*C*CO(Q)], 127.8, 128.4, 128.6, 130.1, 130.5, 132.8 and 134.8 [10 × CH(Ph) and 4 × CH(Q)], 135.0 and 135.5 [2 × *C*(Ph)], 147.3 [*C*N=C(Q)], 157.4 [*C*=N(Q)], 160.5, [CO(Q)], 170.1 and 170.9 (2 × CO); *m*/*z* (%) (FAB), 528 (MH^+, 100) and 470 (70).

Further elution with the same solvent mixture gave unreacted MAQ[3] **11** as colourless crystals (1.5 g).

3-(*N*-Benzoyl-*N*-2-methylpropanoylamino)-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methylpropyl]quinazolin-4(3*H*)-one 8. General procedure **II** for diacylation was followed using 3-benzoylaminoquinazolinone **7** (1 g, 2.2 mmol), dry dichloromethane (2 cm^3), dry pyridine (0.36 g, 4.6 mmol, 2 eq.) and 2-methylpropanoyl chloride (0.47 g, 4.7 mmol) and the mixture stirred at room temperature for 5 days. The yellow oil obtained on work-up (1.2 g) was purified by flash chromatography over silica gel and elution with light petroleum–ethyl acetate (5 : 1) to give *DAQ*^{I} **8** (R_f 0.48) as a colourless oil (1 g, 83%) and as a mixture of diastereoisomers. Re-chromatography using kieselgel with light petroleum–ethyl acetate (10 : 1) as eluent gave the faster running *DAQ*^{I} *diastereoisomer* **8a** as a viscous

colourless oil (0.26 g, 23%) (R_f 0.42) (Found: MH^+, 522.2789. $C_{29}H_{39}N_3O_4Si$ requires MH^+, 522.2789); ν_{max}/cm^{-1} 1700s and 1605s; δ_H −0.13 and 0.01 (6H, 2 × s, CH_3SiCH_3), 0.98 [9H, s, (CH_3)$_3$CSi], 1.05 and 1.13, 1.28 and 1.39 (12H, 4 × d, J 6.6, 2 × CH_3CHCH_3), 2.2 [1H, m, (7 peaks), CH$_3$CHCH$_3$], 2.95 [1H, h, J 6.6, (CH$_3$)$_2$CH], 4.62 (1H, br d, J 5.0, CHOSi), 7.50–7.75 [4H, m, 3 × CH(Ph) and 6-H(Q)], 7.8–8.10 [4H, m, 7- and 8-H(Q) and 2 × CH(Ph)] and 8.42 [1H, dd, J 8.0 and 1.3, 5-H(Q)]; δ_C −4.9 and −3.7 (CH_3SiCH_3), 18.8 [(CH$_3$)$_3$CSi], 19.7, 20.6, 20.9, 32.3 and 35.3 (4 × CH_3 and 2 × CH), 26.3 [(CH_3)$_3$C], (CHOSi missing), 121.6 [CCO(Q)], 127.7, 127.8, 128.4, 129.2, 129.3, 133.7 and 135.5 [5 × CH(Ph) and 4 × CH(Q)], 134.1 [C(Ph)], 146.7 [CN=C(Q)], 156.6 [C=N(Q)], 160.5 [CO(Q)] and 170.2 and 178.8 [2 × CO]; m/z (%), (FAB) 522 (MH^+, 66%), 452 (80), 436 (21), 394 (100), 275 (60), 232 (47) and 187 (33).

Further elution with the same solvent mixture gave the major more polar *DAQ*^{1} *diastereoisomer* **8b** (R_f 0.37) as colourless crystals (0.46 g, 40%); mp 126–128 °C (from light petroleum) (Found: C, 66.8; H, 7.5; N, 8.1. $C_{29}H_{39}N_3O_4Si$ requires C, 66.8; H, 7.5; N, 8.1%); ν_{max}/cm^{-1} 1700s and 1605s; δ_H −0.02 and 0.07 (6H, 2 × s, CH_3SiCH_3), 0.89 [9H, s, (CH_3)$_3$CSi], 1.08, 1.14, 1.20 and 1.36 (12H, 4 × d, J 6.6, 2 × CH_3CHCH_3), 2.23 [1H, m, (7 lines), CH$_3$CHCH$_3$], 2.78 [1H, h, J 6.6, (CH$_3$)$_2$CHCO], 4.66 (1H, d, J 7.2, CHOSi), 7.53–7.67 [4H, m, 3 × CH(Ph) and 6-H(Q)], 7.8–7.94 [2 H, m, 7- and 8-H (Q)], 7.95–8.05 [2H, m, 2 × CH(Ph)] and 8.42 [1H, dd, J 8.3 and 1.0, 5-H(Q)]; δ_C −4.6 and −3.8 (CH_3SiCH_3), 18.9 [(CH$_3$)$_3$CSi], 19.6, 20.3, 21.0, 32.5 and 35.6 (4 × CH_3 and 2 × CH), 26.4 [(CH_3)$_3$C], (CHOSi missing), 121.7 [CCO(Q)], 127.7, 128.3, 135.4, 129.1, 129.7, 133.5 and 136.4 [5 × CH(Ph) and 4 × CH(Q)], 135.0 [C(Ph)], 146.8 [CN=C(Q)], 156.3 [C=N(Q)], 160.4 [CO(Q)] and 169.9 and 179.4 (2 × CO). From comparison of signals at δ 2.78 and 2.95 in NMR spectrum of the crude reaction product the ratio of **8b**–**8a** was 1.6 : 1; m/z (%) (FAB) 522 (MH^+, 66%), 452 (80), 436 (21), 394 (100), 275 (60), 232 (47) and 187 (33). An X-ray structure determination was carried out on a crystal of diastereoisomer **8b** obtained from ethanol.[3b]

DAQ^1 **8b** (25 mg) was dissolved in $CDCl_3$ (0.5 cm^3) and heated at 60 °C for 14 h to give a 1 : 1 ratio of **8a**–**8b** by comparison of the NMR spectrum of the solution with those of authentic samples above.

***N*-Benzoyl-*N*-ethanoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methylpropyl]quinazolin-4(3*H*)-one 9.** General procedure **II** for diacylation was followed using 3-benzoylaminoquinazolinone **7** (1 g, 2.22 mmol) dissolved in dry dichloromethane (2 cm^3) containing dry pyridine (0.15 g, 1.9 mmol) with acetyl chloride (0.29 g, 3.7 mmol) added dropwise over 5 min, and the mixture stirred for 3 days with heating under reflux. The yellow oil obtained on work-up (1.2 g) was purified by flash chromatography over silica gel with light petroleum–ethyl acetate (4 : 1) as eluent to give *DAQ*^{1} **9** (R_f 0.56) as colourless crystals (0.84 g, 76%), mp 136–138 °C (from light petroleum), $[\alpha]_D$ = −222.4 (c 2.0, $CHCl_3$) (Found: C, 65.0; H, 7.1; N, 8.4; $C_{27}H_{35}N_3O_4Si$ requires C, 65.1; H, 7.1; N, 8.5%) (Found: MH^+ 494.2475. $C_{27}H_{35}N_3O_4Si$ requires MH^+ 494.2475); ν_{max}/cm^{-1} 1700s and 1600s; δ_H −0.02 and 0.02 (6H, 2 × s, CH_3SiCH_3), 0.82 [9H, s, (CH_3)$_3$CSi], 1.09 and 1.24 (6H, 2 × d, J 6.6, CH_3CHCH_3), 2.23 (3H, s, CH_3CO), 2.45 [1H, m, (7 peaks), CH$_3$CHCH$_3$], 4.63 (1H, d, J 8.2, CHOSi), 7.59–7.74 [4H, m, 3 × CH(Ph) and 6-H(Q)], 7.83–8.08 [4H, m, 7- and 8-H(Q) and 2 × CH(Ph)] and 8.43 [1H, d, J 8.2, 5-H(Q)]; δ_C −4.6 and −3.9 (CH_3SiCH_3), 18.9 [(CH$_3$)$_3$C], 19.1 and 20.07 (CH_3CHCH_3), 26.1 (CH$_3$CHCH$_3$), 26.4 [(CH_3)$_3$C], 32.5 (CH_3CO), 82.9 (CHOSi), 121.6 [CCO(Q)], 127.8, 127.9, 128.4, 129.1, 129.4, 130.2 and 135.5 [5 × CH(Ph) and 4 × CH(Q)], 134.8 [C(Ph)], 146.9 [CN=C(Q)], 155.8 [CN(Q)], 160.4 [CO(Q)] and 169.3 and 171.8 (CO); m/z (%) (FAB) 494 (MH^+, 100), 436 (63) and 394 (65). The 1H NMR spectrum of a sample that had been heated at 137 °C for ~1 min showed no change.

A crystal suitable for X-ray crystallographic structure determination was obtained from ethanol (Fig. 1).

3-[*N*-(*S*)-2-Acetoxypropanoyl-*N*-ethanoylamino]-2-diphenylmethylquinazolin-4(3*H*)-one 31. General procedure **II** was followed using MAQ[2] **30** (1.1 g, 2.7 mmol), dichloromethane (2 cm^3), pyridine (0.4 g, 5.1 mmol) and (*S*)-2-acetoxypropanoyl chloride (0.82 g, 5.4 mmol) and the mixture stirred at room temperature for 24 h. Chromatography of the yellow oil (0.95 g) obtained using flash silica and light petroleum–ethyl acetate (2 : 1) as eluent gave the minor diastereoisomer **31a** as colourless crystals (0.43 g, 33%); mp 163–165 °C (from methanol) (R_f 0.43) (Found: MH^+ 484.1873. $C_{28}H_{25}N_3O_5$ requires MH^+ 484.1873); ν_{max}/cm^{-1} 1745s, 1710s, 1610 and 1602s; δ_H 1.08 (3H, s, CH_3CO), 1.51 (3H, d, J 6.9, CH_3CHOAc), 2.03 (3H, s, CH_3CO$_2$), 5.48 (1H, s, PhCHPh), 6.01 (1H, q, J 6.9, CH$_3$CH-OAc), 7.03–7.26 [10H, m, 10 × CH(Ar)], 7.31 [1H, ddd, J 8.3, 6.6 and 1.3, 6-H(Q)], 7.50 [1H, dd, J 8.2 and 1.3, 8-H(Q)], 7.59 [1H, ddd, J 8.2, 6.6 and 1.3, 7-H(Q)] and 8.05 [1H, dd, J 8.2 and 1.3, 5-H(Q)]; The ^{1}H NMR spectrum at 400 MHz at −50 °C remained unchanged; δ_C 16.2, 20.9, and 22.0 (3 × CH$_3$), 52.9 (PhCHPh), 72.2 (CH$_3$$C$HOAc), 121.0 [CCO(Q)], 127.2, 127.8, 128.1, 128.6, 128.9, 129.2, 129.8, 129.9, 130.3 and 135.8 [10 × CH(Ar) and 4 × CH(Q)], 138.1 and 140.0 [2 × C(Ph)], 147.0 [CN=C(Q)], 157.9 [C=N(Q)], 160 [CO(Q)] and 171.8, 172.5, and 172.7 (3 × CO); m/z (%) (FAB), 484 (MH^+, 100), 154 (100), 136 (82) and 115 (40).

An X-ray structure determination was obtained on a crystal from methanol (Fig. 3a).

Further elution with the same solvent mixture gave the *DAQ*^{2} diastereoisomer **31b** (R_f 0.23) as colourless crystals (0.45 g, 35%) mp 153–155 °C (from ethyl acetate) (Found: MH^+ 484.1873. $C_{28}H_{25}N_3O_5$ requires MH^+ 484.1873); ν_{max}/cm^{-1} 1740s, 1705s, 1608 and 1600s; δ_H 1.25 (3H, s, CH_3CO), 1.82 (3H, d, J 6.6, CH_3CHOAc), 2.24 (3H, s, CH_3CO), 5.44 (1H, s br, PhCHPh), 6.07 (1H, q br, J 6.6, CH$_3$CHOAc), 7.25–7.53 [10H, m, 10 × CH(Ar)], 7.57 [1H, ddd, J 8.2, 7.1 and 1.3, 6-H(Q)], 7.50 [1H, dd, J 8.2 and 1.3, 8-H(Q)], 7.59 [1H, ddd, J 8.2, 7.1 and 1.3, 7-H(Q)] and 8.05 [1H, dd, J 8.2 and 1.3, 5-H(Q)]; δ_C 17.4, 21.4, and 23.1 (3 × CH_3), 53.9 [(Ph)$_2$CH], 71.0 (CH$_3$$C$HOAc), 121.3 [CCO(Q)], 127.5, 127.9, 128.0, 128.6, 128.8, 129.8, 130.0 and 135.7 [10 × CH(Ar) and 4 × CH(Q)], 137.4 and 139.6 [2 × C(Ph)], 146.7 [CN=C(Q)], 157.3 [C=N(Q)], 159.9 [CO(Q)] and 170.4, 171.5, and 171.9 (3 × CO); from comparison of signals δ_H 6.07 and 6.01 in the NMR spectrum of the product obtained after the first column chromatography, the ratio of **31b**–**31a** diastereoisomers present was 1.1 : 1; the signals at δ 6.07 and 5.44 above showed (400 MHz) the following temperature dependence: 0 °C ~6.0, s, br (coalescence) and 5.29 s, br; −25 °C 6.1 s, br and 5.11 s, br; 40 °C 6.09, q, sharp and 5.1 s, sharp, respectively; m/z (%) (FAB), 484 (MH^+, 74), 154 (100), 136 (82) and 115 (40).

An X-ray structure determination was obtained on a crystal from methanol (Fig 3b).

3-{Bis[(*S*)-2-acetoxypropanoyl]amino}-2-diphenylmethylquinazolin-4(3*H*)-one 37a. Using general procedure **II**, a mixture of 3-[(*S*)-2-acetoxypropanoyl]aminoquinazolinone **32**[4] (1.1 g, 2.5 mmol), dichloromethane (3 cm^3), pyridine (0.39 g, 5.0 mmol) and distilled (*S*)-2-acetoxypropanoyl chloride (0.56 g, 3.74 mmol) was stirred continuously for 24 h at room temperature. The brown oil obtained after work-up was purified by column chromatography on silica using light petroleum–ethyl acetate (2 : 1) as eluent to give a colourless oil (R_f 0.43) which solidified on standing. Crystallisation afforded *DAQ*^{2} **37a** (1.2 g, 87%) as a colourless solid, mp 169–170 °C (from methanol) (Found: C, 66.9; H, 5.2; N, 7.6. $C_{31}H_{30}N_3O_7$ requires C, 67.0; H, 5.2; N, 7.6%) (Found: MH^+ 556.2083. $C_{31}H_{30}N_3O_7$ requires MH^+ 556.2084); ν_{max}/cm^{-1} 1750s, 1689s and 1600s; δ_H 1.51 (6H, br d, J 6.7, CH_3CHOAc), 2.10 and 2.25 (6H, 2 × s,

2 × CH_3CO$_2$), 5.08 and 6.03 (2H, 2 × q br, C*H*OAc), 5.84 (1H, br s, PhC*H*Ph), 7.31–7.72 [11H, m, 10 × CH(Ar) and 6-H(Q)], 7.86 [1H, dd, *J* 8.3 and 1.0, 8-H(Q)], 7.95 [1H, ddd, *J* 8.3, 7.0 and 1.0, 7-H(Q)] and 8.35 [1H, dd, *J* 8.0 and 1.0, 5-H(Q)]; δ_H (400 MHz, −50 °C) 1.26 and 1.52 (6H, 2 × d, *J* 6.6, 2 × CH_3CHOAc), 2.0 and 2.4 (6H, 2 × s, 2 × CH$_3$CO$_2$), 4.54 and 6.11 (2H, 2 × q, *J* 6.6, 2 × CH$_3$C*H*OAc), 5.82 (2H, s, PhC*H*Ph) additional signals (~20% of those given previously) were present at δ 4.40 (br s), 5.07 (s), 6.07 (br s) and 7.07 (br s); δ_C (25 °C) 16.8, 20.7, 20.9 and 21.3 (4 × *C*H$_3$), 52.8 (Ph*C*HPh), 69.6 and 70.9 (2 × *C*HOAc), 120.9 [*C*CO(Q)], 127.6, 127.8, 128.2, 128.6, 128.8, 128.9, 129.2, 129.8, 129.9 and 136.2 [10 × CH(Ph) and 4 × CH(Q)], 139.0 and 139.6 [2 × C(Ph)], 146.6 [*C*N=C(Q)], 157.3 (C=N), 160.7 [CO(Q)] and 169.9, 170.7, 171.5 and 172.3 (4 × CO); *m*/*z* (%) (FAB), 156 (MH$^+$, 100), 442 (96), 311 (51) and 167 (99).

A crystal grown from methanol was suitable for X-ray structure determination (Fig. 4).

Preparation of *meso*-bis[(*S*)-2-acetoxypropanoylamino]-2-diphenylmethylquinazolin-4(3*H*)-one 37b. Using general procedure **II**, a mixture of 3-[(*S*)-2-acetoxypropanoylamino]-quinazolinone **32** (0.7 g, 1.5 mmol), dichloromethane (2 cm^3), pyridine (0.23 g, 2.96 mmol) and racemic-2-acetoxypropanoyl chloride (0.33 g, 2.2 mmol) was stirred continuously for 24 h at room temperature. Flash column chromatography of the yellow oil obtained on work-up over silica with light petroleum–ethyl acetate (2 : 1) as eluent gave a colourless solid whose TLC showed two spots at R_fs 0.43 and 0.37.

Further elution with light petroleum–ethyl acetate (1 : 1) gave unchanged MAQ[2] **32** as a colourless oil (0.49 g) (R_f 0.5, 1 : 1 light petroleum–ethyl acetate).

Re-chromatography of the solid mixture above using a chromatotron and light petroleum–ethyl acetate (2 : 1) as eluent gave DAQ[2] **37a** as a colourless solid (0.08 g, 10%) (R_f 0.43) identical with that isolated previously.

Further elution with the same solvent mixture gave *meso-DAQ*[2] **37b** (R_f 0.37) as a colourless oil (0.01 g, 1%) (Found: MH$^+$ 556.2085. $C_{31}H_{30}N_3O_7$ requires *MH*$^+$ 556.2084); δ_H 1.3 (6H, d, *J* 6.7, 2 × C*H*$_3$CHOAc), 2.06 (6H, s, 2 × CH$_3$CO$_2$), 5.45 (2H, br q, *J* 6.7, 2 × CH$_3$C*H*OAc), 5.91 (1H, s, PhC*H*Ph), 7.2–7.9 [13H, m, 10 × CH(Ar) and 6-, 7- and 8-H(Q)] and 8.26 [1H, dd, *J* 8.0 and 1.0, 5-H(Q)]. In variable-temperature NMR studies (400 MHz) (27, 0, −25 and −44 °C) the broadened signal at δ 5.45 of CH$_3$C*H*OAc was split into two broad signals (δ 5.0 and 5.80) with a coalescence temperature at ~0 °C.

***N*-[(*S*)-2-Acetoxypropanoyl-*N*-ethanoylamino]phthalimide 41.** General procedure **II** was followed using *N*-acetylaminophthalimide **40**[12] (0.6 g, 2.94 mmol), dichloromethane (2 cm^3), pyridine (0.46 g, 5.9 mmol) and (*S*)-2-acetoxypropanoyl chloride (0.89 g, 5.9 mmol) with stirring at room temperature for two days. The pale brown oil (1.1 g) obtained was purified by flash column chromatography using light petroleum–ethyl acetate (1 : 1) as eluent to give *N-phthalimido-imide* **41** as a colourless oil (0.7 g, 75%) (R_f 0.67) (Found: MH$^+$ 319.0930. $C_{15}H_{14}N_2O_6$ requires *MH*$^+$ 319.0930); ν_{max}/cm^{-1} 1800s, 1730s, and 1360s; δ_H 1.54 (3H, d, *J* 6.9, C*H*$_3$CHOAc), 2.08 (3H, s, C*H*$_3$CO$_2$), 2.43 (3H, s, C*H*$_3$CO), 5.72 (1H, q, *J* 6.9, C*H*OAc) and 7.83–8.20 [4H, m, C*H*(Ar)]; δ 16.8, 20.7 and 24.6 (3 × *C*H$_3$), 70.1 (CH$_3$*C*HOAc), 124.8, 124.9, 135.6 and 135.8 [4 × CH(Ar)], 130.2, 130.3 [2 × C(Ar)] and 164.8, 170.2, 170.4 and 171.1 (5 × CO); *m*/*z* (%) (FAB), 319 (MH$^+$, 48), 277 (45), 259 (100), 154 (60), 137 (62) and 115 (71).

Competitive reactions of pyrrolidine and piperidine with DAQs 2 and 3

A solution of DAQ **2** (0.1 g, 0.25 mmol), pyrrolidine (18 mg, 0.25 mmol) and piperidine (21 mg, 0.25 mmol) in deuterochloroform (0.5 cm^3) was stirred for 6 h at 0 °C. An ^{1}H NMR spectrum (400 MHz) showed the ratio of *N*-acetylpyrrolidine to *N*-acetylpiperidine was 20 : 1 from comparison of signals at δ 3.42 and 3.50 with those in the spectra of authentic samples.

The same procedure was carried out using DAQ **3** (0.1 g, 0.19 mmol), pyrrolidine (14 mg, 0.19 mmol) and piperidine (16 mg, 0.19 mmol) in deuterochloroform (0.5 cm^3) for 4 h at −10 °C. An ^{1}H NMR spectrum (400 MHz) showed the ratio of *N*-benzoylpyrrolidine to *N*-benzoylpiperidine was ~30 : 1 from comparison of signals at δ 3.6 and 3.7 with those in the spectra of authentic samples.

General procedure III for enantioselective acylation (kinetic resolution) of racemic amines

To the DAQ (1 eq.) dissolved in the dichloromethane (1 cm^3 100 mg^{-1}) was added racemic amine (2 eq.) and the solution stirred at −20 to −10 °C and then at 5 °C for the time given, monitoring the disappearance of the starting material by TLC at 5 °C. To work up, further dichloromethane (2 cm^3 100 mg^{-1}) was added and the solution washed with hydrochloric acid (2 M) to remove unreacted amine, then with water, dried, and evaporated under reduced pressure. Separation of product was carried out using a chromatotron or flash chromatography. The unreacted amine was recovered from the aqueous acid extract as the hydrochloride salt by evaporation of the bulk of the acid-water under reduced pressure first using an oil pump and then drying in a desiccator containing P_2O_5 for 24 h. For NMR spectroscopic examination of the progress of the reactions, deuterochloroform was substituted for dichloromethane in the procedure above. Yields of amide were based on the (eq. amine used)/2.

Reaction of DAQ[1] 8a with a 2-methylpiperidine. General procedure **III** was followed using DAQ[1] **8a** (0.1 g, 0.19 mmol) and racemic 2-methylpiperidine (38 mg, 0.38 mmol) in dichloromethane (1 cm^3) and the mixture stirred at −20 °C for 2 h and then at 5 °C for 12 h. Flash chromatography of the product with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **13** (69 mg, 86%) (R_f 0.38, 3 : 1 light petroleum–ethyl acetate) identical with an authentic sample prepared as described above.

Further elution with the same solvent mixture gave (*R*)-*N*-benzoyl-2-methylpiperidine **12** as a colourless oil (33 mg, 85%); $[\alpha]_D$ = −31.4 (*c* 0.8, CHCl$_3$), ee 95% by comparison with an authentic sample prepared as described below.

General procedure IV; derivatization of the unreacted amine

(i) With benzoyl chloride. The unreacted 2-methylpiperidine enantiomer was recovered as the hydrochloride acid salt from the experiment above as a colourless solid (25 mg, 96%). This salt (22 mg, 0.16 mmol) was dissolved in pyridine (0.5 cm^3), benzoyl chloride (34.2 mg, 0.24 mmol) added and the reaction mixture stirred for 2 h at room temperature. After addition of dichloromethane (1 cm^3) the solution was washed with hydrochloric acid (2 M; 0.5 cm^3) followed by water, dried and evaporated and the pale yellow oil (41 mg) obtained was purified by column chromatography over silica with light petroleum–ethyl acetate (3 : 1) as eluent to give (*S*)-*N*-benzoyl-2-methylpiperidine **12** as a colourless oil (23.1 mg, 70%); $[\alpha]_D$ = +30 (*c* 0.64, CHCl$_3$), ee 91% by comparison with an authentic sample $[\alpha]_D$ = +32.8 (*c* 0.64, CHCl$_3$) (see below).

(ii) With (*S*)-2-acetoxypropanoyl chloride. The aqueous acid extract in another experiment using DAQ[1] **8a** carried out as described above, containing unreacted 2-methylpiperidine hydrochloride, was made alkaline with sodium hydroxide (2 M) and the solution extracted with ether (3 × 1 cm^3), the combined ether layers, dried over powdered potassium hydroxide, pyridine (24 mg, 0.3 mmol) and (*S*)-2-acetoxypropanoyl chloride (46 mg, 0.3 mmol) added and the mixture stirred for 2 h at

room temperature. Work-up as described above gave amide **14** (24 mg, 72%) whose ^{1}H NMR (400 MHz, 50 °C) showed it to contain an 18 : 1 mixture of (*S*,*S*)–(*R*,*S*) diastereoisomers **14a**–**14b** (de 89%) from comparison of the intensities of signals in its NMR spectrum at δ 2.09 and 2.10 respectively, adding incremental amounts of an authentic sample of the (*R*,*S*) diastereoisomer, prepared as described below, and monitoring the increase in the signal at 2.10 ppm.

Reaction of DAQ^1 8b with a 2-methylpiperidine

General procedure **III** was followed using DAQ^1 **8b** (0.1 g, 0.19 mmol) and 2-methylpiperidine (38 mg, 0.38 mmol) in deuterochloroform (0.5 cm^3) and the mixture stirred at −20 °C for 2 h and then at 5 °C for 30 h. Flash chromatography of the product with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ^1 **13** (69 mg, 86%) (R_f 0.38, 3 : 1 light petroleum–ethyl acetate) identical with that isolated previously.

Further elution with the same solvent mixture gave (*S*)-*N*-benzoyl-2-methylpiperidine **12** as a colourless oil (32 mg, 82%); $[\alpha]_D$ = +26.7 (*c* 0.75, $CHCl_3$) ee 81% by comparison with an authentic sample (see below).

The unreacted 2-methylpiperidine enantiomer was recovered as its hydrochloride salt from the extraction with hydrochloric acid (2 M) as a colourless solid (28 mg, 97%). Following general procedure **IV** this salt (26 mg, 0.19 mmol), dissolved in pyridine (0.5 cm^3) was treated with benzoyl chloride (54 mg, 0.38 mmol) and the reaction mixture stirred for 2 h at room temperature. After work-up, the pale yellow oil (70 mg) obtained was purified by column chromatography over silica with light petroleum–ethyl acetate (3 : 1) as eluent to give (*R*)-*N*-benzoyl-2-methylpiperidine **12** as a colourless oil (27 mg, 69%); $[\alpha]_D$ = −26.7 (*c* 0.7, $CHCl_3$) ee 81% (see above).

Reaction of DAQ^1 9 with 2-methylpiperidine

General procedure **III** was followed using DAQ^1 **9** (0.1 g, 0.2 mmol) and racemic 2-methylpiperidine (40 mg, 0.4 mmol) in dichloromethane (1 cm^3) and the mixture stirred at −20 °C for 2 h and then at 5 °C for ~30 h. After work-up, a proton NMR spectrum of the crude reaction product showed the presence of a ~2.5 : 1 ratio of *N*-benzoyl-2-methylpiperidine to *N*-ethanoyl-2-methylpiperidine, inferred from comparison of signals at δ 8.20 [5-H(Q) for MAQ^{1}s **16** and **7**] and δ 8.0 [2 × CH(Ph) for MAQ^1 **7**] respectively. Chromatotron chromatography with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ^1 **7** as colourless crystals (16 mg, 17%), identical with that isolated previously.

Further elution with the same solvent mixture gave MAQ^1 **16** as a colourless oil (35 mg, 41%), identical with that isolated previously.

Further elution with the same solvent mixture gave (*S*)-*N*-benzoyl-2-methylpiperidine **12** as a colourless oil (17 mg, 41%), $[\alpha]_D$ = +30 (*c* 0.5, $CHCl_3$), ee 91% by comparison with an authentic sample (see below).

The unreacted 2-methylpiperidine was obtained as its hydrochloride salt as a colourless solid (23 mg, 83%); $[\alpha]_D$ = +0.5 (*c* 2, H_2O), ee 11% by comparison with (*R*)-2-methylpiperidine hydrochloride, prepared from the *R*-enantiomer of the amine; $[\alpha]_D$ = +4.6 (*c* 2.2, H_2O).

Reaction of DAQ^1 9 with a 3-methylpiperidine

General procedure **III** was followed using DAQ^1 **9** (0.1 g, 0.2 mmol) and racemic 3-methylpiperidine (0. 04 g, 0.4 mmol) in deuterochloroform (1 cm^3) and the mixture stirred at −20 °C for 2 h and then at 5 °C for 30 h. An ^{1}H NMR spectrum of the solution showed the presence of 3 : 1 ratio of *N*-benzoyl-3-methylpiperidine **17** to *N*-ethanoyl-3-methylpiperidine **18** respectively, inferred from comparison of signals at δ 8.20 [5-H(Q) of MAQ^{1}s **16** and **7**] and δ 8.0 [2 × CH(Ph) of MAQ^1 **7**] respectively. Chromatotron chromatography with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ^1 **7** as colourless crystals (18 mg, 20%), (R_f 0.50), identical with that isolated previously.

Further elution with the same solvent mixture gave a mixture of MAQ^1 **16** and amide **17** which was dissolved in THF (1 cm^3), an excess of TBAF in THF (1 M, 0.3 g) added and the mixture stirred for 6 h at room temperature. The bulk of the solvent was removed under reduced pressure, the residual oil dissolved in dichloromethane (3 cm^3) and the solution washed successively with saturated aqueous sodium hydrogen carbonate, brine, and water, then dried to give a yellow oil (0.11 g). Flash column chromatography with light petroleum–ethyl acetate (2 : 1) as eluent gave *N*-benzoyl-3-methylpiperidine **17** as a colourless oil (13 mg, 32%), $[\alpha]_D$ = +36.7 (*c* 0.3, $CDCl_3$); ee 85% based on an enantiopure sample prepared as described below.

Further elution with the same solvent mixture gave 3-ethanoylamino-2-(1-hydroxy-2-methylpropyl)quinazolinone **19** as a colourless oil (23 mg, 41%) (Found: MH^+ 276.1348. $C_{14}H_{17}N_3O_3$, requires MH^+ 276.1348); ν_{max}/cm^{-1} 3380w, 3240w, 1700s and 1612s; δ_H (mixture of *N*–*N* bond rotamers) major rotamer 0.95 and 1.03 (6H, 2 × d, *J* 6.9, CH_3CHCH_3), 2.40 (1H, m CH$_3$C*H*CH$_3$), 2.52 (3H, s, CH$_3$CO), 4.74 (1H, d, *J* 3.3, C*H*OH), 7.59–7.75 [1H, m, 6-H(Q)], 7.8–8.08 [2H, m, 8- and 7-H(Q)] and 8.36 [1H, d, *J* 8.1, 5-H(Q)]; minor rotamer (observable signals), 2.49 (3H, s, CH$_3$CO) and 4.93 (1H, d, *J* 3.0, C*H*OH); δ_C 20.6, 20.8 and 21.3 (3 × CH$_3$), 32.9 [(CH$_3$)$_2$*C*H], 72.9 (CHOH), 120.8 [*C*CO(Q)], 127.3, 127.5, 127.8 and 135.7 [4 × CH(Q)], 146.2 [*C*–C=N(Q)], 158.4 [*C*=N(Q)], 160.1 [*C*O(Q)] and 171.0 (CO). From comparison of the intensities of signals at δ 4.74 and δ 4.93 the ratio of rotamers is 1.5 : 1; *m*/*z* (%) (FAB) 276 (MH^+, 100), 216 (46) and 154 (51).

The unreacted 3-methylpiperidine was obtained as its hydrochloride salt as a colourless solid (21 mg, 78%).

Reaction of DAQ^1 9 with 1-phenylethylamine

General procedure **III** was followed using DAQ **9** (0.1 g, 0.2 mmol) and 1-phenylethylamine (49 mg, 0.4 mmol) in deuterochloroform (0.5 cm^3) and the solution reaction stirred at −20 °C for 2 h and then at 5 °C for 12 h. A proton NMR spectrum of the solution showed the presence of *N*-benzoyl- and *N*-acetyl-1-phenylethylamine **20** and **21** in a ratio of 3 : 1 by comparison of signals at δ 6.60 and 5.97 respectively with those of authentic samples at (δ 6.61 and 5.90) and by comparison of signals at δ 8.20 [5-H(Q) for both MAQs **7** and **16**] and 8.0 [2 × CH(Ar) for MAQ^1 **7**]. Chromatotron chromatography with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ^1 **7** (17 mg, 19%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide (*S*)-**20** as a colourless solid (21 mg, 46%); $[\alpha]_D$ = −16.3 (*c* 0.4, $CHCl_3$), ee 82% by comparison with an authentic sample $[\alpha]_D$ = −20 (*c* 0.4, $CHCl_3$).

Further elution with the same solvent mixture gave MAQ^1 **16** (32 mg, 41%) identical with that isolated previously.

Further elution with ethyl acetate gave amide (*R*)-**21** as a colourless solid (8 mg, 23%) $[\alpha]_D$ = +94 (*c* 0.5, $CHCl_3$) ee 76% by comparison with authentic sample $[\alpha]_D$ = +124 (*c* 0.5, $CHCl_3$).

The hydrochloride salt of unreacted 1-phenylethylamine was obtained as a colourless solid (26 mg, 80%), $[\alpha]_D$ = −1.1 (*c* 2.6, H_2O) ee 16% by comparison with hydrochloride salt prepared from enantiopure material $[\alpha]_D$ = +6.6 (*c* 2.7, H_2O).

Reaction of DAQ^1 9 with valine methyl ester hydrochloride

A solution of racemic valine methyl ester hydrochloride (68 mg, 0.4 mmol) in water (1 cm^3) was treated with aqueous sodium hydrogen carbonate and extracted with dichloromethane (1 cm^3). After drying and following general procedure **III**, the dichloromethane solution was added to a cold solution of

DAQ[1] **9** (0.1 g, 0.2 mmol) in dichloromethane (0.5 cm^3) and the mixture stirred at −10 °C for 2 h and then at 5 °C for 12 h. Unreacted alanine ethyl ester was extracted with aqueous hydrochloric acid (2 M, 1 cm^3). Chromatotron chromatography of the product from the organic extract with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **7** (3 mg, 3%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide (*S*)-**22** as a colourless solid (32 mg, 67%), mp 110–112 °C (from light petroleum) (lit.[13] mp 110.5–111 °C) $[\alpha]_D$ = +43.7 (*c* 0.65, $CHCl_3$), 94% ee by comparison with an enantiopure authentic sample $[\alpha]_D$ = +46.2 (*c* 0.65, $CHCl_3$), lit.[13] $[\alpha]_D$ = +46.0 (*c* 0.4, $CHCl_3$); δ_H 0.99 and 1.02 (6H, 2 × d, *J* 6.6, CH_3CHCH_3), 2.28 (1H, dh, *J*, 6.6 and 4.8, CH_3CHCH_3), 3.78 (3H, s, OCH_3), 4.79 (1H, dd, *J* 8.3 and 4.8, CHNH), 6.63 (1H, d, *J* 8.3, NH), 7.4–7.57 [3H, m, CH(Ar)] and 7.78–7.85 [2H, m, CH(Ar)].

Further elution with the same solvent mixture gave MAQ[1] **16** (51 mg, 65%) identical with that isolated previously.

The (*R*)-hydrochloride salt of valine methyl ester was recovered as a colourless solid (29 mg, 85%), $[\alpha]_D$ = −13.3 (*c* 0.9, H_2O), ee 92% by comparison with enantiopure (*S*)-valine methyl ester hydrochloride $[\alpha]_D$ = +14.4 (*c* 0.9, H_2O) lit.[14] $[\alpha]_D$ = +15.7 (*c* 2, H_2O).

Reaction of DAQ[1] 24a with 1-phenylethylamine

General procedure **III** was followed using DAQ[1] **24a** (80 mg, 0.15 mmol) and 1-phenylethylamine (36 mg, 0.30 mmol) and the solution stirred at −10 °C for 2 h and then at 5 °C for 35 h. After work-up, a proton NMR spectrum of the crude product showed presence of only MAQ[1] **13** and amide **25**. Chromatotron chromatography with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **13** (43 mg, 68%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide **25** as a colourless oil (22 mg, 63%) whose ^{1}H NMR spectrum showed it to contain a 8 : 1 mixture of diastereoisomers **25a**–**25b** (*R*,*R* : *S*,*R*) from comparison of signals at δ 2.15 and 2.16 with those of authentic samples.

The (*S*)-hydrochloride salt of unreacted 1-phenylethylamine was recovered as a colourless solid (19 mg, 81%), $[\alpha]_D$ = −4.6 (*c* 1.9, H_2O) (70% ee) by comparison with the rotation of an enantiopure sample $[\alpha]_D$ = +6.5 (*c* 2, H_2O).

Reaction of DAQ[1] 24b with 1-phenylethylamine

General procedure **III** was followed using DAQ[1] **24b** (0.1 g, 0.19 mmol) and 1-phenylethylamine (0.046 g, 0.38 mmol) and the reaction mixture stirred at −10 °C for 2 h and then at 5 °C for 24 h. After work-up, a proton NMR spectrum of the crude product showed the presence of amides **25** and **26** in a 2 : 1 ratio from integration comparison of signals at δ 6.42 and 5.81 in authentic samples (see below) together with the corresponding MAQ[1]s **13** and **27**.[5] Chromatotron chromatography with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **13** (17 mg, 22%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide **25** as a colourless solid (19 mg, 42%) whose ^{1}H NMR showed it to contain a ≥12 : 1 mixture of diastereoisomers **25d**–**25c** (*S*,*S* : *R*,*S*) (de 85%) by comparison of the intensities of signals at δ 2.16 and 2.17 with those of authentic samples (see below).

Further elution with the same solvent mixture gave a mixture of MAQ[1] **27** and amide **26** (~0.075 g) from comparison of signals at δ 5.50 to 5.12.

The hydrochloride salt of unreacted 1-phenylethylamine was recovered as a colourless solid (24 mg, 80%), $[\alpha]_D$ = −0.5 (*c* 2, H_2O) 7.7% ee by comparison with the rotation of an enantiopure sample of (*R*)-1-phenylethylamine hydrochloride, $[\alpha]_D$ = +6.5 (*c* 2, H_2O).

Reaction of DAQ[1] 24c with amines

(i) With 1-phenylethylamine. General procedure **III** was followed using DAQ[1] **24c** (0.1 g, 0.19 mmol) and 1-phenylethylamine (45 mg, 0.38 mmol) in dichloromethane (1 cm^3) and the solution stirred at −10 °C for 6 h. After work-up a proton NMR spectrum of the crude mixture showed the presence of only MAQ[1] **13** and amide **25**. Chromatotron chromatography with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **13** (64 mg, 82%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide **25** as a colourless oil (24 mg, 77%) whose ^{1}H NMR showed it to contain a 15 : 1 mixture of diastereoisomers **25c**–**25d** (de 88%) by comparison of the signals at δ 2.12 and 2.11 in the NMR spectrum with those of authentic samples.

The (*S*)-hydrochloride salt of unreacted 1-phenylethylamine was recovered as a colourless solid (26 mg, 90%), $[\alpha]_D$ = −5.9 (*c* 1.9, H_2O), 91% ee by comparison with the rotation of the enantiopure material $[\alpha]_D$ = −6.4 (*c* 1.9, H_2O).

(ii) With 2-methylpiperidine. General procedure **III** was followed using DAQ[1] **24c** (0.1 g, 0.19 mmol) and racemic 2-methylpiperidine (37 mg, 0.37 mmol) the mixture stirred at −20 °C for 2 h and then at 5 °C for 24 h. After work-up, flash chromatography with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **13** (61 mg, 77%) (R_f 0.38, 3 : 1 light petroleum–ethyl acetate) identical with an authentic sample.

Further elution with the same solvent mixture gave amide **28** as a colourless oil which crystallised on standing (37 mg, 79%) whose ^{1}H NMR (400 MHz, at 50 °C) showed it to contain a ~45 : 1 mixture of diastereoisomers **28a**–**28b** (de 95%) from comparison of the intensities of signals at δ 2.11 and 2.12.

The unreacted 2-methylpiperidine enantiomer was recovered as the colourless, solid hydrochloride (22 mg, 88%) and, following general procedure **IV**, was dissolved in pyridine and derivatised by reaction with (*S*)-2-acetoxypropanoyl chloride to give amide **28** (24 mg, 81%) whose ^{1}H NMR (at 400 MHz and 50 °C) showed it to contain a 17 : 1 mixture of diastereoisomers **28b**–**28a** (de 89%) by comparison of the signals at δ 2.10 and 2.09 respectively with those of authentic samples.

(iii) With 2-propylpiperidine. General procedure **III** was followed using DAQ[1] **24c** (0.1 g, 0.19 mmol), in dichloromethane with racemic 2-propylpiperidine (48 mg, 0.38 mmol) and the reaction mixture stirred at 5 °C for 24 h. After work-up, a proton NMR spectrum of the crude mixture showed the presence of only MAQ[1] **13** and amide **29**. Separation of these compounds was carried out using flash chromatography with light petroleum–ethyl acetate (3 : 1) as eluent to give MAQ[1] **13** (65 mg, 82%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide **29** as a colourless oil which crystallised on standing (32 mg, 71%) whose ^{1}H NMR spectrum showed it to contain a 50 : 1 mixture of diastereoisomers **29a**–**29b** (de 96%) from comparison of the intensities of signals at δ 2.11 and 2.13 in the NMR spectrum at 400 MHz and 50 °C. Assignment of absolute configuration to **29a** and **29b** (*S*,*S* and *S*,*R* respectively) was based on the *R*-configuration of the unreacted 2-propylpiperidine enantiomer, recovered as the colourless hydrochloride salt (27 mg, 87%); mp 219–221 °C (lit.[15] 218 °C); δ_H 1.0 (3H, t, *J* 6.7, CH_3), 1.3–2.2 (10H, m, 5 × CH_2), 2.8–3.1 (2H, m, NCH_2), 3.50 (1H, br d, *J* 6.7, CHN) and 9.28 and 9.60 (2H, 2 × s br, NHH); $[\alpha]_D$ = −6.7 (*c* 0.42, ethanol), lit.[10] $[\alpha]_D$ = −7.3 (*c* 0.33, ethanol). The ee of this salt is therefore ~90%.

Reaction of DAQ[1] 24d with 1-phenylethylamine

General procedure **III** was followed using DAQ[1] **24d** (0.1 g, 0.19 mmol) and 1-phenylethylamine (46 mg, 0.38 mmol) and the mixture stirred at −10 °C for 8 h. After work-up, an ^{1}H NMR spectrum of the crude reaction mixture showed the presence of

only MAQ[1] **13** and amide **25**. Chromatotron chromatography with light petroleum–ethyl acetate (3 : 1) as eluent gave MAQ[1] **13** (63 mg, 80%) identical with an authentic sample.

Further elution with the same solvent mixture gave amide **25** as a colourless oil whose ^{1}H NMR spectrum showed it to contain an 8 : 1 (78% de) mixture of diastereoisomers **25b** –**25a** by comparison of signals at δ 2.13 and 2.12 with those of authentic samples.

The (*R*)-hydrochloride salt of unreacted 1-phenylethylamine was recovered as a colourless solid (26 mg, 87%) $[\alpha]_D = +5$ (*c* 2, H_2O), 77% ee by comparison with enantiopure material $[\alpha]_D = +6.5$ (*c* 2, H_2O).

Reactions of DAQ[2] 31a

(i) With 1-phenylethylamine. General procedure **III** was followed using DAQ[2] **31a** (87 mg, 0.18 mmol) and 1-phenylethylamine (44 mg, 0.36 mmol) at −10 °C for 10 h. After work-up, a proton NMR spectrum of the crude reaction mixture showed the ratio of amides **21** to **25** was >23 : 1 from comparison of signals at δ 5.90 and 6.39 with those of authentic samples (δ 590 and 6.35) respectively (see below). Chromatotron chromatography with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ[2] **32** as a colourless solid (48 mg, 61%), identical with that isolated previously.

Further elution with the same solvent mixture gave MAQ[2] **30** as a colourless solid (3 mg, 4%) identical with that isolated previously.

Further elution with ethyl acetate gave (*R*)-*N*-(1-phenylethyl)acetamide **21** (19 mg, 63%); $[\alpha]_D = +116$ (*c* 0.5, $CHCl_3$), ee 93% by comparison with an authentic sample $[\alpha]_D = +124$ (*c* 0.5, $CHCl_3$); lit.[16] $[\alpha]_D = +129.5$ (*c* 1, $CHCl_3$).

Unreacted (*S*)-1-phenylethylamine was recovered as its hydrochloride salt as a colourless solid (25 mg, 87%); $[\alpha]_D = -5$ (*c* 2, H_2O), ee 77%, by comparison with an authentic sample $[\alpha]_D = +6.5$ (*c* 1, H_2O).

(ii) With alanine ethyl ester. A solution of racemic alanine ethyl ester hydrochloride (0.114 g, 0.74 mmol) was treated with excess sodium hydrogen carbonate and the free amino acid ester extracted into dichloromethane (2 cm^3). After drying, and following general procedure **III**, the dichloromethane solution was added to a cold solution of DAQ[2] **31a** (90 mg, 0.19 mmol) in dichloromethane (0.5 cm^3) and the mixture stirred at −10 °C for ~10 h. Unreacted alanine ethyl ester was extracted with aqueous hydrochloric acid (2 M, 1 cm^3). The ratio of amides **33** and **34** in the crude product was ~1 : 1 by comparison of the signals at δ 6.67 and 6.13 with those of authentic samples (δ 6.68 and 6.13) respectively. Chromatotron chromatography of the crude product with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ[2] **32** (32 mg, 39%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide **33** as a colourless oil (16 mg, 36%) whose ^{1}H NMR spectrum showed it to contain a 1 : 1 mixture of diastereoisomers **33a**–**33b** (*R*,*S*–*S*,*S*) from comparison of the intensities of signals *inter alia* at δ 5.12 and 5.16 with those in the NMR spectra of an authentic mixture (see below).

Further elution with the same solvent mixture gave MAQ[2] **30** as colourless crystals (23 mg, 33%) identical with an authentic sample.

Further elution with ethyl acetate gave (*R*)-amide **34** as a colourless oil (7 mg, 23%); δ_H 1.29 (3H, t, *J* 7.1, CH_3CH_2O), 1.39 (3H, d, *J* 7.4, CH_3CHN), 2.02 (3H, s, CH_3CO), 4.21 (2H, q, *J* 7.1, CH_3CH_2O), 4.58 (1H, dq, *J* 7.4 and 7.0, CH_3CHNH) and 6.1 (1H, br, NH), $[\alpha]_D = -15.7$ (*c* 0.7, $CDCl_3$), ee > 97% by comparison with an authentic sample of the (*S*)-enantiomer $[\alpha]_D = +15.7$ (*c* 0.7, $CDCl_3$) (see below).

The hydrochloride salt of alanine ethyl ester was recovered as a colourless solid (51 mg, 79%).

Enantiopurity assay of DAQ[2] 31a

The reaction above was repeated under the same conditions but using pure (*S*)-alanine ethyl ester hydrochloride (98 mg, 0.64 mmol) and DAQ[2] **31a** (62 mg, 0.13 mmol). After separation using chromatotron chromatography as above, a proton NMR spectrum of the crude product showed the presence of only one amide ester diastereoisomer **33b** (*S*,*S*).

Reactions of DAQ[2] 31b

(i) With 1-phenylethylamine. General procedure **III** was followed using DAQ[2] **31b** (80 mg, 0.17 mmol) and racemic 1-phenylethylamine (40 mg, 0.33 mmol). After work-up, a proton NMR spectrum of the crude mixture showed the ratio of amides **21** to **25** was ~1 : 1 respectively by comparison of signals at δ 6.10 and 6.41 with those of authentic samples and confirmed by product isolation (see below). Chromatotron chromatography with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ[2] **30** as a colourless solid (27 mg, 37%) identical with that isolated previously.

Further elution with the same solvent mixture gave amide **25** as a colourless oil (13 mg, 33%) whose ^{1}H NMR spectrum showed it to contain a 9 : 1 mixture of diastereoisomers **25c**–**25d** (*S*,*R*)–(*S*,*S*) from comparison of signals at δ 2.13 and 2.12 with those of authentic samples (see below).

Further elution with the same solvent mixture gave MAQ[2] **32** as a colourless solid (21 mg, 34%) identical with that isolated previously.

Further elution with ethyl acetate gave (*S*)-*N*-(1-phenylethyl)acetamide **21** (9 mg, 33%); $[\alpha]_D = -100$ (*c* 0.4, $CHCl_3$) ee 85% by comparison with an authentic sample $[\alpha]_D = +117$ (*c* 0.4, $CHCl_3$), prepared as described below.

Unreacted 1-phenylethylamine was recovered as hydrochloride salt as a colourless solid (21 mg, 80%); $[\alpha]_D = -0.5$ (*c* 2.1, H_2O), ee 7.7%, by comparison with the rotation of an enantiopure sample $[\alpha]_D = +6.5$ (*c* 2, H_2O).

(ii) With alanine ethyl ester. A solution of racemic alanine ethyl ester hydrochloride (60 mg, 0.39 mmol) in water (1 cm^3) was converted to free amine by addition of aqueous sodium hydrogen carbonate and extracted into dichloromethane (1 cm^3). After drying, and following general procedure **III**, the dichloromethane solution was added to a cold solution of DAQ[2] **31b** (0.09 g, 0.19 mmol) in dichloromethane (0.5 cm^3) and the mixture stirred at −10 °C for 6 h. The ratio of amides **33** to **34** was ~20 : 1 based on yields of recovered MAQ[2] **30** and MAQ[2] **32** (see below). Separation of these compounds was carried out using a chromatotron with light petroleum–ethyl acetate (2 : 1) as eluent and gave MAQ[2] **32** (3.5 mg, 3%) as colourless crystals (R_f 0.32), mp 183–185 °C (from light petroleum) identical with an authentic sample (see above).

Further elution with the same solvent mixture gave *amide* **33** as a colourless oil (34 mg, 77%) whose ^{1}H NMR spectrum showed it to contain a ~30 : 1 mixture of diastereoisomers **33b**–**33a** (*S*,*S*–*R*,*S*) from comparison of the intensities of signals at δ 5.23 and 5.19 with those at δ 5.16 and 5.12 in the spectra of authentic samples (Found: MH^+ 232.1185. $C_{10}H_{17}NO_5$ requires MH^+ 232.1185); ν_{max}/cm^{-1} 3440s, 1740s, 1680s, 1525s and 1455s; δ_H 1.30 (3H, t, *J* 7.1, CH_3CH_2O), 1.42 (3H, d, *J* 7.1, CH_3CHN), 1.47 (3H, d, *J* 6.9, CH_3CHOAc), 2.17 (3H, s, CH_3CO_2), 4.23 (2H, q, *J* 7.1, CH_3CH_2O), 4.56 (1H, m, CH_3CHNH), 5.23 (1H, q, *J* 6.9, CH_3CHOAc) and 6.68 (1H, d br, *J* 6.4, NH); minor diastereoisomer (observable signal) 5.22 (1H, q, *J* 6.9, CH_3CHOAc).

Further elution with the same solvent mixture gave MAQ[2] **30** as colourless crystals (49 mg, 71%); (R_f 0.34; 1 : 1 ethyl acetate–petroleum ether) identical with an authentic sample (see above).

The hydrochloride salt of unreacted (*R*)-alanine ethyl ester was recovered as a colourless solid (49 mg, 86%), $[\alpha]_D = -7.5$

(*c* 2, MeOH) ee 93% by comparison with an authentic sample $[\alpha]_D = -8$ (*c* 2, MeOH).

Reaction of DAQ 35 with 1-phenylethylamine

General procedure **III** was followed using DAQ **35** (subsequently shown to be enantio-impure; see below) (75 mg, 0.19 mmol) and 1-phenylethylamine (45 mg, 0.37 mmol) and the solution stirred at −20 °C for 2 h and then at 0 °C for 10 h. After work-up, chromatotron chromatography of the product with light petroleum–ethyl acetate (1 : 1) as eluent gave amide **25** as a colourless oil (33 mg, 75%) as a 2 : 1 ratio of diastereoisomers **25c**–**25d** by comparison of the signals at δ 2.11 and 2.10 with those of authentic samples

Further elution with the same solvent mixture gave MAQ **39** (30 mg, 60%) (R_f 0.36) identical with authentic material.[5]

The hydrochloride salt of unreacted (*S*)-amine was obtained as a colourless solid (17 mg, 76%), $[\alpha]_D = -2.2$ (*c* 1.7, H_2O) ee 34% by comparison with the specific rotation of authentic sample $[\alpha]_D = -6.5$ (*c* 2, H_2O).

Enantiopurity assay of DAQ 35

The reaction was repeated under the same conditions but using pure (*S*)-1-phenylethylamine (72 mg, 0.60 mmol) and DAQ **35** (60 mg, 0.15 mmol). An NMR spectrum of the crude product showed the presence of an 8 : 1 ratio of amide diastereoisomers **25c**–**25d**; DAQ **35** is therefore of 77% ee.

Reaction of DAQ[2] 37a with amines

(i) With 1-phenylethylamine (2 eq.). General procedure **III** was followed using DAQ[2] **37a** (76 mg, 0.14 mmol) and racemic 1-phenylethylamine (33 mg, 0.27 mmol) in dichloromethane (0.5 cm^3) and the solution stirred at −20 °C for 2 h. After work-up, chromatotron chromatography of the product with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ[2] **32** (51 mg, 85%) (R_f 0.32), identical with that prepared above.

Further elution with the same solvent mixture gave amide **25** as a colourless oil (25 mg, 75%) as a 5 : 1 ratio of diastereoisomers **25c**–**25d** (67% de) by NMR spectroscopy and comparison with authentic samples as previously.

The hydrochloride salt of unreacted (*S*)-amine was obtained as a colourless solid (18 mg, 84%), $[\alpha]_D = -3.9$ (*c* 1.5, H_2O), ee 60% comparison with an authentic sample $[\alpha]_D = -6.5$ (*c* 1.5, H_2O).

(ii) With 1-phenylethylamine (5 eq.). Repetition of the experiment above using 5 eq. of 1-phenylethylamine gave amide **25** as a colourless oil as an 8 : 1 ratio of diastereoisomers **25c**–**25d** (78% de).

Enantiopurity assay on DAQ[2] 37a

The reaction above was repeated under the same conditions but using pure (*R*)-1-phenylethylamine (22 mg, 0.18 mmol) and DAQ[2] **37a** (33 mg, 0.06 mmol). An ^{1}H NMR spectrum of the crude product showed only one signal for the CH_3CO_2 of amide **25c** showing DAQ[2] **37a** is enantiopure.

(iii) With 2-methylpiperidine (2 eq.). General procedure **III** was followed using DAQ[2] **37a** (86 mg, 0.16 mmol) and racemic 2-methylpiperidine (32 mg, 0.32 mmol) in dichloromethane (0.5 cm^3) and the solution stirred at −30 °C for 3 h and then at 5 °C for ~24 h. After work-up, a ^{1}H NMR spectrum of the crude mixture (at 50 °C and 400 MHz) showed the presence of *N*-2-[(*S*)-acetoxypropanoyl]-2-methylpiperidine **28a**–**28b** as a 33 : 1 ratio of diastereoisomers (94% de) by comparison of the signals at δ 2.096 and 2.103 with those of authentic samples (see below).

The unreacted 2-methylpiperidine was recovered as the solid, colourless hydrochloride salt (18 mg, 90%). A solution of this salt (18 mg) in water (1 cm^3) was basified with sodium hydroxide (2 M), the 2-methylpiperidine was extracted with ether (2 × 1.5 cm^3), and the combined extracts were dried over powdered sodium hydroxide and the ether removed carefully under reduced pressure to give (*R*)-2-methylpiperidine (9 mg, 69%) $[\alpha]_D = -7.8$ (*c* 0.9, ethanol) ee 89% by comparison with the specific rotation of an enantiopure sample $[\alpha]_D = -8.7$ (*c* 1.5, ethanol) (see below).

(iv) With 2-methylpiperidine (5 eq.). Repetition of the experiment above using 5 eq. of 2-methylpiperidine gave amides **27a** and **27b** in a ratio of ~40 : 1 (de 95%).

(v) With 2-propylpiperidine (4 eq.). As in the previous experiment, a solution of DAQ[2] **37a** (0.1 g, 0.18 mmol) and 2-propylpiperidine (coniine) (0.092 g, 4 eq.) in dichloromethane (1 cm^3) was stirred at 5 °C for ~16 h. After work-up, chromatotron chromatography with light petroleum–ethyl acetate (2 : 1) as eluent gave MAQ[2] **32** (65 mg, 82%) (R_f 0.32).

Further elution with the same solvent mixture gave *N*-((*S*)-2-acetoxypropanoyl)-2-propylpiperidine **29** as a colourless oil (31 mg, 71%) as a ~45 : 1 ratio of diastereoisomers **29a**–**29b** (*S*,*S*–*R*,*S*) (96% de) by comparison of signals at δ 2.094 and 2.107 with those of the mixture isolated previously (using DAQ[1] **24c**).

Reaction of *N*-[(*S*)-2-acetoxypropanoyl-*N*-ethanoylamino]-phthalimide (DAP) 41 with 1-phenylethylamine

General procedure **III** was followed using DAP **41** (0.1 g, 0.31 mmol) and racemic 1-phenylethylamine (76 mg, 0.62 mmol) in dichloromethane and the reaction mixture stirred for 6 h at −10 °C (0.5 cm^3). After work-up, a ^{1}H NMR spectrum of the crude mixture showed the ratio of amides **21** to **25** was 1.2 : 1 respectively by comparison of signals at δ 5.90 and 6.39 with those of authentic samples. Chromatotron chromatography with light petroleum–ethyl acetate (1 : 1 containing 2% methanol) as eluent gave a 52 : 48 ratio of amides **25d**–**25c** by comparison with authentic samples (see below).

Further elution with the same solvent mixture gave a pure sample of amide **21** (15 mg, 30%) $[\alpha]_D = +8.9$ (*c* 0.4, $CHCl_3$), ee 7.8% by comparison with an authentic sample.

Enantiopurity assay on DAP 41

The reaction above was repeated under the same conditions but using pure (*S*)-1-phenylethylamine (0.085 g, 0.7 mmol) and DAP **41** (0.11 g, 0.35 mmol). After work-up, a ^{1}H NMR spectrum of the crude product showed the same ratio of amides **21**–**25** (1.2 : 1 respectively). After separation using chromatotron as above, a proton NMR spectrum showed the presence of only one diastereoisomer (**25d**) of amide **25**: DAP **41** is therefore enantiopure.

Preparation of authentic samples

General procedure V for *N*-acylation of amines. To a stirred solution of the amine (0.2 g) in dichloromethane was added pyridine (2 eq.) followed by dropwise addition of the acid chloride (1.3 eq.). After 1 h, further dichloromethane (10 ml) was added, the solution was then washed successively with saturated aqueous sodium hydrogen carbonate, hydrochloric acid (2 M), water, then dried and the solvent removed under reduced pressure to give the amide.

The following were prepared by the above method.

(i) *N*-Acetylpyrrolidine as a pale yellow oil (84%), δ_H (300 MHz) 1.89–2.0 (4H, m, 2 × CH_2), 2.1 (3H, s, CH_3CO) and 3.42 (4H, struct. m, 2 × CH_2N), lit.[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86–2.0 (m, 4H), 2.06 (s, 3H) and 3.45 (dd, *J* 7.1, 16.0, 4 H).

(ii) *N*-Acetylpiperidine as a pale yellow oil (83%), δ_H (300 MHz) 1.45–1.65 (6H, m, 3 × CH_2), 2.05 (3H, s, CH_3CO) and 3.37 and 3.54 (4H, 2 × t, *J* 5.6, 2 × CH_2N); lit.[18] ^{1}H NMR

($CDCl_3$) δ 1.61 (m, 6H, 3 × CH_2), 2.06 (s, 3H, $COCH_3$) and 3.50 (m, 4H, 2 × CH_2).

(iii) *N*-Benzoylpyrrolidine as a light brown oil (76%), δ_H 1.72–1.96 (4H, m, 2 × CH_2), 3.40 and 3.60 (4H, 2 × t, *J* 6.6, 2 × CH_2N), 7.3–7.4 [3H, m, 3 × CH(Ph)] and 7.45 [2H, m, 2 × CH(Ph)]; lit.[19] δ_H 1.80–2.00 (4H, m, 2 × CH_2), 3.40, 3.64 (2 × 2H, 2 × t, *J* 6.4, 2 × CH_2N), 7.35–7.50 (5H, m, ArH).

(iv) *N*-Benzoylpiperidine as a pale yellow oil (81%), δ_H 1.3–1.9 (6H, m, 3 × CH_2), 3.30 and 3.70 (4H, 2 × s, br, 2 × CH_2N) and 7.3–7.4 [5H, m, CH(Ph)]; lit.[20] 7.42–7.36 (m, 5H), 3.72 (br s, 2H), 3.34 (br s, 2H), 1.68 (m, 4H) and 1.52 (m, 2H).

(v) (*S*)-*N*-Benzoyl-1-phenylethylamine **20** from (*S*)-1-phenylethylamine as a pale yellow oil (0.30 g, 81%), δ_H 1.55 (3H, d, *J* 6.9, CH_3CHNH), 5.3 (1H, q, CH_3C*H*NH), 6.61 (1H, br d, *J* 6.9, NH) and 7.1–7.9 [10H, m, CH(Ph)]; $[\alpha]_D$ = −20 (*c* 0.4, $CHCl_3$), lit.[21] $[\alpha]_D$ = −20.07 (1.02, $CHCl_3$).

(vi) (*R*)-*N*-Acetyl-1-phenylethylamine **21** from (*R*)-1-phenylethylamine as a light yellow oil (0.23 g, 85%), δ_H 1.29 (3H, d, *J* 7.0, CH_3CHNH), 1.76 (3H, s, CH_3CO), 4.9 (1H, m, CH_3C*H*NH), 5.90 (1H, s br, NH) and 7.0–7.2 [5H, m, CH(Ph)]; $[\alpha]_D$ = +117 (*c* 0.4, $CHCl_3$); 124 (*c* 0.5, $CHCl_3$) lit.[16] $[\alpha]_D$ = +129.5 (*c* 1, $CHCl_3$).

(vii) (2*S*,1′*R*)-2-Acetoxy-*N*-(1-phenylethyl)propanamide **25c** using (*R*)-1-phenylethylamine and (*S*)-2-acetoxypropanoyl chloride as colourless crystals (82%); δ_H 1.55 and 1.60 (6H, 2 × d, *J* 6.9, 2 × CH_3), 2.12** (3H, s, CH_3CO_2), 5.11–5.30 (2H, m, 2 × C*H*), 6.35 (1H, br, NH) and 7.30–7.48 [5H, m, 5 × CH(Ph)].

(viii) (2*S*,1′*S*)-2-Acetoxy-*N*-(1-phenylethyl)propanamide **25d** using (*S*)-1-phenylethylamine and (*S*)-2-acetoxypropanoyl chloride as a colourless oil (92%); δ_H 1.46 and 1.51 (6H, 2 × d, *J* 6.9, 2 × CH_3), 2.11 (3H, s, CH_3CO_2), 5.08–5.20 (2H, m, 2 × C*H*), 6.40 (1H, br d, *J* 7.4, NH) and 7.20–7.38 [5H, m, 5 × CH(Ph)].

(ix) (*R*)-*N*-(2-Methylpropanoyl)-1-phenylethylamine **26** from (*R*)-1-phenylethylamine as a colourless solid (from ethyl acetate) (84%) δ_H 1.14 (6H, 2 × d, *J* 6.6, CH_3CHCH_3), 1.47 (3H, *J* 6.9, CH_3CH), 2.34 (1H, h, CH_3C*H*CH_3), 5.12 (1H, m, CH_3C*H*OAc), 5.81 (1H, br s, NH) and 7.2–7.38 [5H, m, 5 × CH(Ar)]; $[\alpha]_D$ = +76.7 (*c* 0.3, $CHCl_3$).

(x) *N*-[(*S*)-2-Acetoxypropanoyl]alanine ethyl ester **33a** and **33b** from racemic alanine ethyl ester hydrochloride and (*S*)-2-acetoxypropanoyl chloride. After work-up the pale yellow oil (0.41 g) obtained was purified by column chromatography over silica with light petroleum–ethyl acetate (2 : 1) as eluent to give amides **33a** and **33b** (ratio 1 : 1) as a colourless oil (0.27 g, 90%) (Found: MH^+ 232.1185. $C_{10}H_{17}NO_5$ requires MH^+ 232.1185); ν_{max}/cm^{-1} 3440s, 1740s, 1680s, 1525s and 1455s; δ_H 1.22 and 1.23 (6H, 2 × t, *J* 7.1, C$H_3$$CH_2O$), 1.35 and 1.37 (6H, 2 × d, *J* 7.1, CH_3CHN), 1.40 and 1.41 (6H, 2 × d, *J* 6.9, CH_3CHOAc), 2.09 (6H, s, CH_3CO_2), 4.14 and 4.15 (4H, 2 × q, *J* 7.1, CH_3CH_2O), 4.49 (2H, m, *J* 7.1, CH_3C*H*NH), 5.12 and 5.16 (2H, 2 × q, *J* 6.9, CH_3C*H*OAc) and 6.68 (2H, d, *J* ~6, NH); δ_C 14.4, 18.1, 18.7 and 21.4 (4 × CH_3), 48.2 (CH_3*C*HNH), 62.0 (CH_3*C*H_2O), 70.8 (*C*HOAc) and 169.8, 170.3 and 173.1 (3 × CO); *m*/*z* (%) (FAB) 232 (MH^+, 100) and 190 (24).

An authentic sample of **33b** was prepared as described above from (*S*)-alanine ethyl ester hydrochloride as a colourless oil δ_H 1.29 (3H, t, *J* 7.1, C$H_3$$CH_2O$), 1.44 (3H, d, *J* 7.1, CH_3CHN), 1.48 (3H, d, *J* 6.9, CH_3CHOAc), 2.16 (3H, s, CH_3CO_2), 4.21 (2H, q, *J* 7.1, $CH_3$$CH_2O$), 4.56 (1H, q, *J* 7.1, CH_3C*H*NH), 5.19 (1H, q, *J* 6.9, CH_3CHOAc) and 6.77 (1H, d, br, *J* 6.4, NH).

(xi) *N*-[(*S*)-2-Acetoxypropanoyl]-(*S*)-2-methylpiperidine **28a** from (*S*)-2-methylpiperidine (0.1 g scale) [prepared by resolution of the racemic amine with (−)-mandelic acid according to the literature method[7] $[\alpha]_D$ = +8.9 (*c* 2, ethanol), lit.[7] $[\alpha]_D$ = 7.2 (*c* 6, 95% ethanol)] and (*S*)-2-acetoxypropanoyl chloride. After work-up, column chromatography of the crude product (0.12 g) over silica gave amide **28a** as a colourless oil (0.15 g, 75%).

(xii) *N*-[(*S*)-2-Acetoxypropanoyl]-(*R*)-2-methylpiperidine **28b** from (*R*)-2-methylpiperidine (0.1 g scale) [prepared by resolution of the racemic amine with (+)-mandelic acid according to the literature method[7] $[\alpha]_D$ = −8.5 (*c* 0.5, methanol)] and (*S*)-2-acetoxypropanoyl chloride. Chromatography of the product as above gave *amide* **28b** as a colourless oil (0.16 g, 80%). For a 1 : 1 mixture of **28a** and **28b** (Found: MH^+ 214.1655. $C_{13}H_{23}NO_3$ requires MH^+ 214.1655); ν_{max}/cm^{-1} 1704s, 1645s, 1510s, 1375s and 1250s; δ_H (mixture of *N*–*C*O rotamers) (2-methyl axial;[22] rotamer A, C=*O*/C_2 *cis*, rotamer B, C=*O*/C_6 *cis*), 1.25–1.45 (6H, m, CH_3CHOAc and CH_3CHN), 1.46–1.80 (6H, m, 3 × CH_2), 2.1 (3H, s, CH_3CO_2), 2.65 [0.5H, ddd, *J* ~12.5, ~12.5 and ~2, H_6-ax. (A or B)], 3.08 [0.5H, ddd, *J* ~12.5, 12.5 and ~2, H_6-ax. (B or A)], 3.52 (0.5H, br d, *J* ~12, H_6-eq. A), 3.95 (0.5H, br m, H_2-eq. B), 4.37 (0.5H, dd, *J* ~12.5 and ~4, H_6-eq. B), 4.83 (0.5H, m, H_2-eq. A) and 5.33 [1H, 2 × q, *J* ~7, CH_3C*H* (A and B)]; from the signals at δ 2.65 and 3.08 the ratio of *N*–*C*O rotamers was 1 : 1. Examination of the product by NMR spectroscopy (400 MHz at +50 °C) showed it to be a 1 : 1 mixture of diastereoisomers from comparison of signals at δ_H 2.11 and 2.12. As for **25c/d** above δ for both signals varied depending on concentration/spectrum reproducibility but $\Delta\delta$ was maintained at 0.01 ppm. δ_C 15.8, 17.2 and 21.2 (3 × CH_3), 19.1 (3 × CH_2), 45.0 (CHN), 67.5 (CH_3C*H*OAc) and 169.1 and 171.0 (2 × CO).

(xiii) (*S*)-2-Acetoxypropanoyl-2-propylpiperidine **29** from racemic 2-propylpiperidine and (*S*)-2-acetoxypropanoyl chloride. After work-up, column chromatography over silica with light petroleum–ethyl acetate (1 : 1) as eluent gave *amide* **29** as a colourless oil (0.164 g, 86%) as a mixture of diastereoisomers (Found: MH^+ 242.1756. $C_{13}H_{23}NO_3$ requires MH^+ 242.1756); ν_{max}/cm^{-1} 1740s, 1643s, 1510s, 1375s and 1250s; δ_H (mixture of *N*–*C*O rotamers) (2-propyl axial; rotamer A, C=*O*/C_2 *cis*, rotamer B, C=*O*/C_6 *cis*) 0.85–1.05, 1.2–1.85 (13H, 2 × m, 5 × CH_2, CH_3), 2.12 (3H, s, CH_3CO_2), 2.66 (0.25H, br dd, *J* ~12.5 and 12.5, H_6-ax. B), 3.17 (0.75H, ddd, *J* 12.5, 12.5 and ~2, H_6 ax.-A), 3.58 (0.75H, br d, *J* 12, H_6-aq. A), 3.93 (0.25H, m, H_2-eq. B), 4.48 (0.25H, br d, *J* ~12, H_6-eq. B), 4.72 (0.75H, m, H_2-eq. A), 5.37 (0.75H, q, *J* 7, CH_3C*H*, A) and 5.48 (0.25H, q, *J* 7, B) (ratio A : B is 3 : 1). Examination of the product by NMR spectroscopy (400 MHz at +50 °C) showed it to be a 1 : 1 mixture of diastereoisomers from comparison of signals at δ_H 2.11 and 2.13; δ_C 14.4, 17.1 and 19.6 (3 × CH_3), 19.2, 25.7, 26.4, 26.6, 28.3 and 28.5 (6 × CH_2), 48.8 (CHN), 68.9 (CH_3C*H*OAc) and 169.2 and 170.8 (2 × CO); *m*/*z* (%) (FAB) 242 (MH^+, 100), 200 (48) and 154 (24).

(xiv) (*S*)-*N*-Benzoyl-2-methylpiperidine **12** from (*S*)-(+)-2-methylpiperidine [prepared by resolution of the racemic amine with (−)-mandelic acid according to the literature method[7] $[\alpha]_D$ = +8.9 (*c* 2, ethanol), lit.[7] $[\alpha]_D$ = 7.2 (*c* 6, 95% ethanol)] as a colourless oil (80%) which solidified after setting aside for two days, mp 43–45 °C (from light petroleum) (lit.[22] 42–43 °C) $[\alpha]_D$ = +32.9 (*c* 0.8, $CHCl_3$). δ_H (1 : 1 mixture of *N*–*C*O rotamers) (2-methyl axial; rotamer A, C=*O*/C_2 *cis*, rotamer B, C=*O*/C_6 *cis*) 1.14 and 1.25 (3H, d, *J* 7, CH_3CHN), 1.40–1.83 (6H, m, 3 × CH_2), 2.91 [0.5H, ddd, *J* ~12, ~12 and ~2, H_6-ax. (A or B)], 3.13 [0.5H, ddd, *J* ~12, ~12 and ~2, H_6-ax. (B or A)], 3.55 (0.5H, br d, *J* ~12, H_6-eq. A), 4.01 (0.5H, m, H_2-eq. B), 4.60 (0.5H, br d, *J* ~12, H_6-eq. B) and 5.06 (0.5H, m, H_2-eq. A).

(xv) *N*-Acetyl-2-methylpiperidine **15** as a colourless liquid (84%), δ_H ($CDCl_3$, 400 MHz, −40 °C) (1 : 1 mixture of NC=O rotamers) (2-methyl axial; rotamer A C=O/C_2 *cis*; rotamer B C=O/C_6 *cis*) 1.15 and 1.25 (3H, 2 × d, *J* 7.0, CH_3CHN), 1.3–1.8 (6H, m, 3 × CH_2), 2.12 and 2.15 (3H, 2 × s, CH_3CO), 2.67 and 3.19 [1H, 2 × ddd, *J* 16.0, 14.0 and 3.0, H_6-ax. (A and B)], 3.61

** The signals at δ 2.12 in **25c** and δ 2.11 in **25d** used for diastereoisomer differentiation, both varied depending on concentration/spectrum reproducibility but the $\Delta\delta$ was 0.010 ± 0.002 ppm with **25d** at higher and **25c** at lower chemical shift as shown by addition of incremental amounts of either one of them and observing the increase in the corresponding resonance. For spectroscopic comparison **25c** ≡ **25b** and **25d** ≡ **25a**.

Table 1 Crystal data

	9	11	31a	31b	37a
Formula	$C_{27}H_{35}N_3O_4Si$	$C_{23}H_{29}N_3O_3Si$	$C_{28}H_{25}N_3O_5$	$C_{28}H_{25}N_3O_5$	$C_{31}H_{29}N_3O_7$
M	493.67	423.58	483.51	483.51	555.57
System	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_1/n$	$P2_12_12_1$	$P2_12_12_1$
a/Å	9.649(2)	8.889(2)	10.167(2)	9.280(2)	11.315(3)
b/Å	9.283(6)	11.391(2)	25.688(3)	14.826(1)	14.210(2)
c/Å	15.152(5)	23.399(4)	10.311(2)	18.246(2)	17.368(5)
α/°	90	90	90	90	90
β/°	96.69(1)	90	115.86(1)	90	90
γ/°	90	90	90	90	90
u/Å^{-3}	1347.9(10)	2369.1(8)	2423.3(7)	2510.4(6)	2792.4(11)
T/K	293	200	200	200	190
Z	2	4	4	4	4
μ(Mo-Kα)/mm^{-1}	0.123	0.126	0.092	0.089	0.095
Refln. measured	3369	2759	5740	3166	3891
Refln. independent	2842	2687	4685	3088	3692
Rint	0.020	0.015	0.049	0.021	0.029
$R1$ $\{I > 2\sigma(I)\}$	0.045	0.054	0.107	0.059	0.054
w$R2(F^2)$ all data	0.099	0.139	0.359	0.144	0.146

(0.5H, dd, J 14.0 and 3.0, H_6-eq. A), 4.13 (0.5H, m, H_2-eq. B), 4.49 (0.5H, dd, J 14.0 and 3.0, H_6-eq. B) and 4.90 (1H, m, H_2-eq. A).

(xvi) (*R*)-*N*-Benzoyl-3-methylpiperidine **17** from (*R*)-3-methylpiperidine [prepared by resolution of the racemic amine with (+)-tartaric acid by the literature method[9] $[\alpha]_D = -3.3$ (c 25, methanol), lit.[9] $[\alpha]_D = -0.61$ (neat)] as a light yellow oil (71%); δ_H (300 MHz) (1 : 1 mixture of *N*–*C*O rotamers) 1.35–1.92 (4H, br m, 2 × CH_2), 2.44 and 2.61 (1H, 2 × m, CH), 2.81 and 2.94 (1H, 2 × m, CH), 3.62 (1H, m, CH), 4.54 (1H, m, CH) and 7.35–7.45 [5H, m, CH(Ph)]; $[\alpha]_D = -43$ (c 0.3, $CHCl_3$) or $[\alpha]_D = -51$ (c 1, methanol); lit.[23] $[\alpha]_D = -51.9$ (c 1, methanol), lit.[24] (for (*S*)-enantiomer) $[\alpha]_D = +49.5$ (c 1, methanol).

(xvii) (*S*)-*N*-Benzoylvaline methyl ester **22** from L-valine methyl ester hydrochloride. Column chromatography of the residual pale yellow oil over silica with light petroleum–ethyl acetate gave (*S*)-*N*-benzoylvaline methyl ester **22** as a viscous colourless oil which crystallised on standing (91%), mp 110–112 °C (from light petroleum), $[\alpha]_D = +46.2$ (c 0.65, $CHCl_3$), lit.[13] mp 110.5–111 °C, $[\alpha]_D = +46.0$ (c 0.4, $CHCl_3$); δ_H 0.99 and 1.01 (6H, 2 × d, J 6.6, CH_3CHCH_3), 2.28 (1H, dh, J 6.6 and 4.8, CH_3CHCH_3), 3.78 (3H, s, OCH_3), 4.78 (1H, dd, J 8.3 and 4.8, CHNH), 6.68 (1H, d, J 8.3, NH), 7.37–7.55 [3H, m, CH(Ar)] and 7.78–7.83 [2H, m, CH(Ar)].

(xviii) (*S*)-*N*-Ethanoylalanine ethyl ester **34** from L-alanine ethyl ester hydrochloride. The pale yellow oil obtained was purified by column chromatography over silica with light petroleum–ethyl acetate to give (*S*)-*N*-ethanoylalanine ethyl ester **34** as a colourless viscous oil which crystallised on standing (0.19 g, 91%). ν_{max}/cm^{-1} 3440s, 1740s, 1670s, 1515s and 1455s; δ_H 1.28 (3H, t, J 7.1, CH_3CH_2O), 1.39 (3H, d, J 7.4, CH_3CHN), 2.02 (3H, s, CH_3CO_2), 4.19 (2H, q, J 7.1, CH_3CH_2O), 4.49 (1H, dq, J 7.4 and ~6.0, CH_3CHNH) and 6.13 (1H, d, J ~6.0, NH); δ_C 13.1, 17.1 and 21.9 (3 × CH_3), 47.1 (CH_3CHNH), 60.4 (CH_3CH_2O) and 169.1 and 172.3 (2 × CO); $[\alpha]_D = +15.7$ (c 0.7 $CHCl_3$) lit.[25] $[\alpha]_D = +10.4$ (c 1, $CHCl_3$); δ_H 1.29 (t, J 7, 3H), 1.4 (d, J 7, 3H), 2.02 (s, 3H), 4.2 (q, J 7, 2H), 4.6 (q, J 7, 1H) and 6.2 (m, 1H).

Crystallography

All data were measured on a Bruker P4 diffractometer and collected using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) (Table 1). Absorption corrections were not applied to the data sets. The structures were solved by direct methods and refined by full-matrix least squares cycles on F^2 for all data, using SHELXTL [SHELXTL–an integrated system for solving, refining and displaying crystal structures. Version 5.10, Bruker Analytical X-ray Systems, Madison, WI, USA, 1997]. All non hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were included in refinement cycles riding on bonded atoms. ††

†† CCDC reference number(s) 167260–167264. See http://www.rsc.org/suppdata/p1/b1/b105917n for crystallographic files in .cif or other electronic format.

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