Asymmetric Intramolecular Conjugate Addition of Amines to Chiral Vinyl Sulphoxides. Total Synthesis of (*R*)-(+)-Carnegine

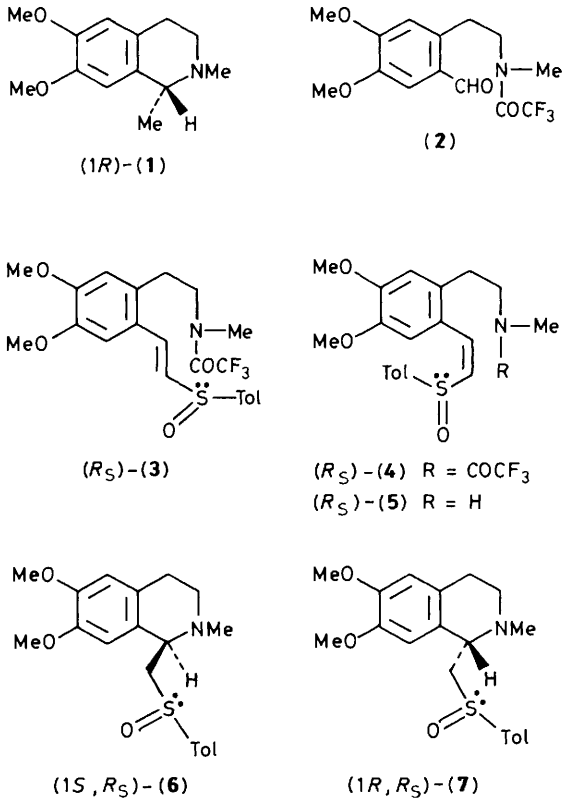
Stephen G. Pyne* and Sandra L. Chapman

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

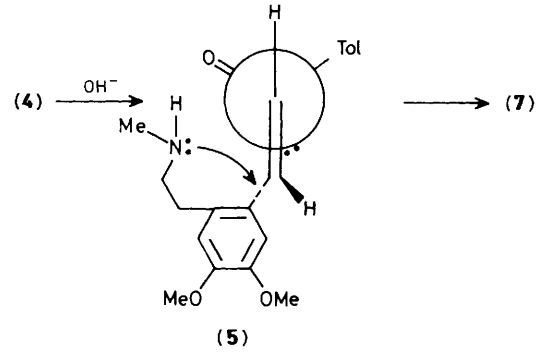
The (*E*)- and (*Z*)-vinyl sulphoxides (**3**) and (**4**) upon treatment with base, undergo cyclization to give chiral isoquinolines one of which was converted into (*R*)-(+)-carnegine.

In the preceding paper[1] we reported the results of the intramolecular conjugate addition of amines to chiral (*E*)-vinyl sulphoximides. Although these reactions proceeded in high overall yield and the diastereoisomeric products could be readily separated, the diastereoselectivity was only modest [48% diastereoisomeric excess (d.e.)]. In the light of the results of Stirling[2] on the intermolecular addition of amines to chiral (*Z*)-vinyl sulphoxides (70% d.e.) we expected that the analogous intramolecular reaction should proceed with high π-face selectivity.[3] Several reports on the highly diastereoselective intramolecular addition of alcohols to chiral vinyl sulphoxides have recently appeared.[4]

The (R_S)-(*E*)-vinyl sulphoxide (**3**) and (R_S)-(*Z*)-vinyl sulphoxide (**4**) were conveniently prepared by the Horner–Wittig reaction of aldehyde (**2**)[1] and (+)-(*R*)-dimethylphosphorylmethyl *p*-tolyl sulphoxide.[5] Vinyl sulphoxides (**3**) and (**4**) (1.8:1, 62% yield) were readily separated by column chromatography. Basic hydrolysis of (*E*)-vinyl sulphoxide (**3**) under a variety of conditions (Table 1) gave a mixture of the diastereoisomeric isoquinolines (**6**) and (**7**) [(**6**):(**7**) 63:37]. An enhanced diastereoselectivity was observed however, from the base hydrolysis of the (*Z*)-vinyl sulphoxide (**4**) (Table 1). This reaction gave (**6**) and (**7**) [(**6**):(**7**), 16:84] in 96% overall yield from which diastereoisomerically pure (**7**) could be obtained in 78% yield after flash chromatography. Reductive desulphurization of (**7**) with Raney Nickel[6] gave (*R*)-(+)-



Tol = *p*-tolyl



Tol = *p*-tolyl

Scheme 1

Table 1. Cyclization of vinyl sulphoxides (**3**) and (**4**).

Sulphoxide	Base[a]	Solvent	*T*/°C[b]	Diastereoisomeric ratio[c,d] (**6**):(**7**)
(**3**)	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	−40	58:42
(**3**)	$[PhCH_2NMe_3]^+[OH]^-$	MeOH	−40	62:38
(**3**)	Li^+OH^-	MeOH–H_2O	0	63:37
(**4**)	$[PhCH_2NMe_3]^+[OH]^-$	CH_2Cl_2	−40	17:83
(**4**)	$[PhCH_2NMe_3]^+[OH]^-$	MeOH	−40	16:84

[a] 3—5 mol equiv. [b] Reaction time *ca.* 1 h. at 0 °C or 40 h at −40 °C. [c] Determined by ^1H n.m.r. spectroscopy. [d] Yield of (**6**) and (**7**) 96% from (**4**) and 65—75% from (**3**).

carnegine (**1**),† [7] {51%, $[\alpha]_D^{18}$ +23.4° (*c* 0.15, EtOH); lit.,[8] (*S*)-(−)-carnegine $[\alpha]_D^{22}$ −24.9° (*c* 4.45, EtOH)}.

Isoquinoline (**7**) was recovered diastereoisomerically pure after exposure to the basic cyclization conditions indicating that (**6**) and (**7**) arise from a kinetically controlled reaction. In contrast with the analogous reaction of vinyl sulphoximides,[1] the diastereoselectivity of these reactions was independent of the nature of the reaction solvent. We suggest a mechanism (Scheme 1) similar to that proposed by Stirling,[2] in which the amino group attacks from the least hindered π-face of the vinyl sulphoxide (**5**). The possibility of H-bonding between the NH of the amino group and the oxygen of the sulphoxide moiety of (**5**)[2] would seem unlikely in the absence of a solvent effect.‡ The possibility of an H-bonded intermediate that incorporates a methanol molecule cannot be excluded however. The application of this methodology to the synthesis of other alkaloids is currently under investigation.

† The ^{1}H n.m.r. of (*R*)-(+)-carnegine was identical with that of (*S*)-(−)-carnegine. See ref. 1.

‡ Recent results from our laboratory on the cyclization of other chiral amino vinyl sulphoxides show dramatic solvent effects.

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