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A practical synthesis of protected β-homolysine

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Abstract

Protected β-homolysine of high enantiomeric purity (ee > 99.5%) is prepared utilizing the stereoselective conjugate addition of lithiated (*S*)-(α-methylbenzyl)benzylamide to (*E*)-7-(tosyloxy)hept-2-enoic acid *tert*-butyl ester, followed by subsequent ammonia substitution, Boc protection and removal of the auxiliary.

1. Introduction

β-Homolysine is an important constituent of a new interesting drug substance GPI-562.[1] Although it could be readily obtained through Arndt–Eistert[2] homologation of L-lysine, this method is not suitable for large scale production in standard multipurpose equipment due to the high risk potential of diazomethane. A more practical way consists in reduction of the carboxyl group of ω-*Z*-lysine methyl ester, activation of the resulting hydroxyl group as a mesylate, substitution with cyanide and final solvolysis to the desired acid derivative.[3] In order to find an alternative to this long pathway we studied the application of the well-documented[4] stereoselective Michael addition of a homochiral amine to a suitable α,β-unsaturated ester. After several attempts[5] we achieved a practical and efficient synthesis of (*S*)-ω-Boc-β-homolysine *tert*-butyl ester **6** as shown in Scheme 1.

2. Results and discussion

Starting from readily available 3,4-dihydropyran and *tert*-butyl diethylphosphonoacetate we obtained directly the acrylate **1** via a Wittig–Horner reaction[6] as a 9:1 *E*:*Z* mixture. Subsequent tosylation of the crude product with tosylanhydride, triethylamine and catalytic amount of 4-(dimethylamino)pyridine (DMAP) in THF gave compound **2**[6] also as a 9:1 *E*:*Z* mixture (use of tosylchloride gave about 10% chloro substituted by-product). The selective addition of (*S*)-(α-methylbenzyl)benzylamine to the crude acrylate **2** in DME was achieved easily by adding

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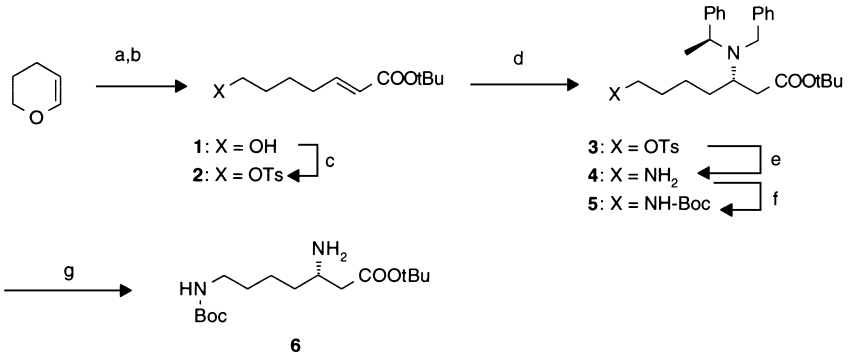
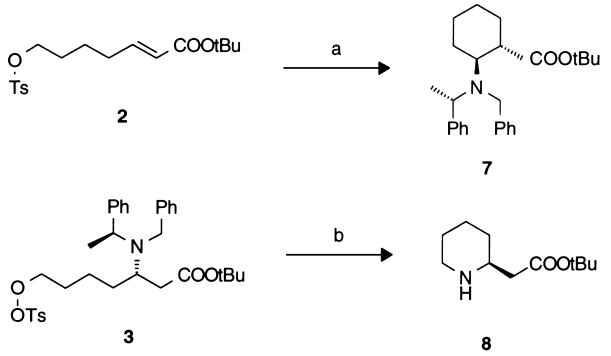


Scheme 1. (a) Catalytic amount of HCl, water; (b) *tert*-butyl diethylphosphonoacetate/K_2CO_3/DMSO; (c) tosylanhydride/triethylamine/DMAP/THF; (d) (i) (*S*)-(α-methylbenzyl)benzylamine, hexyllithium/DME, –60°C, (ii) AcOH; (e) ammonia/ethanol; (f) BOC_2O/AcOEt/K_2CO_3, water; (g) Pd/C, EtOH, AcOEt, oxalic acid

hexyllithium at –60°C to the mixture of the two substrates. The reaction can be monitored by on-line FT-IR, which shows nicely the disappearance of the absorption at 1656 cm^{-1} attributed to the C=C stretching as well that of the carbonyl at 1711 cm^{-1}. After an acidic quench at –60°C and an aqueous work-up we obtained adduct **3** as the main product. At this stage it was not possible to determine the diastereomeric purity by NMR or HPLC. Intermediate **3** was contaminated with about 10% starting material **2**, but it was free of the cyclohexane derivative **7** which may occur through cyclization of the intermediate anion by displacement of the tosylate.[7] Compound **7** was only obtained when the reaction mixture was slowly warmed up to 0°C before aqueous quench[8] (Scheme 2). Transformation of **3** to the amine **4** proved to be quite difficult, as compound **3** did not react under Gabriel conditions[9] (potassium salt of phthalimide, hexamethyldisilylazane, di-*tert*-butyl imidodicarbonate/dimethylformamide at 100°C) nor with sodium azide. However, the tosylate reacted slowly with benzylamine in toluene at reflux or with excess ammonia in ethanol at 50°C in a closed vessel. Under these conditions it was possible to transform smoothly the tosylate **3** to the primary amine **4**. With an acidic work up, it was possible to get rid of the main by-product accumulated in the previous steps.

In contrast to the low reactivity of tosylate **3**, it is rapidly transformed under hydrogenolysis to the cyclization product **8** by an intramolecular displacement (Scheme 2).



Scheme 2. (a) (*S*)-(α-Methylbenzyl)benzylamine, hexyllithium/DME, –60 to 0°C; (b) H_2, Pd/C, EtOH

After Boc protection of **4** under the usual conditions, the subsequent removal of the benzyl groups of **5** by hydrogenolysis with palladium on charcoal failed in the first attempt. However, we observed a dramatic increase in reactivity by adding oxalic acid to the hydrogenation mixture, the *t*-butyl groups remained untouched. After aqueous work up the target molecule **6** was obtained as the crystalline oxalate salt in pure form. The enantiomeric excess was determined by HPLC after derivatisation with Marfey's reagent,[10] and proved to be about 96% for the crude base and >99.5% for the oxalate salt. The absolute configuration has been confirmed after hydrolysis with 6N HCl and compared with an authentic sample of *S*-(+)-homolysine dihydrochloride derived from L-lysine.[3] In conclusion, we have achieved a new synthesis of the β-homolysine derivative **6** in about 20% overall yield, using inexpensive and readily available starting materials.

3. Experimental

All chemicals and solvents were purchased by Fluka as synthetic grade and used without further purification. Hexyllithium was obtained from Chemetall GmBH in bulk and titrated[11] before use. Reactions with hexyllithium were performed under argon. Melting points were determined on a Büchi 535 in open capillary tubes and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with a 1.0 dm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. NMR spectra were recorded on a Bruker–Spectrospin DPX-300 instrument (^{1}H spectra at 300 MHz, ^{13}C spectra at 75 MHz) in $CDCl_3$ solutions, unless otherwise specified. Chemical shifts are given in ppm downfield from TMS internal standard; coupling constants are given in hertz. IR spectra were recorded on a Bruker IFS66 FT-IR spectrophotometer. HPLC analysis were performed on a Merck–Hitachi instrument equipped with a UVD-L 4000, using reversed-phase (Macherey–Nagel) RP-18, 125/4 mm columns, eluted with a gradient of diammoniumhydrogenphosphate at pH 2 and acetonitrile.

3.1. tert-*Butyl (*E*)-7-Hydroxyhept-2-enoate* ***1***

3,4-Dihydropyran [84.1 g (799 mmol)], 270 ml water and 1.7 ml concd HCl were stirred for about 3 h at 0°C; then, 133 g of potassium carbonate, 670 ml dimethylsulfoxide and 100.0 g (340 mmol) *tert*-butyl diethylphosphonoacetate were added and the resultant mixture stirred overnight at 50°C. After dilution with water and extraction with isopropyl acetate, the organic phase was dried ($MgSO_4$) and evaporated to give 78.4 g of **1** as a colorless oil (crude yield >100% as a 9:1 *E*:*Z* mixture). ^{1}H NMR: 1.48 (9H, s, C(C*H*$_3$)$_3$), 1.43–1.65 (4H, m, *H*$_2$C(5), *H*$_2$C(6)), 1.74 (1H, 's', CH$_2$O*H*), 2.21 (2H, m, *H*$_2$C(4)), 3.65 (2H, m, *H*$_2$C(7)), 5.75 (1H, dt, *J*=15.6, 1.5, *H*C(2)), 6.85 (1H, dt, *J*=15.6, 6.9, *H*C(3)).

3.2. tert-*Butyl (*E*)-7-[[(4-methylphenyl)sulfonyl]oxy]hept-2-enoate* ***2***

To a mixture of 30.5 g (122 mmol) of **1**, 47.8 g (146 mmol) tosylanhydride and 40 ml triethylamine in 250 ml tetrahydrofuran was added a catalytic amount of 4-(dimethylamino)pyridine. This was stirred overnight at room temperature, then diluted with water and extracted with isopropyl acetate; the organic phase was dried ($MgSO_4$) and evaporated to give 50.6 g of **2** as a brown liquid (yield 93.7%, as a 9:1 *E*:*Z* mixture). ^{1}H NMR: 1.48 (9H, s, C(C*H*$_3$)$_3$), 1.40–1.54 (2H, m, *H*$_2$C), 1.62–1.71 (2H, m, *H*$_2$C), 2.12 (2H, m, *H*$_2$C(4)), 2.45 (3H, s, C*H*$_3$ of TsO), 4.03 (2H,

t, $J=6.2$, $H_2C(7)$), 5.69 (1H, dt, $J=15.6$, 1.5, $HC(2)$), 6.76 (1H, dt, $J=15.6$, 6.9, $HC(3)$), 7.35 (2H, d, $J=8.1$, TsO), 7.79 (2H, d, $J=8.3$, TsO). ^{13}C NMR: 21.6 (CH_3 of TsO), 23.9 (CH_2), 28.1 ($OC(CH_3)_3$), 28.3 (CH_2), 31.1 (CH_2), 70.0 (CH_2), 80.2 ($OC(CH_3)_3$), 123.7 (CH), 127.9 (CH), 129.9 (CH), 133.1 (C of TsO), 144.8 (C of TsO), 146.6 (CH), 165.9 (COO^tBu).

3.3. tert-*Butyl (3S,αS)-3-(N-benzyl-N-α-methylbenzylamino)-7-[[(4-methylphenyl)sulfonyl]oxy]-heptanoate* **3**

To a stirred mixture of 10.0 g (28.2 mmol) crude **2**, 5.96 g (28.2 mmol) of (*S*)-(α-methylbenzyl)-benzylamine in 280 ml anhydrous dimethoxyethane at –60°C was added dropwise 18.5 ml (42.3 mmol) of a 2.3 M solution of hexyllithium in hexane. The reaction was quenched after 15 min by addition of 3.2 ml (56.4 mmol) acetic acid, followed by dilution with water, acidification to pH 2 and extraction with isopropyl acetate. After treatment with aqueous potassium carbonate, the organic phase was dried over $MgSO_4$. Subsequent evaporation of the solvent yielded 12.1 g of **3** as a yellow oil (yield: 75%). Unreacted amine (1.54 g, 25%) can be recovered from the first water phase upon treatment with potassium carbonate and extraction with isopropyl acetate. ^1H NMR: 1.27 (3H, d, $J=7.0$, $PhCH(CH_3)N$), 1.13–1.65 (6H, m, $H_2C(4)$, $H_2C(5)$, $H_2C(6)$), 1.37 (9H, s, $C(CH_3)_3$), 1.82 (1H, dd, $J=14.8$, 9.5, $HC(2)$), 1.94 (1H, dd, $J=14.8$, 3.3, $HC(2)$), 2.40 (3H, s, CH_3 of TsO), 3.22 (1H, m, HC(3)), 3.45 (1H, d, $J=15.0$, $PhCH_2N$), 3.72 (1H, d, $J=14.9$, $PhCH_2N$), 3.78 (1H, q, $J=7.0$, $PhCH(CH_3)N$), 3.99 (2H, m, $H_2C(7)$), 7.19–7.39 (12H arom.), 7.77 (2H, d, $J=8.3$, TsO). ^{13}C NMR: 20.6 ($PhCH(CH_3)N$), 21.6 (CH_3 of TsO), 22.7 (CH_2), 28.1 ($OC(CH_3)_3$), 28.7 (CH_2), 32.8 (CH_2), 37.4 (C(2)), 50.1 ($PhCH_2N$), 53.5 (C(3)), 58.4 ($PhCH(CH_3)N$), 70.6 ($TsOCH_2$), 80.1 ($OC(CH_3)_3$), 126.7–128.5 (CH arom.), 129.8 (CH arom.), 133.4 (C TsO), 141.8 (C Ph), 143.0 (C Ph), 144.6 (C TsO), 172.0 (COO^tBu).

3.4. tert-*Butyl (3S,αS)-7-amino-3-(N-benzyl-N-α-methylbenzylamino)heptanoate* **4**

Crude **3** [12.1 g (21.3 mmol)] and 110 ml ammonia in ethanol (10% w/v) were heated for 48 h at 50°C in a closed vessel. After evaporation of the solvent, the oily residue was diluted with isopropyl acetate, water and acidified to pH 2 with dilute HCl. The organic phase was then separated, the pH of the aqueous phase was raised to 9 with potassium carbonate and the product was extracted into isopropyl acetate. After drying over $MgSO_4$, the organic phase was concentrated to give 3.94 g of the crude amine **4** in about 45% yield. ^1H NMR: 1.17–1.65 (6H, m, $H_2C(4)$, $H_2C(5)$, $H_2C(6)$), 1.31 (3H, d, $J=7.0$, $PhCH(CH_3)N$), 1.38 (9H, s, $C(CH_3)_3$), 1.85 (1H, dd, $J=14.8$, 9.0, $H_2C(2)$), 1.94 (1H, dd, $J=14.8$, 3.7, $H_2C(2)$), 2.74 (2H, m, $H_2C(7)$), 3.27 (1H, m, $HC(3)$), 3.47 (1H, d, $J=15.0$, $PhCH_2N$), 3.75 (1H, d, $J=15.0$, $PhCH_2N$), 3.80 (1H, q, $J=7.0$, $PhCH(CH_3)N$), 4.31 (2H, s, NH_2), 7.12–7.40 (10H, Ph). ^{13}C NMR: 20.5 ($PhCH(CH_3)N$), 24.1 (CH_2), 28.1 ($C(CH_3)_3$), 31.3 (CH_2), 33.1 (CH_2), 37.6 (C(2)), 41.3 (C(7)), 50.1 ($PhCH_2N$), 53.8 (C(3)), 58.3 ($PhCH(CH_3)N$), 80.0 ($OC(CH_3)_3$), 126.5–128.3 (CH Ph), 141.8 (C Ph), 143.0 (C Ph), 172.1 (COO^tBu). *m/z* (FAB): 411 ($[MH]^+$, 100), 355 (13), 251 (46), 196 (14), 178 (30).

3.5. tert-*Butyl (3S,αS)-7-(tert-butyloxycarbonylamino)-3-(N-benzyl-N-α-methylbenzylamino)-heptanoate* **5**

Compound **4** [3.94 g (9.60 mmol)], 2.2 g (10.1 mmol) di-*tert*-butyl dicarbonate and 2.0 g of potassium carbonate were stirred for 30 min in 80 ml isopropyl acetate:water, 1:1. After the layers

were separated, the organic phase was evaporated to dryness to give 5.71 g of crude **5** (>100%). ^{1}H NMR: 1.20–1.66 (6H, m, H_2C(4), H_2C(5), H_2C(6)), 1.32 (3H, d, J=7.0, PhCH(CH_3)N), 1.39 (9H, s, $CH_2COOC(CH_3)_3$), 1.46 (9H, s, C(CH_3)$_3$ Boc), 1.86 (1H, dd, J=14.7, 9.4, H_2C(2)), 1.97 (1H, dd, J=14.7, 3.4, H_2C(2)), 3.07 (2H, m, H_2C(7)), 3.27 (1H, m, HC(3)), 3.48 (1H, d, J=15.1, PhCH_2N), 3.79 (1H, d, J=13.3, PhCH_2N), 3.80 (1H, q, J=7.0, PhCH(CH$_3$)N), 4.46 (1H, 's', BocNH), 7.21–7.42 (10H, Ph).

3.6. tert-*Butyl* (S)-3-amino-7-(tert-*butyloxycarbonylamino*)heptanoate **6**

A mixture of 5.71 g crude **5** and 1 g oxalic acid was hydrogenated with 0.2 g palladium on charcoal (10%) in 50 ml ethanol under 1 atm of hydrogen at 50°C during 5 h. After removal of the catalyst and solvent, the residue thus obtained was partitioned with water and isopropyl acetate. After removal of the organic phase, the aqueous phase was treated with potassium carbonate (2.0 g) and extracted with isopropyl acetate. Evaporation of the solvent yielded the crude base as a colorless oil. Upon treatment with oxalic acid (0.8 g, 8.9 mmol) in ethyl acetate: ethanol 4:1 (25 ml) we obtained: 2.42 g of the salt **6** as brilliant plates in 62% yield based on the amine derivative **4**. Mp: 134–135°C. $[\alpha]_D^{24}$=+7.62 (*c* 1.57, ethanol). MA: C: 52.94 (53.19), H: 8.15 (8.43), N: 6.87 (6.89), O: 31.81 (31.49). ^{1}H NMR (d_6-DMSO, 360 MHz): 1.24–1.59 (6H, m, H_2C(4), H_2C(5), H_2C(6)), 1.37 (9H, s, $CH_2COOC(CH_3)_3$), 1.42 (9H, s, C(CH_3)$_3$ Boc), 2.49 (1H, dd, J=16.7, 6.8, H_2C(2)), 2.59 (1H, dd, J=16.7, 5.9, H_2C(2)), 2.89 (2H, m, H_2C(7)), 3.34 (1H, m, HC(3)), 6.74 (1H, t (dd), J=5.4, BocNH), 8.48 (3H, NH_3^+). ^{13}C NMR (d_6-DMSO, 75 MHz): 24.7 (H_2C(5)), 30.7 (C(CH$_3$)$_3$), 31.3 (C(CH$_3$)$_3$), 32.0 (H_2C(4)), 34.9 (H_2C(6)), 40.8 (H_2C(2)), 42.5 (H_2C(7)), 50.2 (HC(3)), 78.2 (C(CH$_3$)$_3$), 81.7 (C(CH$_3$)$_3$), 165.5 (C=O), 170.25 (C=O). m/z (EI): 317 ([MH]$^+$, 32), 261 ([MH–C_4H_8]$^+$, 14), 205 ([MH–2×C_4H_8]$^+$, 24), 88 (100), 57 ([C_4H_9]$^+$, 97). IR (KBr): 2978 (m), 2942 (m), 1730 (s), 1693 (s), 1597 (m), 1547 (m), 1518 (s), 1460 (m), 1398 (m), 1367 (m), 1250 (s), 1223 (m), 1155 (s), 720 (m) cm^{-1}.

3.7. (S)-3,7-Diaminoheptanoic acid dihydrochloride

Compound **6** (free base) [250 mg (0.79 mmol)] were refluxed overnight in 3 ml of 6N HCl. After concentration and dilution with ethanol, 137 mg of the amino acid salt (β-homolysine dihydrochloride) in 78% yield were obtained. Mp: 198–200°C; $[\alpha]_D^{24}$=+15.1 (*c* 2.00, water).[12] A sample obtained via homologation of L-lysine gave the following data: mp: 198–200°C; $[\alpha]_D^{24}$=+15.3 (*c* 2.00, water). MA: C: 35.87 (36.06), H: 7.49 (7.78), N: 11.88 (12.02), O: 13.69 (13.73). ^{1}H NMR (CD_3OD, 360 MHz): 1.53 (2H, m, H_2C(5)), 1.76 (4H, m, H_2C(4), H_2C(6)), 2.69 (1H, dd, J=17.6, 7.6, H_2C(2)), 2.80 (1H, dd, J=17.5, 4.9, H_2C(2)), 2.98 (2H, 't', J=7.4, H_2C(7)), 3.58 (1H, m, HC(3)). ^{13}C NMR (CD_3OD, 90 MHz): 23.3 (C(5)), 28.1 (C(4)), 33.1 (C(6)), 36.9 (C(2)), 40.4 (C(7)), 49.5 (C(3)), 173.6 (C(1)).

3.8. tert-*Butyl* (1S,2S,αS)-2-(N-*benzyl*-N-α-*methylbenzylamino*)*cyclohexanecarboxylate* **7**

A mixture of 5.00 g (14.1 mmol) of crude **2** and 3.28 g (15.5 mmol) of (*S*)-(α-methylbenzyl)-benzylamine in 140 ml anhydrous dimethoxyethane was cooled to –60°C before adding 7.8 ml (18.3 mmol) of a 2.36 M solution of hexyllithium in hexane. After stirring at –60°C for 30 min, the temperature was allowed to rise slowly to 0°C during 2.5 h and maintained at 0°C for 1 h. The reaction mixture was then quenched with 100 ml of water, acidified to pH=1 with HCl (10%),

and extracted with 100 ml of isopropyl acetate. The organic phase was treated with 100 ml of a 10% aqueous potassium carbonate solution, dried over $MgSO_4$ and evaporated to dryness leaving 2.95 g of crude product **7** as a yellow oil. Flash column chromatography over silica gel with hexane:ethyl acetate (20:1) as eluent yielded 1.54 g (28%) of **7** as a colorless oil. $[\alpha]_D^{24}=+26.0$ (*c* 1.25, $CHCl_3$); lit.:[7] $[\alpha]_D^{24}=+30.4$ (c 1.00, $CHCl_3$). ^{1}H NMR: 0.83–1.80 (8H, m, H_2C(3,4,5,6)), 1.37 (3H, d, $J=7.0$), 1.46 (9H, s, C(CH_3)$_3$), 2.22 (1H, ddd, 'dt', $J=11.4$, 11.4, 3.7, *H*C(1)), 3.03 (1H, ddd, 'dt', $J=11.4$, 11.4, 3.3, *H*C(2)), 3.69 (1H, d, $J=14.5$, PhCH_2N), 3.75 (1H, d, $J=14.5$, PhCH_2N), 4.07 (1H, q, $J=6.9$, PhC*H*(CH$_3$)N), 7.15–7.32 (10H, Ph). ^{13}C NMR: 19.1 (PhCH(*C*H$_3$)N), 25.2 (CH$_2$), 25.7 (CH$_2$), 28.0 (CH$_2$), 28.1 (C(*C*H$_3$)$_3$), 30.7 (CH$_2$), 49.5 (Ph*C*H$_2$N), 50.1 (CH), 60.0 (CH), 60.2 (CH), 79.4 (*C*(CH$_3$)$_3$), 125.9 (CH Ph), 126.3 (CH Ph), 126.4 (CH Ph), 127.7 (CH Ph), 128.0 (CH Ph), 128.9 (CH Ph), 141.9 (C Ph), 144.7 (C Ph), 175.0 (*C*OO^{t}Bu). *m*/*z* (CI): 422 ([M+C$_2$H$_5$]$^+$, 6), 394 ([M+H]$^+$, 94), 393 (M$^+$, 97), 338 ([M–^{t}Bu+2H]$^+$, 100), 288 ([M–PhMeCH]$^+$, 38), 234 (62), 105 ([PhMeCH]$^+$, 23), 91 ([Bn]$^+$, 17).

3.9. tert-*Butyl (*S*)-piperidine-2-acetate* ***8***

Crude **3** [10.0 g (17.6 mmol)] in 200 ml ethanol were hydrogenated at 50°C with 3 g palladium on charcoal under 20 bar of hydrogen during 5 h. After removal of the catalyst, concentration of the solution and addition of ether, the toluenesulfonic acid salt of **8** was obtained as white crystals (3.20 g, 48.9%); mp: 112°C, $[\alpha]_D^{24}=+11.7$ (*c* 1.65, MeOH). MA: C: 57.35 (58.20), H: 7.48 (7.87), N: 3.86 (3.77), O: 21.74 (21.53). Treatment of this salt in CH_2Cl_2 with 10% aqueous K_2CO_3 led to the free base **8** as a colorless liquid. $[\alpha]_D=+8.3$ (*c* 1.35, CH_2Cl_2). MA: C: 65.60 (66.29), H: 10.58 (10.62), N: 6.90 (7.03), O: 16.25 (16.06). ^{1}H NMR: 1.10–1.51 (3H, m, H_{ax}C(3,4,5)), 1.44 (9H, s, C(CH_3)$_3$), 1.55–1.81 (3H, m, H_{eq}C(3,4,5)), 2.12 (1H, s, NH), 2.29 (2H, 'd', $J=6.5$, CH_2COO^{t}Bu), 2.66 (1H, m, H_{ax}C(6)), 2.87 (1H, m, HC(2)), 3.05 (1H, m, H_{eq}C(6)). ^{13}C NMR: 24.4 (H_2C), 25.8 (H_2C), 27.9 (C(*C*H$_3$)$_3$), 32.2 (H_2C), 42.5 (H_2C), 46.6 (H_2C), 53.3 (H*C*(2)), 80.3 (*C*(CH$_3$)$_3$), 171.6 (*C*OO^{t}Bu). Hydrolysis with 6N HCl (overnight at 100°C) and recrystallization from methanol–ether gave piperidine-2-acetic acid hydrochloride in quantitative yield. Mp: 178–179°C; $[\alpha]_D^{24}=+28.0$ (*c* 1.10, water). Lit.:[13] mp: 180–182°C. The free amino acid was isolated over DOWEX 50 W X 4 (NH_4) and recrystallized from methanol–ether. Mp: 229°C; $[\alpha]_D^{24}=+41.7$ (*c* 1.02, water). Lit.:[14] mp: 234–235°C; $[\alpha]_D^{24}=+33.5$ (*c* 0.60, water). ^{1}H NMR (D_2O, 300 MHz): 1.32–1.50 (3H, m, H_{ax}C(3,4,5)), 1.71–1.79 (3H, m, H_{eq}C(3,4,5)), 2.34 (2H, 'd', $J=6.6$, CH_2COOH), 2.85 (1H, m, H_{ax}C(6)), 3.19–3.28 (2H, m, HC(2) and H_{eq}C(6)). ^{13}C NMR (D_2O, 75 MHz): 22.8 (H_2C), 23.3 (H_2C), 29.5 (H_2C), 41.3 (H_2C), 45.9 (H_2C), 55.9 (H*C*(2)), 178.8 (*C*OOH).

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