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1,3-ASYMMETRIC INDUCTION: HIGHLY ENANTIOSELECTIVE SYNTHESIS OF α-AMINO ACIDS VIA 2,5-TRANS DISUBSTITUTED IMIDAZOLIDIN-4-ONES

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Summary : 2,5-Trans imidazolidin-4-ones have been obtained from mercury promoted cyclisation of unsaturated amidals containing a stereogenic centre. A new enantioselective synthesis of α-amino acids has been devised.

The synthetic usefulness of electrophilic cyclofunctionalisations of double bonds is principally due to the high degree of stereoselectivity obtained when substituents are present on the tether. In fact substituent interactions play an important role during the formation of the heterocycle, owing to 1,2 and 1,3 conformational constraints in the transition state. Furthermore different results can be obtained whether kinetic or thermodinamic conditions are employed [1].

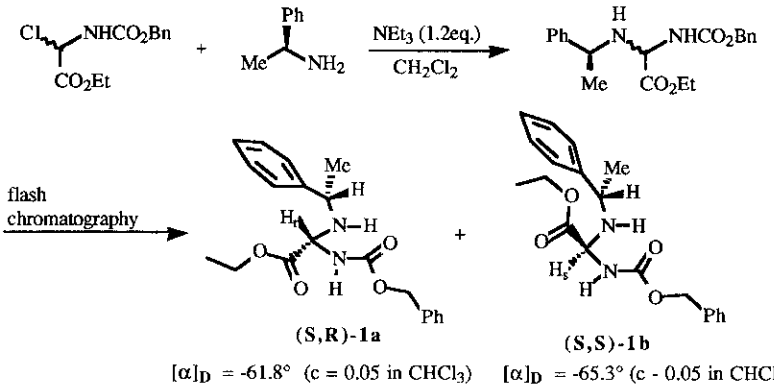
In this field an important contribution to the synthesis of 2,5-trans and 2,5-cis disubstituted tetrahydrofurans starting from ethers has been reported by Bartlett [2]. A similar behaviour has been described by Harding for the synthesis of 2,5-disubstituted pyrrolidines [3]. Furthermore a high 1,3 asymmetric induction has been reported for the halolactonisation of α- and α,β-substituted-γ,δ-unsaturated amides, ascribed to a 1,3 strain between the substituents [4].

In order to prepare chiral aminoalcohols under high stereocontrol, a total 1,3 asymmetric induction has been recently reported in the intramolecular amidomercuration reaction of substrates containing an intraannular N,O-acetal stereogenic centre [5] and in the cyclisation of chiral N-acylaminomethyl ether derivatives [6].

In this work we wish to report an enantioselective synthesis of α-amino acids [7] through the 1,3 asymmetric induction of mercury mediated intramolecular cyclisation of amidals. With this aim a new chiral synthon has been depicted, starting from ethyl glyoxylate and (S)-1-phenylethylamine. We have previously demonstrated the synthetic utility of the (S)-1-phenylethylamine in the preparation of polifunctionalised compounds, due to the preferential conformation that the stereogenic centre assumes when a carbonyl group is present in the α position [8].

By treatment of α-chloro-N-benzyloxycarbamoylglycine [9] with (S)-1-phenylethylamine [10] and triethylamine in dichloromethane, the ethyl N-benzyloxy-N'-phenylethyl-1,1-diaminoacetates **1a** and **1b** have

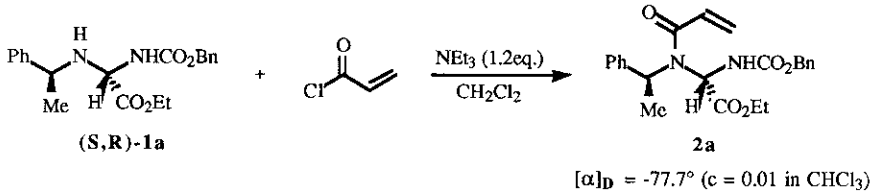
been obtained quantitative yield in 1 : 1 diastereoisomeric ratio. The two diastereoisomers have been separated by silica gel chromatography (Scheme 1) [11].



Scheme 1

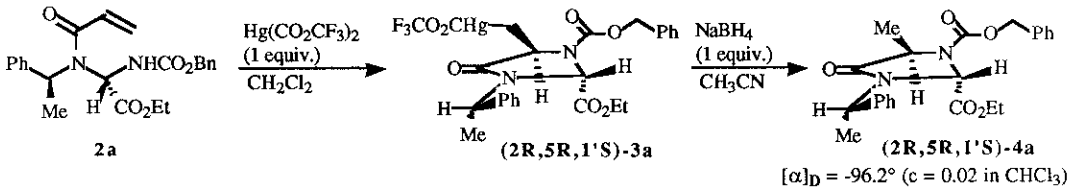
The absolute configuration of the newly formed chiral centre was assigned on comparison of ^{1}H NMR spectra of **(S,R)-1a** (H_r 4.75 ppm; O<u>CH</u>$_2$CH$_3$ 4.18 ppm) and **(S,S)-1b** (H_s 5.10 ppm, O<u>CH</u>$_2$CH$_3$ 3.95 ppm), that show a difference in the chemical shifts that may be attributed to the phenyl group shielding [8]. Due to the NH and carbonyl groups interactions that influence the molecular conformations, the PCMODEL [12] shows a preferential conformation for each compound, that accounts for the ^{1}H NMR indications: in the diastereoisomer **(S,R)-1a** H_r is shielded by the phenyl of the amine residue; on the other hand in **(S,S)-1b** the phenyl shields the hydrogens of the methylene of the ethyl group [13] (Scheme 1).

The N-benzyloxy aminal **(S,R)-1a** was converted into the corresponding acrylamide **2a** in 95% yield by addition of triethylamine and acryloyl chloride in dichloromethane (Scheme 2).



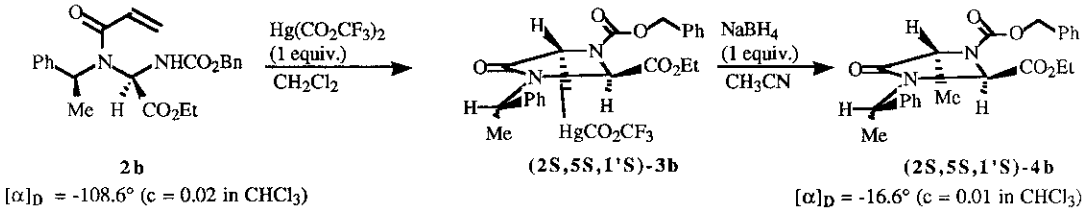
Scheme 2

The cyclisation of amidal **2a** (Scheme 3) with mercuric triflouroacetate in dichloromethane afforded at room temperature the organomercurial **3a** in 2 hours. The reductive cleavage of the carbon-mercury bond was performed in acetonitrile with sodium boron hydride at room temperature for 20 minutes under argon. A single compound in 80% overall yield was obtained, as shown in GLC analysis and ^{13}C NMR. Furthermore, as a result of hindered rotation of the carbamate group around the amide bond [14], the ^{1}H NMR spectrum is rather complex and shows a 1 : 1 mixture of rotamers [15].



Scheme 3

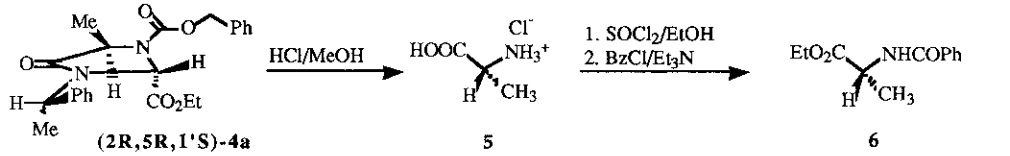
With the same procedure, the cyclisation of amidal **2b**, obtained from compound **(S,S)-1b** and acryloyl chloride, afforded, after reduction, the imidazolidin-4-one **4b** in 75% overall yield as a single product (Scheme 4).



Scheme 4

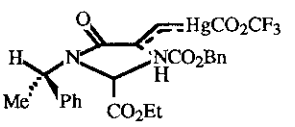
The absolute configuration of the new stereogenic centre C-5 of the imidazolidin-4-ones **4a** and **4b** was determined by comparison of the **4a** and **4b** ^{1}H NMR spectra [15].

Moreover the attribution was confirmed by hydrolysis of **4a** in concentrated HCl and methanol (Scheme 5). A mixture of starting (S)-1-phenylethylamine hydrochloride and D-alanine hydrochloride was obtained. The α-amino acid was characterised as its ethyl benzoyl derivative **6**, for which $[\alpha]_D$ value confirms the chiral purity and the absolute configuration of **4a** [16].

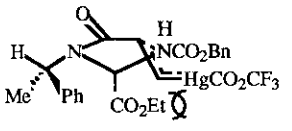


Scheme 5

In conclusion this work describes the complete 1,3 asymmetric induction obtained with the chiral synthons **1a** and **1b** that allows to obtain exclusively the 2,5-trans imidazolidin-4-ones **4a** and **4b**. In fact between the two possible transition states A and B, the 1,3 diaxial-like interaction disfavours the cis configuration of B, favouring the more stable transition state A.



A



B

Moreover the synthons **(S,R)-1a** and **(S,S)-1b** are inexpensive, easily prepared, and the chiral auxiliary (S)-1-phenylethylamine is completely recovered after the hydrolysis of the heterocycle.

Acknowledgement

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8. (a) Bongini A., Cardillo G., Orena M., Porzi G., Sandri S. *Chemistry Lett.* **1988**, 87; (b) Cardillo G., Orena M. *Tetrahedron* **1990**, *46*, 3321.
9. Bernstein Z., Ben-Ishai D. *Tetrahedron* **1977**, *33*, 881.
10. (S)-1-Phenylethylamine was purchased by Janssen and distilled. The experimental $[\alpha]_D$ value was -36° (neat).
11. All new compounds have been fully characterised by IR, ^1H NMR, ^{13}C NMR and high resolution MS.
12. PCMODEL, Serena Software, BOX 3076, Bloomington, IN 47402-3076.
13. **(S,R)-1a**: 300 MHz 1H NMR ($CDCl_3$) δ (ppm) 1.26 (t, 3H, $CH_2\underline{CH_3}$), 1.35 (d, 3H, N-CH-$\underline{CH_3}$), 2.38 (bs, 1H, NH), 3.97 (q, 1H, N-$\underline{CH}$-CH_3), 4.18 (q, 2H, $O\underline{CH_2}CH_3$), 4.75 (d, 1H, N-CH-N), 5.12 (s, 2H, OCH_2Ph), 5.40 (d, 1H, $NHCO_2Bn$), 7.35 (m, 10H, Ph).

    (S,S)-1b: 300 MHz 1H NMR ($CDCl_3$) δ (ppm) 1.25 (t, 3H, $CH_2\underline{CH_3}$), 1.40 (d, 3H, N-CH-$\underline{CH_3}$), 2.40 (bs, 1H, NH), 3.95 (q, 2H, $O\underline{CH_2}CH_3$), 4.10 (q, 1H, N-$\underline{CH}$-CH_3), 5.10 (m, 3H, N-CH-N + OCH_2Ph), 5.50 (d, 1H, $NHCO_2Bn$), 7.35 (m, 10H, Ph)
14. Hiemstra H., Fortgens H. P., Stegenga S., Speckamp W. N. *Tetrahedron Lett.* **1985**, *26*, 3151.
15. **(2R,5R,1'S)-4a**: 300 MHz 1H NMR ($CDCl_3$) δ (ppm) 1.02 and 1.26 (t, 3H, J = 6.3 Hz, $OCH_2\underline{CH_3}$), 1.48 and 1.57 (d, 3H, J = 7.0 Hz, OC-CH-$\underline{CH_3}$), 1.52 and 1.55 (d, 3H, J = 7.3 Hz, N-CH-$\underline{CH_3}$), 3.78 and 4.19 (q, 2H, J = 6.3 Hz, $O\underline{CH_2}CH_3$), 4.36 and 4.39 (q, 1H, J = 7.0 Hz, OC-$\underline{CH}$-CH_3), 4.87 and 4.90 (s, 1H, N-CH-N), 5.08 (AB, 2H, CH_2Ph), 5.48 and 5.51 (q, 1H, J = 7.3 Hz, N-$\underline{CH}$-CH_3), 7.35 (m, 10H, Ph).

    (2S,5S,1'S)-4b: 300 MHz 1H NMR ($CDCl_3$) δ (ppm) 0.75 and 0.96 (t, 3H, J = 7.1 Hz, $OCH_2\underline{CH_3}$), 1.53 and 1.61 (d, 3H, J = 6.7 Hz, OC-CH-$\underline{CH_3}$), 1.72 and 1.73 (d, 3H, J = 7.1 Hz, N-CH-$\underline{CH_3}$), 3.14 and 3.47 (ABX_3, 2H, J = 6.3 Hz, $O\underline{CH_2}CH_3$), 4.38 and 4.42 (q, 1H, J = 6.7 Hz, OC-$\underline{CH}$-CH_3), 5.10 (AB, 2H, CH_2Ph), 5.29 and 5.32 (s, 1H, N-CH-N), 5.55 (q, 1H, J = 7.1 Hz, N-$\underline{CH}$-CH_3), 7.35 (m, 10H, Ph).
16. The $[\alpha]_D$ value of ethyl benzoyl L-alanine is - 7.78° (c = 0.73 in EtOH): Andersen T. P., Ghattas A.-B. A. G., Lawesson S.-O. *Tetrahedron* **1983**, *39*, 3419.

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