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Synthesis and Properties of Enantiopure Bicyclic Amidines

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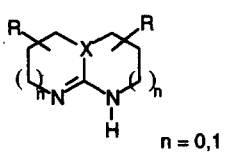
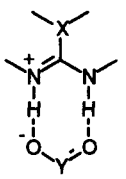
Abstract: The enantiopure bicyclic amidine bases **5a-c** were synthesized from alcohol **8**, *via* alkylation of the appropriate nitriles. The phenylsulphonylamidine **5a** was subjected to X-ray crystallography as its nitrate salt, and was shown by ^{1}H NMR to differentiate analytically between the enantiomers of chiral carboxylic acids.

Bicyclic amidines and guanidines **1a/b** have featured prominently in studies of oxo-anion recognition, through formation of hydrogen-bonded complexes of general form **2**.[1] The two heterocyclic systems may be seen as complementary to each other, the amidines **1a** being more complex structurally (in that they possess an additional sp^3-hybridised centre), less basic and (correspondingly) stronger H-bond donors after protonation. However, despite the early introduction of the pentamethyl amidine **3** by Eschenmoser and co-workers,[1a] recent work has neglected the amidines **1a** in favour of the more accessible guanidines **1b**. In particular, there have been no reports of chiral bicyclic amidines to match the chiral guanidines, e.g. of form **4**,[1c-f] which have been described by several laboratories.[1c-f, h, k; 2]

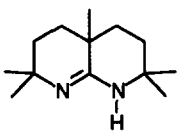


n = 0,1

1a X = CR'
1b X = N



2 Y = C, P, N etc.



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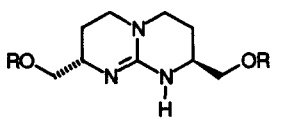

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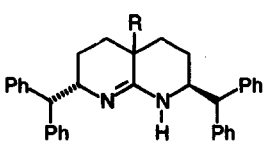
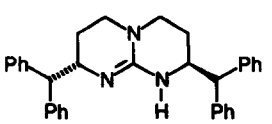
We now describe the syntheses of amidines **5a-c**, the first enantiomerically pure bases of type **1a**. We also describe the X-ray crystal structure of a salt of phenylsulphonylamidine **5a**, and evidence for the enantiodifferentiating recognition of chiral carboxylic acids by this base.



5a R = SO_2Ph **5b** R = H **5c** R = Ph



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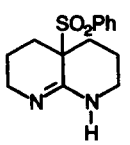

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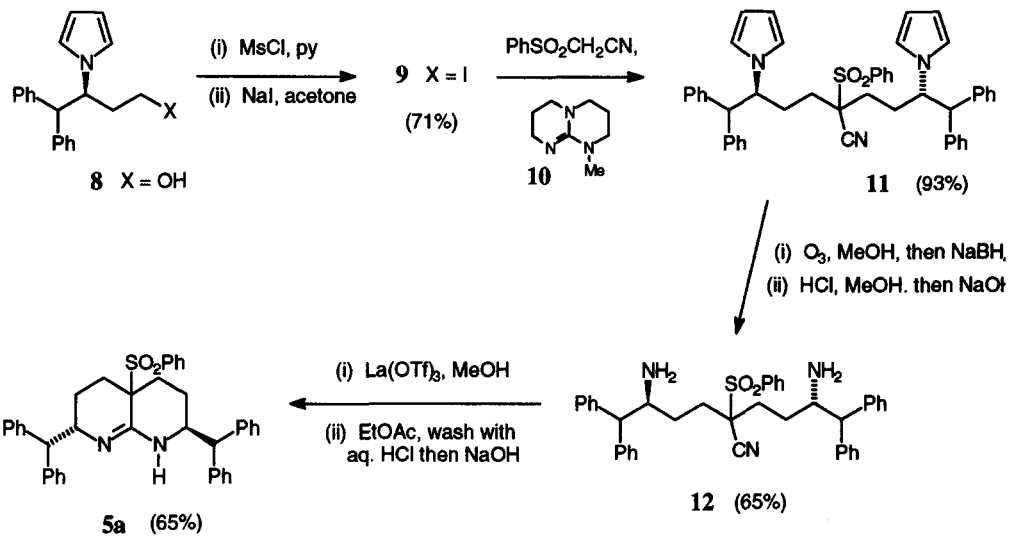
The design and synthesis of **5a-c** relate to our previous work on guanidine **6**[1k] and on the achiral phenylsulphonylamidine **7**.[1m] The diphenylmethyl substituents were chosen to provide hindered, chiral environments in the "binding regions" of the amidines, and to allow synthesis from the enantiopure alcohol **8** employed in the earlier project. Once again, we planned to use the pyrrolyl substituent in **8** as a masked amino group, compatible with a nucleofugal leaving group even under strongly basic conditions. The synthetic pathway to **5a** is summarised in Scheme 1. After conversion of **8** to iodide **9** the latter was used to bis-alkylate phenylsulphonylacetonitrile, employing the hindered guanidine 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, **10**)[3] as base. Deprotection of the product **11** gave diamine **12**, in 40% overall yield from **8**. Our experience in an earlier synthesis of **7** suggested that **12** might cyclise spontaneously under the deprotection conditions.[1m] Although this did not occur, treatment of **12** with lanthanum triflate[4] in methanol gave **5a** in an acceptable yield of 65%.



Scheme 1

Amidine **5a** was purified by recrystallisation of its nitrate, and characterised by NMR and LSI-MS.[5] Crystals of the nitrate grown carefully from benzene were of sufficient quality for a preliminary X-ray crystal structure (R = 0.11).[6] The unit cell was found to contain two distinct **5a**H^+.NO_3^- ion pairs, as shown in Figure 1. In (A), the bicyclic nucleus of the cation adopts a bis(half-chair) conformation, so that one $CHPh_2$ substituent must take a pseudoaxial position. In (B), one of the nuclear rings takes up a boat-like conformation, allowing both substituents to be pseuodequatorial. In both cases the "binding region" of the amidinium is flanked by a phenyl group from each substituent, creating a hindered, chiral environment.[7] The usual pattern of parallel NH...O hydrogen bonds is not observed, the nitrate anions being sandwiched between the aromatic rings and held at obtuse angles to the planes of the amidinium units.[8] In (A) the anion is disordered, apparently occurring in two sites with 50% occupancy.[9] For one of these, it is positioned such that one oxygen is within H-bonding distance of both NH's (NH...O distances of 2.03 and 1.94Å). A similar environment is observed for the anion in (B) (NH...O distances of 1.89 and 1.98Å).

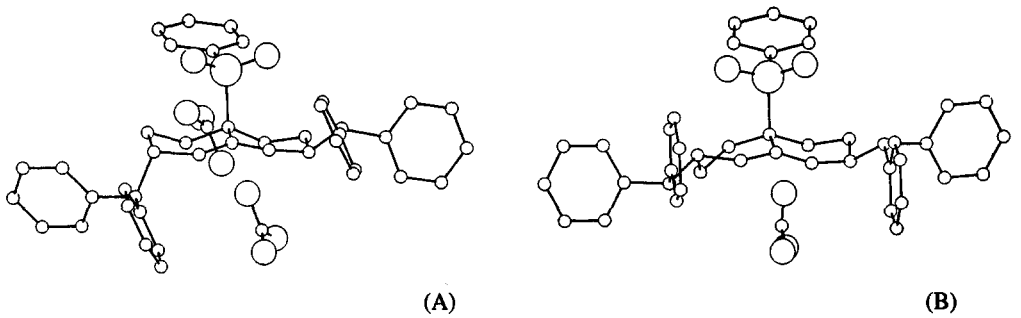
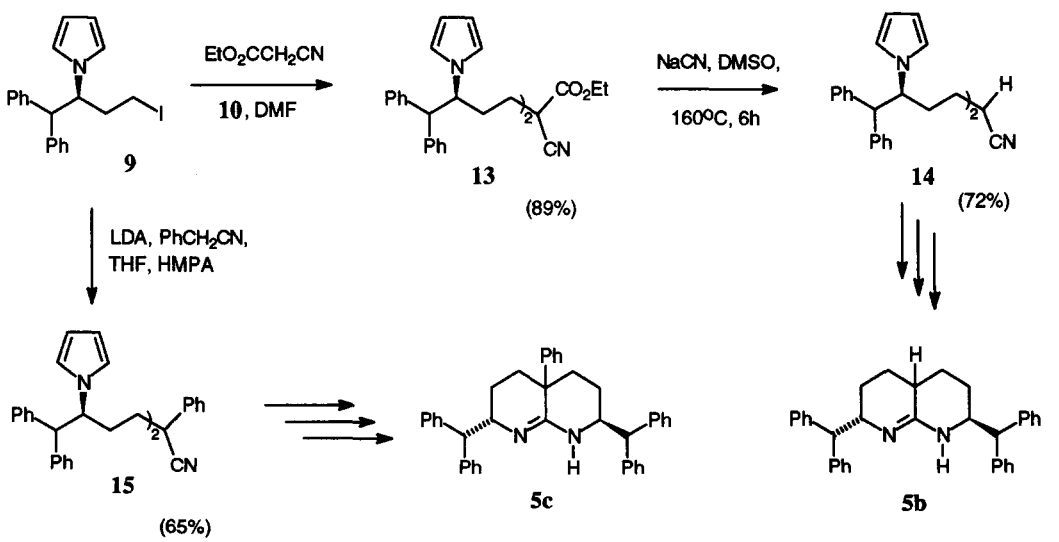


Figure 1: $\mathbf{5aH^+}.NO_3^-$ ion pairs, as present in the crystal structure. Only non-hydrogen atoms are shown.

^{1}H NMR experiments demonstrated that $\mathbf{5aH^+}$, like $\mathbf{6H^+}$,[1k] can differentiate (in an analytical sense) between the enantiomers of chiral carboxylates. For example, stirring $CHCl_3$ solutions of $\mathbf{5aH^+}.NO_3^-$ with aqueous solutions of sodium L- or D,L-*N*-(BOC)-phenylalaninate resulted in extraction of carboxylate anions into the organic phase. ^{1}H NMR spectra of the resulting salts showed significant movements for several of the amidinium signals relative to $\mathbf{5aH^+}.NO_3^-$ (e.g. $\Delta\delta$ of up to 0.27 p.p.m. for Ph_2CH), suggesting the formation of tightly bound complexes. When the D,L-phenylalaninate was used, splittings were observed for some of the signals resulting from protons on the carboxylate (e.g. NH peaks separated by 0.1 p.p.m.), presumably due to the formation of diastereomeric complexes. However, as the peaks were of roughly equal intensity, it seems that extraction did not take place with significant enantioselectivity.

To access enantiopure bicyclic amidines without the electron-withdrawing sulphonyl group, we extended the methodology in Scheme 1 in two respects. Firstly, as shown in Scheme 2, we performed the guanidine-catalysed alkylation on ethyl cyanoacetate, giving an intermediate **13** which could be de-ethoxycarbonylated to nitrile **14**. Unmasking of the amino groups and bicyclisation, as in Scheme 1, gave



Scheme 2

amidine **5b**. Secondly, the bis-alkylation of phenylacetonitrile using LDA as base[10] led to nitrile **15** (Scheme 2), which was transformed as before into bicyclic amidine **5c**. The success of these sequences means that a range of hindered, chiral bicyclic amidines is now available, to complement the guanidine **6** in studies of anion recognition and catalysis.

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References and Footnotes

1. See e.g.: (a) Heinzer, F.; Soukup, M.; Eschenmoser, A. *Helv. Chim. Acta* **1978**, *61*, 2851. (b) Müller, G.; Riede, J; Schmidtchen, F.P. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1516. (c) Gleich, A.; Schmidtchen, F.P.; Mikulcik, P.; Müller G. *J. Chem. Soc., Chem. Commun.* **1990**, 55. (d) Schiessl, P.; Schmidtchen, F.P. *J. Org. Chem.*, **1994**, *59*, 509. (e) Galán, A.; Andreu, D.; Echavarren, A.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511. (f) Deslongchamps, G.; Galán, A.; de Mendoza, J.; Rebek, J. Jr. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 61. (g) Chicharro, J.-L.; Prados, P.; de Mendoza, J. *J. Chem. Soc., Chem. Commun.* **1994**, 1193. (h) Corey, E.J.; Ohtani, M. *Tetrahedron Lett.*, **1989** *30*, 5227. (i) van Aken, E.; Wynberg, H; van Bolhuis, F. *J. Chem. Soc., Chem. Commun.* **1992**, 629. Contributions from this laboratory: (j) Boyle, P.H.; Convery, M.A.; Davis, A.P.; Hosken, G.D.; Murray, B.A. *J. Chem. Soc., Chem. Commun.* **1992**, 239. (k) Boyle, P.H.; Davis, A.P.; Dempsey, K.J.; Hosken, G.D. *J. Chem. Soc., Chem. Commun.* **1994**, 1875. (m) Convery, M.A.; Davis, A.P.; Dunne, C.J.; MacKinnon, J.W. *J. Chem. Soc., Chem. Commun.* **1994**, 2557.
2 For C_2-symmetric acyclic and monocyclic chiral amidines/guanidines, see: (a) Chinchilla, R.; Nájera, C.; Sánchez-Agulló, P. *Tetrahedron: Asymmmetry* **1994**, *5*, 1393. (b) Dauwe, C.; Buddrus, J. *Synthesis* **1995**, 171.
3. Schwesinger, R. *Chimia* **1985**, *39*, 269.
4. Lanthanide triflates had previously been used to promote the addition of amines to nitriles in the absence of solvent: Forsberg, J.H.; Spaziano, V.T.; Balasubramanian, T.M., Liu, G.K.; Kinsley, S.A.; Duckworth, C.A.; Poteruca, J.J.; Brown, P.S.; Miller, J.L. *J. Org. Chem.* **1987**, *52*, 1017. Others have found that these Lewis acids can be surprisingly effective in protic solvents. See e.g.: Kobayashi, S. *Chem. Lett.* **1991**, 2087.
5. Selected data: LSI-MS (**5a**) 611.2732 (MH^+), m.p. 115-116 °C, $[\alpha]_D^{20}$ = +16.3 (*c* = 2.1 in CH_2Cl_2); δ_H(**5a**H$^+$.NO_3^-, 300 MHz, $CDCl_3$) 9.57 (1H, s, N*H*), 9.21 (1H, s, N*H*), 7.97-7.09 (25H, m, Ar), 4.44, 4.09 (2 x 1H, m, Ph_2CH-C*H*), 3.93 (1H, d, *J* 10.8 Hz, Ph_2CH-CH), 3.45 (1H, d, *J* 11.1 Hz, Ph_2CH-CH), 2.60-2.41 (2H, m), 2.01-1.1 (6H, m).
6. Formula = $C_{81.5}H_{78}O_{10}N_6S_2$, a = 12.258(5), b = 12.360(6), c = 14.964(8) Å, α = 113.07(2), β = 113.63(2), γ = 90.91(3)°, U = 1870(2) Å^3. Data was collected using an Enraf-Nonius CAD4 diffractometer. It was necessary to use several crystals, mounted in capillaries, because of decay in the X-ray beam. No symmetry higher than *P*1 was observed. Two **5a**H$^+$cations were present in the asymmetric unit. Three NO_3^- positions were located, one with full occupancy and the other two refined with half occupancy. A further isolated area of high electron density was located but could not be assigned as a particular molecule. It was refined as three half-occupied carbon positions. The structure was solved using the direct method of SHELXS-86; final R = 0.1105. Atomic co-ordinates, bond lengths and angles, and thermal parameters, have been deposited at the Cambridge Crystallographic Data Centre.
7. The *anti* arrangement for Ph_2CH-CH in the crystalline salt correlates with vicinal ^{1}H NMR couplings of *ca* 11 Hz observed for **5a**, its nitrate, and also its carboxylate salts, in $CDCl_3$ solution.
8. *Cf.* the roughly coplanar arrangement observed for a guanidinium nitrate in ref. 1c.
9. Considering the rather high R value, the location of this anion must be regarded as tentative.
10. Chelucci, G. *Synthesis* **1991**, 474.

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