SEMISYNTHETIC CEPHALOSPORINS. III[1]

SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF NOVEL ORALLY ACTIVE 7-[4-HYDROXY-3-(SUBSTITUTED METHYL)PHENYL]-ACETAMIDO-3-CEPHEM-4-CARBOXYLIC ACIDS

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A family of novel optically active α-amino-3-substituted-methyl-4-hydroxy benzene acetic acids (**3**) have been prepared. A number of these amino acids were converted to a group of cephalosporins (**12**). Compound **12A** showed the most interesting activity *in vitro* and *in vivo*, primarily against Gram-positive organisms and was shown to be well absorbed orally.

This paper describes the synthesis of a novel family of optically active α-amino aryl acetic acids which when coupled to 7-aminocephalosporanic acids gave a group of cephalosporins some of which had desirable oral activity.

Chemistry

The majority of the semisynthetic cephalosporins are not effective when administered orally. The main exceptions are cephalexin and cephradine, and recently reported compounds such as cefaclor[2], cefadroxil[3] and cefatrizine[4]. In view of the fact that oral activity is observed primarily in derivatives of α-amino aryl acetic acids, we designed our synthetic course on the basis of modification of the aryl part of a readily available α-amino acid, in such a way that initial functionalization of the aromatic ring would provide a "handle", which could in turn be easily converted into a variety of functional groups. The second important criterion was the necessary optical activity of the amino acids. In order to avoid the resolution of each individual compound thus obtained, it was deemed important to start with an optically active amino acid whose modification would proceed without racemization. These two requirements were fulfilled upon chloromethylation of D-α-amino-4-hydroxyphenyl acetic acid **1**. This reaction proceeded in high yield, and the isolated product **2** was devoid of side products derived from poly-chloromethylation, N-formylation, polymerization, *etc.* Amino acid **2** was in turn readily converted to a series of novel optically active acids **3**, primarily by simple nucleophilic displacement of the benzylic chloride (Table 1). The most convenient method for the preparation of the methoxy derivative **3F** involved initial conversion to the methoxy ester **4** upon reflux in methanol. Neutralization of hydrochloride of **4** to the free base **4A** followed by facile hydrolysis gave the desired **3F**.

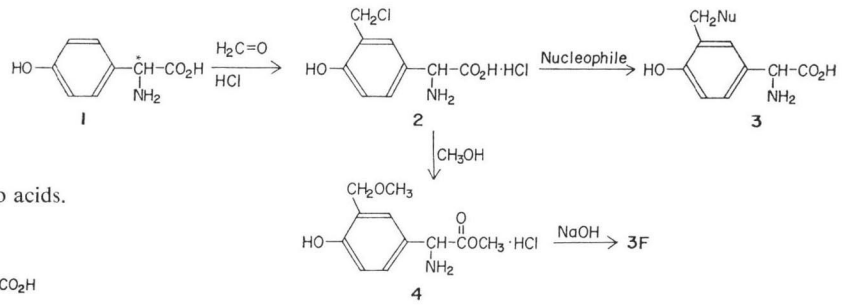
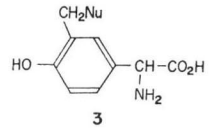
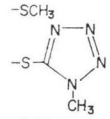
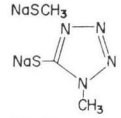
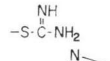
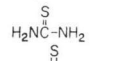
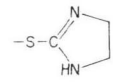
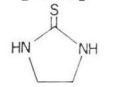
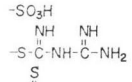
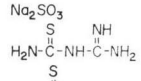
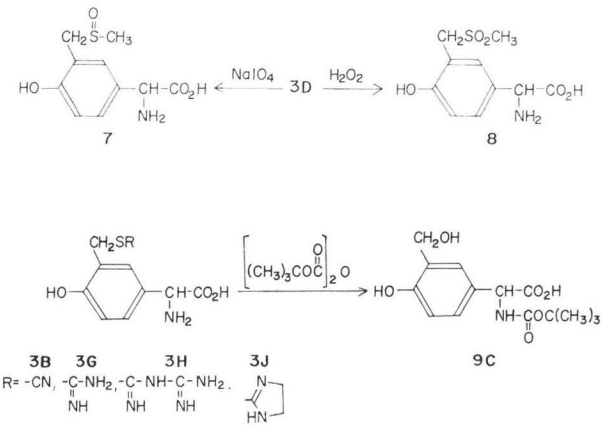


Table 1. Novel amino acids.



	Nu	Reagent
A	$-N_3$	NaN_3
B	-SCN	KSCN
C	-OH	$NaHCO_3$
D	$-SCH_3$	$NaSCH_3$
E		
F	$-OCH_3$	CH_3OH
G		
H		
I	$-SO_3H$	Na_2SO_3
J		
K	-SCOEt	Na-SCOEt
L	-H	$H_2/Pd/C$



The conversion of **3** to the corresponding N-tert-butoxycarbonyl (Boc) derivatives **9** proceeded smoothly with compounds **3A**, **3C**, **3D**, **3E**, **3K**, **3L**, **7** and **8** by standard procedures[5] where the preferred reagent used was di-tert-butyldicarbonate. The attempted conversion of amino acids **3B**, **3G**, **3H** and **3J** to the Boc-derivatives failed in view of the easy concomitant hydrolysis of the RS-substituent under the basic reaction conditions to give **9C**.

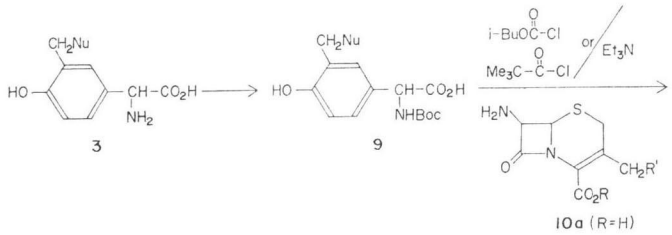
Some of **3** were obtained as mixtures with equilvalent amounts of sodium chloride upon lyophilization of the aqueous solution in which the reactions were carried out. They were used subsequently without further purification. Compound **3L** was obtained by hydrogenolytic reduction of the chloride in a Parr hydrogenator. Selective oxidations of **3D** gave sulfoxide **7** and sulfone **8**.

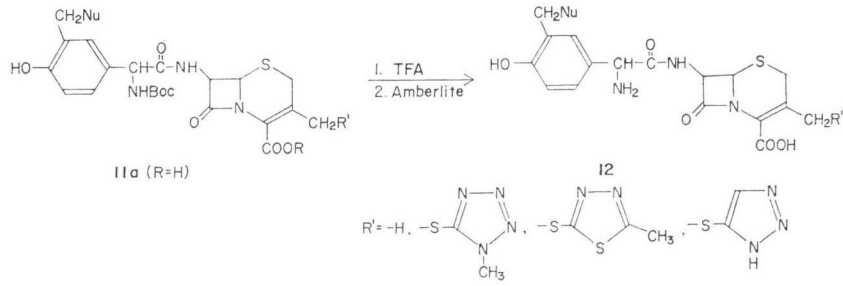
The Boc-derivative of **3I** could not be isolated and unambiguously identified due to the strong acidic conditions necessary to free the sulfonic acid group from its sodium salt, which caused extensive decomposition of the Boc-protecting group.

The coupling of the acids **9** to the respective 7-aminocephems[6] **10** was carried out by the general mixed anhydride procedure of SPENCER *et al.*[7] using *i*-butyl chloroformate or pivaloyl chloride.

Alternatively coupling could be carried out with the esters **10B**[8] in the presence of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ).

The final products **12** were obtained upon treatment of **11** with trifluoroacetic acid followed by neutralization with basic Amberlite IR-45 resin[6].





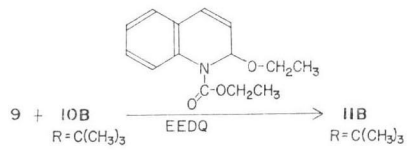
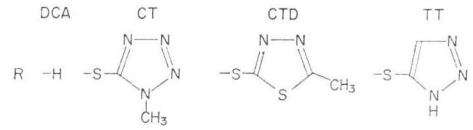
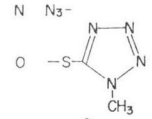


Table 2. Novel cephalosporins **12**.



12	Nu	R'
A	CH_3S-	DCA
B	CH_3S-	CTD
C	CH_3S-	CT
D	CH_3S-	TT
E	CH_3O-	DCA
F	CH_3O-	CTD
G	CH_3O-	CT
H	CH_3O-	TT
I	HO-	DCA
J	HO-	CTD
K	HO-	CT
L	N_3-	DCA
M	N_3-	CTD
N	N_3-	CT
O		DCA
P	$CH_3-\overset{O}{\overset{\|}{S}}-$	CTD
Q	$-S-\overset{S}{\overset{\|}{C}}-O-CH_2CH_3$	CTD
R	CH_3SO_2-	CT
S	$-S-\overset{S}{\overset{\|}{C}}-O-CH_2CH_3$	CT

Biological Results and Discussion

The activity *in vitro* of compounds **12A**~**S** (Table 2) against selected Gram-positive and Gram-negative organisms is shown in Table 3. All of the compounds were inactive against *Pseudomonas aeruginosa*, and all were either inactive or only weakly active against *Streptococcus faecalis, Enterobacter aerogenes, Enterobacter cloacae, Proteus vulgaris, Providencia stuartii*, and *Serratia marcescens*. Of the compounds bearing the 7-aminodesacetoxycephalosporanic acid (7-ADCA) nucleus, **12A** was the most potent. Of the compounds substituted at the 3-position by heteroarylthiomethyl groups, **12C**, **12D**, **12F**, **12J**, **12N** and **12R** generally were more potent than the other 3-substituted compounds.

When tested for efficacy against lethal infections in mice, the most effective compounds were those shown in Table 4. As indicated, the compounds were compared to cephalexin in separate tests. With respect to **12A** and cephalexin and regardless of the route of administration, **12A** was superior in protecting against streptococcal infections, inferior in protecting against Gram-negative bacterial infections while the two were equipotent against the infection with the resistant strain of *Staphylococcus aureus*. Regarding the compounds bearing a heterothiomethyl group in the 3-position, all were superior to

Table 3. Minimal inhibitory concentrations of compounds **12** and cephalexin.

Compound	Minimal inhibitory concentration (μg/ml)[a]								
	S.a. (R)[b]	*S.a.* (S)[b]	*S.e.* (R)[b]	*S.pn.*[b]	*S.p.*[b]	*E.c.*[b]	*K.p.*[b]	*P.m.*[b]	*S.s.*[b]
A	6.2	3.1	12.5	0.4	0.4	50	25	100	25
B	12.5	3.1	12.5	0.2	0.2	100	50	>100	25
C	12.5	3.1	6.2	≤0.05	0.2	12.5	12.5	25	6.2
D	6.2	0.8	3.1	0.1	0.1	25	12.5	50	3.1
E	12.5	3.1	12.5	1.6	0.4	50	25	100	25
F	12.5	1.6	6.2	0.2	0.2	25	12.5	>100	12.5
G	12.5	1.6	12.5	0.4	0.2	12.5	6.2	50	6.2
H	12.5	1.6	12.5	0.8	0.4	50	12.5	100	6.2
I	50	12.5	50	6.2	0.8	100	50	>100	50
J	12.5	3.1	12.5	0.2	0.2	12.5	12.5	50	6.2
K	25	6.2	25	0.4	0.4	6.2	6.2	50	3.1
L	25	12.5	50	3.1	0.8	100	50	>100	50
M	25	6.2	25	0.4	0.8	50	100	>100	25
N	25	6.2	12.5	0.4	0.2	6.2	6.2	12.5	6.2
O	100	25	100	12.5	3.1	>100	100	>100	100
P	25	6.2	50	0.8	0.8	50	25	>100	12.5
Q	12.5	1.6	6.2	≤0.05	0.1	100	25	>100	12.5
R	12.5	6.2	12.5	0.4	0.4	12.5	6.2	25	1.6
S	25	6.2	25	0.1	0.2	50	12.5	50	12.5
Cephalexin[c]	6.2~12.5	0.8~1.6	12.5~25	1.6~3.1	0.4~0.8	6.2~12.5	3.1~6.2	12.5~25	3.1~6.2

a Determined by serial two-fold dilution of compound in MUELLER-HINTON agar and inoculation of the agar surface with an appropriately diluted 18~24-hour broth culture. Agar plates were incubated at 37°C for 17 hours and the lowest concentration causing complete or virtually complete inhibition of visible growth was considered to be the minimal inhibitory concentration.

b *S.a.* (R), *Staphylococcus aureus* (benzylpenicillin-resistant); *S.a.* (S), *Staphylococcus aureus* (benzylpenicillin-sensitive); *S.e.*, *Staphylococcus epidermidis* (benzylpenicillin-resistant); *S.pn.*, *Streptococcus pneumoniae*; *S.p.*, *Streptococcus pyogenes*; *E.c.*, *Escherichia coli*; *K.p.*, *Klebsiella pneumoniae*; *P.m.*, *Proteus mirabilis*; *S.s.*, *Salmonella schottmuelleri*.

c Range of MICs obtained with cephalexin during the testing of compounds **12** A~S.

cephalexin against streptococcal infections whether administered s.c. or p.o. None was superior to cephalexin against the two Gram-negative bacterial infections when the compounds were administered p.o., and two of the three compounds, **12J** and **12C** were inferior to cephalexin against the *S. aureus* infection whether administered parenterally or orally. Thus, **12A**, which has the same nucleus as cephalexin, is the most interesting compound of all of those studied by virtue of its activity against the Gram-positive organisms *in vitro* and *in vivo* and the fact that it appears to be well absorbed orally.

Experimental Section

Satisfactory elemental analyses were obtained for all new compounds. The NMR spectra of all cephalosporin derivatives were consistent with their expected structure.

(−)-α-Amino-3-(chloromethyl)-4-hydroxybenzene acetic acid hydrochloride (**2**)

To a solution of (−)-α-amino-4-hydroxybenzene acetic acid (100 g, 0.6 mole) in concentrated hydrochloric acid at 35~40°C, 50 ml of aqueous formaldehyde (35~37%) (0.6 mole) was added at once, and bubbling of hydrogen chloride was started. After 5~10 minutes, a solid began to precipitate. Stirring was continued for 30 minutes, and the solid was then collected. The crude product was washed

Table 4. Activity of **12A**, **12J**, **12F**, **12C** and cephalexin against mouse infections.

Compound	ED_{50} (mg/kg/dose)[a]									
	S.a. (R)[b]		*S.pn.*[b]		*S.p.*[b]		*E.c.*[b]		*S.s.*[b]	
	s.c.[c]	p.o.[c]	s.c.	p.o.	s.c.	p.o.	s.c.	p.o.	s.c.	p.o.
12A	<2.5	5.9	12.4	5.0	<0.5	<0.5	14.3	40	18.6	>40
Cephalexin	<2.5	6.1	30.6	29.6	2.8	1.2	3.2	10	4.6	14.9
12J	>40	>40	1.2	3.1	0.25	0.33	2.9	10	<2.5	11.3
Cephalexin	7.9	18.7	36.8	34.4	1.2	1.4	<2.5	2.9	8.6	13.5
12F	2.9	8.9	<1.25	<5.0	0.17	0.39	11.1	>40	8.3	23.8
Cephalexin	<2.5	6.1	45.3	37	NT[d]	2.0	4.5	12.4	5.8	18.2
12C	20	>40	1.3	5.8	0.13	0.54	4.6	6.6	1.3	14.8
Cephalexin	7.9	18.7	40	22.7	NT[d]	1.2	3.2	10.0	4.6	14.9

a Male albino CD-1 mice weighing 20 (±1) g were infected by intraperitoneal injection of a bacterial suspension to produce uniformly lethal infections. Groups of ten mice each were treated subcutaneously or orally with aqueous solutions of appropriate concentrations of antibiotic at 1 and 4 hours after infection. The number of mice in each group surviving the challenge for 4 days was recorded and the ED_{50} (the dose in mg/kg required to protect 50% of the infected mice) determined by the method of REED and MUENCH, Am. J. Hyg., 27, 493 (1938).

b See footnote b, Table 3.

c s.c., compound administered subcutaneously; p.o., compound administered *per os*.

d NT, not tested.

with ether and with acetone. A second crop was obtained from the filtrate after standing at room temperature overnight. Collected 102 g (67%): m.p. >300°C, $[\alpha]_D^{18}$ −134° (*c* 4.75, CH_3OH), NMR (Me_2SO-d_6) δ 4.68 (s, 2), 4.9 (broad s, 1), 6.9~7.6 (superimposed q and s, 3).

(−)-α-Amino-3-(azidomethyl)-4-hydroxybenzene acetic acid (**3A**)

To a solution of **2** (252 mg, 1 mmole) in 4 ml of methyl alcohol was added sodium azide (156 mg, 2.4 mmole). The mixture was stirred at *ca.* 40°C for a few minutes. After some 10 minutes the product began to precipitate. The mixture was cooled, filtered and the product was washed with a small amount of methyl alcohol and acetone. Collected 210 mg (95% yield): m.p. >300°, $[\alpha]_D^{18}$ −98.68° (*c* 0.633, dilute HCl), NMR (Me_2SO-d_6) δ 4.22 (s, 1), 4.35 (s, 2), 6.7~7.5 (superimposed q and s, 3).

(−)-α-Amino-3-(thiocyanatomethyl)-4-hydroxybenzene acetic acid (**3B**)

A solution of **2** (0.5 g, 1.98 mmole) and potassium thiocyanate (0.4 g, 4.12 mmole) in 10 ml of methanol was stirred at room temperature for 16 hours. The precipitated potassium chloride was filtered, the filtrate was evaporated and to the residue was added saturated aqueous sodium bicarbonate until pH 7. The product precipitated as a white powder which was filtered and dried. Obtained 1.83 g (78% yield): NMR (TFA-d + D_2O) δ 4.1 (s, 2), 5.08 (s, 1), 6.9~7.3 (m, 3).

(−)-α-Amino-3-(hydroxymethyl)-4-hydroxybenzene acetic acid (**3C**)

To a solution of **2** (0.5 g 1.98 mmole) in 10 ml water was added saturated aqueous sodium bicarbonate until a pH of 7 was reached. The solution was stirred overnight and was then lyophilyzed to give a quantitative yield of the title compound combined with two equivalents of sodium chloride: $[\alpha]_D^{25}$ −84.4° (*c* 6.4, CH_3OH), NMR (TFA-d + D_2O) δ 1.73 (s, 2), 5.1 (s, 1), 6.9~7.3 (m, 3).

(−)-α-Amino-3-(thiomethoxymethyl)-4-hydroxybenzene acetic acid (**3D**)

To a solution of methyl thiol (3 g, 0.04 mole) in 250 ml of water was added sodium hydroxide (1.6 g, 0.04 mole) followed by **2** (5 g, 0.02 mole). The solution obtained was stirred overnight. Removal of the solvent by flash evaporation gave a quantitative yield of the title compound combined with

two equivalents of sodium chloride: $[\alpha]_D^{25}$ −99.36° (*c* 7.82, dilute HCl), NMR (TFA-d + D_2O) δ 2.14 (s, 3), 3.78 (s, 2), 5.18 (s, 1), 6.9 ~ 7.3 (m, 3).

(−)-α-Amino-3-[(aminoiminomethyl)thiomethyl]-4-hydroxybenzene acetic acid (**3G**)

A solution of **2** (2 g, 8 mmole) and thiourea (0.61 g, 8 mmole) in 10 ml of water was stirred at room temperature for 4 hours. Removal of the solvent by lyophilyzation gave a quantitative yield of the product isolated as its dihydrochloride: $[\alpha]_D^{25}$ −69.2° (*c* 10.4, H_2O), NMR (TFA-d) δ 4.34 (s, 2), 5.4 (s, 1), 6.8 ~ 7.6 (m, 3).

Compounds **3E**, **3H**, **3J** were obtained analogously to compound **3G** when thiourea was replaced by 1-methyl-1H-tetrazol-5-ylthiol, ethylenethiourea and 1-amidino-2-thiourea respectively.

(−)-α-Amino-4-hydroxy-3-(1-methyl-1H-tetrazol-5-yl)thiomethylbenzene acetic acid (**3E**)

$[\alpha]_D^{25}$ −47.8° (*c* 11.86, H_2O), NMR (TFA-d + D_2O) δ 3.96 (s, 3), 4.42 (s, 2), 5.17 (s, 1), 6.8 ~ 7.6 (m, 3).

(−)-α-Amino-3-(4,5-dihydro-1H-imidazol-2-yl)thiomethyl-4-hydroxybenzene acetic acid (**3H**)

$[\alpha]_D^{25}$ −53.41° (*c* 9.4, H_2O), NMR (TFA-d + D_2O) δ 4.05 (s, 4), 4.41 (s, 2), 5.16 (s, 1), 6.9 ~ 7.7 (m, 3).

(−)-α-Amino-3-[(amino[(aminoiminomethyl)imino]methyl]thiomethyl]-4-hydroxybenzene acetic acid (**3J**)

NMR (TFA-d + D_2O) δ 4.2 (s, 2), 5.2 (s, 1), 6.8 ~ 7.3 (m, 3).

(−)-α-Amino-4-hydroxy-3-(sulfomethyl)-benzene acetic acid (**3I**)

Compound **3I** was obtained after three-hour reflux of an aqueous solution of sodium sulfite (4 mmole) and **2** (1 g, 4 mmole) in 15 ml of water. Lyophilization of the solvent gave the product as its sodium salt. NMR (TFA-d + D_2O) δ 4.1 (s, 2), 5.0 (s, 1), 6.7 ~ 7.4 (m, 3).

(−)-α-Amino-3-[(ethoxythiocarbonyl)thiomethyl]-4-hydroxybenzene acetic acid (**3K**)

To a solution of **2** (1 g, 0.004 mole) in 200 ml of water was added potassium ethylxanthate (1.26 g, 0.08 mole). Within a few minutes a precipitate began to form. The mixture was stirred at room temperature for 3 hours. The solid precipitate was filtered, washed with water and dried to give 58.3% of the product: $[\alpha]_D^{25}$ −81.1° (*c* 5.82, CH_3OH), NMR (TFA-d + D_2O) δ 1.4 (t, 3), 4.37 (s, 2), 4.6 (q, 2), 5.03 (s, 2), 6.7 ~ 7.5 (m, 3).

α-Amino-4-hydroxy-3-methylbenzene acetic acid (**3L**)

A quantitative yield of compound **3L** was obtained upon 16-hour, aqueous, catalytic hydrogenation of **2** (1 g, 0.004 mole) on 10% palladium on charcoal. The product was isolated upon filtration of the catalyst and lyophilization of the solvent: $[\alpha]_D^{25}$ −116.7° (*c* 6.52, dilute HCl), NMR (TFA-d) δ 2.31 (s, 3), 5.30 (s, 1), 7.05 ~ 7.58 (m, 3).

(−)-α-Amino-3-(methoxymethyl)-4-hydroxybenzene acetic acid methyl ester hydrochloride (**4**)

A solution of **2** (1 g, 3.96 mmole) in 10 ml of methanol was refluxed for 30 hours. The solvent was then removed under vacuum and the product was isolated in quantitative yield as a bright hygroscopic powder. NMR (Me_2SO-d_6 + D_2O) δ 3.40 (s, 3), 3.78 (s, 3), 4.47 (s, 2), 5.20 (s, 1), 7 ~ 7.7 (m, 3).

(−)-α-Amino-3-(methoxymethyl)-4-hydroxybenzene acetic acid methyl ester (**4A**)

Compound **4** was dissolved in a minimum amount of methanol. To the obtained solution was added methanolic potassium hydroxide until a basic reaction to phenolphthalein was observed. The potassium chloride which precipitated was filtered, the solvent was removed under vaccum to give a quantitative yield of the free base **4A**. NMR (Me_2SO-d_6 + D_2O) δ 3.32 (s, 3), 3.64 (s, 3), 4.4 (superimposed s, 2 and s, 1), 6.6 ~ 7.3 (m, 3).

(−)-α-Amino-3-(methoxymethyl)-4-hydroxybenzene acetic acid (**3F**)

Compound **4A** was dissolved in aqueous 1 N sodium hydroxide and the solution was stirred at 40 ~ 50°C for one hour. The solution was acidified with 6 N hydrochloric acid to pH 7. Evaporation of the solvent gave the title compound in a 90% overall yield: $[\alpha]_D^{25}$ −84.1° (*c* 7.1, dilute HCl), NMR (D_2O) δ 3.42 (s, 3), 4.56 (s, 2), 5.2 (s, 1).

(−)-α-Amino-4-hydroxy-3-[(methylsulfinyl)methyl]benzene acetic acid (**7**)

To an aqueous solution (500 ml) of **3D** (3.49 g, 0.01 mole) was added sodium metaperiodate (0.01 mole). The mixture was stirred at room temperature for 5 hours, it was filtered and the filtrate was lyophilyzed to give a quantitative yield compound **7**. NMR (Me_2SO-d_6 + D_2O) δ 2.65 (s, 3), 4.12 (s, 2), 4.5 (s, 1), 6.8~7.5 (m, 3).

(−)-α-Amino-4-hydroxy-3-[(methylsulfonyl)methyl]benzene acetic acid (**8**)

A solution of **3D** (3 g, 8.7 mmole) and 30 ml of 30% hydrogen peroxide in 300 ml of acetic acid was stirred at room temperature for 17 hours. The mixture was filtered and the filtrate was flash concentrated at 35°C. The residue was mixed with methanol to give a solid which was washed with ether, filtered and dried to give compound **8** in 92% yield: $[\alpha]_D^{25}$ −82.07° (*c* 9.48, dilute HCl), NMR (TFA-d + D_2O) δ 2.75 (s, 3), 4.17 (s, 2), 4.8 (s, 1), 6.5~7.3 (m, 3).

General procedure for the preparation of the N-*tert*-butyloxycarbonyl (Boc) derivatives **9** of amino acids **3**

To a well stirred solution of an amino acid **3** (0.5 mole) and sodium hydroxide (0.5 mole) in 50 ml of water and 100 ml of *tert*-butanol was added di-*tert*-butyl dicarbonate [$(Boc)_2O$] (0.55 mole). The mixture was stirred overnight. The turbid solution obtained was diluted with water (250 ml) and extracted with three portions of pentane (300 ml each). The aqueous phase was cooled, acidified to pH 2~3 with potassium hydrogen sulfate, and extracted with four 400-ml portions of ethyl acetate. The combined organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed under reduced pressure. The desired N-*tert*-butyloxycarbonyl amino acids **9** were usually obtained as solid foams. The yields of the products were in the range of 40~90%.

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