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Synthesis of Amino Acid and 4,5-Dihydro-6H-1,3-thiazine Derivatives for the Preparation of Cephalosporin Compounds

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Several β-hydroxy-α-halogeno-α-amino acid derivatives (**3**—**5**) were prepared from *tert*-butyl N-benzylideneglycinate (**1**) and α-haloketones or an α-haloaldehyde for utilization in the synthesis of 4,5-dihydro-6H-1,3-thiazine derivatives (**7** and **12**). An alternative thiazine synthesis starting from *tert*-butyl glycinate (**13**) was found to proceed stereoselectively, giving rise to **12a**. The two thiazine derivatives **7** and **12a** were converted into cephalosporin derivatives (**10** and **17**, respectively) by reaction with azidoacetyl chloride. The 7-azido-3-methylcephem derivative (**17**) was further led to 7-aminodeacetoxycephalosporanic acid (7-ADCA, **22**).

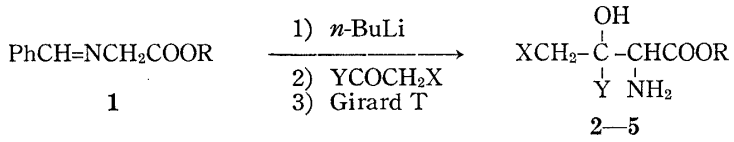
Keywords——amino acid; 1,3-thiazine; cephalosporin derivative; 7-aminodeacetoxycephalosporanic acid; N-benzylideneglycinate; cycloaddition reaction; stereoselectivity; *trans*→*cis* conversion

1,3-Thiazine derivatives are key intermediates for the total synthesis of cephalosporin derivatives, as demonstrated by Ratcliffe and Christensen.[2] An earlier paper dealing with the total synthesis of 3-trifluoromethylcephalosporin derivatives[3] described a new route to 4,5-dihydro-6H-1,3-thiazines. This synthetic method involves the reaction of the anion of **1** with the highly reactive α-haloketone CF_3COCH_2Br to give diastereomeric amino acids, **2a** and **2b**, which were converted to the 4,5-dihydro-6H-1,3-thiazines. With the aim of widening the scope of this useful amino acid synthesis and the subsequent 1,3-thiazine preparation, the anion generated from **1** was reacted with some other haloketones and a haloaldehyde. This paper reports a synthetic method for preparing several new amino acid derivatives which may be converted into 1,3-thiazine derivatives useful for cephalosporin synthesis. The present work exemplifies the usefulness of these compounds as intermediates for cephalosporin compounds.

tert-Butyl glycinate was treated with *n*-BuLi in tetrahydrofuran at −78° followed by reaction with α-haloketones or an α-haloaldehyde to give α-amino acid derivatives. When 1,3-dichloroacetone was used as the α-haloketone, the corresponding α-amino acid derivative (**3**) was obtained in excellent yield. The dichloro compound is extremely interesting in that it is suitably functionalized for the synthesis of cephalosporin or other β-lactam antibiotics. In fact, **3** could be converted into the 1,3-thiazine derivative (**7**) by treatment with ethyl thioformate in carbon tetrachloride and then with potassium carbonate in acetone. The intermediate compounds **6** and **7** were produced in 77% and 70% yields, respectively.

The 1,3-thiazine (**7**) was, after being mesylated with methanesulfonyl chloride and triethylamine, subjected to [2+2] cycloaddition reaction with azidoacetyl chloride in the presence of triethylamine to give the cepham derivative (**8**) in 26% yield. The stereochemical relationship of the C-6 and C-7 hydrogens was shown to be *trans* by the nuclear magnetic resonance

1) Location: *1-2-58 Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
2) R.W. Ratcliffe and B.G. Christensen, *Tetrahedron Lett.*, **1973**, 4649.
3) T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto, M. Nagano, and T. Miyadera, *Tetrahedron Lett.*, **1977**, 3053; T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto, and T. Miyadera, *Chem. Pharm. Bull.*, **28**, 62 (1980).



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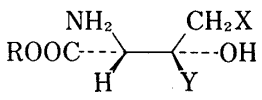
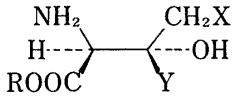


a



b

Compound	Y	X	R	Yield	a/b
2	CF_3	Br	*t*-Bu	70	3/1
3	CH_2Cl	Cl	*t*-Bu	90	—
4	CH_3	Cl	*t*-Bu	65	1/2
5	H	Cl	Et	31	3/2 or 2/3

Chart 1

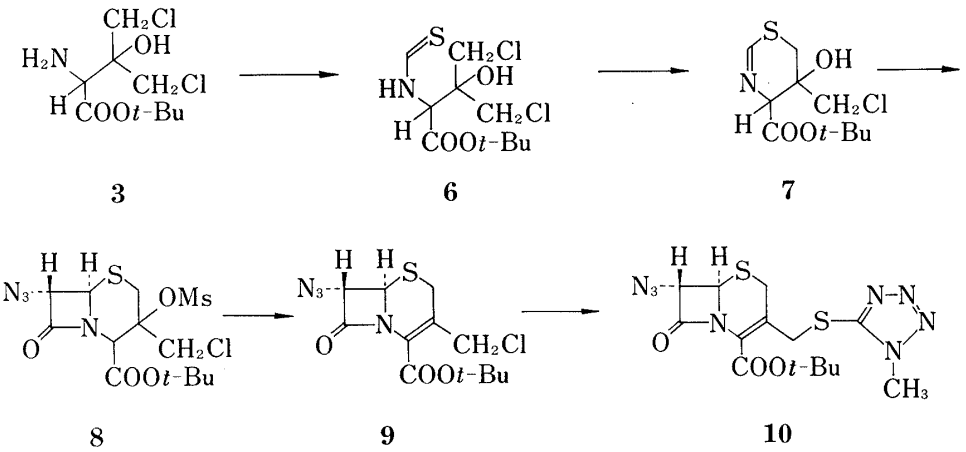


Chart 2

(NMR) spectrum, in which the two hydrogens coupled with a coupling constant of 2.0 Hz. The C-4 hydrogen was assumed to be located on the α-side in the light of previous work.[3] The elimination reaction of **8** to provide the cephem derivative (**9**) was carried out by heating with pyridine in benzene according to the procedure reported previously.[3] The chlorine atom can be displaced by nucleophilic reagents to obtain useful derivatives. As an example of such substitution, **9** was reacted with 1-methyl-5-mercapto-1H-tetrazole to afford the 3-tetrazolylthiomethyl derivative (**10**). The reduction of the azido group to an amino group and subsequent epimerization may be performed, if desired, as demonstrated in the total synthesis of 3-trifluoromethylcephalosporins[3] and 7-aminodeacetoxycephalosporanic acid (7-ADCA).[4]

Similar treatment of the anion of **1** with chloroacetone yielded two diastereomers (**4a**, more polar, and **4b**, less polar). Stereochemical assignments for the two isomers became possible by leading them to the 1,3-thiazine derivatives, one of which has been unambiguously identified as the *cis* isomer.[4] The more polar isomer **4a**, when treated with ethyl thioformate and subsequently with potassium carbonate, afforded the 1,3-thiazine derivative (**12a**) as the

4) T. Hashimoto, T. Watanabe, Y. Kawano, T. Tanaka, and T. Miyadera, *Heterocycles*, **11**, 207 (1978).

major product. Although the ring closure of **11a** is accompanied by isomerization of **12a** to **12b**, **12a** was shown to be the initially formed thiazine by chromatographic monitoring on thin layer plates. The major product was identified by comparison of the NMR spectrum with that of an authentic sample which was obtained by stereoselective cyclization of *tert*-butyl N-acetonylthiomethylideneglycinate (**15**) as described later.

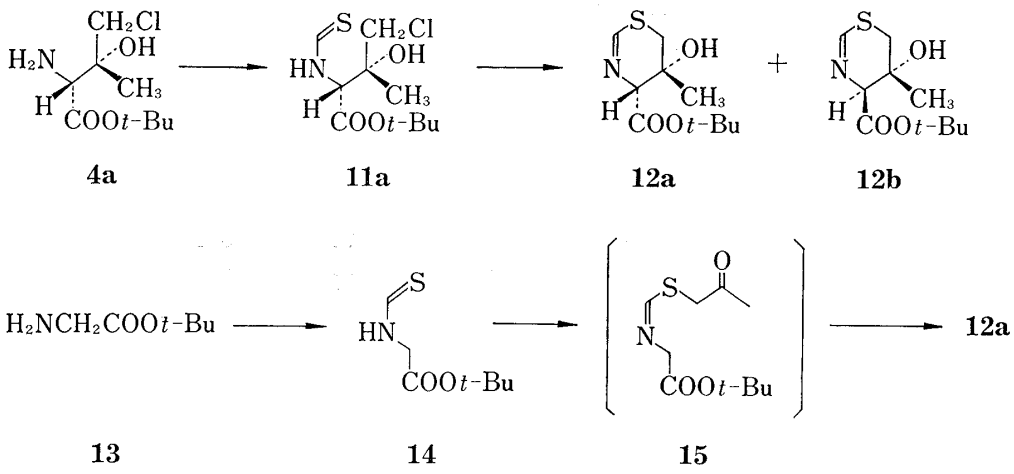


Chart 3

α-Chloroacetaldehyde also underwent reaction with the anion of **1** to give a diastereomeric mixture of **5a** and **5b** in a ratio of 3 : 2 or 2 : 3 . The stereochemistries of the isomers remain to be determined.

As an extension of the preceding 1,3-thiazine synthesis, an alternative synthetic route has been successfully established as already reported in a preliminary paper.[4] In contrast to the above, this method involves thiazine ring formation by ring closure between the C-4 and C-5 carbons in the final step. *tert*-Butyl glycinate was first treated with ethyl thioformate in carbon tetrachloride to give the thioformamido derivative (**14**) in 80% yield. The thioamide was treated with one mole-equivalent of sodium hydride in tetrahydrofuran at 0°, followed by reaction with bromoacetone. The possible intermediate (**15**) underwent spontaneous cyclization in the reaction medium, giving rise to **12a** in 69% yield. The thiazine formation seemed to proceed stereoselectively to give one diastereomer (**12a**) almost exclusively; the hydroxyl and carboxylate groups are *cis* in this compound. The stereochemistry of **12a** was assumed, based on the infrared (IR) spectra of the two isomers,[4] and was finally confirmed by X-ray crystallographic analysis.[5] The stereoselective ring closure can be explained on the assumption that it may favor the transition state in which the carboxylate group is located *cis* to the carbonyl oxygen through metal ion participation.[4]

The thiazine thus formed was utilized to obtain the desired cephalosporin derivative by the established method. The thiazine (**12a**), after being acetylated with acetic anhydride in pyridine, was treated with azidoacetyl chloride and triethylamine in tetrahydrofuran to give the *trans* 7-azido-3-cephem derivative (**17**). Following the catalytic hydrogenation of **17** to the amino compound (**18**), **18** was converted into the *cis* isomer (**21**) by the method of Hiraoka and co-workers.[6] The *trans* amino compound **18** was treated with *o*-nitrobenzenesulfenyl chloride in the presence of triethylamine in tetrahydrofuran at room temperature to give the *trans* sulfenylamido derivative (**19**) in 80% yield. Oxidation of **19** with excess manganese dioxide in methylene chloride and successive reduction with sodium borohydride in

5) T. Hata and C. Tamura, unpublished results.
6) T. Kobayashi, K. Iino, and T. Hiraoka, *J. Am. Chem. Soc.*, **99**, 5505 (1977); *idem*, *Chem. Pharm. Bull.*, **27**, 2727 (1979).

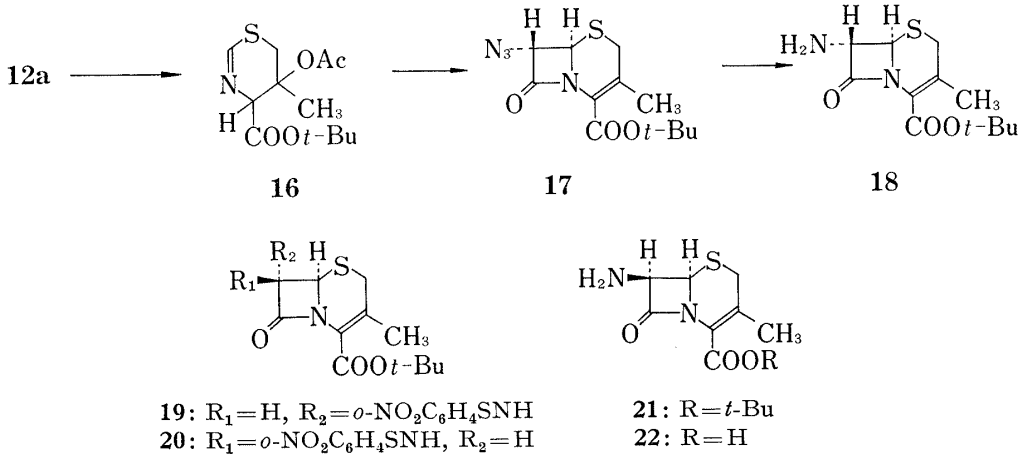


Chart 4

dimethyl sulfoxide-tetrahydrofuran afforded the *cis* sulfenamido compound (**20**), together with a small amount of the *trans* isomer (**19**). In this reduction it has been shown that the reducing agent can be replaced by diborane[3] or lithium tri-*tert*-butoxyaluminum hydride.[6] The deprotection of the sulfenyl group of **20** was carried out with potassium iodide and $Na_2S_2O_3$ in methanol-acetic acid at room temperature. The resulting *cis* 7-amino compound (**21**) was formed in 32% yield starting from the *trans* sulfenamide (**19**). The *tert*-butyl group of **21** was removed by treatment with trifluoroacetic acid at room temperature to yield (±)-7β-amino-deacetoxycephalosporanic acid as the trifluoroacetic acid salt.

Experimental

The silica gel plates used for preparative thick layer chromatography were obtained from E. Merck, Darmstadt, West Germany. All melting points are uncorrected. NMR spectra were recorded on a Varian A-60, a Hitachi R-24 or a Varian HA-100 spectrometer and signals are given in δ units downfield from tetramethylsilane as an internal standard. IR spectra were measured on a Nihon-Bunko Jasco IR-A or a Perkin Elmer 225 spectrometer. A Nihon-Denshi JMS-01-SG spectrometer was used to obtain mass spectra.

***tert*-Butyl 2-Amino-4-chloro-3-chloromethyl-3-hydroxybutyrate (3)**——A solution of *n*-BuLi in *n*-hexane (24.6 ml, 1 mmol=0.614 ml) was added dropwise at −70° to a solution of **1** (R=*t*-Bu, 8.76 g) in tetrahydrofuran (THF, 160 ml) and the mixture was stirred for 0.5 hr. A solution of 1,3-dichloroacetone (5.18 g) in THF (4 ml) was added and the mixture was allowed to warm to −20°, stirred for an additional 0.5 hr and recooled to −70°. After addition of AcOH (2.4 ml), the reaction mixture was poured into ice-water and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in MeOH (80 ml) and treated with Girard reagent T (7.2 g) for 2 hr at room temperature. After removal of the solvent, the residue was taken up in AcOEt, washed with aq. NaCl solution, dried over Na_2SO_4 and freed of the solvent. The crude product was chromatographed on a column of silica gel with benzene–AcOEt (5: 1), affording 1.91 g of oily **3**. Yield, 90%. NMR ($CDCl_3$) δ: 1.51 (9H, s, *t*-Bu), 2.90 (3H, bs, OH, NH_2), 3.73 (3H, s, C_2–H, CH_2Cl), 3.87 (2H, s, CH_2Cl). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3400, 3320 (NH_2, OH), 1730 (ester).

***tert*-Butyl 4-Chloro-3-chloromethyl-3-hydroxy-2-thioformamidobutyrate (6)**——Ethyl thioformate (408 mg) was added to a solution of the amino alcohol **3** (970 mg) in CCl_4 (10 ml). After stirring at room temperature for 3 hr, the mixture was concentrated *in vacuo* and the residue was triturated with *n*-hexane–ether to give 880 mg of **6** as crystals. Yield, 77%. NMR ($CDCl_3$) δ: 1.54 (9H, s, *t*-Bu), 3.87 (4H, s, $2\times CH_2Cl$), 3.5—4.0 (1H, bs, OH), 5.78 (1H, d, J=8.5 Hz, C_2–H), 8.5 (1H, bs, NH), 9.68 (1H, d, J=6.0 Hz, HC=S). IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH, OH), 1720 (ester). MS *m/e*: 302 (M^+).

***tert*-Butyl 5-Chloromethyl-5-hydroxy-4,5-dihydro-6H-1,3-thiazine-4-carboxylate (7)**——The thioformamide **6** (302 mg) was added to a suspension of K_2CO_3 (415 mg) in acetone (10 ml), and the mixture was stirred for 50 min at room temperature and then filtered. The filtrate was concentrated *in vacuo* and the residue was triturated with ether. The crystalline product was collected by filtration and dried, affording 161 mg of **7**, mp 149—150° (from benzene). Furthermore, 24 mg of **7** was obtained from the filtrate by chromatography on a column of silica gel, eluting with benzene–AcOEt=5: 1. Yield, 70%. NMR (DMSO-d_6) δ: 1.43 (9H, s, *t*-Bu), 2.95 (1H, d-d-d, J=12.0, 2.0, 2.0 Hz, C_6–H), 3.21 (1H, bs, OH), 3.37 (1H, d, J=12.0 Hz, C_6–H), 3.62 (2H, s, CH_2Cl), 4.37 (1H, d-d, J=2.0, 2.0 Hz, C_4–H), 8.28 (1H, d-d, J=2.0, 2.0 Hz, C_2–H). IR

ν_{max}^{Nujol} cm^{-1}: 3000 (OH), 1720 (ester). *Anal.* Calcd for $C_{10}H_{16}ClNO_3S$: C, 45.19, H, 6.06; N, 5.27; Cl, 13.34; S, 12.06. Found: C, 45.15; H, 6.33; N, 5.23; Cl, 13.25; S, 12.15. MS *m/e*: 266 (M^+).

***tert*-Butyl (±)-7α-Azido-3-chloromethyl-3-methanesulfonyloxycepham-4-carboxylate (8)**——An ice-cooled solution of the thiazine **7** (133 mg) in THF (5 ml) was treated with triethylamine (140 μl) and methanesulfonyl chloride (39 μl). After stirring at 0° for 0.5 hr, the reaction mixture was cooled at −70°, and triethylamine (70 μl) and then azidoacetyl chloride (44 μl) were added. The mixture was allowed to warm slowly to room temperature, stirred for an additional 0.5 hr, poured into ice-water and extracted with AcOEt. The extract was washed successively with 5% aq. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was chromatographed on a column of silica gel with benzene–AcOEt (10: 1) to give 55 mg of **8** as colorless crystals. Yield, 26%. NMR ($CDCl_3$) δ: 1.53 (9H, s, *t*-Bu), 3.20 (3H, s, CH_3SO_3), 3.35, 4.07 (2H, AB-q, J=15.0 Hz, C_2–H_2), 4.50 (2H, s, CH_2Cl), 4.59 (1H, d, J=2.0 Hz, C_7–H), 5.02 (1H, s, C_4–H), 5.13 (1H, d, J=2.0 Hz, C_6–H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), 1782 (β-lactam), 1730 (ester).

***tert*-Butyl (±)-7α-Azido-3-chloromethyl-3-cephem-4-carboxylate (9)**——A solution of the cepham **8** (100 mg) in dry benzene (5 ml) was treated with pyridine (0.6 ml). The mixture was heated for 20 hr at 50°, poured into ice-water and extracted with AcOEt. The extract was washed successively with 5% aq. HCl, H_2O, 5% aq. $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel, eluting with benzene, to give 25 mg of crystalline **9**, and 46 mg of the starting material **8**. NMR ($CDCl_3$) δ: 1.56 (9H, s, *t*-Bu), 3.40, 3.77 (2H, AB-q, J=18.0 Hz, C_2–H_2), 4.47 (2H, s, CH_2Cl), 4.56 (1H, d, J=2.0 Hz, C_7–H), 4.67 (1H, d, J=2.0 Hz, C_6–H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), 1795 (β-lactam), 1730 (ester). MS *m/e*: 331 (M^+).

***tert*-Butyl (±)-7α-Azido-3-(1-methyl-1H-tetrazol-5-yl)thiomethyl-3-cephem-4-carboxylate (10)**——A solution of **9** (98 mg) in DMF (3 ml) was cooled to −70°, then 5-mercapto-1-methyl-1H-tetrazole (38 mg) and triethylamine (41 μl) were added. The mixture was stirred for 1 hr at −70°, warmed slowly to room temperature, poured into ice-water and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel with benzene–AcOEt (8: 1) to give 75 mg of **10** as colorless crystals. NMR (DMF-d_7) δ: 1.56 (9H, s, *t*-Bu), 3.73, 4.00 (2H, AB-q, J=18.0 Hz, C_2–H_2), 4.06 (3H, s, NCH_3), 4.29, 4.61 (2H, AB-q, J=14.0 Hz, C_3–CH_2), 5.01 (1H, d, J=2.0 Hz, C_6–H or C_7–H), 5.26 (1H, d, J=2.0 Hz, C_6–H or C_7–H), IR ν_{max}^{KBr} cm^{-1}: 2110 (N_3), 1780 (β-lactam), 1715 (ester).

***tert*-Butyl 2-Amino-3-chloromethyl-3-hydroxybutyrate (4a and 4b)**——Using the procedure described for the preparation of **3**, the anion generated from N-benzylideneglycinate **1** (R=*t*-Bu, 2.19 g) and *n*-BuLi (6.2 ml, 1 mmol=0.614 ml) was treated with chloroacetone (0.84 ml) followed by Girard reagent T (1.8 g). The crude product was purified by silica gel column chromatography with benzene–AcOEt (2: 1) to give 189 mg of the less polar thiazine isomer **4b**, 1.054 g of a mixture of **4a** and **4b**, and 203 mg of the more polar isomer **4a**. Yield, 66%. **4a**: NMR ($CDCl_3$) δ: 1.20 (3H, s, CH_3), 1.50 (9H, s, *t*-Bu), 2.61 (3H, s, OH, NH_2), 3.61 (1H, s, C_2–H), 3.71 (2H, s, CH_2Cl). IR $\nu_{max}^{Liq.}$ cm^{-1}: 3390, 3310 (OH, NH_2), 1730 (ester). **4b**: NMR ($CDCl_3$) δ: 1.31 (3H, s, CH_3), 1.51 (9H, s, *t*-Bu), 2.48 (3H, s, OH, NH_2), 3.47, 3.76 (2H, AB-q, J=12.0 Hz, CH_2Cl), 3.52 (1H, s, C_2–H). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3320 (OH, NH_2), 1730 (ester).

***tert*-Butyl 3-Chloromethyl-3-hydroxy-2-thioformamidobutyrate (11a)**——Using the procedure described for the preparation of **6**, the more polar amino alcohol **4a** (180 mg) was treated with ethyl thioformate (80 mg). The crude product was purified by column chromatography, eluting with benzene–AcOEt (3: 1), to give 137 mg of **11a** as colorless crystals, mp 101—104° (from ether–pet. ether). Yield, 63%. NMR ($CDCl_3$) δ: 1.40 (3H, s, CH_3), 1.52 (9H, s, *t*-Bu), 3.28 (1H, s, OH), 3.55, 3.78 (2H, AB-q, J=12.5 Hz, CH_2Cl), 5.51 (1H, d, J=8.5 Hz, C_2–H), 8.3 (1H, bs, NH), 9.65 (1H, d, J=6.0 Hz, CH=S). IR ν_{max}^{KBr} cm^{-1}: 3350, 3300 (OH, NH), 1710 (ester). MS *m/e*: 268 (M^+, $C_{10}H_{18}ClNO_3S$).

Ethyl 2-Amino-4-chloro-3-hydroxybutyrate (5a and 5b)——Using the above procedure, **5** was obtained from **1** (R=Et, 1.91 g) and chloroacetaldehyde (808 mg). The crude product was chromatographed on a column of silica gel with benzene–AcOEt (1: 1) to afford 391 mg of the less polar amino alcohol (**5a** or **5b**) and 250 mg of the more polar amino alcohol (**5b** or **5a**). The less polar isomer, NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.0 Hz, CH_3), 2.43 (3H, s, OH, NH_2), 3.58—3.77 (3H, m, CH_2Cl, C_2–H), 4.01—4.30 (1H, m, C_3–H), 4.27 (2H, q, J=7.0 Hz, $C\underline{H}_2CH_3$). The more polar isomer, NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2$), 2.54 (3H, s, OH, NH_2), 3.60—3.80 (3H, m, CH_2Cl, C_2–H), 3.9—4.2 (1H, m, C_3–H), 4.27 (2H, q, J=7.0 Hz, $CH_3C\underline{H}_2$).

Cyclization Reaction of 11a with K_2CO_3——Powdered K_2CO_3 (97 mg) was added to a solution of **11a** (54 mg) in acetone (3 ml), and the mixture was stirred for 3 hr at room temperature. After the insoluble material had been filtered off, the solvent was removed and the residue was triturated with ether to give 15 mg of the thiazine **12a** as colorless crystals, mp 140—142° (from benzene). This product was identical with the thiazine **12a** as judged by comparison of the NMR spectra.

***tert*-Butyl 2-Thioformamidoacetate (14)**——Ethyl thioformate (4.51 g) was added to a solution of *tert*-butyl glycinate **13** (5.86 g) in CCl_4 (20 ml) with stirring at 0° and the mixture was stirred for 15 min. After removing the solvent, the residue was chromatographed on a column of silica gel, eluting with benzene–AcOEt (6: 1), to give 6.45 g of **14** as crystals, mp 50—51° (from ether–pet-ether). Yield, 80%. NMR ($CDCl_3$) δ: 1.52 (9H, s, *t*-Bu), 4.36 (2H, d-d, J=1.2, 4.8 Hz, CH_2), 7.5—9.3 (1H, bs, NH), 9.57 (1H, d-t, J=1.2, 6.0 Hz, HC=S). IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1735 (ester). *Anal.* Calcd for $C_7H_{13}NO_2S$: C, 47.97; H, 7.47; N, 7.99;

S, 18.29. Found: C, 47.76; H, 7.42; N, 7.83; S, 18.57.

***tert*-Butyl (±)-5α-Hydroxy-5β-methyl-4,5-dihydro-6H-1,3-thiazine-4α-carboxylate (12a)**——The thioformamide **14** (1.05 g) was added to a suspension of NaH (144 mg) in THF (50 ml) with stirring at 0° under nitrogen, and 10 min later bromoacetone (504 mg) was added. After stirring for 20 min, the reaction mixture was poured into an ice-cooled 10% K_2HPO_4 solution and extracted with AcOEt. The extract was dried over $MgSO_4$, and concentrated *in vacuo* to give an oily product (952 mg), which was crystallized from ether. Recrystallization from benzene gave **12a** as colorless crystals, mp 140—141°. Yield, 69%. NMR ($CDCl_3$) δ: 1.38 (3H, s, CH_3), 1.54 (9H, s, *t*-Bu), 2.88 (1H, d-d, $J=1.3$, 12.5 Hz, C_6–H), 3.01 (1H, d, $J=12.5$ Hz, C_6–H), 3.50 (1H, s, OH), 4.07 (1H, m, C_4–H), 8.33 (1H, d, $J=2.5$ Hz, C_2–H). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3500 (OH), 1719 (ester). *Anal.* Calcd for $C_{10}H_{17}NO_3S$: C, 51.92; H, 7.40; N, 6.05; S, 13.86. Found: C, 51.98; H, 7.44; N, 5.78; S, 14.41. MS *m/e*: 231 (M^+).

***tert*-Butyl (±)-7α-Azido-3-methyl-3-cephem-4-carboxylate (17)**——Acetic anhydride (1 ml) was added to a solution of **12a** (231 mg) in pyridine (6 ml) and the mixture was stirred at 60° for 2 days, then poured into an ice-cooled 10% K_2HPO_4 solution and extracted with AcOEt. The extract was dried over $MgSO_4$ and concentrated *in vacuo* to afford crude acetate **16**. The acetate was dissolved in CH_2Cl_2 (18 ml) and cooled with ice-water, then triethylamine (168 μl) and azidoacetyl chloride (106 μl) were added under nitrogen, and the mixture was stirred for 1 hr at 0° and 1 hr at room temperature. After dilution with CH_2Cl_2 (20 ml), the mixture was washed successively with 5% HCl, 5% aq. $NaHCO_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by preparative thin-layer chromatography (TLC) with benzene–AcOEt (4: 1) to give 60 mg of **17** as colorless crystals, mp 82—83° (from *n*-hexane). Yield,20%. NMR ($CDCl_3$) δ: 1.55 (9H, s, *t*-Bu), 2.07 (3H, d, $J=1.0$ Hz, CH_3), 3.16 (1H, d, $J=18.0$ Hz, C_2–H), 3.48 (1H, d-q, $J=1.0$, 18.0 Hz, C_2–H), 4.42 (1H, d, $J=1.8$ Hz, C_7–H), 4.59 (1H, d, $J=1.8$ Hz, C_6–H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_3), 1778 (β-lactam), 1715 (ester), 1640 (C=C). MS *m/e*: 296 (M^+). *Anal.* Calcd for $C_{12}H_{16}N_4O_3S$: C, 48.36; H, 5.44; N, 18.90; S, 10.81. Found: C, 48.67; H, 5.33; N, 18.67; S, 10.99.

***tert*-Butyl (±)-7α-Amino-3-methyl-3-cephem-4-carboxylate (18)**——The azide **17** (277 mg) was hydrogenated over 10% Pd-C (277 mg) in THF (30 ml) containing *p*-toluenesulfonic acid monohydrate (179 mg). When the starting material had disappeared, the catalyst was filtered off and washed with AcOEt. The filtrate and the washings were combined, washed successively with 5% aq. $NaHCO_3$, H_2O and aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo* to give 212 mg of **18** as a powder. NMR ($CDCl_3$) δ: 1.56 (9H, s, *t*-Bu), 1.96 (2H, s, NH_2), 2.01 (3H, splintered s, CH_3), 3.07 (1H, d, $J=18.0$ Hz, C_2–H), 3.47 (1H, d-q, $J=1.0$, 18.0 Hz, C_2–H), 4.07 (1H, d, $J=2.0$ Hz, C_7–H), 4.42 (1H, d, $J=2.0$ Hz, C_6–H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3300 (NH_2), 1775 (β-lactam), 1720 (ester), 1640 (C=C).

***tert*-Butyl (±)-3-Methyl-7α-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (19)**——*o*-Nitrobenzenesulfenyl chloride (152 mg) and triethylamine (112 μl) were added with cooling at 0° to a solution of **18** (212 mg) in THF (5 ml). The reaction mixture was stirred for 15 min at 0° and for 1.5 hr at room temperature, then diluted with AcOEt. The mixture was washed successively with aq. NaCl, 5% aq. $NaHCO_3$ and aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel, eluting with benzene–AcOEt (10: 1), to give 266 mg of **19** as crystals. Yield, 54%. NMR ($CDCl_3$) δ: 1.42 (9H, s, *t*-Bu), 1.99 (3H, s, CH_3), 3.03, 3.51 (2H, AB-q, $J=18.5$ Hz, C_2–H_2), 4.03 (1H, d, $J=7.0$ Hz, NH), 4.41 (1H, d-d, $J=2.0$, 7.0 Hz, C_7–H), 4.68 (1H, d, $J=2.0$ Hz, C_6–H), 7.1—8.4 (4H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1770 (β-lactam), 1715 (ester), 1635 (C=C).

***tert*-Butyl (±)-3-Methyl-7β-*o*-nitrobenzenesulfenamido-3-cephem-4-carboxylate (20)**——A solution of **19** (164 mg) in CH_2Cl_2 (2.5 ml) was added to a suspension of activated MnO_2 (4.92 g) in CH_2Cl_2 (2.5 ml) with ice-cooling. After stirring for 50 min at room temperature, the insoluble material was filtered off and washed with AcOEt. The filtrate and the washings were combined and concentrated *in vacuo* to give 118 mg of *tert*-butyl (±)-3-methyl-7-*o*-nitrobenzenesulfenimino-3-cephem-4-carboxylate as yellow crystals. The resulting sulfenimine was dissolved in THF (11 ml)-dimethyl sulfoxide (DMSO, 1.6 ml), then a solution of $NaBH_4$ (46 mg) in THF (11 ml)–DMSO (1.6 ml) was added with ice-cooling. After stirring for 10 min, the mixture was quenched with AcOH (0.48 ml) and extracted with AcOEt. The extract was washed successively with H_2O, 5% aq. $NaHCO_3$ and aq. NaCl, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative TLC with benzene–AcOEt (4: 1) to afford 54 mg of **20** as crystals, mp 208—209° (from isopropyl ether–$CHCl_3$). Yield, 33%. NMR (DMF-d_7) δ: 1.51 (9H, s, *t*-Bu), 2.02 (3H, s, CH_3), 3.37, 3.70 (2H, AB-q, $J=18.0$ Hz, C_2–H_2), 5.01 (1H, d-d, $J=5.0$, 8.5 Hz, C_7–H), 5.13 (1H, d, 5.0 Hz, C_6–H), 5.72 (1H, d, $J=8.5$ Hz, NH), 7.3—8.4 (4H, m, aromatic H). IR ν_{max}^{KBr} cm^{-1}: 3450 (NH), 1750 (β-lactam), 1710 (ester), 1635 (C=C).

***tert*-Butyl (±)-7β-Amino-3-methyl-3-cephem-4-carboxylate (21)**——A solution of KI (108 mg) in a mixture of MeOH (1.5 ml) and AcOH (0.22 ml) was added with ice-cooling to a solution of **20** (27 mg) in CH_2Cl_2 (0.5 ml), then aq. $Na_2S_2O_3$ (1 M solution, 0.135 ml) was added to the mixture. The whole was stirred for 5 hr at room temperature, diluted with AcOEt, washed with 5% aq. $NaHCO_3$ and aq. NaCl, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel with CH_2Cl_2–AcOEt (1: 1) to give 17 mg of **21**. Yield, 98%. NMR ($CDCl_3$) δ: 1.51 (9H, s, *t*-Bu), 1.85 (2H, bs, NH_2), 2.04 (3H, s, CH_3), 3.08, 3.55 (2H, AB-q, $J=19.0$ Hz, C_2–H_2), 4.68 (1H, d, $J=5.5$ Hz, C_6–H), 4.97 (1H, d, $J=5.5$ Hz, C_7–H). IR ν_{max}^{KBr} cm^{-1}: 3400, 3320 (NH_2), 1770 (β-lactam), 1715 (ester), 1640 (C=C).

(±)-7β-Aminodeacetoxycephalosporanic Acid·CF_3COOH (22)——The *tert*-butyl ester **21** (17 mg) was dissolved in CF_3COOH (1 ml) and the solution was stirred for 50 min at room temperature. After removal of the CF_3COOH, the residue was redissolved in benzene containing a small amount of MeOH and lyophilized to give 16 mg of **22** as a powder. NMR (CF_3COOD) δ: 2.50 (3H, s, CH_3), 3.41, 3.78 (2H, AB-q, $J=17.0$ Hz, C_2–H_2), 5.36 (1H, d, $J=4.0$ Hz, C_6–H), 5.47 (1H, d, $J=4.0$ Hz, C_7–H). IR ν_{max}^{KBr} cm^{-1}: 1790 (β-lactam). The spectroscopic data for **22** were consistent with those of 7-aminodeacetoxycephalosporanic acid·CF_3COOH[7] derived from natural penicillin.

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7) The salt was prepared by treatment of optically active 7-ADCA with CF_3COOH.