Asymmetric Intramolecular Conjugate Addition of Amines to Chiral Vinyl Sulphoximides. Total Synthesis of (*R*)-(+)- and (*S*)-(−)-Carnegine

Stephen G. Pyne

Department of Chemistry, University of Wollongong, Wollongong, N.S.W. 2500, Australia

The chiral vinyl sulphoximides (**3a**) and (**3b**) upon treatment with base, undergo cyclization to give chiral isoquinolines which were converted into (*R*)-(+) and (*S*)-(−)-carnegine.

Recently we reported that chiral vinyl sulphoximides underwent conjugate addition with organocopper reagents with high asymmetric induction.[1,2] We report here on the results of a study on the intramolecular conjugate addition of amines to chiral vinyl sulphoximides.[3]

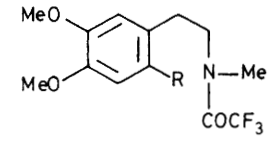
It was envisaged that a synthesis of optically active carnegine (**5c**) could be realized from an intramolecular conjugate addition of the chiral amino vinyl sulphoximide (**4**) followed by reductive removal of the sulphoximide moiety.[4] The chiral vinyl sulphoximides (**3a**) and (**3b**) were prepared as follows. 2-(3,4-Dimethoxyphenyl)ethylamine was converted into its trifluoroacetamide and then *N*-methylated[5] to give trifluoroacetamide (**1**) in 95% overall yield. Vilsmeir formylation [$POCl_3$, dimethylformamide (DMF), 80 °C, 3 days] of (**1**) gave the aldehyde (**2**) (45%). Treatment of (**2**) with the lithium carbanion of either (R_S)-sulphoximide (**7a**)[2] or (S_S)-sulphoximide (**7b**)[1] followed by mesylation[1] and then elimination[1] {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), CH_2Cl_2, 25 °C} furnished (*E*)-vinyl sulphoximides (**3a**) and (**3b**) respectively (50—55%).

Basic hydrolysis of (**3a**) or (**3b**), under a variety of conditions (Table 1), led directly to mixtures of the cyclized products (**5**) and (**6**) in high overall yield but with modest diastereoselectivity. The diastereoisomeric products (**5**) and (**6**) could be readily separated by flash chromatography. For example, diastereoisomerically pure isoquinolines (**5b**) and

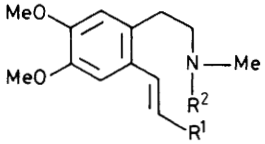
Table 1. Cyclization of vinyl sulphoximides (**3a**) and (**3b**).[a]

Sulphoximide	Base[b]	Solvent	T/°C[c]	Diastereoisomeric ratio[d,e] (**5**) : (**6**)
(**3a**)	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	0	26 : 74
(**3a**)	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	−40	28 : 72
(**3a**)	$[PhCH_2NMe_3]^+[OH]^-$	MeOH	0	58 : 42
(**3a**)	Li^+OH^-	MeOH–H_2O(2 : 1)	0	65 : 35
(**3b**)	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	0	71 : 29
(**3b**)	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	−40	68 : 32
(**3b**)	$[PhCH_2NMe_3]^+[OH]^-$	MeOH	0	54 : 46
(**3b**)	Li^+OH^-	MeOH–H_2O(2 : 1)	0	65 : 35

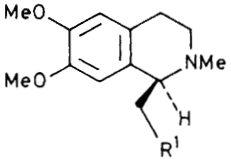
[a] It is assumed that (**5**) and (**6**) arise from the cyclization of (**4**), although this compound could not be isolated. [b] 3—5 mol equiv. [c] Reaction time *ca.* 1 h at 0 °C or 40 h at −40 °C. [d] Determined by ^{1}H n.m.r. spectroscopy. [e] Yield of (**5**) and (**6**), 88—96%.



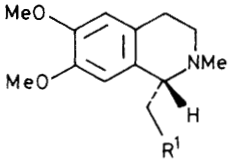
(**1**) R = H
(**2**) R = CHO



(**3**) R^2 = $COCF_3$
(**4**) R^2 = H

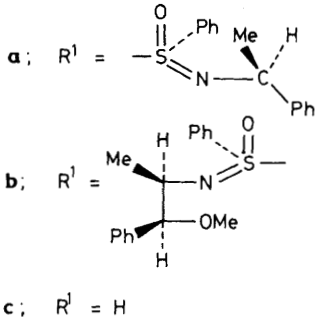


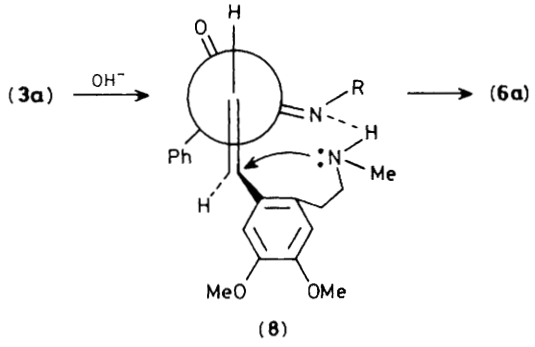
(1*S*)-(**5**)



(1*R*)-(**6**)

MeR^1 (**7**)





Scheme 1

(**6a**) (Table 1) could be obtained in 59% and 65% yield after chromatographic purification. Reductive desulphurization of (**5b**) and (**6a**) with Raney nickel[4] gave (*S*)-(−)-carnegine (**5c**){68%, $[\alpha]_D^{18}$ −23.5° (*c* 0.15, EtOH); lit.,[6] $[\alpha]_D^{22}$ −24.9° (*c* 4.45, EtOH)} and (*R*)-(+)-carnegine (**6c**)†[7] {76%, $[\alpha]_D^{18}$ +23.2° (*c* 0.18, EtOH)} respectively.

Isoquinoline (**6b**) was returned diastereoisomerically pure after exposure to the basic cyclization conditions indicating that (**5**) and (**6**) arise from a kinetically controlled cyclization of amine (**4**). The stereochemical outcome of these cyclizations seems largely governed by the chirality at sulphur of (**4**) and not by the chiral auxiliary ligand. Changing the reaction solvent from methylene chloride (CH_2Cl_2) to methanol (MeOH) in the reaction of (**3**) with benzyltrimethylammonium hydroxide ($[PhCH_2NMe_3]^+[OH]^-$) dramatically affects the diastereoselectivity (from 48% to 16%). Surprisingly, the reaction temperature had little effect on the diastereoselectivity. We propose that in non-polar aprotic solvent (CH_2Cl_2) the reaction proceeds *via* the intermediate (**8**) (Scheme 1) in which there is H-bonding between the NH of the amino group and the nitrogen of the sulphoximide moiety.

We thank the Australian Research Grants Scheme for financial support, Professor R. A. Raphael for useful discussions, and Professor M. G. Reinecke for generously providing a sample of (*S*)-carnegine and informing us of the error in the ^{1}H n.m.r. data reported in reference 7.

Received, 18th June 1986; Com. 844

† Our ^{1}H n.m.r. spectra of (**5c**) and (**6c**) [δ ($CDCl_3$) 6.58 (s, 1H), 6.56 (s, 1H), 3.84 (s, 6H), 3.54 (q, *J* = 6.5 Hz, 1H), 3.12—2.53 (m, 4H), 2.47 (s, 3H), 1.37 (d, *J* = 6.5 Hz, 3H)] were identical with that of (*S*)-(−)-carnegine.

References

1 S. G. Pyne, *J. Org. Chem.*, 1986, **51**, 81.
2 S. G. Pyne, *Tetrahedron Letters*, 1986, **27**, 1691.
3 For the analogous intermolecular case see, R. Annunziata and M. Cinquini, *J. Chem. Soc., Perkin Trans. I*, 1979, 1684.
4 C. R. Johnson and C. J. Stark, Jr., *J. Org. Chem.*, 1982, **47**, 1193.
5 R. A. W. Johnstone, D. W. Payling, and C. Thomas, *J. Chem. Soc.* (C), 1969, 2223.
6 A. R. Battersby and T. P. Edwards, *J. Chem. Soc.*, 1960, 1214.
7 S. D. Brown, J. E. Hodgkins, J. L. Massingill, Jr., and M. G. Reinecke, *J. Org. Chem.*, 1972, **37**, 1825.