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New access to racemic β^3-amino acids

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Abstract—A general simple procedure having the potential for large scale preparations of racemic β^3-amino acids has been developed. The procedure involves base-catalyzed Michael-type addition of sodium diethyl malonate to *N*-Boc-α-amidoalkyl-*p*-tolyl sulfones in tetrahydrofuran. Hydrolysis of the adducts by refluxing with 6 M aqueous hydrochloric acid affords β^3-amino acid hydrochlorides in high yield and excellent purity.

1. Introduction

In recent years, there has been increased interest in β-amino acids due mainly to the fact that the corresponding oligomers, the β-peptides, display a high tendency towards the formation of secondary structures including helices, sheets, and reverse turns.[1] Furthermore, some representatives of β^3-amino acids are found in nature in free form or as components of naturally occurring biologically active peptides.[2] In this respect, several methods for the synthesis of racemic β-amino acids have been developed.[3] Recently, stereoselective syntheses of β-amino acids have been the subject of a series of review articles.[4–6] The effective route to enantiopure β^3-amino acids by 1,3-dipolar cycloaddition has been also recently described by Mapp and co-workers.[7] The wide implementation of numerous stereoselective methods into synthetic practice, especially for large scale production, is, however, hampered by the use of expensive reagents and/or often multistep procedures. Fortunately, it has been well established that β-amino acid/ester racemates can be easily resolved using a variety of techniques including enzymatic or chemical resolution.[8]

In a search for a simple, effective, and economic approach to racemic β^3-amino acids, which could be applicable especially for multigram scale, we have focused our attention on Michael-type addition of sodium diethyl malonate to *N*-Boc imines.

2. Results and discussion

Nucleophilic addition to *N*-Boc imines generated in situ from α-amidoalkyl-*p*-tolyl(phenyl)sulfones by base-induced elimination has been nowadays the subject of extensive studies.[9] The easily available *N*-Boc imines can be considered as natural precursors of primary amines because the Boc group can function both as C=N bond activator and be easily detached once nucleophilic addition has been attained. We found that *N*-Boc-α-amidoalkyl-*p*-tolyl sulfones **1** readily underwent base induced elimination and the *N*-Boc imines **2** thus formed reacted smoothly with sodium diethyl malonate to give the respective adducts **3a–h** in high yields (Scheme 1).

The reaction was carried out at room temperature by adding 1 equiv of diethyl malonate to the suspension of 2 equiv of sodium hydride and 1 equiv of the sulfone **1** in tetrahydrofuran. The strongly exothermic process was moderated by occasional cooling with cold water. Crude adducts **3a–h** obtained by quenching the reaction mixture with aqueous ammonium chloride followed by extraction with dichloromethane were spectroscopically pure (NMR). They could be directly used for subsequent hydrolysis without additional purification.

Upon refluxing with 6 M (ca. 20%) hydrochloric acid for 1 h the adducts **3a–h** were transformed into β^3-amino acid hydrochlorides **4a–h** by amino group deprotection, hydrolysis, and decarboxylation (Scheme 2).

Aqueous solutions of **4a–h** decolorized with active charcoal, evaporated to dryness, washed with ether and dried over phosphorus pentoxide afforded pure, crystalline β^3-amino acid hydrochlorides **4a–h** in excellent yields (see Table 1) and analytical purity.

Keywords: Michael-type addition; *N*-Boc imines; Diethyl malonate.
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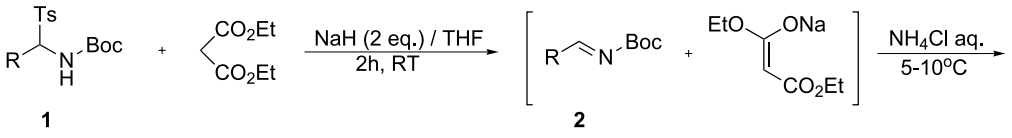
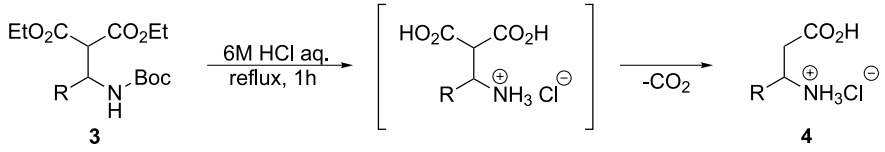


3	R	Yield (%)	3	R	Yield (%)
a	H	88	e	*i*-Bu	96
b	Me	94	f	*c*-C_6H_{11}	99
c	Et	98	g	Ph	81
d	*i*-Pr	98	h	*p*-MeO-C_6H_4	99

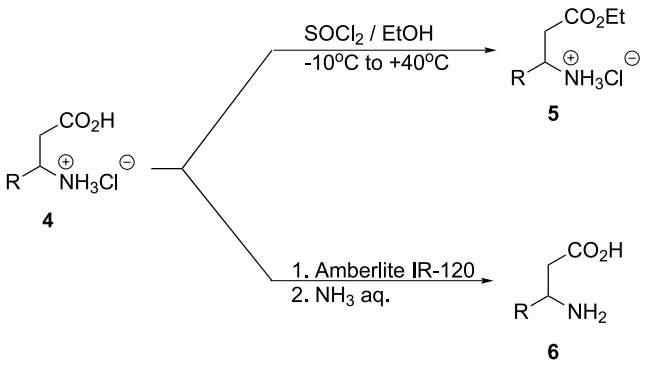
Scheme 1.



Scheme 2.

Ethyl ester hydrochlorides **5a–h** could be easily obtained from **4a–h** by the modified method described earlier.[10] This esterification procedure involved the treatment of **4a–h** with ethanol–thionyl chloride mixture at −10 °C followed by heating at 40 °C for ca. 3 h. The reaction progress was monitoring by thin-layer chromatography, (disappearance of starting material) (Scheme 3).

β^3-Amino acid hydrochlorides **4a–h** could be also almost quantitatively transformed into free β^3-amino acids **6a–h** using a column packed with Amberlite IR-120 ion-exchange resin. Compounds **6a–h** were spectroscopically pure (^{1}H NMR) and had melting points fully consistent with the literature data (see Section 4). The yields of compounds **5a–h** and **6a–h** are collected in Table 1.



Scheme 3.

Table 1. β^3-Amino acid hydrochlorides (**4a–h**), β^3-amino acid ethyl ester hydrochlorides (**5a–h**) and β^3-amino acids (**6a–h**)

Entry	R	(**4**) Yield (%)[a]	(**5**) Yield (%)[a]	(**6**) Yield (%)[a]
a	H	84	99	96
b	Me	96	99	93
c	Et	83	94	99
d	*i*-Pr	92	95	92
e	*i*-Bu	89	94	92
f	*c*-C_6H_{11}	92	90	99
g	Ph	92	84	91
h	*p*-MeO–C_6H_4	85	91	89

[a] Yields of crude, analytically pure products.

3. Conclusion

The outlined procedure for the synthesis of racemic β^3-amino acids represents a versatile and cost-effective approach to these compounds from easily available starting materials. It is operationally simple and can be conveniently applied for multigram scale preparation.

4. Experimental

4.1. General

Melting points (determined in open capillary tubes) are uncorrected. IR spectra (liquid films or KBr discs) were measured using a Specord M 80 (C. Zeiss) instrument. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX-250 spectrometer operating at 250 or 63 MHz, using $CDCl_3$ solutions unless otherwise stated. MS/CI were measured on Finnigan Mat mass spectrometer. FAB/MS were measured on an APO Electron (Ukraine) Model MI 12001 mass spectrometer. All commercially available starting materials were purchased from Fluka and used without additional purification. *N*-Boc-α-amidoalkyl-*p*-tolyl sulfones **1** were prepared as described before.[11]

4.2. Addition of sodium diethyl malonate to *N*-Boc imines (2)

General procedure. A solution of diethyl malonate (6.4 g,

0.04 mol) in THF (50 mL) was added dropwise with stirring and occasional cooling for ca. 30 min to a suspension of sodium hydride (1.92 g, 0.08 mol) and the corresponding sulfone **1** (0.04 mol) in anhydrous THF (100 mL). Stirring was continued for 2 h at room temperature. The mixture was then cooled to 10 °C and quenched with saturated NH_4Cl aq (30 mL). Water (20 mL) was then added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). Combined extracts were dried ($MgSO_4$) and the solvent evaporated in vacuo to give spectroscopically pure adducts **3a–h**.

4.2.1. Diethyl 2-(*N*-Boc-aminomethyl)malonate (3a). Yield 88%, colorless oil; [Found: C, 53.7; H, 7.9; N, 5.0. $C_{13}H_{23}NO_6$ requires C, 53.97; H, 8.01; N, 4.84%]; ν_{max} (liquid film) 3400, 3000, 2960, 1730, 1528, 1508, 1488, 1460, 1400, 1374, 1300, 1256, 1170, 1100, 1036, 960, 900, 870, 784, 650 cm^{-1}; δ_H 1.28 (6H, t, J=7.1 Hz, CH_3CH$_2$O), 1.43 (9H, s, *Me*$_3$C), 3.60–3.65 (3H, m, C*H*CH_2NH), 4.21 (4H, q, J=7.1 Hz, CH$_3$CH_2O), 5.15 (1H, br s, N*H*); δ_C 13.6, 27.9, 38.9, 51.6, 61.2, 79.1, 155.3, 167.8; FAB/MS: 290 (26, M+1), 234 (100), 190 (78%).

4.2.2. Diethyl 2-(1-*N*-Boc-aminoethyl)malonate (3b). Yield 94%, colorless solid; [Found: C, 55.6; H, 8.1; N, 4.8. $C_{14}H_{25}NO_6$ requires C, 55.43; H, 8.31; N, 4.62%]; ν_{max} (liquid film) 3370, 2980, 2930, 1750, 1708, 1528, 1460, 1380, 1368, 1308, 1250, 1176, 1156, 1100, 1080, 1050, 1020, 856, 834, 750, 660, 630 cm^{-1}; δ_H 1.24–1.32 (6H, m, CH_3CH$_2$O), 1.24–1.32 (3H, m, CH_3CH), 1.42 (9H, s, *Me*$_3$C), 3.56 (1H, d, J=4.5 Hz, C*H*(CO$_2$Et)), 4.13–4.30 (4H, m, CH$_3$CH_2O), 4.30–4.45 (1H, m, NHC*H*), 5.27–5.43 (1H, m, N*H*); δ_C 13.8, 18.9, 28.1, 45.75, 55.9, 61.2, 61.35, 79.1, 154.8, 167.55, 168; FAB/MS: 304 (46, M+1), 248 (100), 204 (28%).

4.2.3. Diethyl 2-(1-*N*-Boc-aminopropyl)malonate (3c). Yield 98%, colorless solid mp 53–55 °C; [Found: C, 56.9; H, 8.5; N, 4.2. $C_{15}H_{27}NO_6$ requires C, 56.77; H, 8.57; N, 4.41%]; ν_{max} (KBr) 3360, 2976, 2936, 1736, 1688, 1532, 1460, 1390, 1368, 1320, 1290, 1244, 1230, 1176, 1150, 1120, 1100, 1070, 1010, 650, 620 cm^{-1}; δ_H 0.95 (3H, t, J=7.4 Hz, CH_3CH$_2$CH), 1.27 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.29 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.42 (9H, s, *Me*$_3$C), 1.50–1.68 (2H, m, CH$_3$CH_2CH), 3.60 (1H, d, J=4.3 Hz, C*H*(CO$_2$Et)), 4.10–4.30 (2H, m, CH$_3$CH_2O), 4.10–4.30 (1H, m, NHC*H*), 5.40 (1H, d, J=10.1 Hz, N*H*); δ_C 10.5, 13.7, 13.8, 28.0, 51.5, 54.6, 61.1, 61.3, 78.7, 155.2, 167.7, 168.15; FAB/MS: 318 (1, M+1), 262 (7), 219 (23%).

4.2.4. Diethyl 2-(1-*N*-Boc-amino-2-methylpropyl)malonate (3d). Yield 98%, colorless oil; [Found: C, 58.2; H, 8.7; N, 4.4. $C_{16}H_{29}NO_6$ requires C, 57.99; H, 8.82; N, 4.23%]; ν_{max} (liquid film) 3440, 3390, 2980, 2930, 2910, 1724, 1500, 1470, 1392, 1368, 1348, 1280, 1264, 1232, 1172, 1100, 1090, 1034, 1010, 870, 660, 630 cm^{-1}; δ_H 0.93 (3H, d, J=6.4 Hz, *Me*$_2$CH), 0.96 (3H, d, J=6.4 Hz, *Me*$_2$CH), 1.27 (3H, t, J=7.1 Hz CH_3CH$_2$O), 1.29 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 1.64–1.82 (1H, m, Me$_2$C*H*), 3.69 (1H, d, J=4.3 Hz, C*H*(CO$_2$Et)), 3.94–4.05 (1H, m, C*H*–NH), 4.10–4.30 (4H, m, CH$_3$CH_2O), 5.55 (1H, d, J=10.5 Hz, N*H*); δ_C 13.7, 13.8, 19.0, 19.6, 28.0, 31.8, 53.1, 55.8, 61.1, 61.5, 78.6, 155.3, 168.0, 168.45; FAB/MS: 332 (42, M+1), 276 (100), 232 (54%).

4.2.5. Diethyl 2-(1-*N*-Boc-amino-3-methylbutyl)malonate (3e). Yield 96%, colorless solid, mp 58–60 °C; [Found: C, 59.0; H, 9.2; N, 4.2. $C_{17}H_{31}NO_6$ requires C, 59.11; H, 9.05; N, 4.05%]; ν_{max} (KBr) 3370, 3000, 2970, 1752, 1720, 1528, 1476, 1450, 1400, 1372, 1320, 1300, 1268, 1236, 1188, 1160, 1070, 1036, 1016, 630, 620 cm^{-1}; δ_H 0.92 (3H, d, J=6.25 Hz, *Me*$_2$CH), 0.95 (3H, d, J=6.25 Hz, *Me*$_2$CH), 1.27 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.29 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 1.46–1.67 (1H, m, Me$_2$C*H*), 3.56 (1H, d, J=4.25 Hz, C*H*(CO$_2$Et)), 4.15–4.26 (4H, m, CH$_3$CH_2O), 4.27–4.35 (1H, m, C*H*–NH), 5.33 (1H, d, J=10.0 Hz, N*H*); δ_C 13.6, 21.5, 22.6, 24.6, 27.9, 42.2, 48.0, 55.1, 60.9, 61.1, 78.5, 154.8, 167.5, 167.9; FAB/MS; 346 (42, M+1), 290 (100), 246 (38%).

4.2.6. Diethyl 2-(*N*-Boc-aminocyclohexylmethyl)malonate (3f). Yield 99%, colorless oil; [Found: C, 61.6; H, 9.1; N, 3.6. $C_{19}H_{33}NO_6$ requires C, 61.43; H, 8.95; N, 3.77%]; ν_{max} (liquid film) 3450, 2990, 2950, 2870, 1736, 1500, 1450, 1400, 1374, 1350, 1316, 1284, 1256, 1174, 1150, 1100, 1046, 1020, 972, 870, 780, 650 cm^{-1}; δ_H 0.94–1.20 (5H, m, ring CH_2), 1.26 (3H, t, J=7.0 Hz, CH_3CH$_2$O), 1.29 (3H, t, J=7.0 Hz, CH_3CH$_2$O), 1.40 (9H, s, *Me*$_3$C), 1.40–1.55 (6H, m, ring CH_2), 3.71 (1H, d, J=4.0 Hz, C*H*(CO$_2$Et)), 4.02 (1H, dt, J=10.0, 4.0 Hz, C*H*NH), 4.10–4.32 (4H, m, CH$_3$CH_2O), 5.54 (1H, d, J=10.0 Hz, N*H*); δ_C 13.6, 13.7, 25.5, 25.6, 25.8, 29.2, 29.9, 28.0, 41.0, 52.45, 54.7, 61.0, 61.4, 78.5, 155.2, 168.1, 168.45; FAB/MS: 372 (20, M+1), 316 (47), 272 (28%).

4.2.7. Diethyl 2-(*N*-Boc-aminophenylmethyl)malonate (3g). Yield 81%, colorless solid, mp 69–70 °C; [Found: C, 62.3; H, 7.6; N, 4.0. $C_{19}H_{27}NO_6$ requires C, 62.45; H, 7.45; N, 3.83%]; ν_{max} (KBr) 3400, 2990, 2950, 1728, 1688, 1520, 1390, 1368, 1316, 1296, 1256, 1236, 1172, 1012, 754, 700 cm^{-1}; δ_H 1.13 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.26 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 3.88 (1H, d, J=4.7 Hz, CH(CO$_2$Et)), 4.01–4.29 (4H, m, CH$_3$CH_2O), 5.49 (1H, br s, C*H*NH), 6.18 (1H, br s, N*H*), 7.20–7.36 (5H, m, H_{arom}); δ_C 13.5, 13.6, 27.95, 53.15, 56.6, 61.2, 61.5, 79.2, 126.0, 127.2, 128.2, 139.4, 154.7, 166.8, 167.7; FAB/MS: 366 (1, M+1), 266 (40%).

4.2.8. Diethyl 2-(*N*-Boc-amino-(4-methoxyphenyl) methyl)malonate (3h). Yield 99%, colorless solid, mp 64–66 °C; [Found: C, 60.5; H, 7.6; N, 3.4. $C_{20}H_{29}NO_7$ requires C, 60.74; H, 7.39; N, 3.54%]; ν_{max} (KBr) 3390, 2990, 1744, 1728, 1684, 1520, 1368, 1300, 1250, 1172, 1104, 1024, 832, 630, 620 cm^{-1}; δ_H 1.16 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.26 (3H, t, J=7.1 Hz, CH_3CH$_2$O), 1.41 (9H, s, *Me*$_3$C), 3.78 (3H, s, CH_3O), 3.84 (1H, d, J=5.0 Hz), C*H*(CO_2Et)), 4.00–4.30 (4H, m, CH$_3$CH_2O), 5.42 (1H, br s, C*H*NH), 6.12 (1H, br s, N*H*), 6.84 (2H, d, J=8.7 Hz, H_{arom}), 7.22 (2H, d, J=8.7 Hz, H_{arom}); δ_C 13.8, 13.9, 28.2, 52.9, 55.2, 57.0, 61.5, 61.8, 79.5, 113.8, 127.4, 131.7, 158.85, 154.9, 167.0, 168.0; FAB/MS: 396 (1, M+1), 294 (11), 279 (38), 180 (100%).

4.3. Preparation of β[3]-amino acid hydrochlorides (4a–h)

General procedure. A mixture of the adduct **3** (0.02 mol) and ca. 20% HCl aq (40 mL) was refluxed for 1 h. Active charcoal (ca. 1 g) was added to the resultant solution, heating was continued for 10 min, and the hot solution was filtered and evaporated to dryness in vacuo. The residue was treated with ether (30 mL) and refrigerated overnight. Crystalline β[3]-amino acid hydrochlorides (**4a–h**) were filtered off, washed with ether and dried over P_2O_5. All crude products were analytically pure.

4.3.1. 3-Aminopropanoic acid hydrochloride (4a). Yield 84%, colorless solid, mp 104–106 °C, mp after recrystallization from isopropyl alcohol—122–124 °C (lit.[12] mp 123–125 °C); [Found: C, 28.6; H, 6.5; N, 11.1. $C_3H_8ClNO_2$ requires C, 28.70; H, 6.42; N, 11.16%]; ν_{max} (CCl_4) 3030, 2920, 1730, 1716, 1700, 1590, 1504, 1480, 1410, 1330, 1304, 1260, 1200, 1130, 1096, 1056, 950, 916, 650 cm^{-1}; δ_H (D_2O) 2.82 (2H, t, J=6.5 Hz, CH_2CO_2H), 3.28 (2H, t, J=6.5 Hz, CH_2NH_3).

4.3.2. 3-Aminobutanoic acid hydrochloride (4b). Yield 96%, colorless solid, mp 94–98 °C (lit.[13] mp 109.5–110.5 °C); [Found: C, 34.5; H, 7.4; N, 10.1. $C_4H_{10}ClNO_2$ requires C, 34.42; H, 7.22; N, 10.03%]; ν_{max} (KBr) 3120, 2940, 2840, 1696, 1616, 1596, 1500, 1436, 1392, 1376, 1306, 1244, 1192, 928, 896, 696 cm^{-1}; δ_H (D_2O) 1.36 (3H, d, J=6.7 Hz, CH_3CH), 2.72 (1H, dd, J=17.5, 7.2 Hz, CH_2CO_2H), 2.80 (1H, dd, J=17.5, 5.8 Hz, CH_2CO_2H), 3.67–3.88 (1H, m, CH_3CH).

4.3.3. 3-Aminopentanoic acid hydrochloride (4c). Yield 83%, colorless solid, mp 118–123 °C; [Found: C, 39.3; H, 8.0; N, 9.0. $C_5H_{12}ClNO_2$ requires C, 39.10; H, 7.87; N, 9.12%]; ν_{max} (KBr) 3400, 2980, 1720, 1600, 1500, 1460, 1408, 1204, 1176, 654, 630 cm^{-1}; δ_H (D_2O) 0.99 (3H, t, J=7.4 Hz, CH_3CH_2), 1.73 (2H, qt, J=7.4 Hz, CH_3CH_2), 2.69 (1H, dd, J=17.6, 8.2 Hz, CH_2CO_2H), 2.85 (1H, dd, J=17.6, 4.6 Hz, CH_2CO_2H), 3.51–3.65 (1H, m, C$H$$NH_3$).

4.3.4. 3-Amino-4-methylpentanoic acid hydrochloride (4d). Yield 92%, colorless solid, mp 162–167 °C; [Found: C, 43.1; H, 8.6; N, 8.4. $C_6H_{14}ClNO_2$ requires C, 42.99; H, 8.42; N, 8.36%]; ν_{max} (KBr) 3270, 2980, 2920, 1720, 1604, 1500, 1472, 1420, 1396, 1220, 1176, 1124, 812, 654 cm^{-1}; δ_H (D_2O) 0.99 (3H, d, J=6.8 Hz, Me_2CH), 1.00 (3H, d, J=6.8 Hz, Me_2CH), 2.02 (1H, 8 lines, J=6.8 Hz, Me_2CH), 2.67 (1H, dd, J=17.8, 9.0 Hz, CH_2CO_2H), 2.86 (1H, dd, J=17.8, 3.9 Hz, CH_2CO_2H), 3.45–3.55 (1H, m, C$H$$NH_3$).

4.3.5. 3-Amino-5-methylhexanoic acid hydrochloride (4e). Yield 89%, colorless solid, mp 154–156 °C; [Found: C, 46.2; H, 9.0; N, 7.8. $C_7H_{16}ClNO_2$ requires C, 46.28; H, 8.88; N, 7.71%]; ν_{max} (KBr) 3100, 2940, 1720, 1608, 1580, 1500, 1428, 1400, 1372, 1278, 1222, 1190, 1134, 1120, 1060, 860, 700 cm^{-1}; δ_H (D_2O) 0.92 (3H, d, J=6.6 Hz, Me_2CH), 0.94 (3H, d, J=6.6 Hz, Me_2CH), 1.56 (2H, t, J=6.6 Hz, CH_2CHNH), 1.69 (1H, 9 lines, J=6.6 Hz, Me_2CH), 2.68 (1H, dd, J=17.5, 8.1 Hz, CH_2CO_2H), 2.85 (1H, dd, J=17.5, 4.5 Hz, CH_2CO_2H), 3.64–3.75 (1H, m, C$H$$NH_3$).

4.3.6. 3-Amino-3-cyclohexylpropanoic acid hydrochloride (4f). Yield 92%, colorless solid, mp 230–232 °C; [Found: C, 52.1; H, 8.8; N, 6.5. $C_9H_{18}ClNO_2$ requires C, 52.5; H, 8.74; N, 6.74%]; ν_{max} (KBr) 3260, 2950, 2870, 1720, 1608, 1590, 1500, 1444, 1420, 1388, 1350, 1230, 1200, 1164, 806, 796, 630, 620 cm^{-1}; δ_H (D_2O) 0.92–1.27 (5H, m, ring CH_2), 1.47–1.73 (6H, m, ring CH_2), 2.62 (1H, dd, J=17.8, 8.75 Hz, CH_2CO_2H), 2.80 (1H, dd, J=17.8, 4.0 Hz, CH_2CO_2H), 3.38–3.43 (1H, m, C$H$$NH_3$).

4.3.7. 3-Amino-3-phenylpropanoic acid hydrochloride (4g). Yield 92%, colorless solid, mp 215–219 °C (lit.[14] mp 217–218 °C); [Found: C, 53.5; H, 6.2; N, 7.1 $C_9H_{12}ClNO_2$ requires C, 53.61; H, 6.00; N, 6.95%]; ν_{max} (KBr) 3060, 3000, 2920, 1730, 1600, 1490, 1416, 1384, 1370, 1224, 1022, 830, 760, 696, 630, 620 cm^{-1}; δ_H (D_2O) 3.12 (1H, dd, J=17.1, 6.8 Hz, CH_2CO_2H), 3.23 (1H, dd, J=17.1, 7.6 Hz, CH_2CO_2H), 7.45–7.55 (5H, m, H_{arom}).

4.3.8. 3-Amino-3-(4-methoxyphenyl)propanoic acid hydrochloride (4h). Yield 85%, colorless solid, mp 198–203 °C (lit.[15] mp 205 °C); [Found: C, 51.9; H, 6.0; N, 6.2. $C_{10}H_{14}ClNO_3$ requires C, 51.84; H, 6.09; N, 6.05%]; ν_{max} (KBr) 2980, 2910, 1710, 1600, 1574, 1522, 1474, 1400, 1304, 1280, 1260, 1176, 1116, 1020, 840, 820, 790, 540 cm^{-1}; δ_H (D_2O) 3.07 (1H, dd, J=17.0, 6.9 Hz, CH_2CO_2H), 3.20 (1H, dd, J=17.0, 7.7 Hz, CH_2CO_2H), 3.85 (3H, s, CH_3), 7.07 (2H, d, J=8.7 Hz, H_{arom}), 7.44 (2H, d, J=8.7 Hz, H_{arom}).

4.4. Preparation of β[3]-amino acid ethyl ester hydrochlorides (5a–h)

General procedure. Thionyl chloride (0.8 mL, 0.011 mol) was added dropwise with efficient stirring to ethanol (12 mL) cooled to −10 °C. Stirring was continued for 30 min at −10 °C, β[3]-amino acid hydrochloride (**4a–h**, 0.01 mol) was then added and the temperature was raised to 20–25 °C. After 1 h at this temperature stirring was continued at 40 °C for approximately 3 h (until disappearance of the substrate spot on TLC plate, $CHCl_3$/MeOH, 3:1 being used as eluent). Ethanol was then evaporated in vacuo and ether or hexane was added to the residual oil. Crystals of **5a–h** obtained on refrigeration were analytically pure.

4.4.1. Ethyl 3-aminopropanoate hydrochloride (5a). Yield 99%, colorless solid, mp 48–50 °C (lit.[12] mp 69–70 °C); [Found: C, 39.2; H, 7.8; N, 9.1. $C_5H_{12}ClNO_2$ requires C, 39.10; H, 7.87; N, 9.12%]; ν_{max} (KBr) 3450, 3000, 1724, 1670, 1600, 1480, 1464, 1404, 1380, 1230, 1100, 1024, 630, 620 cm^{-1}; δ_H (D_2O) 1.26 (3H, t, J=7.2 Hz, CH_3CH_2O), 2.81 (2H, t, J=6.5 Hz, CH_2CO), 3.29 (2H, t, J=6.5 Hz, CH_2NH_3), 4.21 (2H, q, J=7.2 Hz, CH_3CH_2O; δ_C (D_2O) 13.3, 31.2, 35.0, 62.1, 172.5; MS/CI 118 (M_K, 100%).

4.4.2. Ethyl 3-aminobutanoate hydrochloride (5b). Yield 99%, colorless oil; [Found: C, 42.9; H, 8.5; N, 8.3. $C_6H_{12}ClNO_2$ requires C, 42.99; H, 8.42; N, 8.36%]; ν_{max} (liquid film) 2980, 2912, 1728, 1600, 1496, 1450, 1396, 1324, 1208, 1186, 1130, 1090, 1024, 650, 624 cm^{-1}; δ_H (D_2O) 1.26 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.35 (3H, d, J=6.6 Hz, CH_3CH), 2.76 (2H, d, J=6.6 Hz, CH_2CO_2Et), 3.77

(1H, 6 lines, J=6.6 Hz, CH_3CH), 4.20 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C (D_2O) 12.6, 16.85, 37.0, 45.0, 61.0, 170.75; MS/CI 132 (M_K, 100%).

4.4.3. Ethyl 3-aminopentanoate hydrochloride (5c). Yield 94%, colorless solid, mp 40–43 °C; [Found: C, 46.1; H, 9.1; N, 7.9. $C_7H_{16}ClNO_2$ requires C, 46.28; H, 8.88; N, 7.71%]; ν_{max} (KBr) 3420, 2920, 1736, 1600, 1512, 1460, 1388, 1374, 1276, 1240, 1200, 1170, 1130, 1100, 1024, 620, 610 cm^{-1}; δ_H (D_2O) 1.01 (3H, t, J=7.4 Hz, CH_3CH_2CH), 1.29 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.75 (2H, qt, J=7.4 Hz, CH_3CH_2CH), 2.73 (1H, dd, J=17.4, 8.0 Hz, CH_2CO_2Et) 2.88 (1H, dd, J=17.4, 4.8 Hz, CH_2CO_2Et), 3.55–3.72 (1H, m, CH_3CH_2CH), 4.23 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C (D_2O) 8.0, 12.4, 24.0, 34.7, 48.4, 61.0, 170.9; MS/CI 146 (M_K, 100%).

4.4.4. Ethyl 3-amino-4-methylpentanoate hydrochloride (5d). Yield 95%, colorless solid, mp 69–71 °C; [Found: C, 49.3; H, 9.1; N, 7.2. $C_8H_{18}ClNO_2$ requires C, 49.10; H, 9.27; N, 7.16%]; ν_{max} (KBr) 3450, 2976, 2920, 1728, 1600, 1500, 1470, 1394, 1380, 1344, 1300, 1240, 1204, 1194, 1170, 1150, 1130, 1024 cm^{-1}; δ_H (D_2O) 1.08 (3H, d, J=6.8 Hz, Me_2CH), 1.10 (3H, d, J=6.8 Hz, Me_2CH), 1.28 (3H, t, J=7.1 Hz,CH_3CH_2O), 2.16 (1H, 8 lines, J=6.8 Hz, Me_2CH), 2.74 (1H, dd, J=16.9, 5.8 Hz, CH_2CO_2Et), 2.88 (1H, dd, J=16.9, 6.8 Hz, CH_2CO_2Et), 3.54 (1H, m, Me_2CHCH), 4.20 (2H, q, J=7.1 Hz, CH_3CH_2O); δ_C (D_2O) 12.2, 15.8, 16.3, 28.75, 32.6, 52.3, 61.2, 171.5; MS/CI 160 (M_K, 100%).

4.4.5. Ethyl 3-amino-5-methylhexanoate hydrochloride (5e). Yield 94%, colorless, low melting solid; [Found: C, 51.5; H, 9.7; N, 6.8. $C_9H_{20}ClNO_2$ requires C, 51.54; H, 9.61; N, 6.68%]; ν_{max} (CCl_4) 3416, 2970, 1740, 1608, 1530, 1512, 1460, 1384, 1370, 1350, 1324, 1250, 1200, 1140, 1032, 650 cm^{-1}; δ_H (D_2O) 0.92 (3H, d, J=6.4 Hz, Me_2CH), 0.93 (3H, d, J=6.4 Hz, Me_2CH), 1.27 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.45–1.58 (2H, m, CH_2CHNH_3), 1.68 (1H, 9 lines, J=6.4 Hz, Me_2CHCH_2), 2.70 (1H, dd, J=17.4, 7.6 Hz, CH_2CO_2Et), 2.85 (1H, dd, J=17.4, 4.6 Hz, CH_2CO_2Et), 3.65–3.77 (1H, m, $CHNH_3$), 4.21 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C (D_2O) 13.3, 21.3, 21.5, 23.7, 36.4, 40.8, 46.5, 62.2, 172.2; MS/CI 174 (M_K, 100%).

4.4.6. Ethyl 3-amino-3-cyclohexylpropanoate hydrochloride (5f). Yield 90%, colorless solid, mp 103–105 °C; [Found: C, 56.0; H, 9.3; N, 6.1. $C_{11}H_{22}ClNO_2$ requires C, 56.04; H, 9.41; N, 5.94%]; ν_{max} (KBr) 3440, 2930, 2870, 1730, 1600, 1504, 1450, 1408, 1380, 1370, 1330, 1300, 1268, 1210, 1184, 1160, 1114, 1040, 630, 620 cm^{-1}; δ_H (D_2O) 0.98 (5H, m, ring CH_2), 1.26 (3H, t, J=7.2 Hz, CH_3CH_2O), 1.64–1.81 (6H, m, ring CH_2), 2.70 (1H, dd, J=17.5, 8.5 Hz, CH_2CO_2Et), 2.87 (1H, dd, J=17.5, 4.25 Hz, CH_2CO_2Et), 3.47–3.54 (1H, m, $CHNH_3$), 4.21 (2H, q, J=7.2 Hz, CH_3CH_2O); δ_C 13.3, 25.2, 25.3, 27.6, 28.0, 33.95, 39.4, 52.6, 62.2, 172.4; MS/CI 200 (M_K, 100%).

4.4.7. Ethyl 3-amino-3-phenylpropanoate hydrochloride (5g). Yield 84%, colorless solid, mp 138–141 °C (lit.[16] mp 134–136 °C); [Found: C, 57.4; H, 7.1; N, 6.0. $C_{11}H_{16}ClNO_2$ requires C, 57.52; H, 7.02; N, 6.10%]; ν_{max} (KBr) 3450, 2880, 1740, 1590, 1500, 1450, 1376, 1364, 1306, 1246, 1176, 1104, 1084, 1026, 1008, 912, 750, 690, 624, 614, 540 cm^{-1}; δ_H (D_2O) 1.17 (3H, t, J=7.1 Hz, CH_3CH_2O), 3.13 (1H, dd, J=16.8, 7.3 Hz, CH_2CO_2Et), 3.22 (1H, dd, J=16.8, 7.3 Hz, CH_2CO_2Et), 4.13 (2H, q, J=7.3 Hz, CH_3CH_2O), 4.82 (1H, t, J=7.3 Hz, $CHNH_3$), 7.42–7.54 (5H, m, H_{arom}); δ_C (D_2O) 12.1, 37.0, 50.3, 61.0, 126.0, 128.2, 128.5, 133.8, 170.0; MS/CI 194 (M_K, 100%).

4.4.8. Ethyl 3-amino-3-(4-methoxyphenyl)-propanoate hydrochloride (5h). Yield 91%, colorless solid, mp 133–137 °C; [Found: C, 55.4; H, 6.9; N, 5.5. $C_{12}H_{18}ClNO_3$ requires C, 55.49; H, 6.99; N, 5.39%]; ν_{max} (KBr) 3470, 3210, 2904, 1736, 1616, 1600, 1520, 1500, 1460, 1380, 1364, 1300, 1264, 1250, 1184, 1110, 1024, 832, 620, 610, 552 cm^{-1}; δ_H ($CDCl_3$) 1.15 (3H, t, J=7.0 Hz, CH_3CH_2O), 3.78 (3H, s, CH_3O), 4.01–4.09 (2H, m, CH_2CO_2Et), 4.64 (1H, m, $CHNH_3$), 6.86 (d, J=8.2 Hz, H_{arom}), 7.44 (2H, d, J=8.2 Hz, H_{arom}), 8.69 (3H, br s, NH_3^+); δ_C (D_2O) 12.0, 36.9, 49.8, 54.2, 61.0, 113.4, 126.2, 127.6, 158.4, 170.1; MS/CI 224 (M_K, 14%).

4.5. Preparation of β³-amino acids (6a–h)

General procedure. Conventional treatment of β³-amino acid hydrochlorides (**4a–h**) with Amberlite IR-120 ion-exchange resin followed by washing the column with 2 M NH_3 aq and evaporation of water in vacuo afforded analytically pure β³-amino acids (**6a–h**) in almost quantitative yields.

4.5.1. 3-Aminopropanoic acid (6a). Yield 96%, colorless solid, mp 197–199 °C (dec) (lit.[17] mp 197–198 °C (dec)); δ_H (D_2O) 2.54 (2H, t, J=6.7 Hz, CH_2NH_2), 3.17 (2H, t, J=6.7 Hz, CH_2CO_2H).

4.5.2. 3-Aminobutanoic acid (6b). Yield 93%, colorless solid, mp 187–191 °C (dec) (lit.[18] mp 187–189 °C (dec)); δ_H (D_2O) 1.31 (3H, d, J=6.8 Hz, CH_3CH), 2.48 (2H, d, J=6.8 Hz, CH_2CO_2H), 3.60 (1H, 6 lines, J=6.8 Hz, CH_3CH).

4.5.3. 3-Aminopentanoic acid (6c). Yield 99%, colorless solid, mp 184–187 °C (dec) (lit.[19] mp 189–191 °C (dec)); δ_H (D_2O) 0.98 (3H, t, J=7.4 Hz, CH_3CH_2CH), 1.67 (2H, qt, J=7.4 Hz, CH_3CH_2CH), 2.41 (1H, dd, J=16.6, 8.2 Hz, CH_2CO_2H), 2.55 (1H, dd, J=16.6, 5.0 Hz, CH_2CO_2H), 3.34–3.48 (1H, m, CH_3CH_2CH).

4.5.4. 3-Amino-4-methylpentanoic acid (6d). Yield 92%, colorless solid, mp 192–195 °C (dec) (lit.[20] mp 202–210 °C (dec)); δ_H (D_2O) 0.98 (3H, d, J=6.8 Hz, Me_2CH), 0.99 (3H, d, J=6.8 Hz, Me_2CH), 1.94 (1H, 8 lines, J=6.8 Hz, Me_2CH), 2.39 (1H, dd, J=16.8, 9.2 Hz, CH_2CO_2H), 2.57 (1H, dd, J=16.8, 4.3 Hz, CH_2CO_2H), 3.28–3.41 (1H, m, $CHNH_2$).

4.5.5. 3-Amino-5-methylhexanoic acid (6e). Yield 92%, colorless solid, mp 225–226 °C (dec) (lit.[21] mp 215–216 °C (dec)); δ_H (D_2O) 0.92 (3H, d, J=6.8 Hz, Me_2CH), 0.93 (3H, d, J=6.8 Hz, Me_2CH), 1.49 (2H, t, J=6.8 Hz, Me_2CHCH_2), 1.66 (1H, 9 lines, J=6.8 Hz, Me_2CHCH_2), 2.39 (1H, dd, J=16.5, 8.0 Hz, CH_2CO_2H), 2.60 (1H, dd, J=16.5, 4.7 Hz, CH_2CO_2), 3.52–3.60 (1H, m, $CHNH_2$).

4.5.6. 3-Amino-3-cyclohexylpropanoic acid (6f). Yield 99%, colorless solid, mp 224–225 °C (dec) (lit.[22] mp 229–230 °C

(dec)); δ_H (D_2O) 0.94–1.33 (5H, m, ring, CH_2), 1.55–1.74 (6H, m, ring CH_2), 2.39 (1H, dd, $J=16.8$, 9.0 Hz, CH_2CO_2H), 2.59 (1H, dd, $J=16.8$, 4.2 Hz, CH_2CO_2H), 3.28–3.36 (1H, m, CHNH_3).

4.5.7. 3-Amino-3-phenylpropanoic acid (6g). Yield 81%, colorless solid, mp 220–222 °C (dec) (lit.[23] mp 221–223 °C (dec)); δ_H (D_2O) 2.82 (1H, dd, $J=16.2$, 6.9 Hz, CH_2CO_2H), 2.93 (1H, dd, $J=16.2$, 6.9 Hz, CH_2CO_2H), 4.65 (1H, dd, $J=6.9$ Hz, CHNH_2), 7.40–7.52 (5H, m, H_{arom}).

4.5.8. 3-Amino-3-(4-methoxyphenyl)-propanoic acid (6h). Yield 89%, colorless solid, mp 226–228 °C (dec) (lit.[23] mp 228–229 °C (dec)); δ_H (D_2O) 2.79 (1H, dd, $J=$ 16.1, 6.8 Hz, CH_2CO_2H), 2.90 (1H, dd, $J=16.1$, 8.0 Hz, CH_2CO_2H), 3.84 (3H, s, CH_3O), 4.61 (1H, m, CHNH_2), 7.05 (2H, d, $J=8.7$ Hz, H_{arom}), 7.41 (2H, d, $J=8.7$ Hz, H_{arom}).

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