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# Variations of the Nature of the Chiral Auxiliary with a Highly Enantioselective Chiral NADH Model

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***Abstract:*** Various chiral amino alcohols have been used as chiral auxiliaries for a highly enantioselective NADH model. Some of these are new reagents which have been obtained by an enzymic resolution method.

Chiral NADH models are promising reagents in asymmetric reductions. In 1975, Ohno reported the first stereoselective reduction of ethyl benzoylformate by a 1,4-dihydronicotinamide derivative bearing a chiral carboxamide at C-3 (1). The corresponding (R)-mandelate was obtained with an enantiomeric excess of 20 %. Since this initial report, a large number of results have been described concerning the obtaining of high e.e. with performant chiral NADH models (2).

In all cases the reductions were performed in the presence of magnesium ions which are involved in a ternary complex model/$Mg^{2+}$/ substrate (3). The occurence of this complex plays an important role in the stereoselective transfer of the hydrogen from the reagent to the substrate.

In our laboratory we have developped a series of chiral models possessing chiral aminoalcohol derivatives at the carbonyl at C-3 of the 1,4-dihydropyridine structure (4). In the ternary complex the rigidity of the chiral auxiliary is assured by the coordination of magnesium ions with the carbonyl group at C-3 and by the supplementary complexation caused by the alcoholic oxygen. By these means good e.e. is obtained with model bearing phenylalaninol at the carbonyl at C3.

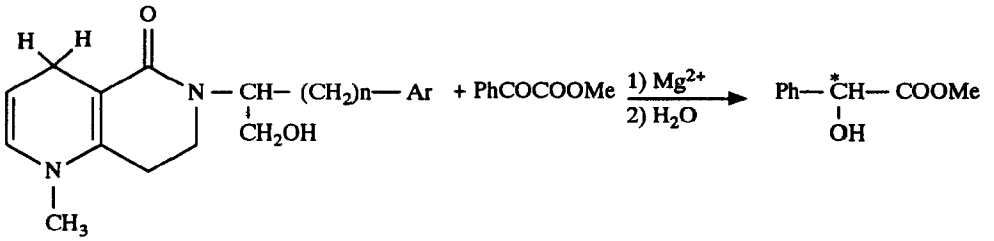
In the past, in the thieno[2,3-b]pyridine series, we have shown that a model bearing a paranitrophenyl group instead of a phenyl group in phenylalaninol, leads to a good improvement of the e.e. (58 % to 75 %) (5). It was suggested that the rigidification of the chiral auxiliary in the ternary complex was enhanced by the establishment of a charge-transfer complex between the poor in electrons paranitrophenyl group and the rich in electrons thienodihydropyridine system.

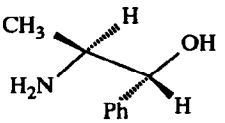
A great improvement in the efficiency of these types of NADH models was carried out by studying

reagents where the free rotating ability around the C3-C=0 bond was suppressed. To attain this objective a cyclised reagent **1a** was synthesized (6).

With this reagent an e.e. of about 90 % was obtained during the reduction of methyl benzoylformate at room temperature. The large enhancement of the e.e. is a result of the following two factors: i) the rigidity of the chiral auxiliary leads to a high stereodifferentiation of the two faces of the 1,4-dihydropyridine structure and ii) the readiness of the formation of the ternary complex.

It could be of interest to modulate the structure of the chiral auxiliary with a view to obtaining better e.e. and to disposing a larger field of performant reagents. With respect to this objective we synthesised and studied new cyclised models of type 1 derived of various chiral amino alcohols **9**.



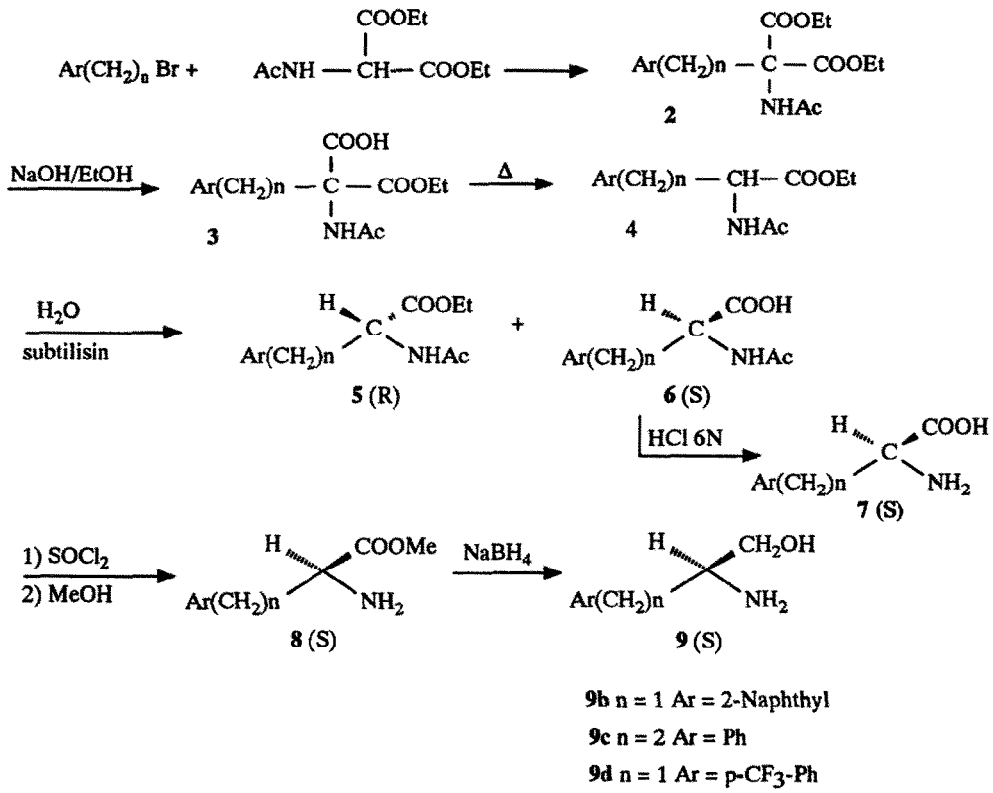

| | aminoalcohol precursor | | |
|---|---|---|---|
| **1a** | **9a** | n = 1 | Ar = Ph |
| **1b** | **9b** | n = 1 | Ar = 2-naphtyl |
| **1c** | **9c** | n = 2 | Ar = Ph |
| **1d** | **9d** | n = 1 | Ar = p $CF_3$-Ph |
| **1e** | **9e** | n = 1 | Ar = p MeO-Ph |
| **1f** | **9f** |  | (1R,2S) - norephedrine |



Scheme 1

The necessary chiral aminoalcohols were obtained in the following ways :

- norephedrine **9f** is a commercial product.
- (S)-phenylalaninol **9a** was obtained by reduction of phenylalanine methyl ester with $NaBH_4$ (5).
- (S)-paramethoxyphenylalaninol **9e**, was obtained in a similar fashion after reduction of methylated tyrosine (5).
- (S)-aminoalcohols **9 b,c,d** were also obtained by reduction of the corresponding (S) amino acid methyl esters. The latter were obtained by enantioselective enzymic hydrolysis (8) of racemic ethyl N-acetylamino acids using the following scheme (9) :



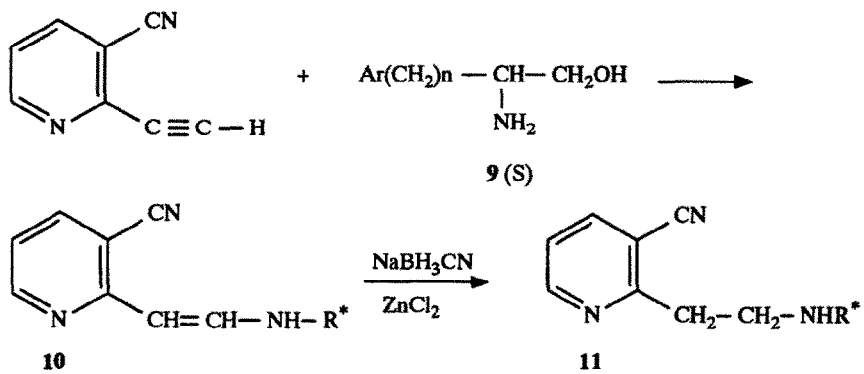
**9b** n = 1 Ar = 2-Naphthyl

**9c** n = 2 Ar = Ph

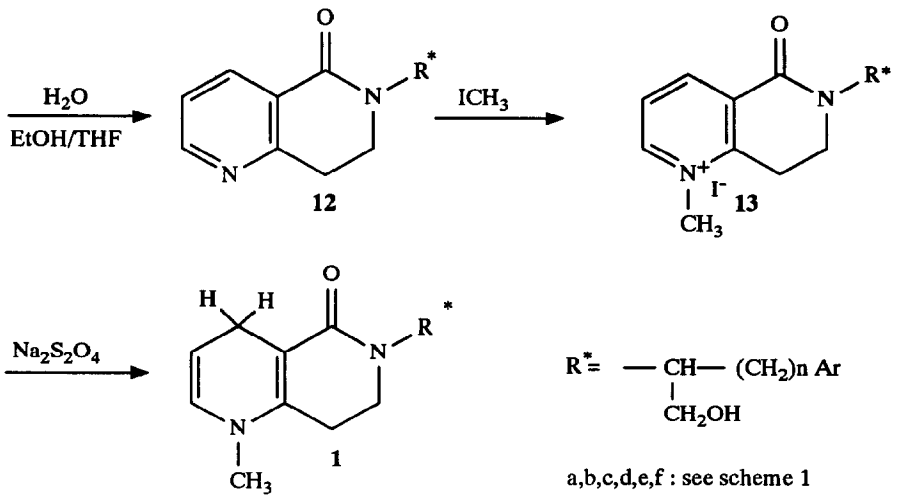
**9d** n = 1 Ar = p-$CF_3$-Ph

Scheme 2

The optical purity of these aminoalcohols was established by GPC analysis of Mosher's derivatives of aminoesters **8b,c,d** (10). Compounds **8** and **9** were shown optically pure. It can be assumed that aminoalcohols **9b,c,d** are also optically pure, the transformation **6** → **9** being non racemizing. All the available chiral aminoalcohols were involved in the synthesis of chiral NADH models **1** by using the previously described method (6b) (scheme 3).



Scheme 3




Scheme 3 (continued)

Nota: it must be noted that an attempt to obtain a model with a (S)-paranitrophenylalaninol as chiral auxiliary was tried. But contrary to the behaviour in the thieno[2,3-b]pyridine series (5), we did not succeed in the reduction of the corresponding pyridinium salt with $Na_2S_2O_4$.

The reduction of methyl benzoyl formate at room temperature with these reagents leads the results shown in table 1.

| Model | Chem Yield | e.e. | Major enantiomer |
|---|---|---|---|
| **1a** | 95 | 88 | R |
| **1b** | 66 | 91 | R |
| **1c** | 55 | 85 | R |
| **1d** | 60 | 79 | R |
| **1e** | 75 | 85 | R |
| **1f** | 62 | 88 | R |

Table 1 : Reduction of methyl benzoylformate with various NADH models **1**

As can be seen the best e.e. is obtained with the β-naphtyl derivative **2a**. The enhancement in the efficiency due to the larger size of the naphtyl group, compared to the phenyl group in **1a** is rather modest. By changing a phenyl group to a naphtyl group in other simpler NADH models the e.e. was improved from 20 % to 28 % (11).

The introduction of a supplementary methylene group in the chain between the phenyl group and the

chiral carbon does not modify significantly the e.e. (model **1c** compared with model **1a**). Despite the greater mobility of the hindering group, the stereodifferentiation of the two faces of the dihydropyridine is always well assured.

The results obtained with models **1d** and **1e** are surprising. It could be assumed that the electron withdrawing $CF_3$ group would favour the formation of a charge transfer complex as was previously proposed for the paranitrophenyl group in the thienopyridine series (5). On the other hand the electron donating MeO group would disfavour this charge transfer complex. As can be seen, the results do not confirm this hypothesis. We believe that, in the thienopyridine series, the charge transfer complex was the result of a strong interaction between the paranitrophenyl substituent and the $\pi$ excessive thiophene ring.

The last substituent is derived from norephedrine. An examination of molecular models suggests that the methyle and phenyle groups could exert an additional influence on the stereodifferentiation of the two faces of the dihydropyridine. It appears that the behaviour of norephedrine is the same as phenylalaninol. However, norephedrine is a cheap, readily available commercial reagent and on this point alone, it can be claimed that model **1f** is a readily available, highly enantioselective chiral NADH model.

## EXPERIMENTAL

(S)-phenylalaninol **9a**, (S)-paramethoxyphenylalaninol **9e** were obtained by previously described methods (5). Norephedrine **9f** was purchased from Aldrich.

***I) Synthesis of chiral amino acids by enzymic methods.***

*1) Diethyl arylalkylacetamidomalonic acids : 2b,c,d (9).* In a flask flushed with argon was introduced 100 ml of anhydrous ethanol and 2.3 g (0.1 mole) of sodium. After reaction and cooling to room temperature, 21.7 g (0.1 mol) of diethyl acetamidomalonate was added followed by, 10 minutes later, 0.11 mol of arylalkyl halogenated derivative $Ar(CH_2)_n$ Br . The mixture was heated to reflux for 15 hours. After cooling, derivatives **2** were isolated by filtration.

**2b** (n = 1, Ar = 2-naphtyl) yield 94 %. IR: $\upsilon$ 1740 $cm^{-1}$; 1640 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.7 - 7.2 (m, 7H) ; 6.5 (s, 1H) ; 4.3 (q, 4H); 3.8 (s, 2H) ; 2.0 (s, 3H) ; 1,3 (t, 6H).

**2c** (n = 2, Ar = Ph) yield 60 %. IR: $\upsilon$ 1740 $cm^{-1}$; 1640 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.2 (s, 5H); 6.9 (s, 1H); 4.2 (q, 4H); 2.6 (m, 4H); 2.0 (s, 3H); 1.2 (t, 6H).

**2d** (n = 1, Ar = p-$CF_3$Ph) yield 94 %. IR: 1740 $cm^{-1}$; 1650 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.5 (d, 2H); 7.1 (d, 2H); 6.6 (s, 1H); 4.3 (q, 4H); 3.7 (s, 2H); 2.0 (s, 3H); 1.3 (t, 6H).

*2) Ethyl arylakylacetamidomonomalonates : 3b,c,d.* The diester **2** (0.1 mol) was dissolved in 200 ml of ethanol. To this solution was added 75 ml of 3.9 M NaOH and the mixture was stirred at room temperature for 40 minutes. After acidification to pH=2, the ethanol was evaporated and the remaining solid was washed with water and dried.

**3b** yield 88 %. IR: $\upsilon$ (C=O) : 1770-1740-1610 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.0-7.0 (m, 9H); 4.1 (q, 2H); 3.5 (s, 2H); 1.9 (s, 3H); 1.1 (t, 3H).

**3c** yield 85 %. IR: $\upsilon$ (C=O) : 1770-1740-1610 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.1 (s, 1H); 7.2 (s, 5H); 4.0 (q, 2H); 2.4 (s, 4H); 1.9 (s, 3H); 1.1 (t, 3H).

**3d** yield 85 %. IR: $\upsilon$ (C=O) : 1770-1740-1620 $cm^{-1}$. $^1H$ NMR: (DMSO-$d_6$): 7.6 (d, 2H); 7.2 (d, 2H); 6.9 (s, 1H); 4.1 (q, 2H); 3.5 (s, 2H); 1.9 (s, 3H); 1.1 (t, 3H).

*3) Ethyl 2-arylalkyl-2 acetamidocarboxylates: 4b,c,d.* A solution of the monoester **3** (0.1 mol) in 400 ml of dioxane, was heated to reflux for 1 hour. After evaporation of the solvent, the residual oil was taken up in

ethyl acetate. The organic phase was washed with a 5 % solution of $NaHCO_3$, then with a saturated solution of NaCl. After drying and evaporation of the solvent, crude ester **4** was obtained in the form of an oil which slowly crystallysed.

**4a** yield 81 %. m.p.= 127°C. IR: υ (C=O) 1750-1650 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.8-7.1 (m, 7H); 6.1 (d, 1H); 4.9 (m, 1H); 4.1 (q, 2H); 3.3 (d, 2H); 1.9 (s, 3H); 1.2 (t, 3H). Anal. Calcd for $C_{17}H_{19}NO_3$ (285.35): C, 71.56; H, 6.71; N, 4.91. Found: C, 71.65; H, 6.92; N, 4.75.

**4b** yield 78 %. m.p.= 72°C. IR: υ (C=O) : 1750-1650 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.2 (m, 5H); 6.1 (d, 1H); 4.7 (m, 1H); 4.2 (q, 2H); 2.7 (m, 2H); 2.2 (m, 2H); 2.0 (s, 3H); 1.2 (t, 3H). Anal. Calcd for $C_{14}H_{19}NO_3$ (249.32): C, 67.45; H, 7.68; N, 5.62. Found: C, 67.37; H 7.75; N, 5.79.

**4c** yield 80 %. m.p.= 112°C. IR: υ (C=O) : 1750-1650 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.6 (d, 2H); 7.2 (d, 2H); 6.2 (d, 1H); 4.9 (m, 1H); 4.2 (q, 2H); 3.2 (d, 2H); 2.0 (4, 3H); 1.2 (t, 3H). Anal. Calcd for $C_{14}H_{16}F_3NO_3$ (303.30): C, 55.44; H, 5.32; N, 4.62. Found: C, 55.68; H, 5.32; N, 4.52.

*4) Enzymic resolution of racemic 4. Synthesis of (S)-2-arylakyl-2-acetamidocarboxylic acids 6 and (R)-ethyl-2-arylalkyl-2 acetamidocarboxylic acids : 5.* Substrate **4** (0.04 mol) was dissolved in 60 ml of acetonitrile, 60 ml of water and 10 ml of a 0.01 M KCl solution. The mixture was vigorously stirred and 0.2 g of $NaHCO_3$ was added followed by 0.02 g of protease (subtilisin type VIII Sigma). The pH was maintained at 7.8 by use of an automatic burette delivering 10 µl fractions of 1M NaOH. The mixture was stirred at room temperature until there was no more NaOH used up (about 5 hours). After evaporation of the solvent the ester (R)-**5** was separated by filtration. The aqueous phase was extracted with ethyl acetate, then acidified (pH = 1) with 6M HCl and the (S)-acid **6** was filtered and dried.

**6b** yield 48 %. m.p.= 208°C. IR: υ (C=O) : 1710-1630 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.2 (d, 1H); 7.8 (m, 3H); 7.7 (s, 1H); 7.4 (m, 3H); 4.5 (m, 1H); 3.3 (m, 2H); 1.8 (s, 3H). Anal. Calcd for $C_{15}H_{15}NO_3$ (257.30): C, 70.02; H, 5.88; N, 5.44. Found: C, 70.76; H, 6.03; N, 5.48.

**6c** yield 48 %. m.p.= 183°C. IR: υ (C=O) : 1700-1630 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.2 (d, 1H); 7.2 (s, 5H); 4.1 (m, 1H); 2.5 (m, 2H); 1.9 (m, 5H). Anal. Calcd for $C_{12}H_{15}NO_3$ (221.26): C, 65.14; H, 6.83; N, 6.33. Found: C, 65.04; H, 6.72; N, 6.20.

**6d** yield 47 %. m.p. = 186°C. IR: υ (C=O) : 1740-1610 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.2 (d, 1H); 7.6 (d, 2H); 7.3 (d, 2H); 4.4 (m, 1H); 3.0 (m, 2H); 1.8 (s, 3H). Anal. Calcd for $C_{12}H_{12}F_3NO_3$ (275.24): C, 52.36; H, 4.40; N, 5.09. Found: C, 52.24; H, 4.25; N, 4.88.

*5) Hydrolysis of compounds 6 : synthesis of (S)-amino acids 7.* The arylalkyl acetamidocarboxylic acid **6** (0.015 mol) was heated to reflux in 100 ml 6M HCl for 4 hours. After cooling, the water was evaporated to dryness and the amino acids were obtained in the form of hydrochloride.

**6b**, HCl : yield 90 %. m.p. > 250°C. IR: υ (C=O) : 1730 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.6 (m, 3H); 7.9-7.4 (m, 7H); 4.2 (m, 1H); 3.3 (d, 2H). Anal. Calcd for $C_{13}H_{14}ClNO_2$ (251.71): C, 62.03; H, 5.61; N, 5.57. Found: C, 61.63; H, 5.80; N, 5.46.

**6c**, HCl : yield 95 % m.p. > 250°C. IR: υ (C=O) : 1730 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.6 (m, 3H); 7.2 (s, 5H); 3.8 (m, 1H); 2.6 (m, 2H); 2.1 (m, 2H). Anal. Calcd for $C_{10}H_{14}ClNO_2$ (251.68): C, 55.69; H, 6.54; N, 6.49. Found: C, 56.42; H, 6.63; N, 6.57.

**6d**, HCl : yield 90 % m.p.= 246 °C. IR: υ (C=O) : 1730 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.6 (m, 3H); 7.7 (d, 2H); 7.5 (d, 2H); 4.2 (m, 1H); 3.3 (d, 2H). Anal. Calcd for $C_{10}H_{11}ClF_3NO_2$ (269.66): C, 44.54; H, 4.11; N, 5.19. Found: C, 44.56; H, 4.04; N, 5.09.

***II) Synthesis of chiral aminoalcohols.***

*1) (S)-methyl aminoesters 8.* To the above chloride of amino acid **7** (0.015 mol) suspended in 15 ml of methanol was added 3 ml of redistilled thionyl chloride (0.041 mol). The solution was heated to reflux for 2 hours. After elimination of all volatile products, the remaining solid was dried and the ester **8** was obtained in the form of an hydrochloride.

**8b**, HCl yield 95 %. m.p.= 195°C. IR: υ (C=O) : 1750 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.8 (m, 3H); 7.85

(m, 4H); 7.45 (m, 3H); 4.35 (m, 1H); 3.7 (s, 3H); 3.3 (t,2 H). Anal. Calcd for $C_{14}H_{16}ClNO_2$ (265.75): C, 63.28; H, 6.07; N, 5.27. Found: C, 63.47; H, 6.03; N, 5.17.

**8c**, HCl yield 94 % m.p.= 194°C. IR: υ (C=O) : 1750 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) : 8.8 (m, 3H); 7.2 (s, 5H); 3.8 (m, 1H); 3.6 (s, 3H); 2.6 (m, 2H); 2.1 (m, 2H). Anal. Calcd for $C_{11}H_{16}ClNO_2$ (229.71): C, 57.51; H, 7.02; N, 6.10. Found: C, 57.45; H, 6.54; N, 5.89.

**8d**, HCl yield 94 %. m.p.= 200°C. IR: υ (C=O) : 1740 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 8.8 (m, 3H); 7.7 (d, 2H); 7.5 (d, 2H); 4.3 (t, 1H); 3.7 (s, 3H); 3.3 (t, 2H). Anal. Calcd for $C_{11}H_{13}ClF_3NO_2$ (283.68): C, 46.57; H, 4.62; N, 4.94. Found: C, 46.49; H, 4.62; N, 4.89.

*2) Determination of optical purity of aminoesters 8b,c,d.* Racemic esters **4b**, **4c**, and **4d** have been prepared by the method precedently described without enzymic resolution. In this way racemic aminoacids **6b,c,d** were obtained and they were transformed into racemic esters **8b,c,d**. For the determination of the optical purity, the Mosher's derivatization method was used (10).

Into a test tube was introduced 5 mg of racemic aminoester. The tube was flushed with argon and 300 µl of anhydrous pyridine was added followed by 50 µl of Mosher's acid chloride. The mixture was stirred for 10 minutes at room temperature. The excess Mosher's reagent was destroyed by adding 50 µl of methanol and the resulting mixture was analysed by GPC.

- chromatograph DELSI SI200
- injector "split" 250°C
- detector FID 250°C
- column DB1 capillary 30x0.25x0.25 (m x mm x µm)
- vector gas : hydrogen (1 bar)
- oven temperature : 200°C for c,d ; 240°C for b.
- retention times (approximately, in minutes) :

| Substituent | enantiomer | |
|---|---|---|
| | R | S |
| 2-Naphtyl | 23 | 25 |
| $CF_3$ | 19 | 21 |
| $PhCH_2CH_2$- | 37 | 41 |

Under the same conditions it was observed that the (S)-aminoesters obtained after enzymic resolution were optically pure.

*3) Reduction of (S)-aminoesters 8b,c,d. Synthesis of (S)-aminoalcohols 9,b,c,d.* To a solution of 1.75 g of $NaBH_4$ (0.046 mol) in 25 ml of a mixture water/ethanol (1/1) was added a solution of aminoester **8** and 25 ml of the same solvent mixture. The resulting mixture was heated to reflux for 4.5 hours, then the ethanol was evaporated. The aqueous phase was saturated with sodium chloride and extracted with ethyl acetate. After drying and evaporation of the solvent a pale yellow oil was obtained which soon crystallised.

**9b** yield 78 % m.p.= 112°C. $^1H$ NMR ($CDCl_3$): 7.8 (m, 3H); 7.6 (s, 1H); 7.4 (m, 2H); 7.3 (m, 1H); 3.7 (dd, 1H); 3.4 (dd, 1H); 3.2 (m, 1H); 3.0 (dd, 1H) ; 2.7 (dd, 1H). Anal. Calcd for $C_{13}H_{15}NO$ (201.27): C, 77.58; H, 7.51; N, 6.96. Found: C, 77.71; H, 7.29; N, 6.67.

**9c** yield 72 % m.p.= 76°C. $^1H$ NMR ($CDCl_3$): 7.2 (m, 5H); 3.6 (dd, 1H); 3.3 (dd, 1H); 2.8 (m, 1H); 2.6 (m, 2H); 1.6 (m, 2H).

**9d** yield 75 % m.p.= 74°C. $^1H$ NMR ($CDCl_3$): 7.6 (d, 2H); 7.3 (d, 2H); 3.6 (dd, 1H); 3.4 (dd, 1H); 3.1 (m, 1H); 2.9 (dd, 1H); 2.6 (dd, 1H). Anal. Calcd for $C_{10}H_{12}F_3NO$ (219.22): C, 54.79; H, 5.52; N, 6.39. Found C, 54.67; H, 5.39; N, 6.02.

*III) Synthesis of models 1*

*1) 5-oxo-5,6,7,8-tetrahydro-1,6-naphtyridines: 12.* A solution of 1.28 g (0.010 mol) of 2-ethynylnicotinonitrile and 0.011 mol of chiral aminoalcohol **9** in 35 ml of anhydrous THF was heated to reflux for 24 hours. The solvent was evaporated and the crude enamine **10** was dissolved in 50 ml of methanol. To the solution was added 1.3 g of $NaBH_3CN$ and 1.4 g of anhydrous $ZnCl_2$. The mixture was stirred at room temperature. One hour later 0.65 g of $NaBH_3CN$ and 0.7 g of $ZnCl_2$ were added and stirring was maintained for 1 hour. After cooling, a solution of 0.1 M NaOH was added and the mixture was extracted with $CH_2Cl_2$. After drying followed by evaporation of the solvent, crude compound **11** was obtained and not further purified. This product was dissolved in 20 ml of a mixture ethanol/water (95/5) and stirred for 48 hours. After evaporation of the solvents, the resulting solid was purified by column chromatography (silica, eluent $CH_2Cl_2$/EtOH : 90/10). (The yields are given with respect to 2-ethynylnicotinonitrile).

**12a** yield 56 % m.p.= 125°C (6b)

**12b** yield 45 % m.p.= 122°C. IR: υ (C=O) : 1620 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 8.5 (dd, 1H); 8.25 (dd, 1H); 7.7 (m, 4H); 7.4 (m, 3H); 7.25 (dd, 1H); 4.85 (m, 1H); 3.9 (m, 2H); 3.5 (m, 2H); 3.2 (m, 3H); 2.9 (m, 2H). Anal. Calcd for $C_{21}H_{20}N_2O_2$ (332.40): C, 75.88; H, 6.06; N, 8.43. Found: C, 76.03; H, 5.89; N, 8.53.

**12c** yield 46 %. IR: υ (C=O) : 1630 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 8.6 (dd, 1H); 8.3 (dd, 1H); 7.2 (m, 6H); 4.8 (m, 1H); 3.8-3.6 (m, 5H); 3.2 (m, 2H); 2.7 (m, 2H); 1.9 (m, 2H). Anal. Calcd for $C_{18}H_{20}N_2O_2$ (296.37): C, 72.95; H, 6.80; N, 9.45. Found: C, 72.76; H, 6.72; N, 9.29.

**12d** yield 39 % m.p.= 136°C. IR: υ (C=O) : 1640 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 8.55 (dd, 1H); 8.25 (dd, 1H); 7.55 (d, 2H); 7.35 (d, 2H); 7.25 (dd, 1H); 4.80 (m, 1H) ; 3.90 (m, 2H); 3.50 (m, 2H); 3.10 (d, 2H); 2.95 (m, 3H). Anal. Calcd for $C_{18}H_{17}F_3NO_2$ (350.35): C, 61.71; H, 6.42; N, 7.99. Found: C, 61.28; H, 5.02; N 8.19.

**12e** yield 71 % m.p.= 104°C. IR: υ (C=O) : 1625 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 8.52 (d, 1H); 8.23 (d, 1H); 7.22 (dd, 1H); 7.13 (d, 2H); 6.77 (d, 2H); 4.78 (m, 1H); 3.73 (s, 3H); 3.65 (m, 2H); 3.48 (t, 2H); 2.92 (m, 4H). Anal. Calcd for $C_{18}H_{20}N_2O_3$ (312.37): C, 69.21; H, 6.45; N, 8.97. Found: C, 69.05; H, 6.51; N, 8.93.

**12f** yield 40 %. IR: υ (C=O): 1630 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 8.3 (dd, 1H); 8.05 (dd, 1H); 7.2 (m, 6H); 4.07 (m, 3H); 3.4 (m, 2H); 2.75 (m, 2H); 1.1 (d, 3H). Anal. Calcd for $C_{17}H_{18}N_2O_2$ (282.34): C, 72.32; H, 6.42; N, 9.92. Found C, 72.04; H, 6.35. N, 9.83.

*2) Quaternization of compounds 12: Synthesis of pyridinium salts 13.* Compound **12** (0.004 mol) was dissolved in 5 ml of acetonitrile. To the solution, 5 ml of methyl iodide was added and the mixture was heated to reflux for 12 hours. After cooling, 2/3 of the volatile compounds were evaporated and diethyl ether was added. The pyridinium salt which precipitated was filtered. The yield was nearly quantitative.

**13a** (6b)

**13b** m.p.= 205°C. IR: υ (C=O) : 1670 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 9.0 (d, 1H); 8.7 (d, 1H); 8.0 (t, 1H); 7.8 (m, 4H); 7.4 (m, 3H); 5.0 (m, 2H); 4.2 (s, 3H); 3.7 (m, 4H); 3.3-3.1 (m, 4H). Anal. Calcd for $C_{22}H_{23}IN_2O_2$ (474.34): C, 55.71; H, 4.89; N, 5.90. Found: C, 55.11; H, 4.79; N, 5.73.

**13c** m.p.= 208°C. IR: υ (C=O) : 1670 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 9.10 (d, 1H); 8.90 (d, 1H); 8.10 (t, 1H); 7.20 (m, 5H); 4.85 (t, 1H); 4.60 (m, 1H); 4.25 (s, 3H); 3.70-3.40 (m, 6H); 2.55 (m, 2H); 1.80 (m, 2H). Anal. Calcd for $C_{19}H_{23}IN_2O_2$ (438.30): C, 52.07; H, 5.29; N, 6.39. Found: C, 52.19; H, 5.24; N, 6.20.

**13d** m.p.= 190°C. IR: υ (C=O) : 1670 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 9.05 (d, 1H); 8.75 (d, 1H); 8.0 (t, 1H); 7.6 (d, 2H); 7.5 (d, 2H); 4.9 (m, 2H); 4.25 (s, 3H); 3.65 (m, 4H); 3.3 (m, 2H); 3.0 (d, 2H). Anal. Calcd for $C_{19}H_{20}F_3IN_2O_2$ (492.28): C, 46.36; H, 4.09; N, 5.69. Found: C, 46.51; H, 4.31; N, 5.63.

**13e** m.p.= 180°C. IR: υ (C=O) : 1670 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$) : 9.06 (d, 1H); 8.78 (d, 1H); 8.02 (t, 1H); 7.15 (d, 2H); 6.80 (d, 2H); 4.92 (t, 1H); 4.82 (m, 1H); 4.25 (s, 3H); 3.67 (s, 3H); 3.60 (m, 4H); 3.25 (m, 2H); 2.82 (m, 2H). Anal. Calcd for $C_{19}H_{23}IN_2O_3$ (454.3): C, 50.23; H, 5.10; N 6.16. Found: C, 49.74; H, 4.84; N, 5.94.

**13f** m.p.= 202°C. IR: υ (C=O) : 1660 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): 9.07 (d, 1H); 8.78 (d, 1H); 8.03 (t, 1H); 7.25 (m, 5H); 5.62 (d, 1H); 4.71 (m, 2H); 4.21 (s, 3H); 3.65 (m, 2H); 3.25 (m, 2H); 1.10 (d, 3H). Anal. Calcd for $C_{18}H_{21}IN_2O_2$ (424.23): C, 50.96; H, 4.99; N, 6.60. Found: C, 50.75; H, 4.97; N, 6.61.

*3) Reduction of pyridinium salts 13 : synthesis of models 1.* The pyridinium salt (0.001 mol) was dissolved at 40°C in 5 ml of water which have been degassed with argon. After dissolution the mixture maintained under argon was returned to room temperature and 0.53 g of $Na_2CO_3$ was added. A solution of 0.70 g of $Na_2S_2O_4$ in 3 ml of degassed water was then added with vigorous stirring. The precipitate was filtered and washed with degassed water, then dried. These compounds were not purified further.

**1a** (6b)

**1b** yield 60 %. $^1H$ NMR ($CDCl_3$): 7.8 (m, 3H); 7.6 (s, 1H); 7.4 (m, 3H); 5.6 (d, 1H); 4.7 (q, 1H); 4.2 (m, 2H); 3.8 (m, 2H); 3.3-3.0 (m, 6H); 2.8 (s, 3H); 2.1 (m, 2H).

**1c** yield 86 %. $^1H$ NMR ($CDCl_3$): 7.25 (m, 5H); 5.7 (d, 1H); 4.75 (q, 1H); 4.35 (m, 1H); 3.7 (m, 2H); 3.3 (m, 2H); 3.15 (m, 2H); 2.95 (s, 3H); 2.65 (m, 2H); 2.4 (m, 2H); 1.9 (m, 2H).

**1d** yield 90 %. $^1H$ NMR ($CDCl_3$): 7.55 (d, 2H); 7.35 (d, 2H); 5.65 (d, 1H); 4.75 (q, 1H); 4.1 (m, 2H); 3.75 (m, 2H); 3.2-3.0 (m, 6H); 2.85 (s, 3H); 2.2 (m, 2H).

**1e** yield 88 %. $^1H$ NMR ($CDCl_3$): 7.13 (d, 2H); 6.82 (d, 2H); 5.65 (d, 1H); 4.76 (q, 1H); 4.15 (m, 2H); 3.79 (m, 5H); 3.2-2.9 (m, 6H); 2.86 (s, 3H); 2.15 (t, 2H).

**1f** yield 88 %. $^1H$ NMR ($CDCl_3$): 7.29 (m, 5H); 5.67 (d, 1H); 4.90 (s, 1H); 4.80 (q, 1H); 4.40 (m, 1H); 3.15-2.75 (m, 7H); 2.25 (t, 2H); 1.18 (d, 3H).

*4) Reduction of methyl phenylglyoxylate with models 1.* For the procedure and the determination of e.e. see ref (7).

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