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A New α-Haloglycine Template for the Asymmetric Synthesis of Amino Acid Derivatives

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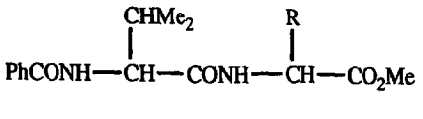
Abstract: Reaction of *(S)-N,N*-diacylvalylglycine anhydride with *N*-bromosuccinimide afforded the corresponding α-bromoglycine derivative, which reacted diastereoselectively with allyltributyltin and deuterium over palladium chloride to give the corresponding α-allyl- and α–deuterio-glycine derivatives, respectively.

There have been many reports of the use of α-haloglycine derivatives in the asymmetric synthesis of amino acids.[1-3] Our recent observation of the selective halogenation of glycine residues in amino acid derivatives[4] resulted in a complementary, though only modestly diastereoselective, method for the elaboration of glycine residues in dipeptides.[5] Thus, for example, reactions of the valyl-α-bromoglycine derivative (**1a**) with allyltributyltin and diethylmalonate anion gave the dipeptide derivatives (**1b**) and (**1c**), respectively, each as a 3:1 mixture of diastereomers. Anticipating that the geometrical constraints imposed by a cyclic system would lead to a greater degree of asymmetric induction, we have now studied analogous reactions of glycine residues in cyclic dipeptides. Prior to this study it had been shown that bis-lactim ethers, such as (**2**), derived from cyclic dipeptides, react with a high degree of asymmetric induction, although they suffer the disadvantage that they are unstable, decomposing by hydrogen chloride elimination with aromatization to give the corresponding pyrazine derivatives.[6]

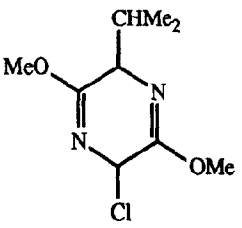
The diketopiperazine (**3b**),[7,8] chosen for this investigation, was obtained by treatment of valylglycine anhydride (**3a**) with excess acetic anhydride. Subsequent treatment with *N*-bromosuccinimide in CCl_4/CH_2Cl_2 (1:1) at reflux under nitrogen, with azobisisobutyronitrile to initiate the reaction, gave the α-bromoglycine derivative (**4**) [^{1}H n.m.r. ($CDCl_3$) δ 0.99 (d, *J* 7 Hz, 3H), 1.19 (d, *J* 7 Hz, 3H), 1.85 (m, 1H), 2.61 (s, 3H), 2.63 (s, 3H), 5.08 (d, *J* 10.5 Hz, 1H) and 6.92 (s, 1H)] as a single diastereomer, in 86% yield. The regioselectivity of this reaction is consistent with the selectivity for reaction of glycine residues observed with acyclic peptides.[4]

When the bromide (**4**) was treated with allyltributyltin in benzene at reflux for 6 h, with azobisisobutyronitrile to initiate the reaction, a single diastereomer of the corresponding allylglycine derivative (**5a**) [^{1}H n.m.r. ($CDCl_3$) δ 0.82 (d, *J* 7 Hz, 3H), 1.00 (d, *J* 7 Hz, 3H), 2.08 (m, 1H), 2.42 (s, 3H), 2.47 (s, 3H), 2.75 (m, 2H), 4.76 (d, *J* 4.5 Hz, 1H), 4.90 (dd, *J* 3.5 and 5.5 Hz, 1H), 5.15 (m, 2H) and 5.60 (m, 1H)] was obtained in 60% yield. Although this material proved to be unsuitable for

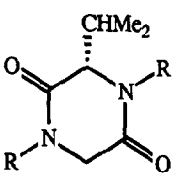


(1)

a) R = Br
b) R = $CH_2CH{=}CH_2$
c) R = $CH(CO_2Et)_2$

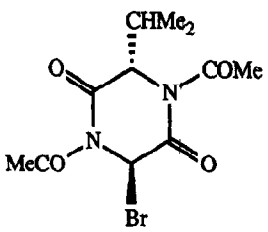


(2)

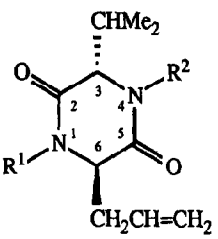


(3)

a) R = H
b) R = COMe

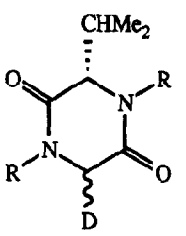


(4)



(5)

a) $R^1 = R^2$ = COMe
b) R^1 = H, R^2 = COMe



(6)

a) R = COMe
b) R = H

X-ray crystallographic analysis, on standing in moist ethyl acetate/light petroleum it underwent hydrolysis to give the monoacyldiketopiperazine derivative (**5b**) [^{1}H n.m.r. ($CDCl_3$) δ 1.00 (d, *J* 7 Hz, 3H), 1.08 (d, *J* 7 Hz, 3H), 2.10 (m, 1H), 2.54 (s, 3H), 2.80 (m, 2H), 4.18 (dd, *J* 3.5 and 9 Hz, 1H), 4.89 (dd, *J* 1.5 and 8.5 Hz, 1H), 5.30 (m, 2H) and 5.70 (m, 1H)], which was shown to be the *trans*-isomer by crystallographic analysis (Figure 1).[9] It is logical to assume that the stereochemistry of this material is the same as that of the diacyldiketopiperazine derivative (**5a**).

In the presence of $Eu(hfc)_3$,[10] the ^{1}H n.m.r. spectrum of the diketopiperazine (**5a**) displayed distinct resonances for each enantiomer. In particular, duplicate signals were observed for one of the methyl groups of the isopropyl substituent and for each *N*-acetyl group. When the above reactions were repeated with the enantiomer of the

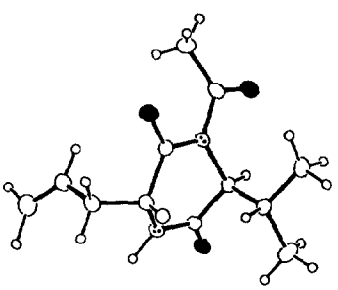


Figure 1. Molecular structure of the monoacyldiketopiperazine derivative (**5b**)

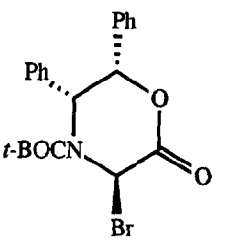
diketopiperazine (**3b**) derived from *(S)*-valine,[11] only one enantiomer of the allylglycine derivative (**5a**) could be detected using this procedure.[12] Thus the elaboration of the glycine derivative (**3b**) occurs without racemization of the valine residue, and the homochiral *(3S,6R)*-diastereomer of the allylglycine derivative (**5a**) is produced under these circumstances.

The bromide (**4**) in THF/D_2O (4:1) was stirred over palladium chloride under an atmosphere of deuterium, at room temperature for 14 h, to give the deuteride (**6a**), with 92% deuterium incorporation, as a 20:1 mixture of diastereomers. That mixture was treated with hydrazine hydrate in DMF[13] to give the deuteriated valylglycine anhydride (**6b**), also as a 20:1 mixture of diastereomers. In the ^1H n.m.r. spectrum (D_2O) of the latter compound, the relative intensity of the resonances at δ 4.20 and 4.37, for the α-hydrogen of the glycine residue in the *cis*- and *trans*-isomers, respectively,[14] showed the *cis*-diastereomer to be predominant. Through correlation, the major diastereomer of the diacyldiketopiperazine derivative (**6a**) can also be assigned the *cis*-stereochemistry.

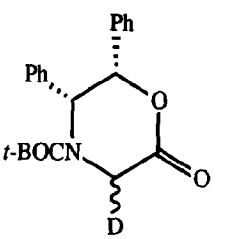
Although the relative stereochemistry of the bromide (**4**) was not separately determined, it is likely that the bromine is incorporated *trans* to the isopropyl substituent. The conversion of the bromide (**4**) to the deuteride (**6a**) would then involve an inversion of configuration.

Treatment of the bromide (**4**) with tributyltin deuteride[5] gave the deuteriated diketopiperazine (**6a**), with 85% deuterium incorporation, as a 2:1 mixture of the *trans*- and *cis*-diastereomers. The predominance of the *trans*-isomers of the diketopiperazines (**5a**) and (**6a**), in the reactions of the bromide (**4**) with allyltributyltin and tributyltin deuteride, respectively, can be attributed to a preference for delivery of deuterium and the allyl group *trans* to the isopropyl group in the radical derived by bromine atom transfer from the halide (**4**).

It is noteworthy that, by analogy with the present work, the palladium-catalysed reaction of the bromide (**7**) with deuterium has been found to be highly stereoselective, affording mainly the deuteride (**8**) through inversion of configuration.[2] The reaction of the bromide (**7**) with tributyltin deuteride was much less stereoselective and gave mainly the deuteride (**8**) resulting from retention of configuration.[2]



(7)



(8)

The synthesis of the bromide (**4**) and its subsequent reactions to give the allylglycine derivative (**5a**) and the deuteriated diketopiperazine (**6a**) illustrate the high degree of diastereoselectivity that can be expected in the elaboration of α-haloglycine derivatives in cyclic dipeptides. On this basis, the bromide (**4**) is likely to have considerable utility as a template for the asymmetric synthesis of amino acid derivatives. In this regard it should be noted that both *(R)*- and *(S)*-valine are inexpensive and readily available, therefore the approach delineated above should prove suitable for the α-substitution of glycine residues to give whichever enantiomer of the product is desired.

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7. All new compounds were fully characterized.
8. Initial reactions and the X-ray crystallographic structure determination of the diketopiperazine (**5b**) were performed using racemic materials.
9. Molecular structure of the diketopiperazine (**5b**): monoclinic space group $P2_1/c$, a = 8.778(2), b = 15.416(1), c = 10.012(3) Å, β = 109.24(1)°, R = 0.050 for 1068 reflections.
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