Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 1, pp. 149–153, 1997

Printed in Great Britain

PII: S0957-4166(96)00495-8

0957-4166/97 $17.00 + 0.00

A short synthesis of (*S*)-2-(diphenylmethyl)pyrrolidine, a chiral solvating agent for NMR analysis

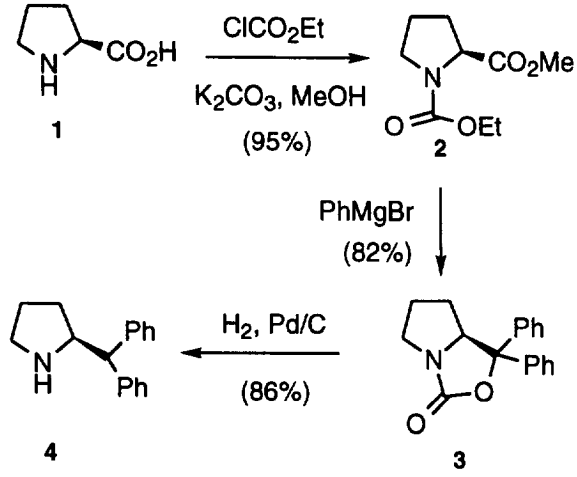
David J. Bailey, David O'Hagan * and Mustafa Tavasli

Department of Chemistry, University of Durham, Science Laboratories, South Road, Durham, DH1 3LE, UK

Abstract: A three step synthesis of (*S*)-2(diphenylmethyl)pyrrolidine **4** is described which allows its preparation on a large scale. The C_2 symmetric diamines **5** and **6** have been prepared from **4** and are attractive as potential ligands for asymmetric transformations. Pyrrolidine **4** has been assessed as a chiral solvating agent for the NMR analysis of chiral compounds. It emerges as a good CSA for carboxylic acids and some secondary alcohols.

(*S*)-2(Diphenylmethyl)pyrrolidine **4** was first reported as its hydrochloride salt in the patent literature in 1969[1] and has more recently been prepared from L-proline by Enders *et al.*[2]. Despite the recent widespread interest focused on homochiral monoamines[3] and C_2 symmetric diamines[4], in various aspects of asymmetric catalysis (deprotonations[3b,5], organo-zinc[6], magnesium[7], tin[8] and palladium[9] reactions, dihydroxylations[10], epoxide ring opening[11], polymerisations[12], conjugate additions[13], amine oxides[14] etc.) to our knowledge **4** has never been evaluated in any of these arenas. We attribute this simply to its lack of availability[15] rather than to any undesirable structural features. On the contrary, the sterically large diphenylmethyl group renders the base potentially attractive for many applications. In the course of our interest in generating suitable pyrrolidines for the preparation of chiral fluorinating agents[16] we report a straightforward three step process to **4** from L-proline as outlined in Scheme 1.

Treatment of (*S*)-L-proline **1** with ethyl chloroformate and potassium carbonate in methanol furnished **2** in excellent yield[17]. Compound **2** could be isolated and purified by chromatography, but for larger scale synthesis the crude product was subjected directly to a Grignard reaction with



Scheme 1.

* Corresponding author. Email: David.O'Hagan@durham.ac.uk

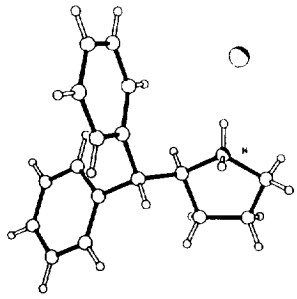
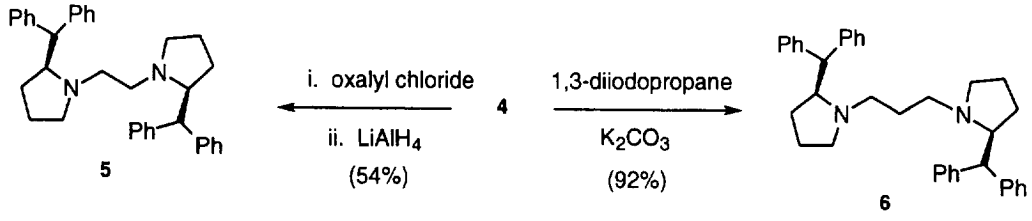


Figure 1. X-Ray structure of HCl salt of (*S*)-**4**.



Scheme 2.

phenylmagnesium bromide (2 equivalents). *In situ* cyclisation generated **3**, which is a solid material and can be purified by recrystallisation from ethyl acetate. The key step in the reaction sequence is the hydrogenation of **3** using palladium on carbon as a catalyst. This results in the loss of the elements of carbon dioxide to generate **4** in an overall yield of 67% from L-proline. The synthesis allows for the large scale preparation of **4** and typically we prepare 20 g batches at a time. The configurational purity of the product was determined to be >98% ee by chiral HPLC analysis[18] and the (*S*) absolute stereochemistry, although not in doubt, was confirmed by X-ray analysis[19,20,23] of a suitable crystal of the hydrochloride salt as shown in Figure 1.

In view of the interest in C_2 symmetric diamines as catalysts in asymmetric organometallic reactions[2–12], the novel diamines **5** and **6** were synthesised from **4** using previous protocols[4b] for related pyrrolidine systems. Both of the diamines **5** and **6** could be prepared in a straightforward manner as shown in Scheme 2.

Chiral solvating agent for NMR analysis

There is a current requirement for good chiral solvating agents (CSAs) to determine the enantiomeric composition of chiral carboxylic acids and alcohols directly by NMR analysis[21,22]. The potential anisotropic influence of the diphenylmethyl group of **4** suggested that it may serve as a chiral solvating agent for the NMR analysis of chiral carboxylic acids. In the event **4** emerged as an excellent CSA[15] for racemic carboxylic acids such as 3-phenylbutyric **7**, 2-bromopropionic **8**, mandelic **9**, 2-phenoxypropionic **10**, 2-phenylpropionic **11** acids and Mosher's acid **12**. The optimal chemical shift non-equivalence between the diastereisomeric salts in solution is established when one equivalent of pyrrolidine base is added consistent with the formation of a 1:1 salt complex in solution. Table 1 indicates the chemical shift nonequivalence in the ^{1}H-NMR spectrum for the CH_3 and CH resonances of **7–12** with one equivalent of **4**.

Some success was achieved for the resolution of the secondary alcohols phenethanol **13** and α-cyclohexyl-benzyl alcohol **14**; however, chiral primary and tertiary alcohols failed to generate resolvable diastereomeric complexes.

Table 1. Chemical shift non-equivalences (in ppm) in the resultant ^{1}H-NMR spectra for 1:1 diastereoisomeric salts of **4** with racemic **7–12**. Typically a solution of 10 mg of racemic acid/alcohol in $CDCl_3$ (0.75 ml) was titrated in each case with a 0.5 M solution of **4** in $CDCl_3$

	Δδ CH/[a]CH_2	Δδ CH_3		Δδ CH	Δδ CH_3
7	0.054[a]	none	**11**	0.007	0.011
8	0.045	0.020	**12**	-	0.006
9	0.028	none	**13**	0.014	0.005
10	none	0.025	**14**	0.007	none

Experimental

(5S)-[3.3.0]-1-Aza-2-oxo-3-oxa-4,4-diphenyl-bicyclooctane 3

A solution of **2** (39.0 g, 193 mmol) in THF (100 ml) was added to a solution of phenylmagnesium bromide in THF (1.0 M, 386 ml, 386 mmol) under an inert atmosphere of N_2 at 0°C. The solution was warmed to 18°C and then heated under reflux for 3 h. The reaction was then added to an ice cold solution of NH_4Cl and the aqueous layer extracted into ethyl acetate (4×100ml). The combined organic extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure to give the title compound as a white crystalline solid, which was recrystallised from ethyl acetate. m.p. 148–149°C, $[\alpha]_D$=−271 (c 0.01, CH_2Cl_2), [lit[24], $[\alpha]_D$=−241.6 (c 0.002, MeOH)], δ_H ($CDCl_3$) 7.53–7.21 (10H, m, ArH), 4.53 (1H, m, CH), 3.64, 3.31 (2H, CH_2N), 1.83 (4H, m, CH_2); δ_C ($CDCl_3$) 160.0, 139.9, 128.2, 126.6, 125.0, 85.4, 68.7, 45.6, 28.5, 24.4; ν_{max} (neat)/cm^{-1} 2969, 2863, 1757 (C=O), 1255 (C–O); m/z (EI) 279.1 (M^+, 27%), 105.0 (100%); (Found; C, 77.40: H, 6.14: N, 5.01. $C_{18}H_{17}NO_2$ requires C, 77.38: H, 6.14: N, 5.02).

(2S)-2(Diphenylmethyl)pyrrolidine 4

A mixture of **3** (15.1 g, 54.0 mmol) and Pd/C (4.0 g) (10%) in methanol (500 ml) was stirred under an atmosphere of hydrogen at room temperature for 48 h. The catalyst was filtered off and the methanol removed under reduced pressure. Purification, over silica gel eluting with ethyl acetate then methanol, or on a larger scale by distillation gave the title compound (11.0 g, 86%) as a colourless oil. b.p. (135°C, 0.01 mmHg), $[\alpha]_D$=−7.84 (c 2.05, $CHCl_3$) [lit[2], $[\alpha]_D$=−7.8 (c 2.11, $CHCl_3$]. δ_H (200 MHz; $CDCl_3$; Me_4Si) 7.28 (10H, m, Ar), 3.89 (2H, m, 2×CH), 2.93, 2.85 (2H, AB-system, CH_2N), 1.69 (3H, m, CH_2) 1.37 (1H, m, CH_2); δ_C ($CDCl_3$) 142.9, 142.8, 128.6, 128.4, 127.9, 126.4, 62.1, 57.2, 45.6, 30.5, 24.3; ν_{max} (neat)/cm^{-1} 3405 (NH), 2962; m/z (CI) 238.4 (M^+, 39%, 84.1 (19%); (Found; C, 74.65: H, 7.62: N, 4.98: Cl, 12.71. $C_{17}H_{20}Cl$ (HCl salt) requires C, 74.69: H, 7.38: N, 5.13: Cl, 12.80).

N,N′-1,2-Ethane-bis((2S)-2(diphenylmethyl)pyrrolidine) 5

Oxalyl chloride (0.82 g, 6.3 mmol) was added to a solution of **4** (3.0 g, 12.6 mmol), triethylamine (2.11 ml, 1.53 g, 15.0 mmol) and DMAP (0.15 g, 1.26 mmol in dichloromethane (50 ml)) at −78°C. After 10 min the solution was warmed to 0°C and stirred for 8 h. The solution was filtered and the solvent removed under reduced pressure to leave a brown solid. This solid was dissolved directly in dry THF (30 ml) and the resulting solution added to a slurry of $LiAlH_4$ (0.71 g, 18.9 mmol) in THF (10 ml) at 0°C. The reaction was quenched after 8 h with NaOH (0.2 M, 5 ml), filtered and the reaction mixture extracted into ethyl acetate (2×20ml). The combined organic extracts were dried ($MgSO_4$) and concentrated to give a yellow oil. Purification over neutral alumina, eluting with n-hexane/ethyl acetate (9:1), gave the title compound (1.70 g, 54%) as a white solid. m.p. 103–104°C; $[\alpha]_D$=−49.54 (c 1.09, $CHCl_3$); δ_H ($CDCl_3$) 7.31 (20 H, m, ArH), 3.96 (2H, d, CH), 3.25 (2H, m, CHN), 3.00, 2.17 (4H, CH_2), 2.47, 2.19 (4 H, CH_2), 1.56–1.92 (8H, m, CH_2); δ_C ($CDCl_3$) 144.7, 144.3, 129.8, 129.6, 128.8, 128.5, 126.7, 126.51, 68.3, 57.4, 55.6, 55.3, 30.3, 24.5; ν_{max} (KBr)/cm^{-1} 2962, 2791 (N–CH_2); m/z (CI) 501.3 (M+H, 25.3%), 236.2 (100%); (Found: M+H, 501.3266. $C_{36}H_{40}N_2$+H requires 501.3269).

*N,N'-1,3-Propane-bis((2S)-2(diphenylmethy)lpyrrolidine) **6***

A solution of **4** (2.0 g, 8.4 mmol) was added to slurry of K_2CO_3 in EtOH (30 ml). After 15 min 1,3-diiodopropane (0.42 ml, 4.2 mmol) was added and the solution heated under reflux for 8 h. The reaction was filtered and then concentrated under reduced pressure. Purification over neutral alumina eluting with n-hexane/ethyl acetate (9:1) gave the title compound (2.0 g, 92%) as a colourless oil which crystallised as a white solid on standing m.p. 73–74°C; $[\alpha]_D$=−25.5 (c 1.73, $CHCl_3$); δ_H ($CDCl_3$) 7.28 (20H, m, Ar) 3.98 (2H, d, CH), 3.20 (2H, m, CHN), 2.0 (10H, m, CH_2), 1.73–1.45 (8H, m, CH_2); δ_C ($CDCl_3$) 144.6, 144.3, 129.6, 129.5, 128.7, 128.5, 126.5, 126.4, 68.4, 57.6, 55.1, 54.9, 30.6, 24.2; ν_{max} (KBr)/cm^{-1} 2959, 2788 (N–CH_2); m/z (CI) 515.4 (M+H, 22.8%), 84 (100%); (Found: M+H, 515.3426. $C_{37}H_{42}N_2$+H requires 515.3426).

Acknowledgements

We thank the Afyon Kocatepe University, Turkey for a Y.O.K studentship (M. T.) and Glaxo Group plc/EPSRC for a CASE studentship (D. J. B.). We also acknowledge Dr Robert Boughtflower (Glaxo) for chiral HPLC analysis and the involvement of Drs U. Dyer and M. Montief in the project at various stages.

References

1. Roussel-UCLAF, Patent [Fr. M 3,638], 1964. [*Chem. Abs.*, **1969**, *70*, 106375m].
2. Enders, D.; Kipphardt, H.; Gerdes, P.; Brena-Valle, L. J.; Bhushan, V. *Bull. Soc. Chim. Belg.*, **1988**, *97*, 691.
3. (a) Chong, J. M.; Clarke, I. S.; Kock, I.; Olbach, P. C.; Taylor, J. T. *Tetrahedron: Asymmetry*, **1995**, *6*, 409; (b) Cox, P. J.; Simkins, N. S. *Tetrahedron: Asymmetry*, **1991**, *2*, 1.
4. (a) Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.*, **1994**, *35*, 3391; (b) Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron*, **1993**, *49*, 9735.
5. Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *Tetrahedron Lett.*, **1994**, *35*, 6159;.
6. Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.*, **1994**, 297; Soai, K.; Niwa, S. *Chem. Rev.*, **1992**, *92*, 833.
7. Nakajima, M.; Tomioka, K.; Koga, K. *Tetrahedron*, **1993**, *49*, 9751.
8. Kobayashi, S.; Kawasuji, T.; Mori, N. *Chem. Lett.*, **1994**, 217.
9. Kubota, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.*, **1993**, *34*, 8135.
10. Wu, Y.-D.; Wang, Y.; Houk, K. N. *J. Org. Chem.*, 1992, **57**, 1362; Oishi, T.; Hirama,. *J. Org. Chem.*, **1989**, *54*, 5834; Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.*, **1989**, *111*, 9243; Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.*, **1990**, *31*, 1741.
11. Asami, M. *Bull. Chem. Soc. Jpn*, **1990**, *63*, 721.
12. Okamoto, Y.; Nakano, T. *Chem. Rev.*, **1994**, *94*, 349.
13. Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. J.; *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2373; Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2385.
14. O'Neil, I. A.; Miller, N. D.; Barkley, J. V.; Low, C. M. R.; Kalindjian, S. B. *Synlett.*, **1995**, 617; **1995**, 619.
15. (*S*)-2-(Diphenylmethyl)pyrrolidine **4** will soon be available from the Aldrich Chemical Company, catalogue number 46,7189.
16. Bailey, D. J., Ph.D Thesis, University of Durham, 1994.
17. Kanth, J. V. B.; Periasamy, M. *Tetrahedron*, **1993**, *49*, 5127.
18. The amine **4** was derivatised as its trifluoroacetyl amine with N-trifluoroacetylimidazole and analysed using a Chiracel ODH HPLC column.
19. Crystal data: $C_{17}H_{19}N.HCl$, M=273.81, orthrombic, a=8.177(2), b=11.766(4), c=16.091(5) Å, V=1548(1) $Å^3$, λ=1.54178 Å, space group $P2_12_12_1$(No 19), Z=4, D_c=1.17 g cm^{-3}, F(000)=584, μ(Cu-Kα)=2.08 mm^{-1}. Data collection and processing: Siemens R3m/V diffractometer, 2322

refelections measured ($3<2t<115°$) of which 2108 were unique and 1509 had $I > 2.0\ \sigma(I)$. Full matrix least squares refinement was employed with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode with individual isotropic temperature factors. Individual weights were applied according to the scheme $w=[\sigma^2(F_o)+0.0008|F_o|^2]^{-1}$ and refinement converged at $R=0.052$, $Rw=0.051$, goodness of fit=1.09. The absolute configuration was unambigously determined by refining the Rogers[20] eta parameter [$\eta=0.92(7)$]. All computations were carried out using the SHELXTL PLUS[23] (μ-VAX II) system of programs.

20. Rogers, D. *Acta Crystallogr., Sect. A*, **1981**, *37*, 734.
21. Parker, D. *Chem. Rev.*, **1991**, *91*, 1441.
22. Fullwood, R.; Parker, D. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 57.
23. Sheldrick, G. M. SHELXTL PLUS – Release 4.11/V (Copyright 1990 Siemens Analytical X-Ray Instr., Inc.).
24. Dleaunay, D.; LeCorre, M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 3041.

(Received in UK 23 October 1996)