Tetrahedron Letters, Vol. 34, No. 24, pp. 3919-3920, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

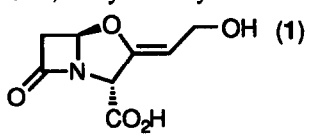
Synthesis of *L*-Ornithines Stereospecifically Deuterated at C-3

Jack E. Baldwin, Kirsten D. Merritt, and Christopher J. Schofield

The Dyson Perrins Laboratory and the Oxford Centre for Molecular Sciences, South Parks Road, Oxford, OX1 3QY, U.K.

Abstract: (2*S*, 3*S*)-[2,3-$^2H_2$]-Ornithine and (2*S*, 3*R*)-[3-$^2H_1$]-ornithine were prepared with high stereoselectivity *via* asymmetric reduction catalysed by {bicyclo[2.2.1]hepta-2,5-diene}{(*R*)-1,2-*bis*(diphenylphosphino)propane}rhodium (I) trifluoromethanesulphonate [(*R*)-Rh-Prophos].

To aid investigations into the biosynthetic pathway to the β-lactamase inhibitor clavulanic acid (**1**),[1] we required syntheses of *L*-ornithines stereospecifically deuterated at C-3 (**2a, b**).[2] Gould *et al* have reported the synthesis of ornithines stereospecifically deuterated at C-3 *via* the reduction of a deuterated aldehyde precursor with *R*- or *S*-Alpine borane[3] and subsequent introduction of the α-amino centre achirally.[4] Their estimated diastereomeric excess was *ca.* 90%, however, the syntheses yielded racemic products.

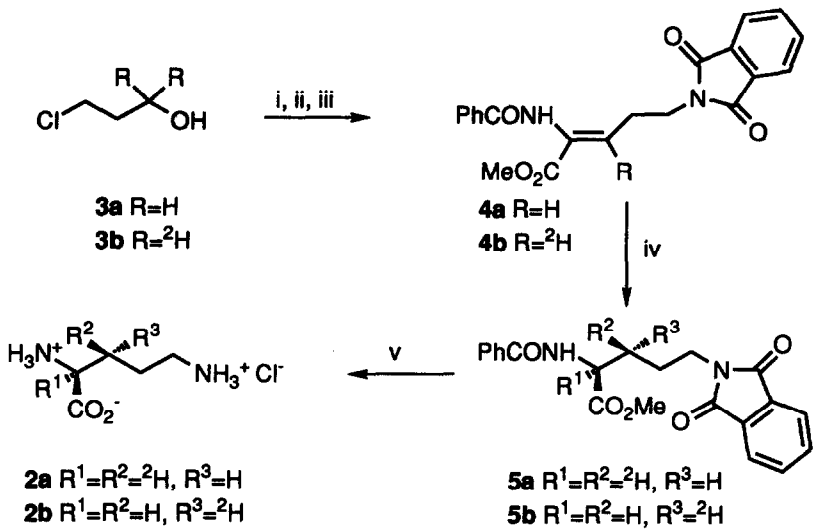


(**1**)

α-Amino acids have been prepared in high enantiomeric excess (up to 99%) *via* hydrogenation of suitably protected *Z*-didehydroamino acids using asymmetric catalysts.[5] Asymmetric hydrogenation or deuteration of an appropriate deuterated or protiated olefin would enable both the required chiral centres to be introduced simultaneously, with complete diastereoselectivity since addition is *syn*.[6] Consideration of the advantages of this proposed strategy over the published route made this the method of choice (Scheme 1).

Having incorporated deuterium into one compound by reduction of ethyl 3-chloropropionate with $LiAlD_4$,[3] both required ornithine stereoisomers were prepared using parallel routes. Thus, phthalimide displacement[7] on (**3a, b**), followed by Swern oxidation[8] and the Schmidt procedure[9] yielded the protected *Z*-olefins (**4a, b**). (The *Z*-configuration of (**4a**) was confirmed by X-ray crystallography.) The olefins (**4a, b**) were then reduced in a *syn*[6] manner using {bicyclo[2.2.1]hepta-2,5-diene}{(*R*)-1,2-*bis*(diphenylphosphino)propane}rhodium (I) trifluoromethanesulphonate [(*R*)-Rh-Prophos] as catalyst.[10] Using a chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato], europium III derivative,[11] the enantiomeric excesses (ee) of (**5a**) and (**5b**) were found to be *ca.* 88%. Recrystallisation[12] yielded (**5a**) of *ca.* 92%ee and (**5b**) of *ca.* 93%ee. Deprotection by refluxing in 6M HCl followed by ion-exchange, adjustment of the pH to 4.0-4.5 and crystallisation from water/ethanol[13] yielded the desired compounds (**2a**) and (**2b**).

Acknowledgements: We would like to thank the SERC for support, Dr. A. J. Edwards for the X-ray crystal structure determination and Drs. J. M. Brown and D. W. Price for helpful discussions.



3a R=H
3b R=^{2}H

4a R=H
4b R=^{2}H

2a R^1=R^2=^{2}H, R^3=H
2b R^1=R^2=H, R^3=^{2}H

5a R^1=R^2=^{2}H, R^3=H
5b R^1=R^2=H, R^3=^{2}H

Scheme 1. Reagents: i, K phthalimide, 18-crown-6, toluene, 104°C (R=H, Yield=82%, R=^{2}H, Yield=66% from ethyl 3-chloropropionate); ii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60°C (R=H, Yield=82%, R=^{2}H, Yield=72%); iii, $PhCONHCH(CO_2Me)PO(OEt)_2$, $^tBuO^-K^+$, CH_2Cl_2 (R=H, Yield=57%, R=^{2}H, Yield=52%); iv, $^2H_2$ or H_2, (*R*)-Rh-Prophos, CH_2Cl_2, 30°C (Yields *ca.* 60% after recrystallisation); v, 6M HCl reflux (R=H, Yield=42%, R=^{2}H, Yield=45%). DMSO=dimethylsulphoxide.

REFERENCES

1. Brown, A. G.; Butterworth, D.; Cole, M.; Hanscomb, G.; Hood, J. D.; Reading, C.; Rolinson, G. N. *J. Antibiot.*, **1976**, *29*, 668-669.
2. Baldwin, J. E.; Merritt, K. D.; Schofield, C. J.; Elson, S. W.; Baggaley, K. H. *J. Chem. Soc., Chem. Commun.*, submitted for publication.
3. Prabhakaran, P. C.; Gould, S. J.; Orr, G. R.; Coward, J. K. *J. Am. Chem. Soc.*, **1988**, *110*, 5779-5784.
4. Prabhakaran, P. C.; Woo, N-T.; Yorgey, P. S.; Gould, S. J. *J. Am. Chem. Soc.*, **1988**, *110*, 5785-5791.
5. Williams, R. M. *Synthesis of optically active α-amino acids*; Pergamon Press; Oxford, 1989; pp239-256, and references cited therein.
6. Detellier, C.; Gelbard, G.; Kagan, H. B. *J. Am. Chem. Soc.*, **1978**, *100*, 7556-7561.
7. Soai, K.; Ookawa, A.; Kato, K. *Bull. Chem. Soc. Jpn.*, **1982**, *55*, 1671-1672.
8. Mancuso, A. J.; Huang, S-L.; Swern, D. *J. Org. Chem.*, **1978**, *43*, 2480-2482.
9. Schmidt, U.; Lieberknecht, A.; Kazmaier, U.; Griesser, H.; Jung, G.; Metzger, J. *Synthesis*, **1991**, 49-55.
10. Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.*, **1978**, *100*, 5491-5494.
11. Goering, H. L.; Eikenberry, J. N.; Koermer, G. S. *J. Am. Chem. Soc.*, **1971**, *93*, 5913-5914.
12. O'Reilly, N. J.; Derwin, W. S.; Lin, H. C. *Synthesis*, **1990**, 550-556.
13. Greenstein, J. P.; Winitz, M. *Chemistry of the amino acids*; John Wiley and Sons, Inc.; New York; 1961; vol. 3; p2479.

(Received in UK 5 April 1993)