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# Stereoisomerism in 3-[*N*-(2-acetoxypropanoyl)-*N*-acylamino]-quinazolin-4(3*H*)-ones, enantioselective acylating agents

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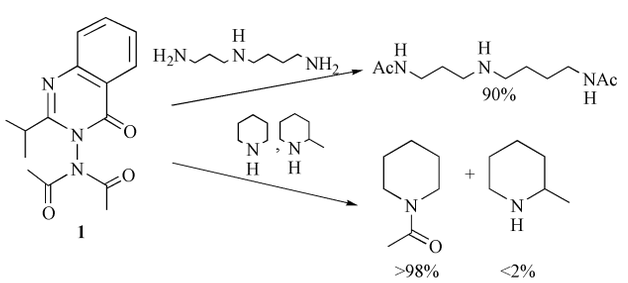
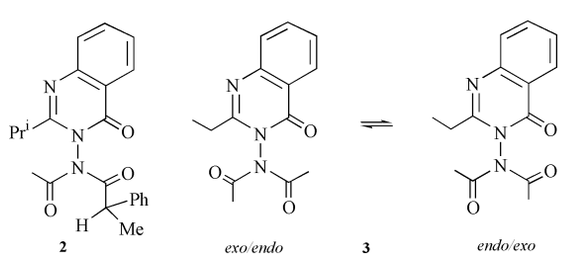
The title compounds diacylaminoquinazolinones (DAQs) are enantioselective acylation agents for amines and a detailed study of their stereostructures was undertaken with the aim of understanding how this enantioselectivity arises. The N–N bond in these DAQs is a chiral axis. Even where both *N*-acyl groups are (*S*)-2-acetoxypropanoyl, the N–N bond is still a chiral axis because in the most stable conformation of the planar imide moiety, one *exo*/*endo* orientation of the carbonyl groups is much preferred over the alternative (*endo*/*exo*) as revealed by NMR spectroscopy. A conformational preference within the 2-acetoxypropanoyl grouping accounts for the presence of a single *exo*/*endo* conformation in solution for some of these DAQs (see above) but an interconverting *exo*/*endo*⇌*endo*/*exo* mixture for others. Where a single *exo*/*endo* conformation is present in solution, evidence is presented that this closely resembles the X-ray determined crystal structure. A mechanism for the second acylation step to form these DAQs is proposed, which involves preliminary *O*-acylation of the 3-(monoacylamino)quinazolinone.

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




**Scheme 1**

When the two *N*-acyl groups in the DAQ are not identical, the N–N bond becomes a chiral axis with the two planes containing the quinazolinone and imide moieties orthogonal to one another. The barrier to N–N bond rotation is sufficiently high to allow separation of diastereoisomers (atropisomers) when there is a chiral centre also present in the DAQ. Thus, the stereostructures of both (racemic) diastereoisomers of

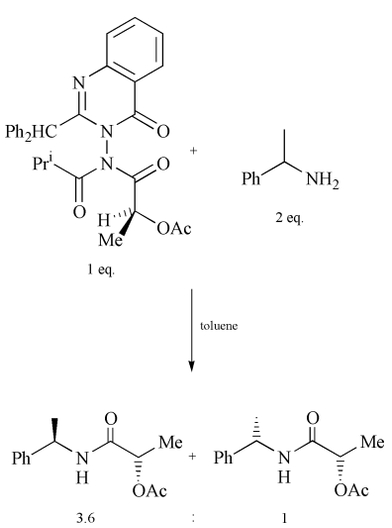



DAQ **2** have been identified by X-ray crystallography determinations: interconversion between them takes place on heating in toluene ($\Delta G^{\ddagger} = 121$ kJ mol$^{-1}$) by rotation around the N–N bond.[2]

There is also a significant, albeit smaller, barrier to stereoisomerism within the imide group in these DAQs. The preferred conformation is an *exo*/*endo* arrangement for the two carbonyl groups and for *e.g.* DAQ **3**, *exo*/*endo*⇌*endo*/*exo* interconversion occurs at room temperature at a restricted enough rate to give rise to broadening of the acetyl methyl signals in its NMR spectrum.

At −83 °C in [$^2H_6$] acetone solution, signals from the two acetyl methyl groups have separated into two singlets of equal intensity and, significantly, the methylene protons of the ethyl substituent become non-equivalent because the N–N bond is now a chiral axis.[2]

The *chemo*selectivity exhibited by *e.g.* DAQ **1** towards amines (Scheme 1) has a *stereo*selective counterpart, the preferred reaction of an enantiopure DAQ with one enantiomer of a racemic amine giving rise to kinetic resolution of the amine[2] (Scheme 2).

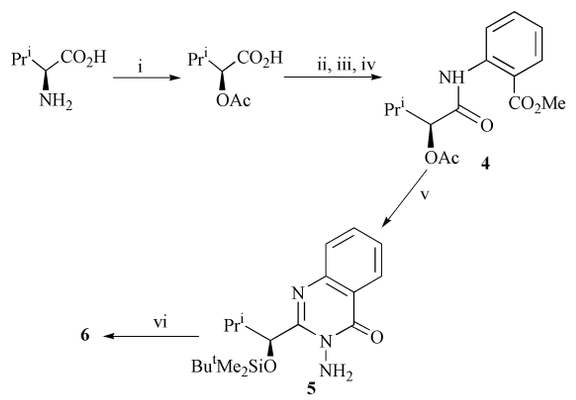



**Scheme 2**

In this paper,[3] the stereoisomerism in DAQs bearing at least one *N*-2-acetoxypropanoyl group is examined with a view to understanding the origin of the enantioselectivity in kinetic resolution of racemic amines using these DAQs.

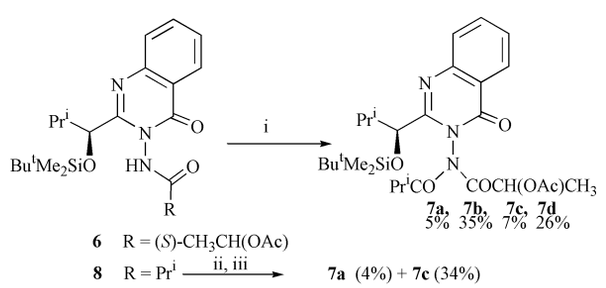
## Results and discussion

3-Aminoquinazolinone **5** was prepared from L-valine by the route shown in Scheme 3 in an overall yield of 46% without the need for chromatographic separation at any stage.



**Scheme 3** *Reagents*: i, $KNO_2$, HOAc; ii, $SOCl_2$; iii, methyl anthranilate; iv, $NH_2NH_2$, EtOH, 147 °C; v, $Bu^tMe_2SiCl$, imidazole; vi, (*S*)-$CH_3CH(OAc)COCl$, pyr. $CH_2Cl_2$.

Acylation of 3-aminoquinazolinone **5** with (*S*)-2-acetoxypropanoyl chloride gave the 3-monoacylaminoquinazolinone (MAQ) **6**. Even a chromatographically purified sample of MAQ **6** showed small additional signals in its NMR spectrum, consistent with the presence of a minor N–N bond rotamer (ratio ~10 : 1).[4] Reaction of MAQ **6** with 2-methylpropanoyl chloride in dichloromethane containing pyridine at room temperature for three days gave a mixture of four diastereoisomeric DAQs **7a**–**d** in order of their elution in chromatography using a chromatotron (Scheme 4).



**Scheme 4** *Reagents and conditions*: i, $Pr^iCOCl$, pyr. $CH_2Cl_2$, 3 days; ii, BuLi, THF; iii, (*S*)-$CH_3CH(OAc)COCl$.

After flash chromatography to remove residual MAQ **6**, the bulk of the major DAQ diastereoisomer **7b** was separated by crystallisation. Pure samples of **7a**, **7c** and **7d** were then obtained by chromatotron chromatography. X-Ray crystal structures of all the DAQs were carried out and reveal their stereostructures as shown[3] (see also Fig. 1).†

Conversion of MAQ **8** into DAQs **7a** (4%) and **7c** (34%) was also possible by formation of its *N*-lithium salt using butyllithium followed by addition of (*S*)-2-acetoxypropanoyl chloride.

These crystal structures confirm that, at least in the crystalline form, an *exo*/*endo* conformation for the carbonyl groups of the imide moiety is preferred. This preference has been previously found in *N*-alkyl-substituted acyclic imides[5] and in most other crystal structures of DAQs we have examined.[2] The

† The crystal structures of **7b**–**d** have been reported previously and are drawn so as to simulate the conformations they take up in the crystal in each case. The crystal structure of **7a** was not previously reported and is reproduced here along with the simulated drawing for comparison with **7b**–**d**. CCDC reference number 207/485. See http://www.rsc.org/suppdata/p1/b0/b005814i/ for crystallographic files in .cif format.

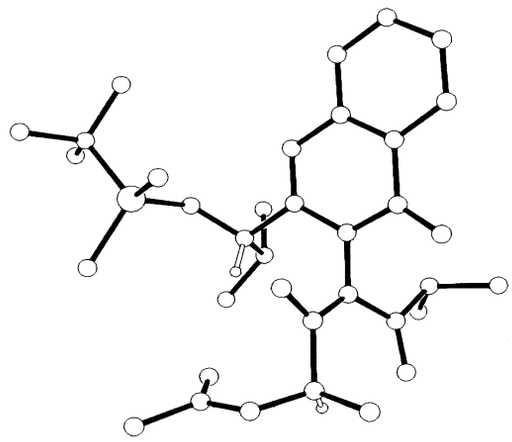
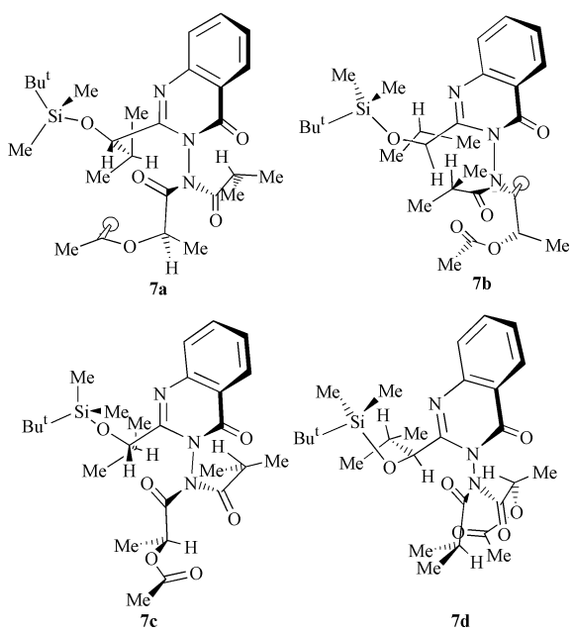


**Fig. 1** The molecular structure of **7a**. H atoms on chiral centres are shown with open bonds, all other H atoms have been omitted for clarity.



NMR spectra of these DAQs (see below) suggest that *exo*/*endo* conformations are also those preferred in solution.

It is noteworthy that in the crystal structure of DAQ **7d**, the 2-methylpropanoyl carbonyl group has an *exo*-conformation whereas in those of DAQs **7a**–**c**, this group has an *endo*-orientation. The conformations around the (Q)$C_2$–C(Me,H,-OSi) bonds in **7b** and **7d** are similar and have the C–OSi bond out of the plane of the Q-ring by 74° and 82° respectively. The conformations around the (Q)$C_2$–C(Me,H,OSi) bonds in **7a** and **7c** are likewise similar, but differ from those around **7b** and **7d** in having the C–OSi bond close to the plane of the Q-ring (21° and 14° respectively).

Diastereoisomers **7a** and **7d** apparently arise by epimerisation at the (*S*)-2-acetoxypropanoyl chiral centres and it was assumed that the (Q)$C_2$-attached chiral centre was stereostable. However, in the X-ray crystal structure determination of DAQ **7a**, the space group $P\bar{1}$ indicates that the molecule was racemic. The bulk of DAQ **7a** was obtained as an oil and only a very small number of small crystals were produced from this oil on standing: one of these crystals was used for the structure determination. The oily material which remained failed to produce any more crystalline material even after setting aside for several months and it was also found to have a significant rotation $[a]_D = +126.8$ (*c* 0.5, $CDCl_3$), so the extent of racemisation is believed to be small: the enantiopurity of these DAQs **7a**–**d** appears to be high based on the high enantioselectivities obtained in their reactions with amines.[3]

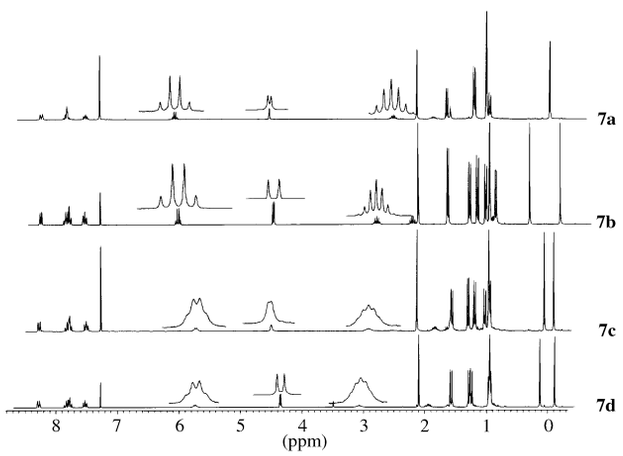



**Fig. 2**

DAQs **7b** and **7c** differ only in the configuration of their N–N axes. Heating pure DAQ **7b** in boiling deuterochloroform for 48 h converted it into a 1:1 mixture of **7b**–**7c** as shown by NMR spectroscopy. Likewise, heating **7d** for 13 h under the same conditions gave a 6:1 mixture of **7a**–**7d**. Both these equilibrations are assumed to take place by rotation around the N–N bond. As expected, there was no interconversion between **7a** and **7c** or between **7b** and **7d**, *i.e.* epimerisation at the 2-acetoxypropanoyl centre does not take place under these conditions.

### Conformations of imide moieties of DAQs 7a–d in solution

The NMR spectra of DAQs **7a**–**d** present a dichotomy in appearance for the C*H*OAc and C*H*Pr$^{i}$ signals of **7a** and **7b**, which are sharp, and those for **7c** and **7d**, which are broadened (Fig. 2).

It seemed likely that these signals for DAQs **7c** and **7d** are broadened because of *exo*/*endo*⇌*endo*/*exo* interconversion in the imide moiety which is becoming slow on the NMR time-scale (*cf*. the temperature-dependent NMR spectrum for DAQ **3** above). In support of this conclusion, the broadened quartet for C*H*OAc in the NMR spectrum of DAQ **7d** at 27 °C ($\delta$ 5.73) separated at −50 °C into a broadened singlet and a broadened quartet ($\delta$ 6.08 and 5.57, ratio 2.9:1, respectively) which we assigned to C*H*OAc protons in *exo*- and *endo*-COCH(OAc)-$CH_3$ groups respectively (see below) (*exo* = 2-acetoxypropanoylcarbonyl *cis* to Q). Likewise, the broadened quartet at $\delta$ 5.71 in the NMR spectrum of DAQ **7c**, run at room temperature, separated into a broadened quartet and a broad singlet at $\delta$ 6.01 and 4.97, ratio 2.7:1 respectively when the spectrum was run at −50 °C.‡

There are a number of possible explanations for the sharpness of the corresponding signals in DAQs **7a** and **7b**:

(a) the interconversion in solution between *exo*/*endo* and *endo*/*exo* forms is faster than for DAQs **7c** and **7d**;

(b) the conformation in solution is *exo*/*exo*, notwithstanding the *exo*/*endo* conformation in solution;§

(c) in solution the *exo*/*endo* conformation is significantly more stable than the *endo*/*exo*.

‡ For simplicity, we have assumed that for DAQ **7d** the major imide conformer is the *exo*/*endo* but, in view of the broadening of the signal at $\delta$ 6.08, it may be in equilibrium with a small concentration of another conformation (*exo*/*exo*?). Likewise for DAQ **7c**, the smaller broadened signal at $\delta$ 4.97 is assumed to be that from the *endo*/*exo* conformer possibly in equilibrium with another minor conformer.

§ In principle, the *endo*/*endo* conformation is also possible but this is probably the least stable of the three possible planar imide conformers and is neglected (it is excluded in any case for the same reasons as the *exo*/*exo*).

Faster *exo*/*endo*–*endo*/*exo* interconversion [explanation (a) above] is unlikely because the NMR spectrum of DAQ **7b** remains unchanged even when run at −40 °C with no visible broadening of the signals: the chemical shifts $\delta$ of the $CH_3CH$(OAc) protons in **7a** and **7b** (see below) do not support (a).

Although at this point it is difficult to exclude (b) above, it is not clear what property it is that **7a** and **7b** share which would lead to both preferring an *exo*/*exo* conformation in solution since they have different configurations both at their N–N chiral axes and their 2-acetoxypropanoyl chiral centres and, at least in the crystalline state, different preferred conformations around the (Q)$C_2$–C(Me,H,OSi) bonds (see above).

The chemical shifts $\delta$ for the C*H*OAc protons in DAQs **7a** and **7b** are 6.06 and 6.00 respectively compared with $\delta$ 5.5 for the corresponding proton in MAQ **6**. Deshielding of the C*H*OAc protons in **7a** and **7b** is ascribed to the proximity in solution of the neighbouring 2-methylpropanoyl carbonyl group in the *exo*/*endo* conformer. It is clear from the crystal structures of **7a** and **7b** that the C*H*OAc proton is also close to the carbonyl of the 2-methylpropanoyl group. The conclusion to be drawn is that there is predominantly one conformation in solution for the imide moieties in DAQs **7a** and **7b** [see (c) above] and that these are similar to the preferred conformations in the respective crystal structures.

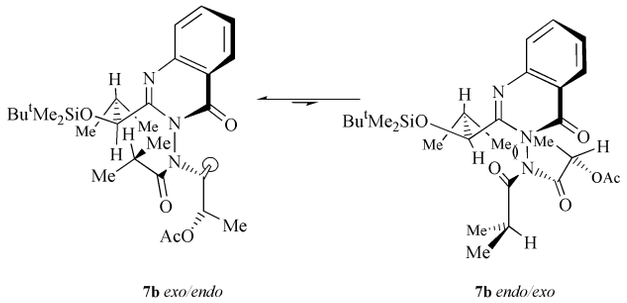
For DAQs **7c** and **7d**, their NMR spectra at −50 °C reveal that the more abundant imide conformation in both cases is also the *exo*/*endo* with the C*H*(OAc)$CH_3$ proton signals deshielded at $\delta$ 6.08 and 6.01 respectively (see above) by the 2-methylpropanoyl carbonyl as for DAQs **7a** and **7b**. Thus, the major imide conformation for DAQ **7c** in solution is the same as that in the crystal structure but for DAQ **7d** it is the minor conformation in solution which corresponds to that found in the crystal structure.

The origin of these *exo*/*endo*–*endo*/*exo* equilibrium positions in DAQs **7a**–**d** is still under investigation but it is clear that it must involve interactions between the substituents on the chiral centre and the quinazolinone when these are *cis* (*i.e.* in the *endo*/*exo* conformation): these interactions are adverse in DAQs **7a** and **7b** but less so in DAQs **7c** and **7d**.

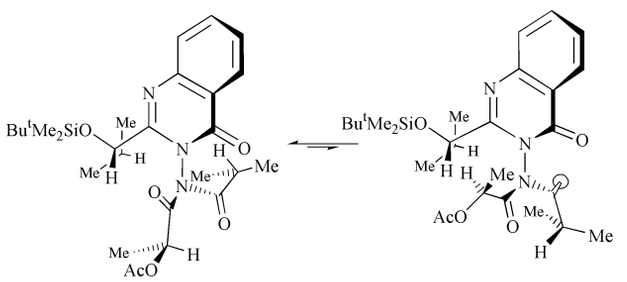
The torsional angles $\phi$ between the C=O and C–O bonds of the –NC(=O)–C(–OAc)H($CH_3$) grouping in nine crystal structures we have which contain 2-acetoxypropanoyl as an *N*-substituent, lie between 19° and 39° for eight of them. If there is a strong preference for retention of this torsional angle in solution, *i.e.* this conformation is much preferred over others, then in the alternative *endo*/*exo* forms of *e.g.* DAQs **7b** and **7c** (Scheme 5), a sterically repulsive interaction between the methyl group (*Me*CHOAc) and the (Q)$C_2$-substituent will result for **7b** *endo*/*exo* but not for **7c** *endo*/*exo*. Consequently a displacement of the equilibrium wholly onto the **7b** *exo*/*endo* side can be accounted for, whereas **7c** will be an interconverting mixture of *exo*/*endo* and *endo*/*exo* forms. An analogous explanation nicely accounts for the differences in the NMR spectra of DAQs **7a** and **7d**.

The conclusion that DAQs **7a** and **7b** are present in solution essentially in one *exo*/*endo* conformation whereas DAQs **7c** and **7d** are present as two rapidly interconverting *exo*/*endo*–*endo*/*exo* conformations is supported by an analogous correlation for the NMR spectra of DAQs **13** and **14** and an X-ray crystallographic structure determination of DAQ **13**.[6] These two compounds were prepared in the usual way by diacylation of the corresponding 3-aminoquinazolinones **9** and **10** with (*S*)-2-acetoxypropanoyl chloride (for **13**) and *rac*-2-acetoxypropanoyl chloride (for **14**) (Scheme 6).

Conversion of MAQ **11** into DAQ **13** is significantly faster than the corresponding reaction of MAQ **6** with 2-methylpropanoyl chloride and pyridine and the degree of epimerisation at the 2-acetoxypropanoyl centre, giving any *meso*-compound (see below) is less.

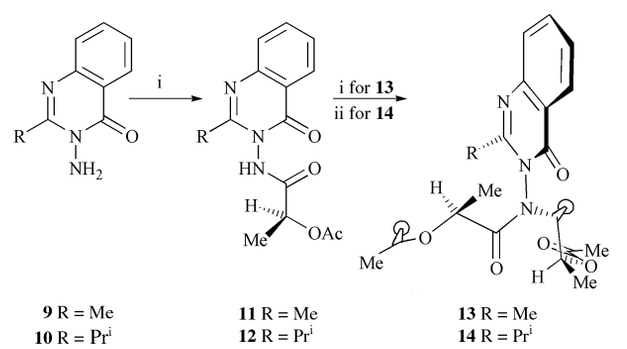


**7b** *exo*/*endo* **7b** *endo*/*exo*



**7c** *exo*/*endo* **7c** *endo*/*exo*

**Scheme 5**



**9** R = Me **11** R = Me **13** R = Me
**10** R = Pr$^i$ **12** R = Pr$^i$ **14** R = Pr$^i$

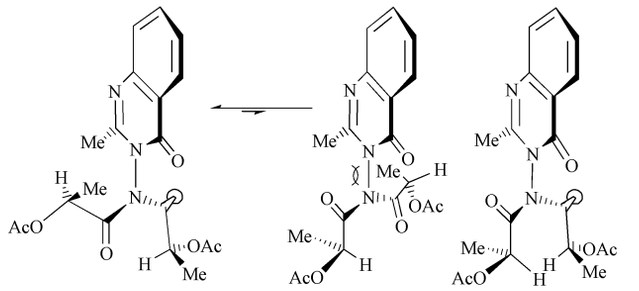
**Scheme 6** *Reagents*: i, (*S*)-$CH_3CH(OAc)COCl$, pyr. $CH_2Cl_2$; ii, *rac*-$CH_3CH(OAc)COCl$, pyr. $CH_2Cl_2$.

As in the X-ray crystal structures of DAQs **7a**–**d**, the preferred conformations for the imide moiety in DAQs **13** is *exo*/*endo* and, for the two 2-acetoxypropanoyl groups, the torsion angles $\phi$ have magnitudes of −25.2° (*endo*) and −20.8° (*exo*) (see above).

The two $CH_3CHOAc$ signals in the NMR spectrum of DAQ **13** appear as widely separated sharp quartets ($\delta$ 5.01 and 5.97) with the lower field signal characteristically deshielded by the neighbouring *endo* carbonyl group; there was no change in the appearance of the spectrum when run at −50 °C in $CDCl_3$. A similarly wide separation of chemical shift ($\delta$ 4.87 and 6.0) was present for the corresponding signals of DAQ **14**.

It is important to point out that, unlike the *exo*/*endo* and *endo*/*exo* conformations of DAQ **3** which are enantiomeric, those for *e.g.* DAQ **13** (**13a** *exo*/*endo* and **13a** *endo*/*exo*; Scheme 7) are diastereoisomeric and, in principle, different in energy. [These two conformations for the imide as in DAQ **1** are interconverted by rotation around the N–N bond and thus the N–N bond is not a chiral axis in this molecule if **13a** *exo*/*endo* ⇌**13a** *endo*/*exo* is occurring.]

If, as previously discussed for DAQs **7a**–**d**, the same small torsion angle $\phi$ between the C=O and C–O bonds is preferred for DAQ **13** in solution as well as in the crystalline form, then the equilibrium position greatly in favour of **13a** *exo*/*endo* becomes clear because **13a** *endo*/*exo* suffers from the same adverse steric interaction between the methyl in the 2-acetoxypropyl group *cis* to the quinazolinone and the methyl



**13a** *exo*/*endo* **13a** *endo*/*exo* **13a** *exo*/*exo*

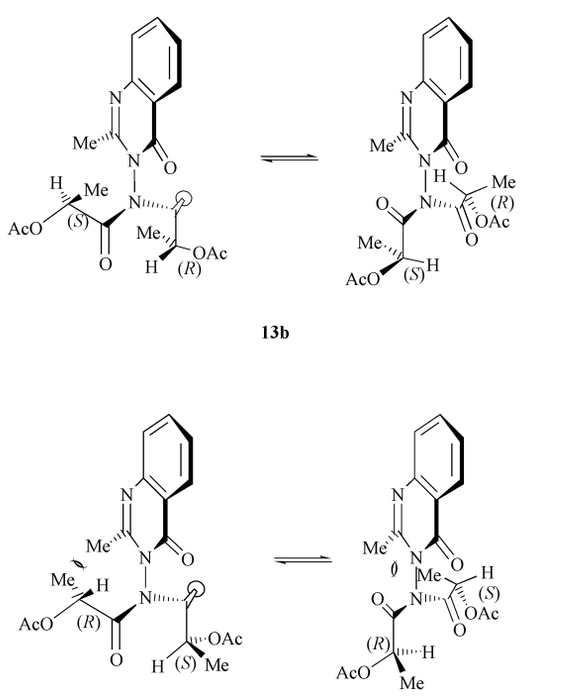
**Scheme 7**

2-substituent of the latter. Thus, DAQs **13** and **14** each exist in solution preferentially in a single *exo*/*endo* conformation for the same reasons that DAQs **7a** and **7b** do, in spite of the fact that in **13** and **14** the two acyl groups on nitrogen are identical.

The NMR spectra of DAQs **13** and **14** do not support *exo*/*exo* conformations (Scheme 7) for them in solution (see earlier discussion for DAQs **7a** and **7b** above). Although the two (*S*)-2-acetoxypropanoyl groups in such *exo*/*exo* conformations would be diastereotopic¶ the magnitude of the chemical shift differences (see above for $CH_3CHOAc$ quartets) is more compatible with single *exo*/*endo* conformations *i.e.* **13a** *exo*/*endo* as above.

### *meso*-DAQ 13b

There are two possible *meso*-compounds as a result of epimerisation at one chiral centre in DAQ **13** (Scheme 8). From our



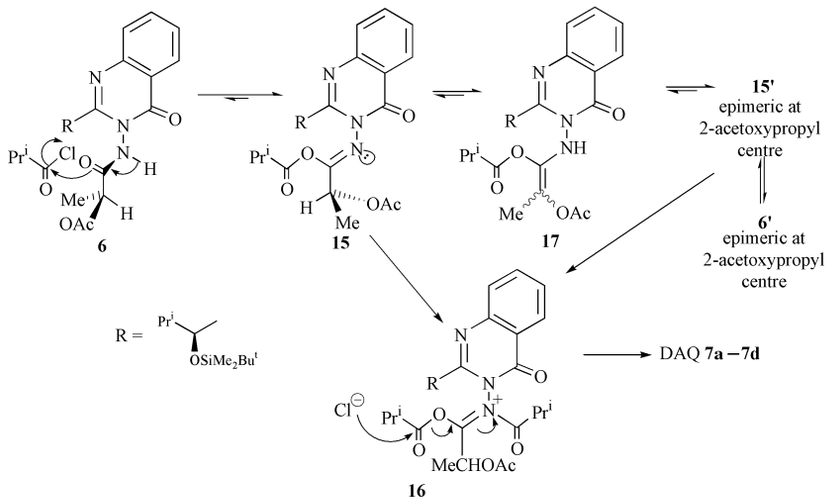
**13b**

**13c**

**Scheme 8**

earlier discussion, the stability of the *meso*-DAQ diastereoisomer **13b** would be expected to be greater than **13c** since both imide conformations in the latter suffer from the previously described adverse steric interactions as indicated. The NMR

¶ If the two carbonyl groups in **13a** *exo*/*exo* (see Scheme 6) were to be replaced in turn by *e.g.* thiocarbonyl groups, the relationship between the two resulting molecules would be a diastereoisomeric one. Hence the two (*S*)-2-acetoxypropanoyl groups are diastereotopic (see R. S. Atkinson, *Stereoselective Synthesis*, Wiley, Chichester, 1995, p.15).




**Scheme 9**

spectrum of a minor component isolated by chromatography of the crude product from acylation of MAQ **11** (Scheme 6) shows, besides the two $CH_3CHOAc$ quartets from DAQ **13a**, two *broadened* quartets at $\delta$ 5.47 and 5.59, possibly from the same proton in both *meso*-diastereoisomers **13b** and **13c**. A pure sample of presumably *meso*-isomer **13b** was isolated by chromatotron chromatography and found to have zero rotation.

A 1 : 1 ratio of *exo*/*endo*–*endo*/*exo* diastereoisomers of DAQ **13b** (and **13c**) would be anticipated‖ with interconversion between the two conformations becoming fast on the NMR timescale (as for DAQs **7c** and **7d**) and hence giving rise to broadening of the quartet signals as in the NMR spectrum above.

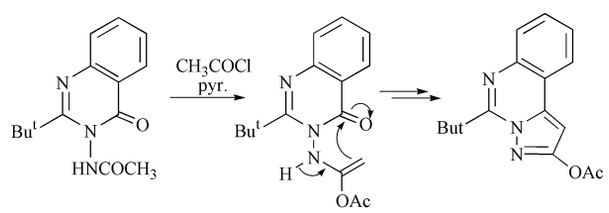
### Formation of DAQs 7a–7d: mechanism of epimerisation in 7a and 7d

Acylation of MAQ **6** with 2-methylpropanoyl chloride and pyridine is a slow reaction requiring three days and some MAQ **6** remains unreacted even after this time. When DAQs **7b** and **7d** were re-submitted to the acylation conditions with 2-methylpropanoyl chloride, pyridine and dichloromethane for 2 days, they were both recovered unchanged which indicated that epimerisation occurred in the acylation of MAQ **6** itself.

In fact, the MAQ **6** recovered from the attempted diacylation reaction was a mixture of diastereoisomers resulting from some epimerisation at the 2-acetoxypropanoyl centre as shown by the appearance in its NMR spectrum of a separated singlet signal just upfield of the $CH_3CHOCOCH_3$ signal of the starting MAQ **6** ($\delta$ 2.21 and 2.24).

The tendency for amides to react with acid chlorides on oxygen will be augmented in MAQ **6** because the quinazolinone ring will hinder attack by the $sp^2$-hybridised exocyclic nitrogen on the acid chloride both sterically and, because of its electron-withdrawing character, electronically. Consequently, the reversibly formed product would be expected to be the *O*-acylimidate **15** (Scheme 9).†† Reversible protonation–deprotonation of the imidate **15** would account for epimerisation at the 2-acetoxypropanoyl centre. Further acylation of this *O*-acylimidate **15** with 2-methylpropanoyl chloride on the now more accessible and more basic nitrogen would deliver the *N*-acyliminium species **16** whose deacylation leads to DAQs **7a**–**d**.

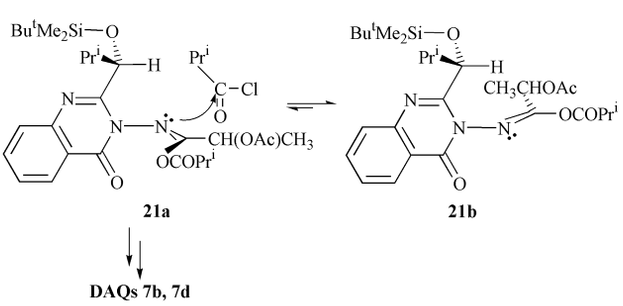
A precedent for the formation of the enamine **17** is the conversion of MAQ **18** into the pyrazolo[1,5-*c*]quinazoline **20** in which an analogous enamine **19** was postulated as an intermediate (Scheme 10).




**Scheme 10**

Deacylation of *O*-acylimidate **15** by *protonation* on the imidate nitrogen (*cf*. acylation to give **16**) would reform MAQ **6**, which would have undergone some epimerisation at the 2-acetoxypropanoyl chiral centre if interconversion with enamine **17** had occurred.

It is noteworthy that the two major diastereoisomers DAQ **7b** and **7d** produced have the same configurations for their N–N chiral axes and that the transition state **21a** leading to their formation (Scheme 11) would have the quinazolinone




**Scheme 11**

2-substituent in what is believed to be a preferred conformation (*cf*. conformations of the $Q_2$-substituent in DAQs **7b** and **7d** in the crystal structures;‡‡ see earlier), with attack by the acid chloride on the lone pair in **21a** (rather than **21b**).

### Summary

Acylation of MAQ **6** with 2-methylpropanoyl chloride and pyridine gives a mixture of four DAQ diastereoisomers **7a**–**d**

‖ The *exo*/*exo* conformation might be expected to be favoured for DAQ **13c** but a pure sample of this compound was not isolated.

†† It is possible that initial acylation takes place on the Q-carbonyl oxygen and the intramolecular transfer to form imidate **15** occurs.

‡‡ If the conformation of the $Q_2$-substituent in the crystal structures of DAQs **7a** and **7c** were used in **21a**, the predicted result would be the same.

resulting from the axial chirality of the N–N bond together with partial epimerisation at the 2-acetoxypropanoyl chiral centre. Diastereoisomers **7a** and **7b**, **13** and **14** show an unexpected preference in solution for one of the two *exo*/*endo* conformations of the imide moiety. The preferred *exo*/*endo* conformation, which corresponds in each case to that present in the X-ray determined crystalline structures of these DAQs, is itself believed to arise from a preferred conformation within the $NCOCH(OAc)CH_3$ grouping which gives rise to an adverse steric effect in the alternative *endo*/*exo* conformation. In diastereoisomers **7c** and **7d**, this unfavourable interaction is absent and an equilibrium mixture of *exo*/*endo* and *endo*/*exo* conformers is present in each case.

The presence of a single conformation for these DAQs in solution makes it more likely that this will be the reacting conformation with amines. Since these DAQs react highly enantioselectively with chiral primary and secondary amines giving kinetic resolution, the findings in this paper will be invaluable in attempts to derive a transition state model to account for the sense of enantioselectivity and hence to make rational changes to maximise the degree of this enantioselectivity.

## Experimental

For general experimental details see ref. 7.

### Preparation of 3-amino-2-[(*S*)-1-hydroxy-2-methylpropyl]quinazolin-4(3*H*)-one 4

2-Hydroxy-3-methylbutanoic acid (13 g) (prepared from L-valine[8]) was dissolved in dry ether (20 $cm^3$) and freshly distilled acetyl chloride (15 $cm^3$) added with stirring. After setting aside overnight, the ether and unreacted acetyl chloride were evaporated under reduced pressure to leave 2-acetoxy-3-methylbutanoic acid as a cloudy oil (17 g) $\delta_H$ 1.02 and 1.05 (6H, 2 × d, *J* 6.6, $CH_3CHCH_3$), 2.16 (3H, s, $CH_3CO$), 2.25 (1H, m, $CH_3CHCH_3$), 4.9 (1H, d, *J* 6.2, CHO) and 10.15 (1H, s, $CO_2H$). This acid (13 g) was converted to its acid chloride by dissolving in dry ether (40 $cm^3$) adding two drops of *N*,*N*-dimethylformamide and then thionyl chloride (12 $cm^3$) dropwise with stirring. After setting aside overnight, ether and unreacted thionyl chloride were removed under reduced pressure to give the acid chloride. To a briskly stirred solution of this acid chloride (13 g) in dry ether (300 $cm^3$) was added methyl anthranilate (23.2 $cm^3$; 2.2 eq.) and the thick white precipitate which formed was stirred for a further 1 h. After setting the reaction mixture aside overnight, the white solid was filtered, washed well with ether and the combined filtrates washed successively with hydrochloric acid (2 M, 5 × 50 $cm^3$), saturated aqueous sodium hydrogen carbonate and saturated brine then dried and the solvent removed by evaporation under reduced pressure to give an oil which solidified over 12 h. *Methyl (S)-N-(2-acetoxy-3-methylpropanoyl)anthranilate* was obtained as a colourless solid (17 g, 86%) mp 44–46 °C (from ethanol) (Found: $M^+$ 293.1263. $C_{15}H_{19}NO_5$, requires $M^+$ 293.1263); $[a]_D = -125.6$ (*c* 1.2, $CHCl_3$); $\nu_{max}/cm^{-1}$ 3320m, 1700m, 1610s and 1590m; $\delta_H$ 0.89 and 0.92 (6H, 2 × d, *J* 5.7, $CH_3CHCH_3$), 2.21 (3H, s, $CH_3CO$), 2.31 [1H, m, $(CH_3)_2CH$], 3.78 (3H, s, $OCH_3$), 5.15 (1H, d, *J* 4.0, HCO), 7.1 [1H, ddd, *J* 8.2, 7.0 and 1.0, 5-H(Ar)], 7.54 [1H, ddd, *J* 8.5, 7.0 and 1.6, 4-H(Ar)], 8.02 [1H, dd, *J* 8.2 and 1.6, 6-H(Ar)], 8.76 [1H, dd, *J* 8.5 and 1.0, 3-H(Ar)]; $\delta_C$ 17.2 and 19.2 ($CH_3CHCH_3$), 21.1 ($CH_3CHCH_3$) 31.1 ($CH_3CO$), 52.6 ($OCH_3$), 78.6 (HCO), 115.2 ($CCO_2Me$), 120.7, 122.6, 131.2 and 135.0 [4 × CH(Ar)], 141.0 [CNH(Ar)] and 168.8, 169.2 and 170.6 (3 × CO); *m*/*z* (%) 293 ($M^+$, 41), 178 (46), 151 (100) and 119 (35). The foregoing anthranilate was dissolved in ethanol (25 $cm^3$) and heated with hydrazine (14.0 $cm^3$) in a closed steel container at 147 °C for 24 h. After cooling, the bulk of the solvent was removed under reduced pressure and the residue dissolved in dichloromethane (40 $cm^3$), the dichloromethane solution washed with water (3 × 25 $cm^3$), dried and the solvent removed under reduced pressure to give *3-amino-2-[(S)-1-hydroxy-2-methylpropyl]quinazolin-4(3H)-one* **4** as a pale yellow oil $[a]_D = -24$ (*c* 1.2, $CHCl_3$) which solidified on standing to give a colourless solid mp 138–140 °C (from ethanol) (11 g, 82%) (Found: C, 62.1; H, 6.6; N, 17.7. $C_{12}H_{15}N_3O_2$ requires C, 61.8; H, 6.5; N, 18.0%) (Found: $MH^+$ 233.1164. $C_{12}H_{14}N_3O_2$, requires $MH^+$ 233.1164); $\nu_{max}/cm^{-1}$ 3300w, 1690 and 1600; $\delta_H$ 0.82 and 1.1 (6H, 2 × d, *J* 6.9, $CH_3CHCH_3$), 2.3 (1H, m, $CH_3CHCH_3$), 3.98 (1H, d, *J* 8.2, OH), 4.75 (2H, s, $NH_2$), 4.91 (1H, dd, *J* 8.2 and 3.5, CHOH), 7.4 [1H, ddd, *J* 8.2, 7.0 and 1.3, 6-H(Q)], 7.6 [1H, ddd, *J* 8.2, 7.0 and 1.3, 7-H(Q)], 7.65 [1H, dd, *J* 8.2 and 1.3, 8-H(Q)] and 8.16 [1H, d, *J* 8.2, 5-H(Q)]; $\delta_C$ 15.5 and 20.5 ($CH_3CHCH_3$), 32.6 ($CH_3CHCH_3$), 73.5 (CHOH), 120.4 [CCO(Q)], 126.9, 127.2, 127.5 and 134.9 [4 × CH(Q)], 146.2 [CN=C(Q)], 158.7 [C=N(Q)] and 162.5 [CO(Q)]; *m*/*z* (%) 233 ($MH^+$, 23), 216 (34), 190 (100), 175 (78) 145 (48), 132 (73) and 84 (74).

### (*S*)-3-Amino-2-(1-*tert*-butyldimethylsilyloxy-2-methylpropyl)-quinazolin-4(3*H*)-one 5

The 3-aminoquinazolinone **4** above (6 g, 26 mmol) was dissolved in *N*,*N*-dimethylformamide (DMF) (15 $cm^3$), *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (7.4 g, 49 mmol) and imidazole (4.4 g, 64 mmol) were added and the solution stirred at room temperature for two days. Light petroleum (30 $cm^3$) was then added, the solution washed with water, dried and evaporated under reduced pressure. Crystallisation of the resulting white solid gave the desired *3-aminoquinazolinone* **5** (8.5 g, 96%), mp 126–128 °C (from light petroleum) (Found: C, 61.9; H, 8.4; N, 12.0. $C_{18}H_{29}N_3O_2Si$ requires C, 62.0; H, 8.4; N, 12.1%); $\nu_{max}/cm^{-1}$ 3336m and 1675m; $[a]_D = -95$ (*c* 1.3, $CHCl_3$); $\delta_H$ −0.12 and 0.1 (6H, 2 × s, $CH_3SiCH_3$), 0.94 and 1.2 (6H, 2 × d, *J* 6.6, $CH_3CHCH_3$), 0.97 [9H, s, $(CH_3)_3CSi$], 2.85 (1H, m, $CH_3CHCH_3$), 4.65 (1H, d, *J* 6.6, CHOSi), 5.86 (2H, s, $NH_2$), 7.59 [1H, ddd, *J* 8.2, 7.0 and 1.6, 6-H(Q)], 7.82 [1H, ddd, *J* 8.2, 7.0 and 1.0, 7-H(Q)], 7.85 [1H, dd, *J* 8.2 and 1.6, 8-H(Q)], 8.39 (1H, dd, *J* 8.2, and ~1.0, 5-H(Q)]; $\delta_C$ −4.8 and −4.5 ($CH_3SiCH_3$), 18.9 [$(CH_3)_3C$], 19.2 and 19.9 ($CH_3CHCH_3$), 26.1 [$(CH_3)_3CSi$], 31.4 ($CH_3CHCH_3$), 82.9 (CHOSi), 120.0 [CCO(Q)], 126.7, 127.2, 128.0 and 134.2 [4 × CH(Q)], 146.6 [CN(Q)], 154.3 [C=N(Q)], and 160.1 [CO(Q)]; *m*/*z* (%) 347 ($M^+$, 9.0), 232 (70), 290 (100), 275 (54), 259 (42), 247 (58), 232 (54), 218 (59), 203 (52), 187 (47), 75 (29) and 59 (43).

### General procedure for the mono-*N*-acylation of 3-aminoquinazolinones

To the 3-aminoquinazolinone dissolved in dry dichloromethane (2 $cm^3$ $g^{-1}$) containing dry pyridine (1.5 mol equiv.) was added the acid chloride (1.5 mol equiv.) dropwise with stirring. After stirring for 12 h at room temperature, more dichloromethane (~50 $cm^3$) was added and the solution washed with saturated aqueous sodium hydrogen carbonate, then water, dried and the solvent removed under reduced pressure.

### General procedure for the preparation of 3-(diacylamino)quinazolinones (DAQs) from 3-(monoacylamino)quinazolinones (MAQs)

To a solution of the MAQ (1 mol equiv.), prepared as described above, in dichloromethane (2 $cm^3$ $g^{-1}$) containing dry pyridine (1.5 mol equiv.), was added the acid chloride (2–3 mol equiv.) dropwise over 10 min and the mixture stirred and heated under reflux for 2–4 days with exclusion of moisture, monitoring the disappearance of the starting MAQ by TLC. After cooling, additional dichloromethane (40 $cm^3$) was added and the solution 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-(*S*)-2-Acetoxypropanoylamino-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methylpropyl]quinazolin-4(3*H*)-one 6

The general procedure for monoacylation was followed using 3-aminoquinazolinone **5** (1 g, 2.9 mmol), pyridine (0.23 g, 2.9 mmol), dichloromethane (4 $cm^3$) and (*S*)-2-acetoxypropanoyl chloride (0.34 g, 4.4 mmol) and the mixture stirred for 24 h at room temperature. The brown oil obtained after work-up as described above was purified by column chromatography on silica using light petroleum–ethyl acetate (3:1) as eluent to give the MAQ **6** as a colourless oil (1.15 g, 88%) ($R_f$ 0.26) (Found: $MH^+$ 462.2425. $C_{23}H_{35}N_3O_5Si$ requires $MH^+$ 462.2424); $\nu_{max}$/$cm^{-1}$ 3260br, 1745s, 1698s and 1610s; $[a]_D = +10.6$ (*c* 1.6, $CHCl_3$); $\delta_H$ 0.0 and 0.14 (6H, 2 × d, *J* 6.6, $CH_3CHCH_3$), 0.94 (9H, s, $(CH_3)_3CSi$), 1.72 (3H, d, *J* 6.9, $CH_3CHOAc$), 2.04 (1H, m, 7 lines, $(CH_3)CH$), 2.24 (3H, s, $CH_3COO$), 4.44 (1H, d, *J* 6.6, CHOSi), 5.50 (1H, q, *J* 6.9, $CH_3CHOAc$), 7.51 [1H, ddd, *J* 8.2, 7.0 and 1.6, 6-H(Q)], 7.76 [1H, dd, *J* 8.2 and 1.6, 8-H(Q)], 7.80 [1H, ddd, *J* 8.2, 7.0 and 1.6, 7-H(Q)], 8.26 [1H, d, *J* 8.2, 5-H(Q)] and 8.65 (1H, s, NH); minor N–N bond rotamer (observable signals) 1.70 (3H, d, *J* 6.6, $CH_3CHOAc$), 2.2 (3H, s, $OCOCH_3$), 4.47 (1H, br d, *J* 5.0, CHOSi) and 8.78 (1H, s, NH). From comparison of signals at $\delta$ 1.72 and 1.70 the ratio of rotamers was ~10:1; $\delta_C$ −4.8 and −4.5 (2 × $CH_3$), 14.6 [$C(CH_3)_3$], 18.2, 18.6, 19.5 and 21.4 (4 × $CH_3$), 26.2 [$(CH_3)_3CSi$], 60.8 and 70.7 (2 × CH), 121.2 [CCO(Q)], 127.4, 127.7, 128.3 and 135.3 [4 × CH(Q)], 146.7 [CN=C(Q)], 156.8 [C=N(Q)], 160.1 [CO(Q)], 170.1 and 175 (2 × CO); *m*/*z* (%) (FAB) 462 ($MH^+$ 89), 404 (63), 307 (22), 275 (22), 216 (20), 154 (100), 136 (93).

### 3-[(2-Methylpropanoyl)amino]-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methylpropyl]quinazolin-4(3*H*)-one 8

The general procedure for monoacylation was followed using 3-aminoquinazolinone **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* **8** as colourless crystals (1.9 g, 79%), mp 116–118 °C (from light petroleum) ($R_f$ 0.38, 5:1 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); $\delta_H$ (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, $(CH_3)_3C$), 1.36 and 1.39 [6H, 2 × d, *J* 6.9, $(CH_3)_2CHCO$], 2.08 (1H, 7 lines $CH_3CHCH_3$), 2.73 [1H, *h*, *J* 6.9, $(CH_3)_2CHCO$], 4.45 (1H, d, *J* 7.0, CHOSi), 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)]; $\delta_C$ −4.9 and −4.4 ($CH_3SiCH_3$), 18.6 [$C(CH_3)_3$], 19.4, 19.7, 33.2 and 34.5 (4 × $CH_3$), 26.2 [$(CH_3)_3C$], 121.4 [CCO(Q)], 127.5, 128.8 and 135.1 [CH(Q)], 146.8 [CN=C(Q)], 160.4 [CO(Q)] and 174.1 (CO) (CHOSi missing); minor rotamer (observable signals) 0.04 and 0.12 (6H, 2 × s, $CH_3SiCH_3$), 2.3 (1H, 7 lines $CH_3CHCH_3$) and 4.65 (1H, d, *J* 7.0, CHOSi); from comparison of the signals at $\delta$ 4.45 and $\delta$ 4.65, the ratio of N–N bond rotamers was 6:1; *m*/*z* (%) (FAB) 418 ($MH^+$, 100), 360 (77), 275 (23) and 216 (31).

### Reaction of 3-aminoquinazolinone 5 with racemic 2-acetoxypropanoyl chloride

Using the same procedure above, monoacylation of 3-aminoquinazolinone **5** (0.3 g, 0.86 mmol) was carried out with pyridine (0.102 g, 1.3 mmol), dichloromethane (2 $cm^3$) and racemic 2-acetoxypropanoyl chloride (0.195 g, 1.3 mmol). The brown oil obtained after work-up was purified by column chromatography on silica using light petroleum–ethyl acetate (3:1) as eluent to give the racemic MAQ **6** as a colourless oil (0.35 g, 88%) ($R_f$ 0.26). Examination of the product by NMR spectroscopy showed it to be a 1:1 mixture of diastereoisomers with signals in addition to those in the spectrum above at $\delta$ 1.63 (3H, d, *J* 6.7, $CH_3CHOAc$) and 2.21 (3H, s, $OCOCH_3$). Partial separation was achieved by re-chromatography using a chromatotron and light petroleum–ethyl acetate (5:1) as eluent to give one fraction containing a 5:1 mixture of diastereoisomers with the major diastereoisomer identical to that obtained previously.

### Preparation of 3-[*N*-(2-acetoxypropanoyl)-*N*-(2-methylpropanoyl)amino-2-[(*S*)-1-*tert*-butyldimethylsilyloxy-2-methylpropyl]quinazolin-4-(3*H*)-ones (7a–d)

A modification of the general procedure for diacylation was followed using MAQ **6** (2 g, 4.34 mmol), dichloromethane (5 $cm^3$), pyridine (0.69 g, 8.7 mmol) with 5 drops of DMF and 2-methylpropanoyl chloride (0.924 g, 8.9 mmol) and stirring continued for five days at room temperature. A pale yellow oil (3.2 g) was obtained on work-up, and TLC of the crude product mixture showed the presence of five major products. Flash column chromatography over silica gel with light petroleum–ethyl acetate (5:1) as eluent gave a colourless oil (~1.9 g) containing four compounds with $R_f$ values in the range 0.58–0.48 (see below).

Further elution with light petroleum–ethyl acetate (1:1) as eluent gave MAQ **6** as a colourless oil (0.1 g, 5%) ($R_f$ 0.26, 3:1 light petroleum–ethyl acetate), identical with the starting material but comprising a 1.9:1 mixture of diastereoisomers by NMR from comparison of the signals at $\delta_H$ 1.63 and 1.72 (see above).

A solution of the oil obtained in the first fraction in methanol (2 $cm^3$) deposited crystals on setting aside to give the major diastereoisomer **7b** (0.55 g, 24%) ($R_f$ 0.55, 5:1 light petroleum–ethyl acetate) as colourless crystals, mp 110–112 °C (from methanol) (Found: $MH^+$, 532.2842. $C_{27}H_{41}N_3O_6Si$ requires $MH^+$ 532.2842) (Found: C, 60.9; H, 7.8; N, 7.9. $C_{27}H_{41}N_3O_6Si$ requires C, 60.5; H, 7.8; N, 7.9%); $\nu_{max}$/$cm^{-1}$ 1740s, 1705s, 1607s and 1265s; $\delta_H$ −0.23 and 0.27 (6H, 2 × s, $CH_3SiCH_3$), 0.82 and 1.0 [6H, 2 × d, *J* 6.6, $CH_3CHCH_3$), 0.93 [9H, s, $(CH_3)_3CSi$], 1.12 and 1.25 (6H, 2 × d, *J* 6.6, $CH_3CHCH_3$), 1.60 (3H, d, *J* 6.9 $CH_3CHOAc$), 2.08 (3H, s, $CH_3CO_2$), 2.19 [1H, m, 7 lines $(CH_3)_2CHCHOSi$], 2.76 [1H, h, *J* 6.6, $(CH_3)_2CHCO$], 4.45 (1H, d, *J* 6.6, CHOSi), 6.00 (1H, q, *J* 6.9, CHOAc), 7.52 [1H, ddd, *J* 8.2, 6.7 and 1.6, 6-H(Q)] and 7.75 [1H, dd, 8.2 and 1.6, 8-H (Q)], 7.83 [1H, ddd, *J* 8.2, 6.7 and 1.6, 7-H(Q)], 8.23 [1H, dd, *J* 8.2 and 1.6, 5-H(Q)]; $\delta_C$ −3.7 and −2.5 ($CH_3SiCH_3$), 16.8, 17.0, 20.0, 20.1, 20.7 and 20.9 (6 × $CH_3$), 19.2 [$(CH_3)_3CSi$], 26.5 [$(CH_3)_3CSi$], 32.5 and 33.4 [2 × ($CH_3CHCH_3$)], 71.5 and 76.3 (2 × CH), 121.4 [CCO(Q)], 127.8, 128.0, 128.4 and 135.9 [4 × CH(Q)], 146.6 [CN=C(Q)], 157.1 [C=N(Q)], 160.3 [CO(Q)] and 170.7, 172.2 and 179.7 (3 × CO); *m*/*z* (%) (FAB) 532 ($MH^+$, 89), 474 (100), 404 (68), 275 (71), 232 (48) and 187 (49). An X-ray structure determination on crystals obtained from methanol, showed that the DAQ **7b** has (*S*)-configurations for both chiral centres and an (*R*)-configuration for the N–N bond.[3]

Evaporation of the methanol after separation of the bulk of DAQ **7b** above and chromatography of the residue using a chromatotron with light petroleum–ethyl acetate (18:1) as eluent gave first DAQ **7a** as a colourless gum (0.12 g, 5%) ($R_f$ 0.58, 5:1 light petroleum–ethyl acetate) (Found $MH^+$, 532.2843. $C_{27}H_{41}N_3O_6Si$ requires $MH^+$ 531.2843); $\delta_H$ −0.01 (6H, s, $CH_3SiCH_3$), 0.94, 1.20 and 1.64 (15H, 5 × d, *J* 6.7, 2 × $CH_3CHCH_3$ and $CH_3CHOAc$), 1.00 [9H, s, $(CH_3)_3CSi$)], 1.87 [1H, m, $(CH_3)_2CH$], 2.11 (3H, s, $CH_3CO_2$), 2.51 [1H, h, *J* 6.7, $(CH_3)_2CHCO$], 4.53 (1H, d, *J* 2.1, CHOSi), 6.06 (1H, q, *J* 6.7 CHOAc), 7.52 [1H, ddd, *J* 8.3, 6.4 and 1.6, 6-H(Q)], 7.80 [1H, dd 8.3 and 1.6, 8-H (Q)], 7.84 [1H, ddd, *J* 8.3, 6.4

and 1.6, 7-H(Q)] and 8.23 [1H, dd, *J* 8.3 and 1.6, 5-H(Q)]; $\delta_C$ −5.1 and −2.2 ($CH_3SiCH_3$), 14.9, 16.4, 20.3, 20.5 and 21.3 (6 × $CH_3$), 18.8 [$(CH_3)_3CSi$], 26.3 ($CH_3)_3CSi$), 32.9 and 33.5 [2 × $(CH_3)_2CH$], 72.0 and 73.5 (2 × *C*H), 121.1 [*C*CO(Q)], 127.5, 127.6, 128.7 and 135.8 [4 × *C*H(Q)], 146.9 [*C*N=C(Q)], 157.6 [C=N(Q)], 160.8 [CO(Q)] and 171.2, 172.6 and 180.5 (3 × CO); *m*/*z* (%) (FAB) 532 ($MH^+$, 45), 474 (51), 404 (54), 275 (56), 232 (32) and 187 (32). A small number of crystals were obtained from the gum on setting aside and were separated by trituration with ethanol. An X-ray structure determination showed the DAQ **7a** was racemic with *S*(*R*) at Q-2 and *R*(*S*) at 2-acetoxypropanoyl centres and an *S*(*R*)-configuration for the N–N axis. The gum obtained after removal of the ethanol after separation of the crystals by trituration failed to crystallise further even on standing for several months, and had $[\alpha]_D$ = +126.8 (*c* 0.5 $CDCl_3$).

Further elution with the same solvent mixture gave more of the major DAQ **7b** ($R_f$ 0.55, 5:1 light petroleum–ethyl acetate) as colourless crystals (0.25 g, overall yield 35%).

Further elution with the same solvent mixture gave DAQ **7c** ($R_f$ 0.52, 5:1 light petroleum–ethyl acetate) as a colourless oil (0.161 g, 7%), which solidified on standing. Recrystallisation gave a colourless solid, mp 106–108 °C (from methanol) (Found $MH^+$ 532.2842. $C_{27}H_{42}N_3O_6Si$ requires $MH^+$, 532.2842); $\nu_{max}$/$cm^{-1}$ 1740s, 1705s, 1605s and 1245s; $\delta_H$ −0.11 and 0.04 (6H, 2 × s, $CH_3SiCH_3$), 0.92 and 1.01 (6H, 2 × d, *J* 6.7, $CH_3$-$CHCH_3$), 0.94 [9H, s, $(CH_3)_3CSi$], 1.17 and 1.28 [6H, 2 × d, *J* 6.7, $(CH_3)_2CHCO$], 1.54 (3H, d, *J* 6.7 $CH_3CHOAc$), 1.82 [1H, m, $(CH_3)_2CHCOSi$], 2.11 (3H, s, $CH_3CO_2$), 2.91 [1H, br h, $(CH_3)_2CH$], 4.49 (1H, br s, CHOSi), 5.71 (1H, br q, *J* 6.7 CHOAc), 7.50 [1H, ddd, *J* 8.0, 6.7 and 1.6, 6-H(Q)], 7.76 [1H, dd, *J* 8.0 and 1.6, 8-H(Q)], 7.82 [1H, ddd, *J* 8.0, 6.7 and 1.3, 7-H(Q)] 8.24 [1H, dd, *J* 8.0 and 1.3, 5-H(Q)]; variable-temperature NMR studies at 400 MHz showed maximum broadening of the quartet signal at $\delta$ 5.71 occurred at 0 °C, and at −50 °C two signals at 4.97 (br q) and 6.01 (br s) were obtained (ratio 1:2.7); $\delta_C$ −4.6 and −3.6 ($CH_3SiCH_3$), 15.3, 17.1, 19.6, 20.7, 20.7 and 21.0 (6 × $CH_3$), 18.9 [$(CH_3)_3CSi$], 26.3 [$(CH_3)_3CSi$), 32.7 and 34.4 [2 × $(CH_3)_2CH$], 70.6 and 74.4 (2 × *C*H), 121.3 [*C*CO(Q)], 127.8, 128.0, 128.5 and 135.8 [4 × *C*H(Q)], 146.6 [*C*N=C(Q)], 156.9 [C=N(Q)], 160.4 [CO(Q)], 170.4, 171.7 and 179.4 (3 × CO); *m*/*z* (%) (FAB) 532 ($MH^+$, 45), 474 (51), 404 (54), 275 (56), 232 (32) and 187 (32). A crystal structure determination showed that DAQ **7c** has (*S*)-configurations for both chiral centres and an (*S*)-configuration for the N–N chiral axis.[3]

Further elution with the same solvent mixture gave DAQ **7d** ($R_f$ 0.48, 5:1 light petroleum–ethyl acetate) as a viscous, colourless oil which crystallized on standing (0.60 g, 26%), mp 68–70 °C (from methanol) (Found $MH^+$ 532.2843. $C_{27}H_{42}N_3O_6Si$ requires $MH^+$, 532.2843); $\nu_{max}$/$cm^{-1}$ 1740s, 1707s, 1610s and 1245s; $\delta_H$ −0.12 and 0.12 (6H, 2 × s, $CH_3SiCH_3$), 0.52 and 0.96 (6H, 2 × d, *J* 6.7, $CH_3CHCH_3$), 0.94 [9H, s, $(CH_3)_3CSi$], 1.23 and 1.27 (6H, 2 × d, *J* 6.7, $CH_3CHCH_3$), 1.56 (3H, d, *J* 6.9 $CH_3CHOAc$), 2.09 (3H, s, $CH_3COO$), 2.92 [1H, m, $(CH_3)_2$-$CHCOSi$], 3.06 [1H, br h, $(CH_3)_2CH$], 4.34 (1H, d, *J* 4.6, CHOSi), 5.73 (1H, br q, *J* 6.7 CHOAc), 7.52 [1H, ddd, *J* 8.3, 6.9 and 1.6, 6-H(Q)], 7.75 [1H, dd, *J* 8.3 and 1.6, 8-H(Q)], 7.82 [1H, ddd, *J* 8.3, 6.9 and 1.3, 7-H(Q)], 8.25 [1H, dd, *J* 8.3 and 1.3, 5-H(Q)]; variable-temperature NMR studies at 400 MHz showed maximum broadening of the quartet signal at $\delta$ 5.73 for the CHOAc signal occurred at 0 °C, and at −50 °C two signals at $\delta$ 5.57 (br q) and 6.08 (br s) were obtained (ratio 1:2.9); $\delta_C$ −4.3 and −3.2 ($CH_3SiCH_3$), 16.2, 17.8, 19.9, 20.3, 20.7 and 20.9 (6 × $CH_3$), 19.0 [$(CH_3)_3CSi$], 26.4 [$(CH_3)_3CSi$], 32.5 and 34.4 [2 × $(CH_3)_2CH$], 70.3 and 75.9 (2 × *C*H), 121.3 [*C*CO(Q)], 127.9, 128.0, 128.4 and 135.8 [4 × *C*H(Q)], 146.6 [*C*N=C(Q)], 156.4 [C=N(Q)], 160.3 [CO(Q)], 170.0, 171.7 and 178.7 (3 × CO); *m*/*z* (%) (FAB) 532 ($MH^+$, 100), 474 (78), 404 (60), 275 (64), 232 (44) and 187 (53).

A crystal grown from methanol was shown by X-ray structure determination to have an (*S*)-configuration at the Q-2 chiral center and an (*R*)-configuration at the 2-acetoxypropanoyl chiral center and (*R*)-configuration for the N–N chiral axis.[3]

### Reaction of MAQ 8 with (*S*)-2-acetoxypropanoyl chloride mediated by butyllithium

To a flame-dried 2-necked flask equipped with 3-way tap and a septum cap and stirring bar was added solution of MAQ **8** (0.3 g, 0.72 mmol) in dry THF (1 ml). The flask was cooled to −78 °C under an atmosphere of nitrogen and a solution of butyllithium (0.6 $cm^3$ of a 1.6 M solution in hexane, 1.2 mmol) in THF (1 ml) was added with stirring *via* a syringe followed by (*S*)-2-acetoxypropanoyl chloride (0.23, 1.4 mmol) also dropwise *via* syringe, with stirring throughout. After 1 h at −78 °C, the mixture was allowed to warm to ambient temperature and water was added. Most of the THF was removed under reduced pressure and the residue extracted with dichloromethane (3 × 5 $cm^3$). The combined organic extracts were washed with brine, dried and evaporated under reduced pressure. Flash chromatography of the residue on silica with light petroleum–ethyl acetate (10:1) as eluent gave DAQ **7a** ($R_f$ 0.58, 5:1 light petroleum–ethyl acetate) (0.016 g, 4%) identical with that isolated above. Further elution with the same solvent gave the DAQ diastereoisomer **7c** ($R_f$ 0.52, 5:1 light petroleum–ethyl acetate) (0.131 g, 34%) identical with that isolated previously.

Further elution with the same solvent gave unreacted starting material **6** (0.152 g) identical with that isolated previously.

### 3-[(*S*)-2-Acetoxypropanoylamino]-2-methylquinazolin-4(3*H*)-one 11

Using the general procedure for monoacylation, 3-aminoquinazolinone **9** (1 g, 5.7 mmol), pyridine (0.9 g, 11.4 mmol), dichloromethane (3 $cm^3$) and (*S*)-2-acetoxypropanoyl chloride (1.72 g, 11.4 mmol) were stirred for 24 h at room temperature. After work-up the yellow oil obtained was purified using column chromatography on silica with light petroleum–ethyl acetate (1:1) as eluent to give MAQ **11** (1.12 g, 68%) ($R_f$ = 0.36) as a colourless oil (1.12 g, 68%) (Found: $MH^+$ 290.1141. $C_{14}H_{15}N_3O_4$ requires $MH^+$ 290.1141); $\nu_{max}$/$cm^{-1}$ 3390m 1740s, 1692s and 1612s; $\delta_H$ (mixture of N–N bond rotamers) major rotamer 1.65 (3H, d, *J* 6.6, $CH_3CHOAc$), 2.22 (3H, s, $CH_3CO$), 2.48 (3H, s, $CH_3$), 5.42 (1H, br q, *J* 6.6, CHOAc), 7.41 [1H, br m, 6-H(Q)], 7.59 [1H, d, *J* 8.0, 8-H(Q)], 7.73 [1H, br m, 7-H(Q)], 8.13 [1H, d, *J* 8.0, 5-H(Q)] and (1H, s, NH); $\delta_C$ 17.7, 21.3 and 21.6 (3 × $CH_3$), 70.2 (*C*HOAc), 120.8 [*C*CO(Q)], 127.1, 127.2, 127.6 and 135.5 [4 × *C*H(Q)], 147.3 [*C*N=C(Q)], 155.5 [CN(Q)], 160.5 [CO(Q)] and 170.7 and 171.4 (2 × CO); $\delta_H$ minor rotamer (observable signals) 1.62 (3H, d, *J* 6.6, $CH_3CHOAc$), 2.20 (3H, s, $CH_3CO$), 2.52 (3H, s, $CH_3$) and (1H, s, NH); *m*/*z* (%) (FAB) 290 ($MH^+$, 48) and 154 (100). From comparison of the signals at $\delta$ 2.22 and 2.20, the ratio of N–N bond rotamers was ~1.2:1.

### 3-{Bis[(*S*)-2-acetoxypropanoyl]amino}-2-methylquinazolin-4(3*H*)-one 13

Using the general procedure for diacylation, amide **11** (1 g, 3.46 mmol), pyridine (0.55, 6.9 mmol) and distilled (*S*)-2-acetoxypropanoyl chloride (1.04 g, 6.9 mmol) were stirred continuously in dichloromethane (3 $cm^3$) for three days at room temperature. The brown oil obtained was purified by column chromatography on silica using light petroleum–ethyl acetate (1:1) as eluent to give the DAQ **13** as a colourless oil. Re-chromatography using a chromatotron and light petroleum–ethyl acetate (3:1) as eluent gave (*S*,*S*)-DAQ **13** as a colourless oil (0.6 g, 43%) which solidified on standing and crystallised to give colourless solid, mp 124–126 °C (from ethanol) (Found: $MH^+$

404.1457. $C_{19}H_{21}N_3O_7$ requires $MH^+$ 404.1458); $\nu_{max}/cm^{-1}$ 1745s, 1700s and 1613s; $\delta_H$ 1.40 and 1.36 (6H, 2 × d, *J* 6.7, 2 × C$H_3$CH), 2.09 and 2.12 (6H, 2 × s, 2 × C$H_3$CO$_2$), 2.36 (3H, s, C$H_3$), 5.01 and 5.97 (2H, 2 × q, *J* 6.7, 2 × C*H*OAc), 7.50 [1H, ddd, *J* 8.3, 7.0 and 1.3, 6-H(Q)], 7.68 [1H, dd, *J* 8.3 and 1.3, 8-H(Q)], 7.81 [1H, ddd, *J* 8.3, 7.0 and 1.3, 7-H(Q)] and 8.19 [1H, dd, *J* 8.3 and 1.3, 5-H(Q)]; $\delta_C$ 16.4, 16.8, 20.7, 20.9 and 21.3 (5 × *C*H$_3$), 68.9 and 71.7 (2 × *C*HOAc), 120.8 [*C*CO(Q)], 127.7, 127.8, 127.9 and 136.2 [4 × *C*H(Q)], 147.2 [*C*N=C(Q)], 156.1 [CN(Q)], 160.0 [CO(Q)] and 170.2, 171.1, 171.3 and 172.0 (4 × CO); *m*/*z* (%) (FAB) 404 ($MH^+$, 48), 290 (40) and 154 (100).

A crystal grown from methanol was shown by an X-ray structure determination to have (*S*)-configurations at both chiral centres.[6]

Variable-temperature NMR studies at 400 MHz were carried out on DAQ **13** at different temperatures (−50, −25, 0 and 27 °C) but there was no change in the spectrum.

Further elution with the same solvent gave a mixture of *meso*-DAQ *diastereoisomers* **13b** and possibly **13c** as a colourless oil (0.06 g, 4%) ($R_f$ 0.53, 1 : 1 light petroleum–ethyl acetate) (Found: $MH^+$ 404.1457. $C_{19}H_{21}N_3O_7$ requires $MH^+$ 404.1458); $\nu_{max}/cm^{-1}$ 1745s, 1700s and 1613s; $\delta_H$ (major diastereoisomer) 1.55 (6H, d, *J* 6.7, C$H_3$CHOAc), 2.10 (6H, s, 2 × C$H_3$CO$_2$), 2.53 [3H, s, CH$_3$(Q)], 5.47 (2H, br q, *J* 6.7, 2 × CH$_3$C*H*OAc), 7.48 [1H, ddd, *J* 8.0, 6.5 and 1.1, 6-H(Q)], 7.66 [1H, dd, *J* 8.0 and 1.1, 8-H(Q)], 7.79 [1H, ddd, *J* 8.0, 6.5 and 1.1, 7-H(Q)] and 8.25 [1H, dd, *J* 8.0 and 1.1, 5-H(Q)]; $\delta_C$ 16.9, 20.7 and 21.2 (5 × *C*H$_3$), 70.1 (2 × *C*HOAc), 121.1 [*C*CO(Q)], 127.6, 127.8, 128.1 and 135.9 [4 × *C*H(Q)], 147.0 [*C*N=C(Q)], 155.2 [C=N(Q)], 160.0 [CO(Q)] and 170.5 and 171.6 (4 × CO); minor diastereoisomer (observable signals) 2.03 (6H, s, 2 × C$H_3$CO$_2$), 2.46 [3H, s, CH$_3$(Q)], 5.59 (2H, br q, *J* 6.7, 2 × CH$_3$C*H*OAc) and 8.20 [1H, dd, *J* 8.0 and 1.1, 5-H(Q)]. From the integration of the signals at $\delta$ 5.47 and 5.59 the ratio of major:minor diastereoisomers is 2.5 : 1; *m*/*z* (%) (FAB) 404 ($MH^+$, 61), 290 (25) and 154 (45). Re-chromatography using a chromatotron and light petroleum–ethyl acetate (5 : 1) as eluent gave a pure sample of the major *meso*-diastereoisomer **13b** as colourless oil (8 mg).

### Racemic 3-[bis(2-acetoxypropanoyl)amino]-2-isopropylquinazolin-4(3*H*)-one 14

3-Aminoquinazolinone **10** (1.5 g, 7.4 mmol), pyridine (1.15 g, 14.7 mmol) and racemic 2-acetoxypropanoyl chloride (3 g, 20 mmol) in dichloromethane (5 cm$^3$) were set aside at room temperature for 4 days. The yellow oil (1.9 g) obtained on work-up used in the general procedure was purified by column chromatography on silica using light petroleum–ethyl acetate (2 : 1) as eluent to give racemic DAQ **14** as colourless crystals (1.8 g, 56%), mp 114–116 °C, [*a*] = −1 (*c* 1, $CHCl_3$) (Found: $MH^+$ 432.1771. $C_{21}H_{25}N_3O_7$ requires $MH^+$ 432.1771); $\delta_H$ 1.16 and 1.39 (6H, 2 × d, *J* 6.6, C$H_3$CHC$H_3$), 1.35 and 1.62 (6H, 2 × d, *J* 6.9, 2 × C$H_3$CHOAc), 2.1 and 2.16 (6H, 2 × s, 2 × C$H_3$CO$_2$), 3.4 (1H, *h*, *J* 6.6, CH$_3$C*H*CH$_3$), 4.87 and 6.0 (2H, 2 × q, *J* 6.9, C*H*OAc), 7.47 [1H, ddd, *J* 8.2, 7.0 and 1.3, 6-H(Q)], 7.73 [1H, dd, *J* 8.2 and 1.3, 8-H(Q)], 7.81 [1H, ddd, *J* 8.2, 7.0 and 1.3, 7-H(Q)] and 8.19 [1H, dd, *J* 8.2 and 1.3, 5-H(Q)]. There was no change in the $^1$H NMR spectrum (at 400 MHz) at temperatures down to −50 °C. $\delta_C$ 16.5, 16.9, 20.7, 20.4, 32.3 and 22.9 (6 × *C*H$_3$), 30.6 (CH$_3$*C*HCH$_3$), 68.9 and 71.5 (2 × *C*HOAc), 120.8 [*C*CO(Q)], 127.5, 127.5, 128.2 and 135.9 [4 × *C*H(Q)], 147.3 [*C*N=C(Q)], 160.7 [CN(Q)], 163.5 [CO(Q)] and 170.5, 170.7, 171.4 and 172.5 (4 × CO); *m*/*z* (%) (FAB) 432 ($MH^+$, 100), 372 (40), 318 (78) and 230 (50).

### Crystal structure determination of 7a

**Crystal data.** $C_{27}H_{41}N_3O_6Si$, $M$ = 531.72, triclinic, space group $P\bar{1}$, $a$ = 10.781(2), $b$ = 11.994(3), $c$ = 12.330(3) Å, $\alpha$ = 79.69(2), $\beta$ = 81.95(2), $\gamma$ = 78.00(3)°, $V$ = 1525.6(6) Å$^3$, $T$ = 200 K, $Z$ = 2, $\mu$(Mo-K$\alpha$) = 0.118 mm$^{-1}$ colourless block, crystal dimensions 0.39 × 0.34 × 0.28 mm. Data were measured on a Siemens P4 diffractometer with graphite monochromated Mo-K$\alpha$ radiation ($\lambda$ = 0.7107 Å) using an ω scan technique. Three standard reflections monitored every 100 scans showed no significant variation in intensity, the reflections were corrected for Lorentz and polarisation effects. 3388 data were measured ($2.7 < \theta < 21°$), with 3265 independent reflections (merging $R_{int}$ = 0.059). No corrections for absorption or crystal decay were required.

The structures were solved by direct methods and refined by full-matrix least squares on $F^2$ using the program SHELXL-97. All hydrogen atoms were included in calculated positions (C–H = 0.96 Å) using a riding model. Full matrix least squares based on $F^2$ gave $R1$ = 0.0699, $wR2$ = 0.149 for all data, for 319 parameters.

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