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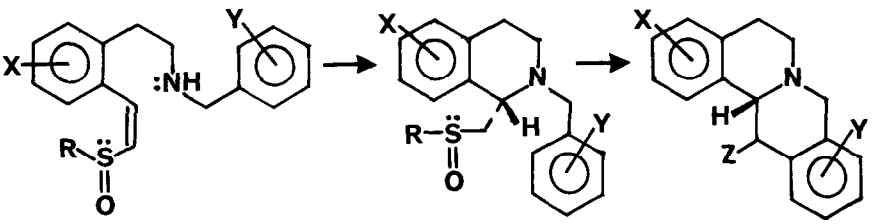
INTRAMOLECULAR ADDITION OF AMINES TO CHIRAL VINYL SULFOXIDES, TOTAL SYNTHESIS OF (R)-(+)-CANADINE

Stephen G. Pyne,
Department of Chemistry, University of Wollongong,
P.O. Box 1144, Wollongong,N.S.W. 2500, Australia.

Abstract: The intramolecular conjugate addition of an amine to the chiral vinyl sulfoxides 3 and 4 to give chiral isoquinolines 5 and 6 is reported. Isoquinoline 5 is converted to (R)-(+)-Canadine via an intramolecular Pummerer reaction.

We recently reported the application of the intramolecular conjugate addition of an amine to a chiral vinyl sulfoxide to the asymmetric synthesis of (R)-(+)-Carnegine[1]. It was envisaged that this methodology in conjunction with the intramolecular Pummerer reaction[2] should allow for the asymmetric synthesis of tetrahydroprotoberberine alkaloids (Scheme).



In this paper we describe the synthesis and cyclization of the chiral vinyl sulfoxides 3 and 4 to give 5 and the conversion of 5 via an intramolecular Pummerer reaction to (R)-(+)-Canadine 8.

The chiral vinyl sulfoxides 3 and 4 were prepared from the 3-isochromanone 1[3] as follows. Reaction of 1 with 2,3-dimethoxybenzylamine[4] (1 mol equiv) in refluxing ethanol (48 hr) gave amide 2a which upon reduction with lithium aluminium hydride (THF, reflux, 18 hr) afforded the amino-alcohol 2b (53% overall). Treatment of 2b with trifluoroacetic anhydride (2.2 mol equiv, pyridine (3 mol equiv), CH_2Cl_2) gave the corresponding trifluoroacetate-trifluoroacetamide which upon selective hydrolysis (anhydrous powdered K_2CO_3(s), dry methanol, 25°,5 hr) and then Collins oxidation (6

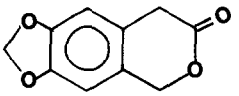
mol equiv of $CrO_3(py)_2$) yielded aldehyde 2c (83%). The Horner-Wittig reaction of 2c with (R)-(+)-dimethylphosphorylmethyl p-tolyl sulfoxide[5] gave a mixture of (Rs)-(E)-vinylsulfoxide 3 (δ 6.14, d, J=15.3 Hz) and (Rs)-(Z)-vinylsulfoxide 4 (δ 6.41, d, J=10.2 Hz) which could be separated by column chromatography (3:4, ca 2:1, 86%). Treatment of either 3 or 4 with benzyltriethylammonium hydroxide (5 mol equiv) in methylene chloride at -40° for 48 hr gave a mixture of the isoquinolines 5 and 6 in which the former predominated. Cyclization of 3 and 4 gave isoquinolines 5 and 6 in a ratio of 3:1 and 4:1 respectively. On a preparative scale the mixture of 3 and 4 obtained from the Horner-Wittig reaction of 2c could be cyclized directly to give after column chromatography diastereomerically pure 5 (47%) and 6 (14%). The ^{1}H NMR of 5 and 6[6] indicated they had the (1R) and (1S) configurations respectively. These assignments were unequivocally established by the conversion of 5 to (R)-(+)-Canadine 8.

Isoquinoline 6 was recovered diastereomerically pure after exposure to the basic cyclization conditions indicating that 5 and 6 arise from a kinetically controlled reaction. The facile cyclization of 3 and 4 is in stark contrast to the corresponding intermolecular conjugate addition reaction of (Z)-β-styryl phenyl sulfoxide with benzylamine, which has a half-life of six days in refluxing ethanol[7] We suggest 5 and 6 arise from the cyclization of an incipient amino anion. The stereochemical outcome of the cyclization of 4 is readily rationalised as arising from cyclization of an incipient amino anion via the conformation 9 which is expected on purely steric grounds[1,8].

Stereoelectronic arguments would favour attack on either conformation 10 or 12 since the incipient α-sulfinyl carbanion would experience maximum stabilisation by the sulfinyl group in the transition state.[10,11] In the case of the (Z)-vinylsulfoxide 4 steric considerations favour 12 (13) over 10 (11) due to severe steric interactions between the tolyl group and the β-aryl group in the latter.

The stereochemical outcome of the cyclization of 4 can therefore be readily rationalised by inferring either conformation 9 or 12.

The stereochemical outcome of the cyclization of 3 to give 5 was unexpected in light of our previous work[1]. The diastereoselectivity for the cyclization of an (E)-vinyl sulfoxide however was poor (26% de) suggesting little difference in free energy between diastereomeric transition states (10 and 12). The difference in free energy between the conformations 10 and 12 in the cyclization of 3 however, is not clear cut, although conformation 10 (11) may be inferred from the stereochemical outcome. Interestingly, the reported stereochemical outcome of the intramolecular addition of a thiourea to a (E)-vinylsulfoxide can be rationalized as proceeding via a transition state



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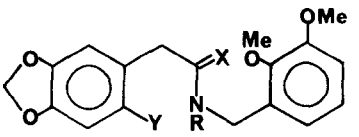
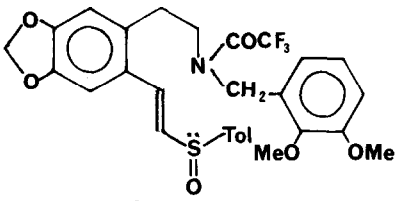


2a X=O, Y=CH_2OH, R=H

2b X=H_2, Y=CH_2OH, R=H

2c X=H_2, Y=CHO, R=$COCF_3$



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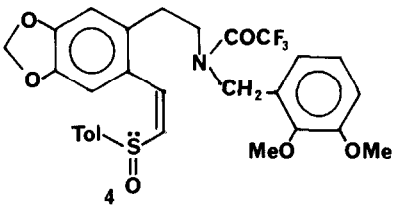

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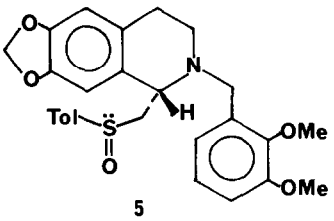

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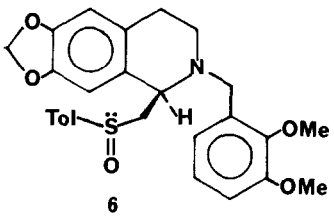

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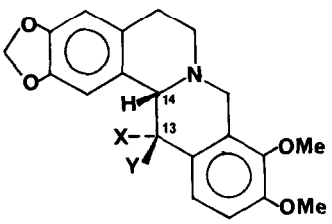
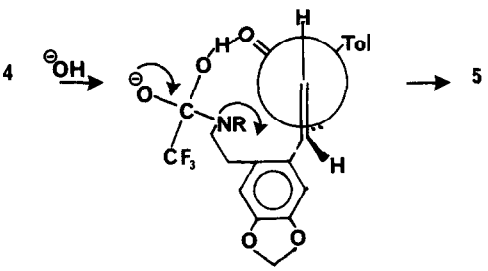


7a X=STol, Y=H

7b X=H Y=STol

8 X=Y=H



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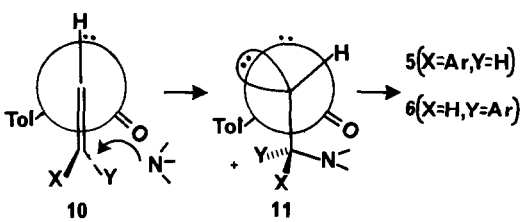
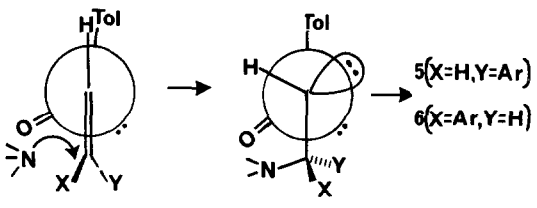


10 11

5(X=Ar,Y=H)

6(X=H,Y=Ar)



12 13

5(X=H,Y=Ar)

6(X=Ar,Y=H)

similar to 12 (13)[12,13,14] Clearly the cyclization reactions of (E)- 3 and (Z)-4 proceed with reverse π-face selectivity.

The Pummerer reaction of 5 with trifluoroacetic anhydride (2 mol equiv, 0°, 10 min, toluene) and then cyclization (90°,3 hr) gave a 1:1 mixture of 7a (δ 4.43, d, J = 1.98, Hz, H-14) and 7b (δ 4.34, d, J = 6.7 Hz, H-14) in 62% yield after chromatography on alumina. The 'H NMR spectra of 7a and 7b were consistent with H-13 and H-14 being in a cis relationship in 7a and a trans relationship in 7b[15]. Consequently 7a and 7b most likely adopt the trans- and cis- quinolizidine conformations respectively[15]. Reductive desulfurization of 7 with Raney Nickel[16] gave (R)-(+)-Canadine 8 (81%, mp 132-133° (from MeOH), $[\alpha]_D^{16}$ + 273° (c 0.04, $CHCl_3$); lit.[17] mp 131-132°, $[\alpha]_D^{15}$ + 299° ($CHCl_3$) which had identical ^1H NMR[18], ^{13}C NMR[19] and MS[18] to that reported. Current research is directed at determining the factors which affect the stereoselectivity of these cyclization reactions with the ultimate goal of enhancing their diastereoselectivities.

References and Notes

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