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Reaction of (*S*)-homoserine lactone with Grignard reagents: synthesis of amino-keto-alcohols and β-amino acid derivatives

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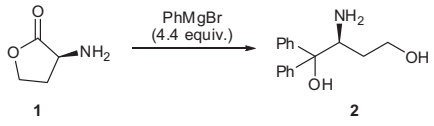
ABSTRACT

The ring-opening reaction of homoserine lactone with phenylmagnesium bromides was systematically examined. A reliable method to achieve β-amino acid precursors was developed by tuning the reaction conditions to favor mono-addition to the carbonyl moiety of the lactone.

1. Introduction

β-Amino acids are important compounds in Nature and synthetic chemistry because they present a broad range of biological properties. Several approaches for the efficient synthesis of these compounds have been developed.[1] One of these approaches involves aspartic acid and methionine. (*S*)-Homoserine lactone can be readily obtained from (*S*)-methionine,[2,3] and the reaction of this lactone with a variety of Grignard reagents yields the corresponding amino alcohols,[3,4] which can then be easily oxidized into β-amino acids. However, treatment of lactone **1** with Grignard reagents yields bis-addition, not mono-addition, of the reagent to the carbonyl group, furnishing tertiary alcohols[2] (Scheme 1).



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Scheme 1. Bis-addition of PhMgBr to homoserine lactone.

To avoid bis-addition, several methodologies have been developed.[5] Seki et al. also reported the synthesis of γ-aryl or alkyl-substituted homochiral β-amino acids from *N*-Cbz-(*S*)-homoserine lactone.[3] The literature reports two main methods for synthesizing amino-keto acids from such compounds: Friedel–Crafts acylation and organometallic reaction with the corresponding anhydride or acyl chloride.[6] Although amino-keto acids are accessible via the Friedel–Crafts reaction with anhydrides or acyl chlorides, the control of regioselectivity is strictly reagent-dependent. In addition, nucleophilic groups containing aryl and alkyl compounds are usually unable to undergo Friedel–Crafts reactions. These are the major drawbacks in the synthesis of aryl amino-keto acids when using the Friedel–Crafts reaction. Although the reaction of organometallics with lactones is well known in the literature, bis-homoserine has not been studied in detail, and its potential in developing easy access to β-amino acid precursors has not been evaluated. Herein we report a straightforward and efficient synthesis of γ-keto-β-amino acids via the ring-opening reaction of homoserine lactone.

2. Results and discussion

We commenced with the synthesis of *N*-Boc-(*S*)-homoserine lactone **1a** from (*S*)-methionine using a known method as described in the literature.[3] (*S*)-Methionine was subjected to *S*-alkylation and nucleophilic displacement of a dialkyl sulfide, and the L-homoserine obtained was then converted into lactone **1** with HCl (Scheme 2).

Two equivalents of PhMgBr prepared[7] in situ from PhBr and Mg turnings in the presence of 1,2-dibromoethane were treated with one equivalent of lactone **1a** at room temperature (Scheme 3). After purification of the crude material, keto-alcohols **6** and **7** were obtained in yields of 70% and 20%, respectively. For this reaction, at least a twofold excess of PhMgBr was necessary: one equivalent for the acidic proton (–*N**H***Boc) and one equivalent to achieve the addition to the carbonyl group of the lactone. In our attempts to improve the synthesis of keto-alcohol **6**, 2.3 equiv of PhMgBr were used and the desired keto-alcohol was obtained in good yield.

It should be noted that depending on the reaction temperature used, an increased ratio of bis-addition product **7** was found. Thus, to eliminate **7**, the reaction was repeated at 0 and −78 °C, however these reactions failed. Despite our failure to eliminate bis-addition product **7**, the synthesis of **6** in good yield encouraged us to expand this simple methodology to a series of in situ prepared Grignard

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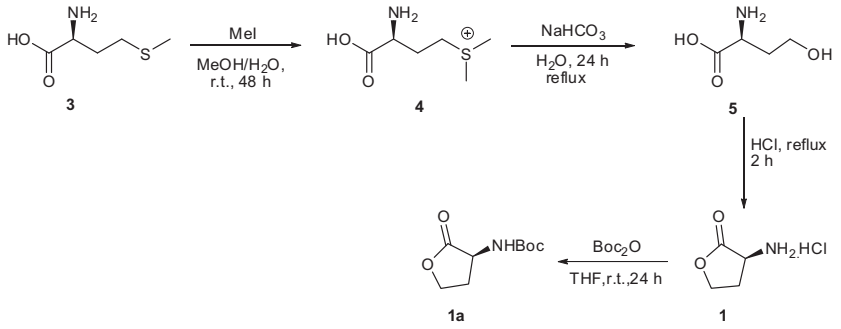
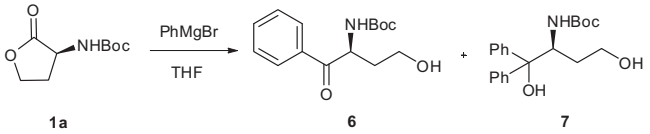


Scheme 2. Synthesis of homoserine lactone.



Scheme 3. The ring-opening reactions of homoserine lactone with PhMgBr.

Table 1
The ring-opening reactions of homoserine lactone with Grignard reagents

Entry	ArMgBr	Products	Yield[a] (%)
1	C_6H_5MgBr	**6**[3]	70
2	2-(MeO)C_6H_4MgBr	**6a**	45
3	4-(MeO)C_6H_4MgBr	**6b**[3]	40
4	3-(F)-4-(MeO)C_6H_3MgBr	**6c**	45
5	2-(Me)C_6H_4MgBr	**6d**	40
6	3-(Me)C_6H_4MgBr	**6e**	55
7	4-(Me)C_6H_4MgBr	**6f**[3]	45
8	2,4-(dimethyl)C_6H_3MgBr	**6g**	45
9	4-(F)C_6H_4MgBr	**6h**	35
10	3,4-(difluoro)C_6H_3MgBr	**6i**	70
11	2,4,5-(trifluoro)C_6H_2MgBr	**6j**	80
12	4-(*N*,*N*-dimethyl)-C_6H_4MgBr	**6k**	50

[a] Isolated yields after column chromatography.

reagents. To prevent sudden temperature increases in the room-temperature reactions, we used glass pieces instead of 1,2-dibromoethane to activate the magnesium.

As can be seen in Table 1, the substituents and their positions on the aromatic ring affect the formation of keto-alcohols. We assume that this dependence stems from the nucleophilicity and steric effect of the aryl group.

Some of the ring-opening reactions of homoserine lactone indicated that it had not completely reacted. An additional study to investigate this phenomenon was performed using the conditions given in Tables 2 and 3. Keto-alcohols **6** were obtained in a good yield as judged by the ^{1}H NMR spectra of the crude products. In contrast to previous reports,[3] the lactone was opened under mild condition (2.7 equiv of ArMgBr at room temperature and 50 °C) to give the amino-keto alcohols in one step. We believe that the syntheses of amino-keto alcohols can be achieved by employing our protocol without any obstacle.

To broaden the scope of this methodology to include alkylmagnesium halides, commercially available isopropylmagnesium bromide and ethylmagnesium bromide were also used to obtain amino-keto-alcohols. Treatment of lactone **1a** with ethylmagnesium bromide at room temperature gave **8a** in 60% yield and **9a** in 15% yield. The use of isopropylmagnesium bromide gave only **8b** in 70% yield without any bis-addition product (Scheme 4), a favorable result that could be attributed to the steric bulkiness of the isopropyl group hampering the bonding of an additional isopropyl group to the same center.

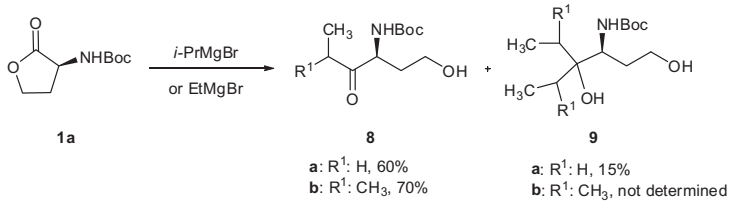
Considering the results obtained, this methodology functions very well and is a very convenient method for preparing amino-keto alcohol **6**, which is a precursor of amino-keto-acids. For example, we also easily obtained amino keto-alcohols **6e**, **6k**, and **8** via this method; these amino-keto-alcohols cannot be synthesized via Friedel–Crafts acylation. At this stage, the synthesized amino-keto-alcohols were successfully converted into the corresponding amino-keto-acids by Jones oxidation in 60%–70% yield (Scheme 5).

Table 2
The ring-opening reactions of homoserine lactone with Grignard reagents

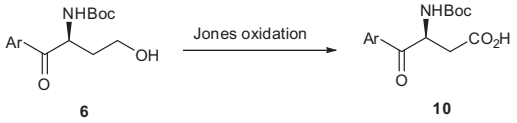
Entry	ArMgBr (2.7 equiv)	Lactone (1 equiv)	Temp. (°C)	Time (h)	Products	Ratio of product (%)
1	2-(MeO)C_6H_4MgBr	**1a**	50	2	**6a:7a**	30:70
2	4-(Me)C_6H_4MgBr	**1a**	50	2	**6f:7f**	40:60
3	4-(F)C_6H_4MgBr	**1a**	50	2	**6h:7h**	50:50
4	3,4-(difluoro)C_6H_3MgBr	**1a**	50	2	**6i:7i**	66:34
5	2,4,5-(trifluoro)C_6H_2MgBr	**1a**	50	2	**6j:7j**	75:25
6	4-(*N*,*N*-dimethyl)C_6H_4MgBr	**1a**	50	2	**6k:7k**	50:50

Table 3
The ring-opening reactions of homoserine lactone with Grignard reagents

Entry	ArMgBr (2.7equiv.)	Lactone (1 equiv)	Temp. (°C)	Time (h)	Products	Ratio of product (%)
1	2-(MeO)C_6H_4MgBr	**1a**	rt	2	**6a:7a**	85:15
2	4-(MeO)C_6H_4MgBr	**1a**	rt	2	**6b:7b**	60:40
3	4-(Me)C_6H_4MgBr	**1a**	rt	2	**6f:7f**	65:35
4	4-(F)C_6H_4MgBr	**1a**	rt	2	**6h:7h**	66:34
5	4-(*N*,*N*-Dimethyl)C_6H_4MgBr	**1a**	rt	2	**6k:7k**	66:34



Scheme 4. Ring-opening reactions of homoserine lactone with EtMgBr and *i*-PrMgBr.



Scheme 5. Oxidation of amino-keto-alcohols.

Table 4
β-Amino-γ-keto amino acid derivatives

Entry	Aryl group	Compound no
1	C_6H_5–	**10**
2	2-(OMe)C_6H_4–	**10a**
3	4-(OMe)C_6H_4–	**10b**
4	4-(OMe)-3-(F)C_6H_3–	**10c**
5	2-(Me)C_6H_4–	**10d**
6	4-(Me)C_6H_4–	**10f**
7	2,4-(Dimethyl)C_6H_3–	**10g**
8	4-(F)C_6H_4–	**10h**
9	3,4-(Difluoro)C_6H_3–	**10i**
10	2,4,5-(Trifluoro)C_6H_2–	**10j**

3. Conclusion

In conclusion we have developed a simple methodology to gain access to amino-keto-alcohols from the readily available serine lactone **1a** and Grignard reagents. The keto-alcohols were advantageously extended to the synthesis of β-amino-γ-keto amino acid derivatives. We believe that this procedure is not only simple and economical, but also applicable for the large scale syntheses of amino-keto-alcohols. The enantiomeric purity was not lost during the ring-opening process, because we used a homochiral starting material (a pure enantiomer) and we did not perform any reactions on the stereogenic center. Therefore, we do not expect a change in the enantiomeric purity. We performed the HPLC analysis of some of these compounds **6j′**, **6k** and **8a′**, which confirmed that there was no racemisation on the stereocenters. Further elaboration of the keto group provided the γ-functionalized-β-amino acids. We believe that this simple and straightforward method will find wide application in the synthesis of pharmacologically important β-amino acid derivatives (Table 4).

4. Experimental

General. All of the reagents used in the experiments are commercially available unless otherwise specified, and all solvents were distilled before use. IR spectra: PerkinElmer Spectrum One FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra: Varian 400 and 100 MHz and Bruker 400 and 100 MHz spectrometers. HR-MS: electron spray technique (M^+/M^-) from solutions in MeOH (Waters LCT PremierTM XE UPLC/MS TOF (Manchester, UK)).

General procedure A: Opening of the homoserine lactone **1a** with Grignard reagents

In an oven-dried flask, dried halogen-group-containing compounds (2.3 equiv) were added to dry THF containing magnesium metal (Mg) (2.3 equiv, with glass pieces to activate the magnesium metal) at room temperature under nitrogen. The reaction mixture was stirred vigorously until Grignard generation occurred. The lactone (1 equiv dissolved in 40 mL of THF) was added dropwise to the Grignard reagent solution, and the mixture was stirred at room temperature for 16 h and monitored by TLC. The mixture was treated with saturated aqueous NH_4Cl (20 mL) and then extracted with AcOEt (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed by an evaporator. The residue was purified by silica-gel column chromatography (AcOEt/hexane). In another experiment, the ring-opening reactions of homoserine lactone with select Grignard reagents were carried out using 2.7 equiv ArMgBr at r.t. and 50 °C for 2 h.

General procedure B: Conversion of alcohols to silylethers

In some reactions, the crude mixture was converted into silylether to avoid the difficulties associated with separating amino-keto-alcohol **6** from other compounds or impurities.*tert*-Butylchlorodimethylsilane (1.1 equiv) was added to a solution of alcohol **6** or **8** (1 equiv) and 1*H*-imidazole (2.2 equiv) in CH_2Cl_2 (30 ml). The mixture was stirred at room temperature for 24 h, quenched with saturated aqueous NH_4Cl (30 ml), and then extracted with CH_2Cl_2 (3 × 50 ml). The combined organic layers were dried over Na_2SO_4, and the crude product was purified by silica-gel column chromatography (AcOEt/hexane).

General procedure C: Oxidation reaction of keto-alcohols

Three milliliters of 2.67 M H_2CrO_4 was added to the keto-alcohol (1 equiv) at room temperature, and the mixture was stirred for 1.5 h. Monitoring by TLC was performed, and the reaction was quenched with 2-propanol. The mixture was stirred until a dark green color was achieved. The solvent was removed by an evaporator, and the residue was dissolved with DCM/AcOEt (1:1). The organic phase was dried over Na_2SO_4 and then filtered, and the solvent was removed by evaporation. The residue was purified by silica gel column chromatography (AcOEt/hexane).

4.1. *tert*-Butyl (*S*)-(4-hydroxy-1-(2-methoxyphenyl)-1-oxobutan-2-yl)carbamate 6a

Brown viscous liquid. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{25} = -4$ (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.50 (m, 1H), 7.03–6.96 (m, 2H), 5.85 (d, *J* = 7.7 Hz, 1H), 5.56 (m, 1H), 3.94 (s, 3H), 3.66 (m, 2H), 2.09 (m, 1H), 1.45 (s, 9H), 1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 159.2, 157.4, 135.0, 131.6, 124.6, 121.1, 112.0, 80.4, 58.7, 56.7, 55.8, 36.6, 28.5. IR (neat, cm^{-1}): 3411, 2976, 1697, 1600, 1493, 1248, 1165, 1024. Elemental analysis: calc. for $C_{16}H_{23}NO_5$C: 62.12; H: 7.49; N: 4.53; found C: 62.08; H: 7.12; N: 4.59.

4.2. *tert*-Butyl (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-1-(3-fluoro-4-methoxyphenyl)-1-oxobutan-2-yl)carbamate 6c′

White solid, R_f = 0.45 (30% AcOEt/hexane) $[\alpha]_D^{27}$ = +36 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 11.8 1.9 Hz, 1H), 6.98 (t, *J* = 8.4 Hz, 1H), 5.55 (d, *J* = 7.7 Hz, 1H), 5.30 (m, 1H), 3.94 (s, 3H), 3.75–3.65 (m, 2H), 2.08 (m, 1H), 1.71

(m, 1H), 1.42 (s, 9H), 0.89 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 155.7, 152.3 (d, $^1J_{CF}$ = 247,8 Hz, C-3) 152.4 (C-4), 152. 3 (C-1), 126.3 (C-6), 116.5 (d, $^2J_{CF}$ = 8 Hz, C-2), 112.6 (C-5), 79.8, 59.6, 56.5, 52.9, 36.2, 28.5, 26.1, −5.3. IR (neat, cm^{-1}): 3416, 2930, 2857, 1712, 1687, 1518. Elemental analysis: calc. for $C_{22}H_{36}FNO_5Si$ C: 59.84; H: 8.22; N: 3.17; found C: 60.23; H: 8.29; N: 2.99.

4.3. *tert*-Butyl (*S*)-(4-hydroxy-1-oxo-1-(*o*-tolyl)butane-2-yl)carbamate 6d

Yellow liquid, R_f = 0.4 (40% AcOEt/hexane) $[\alpha]_D^{25}$ = +18 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 1H), 7.44–7.40 (m, 1H), 7.30–7.25 (m, 2H), 5.82 (d, *J* = 7.0 Hz, 1H), 5.36–5.29 (m, 1H), 3.80 (brs, 1H) 3.70–3.64 (m, 2H), 2.47 (s, 3H), 2.06–1.98 (m, 1H), 1.48 (s, 9H), 1.47–1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 157.3, 139.5, 134.7, 132.4, 129.1, 126.3 (×2), 80.7, 58.4, 54.3, 36.8, 28.4, 21.4. IR (neat, cm^{-1}): 3435, 2925, 1684, 1637, 1455. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{23}NO_4$: 293.1623, found: 293.1627.

4.4. *tert*-Butyl (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-1-oxo-1-(*m*-tolyl)butan-2-yl)carbamate 6e′

Yellow liquid, R_f = 0.7 (30% AcOEt/hexane) $[\alpha]_D^{25}$ = +20 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.79 (m, 2H), 7.38–7.29 (m, 2H), 5.65 (d, *J* = 7.4 Hz, 1H), 5.41–5.38 (m, 1H), 3.75–3.63 (m, 2H), 3.38 (s, 3H), 2.16–2.07 (m, 1H), 1.76–167 (m, 1H), 1.43 (s, 9H). 0.89 (s, 6H), −0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.7, 155.8, 138.7, 134.4, 129.4, 128.8, 126.5, 122.9, 79.7, 59.7, 53.4, 36.0, 28.5, 28.4, 26.1, 21.5, −5.3. IR (neat, cm^{-1}): 3414, 2955, 2929, 1717, 1686, 1499. HRMS (ESI) *m*/*z* calc. for $C_{22}H_{37}NO_4Si$: 408.2491, found: 408.2157.

4.5. *tert*-Butyl (*S*)-(1-(2,4-dimethylphenyl)-4-hydroxy-1-oxobutan-2-yl)carbamate 6g

Yellow viscous liquid, R_f = 0.3 (30% AcOEt/hexane) $[\alpha]_D^{20}$ = −3.6 (*c* 1, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.0 Hz, 1H), 7.15–7.09 (m, 2H), 5.85 (d, *J* = 7.0 Hz, 1H), 5.44–5.40 (m, 1H), 3.95 (brs, 1H), 3.72–3.69 (m, 2H), 2.49 (s, 3H), 2.38 (s, 3H), 2.26–2.24 (m, 1H), 1.46 (s, 9H), 146–1.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 157.2, 143.2, 140.1, 133.3, 131.6, 129.7, 126.9, 80.5, 58.4, 54.0, 37.0, 28.5, 28.3, 20.9. IR (neat, cm^{-1}): 3416, 2975, 2929, 1679, 1612, 1492. HRMS (ESI) *m*/*z* calc. for $C_{17}H_{25}NO_4$: 306.1783, found: 306.1705.

4.6. *tert*-Butyl (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-1-(4-fluorophenyl)-1-oxobutan-2-yl) carbamate 6h′

Colorless viscous liquid, R_f = 0.7 (40% AcOEt/hexane) $[\alpha]_D^{26}$ = +22 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–8.03 (m, 2H), 7.13–7.09 (m, 2H), 5.59 (d, *J* = 7.3 Hz, 1H), 5.38–5.33 (m, 1H), 3.73–3.64 (m, 2H), 2.14–2.05 (m, 1H), 1.76–1.68 (m, 1H), 1.41 (s, 9H), 0.88 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.0, 166.1 (d, $^1J_{CF}$ = 254 Hz, C-4), 155.8, 131.7 (d, $^3J_{CF}$ = 9.2 Hz, C-2/6), 116.0 (d, $^2J_{CF}$ = 22 Hz, C-3/5), 79.8, 59.6, 53.2, 35.9, 28.2, 25.9, 18.4, −5.4. IR (neat, cm^{-1}): 3355, 2956, 2930, 1693, 1600, 1509, 1367, 1233, 1156. HRMS (ESI) *m*/*z* calc. for $C_{21}H_{34}FNO_4Si$: 412.2314, found: 412.2315.

4.7. *tert*-Butyl (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-1-(3,4-difluorophenyl)-1-oxobutan-2-yl)carbamate 6i′

Yellow liquid, R_f = 0.7 (30% AcOEt/hexane) $[\alpha]_D^{27}$ = +9 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89–7.81 (m, 2H), 7.26–7.18 (m, 1H), 5.60 (d, *J* = 7.5 Hz, 1H), 5.34–5.29 (m, 1H), 3.75–3.65 (m, 2H), 2.13–2.02 (m, 1H), 1.76–1.66 (m, 1H), 1.40 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 155.8, 154.0 (dd, $^1J_{CF}$ = 256 Hz, $^2J_{CF}$ = 13 Hz, C-4) 150.6 (dd, $^1J_{CF}$ = 250 Hz, $^2J_{CF}$ = 13 Hz, C-3), 132.2 (C-1), 126.0 (m, C-6), 118.3 (d, $^2J_{CF}$ = 18 Hz, C-2), 117.8 (d, $^2J_{CF}$ = 18 Hz, C-5), 80.0, 59.6, 53.3, 35.7, 28.5, 26.0, 18.4, −5.45 IR (neat, cm^{-1}): 3355, 2956, 2931, 2858, 1700, 1612, 1518, 1283, 1170. HRMS (ESI) *m*/*z* calc. for $C_{15}H_{19}F_2NO_4$: 314.1209, found: 314.1201.

4.8. *tert*-Butyl (*S*)-(4-((*tert*-butyldimethylsilyl)oxy)-1-oxo-1-(2,4,5-trifluorophenyl)butan-2-yl)carbamate 6j′

Yellow viscous, R_f = 0.4 (30% AcOEt/hexane). $[\alpha]_D^{25}$ = −9 (*c* 1, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.72 (m, 1H), 7.03–6.96 (m, 1H), 5.76 (d, *J* = 8 Hz, 1H), 5.10–5.04 (m, 1H), 3.74–3.64 (m, 2H), 2.16–2.06 (m, 1H), 1.83–1.75 (m, 1H), 1.40 (s, 9H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.3, 157.2 (dd, $^1J_{CF}$ = 262 Hz, $^2J_{CF}$ = 10 Hz, C-2), 155.7, 153.5 (dt, $^1J_{CF}$ = 259 Hz, $^2J_{CF}$ = 14 Hz, C-4), 147.4 (ddd, $^1J_{CF}$ = 247 Hz, $^2J_{CF}$ = 13 Hz, $^3J_{CF}$ = 3 Hz C-5), 120.60 (d, $^2J_{CF}$ = 16 Hz, C-1), 119.4 (d, $^2J_{CF}$ = 20 Hz, C-6), 106.9 (dd, $^2J_{CF}$ = 30.2 Hz, C-3), 79.9, 60.0, 57.9, 33.8, 28.5, 26.0, −5.5.

4.9. *tert*-Butyl (*S*)-(1-(4-(dimethylamino)phenyl)-4-hydroxy-1-oxobutan-2-yl) carbamate 6k

Yellow solid, mp: 185–187 °C, R_f = 0.2 (40% AcOEt/hexane) $[\alpha]_D^{25}$ = +75 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 5.92 (d, *J* = 7.7 Hz, 1H), 5.36 (m, 1H), 4.10 (m, 1H), 3.72–3.69 (m, 2H), 3.07 (s, 6H), 2.11 (m, 1H), 1.46 (s, 1H), 1.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.1, 157.5, 154.1, 131.4, 121.2, 111.0, 80.4, 58.6, 51.4, 40.2, 38.6, 28.5. IR (neat, cm^{-1}): 3412, 2976, 1706, 1656, 1597, 1531, 1368, 1167. HRMS (ESI) *m*/*z* calc. for $C_{17}H_{26}N_2O_4$: 323.1892, found: 323.1967.

4.10. *tert*-Butyl (*S*)-(1-((*tert*-butyldimethylsilyl)oxy)-4-oxohexan-3-yl)carbamate 8a′

Colorless viscous liquid. R_f = 0.63 (20% AcOEt/hexane) $[\alpha]_D^{20}$ = +17.3 (*c* 1, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.71 (d, *J* = 6.4 Hz, 1H), 4.24–4.20 (m, 1H), 3.59 (t, *J* = 5.6 Hz, 2H), 2.57–2.38 (m, 1H), 1.98–1.77 (m, 2H), 1.34 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.80 (s, 9H), −0.05 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.3, 155.7, 79.5, 59.9, 58.1, 33.6, 32.6, 28.5, 26.0, 18.3, 7.7, −5.5 (×2). Elemental analysis: calc. for $C_{17}H_{35}NO_4Si$ C: 59.09; H: 10.21; N: 4.05; found C: 59.10; H: 9.81; N: 3.99.

4.11. *tert*-Butyl (*S*)-(1-((*tert*-butyldimethylsilyl)oxy)-5-methyl-4-oxohexan-3-yl)carbamate 8b′

Colorless viscous liquid. R_f = 0.66 (20% AcOEt/hexane). $[\alpha]_D^{20}$ = +22.3 (*c* 1, CH_2Cl_2) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (d, *J* = 6.8 Hz, 1H), 4.50–4.45 (m, 1H), 3.64 (t, *J* = 5.8 Hz, 2H), 2.86 (sep, *J* = 6.8 Hz, 1H), 2.06–1.72 (m, 2H), 1.39 (s, 9H), 1.10 (d, *J* = 6.8 Hz, 1H), 1.05 (d, *J* = 6.8 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 213.6, 155.7, 79.6, 60.2, 60.0, 56.3, 37.4, 33.9, 26.1, 19.3, 18.0, −5.5(×2). Elemental analysis: calc. for $C_{18}H_{37}NO_4Si$ C: 60.12; H: 10.37; N: 3.90; found C: 59.84; H: 9.98; N: 3.58.

4.12. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-oxo-4-phenyl butanoic acid 10

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-oxo-4-phenyl butanoic acid **10** was obtained in a 70% yield. White solid. mp: 152–154 °C

R_f = 0.3 (60% AcOEt/hexane) $[\alpha]_D^{25}$ = −24 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (brs, 1H), 7.95 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.55–7.45 (m, 2H), 5.72 (d, *J* = 8.4 Hz, 1H), 5.50 (brs, 1H), 2.94 (dd, AB system, *J* = 16.4, 4.8 Hz, 1H), 2.87–2.74 (dd, AB system, *J* = 12.5, 4.4 Hz, 1H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.6, 176.2, 155.5, 134.7, 133.8, 128.7, 128.9, 80.8, 52.2, 37.0, 28.4. IR (neat, cm^{-1}): 3343, 2979, 1691, 1508, 1368, 1250, 1164. Elemental analysis: calc. for $C_{18}H_{37}NO_4Si$ C: 61.42; H: 6.53; N: 4.78; found C: 61.22; H: 6.59; N: 4.63.

4.13. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(2-methoxyphenyl)-4-oxo-butanoic acid 10a

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(2-methoxyphenyl)-4-oxobutanoic acid (**10a**) was obtained in a 60% yield. Yellow viscous. R_f = 0.4 (60% AcOEt/hexane), $[\alpha]_D^{25}$ = −6 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.7 Hz, 1H), 7.52–7.47 (m, 1H), 7.02 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 5.85 (d, *J* = 7.2 Hz, 1H), 5.44–5.37 (m, 1H), 3.91 (s, 3H), 2.98 (dd, AB system, *J* = 16.8, 4.4 Hz, 1H), 2.77 (dd, *J* = 16.8, 5.1 Hz, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 175.3, 158.2, 156.2, 134.7, 131.8, 121.3, 111.5, 80.6, 56.8, 55.8, 37.9, 28.5. IR (neat, cm^{-1}): 3416, 2978, 2929, 1713, 1599, 1487, 1248, 1163. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{21}NO_6$: 322.1296, found: 322.1294.

4.14. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(4-methoxyphenyl)-4-oxobutanoic acid 10b

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(4-methoxyphenyl)-4-oxobutanoic acid **10b** was obtained in a 70% yield. Brown viscous, R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{26}$ = +1 (*c* 1, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.99 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.48–5.44 (m, 1H), 4.89–4.87 (m, 1H), 3.85 (s, 3H), 2.83 (dd, *J* = 16.1, 5.9 Hz, 1H), 2.5 (dd, *J* = 16.0, 7.0 Hz, 1H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ = 197.3, 177.0, 164.3, 156.5, 130.9, 127.8, 113.7, 79.7, 54.9, 52.4, 38.2, 27.5. IR (neat, cm^{-1}): 3401, 2977, 1676, 1601, 1569, 1421, 1256, 1169. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{21}NO_6$: 322.1296, found: 322.1294.

4.15. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanoic acid 10c

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(3-fluoro-4-methoxyphenyl)-4-oxobutanoic acid **10c** was obtained in a 60% yield. White solid. mp: 182–184 °C R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{26}$ = −3 (*c* 1, MeOH) ^{1}H NMR (400 MHz, CD_3OD): δ = 10.11 (brs, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 12.0 Hz, 1H), 7.06–6.927 (m, 1H), 5.72 (d, *J* = 9.0 Hz, 1H), 5.44–5.42 (m, 1H), 3.92 (s, 3H), 2.90 (dd, AB system, *J* = 16.4, 5.1 Hz, 1H), 2.76 (dd, AB system, *J* = 16.5, 4.5 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ = 195.3, 175.9, 155.4, 152.2 (d, $^1J_{CF}$ = 247,8 Hz, C-3) 152.4 (C-4), 152. 3 (C-1), 126.3 (C-6), 116.6 (d, $^2J_{CF}$ = 19 Hz, C-2), 112.6 (C-5), 80.8, 56.5, 51.6, 36.9, 28.4. IR (neat, cm^{-1}): 3355, 2979, 1679, 1573, 1520, 1436, 1280, 1166. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{20}FNO_6$ 340.1202; found 340.1204.

4.16. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-oxo-4-(*o*-tolyl) butanoic acid 10d

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-oxo-4-(*o*-tolyl) butanoic acid **10d** was obtained in a 60% yield. Pale yellow viscous. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{27}$ = +7 (*c* 1, EtOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.70 (d, *J* = 7.3 Hz, 1H), 7.38–7.34 (m,1H), 7.25 (d, *J* = 7.3 Hz, 2H), 5.19–5.15 (m, 1H), 4.88–4.85 (m, 1H), 2.72 (d, *J* = 15.1 Hz, 1H), 2.51 (d, *J* = 16.1 Hz, 1H), 2.40 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ = 203.7, 178.1, 156.6, 138.1, 136.8, 131.3, 130.9, 127.9, 125.3, 79.4, 55.7, 38.0, 27.5, 19.4. IR (neat, cm^{-1}): 3416, 2975, 2929, 1679, 1612, 1492. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{21}NO_5$ 306.1419; found 306.1383.

4.17. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-oxo-4-(*p*-tolyl)butanoic acid 10f

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-oxo-4-(*p*-tolyl)butanoic acid **10f** was obtained in a 65% yield. White solid, mp: 60–62 °C. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{27}$ = −15 (*c* 1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 5.68 (d, *J* = 7.6 Hz 1H), 5.51–5.47 (m, 1H), 2.93 (dd, AB system, *J* = 16.4, 5.1 Hz 1H), 2.77 (dd, AB system, *J* = 16.1, 5.1 Hz, 1H), 2.41 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 175.6, 155.5, 145.0, 131.9, 129.7, 129.1, 80.7, 52.0, 37.4, 28.5, 21.9. IR (KBr) (cm^{-1}): 3345, 2926, 2855, 1713, 1702, 1607, 1504. HRMS (ESI) *m*/*z* calc. for $C_{16}H_{21}NO_5$ 306.1419; found 306.1383.

4.18. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(2,4-dimethylphenyl)-4-oxobutanoic acid 10g

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(2,4-dimethylphenyl)-4-oxobutanoic acid **10g** was obtained in a 60% yield. Pale yellow viscous. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{27}$ = −4 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.82 (brs, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.05–7.01 (m, 2H), 5.74 (d, *J* = 8.4 Hz, 1H), 5.29–5.25 (m, 1H), 2.94–2.82 (m, 2H), 2.39 (s, 3H), 2.32 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.4, 176.4, 155.7, 142.5, 139.6, 133.1, 132.3, 128.7, 126.4, 80.5, 53.9, 37.0, 28.5, 21.6, 20.8. IR (neat, cm^{-1}): 3340, 2979, 2930, 1711, 1612, 1498, 1251, 1165. HRMS (ESI) *m*/*z* calc. for $C_{17}H_{23}NO_5$ 320.1503; found 320.1500.

4.19. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(4-fluorophenyl)-4-oxobutanoic acid 10h

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(4-fluorophenyl)-4-oxobutanoic acid **10h** was obtained in a 80% yield. White solid. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{25}$ = −11 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (brs, 1H), 8.03–7.98 (m, 2H), 7.16–7.11 (m, 2H), 5.64 (d, *J* = 9.0 Hz, 1H), 5.48–5.42 (m, 1H), 3.28 (t, *J* = 6.6 Hz, 1H), 2.79 (t, *J* = 6.4 Hz, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.5, 178.2, 166.1 (d, $^1J_{CF}$ = 254 Hz, C-4), 155.8, 131.7 (d, $^3J_{CF}$ = 9.2 Hz, C-2/6), 116.0 (d, $^2J_{CF}$ = 22 Hz, C-3/5), 80.9, 51.9, 36.8, 33.3, 28.5. IR (neat, cm^{-1}): 3353, 2979, 2924, 1690, 1612, 1599, 1509. HRMS (ESI) *m*/*z*, calc. for $C_{15}H_{18}FNO_5$ 311.1169; found 311.1112.

4.20. (*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(3,4-difluorophenyl)-4-oxobutanoic acid 10i

(*S*)-3-((*tert*-Butoxycarbonyl)amino)-4-(3,4-difluorophenyl)-4-oxobutanoic acid **10i** was obtained in a 70% yield. White solid. mp: 212–214 °C. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{25}$ = −4 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, CD_3OD): δ = 7.91–7.81 (m, 2H), 7.40–7.33 (m, 1H), 5.41–5.36 (m, 1H), 4.87–4.85 (m, 1H), 2.87–2.78 (m, 1H), 2.55–2.49 (m, 1H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD): δ = 196.4, 177.8, 156.4, 154.0 (dd, $^1J_{CF}$ = 256 Hz, $^2J_{CF}$ = 13 Hz, C-4) 150.6 (dd, $^1J_{CF}$ = 250 Hz, $^2J_{CF}$ = 13 Hz, C-3), 132.2 (C-1), 126.0 (m, C-6), 118.3 (d, $^2J_{CF}$ = 18 Hz, C-2), 117.8 (d, $^2J_{CF}$ = 18 Hz, C-5),79.8, 52.9, 38.1, 27.4. IR (neat, cm^{-1}): 3416, 2975, 2929, 1679, 1612, 1492. HRMS (ESI) *m*/*z* calc. for $C_{15}H_{17}F_2NO_5$ 328.1002; found 328.0994.

4.21. (*S*)-3-(((Benzyloxy)carbonyl)amino)-4-oxo-4-(2,4,5-trifluorophenyl)butanoic acid 10j

(*S*)-3-(((Benzyloxy)carbonyl)amino)-4-oxo-4-(2,4,5-trifluorophenyl)butanoic acid **10j** was obtained in a 80% yield. White solid. mp: 55–57 °C. R_f = 0.4 (50% AcOEt/hexane) $[\alpha]_D^{25}$ = +5 (*c* 1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (brs, 1H), 7.66–7.60 (m, 1H), 7.38–7.27 (m, 5H), 7.01–6.95 (m, 1H), 5.92 (d, *J* = 7.7 Hz, 1H), 5.16–5.13 (m, 1H), 5.10 (s, 6H), 3.13 (dd, *J* = 17.2, 4.7 Hz, 1H), 2.91 (dd, *J* = 17.0, 5.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.4, 175.5, 157.2 (dd, $^1J_{CF}$ = 262 Hz, $^2J_{CF}$ = 10 Hz, C-2), 155.9, 153.5 (dt, $^1J_{CF}$ = 259 Hz, $^2J_{CF}$ = 14 Hz, C-4), 147.4 (ddd, $^1J_{CF}$ = 247 Hz, $^2J_{CF}$ = 13 Hz, $^3J_{CF}$ = 3 Hz, C-5), 136.1, 128.8,128,5,128,3, 120.4 (d, $^2J_{CF}$ = 16 Hz, C-1), 119.4 (d, $^2J_{CF}$ = 19 Hz, C-6), 106.7 (dd, $^2J_{CF}$ = 30,2 Hz, C-3), 67.6, 56.6, 35.8. IR (KBr) (cm^{-1}): 3371, 3067, 2983, 1719, 1625, 1513. Elemental analysis: calc. for $C_{18}H_{14}F_3NO_5C$: 56.70; H: 3.70; N: 3.67; found C: 56.40; H: 3.66; N: 3.42.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.08.009.

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