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Synthesis of aziridine-2-carboxylates via conjugate addition of an amine to 2-(5*H*)-furanon-3-yl methanesulfonate: application to the preparation of α-amino-β-hydroxy-γ-butyrolactone

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Abstract

Conjugate addition of benzylamine to 2-(5*H*)-furanon-3-yl methanesulfonate in methanol afforded a 7:1 mixture of the *trans* and *cis* methyl *N*-benzyl-2-hydroxymethylaziridine-2-carboxylates **7** and **8**, respectively. Treatment of **7** with benzyl alcohol in the presence of $BF_3 \cdot OEt_2$ then furnished, after hydrogenolysis, *rac–cis* α-amino-β-hydroxy-γ-butyrolactone (**1**).

α-Amino-β-hydroxy-γ-butyrolactone (**1**) represents a valuable building block in organic synthesis by virtue of the high concentration of varied functional groups present on a relatively small framework. The *cis* derivative of **1** has, for example, been used for the preparation of complex β-lactam antibiotics[1,2] and both the *cis* and *trans* forms are precursors of the biologically important class of α-amino-β-hydroxy acids.[3]

Several methods for the synthesis of racemic or chiral **1** have been described. These include: via ammonolysis of epoxysuccinic acid,[1] by treatment of α-bromo-β-hydroxy-γ-butyrolactone with sodium azide,[3] by a Strecker reaction starting from D-glyceraldehyde acetonide,[4] by selective bromination of L-threonic acid[2] and by a chemo-enzymatic route starting from glycine.[5] Most of these procedures require multiple steps, or produce **1** in modest overall yields.

It occurred to us that an efficient route to **1** could be based on the conjugate addition of an amine to an unsaturated furanone substrate bearing a leaving group at the α-position (e.g. **2**, X=leaving group) to give an intermediate of type **3** (Scheme 1). Intramolecular displacement of the leaving group by the amine would then give rise to the aziridino-γ-lactone **4**. As work from our laboratory has previously shown, related aziridino-γ-lactones (prepared from carbohydrate derivatives) are opened at the β-position by alcohols in the presence of a Lewis acid.[6–9] With a substrate such as **4** this would furnish the desired

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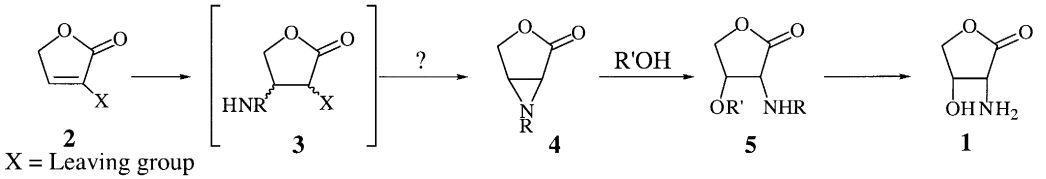
trans α-amino-β-alkoxy-γ-butyrolactone **5** which could, presumably, be transformed into **1** by a choice of appropriate R and R′ groups.

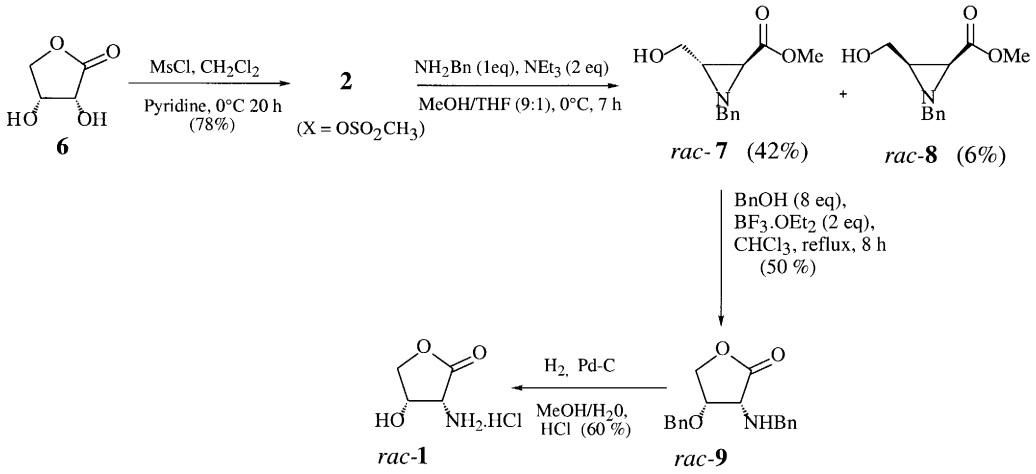


Scheme 1.

While conjugate additions of amines to 2-(5*H*)-furanones (i.e. **2**, X=H) have been well documented,[10–18] examples of such reactions on substrates having a leaving group at the α-position are less well known. Farina and co-workers[19] have examined the reaction of benzylamine with the α-bromo-γ-methoxy derivative of **2** in CCl_4. Conjugate addition was observed, but the reaction was incomplete and the products (a mixture of diastereomers) were too unstable to allow full characterization. Use of the α-chloro analogue led, in contrast, essentially to the product of 1,2-attack. There was no evidence, in either case, of formation of aziridine derivatives.

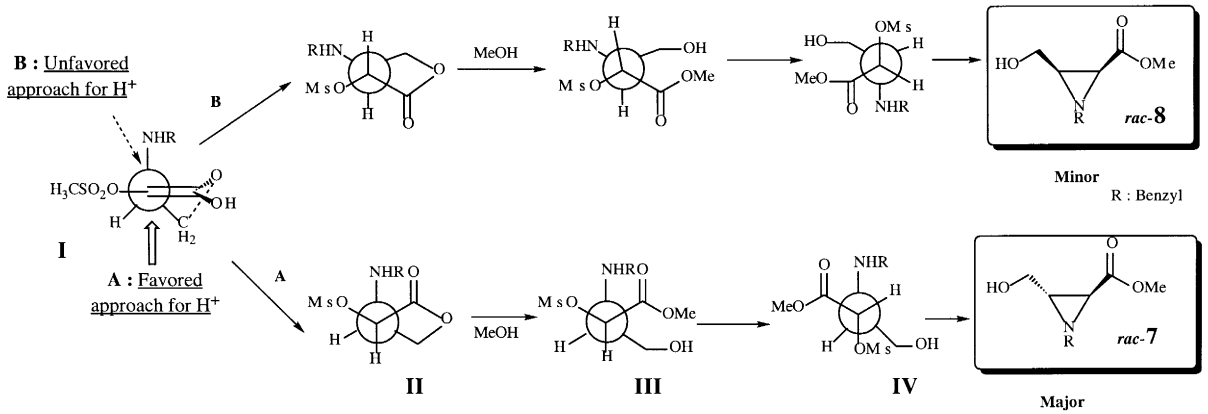
In view of this apparent instability of the α-halo-γ-lactone derivatives, we decided to pursue our objectives using the α-*O*-mesylate **2** (X=OSO_2CH_3). The latter was prepared by treatment of commercial D-erythronic γ-lactone **6** with excess methanesulfonyl chloride in pyridine and dichloromethane at 0°C for 20 h (Scheme 2).[20] Conjugate addition of benzylamine was then effected using conditions analogous to those described by Collis and Perlmutter[11] for reaction of this same nucleophile with a simple butenolide (i.e. having no leaving group at the α-position). Thus, compound **2** (X=OSO_2CH_3), in methanol and THF (added to allow its complete solubilization) containing 2 equivalents of triethylamine (to neutralize any methanesulfonic acid released during the reaction), was treated with 1 equivalent of benzylamine for 7 h at 0°C. Two principal products were formed which were easily separated by column chromatography on silica gel (ethyl acetate:heptane, 2:3). Proton NMR and mass spectral analysis of these two compounds showed that both were methyl *N*-benzylaziridine-2-carboxylates. The major product (*rac*-**7**, 42%) was attributed the *trans* configuration based on the H2–H3 coupling constant of 2.4 Hz while the minor product (*rac*-**8**, 6%), having a larger H2–H3 coupling constant (*J*=6.7 Hz), corresponded to the *cis* isomer.[21–23] While small amounts of the benzylcarboxamides corresponding to **7** and **8** were also isolated from the reaction mixture (overall yield <5%), there was no evidence for the formation of the anticipated aziridine-γ-lactone species of type **4**. Nevertheless, reaction of the *trans* aziridine-2-carboxylate **7** with benzyl alcohol at reflux in chloroform in the presence of 2 equivalents of boron trifluoride etherate then provided the *rac–cis* α-benzylamino-β-benzyloxy-γ-lactone **9** in 50% yield (non-optimized).[6,24] Finally, hydrogenolytic removal of the two benzyl groups of **9** in methanol–water containing HCl gave *rac–cis* α-amino-β-hydroxy-γ-butyrolactone (**1**) as the hydrochloride salt, whose physical and spectroscopic characteristics corresponded to literature values.[3,4,25]

Formation of the *trans* aziridine **7** as the major product of conjugate addition of benzylamine to butyrolactone **2** (X=OSO_2CH_3) can be rationalized in terms of selective facial protonation of the initially formed enol **I** (Scheme 3). Based on a model proposed by Cram and Elhafez[26] and exploited by Cromwell et al.,[27] protonation of the α-position during the course of tautomerization of the enol would be expected to occur from the least hindered side of the ring; that is, on the side opposite the benzylamine group, to give the *cis* α-methanesulfonyloxy-β-amino-butyrolactone **II** (pathway A). The latter then reacts with methanol to afford ester **III** which assumes a conformation **IV** allowing S_N2 displacement of the mesylate by the amine. This process thus provides aziridine **7** as the major product. It is interesting



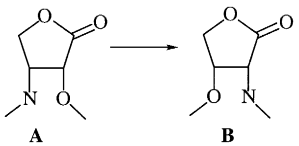
Scheme 2.

to note that no conjugate addition products were observed in the absence of methanol.[28] A similarly high stereoselectivity of conjugate addition of benzylamine to acrylates in the presence of methanol has recently been reported.[29]



Scheme 3.

The two-step reaction process described herein consists, in fact, of five transformations (conjugate addition, lactone opening, aziridine formation, aziridine opening, relactonization) which allows efficient inversion of the nitrogen and oxygen functionalities on the α- and β-positions of the γ-butyrolactone (**A**→**B**). Furthermore, while the expected aziridino-γ-lactone **4** was not obtained, the aziridine-2-carboxylates **7** and **8**, produced instead by this novel methodology, represent highly interesting synthetic tools.[30]



This model study presented to test the feasibility of the approach does not permit preparation of chirally pure products. However, because it has been shown that the presence of a substituent at the γ-position of γ-butyrolactones allows almost complete stereocontrol of conjugate addition of amines,[11,14–17] extension

of our methodology to such substrates should, in principle, lead to enantiomerically pure products. This possibility is currently under study.

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