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LETTERS

# Completely diastereoselective aziridination of α,β-unsaturated acids via intramolecular reaction of 3-acetoxyaminoquinazolin-4(3*H*)-ones

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**Abstract**—(*R*)-3-Amino-2-[1-(2-hydroxyethoxy)ethyl]quinazolin-4(3*H*)-one **10** was prepared in 62% yield without the need for chromatography and *O*-cinnamoylated; reaction with lead tetra-acetate gave aziridine **12** as a single diastereoisomer in quantitative yield which was converted into the β-amino acid ester **15** corresponding to overall enantioselective addition of ammonia to the double bond of cinnamic acid. © 2002 Elsevier Science Ltd. All rights reserved.

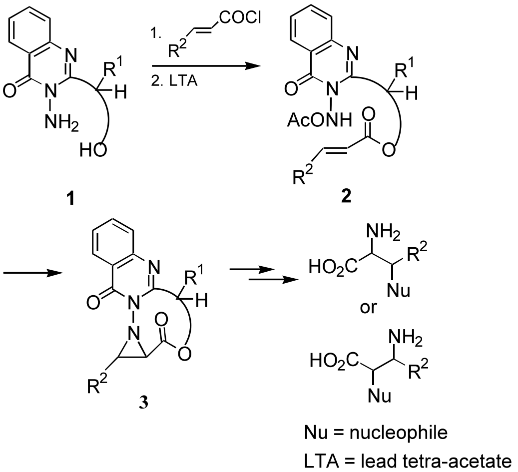
The reaction in Scheme 1 was envisaged as a means by which α,β-unsaturated acids could be converted into single enantiomers of α- or β-amino acid derivatives by the use of 3-aminoquinazolinone **1** as a chiral auxiliary/appended pro-reagent.[1]

For the conversion of 3-acetoxyaminoquinazolinone (QNHOAc) **2** into a single diastereoisomer of lactone **3** in Scheme 1, the chiral centre in the tether must control the face of the α,β-unsaturated ester which is aziridinated.

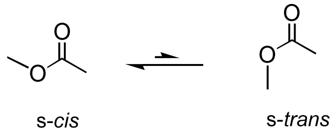
Esters have previously been used as fissionable groups in tethers, e.g. in intramolecular Diels–Alder reactions.[2] When the tether including the ester comprises a limited number of atom links (≤5) reaction is only feasible from the less stable[3] s-*trans* conformation (Scheme 2).

However, whereas a Diels–Alder reaction can if necessary be heated, in the case of QNHOAc **2**, its thermal instability above 0°C[4] precludes heating and means that the s-*cis*-conformational preference of the ester must be accommodated by increasing the number of connecting atoms in the remainder of the tether to allow the transition state (TS$^{\neq}$) geometry of the aziridination to become accessible.

In order to determine the optimum number of additional atoms required in the tether, a series of 2-(ω-hydroxyalkyl)-3-aminoquinazolinones **4** was prepared with $n=3$, 4 and 5 and each was reacted with cin-



**Scheme 1.**



**Scheme 2.**

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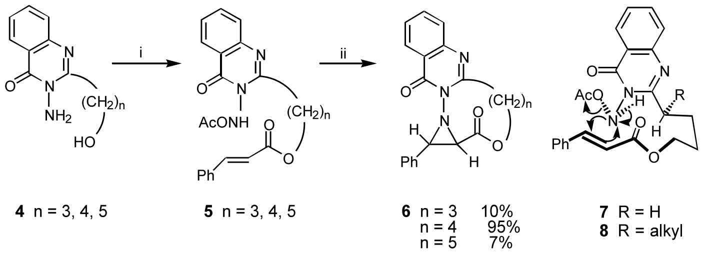


**Scheme 3.** *Reagents and conditions*: (i) PhCH=CHCOCl (1.1 equiv.), pyridine, $CH_2Cl_2$ −40→0°C; **5** $n=3$, 48%; $n=4$, 54%; $n=5$, 56%; (ii) LTA (1.1 equiv.), HMDS (2 equiv.), $CH_2Cl_2$.

namoyl chloride in the presence of pyridine. In each case, only *O*-acylation occurred, the nucleophilicity of the 3-amino group being greatly reduced by the electron-withdrawing Q-group. The corresponding *O*-cinnamoyl esters **5** were each oxidised with lead tetra-acetate in the presence of hexamethyldisilazane (HMDS)[5] and the isolated yields of aziridines **6** determined (Scheme 3).

That ester **5**, $n=4$ gives the highest yield of aziridine is accounted for by the presumed TS$^{\#}$ **7** in which the conformation of the tether is assumed to resemble closely that in the product aziridine **6**, $n=4$. This TS$^{\#}$ model **7** reveals the following favourable features (i) an orthogonal approach of C=C and Q–N bonds contained in almost parallel planes as required for the aziridination,[4] (ii) an s-*cis* (see above) and planar ester functionality, (iii) a staggered conformation for the tetramethylene segment of the tether forming a chair-like motif and (iv) overlap of the ester carbonyl oxygen with the Q-group, a factor believed to be mandatory for successful intermolecular aziridination of α,β-unsaturated esters with QNHOAc compounds.[6] In addition, this model strongly suggested that a substituent R on the carbon linking the tether to the Q-group would greatly prefer an 'equatorial' location on the chair motif as shown in TS$^{\#}$ **8**, i.e. would direct aziridination onto the face of the α,β-unsaturated ester indicated with 1,7-chirality induction (these aziridinations are *syn*-stereospecific).

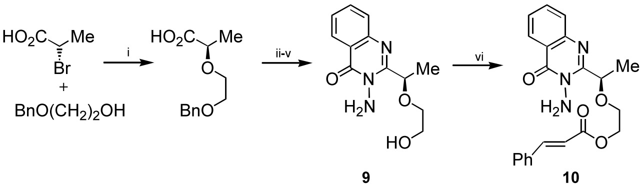
For ease of incorporation of the chiral centre, we synthesised crystalline 3-aminoquinazolinone ($QNH_2$) **9** which includes an ether linkage in the tether by the route shown in Scheme 4 in an overall yield of 62% without the need for chromatography at any stage.

The enantiopurity of $QNH_2$ **9** was confirmed by derivatisation with (*R*)-myrtenal and comparison of the NMR spectrum of the product with the diastereoisomer mixture using racemic $QNH_2$ **9**.

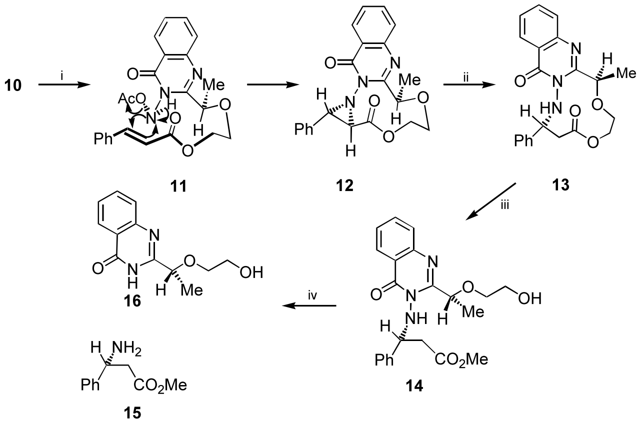
*O*-Cinnamoylation of $QNH_2$ **9** and then addition of ester **10** and LTA alternately in small portions to a stirred dichloromethane solution gave an almost quantitative yield of aziridine **12** as a single crystalline diastereoisomer via, it is assumed, TS$^{\#}$ **11** (Scheme 5).

Reduction of aziridine **12** with samarium(II) iodide[7] took place regiospecifically to give crystalline lactone **13** (84%) which was ring-opened quantitatively to ester **14** with sodium methoxide in methanol. Further reaction with samarium(II) iodide in the presence of β-dimethylamino ethanol gave clean reduction to a mixture of β-amino ester **15** and $QNH_2$ **16** which was separated by chromatography.[8] Comparison of the specific rotation of this amino ester $[\alpha]_D=21$ (*c* 0.46, $CHCl_3$) with that in the literature[9] $\{[\alpha]_D=22.3$ (*c* 1.99 $CHCl_3$)$\}$ shows that it is *R*-configured in accordance with TS$^{\#}$ model **11**.[10]

We have previously described the completely diastereoselective intermolecular aziridination of methyl acrylate and also of electron-available alkenes, e.g.



**Scheme 4.** *Reagents and conditions*: (i) NaH (2 equiv.), $BnOCH_2CH_2OH$, THF then (*S*)-$MeCHBrCO_2H$ (89%); (ii) NaOMe (1 equiv.), MeOH→sodium salt, $(COCl)_2$, pyridine, benzene; (iii) methyl anthranilate (2.2 equiv.), ether (99%); (iv) Pd/C, $H_2$, AcOH (91%); (v) $NH_2NH_2$, EtOH, 130°C, 4 h (78%); (vi) PhCH=CHCOCl (1.2 equiv.), pyridine, $CH_2Cl_2$, −20°C→rt (62%; 91% based on recovered **9**).



**Scheme 5.** *Reagents and conditions*: (i) LTA (1.1 equiv.), HMDS (2 equiv.), $CH_2Cl_2$ (>95%); (ii) $SmI_2$, THF, $Bu^tOH$ (84%); (iii) MeOH, MeONa (>95%); (iv) $SmI_2$, THF, $Me_2N(CH_2)_2OH$ (40%).

butadiene and styrene with an enantiopure QNHOAc compound and the conversion in some cases into Q-free chirons[11] but the method is less diastereoselective with more substituted alkenes. The present method is potentially applicable to a wide variety of α,β-unsaturated acids and is likely to be tolerant of additional substituents on the α- and on the β-positions.[12] Regiocomplementary ring-opening of the intramolecular aziridination products, e.g. **12** can be anticipated by appropriate choice of reagents.[13]

## Acknowledgements

We thank the EPSRC and Roche for support.

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10. The ester of a racemic alcohol related to **9** (Ph replacing Me) with *E*-2,3-dimethylacryloyl chloride (tiglyl chloride) similarly underwent intramolecular aziridination with LTA and an X-ray structure determination of the product shows it to have the same relative configuration as aziridine **12** but a boat motif for the (Q)C–O$(CH_2)_2$O segment of the ten-membered ring.
11. (a) Atkinson, R. S.; Ayscough, A. P.; Gattrell, W. T.; Raynham, T. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3096–3106; (b) Atkinson, R. S.; Meades, C. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1518–1527.
12. Intermolecular aziridination of methyl methacrylate according to Ref. 11a gave a 6:1 ratio of diastereoisomers in 45% yield.
13. Ring-opening of aziridine **12** with acid, e.g. TFA, takes place at the benzylic position.