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[1,2] Boc migration during pyroglutamate alkylations

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Abstract—Treatment of *N*-Boc protected pyroglutamates with strong bases lead to a Boc migration from the N-atom to the C2 position when no or poor electrophiles are being used.

1. Introduction

Pyroglutamates and their syntheses have received a lot of attention over the years because of their importance in several domains. Pyroglutamic acid is a very useful and versatile starting material for the synthesis of both natural and unnatural products. Intensive study of glutamate analogues resulted in specific inhibitors of different receptor types of the mammalian central nervous system.[1] It has also been used for the synthesis of pyrrolidine alkaloids,[2] kainoids,[3] (−)-bulgecinine,[4] (−)-domoic acid,[5] enantiomerically pure glycine and proline derivatives,[6] a wide variety of non-proteinogenic amino acids,[7] etc.

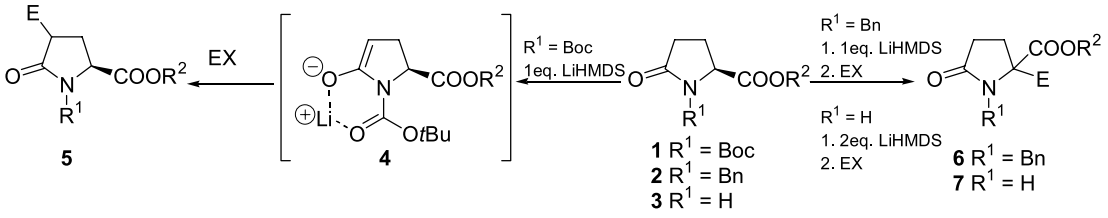
Alkylation of pyroglutamates has therefore been essential in order to expand the range of glutamate analogues and to study their biological properties. The attractiveness of pyroglutamates as a building block lies in the fact that the site of alkylation can be directed by changing the protecting group on *N* (Scheme 1). Alkylation of *N*-Boc protected pyroglutamates **1** results in C4 functionalized derivatives **5** whereas alkylation of *N*-benzyl **2** or N-unprotected **3** pyroglutamates occurs at the 2-position, resulting in **6** and **7**.[8]

The regioselectivity of the alkylation of *N*-Boc protected pyroglutamates was explained by the formation of a stabilized Li-salt **4** which directs the alkylation to the 4-position. This stabilized intermediate cannot be formed in *N*-benzyl or N-unprotected derivatives, thus resulting in alkylation at the 2-position.

This proves that the Boc protecting group plays a crucial role in pyroglutamate chemistry. The reactivity of this carbamate group, however, is often an underestimated feature. There are numerous reports of cases where the Boc group reacts as an electrophile or a nucleophile, resulting in unexpected and often undesired side reactions.[9]

2. Results and discussion

During an ongoing project on the synthesis of 2,4-methanoproline **9**,[10] pyroglutamate derivative **8** was



Scheme 1.

Keywords: Boc migration; Pyroglutamate; Alkylation; Carbamates.
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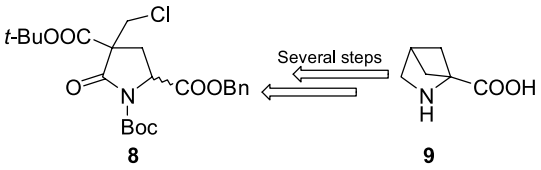


Scheme 2.

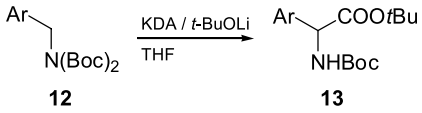
synthesized,[11] as a possible precursor for this interesting amino acid (Scheme 2).

It was observed however, that treating **8** with 1.5 equiv of LiHMDS did not lead to the envisaged 2-azabicyclo[2.1.1]-hexane skeleton, although the starting material was completely converted to a new product. In the ^{1}H-spectrum, the CH proton at the C2-position had disappeared and the remaining CH_2 of the ring was reduced from a ABX-system to a AB-system. Furthermore a broad singlet appeared around 6.41 ppm, which is typical for a NH proton of an amide. In the ^{13}C-spectrum the carbonyl of the Boc group, which is normally around 150 ppm was missing, but two *t*-Butyl groups were still present. Taking all this information into account, structure **10** was deduced, proving that the Boc-group migrated from the N-atom to the C2 position.

The proposed mechanism is depicted in Scheme 3. The formed anion at the 2-position is unreactive towards the chloromethyl group, probably because of the high ring strain involved in the formation of a four-membered ring within a five-membered ring, combined with the planar character of the lactam functionality. However, at room temperature the anion is reactive enough to attack the adjacent *N*-Boc group. The formed bicyclic intermediate **11** is not stable and opens again to form **10** upon work up.

Although there are reports of the Boc moiety reacting as an electrophile, these reactions are usually limited to intramolecular attacks by oxygen or nitrogen nucleophiles.[9] In the literature, only two cases of intramolecular attack on a Boc group by a carbon nucleophile followed by Boc migration were reported. Snieckus mentioned the migration of the Boc group from N to the *ortho* carbon atom of aniline derivatives after directed *ortho* metallation leading to anthranilate esters.[12] Kise et al. described that the reaction of *N*,*N*-di-Boc-protected benzylamines **12** with KDA/*t*-BuOLi at −78 °C gave *N*-Boc protected *t*-Butyl phenylglycines **13** (Scheme 4).[13]

These examples show the Boc migration under quite extreme reaction conditions, whereas in the case of pyroglutamate alkylation, the Boc migration can really compete with the alkylation reaction. In order to investigate the generality of this reaction, a number of pyroglutamate



Scheme 4.

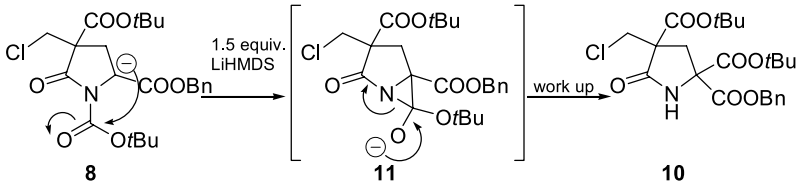
derivatives were synthesized and subjected to the same reaction conditions (Table 1). In this way, we found that esters with a varying substitution pattern underwent the same reaction. Although deprotonation of the pyroglutamates in entries b and h could result in theory in intramolecular substitution of the chloride with formation of a six-membered ring, only the [1,2] Boc migrated product was observed. When there is no or only one substituent present on the C4 position, a double amount of base is needed since the first equivalent is consumed in deprotonating this position. In this case, the Boc migration occurs via a dianion. Some of the Boc migrated products proved to be quite unstable on silica gel during purification (e.g., entries g and h), leading to a substantial loss of material.

When no substituent is present on the C4 position (entries i and j), no Boc migration was observed. Instead, the ring-opened products were isolated. Apparently, in these cases, the formed dianions are unstable and the esters fragment with formation of alkoxide anions. These anions in turn attack another pyroglutamate molecule and induce ring-opening with formation of racemic glutamate derivatives **15i**, **j** (no optical rotation). In this fashion, the yield is limited to 50% and explains the low yield of the isolated products.

In summary, we have shown that deprotonation of *N*-Boc protected pyroglutamates at the C2 position can result in the [1,2] Boc migration in the absence of good electrophiles resulting in the formation of functionalized γ-lactam *gem* dicarboxylates. This is the first example of an intramolecular nucleophilic attack of an ester enolate onto a Boc-protecting group. Not only should this side reaction be taken into account when working with pyroglutamates, γ-lactam *gem* dicarboxylates are useful intermediates in organic synthesis.[14]

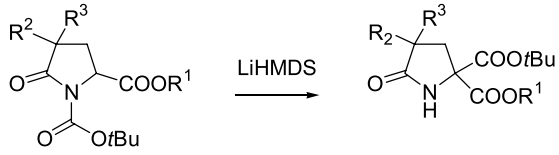
3. Experimental

High-resolution ^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) spectra were run with a Jeol JNM-EX 270 NMR spectrometer or on a Jeol JNM-EX 300 NMR. Peak assignments were obtained with the aid of DEPT, 2D-HETCOR, 2D-COSY spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. Mass spectra were recorded on a Varian

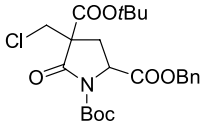
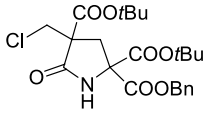
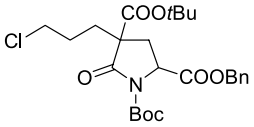
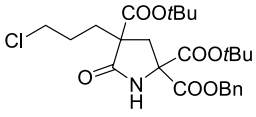
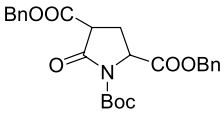
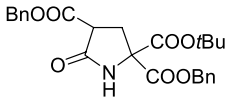
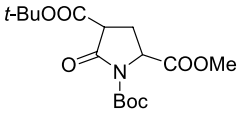
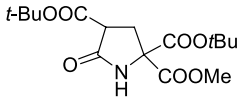
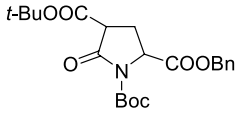
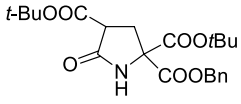
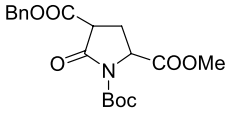
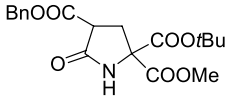
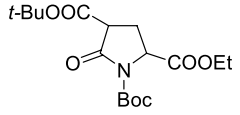
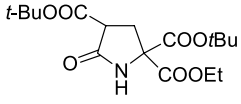
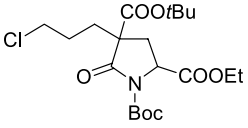
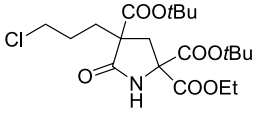
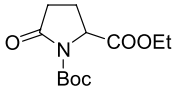
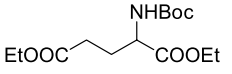
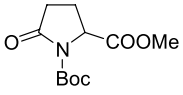
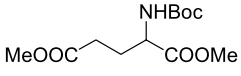


Scheme 3.

Table 1. [1,2] Boc migration observed for different *N*-Boc protected pyroglutamates upon treatment with LiHMDS in THF



14 **15**

Entry	Substrate	LiHMDS (equiv)	Product	Conversion[a]	Yield[b]
a		1.5		100%	61%
b		1.5		91%	64%
c		3		90%	72%
d		3		82%	56%
e		3		86%	62%
f		3		81%	69%
g		3		79%	[c]
h		1.5		91%	[c]
i		3		77%	36%
j		3		71%	32%

[a] Conversion determined by ^{1}H NMR on the crude reaction mixture.
[b] Yield after purification by flash chromatography.
[c] The product could not be obtained in sufficient purity.

MAT 112 spectrometer (70 eV), using either GC–MS coupling or a direct inlet system. Some volatile samples were recorded on an HP 6890 GC coupled with a HP 5973 MSD (Mass selective detector; quadrupole). Mass spectra of molecules with a high molecular weight were recorded on an Agilent 1100 Series VS (ES, 4000 V) mass spectrometer. IR-spectra were obtained from a Perkin–Elmer Spectrum One infrared spectrometer. For liquid samples, the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline

compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and are uncorrected. The elemental analysis was performed on a Perkin–Elmer 2400 Elemental Analyzer. The purification of reaction mixtures was performed by flash chromatography using a glass column with silica gel (Across, particle size 0.035–0.070 mm, Pore diameter ca. 6 nm).

4-Alkoxycarbonyl-2-alkyl-1-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylates (**14c**, **14d**, **14e**, **14f**, **14g**) were prepared following the literature procedure.[11]

3.1. General procedure for the alkylation of 2,4-dialkyl 1-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate at the 4-position

In a classical experiment, 1 g of 2-benzyl 1,4-di-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (2.3 mmol) was dissolved in 10 ml of dry THF and kept under a positive N_2-pressure. 0.29 g of KO*t*Bu (1.1 equiv) was added and the mixture was stirred for 30 min after which the electrophile (2 equiv) was added. The reaction mixture was subsequently refluxed overnight. After cooling, the solution was poured in water and extracted with diethyl ether. The organic layers were combined and dried with $MgSO_4$. Filtering off the drying agent and evaporating the solvent led to a mixture which was purified by chromatography to remove the excess of electrophile.

3.1.1. 2-Benzyl 1,4-di-*t*-butyl 4-(chloromethyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate (14a). The reaction was performed on 2.3 mmol of starting material. Chloroiodomethane was used as electrophile (yield=58%, major/minor 53/47). The product was obtained as a white powder.

^{1}H NMR (270 MHz, $CDCl_3$) δ: *major*: 1.41 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 2.54 (1H, dd, J=13.9, 10.2 Hz, CH_aH$_b$ ring), 2.81 (1H, dd, J=13.9, 2.6 Hz, CH$_a$$H_b$ ring), 3.83 (1H, d, J=11.2 Hz, CH_aH$_b$Cl), 3.96 (1H, d, J=11.2 Hz, CH$_a$$H_b$Cl), 4.69 (1H, dd, J=10.2, 2.6 Hz, CH ring), 5.15 (1H, d, J=12.2 Hz, CH_aH$_b$Ph), 5.26 (1H, d, J=12.2 Hz, CH$_a$$H_b$Ph), 7.35−7.38 (5H, m, CH, Ph). *Minor*: 1.43 (9H, s, *t*-Bu), 1.47 (9H, s, *t*-Bu), 2.22 (1H, dd, J=13.3, 6.9 Hz, CH_aH$_b$ ring), 2.87 (1H, dd, J=13.9, 8.9 Hz, CH$_a$$H_b$ ring), 3.80 (1H, d, J=11.3 Hz, CH_aH$_b$Cl), 3.99 (1H, d, J=11.3 Hz, CH$_a$$H_b$Cl), 4.69 (1H, dd, J=9.0, 6.9 Hz, CH ring), 5.21 (1H, d, J=12.5 Hz, CH_aH$_b$Ph), 5.23 (1H, d, J=12.5 Hz, CH$_a$$H_b$Ph), 7.35–7.38 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.64 (*t*-Bu), 27.73 (*t*-Bu), 28.77 (CH_2 ring), 29.29 (CH_2 ring), 45.30 (CH_2Cl), 47.08 (CH_2Cl), 56.39 (CH, ring), 56.78 (CH, ring), 59.19 ($C_{quat.}$, C4), 59.55 ($C_{quat.}$, C4), 67.46 (CH_2Ph), 67.55 (CH_2Ph), 84.06 ($C_{quat.}$, *t*-Bu), 84.15 ($C_{quat.}$, *t*-Bu), 84.47 ($C_{quat.}$, *t*-Bu), 128.50 (CH), 128.53 (CH), 128.61 (CH), 128.71 (CH), 134.82 ($C_{quat.}$, Ph), 135.09 ($C_{quat.}$, Ph), 148.80 (C=O, Boc), 165.87 (C=O), 166.50 (C=O), 167.92 (C=O), 169.93 (C=O), 170.71 (C=O). IR (cm^{-1}) ν_{max}: (KBr) 1782, 1742. MS: *m*/*z* (%): (ES, Pos) no M^+, 314 (12), 312 (28), 91 (100). Chromatography: Hex/EtOAc 80/20 R_f=0.22 and 0.19. Mp 89.2–90.3 °C. Anal. Calcd $C_{23}H_{30}ClNO_7$: C 59.03%, H 6.46%, N 2.99%; found: C 58.89%, H 6.56%, N 3.10%.

3.1.2. 2-Benzyl 1,4-di-*t*-Butyl 4-(3-chloropropyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate (14b). The reaction was performed on 2.3 mmol of starting material. 3-Bromo-1-chloro-propane was used as electrophile (yield =82%, major/minor 54/46). The product was obtained as a white powder.

Major. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.44 (9H, s *t*-Bu), 1.45 (9H, s, *t*-Bu), 1.37–1.5 (2H, m, CH_2CH$_2$CH$_2$Cl), 1.79–1.88 (2H, m, CH$_2$CH_aH$_b$CH$_2$Cl+CH_aH$_b$ ring), 2.05–2.14 (1H, m, CH$_2$CH$_a$$H_bCH_2$Cl), 2.76 (1H, dd, J=13.5, 8.9 Hz, CH$_a$$H_b$ ring), 3.46 (2H, t, J=5.9 Hz, CH$_2$Cl), 4.64 (1H, dd, J=8.9, 7.3 Hz, CH ring), 5.19 (1H, d, J=12.0 Hz, CH_aH$_b$-Ph), 5.22 (1H, d, J=12.0 Hz, CH$_a$$H_b$Ph), 7.37 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.60 ($CH_2CH_2CH_2$), 27.78 (*t*-Bu), 30.67 ($CH_2CH_2CH_2$), 31.18 (CH_2 ring), 44.64 (CH_2Cl), 56.85 (CH, C2), 56.99 ($C_{quat.}$, C4), 67.51 (CH_2Ph), 83.22 ($C_{quat.}$, *t*-Bu), 84.15 ($C_{quat.}$, *t*-Bu), 128.71 (CH), 128.77 (CH), 134.86 ($C_{quat.}$, Ph), 149.09 (C=O, Boc), 168.68 (C=O), 170.58 (C=O), 170.92 (C=O). IR (cm^{-1}) ν_{max}: 1793, 1724. MS: *m*/*z* (%): (ES, Pos) no M^+, 342 (17), 340 (50), 91 (100). Chromatography: Hex/EtOAc 80/20 R_f=0.27. Mp 79.2–83.1 °C. Anal. Calcd $C_{25}H_{34}ClNO_7$: C 60.54%, H 6.91%, N 2.82%; found: C 60.40%, H 6.99%, N 2.89%.

Minor. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.36–1.50 (1H, m, CH_aH$_b$CH$_2$CH$_2$Cl), 1.41 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.64–1.87 (2H, m, CH$_a$$H_bCH_2CH_2$Cl+CH$_2CH_aH_bCH_2$Cl), 2.13–2.25 (1H, m, CH$_2$CH$_a$$H_bCH_2$Cl), 2.17 (1H, dd, J=13.5, 9.9 Hz, CH_aH$_b$ ring), 2.82 (1H, dd, J=13.5, 2.0 Hz, CH$_a$$H_b$ ring), 3.52 (2H, t, J=5.8 Hz, CH$_2$Cl), 4.61 (1H, dd, J=9.9, 2.0 Hz, CH ring), 5.12 (1H, d, J=12.0 Hz, CH_aH$_b$-Ph), 5.24 (1H, d, J=12.0 Hz, CH$_a$$H_b$Ph), 7.34–7.38 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.69 (*t*-Bu), 27.74 (*t*-Bu), 27.92 ($CH_2CH_2CH_2$), 30.98 (CH_2 ring), 33.24 ($CH_2CH_2CH_2$), 44.47 (CH_2Cl), 56.24 (CH, C2), 56.73 ($C_{quat.}$, C4), 67.42 (CH_2Ph), 83.16 ($C_{quat.}$, *t*-Bu), 83.83 ($C_{quat.}$, *t*-Bu), 128.48 (CH), 128.54 (CH), 128.61 (CH), 135.09 ($C_{quat.}$, Ph), 149.09 (C=O, Boc), 167.94 (C=O), 170.19 (C=O), 170.22 (C=O). IR (cm^{-1}) ν_{max}: 1792, 1725. MS: *m*/*z* (%): (ES, Pos) no M^+, 342 (15), 340 (45), 91 (100). Chromatography: Hex/EtOAc 80/20 R_f=0.19. Mp 91.5–93.0 °C. Anal. Calcd $C_{25}H_{34}ClNO_7$: C 60.54%, H 6.91%, N 2.82%; found: C 60.42%, H 7.11%, N 2.88%.

3.1.3. 1,4-Di-*t*-Butyl 4-(3-chloropropyl) 2-ethyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14h). The reaction was performed on the diastereoisomeric mixture of **14g**. 3-Bromo-1-chloro-propane was used as electrophile (yield= 80%, major/minor 52/48). The product was obtained as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.41–1.55 (1H, m, CH_AH$_B$CH$_2$CH$_2$Cl); 1.45 (9H, s, *t*-Bu); 1.46 (9H, s, *t*-Bu); 1.50 (9H, s, *t*-Bu); 1.71–1.80 (2H, m, CH$_A$$H_BCH_2CH_2$Cl+CH$_2CH_AH_BCH_2$Cl); 1.82–1.91 (2H, m, CH$_2$CH_AH$_B$CH$_2$Cl+CH-$_A$H$_B$ ring); 2.11–2.25 (1H, m, CH$_2$CH$_A$$H_BCH_2$Cl); 2.11–2.25 (2H, m, CH$_2$CH$_A$$H_BCH_2$-Cl+C$H$-$_AH_B$ ring); 2.78 (1H, dd, J=13.5, 8.5 Hz, CH$_A$$H_B$

ring); 2.80 (1H, dd, $J=14.1$, 2.5 Hz, CH-$_A H_B$ ring); 3.53 (2H, t, $J=6.1$ Hz, CH_2Cl); 3.53 (2H, t, $J=6.0$ Hz, CH_2Cl); 4.13–4.29 (2H, m, CH_2CH_3); 4.13–4.29 (2H, m, CH_2CH_3); 4.55 (1H, dd, $J=10.0$, 2.1 Hz, CH ring); 4.59 (1H, dd, $J=8.6$ Hz, $J=7.7$ Hz, CH ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 14.13 (CH_2CH_3–); 14.13 (CH_2CH_3–); 27.72 (*t*-Bu); 27.84 (*t*-Bu); 27.95 (CH_2CH_2-CH_2); 28.29 (CH-$_2CH_2CH_2$); 30.97 ($CH_2CH_2CH_2$); 31.16 (CH_2 ring, C3); 31.29 (CH_2 ring, C3); 33.32 ($CH_2CH_2CH_2$); 44.47 (CH-$_2$Cl); 44.70 (CH_2Cl); 56.21 (CH ring, C2); 56.71 (C_{quat}, C4); 56.96 (CH ring, C2); 57.04 (C_{quat}, C4); 61.69 (CH_2CH_3); 61.81 (CH_2CH_3); 83.02 (C_{quat}, *t*-Bu); 83.19 (C_{quat}, *t*-Bu); 83.68 (C_{quat}, *t*-Bu); 84.03 (C_{quat}, *t*-Bu); 149.15 (C=O, *N*-Boc); 149.15 (C=O, *N*-Boc); 167.94 (C=O); 168.74 (C=O); 170.25 (C=O); 170.32 (C=O); 170.65 (C=O); 171.12 (C=O). IR (cm^{-1}) ν_{max}: 1725 (C=O); 1794 (C=O). MS: *m*/*z* (%): (ES, pos) no M^+; 366 (13); 325 (7); 280 (41); 279 (14); 278 (100); 234 (6); 232 (11); 202 (16); 158 (9). Anal. Calcd $C_{20}H_{32}ClNO_7$: C 55.36%, H 7.43%, N 3.23%; found: C 55.18%, H 7.62%, N 3.46%.

3.1.4. 2-Benzyl 2,4-di-*t*-butyl 4-(chloromethyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate (15a). To a solution of 0.1 g (0.2 mmol) of the major diastereoisomer of **14a** in 2 ml of dry THF, 0.32 ml (1.5 equiv) of a LiHMDS solution (1 M in hexanes) was added at −78 °C and under a N_2-atmosphere. The mixture was stirred for 30 min at this temperature. After allowing the reaction to warm up overnight to room temperature, it was quenched with a saturated NH_4Cl/NH_4OH solution and extracted with EtOAc. The organic phase was washed with water and dried with $MgSO_4$. Filtering off the $MgSO_4$ and evaporating the filtrate gave the crude product that was purified by column chromatography which led to 0.061 g of **15a** as a clear oil (yield =61%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.34 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 2.90 (1H, d, $J=14.5$ Hz, CH_aH_b ring), 3.23 (1H, d, $J=14.5$ Hz, CH_aH_b ring), 3.86 (1H, d, $J=11.4$ Hz, CH_aH_bCl), 3.90 (1H, d, $J=11.4$ Hz, CH_aH_bCl), 5.22 (1H, d, $J=11.9$ Hz, CH_aH_bPh), 5.26 (1H, d, $J=11.9$ Hz, CH_aH_bPh), 6.41 (1H, br. s, NHCO), 7.36 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.53 (*t*-Bu), 27.66 (*t*-Bu), 34.44 (CH_2 ring), 45.48 (CH_2Cl), 57.68 ($C_{quat.}$, C4), 66.31 ($C_{quat.}$, C2), 68.18 (CHC=O_2Ph), 83.74 ($C_{quat.}$, Ph), 84.46 ($C_{quat.}$, *t*-Bu), 128.70 (CH), 128.79 (CH), 128.88 (CH), 134.72 ($C_{quat.}$, Ph), 167.33 (C=O), 167.96 (C=O), 170.83 (C=O). IR (cm^{-1}) ν_{max}: 1739. MS: *m*/*z* (%): (ES, Pos) no M^+, 358 (10), 356 (20), 91 (100). Chromatography: 80/20 Hex/EtOAc R_f= 0.30. Anal. Calcd $C_{23}H_{30}ClNO_7$: C 59.03%, H 6.46%, N 2.99%; found: C 59.10%, H 6.39%, N 3.08%.

3.1.5. 2-Benzyl 2,4-di-*t*-butyl 4-(3-chloropropyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate (15b). The reaction is similar to that of the conversion of **14a**–**15a**. The reaction was performed on the major diastereoisomer of **14b**. The product was obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.33 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.39–1.47 (2H, m, $CH_2CH_2CH_2Cl$), 1.78–1.87 (1H, m, $CH_2CH_aH_bCH_2Cl$), 2.05–2.12 (1H, m, $CH_2CH_aH_bCH_2$-Cl), 2.53 (1H, d, $J=14.3$ Hz, CH_aH_b ring), 3.16 (1H, d, $J=14.3$ Hz, CH_aH_b ring), 3.53–3.55 (2H, m, CH_2Cl), 5.22 (2H, br. s, CH_2Ph), 6.39 (1H, br. s, NHC=O), 7.36 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.61 (*t*-Bu), 27.78 (*t*-Bu), 27.78 ($CH_2CH_2CH_2Cl$), 31.75 ($CH_2CH_2CH_2Cl$), 36.39 (CH_2 ring), 44.80 (CH_2Cl), 55.20 ($C_{quat.}$, C4), 66.39 ($C_{quat.}$, C2), 68.11 ($COOCH_2Ph$), 82.79 ($C_{quat.}$, *t*-Bu), 84.44 ($C_{quat.}$, *t*-Bu), 128.77 (CH), 129.22 (CH), 134.86 ($C_{quat.}$, Ph), 166.97 (C=O), 168.35 (C=O), 169.36 (C=O), 173.70 (C=O). IR (cm^{-1}) ν_{max}: 1742, 2978. MS: *m*/*z* (%): (ES, Pos) no M^+, 386 (20), 384 (57), 91 (100). Chromatography: Hex/EtOAc 70/30 R_f=0.21. Anal. Calcd $C_{25}H_{34}ClNO_7$: C 60.54%, H 6.91%, N 2.82%; found: C 60.38%, H 7.09%, N 3.02%.

3.1.6. 2,4-Dibenzyl 1-*t*-butyl-5-oxo-1,2,4-pyrrolidinetricarboxylate (14c). Yield 83% (major/minor 80/20), the product is obtained as a brown oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ: *major*: 1.43 (9H, s, *t*-Bu), 2.23 (1H, dd, $J=13.4$, 2.3 Hz), 2.71 (1H, ddd, $J=13.5$, 9.1, 10.2 Hz, CH_aH_b ring), 3.71 (1H, dd, $J=10.7$ Hz, $J=9.1$ Hz, CH, C4), 4.70 (1H, dd, $J=9.6$, 2.3 Hz, NCH). *Minor*: 1.41 (9H, s, *t*-Bu), 2.52–2.59 (2H, m, CH_aH_b ring), 3.58 (1H, dd, $J=8.9$, 5.6 Hz, CH, C4) 4.64 (1H, dd, $J=8.6$, 5.0 Hz, NCH), *not assigned* 5.07–5.26 (4H, m, CH_2Ph), 7.33–7.39 (10H, m, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.65 (CH_2), 25.3 (CH_2), 27.31 (*t*Bu), 27.71 (*t*Bu), 48.44 (CH, C4), 48.75 (CH, C4), 57.19 (NCH), 57.63 (NCH), 67.35 (CH_2Ph), 67.49 (CH_2Ph), 67.62 (CH_2Ph), 83.99 (C_{quat}), 84.15 (C_{quat}), 128.15 (CH), 128.3 (CH), 128.37 (CH), 128.49 (CH), 128.57 (CH), 128.67 (CH), 134.89 (C_{quat}, Ph), 135.11 (C_{quat}, Ph), 148.85 (C=O, Boc), 148.94 (C=O, Boc), 167.74 (C=O), 167.81 (C=O), 170.17 (C=O, Boc), 170.65 (C=O, Boc). IR (cm^{-1}) ν_{max}: 1795, 1733. MS: *m*/*z* (%): no M^+, 353 (23), 219 (19), 200 (32), 180 (18), 107 (38), 92 (38), 91 (100), 65 (22), 57 (93). Chromatography: Hex/EtOAc 80/20 R_f=0.12. Anal. Calcd $C_{25}H_{27}NO_7$: C 66.21%, H 6.00%, N 3.09%; found: C 65.92%, H 6.12%, N 3.25%.

3.1.7. 2,4-Dibenzyl 2-*t*-butyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15c). The reaction is similar to that of the conversion of **14a**–**15a**.The reaction was performed on the diastereoisomeric mixture of **14c** and gave **15c** as a clear oil. (Major/minor 54/46).

^{1}H NMR (270 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.32 (9H, s, *t*-Bu), 1.34 (9H, s, *t*-Bu), 2.82–2.94 (2H, m, CH_2), 3.57–3.64 (1H, m, $CHCH_2$), 5.13–5.26 (4H, m, $COOCH_2Ph$), 6.54 (1H, NH), 7.26–7.37 (10H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: MAJOR, MINOR, not assigned: 27.51 (*t*-Bu), 27.55 (*t*-Bu), 31.21 (CH_2 ring), 31.32 (CH_2 ring), 47.12 (CH, C4), 47.19 (CH, C4), 66.88 ($C_{quat.}$, C2), 67.21 ($C_{quat.}$, C2), 67.49 ($COOCH_2Ph$), 67.53 ($COOCH_2Ph$), 68.03 ($COOCH_2Ph$), 68.21 ($COOCH_2Ph$), 84.17 ($C_{quat.}$, *t*-Bu), 84.31 ($C_{quat.}$, *t*-Bu), 128.30 (CH), 128.34 (CH), 128.43 (CH), 128.55 (CH), 128.66 (CH), 128.69 (CH), 134.55 ($C_{quat.}$, Ph), 134.70 ($C_{quat.}$, Ph), 135.27 ($C_{quat.}$, Ph), 135.33 ($C_{quat.}$, Ph), 166.41 (C=O), 166.75 (C=O), 167.98 (C=O), 168.35 (C=O), 170.83 (C=O). ^{1}H NMR (270 MHz, C_6D_6) δ: 1.18 (9H, s, *t*-Bu), 1.21 (9H, s, *t*-Bu), 2.62 (1H, dd, $J=13.9$, 9.2 Hz, CH_aH_b), 2.68 (1H, dd, $J=13.7$, 9.6 Hz, CH_aH_b), 3.04 (1H, dd, $J=13.7$, 10.6 Hz, CH_aH_b), 3.06 (1H, dd, $J=13.9$, 11.2 Hz, CH_aH_b), 3.39–3.46

(1H, m, CH), 4.86–4.99 (4H, m, CH_2Ph), 7.04–7.24 (10H, m, CH, Ph), 8.07(1H, br. s, NH), 8.10 (1H, br. s, NH). ^{13}C NMR (68 MHz, C_6D_6) δ: 27.39 (*t*-Bu), 27.46 (*t*-Bu), 31.59 (CH_2 ring), 31.46 (CH_2 ring), 47.69 (CH, C4), 47.76 (CH, C4), 67.24 (CH_2Ph), 67.31 (CH_2Ph), 67.67 (CH_2Ph), 67.74 (CH_2Ph), 67.82 ($C_{quat.}$, C2), 68.00 ($C_{quat.}$, C2), 83.36 ($C_{quat.}$, *t*-Bu), 83.49 ($C_{quat.}$, *t*-Bu), 128.21 (CH), 128.25 (CH), 128.39 (CH), 128.66 (CH), 128.75 (CH), 135.56 ($C_{quat.}$, Ph), 135.70 ($C_{quat.}$, Ph), 136.15 ($C_{quat.}$, Ph), 136.21 ($C_{quat.}$, Ph), 167.04 (C=O), 167.36 (C=O), 168.51 (C=O), 168.75 (C=O), 168.78 (C=O), 168.87 (C=O), 171.79 (C=O), 171.86 (C=O). IR (cm^{-1}) ν_{max}: 3032, 1610, 1495, 1454, 1741, 1714. MS: *m/z* (%): (ES, Pos) 454 ($M+H^+$, 25), 398 (100), 181 (34), 91 (35). Chromatography: Hex/EtOAc 70/30 $R_f=0.19$. Anal. Calcd $C_{25}H_{27}NO_7$: C 66.21%, H 6.00%, N 3.09%; found: C 65.99%, H 6.10%, N 3.18%.

3.1.8. 1,4-Di-*t*-butyl 2-methyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14d). ^1H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.47 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 1.50 (9H, s, *t*-Bu); 2.18 (1H, ddd, $J=13.4$, 9.0, 2.5 Hz, CH_AH_B); 2.43–2.59 (2H, m, CH_2 ring); 2.68 (1H, ddd, $J=13.4$, 10.2, 9.4 Hz, CH_AH_B); 3.47 (1H, dd, $J=9.4$, 5.8 Hz, CH, C4); 3.56 (1H, dd, $J=10.2$, 9.0 Hz, CH, C4); 3.78 (3H, s, OCH_3); 3.79 (3H, s, CH_3); 4.61 (1H, dd, $J=9.1$, 5.0 Hz, CH, C2); 4.67 (1H, dd, $J=9.4$, 2.5 Hz, CH, C2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.81 (CH_2 ring); 25.33 (CH_2 ring); 27.82 (*t*-Bu); 27.91 (*t*-Bu); 49.36 (CH, C4); 49.68 (CH, C4); 52.49 (CH_3); 52.67 (OCH_3); 57.12 (CH, C2); 57.50 (CH, C2); 82.66 (C_{quat}, *t*-Bu); 83.71 (C_{quat}, *t*-Bu); 83.93 (C_{quat}, *t*-Bu); 149.03 (C=O, *N*-Boc); 149.03 (C=O, *N*-Boc); 166.38 (C=O); 167.14 (C=O); 168.10 (C=O); 168.41 (C=O); 171.03 (C=O); 171.49 (C=O). IR (cm^{-1}) ν_{max}: 1729 (C=O); 1753 (C=O); 1797 (C=O). MS: *m/z* (%): (ES, neg) 342 ($M-H^+$, 100). Anal. Calcd $C_{16}H_{25}NO_7$: C 55.97%, H 7.34%, N 4.08%; found: C 56.30%, H 7.52%, N 4.29%.

3.1.9. 2,4-Di-*t*-butyl 2-methyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15d). The reaction is similar to that of the conversion of **14a**–**15a**. The reaction was performed on the diastereoisomeric mixture of **14d** and gave **15d** as a clear oil (major/minor 53/47).

^1H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.46 (9H, s, *t*-Bu); 1.48 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 2.82–2.88 (2H, m, CH_2 ring, C3); 3.43 (1H, dd, $J=8.9$, 5.9 Hz, CH ring, C4); 3.45 (1H, dd, $J=9.1$, 7.2 Hz, CH ring, C4); 3.80 (3H, s, CH_3); 3.82 (3H, s, CH_3); 6.51 (1H, br. s, NH); 6.53 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.71 (*t*-Bu); 27.74 (*t*-Bu); 27.91 (*t*-Bu); 27.94 (*t*-Bu); 31.38 (CH_2 ring, C3); 31.50 (CH_2 ring, C3); 48.03 (CH ring, C4); 48.13 (CH ring, C4); 53.32 (CH_3); 53.44 (CH_3); 66.77 (C_{quat}, C2); 67.15 (C_{quat}, C2); 82.48 (C_{quat}, *t*-Bu); 82.54 (C_{quat}, *t*-Bu); 84.11 (C_{quat}, *t*-Bu); 84.30 (C_{quat}, *t*-Bu); 166.68 (C=O); 167.14 (C=O); 167.64 (C=O); 168.88 (C=O); 169.31 (C=O); 171.48 (C=O); 171.51 (C=O). IR (cm^{-1}) ν_{max}:1717 (C=O); 1739 (C=O, br.). MS: *m/z* (%): (ES, neg) 342 ($M-H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.34$. Anal. Calcd $C_{16}H_{25}NO_7$: C 55.97%, H 7.34%, N 4.08%; found: C 55.85%, H 7.46%, N 4.19%.

3.1.10. 2-Benzyl 1,4-di-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14e). Di-*t*-butyldicarbonate (1.5 equiv) was used as electrophile and once it was added the reaction was allowed to warm to room temperature. The product crystallizes as a white powder (major/minor 78/22).

^1H NMR (270 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.40 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.45 (9H, s, *t*-Bu), 1.47 (9H, s, *t*-Bu), 2.18 (1H, ddd, $J=13.4$, $J=9.0$, 2.3 Hz, CH_aH_b), 2.47–2.53 (2H, m, CH_2 ring), 2.67 (1H, ddd, $J=13.5$, 10.1, 9.9 Hz, CH_aH_b), 3.42 (1H, dd, $J=6.4$, 8.4 Hz, CH), 3.53 (1H, dd, $J=10.4$, 9.1 Hz, CH), 4.61 (1H, dd, $J=5.9$, 7.9 Hz, NCH), 4.68 (1H, dd, $J=9.6$, 2.3 Hz, NCH), 5.13–5.28 (2H, m, $COOCH_2Ph$), 7.26–7.45 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.71 (CH_2 ring), 25.23 (CH_2 ring), 27.67 (*t*-Bu), 27.76 (*t*-Bu), 27.85 (*t*-Bu), 28.23 (*t*-Bu), 49.29 (CH, C4), 49.67 (CH, C4), 57.18 (NCH), 57.56 (NCH), 67.24 ($COOCH_2Ph$), 67.38 ($COOCH_2Ph$), 82.59 ($C_{quat.}$, *t*-Bu), 83.63 ($C_{quat.}$, *t*-Bu), 83.84 ($C_{quat.}$, *t*-Bu), 128.44 (CH), 128.50 (CH), 128.55 (CH), 128.66 (CH), 135.02 ($C_{quat.}$, Ph), 135.16 ($C_{quat.}$, *t*-Bu), 148.93 (C=O, Boc), 148.98 (C=O, Boc), 156.6 (C=O), 166.45 (C=O), 167.09 (C=O), 168.14 (C=O), 168.43 (C=O), 170.42 (C=O), 170.83 (C=O). IR (cm^{-1}) ν_{max}: 1703, 1726. MS: *m/z* (%): (direct inlet) no M^+, 308 (7), 264 (25), 129 (19), 128 (98), 110 (37), 91 (87), 57 (100). Chromatography: Hex/EtOAc 70/30 $R_f=0.31$ Mp 84–86.5 °C (yield =77%). Anal. Calcd $C_{22}H_{29}NO_7$: C 62.99%, H 6.97%, N 3.34%; found: C 62.71%, H 7.25%, N 3.25%.

3.1.11. 2-Benzyl 2,4-di-*t*-butyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15e). The reaction is similar to that of the conversion of **14a**–**15a**. The reaction was performed on the diastereoisomeric mixture of **14e** and gave **15e** as a clear oil. (Major/minor 52/48).

^1H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.33 (9H, s, *t*-Bu); 1.36 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 2.82–2.87 (2H, m, CH_2 ring, C3); 3.41 (1H, dd, $J=9.4$, 2.5 Hz, CH ring, C4); 3.44 (1H, dd, $J=9.1$, 3.0 Hz, CH ring, C4); 5.14–5.28 (2H, m, CH_2Ph); 6.56 (1H, br. s, NH); 6.58 (1H, br. s, NH); 7.31–7.36 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.54 (*t*-Bu); 27.59 (*t*-Bu); 27.93 (*t*-Bu); 31.27 (CH_2 ring, C3); 31.41 (CH_2 ring, C3); 48.00 (CH ring, C4); 48.14 (CH ring, C4); 66.83 (C_{quat}, C2); 67.15 (C_{quat}, C2); 68.03 (CH_2Ph); 68.16 (CH_2Ph); 82.45 (C_{quat}, *t*-Bu); 82.49 (C_{quat}, *t*-Bu); 84.04 (C_{quat}, *t*-Bu); 84.20 (C_{quat}, *t*-Bu); 126.97 (CH, Ph); 128.60 (CH, Ph); 128.66 (CH, Ph); 128.71 (CH, Ph); 128.74 (CH, Ph); 128.82 (CH, Ph); 134.62 (C_{quat}, Ph); 134.77 (C_{quat}, Ph); 166.53 (C=O); 166.94 (C=O); 167.63 (C=O); 167.67 (C=O); 168.12 (C=O); 168.54 (C=O); 171.51 (C=O). IR (cm^{-1}) ν_{max}:1732 (C=O, br.). MS: *m/z* (%): (ES, neg) 418 ($M-H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.40$. Anal. Calcd $C_{22}H_{29}NO_7$: C 62.99%, H 6.97%, N 3.34%; found: C 62.78%, H 7.26%, N 3.42%.

3.1.12. 4-Benzyl 1-*t*-butyl 2-methyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14f). Yield 80% (major/minor 77/23), the product is obtained as a white powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.50 (9H, s, *t*-Bu); 2.25 (1H, ddd, $J=13.5$, 8.8, 2.5 Hz, CH_AH_B ring, C3); 2.52–2.57 (2H, m, CH_2 ring, C3); 2.74 (1H, ddd, $J=13.5$, 10.4, 9.4 Hz, CH_AH_B ring, C3); 3.59 (1H, dd, $J=8.3$, 6.6 Hz, CH ring, C4); 3.69 (3H, s, CH_3); 3.74 (1H, dd, $J=10.4$. 8.8 Hz, CH ring, C4); 3.78 (3H, s, CH_3); 4.61 (1H, dd, $J=7.8$, 5.9 Hz, CH ring, C2); 4.68 (1H, dd, $J=9.4$, 2.5 Hz, CH ring, C2); 5.11 (2H, s, CH_2Ph); 5.22 (2H, s, CH_2Ph); 7.30–7.40 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.69 (CH_2 ring, C3); 25.37 (CH_2 ring, C3); 27.85 (*t*-Bu); 27.85 (*t*-Bu); 48.53 (CH ring, C4); 48.82 (CH ring, C4); 52.57 (CH_3); 52.77 (CH_3); 57.12 (CH ring, C2); 57.57 (CH ring, C2); 66.86 (CH_2Ph); 67.75 (CH_2Ph); 84.18 (C_{quat}, Ph); 84.32 (C_{quat}, Ph); 128.13 (CH, Ph); 128.24 (CH, Ph); 128.41 (CH, Ph); 128.47 (CH, Ph); 128.55 (CH, Ph); 128.58 (CH, Ph); 128.62 (CH, Ph); 135.08 (C_{quat}, Ph); 135.14 (C_{quat}, Ph); 148.99 (C=O, *N*-Boc); 148.99 (C=O, *N*-Boc); 167.76 (C=O); 167.91 (C=O); 170.79 (C=O); 171.37 (C=O). IR (cm^{-1}) ν_{max}:1737 (C=O); 1777 (C=O, br.). MS: *m*/*z* (%): (ES, neg) 376 ($M-H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.19$. Mp 94–97 °C. Anal. Calcd $C_{19}H_{23}NO_7$: C 60.47%, H 6.14%, N 3.71%; found: C 60.58%, H 6.24%, N 3.88%.

3.1.13. 4-Benzyl 2-*t*-butyl 2-methyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15f). The reaction is similar to that of the conversion of **14a**–**15a**. The reaction was performed on the diastereoisomeric mixture of **14f** and gave **15f** as a clear oil. (Major/minor 51/49).

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.45 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 2.89 (2H, m, CH_2 ring, C3); 3.58–3.66 (1H, m, CH ring, C4); 3.76 (3H, s, CH_3); 3.79 (3H, s, CH_3); 5.16–5.27 (2H, m, CH_2Ph); 6.62 (1H, br. s, NH); 7.28–7.40 (5H, m, Ph). ^{13}C^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.70 (*t*-Bu); 31.31 (CH_2 ring, C3); 31.42 (CH_2 ring, C3); 47.13 (CH ring, C4); 47.19 (CH ring, C4); 53.35 (CH_3); 53.51 (CH_3); 66.80 (C_{quat}, C2); 67.18 (C_{quat}, C2); 67.56 (CH_2Ph); 67.61 (CH_2Ph); 84.29 (C_{quat}, *t*-Bu); 84.45 (C_{quat}, *t*-Bu); 128.16 (CH, Ph); 128.27 (CH, Ph); 128.34 (CH, Ph); 128.39 (CH, Ph); 128.57 (CH, Ph); 128.66 (CH, Ph); 128.72 (CH, Ph); 128.86 (CH, Ph); 135.24 (C_{quat}, Ph); 135.31 (C_{quat}, Ph); 166.57 (C=O); 166.96 (C=O); 168.36 (C=O); 168.71 (C=O); 169.11 (C=O); 170.80 (C=O); 170.83 (C=O). IR (cm^{-1}) ν_{max}:1740 (C=O, br.). MS: *m*/*z* (%): (ES, Pos) 378 ($M+H^+$, 43); 323(17); 322 (100). Chromatography: Hex/EtOAc (70/30) $R_f=0.09$ and 0.17. Anal. Calcd $C_{19}H_{23}NO_7$: C 60.47%, H 6.14%, N 3.71%; found: C 60.35%, H 6.53%, N 3.86%.

3.1.14. 1,4-Di-*t*-butyl 2-ethyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14g). Di-*t*-butyldicarbonate (1.5 equiv) was used as electrophile and once it was added the reaction was allowed to warm to room temperature. **14g** is obtained (yield 80% major/minor 70/30) as a brown oil.

H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.30 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.45 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 1.50 (9H, s, *t*-Bu); .2.20 (1H, ddd, $J=13.5$, 8.8, 2.5 Hz, CH_AH_B ring); 2.48–2.53 (2H, m, CH_2 ring); 2.68 (1H, ddd, $J=13.5$, 10.5, 9.6 Hz, CH_AH_B ring); 3.44 (1H, dd, $J=7.7$, 7.4 Hz, CH ring, C4); 3.56 (1H, dd, $J=10.5$, 8.8 Hz, CH ring, C4); 4.19–4.27 (2H, m, CH_2CH_3); 4.19–4.27 (2H, m, CH_2CH_3); 4.56 (1H, dd, $J=7.2$, 6.6 Hz, CH ring, C2); 4.64 (1H, dd, $J=9.6$, 2.5 Hz, CH ring, C2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 14.24 (CH_2CH_3–); 14.24 (CH_2CH_3–); 24.88 (CH_2 ring, C3); 25.46 (CH_2 ring, C3); 27.75 (*t*-Bu); 27.93 (*t*-Bu); 28.03 (*t*-Bu); 28.30 (*t*-Bu); 49.45 (CH, C4); 49.77 (CH, C4); 57.28 (CH ring, C2); 57.63 (CH ring, C2); 61.81 (CH_2CH_3); 61.92 (CH_2CH_3); 82.90 (C_{quat}, *t*-Bu); 82.98 (C_{quat}, *t*-Bu); 83.95 (C_{quat}, *t*-Bu); 84.11 (C_{quat}, *t*-Bu); 149.22 (C=O, *N*-Boc); 149.22 (C=O, *N*-Boc); 166.40 (C=O); 167.26 (C=O); 168.13 (C=O); 168.46 (C=O); 170.55 (C=O); 172.09 (C=O). IR (cm^{-1}) ν_{max}:1729 (br., C=O); 1796 (C=O). MS: *m*/*z* (%): (ES, pos) No M^+; 297 (8); 254 (12); 203 (8); 202 (100). Anal. Calcd $C_{17}H_{27}NO_7$: C 57.13%, H 7.61%, N 3.92%; found: C 57.00%, H 7.89%, N 3.88%.

3.1.15. 2,4-Di-*t*-butyl 2-ethyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15g). The reaction is similar to that of the conversion of **14a**–**15a**. The reaction was performed on the diastereoisomeric mixture of **14g** and gave **15g** as a brown oil. (Major/minor 51/49, purity 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.29 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.31 (3H, t, $J=7.0$ Hz, CH_2CH_3); 1.46 (9H, s, *t*-Bu); 1.48 (9H, s, *t*-Bu); 1.48 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 2.82–2.85 (2H, m, CH_2 ring); 3.41–3.48 (1H, m, CH ring); 4.23–4.30 (2H, m, CH_2CH_3); 4.23–4.30 (2H, m, CH_2CH_3); 6.30 (1H, br. s, NH); 6.32 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 13.97 (CH_2CH_3); 14.01 (CH_2CH_3); 27.66 (*t*-Bu); 27.71 (*t*-Bu); 27.87 (*t*-Bu); 28.01 (*t*-Bu); 31.23 (CH_2 ring, C3); 31.35 (CH_2 ring, C3); 48.12 (CH ring, C4); 48.20 (CH ring, C4); 62.41 (CH_2CH_3); 62.59 (CH_2CH_3); 66.93 (C_{quat}, C2); 67.23 (C_{quat}, C2); 82.27 (C_{quat}, *t*-Bu); 82.32 (C_{quat}, *t*-Bu); 83.77 (C_{quat}, *t*-Bu); 83.98 (C_{quat}, *t*-Bu); 166.80 (C=O); 167.27 (C=O); 167.74 (C=O); 167.74 (C=O); 168.32 (C=O); 168.80 (C=O); 171.82 (C=O); 171.82 (C=O). IR (cm^{-1}) ν_{max}: 1736 (br.); 1793 (C=O). MS: *m*/*z* (%): (ES, pos) No M^+; 247 (15); 246 (100); 202 (11).

3.1.16. 1,5-Diethyl-2-[(*t*-butoxycarbonyl)amino]pentanedioate (15i). The reaction is similar to that of the conversion of **14a**–**15a**.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.28 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.44 (9H, s, *t*-Bu); 1.88–2.01 (1H, m, $COCH_2CH_AH_B$); 2.12–2.24 (1H, m, $COCH_2CH_AH_B$); 2.36–2.43 (2H, m, $COCH_2$); 4.14 (2H, q, $J=7.2$ Hz, CH_2CH_3); 4.20 (2H, q, $J=7.2$ Hz, CH_2CH_3); 4.31 (1H, dd, $J=13.1$ Hz, $J=8.4$ Hz, COCH); 5.19 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.16 (CH_2CH_3); 14.19 (CH_2CH_3); 27.84 ($COCH_2CH_2$); 28.29 (*t*-Bu); 30.37 ($COCH_2$); 52.98 (CH); 60.65 (CH_2CH_3); 61.52 (CH_2CH_3); 79.96 (C_{quat}, *t*-Bu); 155.39 (C=O, NH-Boc); 172.26 (C=O); 172.79 (C=O). IR (cm^{-1}) ν_{max}:1719 (C=O); 1737 (C=O). MS: *m*/*z* (%): (ES, pos) no M^+; 204 ($M-Boc+H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.43$.

3.1.17. 1,5-Dimethyl-2-[(*t*-butoxycarbonyl)amino]pentanedioate (15j). The reaction is similar to that of the conversion of **14a**–**15a**.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.44 (9H, s, *t*-Bu); 1.99–2.02 (1H, m, $COCH_2CH_AH_B$); 2.13–2.25 (1H, m, $COCH_2CH_A$-H_B); 2.39–2.45 (2H, m, $COCH_2$); 3.68 (3H, s, CH_3); 3.75 (3H, s, CH_3); 4.30–4.37 (1H, m, COCH); 5.19 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.78 ($COCH_2CH_2$); 28.32 (*t*-Bu); 30.09 ($COCH_2$); 51.81 (CH_3); 52.44 (CH_3); 52.91 (CH); 80.04 (C_{quat}, *t*-Bu); 155.42 (C=O, NH-Boc); 172.72 (C=O); 173.21 (C=O). IR (cm^{-1}) ν_{max}: 1714 (C=O); 1736 (C=O); 1793 (C=O). MS: *m/z* (%): (ES, pos) no M^+; 176 ($M-Boc+H^+$, 100); 144 (24). Chromatography: Hex/EtOAc (70/30) R_f=0.31.

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