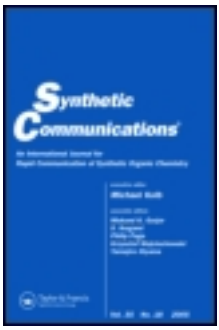

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A Selective Protection of 2,3-Diaminopropionic Acid

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A SELECTIVE PROTECTION OF 2,3-DIAMINOPROPIONIC ACID

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ABSTRACT: A two step selective protection of 2,3-diaminopropionic acid yields the useful diaminopropionic acid methyl ester **3a**. Further manipulation yields 2(S)-(N-benzyloxycarbonylamino)-3-aminopropionic acid methyl ester hydrochloride **5** in >99.9%ee.

The differentially protected amino acids **3a** and **5** are useful structures for the synthesis of amino acid derivatives. Previously reported preparations of compound **3a** require several steps, beginning with Curtius rearrangements of asparagine derivatives,[1] or Mitsunobu displacement of the hydroxyl group of serine.[2] These preparations lead to a selectively protected amino acid, wherein manipulation of protecting groups and esterification yields **3a** or **5**.[3] We report a synthetic route that yields compound **3a** in two-steps and demonstrate the derivatization of **3a** to **5** with retention of high enantiomeric purity.

The 2,3-diaminopropionic acid monohydrochloride[4] (1) yields the methyl ester dihydrochloride salt **2** in excellent yield when treated with

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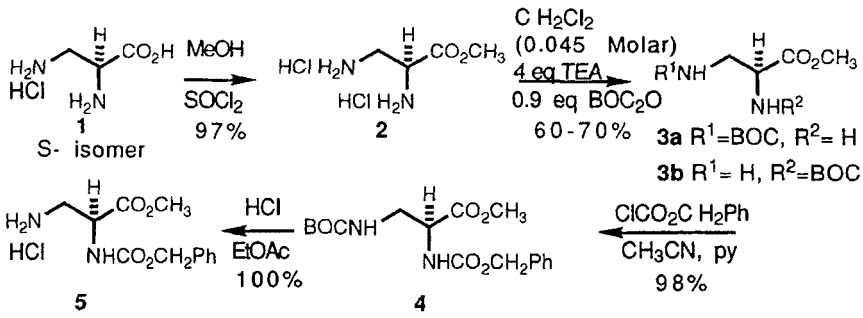

FIG. 1

thionyl chloride in methanol. The ester is then selectively protected as the mono-BOC derivative using di-*tert*-butyldicarbonate / triethylamine in methylene chloride at -78°C, to give an 8:1 ratio of **3a**:**3b** in 70% yield.

During the formation of **3a/3b** dilute reaction conditions (0.045 molar) were used to maximize the solubility of the starting diamino acid and thus obtain a homogenous reaction mixture. To obtain **3a/3b** in high enantiomeric purity, triethylamine was added at -78°C followed by warming to 0°C.[5] N-methylmorpholine could not be substituted for triethylamine, as the time required for reaction increased substantially and less selectivity was observed. Although less than an equivalent of BOC_2O was used, not all appeared to react, and bis-protection was observed in significant amounts if the unreacted reagent was not removed prior to concentration. The two monoprotected amines could be readily separated from one another by column chromatography on silica gel in 2.5% MeOH / EtOAc.

Compound **3a** was further derivatized with minimal racemization by treatment with benzyl chloroformate in acetonitrile containing pyridine at

0°C to yield **4** in 98% yield. Deprotection of benzyl urethane **4** with HCl/EtOAc led to **5** in quantitative yield. The enantiomeric purity of **5** was determined to be >99.9% by derivatization with 3,5-dinitrobenzoyl chloride and direct HPLC comparison to the R-enantiomer.[6]

In summary, a convenient method for the preparation of compound **3a** in good yield has been described. The benzyloxycarbonyl derivative of compound **3a** was prepared with minimal racemization using conditions which can in principle be extended to the preparation of other nitrogen derivatives.

EXPERIMENTAL SECTION

Methyl 2(S),3-diaminopropionate (2)

Methanol (400mL) was cooled to 0°C and thionyl chloride (217 mL, 3.0 mole, 20 eq) was added dropwise under argon. After addition was completed, the solution was warmed to room temperature for 20 min. 2(S),3-Diaminopropanoic acid (1) (20g, 0.143 mole) was crushed to a fine powder and added to the solution. The reaction mixture was heated at reflux for 48 hrs, at which time TLC showed a small amount of starting material remaining. An additional portion of methanol (100 mL) and thionyl chloride (72 mL) was prepared as before and added to the reaction at room temperature; the reaction was then stirred overnight at room temperature. The solvent was removed at 40°C in vacuo to provide **2** as a white foam (26.4g, 97%). Rf 0.72 (9 : 1 : 1 EtOH / H_2O / NH_4OH). ^1H NMR (400 MHz, D_2O) δ 4.55 (dd, J=5.4, 8.2 Hz, 1H), 3.92 (s, 3H), 3.64

(dd, J=8.2,13.8 Hz, 1H), 3.55 (dd, J=5.4, 13.8 Hz, 1H). Exact mass (FAB, calculated for $C_4H_{10}N_2O_2$ + 1 = 119.0820, found 119.0828).

Methyl 2(S)amino-3(N-t-butyloxycarbonylamino)propionate (3a)

Methyl 2(S),3-diaminopropionate (2) (6.0 g, 31.5 mmole) was crushed to a fine powder, suspended in 1L of CH_2Cl_2, and cooled to -78°C under argon. Triethylamine (17.5 mL, 0.126 mole, 4 eq) was added dropwise; the solution gradually became homogenous. Di-t-butyldicarbonate (6.18 g, 2.83 mmole, 0.9 eq) was dissolved in 50 mL CH_2Cl_2 and added dropwise to the solution. After the addition was completed, the reaction was placed in an ice bath and stirred for 1.5 hours. The reaction was transferred to a separatory funnel and extracted with 3 X 50 mL of 10% $KHSO_4$ solution. The aqueous layer was washed with 3 X 10 mL of CH_2Cl_2, the pH was raised to 10 with saturated $NaHCO_3$ and 3N NaOH solution, and the aqueous layer was extracted with 10 X 100 mL of CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered and concentrated to give 4.9 g of a pale yellow oil. Column chromatography on silica gel in 2.5% MeOH / EtOAc gave 4.32g (70%) of **3a** and 0.540g (9%) of the minor isomer **3b** as oils. Rf **3a** 0.39 (5% MeOH / EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.0 (bs, 1H), 3.72 (s, 3H), 3.56 (t, J = 5.7 Hz, 1H), 3.46 (m, 1H), 3.23 (m, 1H), 1.55 (bs, 2H), 1.42 (s, 9H). Exact mass (FAB, calculated for $C_9H_{18}N_2O_4$ + 1 = 219.1344, found 219.1363).

Methyl 2(S)-(N-benzyloxycarbonylamino)-3(N-t-butyloxycarbonyl-amino) propionate (4)

Methyl 2(S)amino-3(N-t-butyloxycarbonylamino) propionate (3a) (1.018g, 4.66 mmole) was dissolved in 25 mL of acetonitrile and cooled to 0°C under argon. Pyridine (1.13 mL, 14 mmole) was added dropwise followed by benzyl chloroformate (0.73 mL, 5.12 mmole). The reaction was removed from the cold bath, allowed to warm to room temperature and stir for 5 hours, and then was diluted with 150 mL EtOAc, washed with 3X10 mL 10% $KHSO_4$, brine, dried over $MgSO_4$, filtered and evaporated to give 1.61g of a clear oil (98% yield). Trituration of this oil with hexanes afforded **4** as a white solid (1.51g, 92%). Rf 0.5 (40% EtOAc/Hexanes). ^1H NMR (400MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.78 (bs, 1H), 5.11(s, 2H), 4.83(bs,1H), 4.41(bs, 1H), 3.76 (s, 3H), 3.55 (bs, 2H), 1.41 (s,9H). Exact mass (FAB, calculated for $C_{17}H_{24}N_2O_6$ + 1 = 353.1712, found 353.1693).

Methyl 2(S)-(N-benzyloxycarbonylamino)-3-aminopropionate (5)

Methyl 2(S)-(N-benzyloxycarbonylamino)-3(N-t-butyloxy-carbonylamino)propionate (4) (0.1g, 0.28 mmole) was dissolved in 5 mL of EtOAc and cooled to -40°C. HCl gas was bubbled through the solution for one minute; the reaction was then warmed to 0°C and stirred for 1/2 hour. Concentration of the solution in vacuo, first at room temperature, then at 40°C yielded **5** as a clear oil which solidified on standing (81 mg, 100%). Crystallization from methanol/ether yielded colorless needles, m.p 169°C (uncorrected). Rf 0.37 ($CHCl_3$ saturated with NH_3). ^1H NMR (400MHz, CD_3OD) δ 7.33 (m, 5H), 5.13 (s, 2H), 4.50 (dd, J=5.0, 8.9 Hz, 1H), 3.71 (s, 3H), 3.43 (dd, J=5.0, 13.2 Hz, 1H), 3.21 (dd, J= 8.9, 13.2 Hz,

1H). Exact mass (FAB, calculated for $C_{12}H_{16}N_2O_4$ + 1 = 253.1188, found 253.1202).

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REFERENCES

1. Rich, D.H.; Jasensky, R.D.; Jueller, G.C.; Anderson, K.E. *J. Med. Chem.* **1981**, *24*, 567.
2. Golding, B.T.; Howes, C. *J. Chem. Res., Synop.* **1984** *(1)* 1.
3. (a) Arnold, L.D.; Kalantar, T.H.; Vederas, J.C. *J. Am. Chem. Soc.* **1985**, *107*, 7105, (b) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis*, **1981**, 266, (c) Scholts, J.M.Bartlett, P.A. *Synthesis*, **1989**, 542. (d) Kjaer, A. *Acta Chemica Scand.*, **1949**, 1087, (e) Grzybowska, J.; Andruszkiewicz, R.; Wojciechowska, H. *Polish J. Chem.* **1979**, 935.
4. The R and S enantiomers of 2,3-diaminopropionic acid were obtained from American Tokyo Kasei and Schweizerhall, respectively.
5. The addition of base at low temperature (-78°C) gives optimum results. Addition of base at 0°C leads to formation of 7% of the enantiomer as determined by derivatization of **3a** with Marfey's reagent and direct HPLC comparison to the R-enantiomer.
6. Samples were prepared in methanol at 1mg per mL and 0.1mg per mL. Aliquots were dried in a speed vacuum apparatus and redissolved in 500uL of methylene chloride. Ten uL of pyridine and

10 uL of 3,5-dinitrobenzoyl chloride solution (6mg/mL in methylene chloride) was added and the reaction maintained at room temperature for one hour. The methylene chloride was removed in a speed vacuum apparatus under reduced pressure with no heat and redissolved in 500uL methanol. Separation was carried out on a chiral AGP column (100 x 4.0 mm, Advanced Separation Technologies) using an isocratic system of 20 mM sodium monobasic phosphate (75%) and methanol (25%) at 1 mL/min. The column was at room temperature and the effluent was monitored at 254 nM. The S isomer had a retention time of 4.6 minutes, the R isomer a retention time of 5.5 minutes. No R isomer was detected in the product **5** prepared by the above method.

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