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Synthesis of the enantiomers and *N*-protected derivatives of 3-amino-3-(4-cyanophenyl)propanoic acid

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Abstract—Racemic ethyl 3-amino-3-(4-cyanophenyl)propanoate was synthesized and the enantiomers separated through enantioselective *N*-acylation by *Candida antarctica* lipase A (CAL-A) in neat butyl butanoate. The free amino acid enantiomers were transformed to the Boc and Fmoc-protected derivatives.

1. Introduction

The design and synthesis of peptide oligomers containing nonnatural amino acids,[1–4] and of other biologically active amino acid derivatives,[5,6] is a challenge in current drug design and peptide secondary structure analysis (β-peptides and foldamers).[7]

For peptide structural studies, it is useful to incorporate amino acid scaffolds which possess easy-to-detect functional groups as internal local environment markers. One good possibility is to introduce a small, intermediately polar nitrile group, which has a characteristic vibrational stretching band in the IR spectrum, and which is sensitive to the environment. For this purpose, the use of cyano derivatives of enantiomerically pure alanine and phenylalanine has been reported recently.[8,9]

Racemic *p*-cyanophenylalanine is applied in the synthesis of aromatase inhibitors,[6] TNFα inhibitors,[10] and antifungal[11] and antiepileptogenic[12] agents. Enantiomerically pure β-amino acid derivatives of *p*-cyanophenylalanine have not yet been described in the literature. Our aim was to find an appropriate method for preparation of the enantiomers of 3-amino-3-(4-cyanophenyl)propanoic acid.

2. Results and discussion

The lipase-catalysed enantioselective acylation strategy has acquired a valued position for the preparation of highly enantiopure compounds, with the advantage that both enantiomers can be obtained. Relying on this strategy, the racemic amino acid **1** was prepared by the modified Rodionov method[13] and transformed to its ethyl ester (±)-**4** in EtOH in the presence of $SOCl_2$. The optimization of the *N*-acylation conditions for (±)-**4** with lipase A from *Candida antarctica* (CAL-A) (Table 1) was started by testing the gram-scale conditions of the previously examined kinetic resolutions of phenyl, thienyl and furyl-substituted 3-aminocarboxylates.[14,15] The reaction of (±)-**4** exhibited almost no selectivity in ethyl butanoate, which was the solvent (and the acyl donor) of choice for the gram-scale resolution of the heteroaryl-substituted analogues (Table 1, entry 5).[14] *N*-Acylation of (±)-**4** with 2,2,2-trifluoroethyl butanoate revealed solvent dependence with the reactivity decreasing in the sequence *i*-Pr_2O, Et_2O, MeCN, THF, with low to moderate enantioselectivities (entries 1–4). The highest enantioselectivity was observed for the reaction in neat butyl butanoate, although the reactivity was then moderate as compared with that observed for acylation with 2,2,2-trifluoroethyl butanoate in solvents other than THF (entry 6). An elevated substrate concentration in butyl butanoate resulted in a decreased enantioselectivity and reactivity (entry 7). It is interesting that, taking the same conditions into consideration, the

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Table 1. *N*-Acylation of (±)-**4** (0.05 M) by CAL-A (15 mg/mL) at room temperature

Entry	Acyl donor	Solvent	Time (h)	c (%)[a]	Ee_s (%)	Ee_p (%)	E[b]
1	$PrCO_2CH_2CF_3$	THF	16	16	17	92	28
2	$PrCO_2CH_2CF_3$	Et_2O	1	52	97	90	83
3	$PrCO_2CH_2CF_3$	*i*-Pr_2O	0.33	51	94	91	80
4	$PrCO_2CH_2CF_3$	MeCN	1.5	53	99	86	68
5	$PrCO_2Et$		1	18	4	19	2
6	$PrCO_2Bu$		9	50	94	95	143
7	$PrCO_2Bu$[c]		12.5	47	83	93	70

[a] $c = ee_s/(ee_s + ee_p)$.
[b] $E = \ln[(1 - ee_s)/(1 - ee_s/ee_p)]/\ln[(1 - ee_s)/(1 + ee_s/ee_p)]$.[17]
[c] 0.1 M substrate concentration.

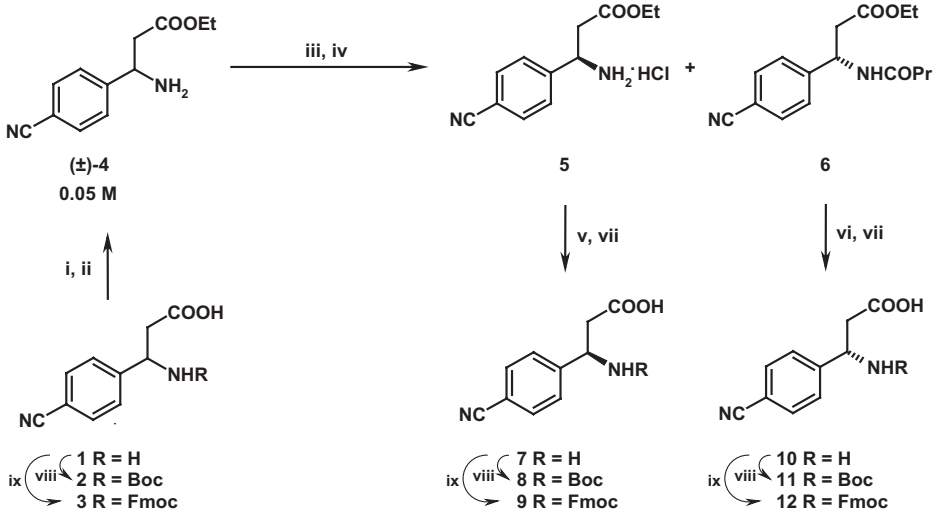
enzyme systematically displayed a lower enantioselectivity for (±)-**4** than for the heteroaryl-substituted analogues (for instance, $E = 580$ and 220 were observed for the reactions of ethyl 3-amino-3-(2-thienyl)propanoate and 3-amino-3-(2-furyl)propanoate, respectively, in neat butyl butanoate).[14] On the other hand, the enantioselectivity was higher than that for the more hydrophobic 3-phenyl-substituted analogue under the same conditions ($E = 75$, in the case of 2,2,2-trifluoroethyl butanoate as acyl donor in diisopropyl ether).[15] Amino ester (±)-**4** was finally subjected to enzymatic *N*-acylation on a gram scale under optimized conditions in neat butyl butanoate at 0.05 M substrate concentration and at 15 mg/mL of the 20% (w/w) CAL-A preparation on Celite.[16]

After the gram-scale resolution was stopped by filtering off the enzyme, the substrate was isolated as the hydrochloride salt **5**, and the product as the butanamide derivative **6**. The isolated enantiomeric compounds were subjected to acid hydrolysis. The ester group of **5** could be easily hydrolysed with 12% HCl at room temperature, while the amide bond of **6** was cleaved with 18% HCl under reflux conditions. Due to the forced conditions of hydrolysis of **6**, cyano group hydrolysis to the amide stage could also be detected. The resulting amino acid hydrochlorides were desalted either by ion-exchange chromatography or by propylene oxide to give **7** and **10** and recrystallized (Scheme 1). The use of ion-exchange resin catalysis for deacylation[18] resulted in hydrolysed product **10** in low yields, too.

For peptide synthetic purposes, we transformed enantiomers **7** and **10** to Boc (**8** and **11**) and Fmoc-protected (**9** and **12**) derivatives. The racemic counterparts of the protected amino acids, **2** and **3**, were also synthesized in parallel.

For all the products reported here, appropriate NMR and IR spectra were taken and mass spectra were recorded by means of CI-MS, except for **1**, **7** and **10**, the mass spectra of which were recorded by means of EI-MS. Physical data on the isolated enantiomerically pure compounds are included in Table 2.

The absolute configurations of the products were established on the basis of the (*S*)-selectivity of CAL-A for the previously resolved aromatic and heteroaromatic 3-amino ester analogues.[14,15] Comparison of their chromatographic behaviour confirmed this conclusion.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, abs EtOH, −10 °C, 3 h rt, 1 h reflux; (ii) Et_3N, CH_2Cl_2, column chromatography: CH_2Cl_2/MeOH = 95:5; (iii) $PrCO_2Bu$, 15 mg/mL CAL-A 20% on Celite; (iv) dry HCl bubbling; (v) 12% aq HCl, 20 h, rt; (vi) 18% aq HCl, 3 h reflux; (vii) ion-exchange chromatography on Varion KS resin or propylene oxide; (viii) K_2CO_3, Boc_2O, dioxane/H_2O = 2:1, 5 h, rt; (ix) $NaHCO_3$, Fmoc-OSu, acetone/H_2O = 1:1, 2 h, 0 °C, then rt.

Table 2. Physical data on the isolated compounds

Compound	Yield (%)[a]	Mp (°C)	Ee (%)[b,c]	$[\alpha]_D^{25}$
5	52	196–199	97	−7 (*c* 0.5, MeOH)
6	74	Oil	90	−66 (*c* 1, MeOH)
7	66	240–242	96	+4 (*c* 0.15, H_2O)
8	83	120–123	98	+50 (*c* 0.53, MeOH)
9	80	170–172	>99	+30 (*c* 0.69, MeOH)
10	15	229–231	99	−4 (*c* 0.16, H_2O)
11	98	127–130	99	−50 (*c* 0.46, MeOH)
12	44	165–170	99	−30 (*c* 0.09, MeOH)

[a] Referring to crude product.

[b] Determined by GC on an L-valine column; **7**, **10**: after derivatization with CH_2N_2, and then acetic anhydride and 1% DMAP/pyridine; **8**, **11**: after derivatization with CH_2N_2; **9**, **12**: after deprotection with 5% piperidine, and then similarly as for **7** and **10**.

[c] After column chromatography and recrystallization; the ee values increased during recrystallization.

3. Experimental

Melting points were determined with a Kofler apparatus at a heating rate of 4 °C/min. ^{1}H NMR spectra were recorded in DMSO-d_6 at ambient temperature on a Bruker DRX400 spectrometer. Chemical shifts are given in δ (ppm) relative to TMS as internal standard; multiplicities were recorded as s (singlet), d (doublet), t (triplet) or m (multiplet). IR spectra were measured in KBr disks on a Perkin Elmer Paragon 1000PC FT-IR spectrometer. MS spectra were recorded on a Finnigan MAT 95 S instrument. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer. Optical rotations were measured with a Perkin–Elmer 341 polarimeter.

3.1. Preparation of racemic compounds

3.1.1. (±)-3-Amino-3-(4-cyanophenyl)propanoic acid 1. Compound (±)-**1** was prepared according to a known procedure.[6] Mp 243–245 °C, lit. mp[19] 233–236 °C. ^{1}H NMR δ 2.41 (2H, d, J = 6.69, CH_2), 4.25–4.35 (1H, m, C*H*), 7.59 (2H, d, J = 8.21 Hz, aromatic), 7.85 (2H, d, J = 8.24 Hz, aromatic). ^{13}C NMR δ 41.9, 52.4, 110.4, 119.3, 2×128.2, 2×132.6, 149.2, 173.1. IR (KBr) ν (cm^{-1}) 2548 (br), 2228, 2161, 1628, 1560, 1394. MS (*m*/*z*, EI) (rel abund.) 190 (4, [M^+]), 172 (4), 144 (10), 131 (100), 129 (20), 104 (20), 77 (10). Anal. Calcd for $C_{10}H_{10}N_2O_2$ C: 63.15%, H: 5.30%, N: 14.73%, found: C: 62.25%, H: 4.85%, N: 14.03%.

3.1.2. (±)-3-(*tert*-Butoxycarbonylamino)-3-(4-cyanophenyl)propanoic acid 2. Amino acid **1** (40 mg, 0.2 mmol) was dissolved in 3 mL of a dioxane/water = 1:1 mixture. K_2CO_3 (276 mg, 2 mmol) and di-*tert*-butyl dicarboxylate (44 mg, 0.2 mmol) were added. After stirring for 5 h, the pH was adjusted to 2 with 1 M HCl, the product was extracted with EtOAc and dried on Na_2SO_4, and the solvent was evaporated off. White crystals (60 mg, 98%), mp 168–171 °C (diisopropyl ether). ^{1}H NMR δ 1.40 (9H, s, *t*-Bu), 2.60–2.80 (2H, m, CH_2), 4.90–5.05 (1H, m, CH), 7.55 (2H, d, J = 8.11, aromatic), 7.61 (1H, d, J = 8.21 Hz, NH), 7.85 (2H, d, J = 7.98, aromatic). ^{13}C NMR δ 40.5, 51.0, 78,1, 109.7, 118.7, 4×127.4, 3×132.2, 148.8, 154.7, 171.4. IR (KBr) ν (cm^{-1}) 3327, 2978, 2627, 2224, 1710, 1530, 1391, 1366. MS (*m*/*z*, CI) (rel abund.) 291 (100, [M + H]$^+$), 263 (10), 245 (4), 235 (20), 217 (20), 191 (24), 174 (12), 130 (32).

3.1.3. (±)-3-(9-Fluorophenylmethoxycarbonylamino)-3-(4-cyanophenyl)propanoic acid 3. Amino acid **1** (40 mg, 0.2 mmol) was dissolved in 1.33 mL of an acetone/water = 1:1 mixture and cooled to 0 °C. $NaHCO_3$ (104 mg, 1.2 mmol) and Fmoc-OSu (83 mg, 0.25 mmol) were added. The mixture was stirred for 2 h at 0 °C and at rt overnight. After removal of the acetone, the pH was adjusted to 2 with 1 M HCl, the product was extracted with EtOAc and dried on Na_2SO_4, and the solvent was evaporated off. White crystals (50 mg, 58%), mp 179–182 °C (diisopropyl ether). ^{1}H NMR δ 2.55–2.80 (2H, m, CH_2), 4.10–4.35 (3H, m, Fmoc CH_2, CH), 4.90–5.10 (1H, m, CH), 7.20–7.95 (12H, m, aromatic), 8.06 (1H, s, NH). ^{13}C NMR δ 40.3, 46.6, 51.4, 65.3, 109.8, 118.7, 2×120.1, 2×125.0, 2×127.0, 2×127.4, 2×127.5, 2×132.3, 2×140.7, 143.6, 143.8, 148.4, 155.3, 171.3. IR (KBr) ν (cm^{-1}) 3353, 2926, 2234, 1703, 1536, 1082. MS (*m*/*z*, CI) (rel abund.) 413 (10, [M+H]$^+$), 196 (64), 191 (2), 178 (100), 165 (60), 157 (4), 131 (1).

3.1.4. Ethyl (±)-3-amino-3-(4-cyanophenyl)propanoate hydrochloride 4·HCl. Absolute EtOH (8 mL) was cooled below −10 °C. $SOCl_2$ (0.7 mL, 9.6 mmol) was added dropwise, the temperature being kept below −10 °C. Amino acid **1** (1.7 g, 8.7 mmol) was added to the mixture, which was then stirred for 0.5 h at 0 °C and 3 h at rt, and finally refluxed for 1 h. The solvent was evaporated off and the hydrochloride of **4** was recrystallized from EtOH/diethyl ether. White crystals (1.75 g, 78%), mp 215–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.09 Hz, CH_3), 2.95–3.25 (2H, ddd, J = 8.75, 16.34, 69.66 Hz, CH_2CO), 3.92–4.10 (2H, m, CH_2CH$_3$), 4.71 (1H, t, J = 7.18 Hz, C*H*), 7.76 (2H, d, J = 8.22 Hz, aromatic), 7.91 (2H, d, J = 8.16 Hz, aromatic), 8.83 (3H, s, $NH_3^+Cl^-$). ^{13}C NMR δ 13.8, 38.2, 50.5, 60.6, 111.6, 118.4, 2×128.9, 2×132.5, 142.0, 168.8. IR (KBr) ν (cm^{-1}) 3056, 2930, 2787, 2227, 2026, 1725, 1510, 1208, 845. Anal. Calcd for $C_{12}H_{15}ClN_2O_2$ C: 56.59%, H: 5.94%, Cl: 13.92%, N: 11.00%, found: C: 56.82%, H: 6.03%, Cl: 13.67%, N: 11.34%.

3.1.5. Ethyl (±)-3-amino-3-(4-cyanophenyl)propanoate 4. The base was released by the addition of 3 equiv of Et_3N to the CH_2Cl_2 suspension of (±)-**4**·HCl. The mixture was stirred for 3 h and the solvent was evaporated off under reduced pressure. The residue was purified by column chromatography, using CH_2Cl_2/MeOH = 95:5 as eluent. A yellow oil (1.33 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.14 Hz, CH_3), 2.24 (2H, s, NH_2), 2.66 (2H, d, J = 6.76 Hz, CH_2CO), 4.14 (2H, q, J = 7.11 Hz, CH_2CH$_3$), 4.50 (1H, t, J = 6.74 Hz, CH), 7.50 (2H, d, J = 8.20 Hz, aromatic), 7.63 (2H, d, J = 8.32 Hz, aromatic). IR (KBr) ν (cm^{-1}) 3377, 2980, 2227, 1728, 1608, 1185. Anal. Calcd for $C_{12}H_{14}N_2O_2$ C: 66.04%, H: 6.47%, N: 12.83%, found: C: 65.44%, H: 6.86%, N: 13.47%.

3.2. Gram-scale resolution of (±)-4

Compound (±)-**4** (1.20 g, 5.50 mmol) was dissolved in butyl butanoate (110 mL) and 1.65 g of 20% CAL-A preparation[16] was added. The reaction vessel was shaken at room temperature. The reaction was stopped at 51% conversion by filtering off the enzyme. The enzyme was washed with CH_2Cl_2, and dry HCl was bubbled through the solution for 2 h. The solvent was evaporated off under vacuum and **5** was crystallized from diisopropyl ether (0.35 g, 52%, diisopropyl ether/EtOH). The mother liquor was evaporated down and **6** was isolated by column chromatographic purification, using CH_2Cl_2/MeOH = 95:5 as eluent (0.61 g, 74%).

3.2.1. Ethyl (*R*)-3-amino-3-(4-cyanophenyl)propanoate hydrochloride 5. The ^{1}H NMR data were identical with those for (±)-**4**·HCl. IR (KBr) ν (cm^{-1}) 3078, 2918, 2786, 2225, 1730, 1516. Anal. Calcd for $C_{12}H_{15}ClN_2O_2$ C: 56.59%, H: 5.94%, Cl: 13.92%, N: 11.00%, found: C: 55.98%, H: 5.95%, Cl: 13.38%, N: 11.14%.

3.2.2. Ethyl (*S*)-3-butanoylamino-3-(4-cyanophenyl)propanoate 6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, J = 7.37 Hz, CH_3CH$_2$CH$_2$), 1.16 (3H, t, J = 7.13 Hz, OCH$_2$CH_3), 1.55–1.75 (2H, m, CH$_3$CH_2CH$_2$), 2.18 (2H, t, J = 7.42 Hz, CH$_3$CH$_2$CH_2), 2.80–2.95 (2H, m, CH_2CO), 4.05 (2H, q, J = 7.12 Hz, OCH_2CH$_3$), 5.40–5.50 (1H, m, CHCH$_2$CO), 6.79 (1H, br d, J = 7.92 Hz, NH), 7.39 (2H, d, J = 8.16 Hz, aromatic), 7.61 (2H, d, J = 8.30 Hz, aromatic). ^{13}C NMR δ 13.8, 14.1, 19.1, 38.7, 39.5, 49.2, 61.2, 111.4, 118.5, 2×127.1, 2×132.5, 146.2, 170.9, 172,4. IR (KBr) ν (cm^{-1}) 3296, 2964, 2228, 1740, 1654. Anal. Calcd for $C_{16}H_{20}N_2O_3$ C: 66.65%, H: 6.99%, N: 9.72%, found: C: 64.56%, H: 7.09%, N: 9.53%.

3.3. Preparation of enantiomeric amino acids and their *N*-protected derivatives

3.3.1. (*R*)-3-Amino-3-(4-cyanophenyl)propanoic acid 7. Compound **5** (0.53 g, 2.08 mmol) was stirred in 12% HCl (21 mL) for 20 h at rt. After evaporation, the residue was dissolved in water and purified by ion-exchange chromatography (0.26 g, 66%). The light-brown solid was recrystallized from water/acetone to give a white powder. The ^{1}H NMR and MS data were identical with those of **1**. IR (KBr) ν (cm^{-1}) 3041, 2230, 1613, 1547, 1417, 1250, 844, 573.

3.3.2. (*R*)-3-(*tert*-Butoxycarbonylamino)-3-(4-cyanophenyl)propanoic acid 8. Prepared similarly to **2**. The ^{1}H NMR and MS data were identical with those for **2**. IR (KBr) ν (cm^{-1}) 3367, 2986, 2229, 1687, 1521, 1271, 1172.

3.3.3. (*R*)-3-(9-Fluorophenylmethoxycarbonylamino)-3-(4-cyanophenyl)propanoic acid 9. Prepared similarly to **3**. The ^{1}H NMR and MS data were identical with those for **3**. IR (KBr) ν (cm^{-1}) 3347, 2919, 2357, 2234, 1700, 1537, 1286, 740.

3.3.4. (*S*)-3-Amino-3-(4-cyanophenyl)propanoic acid 10. Compound **6** (0.5 g, 1.73 mmol) was refluxed in 18% HCl (50 mL) for 3 h. After evaporation, the residue was dissolved in MeOH and the solution was stirred with an excess of propylene oxide and then evaporated down. The residue was dissolved in hot MeOH and filtered, and the solvent was removed under reduced pressure (50 mg, 15%). The light-brown solid was recrystallized from water/acetone to give a white powder which contained the hydrolysed amide product according to the NMR. The characteristic ^{1}H NMR and MS lines were identical with those for **1**; the IR data were identical with those for **7**. MS (m/z, EI) (rel abund.) 208 (16) for the amide by-product.

3.3.5. (*S*)-3-(*tert*-Butoxycarbonylamino)-3-(4-cyanophenyl)propanoic acid 11. Prepared similarly to **2**. The ^{1}H NMR and MS data were identical with those for **2**. The IR was identical with that for **8**.

3.3.6. (*S*)-3-(9-Fluorophenylmethoxycarbonylamino)-3-(4-cyanophenyl)propanoic acid 12. Prepared similarly to **3**. The ^{1}H NMR and MS data were identical with those for **3**. The IR spectrum was identical with that for **9**.

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