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Enantioselective Syntheses of (*R*)-3-Phenyl GABA, (*R*)-Baclofen and 4-Arylpyrrolidin-2-ones

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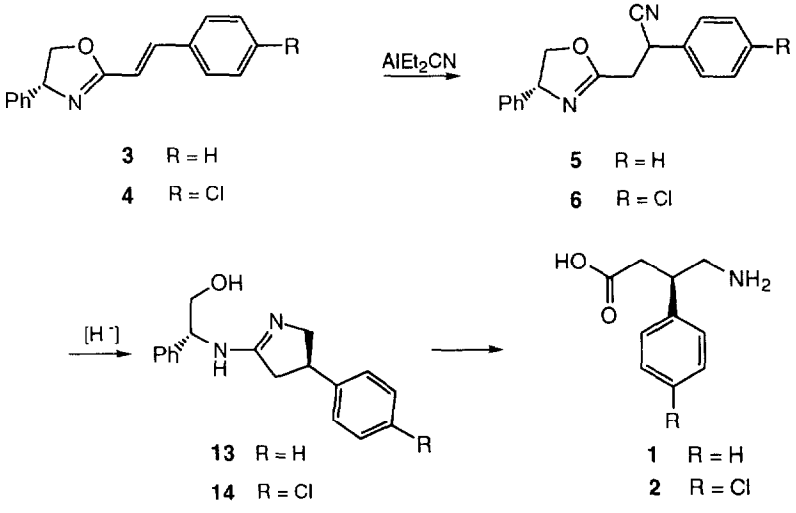
Abstract : Enantioselective synthesis of (R)-4-amino-3-phenylbutyric acid and (R)-baclofen has been achieved through a diastereoselective conjugate addition of cyanide to enantiomerically pure 2-(2-arylethenyl)oxazolines, followed by chemoselective reduction into cyclic amidines. Copyright © 1996 Elsevier Science Ltd

β-substituted GABA derivatives,[1] particularly 4-amino-3-phenylbutyric acid **1**[2] and 4-amino-3-(*p*-chlorophenyl) butyric acid (baclofen) **2**,[3] play an important role in several nervous system functions. The biological activity of these two compounds has been related to their (*R*) enantiomers, and (*R*)-baclofen **2** is known to be an useful selective agonist of the $GABA_B$ receptor. However, the resolution of the corresponding racemates involves some tedious steps[2] and only a few enantioselective syntheses have been achieved.[4-7]

A new strategy was studied, starting from α,β-unsaturated oxazolines **3** and **4** derived from (*R*)-phenyl glycinol : this involved their stereoselective hydrocyanation with $AlEt_2CN$[8] followed by chemoselective reduction of the nitrile function and subsequent hydrolysis as depicted in Scheme 1.



3 R = H
4 R = Cl
5 R = H
6 R = Cl
13 R = H
14 R = Cl
1 R = H
2 R = Cl

Scheme 1

The oxazoline **4** was obtained in 87% yield from (*R*)-phenylglycinol[9] through (2*R*)-2-(*N*-*p*-chlorocinnamoyl)amino-2-phenylethanol (100% yield), as previously described for the preparation of **3**.[10,11]

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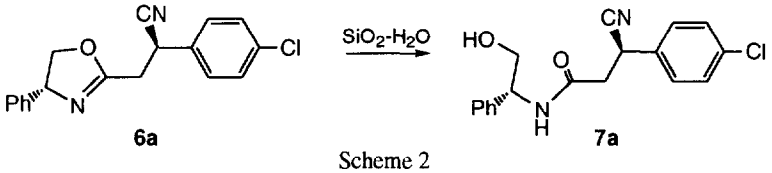
Both oxazolines **3** and **4** gave closely related results in the hydrocyanation reactions with $AlEt_2CN$ in dichloromethane. Electronic factors due to the presence of the aryl group on the double bond could explain that the conjugate addition proceeded slowly at room temperature. The conversion of **3** and **4** was incomplete after 48 h and the 2-(2-aryl-2-cyanoethyl)oxazolines **5** and **6** were isolated in the range of 40-50% yield, the diastereoselectivity, evaluated by ^1H NMR, being *ca* 50% of the required 2'*R* configuration. The formation of some bis-oxazolines has been observed as by-products resulting from self conjugate addition, particularly when the reactions were performed on a large scale.[10,11] This disadvantage could be avoided by adding powdered molecular sieves to the reaction mixture. The yield of **5** was improved to 65% but the diastereoselectivity decreased to 26%.

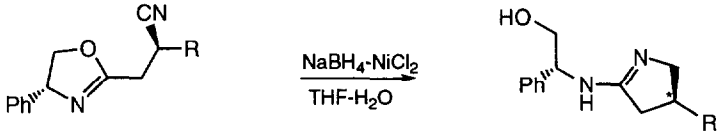
The two diastereoisomers of **5** and **6** could be separated by flash chromatography on silicagel, without epimerisation of the newly created asymmetric center and this result was noteworthy owing to the acidity of the α-cyanobenzylic proton. Some hydrolysis of the oxazolines was possible with prolonged contact with silicagel, giving rise to small amounts of the corresponding amides **7** (IR : ν = 1678 cm^{-1}, NC=O). The cleavage of the oxazoline ring however proceeded with retention of the configuration at the α–cyano carbon (Scheme 2, for example).



6a **7a**

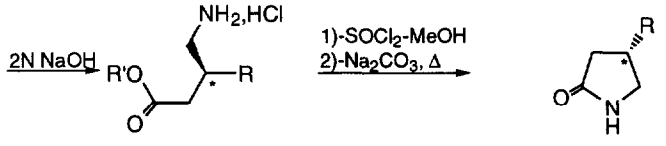
Scheme 2

Selective reduction of (4*R*)-2-(2-cyanopropyl)-4-phenyl-4,5-dihydrooxazole **8** with $LiAlH_4$ led to amidines **9** in 99% yield,[11,12] but the attempts to extend this reaction to 2-(β-aryl-β-cyanoethyl)oxazolines **5** and **6** were unsatisfactory, and it was necessary to investigate other conditions (Scheme 3).



8 R = CH_3 (d.e. 48%)
5a R = Ph
6a R = *p*-ClPh

9 R = CH_3
13 R = Ph
14 R = *p*-ClPh



10 R = CH_3, R' = H → **11** R' = CH_3
1, HCl R = Ph, R' = H → **15** R' = CH_3
2, HCl R = *p*-ClPh, R' = H → **16** R' = CH_3

12 R = CH_3
17 R = Ph
18 R = *p*-ClPh

Scheme 3

The use of sodium borohydride in the presence of several metal chlorides to reduce nitriles into the corresponding primary amines is a well documented method,[13-17] but the system $NaBH_4$-$CoCl_2$[14] was not found to be reactive enough to efficiently reduce the nitriles **5**.[11] The reaction with $NaBH_4$-$NiCl_2$[16], in the experimental conditions used to reduce aromatic nitro groups[18] was more efficient but some epimerisation was observed in methanol. The use of a mixture THF-H_2O 2 : 1 as solvent gave better results and allowed the reduction of the major (2'*R*, 4*R*)-2-(2-aryl-2-cyanoethyl)-4-phenyl-4,5-dihydrooxazoles **5a** and **6a** into the amidines **13** and **14** in nearly quantitative yields. The crude reduction products contained only traces of the corresponding primary alcohols (ex : 2-[(2-*p*-chlorophenyl-3-hydroxy)propyl]-4-phenyl-4,5-dihydrooxazole from **6a**) as the sole by-products formed *via* partial reduction of the nitrile function, and they could be used advantageously in the next step without purification. After chromatography on silicagel, the amidines **13** and **14** were isolated respectively in 86% and 80% yield. We observed no hydrogenolysis of *p*-chloro substituent of the phenyl group[19] in the reduction of major diastereomer **6a**, as seen in some cases of catalytic reductive hydrogenation of cyano groups.[20] The compounds **13** and **14** were less reactive than **9** towards acid hydrolysis (6N HCl at reflux) and alkaline conditions were preferred for this purpose.[21] Therefore, the amidines **13** and **14** were treated with 2N NaOH-EtOH 2.5 : 1 to afford quantitatively 4-amino-3-arylbutyric acid sodium salts. The aminoacids **1** and **2** were obtained in excellent yields after acidification and ion-exchange resin column. Thus, (3*R*)-4-amino-3-phenylbutyric acid **1** and (*R*)-baclofen **2** were synthesized from the 2-(2-aryl-2-cyanoethyl)-4-phenyl-4,5-dihydrooxazoles **5a** and **6a** in 94% and 96% yield respectively.

The hydrochlorides of aminoacids **1, 2** and **10** were converted into their methyl ester hydrochlorides by treatment with thionylchloride in anhydrous methanol. 4-Methylpyrrolidin-2-one **12**[22] was directly obtained by basification of methyl 4-amino-3-methylbutyrate hydrochloride **11**. In the same conditions, the cyclization of the aminoesters **15** and **16** to lactams was incomplete and simple heating of their dilute solution in toluene in the presence of Et_3N (2-4%) afforded the corresponding (*R*)-4-arylpyrrolidin-2-ones **17** (68%)[23] and **18** (64%)[4]. The $[\alpha]_D$ value of **17** and **18** demonstrated the absence of epimerisation during the reduction of **5a** and **6a** and during the subsequent steps.

Thus, the synthesis of (*R*)-β-phenyl GABA **1** and (*R*)-baclofen **2** has been achieved following a new and efficient strategy. This work constitutes a formal enantioselective synthesis of the corresponding 3-arylpyrrolidines and analogues of pharmacological interest.[23,24]

EXPERIMENTAL SECTION

Melting points were taken on a microscope Leitz (unless otherwise indicated). Optical rotations were measured on a Perkin-Elmer 241 ; the concentrations in $CHCl_3$ solution (unless otherwise indicated) were given in g/100 mL. IR spectra (ν cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H NMR spectra were obtained ($CDCl_3$, Me_4Si, δ = 0 ppm) from Bruker AC 200, AC250, AM300 or AM400 ; coupling constants *J* values are given in Hertz (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets and multiplet respectively). ^{13}C NMR spectra were recorded on AC 200 (50.0 MHz), AC250 (62.5 MHz) or AM300 (75.0 MHz). Mass spectra and high resolution mass spectra (m/z) were respectively measured on an AEI MS50 and on a Kratos MS80 spectrometer . Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that the organic layer was dried over magnesium sulfate, filtered and evaporated under reduced pressure.

(2*R*)-2-(*N*-*p*-chlorocinnamoyl)amino-2-phenylethanol.

Cinnamoyl chloride (3.20 g, 15.7 mmol) was added dropwise to a vigorously stirred mixture of (*R*)-phenylglycinol (1.80 g, 13.1 mmol) in CH_2Cl_2 (63 mL) and Na_2CO_3 (1.70 g, 15.7 mmol) in water (32 mL). The reaction was stirred at room temperature (r.t.) until completion, 2N NaOH (40 mL) and MeOH (40 mL) were then added. The mixture was stirred for 10 minutes at r.t. and extracted with CH_2Cl_2 (3 x 80 mL). The amide obtained after usual workup (4.0 g, 100%) was crystallized from dichloromethane as white crystals : mp : 160-161°C. $[\alpha]_D^{20}$ = + 40 (c = 0.9). IR : 3422, 1669, 1629, 1609, 1503. ^{1}H NMR (250 MHz, DMSO-d_6) : 8.70 (d, 1H, *J* = 8, NH), 7.70 (2H, H-Ar), 7.54 (d, 1H, *J* = 16, HC=), 7.47 (m, 7H, H-Ar), 6.95 (d, 1H, *J* = 16, HC=), 5.15 (2m, 2H, H-2, OH), 3.78 (d, 2H, *J* = 6, H-1). ^{13}C NMR (62.5 MHz, DMSO-d_6) : 164.4 (CO), 141.0 (qC, Ar), 137.3 (HC=), 133.9, 133.8 (qC, Ar), 129.0, 128.9, 128.0, 126.9 (CH, Ar), 123.2 (HC=), 64.6 (C-1), 55.1 (C-2). (CI)MS : 304 $(M + H)^+$, 302 $(M + H)^+$. Anal. calcd for $C_{17}H_{16}ClNO_2$: C, 67.66; H, 5.34; N, 4.64 ; found : C, 67.25, H, 5.36; N, 4.46.

(4*R*)-2-[(*E*)-2-(*p*-chlorophenyl)ethenyl]-4-phenyl-4,5-dihydrooxazole 4.

$POCl_3$ (9.3 mL, 103 mmol) was slowly added to a stirred mixture of (2*R*)-2-(*N*-*p*-chlorocinnamoyl)amino-2-phenylethanol (3.1 g, 10.3 mmol) in anhydrous toluene (30 mL) at room temperature under argon. Following completion of the reaction, solvent and excess reagent were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL), an aqueous solution of Na_2CO_3 (10% w/v, 40 mL) was then added and the mixture was stirred for 0.5 h. After extraction with CH_2Cl_2 the crude oxazoline **4** was obtained (2.9 g, 100%) and crystallized from Et_2O to give white crystals (2.53 g, 87%) : mp : 107-108°C. $[\alpha]_D^{24}$ = + 79 (c = 0.98). IR : 2982, 1656, 1630, 1609, 1593, 1496, 1456, 1410, 1364. ^{1}H NMR (300 MHz) : 7.27 (m, 10H, 9 x H-Ar, H-2'), 6.59 (d, 1H, *J* = 16, H-1'), 5.21 (dd, 1H, *J* = 10, *J'* = 8, H-4), 4.60 (dd, 1H, *J* = 8, *J'* = 10, Ha-5), 4.09 (dd, 1H, *J* = *J'* = 8, Hb-5). ^{13}C NMR (75.0 MHz) : 164.26 (C-2), 142.23 (qC, Ar), 139.18 (HC=), 135.50 (qC, Ar), 129.18, 128.74, 127.69, 126.69 (CH, Ar), 115.73 (HC=), 74.49 (C-5), 70.12 (C-4). MS : 285 ($M^{+\cdot}$), 284, 283 ($M^{+\cdot}$), 282 (100%), 253, 252, 218, 165, 91, 89. Anal. calcd for $C_{17}H_{14}ClNO$: C, 71.95 ; H, 4.97 ; N, 4.94 ; found : C, 71.87 ; H, 5.18 ; N, 4.97.

(4*R*)-2-[(2-cyano-2-phenyl)ethyl]-4-phenyl-4,5-dihydrooxazoles 5.

method A : To a stirred solution of (4*R*)-4-phenyl-2-[(*E*)-2-phenylethenyl]-4,5-dihydrooxazole **3** (431 mg, 1.73 mmol) in anhydrous CH_2Cl_2 (3.46 mL) at -30°C was added Et_2AlCN (1M in toluene, 2.6 mL) under an argon atmosphere. The mixture was allowed to warm and was stirred at r.t. for 24 h. Et_2AlCN (1M, 2.6 mL) was added and the same addition was repeated after 24h. After being stirred for additional 64 h, an aqueous solution of Na_2CO_3 (10% w/v, 10 mL) was added to the reaction. The mixture was extracted with CH_2Cl_2. The residue obtained after usual workup was rapidly chromatographed on silica gel (eluent : dichloromethane-MeOH 98 : 2) to afford unreacted oxazoline **3** (179 mg, 33%) and nitriles **5** as white crystals (229 mg, 48%). Diastereomers **5a** : **5b** = 76 : 24 (d.e. 52%).

method B : Anhydrous CH_2Cl_2 (4.0 mL) was added to a mixture of oxazoline **3** (494 mg, 1.98 mmol) and dry powdered 3Å molecular sieves (566 mg). The mixture was stirred at -30°C and Et_2AlCN (1M in toluene, 3.0 mL) was added under argon. After 2 h, the cooling bath was removed and the mixture was stirred at r.t. for an addditional 72 h. The same workup as described for method A afforded starting oxazoline (23% yield) and nitriles **5** obtained in 65% yield. Diastereomers **5a** : **5b** = 63 : 37 (d.e. 26%).

Careful chromatography of **5** on silica gel (eluent : pentane-ether 1 : 1) allowed isolation of major diastereomer

(2'*R*, 4*R*) **5a** as white crystals (d.e. > 97 %) : mp : 120-1°C (Et_2O). $[\alpha]_D^{24}$ = + 37 (c = 1.08). IR : 3000, 2250, 1669, 1600, 1494, 1475, 1456. ^1H NMR (300 MHz) : 7.46 (m, 5H, H-Ar), 7.33 (m, 3H, H-Ar), 7.12 (m, 2H, H-Ar), 5.22 (dd, 1H, $J_{4,5a}$ = 10, $J_{4,5b}$ = 8.5, H-4), 4.65 (dd, 1H, $J_{5a,4}$ = 10, $J_{5a,5b}$ = 8.5, Ha-5), 4.41 (dd, 1H, $J_{2',1'a}$ = 8.5, $J_{2',1'b}$ = 7, H-2'), 4.08 (dd, 1H, $J_{5b,5a}$ = $J_{5b,4}$ = 8.5, Hb-5), 3.10 (ddd, 1H, $J_{1'a,1'b}$ = 15.5, $J_{1'a,2'}$ = 8.5, $J_{1'a,4}$ = 1.2, Ha-1'), 2.95 (ddd, 1H, $J_{1'b,1'a}$ = 15.5, $J_{1'b,2'}$ = 7, $J_{1'b,4}$ = 1.3, Hb-1'). ^{13}C NMR (75.0 MHz) : 164.19 (C-2), 141.78, 134.64 (qC, Ar), 129.41, 128.81, 128.69, 127.72, 127.58, 126.58 (CH, Ar), 120.09 (CN), 75.33 (C-5), 69.76 (C-4), 34.46 (C-2'), 34.28 (C-1'). MS : 276 ($M^{+\cdot}$), 130, 103 (100%), 91, 77. HRMS : ($M^{+\cdot}$) calcd for $C_{18}H_{16}N_2O$: 276.1263 ; found : 276.1253.

Minor diastereomer (2'*S*, 4*R*) **5b** was purified by preparative TLC (eluent : pentane-ether 4 : 6) as white crystals, d.e. 95%). mp : 118-120°C $[\alpha]_D^{26}$ = + 37 (c = 0.77). IR : 3000, 2247, 1669, 1603, 1496, 1450. ^1H NMR (300 MHz) : 7.42 (m, 5H, H-Ar), 7.32 (m, 3H, H-Ar), 7.15 (m, 2H, H-Ar), 5.21 (br dd, 1H, $J_{4,5a}$ = 10, $J_{4,5b}$= 8, H-4), 4.67 (dd, 1H, $J_{5a,4}$ = 10, $J_{5a,5b}$ = 8, Ha-5), 4.42 (dd, 1H, $J_{2',1'a}$ = 9, $J_{2',1'b}$ = 6.5, H-2'), 4.11 (dd, 1H, $J_{5b,5a}$ = $J_{5b,4}$ = 8, Hb-5), 3.10 (ddd, 1H, $J_{1'a,1'b}$ = 16, $J_{1'a,2'}$ = 9, $J_{1'a,4}$ = 1, Ha-1'), 2.93 (ddd, 1H, $J_{1'b,1'a}$ = 16, $J_{1'b,2'}$ = 6.5, $J_{1'b,4}$ = 1, Hb-1'). ^{13}C NMR (75.0 MHz) : 164.21 (C-2), 141.72, 134.76 (qC, Ar), 129.40, 129.17, 128.86, 128.14, 127.83, 127.09, 125.51 (CH, Ar), 120.07 (CN), 75.29 (C-5), 69.89 (C-4), 34.43 (C-2'), 34.22 (C-1'). MS : 276 ($M^{+\cdot}$, 100%), 130, 103, 91, 77. HRMS : ($M^{+\cdot}$) calcd for $C_{18}H_{16}N_2O$: 276.1263 ; found : 276.1249.

(4*R*)-2-[(2-*p*-chlorophenyl-2-cyano)ethyl]-4-phenyl-4,5-dihydrooxazoles 6.

Method A : To a stirred solution of (4*R*)-2-[(*E*)-2-(*p*-chlorophenyl)ethenyl]-4-phenyl-4,5-dihydrooxazole **4** (131 mg, 0.46 mmol) in anhydrous CH_2Cl_2 (0.92 mL) at -30°C was added Et_2AlCN (1M in toluene, 0.70mL) under argon. The mixture was allowed to reach r.t. and was stirred for 22 h before a second addition of Et_2AlCN (1M, 0.70 mL). After being stirred for additional 24 h, CH_2Cl_2 (10 mL) and an aqueous solution of Na_2CO_3 (10% w/v, 5 mL) were successively added to the reaction mixture followed by extraction with CH_2Cl_2. The residue obtained after usual workup (145 mg) was rapidly chromatographed on silica gel (eluent : CH_2Cl_2-MeOH 99 : 1) to afford unreacted oxazoline **4** (55.0 mg, 42%), nitriles **6** as white crystals (56.0 mg, 39%) and more polar products (22 mg). Diastereomers **6a** : **6b** = 74 : 26 (d.e. 48%).

Method B : Anhydrous CH_2Cl_2 (3.6 mL) was added to a mixture of oxazoline **4** (514 mg, 1.81 mmol) and dry powdered 3Å molecular sieves (554 mg). The mixture was stirred at -30°C and Et_2AlCN (1M in toluene, 2.7 mL) was added under argon. After 1 h, the cooling bath was removed and the mixture was stirred at r.t. for an additional 74 h. After the same workup as described in the method A, starting oxazoline was recovered in 40% yield and nitriles **6** were obtained in 55% yield. Diastereomers **6a** : **6b** = 63 : 37 (d.e. 26%).

Chromatography of **6** on silica gel (eluent : pentane-ether 1 : 1) allowed separation of diastereomers. Major diastereomer (2'*R*, 4*R*) **6a** (white crystals) : mp : 133-5°C (Et_2O). $[\alpha]_D^{22}$ = + 13 (c = 0.42). IR : 3000, 2950, 2248, 1673, 1603, 1494. ^1H NMR (300 MHz) : 7.39 and 7.33 (m, 7H, H-Ar), 7.07 (dd, 2H, J = 7.5, J' = 1, H-Ar), 5.21 (dd, 1H, $J_{4,5a}$ = 10, $J_{4,5b}$ = 8, H-4), 4.65 (dd, 1H, $J_{5a,4}$ = 10, $J_{5a,5b}$ = 8, Ha-5), 4.37 (dd, 1H, $J_{2',1'a}$ = 8, $J_{2',1'b}$ = 7, H-2'), 4.07 (dd, 1H, $J_{5b,5a}$= $J_{5b,4}$ = 8, Hb-5), 3.08 (ddd, 1H, $J_{1'a,1'b}$ = 16, $J_{1'a,2'}$ = 8, $J_{1'a,4}$ ~ 1, Ha-1'), 2.95 (ddd, 1H, $J_{1'b,1'a}$ = 16, $J_{1'b,2'}$ = 7, $J_{1'b,4}$ ~ 1, Hb-1'). ^{13}C NMR (75.0 MHz) : 163.86 (C-2), 141.59, 134.80, 133.00 (qC, Ar), 129.59 129.05, 128.82, 128.49, 127.79, 126.47 (CH, Ar), 119.68 (CN), 75.34 (C-5), 69.62 (C-4), 34.04 (C-1'), 33.77 (C-2'). MS : 312, 310 ($M^{+\cdot}$, 100%), 150, 130, 120, 103, 91, 89, 77. HRMS ($M^{+\cdot}$) calcd for $C_{18}H_{15}{}^{37}ClN_2O$: 312.0844, found : 312.0838 ; for $C_{18}H_{15}{}^{35}ClN_2O$: 310.0872, found : 310.0881.

Minor diastereomer (2'*S*, 4*R*) **6b** (white crystals, d.e. 97%) : mp : 136-7°C (Et_2O). $[\alpha]_D^{27}$ = + 55 (c = 0.60). IR : 3000, 2250, 1669, 1494. ^1H NMR (300 MHz) : 7.39 and 7.33 (m, 7H, H-Ar), 7.10 (dd, 2H, J = 7.5, J' = 1.5, H-Ar), 5.21 (dd, 1H, $J_{4,5a}$ = 10, $J_{4,5b}$ = 8, H-4), 4.66 (dd, 1H, $J_{5a,4}$ = 10, $J_{5a,5b}$ = 8, Ha-5), 4.39 (dd, 1H, $J_{2',1'a}$ = 8, $J_{2',1'b}$ = 7, H-2'), 4.12 (dd, 1H, $J_{5b,5a}$ = $J_{5b,4}$ = 8, Hb-5), 3.08 (ddd, 1H, $J_{1'a,1'b}$ = 16, $J_{1'a,2'}$ = 8, $J_{1'a,4}$ = 1, Ha-1'), 2.94 (ddd, 1H, $J_{1'a,1'b}$ = 16, $J_{1'a,2'}$ = 7, $J_{1'b,4}$ = 1, Hb-1'). ^{13}C NMR (75.0 MHz) : 163.82 (C-2), 141.60, 134.80, 133.10 (qC, Ar), 129.64, 129.05, 128.87, 127.88, 126.88 (CH, Ar), 119.67 (CN), 75.25 (C-5), 69.83 (C-4), 33.97 (C-1'), 33.74 (C-2'). MS : 312, 310 ($M^{+\cdot}$, 100%), 150, 130, 120, 103. HRMS ($M^{+\cdot}$) calcd for $C_{18}H_{15}{}^{37}ClN_2O$: 312.0844 ; found : 312.0852 ; for $C_{18}H_{15}{}^{35}ClN_2O$: 310.0872; found : 310.0860.

(2'*R*, 3*R*)-2-[(*N*-3-*p*-chlorophenyl-3-cyano)propanoyl)amino]-2-phenylethanol 7a.

Silica gel (230-400 mesh, 10 g) was added to a solution of the nitrile **6a** (40.0 mg, 0.129 mmol) in CH_2Cl_2 (10 mL), pentane (4 mL) and Et_2O (6 mL). The mixture was stirred at room temperature for 42 h, filtered, and the silica gel was washed with CH_2Cl_2-MeOH 9 : 1. The solvents were removed under reduced pressure and the residue was purified by preparative TLC (eluent : CH_2Cl_2-MeOH 95 : 5) to afford the amide **7a** as white crystals (40.0 mg, 94%). mp : 110-112°C . $[\alpha]_D^{25}$ = - 31 (c = 0.62). IR : 3429, 3027, 2928, 2249 (weak), 1678, 1511, 1494. ^1H NMR (200 MHz) : 7.4-7.2 (m, 9H, H-Ar), 6.29 (br d, J = 6.7, NH), 5.02 (m, 1H, H-2), 4.40 (dd, 1H, $J \sim J'$ = 7.2, H-3'), 3.80 (2dd, 2H, H_2-1), 2.92 (dd, 1H, J = 14.8, J' = 7.2, Ha-2'), 2.73 (dd, 1H, J = 14.8, J' = 7.5, Hb-2'), 2.35 (br s, exch., OH). ^{13}C NMR (50.0 MHz) : 168.1 (C-1'), 138.3, 134.7, 133.2 (qC, Ar), 129.5, 129.0, 128.9, 128.1, 126.7 (CH, Ar), 120.1 (CN), 65.8 (C-1), 55.8 (C-2), 42.0 (C-2'), 33.0 (C-3'). (CI)MS : 331, 329 [(M + H)$^+$, 100%], 295. Anal. calcd for $C_{18}H_{17}ClN_2O_2$: C, 65.75 ; H, 5.21 ; N, 8.52 ; found : C, 65.64 ; H, 5.49 ; N, 8.32. The same protocol applied to a mixture of diastereomers **6** (d.e. 26%) led to the corresponding amides **7** without change of the diastereomeric excess (evaluated by ^1H NMR).

(4*R*)-2-(2-cyanopropyl)-4-phenyl-4,5-dihydrooxazoles 8.

Et_2AlCN (1M in toluene, 3.67 mL) was added dropwise under argon to a stirred solution of oxazoline (4*R*)-4-phenyl-2-(*E*)-propenyl-4,5-dihydrooxazole (457 mg, 2.44 mmol) in anhydrous toluene (4.9 mL) at -30°C. The cooling bath was removed and the mixture was stirred at r.t. for 48 h. Dichloromethane (20 mL) and an aqueous solution of Na_2CO_3 (10% w/v, 10 mL) were successively added and the crude product was extracted with CH_2Cl_2. The residue obtained after usual workup was rapidly purified by chromatography on silica gel (eluent : CH_2Cl_2-MeOH 98 : 2) to afford unreacted α,β-unsaturated oxazoline (13.0 mg, 3%), 2-β-cyanopropyloxazolines **8** (oil, 316 mg, 60%, d.e. 48%) and more polar products (63 mg). **8** : IR : 2244, 1667, 1500, 1450. ^1H NMR (400 MHz) : 7.37 (m, 2H, H-Ar), 7.27 (m, 3H, H-Ar), 5.25 (dd, 1H, $J_{4,5a}$ = 10, $J_{4,5b}$ = 8.5, H-4), 4.70 (dd, 1H, $J_{5a,5b}$= 8.5, $J'_{5a,4}$ = 10, Ha-5), 4.13 (dd, $J_{5b,5a}$ = $J_{5b,4}$ = 8.5, Hb-5), (4.14, minor diast.), 3.21 (m, $J_{2',1'a}$ = $J_{2',1'b}$ = 8, H-2'), (3.19, minor diast.), 2.79 (ddd, 1H, $J_{1'a,1'b}$ = 16, $J_{1'a,2'}$ = 8, $J_{1'a,4}$ = 1.2, Ha-1'), 2.61 (ddd, 1H, $J_{1'b,1'a}$ = 16, $J_{1'b,2'}$ = 8, $J_{1'b,4}$ = 1.5, Hb-1'), 1.46 (d, J = 8, CH_3), (1.47, minor diast.). ^{13}C NMR (62.5 MHz) : 164.7 (C-2), 141.8 (qC, Ar), 128.8, 127.7, 126.5 (CH, Ar), 121.9 (CN), 75.1 (C-5), 69.7 (C-4), 32.4 (C-1'), 23.0 (C-2'), 17.9 (CH_3). MS : 214 ($M^{+\cdot}$), 213, 199, 186, 184, 171, 161, 130 (100%), 119, 103, 77. HRMS : ($M^{+\cdot}$) calcd for $C_{13}H_{14}N_2O$: 214.1108 ; found : 214.1106.

(2*R*)-2-(4-methylpyrrolin-2-yl)amino-2-phenylethanol 9.

$LiAlH_4$ (95 mg, 2.5 mmol) in anhydrous THF (6.6 mL) was heated under reflux for 1 h and cooled to room temperature. A solution of 2-cyanopropyloxazolines **8** (270 mg, 1.26 mmol) in THF (6.6 mL) was then added and the mixture was stirred for 5 minutes. After being cooled to 0°C, excess of hydride was removed by addition of some drops of EtOAc and saturated aqueous Na_2SO_4 solution. After being stirred for 1 h, the mixture was filtered and the solid was washed with THF. Evaporation of solvent under reduced pressure afforded the amidines **9** as a pale yellow solid (272 mg, 99%) : IR : 3435, 2970, 1696 (sh), 1636, 1509, 1460. ^1H NMR (300 MHz) : 7.33 (m, 5H, H-Ar), 4.67 (br d, 1H, J = 8, H-2), 3.89 (m, 1H, Ha-1), 3.76 (m, 2H, Hb-1, Ha-5'), 3.23, 3.14 (2dd, 1H, J = 12, J' = 6, Hb-5'), 2.63 (dd, 1H, J = 15.5, J' = 8.5, Ha-3'), 2.48 (m, 1H, H-4'), 2.11 (dd, 1H, J = 15.5, J' = 6, Hb-3'), 1.08, 1.06 (2d, J = 6.7, CH_3-4'). ^{13}C NMR (62.5 MHz) : 167.7 (C-2'), 140.3 (qC, Ar), 129.0, 127.9, 126.8 (CH, Ar), 68.5 (C-1), 62.3 (C-2), 60.2 (C-5'), 40.1 (C-3'), 31.8 (C-4'), 19.6 (CH_3). MS : 218 ($M^{+\cdot}$), 217, 201, 187 (100%), 106, 99, 91, 77. HRMS ($M^{+\cdot}$) calcd for $C_{13}H_{18}N_2O$: 218.1419 ; found : 218.1418.

4-Methylpyrrolidin-2-one 12.

6N HCl (40 mL) was added to the amidines **9** (265 mg, 1.21 mmol, d.e. 48%). The mixture was stirred for 15 min at room temperature under argon and heated under reflux for 72 h before evaporation to dryness. To a stirred solution of the crude aminoacid hydrochloride **10** in anhydrous MeOH (11 mL) at -20°C, was added $SOCl_2$ (1.0 mL) and the mixture was stirred at room temperature for 24 h. After evaporation of solvent and excess reagent under reduced pressure, the crude amino methyl ester hydrochloride **11** was dissolved in a mixture of CH_2Cl_2-Na_2CO_3 5%, stirred for 20 min. at r.t. and extracted 4 times with CH_2Cl_2. Purification of the crude product by preparative TLC (eluent : Et_2O) afforded the pyrrolidinone **12** (69 mg, 58%). $[\alpha]_D^{30}$ = -10 (c = 1.18) e.e. 50%, lit. (*S*) enantiomer : $[\alpha]_D$ = -20 (c = 0.6). Comparison of IR, ^1H NMR, ^{13}C NMR and MS data.[22] ^1H NMR (400 MHz) : 5.74 (m, 1H, NH), 3.51 (dd, 1H, J = J' = 9, Ha-5), 2.98 (dd, 1H, J = 9, J' = 6, Hb-5), 2.58 (m, 1H, H-4), 2.46 (dd, 1H, J = 16.5, J' = 8.5, Ha-3), 1.95 (dd, 1H, J = 16.5, J' = 7, Hb-3), 1.15 (d, 3H, J = 7, CH_3). ^{13}C NMR (75.0 MHz) : 178.92 (C-2), 49.73 (C-5), 38.59 (C-3), 29.45 (C-4), 19.66 (CH_3).

(2*R*,4'*R*)-2-phenyl-2-[(4-phenylpyrrolin-2-yl)amino]ethanol 13.

To a stirred solution of (2'*R*, 4*R*)-2-[(2-cyano-2-phenyl)ethyl]-4-phenyl-4,5-dihydrooxazole **5a** (d.e. 96%, 369.7 mg, 1.34 mmol) in a mixture THF-H_2O 2 : 1 (25.0 mL) was added $NiCl_2$. $6H_2O$ (634. mg, 2.67 mmol) at room temperature. After being stirred for 5 minutes, $NaBH_4$ (220 mg, 5.81 mmol) was added in 8 portions over 40 minutes and the black reaction mixture was stirred for 20 min. before the addition of NH_4OH (28%, 2.0 mL) and a mixture CH_2Cl_2-MeOH-28% NH_4OH 8 : 2 : 0.2. The crude amidine **13** (446.4 mg) was obtained as a pale yellow foam after filtration on a short column of silica gel. It could be used in the next step without purification or purified in 86% yield by preparative TLC (eluent : CH_2Cl_2-MeOH-28% NH_4OH 9 : 1 : 0.2) as a white foam. $[\alpha]_D^{24}$ = - 85 (c = 0.97). IR : 3438, 3181, 2950, 1682, 1638, 1604 (weak), 1509, 1494. ^1H NMR (250 MHz, $CDCl_3$, D_2O-NaOD) : 7.4-7.15 (10H, Ar-H), 4.80 (m, 1H, H_2), 4.09 (m, 1H, Ha-5'), 3.93 (dd, 1H, J = 11.4, J' = 7.8, Ha-1), 3.81 (dd, 1H, J = 11.4, J' = 2.7, Hb-1), 3.62 (m, 2H, H-4', Hb-5'), 2.93 (dd, 1H, J = 15, J' = 9, Ha-3'), 2.62 (dd, 1H, J = 15, J' = 7.5, Hb-3'). ^{13}C NMR (62.5 MHz) : 167.0 (C-2'), 142.8 (qC, Ar), 139.6 (qC, Ar), 128.9, 128.8, 127.9, 126.8 (CH, Ar), 67.5 (C-1), 61.6 (C-2), 60.4 (C-5'), 42.6 (C-4'), 40.2 (C-3'). (CI) HRMS $(M + H)^+$ calcd for $C_{18}H_{21}N_2O$: 281.1654 ; found : 281.1606;

for $C_{18}H_{20}N_2O$: 280.1576 ; found : 280.1542.

(2*R*, 4'*R*)-2-[(4-*p*-chlorophenylpyrrolin-2-yl)amino]-2-phenylethanol 14.

The (2'*R*, 4*R*)-2-[(2-*p*-chlorophenyl-2-cyano)ethyl]-4-phenyl-4,5-dihydrooxazole **6a** was reduced following the same protocol. To a solution of **6a** (215.9 mg, 0.69 mmol) in THF-H_2O 2 : 1 (14 mL) was added under stirring at room temperature, $NiCl_2$. $6H_2O$ (330.3 mg, 1.39 mmol) and $NaBH_4$ (111.5 mg, 2.95 mmol) in portions over 35 min. After being stirred for additional 25 min, the reaction mixture was treated as described above to afford the crude amidine **14** (251 mg) which could be purified by flash chromatography (eluent : CH_2Cl_2-MeOH-NH_4OH 9 : 1: 0.2) in 80% yield as a white foam : $[\alpha]_D^{22}$ = - 91 (c = 1.22). IR : 3438, 3325, 3170, 2950, 1683, 1638, 1510, 1494. ^1H NMR (250 MHz, D_2O-NaOD) : 7.34 (m), 7.25 (d, *J* = 8.5) and 7.12 (d, *J* = 8.5) : H-Ar, 4.80 (m, H-2), 4.09 (m, 1H, Ha-5'), 3.94 (dd, 1H, *J* = 11, *J'* = 7.6, Ha-1), 3.81 (dd, 1H, *J* = 11, *J'* = 2.5, Hb-1), 3.59 (m, 2H, H-4', Hb-5), 2.94 (dd, 1H, *J* = 16, *J'* = 9.8, Ha-3'), 2.55 (dd, 1H, *J* = 16, *J'* = 7.6, Hb-3'). ^{13}C NMR (62.5 MHz) : 166.6 (C-2'), 141.4, 139.5, 132.2 (qC, Ar), 128.6, 128.0, 127.7, 126.6 (CH, Ar), 67.1 (C-1), 61.1 (C-2), 60.5 (C-5'), 41.9 (C-4'), 40.0 (C-3'). (FAB) MS : 317, 315 (MH^+, 100%), 281, 195. Anal. calcd for $C_{18}H_{19}ClN_2O.H_2O$: C, 64.95 ; H, 6.36 ; N, 8.42 ; found : C, 65.17 ; H, 6.13 ; N, 8.31.

A by-product was also isolated in *ca* 2% and was identified as 2-[(2-*p*-chlorophenyl-3-hydroxy)propyl]-4-phenyl-4,5-dihydrooxazole : IR : 3294, 2981, 1663, 1494. ^1H NMR (250 MHz) : 7.26 (m, 7H, H-Ar), 6.85 (2H, H-Ar), 5.09 (dd, 1H, *J* = 10, *J'* = 8.4, H-4), 4.56 (dd, 1H, *J* = 8.4, *J'* = 10, Ha-5), 3.96 (dd, 1H, *J* = *J'* = 8.4, Hb-5), 3.83 (2H, H_2-3'), 3.34 (m, 1H, H-2'), 2.88 (dd, 1H, *J* = 15, *J'* = 7, Ha-1'), 2.74 (dd, 1H, *J* = 15, *J'* = 8, Hb-1'). ^{13}C NMR (62.5 MHz) : 167.6 (C-2'), 142.0, 139.8, 133.0 (qC, Ar), 129.5, 129.0, 128.8, 127.7, 126.5 (CH, Ar), 75.0 (C-5), 69.5 (C-4), 67.1 (C-3'), 44.8 (C-2'), 31.7 (C-1'). (CI)MS : 318 $(M + H)^+$, 316 [$(M + H)^+$, 100%]. (CI)HRMS : $(M + H)^+$ calcd for $C_{18}H_{19}{}^{37}ClNO_2$: 318.1075 ; found : 318.1079 ; for $C_{18}H_{19}{}^{35}ClNO_2$: 316.1104 ; found : 316.1102.

(3*R*)-4-amino-3-phenylbutyric acid 1.

A mixture of the crude amidine **13** (215.5 mg, obtained from 0.65 mmol of 2–cyanoalkyloxazoline **5a**) in 2N NaOH (10 mL) and EtOH (95%, 4 mL) was heated at 100°C under argon for 14 h. Ethanol was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 to remove the (*R*)-phenylglycinol (100%). The aqueous phase was acidified with 6N HCl and extracted with CH_2Cl_2 before filtration and purification by ion-exchange resin [Amberlite IR-120 (H^+), eluent : 10% aqueous NH_4OH] to afford the aminoacid as a white solid (109 mg, 94%) : mp : 193°C (Kofler apparatus, subl.), lit. : 193-194°C (subl.). $[\alpha]_D^{23}$ = - 5.8 (c = 0.72, H_2O), e.e. 97% ; lit. $[\alpha]_D$ = - 6 (c = 2.5, H_2O).[2] Comparison of IR (nujol) and ^1H NMR (D_2O-NaOD) data.[2] The aminoacid (96.7 mg, 0.45 mmol) was converted to its hydrochloride by addition of 2N HCl, filtration of the solution and evaporation to dryness to give the HCl salt as white crystals (107.9 mg, 93%).

(3*R*)-4-amino-3-(*p*-chlorophenyl)butyric acid [(*R*)-Baclofen] 2.

The crude amidine **14** (179 mg, 0.50 mmol) was treated as described above to afford (*R*)-phenylglycinol (100%) and (*R*)-Baclofen as a white solid (101.3 mg, 96%). Comparison of ^1H NMR (D_2O-NaOD).[6]

(*R*)-Baclofen (92.9 mg, 0.43 mmol) was converted to its hydrochloride as described for **1** and was isolated as white crystals (102.8 mg, 95%). mp : 216°C (dec.), lit. : 215°C (dec.)[3b]. $[\alpha]_D^{22}$ = -1.2 (c = 0.24, H_2O), lit. $[\alpha]_D^{25}$ = -1.3 (c = 0.2, H_2O).[7]

(*R*)-4-Phenylpyrrolidin-2-one 17.

To a solution of (3*R*)-4-amino-3-phenylbutyric acid hydrochloride (107 mg, 0.50 mmol) in anhydrous methanol (18 mL), stirred under argon at -65°C was slowly added $SOCl_2$ (2.0 mL). After being stirred for 1h, the cooling bath was removed and the mixture was stirred at room temperature for an additional 24 h. Solvent and reagent in excess were removed *in vacuo*, CH_2Cl_2 (20 mL) and aqueous Na_2CO_3 (10%, 6 mL) were added and the mixture was stirred for 0.5 h at r.t. and then extracted 4 times with CH_2Cl_2. The crude products obtained after usual workup (aminoester **15** and pyrrolidinone **17** (64.7 mg) were dissolved in a mixture of toluene (5 mL) and Et_3N (0.2 mL) and the solution was heated at 110°C for 8 h. After evaporation to dryness, the residue was purified by preparative TLC (eluent : CH_2Cl_2-MeOH 93:7) to afford (*R*)-4-phenylpyrrolidin-2-one **17** as white crystals (54.2 mg, 68%) : mp = 98-99°C, lit. : mp : 96-7°C ; $[\alpha]_D^{24}$ = -37 (c = 1.09, MeOH), lit. $[\alpha]_D^{25}$ = -37.8 (c = 0.95, MeOH).[23] IR : 3440, 3225, 3020, 1694, 1494, 1428. ^{1}H NMR (250 MHz) : 7.40-7.24 (5H, H-Ar), 5.93 (br s, 1H, NH), 3.79 (dd, 1H, $J \sim J' \sim 8.2$, Ha-5), 3.72 (m, 1H, H-4), 3.43 (dd, 1H, $J = 8.2$, $J' = 7$, Hb-5), 2.74 (dd, 1H, $J = 17$, $J' = 8.6$, Ha-3), 2.52 (dd, 1H, $J = 17$, $J' = 8.7$, Hb-3). ^{13}C NMR (62.5 MHz) : 178.1 (C-2), 142.2 (qC, Ar), 128.9, 127.1, 126.8 (CH, Ar), 49.7 (C-5), 40.3 (C-4), 38.2 (C-3).

(*R*)-4-p-chlorophenylpyrrolidin-2-one 18.

(*R*)-Baclofen hydrochloride (102.8 mg, 0.41 mmol) was treated as described above to provide the crude amino methylester **16** (68 mg, 73%). A solution of this compound in a mixture toluene (9 mL)-pyridine (1mL)-Et_3N (0.2 mL) was heated at 110°C for 40 h. After removing the solvents *in vacuo*, the pyrrolidinone **18** was purified by preparative TLC (eluent : CH_2Cl_2-MeOH 95 : 5) and obtained as a white solid (51.4 mg, 64%) : mp : 112-113.°C, lit. : mp : 112°C.[4] $[\alpha]_D^{25}$ = - 40 (c = 1.06, 99% EtOH), lit. $[\alpha]_D$ = -39 (c = 1, EtOH).[4] IR : 3440, 3225, 3010, 1694, 1496, lit. : 1697. Comparison of ^{1}H NMR and ^{13}C NMR data.[4]

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