Synthesis of N^2-Protected L-2,3-Diaminopropanoic Acids

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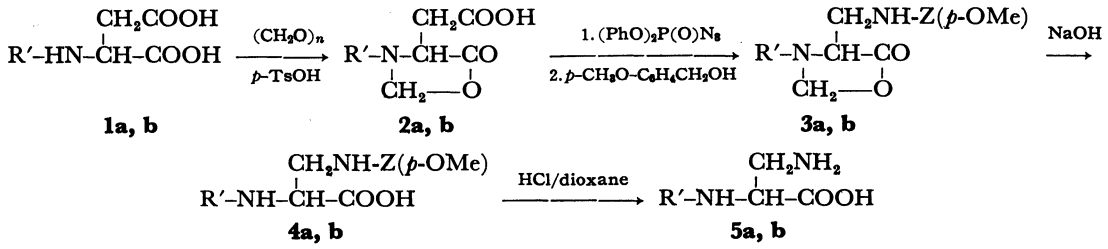
Synopsis. The title compounds have been synthesized from *N*-protected L-aspartic acid *via* Curtius rearrangement.

In the course of synthetic studies of 3-aminonocardicinic acid (the nucleus of nocardicins),[1] we needed N^2-protected L-2,3-diaminopropanoic acid. L-2,3-Diaminopropanoic acid (L-DAPr) is well known as a constituent amino acid of several antibiotics including tuberactinomycins[2] and bleomycins.[3] Although N^2- or N^3-protected L-DAPr and $N^{2,3}$-diprotected L-DAPr have been required for constructing these antibiotics,[4] many of previous methods for the synthesis of these L-DAPr derivatives employ inconvenient procedure.[5,6] We report here a simple synthesis of N^2-protected L-DAPr and $N^{2,3}$-diprotected L-DAPr from *N*-protected L-aspartic acid *via* Curtius rearrangement.

The α-carboxyl groups of *N*-(2,2,2-trichloroethoxycarbonyl)-L-aspartic acid (**1a**) and *N*-benzyloxycarbonyl-L-aspartic acid (**1b**) were protected by the formation of the oxazolidines **2a** and **2b** according to the published method.[7] The oxazolidine **2a** was treated with diphenyl phosphorazidate[8] in benzene to give the acid azide, which was subsequently heated with *p*-methoxybenzyl alcohol in refluxing benzene to produce **3a** in 70% yield. Ring-opening of **3a** with aqueous sodium hydroxide provided the diprotected diamino acid **4a** as an oil, which produced the crystalline dicyclohexylammonium salt. Similarly, the oxazolidine **2b** gave **4b** as crystals. Removal of *p*-methoxybenzyl groups of **4a** and **4b** was carried out with hydrogen chloride in dioxane to give the N^2-protected diamino acids **5a** and **5b** in 73% and 92% yields, respectively. The physical data of the products are shown in Table 1.

Reductive deprotection of **5a** with zinc in formic acid gave L-DAPr, the hydrochloride of which had identical $[\alpha]_D$ value with that reported.[5a] The total synthesis of 3-aminonocardicinic acid using **4** as a starting material will be reported elsewhere.



a: R′ = Cl_3CCH_2OCO
b: R′ = $C_6H_5CH_2OCO$

Experimental

Melting points (capillary) were uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. IR spectra were determined on a JASCO IRA-1 spectrometer. Elemental analyses were performed in the material analysis center of this institute.

(S)-3-(2,2,2-Trichloroethoxycarbonyl)-5-oxo-4-oxazolidineacetic Acid (2a). This compound was prepared in 75% yield by heating **1a** with paraformaldehyde and *p*-toluenesulfonic acid in refluxing benzene according to the procedure described for the preparation of **2a**.[7] The product was crystallized from benzene–hexane; mp 87—88 °C (dec); $[\alpha]_D^{25}$ +177.5° (*c* 1.0, MeOH). Found: C, 30.21; H, 2.49; N, 4.46%. Calcd for $C_8H_8NO_6Cl_3$: C, 29.98; H, 2.51; N, 4.37%.

(S)-4-(p-Methoxybenzyloxycarbonylaminomethyl)-3-(2,2,2-trichloroethoxycarbonyl)-5-oxazolidinone (3a). A solution of **2a**

Table 1. Yields and physical properties of N^2-protected and $N^{2,3}$-diprotected L-2,3-diaminopropanoic acids

Compound	Yield[a] %	Mp θ_m/°C	$[\alpha]_D^{25}$/°	Formula	Found (Calcd) (%) C	H	N
4a·DCHA[b]	50	190—191	+3.7 (*c* 0.9, MeOH)	$C_{27}H_{40}N_3O_7Cl_3$	51.75 (51.89)	6.44 (6.45)	6.52 (6.72)
4b	61	145—147	−13.7 (*c* 0.76, MeOH)	$C_{20}H_{22}N_2O_7$	59.58 (59.69)	5.48 (5.51)	6.90 (6.96)
4b·DCHA[b]		178—180	+4.1 (*c* 0.8, MeOH)	$C_{32}H_{45}N_3O_7$	65.59 (65.84)	7.80 (7.77)	7.21 (7.20)
5a	38	179—180	−15.5 (*c* 0.7, 1 M NaOH)	$C_6H_9N_2O_4Cl_3$	25.68 (25.78)	3.19 (3.25)	9.95 (10.02)
5b	56	213—214 dec[c]	−9.5[c] (*c* 0.4, 1 M NaOH)	$C_{11}H_{14}N_2O_4$	55.20 (55.46)	5.96 (5.92)	11.54 (11.76)

a) Isolated yield on the basis of **1**. b) Dicyclohexylammonium salts. c) Lit,[9] mp 240—241 °C dec, $[\alpha]_D^{22}$ −7.4° (*c* 0.4, 1 M NaOH).

(9.65 g, 0.03 mol) in anhydrous benzene (150 ml) was treated with diphenyl phosphorazidate (9.1 g, 0.033 mol) and triethylamine (3.36 g, 0.033 mol). After the mixture was stirred for 15 h, *p*-methoxybenzyl alcohol (4.14 g, 0.03 mol) was added and the mixture was refluxed for 3 h. The solution was cooled, washed with saturated aqueous $NaHCO_3$, 5% hydrochloric acid and water, dried ($MgSO_4$), and then concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene–ethyl acetate to give **3a** (9.6 g, 70%) as a pale yellow oil; IR (CH_2Cl_2) 1810 and 1735 cm^{-1}.

(S)-3-Benzyloxycarbonyl-4-(p-methoxybenzyloxycarbonylaminomethyl)-5-oxazolidinone (3b). This compound was prepared from **2b** by the procedure described for **3a** in 80% yield.

N^3-*(p-Methoxybenzyloxycarbonyl)*-N^2-*(2,2,2-trichloroethoxycarbonyl)*-L-*2,3-diaminopropanoic Acid (4a).* To a solution of **3a** (9.1 g, 0.02 mol) in aqueous acetone (80 ml), 1 M aqueous NaOH (20 ml) was added dropwise at 0 °C over 1 h. After being stirred for 2 h at 0—5 °C, the solution was concentrated *in vacuo*. The residue was diluted with water (20 ml), washed with ether, acidified with 20% hydrochloric acid, and then extracted with ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give **4a** (8.71 g, 98%) as a pale yellow oil.

The oily product (464 mg) was treated with dicyclohexylamine (227 mg) in ethanol (10 ml) to yield the dicyclohexylammonium salt (595 mg, 91%); mp 190—191 °C.

N^2-*Benzyloxycarbonyl*-N^3-*(p-methoxybenzyloxycarbonyl)*-L-*2,3-diaminopropanoic Acid (4b).* This compound was prepared from **3b** according to the procedure described for **4a** in 95% yield. The product was crystallized by trituration in ether; mp 145—147 °C. This compound also produced the crystalline dicyclohexylammonium salt; mp 178—180 °C.

N^2-*(2,2,2-Trichloroethoxycarbonyl)*-L-*2,3-diaminopropanoic Acid (5a).* A solution of **4a** (8.7 g, 0.0195 mol) in dioxane (100 ml) was treated with a 4 M HCl–dioxane solution (100 ml). After being stirred for 3 h, the solution was concentrated *in vacuo* and the remaining solid was dissolved in ethanol. The solution was ajusted to pH 7 with triethylamine and left in a refrigerator overnight. The white precipitates were collected by filtration, washed with chilled ethanol, and dried *in vacuo* to give **5a** (4.0 g, 73%); mp 179—180 °C.

N^2-*Benzyloxycarbonyl*-L-*2,3-diaminopropanoic Acid (5b).* This compound was prepared from **4b** by the procedure described for **5a** in 92% yield; mp 213—214 °C (dec) [Lit,[9] mp 240—241 °C (dec)].

L-*2,3-Diaminopropanoic Acid Hydrochloride.* The compound **5a** (280 mg) was dissolved in formic acid (10 ml) and cooled in an ice bath. Activated zinc dust (654 mg) was added with vigorous stirring and stirring was continued for 3 h at 0—5 °C. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with water, treated with H_2S, and then filtered. A few drops of 20% hydrochloric acid was added to the filtrate and the solvent was evaporated *in vacuo*. The residue was crystallized from water–ethanol to give 99 mg (71%); mp 233—235 °C (dec); $[\alpha]_D^{25}$ +19.4° (*c* 1, H_2O). [Lit,[5a] mp 236 °C (dec); $[\alpha]_D^{12}$ +19° (*c* 1, H_2O)].

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