Synthesis of achiral and chiral *N*-protected γ-amino-β-ketones and β-ketoesters

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Dedicated to Prof. Nouria Al-Awadi on the occasion of her 55th anniversary

Abstract

Novel chiral *N*-carbamate-protected γ-amino-β-ketones **3a**–**c** and the known *N*-carbamate-protected nitroketone **3d** were prepared from the corresponding 1-(*N*-protected α-aminoacyl)benzotriazoles **1** by reaction with nucleophiles **2a–d** in the presence of bases under mild conditions. Similarly achiral and chiral *N*-protected γ-amino-β-ketoesters **3e–l** were prepared by reaction with acetoacetates in the presence of sodium hydride.

Keywords: Benzotriazole, achiral, chiral, protected, ketones, ketoesters

Introduction

Synthesis and development of *N*-protected γ-amino β-ketones and β-ketoesters has attracted interest for decades since they afford building blocks for intermediates and bioactive pharmaceuticals. Thus optically active α-amino ketones, which can be prepared *via* decarboxylation of *N*-protected γ-amino-β-ketoesters, are useful chiral building blocks for the preparation of biologically active natural products including polyfunctional amino acids, amino polyols such as amino sugars and peptide mimics which may act as enzyme inhibitors.[1,2]

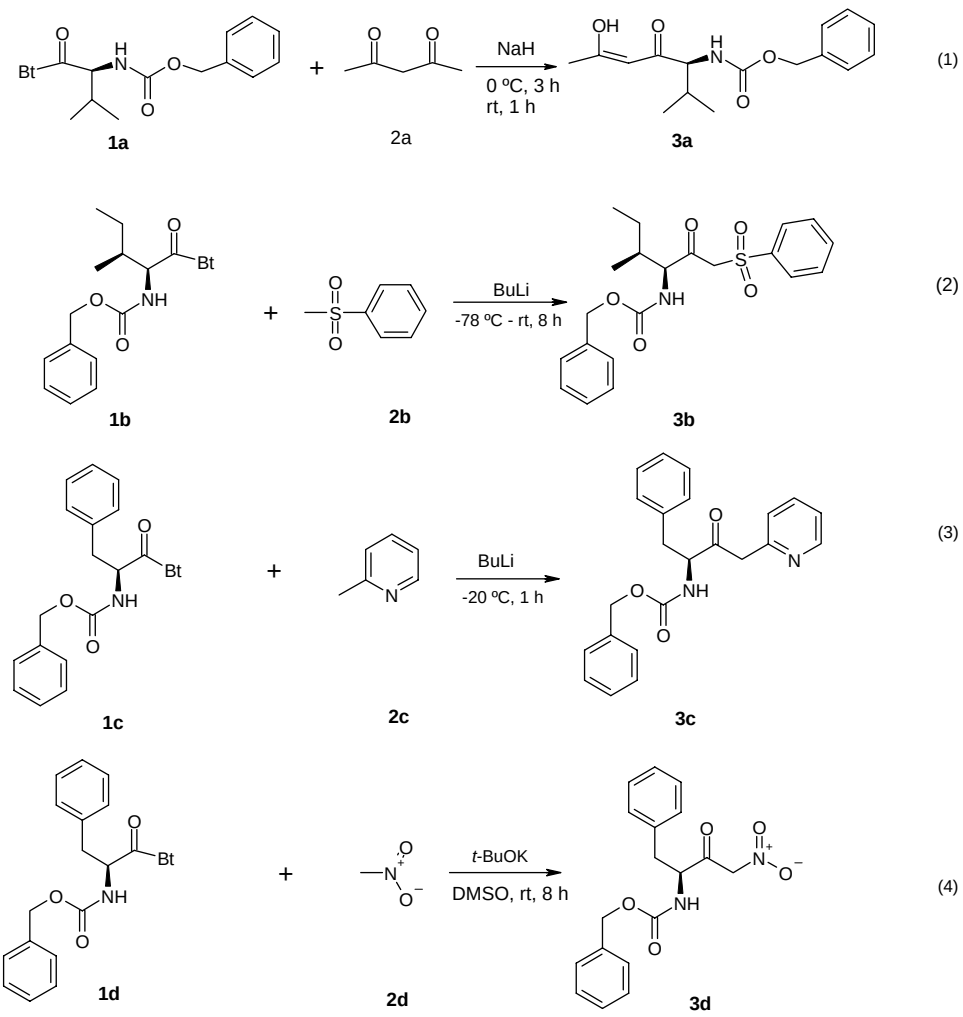
Benzotriazole has been employed extensively as a synthetic auxiliary.[3] 1-Acylbenzotriazoles are stable, may be prepared directly from carboxylic acids in high yields[4] and have been widely used in *N*-,[4b,5] *C*-,[6] *O*-,[6d,7] and *S*-acylations.[8]

Recently we prepared β-keto esters and β-diketones by *C*-acylative/deacetylation of acetoacetic esters and acetonyl ketones with 1-acylbenzotriazoles.[6d] We have now extended this methodology to the preparation of achiral and chiral *N*-protected γ-amino-β-keto esters *via* *C*-acylation of acetoacetic esters with achiral and chiral 1-(*N*-protected α-aminoacyl)benzotriazoles, followed by spontaneous deacetylation. More importantly however, we have used similar benzotriazole technology to prepare the first reported representatives of these new classes of functionalized chiral

γ-amino-β-ketones: γ-amino-β-diketo carbamate **3a**, the γ-amino-β-keto-α-sulfonyl-carbamate **3b** and the γ-amino-β-keto-α-pyridinyl-carbamate **3c**.

Results and Discussion

Chiral *N*-carbamate-protected γ-amino-β-ketones **3a**–**d** were prepared in 41–83% by reaction of the corresponding chiral 1-(*N*-protected α-aminoacyl)benzotriazoles **1a**–**d** with nucleophiles **2a**–**d** in the presence of various bases as shown in Scheme 1 and Table 1.



Scheme 1

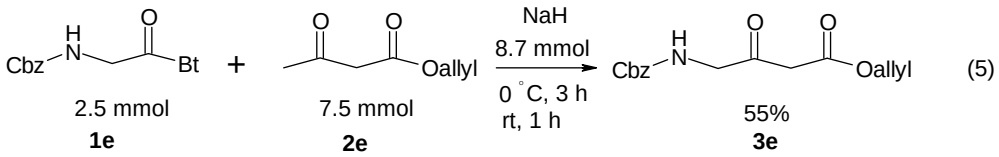
All the above reactions gave good yields except reaction 3, which produced several unidentified by-products (Table 1).

Table 1. Preparation of **3a**–**d**

Entry	**1**	**2**	**3**, Yield (%) (lit. ref.)
a	Z-L-VAL-Bt	**a**	76
b	Z-L-ILE-Bt	**b**	67
c	Z-L-PHE-Bt	**c**	41
d	Z-L-PHE-Bt	**d**	83 (9)

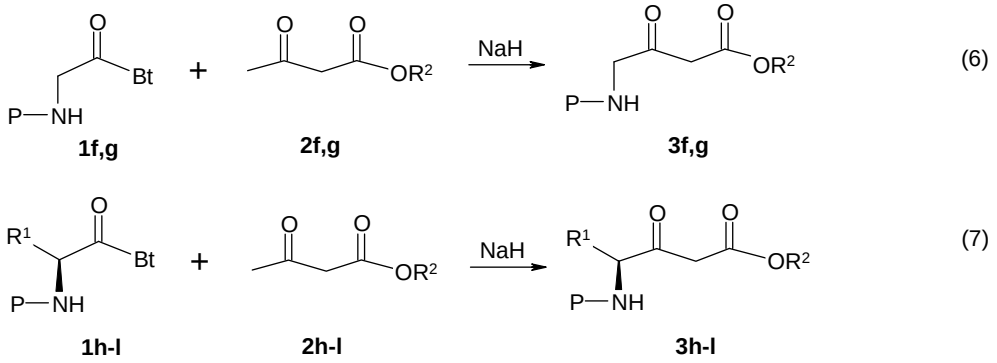
The structures of chiral *N*-carbamate-protected γ-amino-β-ketones **3a**–**d**, are supported by spectroscopic data and microanalyses. The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ indicate that **3a** exists essentially in the enol form with a trace of the keto form, consistent with previously reported l studies.[6d,10] Compound **3c** is a mixture of keto and enol forms (10 : 7) and **3b** and **3d** are fully keto forms. Thus the ^{1}H NMR spectrum of **3a** shows a singlet at 5.57 ppm (enolic methine proton) and a broad singlet at 15.11 ppm (enol hydrogen) and its ^{13}C NMR spectrum shows a signal at 99.0 ppm (enolic methine carbon). The ^{1}H spectrum of **3c** shows an AB quartet at 3.90 and 4.06 ppm (α-methylene protons of the keto form) and a singlet at 5.26 ppm (enolic methine proton of the enol form), and its ^{13}C NMR spectrum shows signals at 49.7 ppm (α-methylene carbon of the keto form) and 93.4 ppm (enolic methine carbon). The ^{1}H NMR spectrum of **3b** shows AB quartets at 4.20 and 4.42 ppm and that of **3d** shows AB quartets at 5.23 and 5.43 ppm (α-methylene protons of the keto forms)[9].

Condensation of the sodium enolate of allyl acetoacetate **2e** with achiral benzyl [2-(1*H*-benzotriazol-1-yl)-2-oxoethyl]carbaminate (Z-GLY-Bt) **1e** in various molar ratios in THF at 0–25 °C gave *N*-protected γ-amino-β-keto ester **3e** in up to 55% isolated yield without *O*-acylation or other by-products (Scheme 2).



Scheme 2

Under similar reaction conditions, the achiral and chiral *N*-protected γ-amino-β-keto esters **3f**–**l** were prepared in 54–78% isolated yields (Scheme 3, Table 2).



Scheme 3

Table 2. Preparation of **3f-l**

Entry	**1**	**R**^{2} in **2** & **3**	**3**, Yield (%) (lit. ref.)
f	Z-GLY-Bt	Me	54 (11)
g	Z-GLY-Bt	*t*-Bu	54
h	Z-L-PHE-Bt	allyl	78
i	Z-L-TRP-Bt	allyl	64
j	Z-L-MET-Bt	allyl	54
k	Z-L-ILE-Bt	allyl	55
l	FMOC-L-PHE-Bt	allyl	72

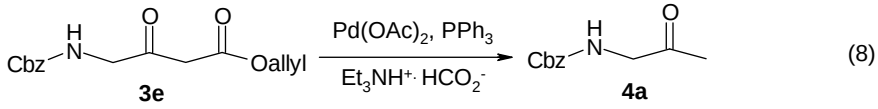
To obtain optimal yields it was crucial to keep the molar ratio of nucleophiles **2** to acylbenzotriazoles **1** at 3 : 1 and the reaction temperature at 0 ºC for a minimum of three hours.

The yields achieved by the synthetic methodology for **3e–l** are comparable or somewhat inferior to those reported in the literature for direct reaction of ethyl acetate anion with *N*-protected amino esters (89%)[12] or by the reaction of allyl or aralkyl acetates with *N*-protected amino acids in the presence of *N*,*N'*-carbonyldiimidazole (75-87%).[13]

The structure of the known *N*-protected γ-amino-β-keto ester **3f** is supported by comparison of its melting point and spectroscopic data with a literature report.[11] The structures of the novel *N*-protected γ-amino-β-keto esters **3e**,**g–l** are supported by spectroscopic data and microanalyses. The ^{1}H NMR spectra of the achiral **3e–g** show new sets of singlets at 3.40–3.59 ppm assigned to the α-methylene protons and their ^{13}C NMR spectra show signals at 46.2–47.9 ppm corresponding to the α-methylene carbons. The ^{1}H NMR spectra of the chiral **3h–j**,**l** show AB quartets at 3.43–3.61 and 3.49–3.64 ppm, due to the presence of two magnetically non-equivalent α-methylene protons. Chiral **3k** is an exception, in which the α-methylene protons are seen as a singlet at 3.58 ppm instead of an AB quartet. The ^{13}C NMR spectra of the chiral **3h–l** contain signals at 46.2–47.1 ppm corresponding to the α-methylene carbons. The ^{1}H and ^{13}C spectra of **3e–g** in $CDCl_3$ show only the keto form whereas ^{1}H and ^{13}C spectra of chiral **3h–l** show mixtures of keto and enol forms with the former predominating. A broad singlet at 12.0–12.13 ppm in the ^{1}H NMR spectra of **3h–l** is assigned to the enol hydrogen. The only olefinic carbon signal detected among the enol forms of

3e–**l** is at 90.0 ppm in chiral β-keto ester **3k**. Apparently steric effects in **3e**–**l** play an important role in determining the tautomeric equilibria. Thus γ-di-substituted **3h–l** tend to stabilize enol forms, while γ-mono-substituted **3e**–**g** do not.

N-Carbamate-protected α-amino ketones **4a**,**b**[14] were prepared *via* β-keto esters **3e**,**h** in 85-86% yields following a literature procedure (Scheme 4 and Table 3).[13b] It should be noted that the method is compatible with a variety of functional groups and carbamate protecting groups.



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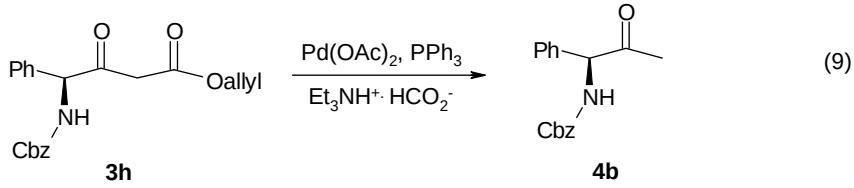

(9)

Scheme 4

Table 3. Preparation of **4a**–**b**

Entry	**3**	**4**, Yield (%) (lit. ref.)
m	**e**	**a**, 85 (14)
n	**h**	**b**, 86 (14)

In summary, procedures for the preparation of achiral/chiral *N*-protected γ-amino-β-ketones and β-ketoesters have been developed by treatment of starting nucleophiles or acetoacetates with achiral/chiral 1-(*N*-carbamate-protected β-amino)acylbenzotriazoles in the presence of a base under mild conditions. The advantages of this method include: (i) most acylbenzotriazoles are stable over months; (ii) the use of acylbenzotriazoles offers mild reaction conditions, operational ease and, importantly, *O*-acylation is greatly reduced; (iii) achiral/chiral *N*-protected γ-amino-β-ketoesters and analogues are obtained in good to excellent yields by one-pot methodology with retention of chirality.

Experimental Section

General Procedures and Materials. Melting points were determined on a hot-stage apparatus and are uncorrected. Optical rotations were measured on a PERKIN-ELMER 241 polarimeter. NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard for ^1H (300 MHz) and $CDCl_3$ as the internal standard for ^{13}C (75 MHz), unless otherwise specified. All reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Anhydrous THF was obtained by

distillation immediately prior to use, from sodium/benzophenone ketyl. Column chromatography was carried out on silica gel S733-1 (200–425 mesh).

Procedure for the preparation of benzyl *N*-[(1*S*,3*Z*)-4-hydroxy-1-isopropyl-2-oxo-3-pentenyl]carbamate (3a). To a solution of 2,4-pentanedione (99%, 1.52 g, 15 mmol) in THF (70 mL) was added NaH (60%, 0.70 g, 17.5 mmol) at 0 ºC and stirring was continued for 30 min under nitrogen. A solution of Z-L-VAL-Bt (1.76 g, 5 mmol) in THF (40 mL) was added by syringe. The resulting mixture was stirred at 0 ºC for 3 h and rt for 1 h. A small amount of silica gel was added and THF was removed under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (6–3/1, v/v) to give the product benzyl *N*-[1*S*,3*Z*)-4-hydroxy-1-isopropyl-2-oxo-3-pentenyl]carbamate (1.10 g, 3.78 mmol) as a colorless oil; yield 76%; $[\alpha]_D^{22}$ = –4.41 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$), the enol form: δ 0.87 (d, *J* = 6.84 Hz, 3H), 0.98 (d, *J* = 6.84 Hz, 3H), 1.98–2.16 (m, 4H), 4.17 (dd, *J* = 9.0, 5.4 Hz, 1H), 5.11 (s, 2H), 5.38 (d, *J* = 9.0 Hz, 1H), 5.57 (s, 1H), 7.27–7.41 (m, 5H), 15.11 (br s, 1H); visible ^{1}H peaks of the keto form: 3.66 (d, *J* = 12.0 Hz, A part of AB system), 3.61 (d, *J* = 12.0 Hz, B aprt of AB system), 1.02 (d, *J* = 6.8 Hz), 0.80 (d, *J* = 6.8 Hz); the enol form: ^{13}C NMR ($CDCl_3$) δ 17.3, 19.5, 23.9, 31.3, 61.7, 67.0, 99.0, 128.1, 128.1, 128.5, 136.2, 156.2, 188.3, 194.5. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.58; H, 7.32; N, 5.24.

Procedure for the preparation of benzyl *N*-{(1*S*,2*S*)-2-methyl-1-[2-(phenylsulfonyl)acetyl] butyl}carbamate (3b). To a solution of methyl phenyl sulfone (0.78 g, 5 mmol) in THF (37 mL) was added BuLi (1.6 M, 6.25 mL, 10 mmol) at –78 ºC and stirring was continued for 1 h under nitrogen. A solution of Z-L-ILE-Bt (1.83 g, 5 mmol) in THF (20 mL) was added by syringe. The resulting mixture was stirred at –78 ºC and the temperature was allowed to rise to rt during 8 h. The mixture was quenched with a solution of saturated aqueous ammonium chloride and extracted with ethyl acetate (150 mL). The extract was washed with aqueous sodium carbonate (1M, 2 x 100 mL), dried over anhydrous magnesium sulfate and solvents removed under reduced pressure, and the residue was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (4–3/1, v/v) to give an impure oily product, which was dissolved in a mixture of ether and hexanes and cooled in the freezer (twice) to give the pure product benzyl *N*-{(1*S*,2*S*)-2-methyl-1-[2-(phenylsulfonyl)acetyl]butyl}carbamate (1.35 g, 3.35 mmol) as colorless needles, mp 83–85 ºC; yield 67%; $[\alpha]_D^{22}$ = +6.62 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 7.2 Hz, 3H), 0.96–1.12 (m, 4H), 1.18–1.32 (m, 1H), 1.83–2.12 (m, 1H), 4.20 (d, *J* = 14.3 Hz, 1H, B part of AB system), 4.40 (dd, *J* = 8.8, 4.4 Hz, 1H), 4.42 (d, *J* = 14.4 Hz, 1H, A part of AB system), 5.11 (s, 2H), 5.36 (d, *J* = 8.7 Hz, 1H), 7.36 (s, 5H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.91 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 11.5, 15.9, 24.0, 35.6, 63.9, 65.3, 67.2, 128.0, 128.2, 128.4, 128.5, 129.2, 134.2, 136.0, 138.8, 156.3, 197.4. Anal. Calcd for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.24; N, 3.47. Found: C, 62.61; H, 6.29; N, 3.45.

Procedure for the preparation of benzyl *N*-[(1*S*)-1-benzyl-2-oxo-3-(2-pyridinyl)propyl] carbamate (3c). To a solution of 2-picoline (99%, 0.47 g, 5 mmol) in THF (20 mL) were added BuLi (1.6 M, 7.5 mL, 12.5 mmol) and HMPA (6 eq, 5.3 g) during 15 min at -78 ºC and stirring was continued for 3 h before the temperature was allowed to rise to -20 ºC. A solution of Z-L-PHE-Bt

(2.0 g, 5 mmol) in THF (20 mL) was added by syringe at -20 ºC under nitrogen. The resulting mixture was stirred at -20 ºC for 1 h, quenched with water (20 mL) and extracted with ethyl acetate (150 mL). The extract was washed with aqueous sodium carbonate (1M, 2 x 100 mL), dried over anhydrous magnesium sulfate and solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (3/1, v/v) to give an impure orange oily product, which was dissolved in a mixture of ether and hexanes and cooled in the freezer to give the product benzyl *N*-[(1*S*)-1-benzyl-2-oxo-3-(2-pyridinyl)propyl]carbamate (0.76 g, 2.03 mmol) as yellow crystals, mp 65–67 ºC; yield 41%; $[\alpha]_D^{22}$ = –2.18 º (c 0.0167g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$), the keto form (59%): δ 2.99–3.21 (m, 2H), 3.90 (d, *J* = 15.6 Hz, 1H, B part of AB system), 4.06 (d, *J* = 15.6 Hz, 1H, A part of AB system), 4.75 (q, *J* = 6.8 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H, B part of AB system), 5.09 (d, *J* = 12 .2 Hz, 1H, A part of AB system), 5.74 (d, *J* = 7.1 Hz, 1H), 7.00 –7.42 (m, 12H), 7.62 (t, *J* = 7.3 Hz, 1H), 8.50 (d, *J* = 4.2 Hz, 1H); the enol form (41%): δ 3.04–3.21 (m, 2H), 4.53 (q, *J* = 7.3 Hz, 1H), 5.05 (d, *J* = 12.2 Hz, 1H, B part of AB system), 5.09 (d, *J* = 12.2 Hz, 1H, A part of AB system), 5.41 (d, *J* = 8.3 Hz, 1H), 5.26 (s, 1H), 7.00–7.42 (m, 10H), 6.77–6.88 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 8.04 (d, *J* = 4.9 Hz, 1H), 15.35 (br s, 1H); ^{13}C NMR ($CDCl_3$), the keto and enol form:δ 37.2, 39.6, 49.7, 56.8, 60.6, 66.6, 66.8, 77.2, 93.4, 117.2, 121.2, 122.1, 124.3, 126.4, 126.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 129.3, 129.4, 136.0, 136.3, 136.5, 136.7, 137.4, 137.4, 141.4, 149.5, 154.0, 155.6, 155.7, 157.2, 169.9, 171.3, 205.4. Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.64; H, 5.85; N, 7.36.

Procedure for the preparation of benzyl *N*-[(1*S*)-1-benzyl-3-nitro-2-oxopropyl]carbamate (3d). A mixture of nitromethane (0.156 g, 2.5 mmol), potassium *t*-butoxide (0.63 g, 5.5 mmol) in DMSO (13 mL) was stirred for 10 min at rt. Z-L-PHE-Bt (1.001 g, 2.5 mmol) in DMSO (13 mL) was added to the resulting solution in one portion and the mixture was stirred for 8 h at rt. The mixture was poured into water (50 mL), acidified with 10% acetic acid (50 mL) and extracted with ethyl acetate (3 x 50 mL). The extracts were washed with water (2 x 50 mL), dried over anhydrous MgSO4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexanes/EtOAc as eluant (6-1/1, v/v) to give benzyl *N*-[(1*S*)-1-benzyl-3-nitro-2-oxopropyl]carbamate as ivory needles (0.71 g, 2.074 mmol) , mp 122-124 ºC [lit.[9] 117–121 °C]; yield 83%; $[\alpha]_D^{22}$ = –33.81 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.12–3.28 (m, 2H), 4.64 (q, *J* = 7.0 Hz, 1H), 5.19 (s, 2H), 5.23 (d, *J* = 15.3 Hz, B part of AB system, 1H), 5.38 (d, *J* = 7.6 Hz, 1H), 5.43 (d, *J* = 15.3 Hz, A part of AB system, 1H), 7.20–7.29 (m, 2H), 7.37–7.51 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 36.6, 59.8, 67.7, 82.0, 127.7, 128.2, 128.5, 128.6, 129.1, 129.2, 134.7, 135.5, 156.0, 195.9. Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.85; H, 5.21; N, 8.02.

General procedure for the preparation of achiral and chiral *N*-protected γ-amino-β-keto esters 3e–l

To a solution of an acetoacetate ester (2a–h, 15 mmol) in THF (60 mL) was added NaH (60%, 0.70 g, 17.5 mmol) at room temperature and stirring was continued for 30 min under nitrogen. The reaction mixture was cooled to 0 ºC for 10 min before a solution of an acylbenzotriazole (1a–h, 5

mmol) in THF (40 mL) was added by syringe. The resulting mixture was stirred at 0 ºC for 3 h and rt for 1 h. A small amount of silica gel was added and THF was removed under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant to give the corresponding achiral and chiral *N*-protected *γ*-amino-*β*-keto esters.

Compound characterization data of 3e–l

Allyl 4-[(benzyloxycarbonyl)amino]-3-oxobutanoate (3e). Colorless oil after chromatography on silica gel using hexanes/ethyl acetate as eluant (20–7/1, v/v); yield 55%; ^{1}H NMR ($CDCl_3$) δ 3.59 (s, 2H), 4.28 (d, *J* = 5.1 Hz, 2H), 4.67 (d, *J* = 5.8 Hz, 2H), 5.18 (s, 2H), 5.30 (dd, *J* = 10.4, 1.1 Hz, 1H), 5.37 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.66 (br s, 1H), 5.87–6.00 (m, 1H), 7.39 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 46.2, 50.8, 66.2, 67.1, 119.0, 127.9, 128.1, 128.4, 131.1, 135.9, 156.3, 166.2, 198.2. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.61; H, 5.92; N, 5.14.

Methyl 4-[(benzyloxycarbonyl)amino]-3-oxobutanoate (3f). Microcrystals after chromatography on silica gel using hexanes/ethyl acetate as eluant (10–2/1, v/v); mp 49–51 °C [lit.[11] 53.5–55.0 °C]; yield 54%; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 2H), 3.74 (s, 3H), 4.21 (d, *J* = 5.1 Hz, 2H), 5.12 (s, 2H), 5.48 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 46.2, 50.8, 52.6, 67.1, 128.1 (2C), 128.2, 128.5 (2C), 136.1, 156.1, 166.8, 197.9.

***t*-Butyl 4-[(benzyloxycarbonyl)amino]-3-oxobutanoate (3g).** Microcrystals after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (20–7/1, v/v); mp 43.0–45.0 °C; yield 54%; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 3.40 (s, 2H), 4.20 (d, *J* = 5.1 Hz, 2H), 5.12 (s, 2H), 5.48 (br s, 1H), 7.35 (s, 5H); ^{13}C NMR ($CDCl_3$) δ 27.9, 47.9, 50.8, 67.1, 82.7, 128.1, 128.2, 128.6, 136.2, 156.2, 165.7, 198.5. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.89; H, 7.06; N, 4.51.

Allyl (4*S*)-4-[(benzyloxycarbonyl)amino]-3-oxo-5-phenylpentanoate (3h). Microcrystals after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (10–6/1, v/v); mp 57.0–59.0 °C; yield 78%; $[\alpha]_D^{22}$ = +3.08 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.97–3.06 (m, 1H), 3.13–3.19 (m, 1H), 3.47 (d, AB, *J* = 17.0 Hz, 1H), 3.53 (d, AB, *J* = 17.0 Hz, 1H), 4.54–4.70 (m, 3H), 5.07 (s, 2H), 5.22–5.35 (m, 3H), 5.81–5.94 (m, 1H), 7.13–7.15 (m, 2H), 7.21–7.38 (m, 8H); visible ^{1}H peaks for enol form: δ 12.09; ^{13}C NMR ($CDCl_3$) δ 37.0, 46.8, 60.8, 66.1, 67.1, 118.9, 127.2, 128.0, 128.2, 128.5, 128.8, 129.2, 129.2, 131.4, 135.6, 155.7, 166.3, 201.2; visible ^{13}C peaks for enol form: δ 38.7, 64.9, 118.4, 126.9, 136.0. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.16; H, 6.05; N, 3.73.

Allyl (4*S*)-4-[(benzyloxycarbonyl)amino-5-(1*H*-indol-3-yl)-3-oxopentanoate (3i). Microcrystals after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (3/1, v/v); mp 62.0–64.0°C; yield 64%; $[\alpha]_D^{22}$ = +1.17 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.26 (dd, *J* = 6.0, 2.1 Hz, 2H), 3.43 (d, *J* = 16.3 Hz, 1H, B part of AB system), 3.48 (d, *J* = 16.1, 1H, A part of AB system), 4.54 (d, *J* = 5.8 Hz, 2H), 4.77 (q, *J* = 6.7 Hz, 1H), 5.07 (s, 2H), 5.20–5.31 (m, 2H), 5.45 (d, *J* = 7.3 Hz, 1H), 5.77–5.91 (m, 1H), 6.94 (d, *J* = 2.1 Hz, 1H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.25–7.38 (m, 6H), 7.59 (d, *J* = 7.8 Hz, 1H), 8.18 (s, 1H); visible ^{1}H peaks for enol form: δ 12.13 (bs, 0.04H); ^{13}C NMR ($CDCl_3$) δ 27.0, 46.9, 60.2, 66.0, 67.1, 109.5, 111.3, 118.6, 118.8, 119.8, 122.4, 123.1, 127.2, 128.1, 128.2, 128.5, 131.4, 136.0, 136.1, 155.9, 166.4,

202.0; visible ^{13}C peaks for enol form: δ 64.3, 111.2, 118.4, 119.7, 122.2, 131.8. Calcd for $C_{24}H_{24}N_2O_5$: C 68.56; H, 5.75; N, 6.66. Found: C, 68.59; H, 5.79; N, 6.58.

Allyl (4*S*)-4-[(benzoxycarbonyl)amino]-6-(methylsulfanyl)-3-oxohexanoate (3j). Yellow oil after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (10–6/1, v/v); yield 54%; $[\alpha]_D^{22}$ = –0.59 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.83–1.96 (m, 1H); 2.08 (s, 3H), 2.17–2.29 (m, 1H), 2.53 (t, *J* = 7.0 Hz, 2H), 3.61 (d, *J* = 15.6 Hz, 1H, B part of AB system), 3.64 (d, *J* = 15.6 Hz, 1H, A part of AB system), 4.55–4.66 (m, 3H), 5.12 (s, 2H), 5.24–5.63 (m, 2H), 5.49 (d, *J* = 8.3 Hz, 1H), 5.83–5.97 (m, 1H), 7.28–7.40 (m, 5H); visible ^{1}H peaks from the enol form: δ 4.75, 12.0; ^{13}C NMR ($CDCl_3$) δ 15.5, 29.9, 30.2, 46.2, 59.2, 66.2, 67.3, 119.1, 128.1, 128.3, 128.6, 131.3, 135.9, 155.9, 166.4, 201.1; visible ^{13}C peaks from the enol form: δ 15.4, 30.1, 32.0, 53.3, 65.0, 67.1, 118.7, 128.8, 128.9, 129.1, 131.7, 138.9, 160.4, 172.1, 174.7. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 59.45; H, 6.35; N, 3.73.

Allyl (4*S*,5*S*)-4-[(benzyloxycarbonyl)amino]-5-methyl-3-oxoheptanoate (3k). Yellow oil after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (10–7/1, v/v); yield 55%; $[\alpha]_D^{22}$ = +5.28 º (c 0.0392 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.85–0.95 (m 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.96–1.18 (m, 1H), 1.24–1.40 (m, 1H), 1.90–2.07 (m, 1H), 3.58 (s, 2H), 4.44 (dd, *J* = 9.0, 4.4 Hz, 1H), 4.63 (d, *J* = 5.5 Hz, 2H), 5.11 (s, 2H), 5.21–5.40 (m, 3H), 5.80–6.01 (m, 1H), 7.20–7.42 (m, 5H); visible ^{1}H peaks for the enol form: 4.04–4.09, 12.0; ^{13}C NMR ($CDCl_3$) δ 11.5, 16.0, 23.9, 36.3, 47.1, 64.6, 66.0, 67.1, 118.8, 128.0, 128.1, 128.4, 131.4, 136.0, 156.3, 166.1, 201.6; visible ^{13}C peaks for the enol form: 11.2, 15.6, 24.7, 36.8, 58.7, 64.8, 66.9, 90.0, 118.4, 131.8, 155.8, 172.0. 175.1. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.50; H, 7.32; N, 4.06.

Allyl (4*S*)-4-[(9*H*-fluoren-9-ylmethoxycarbonyl)amino]-3-oxo-5-phenylpentanoate (3l). Microcrystals after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (7/1–4/1, v/v); mp 89-91 ºC; yield 72%; $[\alpha]_D^{22}$ = +0.56 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.02 (dd, *J* = 14.1, 7.1 Hz, B part of AB system, 1H), 3.17 (dd, *J* = 14.1, 6.2 Hz, A part of AB system, 1H), 3.46 (d, *J* = 16.2 Hz, B part of AB system, 1H), 3.50 (d, *J* = 16.2 Hz, A part of AB system, 1H), 4.18 (t, *J* = 6.7 Hz, 1H), 4.36–4.50 (m, 2H), 4.51–4.76 (m, 3H), 5.21–5.41 (m, 3H), 5.80–6.00 (m, 1H), 7.14 (d, *J* = 7.1 Hz, 2H), 7.20–7.38 (m, 5H), 7.41 (t. *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 6.9 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 2H); visible ^{1}H peaks for the enol form: δ 2.66, 2.84, 5.05, 6.95, 7.05, 12.11 (br s); ^{13}C NMR ($CDCl_3$) δ 36.8, 46.7, 47.1, 60.8, 66.0, 66.8, 119.0, 119.9, 125.0, 127.0, 127.1, 127.7, 128.7, 129.2, 131.4, 135.7, 141.3, 143.6, 155.7, 166.3, 201.2; visible ^{13}C peaks for the enol form: δ 60.3, 64.9, 118.4, 128.6, 131.7, 136.0, 155.4, 172.1; Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98. Found: C, 74.14; H, 5.75; N, 2.98.

General procedure for the preparation of *N*-carbamate-protected α-amino ketones 4a,b

To a stirred solution of palladium acetate (20.74 mg, 0.092 mmol), PPh_3 (49.44 mg, 0.189 mmol), formic acid (0.29 mL, 7.25 mmol), and Et_3N (1.31 mL, 9.4 mmol) in dry THF (15 mL) was added dropwise a solution of the corresponding allyl esters **3a** or **3d** (3.77 mmol) in THF (29 mL) at room temperature under nitrogen. The mixture was stirred for 8 h for **6a** and 45 h for **6b**. After the filtrate

was concentrated, the residue was purified by column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant to give the corresponding *N*-carbamate-protected α-amino ketones.

Benzyl *N*-(2-oxopropyl)-carbamate (4a). Colorless prisms after chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (1/1, v/v); mp 76-77 ºC; [lit.[14] 77°C] yield 85%; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 4.08 (d, *J* = 4.7 Hz, 2H), 5.11 (s, 2H), 5.57 (br s, 1H), 7.26–7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.0, 51.1, 66.9, 128.0, 128.1, 128.4, 136.2, 156.0, 202.8.

Benzyl *N*-[(1*S*)-2-oxo-1-benzylpropyl]-carbamate (4b). Colorless prisms after column chromatography on silica gel using a mixture of hexanes/ethyl acetate as eluant (4-2/1, v/v) and recrystallization from ether and hexanes (3/1, v/v); mp 78–79 ºC; [lit.[14] 79.0–80.0°C] yield 86%; $[\alpha]_D^{22}$ = +6.33 º (c 0.0334 g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.04 (dd, *J* = 14.1, 6.1 Hz, 1H, B part of AB quartet of doublets), 3.14 (dd, *J* = 14.0, 6.5 Hz, 1H, A part of AB quartet of doublets), 4.64 (q, *J* = 6.7 Hz, 1H), 5.10 (s, 2H), 5.41 (d, *J* = 6.6 Hz, 1H), 7.09–7.18 (m, 2H), 7.23–7.41 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 27.9, 37.4, 61.0, 66.9, 127.1, 128.0, 128.1, 128.5, 128.7, 129.2, 135.7, 136.2, 155.6, 206.2. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.41; H, 6.48; N, 4.65.

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