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SYNTHESIS OF CHIRAL 1,2-DIAMINES

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Summary: (1'S,5R,S)-(1'-phenyleth-1'-yl)-5-iodomethyl-imidazolines **4a,b** have been synthesised and easily resolved by silica gel chromatography. The correlation between the configuration and the ^1H NMR chemical shifts allows to assign the configuration at the C-5 of these intermediates. Each pure diastereomer has been converted to R(-)- and to S(+)-1,2-propyldiamine, respectively.

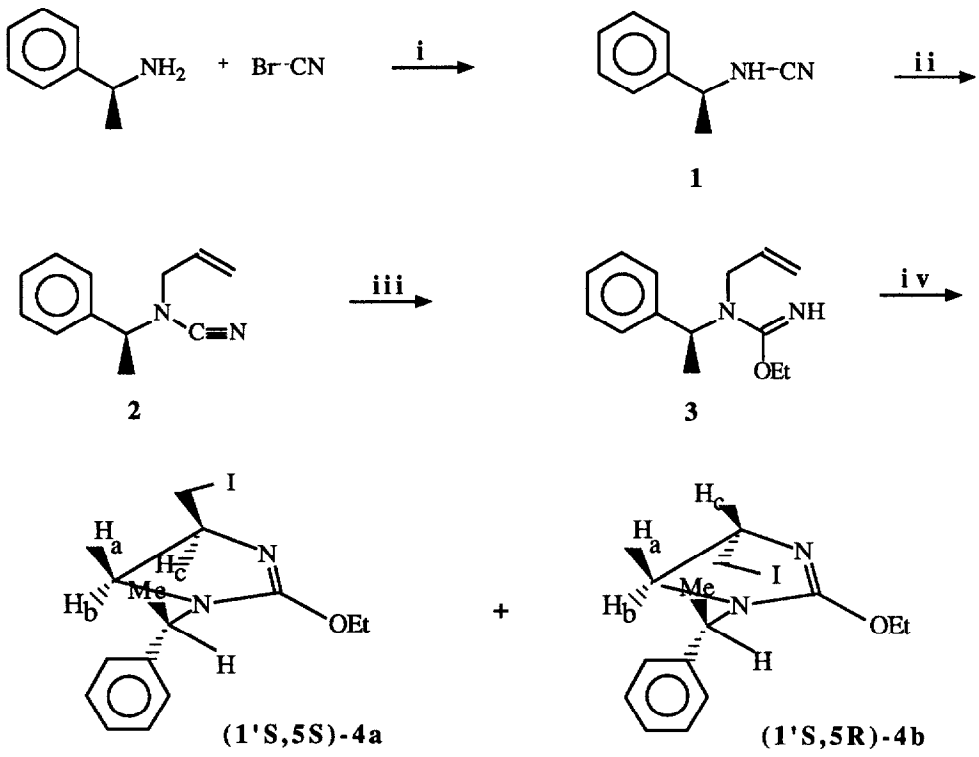
The introduction of neighbouring functional groups in a sequence directed towards the total synthesis of biologically active compounds is of great interest in modern synthetic strategy. In the last few years the halocyclofunctionalisation of double bonds of unsaturated alcohol or amine derivatives has been extensively studied with the aim of synthesising vicinal aminoalcohols under high regio and stereocontrol (1).

In connection with our interest in the development of new methods for the stereoselective functionalisation of acyclic allylic amines, we describe here a convenient approach to chiral 1,2-diamines. This method involves the iodocyclofunctionalisation of unsaturated amidines (2) containing the commercially available (S)-1-phenylethylamine as the chiral moiety (3).

The procedure is outlined in **Scheme 1.** The (S)-1-phenylethylamine is readily converted into the corresponding cyanamide **1**, simply by stirring overnight the amine (1 equiv) and cyanogen bromide (1.1 equiv) in dry THF in the presence of triethylamine (1.5 equiv) (4). The treatment of cyanamide **1** with NaH in dry THF, followed by the addition of allyl bromide, affords the cyanamide **2** in good yield. The addition of HCl (1.1 equiv) to **2** in dry ethanol at room temperature for four days,

gives the corresponding isourea **3** (4). The subsequent cyclisation is effected by treatment of **3** (1 equiv) in $CHCl_3$ with N-iodosuccinimide (NIS, 1 equiv) for a period of 1 hour. A roughly 1:1 diastereomeric mixture of the imidazolines **4a** and **4b** is obtained in 90% yield and easily separated by silica gel chromatography (5).

Scheme 1

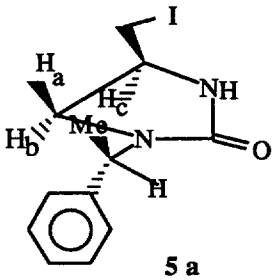


i) Et_3N (1.5 equiv), THF, r.t.; ii) NaH (1 equiv), THF, r.t., then $H_2C{=}CHCH_2Br$; iii) HCl (1.1 equiv), dry EtOH, r.t., 4 days, then aq NaOH; iv) NIS (1 equiv), $CHCl_3$, r.t.

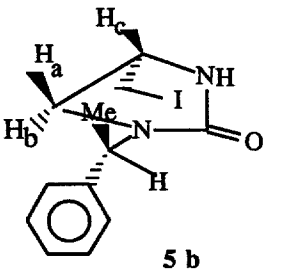
From the analysis of the ^1H NMR spectrum of each diastereomer, the absolute configuration at C-5 is assigned, on the basis of the values of the chemical shifts and of the coupling constants (3a,b). From the inspection of the molecular models, the reported conformers of **4a** and **4b** account for ^1H NMR patterns: owing to the shieldings of the phenyl and CH_2I groups, the ^1H NMR spectra of the diastereomers **4a** and **4b** show the non equivalence of H_a and H_b (6). In fact in **4a** H_a resonates at 3.32 ppm, due to the CH_2I shielding, while in **4b** it resonates at 3.48 ppm. In addition, in **4b** H_b is shielded by the phenyl and by the CH_2I groups and resonates at 3.24 ppm, upfield in respect to H_a, that resonates at 3.48 ppm.

Moreover the correct assignment of the configuration at C-5 in **4a** and **4b** is confirmed by the isomerisation under acidic conditions of **4a** and **4b** into the

corresponding 4-iodomethyl imidazolidin-2-ones **5a** and **5b**, respectively (7). The ^1H NMR of these molecules show for H_a and H_b the same trend of the chemical shifts previously observed by us for the analogous oxazolidin-2-ones (3).



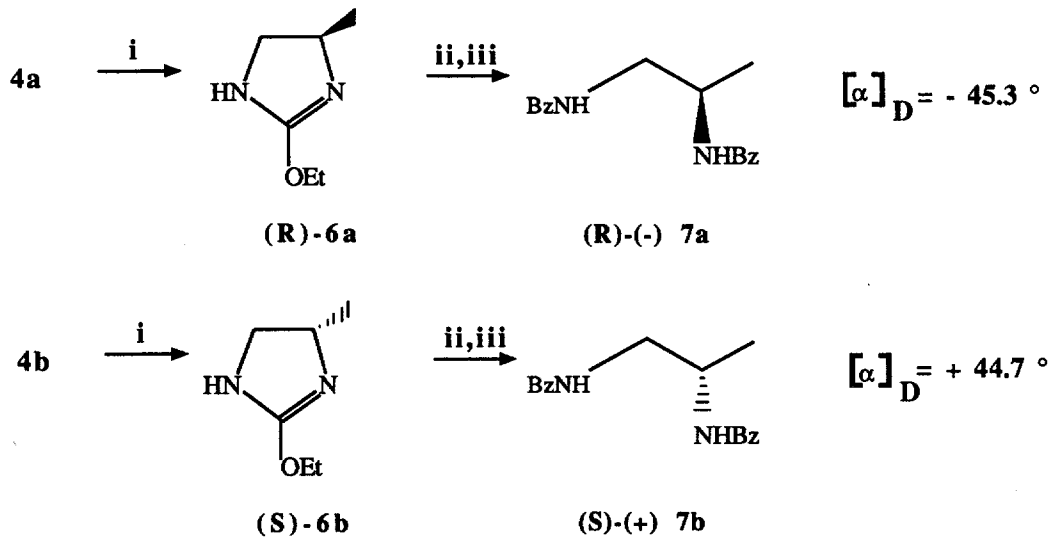
5 a



5 b

The reaction of both **4a** and **4b** with Li/NH_3 affords the methyl imidazolines **(5R)-6a** and **(5S)-6b** respectively, by means of the cleavage of the C-I and the benzylic C-N bonds (**Scheme 2**).

Scheme 2



i) Li (7 equiv), NH_3, -60 °C, 5 min; ii) conc. HCl, reflux, 3 hours; iii) BzCl (1.1 equiv), $NaHCO_3$, acetone, ice bath.

The successive hydrolysis of the heterocyclic rings of **6a** and **6b** in concentrated HCl for 3 hours produces the 1,2-diamines that are directly converted into the corresponding benzoates **7a** and **7b**. The rotational powers and the melting points of these derivatives are in perfect agreement with the data reported in the literature (8).

This synthetic strategy can be extended to allylic and homoallylic amines with substituted double bonds, opening a way to chiral synthons containing diamino groups with the stereogenic centres in the required configuration.

Aknowledgement: We thank the M.P.I. (40%) for the financial support of this research.

REFERENCES AND NOTES

(1) For recent examples see:
(a) G. Cardillo, M. Orena, S. Sandri ***Pure Appl. Chem.*** **1988** *60* , 1679;
(b) S. Knapp, P. J. Kukkola, S. Sharma, S. Pietranico ***Tetr. Lett.*** **1987** *28* , 5399;
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and references therein.

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(b) A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri ***Tetrahedron*** **1987** *43* , 4377;
(c) A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri ***Chem. Lett.*** **1988** 87.

(4) R. Carrau, R. Freire, R. Hernandez, E. Suarez ***J. Chem. Soc., Chem. Comm.*** **1986** 1055. In order to obtain a good yield of **1**, the addition of 1.5 equivalents of triethylamine is required.

(5) All the new compounds have been characterised by IR, ^1H NMR and ^{13}C NMR spectroscopy.

(6) **4a**: ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H), 1.48 (d, 3H), 3.08 (t, 1H, H_b, $J_{ab} = J_{bc} = 9.5$ Hz), 3.15 (ABX, 2H, CH_2I), 3.32 (dd, 1H, H_a, $J_{ab} = 9.5$ Hz, $J_{ac} = 3.5$ Hz), 3.82 (m, 1H, H_c), 4.29 (q, 2H), 4.92 (q, 1H), 7.30 (m, 5H).
4b: ^1H NMR ($CDCl_3$) δ 1.34 (t, 3H), 1.49 (d, 3H), 2.82 (ABX, 2H, CH_2I), 3.24 (dd, 1H, H_b, $J_{bc} = 9.5$ Hz, $J_{ab} = 3.5$ Hz), 3.48 (t, 1H, H_a, $J_{ab} = J_{ac} = 9.5$ Hz), 3.93 (m, 1H, H_c), 4.29 (q, 2H), 4.91 (q, 1H), 7.30 (m, 5H).

(7) **5a**: ^1H NMR ($CDCl_3$) δ 1.55 (d, 3H), 3.08 (ABX, 2H, CH_2I), 3.14 (dd, 1H, H_a, $J_{ab} = 9$ Hz, $J_{ac} = 5$ Hz), 3.15 (t, 1H, H_b, $J_{ab} = J_{bc} = 9$ Hz), 3.69 (m, 1H, H_c), 5.24 (q, 1H), 5.89 (bs, 1H), 7.32 (m, 5H).
5b: ^1H NMR ($CDCl_3$) δ 1.52 (d, 3H), 2.74 (dd, 1H, H_b, $J_{ab} = 9$ Hz, $J_{bc} = 5$ Hz), 3.05 (ABX, 2H, CH_2I), 3.52 (t, 1H, H_a, $J_{ab} = J_{ac} = 9$ Hz), 3.85 (m, 1H, H_c), 5.25 (q, 1H), 6.08 (bs, 1H), 7.32 (m, 5H).

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