Asymmetric Induction in Radical Reactions: Enantioselective Syntheses of (*S*)-2-Deuterioglycine and (*R*)-2-Deuterioglycine

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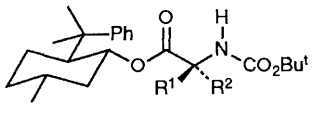
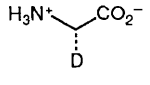
The (−)-8-phenylmenthol ester of *N*-Boc-glycine is brominated with *N*-bromosuccinimide and the bromo-compound is reduced with tri-n-butyldeuteriostannane to give the chiral glycine derivative in high optical yield which upon hydrolysis yields the amino acid without racemisation.

Although there are numerous examples of polar reactions in which the acyclic control of absolute stereochemistry has been described, few examples have been reported of similar control involving acyclic radical intermediates.[1] Observations which we have made show that reactions which are considered to involve radicals may proceed with high asymmetric induction at the radical site and that such reactions can be useful in the synthesis of α-amino acids.



1 $R^1 = R^2 = H$
2a $R^1 = Br$, $R^2 = H$
2b $R^1 = Br$, $R^2 = D$
3a $R^1 = D$, $R^2 = H$
3b $R^1 = H$, $R^2 = D$



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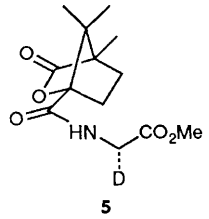

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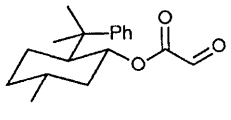

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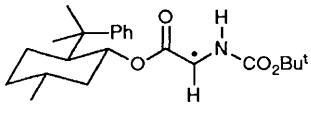

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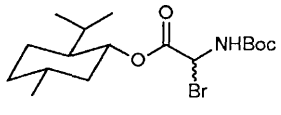

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There is a continuing interest in new routes to the synthesis of chiral glycine.[2] This stems from the fact that many of the routes are long and do not produce a product of high optical purity. Chiral glycine of high optical purity is required[2] as a probe for the elucidation of biosynthetic pathways, enzymic mechanisms and the conformations of peptides in solution.

We now describe our observations which have led to syntheses of the title compounds, in high optical purity, by a route in which the induction step involves an acyclic radical reaction, namely the reaction of a bromo compound with tri-n-butyldeuteriostannane.[3]

The *N*-Boc derivative of glycine was esterified with 8-phenylmenthol[4] to give the enantiomerically pure derivative **1**.† Bromination of this compound with *N*-bromosuccinimide (NBS) in refluxing CCl_4, under irradiation with a sun-lamp, gave the bromo compound **2a** in essentially quantitative yield. Contrary to an earlier report,[5] in which the reaction was done at room temperature, this compound appears to be mainly one

† Spectral data (300 MHz ^{1}H NMR): compound **1**: δ ($CDCl_3$): 7.1–7.4 (complex, 5H) 4.87 (dt, *J* 4.2, 10.7 Hz, 1H), 4.38 (br t, *J* 5.5 Hz, 1H) 3.29 and 3.05 (each dd, *J* 5.5, 18.2 Hz, 1H), 1.43 (s, 9H), 1.29 (s, 3H), 1.18 (s, 3H), 0.87 (d, *J* 6.6 Hz, 3H) and 2.1–0.8 (complex, methylene envelope).

Compound **2**: δ (CCl_4): 7.0–7.3 (complex, 5H), 5.45 (br d, *J* 10.7 Hz, 1H), 4.87 (d, *J* 10.7 Hz, 1H), 4.82 (dt, *J* 4.2, 10.8 Hz, 1H), 1.50 (s, 9H), 1.29 (s, 3H), 1.20 (s, 3H), 0.94 (d, *J* 6.5 Hz, 3H) and 0.85–2.15 (complex, methylene envelope).

Compound **8**: δ (CCl_4): 6.18 and 6.17 (each d, *J* 10.6 Hz, 1H), 5.74 (br d, *J* 10.6 Hz, 1H), 4.73 and 4.67 (each dt, *J* 4.4, 11.0 Hz, 1H total in the ratio *ca.* 1 : 1), 1.48 (br s, 9H), 0.97, 0.95, 0.92, 0.91 (each d, *J* 7.2 Hz, in ratio *ca.* 1 : 1 : 1 : 1, 6H), 0.78(4), 0.77(6) (each d, *J* 6.9 Hz, ratio *ca.* 1 : 1, 3H) and 0.75–2.15 (complex, methylene envelope).

Compounds **3a** and **3b** have NMR spectra identical with that of compound **1** except for the region described in the text.

diastereoisomer,‡ by 300 MHz ^{1}H NMR spectroscopy, but it was unstable and could not be fully characterised.†§ Treatment of this bromo compound with tri-n-butyldeuteriostannane (from tri-n-butylchlorostannane and 99 atom% $LiAlD_4$) in ether or toluene (−78 °C to room temp.) gave the deuterio derivative **3a**,† in 60–70% yield, after chromatography, and greater than 90% diastereoisomeric excess (d.e.). The estimation for the diastereoisomeric ratio (95 : 5) was obtained from the 300 MHz ^{1}H NMR (C_6D_6) spectrum. The region for the diastereotopic protons in the starting glycine derivative appears as an AB quartet at δ 3.34 and 3.22 (*J* 18.1 Hz) further coupled to the amide proton (*J* = 5.5 and 6.0 Hz respectively). The deuteriated derivative **3a** has absorption in this region at δ 3.20 (broadened d, *J ca.* 5.5 Hz) and δ 3.32 (broadened d, *J ca.* 4.7 Hz) in the ratio 95 : 5. Clearly, mainly one diastereotopic proton has been replaced by deuterium. Acid-catalysed hydrolysis¶ of the deuteriated derivative, followed by ion exchange chromatography, gave deuterioglycine **4**,[2] with no detectable loss of deuterium as determined by mass spectrometry and which therefore shows that no racemisation has occurred. Conversion of this amino acid to the camphanic acid amide, methyl ester derivative **5**, following the procedure of Armarego,[8] allowed the determination of the absolute configuration as (*S*) for this deuteriated glycine.

Bromination of the deuterioglycine derivative **3a** with NBS, under the same conditions as described above, and then removal of the bromine with tri-n-butylstannane, gave essentially only the undeuteriated glycine derivative **1**. This indicates that in the bromo derivative **2a** the bromine atom probably has the same configuration as the deuterium in compound **3a**. Compound **2a** is also (*S*) at C-2.

These data would seem to indicate that in both the bromination reaction and the stannane reduction, the same radical, with the same configuration, is formed in both cases. It is reasonable to assume that the bromo compound **2a**, at low temperature, would have a preferred conformation for reaction with the stannane. Once the radical has formed it is expected that it would be configurationally stable at that temperature since it is an extensively delocalised captodative radical.[9] At low temperature it is reasonable to assume that it also has a preferred conformation for reaction with the stannane. Whitesell has shown this to be the case with related glyoxalates **6** which also have an sp^2 carbon at this centre.[10] If this reasoning is correct, then what is remarkable is that the bromination, which occurs in refluxing CCl_4, also gives rise to mainly one diastereoisomer, as is indicated by the NMR data.‡ Reaction of the bromo compound with tri-n-butyldeuteriostannane in refluxing benzene gave lower, but still appreciable asymmetric induction (38% d.e.).

Owing to the lability of the bromo compound **2a**, we have not been able to establish whether this is a kinetic or thermodynamic product. It is difficult to rationalise a preferred conformation for the glycine radical **7** in refluxing carbon tetrachloride. It could be argued that this radical reaction is not stereoselective but that equilibration of the first-formed bromo compounds occurs to give the thermodynamic product which happens to be mainly one diastereoisomer. Subsequent reaction of that bromo compound with an initiating radical then produces a radical which is configurationally and conformationally stable, at least at low temperature. Reaction of that radical with deuteriostannane then gives the observed product. From this it can be inferred that the bromo compound obtained has the (2*S*) configuration. The configuration observed for the deuterio compound is consistent with the conformation shown for the presumed radical intermediate **7**. Whether hydrogen bonding between the NH and ester carbonyl could account for this arrangement is an open question.[11] Alternatively, perhaps tin plays a more intimate role in controlling the stereochemistry.

Using similar chemistry but starting from 2,2-dideuterioglycine (Aldrich 98 atom% D) the bromo derivative **2b** was prepared. Reduction of this bromo compound with tri-n-butylstannane gave the (*R*)-2-deuterioglycine derivative **3b** of similar optical purity. The high field ^{1}H NMR spectrum gave broadened doublets at δ 3.32 (*J* 4.7 Hz) and 3.20 (*J* 5.5 Hz) which were in the ratio 90 : 10. Further experiments indicate that asymmetric induction is also observed in carbon–carbon bond-forming reactions[12] ‖ with this radical intermediate and these will be reported in due course.

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‡ Mainly one set of peaks was observed in the 300 MHz ^{1}H NMR spectrum. In our experience, mixtures of diastereoisomers of other amino acid derivatives of this type invariably give twinning of some of the resonances. Bromination of the corresponding menthyl ester under the same conditions, gave an almost equal mixture of two diastereoisomers **8** as shown by ^{1}H NMR spectroscopy.†

§ Both Williams[6] and Seebach[7] have reported stereoselective brominations of this type but these cases involved cyclic systems in which rotation about single bonds is not possible and approach to one side is sterically less encumbered.

¶ We were working on the same approach to the asymmetric synthesis of amino acids as appeared recently.[5] Those workers reported that racemisation of the amino acids occurred on attempted acid-catalysed hydrolysis of derivatives of this type. We have found that the use of CF_3CO_2H, at room temperature, followed by CF_3CO_2H–6 mol dm^{-3} HCl at reflux effects hydrolysis without racemisation (manuscript in preparation).

‖ Stereoselective formation of carbon–carbon bonds with acyclic amide radicals appeared while this manuscript was in preparation.[13] The captodative radical described here is important because it allows the stereoselective synthesis of α-amino acids.