Tin(II) chloride assisted synthesis of N-protected γ-amino β-keto esters through semipinacol rearrangement†

Anupam Bandyopadhyay, Neha Agrawal, Sachitanand M. Mali, Sandip V. Jadhav and Hosahudya N. Gopi*

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A facile synthetic route for the preparation of N-protected γ-amino β-keto esters from amino aldehydes and ethyl diazoacetate is described. The two component coupling is facilitated by tin(II) chloride followed by semipinacol rearrangement leading to the product in quantitative yield. The reaction is mild, instantaneous and compatible with Boc-, Fmoc- and Cbz-amino protecting groups.

Introduction

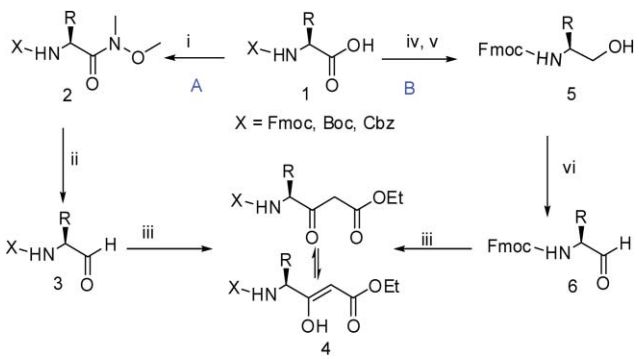
γ-Amino β-keto acids are highly versatile non-natural amino acids present in several biologically active peptides.[1,2] γ-Amino β-keto esters have been widely used as intermediates for the synthesis of many biologically relevant molecules such as statins,[3a,b] ketomethylene dipeptide isosteres,[3c] β-lactams,[3d] tricarbonyl compounds,[3e] rhodopeptins,[3f] substituted pyridines,[3g] fluorescent amino acid tags,[3h,i] cholecystokinin (CCK) receptor antagonists,[3j] γ-amino α,β-unsaturated esters,[3k] and α-azo-β carbonyl compounds.[3l] Several methods exist for the synthesis of γ-amino β-keto esters.[4] The most commonly used method involves the Claisen ester type condensation of activated carboxylic acid followed by nucleophilic substitution either with lithium enolate of alkyl acetates[3b,5a–c] or magnesium enolates of alkyl malonates[3a,l] or mono alkyl malonates in the presence of magnesium chloride.[5d] *N*,*N*′-Carbonyldiimidazole (CDI) is normally used for the carbonyl activation.[6] The other carbonyl activating groups such as pentafluorophenyl esters,[5a] N-carboxyanhydrides (NCAs),[7a,b] and mixed anhydrides[5b] of N-protected amino acids are also utilized in the Claisen ester type condensation. Similarly, C-acylation of protected amino acids with Meldrum's acid *via* mixed anhydride method followed by the hydrolysis leading to β-keto esters has also been reported.[8] The success of these methods varies for reasons including functional group compatibility, multistep procedures for nucleophile preparation, poor yields, harsh reaction conditions and longer duration of reactions. Consequently, there is a need for the development of new and efficient methods for the synthesis of γ-amino β-keto esters.

Reaction between diazomethane and aldehydes leading to ketones is a classic organic reaction.[9] The versatility of metal mediated diazocoupling reactions is well explored in organic synthesis.[10] Participation of diazoacetates in aldol[11] and Mannich[12] type reactions, and diazoacetamides as well as diazoacetates in Darzens[13] and aziridination[14] reactions in the presence of Lewis acid catalysts are well documented. In addition, Holmquist and Roskamp reported the Lewis acid mediated synthesis of rearranged β-keto esters from aliphatic and aromatic aldehydes with ethyl diazoacetate.[15]

We have been interested in the synthesis, conformational analysis and the biological activities of β-, γ- and γ-amino β-keto acids containing peptides. We envisioned that γ-amino β-keto acids could be obtained from the reaction between N-protected amino aldehydes and ethyl diazoacetate. Herein, we report the facile and efficient synthesis of γ-amino β-keto esters using N-protected amino aldehydes and ethyl diazoacetate in the presence of a catalytic amount of anhydrous tin(II) chloride at ambient temperature. In addition, this method was found to be compatible with Boc-, Cbz-, and Fmoc-N-protecting groups, as well as other side chain protecting groups.

Results and discussion

To explore the feasibility of this method we began with Boc-protected amino aldehydes. Scheme 1A shows the synthesis of amino aldehydes starting from Weinreb amide **2**. The protected amino acid **1** was converted to **2** following the reported procedure.[16] The column purified Weinreb amides were subjected to LAH reduction to give corresponding aldehydes.



Scheme 1 Synthesis of N-protected γ-amino β-keto esters from the coupling reaction between amino aldehydes and ethyl diazoacetate in the presence of tin(II) chloride. Reagents and conditions: (i) HBTU, HOBT, DiPEA, HCl·NH(OMe)Me, 2 h, 93–97%; (ii) LAH, THF, 0 °C, 30 min, 86–92%; (iii) ethyl diazoacetate, DCM, 20 mol% $SnCl_2$, 76–84%; (iv) isobutyl chloroformate, DiPEA, THF; (v) $NaBH_4$, H_2O, 90–98%; (vi) Dess–Martin periodinane, DCM, 84–95%.

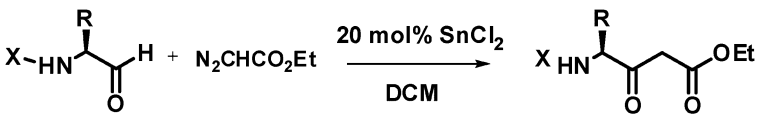
Department of Chemistry, Indian Institute of Science Education and Research, Garware Circle, Pashan, Pune, 411021, India. E-mail: hn.gopi@iiserpune.ac.in

† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR and mass spectra for all compounds. See DOI: 10.1039/c0ob00199f

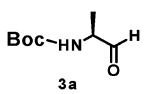
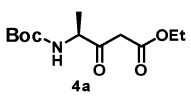
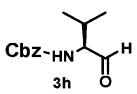
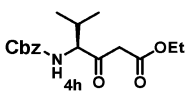
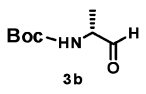
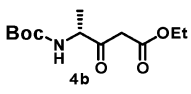
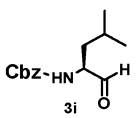
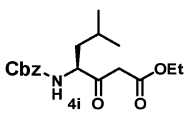
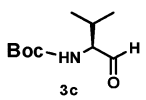
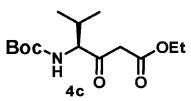
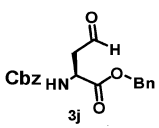
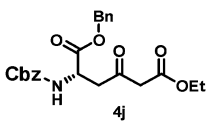
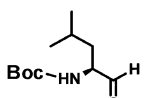
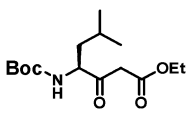
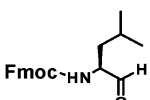
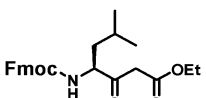
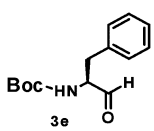
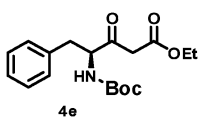
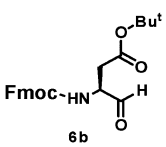
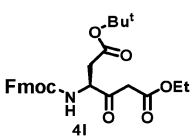
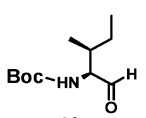
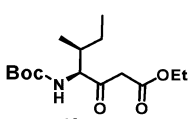
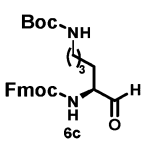
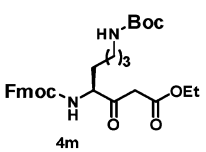
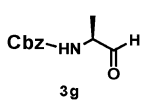
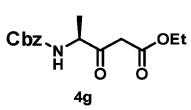
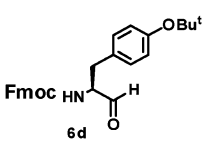
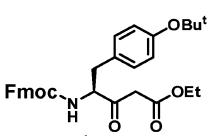
These amino aldehydes were directly used for the next step without purification. In an initial reaction, we subjected Boc-alaninal, **3a** to the coupling reaction with ethyl diazoacetate. In a typical reaction procedure, **3a** was dissolved in dichloromethane and pre-activated by adding 20 mol% of anhydrous tin(II) chloride at room temperature. To this ethyl diazoacetate was added slowly. We observed immediate evolution of nitrogen gas after the addition of ethyl diazoacetate, and it ceased within 30 min indicating the complete consumption of aldehyde. In the course of the reaction, we found that 20 mol% of catalyst is optimum for the reaction to obtain a quantitative yield.

Different Lewis acid catalysts such as $ZnCl_2$, BF_3, $GeCl_2$ and $TiCl_4$ were also reported in a similar type of reaction; however, we restricted our reactions to tin(II) chloride catalyst,[15,17,18] because $TiCl_4$ and zinc Lewis acid catalysts have also been used in the Mukaiyama-aldol type reactions[11c] with aldehydes and diazoacetates. In addition, although BF_3 has been used as a catalyst for the synthesis of Boc-protected γ- amino β-keto esters, the yields were lower than the tin(II) chloride assisted synthesis.[19] Reactions using tin chloride were found to be insensitive to the atmosphere and all reactions were performed in open flasks. In a control reaction, **3a** with ethyl diazoacetate in the absence of catalyst, no reaction occurred, and we isolated starting aldehyde. We further extended this reaction to other Boc-protected amino aldehydes, **3b–f**. The reactions were instantaneous and all Boc-protected β-keto esters, **4a–f**, were isolated in good yields (76–84%) and purity after simple aqueous work-up, and are given in Table 1. The yields are better or comparable to the nucleophilic substitution reactions. Having

Table 1 List of N-protected γ-amino β-keto esters synthesized from the N-protected amino aldehydes and ethyl diazoacetate in the presence of 20 mol% tin(II) chloride



3a-j or 6a-d — 4a-n

Entry	Substrate	Product	Yield (%)	Entry	Substrate	Product	Yield (%)
1	 3a	 4a	76	8	 3h	 4h	75
2	 3b	 4b	78	9	 3i	 4i	83
3	 3c	 4c	84	10	 3j	 4j	69
4	 3d	 4d	79	11	 6a	 4k	77
5	 3e	 4e	78	12	 6b	 4l	77
6	 3f	 4f	76	13	 6c	 4m	80
7	 3g	 4g	80	14	 6d	 4n	83

identified mild conditions for the synthesis of Boc-protected γ-amino β-keto esters, the scope and generality of the reaction was further examined with Cbz- and Fmoc- protected amino acids. We observed quantitative conversion of **2** to **4** in the case of Cbz-protected amino acids; however in the case of Fmoc-protected amino acids yields were lower than expected. We synthesized Cbz-protected β-keto esters, **4g–j** starting from Cbz-protected amino aldehydes, **3g–j** using the same protocol as described for Boc-amino aldehydes (Table 1).

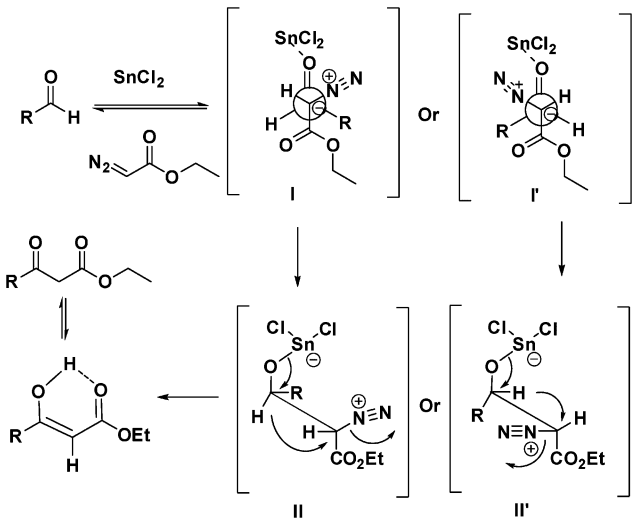
We anticipated that lower yields in the case of Fmoc-amino Weinreb amides may be due to the untimely cleavage of the Fmoc-group in the presence of LAH.[20] This was further confirmed by the ninhydrin test of the reaction mixture. To avoid premature departure of Fmoc- group in the LAH reduction, we adopted a different strategy for the synthesis of **6**. The schematic representation is shown in Scheme 1B. The Fmoc-amino alcohol **5** was readily synthesized starting from Fmoc- amino acid **1** through the mild $NaBH_4$ reduction of corresponding mixed anhydride.[21] The Fmoc- amino alcohol **5** was then subjected to Dess–Martin periodinane oxidation[22] to obtain **6a–d** in quantitative yield. The protected amino aldehydes were directly used for the next step without purification. The Fmoc-γ-amino β-keto esters, **4k–n**, are given in the Table 1. A similar protocol was used for the synthesis of compound **3j** (Table 1, entry 10). All β-keto esters are purified through silica gel column chromatography using ethyl acetate/pet ether as eluent. Notably, all N-protected β-keto esters were isolated in comparable yields indicating that reaction was insensitive to the protecting groups. Out of all β-keto esters **4e**, **4j** and **4m** were isolated as solids and their melting points were recorded and other compounds were isolated as oils. The specific rotations are given in the experimental section.

The ^{1}H and ^{13}C NMR of the N-protected γ-amino β-keto esters were recorded in $CDCl_3$. We observed a doublet of doublet for α-active methylene protons in AB coupling pattern at δ 3.5 ppm along with two distinct and common peaks at around δ 5.5 and δ 12 ppm for enol protons, respectively. The ratio of keto/enol form was found to be ≥10 : 1. Notably, we did not observe any change in the ratio of keto/enol tautomers even with a range of temperatures from –40 to 30 °C (see the ESI†).

On the basis of results observed from this work and the results reported in the literature, we propose a plausible reaction mechanism for the formation of β-keto esters (Scheme 2). We anticipate that formation of protected γ-amino β-keto esters proceeds *via* β-hydroxy-α-diazo ester intermediate. Activation of aldehyde by coordination with the tin(II) chloride and subsequent *re* or *si*-face nucleophilic addition of ethyl diazoacetate leads to the favorable formation of intermediate II or II′, respectively. To achieve this, the diazo group must proceed with *gauche* conformation with the R group as shown in I or I′. The *gauche* conformation may be stabilized by ionic interactions between the charged intermediates. Furthermore, the intermediate II or II′ subsequently loses nitrogen followed by 1,2-hydride shift to give β-keto esters. Overall, the formation of β-keto esters proceeds through the semipinacol rearrangement.

Conclusions

In conclusion, we have described the facile synthesis of N-protected γ-amino β-keto esters from readily accessible amino aldehydes and commercially available ethyl diazoacetate. The reaction is insensitive to the Boc-, Cbz- and Fmoc- protecting groups as well as atmospheric conditions.



Scheme 2 Proposed mechanism for the formation of β-keto ester from aldehyde and ethyl diazoacetate.

Experimental section

All amino acids, ethyl diazoacetate, LAH, DiPEA, tin(II) chloride and Cbz–Cl were purchased from Aldrich. THF, DCM and DMF were purchased from Merck. Isobutyl chloroformate, $NaBH_4$, HBTU, HOBt, di-*tert*-butyl dicarbonate and Fmoc–OSu, were obtained from spectrochem and used without further purification. THF and DiPEA were dried over sodium and distilled immediately prior to use. Column chromatography was performed on Merck silica gel (120–200 mesh) and flash chromatography (Combi Flash R_f). The ^{1}H spectra were recorded on Brucker 500 MHz (or 125 MHz for ^{13}C) and Jeol 400 MHz (or 100 MHz for ^{13}C) spectrometers using residual solvent signals as an internal reference ($CDCl_3$ δ_H, 7.24 ppm, δ_C 77.0 ppm). The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. Specific rotations were recorded using MeOH as a solvent (Rudolph Analytical Research). High-resolution mass spectra were obtained from HRMS-ESI (Waters), LCMS/MS (Waters) and MALDI TOF/TOF (Applied Biosciences).

General procedure for the synthesis of N-protected γ-amino β-keto ester

The N-protected amino aldehyde (2.0 mmol) was dissolved in 15 mL of DCM at room temperature (20–25 °C) and then 0.0756 g (20 mol%) of tin(II) chloride was added followed by 0.239 g (2.1 mmol) of ethyl diazoacetate. Immediate gas evolution was observed. The reaction mixture was stirred and the progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with 10 mL of 0.5 N HCl and the reaction mixture was extracted with DCM (30 mL × 3). The combined organic layer was washed with 20 mL of brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to get a greenish oily crude product which was purified on silica gel column chromatography.

(*S*)-ethyl 4-(*tert*-butoxycarbonylamino)-3-oxopentanoate (4a)

The representative procedure was employed for the coupling of **3a** with ethyl diazoacetate. The procedure gave the title compound 4a as a colorless liquid (0.398 g, 76%) after purification by column chromatography using 15% ethyl acetate/pet-ether (60–80 °C) as eluent. $[\alpha]_D^{25} = -35.69$ ($c = 1$, MeOH, lit [7b] $[\alpha]_D^{25} = -24$), ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.13 (s, 1H enolic 3.5%), 5.17 (b, s, 1H, NH), 4.43–4.37 (m, 1H, CH), 4.24–4.20 (q, $J = 7$ Hz, 2H, OCH_2), 3.62–3.54 (dd, $J = 14.5$ Hz, J = 10.5 Hz, 2H, CH_2, AB coupling), 1.46 (s, 9H, $C(CH_3)_2$, Boc), 1.38–1.36 (d, $J = 6.5$ Hz, 3H, CH_3), 1.31–1.28 (t, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.50, 166.96, 155.19, 80.14, 61.57, 55.42, 45.91, 28.32, 17.11, 14.11; HR-MS m/z calcd for [M+Na$^+$] 282.1317, obsrvd. 282.1317.

(*R*)-ethyl 4-(*tert*-butoxycarbonylamino)-3-oxopentanoate (4b)

Colorless liquid (0.405 g, 78%); $[\alpha]_D^{25} = +35.16$ ($c = 1$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 (s, 1H enolic 7.5%), 5.11–5.12 (d, $J = 5.5$ Hz, 1H, NH), 4.48–4.33 (m, 1H, CH), 4.20–4.15 (q, $J = 7.3$ Hz, 2H, CH_2), 3.58–3.48 (dd, $J = 14.5$ Hz, $J = 10.5$ Hz, 2H, CH_2, AB coupling), 1.42 (s, 9H, $C(CH_3)_3$, Boc-), 1.34–1.32 (d, $J = 7.3$ Hz, 3H, CH_3), 1.27–1.23 (t, $J = 7.3$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.55, 167.02, 155.24, 80.19, 61.63, 55.48, 45.96, 28.37, 17.17, 14.16; MALDI TOF/TOF- m/z Calcd. for $C_{12}H_{21}NO_5$ [M+Na]$^+$ 282.1317, obsrvd. 282.1317.

(*S*)-ethyl 4-(*tert*-butoxycarbonylamino)-5-methyl-3-oxohexanoate (4c)

Colorless liquid (0.48 g, 84%); $[\alpha]_D^{25} = -32.64$ ($c = 1$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.11 (s, 1H enolic form 6.5%), 5.06 (s, b, 1H, NH), 4.35–4.32 (m, 1H, CH), 4.22–4.18 (q, $J = 7$ Hz, 2H, –OCH_2), 3.57–3.50 (dd, $J = 15.5$ Hz, $J = 3$ Hz, 2H, CH_2, AB coupling), 2.27–2.23 (m, 1H, $CH(CH_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$, Boc-), 1.29–1.26 (t, $J = 7$ Hz, 3H, CH_3), 1.02–0.82 (m, 6H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.23, 166.75, 155.86, 80.03, 64.38, 61.55, 47.14, 29.56, 28.31, 19.84, 16.67, 14.10; HR-MS m/z Calcd. for $C_{14}H_{25}NO_5$ [M+Na]$^+$ 310.1630, obsrvd. 310.1620.

(*S*)-ethyl 4-(*tert*-butoxycarbonylamino)-6-methyl-3-oxoheptanoate (4d)

Light yellowish liquid (0.476 g, 79%); $[\alpha]_D^{25} = -53.70$ ($c = 1$, MeOH, lit.[3a] $[\alpha]_D^{25} = -51.3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.10 (s, 1H, enolic 5.5%), 4.96–4.94 (d, $J = 9.5$ Hz, 1H, NH), 4.40–4.36 (m, 1H, CH), 4.24–4.20 (q, $J = 7$ Hz, 2H, –OCH_2), 3.63–3.53 (dd, $J = 16.0$ Hz, $J = 18.5$ Hz, 2H, CH_2, AB coupling), 1.74–1.67 (m, 3H, CH_2, CH), 1.46 (s, 9H, $C(CH_3)_3$, Boc-), 1.32–1.29 (t, $J = 7$ Hz, 3H, CH3), 0.97 (b, s, 6H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.02, 167.07, 155.55, 80.15, 61.51, 58.19, 46.35, 39.90, 28.31, 24.83, 23.28, 21.59, 14.12; HR-MS m/z Calcd. for $C_{15}H_{27}NO_5$ [M+Na]$^+$ 324.1786 obsrvd. 324.1784.

(*S*)-ethyl 4-(*tert*-butoxycarbonylamino)-3- oxo-5-phenylpentanoate (4e)

White crystal (0.521 g, 78%); melting point = 61.4 °C; $[\alpha]_D^{25} = -54.5$ ($c = 0.6$, MeOH, lit.[3a] $[\alpha]_D^{25} = -56.3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.16 (s, 1H, enolic 17%), 7.24–7.15 (m, 5H, C_6H_5), 5.03–5.01 (d, $J = 7.3$ Hz, 1H, NH), 4.57–4.52 (q, $J = 6.4$ Hz, 1H, CH), 4.18–4.12 (q, $J = 7.2$ Hz, 2H, –OCH_2), 3.51–3.40 (dd, $J = 16$ Hz, $J = 11.4$ Hz, 2H, CH_2, AB coupling), 3.15–2.95 (m, 2H, CH_2Ph), 1.38 (s, 9H, $C(CH_3)_3$), 1.26–1.22 (t, $J = 7.2$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.96, 166.86, 155.18, 136.04, 129.24, 128.67, 127.00, 80.21, 61.45, 60.43, 46.86, 36.89, 28.20, 14.02; HR-MS m/z Calcd. for $C_{18}H_{25}NO_5$ [M+Na]$^+$ 358.1630, obsrvd 358.1633.

(4*S*,5*R*)-ethyl 4-((*tert*-butoxycarbonyl)amino)-5-methyl-3-oxoheptanoate (4f)

Colorless liquid (0.453 g, 76%); $[\alpha]_D^{25} = -25.08$ ($c = 1$, MeOH, lit.[7b] $[\alpha]_D^{25} = -23$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.09 (s, 1H, enolic 7.5%), 5.03–5.01(d, $J = 8.24$ Hz,1H, NH), 4.31–4.28 (m, 1H, CH), 4.19–4.13 (q, $J = 6.88$ Hz, 2H, –OCH_2), 3.51 (s, 2H, αCH_2), 1.97–1.90 (m, 1H, CH), 1.63–1.57 (m, 2H, CH_2), 1.41 (s, 9H, $C(CH_3)_3$, Boc-), 1.27–1.23 (t, $J = 7.2$ Hz, 3H, CH_3), 0.97–0.95 (dd, $J = 3.64$ Hz, $J = 3.24$ Hz, 3H, CH_3), 0.89–0.85 (t, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.38, 166.72, 155.74, 79.99, 64,26, 61.47, 47.28, 36.28, 28.25, 24.00, 16.02, 14.05, 11.60; MALDI TOF/TOF- m/z Calcd. for $C_{15}H_{27}NO_5$ [M+Na]$^+$ 324.1787, obsrvd. 324.1709.

(*S*)-ethyl 4-(benzyloxycarbonylamino)-3-oxopentanoate (4g)

Colorless liquid (0.469 g, 80%); $[\alpha]_D^{25} = -14.06$ ($c = 1$, MeOH, lit.[7b] $[\alpha]_D^{25} = -10$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.20 (s, 1H, enolic 4.5%), 7.40 (s, 5H, C_6H_5), 5.53 (b, s, 1H, NH), 5.14 (s, 2H, OCH_2Ph), 4.54–4.48 (m, 1H, CH), 4.23–4.18 (q, $J = 7.5$ Hz, 2H, OCH_2), 3.63–3.55 (dd, $J = 16.5$ Hz, $J = 11.5$ Hz, 2H, CH_2, AB coupling), 1.43–1.42 (d, $J = 7$ Hz, 3H, CH_3), 1.31–1.28 (t, $J = 7$ Hz, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.83, 166.74,155.68, 136.16, 128.60, 128.29, 128.16, 67.09, 61.69, 55.84, 45.93, 17.26, 14.09; LCMS-MS m/z Calcd. for $C_{15}H_{19}NO_5$ [M+K]$^+$ 332.0900, obsrvd. 332.0912.

(*S*)-ethyl 4-(benzyloxycarbonylamino)-5-methyl-3-oxohexanoate (4h)

Yellowish liquid (0.481 g, 75%); $[\alpha]_D^{25} = -24.37$ ($c = 1$, MeOH, lit.[23] $[\alpha]_D^{25} = -22$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.12 (s, 1H, enolic 6.5%), 7.367 (s, 5H, C_6H_5), 5.38–5.36 (d, $J = 8.5$ Hz, 1H, NH), 5.11 (s, 2H, –OCH_2Ph), 4.47–4.44 (m, 1H, CH), 4.21–4.17 (q, $J = 7$ Hz, 2H, CH_2, OCH_2), 3.54–3.54 (m, 2H, CH_2, AB coupling), 2.30–2.26 (m, 1H, CH), 1.286–1.25 (t, $J = 7$ Hz, 3H, CH_3), 1.05–0.81 (m, 6H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.72, 166.60, 156.48, 136.17, 128.60, 128.29, 128.15, 127.00, 67.20, 64.81, 61.64, 47.13, 29.67, 19.85, 16.55, 14.08; MALDI TOF/TOF m/z Calcd. for $C_{17}H_{23}NO_5$ [M+K]$^+$ 360.1213, obsrvd. 360.125.

(*S*)-ethyl 4-(benzyloxycarbonylamino)-6-methyl-3-oxoheptanoate (4i)

Colorless liquid (0.554 g, 83%); $[\alpha]_D^{25} = -32.50$ ($c = 1$, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.11 (s, 1H enolic 6%), 7.37 (s, 5H,C_6H_5), 5.33–5.32 (d, $J = 7$ Hz, 1H, NH), 5.13 (s, 2H, –OCH_2Ph), 4.51–4.47 (m, 1H, CH), 4.23–4.19 (q, $J = 7$, 2H, –OCH_2), 3.62–3.53 (dd, $J = 15.75$ Hz, $J = 13.5$ Hz, 2H, CH_2, AB coupling), 1.80–1.66 (m, 2H, CH_2), 1.46–1.42 (t, $J = 11$ Hz, 1H, CH), 1.30–1.27 (t, $J = 7$ Hz, 3H, CH_3), 0.99–0.95 (dd, $J = 6.2$ Hz,

J = 8 Hz, 6H, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.48, 166.89, 156.15, 136.16, 128.59, 128.28, 128.11, 67.16, 61.60, 58.60, 46.41, 39.98, 24.81, 23.29, 21.54, 14.09; MALDI TOF/TOF m/z Calcd. for $C_{18}H_{25}NO_5$ $[M+K]^+$ 374.1370, obsrvd. 374.1369.

(*S*)-1-benzyl 6-ethyl 2-(benzylcarbonylamino)-4-oxohexanedioate (4j)

White solid (0.589 g, 69%); melting point = 68.3 °C; $[\alpha]_D^{25}$ = −16.30 (c = 1, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 12.06 (s, 1H, enolic), 7.33–7.28 (m, 10H, aromatic), 5.75–5.72 (d, J = 8.2 Hz, 1H, NH), 5.63–5.59 (m, 1H, CH), 5.14 (s, 2H, –OCH_2Ph), 5.08 (s, 2H, –OCH_2Ph), 4.17–4.11 (q, J = 7 Hz, 2H, –OCH_2Me), 3.39 (s, 2H, CH_2, AB coupling), 3.33–3.10 (m, 2H, CH_2), 1.24–1.21 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.78, 170.51, 166.42,155.99, 136.02, 135.10, 128.57, 128.50,128.42, 128.21, 128.03, 67.57, 67.08, 61.59, 49.88, 49.07, 44.59, 14.01; MALDI TOF/TOF m/z Calcd. for $C_{23}H_{25}NO_7$ $[M+K]^+$ 466.1268, obsrvd. 466.1276.

(*S*)-ethyl 4-(((9*H*-fluoren-9-yl)mehtoxy)carbonylamino)-6-methyl-3-oxoheptanoate (4k)

Colorless liquid (0.651 g, 77%); $[\alpha]_D^{25}$ = −28.9 (c = 1, MeOH); ^1H NMR (500 MHz, $CDCl_3$): δ 12.16 (s, 1H, enolic), 7.80–7.79 (d, J = 7.5 Hz, 2H, aromatic, Fmoc-), 7.63–7.61 (t, J = 6.5 Hz, 2H, aromatic, Fmoc-), 7.44–7.42 (t, J = 7.5 Hz, 2H, aromatic, Fmoc-), 7.36–7.33 (t, J = 7.5 Hz, 2H, aromatic, Fmoc-), 5.26–5.24 (d, J = 8 Hz, 1H, NH), 4.50–4.45 (m, 3H, CH, CH_2), 4.26–4.21 (m, 3H,–OCH_2, CH-Fmoc), 3.59–3.50 (dd, J = 16 Hz, J = 13 Hz, 2H, CH_2, AB coupling), 1.71–1.68 (m, 2H, CH_2), 1.47–1.43 (m, 1H, CH), 1.34–1.30 (t, J = 7 Hz, 3H, CH_3), 1.00–0.97 (m, 6H, $C(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.54, 166.91, 156.13, 143.72, 141.38, 127.78, 127.11, 125.08, 120.05, 66.87, 61.63, 58.56, 47.28, 46.35, 39.93, 24.80, 23.33, 21.54, 14.13; MALDI TOF/TOF m/z Calcd. for $C_{25}H_{29}NO_5$ $[M+K]^+$ 462.1683, obsrvd. 462.1631.

(*S*)-1-*tert*-butyl 6-ethyl 3-(((9*H*-fluoren-9-yl)methoxy)-carbonylamino)-4-oxohexanedioate (4l)

Colorless liquid (0.742 g, 77.2%); $[\alpha]_D^{25}$ = 1.43 (c = 1, MeOH); ^1H NMR (500 MHz, $CDCl_3$): δ 12.11 (s, 1H, enolic 5.5%), 7.78–7.32 (m, 8H, aromatic, Fmoc), 5.91 (b, s, 1H, NH), 4.60–4.51 (m, 2H, CH_2), 4.45–4.41 (m, 1H, CH), 4.24–4.18 (m, 3H,–OCH_2, CH–Fmoc), 3.56 (s, 2H, αCH_2), 2.94–2.69 (dd, J = 16.5 Hz, J = 13.8 Hz, 2H, –$CH_2CO_2{}^tBu$), 1.44 (s, 9H, –$OC(CH_3)_3$), 1.28–1.25 (t, J = 7.3 Hz, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.05, 170.52, 166.87, 156.00, 143.67, 141.39, 127.83, 127.11, 125.08, 120.09, 82.17, 67.13, 61.57, 56.70, 47.23, 46.03, 36.57, 28.035, 14.10; HR-MS m/z Calcd. for $C_{27}H_{31}NO_7$ $[M+K]^+$ 520.1738, obsrvd. 520.1722.

(*S*)-ethyl 4-(((9*H*-fluoren-9-yl) mehtoxy)carbonylamino)-8-(*tert*-butoxycarbonylamino)-3-oxooctanoate (4m)

White solid (0.862 g, 80.2%); melting point = 114 °C; $[\alpha]_D^{25}$ = −81.53(c = 1, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 12.11 (s, 1H, enolic), 7.760–7.28 (m, 8H, aromatic, Fmoc-), 5.57–5.56 (d, J = 7.3 Hz, 1H, NH–Fmoc), 4.59 (s, b,1H, NH-Boc), 4.45–4.39 (m, 3H, CH, CH_2), 4.21–4.16 (m, 3H, –OCH_2, CH–Fmoc), 3.55–3.45 (dd, J = 15.6 Hz, J = 9.16 Hz, 2H, CH_2, AB coupling), 3.12–3.02 (q, J = 7.3 Hz, 2H, CH_2NH–Boc), 1.95–1.84 (m, 2H, CH_2), 1.71–1.41 (m, 4H,–CH_2 CH_2–), 1.37 (s, 9H, $C(CH_3)_3$, Boc), 1.27–1.23 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.96, 166.89, 156.27, 143.80, 141.41, 127.84, 127.18, 125.12, 120.09, 79.34, 67.00, 61.74, 60.01, 47.28, 46.27, 39.86, 30.34, 29.78, 28.50, 22.19, 14.18; HR-MS m/z Calcd. for $C_{30}H_{38}N_2O_7$ $[M+Na]^+$ 561.2576, obsrvd. 561.2577.

(*S*)-ethyl 4-(((9*H*-fluoren-9-yl)methoxy)carbonylamino)-5-(4-*tert*-butoxyphenyl)-3-oxopentanoate (4n)

Colorless gummy (0.88 g, 83.3%); $[\alpha]_D^{25}$ = −37.45 (c = 1, MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 12.17 (s, 1H, enolic), 7.75–7.28 (m, 8H, aromatic, Fmoc-), 7.03–7.01 (d, J = 8.3 Hz, 2H, aromatic, Ph–), 6.90–6.88 (d, J = 8.3 Hz, 2H, aromatic, Ph–), 5.33–5.31 (d, J = 7.8 Hz, 1H, NH), 4.64–4.587 (m, 1H, CH), 4.39–4.38 (d, J = 6.9 Hz, 2H, CH_2), 4.19–4.10 (m, 3H, –OCH_2, CH–Fmoc), 3.44–3.34 (dd, J = 16 Hz, J = 11.4 Hz, 2H, CH_2, AB coupling), 3.09–2.94 (m, 2H, –CH_2Ph–O^{t}Bu), 1.30 (s, 9H, –$C(CH_3)_3$, O^{t}Bu), 1.25–1.22 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5121, 166.6250, 155.6698,154.4971, 143.6181, 141.2917, 130.39, 129.69, 127.73, 1.27.68, 127.04, 124.97, 124.36,124.24, 124.19, 119.97, 78.87, 66.90, 61.54, 60.81, 47.14, 46.97, 36.43, 28.77, 14.04; HR-MS m/z Calcd. for $C_{32}H_{35}NO_6$ $[M+Na]^+$ 552.2362, obsrvd. 552.2363.

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