# A Convenient Differential Protection Strategy for Functional Group Manipulation of Aspartic and Glutamic Acids

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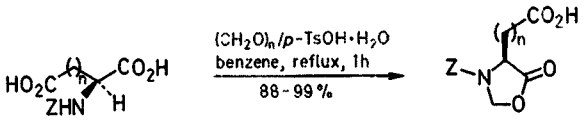
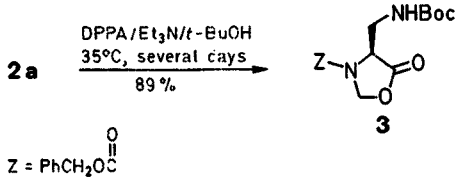
Procedures are provided for selective protection of the α-carboxyl groups of aspartic and glutamic acids via the 5-oxazolidinones **2**. A convenient synthesis of a differentially protected derivative of (*S*)-2,3-diaminopropanoic acid, **3**, is described, along with examples of selective manipulation of the γ-carboxyl group of glutamic acid.

The differential protection of α-amino acids with side chains containing either amino or carboxy functional groups can involve difficult and tedious manipulations. Previous strategies for simultaneous protection of α-amino acids have included copper(II) complexes[1,2] and oxazaborolidones.[3] Use of the *N*-benzyloxycarbonyl-5-oxazolidinone moiety, as first described by Ben-Ishai[4] and illustrated for aspartic and glutamic acids **2**, provides a simple and reliable method of achieving this goal.[5,6] Starting with the commercially available *N*-benzyloxycarbonyl-(L)-aspartic acid (**1a**) or -glutamic acid (**1b**), the crystalline 5-oxazolidinones **2** can be prepared in high yield with paraformaldehyde and a catalytic amount of *p*-toluenesulfonic acid with azeotropic removal of water.[4,6] In this report, we describe the combination of this protection strategy with the modified Curtius-type degradation using diphenyl phosphoroazidate [DPPA; $(PhO)_2P(O)N_3$][7] for a convenient and high yielding route to the differentially protected 2,3-diaminopropanoate derivative **3**. Additional examples of selective transformations of the γ-carboxyl group of glutamate are also provided.

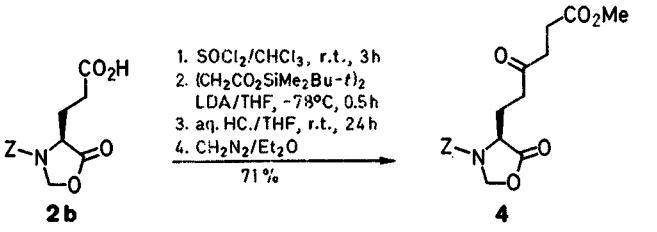


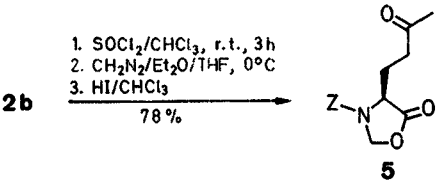



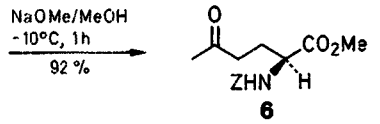

(*S*)-2,3-Diaminopropanoic acid (DAP) is a constituent amino acid of a number of peptidyl antibiotics, including edeines,[8] tuberactinomycins,[9] and some clinically useful bleomycins,[10] as well as the cytostatic cyclic tetrapeptide chlamydocin.[11] DAP has also been used in the synthesis of ethylenediaminetetraacetic acid (EDTA) analogues,[12] 2,8-diaminopurines,[13] 4-unsubstituted monocyclic β-lactams,[14] analogues of asparagine[15] and methotrexate,[16] and as a precursor to didehydroalanine-containing peptides.[17]

As an example fo the synthetic utility of **2a**, the differentially protected 2,3-diaminopropanoic acid derivative **3** is formed directly using a modified Curtius-type rearrangement under mild conditions with diphenyl phosphoroazidate DPPA and triethylamine in *tert*-butyl alcohol.[7,18] This route offers advantages over previously described syntheses[11,15,19] of analogous derivatives in convenience and number of steps as well as in yield. Compound **3** is formed in this sequence without any evidence of racemization, as demonstrated by conversion to the Mosher amides.[20]

The side chain carboxyls of the protected derivatives **2** can also be manipulated in a variety of ways without the interference of either the α-amino or α-carboxyl groups. In addition to conventional diimide coupling reactions, the ω-carboxyl groups of **2a** and **2b** can be converted to the acid chlorides and utilized in Grignard[21] or enolate acylation reactions. This is particularly convenient in the case of **2b**, since cyclization to the pyroglutamate derivative is precluded. As an example, **2b** was converted to the γ-acid chloride and acylated with the enolate derived from bis(*tert*-butyldimethylsilyl) succinate. After desilylation and decarboxylation, the γ-ketoacid derivative **4** was formed exclusively, with no evidence of reaction at the oxazolidinone carbonyl.




The oxazolidinone moiety is stable to trifluoroacetic acid under conditions for removal of *tert*-butoxycarbonyl protecting groups. On removal of the benzyloxycarbonyl group by hydrogenolysis, the oxazolidinone decomposes, and the free α-amino acid is liberated.[5] Alternatively, the oxazolidinone can be treated with an alcohol under alkaline conditions to form the α-benzyloxycarbonylamino, α-alkyl ester, as shown above in the synthesis of methyl ketone **6**. The oxazolidinone **2b** is converted to the acid chloride, homologated with diazomethane and reduced with hydrogen iodide[22] to form the methyl ketone **5**. Cleavage of the oxazolidinone with sodium methoxide/methanol at −10°C affords the methyl ester **6**.

Benzene, $Et_3N$, *i*-$Pr_2NH$, and *t*-BuOH were distilled from $CaH_2$ and used immediately or stored over 4Å molecular sieves under nitrogen. THF and $Et_2O$ were distilled from Na/benzophenone. All other reagents were used as obtained commercially. Gaseous nitrogen was dried by passage over Drierite and potassium hydroxide columns. Molecular sieves were activated prior to use by heating to 150°C at 0.2 Torr for 18 h, and were stored under vacuum. IR spectra were obtained in $CHCl_3$ and NMR spectra in $CDCl_3$.

Unless otherwise indicated, reaction work-ups culminated in washing the organic layer with 5% aq. $NaHCO_3$, $H_2O$, 0.5 N HCl, and brine, drying over $MgSO_4$, and evaporating the solvent under reduced pressure. Chromatography refers to silica gel chromatography as described by Still, Kahn, and Mitra.[23]

**(*S*)-3-Benzylcarbonyl-5-oxo-4-oxazolidineacetic Acid (2a):**
A mixture containing N-benzyloxycarbonyl-L-aspartic acid (26.7 g, 100 mmol), paraformaldehyde (6.0 g, 200 mmol), and *p*-TsOH · $H_2O$ (1.2 g, 6 mmol) in benzene (750 mL) is heated at reflux for 60 min, with removal of water with a Dean-Stark trap. EtOAc (100 mL) is added, the solution is washed with 0.3 M aq. $K_2CO_3$ (10 mL) and $H_2O$ (3 × 10 mL) and dried ($MgSO_4$), and the solvent is evaporated to give a colorless syrup which crystallizes on standing overnight at 0 °C. The product is isolated as a white solid in 94–99% yield, mp 85–87 °C; recrystallized from EtOAc (85–90% recovery) provided a sample for analytical characterization: mp 87–88.5 °C; $[\alpha]_D^{23} = +125.7°$ ($c$ = 3.53, MeOH); (Lit.[5] oil).

| | | | | |
|---|---|---|---|---|
| $C_{13}H_{13}NO_6$ | calc. | C 55.91 | H 4.69 | N 5.01 |
| (280.3) | found | 55.85 | 4.68 | 4.99 |

IR: $\nu$ = 3500–2600, 3010, 1805, 1720, 1510, 1450, 1410, 1135 $cm^{-1}$.

$^1$H-NMR: $\delta$ = 3.05–3.15 (m, 1 H, $H_\alpha$); 3.25–3.35 (m, 1 H, $H_\alpha$); 4.36 (dd, 1 H, $J$ = 5.84, 5.81, H-4); 5.19 (s, 2 H, $PhCH_2$); 5.30 (d, 1 H, $J$ = 3.4, H-2); 5.55 (br s, 1 H, H-2), 7.37 (s, 5 H, ArH).

$^{13}$C-NMR: $\delta$ = 34.1, 51.3, 68.1, 78.2, 128.3, 128.6, 135.0, 152.7, 171.5, 174.9, 178.2.

**(*S*)-3-Benzyloxycarbonyl-5-oxo-4-oxazolidinepropanoic Acid (2b):**
The glutamate homolog **2b** is prepared in an analogous manner from *N*-benzyloxycarbonyl-L-glutamic acid in 88–94% yield: mp 68–69 °C; $[\alpha]_D^{23} = +78.4°$ ($c$ = 3.05, MeOH); (Lit.[5,6] oil; $[\alpha]_D^{25} = +77.6°$ ($c$ = 1.0, MeOH)[6]).

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{15}NO_6$ | calc. | C 57.33 | H 5.15 | N 4.77 |
| (294.4) | found | 57.15 | 5.12 | 4.74 |

IR: $\nu$ = 3400–2600, 3015, 1805, 1720, 1505, 1460, 1400, 1130 $cm^{-1}$.

$^1$H-NMR: $\delta$ = 2.15–2.40 (m, 2 H, $H_\alpha$); 2.40–2.55 (m, 2 H, $H_\beta$); 4.39 (dd, 1 H, $J$ = 5.86, 5.80, H-4); 5.18 (s, 2 H, $PhCH_2$); 5.22 (d, 1 H, $J$ = 4.59, H-2); 5.73 (br s, 1 H, H-2); 7.36 (s, 5 H, ArH).

$^{13}$C-NMR: $\delta$ = 25.8, 29.3, 53.9, 68.2, 77.8, 128.3, 128.6, 135.1, 153.1, 171.7.

**(*S*)-3-Benzyloxycarbonyl-4-[(*N*-*tert*-butoxycarbonyl)aminomethyl]-5-oxazolidinone (3):**
A solution of the aspartate derivative **2a** (1.92 g, 6.89 mmol) in distilled *t*-BuOH (40 mL) is stirred under an atmosphere of nitrogen. DPPA (1.49 mL, 6.89 mmol) and distilled $Et_3N$ (0.96 mL, 6.89 mmol) are added, and the solution is heated to 35 °C for 2 h. At this point, the conversion to the isocyanate is essentially complete. The reaction mixture is allowed to stir for several days at 35 °C to permit the isocyanate to react with *t*-BuOH. The disappearance of the isocyanate infrared peak at 2260 $cm^{-1}$ is used to monitor this reaction. The solvent is removed by evaporation at reduced pressure, and the residue is partitioned between $CHCl_3$ (200 mL) and 5% aq. $NaHCO_3$ (100 mL). The organic layer is worked up to give 2.16 g (89%) of analytically pure **3** as a colorless oil: $[\alpha]_D^{23} + 11.8°$ ($c$ = 3.46, MeOH).

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|---|---|---|---|---|
| $C_{17}H_{22}N_2O_6$ | calc. | C 58.27 | H 6.32 | N 7.99 |
| (351.7) | found | 58.41 | 6.27 | 7.99 |

IR: $\nu$ = 3480, 3020, 2995, 1805, 1725, 1420 $cm^{-1}$.

$^1$H-NMR: $\delta$ = 1.40 (s, 9 H, *t*-$C_4H_9$); 3.48–3.62 (m, 1 H, $H_\alpha$); 3.62–3.95 (m, 1 H, $H_\alpha$); 4.28 (dd, 1 H, $J$ = 5.4, 5.2, H-4); 5.19 (s, 2 H, $PhCH_2$); 5.22 (d, 1 H, $J$ = 4.6, H-2); 5.40 (br s, 1 H, H-2); 5.50 (br s, 1 H, NH); 7.35 (s, 5 H, ArH).

$^{13}$C-NMR: $\delta$ = 28.1, 40.3, 55.5, 67.8, 78.2, 79.9, 128.2, 128.5, 135.3, 152.4, 155.7, 170.9.

**Mosher Amide Derivatives of 3:**
The stereochemical integrity of the 2,3-diaminopropanoic acid derivative **3** was determined by forming the diastereomeric Mosher amide derivatives. Oxazolidinone **3** is cleaved with NaOMe in MeOH to give the methyl ester[11] in the same manner as that described below in the synthesis of **6**. The α-amino compound[11] is formed by hydrogenolytic removal of the benzyloxycarbonyl moiety under standard conditions. Separate acylation with the *R*(+)- and *S*(−)-Mosher acid chlorides under the prescribed conditions[17] affords samples of both diastereomeric amides, which are demonstrated by both $^1$H- and $^{19}$F-NMR to be uncontaminated with each other.

*R*(+)-Amide: $^1$H-NMR (250 MHz: $\delta$ = 3.40 (OMe).

$^{19}$F-NMR (236 MHz, $CFCl_3/CDCl_3$, sealed capillary): $\delta$ = −69.42 ($CF_3$).

*S*(−)-Amide: $^1$H-NMR (250 MHz): $\delta$ = 3.37 (OMe).

$^{19}$F-NMR (236 MHz, $CFCl_3/CDCl_3$, sealed capillary): $\delta$ = −69.22 ($CF_3$); these resonances are readily distinguished in an authentic 1:1 mixture of the two diastereoisomers.

**Methyl (*S*)-3-Benzyloxycarbonyl-γ,5-dioxo-4-oxazolidinehexanoate (4):**
A solution of glutamate derivative **2b** (680 mg, 2.32 mmol) in ethanol-free $CHCl_2$ (10 mL) is treated with $SOCl_2$ (0.21 mL, 2.90 mmol) with stirring at r.t. After 3 h, the volatile materials are removed under vacuum, and the residue is dissolved in $CHCl_3$ and reevaporated to remove traces of $SOCl_2$. THF (5 mL) is added, and the solution is cooled to −78 °C with stirring under an atmosphere of $N_2$.

In a separate flask, bis(*tert*-buyldimethylsilyl) succinate (1.69 g, 5.00 mmol) is added to a solution of LDA (5.05 mmol of *i*-$Pr_2NH$ and 3.45 mL of a 1.48 M solution of *n*-BuLi in hexanes) in THF (20 mL) at −78 °C under an atmosphere of $N_2$. The enolate is allowed to warm to −40 °C over 20 min and then cooled back to −78 °C and cannulated into the solution of acid chloride over 30 min. The reaction is stirred at −78 °C for 30 min, warmed to −40 °C over an additional 30 min, and quenched with a solution of THF/0.5 N HCl (10 mL, 4:1). The resulting solution is partitioned between EtOAc (100 mL) and 1 N HCl (50 mL), and the aqueous layer is washed with additional EtOAc. The organic layers are combined, washed with brine, and dried ($Na_2SO_4$), and the solvent is removed under reduced pressure, and the resulting oil is dissolved in THF (10 mL). The desilylation and decarboxylation are accomplished by stirring the crude product with a solution of THF/0.5 N HCl (10 mL, 4:1) for 24 h. The acid is isolated after a standard aqueous work-up as an oil; yield: 576 mg (71%). For characterization the methyl ester **4** is prepared quantitatively by treating a solution of the acid in $Et_2O$ with diazomethane in $Et_2O$: mp 72–73 °C.

| | | | | |
|---|---|---|---|---|
| $C_{18}H_{21}NO_7$ | calc. | C 59.49 | H 5.82 | N 3.87 |
| (582.6) | found | 59.25 | 5.60 | 3.99 |

IR: $\nu$ = 3020, 2990, 1720, 1710, 1480, 1420, 1300, 1280, 1140, 1120 $cm^{-1}$.

$^1$H-NMR: $\delta$ = 1.67 (t, 2 H, $J$ = 7.2, $H_\epsilon$); 1.87–1.92 (m, 2 H, $H_\gamma$); 2.36 (t, 2 H, $J$ = 6.9, $H_\delta$); 2.46–2.52 (m, 2 H, $H_\beta$); 3.69 (s, 3 H, $CH_3$); 4.34 (dd, 1 H, $J$ = 4.9, 5.3, H-4); 5.18 (s, 2 H, $PhCH_2$); 5.20 (d, 1 H, $J$ = 4.5, H-2); 5.35 (br s, 1 H, H-2); 7.28 (s, 5 H, ArH).

$^{13}$C-NMR: $\delta$ = 22.1, 23.5, 26.2, 30.0, 38.2, 54.2, 66.8, 78.1, 128.0, 128.1, 128.4, 135.2, 154.1, 156.2, 172.4, 206.4.

**(*S*)-3-Benzyloxycarbonyl-4-(3-oxobutyl)-5-oxazilidinone (5):**
A solution of glutamate derivative **2b** (794 mg, 2.71 mmol) in ethanol-free $CHCl_3$ (5 mL) is treated with $SOCl_2$ (0.24 mL, 3.24 mmol) with stirring at r.t. After 3 h, the volatile materials are removed, and the residue is dissolved in $CHCl_3$ and reevaporated to remove traces of $SOCl_2$. THF (2 mL) is added and the solution is cooled to 0 °C. An ether solution of $CH_2N_2$ is added until the yellow color of excess $CH_2N_2$ persisted. The resulting diazoketone is reduced with HI in $CHCl_3$ (3 mL of 59% HI and 3 mL of $CHCl_3$). After 15 min, the solution is partitioned between $CHCl_3$ (100 mL) and $H_2O$ (50 mL), and the organic layer is worked up to give ketone **5** as a yellowish solid (610 mg, 78%), which is recrystallized from EtOAc: mp 102–103 °C.

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|---|---|---|---|---|
| $C_{15}H_{17}NO_5$ | calc. | C 61.84 | H 5.88 | N 4.83 |
| (292.5) | found | 62.01 | 5.72 | 4.85 |

IR: $\nu$ = 3020, 2990, 1805, 1725, 1485, 1415, 1315, 1140, 1120 $cm^{-1}$.

$^1$H-NMR: $\delta$ = 1.87–1.94 (m, 2 H, $H_\alpha$); 2.07 (s, 3 H, $CH_3$); 2.48–2.54 (m, 2 H, $H_\beta$); 4.39 (br s, 1 H, H-4); 5.18 (s, 2 H, $PhCH_2$); 5.22 (d, 1 H, $J$ = 4.6, H-2); 5.35 (br s, 1 H, H-2); 7.28 (s, 5 H, ArH).

$^{13}$C-NMR: $\delta$ = 26.2, 30.0, 39.1, 54.2, 67.0, 78.0, 128.1, 128.3, 135.4, 156.5, 175.1, 207.1

**Methyl (*S*)-2-(Benzyloxycarbonylamino)-5-oxohexanoate (6):**
Methyl ketone **5** (165.8 mg, 0.57 mmol) is added to a solution of NaOMe in MeOH (from 30 mg (1.30 mmol) of Na in 12 mL of MeOH) at −10 °C with stirring under an atmosphere of nitrogen. After stirring for 60 min, the solution is warmed to r.t. and partitioned between EtOAc (50 mL) and 1 N HCl (20 mL), and the organic layer is worked up to give ester **6** as a clear oil (153 mg, 92%).

| | | | | |
|---|---|---|---|---|
| $C_{15}H_{19}NO_5$ | calc. | C 61.41 | H 5.53 | N 4.80 |
| (294.5) | found | 61.19 | 5.38 | 4.78 |

IR: $\nu$ = 3015, 2990, 1740, 1725, 1480, 1415, 1300, 1130, 1120 $cm^{-1}$.

$^1$H-NMR: $\delta$ = 1.85–1.93 (m, 2 H, $H_\gamma$); 2.09 (s, 3 H, $CH_3$); 2.48–2.55 (m, 2 H, $H_\beta$); 3.69 (s, 3 H, $COOCH_3$); 4.40 (ddd, 1 H, $J$ = 4.2, 4.9, 7.2, H-4); 5.21 (s, 2 H, $PhCH_2$); 5.43 (d, 1 H, $J$ = 7.4, NH); 7.30 (s, 5 H, ArH).

$^{13}$C-NMR: $\delta$ = 26.2, 29.9, 39.1, 52.4, 53.2, 66.9, 128.0, 128.1, 128.4, 136.0, 155.8, 172.4, 207.3.

*This work was supported by a grant from the National Institutes of Health (grant no. CA-22747).*

Received: 20 September 1988; revised: 5 January 1989

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