Tetrahedron: Asymmetry Vol. 1, No. 9, pp. 611-620, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Resolution of Multifunctional Carbon Compounds Derivated from N-Protected 2-Cyano Glycinates

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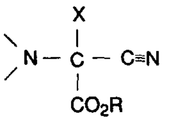
(*Received* 9 *July* 1990)

Abstract : Synthesis and resolution of covalent diastereoisomers from some N-protected 2-cyanoglycinates using (S)-(-)-ethyl lactate as a resolving reagent, give rise after transesterification with titanium tetraisopropoxide, to chiral multifunctional carbon compounds **1**, valuable chiral auxiliaries as key precursors in organic synthesis.

We recently reported[1] the synthesis of racemic compounds **1** bearing several functional groups directly attached to a central carbon atom, derivated from N-protected 2-cyanoglycinates:



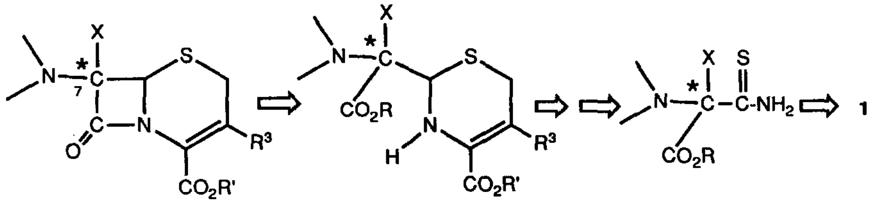
$$\mathrm{>N-C(X)(CO_2R)-C{\equiv}N}$$

1

X = H, F, Cl, Br, Me, $CH_2CH{=}CH_2$, $CH_2C{\equiv}CH$, OMe, OAc.
R = Me, t-Bu.

These α-disubstituted aminoesters **1**, especially in their homochiral forms of known absolute configuration, are of special significance to serve as chiral auxiliaries and versatile chirons for the syntheses of optically active natural products[2]. Furthermore, they can be convenient models for spectroscopic study and research, compared to applicable reagents described for the practical method of determining the enantiomeric purity of optically active compounds[3].

In our case, chiral nitriles **1**, precursors of the corresponding thioamides are especially versatile for subsequent conversions and are key intermediates in the enantioselective route for the total synthesis of cephems, cephalosporins and cephamycins, using a strategy previously investigated on racemic models[4].

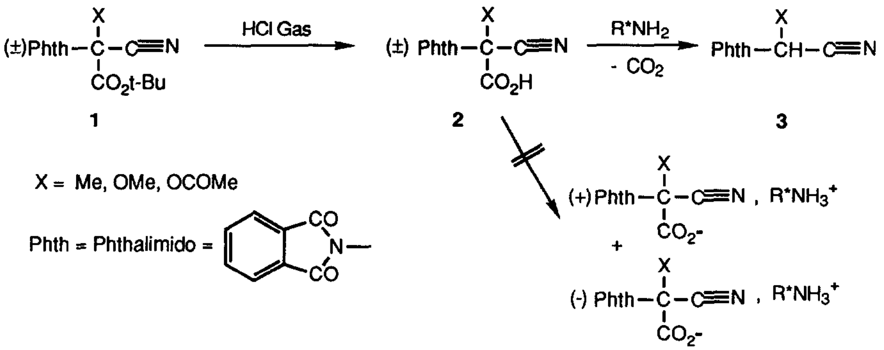


The determination of the absolute configuration of these compounds **1** is difficult because of the problem of derivatization in order to compare them to known chiral structures. X-ray analysis of crystalline derivatives of resolved covalent diastereoisomers bearing a known chiral auxiliary would be the most reliable method.

In this paper we present the results on the synthesis and the resolution of some covalent diastereoisomers of type **1**, on a preparative scale using either chromatography or crystallization techniques, as a prelude to our planned syntheses.

Results and discussion

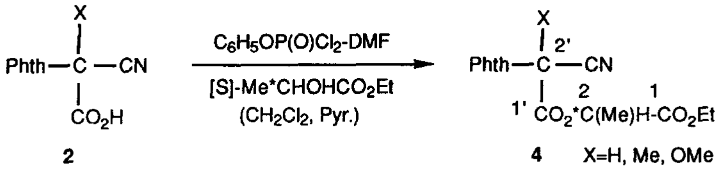
The resolution of racemic acids by separation as crystalline diastereoisomer salts formed from a chiral auxiliary is well known[5,6]. In our case, the 2-cyano-2-phthalimido acetic acids **2**, obtained quantitatively by cleavage of corresponding tert-butyl esters in acidic medium, opposed to chiral amines R^*NH_2 did not lead to the expected diastereoisomeric salts. Their malonic structure explains the partial or total decarboxylation observed in basic medium.



The formation of covalent diastereoisomers by coupling racemic acids **2** with a chiral alcohol[6] presupposed the same difficulties. Effectively, classic methods of coupling: DCC + DMAP[7], $MeSO_2Cl$ + Et_3N[8], etc... carried out in basic medium, only gave small amounts of required esters. The reactions gave, for the most part, the same decarboxylated products **3** as written above.

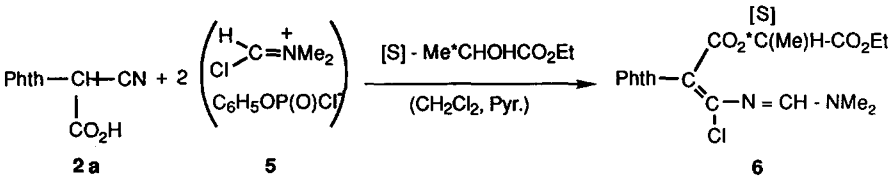
On the other hand, the coupling using the phenyl dichlorophosphate/N,N-dimethylformamide complex, indicated by C. Palomo[9] for activation of carboxylic acids and particularly useful for the esterification of substituted malonic acids which easily undergo decarboxylation, gave in our case the required diastereoisomers **4** with yields of the order of 90% (except for X = OCOMe where only the decarboxylated product was obtained). More recently, we tested this coupling using the Vilsmeier-Haack phosphorus oxychloride/N,N-dimethylformamide reagent. Depending of the runs, the same results were obtained but with yields lower by 5 to 10%.

We took advantage of this mild method of coupling to investigate different chiral alcohols: (S)-(-)-ethyl lactate, (R)-(+)-ethyl mandelate and (-)-menthol, with 2-cyano-2-phthalimido acetic acid **2** (for X = H, Me and OMe). We finally decided upon the diastereoisomers **4** obtained from (S)-ethyl lactate due to their better yields, easier crystallization of the compounds, better resolved ^1H NMR signals and easier evaluation of the diastereoisomer ratios. Morever, the low cost of this chiral auxiliary allowed us to work on preparative scales for the syntheses of the planned cephems mentioned in the introduction.



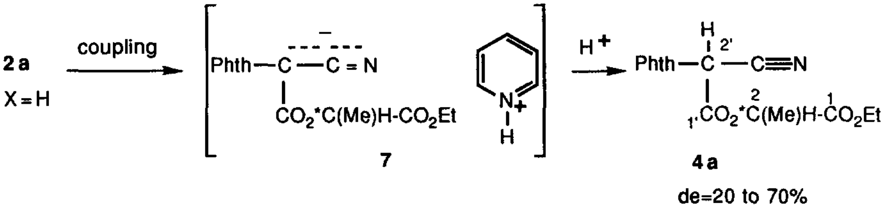
The ^1H NMR spectra of the compounds **4** clearly showed a splitting of most of the proton signals of the two diastereoisomers 2S-2'R and 2S-2'S.

For X = H, an excess of phenyl dichlorophosphate/N,N-dimethylformamide led to the formation of a secondary product **6**, resulting from the supplementary reaction on the nitrile group. We verified that the action of at least two equivalents of the reagent **5** gave, with a yield of 73%, exclusively the α-chloroenamidine **6**.



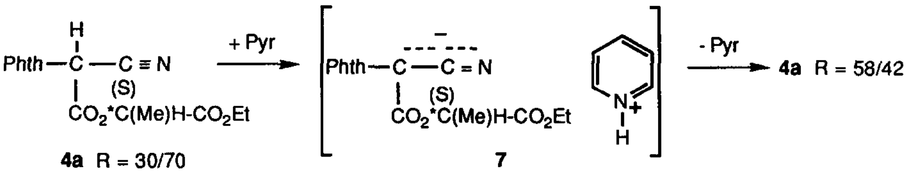
This second reaction should be compared with the work of J. Liebscher on the preparation of 3-chloro-2-aza-2-propeniminium compounds by addition of imidic chloride quaternary salts to nitriles[10].

Anyway, for X = H, **4a** was obtained with good yields using a single equivalent of coupling reagent. Moreover a deracemization[11]was observed, resulting from a diastereoselective protonation at the end of the reaction:



During the acid **2a**/chiral alcohol coupling, the racemic compound (the pair of the 2S-2'R and 2S-2'S diastereoisomers) was transformed into a prochiral intermediary **7** by loss of the proton in the 2'position. The diastereoisomeric excesses varied from 20 to 70% according to the conditions of hydrolysis at the end of the reaction.

A study by ^1H NMR allowed us to confirm this deracemization by highlighting a rapid exchange of the hydrogen in the 2'position with pyridine:



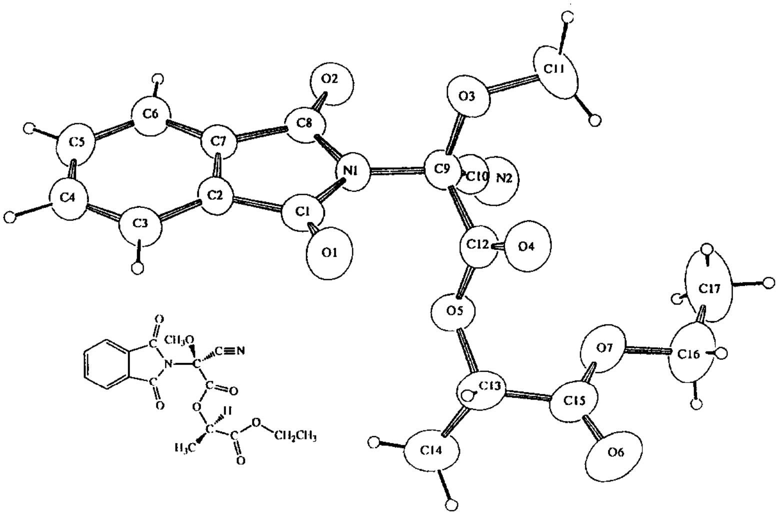
R = ratio diastereoisomer A/diastereoisomer B

After stœchiometric addition of pyridine to a mixture of diastereoisomers **4a** in a ratio R determined beforehand, the formation of the pyridinium salt **7** accompanied by the loss of splitting of the proton signals of **4a** was effectively observed. By progressive elimination of the pyridine under reduced pressure, the progressive disappearance of the complex was followed by ^1H NMR, then finally the formation of the mixture of diastereoisomers **4a** appears in a different ratio from the one initially measured, resulting from a diastereoselective reprotonation. The structure of the intermediary complex **7** was confirmed by ^{13}C NMR, as the pyridine was replaced by the triethylamine (see experimental section). In particular, the displacement of the signal to lower fields which can be attributed to the carbon of the nitrile group, is in favor of the delocalisation of the negative charge on this group (C=N double bond character).

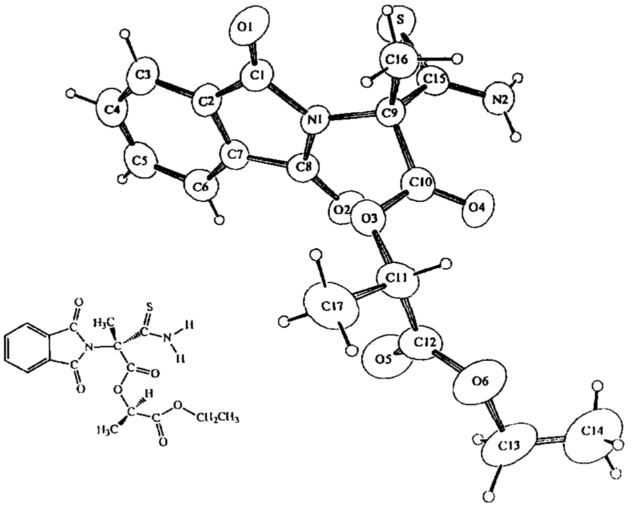
The resolution of the diastereoisomer pairs **4** has been realized by fractional crystallizations in methanol (X = H, OMe), by HPLC or silica gel chromatography (X=Me). The control of the resolution of the racemic mixtures was easily followed by ^1H NMR. It has been possible to totally resolve the diastereoisomers **4b**. A single pure diastereoisomer has been isolated in the cases of **4a** and **4c**. The results are set out in the table below.

4a (X = H)	**4b** (X = Me)	**4c** (X = OMe)
1 pure diastereoisomer isolated by fractional crystallizations: diastereoisomer **A**: $[\alpha]_D$ = -30,5 (c 1, $CHCl_3$) mp = 88-90°C	2 pure diastereoisomers resolved by chromatography: diastereoisomer **A**: 2S-2'R $[\alpha]_D$ = -3,6 (c 2.5, $CHCl_3$) mp = 47-48°C and diastereoisomer **B**: 2S-2'S $[\alpha]_D$ = -30,4 (c = 1,8, $CHCl_3$) mp = 90-91°C	1 pure diastereoisomer isolated by fractional crystallizations: diastereoisomer **A**: 2S-2'S $[\alpha]_D$ = +11,7 (c 1, $CHCl_3$) mp = 129-131°C and diastereoisomer **B**: 2S-2'R (enriched: d.e.>60%)

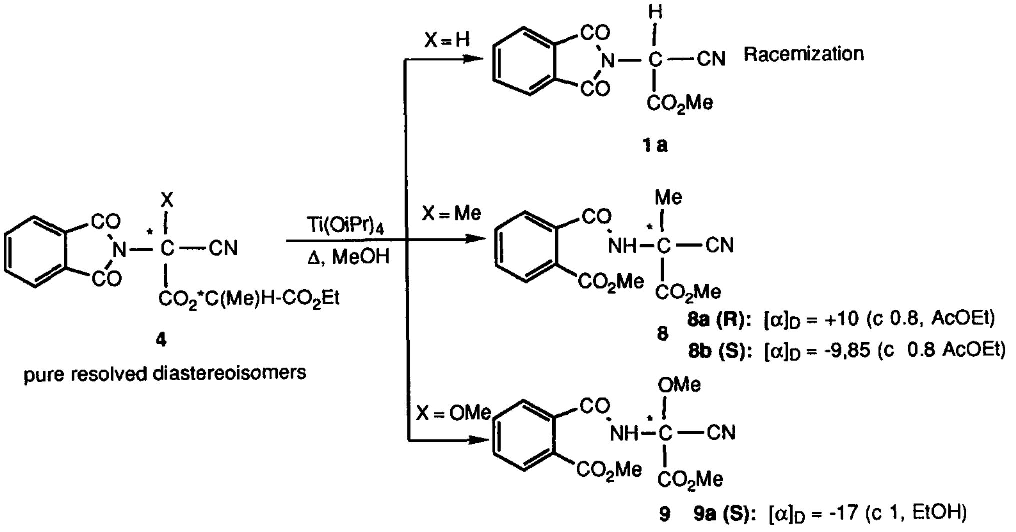
An X-ray crystallography analysis of pure crystals of the diastereoisomer **A** coming from **4c** gave the 2S-2'S configuration illustrated in the ORTEP diagram below:



Because of their too small size, the crystals resulting from **4b** could not be analysed by X-ray. The attribution of the configurations of the pure diastereoisomers **A** and **B** results from the structure determined by X-ray on 2'-methyl-2'-phthalimido-2'-thiocarbamoyl-2-acetoxy ethyl propanoate given by the diastereoisomer **A**, by conversion of the nitrile group into thioamide (by addition of hydrogen sulphide: CN ---> $C(S)NH_2$). We made sure that this transformation carried out in pyridine/Et_3N did not give rise to any epimerization of the carbon atom of the chiral auxiliary. The ORTEP diagram below illustrates the 2S-2'S structure of the pure thioamide diastereoisomer.



Starting from the pure resolved diastereoisomers **4**, we tested the access to the corresponding enantiomers by transesterification using methanol in the presence of titanium tetraisopropoxide[3a,12] or triethylamine. There was racemization for X = H, but the required enantiomers **8** (**8a** and **8b**) and **9a** respectively for X = Me and X = OMe can be isolated. We verified, for the latter, the absence of racemization about the tetrafunctional asymmetric centre. This transesterification reaction was always accompanied by methanolysis of the phthaloyl group to *o*-methoxycarbonyl[1]:



We are pursuing the study of these chiral synthons with multifunctional carbon derived from α-aminoesters, which are of great use for our next syntheses. Let us point out that these multistep syntheses of cephems can also be carried out, starting from the chirons **8** and **9**, as well as from the resolved diastereoisomers **4**.

Experimental:

^1H and ^{13}C NMR spectra were recorded on a JEOL instrument J.N.M. FX 90-MHz. Chemical shifts are reported as δ values in ppm down field from internal standard (Me_4Si) with notations specifying the number of protons, the multiplicity of the signal: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and the coupling constants. IR spectra were measured in KBr with a PERKIN-ELMER 1420 spectrophotometer. Mass spectra were recorded on a Varian MAT 311 spectrometer at 70 eV. Optical rotatory powers were measured at 20°C using a AA.10 OPTICAL ACTIVITY polarimeter.

The compounds purity was monitored by thin layer chromatography (TLC) on silica gel plates. Column chromatography was carried out on silica gel (Merck, Kieselgel 60). The resolution of diastereoisomers was tested by means of HPLC: Milton Roy CM 4000 pump - LDC 3100 detector (254 nm) - equipped with a Spherisorb 5 column - eluent: CH_2Cl_2, flow: 1mL/mn. Elemental microanalyses were performed by the Central Service of Microanalysis of the CNRS (Vernaison, France). Melting points were determined using a microscope with a Kofler hot stage and are uncorrected.

Acids 2: general experimental procedure starting from corresponding 2-cyano-2-phthalimido tert-butyl glycinates[1] 1. A stream of dry HCl gas was passed through a solution of 7 mmol of tert-butyl glycinate **1** in 40 mL of anhydrous $MeNO_2$, cooled at 0°C, until saturation. The mixture was stirred for 3 h at 0°C, the solvent was then removed under reduced pressure. The acids obtained quantitatively were used directly in the coupling reactions without subsequent purification .

2-cyano-2-phthalimido acetic acid 2a: White crystals ($MeNO_2$), mp = 103-104°C. ^1H NMR (CD_3COCD_3) δ: 6.38 (s,1H, CH), 7.98 (s, 4H, Phth), 10.20 (br s, 1H, COOH). MS: m/e (I%): 186 (94), 160 (6), 142 (16), 132 (70), 104 (100), 76 (75), 44 (90).

2-cyano-2-methyl-2-phthalimido acetic acid 2b: White crystals ($MeNO_2$), mp = 87-90°C. ^1H NMR ($CDCl_3$) δ: 2.37 (s, 3H, Me), 7.84 (s, 4H, Phth), 8.40 (br s, 1H, COOH).

2-cyano-2-methoxy-2-phthalimido acetic acid 2c: White crystals (Me_2CO), mp = 115-118°C. ^1H NMR (DMSO) δ: 3.56 (s, 3H, OMe), 7.99 (s, 4H, Phth), 10.11 (br s, 1H, COOH).

2-Phthalimido ethanenitriles 3b, 3c and 3d: They are coming from the decarboxylation of the corresponding acids **2** in alkaline solution, whatever the experimental conditions .

2-Phthalimido propanenitrile 3b: White crystals (AcOEt/petroleum ether), mp = 132°C. ^1H NMR ($CDCl_3$) δ: 1.81 (d, J = 7.2 Hz, 3H, Me), 5.28 (q, J = 7.2 Hz, 1H, CH), 7.85 (s, 4H, Phth). IR (KBr) cm^{-1}: 2230 (CN), 1780, 1720 (C=OPhth). MS: m/e (I%): 200 (74), 185 (100), 173 (57), 157 (26), 147 (48), 105 (85), 104 (68), 76 (69).

2-Methoxy-2-phthalimido ethanenitrile 3c: White crystals (MeOH), mp = 80-81°C. ^1H NMR ($CDCl_3$) δ: 3.56 (s, 3H, OMe), 6.04 (s, 1H, CH), 7.90 (s, 4H, Phth). IR (KBr) cm^{-1}: 1770, 1730 (C=OPhth), 1080 (C-O ether). MS: m/e (I%): 216 (1), 201 (4), 186 (83), 185 (100), 174 (21), 158 (29), 132 (22), 104 (37), 76 (47).

2-Acetoxy-2-phthalimido ethanenitrile 3d: White crystals (MeOH). mp = 152-154°C. ^1H NMR ($CDCl_3$) δ: 2.18 (s, 3H, OCOMe), 7.26 (s, 1H, CH), 7.96 (s, 4H, Phth). IR (KBr) cm^{-1}: 1780, 1730

(C=OPhth), 1760 (C=O ester). MS: m/e (I%): 202 (52), 201 (16), 185 (100), 174 (16), 158 (19), 147 (17), 130 (14), 104 (38), 76 (42), 43 (65).

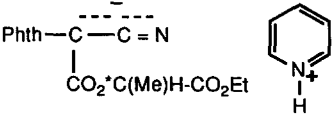
Coupling reactions of the acids 2 with (S)(-)ethyl lactate: general experimental procedure: To 1.05 mL (11.6 mmol) of DMF in a round bottomed flask at 0°C, 1.32 mL (8.75 mmol) of phenyl dichlorophosphate were added . After stirring for 5 mn, 35 mL of anhydrous CH_2Cl_2 were poured, followed by 7 mmol of acid **2**. The solution was brought back to room temperature and stirred for 10 mn. Then 1.6 mL (14 mmol) of (S)(-)ethyl lactate were added. After a further 10 mn stirring, 2.1 mL (26.2 mmol) of pyridine was finally put in. The reaction mixture was stirred overnight, and then dissolved in 150 mL of AcOEt. The resulting solution was washed successively with 2 x 50 mL of a 10% aqueous solution of HCl, 3 x 50 mL of brine, dried (Na_2SO_4), and then concentrated. The residue was purified by silica gel chromatography (petroleum ether/AcOEt 1/1).

2'-Cyano-2'-phthalimido-2-acetoxy ethyl propanoate 4a: Yield = 85%. The diastereoisomers not separated by chromatogaphy (no detectable separation in TLC) gave the most abundant isomer A, resulting from the observed deracemization, by fractional crystallizations:

Pure diastereoisomer A: White crystals (MeOH), mp = 88-90°C. $[\alpha]_D$ = -30.5 (c = 1.02; $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.33 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.56 (d, J = 7 Hz, 3H, Me-CH), 4.24 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.25 (q, J = 7 Hz, 1H, Me-CH), 5.92 (s, 1H, CH), 7.88 (s, 4H, Phth). ^{13}C (C_6D_6) δ: 13.86 and 16.33 (MeCH and MeCH_2), 41.44 (N-CH-CN), 61.74 (CH_2-Me), 72.34 (O-CH-Me), 112.03 (CN), 124.00; 131.48 and 134.54 (C_6H_4), 161.67 and 169.02 (CO esters), 165.31 (CO-Phth). IR (KBr) cm^{-1}: 1770, 1720 (C=OPhth), 1765, 1745 (C=O ester). Anal. Calcd for $C_{16}H_{14}N_2O_6$ (330.29): C 58.18 H 4.27 N 8.48. Found : C 57.96 H 4.21 N 8.51.

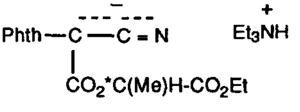
Enriched diastereoisomer B: ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.64 (d, J = 7 Hz, 3H, Me-CH), 4.21 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.25 (q, J = 7 Hz, 1H, Me-CH), 5.94 (s, 1H, CH), 7.88 (s, 4H, Phth). MS: m/e (I%): 286 (9), 258 (13), 213 (27), 186 (69), 185 (100), 158 (15), 132 (36), 76 (23), 73 (28).

Complex 7: (4a + Pyridine):



^{1}H NMR ($CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.60 (d, J = 7 Hz, 3H, Me-CH), 4.22 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.26 (q, J = 7 Hz, 1H, Me-CH), 7.32 (m, 2H), 7.65 (m, 1H) and 8.64 (m, 2H) (5H Pyr), 7.88 (s, 4H, Phth), NH^+ absent (rapid exchange).

Complex 7: (4a + triethylamine):



^{1}H NMR (C_6D_6) δ: 1.01 (t, J = 7 Hz, 3H, Me-CH_2), 1.09 (t, J = 7.3 Hz, 9H, [Me-CH_2]$_3$N), 1.26 (d, J = 7 Hz, 3H, Me-CH), 2.81 (q, J = 7.3 Hz, 6H, [Me-CH_2]$_3$N), 3.97 (q, J = 7 Hz, 2H, Me-CH_2), 5.07 (q, J = 7 Hz, 1H, Me-CH), 6.78 (s, 1H, NH^+), 7.08 and 7.46 (2 m, 4H, Phth). ^{13}C δ :

10.08 ([Me-CH_2]$_3$N), 14.12 and 17.37 (MeCH and MeCH_2), 46.78 ([Me-CH_2]$_3$N), 49.64 (N-C-C=N), 60.83 (CH_2-Me), 68.83 (O-CH-Me), 123.87 (N-C-C=N), 123.22; 132.65 and 133.76 (C_6H_4), 167.79 and 171.95 (CO esters), 168.37 (CO-Phth).

2'-Cyano-2'-methyl-2'-phthalimido-2-acetoxy-2 ethyl propanoate 4b: Yield = 91%. The diastereoisomers were separated by silica gel chromatography (toluene/AcOEt, 9/1) and the different fractions obtained were controled by TLC:

Pure diastereoisomer A (2S-2'R): White crystals (MeOH), mp = 47-48°C. HPLC: rt(mn): 16.24 (CH_2Cl_2), flow: 1 mL/mn. TLC: Rf = O.45 (toluene/AcOEt, 9/1). $[\alpha]_D$ = -3.6 (c = 2.51; $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.64 (d, J = 7 Hz, 3H, Me-CH), 2.43 (s, 3H, Me), 4.22 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.26 (q, J = 7 Hz, Me-CH), 7.83 (s, 4H, Phth). ^{13}C δ: 14.08 and 16.55 (MeCH and MeCH_2), 22.18 (MeC), 54.97 (N-C-CN), 61.87 (CH_2Me), 71.60 (O-CH-Me), 115.41 (CN), 124.03; 131.19 and 135.00 (C_6H_4), 164.92 and 169.35 (CO esters), 166.45 (CO-Phth). IR (KBr) cm^{-1}: 1787, 1733 (C=OPhth), 1776, 1751 (C=O ester). Anal. Calcd for $C_{17}H_{16}N_2O_6$ (344.31): C 59.30 H 4.68 N 8.14. Found: C 59.47 H 4.70 N 8.17.

Pure diastereoisomer B (2S-2'S): White crystals (MeOH), mp = 90-91°C. HPLC: rt(mn): 23.7 (CH_2Cl_2), flow: 1 mL/mn. TLC: Rf = O.38 (toluene/AcOEt, 9/1). $[\alpha]_D$ = -30.4 (c = 1.81; $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.28 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.51 (d, J = 7 Hz, 3H, Me-CH), 2.41 (s, 3H, Me), 4.22 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.23 (q, J = 7 Hz, Me-CH), 7.83 (s, 4H, Phth). ^{13}C δ: 14.05 and 16.65 (MeCH and MeCH_2), 22.31 (MeC), 55.56 (N-C-CN), 61.93 (CH_2), 71.63 (CH), 115.35 (CN), 124.07; 131.09 and 135.13 (C_6H_4), 164.66 and 169.15 (CO esters), 166.35 (CO-Phth). IR (KBr) cm^{-1}: 1791, 1737 (C=OPhth), 1766, 1745 (C=O ester). MS: m/e (I%): 300 (10), 227 (20), 201 (55), 200 (100), 173 (19), 172 (89), 132 (33), 104 (13), 76 (26), 73 (16).

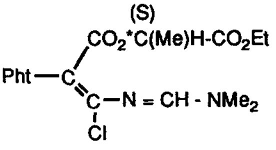
2'-Cyano-2'-methoxy-2'-phthalimido-2-acetoxy ethyl propanoate 4c: The trials to separate the diastereoisomers by TLC did not succeed. It was only possible to obtain one single pure diastereoisomer by fractional crystallizations in MeOH.

Pure diastereoisomer A (2S-2'S): White crystals (MeOH), mp = 129-131°C. Yield = 62%. $[\alpha]_D$ = +11.8 (c = 1.01; $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.30 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.52 (d, J = 7 Hz, 3H, Me-CH), 3.71 (s, 3H, OMe), 4.26 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.36 (q, J = 7 Hz, 1H, Me-CH), 7.91 (s, 4H, Phth).^{13}C δ: 14.05 and 16.59 (Me-CH and Me-CH_2), 55.49 (OMe), 62.00 (CH_2Me), 72.05 (O-CH-Me), N-C-CN (masked under $CDCl_3$ signal): 77.71 (in CD_3COCD_3), 110.53 (CN), 124.52; 130.70 and 135.48 (C_6H_4), 160.14 and 169.02 (CO esters), 165.15 (CO-Phth). IR (KBr) cm^{-1}: 1790, 1740 (C=OPhth), 1780, 1745 (C=O ester).

Enriched diastereoisomer B (2S-2'R) (d.e>60%): ^{1}H NMR ($CDCl_3$) δ: 1.25 (t, J = 7.2 Hz, 3H, Me-CH_2), 1.65 (d, J = 7 Hz, 3H, Me-CH), 3.71 (s, 3H, OMe), 4.21 (q, J = 7.2 Hz, 2H, Me-CH_2), 5.39 (q, J = 7 Hz, 1H, Me-CH), 7.91 (s, 4H, Phth).

The ^{1}H NMR spectrum of the mixture clearly shows a splitting of the proton signals due to the presence of the two diastereoisomers, except for the OMe group signal for which the splitting differences are clearly observed by addition of Eu(fod)$_3$. MS: m/e (I%): 329 (<1), 315 (<1), 243 (3), 215 (100), 174 (30), 130 (34), 104 (26), 76 (27). Anal. Calcd for $C_{17}H_{16}N_2O_7$ (360.31): C 56.66 H 4.48 N 7.77. Found: C 56.86 H 4.22 N 7.48.

α-Chloroenamidine 6: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To 2.4 mL (31 mmol) of DMF in a round bottomed flask at 0°C, 3 mL (20 mmol) of phenyl dichlorophosphate were added. After stirring for 5 mn, 35 mL of anhydrous CH_2Cl_2, then 1.84 g (7 mmol) of acid **2a** were added. After a further 10 mn stirring at 0°C, 1.9 mL (16 mmol) of (S)(-)ethyl lactate were added, then followed 10 mn later by dropwise addition of a solution of 2.4 mL (30 mmol) of pyridine in 15 mL of CH_2Cl_2. The reaction mixture was stirred at 0°C for 1 h, then overnight at room temperature, concentrated under reduced pressure. The residue was dissolved in 150 mL of AcOEt, washed successively with 50 mL of a 10% aqueous solution of HCl and 2 x 50 mL of brine. The solution was dried (Na_2SO_4), concentrated and purified by silica gel chromatography (AcOEt), giving 2.44 g of a yellow fluorescent foam. Yield = 73%. $[\alpha]_D = +31.7$ (c = 1; $CHCl_3$). ^1H NMR ($CDCl_3$): Two forms are observed due to the restricted rotation about the C=N double bond. **Form A (30%)**: δ : 1.20 (t, J = 7.2 Hz, 3H, $MeCH_2$), 1.42 (d, J = 7 Hz, 3H, MeCH), 2.73 and 3.10 (2s, 6H, NMe_2), 4.13 (q, J = 7.2 Hz, 2H, $MeCH_2$), 5.14 (q, J = 7 Hz, MeCH), 7.82 (br s, 4H, C_6H_4), 8.05 (s, 1H, =CH). **Form B (70%)**: same spectrum except δ : 3.20 and 3.24 (2s, NMe_2). ^{13}C δ: 14.02 and 17.17 (Me-CH and Me-CH_2), 35.62 and 41.34 (NMe_2 form A), 36.20 and 41.15 (NMe_2 form B), 61.12 (CH_2), 68.96 (CH), 101.75 (form B) and 102.63 (form A) (C=C-Cl), 149.31 (form A) and 153.99 (form B) (C=C-Cl), 123.61; 132.30 and 134.09 (C_6H_4), 156.92 (HC=N form A), 157.25 (HC=N form B), 162.26 (form B), 162.91 (form. A) and 170,84 (for the two forms) (C=O esters), 167.46 (C=O C_6H_4). IR (KBr) cm^{-1}: 1780, 1754, 1737, 1722 (C=O), 1632 (C=N), 1382 (C-O-), 864 (C-Cl). MS: m/e (I%): 421/423 (37), 386 (28), 304/306 (22), 277 (13), 213 (21), 186 (36), 185 (58), 132 (27), 104 (100), 99 (74), 76 (68), 44 (96). Anal. Calcd for $C_{19}H_{20}N_3O_6Cl$ (421.83): C 54.09 H 4.78 N 9.96. Found: C 54.33 H 4.81 N 9.66.

Transesterification reactions of the esters 4: General experimental procedure: To 0.25 mmol of ester **4** (pure diastereoisomer) in 3 mL of anhydrous MeOH, 0.06 mL (0.2 mmol) of $Ti(OiPr)_4$ was added under an atmosphere of dry nitrogen. The advancement of the reaction brought to reflux was monitored by TLC. It was observed that the kinetic of the methanolysis of the phthaloyl group was greater than that of the transesterification. After about 4 hours (completion of the reaction was determined by TLC) the residue was concentrated and dissolved in 15 mL of AcOEt. The solution was washed with 10 mL of 0,5 N HCl aqueous solution, then with 2 x 10 mL of brine, dried ($MgSO_4$), concentrated and purified by silica gel chromatography (petroleum ether /AcOEt 3/7).

2-Cyano-2-*o*-methoxycarbonylbenzamido methyl propanoates, enantiomers 8a (R) and 8b (S): White crystals (AcOEt/petroleum ether), mp = 125-126°C (mp = 104-106°C for the racemate[1]). Yield = 75%. **8a (R)**: $[\alpha]_D = +10$ (c = 0.8; AcOEt) and **8b (S)**: $[\alpha]_D = -9.85$ (c = 0.8; AcOEt). ^1H NMR ($CDCl_3$) δ: 1.97 (s, 3H, Me), 3.89 and 3.93 (2s, 6H, 2 CO_2Me), 7.50 (br s, 4H, C_6H_4), 7.82 (s, 1H, NH). ^{13}C δ: 23.45 (Me), 52.96 and 54.39 (CO_2Me), 53.77 (NH-C-CN), 116.85 (CN), 128.13; 129.17; 130.38; 130.44; 132.13 and 135.48 (C_6H_4), 167.10 (CO_2Me), 167.33 (CO-NH), 168.66 (CO_2Me). IR (KBr) cm^{-1}: **8a** 3200 (NH), 1759 (C=O ester), 1746 (C=O OMCB), 1646 (C=O amide I) and 1539 NH amide II). **8b** 3200 (NH), 1758

(C=O ester), 1746 (C=O OMCB), 1646 (C=O amide I) and 1539 NH amide II). MS: m/e (I%): 290 (2), 259 (2), 231 (8), 214 (5), 199 (19), 172 (23), 163 (100).

2-Cyano-2-methoxy-2-*o*-methoxycarbonylbenzamido methyl ethanoate 9a (S): Only one pure enantiomer was obtained from the corresponding pure diastereoisomer **4c** (2S-2'S). White crystals (MeOH), mp = 68-69°C (mp = 134-135°C for the racemate[1]). Yield = 80%. $[\alpha]_D$ = -17 (c = 1; EtOH). ^{1}H NMR ($CDCl_3$) δ: 3.66 (s, 3H, OMe), 3.89 and 3.98 (2s, 6H, 2 CO_2Me), 7.56 (br s, 4H, C_6H_4), 7.86 (s, 1H, NH). IR (KBr) cm^{-1}: 3250 (NH), 1760, 1710 (C=O esters), 1670 (C=O amide I), 1525 (NH amide II). MS: m/e (I%): 280 (5), 248 (6), 215 (5), 190 (8), 174 (10), 163 (100).

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