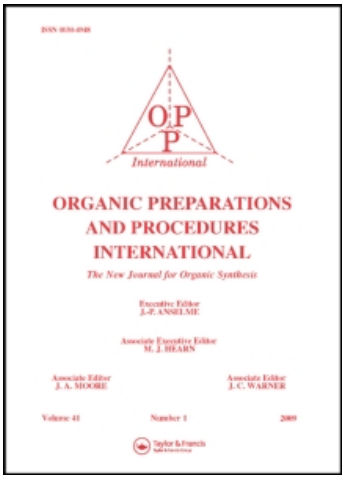

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AN EFFICIENT ONE-POT CONVERSION OF α-AMINO ACID ESTERS TO γ-AMINO-α,β-UNSATURATED CARBOXYLATES

Z. Y. Wei[a]; E. E. Knaus[a]
[a] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, CANADA

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AN EFFICIENT ONE-POT CONVERSION OF α-AMINO ACID ESTERS TO γ-AMINO-α,β-UNSATURATED CARBOXYLATES

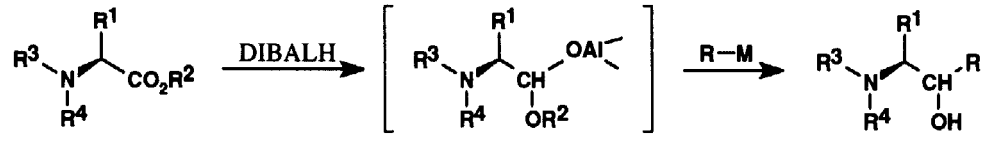
Z. Y. Wei and E. E. Knaus*

Faculty of Pharmacy and Pharmaceutical Sciences
University of Alberta
Edmonton, Alberta, CANADA T6G 2N8

Chiral γ-amino-α,β-unsaturated carboxylates are useful precursors for the synthesis of a variety of biologically important compounds such as -amino acids,[1] pyrrolidines,[2] 2-pyrrolidinones[3] and as synthetic intermediates for the synthesis of natural products.[4] Although chiral γ-amino-α,β-unsaturated carboxylates may be prepared from the corresponding γ-amino acid esters by successive selenation of the enolate, oxidation, and selenoxide elimination,[5] the limited availability of -amino acids detracts from its generality. An alternate synthesis using the Wittig-Horner reaction of the corresponding -amino aldehydes,[6] which may be obtained by a two-step sequence, or direct reduction, from -amino acid esters,[7] is the most efficient and straight forward method for their preparation. However, chiral α-amino aldehydes may undergo racemization due to enolization under a variety of conditions[8] which gives rise to optically impure products..

In order to improve product enantiomeric excess (ee) for syntheses involving chiral α-amino aldehydes, two strategies have been employed. The first strategy, which involves diprotection of the amino group by Boc or benzyl and a second protecting group,[9] did minimize racemization of the α-amino aldehydes although enolization is still possible. A second more attractive strategy involves performing consecutive reactions in a one-pot procedure. Thus, reduction of -amino acid esters (**1**) with DIBALH, followed by direct treatment of the intermediate aluminoxy acetal (**2**) with organometallic reagents, afforded the 2-amino alcohols (**3**) without racemization since the possibility of enolization associated with isolation of the intermediate -amino aldehydes is avoided[10] (Scheme 1). It was envisioned that a similar one-pot strategy could also be utilized for the enantioselective syntheses of γ-amino-α,β-unsaturated carboxylates since α,β-unsaturated esters can be prepared directly from esters.[11]

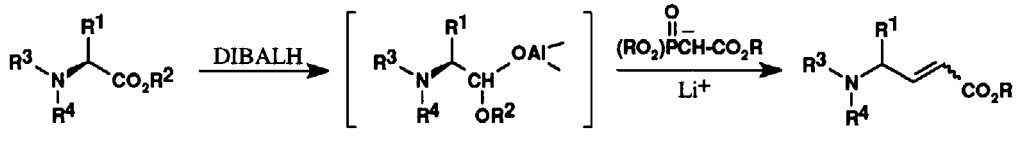
We report here the reaction of N-protected α-amino esters (**1**) with diisobutylaluminum hydride in the presence of a lithium trialkylphosphonoacetate, prepared from a trialkylphosphonoacetate and *t*-butyl lithium, affords N-protected γ-amino-α,β-unsaturated carboxylates (**4**) in high ee (>



1 2 3

Scheme 1

95 to >99%) (Scheme 2). Representative results are shown in Table 1. Thus, DIBALH reduction of N-protected α-amino esters (**1**) in dry THF at -78° presumably affords the intermediate (**2**). The lithium trialkylphosphonoacetate, which is present in the reaction mixture, reacts with the intermediate aluminoxy acetal (**2**) to afford the N-protected γ-amino-α,β-unsaturated carboxylate (**4**). The α,β-unsaturated carboxylate products **4a-e** consisted of a mixture of (E)- and (Z)-stereoisomers where the (E):(Z) ratio varied from 63:37 to 94:6. The (E)- and (Z)-isomers of **4d** were successfully separated by silica gel flash column chromatography.



1 2 4

Scheme 2

The optical purity of the N-protected γ-amino-α,β-unsaturated carboxylates (**4a-c**) was determined by their conversion to, and comparison with, the corresponding chiral γ-lactams reported previously.[3] ^{19}F NMR analysis of the (S)-Mosher's diastereomeric amides of **4d**, which were prepared by removal[12] of the amino protecting group and coupling with (R)-Mosher's acid chloride,[13] indicated that the enantiomeric excess of **4d** was > 95%. The optical purity of **4e** was determined by ^1H NMR analysis of the diastereomeric ureides prepared by reaction with (R)-1-phenylethyl isocyanate.[14]

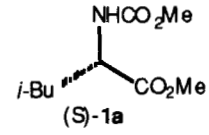
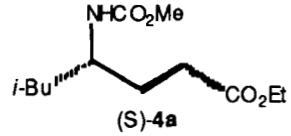
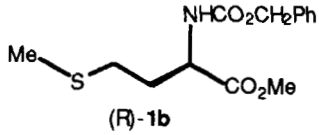
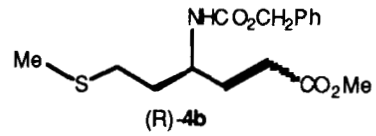
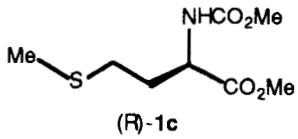
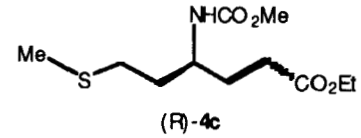
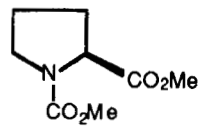
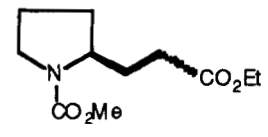
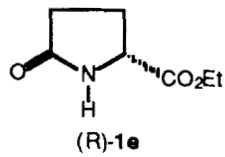
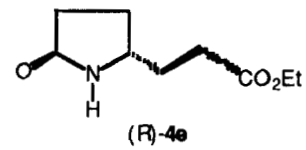
In summary, an efficient procedure has been developed for the synthesis of N-protected γ-amino-α,β-unsaturated carboxylates from N-protected -amino acid esters. This method afforded the target compounds **4** in good chemical yields (54-76%) and high ee (> 95 to >99% ee) which indicates that racemization does not occur, or is minimal, in this one-pot procedure.

EXPERIMENTAL SECTION

All moisture-sensitive reactions were carried out under a positive pressure of nitrogen gas. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl. DIBALH, trimethyphosphonoacetate, triethylphosphonoacetate and ethyl (R)-(-)-2-pyrrolidone-5-carboxylate (**1e**) were purchased from the Aldrich Chemical Co. The N-protected -amino esters (**1a-d**) were prepared from (S)-(+)-leucine (**1a**), (R)-(-)-methionine (**1b-c**) and (S)-(-)-proline (**1d**) using a literature procedure.[15] Nuclear

magnetic resonance spectra (^{1}H NMR, ^{13}C NMR) were acquired on a Bruker AM-300 spectrometer. Infrared spectra were recorded using a Nicolet 5DX FT spectrometer, and only selected absorptions are reported. Optical rotations were obtained using a Optical Activity Ltd polarimeter at 25°.

Table 1. Synthesis of Chiral N-Protected γ-amino-α,β-unsaturated Esters

1	4	Yield, % (E:Z ratio)	ee, %
 (S)-**1a**	 (S)-**4a**	65 (80:20)	> 99
 (R)-**1b**	 (R)-**4b**	68 (65:35)	> 97
 (R)-**1c**	 (R)-**4c**	62 (80:20)	98
 (S)-**1d**	 (S)-**4d**	76 (63:37)	> 95
 (R)-**1e**	 (R)-**4e**	54 (96:4)	> 99

General Procedure for the Preparation of γ-Amino-α,-unsaturated Carboxylates (4).- A solution of *t*-butyl lithium in hexane (6.5 mL of a 1.7 M solution, 11.0 mmol) was added dropwise to a solution of the trialkylphosphonoacetate (11.0 mmol) in THF (50 mL) at -78°. After stirring for 30 min, a solution of the -amino acid ester (**1**, 10.0 mmol) in THF (10 mL) and then a solution of DIBALH in toluene (13 mL of a 1.5 M solution, 19.5 mmol) was added. The resulting mixture was stirred for 5 hrs at -78° prior to warming to 25°. Water (10 mL) and then 2N hydrochloric acid (20 mL) was added, the organic layer was separated, and the aqueous mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic fractions were washed with saturated brine, the organic fraction was dried ($MgSO_4$), filtered, and the solvent was removed in *vacuo*. The products were purified by silica gel flash chromatography to yield the γ-amino-α,β-unsaturated carboxylates (**4**).

Ethyl (4S)-4-(methoxycarbonylamino)-6-methyl-2-heptenoate(4a).- Reaction of **1a** (2.03 g, 10 mmol) with triethyl phosphonoacetate (2.47 g, 11.0 mmol) / *t*-butyl lithium (11.0 mmol) and DIBALH (19.5 mmol) as described in the general procedure, and purification of the product by silica gel flash column chromatography using ethyl acetate:hexane (15:85, v/v) as eluent, afforded **4a** as a colorless oil (E:Z ratio = 80:20, 1.58 g, 65%); $[\alpha]_D$ = -27.0° (c 16, MeOH); IR (film): 3346 (m), 3022 (s), 2875 (m), 1715 (s), 1657 (m), 1510 (m), 1216 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (E) and 0.97 (Z) (two d, *J* = 6.6 Hz, 6H total), 1.29 (E) and 1.30 (Z) (two t, *J* = 7.1 Hz, 3H total), 1.41 (m, 2H), 1.70 (m, 1H), 3.65 (Z) and 3.68 (E) (two s, 3H total), 4.19 (E) and 4.20 (Z) (two q, *J* = 7.1 Hz, 2H total), 4.39 (m, 0.8H, E), 4.91 (E) and 5.20 (Z) (two br s, H total), 5.20 (m, 0.2H, Z), 5.77 (d, *J* = 11.5 Hz, 0.2H, Z), 5.93 (dd, *J* = 15.6, 1.3 Hz, 0.8H, E), 6.05 (m, 0.2H, Z), 6.83 (dd, *J* = 15.6, 5.7 Hz, 0.8H, E); ^{13}C NMR ($CDCl_3$): δ 14.0, 21.5 (Z), 21.8, 22.5, 22.9 (Z), 24.4, 43.1 (Z), 43.3, 47.7 (Z), 50.1, 51.9, 60.0 (Z), 60.2, 119.4 (Z), 120.3, 148.4, 149.6 (Z), 156.3, 165.5 (Z), 166.2.

Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.22; H, 8.70; N, 5.76. Found: C, 59.49; H, 8.57; N, 5.77

Methyl (4R)-4-(benzyloxycarbonylamino)-6-methylthio-2-hexenoate(4b).- Treatment of **1b** (1.49 g, 5.0 mmol) with trimethyl phosphonoacetate (1.0 g, 5.5 mmol) / *t*-butyl lithium (5.5 mmol) and DIBALH (10.0 mmol) as described in the general procedure, and purification of the product by silica gel flash column chromatography using ethyl acetate:hexane (20:80, v/v) as eluent, afforded **4b** as a colorless oil (E:Z ratio = 65:35, 1.10 g, 68%); $[\alpha]_D$ = +15.8° (c 14.6, $CHCl_3$); IR (film): 3339 (m), 3030 (w), 2952 (m), 2917 (m), 1722 (s), 1701 (s), 1659 (m), 1511 (m), 1441 (m), 1223 (m), 1047 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.80 (m, 2H), 2.04 (E) and 2.06 (Z) (two s, 3H total), 2.45 (m, 2H), 3.69 (s, 3H), 4.44 (m, 0.65H, E), 5.05 (E) and 5.07 (Z) (two s, 2H total), 5.20 (m, 0.35 H, Z), 5.3-5.7 (m, 1H), 5.79 (d, *J* = 10.8 Hz, 0.35H, Z), 5.94 (d, *J* = 15.6 Hz, 0.65H, E), 6.10 (m, 0.35H, Z), 6.82 (dd, *J* = 15.6, 5.3 Hz, 0.65H, E), 7.30 (m, 5H).

Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.59; H, 6.60; N, 4.36

Ethyl (4R)-4-(methoxycarbonylamino)-6-methylthio-2-hexenoate(4c).- Treatment of **1c** (2.21 g, 10 mmol) with triethyl phosphonoacetate (2.47 g, 11.0 mmol) / *t*-butyl lithium (11.0 mmol) and DIBALH (19.5 mmol) as described in the general procedure, and purification of the product by silica gel flash column chromatography using ethyl acetate:hexane (20:80, v/v) as eluent, afforded **4c** as a colorless oil (E:Z ratio = 80:20, 1.62 g, 62%); $[\alpha]_D$ = +19.6° (c 14.2, $CHCl_3$); IR (film): 3339 (m), 2959 (m), 2917 (m), 1715 (s), 1659 (m), 1511 (m), 1448 (m), 1370 (m), 1279 (m), 1195 (m), 1047 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27 (E) and 1.29 (Z) (two t, *J* = 7.2 Hz, 3H total), 1.88 (m, 2H), 2.11 (s, 3H), 2.55 (m, 2H), 3.63 (Z) and 3.68 (E) (two s, 3H total), 4.19 (q, *J* = 7.2 Hz, 2H), 4.46 (m, 0.8H, E), 5.14 (Z) and 5.35 (E) (two d, *J* = 8.5 Hz, 1H total), 5.55 (m, 0.2H, Z), 5.80 (d, *J* = 11.5 Hz, 0.2H, Z), 5.96 (dd, *J* = 15.6, 1.6 Hz, 0.8H, E), 6.14 (m, 0.2H, Z), 6.85 (dd, *J* = 15.6, 5.6 Hz, 0.8H, E); ^{13}C NMR ($CDCl_3$): δ 14.0, 15.3, 30.1, 33.6, 49.1, 51.3, 60.3, 121.3, 147.0, 156.2, 165.9.

Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.56; H, 7.33; N, 5.36. Found: C, 50.21; H, 7.38; N, 5.33

(2S)-1-(Methoxycarbonyl)-2-(2-ethoxycarbonylvinyl)-pyrrolidine (4d).- Treatment of **1d** (0.94 g, 5.0 mmol) with triethyl phosphonoacetate (1.24 g, 5.5 mmol) / *t*-butyl lithium (5.5 mmol) and

DIBALH (6.0 mmol) as described in the general procedure, and purification of the product by silica gel flash column chromatography using ethyl acetate:hexane (15:85, v/v) as eluent, afforded (Z)-**4d** (0.32 g) and (E)-**4d** (0.54 g) as colorless oils (E:Z ratio = 63:37, 76%); (Z)-**4d,** $[\alpha]_D$ = -20.1° (c 1.1, $CHCl_3$); IR (film): 3023 (m), 2988 (w), 1687 (s), 1455 (s), 1384 (s), 1209 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.67 (m, 1H), 1.82 (m, 2H), 2.30 (m, 1H), 3.42 (m, 2H), 3.61 (s, 3H), 4.13 (q, *J* = 7.1 Hz, 2H), 5.26 (m, 1H), 5.71 (d, *J* = 11.4 Hz, 1H), 6.14 (m, 1H).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.49; H, 7.84; N, 6.16

(E)-**4d**; $[\alpha]_D$ = -17.6° (c 2.6, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.24 (t, *J* = 6.8 Hz, 3H), 1.84 (m, 3H), 2.03 (m, 1H), 3.42 (m, 2H), 3.62 and 3.65 (both s, 3H total), 4.13 (q, *J* = 6.8 Hz, 2H), 4.44 (m, 1H), 5.76 and 5.80 (two d, *J* = 15.5 Hz, 1H total), 6.78 (dd, *J* = 15.5, 4.8 Hz, 1H).

Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.01; H, 7.57; N, 6.11

(5R)-5-(2-Ethoxycarbonylvinyl)-2-pyrrolidinone (4e).- Treatment of **1e** (0.79 g, 5.0 mmol) with triethyl phosphonoacetate (1.24 g, 5.5 mmol) / *t*-butyl lithium (5.5 mmol) and DIBALH (10.0 mmol) as described in the general procedure, and purification of the product by silica gel flash column chromatography using methanol:ethyl acetate (2:98, v/v) as eluent, afforded **4e** as a colorless oil (E:Z ratio = 94:6, 0.49 g, 54%); $[a]_D$ = -11.5° (c 3.5, $CHCl_3$); IR (film): 3438 (m), 3029 (m), 2938 (m), 1708 (s), 1644 (s), 1518 (m) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (E) and 1.23 (Z) (t, *J* = 7.1 Hz, 3H total), 1.78 (m, 1H), 2.26 (m, 3H), 4.08 (q, *J* = 7.1 Hz, 2H), 4.24 (m, 0.96H, E), 5.17 (m, 0.04H, Z), 5.73 (dd, *J* = 11.5, 1.0 Hz, 0.04H, Z), 5.87 (dd, *J* = 15.5, 1.3 Hz, 0.96H, E), 6.09 (dd, *J* = 11.5, 8.2 Hz, 0.04H, Z), 6.78 (dd, *J* = 15.5, 6.0 Hz, 0.96H, E), 7.70 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 26.9, 27.4 (Z), 29.4, 29.8 (Z), 51.7 (Z), 54.5, 60.1 (Z), 60.3, 120.9, 147.1, 149.2 (Z), 165.7, 178.7.

Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.79; H, 7.25; N, 7.52

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