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Regioselective Ring Opening of Chiral N-Boc Protected Pyroglutamate and Pyroaminoadipate Ethyl Esters with Heteronucleophiles

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ABSTRACT: Mixed diesters, ω-amide and ω-thioesters are obtained from both N-Boc ethyl pyroglutamate and pyroaminoadipate under neutral or basic conditions.Under neutral conditions, the reaction is catalyzed by KCN and the use of Ultrasound speeds up the process. In basic conditions, reaction times are even shorter. In both cases, no transesterification of the α-ester was observed and the chirality of the α-amino acid was preserved.

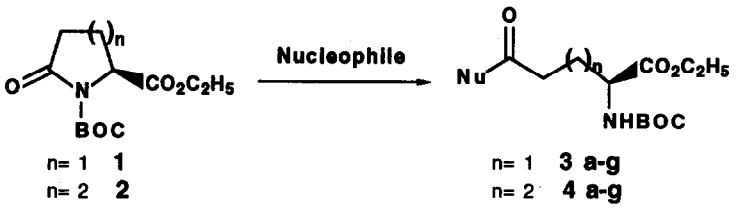
The use of α-amino acids as starting materials for the synthesis of enantiomerically-pure compounds has been well documented,[1] because the single chiral centre present in the naturally-occurring α-amino acid provides a building block for asymmetric synthesis.[2] When dealing with dicarboxylic acids, such as glutamic or α-aminoadipic acids, one of the major problems is to achieve *differentiation* between the carboxyl groups. For instance, this is necessary in peptide synthesis, since only the α-carboxyl group forms the peptide bond and the other group gives the polypeptide an acid character.[3] This differentiation could be achieved by common protection-deprotection protocols[4] which usually are long and tedious and in many cases are not site-specific.

Both N-protected pyroglutamate and pyroaminoadipate esters **1** and **2** can be recognized as internal protection of the terminal carboxylic group, allowing an easy differentiation of the two carbonyl moieties present in the corresponding amino acids. Thus, the N-Boc protected pyroglutamate undergoes a ring opening reaction with Grignard reagents with excellent regioselectivity[5] and, as we have recently reported, with lithium enolates.[6] Also Mann[7] has reported that mixed diesters of glutamic acid can be prepared by reacting N-Boc protected pyroglutamate esters with at least two equivalents of an alcohol in the presence of KCN as catalyst in THF, but the reaction times were long (24 hrs.), the role of the catalyst was unexplained and no mention was made regarding the optical integrity of the asymmetric centre.

As part of our ongoing programme in non proteinogenic amino acids, in this paper we want to report a further extension of this reaction applied to the preparation of various mixed ω-diesters, ω-amides and ω-thioesters derived from both glutamic and α-aminoadipic acids.

Both pyroglutamate and pyroaminoadipate ethyl esters were prepared from the corresponding amino acids[8] and protected as tert-butyl carbamates following standard procedures.[9] The ring opening was achieved reacting **1** and **2** with different heteronucleophiles. Results on **1** and **2** are presented in Table I.

TABLE I

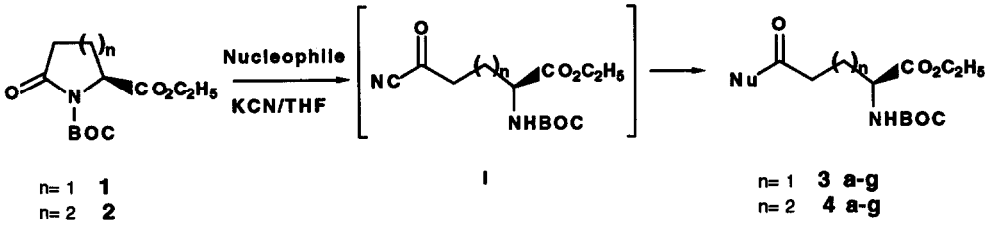


Entry	Subs.	Comp.	Nucleophile	Equiv.	Method A[a]	Method B[b]	Method C[c]	Yield (%)[d]
					Time (h)			
1	1[e]	**3a**	$HC{\equiv}CCH_2OH$	2	18	5		97
2	**2**	**4a**	$HC{\equiv}CCH_2OH$	2		9		83
3	1[e]	**3b**	$H_2C{=}CHCH_2OH$	2	25	8	0.5	79 (87)
4	**2**	**4b**	$H_2C{=}CHCH_2OH$	8		20		76
5	1[e]	**3c**	$C_6H_5CH_2OH$	2	25	9	0.5	64 (76)
6	2[e]	**4c**	$C_6H_5CH_2OH$	1		--	0.5	---[f] (66)
7	1[e]	**3d**	p-$MeOC_6H_4CH_2OH$	2	25	7	0.5	68 (74)
8	2[e]	**4d**	p-$MeOC_6H_4CH_2OH$	1		--	0.5	---[f] (95)
9	1[e]	**3e**	$H_2C{=}CHCH_2NH_2$	6	72	8		95
10	2[e]	**4e**	$H_2C{=}CHCH_2NH_2$	6		10		40
11	**1**	**3f**	$C_6H_5CH_2NH_2$	6	96	15		95
12	**2**	**4f**	$C_6H_5CH_2NH_2$	6		20		87
13	1[e]	**3g**	$C_6H_5CH_2SH$	4		9		32
14	2[e]	**4g**	$C_6H_5CH_2SH$	4		10		35

[a] **Method A**: Reactions performed with KCN as catalyst stirring at room temperature (Mann's procedure). [b] **Method B**: Reactions performed with Ultrasound. [c] **Method C**: Reactions performed at -78°C, in THF with the corresponding sodium alkoxide. [d] Isolated yield with ultrasound (Method B). Yields without Ultrasound (Method A) are roughly the same. In brackets, isolated yield with sodium alkoxide (Method C). [e] Reactions also carried out on the D-enantiomer. [f] The reaction was monitored by ^{1}H-NMR and the crude was not isolated.

When the reactions were performed following Mann's procedure (Method A) on **1** (entries,1, 3, 5, 7, 9, 11), long reaction times were needed (18-96 hrs.). The reaction takes place under mild and neutral conditions and no transesterification at the α-amino ester moiety was observed. The high regioselectivity of

this process can be explained by the nucleophilic attack of the cyanide on the amide carbonyl group (Scheme I).



Scheme I

The heteronucleophile displaces the cyanide in the highly reactive acyl cyanide[10] intermediate **I**, delivering the acyclic products **3** and **4**. The long reaction times may be due to the low solubility of KCN in the reaction medium. Despite their solubility in THF, other catalysts such as imidazole or N-methyl imidazole proved to be less effective than cyanide due to their lower nucleophilicity.

In order to speed up the process we decided to apply ultrasonic irradiation[11] (Method B) to the reaction using KCN as catalyst. Under these conditions, reaction times were considerably shortened (5-15 hrs).

When the reaction was carried out on the N-Boc protected pyroaminoadipate **2** (entries, 2, 4, 10, 12, 14) it was necessary to increase the amount of the nucleophile, observing longer reaction times (9-20 hrs.), even with the aid of ultrasound. In fact, when benzyl and 4-methoxy benzyl alcohols were reacted with the pyroaminoadipate **2**, reaction times were so long that partial decomposition of the reaction products took place and in addition to this, the resulting diesters **4c** and **4d** proved to be difficult to separate from the excess of the reacting alcohol.

These problems could be circumvented employing a different strategy. Thus, reaction between one equivalent of sodium benzyl and 4-methoxybenzyl alkoxides (Method C) with pyroaminoadipate **2** occurred smoothly at -78°C, in 30 minutes, affording the mixed diesters **4c** and **4d** in 66 and 95% yield respectively. Again, no transesterification took place and the reaction proceeded only by ring-opening at the acyl-nitrogen bond. Although these results are in agreement with those reported on reactions between N-benzyloxycarbonyl aziridine-2-ones and alkoxides,[12] Hon and coworkers have recently reported the cleveage of the Boc group when a 2-pyrrolidone derivative was exposed to methanolic sodium methoxide.[13]

At this stage we reinvestigated the formation of other diesters using alkoxide and, as expected, the reaction proceeded very smoothly and with high yields (entries 3, 5, 7).

Amines behave as good nucleophiles, and they react readily with **1** and **2** yielding the corresponding ω-carboxamide derivatives **3** and **4** (entries 9-12). This method is simpler than the reported procedures which involve the use of aluminium compounds[14] or high pressure equipment.[15] Finally, when benzyl thiol was employed yield decreased to 32-35%. The use of sodium benzyl thiolate did not improve the reaction yield.

To investigate the optical purity of the resulting compounds, D-enantiomers were also prepared from the corresponding N-Boc D-pyroglutamate and D-pyroaminoadipate ethyl esters, respectively.

^{1}H-NMR spectra of both enantiomeric series arising from pyroglutamate were recorded after addition of the chiral shift reagent (+)-Eu(tfc)$_3$. The ee were found to be greater than 95% in all cases.[16]

In the case of diesters derived from L- and D-pyroaminoadipate the stereochemical integrity of the chiral centre was determined by chemical correlation. Thus, when **4c** and **4d** were hydrolyzed with 6N HCl, enantiomerically pure (L)-2-aminoadipic acid was obtained ($[\alpha]_D^{25}$=+22, c=2, 5N HCl).[17] In the same way the corresponding D-enantiomers of **4c** and **4d** afforded upon hydrolysis pure (D)-2-aminoadipic acid ($[\alpha]_D^{25}$= -24, c=1, 6N HCl).[17]

In summary, two methods for the regioselective heteronucleophilic ring opening of chiral (L-) and (D)-N-Boc pyroglutamate and pyroaminoadipate ethyl esters are presented, under neutral and basic conditions, allowing for the preparation of different diesters, ω- amides and ω- thioesters in moderate to excellent yields. The use of ultrasound considerably reduces the reaction times, compared with previous described methods. Under basic conditions the reaction time is even shorter and the heteronucleophile is used in stoichiometric amount. In both methods, the chirality of the asymmetric centre is not affected. The method of choice will depend on the nature of the nucleophile and/or the substrate.

EXPERIMENTAL SECTION

^{1}H-NMR and ^{13}C-NMR data were recorded on a Varian-Gemini (200 MHz) and Bruker AC-200P (200 MHz). IR spectra were obtained on a Shimadzu IR-435 and Nicolet 510 P-FT (film and KBr). MS were measured on a VG-12-250 spectrometer (70 eV). Melting points were determined on a Kofler apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. TLC analyses were carried out by using Merck aluminium sheets precoated with silica gel 60 F_{254} (UV, 254 nm and anisaldehyde). Chromatographic separations were performed by using 230-400 mesh silica gel (Merck). Ultrasonic reactions were carried out in a Branson ultrasonic cleaning bath. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under argon. Propargyl, allyl, benzyl, 4-methoxy benzyl alcohols and allyl and benzyl amines were distilled before use.

General procedure for heteronucleophilic ring opening with Ultrasound. (METHOD B)

To a solution of **1** or **2** (0.5 mmol) in dry THF (2 ml) in a conical flask[18], under argon was added the corresponding heteronucleophile (see Table I for the appropriate number of equivalents) and potassium cyanide (0.05 mmol). After stirring in an ultrasonic laboratory cleaning bath (see Table for reaction times), the solvent was removed under reduced pressure. The residue was directly purified by flash chromatography (hexane/ethyl acetate) to give the desired products **3a-g** or **4a-g.**

General procedure for heteronucleophilic ring opening with sodium alkoxides. (METHOD C)

To a suspension of NaH (0.5 mmol) in dry THF (2 ml) the desired alcohol (0.5 mmol) was added and the solution cooled at -78°C under argon. A solution of **1** or **2** (0.5 mmol) in dry THF (2 ml) was added and the resulting solution stirred at -78°C for 30 min. The reaction was quenched with acetic acid (0.2 ml), diluted with water and extracted with CH_2Cl_2 .The organic layer was dried over Na_2SO_4 , the solvent removed under

reduced pressure and the residue purified by flash chromatography (hexane/ethyl acetate) to give the desired products **3b-d** or **4c-d.**

(L)-N-Boc glutamate α-ethyl, γ-propargyl diester (3a)

$[\alpha]_D^{25}$= +7 (c = 2.6, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 5.11 (d, J = 8.0 Hz, 1H, N*H*), 4.61 (d, J = 2.4 Hz, 2H, HCC-C*H*$_2$), 4.24 (m, 1H, C*H*-NH), 4.12 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH$_3$), 2.43 (s, 1H, *H*-CC), 2.39 (m, 2H, OCO-C*H*$_2$-CH$_2$), 2.13 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.90 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.36 (s, 9H, (C*H*$_3$)$_3$C), 1.21 (t, J = 7.15 Hz, 3H, COO-CH$_2$-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 171.96, 171.89, 155.24, 79.85, 77.37, 74.95, 61.45, 52.66, 52.00, 29.89, 28.15, 27.53, 14.02. IR (film) 3380, 3280, 2120, 1745, 1680 cm^{-1}. MS, m/e 314 (1), 258 (6), 140 (47), 84 (40), 57 (100). Anal. Calcd. for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.39; N, 4.46. Found: C, 57.45; H, 7.60; N, 4.70.

(L)-N-Boc glutamate α-ethyl, γ-allyl diester (3b)

$[\alpha]_D^{25}$= +6 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 5.88 (dddd, J = 16.0, 10.3, 5.7 and 1.0 Hz, 1H, CH$_2$=C*H*), 5.28 (m, 2H, C*H*$_2$=CH), 5.21 (m, 1H, C*H*$_2$=CH), 5.08 (d, J = 7.7 Hz, 1H, N*H*), 4.55 (ddd, J = 5.7, 2.6 and 1.2 Hz, 2H, CH$_2$=CH-C*H*$_2$), 4.28 (m, 1H, C*H*-NH), 4.18 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH$_3$), 2.41 (m, 2H, OCO-C*H*$_2$-CH$_2$), 2.14 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.90 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.42 (s, 9H, (C*H*$_3$)$_3$C), 1.26 (t, J = 7.1 Hz, 3H, COO-CH$_2$-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 172.27, 172.07, 155.24, 131.89, 118.22, 79.75, 65.19, 61.36, 52.75, 30.10, 28.13, 27.57, 14.00. IR (film) 3350, 1720, 1680, 1514 cm^{-1}. MS, m/e 259 (3), 242 (10), 214 (6), 186 (19), 142 (66), 84 (45), 57 (100). Anal. Calcd. for $C_{15}H_{25}NO_6$: C, 57.12; H, 7.99; N, 4.44. Found: C, 57.35; H, 8.15; N, 4.71.

(L)-N-Boc glutamate α-ethyl, γ-benzyl diester (3c)

M.p.: 46-8° (acetone-hexane). $[\alpha]_D^{25}$= +6 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 5H, *Ph*), 5.12 (s, 1H, N*H*), 5.09 (s, 2H Ph-C*H*$_2$), 4.29 (m, 1H, C*H*-NH), 4.14 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH$_3$), 2.43 (m, 2H, OCO-C*H*$_2$-CH$_2$), 2.15 (m, 1H, OCO-CH$_2$-C*H*$_2$)), 1.94 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.40 (s, 9H, (C*H*$_3$)$_3$C), 1.24 (t, J = 7.1 Hz, 3H, COO-CH$_2$-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 172.52, 172.15, 155.31, 135.67, 128.55, 128.51, 128.23, 79.91, 66.43, 61.49, 52.80, 30.23, 28.22, 27.75, 14.09. IR (KBr) 3350, 1740, 1728, 1680, 740, 690cm^{-1}. MS, m/e 265 (2), 264 (2), 236 (13), 192 (40), 157 (1), 107 (3), 91 (100). Anal. Calcd. for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.44; N, 3.82. Found: C, 62.47; H, 7.59; N, 4.00.

(L)-N-Boc glutamate α-ethyl, γ-4-methoxy benzyl diester (3d)

$[\alpha]_D^{25}$= +5 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.27-6.86 (AA'BB', 4H, *Ar*), 5.03 (s, 2H, Ar-C*H*$_2$), 5.09 (m, 1H, N*H*)), 4.28 (m, 1H, C*H*-NH), 4.16 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH$_3$), 3.78 (s, 3H, C*H*$_3$O), 2.40 (m, 2H, OCO-C*H*$_2$-CH$_2$), 2.16 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.94 (m, 1H, OCO-CH$_2$-C*H*$_2$), 1.40 (s, 9H, (C*H*$_3$)$_3$C), 1.24 (t, J = 7.1 Hz, 3H, COO-CH$_2$-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 172.58, 172.15, 159.57, 155.29, 130.09, 127.73, 113.86, 79.66, 66.26, 61.46, 55.21, 52.61, 30.27, 28.22, 27.73, 14.06. IR (film) 3360, 1740, 1620, 1025, 780 cm^{-1}. MS, m/e 339 (3), 230 (1), 214 (14), 185 (27), 158 (15), 137 (32), 121 (98), 91 (98), 57 (100).

(L)-N-Boc glutamate α-ethyl ester, γ-allyl amide (3e)

M.p.: 77-9 °C (acetone-hexane). $[\alpha]_D^{25}$= +2 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 6.19 (s, 1H, N*H*-CO), 5.80 (ddt, J = 16.8, 11.5 and 5.6 Hz, 1H, CH$_2$=C*H*), 5.16 (ddd, J = 16.8, 2.8 and 1.5 Hz, 1H, C*H*$_2$=CH), 5.11 (d, J= 7.3 Hz, 1H, N*H*-CO$_2$), 5.09 (ddd, J = 11.5, 2.8 and 1.4 Hz, 1H, C*H*$_2$=CH), 4.21 (m, 1H, C*H*-NH-CO$_2$), 4.15 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH$_3$), 3.84 (tt, J = 5.6 and 1.3 Hz, 2H, CH$_2$=CH-C*H*$_2$), 2.24 (m, 2H, NHCO-C*H*$_2$-CH$_2$), 2.14 (m, 1H, NHCO-CH$_2$-C*H*$_2$), 1.87 (m, 1H, NHCO-CH$_2$-C*H*$_2$), 1.40 (s, 9H,

(CH_3)$_3$C), 1.23 (t, J = 7.14Hz, 3H, COO-CH_2-CH_3). ^{13}C-NMR ($CDCl_3$) δ 172.23, 171.79, 155.79, 134.07, 116.18, 79.94, 61.44, 53.03, 41.00, 32.51, 28.90, 28.19, 14.05. IR (KBr) 3350, 1720, 1680, 1640, 1528 cm^{-1}. MS, m/e 315 (1), 258 (6), 241 (23), 213 (5), 185 (11), 141 (32), 84 (42), 57 (100). Anal. Calcd. for $C_{15}H_{26}N_2O_5$: C, 57.30; H, 8.33; N, 8.91. Found: C, 57.02; H, 8.41; N, 9.03.

(L)-N-Boc glutamate α-ethyl ester, γ-benzyl amide (3f)

M.p.: 102-4°C (acetone-hexane). $[\alpha]_D^{25}$= +14 (c = 1, MeOH). ^{1}H-NMR ($CDCl_3$) δ 7.24 (s, 5H, *Ph*), 6.59 (s, 1H, N*H*-CO), 5.38 (d, J = 8.0 Hz, 1H, N*H*-CO_2), 4.36 (d, J = 5.7 Hz, 2H, Ph-CH_2), 4.20 (m, 1H, C*H*-NH-CO_2), 4.12 (q, J = 7.1 Hz, 2H, COO-CH_2-CH_3), 2.25 (m, 2H, NHCO-CH_2-CH_2), 2.13 (m, 1H, NHCO-CH_2-C*H*$_2$), 1.88 (m, 1H, NHCO-CH_2-C*H*$_2$), 1.37 (s, 9H, (CH_3)$_3$C), 1.21 (t, J = 7.1 Hz, 3H, COO-CH_2-CH_3). ^{13}C-NMR ($CDCl_3$) δ 172.23, 171.81, 155.77, 138.15, 128.51, 127.63, 127.26, 79.91, 61.41, 52.97, 43.49, 32.43, 28.84, 28.17, 14.04. IR (film) 3300, 1732, 1680, 1640, 1528 cm^{-1}. MS, m/e 365 (0.6), 308 (4), 291 (8), 264 (9), 191 (21), 106 (54), 91 (73), 57.2 (100) . Anal. Calcd. for $C_{19}H_{28}N_2O_5$: C, 62.61; H, 7.74; N, 7.68. Found: C, 62.47; H, 8.01; N, 7.90.

(L)-N-Boc glutamate α-ethyl ester, γ-benzyl thioester (3g)

$[\alpha]_D^{25}$= +7 (c = 1.2, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.25 (s, 5H, *Ph*), 5.09 (m, 1H, N*H*)), 4.30 (m, 1H, C*H*-NH), 4.15 (q, J = 7.1 Hz, 2H, COO-CH_2-CH_3), 4.09 (s, 2H, Ph-CH_2), 2.64 (m, 2H, SCO-CH_2-CH_2), 2.21 (m, 1H, SCO-CH_2-C*H*$_2$), 1.97 (m, 1H, SCO-CH_2-C*H*$_2$), 1.41 (s, 9H, (CH_3)$_3$C), 1.24 (t, J = 7.1 Hz, 3H, COO-CH_2-CH_3). ^{13}C-NMR ($CDCl_3$) δ 197.63, 171.95, 155.24, 137.31, 128.75, 128.58, 127.25, 80.00, 61.57, 52.72, 39.53, 33.18, 28.23, 28.12, 14.10. IR (film) 3360, 1740, 1680 cm^{-1}. MS, m/e 325 (0.7), 308 (0.8), 158 (52), 91 (48), 57 (100). Anal. Calcd. for $C_{19}H_{27}NO_5S$: C, 59.83; H, 7.13; N, 3.67; S, 8.40. Found: C, 60.03; H, 7.45; N, 3.62; S, 8.15.

(L)-N-Boc 2-aminoadipate α-ethyl, δ-propargyl diester (4a)

$[\alpha]_D^{25}$= +5 (c = 2.4, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 5.05 (d, J = 7.9 Hz, 1H, N*H*), 4.62 (d, J = 2.4 Hz, 2H, HCC-CH_2), 4.25 (m, 1H, C*H*-NH), 4.14 (q, J = 7.1 Hz, 2H, COO-CH_2-CH_3), 2.43 (t, J = 2.4 Hz, 1H, *H*-CC), 2.34 (m, 2H, OCO-CH_2-CH_2), 1.66 (m, 4H, OCO-CH_2-CH_2-CH_2), 1.39 (s, 9H, (CH_3)$_3$C), 1.22 (t, J = 7.1 Hz, 3H, COO-CH_2-CH_3). ^{13}C-NMR ($CDCl_3$) δ 172.44, 172.13, 155.28, 79.80, 77.53, 74.84, 61.33, 53.04, 51.84, 33.20, 31.91, 28.22, 20.51, 14.10. IR (film) 3360, 3280, 2120, 1740, 1684 cm^{-1}. MS, m/e 328 (1), 272 (4), 254 (9), 228 (7), 154 (44), 98 (33), 57 (100). Anal. Calcd. for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.69; N, 4.27. Found: C, 58.66; H, 7.80; N, 4.40.

(L)-N-Boc 2-aminoadipate α-ethyl, δ-allyl diester (4b)

$[\alpha]_D^{25}$= +3 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 5.89 (dddd, J = 16.0, 10.4, 5.7 and 1.0 Hz, 1H, CH_2=C*H*), 5.28 (m, 1H, C*H*$_2$=CH), 5.21 (m, 1H, C*H*$_2$=CH), 5.03 (d, J = 8.6 Hz, 1H, N*H*), 4.55 (ddd, J = 5.7, 2.7 and 1.3 Hz, 2H, CH_2=CH-C*H*$_2$), 4.27 (m, 1H, C*H*-NH), 4.17 (q, J = 7.1 Hz, 2H, COO-CH_2-CH_3), 2.35 (m, 2H, OCO-CH_2-CH_2), 1.67 (m, 4H, OCO-CH_2-CH_2-CH_2), 1.42(s, 9H, (CH_3)$_3$C), 1.25 (t, J = 7.1 Hz, 3H, COO-CH_2-CH_3). ^{13}C-NMR ($CDCl_3$) δ 172.57, 172.44, 155.25, 132.00, 118.13, 79.67, 64.97, 61.23, 53.01, 33.39, 31.90, 28.96, 20.57, 14.04. IR (film) 3361, 1738, 1716 cm^{-1}. MS, m/e 330 (0.6), 273 (1), 256 (5), 156 (45), 57 (100).

(L)-N-Boc 2-aminoadipate α-ethyl, δ-benzyl diester (4c)

$[\alpha]_D^{25}$= +7 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.35 (s, 5H, *Ph*), 5.11 (s, 2H Ph-CH_2), 5.04 (d, J = 8.4 Hz, 1H, N*H*), 4.28 (m, 1H, C*H*-NH), 4.18 (q, J = 7.1 Hz, 2H, COO-CH_2-CH_3), 2.39 (m, 2H, OCO-CH_2-CH_2), 1.73 (m, 4H, OCO-CH_2-CH_2-CH_2), 1.43 (s, 9H, (CH_3)$_3$C), 1.26 (t, J = 7.12Hz, 3H, COO-CH_2-CH_3).

^{13}C-NMR ($CDCl_3$) δ 173.35, 172.98, 156.00, 136.38, 129.05, 128.70, 80.45, 66.74, 64.85, 53.63, 34.11, 32.59, 28.79, 21.22, 14.65. IR (film) 3350, 1740, 1685 cm^{-1}. MS, m/e 380 (2), 306 (6), 280 (10), 206 (59), 91 (94), 57 (100).

(L)-N-Boc 2-aminoadipate α-ethyl, δ-4-methoxi benzyl diester (4d)

$[\alpha]_D^{25}$= +1 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.27-6.87 (AA'BB', 4H, *Ar*), 5.07 (s, 1H, N*H*CO_2), 5.03 (s, 2H, Ar-C*H*$_2$), 4.28 (m, 1H, C*H*-NH), 4.17 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH_3), 3.79 (s, 3H, C*H*$_3$O), 2.35 (m, 2H, OCO-C*H*$_2$-CH_2), 1.71 (m, 4H, OCO-CH_2-C*H*$_2$-C*H*$_2$), 1.42 (s, 9H, (C*H*$_3$)$_3$C), 1.25 (t, J = 7.1 Hz, 3H, COO-CH_2-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 173.41, 173.02, 160.11, 155.50, 130.56, 128.52, 114.13, 80.32, 66.55, 61.82, 55.75, 53.66, 34.15, 32.56, 28.78, 21.22, 14.69. IR (film) 3360, 1740, 1700, 1024, 820 cm^{-1}. MS, m/e 410 (11), 353 (5), 241 (12), 121 (100), 57 (42). Anal. Calcd. for $C_{21}H_{31}NO_7$: C, 61.59; H, 7.63; N, 3.42. Found: C, 61.85; H, 7.83; N, 3.70.

(L)-N-Boc 2-aminoadipate α-ethyl ester, δ-allyl amide (4e)

$[\alpha]_D^{25}$= +3 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 5.85-5.71 (m, 2H, CH_2=C*H* and N*H*CO), 5.17-5.05 (m, 3H, C*H*$_2$=CH and N*H*CO_2), 4.24 (m, 1H, C*H*-NH-CO_2), 4.15 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH_3), 3.82 (m, 2H, CH_2=CH-C*H*$_2$), 2.23 (m, 2H, NHCO-C*H*$_2$-CH_2), 1.70 (m, 4H, NHCO-CH_2-C*H*$_2$-C*H*$_2$), 1.39 (s, 9H, (C*H*$_3$)$_3$C), 1.23 (t, J = 7.2 Hz, 3H, COO-CH_2-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 172.52, 172.27, 155.49, 134.18, 116.10, 79.76, 61.28, 52.72, 41.74, 35.43, 32.11, 28.19, 21.51, 14.04. IR (film) 3300, 1740, 1640, 1532 cm^{-1}. MS, m/e 328 (0.1), 171 (2), 155 (3), 98 (100), 55 (40). Anal. Calcd. for $C_{16}H_{28}N_2O_5$: C, 58.51; H, 8.59; N, 8.52. Found: C, 58.21; H, 8.68; N, 8.77.

(L)-N-Boc 2-aminoadipate α-ethyl ester, δ-benzyl amide (4f)

$[\alpha]_D^{25}$= +4 (c = 1, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.29 (s, 5H, *Ph*), 6.07 (s, 1H, N*H*-CO), 5.15 (d, J = 8.1 Hz, 1H, N*H*-CO_2), 4.41 (d, J = 5.9 Hz, 2H Ph-C*H*$_2$), 4.27 (m, 1H, C*H*-NH-CO_2), 4.17 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH_3), 2.24 (m, 2H, NHCO-C*H*$_2$-CH_2), 1.74 (m, 4H, NHCO-CH_2-C*H*$_2$ -C*H*$_2$), 1.40 (s, 9H, (C*H*$_3$)$_3$C), 1.26 (t, J = 7.1 Hz, 3H, COO-CH_2-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 172.45, 172.19, 155.43, 138.15, 128.50, 127.60, 127.28, 79.75, 61.26, 52.64, 43.37, 35.45, 32.15, 28.11, 21.45, 14.01. IR (film) 3320, 1740, 1644, 1520 cm^{-1}. MS, m/e 379 (10), 323 (14), 278 (69), 249 (17), 205.2 (100), 172 (12), 162 (11), 149 (10), 106 (95), 57 (74), 91 (78).

(L)-N-Boc 2-aminoadipate α-ethyl ester, δ-benzyl thioester (4g)

$[\alpha]_D^{25}$= +9 (c = 1.3, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ 7.24 (s, 5H, *Ph*), 5.02 (d, J = 8.1 Hz, 1H, N*H*)), 4.25 (m, 1H, C*H*-NH), 4.15 (q, J = 7.1 Hz, 2H, COO-C*H*$_2$-CH_3), 4.08 (s, 2H, Ph-C*H*$_2$), 2.57 (t, J = 6.8, 2H, SCO-C*H*$_2$-CH_2), 1.70 (m, 4H, SCO-CH_2-C*H*$_2$-C*H*$_2$), 1.41 (s, 9H, (C*H*$_3$)$_3$C), 1.24 (t, J = 7.1 Hz, 3H, COO-CH_2-C*H*$_3$). ^{13}C-NMR ($CDCl_3$) δ 198.07, 172.41, 155.29, 137.45, 128.72, 128.57, 127.21, 79.85, 61.37, 53.01, 42.90, 33.09, 31.85, 28.24, 21.25, 14.14. IR (film) 3360, 1740, 1680 cm^{-1}. MS, m/e 396 (0.4), 339 (0.9), 172 (79), 98 (80), 57 (100). Anal. Calcd. for $C_{20}H_{29}NO_5S$: C, 60.73; H,7.39 N, 3.54 Found: C, 60.49; H, 7.09; N, 3.80.

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