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Diastereoselective esterification of (±)-*N*-trifluoroacetyl pipecolic acid using (*S*)-α-methyl pantolactone: synthesis of (*S*)-*N*-Boc pipecolic acid and (*S*)-*N*-Boc-2-piperidinemethanol

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Abstract—Racemic *N*-trifluoroacetyl pipecolic acid has been converted into (*S*)-*N*-Boc-pipecolic acid or (*S*)-*N*-Boc-2-piperidinemethanol by DCC/DMAP-induced diastereoselective esterification with (*S*)-α-methyl pantolactone, followed by a saponification or a reduction reaction and *N*-Boc protection.

1. Introduction

(*S*)-(−)-Piperidine-2-carboxylic acid ((*S*)-(−)-pipecolic acid) is a non proteinogenic amino acid present in several biologically active products. For example, the immunosuppressants FK 506[1] and rapamycin[2] as well as simple analogs of FK506 contain a pipecolic acid moiety. As a proline homologue, (*S*)-(−)-pipecolic acid has also been used in peptide chemistry because it favors formation of β-turn structures. This modification of the secondary structure can result in an interesting modification of biological properties.[3] In addition, simple reduction of (*S*)-(−)-pipecolic acid allowed preparation of (*S*)-2-piperidinemethanol which is an important chiral building block useful for the synthesis of enantiomerically pure piperidine alkaloids.[4]

Racemic pipecolic acid **1** (R = H) is readily available. The current route to pure enantiomers is a resolution of the racemate by fractional crystallization as the tartrate salt[5] or as chiral palladium(II) complexes.[6] Moreover, efficient kinetic resolutions of (±)-pipecolic acid esters[7] or amides[8] catalyzed by lipases have also been described.

We have recently reported a dynamic kinetic resolution of racemic acyclic amino acids by stereoselective esterification of the corresponding *N*-phthalyl derivatives using (*S*)-α-methyl pantolactone as the chiral auxiliary.[9] This method provides an easy access to optically active carboxylic acid derivatives starting from the corresponding racemic mixture. Therefore, we decided to examine this reaction in the case of a racemic *N*-heterocyclic amino acid: (*RS*)-pipecolic acid **1** (R = H).

2. Results and discussion

In the first attempt we used the same experimental conditions as previously described for the resolution of *N*-phthalyl α-amino acids, i.e. 15 h treatment at room temperature of the *N*-protected pipecolic acid in toluene with one equivalent each of DCC, DMAP and the enantiomerically pure alcohol (*S*)-**2**.[9]

Under these experimental conditions, low to moderate chemical yields were obtained depending on the nature of the amine protecting group (Table 1, entries 1–3). The best result was obtained using the *N*-trifluoroacetyl compound **1a** as starting material. Furthermore, no noticeable increase in yield was obtained when the reaction mixture was allowed to stand for several days at room temperature (Table 1, entries 4, 5). Toluene produced slightly higher results than dichloromethane (Table 1, entries 1, 6) and it allowed an easier elimination of the remaining α-methyl pantolactone during workup. LC/MS analysis of the crude **3a**, obtained after DCU filtration and HCl neutralization showed that the corresponding *N*-acylurea and some unidentified by-products were formed together with the ester.

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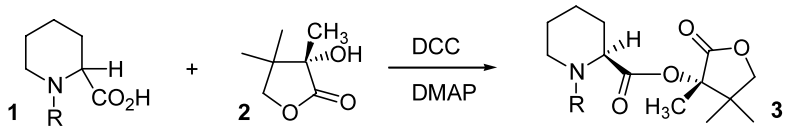
Table 1. Esterification of racemic pipecolic acid **1** using α-(*S*)-methyl pantolactone **2**



a: R = Trifluoroacetyl; b: R = Benzyl; c: R = Fmoc

Entries	Acid	R*OH equiv.	DCC/DMAP equiv.	Solvent/reaction time	Yield (%)
1	**1a**	1	1/1	Toluene/15 h	43* (35**)
2	**1b**	1	1/1	Toluene/15 h	<5
3	**1c**	1	1/1	Toluene/15 h	18
4	**1a**	1	1/1	Toluene/24 h	43*
5	**1a**	1	1/1	Toluene/48 h	45*
6	**1a**	1	1/1	CH_2Cl_2/15 h	37*
7	**1a**	1	1/cat.	Toluene/15 h	8*
8	**1a**	1	1/cat.	CH_2Cl_2/15 h	7*
9	**1a**	0.5	1/1	Toluene/15 h	75*** (83*)
10	**1a**	0.5	0.5/0.5	Toluene/15 h	53*

* Yields of the crude product.
** Yields after column chromatography.
*** Yields toward the alcohol **2** and after chromatography.

When DMAP was used in catalytic amount *N*-acylurea formation was not observed but the esterification yield was drastically decreased (<10%; Table 1, entries 7, 8). Furthermore, when esterification of **1a** was carried out using different activating reagents (DCC alone, DCC/HOBT, BOP…) only low chemical yields were obtained (<5%).

Ester **3a** can be easily isolated in pure form after column chromatography on silica gel eluting with hexane/ethyl acetate (7/3) and recrystallisation (diethyl ether). However, due to formation of by-products, we were not able to recover the non esterified compound. ^{1}H NMR analysis (in $CDCl_3$ or DMSO) of pure compound **3a** led to a complex spectrum where most of the signals were split. ^{1}H and ^{19}F NMR coalescence studies (in DMSO) established that spectral complexity results from the presence in solution of two conformers (coalescence temperature: 120°C). Concerning the diastereomeric excess of compound **3a**, it was difficult to conclude directly on its homogeneity since whatever the conditions and the chiral columns that were used we only obtained one peak on the HPLC chromatograms. Nevertheless, a large NMR and HPLC separation was generally observed in the case of the (*S*)-α-methyl pantolactonyl ester diastereoisomeric mixtures of amino acid.[9] The configuration within (*S*,*S*)-**3a** was assigned on the basis of an X-ray crystal structure determination (Fig. 1).

To explain the diastereoselective esterification, it was reasonable to speculate that under the experimental conditions used, the esterification rate of the acyl (4-dimethylamino)pyridinium salt intermediate could be fast for the (*S*) enantiomer and low for the (*R*) enantiomer thus promoting by-product formation. Concerning the stoichiometry of the process, we have found that it was necessary to use 1 equiv. each of DCC and DMAP but 0.5 equiv. of the chiral alcohol was enough since a dynamic kinetic resolution was not observed (Table 1, entries 1, 9, 10).

Saponification of the diastereoisomerically pure (*S*,*S*)-**3a** afforded the corresponding (*S*)-pipecolic acid which was directly converted into its *N*-Boc derivative **4** using di-*tert*-butyldicarbonate. However, chiral HPLC analysis, either directly or more accurately after transformation of an aliquot to the corresponding benzyl amide derivative, showed that this reaction took place with a lower but significant degree of epimerization (8–10%).

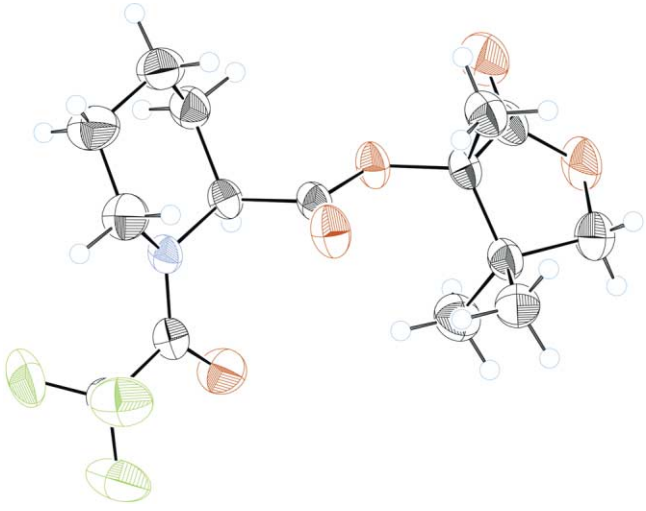
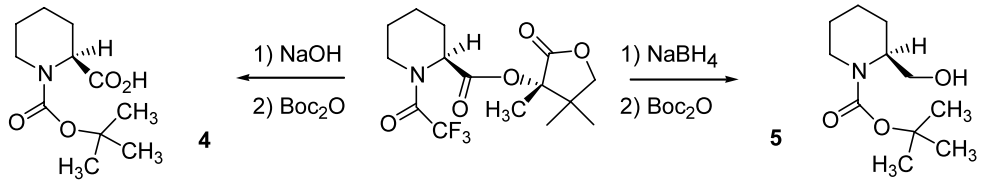


Figure 1. ORTEP drawing of ester (*S*,*S*)-**3a**.



It has been shown that the trifluoroacetyl amine protecting group[10] can also be removed under mild conditions using sodium borohydride. In addition, lithium aluminum hydride[11] and sodium borohydride[12] have been used for the reductive removal of pantolactonyl esters to give the corresponding alcohols. Therefore, we considered the possible simultaneous reduction of the trifluoroacetyl group and the α-methyl pantolactonyl ester of the diastereomerically pure compound (*S*,*S*)-**3a**. The best results were obtained when sodium borohydride in excess (6 equiv.) was used, for 1 h at room temperature, followed by reflux for 30 min. After *N*-Boc protection the corresponding (*S*)-*N*-Boc 2-piperidinemethanol **5** was isolated in moderate yield (57%). Enantiomeric excess of compound **5** was determined by comparison of its specific rotation value with those previously described[13] and more accurately by chiral HPLC after transformation of an aliquot to the corresponding (1*S*)-camphanic ester (e.e. = 84%).

3. Experimental

All reagents were used as purchased from commercial suppliers without further purification. Solvents were dried and purified by conventional methods prior to use. Melting points were determined with a IA 9400 electrothermal or Kofler Heizbank apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. ^{1}H or ^{19}F NMR spectra were recorded with a Bruker AC 250 spectrometer. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, coupling constants (J) in Hz. The ESI mass spectra were recorded with a platform II quadrupole mass spectrometer (Micromass, Manchester, UK) fitted with an electrospray source. HPLC analysis were performed with a Waters model 510 instrument with variable detector at 214 nm using: column I; reverse phase Nucleosil C_{18}, 5μ, (250×10 mm), flow 1 ml/min, H_2O/CH_3CN/0.1% TFA gradient 0→100% (15 min) and 100% (4 min); column II; Chiracel OD, 5μ, (250×10 mm), flow 1 ml/min, condition A: hexane/2-propanol, 98/2; condition B: hexane/2-propanol, 95/5; column III; Welk 01, 5μ, (250×10 mm), flow 1 ml/min, hexane/2-propanol, 90/10; column IV; Chiracel OJ-R, 5μ, (150×4.6 mm), flow 1 ml/min, H_2O/CH_3CN/TFA, 85/15/0.1.The chiral auxiliary (*S*)-α-methyl pantolactone **2** was prepared as previously described.[9]

3.1. (±)-*N*-Trifluoroacetyl pipecolic acid 1a

Trifluoroacetylation of racemic pipecolic acid was carried out as previously described,[14] using ethyl trifluoroacetate and triethylamine in dry methanol. Compound **1a** (72% yield), was obtained as a colorless solid after flash chromatography (eluent AcOEt/hexane/AcOH, 7/3/0.1) R_f = 0.3; mp 70°C; HPLC: R_t = 9.3 min (column I); ^{1}H NMR ($CDCl_3$) δ = 1.50 (m, 2H, CH_2), 1.75 (m, 3H, CH_2 and HCH), 2.37 (d, 1H, J = 13.7 Hz, HCH), 3.00 and 3.34 (t, 1H, $J_1 = J_2$ = 13.8 Hz, HCH-N) (two rotamers 18/82), 3.95 and 4.48 (d, 1H, J = 13.8 Hz, HCH-N) (two rotamers 82/18), 4.77 and 5.30 (d, 1H, J = 5.2 Hz, CH-CO_2H) (two rotamers 18/82); ^{13}C NMR ($CDCl_3$) δ = 20.95 and 21.02 (CH_2, two rotamers), 24.60 and 25.21 (CH_2, two rotamers), 26.63 and 27.74 (CH_2CHCO$_2$H, two rotamers), 41.64 and 44.18 (CH_2N, two rotamers), 53.71 and 56.28 (CHCO$_2$H, two rotamers), 116.65 (q, J = 287 Hz, CF_3), 157.63 (q, J = 36 Hz, COCF$_3$), 175.74 and 176.24 (CO_2H); MS (ESI) m/z: 226.0 [(M+H)$^+$].

3.2. Diastereoselective esterification of racemic *N*-trifluoroacetyl pipecolic acid

To racemic *N*-trifluoroacetyl pipecolic acid **1a** (450 mg; 2 mmol), (*S*)-α-methyl pantolactone **2** (144 mg; 1 mmol) and 4-dimethylaminopyridine (244 mg, 1 mmol) in 3 ml of anhydrous toluene, was added 1 mmol of dicyclohexylcarbodiimide (412 mg) at 0°C. Mixture was then stirred at rt for an additional 15 h. The resulting mixture was filtered, diluted with ethyl acetate and then a 1N HCl solution was added until pH 2–3. The organic layer was separated and the aqueous phase extracted with ethyl acetate. The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Column chromatography on silica gel, eluting with hexane/ethyl acetate (7/3; R_f = 0.5) yielded pure compound **3** as a colorless solid (263 mg, 0.75 mmol, 75%). Diastereomerically pure (*S*,*S*)-**3** (210 mg, 60%) was obtained after recrystallization (diethyl ether); mp 108–110°C; $[\alpha]_D^{20}$ −88.6 (*c* 1.7, CH_2Cl_2); HPLC: R_t = 11.6 min (column I) and R_t = 14.7 (column II, condition A); ^{1}H NMR ($CDCl_3$) δ = 1.07 and 1.10 (s, 3H, CH_3) (two rotamers, 21/79), 1.19 and 1.22 (s, 3H, CH_3) (two rotamers, 79/21), 1.32–1.48 (m, 2H, CH_2), 1.59 and 1.61 (s, 3H, CH_3) (two rotamers, 79/21), 1.66–1.75 (m, 3H, CH_2 and HCH), 2.32 (m, 1H, HCH), 3.03 and 3.34 (t, 1H, $J_1 = J_2$ = 13.6 Hz, HCH-N) (two rotamers 21/79), 3.85 and 3.88 (d, 1H, J = 8.8 Hz, HCH-O) (two rotamers, 79/21), 3.90 and 4.40 (d, 1H, J = 13.6 Hz, HCH-N) (two rotamers 79/21), 3.98 and 4.00 (d, 1H, J = 8.8 Hz, HCH-O) (two rotamers, 21/79), 4.75 and 5.18 (d, 1H, J = 5.1 Hz, CHCO) (two rotamers 21/79); ^{19}F NMR (DMSO-d_6) δ = −67.6 and −68.0 (two rotamers, 22/78); ^{13}C NMR ($CDCl_3$) δ = 16.84 and 19.89 (CH_3, two rotamers), 20.90 (CH_2), 21.05 and 21.12 (CH_3, two rotamers), 22.05 and 22.26 (CH_3, two rotamers), 24.63 and 25.17 (CH_2, two rotamers), 26.75 and 28.03 (CH_2, two rotamers), 41.47 and 44.06

(CH_2N, two rotamers), 43.19 ($C(CH_3)_2$), 53.82 and 56.37 ($CHCO$, two rotamers), 77.54 and 77.61 (CH_2O, two rotamers), 84.97 and 85.38 ($C(CH_3)$-O, two rotamers), 116.75 (q, $J=287$ Hz, CF_3), 157.61 (q, $J=35.8$ Hz, $COCF_3$), 168.8 (CO), 174.29 and 174.41 (CO); MS (ESI) m/z: 352.2 [$(M+H)^+$], 373.9 [$(M+Na)^+$], 725.2 [$(2M+Na)^+$].

3.3. Crystal data for (*S*,*S*)-3a

The diffraction data were collected on a Enraf–Nonius Kappa CCD diffractometer using graphite-monochrome Mo Kα radiation and the ϕ-scan technique up to $\theta=26.34$.

Molecular formula $C_{15}H_{20}F_3NO_5$, molecular weight = 351, orthorhombic, space group $P2_12_12_1$, cell constants: $a=7.0710$ (10) Å, $b=10.4730$ (10) Å, $c=22.0460$ (10) Å, $V=1632.6$ (3) Å^3, $Z=4$, $D_{calcd}=1.397$ mg m^{-3}, $T=298$ K, final $R=0.038$, final $R_w=0.046$. Details of the crystal structure determination have been deposited at the Cambridge Crystallographic Data Centre (deposition number 201754).

3.4. (*S*)-*N*-(*tert*-Butoxycarbonyl)pipecolic acid 4

To a stirred solution of the α-methylpantolactonyl ester (*S*,*S*)-**3a** (175 mg, 0.50 mmol), was added NaOH (60 mg, 1.5 mmol, 3 equiv.) in a solution of THF/H_2O (7/3) (18 ml). The mixture was stirred for 12 h at rt. The THF was eliminated at reduced pressure and the mixture was diluted with dioxane (10 ml). To the solution of this deprotected pipecolic acid was added di-*tert*-butyldicarbonate (163 mg, 0.75 mmol, 1.5 equiv.) and NaOH (20 mg, 1 equiv.). After stirring for 12 h at rt, the dioxane was eliminated at reduced pressure, the mixture was diluted with water (10 ml) and washed with ethyl acetate (10 ml). The aqueous phase was acidified to pH 3–4 and extracted with dichloromethane (3×10 ml). The organic layer was dried and concentrated in vacuo. Column chromatography on silica gel, eluting with hexane/ethyl acetate (7/3); $R_f=0.5$) yielded the pure compound **4** as a colorless solid (97 mg, 0.42 mmol, 85%). ^{1}H NMR ($CDCl_3$) $\delta=1.28$–1.43 (br m, 2H), 1.41 (s, 9H), 1.63 (br m, 3H), 2.15 (br d, 1H), 2.91 (br m, 1H), 3.92 (br m, 1H), 4.72 and 4.88 (br s, 1H). HPLC (column IV): (*S*)-**4**: 92–90%, $R_t=23.7$ min, (*R*)-**4**: 8–10%, $R_t=26.7$ min (broad signals); column I: $R_t=9.7$ min; MS (ESI) m/z: 129.9, 173.9, 229.9 [$(M+H)^+$], 459.1 [$(2M+H)^+$].

3.5. *N*-(*tert*-Butoxycarbonyl)-2-piperidinecarboxylic acid benzylamide

The benzylamide derivative of (*S*)-**4** was obtained as previously described,[15] using 2-chloro-1-methylpyridinium iodide, benzylamide and triethylamine. HPLC: column III: (*S*)-enantiomer: 92–90%, $R_t=17.3$ min, (*R*)-enantiomer: 8–10%, $R_t=14.3$ min. Racemic sample was prepared after *N*-Boc protection of the commercially available racemic pipecolic acid.

3.6. (*S*)-*N*-(*tert*-Butoxycarbonyl)-2-piperidinemethanol 5

To a stirred solution of the α-methylpantolactonyl ester (*S*,*S*)-**3a** (175 mg, 0.50 mmol) in ethanol was slowly added sodium borohydride (114 mg, 6 equiv.). After stirring for 1 h at rt and then 0.5 h at reflux TLC indicated complete consumption of the starting material. Glacial acetic acid was added dropwise to adjust the pH to 2–3 and the mixture was stirred at rt for 1 h. The reaction mixture was neutralized to pH 7 and the solvent was eliminated at reduce pressure.

The residue was dissolved in 20 ml of a mixture dioxane/H_2O followed by addition of di-*tert*-butyldicarbonate (1.5 equiv.) and NaOH (1.5 equiv.). After stirring for 12 h at rt, dioxane was eliminated at reduce pressure, the mixture was diluted with water (10 ml) and washed with ethyl acetate (10 ml). The aqueous phase was acidified to pH 3–4 and extracted with dichloromethane (3×10 ml). The organic layer was dried and concentrated in vacuo. Column chromatography on silica gel, eluting with hexane/ethyl acetate (1/1); $R_f=0.4$), yielded the pure compound **4** as a colorless solid (62 mg, 0.29 mmol, 57%). HPLC: $R_t=8.9$ min (column I); $[\alpha]_D^{20}$ −31.2 (*c* 2, $CHCl_3$); [Ref. 13b $[\alpha]_D^{20}$ −40.5 (*c* 1, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) $\delta=1.30$–1.39 (m, 2H, CH_2), 1.39 (s, 9H, $C(CH_3)_3$), 1.52–1.60 (m, 4H, CH_2), 2.80 (br t, 1H, $J=11.6$ Hz, HCH-N), 3.54 (dd, 1H, $J_1=5.8$ Hz and $J_2=11.0$ Hz, HCH-OH), 3.74 (t, 1H, $J_1=J_2=11.0$ Hz HCH-OH), 3.87 (br d, 1H, $J=11.6$ Hz, HCH-N), 4.22 (m, 1H, CH-CH_2OH); ^{13}C NMR ($CDCl_3$) $\delta=20.04$ (CH_2), 25.63 (CH_2), 25.67 (CH_2), 28.84 ($C(CH_3)_3$), 40.37 (CH_2), 52.90 (CH), 62.16 (CH_2), 80.24 ($C(CH_3)_3$), 156.8 (CO); MS (ESI) m/z: 116.0, 159.5, 215.9 [$(M+H)^+$].

3.7. (1*S*)-Camphanic acid ester of *N*-(*tert*-butoxycarbonyl)-2-piperidinemethanol

To a mixture of (*S*)-*N*-(*tert*-butoxycarbonyl)-2-piperidinemethanol (21 mg, 0.1 mmol) and (1*S*)-camphanic acid chloride (24 mg, 0.11 mmol, 1.1 equiv.) in 0.5 ml of dry CH_2Cl_2 were added at 0°C triethylamine (17 μl, 0.12 mmol, 1.2 equiv.) and a catalytic amount of 4-dimethylaminopyridine. The mixture was then stirred at rt for 12 h. The resulting mixture was diluted with CH_2Cl_2 (5 ml), washed successively with a 1N HCl solution (5 ml) and a saturated $NaHCO_3$ solution (5 ml), dried with Na_2SO_4 and concentrated in vacuo to afford the expected ester in quantitative yield.

HPLC: column II condition B: (1*S*,2′*S*)-enantiomer: 92%, $R_t=9.6$ min, (1*S*,2′*R*)-enantiomer: 8%, $R_t=11.4$ min. Racemic sample was prepared after *N*-Boc protection of the commercially available racemic 2-piperidinemethanol.

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