Pergamon

Tetrahedron 57 (2001) 6505–6509

TETRAHEDRON

Asymmetric synthesis of (*S*)-(+)-carnitine and analogs

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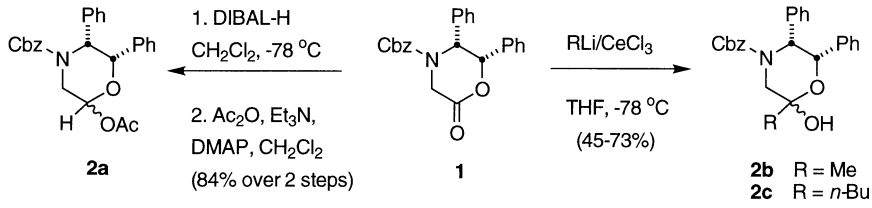
Received 12 February 2001; revised 23 March 2001; accepted 13 April 2001

Abstract—A general asymmetric route to enantiomerically pure (S)-(+)-carnitine and analogs has been investigated that involves monoaddition of organometallic reagents to the lactone carbonyl group of (*5R,6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one and Lewis acid promoted stereoselective allylation of the resulting hemiacetals. The diastereomerically pure allyl oxazines thus obtained were readily converted into enantiomerically pure (*S*)-(+)-carnitine and two substituted analogs.

The asymmetric synthesis of carnitine and its analogs has attracted considerable interest in recent years due to their important biological activities. (*R*)-(−)-carnitine plays an important role in biochemical pathways for β-oxidation of fatty acids and is involved in other important metabolic functions, both as free carnitine and as acyl carnitines.[1,2] In addition, it has been found that this substance has clinical applications as a hypolipidemic agent in hemodialysis patients[3] as well as in the treatment of myocardial ischemia[4] and seizure.[5] Interestingly, the antipode, (*S*)-(+)-carnitine acts as a competitive inhibitor of carnitine acyltransferase[6] causing depletion of carnitine.

Several approached have been reported in the literature for the synthesis of carnitine and its analogs including asymmetric syntheses,[7] utilization of chiral starting materials,[8] chemical resolution,[9] enzymatic or microbial techniques[10] and others.[11] Herein, we report a general method for the synthesis of (S)-(+)-carnitine and its analogs using commercially available (*5R,6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1**)[12] as a starting material.

The approach that was examined involved the sequential nucleophilic addition of organometalic agents to the lactone carbonyl group of **1**, with the objective of creating a quaternary stereogenic center with high diastereoselectivity. Initial investigations were conducted with MeLi as the first nucleophile. Thus, reaction of **1** with MeLi at −78°C in a variety of etheral solvents (Et_2O, THF, DME) resulted in the formation of the desired monoaddition product **2b** as a minor product (<25%) with recovery of a significant amount of unreacted starting material (Scheme 1). This was rationalized due to the competing enolization of **1** as a result of abstraction of the α-hydrogen by the alkyl lithium. However, addition of anhydrous $CeCl_3$ proved beneficial and the reaction of **1** with MeLi/$CeCl_3$[13] (THF, −78°C, 4 h) generated the desired hemiacetal **2b** in 73% yield as a mixture of diastereomers at C2. Reaction of **1** with *n*-BuLi under identical conditions generated **2c** in 45% yield (74% yield of **2c** on the basis of recovered starting material) obtained as a mixture of diastereomers at C2. Conversion of **1** into the unsubstituted acetoxy hemiacetal **2a** was achieved by reaction with DIBAL-H (CH_2Cl_2, −78°C, 30 min) followed by acetylation of the intermediate



Scheme 1.

Keywords: amino acids; carnitine; asymmetric synthesis.

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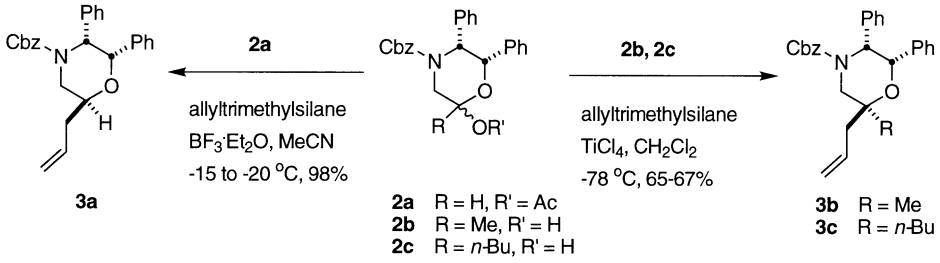


Scheme 2.

hemiacetal (Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C-rt, 12 h), as reported previously by our group[14] (Scheme 1).

Reaction of **2b** and **2c** with allyltrimethylsilane/$TiCl_4$ (CH_2Cl_2, −78°C, 1 h) proceeded with a high degree of diastereoselectivity to generate the desired coupling products **3b** (67% yield) and **3c** (65% yield) as single diastereomers (as evidenced by ^1H NMR analysis of the crude reaction products). The relative stereochemistry of the newly created stereogenic center in **3b** and **3c** was determined as '*S*' by ^1H NMR NOE measurements on **3b** and **3c**. Conversion of **2a** to **3a** was achieved by treatment with allyltrimethylsilane/$BF_3{\cdot}Et_2O$ (CH_3CN, −15 to −20°C, 30 min) as reported previously[14] (Scheme 2).

Modeling of the conformation of the putative oxocarbenium ion intermediate that is presumed to result from Lewis-acid-mediated removal of the acetoxy group from **2b** and **2c**, reveals that the oxazine ring adopts a boat-like conformation placing the phenyl ring adjacent to the ring nitrogen atom in *pseudo*-equatorial disposition mandating that the phenyl ring adjacent to the ring oxygen atom adopt an axial orientation (Fig. 1). The significantly less hindered face of this intermediate thus suffers nucleophilic attack by the allyl group to furnish the *anti*-isomers **3b** and **3c** (Fig. 1).

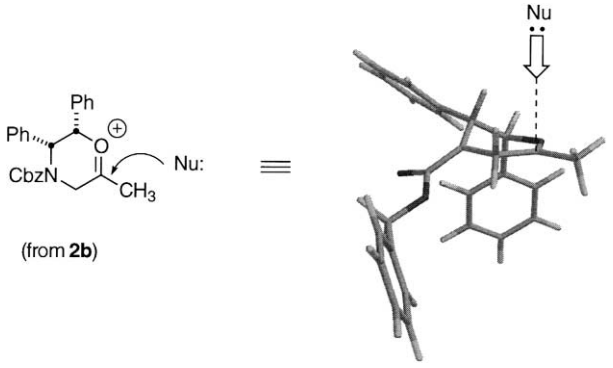
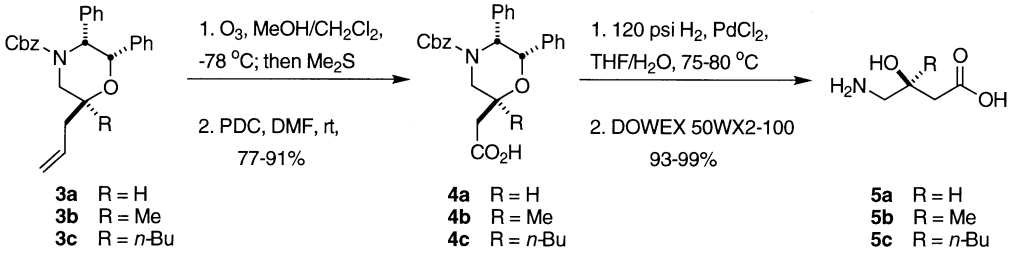


Figure 1. PM3 geometry optimization of the putative oxocarbenium ion intermediate using Spartan, C2 trivalent, overall molecular charge +1.

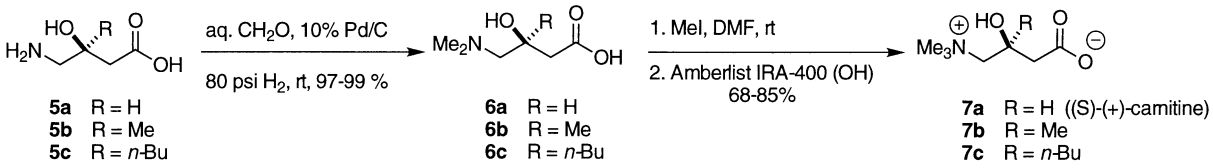
Oxidative cleavage of the allylic double bond in **3b** and **3c** with O_3 ($MeOH/CH_2Cl_2$, −78°C, then Me_2S) followed by treatment with PDC (DMF, rt, 24 h) cleanly generated the carboxylic acids **4b** and **4c** in excellent yields (88–91% over two steps). Conversion of **3a** to **4a** was achieved in a similar way as reported previously.[14] Removal of the chiral auxiliary in **4a–c** by hydrogenolysis ($PdCl_2$, 120 psi H_2, THF/H_2O, 75–80°C, 3 h) followed by treatment with DOWEX® 50WX2-100 ion-exchange resin generated the desired β-hydroxy-γ-amino acids **5a–c**[11a,15] in essentially quantitative yields (Scheme 3).

Reductive methylation of **5a–c** with aqueous formaldehyde (10% Pd/C, 80 psi H_2, rt, 36 h) generated the desired dimethylamino compounds **6a–c** in essentially quantitative yields. Quaternization of **6a–c** with MeI (DMF, rt, 12 h) followed by treatment with Amberlite® IRA-400 (HO-) ion-exchange resin generated (*S*)-(+)-carnitine **7a** ($[\alpha]_D^{25}=+28.1$ (*c* 1, H_2O); lit.[9c] $[\alpha]_D=-30.9$ (*c* 1, H_2O) for the enantiomer) and the carnitine analogs **7b**[11a] ($[\alpha]_D^{25}=+18.3$ (*c* 1, H_2O)) and **7c** ($[\alpha]_D^{25}=+4.6$ (*c* 1, H_2O)) in 68–85% yields (Scheme 4).

In summary, enantioselective syntheses of (*S*)-(+)-carnitine and two analogs have been achieved by the sequential mono-addition of organometallic reagents to the lactone carbonyl of (*5R,6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one, followed by Lewis acid-promoted stereoselective allylation of the resulting hemiacetals. Since (*5S,6R*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one is also commercially available,[12] the methodology described here provides convenient access to (*R*)-(−)-carnitine and the corresponding analogs in the (*R*)-enantiomer series. Current efforts in these laboratories are devoted to expanding this



Scheme 3.



Scheme 4.

methodology to preparation of other amino acids, peptide isosteres and alkaloids of biomedical significance.

1. Experimental

All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven dried glassware (120°C) that was cooled under argon. THF was distilled from sodium benzophenone ketyl and dichloromethane was distilled from CaH_2. Column chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh).^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 300 or 400 MHz spectrometer. Mass spectra were obtained on Fisons VG Autospec. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Optical rotations were obtained on a Rudolph Research automatic polarimeter Autopol III. Compounds **2a**, **3a**, and **4a** were prepared according to the reported procedures.[14]

1.1. General

1.1.1. General procedure for addition of alkyl lithium reagents to of (*5R,6S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one. To anhydrous cerium chloride[13] (1.2 equiv.) at 0°C was added anhydrous THF with vigorous stirring and the resulting suspension was warmed to and stirred at ambient temperature for 12 h after which the mixture was cooled to −78°C and the alkyl lithium was added over a period of 5 min. The resulting yellow suspension was stirred at the same temperature for 30 min after which a solution of **1** in anhydrous THF was added dropwise over a period of 15 min. The mixture was stirred at the same temperature for 4 h, quenched with saturated aq. NH_4Cl and warmed to ambient temperature. Dilute HCl was added and the mixture was extracted with ethyl acetate. The combined organic layer was dried (Na_2SO_4) and evaporated under reduce pressure to furnish the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixtures as eluents.

1.1.2. (*5R,6S*)-2-Hydroxy-2-methyl-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (2b). Prepared from anhydrous $CeCl_3$ (1.65 g, 6.7 mmol) in 20 mL THF, MeLi (1.4 M in Et_2O, 4.78 mL, 6.7 mmol) and **1** (2.12 g, 5.5 mmol) in 100 mL THF. Purification of the crude product by flash chromatography on silica gel (8:2 petroleum ether: ethyl acetate) furnished 1.6 g (73%) of **2b** as a white foam (mixture of diastereomers at C2). **^{1}H NMR** (300 MHz, $CDCl_3$, 300K) δ 7.50–7.00 (m, 15H), 5.80–5.00 (m, 4H), 4.13 and 4.03 (d, 1H, *J*=13.5 Hz), 3.22 (d, 1H, *J*=13.5 Hz), 2.69 and 2.57 (s, 1H), 1.68 and 1.64 (s, 3H); **IR** ($CHCl_3$) 3409, 1678 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{25}H_{26}NO_4$ (*m/z*) 404.1861, found (*m/z*) 404.1865.

1.1.3. (*5R,6S*)-2-Hydroxy-2-butyl-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (2c). Prepared from anhydrous $CeCl_3$ (0.99 g, 4 mmol) in 15 mL THF, *n*-BuLi (2.3 M in hexane, 1.74 mL, 4 mmol) and **1** (1.28 g, 3.3 mmol) in 50 mL THF. Purification of the crude product by flash chromatography on silica gel (8:2 petroleum ether: ethyl acetate) furnished 0.663 g (45%) of **2c** as a white foam (mixture of diastereomers at C2) and 0.509 g of unreacted **1** as a white solid (74% yield of **2c** on the basis of recovered **1**). **^{1}H NMR** (300 MHz, $CDCl_3$, 300K) δ 7.50–7.10 (m, 15H), 5.75–5.10 (m, 4H), 4.13 and 4.03 (d, 1H, *J*= 13.5 Hz), 3.23 (d, 1H, *J*=13.5 Hz), 2.81 and 2.65 (s, 1H), 2.00–0.80 (m, 6H), 1.04 (t, 3H, *J*=7.2 Hz); **IR** ($CHCl_3$) 3416, 1679, 1604, 1585 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{28}H_{32}NO_4$ (*m/z*) 446.2331, found (*m/z*) 446.2331.

1.1.4. General procedure for allylation of hemiacetals 2b and 2c. To a solution of **2b** and **2c** in anhydrous CH_2Cl_2 was added allyltrimethylsilane at −78°C followed by $TiCl_4$ (1 M solution in CH_2Cl_2) over a period of 15 min and the solution was stirred at −78°C for 1 h, after which it was quenched with saturated aq. NH_4Cl and warmed to ambient temperature. Water was added to dissolve the precipitated solids, and the solution was extracted with CH_2Cl_2. The combined organic phase was dried and concentrated to furnish the crude product which was purified by flash chromatography on silica gel using petroleum/ethyl acetate mixtures as eluents.

1.1.5. (*2S,5R,6S*)-2-Methyl-2-(2-propenyl)-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (3b). Prepared from **2b** (1 g, 2.48 mmol), allyltrimethylsilane (3.94 mL, 24.8 mmol) $TiCl_4$ (1 M solution in CH_2Cl_2, 9.92 mL, 9.92 mmol) in dichloromethane (10 mL). Purification of the crude product by flash chromatography on silica gel (9:1 petroleum ether:ethyl acetate) furnished 0.710 g (67%) of **3b** as a clear colorless gum. $[\alpha]_D^{25}$=−133.78 (*c* 1.9, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6, 393K) δ 7.35–7.02 (m, 15H), 5.84–5.70 (m, 1H), 5.45 (d, 1H, *J*= 3.6 Hz), 5.32 (d, 1H, *J*=3.6 Hz), 5.20 (d, 1H, *J*=12.6 Hz),), 5.12 (d, 1H, *J*=12.6 Hz), 5.14–5.03 (m, 2H), 3.79 (d, 1H, *J*=13.5 Hz), 3.02 (d, 1H, *J*=13.5 Hz), 2.71 (dd, 1H, *J*=7.2, 14.7 Hz), 2.37 (dd, 1H, *J*=7.5, 14.7 Hz), 1.33 (s, 3H); **IR** ($CHCl_3$) 1697 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{28}H_{30}NO_3$ (*m/z*) 428.2225; found (*m/z*) 428.2208.

1.1.6. (*2S,5R,6S*)-2-Butyl-2-(2-propenyl)-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (3c). Prepared from **2c** (0.250 g, 0.56 mmol), allyltrimethylsilane (0.89 mL, 5.6 mmol), $TiCl_4$ (1 M solution in CH_2Cl_2, 2.24 mL, 2.24 mmol) in dichloromethane (3 mL). Purification of the

crude product by flash chromatography on silica gel (9:1 petroleum ether:ethyl acetate) furnished 0.173 g (65%) of **3c** as a clear colorless gum. $[\alpha]_D^{25}=-94.3$ (*c* 1, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6, 393K) δ 7.37–7.05 (m, 15H), 5.85–5.71 (m, 1H), 5.51 (d, 1H, *J*=3.6 Hz), 5.38 (d, 1H, *J*=3.6 Hz), 5.23 (d, 1H, *J*=12.3 Hz),), 5.16 (d, 1H, *J*=12.3 Hz), 5.14–5.05 (m, 2H), 3.77 (d, 1H, *J*=13.8 Hz), 3.06 (d, 1H, *J*=13.8 Hz), 2.70 (dd, 1H, *J*=6.6, 14.7 Hz), 2.47 (dd, 1H, *J*=7.2, 14.7 Hz), 1.73–1.65 (m, 2H), 1.54–1.34 (m, 4H), 0.95 (t, 3H, *J*=7.5 Hz); **IR** ($CHCl_3$) 1693, 1639, 1604, 1585 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{31}H_{36}NO_3$ (*m/z*) 470.2695; found (*m/z*) 470.2628.

1.1.7. General procedure for the oxidation of allyl oxazines 3b and 3c. To a solution of **3a** and **3b** in anhydrous MeOH and anhydrous CH_2Cl_2 was bubbled O_3 at −78°C until the solution turned blue. At this point Ar gas was bubbled through the solution for 5 min to remove excess of O_3. Me_2S was added and the mixture was warmed to and stirred at ambient temperature overnight. The residue obtained after the evaporation of solvent was taken up in water and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and evaporated to provide the crude aldehyde which was treated with PDC (3.5 equiv.) in anhydrous DMF for 24 h. Water was added followed by brine and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated to furnish the crude product which was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate mixtures as eluents.

1.1.8. (*2S,5R,6S*)-2-Methyl-2-(2-carboxyethyl)-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (4b). Prepared from **3b** (0.5 g, 1.17 mmol) in dichloromethane (10 mL) and MeOH (20 mL) to obtain 0.486 g of crude aldehyde which was treated with PDC (1.5 g, 3.98 mmol) in anhydrous DMF (4 mL) to obtain crude **4b** which on purification by flash chromatography on silica gel (1:1 petroleum ether:ethyl acetate) furnished 0.46 g of **4b** as a white foam (88% yield over two steps). $[\alpha]_D^{25}=-118.3$ (*c* 1, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6, 373K) δ 11.80 (br, 1H), 7.37–7.07 (m, 15H), 5.48 (d, 1H, *J*=3.6 Hz), 5.43 (d, 1H, *J*=3.6 Hz), 5.21 (d, 1H, *J*=12.9 Hz),), 5.14 (d, 1H, *J*=12.9 Hz), 4.01 (d, 1H, *J*=14.1 Hz), 3.04 (d, 1H, *J*=14.1 Hz), 2.85 (d, 1H, *J*=14.4 Hz), 2.72 (d, 1H, *J*=14.4 Hz), 1.54 (s, 3H); **IR** ($CHCl_3$) 3500–2700 (br), 1704, 1603, 1585 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{27}H_{28}NO_5$ (*m/z*) 446.1967; found (*m/z*) 446.1969.

1.1.9. (*2S,5R,6S*)-2-Butyl-2-(2-carboxyethyl)-5,6-diphenyl-morpholine-4-carboxylic acid benzyl ester (4c). Prepared from **3c** (0.5 g, 1.06 mmol) in dichloromethane (10 mL) and MeOH (20 mL) to obtain 0.482 g of crude aldehyde which was treated with PDC (1.5 g, 3.98 mmol) in anhydrous DMF (4 mL) to obtain crude **4c** which on purification by flash chromatography on silica gel (1:1 petroleum ether: ethyl acetate) furnished 0.47 g of **4c** as a white foam (91% yield over two steps). $[\alpha]_D^{25}=-127.8$ (*c* 1, $CHCl_3$); **^{1}H NMR** (300 MHz, DMSO-d_6, 373K) δ 11.80 (br, 1H), 7.37–7.07 (m, 15H), 5.51 (d, 1H, *J*=4.2 Hz), 5.45 (d, 1H, *J*=4.2 Hz), 5.21 (d, 1H, *J*=12.3 Hz),), 5.14 (d, 1H, *J*=12.3 Hz), 4.01 (d, 1H, *J*=13.5 Hz), 3.06 (d, 1H, *J*=13.5 Hz), 2.79 (s, 2H), 1.94–1.87 (m, 2H), 1.60–1.34 (m, 4H), 0.95 (t, 3H, *J*=7.5); **IR** ($CHCl_3$) 3400–2800 (br), 1704, 1604, 1581 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{30}H_{34}NO_5$ (*m/z*) 488.2436; found (*m/z*) 488.2433.

1.1.10. General procedure for the hydrogenolysis of carboxylic acids 4a–c. A solution of **4a–c** in THF: water (6:4, v/v) was hydrogenated with $PdCl_2$ (3 equiv.) at 75–80°C and 120 psi of H_2 for 3 h. The mixture was then cooled to ambient temperature, the catalyst was removed by filtration through a plug of Celite and the filtrate concentrated and triturated with Et_2O. The residue thus obtained was dissolved in water and passed through DOWEX® 50WX2-100 ion exchange resin and the resin was washed with distilled water. Elution of the resin with 2% aq. NH_4OH furnished the amino acids **5a–c** which were pure by ^{1}H nmr analysis.

1.1.11. (*S*)-4-Amino-3-hydroxybutanoic acid (5a).[15] Prepared by hydrogenolysis of **4a** (0.12 g, 0.28 mmol) with $PdCl_2$ (0.15 g, 0.84 mmol) in THF (6 mL): water (4 mL) to provide 0.031 g (93%) of **5a** as a white amorphous solid after ion exchange chromatography. $[\alpha]_D^{25}=+19.1$ (*c* 1, H_2O); lit.[10d] $[\alpha]_D^{25}=+20.7$ (*c* 1.9, H_2O); **^{1}H NMR** (300 MHz, D_2O) δ 4.24–4.10 (m, 1H), 3.15–3.10 (m, 1H), 2.94–2.87 (m, 1H), 2.39 (d, 2H, *J*=8.0 Hz).

1.1.12. (*S*)-4-Amino-3-methyl-3-hydroxybutanoic acid (5b).[11a] Prepared by hydrogenolysis of **4b** (0.13 g, 0.29 mmol) with $PdCl_2$ (0.16 g, 0.9 mmol) in THF (6 mL): water (4 mL) to provide 0.038 g (97%) of **5b** as a white amorphous solid after ion exchange chromatography. $[\alpha]_D^{25}=+8.4$ (*c* 1, H_2O); **^{1}H NMR** (300 MHz, D_2O) δ 3.06 (d, 1H, *J*=12.9 Hz), 3.00 (d, 1H, *J*=12.9 Hz), 2.46 (s, 2H), 1.29 (s, 3H); **^{13}C NMR** (75 MHz, D_2O) δ 174.4, 64.4, 43.5, 41.8, 19.8; **IR** (KBr) 3700–2500 (br), 1638, 1561 cm^{-1}; **HRMS** (FAB+) Calcd for $C_5H_{12}NO_3$ (*m/z*) 134.0817; found (*m/z*) 134.0822.

1.1.13. (*S*)-4-Amino-3-butyl-3-hydroxybutanoic acid (5c). Prepared by hydrogenolysis of **4c** (0.13 g, 0.26 mmol) with $PdCl_2$ (0.15 g, 0.84 mmol) in THF (6 mL): water (4 mL) to provide 0.047 g (99%) of **5c** as a white amorphous solid after ion exchange chromatography. $[\alpha]_D^{25}=+3.1$ (*c* 1.4, H_2O); **^{1}H NMR** (300 MHz, D_2O) δ 3.13 (d, 1H, *J*=9.9 Hz), 3.06 (d, 1H, *J*=9.9 Hz), 2.48 (s, 1H), 1.60–1.56 (m, 2H), 1.34–1.29 (m, 4H), 0.88 (t, 3H, *J*=5.4 Hz); **^{13}C NMR** (75 MHz, D_2O) δ 173.7, 65.4, 41.2, 38.2, 32.3, 19.5, 17.1, 7.8; **IR** (KBr) 3500–2400 (br), 1628, 1560 cm^{-1}; **HRMS** (FAB+) Calcd for $C_8H_{18}NO_3$ (*m/z*) 176.1286; found (*m/z*) 176.1285.

1.1.14. General procedure for conversion of amino acids 5a–c into 7a–c. A solution of amino acids **5a–c** in distilled water was hydrogenated over 10% Pd/C in the presence of excess of 37% aq. formaldehyde at 80 psi of H_2 and ambient temperature for 36 h. The catalyst was removed by filtration through Celite and was washed with hot distilled water. The combined aqueous layer was passed through DOWEX® 50WX2-100 ion exchange resin and the resin was washed with distilled water. Elution of the resin with 2% aq. NH_4OH furnished the amino acids **6a–c** which were pure by ^{1}H NMR analysis. The amino acids **6a–c** were stirred with MeI in anhydrous DMF for 12 h at ambient temperature.

The solvent was removed under reduced pressure (2 mm) at ambient temperature to obtain the crude product which was dissolved in distilled water and passed through Amberlite® IRA-400 (OH) ion exchange resin eluting with water to furnish the amino acids **7a–c**.

1.1.15. (*S*)-(+)-Carnitine (7a). Prepared by hydrogenation of **5a** (0.03 g, 0.25 mmol) in distilled water (4 mL) and formaldehyde (37 wt. % solution in water, 0.5 mL, excess) with 10% Pd/C (0.01 g, 33% w/w) to provide 0.037 g (99%) of **6a** as a white amorphous solid after DOWEX® 50WX2-100 ion exchange chromatography. **^{1}H NMR** (300 MHz, D_2O) δ 4.40–4.26 (m, 1H), 3.22–3.10 (m, 2H), 2.90 (s, 6H), 2.39 (d, 2H, *J*=6.3 Hz). Treatment of **6a** (0.035 g, 0.23 mmol) with MeI (1 mL) and DMF (1 mL) followed by ion exchange chromatography using Amberlite® IRA-400 (OH) ion exchange resin furnished 0.03 g (78%) of **7a** as a clear colorless gum. $[\alpha]_D^{25}$=+28.1 (*c* 1, H_2O); lit.[9c] $[\alpha]_D$=−30.9 (*c* 1, H_2O) for the enantiomer; **^{1}H NMR** (300 MHz, D_2O) δ 4.60–4.52 (m, 1H), 3.44–3.42 (m, 2H), 2.22 (s, 9H), 2.50–2.36 (m, 2H).

1.1.16. (*S*)-3-Hydroxy-3-methyl-4-(trimethylammonio)-butanoic acid (7b).[11a] Prepared by hydrogenation of **5b** (0.03 g, 0.22 mmol) in distilled water (4 mL) and formaldehyde (37 wt. % solution in water, 0.5 mL, excess) with 10% Pd/C (0.01 g, 33% w/w) to provide 0.036 g (99%) of **6b** as a white amorphous solid after DOWEX® 50WX2-100 ion exchange chromatography. **^{1}H NMR** (300 MHz, D_2O) δ 3.32 (d, 1H, *J*=13.8 Hz), 3.23 (d, 1H, *J*=13.8 Hz), 2.95 (s, 3H), 2.93 (s, 3H), 2.57 (s, 2H), 1.31 (s, 3H); **^{13}C NMR** (75 MHz, D_2O) δ 173.8, 64.8, 61.9, 43.0, 4 1.0, 21.8. Treatment of **6b** (0.030 g, 0.18 mmol) with MeI (1 mL) and DMF (1 mL) followed by ion exchange chromatography using Amberlite® IRA-400 (OH) ion exchange resin furnished 0.028 g (85%) of **7b** as a white amorphous solid. $[\alpha]_D^{25}$=+18.3 (*c* 1, H_2O); **^{1}H NMR** (300 MHz, D_2O) δ 3.52 (d, 1H, *J*=14.1 Hz), 3.47 ((d, 1H, *J*=14.1 Hz), 3.25 (s, 9H), 2.45 (s, 2H), 1.46 (s, 3H); **^{13}C NMR** (75 MHz, D_2O) δ 173.2, 66.5, 65.3, 50.0, 42.6, 21.7; **IR** (KBr) 1655, 1596 cm^{-1}; **HRMS** (FAB+) Calcd for $C_8H_{18}NO_3$ (*m/z*) 176.1286; found (*m/z*) 176.1284.

1.1.17. (*S*)-3-Hydroxy-3-butyl-4-(trimethylammonio)-butanoic acid (7c). Prepared by hydrogenation of **5c** (0.03 g, 0.25 mmol) in distilled water (4 mL) and formaldehyde (37 wt. % solution in water, 0.5 mL, excess) with 10% Pd/C (0.01 g, 33% w/w) to provide 0.034 g (97%) of **6c** as a white amorphous solid after DOWEX® 50WX2-100 ion exchange chromatography. **^{1}H NMR** (300 MHz, D_2O) δ 3.29 (d, 1H, *J*=14.1 Hz), 3.17 (d, 1H, *J*=14.1 Hz), 2.90 (s, 6H), 2.57 (s, 2H), 1.60–1.48 (m, 2H), 1.36–1.20 (m, 4H), 0.85 (t, 3H, *J*=6.0 Hz); **^{13}C NMR** (75 MHz, D_2O) δ 173.9, 67.1, 61.2, 41.0, 40.4, 35.0, 20.1, 17.8, 8.7. Treatment of **6c** (0.030 g, 0.14 mmol) with MeI (1 mL) and DMF (1 mL) followed by ion exchange chromatography using Amberlite® IRA-400 (OH) ion exchange resin furnished 0.022 g (68%) of **7c** as a clear colorless gum. $[\alpha]_D^{25}$=+4.6 (*c* 1, H_2O); **^{1}H NMR** (300 MHz, D_2O) δ 3.52 (d, 1H, *J*=10.5 Hz), 3.46 (d, 1H, *J*=10.5 Hz), 3.26 (s, 9H), 2.52 (s, 2H), 1.80–1.64 (m, 2H), 1.36–1.26 (m, 4H), 0.87 (t, 3H, *J*=6.9 Hz); **^{13}C NMR** (75 MHz, D_2O) δ 173.4, 67.6, 65.0, 50.1, 38.8, 34.5, 19.8, 17.0, 7.8; **IR** (KBr) 1587 cm^{-1}; **HRMS** (FAB+) Calcd for $C_{11}H_{24}NO_3$ (*m/z*) 218.1756; found (*m/z*) 218.1753.

Acknowledgements

This work was supported by National Science Foundation (grant CHE 9731947).

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