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Enantioselective synthesis of α-carbon deuterium-labelled L-α-amino acids

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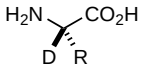
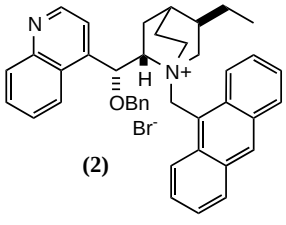
Abstract—In this paper we describe a simple and efficient method for the synthesis of α-carbon deuterium labelled L-α-amino acids via asymmetric alkylation of a benzophenone-derived glycine imine. The key alkylation step employs a chiral quaternary ammonium salt derived from cinchonidine in conjunction with KOD in D_2O enabling both side-chain and isotopic label to be incorporated in a single reaction step. Mild acid hydrolysis of the resulting imines then furnishes the labelled amino acid esters in good overall yield and high enantiomeric excess.

α-Carbon deuterium-labelled L-α-amino acids **1** have found utility in the elucidation of biosynthetic pathways and the mechanistic investigation of amino acid processing enzymes.[1] In addition their incorporation into peptides and proteins can be useful in facilitating the assignment of spectroscopic data and in the investigation of secondary and tertiary structure.[2,3]



(1)

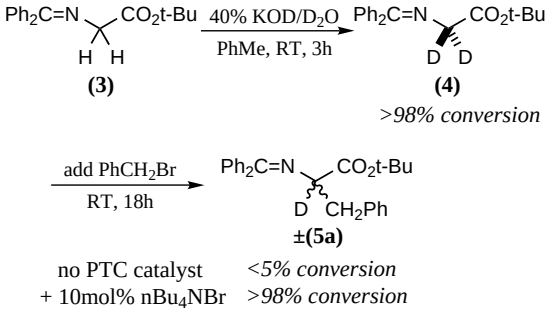
As a consequence a variety of methods for the synthesis of these materials have been developed.[4] Many of these involve the preparation of racemic ^{2}H-2 amino acids followed by resolution[5] or chiral chromatography.[6] However, a number of asymmetric approaches have also been developed including enzyme mediated deuteration of amino acids,[1b,7] enzymatic reductive amination of pyruvates,[3a,8] auxiliary-based asymmetric alkylation of glycine derivatives,[9] and chiral memory-based asymmetric alkylations.[10]



(2)

We have recently been involved in expanding the utility of cinchona alkaloid derived chiral phase-transfer catalysts (PTCs) (e.g. **2**) and have primarily focused on the identification and development of highly practical ambient temperature processes that utilize these materials.[11] A significant part of this work has been concerned with optimization of the asymmetric alkylation of amino acid derived imines (e.g. **3**), a process that was originally developed by O'Donnell, and has recently received attention from a number of groups.[12] This work has led to the development of highly efficient methods for the synthesis of α-amino acids, and in this paper we examine its application in the preparation of α-carbon deuterium-labelled α-amino acids.

Initially we investigated the rate of ^{1}H/^{2}H exchange for imine **3** under typical liquid–liquid phase-transfer alkylation conditions (Scheme 1). It was found that, even in the absence of a PTC, imine **3** was rapidly deuterated at



(3) **(4)** **±(5a)**

Scheme 1.

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C-2. In contrast, alkylation of imine **3** (or **4**) with 1 equiv. benzyl bromide requires 5–10 mol% of a PTC in order to achieve reasonable rates of reaction.[13] This may indicate that in the absence of a PTC, interfacial deprotonation takes place generating a hydrated enolate that is relatively unreactive towards the hydrophobic alkyl halide. Addition of a quaternary ammonium ion PTC could then promote alkylation by reducing the hydration state and/or extracting the enolate into the organic reaction phase.[14]

These observations suggest that it should be straightforward to access α-carbon deuterium-labelled L-α-amino acids directly from imine **3**, simply by pre-mixing with commercially-available 11.7 M KOD/D_2O prior to addition of the PTC and alkylating agent.[15] In order to test this hypothesis we applied these conditions in the reaction of imine **3** with a range of alkylating agents (Table 1). For this study we chose to use chiral PTC catalyst **2**, since previous work in our group had indicated that this is the optimal catalyst for the generation of L-amino acid derivatives.[11a,f]

In all cases the alkylation product **5** was obtained typically with $=95\%$ ^2H incorporation at H-2 as determined by ^1H NMR and mass spectrometric analysis. In addition, high levels of asymmetric induction (>90% e.e.) were obtained with most alkylating agents. This, coupled with the simplicity of the reaction conditions, suggests that asymmetric PTC alkylation is a highly effective means of accessing materials of this type.[15]

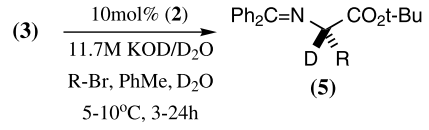
It is interesting to note that when propargyl bromide was used as the alkylating agent, substantial deuteration of the acetylenic position occurred (Table 1, entry f). This suggests that the reaction conditions employed will effect efficient $^1H/^2H$ exchange of C–H acidic groups with $pK_a(H_2O)\leq 23$. This offers a means of introducing additional isotopic substitution, but is not a limitation of the chemistry since any undesired exchange in the side-chain can be reversed by treatment with KOH/H_2O (Scheme 2). Using these conditions, no significant levels of exchange at C-2 could be detected.

Hydrolysis of the imine functions under standard conditions[12] proceeds without loss of deuterium label and furnishes the α-carbon deuterium-labelled L-α-amino acid esters **6a–g** in good overall yield (Table 2).

Thus this constitutes a simple two-step method for the preparation of α-carbon deuterium-labelled L-α-amino acid esters suitable for incorporation into peptide synthesis. This chemistry is compatible with the use of isotopically labelled alkylating agents and so could be utilized in the synthesis of a wide variety of multiply labelled amino acid derivatives.

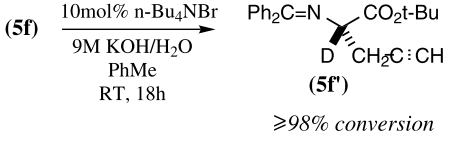
In conclusion, we have demonstrated that the phase-transfer asymmetric alkylation of glycine imine **3** using KOD/D_2O, followed by cleavage of the imine function, is a highly effective strategy for the preparation of α-carbon deuterium labelled L-α-amino acids. Extension of this methodology to other important amino acid derivatives is currently under investigation.

Table 1.



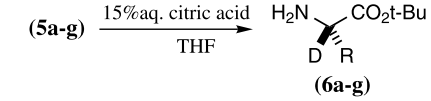
Entry	Product	% e.e.[a]
a	$Ph_2C{=}N$, $CO_2t\text{-}Bu$, D, CH_2Ph	94
b	$Ph_2C{=}N$, $CO_2t\text{-}Bu$, D, $CH_2$4-BrPh	95
c	$Ph_2C{=}N$, $CO_2t\text{-}Bu$, D, $CH_2$2-naphthyl	94
d	$Ph_2C{=}N$, $CO_2t\text{-}Bu$, D, $CH_2CH{=}CH_2$	92
e	$Ph_2C{=}N$, $CO_2t\text{-}Bu$, D, $CH_2C(CH_3){=}CH_2$	96
f	$Ph_2C{=}N$, $CO_2t\text{-}Bu$, D, $CH_2C\equiv CD$	86
g	$t\text{-}BuO_2C$, $N{=}CPh_2$, D, D, $Ph_2C{=}N$, $CO_2t\text{-}Bu$	≥95[b] (90%d.e.)

[a] ±3% via HPLC (Chiralcel OD-H) of the corresponding *N*-Fmoc derivatives. [b] ±3% via HPLC (Chiralcel AD) of the corresponding *N*-Fmoc derivative.



Scheme 2.

Table 2.



Product	Atom% ^2H[a]	% Yield[b]
6a	≥94	90
6b	≥95	80
6c	≥95	84
6d	≥95	92
6e	≥95	70
6f	≥95	74
6g	≥90	86

[a] At C-2 via H NMR/mass spectrometry.
[b] Overall yield for alkylation/hydrolysis.

Acknowledgements

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References

1. See for example: (a) Furuta, T.; Takahashi, H.; Kasuya, Y. *J. Am. Chem. Soc.* **1990**, *112*, 3633; (b) Stevenson, D. E.; Akhtar, M.; Gani, D. *Tetrahedron Lett.* **1986**, *27*, 5661; (c) Baldwin, J. E.; Adlington, R. M.; Ting, H. H.; Arigoni, D.; Graf, P.; Martinoni, B. *Tetrahedron* **1985**, *41*, 3339.
2. See for example: Sack, I.; Balazs, Y. S.; Rahimipour, S.; Vega, S. *J. Am. Chem. Soc.* **2000**, *122*, 12263.
3. This can be particularly effective if multiply-labelled systems can be accessed, see for example: (a) Raap, J.; Nieuwenhuis, S.; Creemers, A.; Hexspoor, S.; Kragl, U.; Lugtenburg, J. *Eur. J. Org. Chem.* **1999**, *10*, 2609; (b) Gardner, K. H.; Kay, L. E. *J. Am. Chem. Soc.* **1997**, *119*, 7599; (c) Lastra, E.; Hegedus, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 87.
4. For recent reviews on the synthesis of labelled amino acids see, (a) Kelly, N. M.; Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **1997**, *14*, 205; (b) Pshenichnikova, A. B.; Karnaukhova, E. N.; Zvonkova, E. N.; Shvets, V. I. *Bioorg. Khim.* **1995**, *21*, 163.
5. See for example: (a) Reider, P. J.; Conn, R. S. E.; Davis, P.; Grenda, V. J.; Zambito, A. J.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 3326; (b) Jones, J. B. *Tetrahedron* **1986**, *42*, 3351; (c) Fujihara, H.; Schowen, R. L. *J. Org. Chem.* **1984**, *49*, 2819.
6. Mitulovi, G.; Lämmerhofer, M.; Maier, N. M.; Lindner, W. *J. Labelled Comp. Rad.* **2000**, *43*, 449.
7. See for example: (a) Mosin, O. V.; Skladnev, D. A.; Shvets, V. I. *Biosci. Biotech. Bioch.* **1998**, *62*, 225; (b) Milne, J. J.; Malthouse, J. P. G. *Biochem. Soc. Trans.* **1996**, *24*, 133S; (c) Faleev, N. G.; Ruvinov, S. B.; Saporovskaya, M. B.; Belikov, V. M.; Zakomyrdina, L. N.; Sakharova, I. S.; Torchinsky, Y. M. *Tetrahedron Lett.* **1990**, *31*, 7051.
8. See for example: Wong, C. H.; Whitesides, G. M. *J. Am. Chem. Soc.* **1983**, *105*, 5012.
9. (a) Elemes, Y.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 1* **1996**, 537; (b) Rose, J. E.; Leeson, P. D.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 157.
10. Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215.
11. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595; (b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599; (c) Lygo, B.; Wainwright, P. G. *Tetrahedron* **1999**, *55*, 6289; (d) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 1385; (e) Lygo, B. *Tetrahedron Lett.* **1999**, *40*, 1389; (f) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671; (g) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391; (h) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403; (i) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron* **2001**, *57*, 6447; (j) Lygo, B.; To, D. M. *Tetrahedron Lett.* **2001**, *42*, 1343.
12. For an authoritative review of the literature relating to the use of chiral PTCs in the asymmetric alkylation of benzophenone glycine imines see O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 1.
13. Similar observations have been noted with phenylacetonitrile, see: Starks, C. M.; Liotta, C. L.; Halpern, M. C. *Phase-Transfer Catalysis—Fundamentals, Applications, and Industrial Perspectives*; Chapman and Hall: New York, 1994; pp. 99–100 chapter 3.
14. For more detailed discussions on the mechanisms that may be operating in alkylations of this type see: Esikova, I. A.; Nahreini, T. S.; O'Donnell, M. J. In *ACS Symposium Series* 659: *Phase-Transfer Catalysis—Mechanisms and Syntheses*; Halpern, M. E., Ed.; ACS: Washington, DC, 1997; p. 89.
15. **Typical procedure**: A solution of glycine imine **3** (0.80 mmol) in toluene (5 ml) under argon, is treated with potassium deuteroxide (0.68 ml of a 11.7 M solution in D_2O). The resulting mixture is stirred vigorously (ca. 1000 rpm) at room temperature (25°C) for 3 h, then cooled to 5–10°C and diluted with deuterium oxide (0.32 ml). Catalyst **2** (0.08 mmol) and the appropriate alkylating agent (0.68 mmol) are added, and stirring continued until the reaction is complete by TLC (3–24 h). The mixture is then extracted with ethyl acetate (3×5 ml). The combined organics are dried (Na_2SO_4) and concentrated under reduced pressure to give the crude imine **5**. This material is dissolved in tetrahydrofuran (4 ml) and 15% aqueous citric acid (1.5 ml) added. The mixture is stirred vigorously at room temperature for 18 h, then diluted with 1 M hydrochloric acid (1 ml). The mixture is extracted with diethyl ether (2×3 ml) to remove the benzophenone, then the aqueous layer is basified (K_2CO_3). Extraction with chloroform (5×3 ml) followed by drying of the extracts (Na_2SO_4) and concentration under reduced pressure gives the crude amino acid *tert*-butyl ester which can generally be purified by passing through a plug of silica.