A Practical and Stereoconservative Synthesis of (*R*)-3-Amino-4-(trimethylammonio)butanoate [(*R*)-Aminocarnitine], and Its Trimethylphosphonium and Simple Ammonium Analogues Starting from D-Aspartic Acid

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We have developed a new stereospecific synthesis of (*R*)-aminocarnitine using D-aspartic acid as the starting material. This strategy, which is simple and amenable to an industrial scale-up, gives the target compound in six steps and in fairly good overall yields (41%). Other aminocarnitine related molecules such as optically pure (*R*)-3-amino-4-(trimethylphosphonio)butanoic acid and (*R*)-3,4-diaminobutanoic acid dihydrochloride have also been prepared according to the same synthetic strategy.

(*R*)-Aminocarnitine **1** and its long chain *N*-acyl derivatives **2** have been described to possess the following interesting pharmacological properties: they inhibit fatty acid oxidation and reduce hyperglycaemia and ketosis.[1] We have recently evaluated some long chain *N*-acylaminocarnitines and related congeners as potential reversible CPT I inhibitors;[2] for example **2b**, a derivative of urea, is in clinical phase 1 at present (Figure 1). Currently available syntheses of (*R*)-aminocarnitine do not allow its large-scale preparation. Even on a laboratory scale, the large number of steps, low yields and the use of hazardous reagents make the synthesis impractical; also, separation of enantiomers is often required.[3] In view of a stereospecific approach, the skeleton of L-aspartic acid has often been selected as a suitable precursor; accordingly, two synthetic strategies have been reported in the literature. One uses *N*-benzyloxycarbonyl-L-asparagine as the starting material; (*R*)-aminocarnitine is synthesized in seven steps with an overall yield of 24%, but the procedure requires diazomethane, silver benzoate and dimethylsulfate.[1e] The other procedure affords (*R*)-aminocarnitine from *N*-benzyloxycarbonyl-L-aspartic acid *tert*-butyl ester, again in seven steps with an overall yield of 22%; diazomethane, silver benzoate, catalytic hydrogenation and methylation with methyl iodide are involved.[3a]

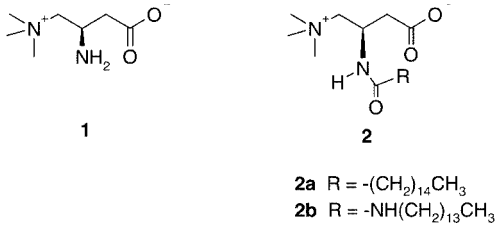

Figure 1. **1**: (*R*)-aminocarnitine; **2a**: (*R*)-(palmitoylamino)carnitine; **2b**: (*R*)-(tetradecylcarbamoylamino)carnitine

A few years ago, we described an original synthesis of (*R*)-aminocarnitine starting from (*R*)-carnitine through a double inversion of configuration of the stereogenic center.[4] Yields were good (49%) and the enantiomeric purity was complete. Nevertheless, reagents and processes are not particularly adequate for a large-scale and especially for an industrial plant. With the aim of pursuing a stereospecific synthesis of (*R*)-aminocarnitine which could be simple and safely performed, and also suitable to an industrial plant, we have explored a new strategy, which again makes use of aspartic acid as the starting material. It actually affords the target compound in six steps in a stereoconservative way. Yields are fairly good (41%) and reagents and processes are safe as well as industrially convenient.[5] Chromatographic steps are not required, using our method. Such a strategy also has the potentiality of leading to other related molecules by a simple route.

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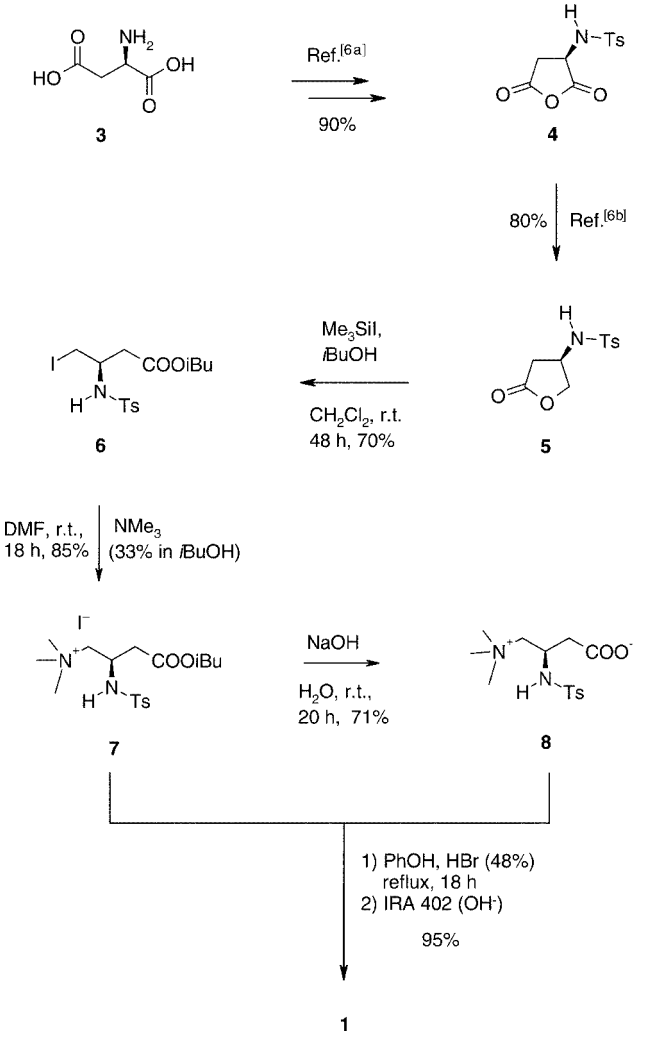
Commercial D-aspartic acid **3** was readily converted into (R)-3-(tosylamino)butano-4-lactone (**5**; Scheme 1) in three steps, according to the literature.[6] In our laboratory, we were able to produce **5** with an overall yield of 72%. Due to possible racemization in the formation of *N*-tosylaspartic anhydride **4**, it is recommended to maintain the bath temperature below 30 °C. This temperature is sufficient for the reaction progress and also prevents any possible racemization during the solvent evaporation step. In fact, at higher reaction temperatures, we observed partial racemization: even at 35 °C, the final product **1** has 76% *ee*. Treatment of lactone **5** with iodotrimethylsilane and isobutyl alcohol in anhydrous dichloromethane, for 48 h at room temperature (as described in the case of the ester formation in ref.[6b]), gave the iodo ester **6** in 70% yield.[7] Nucleophilic substitution on **6** with trimethylamine in isobutanol was performed in DMF (18 h at room temperature). (*R*)-*N*-(Tosylamino)carnitine isobutyl ester **7** was obtained in 85% yield. Compound **7** was then fully deprotected by using 48% hydrobromic acid and phenol (18 h reflux) to give **1** as the dihydrobromide salt; final ion-exchange resin treatment (IRA, 402, OH^- form) gave **1** (free base, inner salt) in 95% yield. The overall yield of (*R*)-aminocarnitine was 41% with 98% *ee* as determined by HPLC after derivatization with *o*-phthalaldehyde and acetyl-L-cysteine.[8]

Alternatively, selective hydrolysis of the isobutyl ester **7** with sodium hydroxide gave **8** in 71% yield. The compound **8** can be considered as a potentially useful (*R*)-aminocarnitine derivative.[1e] Deprotection of the tosyl group was also performed as described for **7**, to give **1** in 95% yield (67% from **7**).

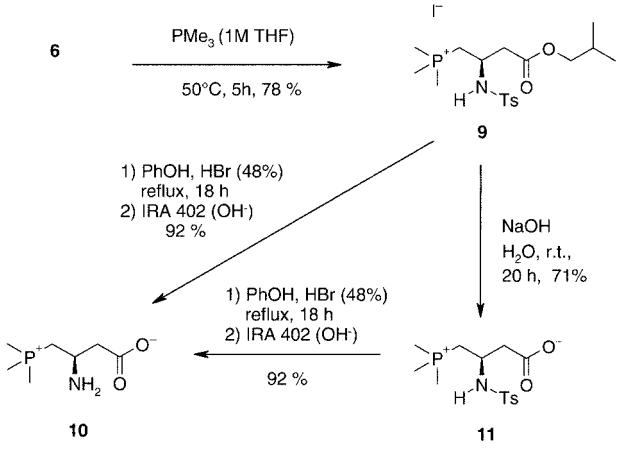
A small-scale preparation is reported in the Exp. Sect. for convenience. However, the entire synthetic procedure has been performed several times by starting from 130 g of D-aspartic acid, with overall yields always above 40%.

The easy preparation of **6** was also exploited for the synthesis of new, potentially pharmacologically interesting compounds. Accordingly (Scheme 2), **9** was obtained from **6** by treatment with trimethylphosphane (THF solution, 5 days at room temperature or 5 h at 50 °C). (*R*)-4-Trimethylphosphonio-3-aminobutyrate (**10**), as well as its tosyl derivative **11**, were prepared following the same procedure used for the synthesis of **1** and **8**, respectively. The enantiopurity of **10** was checked by HPLC as described in ref.[8]. The synthesis of *N*-functionalized derivatives of **10** is also in progress in our laboratory, in order to evaluate their pharmacological activity.

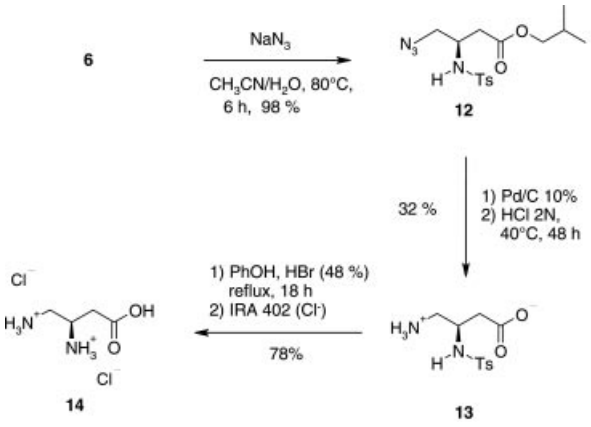
Intermediate **6** is also a useful chiral building block for the synthesis of (*R*)-3,4-diaminobutyric acid dihydrochloride (**14**; Scheme 3),[3d,9] an (*R*)-aminocarnitine congener. Compound **12** was obtained through a nucleophilic substitution of iodine on **6** with sodium azide. Subsequent reduction of the azido group with Pd/C in HCl, followed by hydrolysis gave **13**, which was finally deprotected and treated with an anion exchange resin in the chloride form to give the (*R*)-3,4-diaminobutyric acid dihydrochloride **14**. The enantiopurity of **14**, as well as that of the intermediates for the whole synthetic procedure was, in the absence of a general method for *ee* assessment, not determined. However, we can confidently assume that they present a high *ee*, based on the checked optical purity of the final products **1** and **10**.



Scheme 1. Synthesis of (*R*)-aminocarnitine starting from D-aspartic acid



Scheme 2. Synthesis of (*R*)-3-amino-4-(trimethylphosphonio)butanoate starting from **6**



Scheme 3. Synthesis of (*R*)-3,4-diaminobutanoic acid dihydrochloride starting from **6**

In conclusion, the synthetic strategy described in this paper allows a stereospecific, straightforward, and practical synthesis of enantiomerically pure (*R*)-aminocarnitine as well as its analogues, which can be employed as useful intermediates for the preparation of biologically active compounds.

Experimental Section

Melting points were determined by the capillary method on a thermal apparatus and are uncorrected. ^{1}H NMR spectra were measured at 300 MHz or at 200 MHz; chemical shifts were expressed in δ values relative to TMS, or DDS in the case of spectra recorded in D_2O. MS (FAB) spectra were recorded on a VG MASSLAB TRIO-2 apparatus. Electrospray mass spectra were recorded in positive mode on an ESI LCQ Classic Thermo-Finnigan ion-trap spectrometer. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 Merck prescored plates (5 cm × 10 cm). All reagents and anhydrous solvents were used as commercially available, with the exception of trimethylamine 33% isobutanolic solution, which was prepared by bubbling gaseous trimethylamine into isobutyl alcohol; a rough measurement of the trimethylamine content was performed by weighing the solution after of the gas.The preparation (*R*)-3-(tosylamino)-γ-butyrolactone (**5**) was performed as described.[6a][6b]

Isobutyl (*R*)-4-Iodo-3-(tosylamino)butanoate (6): Iodotrimethylsilane (6.55 mL, 48.18 mmol) was added to a solution of **5** (4.1 g, 16.06 mmol) and isobutyl alcohol (7.4 mL, 80.3 mmol) in anhydrous CH_2Cl_2 (47 mL) chilled to 0 °C with an ice-bath. The resulting dark solution was stirred at room temperature for 48 hours. H_2O was added and stirring was continued for 5 min. The organic layer was washed with 5% $Na_2S_2O_3$ solution, then H_2O, dried over anhydrous Na_2SO_4, and finally evaporated. The crude product was purified by crystallization from Et_2O/hexane to give **6** in 70% yield; m.p. 82−83 °C. $[\alpha]_D^{20}$ = +15.2 (*c* = 1% in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.90 [d, $^3J_{H,H}$ = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.85 [m, 1 H, $CH(CH_3)_2$], 2.40 [s, 3 H, $PhCH_3$], 2.50 [dd, ^2J = 16.6, $^3J_{H,H}$ = 6.2 Hz, 1 H, $CHHCOOiBu$], 2.70 [dd, ^2J = 16.6, $^3J_{H,H}$ = 5.0 Hz, 1 H, $CHHCOOiBu$], 3.20 [dd, ^2J = 10.3, $^3J_{H,H}$ = 6.7 Hz, 1 H, $ICHH$], 3.30 [dd, ^2J = 10.3, $^3J_{H,H}$ = 4.1 Hz, 1 H, $ICHH$], 3.50 [m, 1 H, C*H], 3.80 [m, 2 H, $CH_2CH(CH_3)_2$], 5.20 [d, $^3J_{H,H}$ = 9.1 Hz, 1 H, NH], 7.30 [d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic], 7.75 [d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic]. MS ESI = 457 [$[M + NH_4]^+$]; $C_{15}H_{22}INO_4S$ (439.3): calcd. C 41.01, H 5.04, N 3.18; found C 41.15, H 5.06, N 3.02.

Isobutyl (*R*)-3-(Tosylamino)-4-(trimethylammonio)butanoate Iodide (7): Trimethylamine (32.7% isobutanolic solution, 1.25 mL, 6.96 mmol) was added to a solution of **6** (1.53 g, 3.48 mmol) in anhydrous DMF (16 mL). The resulting solution was stirred at room temperature for 18 h. After complete precipitation with diethyl ether, the white solid residue was triturated with diethyl ether (3×) to give **7** (1.47 g, 85%); m.p. 173−175 °C. $[\alpha]_D^{20}$ = +13.2 (*c* = 0.49% in MeOH). ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 0.85 [d, $^3J_{H,H}$ = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.80 [m, 1 H, $CH(CH_3)_2$], 2.00 (dd, ^2J = 17.6, $^3J_{H,H}$ = 3.2 Hz, 1 H, $CHHCOOiBu$), 2.35 (dd, ^2J = 17.6, $^3J_{H,H}$ = 8.6 Hz, 1 H, $CHHCOOiBu$), 2.45 (s, 3 H, $PhCH_3$), 3.30 [s, 9 H, $N^+(CH_3)_3$], 3.50 (dd, ^2J = 14, $^3J_{H,H}$ = 1.7 Hz, 1 H, N^+CHH), 3.60 (dd, ^2J = 14, $^3J_{H,H}$ = 9.6 Hz, 1 H, N^+CHH), 3.80 [m, 2 H, $CH_2CH(CH_3)_2$], 4.30 [m, 1 H, C*H], 7.45 [d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic], 7.80 [d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic] ppm. MS ESI = 371 [M − I]$^+$; $C_{18}H_{31}IN_2O_4S$ (498.4): calcd. C 43.37, H 6.27, N 5.62; found C 43.01, H 6.47, N 5.38.
Alternatively, the reaction was carried out in anhydrous dichloromethane at room temperature for 5 days. After evaporation of the solvent and trituration with diethyl ether of the residue, the product was isolated in the same yield.

(*R*)-3-(Tosylamino)-4-(trimethylammonio)butanoate (8): A solution of **7** (153 mg, 0.3 mmol) in NaOH (1.2 mL, 1 N), was stirred at room temperature for 20 h, then the aqueous phase was evaporated under vacuum and the crude product was purified by flash chromatography (using as eluent a gradient of $CHCl_3$/CH_3OH starting from 5:5 to 2:8) to give 66.9 mg of (*R*)-(tosylamino)carnitine inner Salt (71%); m.p. 204−206 °C (decomp). $[\alpha]_D^{20}$ = +40.5 (*c* = 0.4% in H_2O). ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 1.75 [dd, ^2J = 16.5, $^3J_{H,H}$ = 2.9 Hz, 1 H, $CHHC(O)O^-$], 1.90 [dd, ^2J = 16.5, $^3J_{H,H}$ = 9.4 Hz, 1 H, $CHHC(O)O^-$], 2.42 (s, 3 H, $PhCH_3$), 3.25 [s, 9 H, $N^+(CH_3)_3$], 3.40 (m, 2 H, N^+CH_2,), 4.15 (m, 1 H, C*H), 7.40 (d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic), 7.80 (d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic) ppm. MS ESI = 315 [M + H]$^+$; $C_{14}H_{22}N_2O_4S$ (314.4): calcd. C 53.48, H 7.05, N 8.91; KF = 5.77%; Calcd. with KF: calcd. C 50.39, H 7.29, N 8.39; found C 50.09, H 7.17, N 8.15.

(*R*)-3-(Amino)-4-(trimethylammonio)butanoate [(*R*)-Aminocarnitine Inner Salt] (1): A round bottom flask containing a mixture of **7** (827 mg, 1.66 mmol), phenol (468 mg, 4.98 mmol) and HBr (48%, 6 mL) was placed in an oil bath previously heated to 130 °C and refluxed for 18 hours. The reaction mixture was then allowed to reach room temperature, diluted with water and extracted twice with EtOAc. The aqueous layer was evaporated under vacuum, the residue was taken up several times with CH_3CN (evaporating under vacuum every time) until a solid residue, insoluble in CH_3CN, was obtained. The solid was filtered and dried to give (*R*)-aminocarnitine as dihydrobromide salt (509 mg, 95%). After dissolving in water (5 mL), elution over an ion-exchange resin IRA 402 (OH^-, 9 mL) and evaporation of the under vacuum, the residue was taken up twice with CH_3CN and then several times with CH_3OH (every time evaporating the solvent under vacuum) to give 252 mg of **1** (quantitative yield for this step); e.e. > 99% (determinate as described in ref.[8]); m.p. 150 °C (decomp). $[\alpha]_D^{20}$ = −21.1 (*c* = 0.4% in H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 2.55 [dd, ^2J = 1.85, $^3J_{H,H}$ = 6.9 Hz, 1 H, $CHHC(O)O$], 2.58 [dd, ^2J = 1.85, $^3J_{H,H}$ = 6.5 Hz, 1 H, $CHHC(O)O$], 3.15 [s, 9 H, $N^+(CH_3)_3$], 3.22 [dd, ^2J = 13.8, $^3J_{H,H}$ = 7.6 Hz, 1 H, N^+CHH], 3.35 (dd, ^2J = 13.8, $^3J_{H,H}$ = 2.6 Hz, 1 H, N^+CHH), 3.50 (m, 1 H, C*H) ppm. MS (FAB) = 161 [M + H]$^+$; $C_7H_{16}N_2O_2$ (160.2): calcd. C 52.47, H 10.06, N 17.48;

KF = 7%; Calcd. with KF: calcd. C 48.79, H 10.14, N 16.26; found C 48.77, H 10.34, N 16.33.

Isobutyl (*R*)-3-(Tosylamino)-4-(trimethylphosphonio)butanoate Iodide (9): Trimethylphosphane was added (1 M in THF, 5.4 mL) to **6** (2 g, 4.5 mmol). The resulting solution was stirred at room temperature for 5 days (or at 50 °C for 5 h in a sealed flask), then the solvent was removed under vacuum and the residue was triturated with diethyl ether (3×) to give **9** (1.81 g, 78%); m.p. 159−161 °C (decomp). $[\alpha]_D^{20}$ = +21.0 (*c* = 0.51% in MeOH). ^{1}H NMR (300 MHz, CD_3OD, 25 °C): δ = 0.82 [d, $^3J_{H,H}$ = 6.8 Hz, 6 H, $CH(CH_3)_2$], 1.80 [m, 1 H, $CH(CH_3)_2$], 2.00 [d, $^2J_{P,H}$ = 14.6 Hz, 9 H, $P^+(CH_3)_3$], 2.10 [m, 1 H, CHHC(O)O], 2.30 [m, 1 H, CHHC(O)O], 2.40 (s, 3 H, $PhCH_3$), 2.60 (m, 2 H, P^+CH_2), 3.70 [d, $^3J_{H,H}$ = 6.6 Hz, 2 H, $CH_2CH(CH_3)_2$], 4.10 (m, 1 H, C*H), 7.40 (d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic), 7.75 (d, $^3J_{1,3}$ = 8.2 Hz, 2 H, aromatic) ppm. $C_{18}H_{31}INO_4PS$ (515.4): calcd. C 41.95, H 6.06, N 2.71, S 6.22; found C 42.33, H 6.16, N 2.88, S 6.22.

(*R*)-3-(Tosylamino)-4-(trimethylphosphonio)butanoate (11): A solution of **9** (1.71 g, 3.3 mmol) in NaOH (15.5 mL, 1 N) was stirred at room temperature for 20 h, then the aqueous phase was evaporated under vacuum and the crude product purified by flash chromatography (using as eluent a gradient of $CHCl_3/CH_3OH$ of 9:1 to 5:5) to give **11** (530 mg, 41.4% yield); m.p. 192−194 °C (decomp). $[\alpha]_D^{20}$ = +45.5 (*c* = 0.5% in MeOH). ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 1.72−1.92 [m, 2 H, $CH_2C(O)O$, and d, $^2J_{P,H}$ = 14.6 Hz, 9 H, $P^+(CH_3)_3$], 2.26−2.50 (m, 5 H, $PhCH_3$, P^+CH_2), 3.86 (m, 1 H, C*H), 7.35 (d, $^3J_{1,3}$ = 8.3 Hz, 2 H, aromatic), 7.66 (d, $^3J_{1,3}$ = 8.3 Hz, 2 H, aromatic) ppm. $C_{14}H_{22}NO_4PS$ (331.4): calcd. C 50.74, H 6.69, N 4.22, S 9.67; KF = 6.1%; Calcd. with KF: calcd. C 47.66, H 6.96, N 3.97, S 9.08; found C 47.50, H 6.85, N 3.92, S 8.78.

(*R*)-3-Amino-4-(Trimethylphosphonio)butanoate (10): A round bottom flask containing a mixture of **9** (1.9 g, 3.7 mmol), phenol (1.04 g, 11.06 mmol) and HBr (27 mL, 48%) was placed in an oil bath previously heated to 130 °C and refluxed for 18 hours. The reaction mixture was then allowed to cool to room temperature, diluted with water and extracted twice with EtOAc. The aqueous layer was evaporated under vacuum, the residue was taken up several times with CH_3CN (evaporating under vacuum every time) until a solid residue, insoluble in CH_3CN, was obtained. The solid was filtered and then dissolved in 5 mL of water and eluted over an exchange ion resin IRA 402 (OH^-, 50 mL). After evaporation under vacuum, the residue was taken up twice with CH_3CN and then several times with CH_3OH (every time evaporating the solvent under vacuum) to give **10** (600 mg, 92% yield); e.e. > 99% (determined as described in ref.[8]); m.p. 66−68 °C (decomp). $[\alpha]_D^{20}$ = −21.3 (*c* = 1% in H_2O). MS = 178M + H]$^+$. ^{1}H NMR (300 MHz, D_2O, 25 °C): δ = 1.75 [d, $^2J_{P,H}$ = 14.6 Hz, 9 H, $P^+(CH_3)_3$], 2.10−2.35 [m, 4 H, $CH_2C(O)O$, P^+CH_2], 3.30 [m, 1 H, C*H] ppm. $C_7H_{16}NO_2P$ (177.2): calcd. C 47.45, H 9.10, N 7.90; KF = 16.3%; Calcd. with KF: calcd. C 39.71, H 9.44, N 6.61; found C 39.98, H 9.49, N 6.79.

Isobutyl (*R*)-4-Azido-3-(tosylamino)butanoate (12): NaN_3 (592 mg, 9.11 mmol) was added to a solution of **6** (1 g, 2.27 mmol) in CH_3CN (10 mL) and H_2O (2 mL). The resulting suspension was stirred at 80 °C for 6 hours, then the solvent was removed under vacuum and the crude residue was diluted with water and extracted twice with diethyl ether. The organic layer was dried over anhydrous Na_2SO_4, and finally evaporated to obtain 790 mg of crude product as a light yellow wax, which was used without further purification (yield = 98%). $[\alpha]_D^{20}$ = +15.2 (*c* = 0.45% in MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.90 [d, $^3J_{H,H}$ = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.85 [m, 1 H, $CH(CH_3)_2$], 2.40 (s, 3 H, $PhCH_3$), 2.50 [m, 2 H, $CH_2C(O)O$], 3.40 (m, 2 H, N_3CH_2), 3.70 (m, 1 H, C*H), 3.80 [m, 2 H, $CH_2CH(CH_3)_2$], 5.30 [d, $^3J_{H,H}$ = 7.5 Hz, 1 H, NH], 7.30 (d, $^3J_{1,3}$ = 8.1 Hz, 2 H, aromatic), 7.75 (d, $^3J_{1,3}$ = 8.1 Hz, 2 H, aromatic) ppm. $C_{15}H_{22}N_4O_4S$ (354.4): calcd. C 50.83, H 6.25, N 15.80; S 9.04; found C 51.15, H 6.34, N 15.41, S 8.71.

(*R*)-4-Amino-3-(tosylamino)butyric Acid Hydrochloride (13): A solution of **12** (1.1 g, 3.0 mmol) in HCl (2 N, 143 mL) was hydrogenated under a H_2 atmosphere overnight at 60 psi. The resulting residue was filtered and the aqueous phase was left to stir for an additional 48 hours at 40 °C. The water was evaporated under vacuum and the residue was taken up twice with CH_3CN (evaporating under vacuum every time) until a solid residue, insoluble in CH_3CN, was obtained. The pale yellow wax was filtered and dried to give of final product (300 mg, 32% yield), which was used without further purification. $[\alpha]_D^{20}$ = +43 (*c* = 0.25% in H_2O). ^{1}H NMR (200 MHz, D_2O, 25 °C): δ = 2.10−2.40 [m, 5 H, $PhCH_3$, $CH_2C(O)O$], 3.00 (m, 2 H, N^+CH_2), 3.75 (m, 1 H, C*H), 7.35 (d, $^3J_{1,3}$ = 8.3 Hz, 2 H, aromatic), 7.70 (d, $^3J_{1,3}$ = 8.3 Hz, 2 H, aromatic) ppm.

(*R*)-3,4-Diaminobutanoic Acid Dihydrochloride (14): A round-bottom flask containing a mixture of **13** (600 mg, 1.94 mmol), phenol (547 mg, 5.82 mmol) and HBr (7.5 mL, 48%) was placed in an oil bath previously heated to 130 °C and refluxed for 18 hours. The reaction mixture was then allowed to cool to room temperature, diluted with water and extracted twice with EtOAc. The aqueous layer was evaporated under vacuum, the residue was taken up several times with CH_3CN (evaporating under vacuum every time) until a solid residue, insoluble in CH_3CN, was obtained. The solid was filtered and dried to give (*R*)-3,4-diaminobutanoic acid as the dihydrobromide salt (230 mg, 95%). The residue was dissolved in 5 mL of water, and after elution over an exchange ion resin IRA 402 (Cl^-, 75 mL) and evaporation under vacuum, taken up twice with CH_3CN and then several times with CH_3OH (every time evaporating the solvent under vacuum) to give **14** (123 mg, 78% yield) as a colorless wax. $[\alpha]_D^{20}$ = +4.3 (*c* = 1% in H_2O). ^{1}H NMR (300 MHz, D_2O, 25 °C, DDS): δ = 2.60 [dd, ^2J = 18, $^3J_{H,H}$ = 7.0 Hz, 1 H, CHHC(O)O], 2.75 [dd, ^2J = 18, $^3J_{H,H}$ = 5.7 Hz, 1 H, CHHC(O)O], 3.35 (m, 2 H, N^+CH_2), 3.85 (m, 1 H, C*H); $C_4H_{12}N_2O_2Cl_2$ (191.1): calcd. C 25.14, H 6.33, N 14.66, Cl 37.11; KF = 21.4%; Calcd. with KF: calcd. C 19.76, H 7.37, N 11.52, Cl 29.17; found C 19.49, H 7.16, N 11.37, Cl 28.80.

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[7] Isobutyl esters are prone to crystallize and less hygroscopic than the ethyl ester derivative. The ethyl ester of **6** has also been prepared: the advantage in this latter case is the possibility of using commercially available 30% trimethylamine in ethanol in the following step. The ethyl ester also gives (*R*)-aminocarnitine in the same yield and *ee* as the isobutyl derivative.

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