# Efficient Synthesis of γ-Oxo- and γ-Hydroxy-α-amino Acids

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**Abstract:** The diastereoselective synthesis of *anti*-γ–oxo-α-aminocarboxylates by aminoalkylation of ketones with in situ generated ternary iminium salts from inexpensive starting materials is described. These compounds are easily transformed diastereoselectively into *syn,anti*- or *anti,anti*–γ-hydroxy-α-aminocarboxylates by the use of different reducing agents. The configuration of the products has been determined by NMR. The aminoalkylation of enamines and imines is also reported.

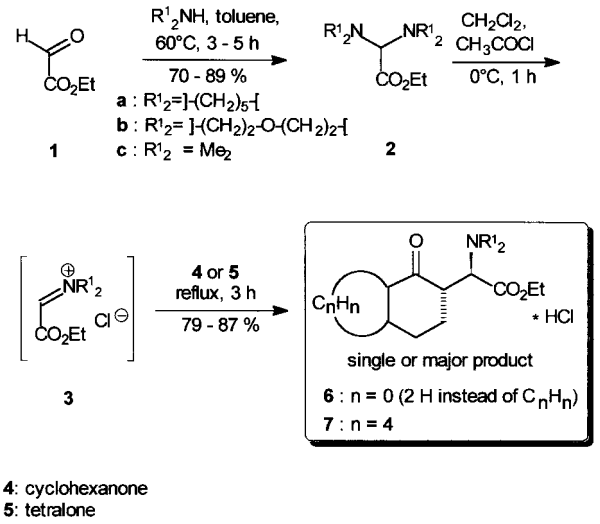
**Key words:** ternary iminium salts, aminoalkylation, diastereoselective reduction, γ-oxo-α-amino acids, γ-hydroxy-α-amino acids

The γ–hydroxy-α-amino acid unit plays an important role in biologically active products, e.g. nikkomycins or neopolyoxins,[1, 2] theonellamide F,[3] scytonemin A,[4] and funebrine.[5] The known synthetic approaches to natural γ–hydroxy-α-amino acid units are distinguished by the involved formation of special key compounds, such as substituted isoxazolines,[1a–f] dihydrooxazine rings,[1g] tetrahydropyrimidines,[1h] β-alkyl homoallylic alcohols[1i] or γ–oxo-α-amino acids.[6] Our goal was the development of a new, inexpensive, and diastereoselective synthetic route using readily available starting materials to yield γ–hydroxy-α-amino acids in a simple manner.

Groß et al.[7] described a facile method for the formation of γ–oxo-α-amino-carboxylates, namely the aminoalkylation of enamines and ketones with preformed ternary iminium salts derived from methyl glyoxylate. However, no information about the relative configuration of the resulting products and the diastereoselectivity of this type of reaction has been described.[6, 7] Furthermore, this methodology was not pursued further, maybe due to the difficult preparation[8] and handling of the described ternary iminium salt.

Recently, we have disclosed that the aminoalkylation of activated carbonyl compounds like enamines[9] or imines[10] (derivatives of aldehydes, cyclic or acyclic ketones) with ternary iminium salts (containing alkyl and aryl groups) provides the corresponding *anti*-β-amino ketones in excellent yields and diastereoselectivities (generally ≥99% ds) after hydrolysis of the initially formed quaternary iminium salts.[9–11] After the simplification of the preparation and handling of the ternary iminium salts derived from alkyl glyoxylates, the aminoalkylation of nucleophiles such as ketones or activated carbonyl compounds, e.g. enamines or enol silyl ethers, should be an efficient way to yield the γ–oxo-α-aminocarboxylates with high diastereoselectivity.

Here we describe the in situ generation of the ternary iminium salts **3a–c** as glycine cation equivalents from easily accessible, substituted ethyl glyoxylate aminals **2a–c** (derived from commercially available ethyl glyoxylate[12]). They are diastereoselectively reacted to give the *anti*-γ–oxo-α-aminocarboxylates **6** and **7** (Scheme 1).




**Scheme 1**

The iminium salt **3** is generated in situ by an electrophilic attack of acetyl chloride on the aminal **2**. The following nucleophilic attack of **4** or **5** on the iminium salt **3** yields the ethyl γ–oxo-α-aminocarboxylates **6** and **7**.

The aminoalkylation of cyclohexanone **(4)** or tetralone **(5)** with **3a** proceeds with the expected high diastereoselectivity. In comparison, conversion of **3b** only leads to one product in the case of **4**, whereas the use of **5** results in an *anti*/*syn* ratio of 3:1. The reaction of the iminium salt **3c** with cyclohexanone **4** produces a mixture of the two diastereoisomers *anti*-**6c** and *syn*-**6c** in a ratio of 5 to 1. The assignment of the relative configuration at the stereogenic centers in **6** and **7** was made by comparison of the coupling constant ($J_{CHN}$) of the resulting lactones **12a** and **13a** with those of analogous compounds.[1h] The results are summarized in Table 1.

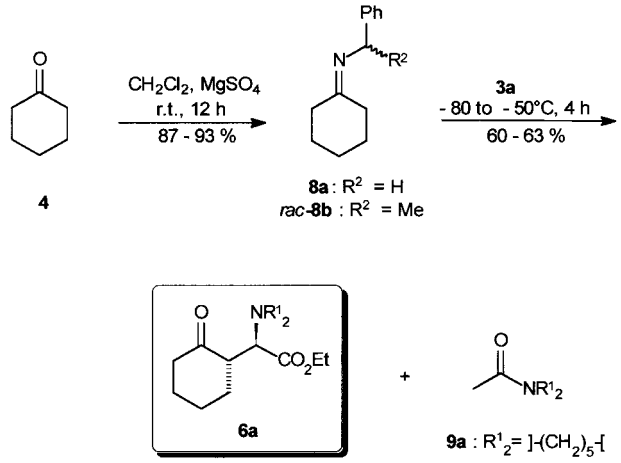
Our recent investigations[10] have shown that imines **8**[13] are suitable compounds for aminoalkylation with ternary iminium salts. The reaction of **8a** and *rac*-**8b** with **3a** gives **6a** with moderate yield and excellent diastereoselectivity (Scheme 2).

The third stereogenic center of the γ–hydroxy-α-amino acid unit is created by the diastereoselective reduction of the carbonyl group (Scheme 3).

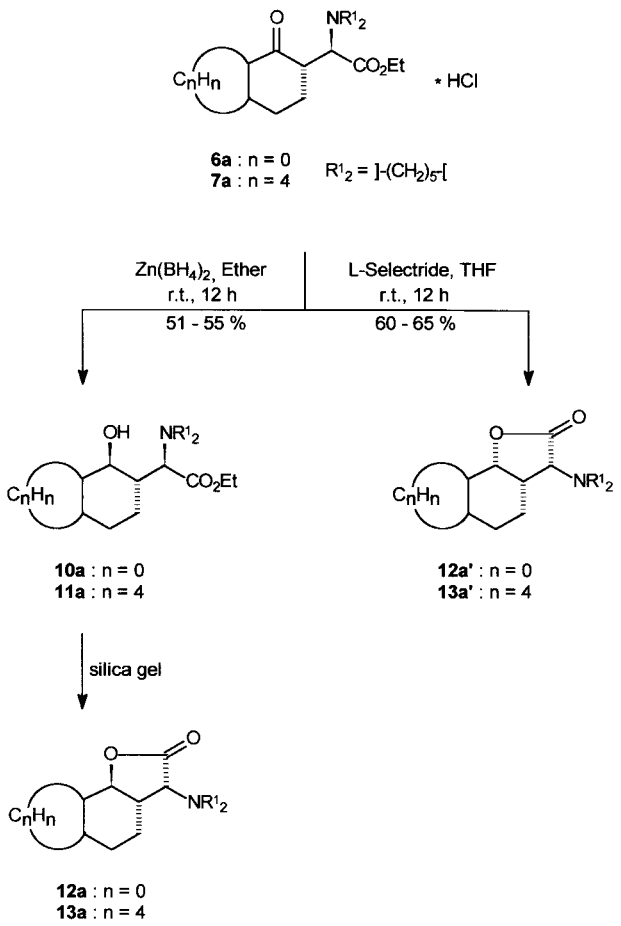
**Table 1.** Diastereoselective Synthesis of γ-Oxo-α-aminocarboxylates by Aminoalkylation of Ketones with in situ Generated Ternary Iminium Salts

| Entry | Ketone | Product | $R^1$ | $R^1$ | Yield (%) | Ratio[a] *anti*/*syn* |
|---|---|---|---|---|---|---|
| 1 | **4** | **6a** | $-(CH_2)_5-$ | | 83 | ≥99: ≤1 |
| 2 | **4** | **6b** | $-(CH_2)_2-O-(CH_2)_2-$ | | 81 | ≥99: ≤1 |
| 3 | **4** | **6c** | Me | Me | 79 | 5:1 |
| 4 | **5** | **7a** | $-(CH_2)_5-$ | | 87 | ≥99: ≤1 |
| 5 | **5** | **7b** | $-(CH_2)_2-O-(CH_2)_2-$ | | 84 | 3:1 |

[a] The *anti*/*syn* ratio was determined from the NMR spectra of the crude product.




**Scheme 2**




**Scheme 3**

Reduction of **6a** with sodium borohydride in ethanol at room temperature produces the *trans,cis*-γ–hydroxy-α-aminolactone **12a** and the diastereoisomeric *cis,cis*-γ–hydroxy-α-aminolactone **12a'** in a ratio of 3 to 1. This result encouraged us to investigate the reduction of **6a** and **7a** with different reducing agents.[3, 6]

The reduction of **6a** with zinc borohydride in diethyl ether at room temperature results in the isolation of the *anti,anti*-γ–hydroxy-α-aminocarboxylate **10a** as a crude product (Scheme 4).[14] During the purification on silica gel lactonization to the *trans,cis*-γ–hydroxy-α-aminolactone **12a** occurs,[15] whereas the use of L-Selectride leads to the *cis,cis*-lactone **12a'** as the single diastereoisomer. The product results from an equatorial attack of the reducing agent (Scheme 4).

Using bulky reducing agents like L-Selectride, the reduction of **7a** takes place with high diastereoselectivity (only the *cis,cis*-lactone **13a'** is isolated). Reduction with sodium borohydride in ethanol at room temperature or zinc borohydride in diethyl ether at room temperature produces a diastereomeric ratio of the aminolactones **13a**/**13a'** of 1:1 and 3.7:1, respectively. The reaction with zinc borohydride results in the formation of the γ–hydroxy-α-aminocarboxylic ester **11a,** which reacts on silica gel in the same way as described before. All results are shown in Table 2.

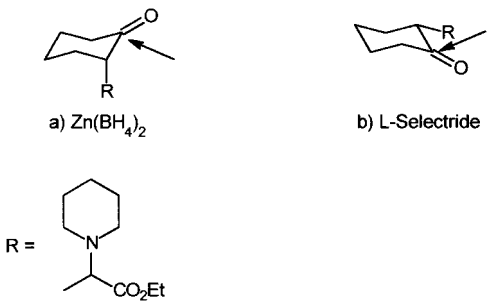
**Table 2.** Reduction of Ethyl γ-Oxo-α-aminocarboxylates **6a** and **7a**

| Entry | Substrate | Reducing Agent | Yield (%)[a] | Ratio[b] (*trans,cis*/*cis,cis*) |
|---|---|---|---|---|
| 1 | **6a** | $NaBH_4$[c] | 70 | 3:1 |
| 2 | **7a** | $NaBH_4$[c] | 75 | 1:1 |
| 3 | **6a** | $Zn(BH_4)_2$[d] | 51 | 95:5[e] |
| 4 | **7a** | $Zn(BH_4)_2$[d] | 55 | 3.7:1[e] |
| 5 | **6a** | L-Selectride[f] | 60 | ≤1: ≥99 |
| 6 | **7a** | L-Selectride[f] | 65 | ≤1: ≥99 |

[a] Combined yields of both diastereoisomers after column chromatography.
[b] The ratio was determined by $^1H$ NMR spectra of the crude product.
[c] Solvent: EtOH.
[d] Solvent: $Et_2O$.
[e] The ratio was determined by $^1H$ NMR spectra of the crude α-hydroxy-γ-aminocarboxylate
[f] Solvent: THF.

In summary, two of the three stereogenic centers of the γ–hydroxy-α-amino acid unit are generated in a highly stereoselective manner by using a simple one-pot procedure. The third stereogenic center is determined by the reducing agent.

Our method only utilized inexpensive, readily available starting materials. Furthermore, there are many notable prospects. Based on the excellent results achieved in the




**Scheme 4**

alkylation of chiral imines derived from 1-phenylethylamine with Michael acceptors,[16] we also expect our method to be suitable for the enantioselective synthesis of γ–hydroxy-α-amino acids.

Anhyd THF was freshly distilled from potassium under argon. $Zn(BH_4)_2$ was synthesized according to literature procedure.[13] Column chromatography on silica gel was performed with Merck Kieselgel 60 (0.040–0.063 mm). $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker ARX 200 spectrometer, using TMS as internal standard. IR spectra were recorded on a Nicolet 510 P FT-IR spectrophotometer. GC/MS data were obtained from a Finnigan MAT Magnum System 240 and MS data from a VG Fisons Autospec. Mps were determined on a Mettler FP61 apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer Elemental Analyser. Satisfactory microanalyses were obtained for the new compounds **2**, **6**, **7**, **12** and **13**: C ±0.34, H ±0.28, N ±0.19.

**Ethyl Glyoxylate Aminals 2; General Procedure:**
A solution of 50% ethyl glyoxylate in toluene (18.8 mL, 0.10 mol, Fluka) in toluene (20 mL) was stirred at 60 °C for 1 h. The secondary amine (0.20 mol) was added slowly (preparation of **2c**: dried $Me_2NH$ was discharged into the solution over 3 h). The mixture was stirred for 2 h at this temperature. Afterwards, $K_2CO_3$ was added to remove the water and the mixture was cooled to r.t. After removal of the solvent in vacuo, the oily crude product was used without further purification.

**Ethyl *anti*-γ-Oxo-α-aminocarboxylates 6 and 7: General Procedure:**
The reactions were conducted under argon. A solution of ethyl glyoxylate aminal **2** (2 mmol) in anhyd $CH_2Cl_2$ was cooled to 0 °C. Acetyl chloride (0.14 mL, 2 mmol) was added in one portion under stirring to generate the iminium salt. After stirring the mixture for 1 h at 0 °C, the ketone **4** or **5** was added and the solution heated under reflux for 3 h. The solvent was removed in vacuo and the crude product was diluted with $Et_2O$ or EtOAc and filtered. The white residue was recrystallized from EtOAc.

**Preparation of the Ethyl *anti*-γ-Oxo-α-aminocarboxylates 6a from Imines:**
The iminium salt **3a** was generated as described above. The solution of the ternary iminium salt was cooled to –80 °C and the imine **8a** or **8b** (2 mmol)[17] added under stirring. Afterwards, the temperature was allowed to rise to –50 °C over 2–3 h. 6 N HCl was added and the aqueous layer was washed with $Et_2O$ several times. The aqueous layer was basified by addition of sat. $NaHCO_3$ and extracted quickly with $CH_2Cl_2$ (3 × 50 mL). The organic layer was dried ($Na_2SO_4$) and the solvent was removed in vacuo. The residue contained the ethyl *anti*-γ-oxo-α-aminocarboxylate **6a** and the piperidine amide **9a**.

**Reduction with $NaBH_4$:**
The *anti*-γ-oxo-α-aminocarboxylate hydrochloride **6a** or **7a** (1 mmol) was dissolved in EtOH (10 mL), $NaBH_4$ (0.10 g, 2.5 mmol[18] was added and the mixture was stirred for 5 h. Afterwards, 6 N HCl was added and the mixture was washed with $Et_2O$ several times. The aqueous layer was basified by the addition of $NH_3$ (25% $NH_3/H_2O$ 1:1). The product was extracted with $CH_2Cl_2$ (3 × 50 mL) and the organic layer was dried ($Na_2SO_4$). The solvent was removed in vacuo and the residue purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 98:2).

**Reduction with $Zn(BH_4)_2$:[13]**
To $NaBH_4$ (1.95 g, 50 mol) in anhyd $Et_2O$ (50 ml) recently fused $ZnCl_2$ (3.4 g, 25 mmol) was added. The mixture was stirred overnight at 0–5 °C. After filtration under $N_2$, the clear solution (ca. 0.5 M) was used immediately. The β-amino ketone **6a** or **7a** (1 mmol) was dissolved in anhyd $Et_2O$ (10 mL). A solution of $Zn(BH_4)_2$ (2 mmol, 1 mL[18]) was added. The mixture was stirred at r.t. overnight. After usual workup, the crude product was identified as the γ-hydroxy-α-aminocarboxylate **10** or **11** which converted to the lactone **12** or **13** during column chromatography.

**Reduction with L-Selectride:**
To the *anti*-γ-oxo-α-aminocarboxylate **6a** or **7a** (1 mmol) in anhyd THF (10 mL) was added 1 M L-Selectride in hexane (2 mL,[18] 2 mmol) at –78 °C. The solution was stirred at r.t. overnight. EtOH was added and when the evolution of gas was complete, 2 N NaOH (1 mL) and 30% $H_2O_2$ (2 mL) were poured into the mixture. The organic layer was extracted with $Et_2O$ (3 × 50 mL), dried and evaporated. The crude product was purified by column chromatography (silica gel, $CH_2Cl_2$/MeOH 98: 2).

**Table 3.** Characterization of Compounds **2a–c**

| Product | $^1H$ NMR ($CDCl_3$/TMS) δ, *J* (Hz) | $^{13}C$ NMR ($CDCl_3$/TMS) δ | IR ν ($cm^{-1}$) | Yield (%) |
|---|---|---|---|---|
| **2a** | 1.33 (t, 3 H, *J* = 7.1, $CH_2CH_3$), 1.40–1.58 [m, 10 H, $N(CH_2)_5$], 2.42–2.58 (m, 8 H, $–CH_2–N–CH_2–$), 3.28 (s, 1 H, –N–CH–N–), 4.25 (q, 2 H, *J* = 7.1, $CH_2CH_3$) | 15.15 (q, $CH_2CH_3$), 25.53, 26.36 [t, $(CH_2)_5$], 50.54 (t, $–CH_2–N–CH_2–$), 60.27 (t, $CH_2CH_3$), 88.08 (d, –N–CH–N–), 169.47 (s, CO) | 2975, 2932, 2851, 2805, 2750, 1741, 1724, 1442, 1174, 1159, 1132, 1123, 1104, 1029 | 89 |
| **2b** | 1.31 (t, 3 H, *J* = 7.1, $CH_2CH_3$), 2.48–2.80 (m, 8 H, $–CH_2–N–CH_2–$), 3.31 (s, 1 H, –N–CH–N–), 3.66–3.79 (m, 8 H, $–CH_2–O–CH_2–$), 4.22 (q, 2 H, *J* = 7.1, $CH_2CH_3$) | 15.07 (q, $CH_2CH_3$), 49.75 (t, $–CH_2–N–C–H_2–$), 60.84 (t, $CH_2CH_3$), 67.37 (t, $–CH_2–O–CH_2–$), 86.91 (d, –N–CH–N–), 168.13 (s, CO) | 2963, 2916, 2854, 1739, 1453, 1269, 1182, 1155, 1115, 1071, 1029 | 83 |
| **2c** | 1.31 (t, 3 H, *J* = 7.0, $CH_2CH_3$), 2.29 [s, 12 H, $N(CH_3)_2$], 2.43 (s, 1 H, –N–CH–N–), 4.25 (t, 2 H, *J* = 7.0, $CH_2CH_3$) | 15.05 (q, $CH_2CH_3$), 41.11 [q, $N(CH_3)_2$], 60.46 (t, $CH_2CH_3$), 87.72 (d, –N–CH–N–), 169.09 (s, CO) | 2972, 2925, 2849, 1738, 1450, 1119, 1099, 1029 | 80 |

**Table 4.** Characterization of Compounds **6a–c** and **7a,b**

| Product | $^1$H NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}$C NMR ($CDCl_3$/TMS) $\delta$ | IR $\nu$ ($cm^{-1}$) | MS (70 eV) $m/z$ (%) | mp (°C) | Yield (%) |
|---|---|---|---|---|---|---|
| **6a** | 1.22 (t, 3 H, $J$ = 7.1, $CH_2CH_3$), 1.26–1.36 (m, 2 H), 1.39–1.95 (m, 4 H), 2.03–2.18 (m, 2 H), 2.29–2.43 (m, 2 H), 2.60–2.64 (m, 1 H), 3.03–3.86 (m, 7 H), 4.09–4.29 (m, 2H, $CH_3CH_2$), 11.90 (br. s, 1 H, NH) | 13.66 (q, $CH_2CH_3$), 21.16, 23.00, 24.91, 26.66, 34.81, 41.65, 47.52, 53.45 [t, $N(CH_2)_5$, $(CH_2)_4$], 52.38 (d, COCHCH), 61.62 (t, $CH_2CH_3$), 66.43 (d, COCHCH), 166.56 (s, CO), 209.08 (s, CO) | 2632, 2529, 2428, 1744, 1713, 1456, 1447, 1227, 1195 | 194 [$M^+$ – HCl–$CO_2Et$] (100), 170 (15), 150 (3), 124 (6), 84 (11), 55 (8) | 204 | 83 |
| **6b** | 1.20 (t, 3 H, $J$ = 7.1, $CH_2CH_3$), 1.29–2.58 [m, 10 H, $(CH_2)_4$, $–CH_2–N–CH_2–$], 2.91–3.26 [m, 2 H, $(CH_2)_4$], 3.56–4.25 (m, 8 H, $–CH_2–O–CH_2–$, COCHCH, COCHCH, $CH_2CH_3$), 12.40 (br. s, 1 H, NH) | 14.17 (q, $CH_2CH_3$), 25.34, 26.99, 34.01, 42.04, 47.42, 52.12 [t, $(CH_2)_4$, $–CH_2–N–CH_2–$], 52.41 (d, COCHCH), 62.37, 64.33 (t, $–CH_2–O–CH_2–$), 66.49 (d, COCHCH), 66.66 (t, $CH_2CH_3$), 166.14 (s, CO), 219.60 (s, CO) | 2945, 2852, 1735, 1678, 1234, 1194 | 315 [$M^+$ – HCl] (0.5), 242 (100), 170 (28), 142 (7), 96 (4), 84 (10) | 198 | 81 |
| **6c** | 1.28 (t, 3 H, $J$ = 7.1, $CH_2CH_3$), 3.95–4.30 (m, 2 H, $CH_2CH_3$), 8.71 (br. s, 1 H, NH)[a] | 13.50 (q, $CH_2CH)_3$, 24.51, 26.52, 33.73, 41.38 [t, $(CH_2)_4$], 39.14 [q, $N(CH_3)_2$], 50.61 (d, COCHCH), 61.70 (t, $CH_2CH_3$), 65.57 (d, COCHCH), 166.33 (s, CO), 208.45 (s, CO)[b]<br>13.76 (q, $CH_2CH_3$), 24.02, 26.37, 34.48, 43.00 [t, $(CH_2)_4$], 39.14 [q, $N(CH_3)_2$], 48.52 (d, COCHCH), 62.17 (t, $CH_2CH_3$), 63.73 (d, COCHCH), 165.75 (s, CO), 206.33 (s, CO)[c] | 2964, 2820, 1742, 1660, 1212, 1196[a] | – | – | 79 |
| **7a** | 0.88 (t, 3 H, $J$ = 7.1 Hz, $CH_3CH_2$), 1.24–1.45 [m, 1 H, $N(CH_2)_5$], 1.66–1.78 [m, 3 H, $N(CH_2)_5$], 1.96–2.16 [m, 1 H, $N(CH_2)_5$], 2.20–2.28 [m, 6 H, $N(CH_2)_5$], 2.33–2.38 (m, 1 H, $PhCH_2CH$H), 2.58–2.94 (m, 1 H, $PhCH_2CH$H), 3.08–3.33 (m, 3 H, –CH–N–CH–, $PhCHCH_2$), 3.59–3.63 (m, 2 H, CHH–N–CHH), 3.82–4.07 (m, 4 H, $CH_2CH_3$, COCHCH, COCHCH), 7.06–7.13 (m, 2 H, Ar–H), 7.27–7.34 (m, 1 H, Ar–H), 7.73–7.76 (m, 1 H, Ar–H), 11.72 (br. s, NH) | 13.44 (q, $CH_2CH_3$), 21.57, 22.89, 23.14, 29.36, 31.41 [t, $N(CH_2)_5$, $PhCH_2CH_2$, $PhCH_2CH_2$], 47.90, 53.31 (t, $–CH_2–N–CH_2–$), 50.19 (d, CHCHN), 61.46 (t, $CH_2CH_3$), 67.29 (d, CHCHN), 126.41, 126.92, 128.56, 131.19 (d, $CH_{arom}$), 133.98, 144.04 (s, $C_{arom}$), 166.10 (s, CO), 196.33 (s, CO) | 2950, 2840, 1748, 1676, 1224, 1196 | 315 [$M^+$ – HCl] (0.5), 242 (100), 170 (28), 142 (7), 96 (4), 84 (10) | 198 | 87 |
| **7b** | 1.08 (t, 3 H, $J$ = 7.1, $CH_2CH_3$), 7.27–7.35 (m, 2 H, Ar–H), 7.51 (d, 1 H, $J$ = 7.6, Ar–H), 7.96 (d, 1 H, $J$ = 7.6, Ar–H), 9.85 (br. s, 1 H, NH)[a] | 13.38 (q, $CH_2CH_3$) 29.30, 30.86 (t, $PhCH_2CH_2$, $PhCH_2CH_2$), 43.09 (t, $–CH_2–N–CH_2–$), 49.12 (d, COCHCH), 60.41 (t, $CH_2CH_3$), 63.33 (t, $–CH_2–N–CH_2–$), 63.85 (t, $–CH_2–N–CH_2–$), 66.91 (d, COCHCH), 126.63, 126.96, 128.82, 131.36 (d, $CH_{arom}$), 134.21, 144.13 (s, $C_{arom}$), 166.07 (s, CO), 196.31 (s, CO)[b]<br>13.78 (q, $CH_2CH_3$), 26.79, 28.04 (t, $PhCH_2CH_2$, $PhCH_2CH_2$), 43.09 (t, $–CH_2–N–CH_2–$), 46.36 (d, COCHCH), 60.41 (t, $CH_2CH_3$), 63.33 (t, $–CH_2–N–CH_2–$), 63.85 (t, $–CH_2–N–CH_2–$), 66.32 (d, COCHCH), 122.95, 127.78 (d, $C_{arom}$), 133.89, 144.13 (s, $C_{arom}$), 165.93 (s, CO), 196.31 (s, CO)[c] | 3025, 2869, 2775, 1708, 1595, 1562, 1228[a] | – | – | 84 |

[a] Both diastereoisomers.
[b] Major product.
[c] Minor product.

**Table 5.** Characterization of Compounds **10**, **11**, **12** and **13**

| Product | $^1$H NMR ($CDCl_3$/TMS) $\delta$, $J$ (Hz) | $^{13}$C NMR ($CDCl_3$/TMs) $\delta$ | IR $\nu$ ($cm^{-1}$) | MS (70 eV) $m/z$ (%) | Yield (%) |
|---|---|---|---|---|---|
| **10a** | – | 14.72 (t, $CH_2CH_3$), 24.64, 24.77, 26.27, 26.40, 28.47, 35.33 [t, $(CH_2)_4$, $N(CH_2)_5$], 42.44 (d, CHCHCH), 52.97 (t, $–CH_2–N–CH_2–$), 60.64 (t, $CH_2CH_3$), 73.24, 74.78 (d, O–CHCHCH, N–CHCHCH), 171.47 (s, CO) | – | – | 55 |
| **11a** | 1.33 (t, 3 H, $J$ = 7.1, $CH_2CH_3$), 1.40–1.78 [m, 8 H, $PhCH_2CH_2$), $N(CH_2)_5$], 2.25–3.06 (m, 6 H, $PhCH_2CH_2$, $–CH_2–N–CH_2–$), 3.14 (d, 1 H, $J$ = 7.4, N–CHCHCH), 4.24 (q, 2 H, $J$ = 7.1, $CH_2CH_3$), 4.87 (d, 1 H, $J$ = 8.1, O–CHCHCH), 7.07–7.65 (m, 4 H, Ar–H)[b] | 15.13 (q, $CH_2CH_3$), 23.43, 24.92, 26.74, 27.16, 28.78 [t, $PhCH_2CH_2$, $PhCH_2CH_2$, $N(CH_2)_5$], 39.97 (d, CHCHCH), 52.53 (t, $CH_2–N–CH_2$), 60.74 (t, $CH_2CH_3$), 71.51 (d, N–CHCHCH), 72.32 (d, O–CHCH), 126.63, 127.43, 127.87, 128.94 (d, $CH_{arom}$), 136.22, 139.28 (s, $C_{arom}$), 171.43 (s, CO)[b] | 3430, 3931, 2851, 1727, 1652, 1535, 1456, 1165[a] | 317 [$M^+$] (1), 271 (1), 244 (100), 227 (24), 170 (33), 142 (34), 124 (35), 114 (13), 98 (33), 84 (25), 41 (10)[a] | 55 |
| | 1.33 (t, 3 H, $J$ = 7.1, $CH_2CH_3$), 1.40–1.78 [m, 8 H, $PhCH_2CH_2$, $N(CH_2)_5$], 2.25–3.06 (m, 6 H, $PhCH_2CH_2$, $–CH_2–N–CH_2–$), 3.29 (d, 1 H, $J$ = 5.6, N–CHCHCH), 4.24 (q, 2 H, $J$ = 7.1, $CH_2CH_3$), 5.52 (d, 1 H, $J$ = 7.3, O–CHCHCH), 7.07–7.65 (m, 4 H, Ar–H)[c] | 15.13 (q, $CH_2CH_3$), 23.43, 24.92, 26.74, 27.16, 28.78 [t, $PhCH_2CH_2$, $PhCH_2CH_2$, $N(CH_2)_5$], 37.34 (d, CHCHCH), 51.65 (t, $–CH_2–N–CH_2–$), 60.74 (t, $CH_2CH_3$), 69.43 (d, N–CHCHCH), 127.21, 128.80, 128.95, 130.50 (d, $CH_{arom}$), 132.50, 137.58 (s, $C_{arom}$), 175.76 (s, CO)[c] | | | |
| **12a** | 1.20–2.26 [m, 15 H, $(CH_2)_4$, $N(CH_2)_5$, CHCHCH], 2.53–2.88 (m, 4 H, $CH_2–N–CH_2$), 3.28 (d, 1 H, $J$ = 12.1, N–CHCHCH), 3.70 (td, 1 H, $J$ = 3.9, $J$ = 10.5, O-CHCHCH) | 24.27, 24.71, 25.59, 28.90, 30.70 [t, $(CH_2)_4$, $N(CH_2)_5$], 26.73 (t, $CH_2$ $CH_2–N–CH_2CH_2$), 45.86 (d, CHCHCH), 51.23 (t, $–CH_2–N–CH_2–$), 70.55 (d, CHCHCH–N), 80.70 (O–CHCHCH), 175.38 (s, CO) | 3415, 2935, 2856, 1781, 1635, 1446, 1169, 1126, 1115, 997 | 224 [$M^+$+1] (100), 179 (23), 150 (19), 124 (52), 110 (13)[d] | 51 |
| **13a** | 1.22–2.10 [m, 8 H, $N(CH_2)_5$, $PhCH_2CH_2$], 2.31–2.42 (m, 1 H, CHCHCH), 2.58 –2.83 (m, 4 H, $–CH_2–N–CH_2–$), 2.85–3.01 (m, 2 H, $PhCH_2CH_2$), 3.51 (d, 1 H, $J$ = 11.9, N–CHCHCH), 4.84 (d, 1 H, $J$ = 10.6, O–CHCHCH), 7.14–7.46 (4 H, Ar–H) | 26.64, 26.61, 26.66, 27.81 [$PhCH_2CH_2$, $PhCH_2CH_2$, $N(CH_2)_5$], 42.48 (CHHHCH), 51.33 ($–CH_2–N–CH_2–$), 71.16 (CHCHCH–N), 78.32 (O–CHCHCH), 126.36, 128.15, 129.22, 130.48 (d, $CH_{arom}$), 134.88, 135.69 (s, $C_{arom}$), 175.42 (s, CO) | 3447, 1652, 1635, 1559, 1384, 1112, 1031 | 271 [$M^+$] (4), 227 (100), 142 (40), 124 (60), 110 (43), 98 (45), 84 (37), 55 (20), 41 (55) | 52 |
| **12a'** | 1.18–1.98 [m, 12 H, $(CH_2)_4$, $N(CH_2)_5$], 2.36–3.00 (m, 4 H, $–CH_2–N–CH_2–$), 3.16 (d, 1 H, $J$ = 7.3, N–CHCHCH), 4.60 (q, 1 H, $J$ = 6.1, OCHCHCH) | 21.44, 21.95, 24.65, 25.76, 29.17 [t, $(CH_2)_4$, $N(CH_2)_5$], 26.73 (t, $CH_2CH_2–N–CH_2CH_2$), 37.38 (d, CHCCH), 51.86 (t, $–CH_2–N–CH_2–$), 68.94 (d, CHCHCHN), 77.34 (d, O-CHCHCH), 175.98 (s, CO) | 3410, 2932, 2855, 1770, 1635, 1450 | | 48 |
| **13a'** | 1.22–2.10 [m, 8 H, $N(CH_2)_5$, $PhCH_2CH_2$], 2.58–2.83 (m, 7 H, $PhCH_2CH_2$, $CH_2–N–CH_2–$, CHCHCH), 3.27 (d, 1 H, $J$ = 5.6, N–CHCHCH), 5.49 (d, 1 H, $J$ = 7.3, O–CHCHCH), 7.14–7.46 (4 H, Ar–H) | 24.22, 24.45, 25.13, 26.61, 27.14 [$PhCH_2CH_2$, $PhCH_2CH_2$, $N(CH_2)_5$], 37.31 (CHCHCH), 51.64 ($–CH_2–N–CH_2$), 69.88 (CHCHCHN), 77.21 (OCHCHCH), 127.19, 127.62, 128.94, 130.48 (d, $CH_{arom}$), 132.45, 137.52 (s, $C_{arom}$), 175.35 (s, CO) | 3447, 1652, 1635, 1559, 1384, 1112, 1031 | 271 [$M^+$] (4), 227 (100), 142 (54), 124 (30), 110 (53), 98 (45), 84 (37), 55 (20), 41 (55) | 65 |

[a] Both diastereoisomers.
[b] Major product.
[c] Minor product.
[d] Determined by GC-MS.

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(18) The hydrochlorides may also be deprotonated with sat. $NaHCO_3$ before reduction. However, the free bases are quite unstable. Therefore, the deprotonation with the reducing agent is useful for a small quantity of the $\gamma$-oxo-$\alpha$-aminocarboxylate hydrochloride.