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A Regioselective Tandem Reduction — Wittig-Horner Reaction Involving the α-Ester Moiety of Diethyl Aspartate or Glutamate

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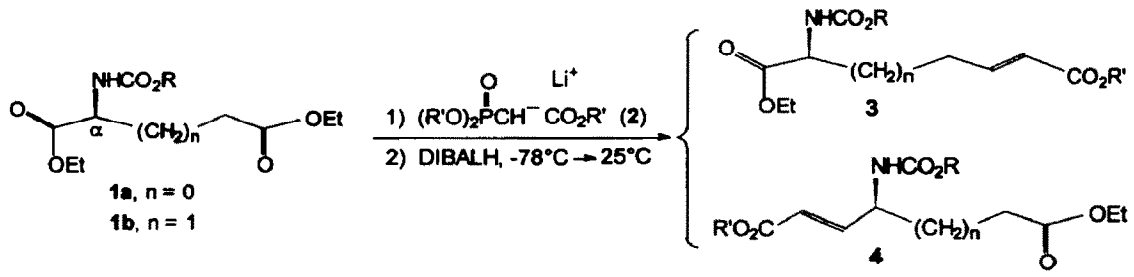
Abstract. The α-ester group of N-protected diethyl aspartate (**1a**) or diethyl glutamate (**1b**) was selectively reduced using diisobutylaluminum hydride (DIBALH) in the presence of a lithium trialkylphosphonoacetate (**2**) to afford N-protected γ-amino-α,β-unsaturated dicarboxylates (**4**).

α-Amino acids constitute a valuable natural source of chiral substrates for use in asymmetric syntheses.[1,2] These natural L-α-amino acids have been employed as synthetic reagents using a diverse array of reactions. However, syntheses utilizing dicarboxylic acids such as aspartic acid or glutamic acid are frequently complicated due to the presence of the two different carboxyl groups. Therefore, selective protection of the two carboxyl groups is often necessary. For example, a strategy for the synthesis of non-proteinogenic α-amino acids starting from L-glutamic acid[3] or L-aspartic acid[4] encompassed selective esterification of the two carboxyl groups prior to a β- or γ-regioselective Aldol-reaction. This regioselectivity was due to the different reactivities of the α-ester, and β- or γ-ester, moieties which was attributed to the different steric effects induced by the respective ester groups.

An efficient methodology[5] for the synthesis of chiral N-protected γ-amino-α,β-unsaturated carboxylates was recently developed. This one-pot procedure afforded the target compounds starting from chiral N-protected α-amino acid esters without loss of optical purity. This methodology has now been applied to L-diethyl aspartate (**1a**) and L-diethyl glutamate (**1b**) (Scheme 1) which affords the γ-amino-α,β-unsaturated dicarboxylates (**4**)[6] as the exclusive, or major, product, respectively. Some examples that illustrate this reaction are shown in Table 1. Thus, reaction of diethyl N-methoxycarbonylaspartate (**1a**, R = Me) with DIBALH in the presence of lithium triethylphosphonoacetate gave **4a** as the exclusive product resulting from reduction and olefination of the α-ester moiety. Similar reactions employing diethyl N-alkoxycarbonylglutamates (**1b**, R = Me, *t*-Bu) gave **4b-d** as the major product together with the minor isomer **3** resulting from reaction of the γ-ester group (ratio **4**:**3** ≥ 13:1). The larger N-*t*-butoxycarbonyl protecting group decreased regioselectivity (**4d**:**3d** ≥ 13:1) relative to the smaller N-methoxycarbonyl substituent (**4b**:**3b** ≥ 40:1). In a typical procedure, a solution of *t*-butyl lithium in hexane (3.3 mL of a 1.7 M solution, 5.6 mmol) was added dropwise to a solution of triethylphosphonoacetate (5.5 mmol) in THF (30 mL) at -78°C. After stirring for 30 min, a solution of diethyl N-methoxycarbonylaspartate (**1a**, 1.24 g, 5.0 mmol) in THF (5 mL) and then a solution of DIBALH in toluene (6 mL of a 1.5 M solution, 9.0 mmol) were added. The resulting mixture was stirred for 5 hr at -78°C prior to warming to 25°C. Water (10 mL) and then 2N hydrochloric acid (10 mL) was added, the organic layer was separated, and the aqueous mixture was extracted with ethyl acetate (3 x 50 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 product was purified by silica gel flash column chromatography to yield the γ-amino-α,β-unsaturated dicarboxylate (**4a**, 0.85 g, 62%).



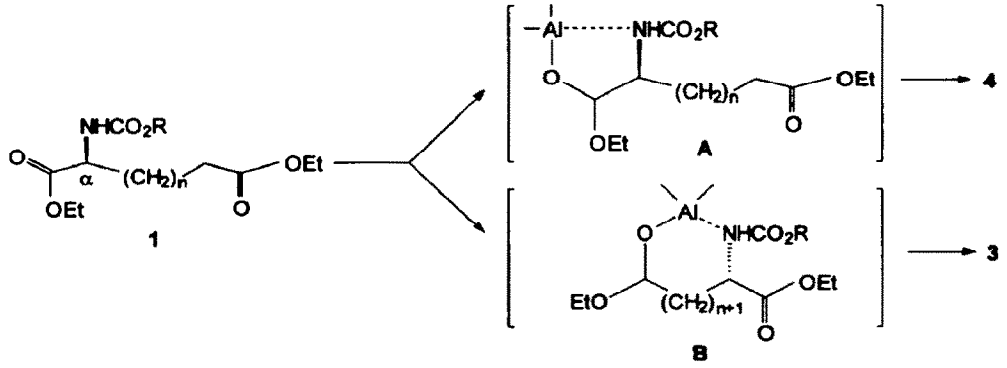
Scheme 1

Table 1. Synthesis of Dialkyl N-alkoxycarbonyl-α,β-unsaturated dicarboxylates (**3, 4**).

Entry	1	2	Ratio 4:3	Yield 4, %
1	n = 0, R = Me	R' = Et	100:0	62 (**4a**)
2	n = 0, R = Me	R' = Et	> 40:1	74 (**4b**)
3	n = 1, R = Me	R' = Me	> 20:1	58 (**4c**)
4	n = 1, R = *t*-Bu	R' = Et	> 13:1	66 (**4d**)

γ-Amino-α,β-unsaturated dicarboxylates (**4**) are likely formed by the Wittig-Horner reaction of the intermediate aluminoxy acetal (**A**) resulting from the regioselective reduction of the α-ester group of **1**, whereas the isomer **3** likely arises via the intermediate aluminoxy acetal (**B**) resulting from reduction of the γ-ester group of **1** (Scheme 2). Although the low temperature reduction of an ester substituent to an aldehyde using DIBALH is a routine reaction, it is difficult to achieve regioslective reduction when more than one ester group is present. One rare example of this controlled chemoselectivity by a steric effect involved a methyl ester which was selectively reduced, in the presence of a *t*-butyl ester, to the corresponding aldehyde using DIBALH.[7]

In the case of the diethyl dicarboxylates (**1**), the α-ester group is more sterically hindered than the β- (**1a**) or γ- (**1b**) ester group. The regioselective reduction of the α-ester group of **1a-b** using DIBALH may be explained by the chelation-controlled transition states **C** and **D** (Figure 1). Since aluminum has a large atomic radius, it is more likely to form a quasi-five-membered ring chelation complex **C**, which would result in preferential reduction of the α-ester group via intermediate aluminoxy acetal **A**, relative to a quasi six- or seven-membered ring chelation complex **D** that would result in the reduction of the β- (**1a**) or γ-ester (**1b**) group to form the intermediate aluminoxy acetal **B**.



Scheme 2

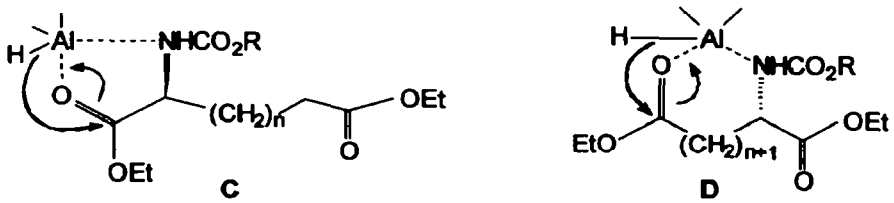
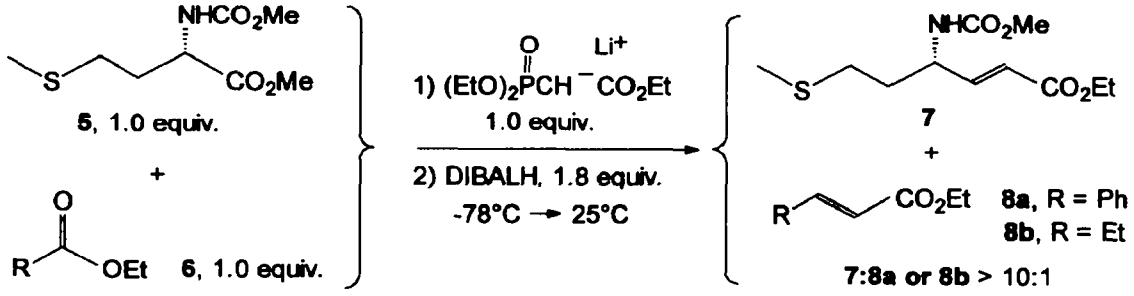
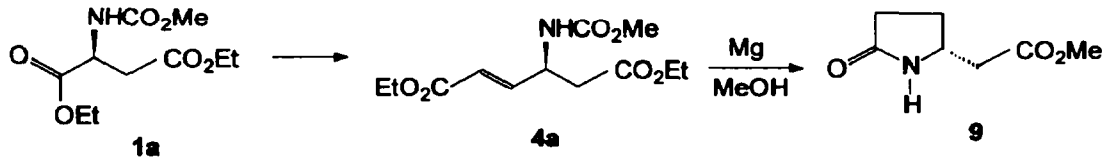


Figure 1. Quasi-ring chelation complexes.



Scheme 3

To our knowledge, this is the first example[8] for the regioselective reduction of one ester group in the presence of a second ester group using DIBALH. This facile regioselective reduction of the α-ester moiety appears to be quite general. For example, a competition experiment showed that the α-amino ester (**5**) was selectively reduced to provide the γ-amino-α,β-unsaturated ester (**7**) in the presence of a second ester compound (**6**) (Scheme 3) which increases the synthetic utility of this reaction. Furthermore, the γ-lactam (**9**) which is a useful synthetic intermediate[9], was synthesized in two steps from diethyl N-methoxycarbonylaspartate (**1a**) in 54% overall yield (**1a** → **4a**, 62%, **4a** → **9**, 87%) as illustrated in Scheme 4.



Scheme 4

ACKNOWLEDGEMENTS. We are grateful to the Medical Research Council of Canada for financial support of this research (Grant No. MT-4888) and the Pharmaceutical Manufacturers Association of Canada and the Medical Research Council of Canada for a joint fellowship to one of us (Z.W.).

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6. NMR and microanalytical data for compounds (**4**):

   4a; oil; ^{1}H NMR ($CDCl_3$) δ: 1.06 (t, J=7.2 Hz, 3H), 1.09 (t, J=7.2 Hz, 3H), 2.50 (d, J=6.0 Hz, 2H), 3.48 (s, 3H), 3.96 (q, J=7.2 Hz, 2H), 3.99 (q, J=7.2 Hz, 2H), 4.57 (m, 1H), 5.80 (dd, J=15.8, 1.7 Hz, 1H), 5.92 (d, J=8.1 Hz, 1H), 6.72 (dd, J=15.8, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.6, 13.7, 38.1, 48.3, 51.6, 60.0, 60.3, 121.2, 145.9, 155.8, 165.5, 169.9. Anal. Calcd. for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.50; H, 6.94; N, 5.03.

   4b; oil; ^{1}H NMR ($CDCl_3$) δ: 1.18 (t, J=7.2 Hz, 3H), 1.21 (t, J=7.2 Hz, 3H), 1.7-1.95 (m, 2H), 2.34 (t, J=7.3 Hz, 2H), 3.59 (s, 3H), 4.06 (q, J=7.2 Hz, 2H), 4.11 (q, J=7.2 Hz, 2H), 4.30 (m, 1H), 5.41 (br s, 1H), 5.87 (dd, J=15.6, 1.4 Hz, 1H), 6.77 (dd, J=15.6, 5.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 29.0, 30.4, 51.5, 52.0, 60.3, 60.5, 121.3, 147.0, 156.3, 165.9, 172.8. Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 53.95; H, 7.29; N, 4.70.

   4c; oil; ^{1}H NMR ($CDCl_3$) δ: 1.24 (t, J=7.2 Hz, 3H), 1.78-2.02 (m, 2H), 2.39 (t, J=7.4 Hz, 2H), 3.66 (s, 3H), 3.72 (s, 3H), 4.12 (q, J=7.2 Hz, 2H), 4.36 (m, 1H), 5.12 (m, 1H), 5.94 (dd, J=15.6, 1.5 Hz, 1H), 6.83 (dd, J=15.6, 5.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.1, 29.0, 30.5, 51.6, 52.2, 60.7, 121.0, 147.3, 156.3, 166.4, 172.9. Anal. Calcd. for $C_{12}H_{19}NO_6$.0.25 H_2O: C, 51.88; H, 6.98; N, 5.04. Found: C, 51.94, H, 7.06; N, 4.98.

   4d; oil; ^{1}H NMR ($CDCl_3$) δ: 1.26 (t, J=7.2 Hz, 3H), 1.29 (t, J=7.2 Hz, 3H), 1.44 (s, 9H), 1.84 (m, 1H), 1.98 (m, 1H), 2.39 (t, J=7.4 Hz, 2H), 4.14 (q, J=7.2 Hz, 2H), 4.19 (q, J=7.2 Hz, 2H), 4.32 (m, 1H), 4.65 (br d, J=9.0 Hz, 1H), 5.92 (dd, J=15.8, 1.6 Hz, 1H), 6.83 (dd, J=15.8, 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.1, 28.2, 29.2, 30.5, 51.0, 60.1, 60.3, 79.6, 121.1, 147.4, 155.1, 166.0, 172.8. Anal. Calcd. for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.28; H, 8.29; N, 4.11.

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