Chem. Pharm. Bull. 28(1) 62—69 (1980)

# 3-Trifluoromethylcephalosporins. I. Total Synthesis of *tert*-Butyl (±)-7-Amino-3-trifluoromethyl-3-cephem-4-carboxylate[1]

Taiichiro Watanabe, Yoichi Kawano, Teruo Tanaka, Toshihiko Hashimoto, and Tetsuo Miyadera

*Central Research Laboratories, Sankyo Co., Ltd.*[2]

(Received June 8, 1979)

*tert*-Butyl (±)-7-amino-3-trifluoromethyl-3-cephem-4-carboxylate (**16**) and the 2-cephem derivative (**21**) were obtained by total synthesis starting from *tert*-butyl N-benzylideneglycinate (**1**). This synthesis is the first example of the reaction of the N-benzylideneglycinate anion with a reactive α-haloketone to give a β-hydroxy-γ-halo-α-amino ester (**5a** and **5b**). The amino esters were treated with ethyl thioformate and then potassium carbonate, leading to the 4,5-dihydro-6H-1,3-thiazine derivatives (**8a** and **8b**). After cycloaddition of **8a** and **8b** with azidoacetyl chloride and catalytic hydrogenation of the azido group, the resulting *trans* 7-aminocephem compound (**12**) was converted to the *cis* isomer (**16**) by the established method, involving reduction of the *o*-nitrobenzenesulfenimino derivative (**14**).

**Keywords**——3-trifluoromethylcephalosporin; total synthesis; N-benzylideneglycine ester; oxazolidine; α-amino acid derivatives; 1,3-thiazine derivatives; cycloaddition reaction; *o*-nitrobenzenesulfenamidocephalosporins; reduction with diborane; *trans-cis* conversion

The chemical modification of cephalosporin derivatives at the C-3 position is of great interest from the viewpoint of structure–activity relationships. As reported in a previous paper,[3] cephalosporin derivatives with a strongly electron-withdrawing group at the C-3 position exhibit higher antibacterial activity *in vitro*. This apparent effect of strongly electron-withdrawing functional groups caused us to consider the synthesis of 3-trifluoromethylcephalosporin compounds bearing the $CF_3$ group. We considered several approaches, involving partial transformation of penicillin,[4] partial transformation of cephalosporin derivatives[5] or total synthesis; however, replacement of a C-3 substituent of the cephem ring with the $CF_3$ group appeared to be impossible by the known methods. The present total synthesis was undertaken taking into account the possibility of its applicability to the preparation of other modified β-lactam antibiotics.

The present synthesis of 3-trifluoromethylcephalosporin derivatives involves a new route to 4,5-dihydro-6H-1,3-thiazines, starting with the reaction of an N-benzylideneglycine ester (**1**) with a reactive α-haloketone (**3**).[6]

The carbonyl group of 1,1,1-trifluoro-3-bromoacetone (**3**) is so reactive that it readily forms the hemiacetal derivative in contact with methanol. The bromoketone activated by

1) Part of this work has been reported in a preliminary communication: T. Watanabe, Y. Kawano, T. Tanaka, T. Hashimoto, M. Nagano, and T. Miyadera, *Tetrahedron Lett.*, **1977**, 3053.
2) Location: *1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan.*
3) T. Hashimoto, Y. Kawano, S. Natsume, T. Tanaka, T. Watanabe, M. Nagano, S. Sugawara, and T. Miyadera, *Chem. Pharm. Bull.*, **26**, 1803 (1978).
4) The Shionogi group has succeeded in obtaining 3-trifluoromethylcephalosporins from a penicillin derivative, and this work was presented at the same meeting as our paper. S. Yamamoto, N. Haga, T. Aoki, S. Hayashi, H. Tanida, and W. Nagata, The 3rd Lecture Meeting sponsored by Yukigosei Kyokai, Tokyo, June, 1977, Abstracts of Papers, p. 25; *Idem*, *Heterocycles*, **8**, 283 (1977).
5) A Du Pont patent (US-3919204) has claimed that 3-trifluoromethylcephalosporin derivatives may be produced from 3-carboxycephalosporin derivatives, but no physical or biological data are given.
6) The N-benzylideneglycinate anion was shown to react with other α-haloketones, T. Miyadera, T. Watanabe, Y. Kawano, T. Tanaka, and T. Hashimoto, Japanese patent provisional publication No. 53-149924.

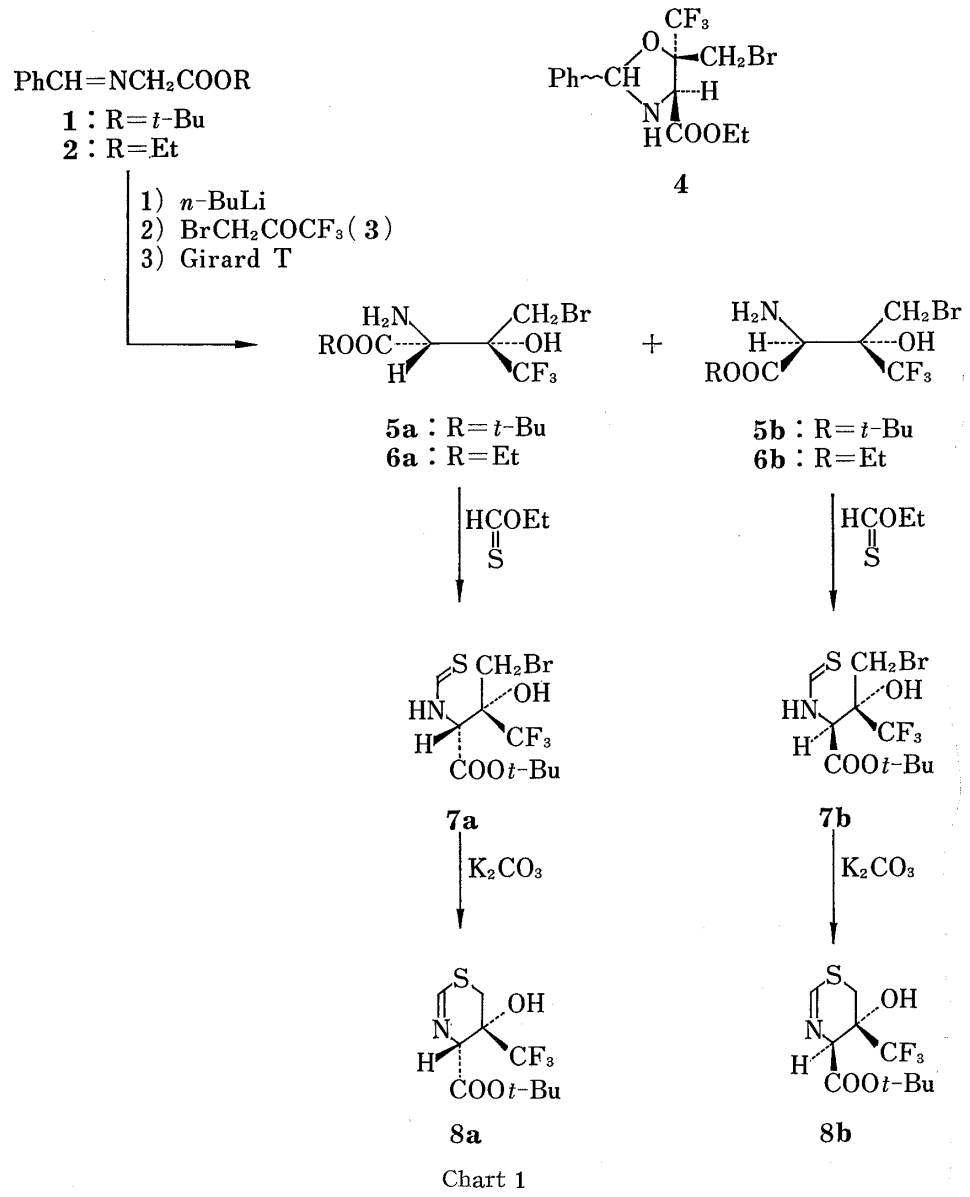


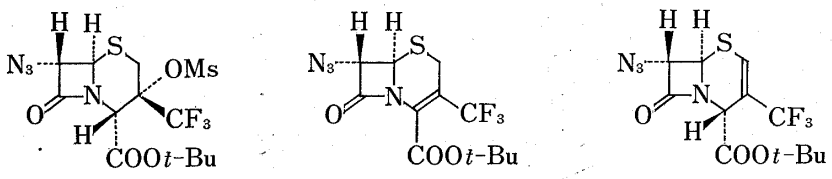

Chart 1

the four halogen atoms underwent reaction with the anion[7] generated from **1** to give the expected products. *tert*-Butyl N-benzylideneglycinate (**1**) was treated with *n*-butyllithium in tetrahydrofuran (THF) at −78°, followed by addition of a solution of **3** in THF. The reaction mixture was quenched with an equimolar amount of acetic acid and the resulting product was treated with Girard reagent T ($(CH_3)_3\overset{+}{N}CH_2CONHNH_2\ Cl^-$) in methanol at room temperature to give a 70% yield of a diastereomeric mixture of **5a** and **5b** in a ratio of approximately 3:1. Similarly, ethyl N-benzylideneglycinate (**2**) was treated with *n*-butyllithium followed by reaction with **3** and then Girard reagent T to yield an approximately

7) Prior to this reaction, we examined the reactivity of the *tert*-butyl N-benzylideneglycinate anion with alkylating agents such as methyl iodide and benzyl bromide, and found that the alkylation reactions proceeded satisfactorily. During this work, alkylation reactions of the N-benzylideneglycinate anion have been reported by two groups: G. Stork, A.Y.W. Leong, and A.M. Touzin, *J. Org. Chem.*, **41**, 3491 (1976); T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* **25**, 2287 (1977). Asymmetric alkylations of the ketimine derived from (−)-menthone and alanine ester were described by the latter group at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1975, Abstracts of Papers, II, p. 4.

3:1 mixture of **6a** and **6b**. In order to examine the intermediates of the above reaction, the reaction mixture of **2** and **3** was worked up after quenching with acetic acid. Column chromatography of the resulting mixture afforded an oxazolidine derivative (**4**) as a presumed intermediate, together with the amino ester (**6a**). The isomeric amino ester **6b** was obtained on treatment of **4** with *p*-toluenesulfonic acid. The proposed structures of **6a** and **6b** were consistent with their spectroscopic data, and stereochemistries were assigned by comparison of their nuclear magnetic resonance (NMR) data with those of **5a** and **5b**. The stereochemical assignments of **5a** and **5b** were finally settled when the isomers were converted into the 4,5-dihydro-6H-1,3-thiazine derivatives (**8a** and **8b**) and also into the cepham derivative (**9**). The less polar amino ester **5a** was treated with ethyl thioformate in carbon tetrachloride at room temperature to give the thioformamide **7a** in 57% yield. Ring closure of the thioformamide to the dihydro-1,3-thiazine derivative **8a** was effected by treatment with powdered potassium carbonate in acetone at room temperature. Similar treatment of the more polar amino ester **5b** with ethyl thioformate afforded the isomeric thioformamide **7b**. This was similarly cyclized to the 1,3-thiazine derivative **8b** by stirring with potassium carbonate in acetone. The stereochemistries of the two isomeric 1,3-thiazines were deduced from the hydroxyl absorption bands in their infrared (IR) spectra. The hydroxyl group of **8a** showed an absorption band at 3488 $cm^{-1}$ in dilute solution (1.7 mmol in $CCl_4$), indicative of intramolecular hydrogen bonding with the ester carbonyl. The IR spectrum of **8b** showed an absorption band at 3585 $cm^{-1}$, assignable to a free hydroxyl group, under the same conditions. From these results the former thiazine was assumed to possess hydroxyl and ester groups in the *cis* configuration. It seems likely that the two functional groups of the other thiazine **8b** are in the *trans* (possibly *quasi-diaxial*) configuration. The stereochemical assignment was supported by X-ray analysis of the cepham derivative **9** derived from **8a**. Based on this determination, the two dihydro-1,3-thiazines **8a** and **8b**, the thioamides **7a** and **7b**, and amino esters **5a** and **5b** could be conclusively assigned as shown in Chart 1.

In the conversion of **8a** into **10**, the hydroxyl group was initially mesylated with methanesulfonyl chloride after treatment with sodium hydride in THF. The mesylated intermediate was, without isolation, subjected to a [2+2]cycloaddition reaction[8] with azidoacetyl chloride in the presence of triethylamine to give **9** and **10** in yields of 70 and 15%, respectively. The formation ratio of **9** and **10** varies over a wide range depending upon the reaction conditions. The mesyloxy group of **9** was eliminated to give **10** by prolonged stirring with alumina in benzene at room temperature. More effectively, the mesylated cepham derivative **9** was transformed to the 3-cephem derivative **10** in excellent yield by treatment with pyridine in benzene at 50° for 70 hr. The 3-cephem compound **10** was also obtained in poorer yield from the other 1,3-thiazine derivative (**8a**) by mesylation and subsequent treatment with azidoacetyl chloride. Treatment of **10** with triethylamine in benzene for 72 hr at room temperature afforded the 2-cephem isomer (**11**)[9] in 69% yield. The structure and




**9** **10** **11**

Chart 2

8) A.K. Bose, B. Anjaneyulu, S.K. Bhattacharya, and M.S. Manhans, *Tetrahedron*, **23**, 4769 (1967); R.W. Ratcliffe and B.G. Christensen, *Tetrahedron Lett.*, **1973**, 4649.
9) The stereochemistry of **11** was tentatively assigned on the basis of reported results: E. van Heyningen and L.K. Ahern, *J. Med. Chem.*, **11**, 933 (1968).

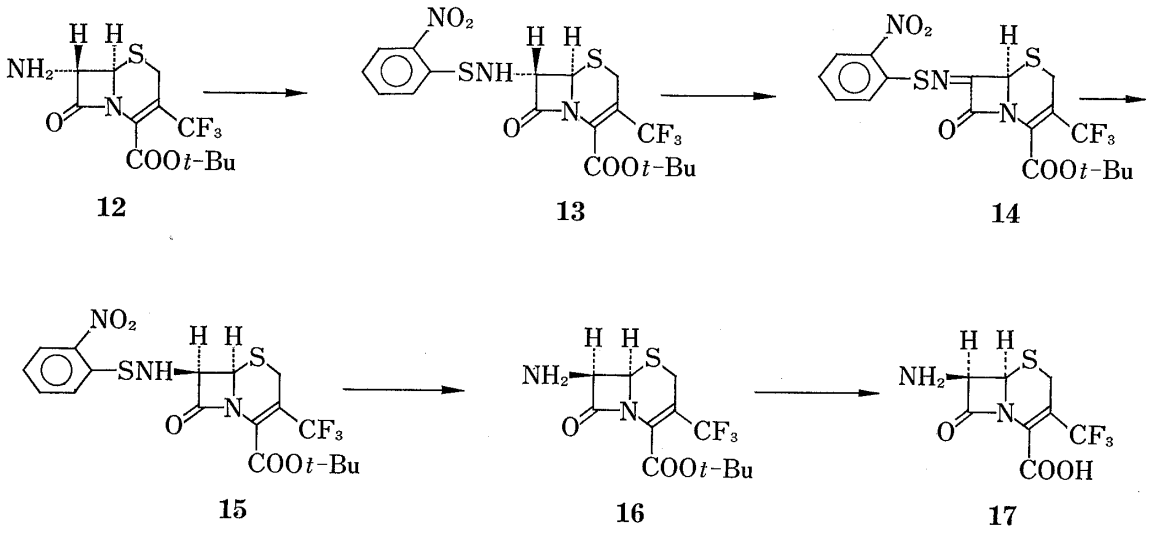



Chart 3

stereochemistry of **9** were assigned on the basis of spectral (NMR and IR) data and mechanistic considerations. The *trans* relationship of the two hydrogens at the C-6 and C-7 positions was indicated by a doublet ($J$=1.5 Hz) at 4.57 ppm due to the C-7 proton in the NMR spectrum. The configuration of the 4-carboxylate group was assigned as *cis* to the C-6 H, since azidoketene generated from azidoacetyl chloride should undergo preferential cycloaddition on the opposite site from the carboxylate group as a result of dipolar repulsion. The stereochemistry of **9** was unambiguously determined by Hata and Tamura[10] in these laboratories. The azido group of **10** was hydrogenated over 10% Pd–C in the presence of *p*-toluenesulfonic acid to give the amino derivative (**12**). In this catalytic hydrogenation the presence of the sulfonic acid appeared to reduce the decomposition of the amino product and improve the yield of **12**. The epimerization of the amino group was initially performed by the method of Christensen and co-workers[11] involving the metalation and protonation of the *p*-nitrobenzylieneamino derivative. However, this method gave rather poor yields, and it was difficult to separate the *cis* isomer from the concomitantly formed *trans* isomer. This difficulty was overcome by utilizing a method recently established by Hiraoka and co-workers,[12] as shown in Chart 3. With this method the *cis* isomer **16** could be obtained in better overall yield. The present paper provides the first example of a successful application to the conversion of a *trans* cephalosporin derivative to the *cis* isomer. The *trans* 7-aminocephem **12** was reacted with *o*-nitrobenzenesulfenyl chloride in the presence of triethylamine at room temperature for 2 hr to give the sulfenamide (**13**) in 85% yield. Treatment of **13** with a large excess of activated manganese dioxide in dichloromethane at 0°—room temperature afforded the 7-*o*-nitrobenzenesulfenimino derivative (**14**). This imino compound was subjected to reduction with diborane in THF without purification. The oxidation and subsequent reduction of **13** afforded the *cis*-*o*-nitrosulfenamide (**15**) in 33% yield, together with a small amount of the *trans* isomer **13**. When sodium borohydride was used in place of diborane for the imine reduction, the yield of **15** was poorer, probably because 3-trifluoromethylcephem compounds are unstable in alkaline media. The major reduction product of **14** was determined to be the *cis* isomer by NMR spectroscopy; the C-6 and C-7 protons were coupled with $J$=5.0 Hz. Treatment of **15** with hydrogen chloride in methanol yielded the

10) T. Hata and C. Tamura, unpublished results.
11) R.A. Firestone, N.S. Maciejewicz, R.W. Ratcliffe, and B.G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).
12) T. Kobayashi, K. Iino, and T. Hiraoka, *J. Am. Chem. Soc.*, **99**, 5505 (1977); *idem*, *Chem. Pharm. Bull.*, **27**, 2727 (1979).

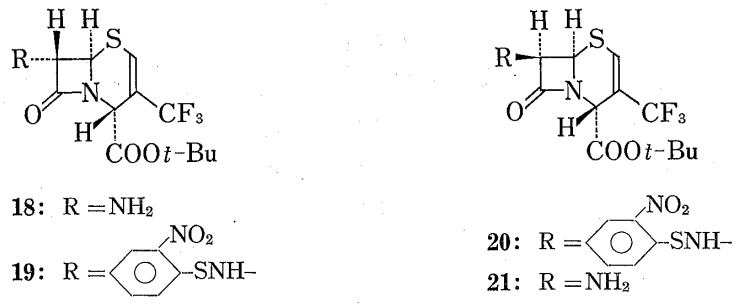



Chart 4

*cis* 7-aminocephem derivative (**16**) in 83% yield. The NMR spectrum of **16** in $CDCl_3$ showed a doublet at 4.79 ppm due to the C-6 H with a coupling constant of 5.0 Hz.

The *cis* 7-amino-2-cephem derivative (**21**) was obtained from the *trans* azido compound **11** by the same procedures, involving catalytic hydrogenation, and the oxidation and reduction of the *o*-nitrobenzenesulfenamido derivative (**19**). The *tert*-butyl group of **16** was removed with trifluoroacetic acid to give the 4-carboxylic acid (**17**). The 7-amino compounds **16** and **17** were converted to acetyl derivative to test for antibacterial activity, as described in the following paper.[13]

## Experimental

Solutions were concentrated below 30° with rotary evaporators under reduced pressure. 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 $\delta$ 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-bromo-3-hydroxy-3-trifluoromethylbutyrate (5a and 5b)**——A solution of *n*-butyllithium in *n*-hexane (102 ml, 0.614 ml=1 mmol) was added to a stirred solution of **1** (32.9 g) in THF (300 ml) with cooling at −78° under nitrogen. After stirring for 5 min, 3-bromo-1,1,1-trifluoroacetone (**3**, 28.7 g) was added dropwise to the above solution and the mixture was gradually warmed to −20°. The reaction mixture was then recooled to −78°, quenched with AcOH (9.0 g) and evaporated to dryness. The residue was partitioned between ether and $H_2O$, and the organic layer was dried over $MgSO_4$, then concentrated to leave a brown oil. The oil was dissolved in MeOH (300 ml) containing Girard reagent T (25.3 g) and the mixture was stirred for 1 hr at room temperature. The solvent was removed and the residue was shaken with ether and $H_2O$. The ether layer was dried over $MgSO_4$ and evaporated to yield a mixture of two diastereomers (**5a**, and **5b**). The mixture was chromatographed on a column of silica gel, eluting with benzene–AcOEt (20: 1), to give **5a** (21.0 g) and **5b** (5.9 g) as an oil. Less polar isomer **5a**: NMR ($CDCl_3$) $\delta$: 1.53 (9H, s, *t*-Bu), 3.19 (3H, bs, $NH_2$, OH), 3.87 (2H, s, $CH_2Br$), 3.95 (1H, q, $J$=1.2 Hz, CHCOO). More polar isomer **5b**: NMR ($CDCl_3$) $\delta$: 1.56 (9H, s, *t*-Bu), 3.40 (3H, bs, $NH_2$, OH), 3.63, 3.91 (2H, AB-q, $J$=11.0 Hz, $CH_2Br$), 3.89 (1H, q, $J$=1.0 Hz, CHCOO).

**Ethyl 2-Amino-4-bromo-3-hydroxy-3-trifluoromethylbutyrate (6a and 6b)**——A solution of *n*-butyllithium in *n*-hexane (68 ml, 0.614 ml=1 mmol) was added to a stirred solution of **2** (21.0 g) in THF (200 ml) with cooling below −60°. After stirring for 1 hr, **3** (19.1 g) was added and the mixture was allowed to warm to −25°. The reaction mixture was then cooled to −60°, acidified with 48% aq. HBr (42 ml) and stirred for 15 min. The solvent was removed by evaporation and the residue was shaken with ether and 5% aq. HBr. The aq. layer was washed with ether, made alkaline with 5% aq. $NaHCO_3$ and extracted with ether. The extract was washed with $H_2O$, dried over $Na_2SO_4$ and evaporated down to give an oil. Chromatography on a column of silica gel with benzene–AcOEt (70: 1) as an eluent afforded **6a** (12.3 g) and **6b** (3.86 g). Less polar isomer **6a**: NMR ($CDCl_3$) $\delta$: 1.31 (3H, t, $J$=7.0 Hz, $CH_2CH_3$), 3.35 (3H, s, $NH_2$, OH), 3.82 (2H, s, $CH_2Br$), 4.06 (1H, s, CHCOO), 4.27 (2H, q, $J$=7.0 Hz, $CH_2CH_3$). More polar isomer **6b**: NMR ($CDCl_3$) $\delta$: 1.32 (3H, t, $J$=7.0 Hz, $CH_2CH_3$), 3.14 (3H, s, $NH_2$, OH), 3.67, 3.88 (2H, AB-q, $J$=11.0 Hz, $CH_2Br$), 3.97 (1H, s, CHCOO).

**Ethyl 5-Bromomethyl-2-phenyl-3-trifluoromethyl-1,3-oxazolidine-4-carboxylate (4) and 5a**——A stirred solution of **2** (955 mg) in THF (10 ml) was treated with *n*-butyllithium (3 ml, 0.614 ml=1 mmol) at −78°

13) Y. Kawano, T. Watanabe, J. Sakai, H. Watanabe, M. Nagano, T. Nishimura, and T. Miyadera, *Chem. Pharm. Bull*, **28**, 62 (1980).

under nitrogen. After stirring for 30 min, **3** (1.22 g) was added and the mixture was warmed to −25° over 1.5 hr. The mixture was then recooled to −78° and quenched with AcOH (0.31 ml). Removal of the solvent gave a brown oil, which was extracted with $CHCl_3$. After washing with $H_2O$ and drying over $MgSO_4$, the solvent was evaporated off and the residual oil was chromatographed on silica gel with benzene as an eluent to afford **4** (163 mg) as a pale yellow oil. NMR ($CDCl_3$) $\delta$: 1.28 (3H, t, $J$=7.0 Hz, Me), 3.80 (2H, s, $CH_2Br$), 4.27 (2H, q, $J$=7.0 Hz, $C\underline{H}_2CH_3$), 4.33 (1H, s, $C_4$–H), 5.58 (1H, bs, $C_2$–H), 7.25—7.85 (5H, m, aromatic H), 3.30 (1H, bs, NH). Further elution of the column with benzene gave **5a** (172 mg).

**Conversion of 4 into 5b**——A solution of **4** (163 mg) and *p*-toluenesulfonic acid hydrate (97 mg) in ether (20 ml) was stirred for 3 hr at room temperature. The reaction mixture was washed successively with $H_2O$, 5% aq. $K_2CO_3$, and $H_2O$. After drying over $MgSO_4$, the solvent was evaporated off and the residual oil was purified by preparative TLC (benzene–AcOEt=4: 1) to give **5b** (27 mg).

***tert*-Butyl 4-Bromo-3-hydroxy-2-thioformamido-3-trifluoromethylbutyrate (7a and 7b)**——A solution of **5a** (18.0 g) and ethyl thioformate (6.2 g) in $CCl_4$ (8 ml) was stirred for 24 hr at room temperature. The colorless crystalline precipitate (**7a**, 4.2 g) was collected by filtration. The filtrate was concentrated to leave a brown oil, which was chromatographed on a column of silica gel, eluting with benzene–AcOEt (4: 1), to yield an additional crop of **7a** (3.7 g). NMR ($CDCl_3$) $\delta$: 1.53 (9H, s, *t*-Bu), 3.77, 4.05 (2H, AB-q, $J$=12.0 Hz, $CH_2Br$), 4.56 (1H, bs, OH), 6.18 (1H, bd, $J$=9.5 Hz, C$\underline{H}$COO), 8.15 (1H, bs, NH), 9.65 (1H, d-d, $J$=9.5, 1.0 Hz, C$\underline{H}$=S).

The more polar amino ester (**5b**, 5.8 g) was treated with ethyl thioformate (3.24 g) in $CCl_4$ (4 ml) for 9 hr at room temperature. Work-up as described above and chromatography on a column of silica gel, eluting with benzene–AcOEt (20: 1), afforded **7b** (2.5 g) as crystals. NMR ($CDCl_3$) $\delta$: 1.54 (9H, s, *t*-Bu), 3.71 (2H, s, $CH_2Br$), 5.96 (1H, bd, $J$=9.0 Hz, C$\underline{H}$COO), 8.41 (1H, b, NH), 9.65 (1H, d, $J$=6.0 Hz, C$\underline{H}$=S).

***tert*-Butyl 5-Hydroxy-5-trifluoromethyl-4,5-dihydro-6H-1,3-thiazine-4-carboxylate (8a and 8b)**——Compound **7a** (6.2 g) was added to a suspension of powdered $K_2CO_3$ (7.03 g) in acetone (110 ml), and the mixture was stirred for 20 min at room temperature. The inorganic material was removed by filtration and washed with acetone. Removal of the acetone by evaporation gave a brown oil which was purified by chromatography on a column of silica gel, eluting with hexane–AcOEt (9: 1), to give **8a** (3.32 g) as colorless crystals, mp 128—130°. *Anal.* Calcd for $C_{10}H_{14}F_3NO_3S$: C, 42.21; H, 4.92; N, 4.92; S, 11.26; F, 20.05. Found: C, 42.34; H, 5.09; N, 4.56; S, 11.01; F, 19.78. IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3488 (OH), 1717 (ester). NMR (100 MHz) ($CDCl_3$) $\delta$: 1.53 (9H, s, *t*-Bu), 3.05 (1H, d-d-d, $J$=13.0, 1.2, 1.0 Hz, $C_6$–H), 3.14 (1H, d, $J$=13.0 Hz, $C_6$–H), 4.19 (1H, d-d, $J$=1.0, 3.0 Hz, $C_4$–H), 5.40 (1H, bs, OH), 8.34 (1H, d-d, $J$=1.2, 3.0 Hz, $C_2$–H).

The isomeric dihydrothiazine (**8b**) was prepared from **7b** (9.62 g) according to the procedure described above. Colorless crystals, mp 159—161°. Yield, 3.31 g. *Anal.* Calcd for $C_{10}H_{14}F_3NO_3S$: C, 42.21; H, 4.92; N, 4.92; S, 11.26; F, 20.05. Found: C, 42.18; H, 5.03; N, 4.76; S, 11.03; F, 19.75. IR $\nu_{max}^{CCl_4}$ $cm^{-1}$: 3585 (0H), 1736 (ester). NMR (100 MHz) ($CDCl_3$) $\delta$: 1.48 (9H, s, *t*-Bu), 2.93 (1H, d-d-d, $J$=13.0, 2.5, 1.5 Hz, $C_6$–H), 3.73 (1H, d, $J$=13.0 Hz, $C_6$–H), 4.62 (1H, d-d, $J$=2.5, 1.5 Hz, $C_4$–H), 8.32 (1H, d-d, $J$=1.5, 1.5 Hz, $C_2$–H).

***tert*-Butyl (±)-7α-Azido-3-trifluoromethyl-3-cephem-4-carboxylate (10) and *tert*-Butyl (±)-7α-azido-3α-mesyloxy-3β-trifluoromethyl-cepham-4α-carboxylate (9)**——A solution of **8a** (9.18 g) in THF (100 ml) was added to a suspension of NaH (1.70 g, 50% mineral oil dispersion, washed with *n*-hexane) in THF (150 ml) with cooling at 0° under nitrogen. After stirring for 15 min methanesulfonyl chloride (2.77 ml) was added and the solution was stirred for 1.5 hr at 0°. The reaction mixture was then recooled to −78°, and triethylamine (5.08 ml) and then azidoacetyl chloride (3.19 g) were added. The mixture was slowly warmed to room temperature over a 2 hr period, poured into aq. NaCl and extracted with AcOEt. The extract was washed successively with 5% HCl, 5% aq. $NaHCO_3$ and aq. NaCl, then dried over $MgSO_4$. Removal of the solvent gave a yellow oil, which was chromatographed on a column of silica gel, eluting with benzene, to give **10** (1.70 g) as colorless crystals. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2100 ($N_3$), 1792 (β-lactam), 1735 (ester). NMR ($CDCl_3$) $\delta$: 1.58 (9H, s, *t*-Bu), 3.50 (2H, m, 2×$C_2$–H), 4.70 (2H, s, $C_6$–H, $C_7$–H). Further elution with benzene–AcOEt (10: 1) gave **9** (10.0 g) as colorless crystals. NMR ($CDCl_3$) $\delta$: 1.56 (9H, s, *t*-Bu), 3.18 (3H, s, OMs), 3.50, 4.18 (2H, AB-q, $J$=14.8 Hz, 2×$C_2$–H), 4.57 (1H, d, $J$=1.5 Hz, $C_7$–H), 4.87 (1H, s, $C_4$–H), 5.05 (1H, bs, $C_6$–H). The crystals were recrystallized from benzene to obtain a sample for X-ray analysis.

The 3-cephem compound (**10**) was also prepared from **8b** (1.57 g) according to the procedure described above. Yield, 279 mg. In this case, the mesyloxycepham compound corresponding to **9** was not obtained.

**Conversion of 9 into 10**——A solution of **9** (8.1 g) and pyridine (10.8 ml) in benzene (800 ml) was stirred for 70 hr at 50°. The reaction mixture was washed successively with $H_2O$, 10% aq. $KHSO_4$ and $H_2O$. The organic layer was dried over $MgSO_4$ and concentrated to give **10** as a pale yellow oil, which was crystallized by trituration with *n*-hexane. Yield, 98.6%.

***tert*-Butyl (±)-7α-Azido-3-trifluoromethyl-2-cephem-4α-carboxylate (11)**——A solution of **10** (1.00 g) in benzene (60 ml) containing triethylamine (1 ml) was allowed to stand at room temperature for 74 hr. The mixture was then concentrated to give an oil, which was chromatographed on silica gel, eluting with benzene, to give the starting material. Further elution with benzene gave **11** in 69% yield. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 2125 ($N_3$), 1765 (β-lactam), 1735 (ester). NMR ($CDCl_3$) $\delta$: 1.49 (9H, s, *t*-Bu), 4.71 (1H, d, $J$=1.0 Hz, $C_6$–H), 5.10 (2H, bs, $C_4$–H, $C_7$–H), 7.13 (1H, d-q, $J$=1.5, 1.5 Hz, $C_2$–H).

***tert*-Butyl (±)-7α-Amino-3-trifluoromethyl-3-cephem-4-carboxylate (12)**——The azide (**11**, 2.71 g) was hydrogenated over 10% Pd-C (2.7 g) in THF (100 ml) containing *p*-toluenesulfonic acid hydrate (2.21 g). When the starting material could no longer be detected on a TLC plate, the catalyst was filtered off and the filtrate was shaken with AcOEt and 5% aq. $NaHCO_3$. The AcOEt layer was washed with $H_2O$, dried over $MgSO_4$, and evaporated down to give **12** (2.49 g) as a yellow powder. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3420, 3340 ($NH_2$), 1780 (β-lactam), 1730 (ester). NMR ($CDCl_3$) δ: 1.55 (9H, s, *t*-Bu), 2.36 (2H, bs, $NH_2$), 3.38, 3.57 (2H, AB-q, $J$=18.0 Hz, $2\times C_2$–H), 4.32 (1H, d, $J$=2.0 Hz, $C_6$–H), 4.57 (1H, d, $J$=2.0 Hz, $C_7$–H). The amino compound was used for the following reaction without further purification.

***tert*-Butyl (±)-7α-(*o*-Nitrobenzenesulfenamido-3-trifluoromethyl-3-cephem-4-carboxylate (13)**——A solution of *o*-nitrobenzenesulfenyl chloride (2.27 g) in THF (15 ml) and then a solution of triethylamine (1.21 g) in THF (5 ml) were added to a solution of **12** (2.59 g) in THF (15 ml) with cooling at 0°. The mixture was stirred for 1.5 hr at room temperature, diluted with AcOEt and then the solution was washed successively with aq. NaCl, 5% aq. $NaHCO_3$ and aq. NaCl. The organic layer was dried over $Na_2SO_4$ and concentrated to give an oil, which was triturated with benzene to give **13** (2.48 g) as crystals. The mother liquor was concentrated and chromatographed on a column of silica gel, eluting with benzene, to yield an additional crop of **13** (0.76 g). NMR ($CDCl_3$) δ: 1.52 (9H, s, *t*-Bu), 3.14 (1H, d, $J$=18.0 Hz, $C_2$–H), 3.54 (1H, d-q, $J$=18.0, 1.0 Hz, $C_2$–H), 3.81 (1H, d, $J$=7.0 Hz, NH), 4.57 (1H, d-d, $J$=7.0, 2.0 Hz, $C_7$–H), 4.81 (1H, d, $J$=2.0 Hz, $C_6$–H), 7.2—8.5 (4H, m, aromatic H).

***tert*-Butyl (±)-7β-(*o*-Nitrobenzenesulfenamido)-3-trifluoromethyl-3-cephem-4-carboxylate (15)**——A solution of **13** (3.24 g) in $CH_2Cl_2$ (50 ml) was added to a suspension of $MnO_2$ (99 g) in $CH_2Cl_2$ (100 ml) with stirring at 0°. After stirring for 40 min at room temperature, the insoluble material was filtered off and washed with AcOEt. The filtrate was concentrated to give *tert*-butyl (±)-7-(*o*-nitrobenzenesulfenimino-3-trifluoromethyl-3-cephem-4-carboxylate (**14**) (2.29 g) as yellow crystals. The crude product was used for the following reaction without further purification. A solution of borane-THF complex in THF (6.35 ml, 1 mmol/ml) was added dropwise to a stirred solution of the crude imine (**14**, 2.29 g) in THF (80 ml) under nitrogen with cooling at −15°. The mixture was maintained at −15° for 1 hr, then quenched with AcOH (3 ml) and shaken with AcOEt and aq. NaCl. The organic layer was washed successively with 5% aq. $NaHCO_3$ and aq. NaCl, dried over $MgSO_4$, and evaporated down to give the crude sulfenamide. The crude product was chromatographed on a column of silica gel, eluting with benzene, to give **15** (1.06 g). NMR ($CDCl_3$) δ: 1.58 (9H, s, *t*-Bu), 3.56 (2H, bs, $2\times C_2$–H), 4.80 (1H, d, $J$=5.0 Hz, $C_6$–H), 5.07 (1H, d, $J$=5.0 Hz, $C_7$–H), 7.2—7.4 (4H, m, aromatic H).

***tert*-Butyl (±)-7β-Amino-3-trifluoromethyl-3-cephem-4-carboxylate (16)**——A stirred solution of **15** (950 mg) in EtOH (35 ml) was treated with anhydrous EtOH (1.02 ml) containing HCl (204 mg) at room temperature. The solution was stirred for 1.5 hr, then evaporated to dryness and the residue was stirred in *n*-hexane. The solvent was removed by decantation and the residue was repeatedly treated with *n*-hexane to give **16** as the HCl salt (600 mg). The salt was stirred in AcOEt (50 ml) and 5% aq. $NaHCO_3$, then the organic layer was washed with $H_2O$, dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed on a column of silica gel, eluting with benzene–AcOEt (7: 3), to give **16** in quantitative yield. NMR ($CDCl_3$) δ: 1.56 (9H, s, *t*-Bu), 1.80 (2H, bs, $NH_2$), 3.46 (2H, m, $2\times C_2$–H), 4.79 (1H, d, $J$=5.0 Hz, $C_6$–H), 4.96 (1H, d, $J$=5.0 Hz, $C_7$–H).

**(±)-7β-Amino-3-trifluoromethyl-3-cephem-4-carboxylic Acid·$CF_3COOH$ (17)**——A solution of **16** (100 mg) in $CF_3COOH$ (5 ml) was stirred for 1.5 hr at room temperature. After removal of the $CF_3COOH$ by evaporation, the residue was dissolved in AcOEt (10 ml) and the solvent was evaporated to dryness. The residue was washed with ether to give **17** (68 mg) as a colorless powder. *Anal.* Calcd for $C_8H_7F_3N_2O_3S$: F, 21.25; N, 10.44; S, 11.35. Found: F, 21.68; N, 10.07; S, 11.16. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 1810 (β-lactam). NMR (DMSO-$d_6$) δ: 3.36 (2H, s, $2\times C_2$–H), 4.96 (1H, d, $J$=5.0 Hz, $C_6$–H), 5.12 (1H, d, $J$=5.0 Hz, $C_7$–H), 5.7—5.8 (bs, $\overset{+}{N}H_3$).

***tert*-Butyl (±)-7α-Amino-3-trifluoromethyl-2-cephem-4α-carboxylate (18)**——The azido-2-cephem (**11**, 520 mg) was hydrogenated over 10% Pd-C (540 mg) in THF (30 ml) containing *p*-toluenesulfonic acid hydrate (310 mg). After usual work-up, the crude product was purified by preparative TLC (benzene–AcOEt=4: 1) to give **18** (268 mg) as a colorless powder, mp 130—131°.

***tert*-Butyl (±)-7α-(*o*-Nitrobenzenesulfenamido)-3-trifluoromethyl-2-cephem-4α-carboxylate (19)**——A solution of *o*-nitrobenzenesulfenyl chloride (152 mg) in THF (1 ml) and triethylamine (81 mg) were added to a solution of **18** (173 mg) in THF (1 ml) at 0° and the solution was stirred for 2 hr at room temperature. The reaction mixture was diluted with AcOEt and washed successively with aq. NaCl, $H_2O$, 5% aq. $NaHCO_3$ and aq. NaCl. The organic layer was dried over $Na_2SO_4$ and evaporated down to give an oil, which was purified by preparative TLC (benzene–AcOEt=16: 1) to afford **19** (217 mg). NMR ($CDCl_3$) δ: 1.44 (9H, s, *t*-Bu), 3.83 (1H, d, $J$=7.0 Hz, NH), 4.60 (1H, d-d, $J$=7.0, 1.5 Hz, $C_7$–H), 5.05 (1H, bs, $C_4$–H), 5.16 (1H, bs, $C_6$–H), 7.12 (1H, m, $C_2$–H), 7.2—8.4 (4H, m, aromatic H).

***tert*-Butyl (±)-7β-(*o*-Nitrobenzenesulfenamido)-3-trifluoromethyl-2-cephem-4-carboxylate (20)**——A solution of **19** (1.00 g) in $CH_2Cl_2$ (31 ml) was stirred with $MnO_2$ (30.5 g) for 1.5 hr at room temperature. The $MnO_2$ was filtered off and washed with AcOEt, and the filtrate was evaporated to dryness to give the crude sulfenimine. The imine was reduced with borane-THF complex as described for **15**. The crude product

was purified by preparative TLC (benzene) to yield **20** (397 mg). NMR ($CDCl_3$) $\delta$: 1.48 (9H, s, *t*-Bu), 3.71 (1H, d, $J$=10.5 Hz, NH), 4.78 (1H, d-d, $J$=10.5, 3.5 Hz, $C_7$–H), 5.09 (1H, bs, $C_4$–H), 5.41 (1H, d, $J$=3.5 Hz, $C_6$–H), 7.22 (1H, m, $C_2$–H), 7.3—8.4 (4H, m, aromatic H).

***tert*-Butyl (±)-7β-Amino-3-trifluoromethyl-2-cephem-4-carboxylate (21)**——The amino compound **21** was prepared from **20** (397 mg) according to the procedure described for **16**. Yield, 240 mg. NMR ($CDCl_3$) $\delta$: 1.48 (9H, s, *t*-Bu), 1.96 (2H, bs, $NH_2$), 4.70 (1H, d, $J$=4.0 Hz, $C_6$–H), 5.03 (1H, bs, $C_4$–H), 5.31 (1H, d, $J$=4.0 Hz, $C_7$–H), 7.15 (1H, t-d, $J$=1.5, 1.5 Hz, $C_2$–H).

**Acknowledgement** We are extremely grateful to Dr. Y. Kishida, the director of chemical research in these laboratories, for his valuable suggestions and encouragement throughout this work. We also thank Dr. C. Tamura and Mr. T. Hata for X-ray crystallographic analysis and Mr. H. Kuwano for measurement of NMR spectra.