2,4,6-TRIPYRIDINIO-1,3,5-TRIAZINE TRICHLORIDE, A NEW AND MILD ESTERIFICATION AGENT FOR PREPARATION OF PENICILLIN ESTERS

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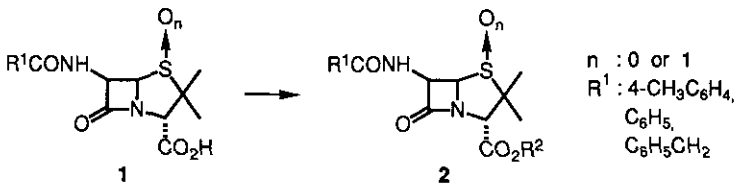
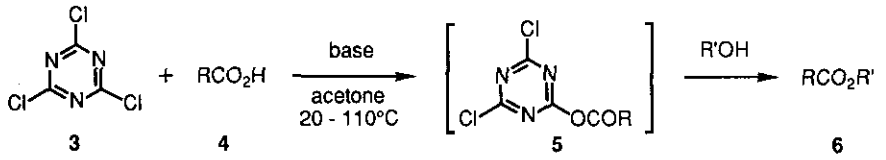
Abstract — Cyanuric chloride reacted with 3 molar equivalents of pyridine to give 2,4,6-tripyridinio-1,3,5-triazine trichloride, which was found to condense penicillins with alcohols under mild conditions to afford penicillin esters in good yields. Application to preparation of cephalosporin esters also is discussed.

Diphenylmethyl esters (**2**) (R^2: $CH(C_6H_5)_2$) of penicillins (**1**) are important intermediates for industrial production of novel β-lactam antibiotics such as latamoxef,[1a] flomoxef,[1b] and ceftibuten.[1c] Of the known esterification agents, diphenyldiazomethane,[2a] diphenylmethyl iodide-triethylamine,[2b] and the combination of diphenylmethanol and a condensing agent such as triphenylphosphine-carbon tetrachloride,[2c] or methanesulfonyl chloride[2d] have been found considerably effective for preparation of penicillin diphenylmethyl esters, but none of them were not satisfactory for industrial production of the esters from the viewpoint of safety and the cost of the agent or the product yield (Scheme 1).



Scheme 1

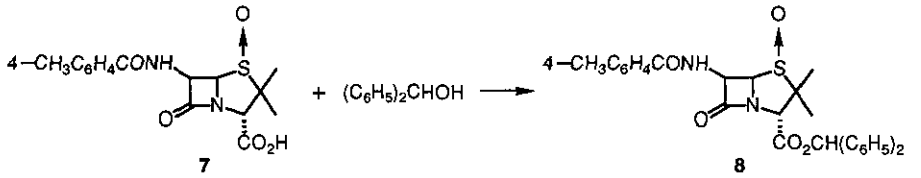
In our extensive search for a new, economical esterification agent, our attention has been focused on the use of inexpensive cyanuric chloride (**3**) which reportedly gives simple carboxylic acid esters (**6**) assumingly via an active ester (**5**) (Scheme 2).[3]



3 : **4** : base = 0.4 : 1 : 2 (molar equiv.)
R : $C_6H_5CH_2CH_2$, $C_6H_5CH_2$, $C_6H_5OCH_2$, $C_6H_5SCH_2$, $CH_3CH=CH$
R' : $C_6H_5CH_2$, $C_6H_{11}C(CH_3)_2$, CH_3
Base :$(C_2H_5)_3N$, $(n\text{-}C_4H_9)_3N$, pyridine, picoline, lutidine

Scheme 2

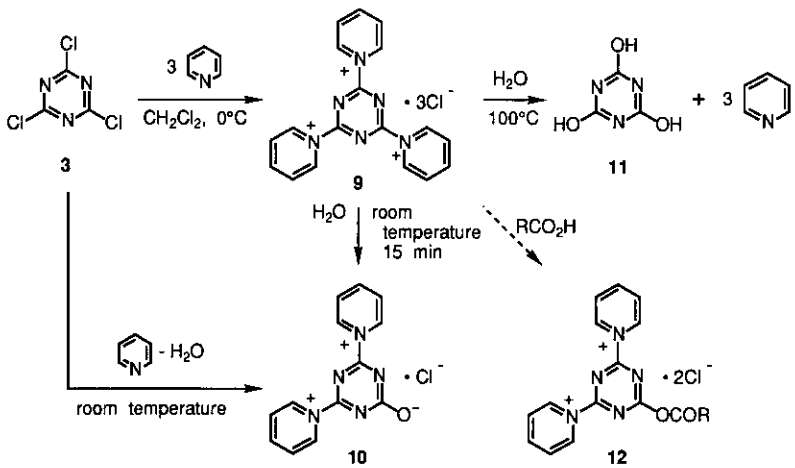
While diphenylmethyl 6β-(4-toluamido)penicillanate 1-oxide (**8**) was obtained only in 20% yield by reaction of the corresponding acid (**7**) with diphenylmethanol, 0.4 molar equivalent of cyanuric chloride, 2 molar equivalents of triethylamine or pyridine in acetone at 20°C, the yield of the ester (**8**) was improved with increasing the amount of pyridine[4] and with lowering the reaction temperature (Scheme 3). These results have led us to investigate reaction of cyanuric chloride and excess pyridine with the hope of finding a new esterification agent. In this paper, we report formation of 2,4,6-tripyridinio-1,3,5-triazine trichloride (**9**) by reaction of cyanuric chloride (**3**) and pyridine, and application of this agent (**9**) to esterification of penicillins and cephalothin, a typical Δ^3-cephem carboxylic acid.



Scheme 3

When cyanuric chloride (**3**) was treated with 3 molar equivalents of pyridine in dichloromethane, a yellow precipitate formed. Because of its extremely high hygroscopicity and handling difficulties, this precipitate was characterized only by ir spectroscopy in nujol. Assignment of structure (**9**) to this precipitate is based on the ir absorptions at 1604, 1591, 1553, 1376, 1158, and 1014 cm^{-1}, characteristic of the pyridinium structure,[5] reaction with water under mild conditions giving 4,6-dipyridinio-2-oxido-1,3,5-triazine chloride (**10**), a known compound derived by reaction of **3** with aqueous pyridine,[6] and complete hydrolysis to cyanuric acid (**11**) and 3 molar equivalents of pyridine, as shown in Scheme 4.

The effectiveness of this new derivative (**9**) for esterification is evident from its facile reaction with the pyridinium salt of acid (**7**) and diphenylmethanol in dichloromethane at 0°C giving the ester (**8**) in 79% yield. Apparently the lower product yield is attributable to rapid hydrolytic decomposition of this agent (**9**) to the ineffective dipyridino compound (**10**) and expectedly the yield should be improved by the use of the



Scheme 4

agent prepared *in situ*. Thus, the yield of product (8) was improved to 95% by omitting the isolation of the agent (9) and lowering the reaction temperature to -17°C. Dichloromethane and acetonitrile were suitable solvents for this esterification, and the use of toluene and ethyl acetate resulted in lower product yields. These results are summarized in Table 1.

Table 1. Esterification of 6β-(4-toluamido)penicillanic acid 1-oxide (7) to its diphenylmethyl ester (8) with diphenylmethanol and 2,4,6-tripyridinio-1,3,5-triazine trichloride (9), prepared *in situ*, in various solvents

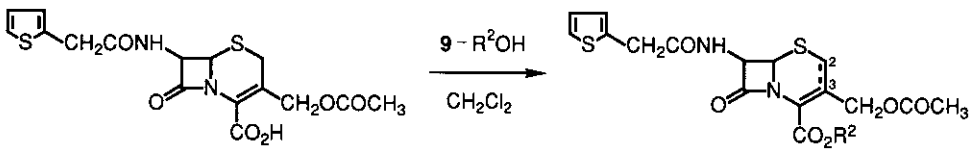
Solvent	Temperature (°C)	Time (h)	Yield of 8 (%)
Dichloromethane	-17 ± 3	1.3	95
Acetonitrile	-15	1.3	90
Toluene	0	20	37
Ethyl acetate	0	20	68

We speculate that the acylating species in this new esterification method is active ester (12) (Scheme 4) whose reactivity is enhanced by two highly electron-withdrawing pyridinio groups. The versatility of this method is shown in Table 2, in which condensation of penicillins (1) irrespective of the sulfoxide (n = 1) or sulfide (n = 0) structure, with primary and secondary alcohols proceeded smoothly. It is noteworthy that *p*-cresol and *tert*-butyl alcohol give penicillin esters, in acceptable yields, which are not prepared easily by conventional methods.

Table 2. Esterification of penicillins (1) to esters (2) with alcohols or *p*-cresol (R^2OH) and 2,4,6-tripyridinio-1,3,5-triazine trichloride (9), prepared *in situ*, in dichloromethane

Penicillin 1		R^2OH	Temperature (°C)	Time (h)	Product 2	
R^1	n				No.	Yield (%)
4-$CH_3C_6H_4$	1	CH_3OH	-7 ± 3	1.5	**2a**	95
4-$CH_3C_6H_4$	1	$C_6H_5CH_2OH$	-7 ± 3	1.3	**2b**	81
4-$CH_3C_6H_4$	1	$(CH_3)_3COH$	0	2	**2c**	53
4-$CH_3C_6H_4$	1	4-$CH_3C_6H_4OH$	-35 ± 2	1.3	**2d**	75
4-$CH_3C_6H_4$	0	$(C_6H_5)_2CHOH$	-15 ± 5	2	**2e**	88
$C_6H_5CH_2$	1	$(C_6H_5)_2CHOH$	-15 ± 5	2	**2f**	92
$C_6H_5CH_2$	0	$(C_6H_5)_2CHOH$	-7 ± 3	1	**2g**	86
$C_6H_5CH_2$	0	$(C_6H_5)_2CHOH$	-6 ± 1	0.7	**2h**	92

Esterification of cephalothin (**13**), a typical Δ^3-cephem carboxylic acid, using the new agent (**9**) was examined (Scheme 5). As shown in Table 3, the condensation with primary alcohols also proceeded smoothly to give the corresponding esters (**14**) in good yields, while the reaction with secondary and tertiary alcohols was accompanied with the double bond isomerization, a common side reaction occurring in the conventional esterification methods.[2b]



13 **14**

Scheme 5

Table 3. Esterification of cephalothin (**13**) to esters (**14**) with various alcohols and 2,4,6-tripyridinio-1,3,5-triazine trichloride (**9**), prepared *in situ*, in dichloromethane

R^2OH	Temperature (°C)	Time (h)	Product 14	
			No. (Δ)	Yield (%)
CH_3OH	-7 ± 1	1.5	**14a** (Δ^3)	87
CCl_3CH_2OH	-9 ± 1	1.3	**14b** (Δ^3)	87
$C_6H_5CH_2OH$	-9 ± 1	1.3	**14c** (Δ^3)	92
$(C_6H_5)_2CHOH$	-10 ± 10	3	**14d** (Δ^3) **14e** (Δ^2)	48
$(CH_3)_3COH$	-8 – 10	8	**14f** (Δ^2)	26

In conclusion, 2,4,6-tripyridinio-1,3,5-triazine trichloride (**9**), prepared *in situ* by reaction of cyanuric chloride and 3 molar equivalents of pyridine in dichloromethane, is found to be a mild esterification agent for preparation of various penicillin esters in good to excellent yields. The new agent is effective also for

condensation of cephem carboxylic acids with primary alcohols. This new esterification procedure, after optimization of reaction conditions and operations, has been successfully applied to industrial production of diphenylmethyl 6β-(4-toluamido)penicillate (**2e**), its 1-oxide (**8**), diphenylmethyl 6β-(2-phenylacetamido)penicillanate (**2g**), and its 1-oxide (**2f**), important intermediates for production of our novel β-lactam antibiotics, latamoxef, flomoxef, and ceftibuten.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were recorded with a JASCO DS-403G spectrophotometer and ^{1}H-nmr spectra with a Varian EM-360L spectrometer using tetramethylsilane as the internal standard. Optical rotations were obtained with a Perkin-Elmer 141 polarimeter.

2,4,6-Tripyridinio-1,3,5-triazine Trichloride (**9**)

To a stirred solution of cyanuric chloride (**3**) (500 mg, 2.71 mmol) in dry CH_2Cl_2 (13 ml) was added with ice-cooling a solution of pyridine (0.66 ml, 8 mmol) in dry CH_2Cl_2 (3 ml) over a period of 3 min. After stirring with ice-cooling for 1 h, the resulting suspension was filtered and washed with dry CH_2Cl_2, and dried in vacuo. The product (**9**), obtained as a yellow precipitate (about 1.1 g), is very hygroscopic and all the above procedures should be carried out under nitrogen. Ir (nujol): 3034, 1604, 1591, 1553, 1376, 1344, 1158, 1014, 775, 651, 634, 614 cm^{-1}.

Reaction of **9** with Water

To the product (**9**), obtained from cyanuric chloride (**3**) (922 mg, 5.0 mmol) and pyridine (12.1 ml, 15 mmol) as described above except for omitting the drying, was added at room temperature under nitrogen water (4 ml) to give a violet solution. Thereto was added, after 15 min, acetone (8 ml) and the resulting violet precipitate was washed with acetone and dried in vacuo to give 0.54 g (35%) of 4,6-dipyridinio-2-oxido-1,3,5-triazine chloride (**10**), mp >300°C. Ir (nujol): 3400, 3340, 3100, 3045, 1660, 1620, 1560, 1500, 1465, 1380 cm^{-1}. ^{1}H-Nmr (D_2O) δ: 8.3-8.6 (m, 2H), 8.8-9.2 (m, 1H), 10.0-10.2 (m, 2H). Anal. Calcd for $C_{13}H_{10}N_5OCl\cdot H_2O$: C, 51.07; H, 3.96; N, 22.91; Cl, 11.60. Found: C, 50.77; H, 3.85; N, 22.74; Cl, 11.69. The ir and ^{1}H-nmr spectra were identical with those of an authentic sample prepared by reaction of cyanuric chloride with pyridine-water (3:1) as reported in the literature.[6]

To the product (**9**), obtained from **3** (9.22 g, 50 mmol) and pyridine (12.1 ml, 150 mmol) as described above, was added water (200 ml) with stirring at room temperature. The colorless CH_2Cl_2 layer was separated and the reddish violet aqueous layer (pH 0.8) was distilled at atmospheric pressure to collect water (155 ml). The resulting suspension was cooled with ice-water and filtered. The colorless crystals were washed with water and dried in vacuo at 55°C to give 6.14 g (95.1%) of cyanuric acid (**11**) whose ir spectrum was identifical with that of an authentic (commercially available) sample of cyanuric acid. The filtrate (pH 1.2)

was adjusted to pH 9 with 48% NaOH and distilled at atmospheric pressure to collect fractions (37 g) boiling at 93-101°C, which were subjected to the gas chromatographic analysis to detect 12.0 g (152 mmol) of pyridine.

Esterification of 6β-(4-Toluamido)penicillanic Acid 1-Oxide (7) to Its Diphenylmethyl Ester (8) with Diphenylmethanol and the New Agent (9) in Dichloromethane

With the Agent (9) Isolated -- To a stirred solution of **7** (526 mg, 1.50 mmol), diphenylmethanol (332 mg, 1.80 mmol), and pyridine (0.24 ml, 3 mmol) in dry CH_2Cl_2 (4 ml) was added with ice-cooling under nitrogen a major part (about 2.5 mmol) of the dried agent (**9**) obtained from **3** (500 mg) as described above. After stirring with ice-cooling for 70 min, the reaction mixture was poured into a mixture of 2*N* H_2SO_4 and ice, and extracted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The organic extracts were combined, washed with an aq. $NaHCO_3$ solution and an aq. NaCl solution, dried with Na_2SO_4, and rotary-evaporated. The residue was crystallized from CH_3OH to give **8** (614 mg, 79%), mp 178-180°C (decomp); ir ($CHCl_3$): 3411, 1801, 1751, 1669, 1613 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 0.93 (s, 3H), 1.70 (s, 3H), 2.37 (s, 3H), 4.78 (s, 1H), 5.05 (1H, d, J = 5 Hz), 6.27 (1H, dd, J = 10, 15 Hz), 7.00 (s, 1H), 7.20 (2H, d, J = 5 Hz), 7.35 (s, 10H), 7.68 (2H, d, J = 8 Hz), 7.83 (1H, d, J = 10 Hz). $[\alpha]_D$ +185° (23.5°C, c = 1.003, $CHCl_3$). Anal. Calcd for $C_{29}H_{28}N_2O_5S$: C, 67.42; H, 5.46; N, 5.42; S, 6.21. Found: C, 67.64; H, 5.14; N, 5.41; S, 6.50.

With the Agent (9), Prepared *in situ* -- To a stirred solution of **3** (14.21 g, 77.1 mmol) in dry CH_2Cl_2 (180 ml) was added with ice-cooling under nitrogen a solution of pyridine (18.7 ml, 231 mmol) in dry CH_2Cl_2 (19 ml) over a period of 10 min. After the stirring was continued for an additional 10 min, to the resulting suspension of **9** was added a solution of **7** (20.0 g, 57.1 mmol), diphenylmethanol (12.6 g, 68.4 mmol), and pyridine (9.0 ml, 111 mmol) in dry CH_2Cl_2 (100 ml) over a period of 40 min. After the stirring was continued at 2-4°C for 45 min, the reaction mixture was worked up in the same way as described above to give **8** (27.1 g, 91.8%). Alternatively and more practically, to a stirred solution of **7** and diphenylmethanol in dry dichloromethane were added at -15 to -20°C pyridine (25.4 ml, 314 mmol) and then a solution of **3** in dry CH_2Cl_2 over a period of 20 min (the amounts of **7**, diphenylmethanol, **3**, and CH_2Cl_2 are the same as above). After the stirring was continued for 80 min, the reaction mixture was worked up in the usual way to give **8** (28.0 g, 94.8%).

Esterification of 7 to 8 in Various Solvents

To a solution of **7** (1.05 g, 3.0 mmol) and diphenylmethanol (718 mg, 3.9 mmol) in a dry solvent (15 ml) were added under nitrogen pyridine (1.33 ml, 16.4 mmol) and **3** (719 mg, 3.9 mmol). The reaction mixture was mixed with CH_2Cl_2 (20 ml) and water (30 ml), and worked up in the same way as described above. The reaction temperature, time and the product yield are shown in Table 1.

Esterification of Penicillins (1) to Esters (2) (Table 2)

Methyl 6β-(4-Toluamido)penicillanate 1-Oxide (2a) -- To a stirred suspension of 7 (3.50 g, 10 mmol) in dry CH_3OH (35 ml) were added at -5°C pyridine (4.45 ml, 55 mmol) and then a solution of cyanuric acid (2.49 g, 13.5 mmol) in dry CH_2Cl_2 over a period of 12 min. The resulting solution was stirred at -5°C to -10°C for 1.5 h and the reaction mixture (suspension) was worked up in the usual way to give ester (2a) (3.47 g, 95.3%), mp 152-154°C [from CH_2Cl_2-$(C_2H_5)_2O$]. Ir ($CHCl_3$): 3408, 1802, 1758, 1740, 1673, 1613 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.25 (s, 3H), 1.75 (s, 3H), 2.38 (s, 3H), 3.80 (s, 3H), 4.70 (s, 1H), 5.12 (1H, d, J = 5 Hz), 6.27 (1H, dd, J = 10, 5 Hz), 7.20 (2H, d, J = 8 Hz), 7.70 (2H, d, J = 8 Hz), 7.83 (1H, d, J = 10 Hz). $[\alpha]_D$ +218° (23.5°C, c = 1.085, $CHCl_3$). Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.02; H, 5.46; N, 7.65; S, 8.74.

Phenylmethyl 6β-(4-Toluamido)penicillanate 1-Oxide (2b) -- To a stirred solution of 7 (3.50 g, 10 mmol) and phenylmethanol (1.35 ml, 13 mmol) in dry CH_2Cl_2 (10 ml) were added under nitrogen at -10°C pyridine (4.45 ml, 55 mmol) and then a solution of 3 (2.49 g, 13.5 mmol) in dry CH_2Cl_2 (20 ml) over a period of 10 min. After stirring at -5 to -10°C for 1.3 h, the reaction mixture was worked up in the usual way to give a crud product (5.03 g), which on SiO_2 chromatography (toluene-ethyl acetate, 4:1 and 2:1) followed by crystallization from $(C_2H_5)_2O$ afforded 2b (3.57 g, 81.0%), mp 157-159°C. Ir ($CHCl_3$): 3412, 1804, 1755, 1673, 1614 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.11 (s, 3H), 1.70 (s, 3H), 2.39 (s, 3H), 4.74 (s, 1H), 5.11 (1H, d, J = 5 Hz), 5.20, 5.31 (2H, ABq, J = 12 Hz), 6.30 (1 H, dd, J = 5, 10 Hz), 7.2-7.7 (m, 9H), 7.81 (1H, d, J = 10 Hz). $[\alpha]_D$ +180° (24.0°C, c = 1.013, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36; S, 7.28. Found: C, 62.88; H, 5.48; N, 6.01; S, 6.81.

tert-Butyl 6β-(4-Toluamido)penicillanate 1-Oxide (2c) -- To a stirred solution of 7 (1.00 g, 2.85 mmol) and *tert*-butanol (2.0 ml, 21 mmol) in dry CH_2Cl_2 (4 ml) were added under nitrogen with ice-cooling pyridine (1.27 ml, 15.7 mmol) and 3 (711 mg, 3.86 mmol). After the stirring was continued for 2 h, the reaction mixture was worked up in the usual way to give, on SiO_2 chromatography (benzene-ethyl acetate, 2:1) followed by crystallization from CH_2Cl_2-$(C_2H_5)_2O$, 2c (612 mg, 52.8%), mp 172.5-175.0°C. Ir ($CHCl_3$): 3413, 1798, 1743, 1669, 1613 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.27 (s, 3H), 1.52 (s, 9H), 1.73 (s, 3H), 2.73 (s, 3H), 4.57 (s, 1H), 5.07 (1H, d, J = 5 Hz), 6.23 (1H, dd, J = 11, 5 Hz), 7.20 (2H, d, J = 8 Hz), 7.67 (2H, d, J = 8 Hz), 7.82 (1H, d, J = 11 Hz). $[\alpha]_D$ +180° (23.5°C, c = 1.003, $CHCl_3$). Anal. Calcd for $C_{20}H_{26}N_2O_5S$: C, 59.09; H, 6.45; N, 6.89; S, 7.89. Found: C, 59.28; H, 6.30; N, 6.67; S, 7.66.

4-Methylphenyl 6β-(4-Toluamido)penicillanate 1-Oxide (2d) -- To a stirred solution of 3 (922 mg, 5.0 mmol) in dry CH_2Cl_2 (20 ml) was added a solution of pyridine (1.22 ml, 15.1 mmol) in dry CH_2Cl_2 (3 ml) at 10-15°C under nitrogen over a period of 5 min. After the stirring was continued for 5 min, the resulting suspension was cooled to -30°C and thereto were added at -34 to -37°C a solution of 7 (1.298 g, 3.70 mmol) and pyridine (0.60 ml, 7.4 mmol) in dry CH_2Cl_2 (3.9 ml) and after 5 min a solution of *p*-cresol (800 mg, 7.4

mmol) in dry CH_2Cl_2 (1.5 ml) over a period of 3-5 min. After the stirring was continued for 75 min, the reaction mixture was worked up in the usual way to give **2d** (1.646 g, 74.7%), mp 162.4-164°C (from CH_2Cl_2-CH_3OH). Ir ($CHCl_3$): 3413, 1802, 1769 1673, 1613 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.40 (s, 3H), 1.85 (s, 3H), 2.33 (s, 3H), 2.38 (s, 3H), 4.90 (s, 1H), 5.13 (1H, d, J = 4 Hz), 6.28 (1H, dd, J = 10, 4 Hz), 6.9-7.8 (m, 8H), 7.85 (1H, d, J = 10 Hz). $[\alpha]_D$ +163° (24.0°C, c = 1.064, $CHCl_3$). Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36; S, 7.28. Found: C, 62.85; H, 5.25; N, 6.64; S, 7.45.

Diphenylmethyl 6β-(4-Toluamido)penicillanate (2e) -- When 6β-(4-toluamido)penicillanic acid (20.85 g, 62.35 mmol) and diphenylmethanol (13.12 g, 71.2 mmol) were treated with pyridine (29.7 ml, 36.7 mmol) and **3** (15.0 g, 81.3 mmol) at -10 to -20°C for 2 h in a similar way to that described for preparation of **2b**, ester (**2e**) (27.40 g, 87.8%), mp 141-143°C [from $(C_2H_5)_2O$] was obtained. Ir ($CHCl_3$): 3444, 1789, 1750, 1674, 1614 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.29 (s, 3H), 1.67 (s, 3H), 2.41 (s, 3H), 4.58 (s, 1H), 5.66 (1H, d, J = 4 Hz), 5.90 (1H, dd, J = 4, 9 Hz), 6.75 (1H, d, J = 9 Hz), 6.96 (s, 1H), 7.2-7.7 (m, 14H). $[\alpha]_D$ +165° (25.0°C, c = 1.008, $CHCl_3$). Anal. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.58; H, 5.64; N, 5.60; S, 6.40. Found: C, 69.57; H, 5.71; N, 5.54; S, 6.37.

Diphenylmethyl 6β-(2-Phenylacetamido)penicillanate 1-Oxide (2f) -- When penicillin G sulfoxide (20.45 g, 58.37 mmol) and diphenylmethanol (13.12 g, 71.2 mmol) were treated with pyridine (28.4 ml, 351 mmol) and **3** (15.0 g, 81.3 mmol) at -10 to -20°C for 2 h in a similar way to that described for preparation of **2b**, ester (**2f**) (27.86 g, 92.4%), mp 148.0-149.5°C (from isopropanol) (reported: mp 146°C[2a]; mp 146-148°C[7]) was obtained. Ir ($CHCl_3$): 3401, 1803, 1750, 1686, 1498 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 0.85 (s, 3H), 1.63 (s, 3H), 3.53 (s, 2H), 4.67 (s, 1H), 4.88 (1H, d, J = 4 Hz), 5.97 (1H, dd, J = 10, 4 Hz), 6.93 (s, 1H), 7.1-7.4 (m, 16H). $[\alpha]_D$ +181° (24.0°C, c = 1.022, $CHCl_3$). Anal. Calcd for $C_{29}H_{28}N_2O_5S$: C, 67.42; H, 5.46; N, 5.42; S, 6.21. Found: C, 66.90; H, 5.51; N, 5.19; S, 6.04.

Diphenylmethyl 6β-(2-Phenylacetamido)penicillanate (2g) -- When penicillin G potassium (3.725 g, 10 mmol) and diphenylmethanol (2.210 g, 12 mmol) were treated with pyridine (4.45 ml, 55 mmol) and **3** (2.49 g, 13.5 mol) at -5 to -10°C for 1 h in a similar way to that described for preparation of **2b**, ester (**2g**) (4.30 g, 85.7%) was obtained on SiO_2 chromatography (toluene-ethyl acetate, 9:1 and 4:1), mp 111.5-112.5°C [from $(C_2H_5)_2O$]. Ir ($CHCl_3$): 3417, 1786, 1747, 1680, 1603 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.21 (s, 3H), 1.40 (s, 3H), 3.64 (s, 2H), 4.46 (s, 1H), 5.53 (1H, d, J = 4 Hz), 5.65 (1H, dd, J = 9, 4 Hz), 6.06 (1H, d, J = 13 Hz), 7.1-7.4 (m, 16H). $[\alpha]_D$ +143° (23.5°C, c = 1.036, $CHCl_3$). Anal. Calcd for $C_{29}H_{28}N_2O_4S$: C, 69.57; H, 5.64; N, 5.60; S, 6.41. Found: C, 69.62; H, 5.63; N, 5.50; S, 6.52.

Diphenylmethyl 6β-(2-Phenoxyacetamido)penicillanate (2h) -- When penicillin V (3.504 g, 10 mmol) was esterified at -5 to -7°C for 40 min in a similar way to that described for preparation of **2g**, ester (**2h**) (4.74 g, 91.8%) was obtained, after SiO_2 chromatography (toluene-ethyl acetate = 4 : 1) as a white foam, ir ($CHCl_3$): 3416, 1790, 1748, 1695, 1602 cm^{-1}. ^1H-Nmr ($CDCl_3$) δ: 1.27 (s, 3H), 1.58 (s, 3H), 4.56 (s, 3H), 5.61 (2H, d, J

= 4 Hz), 5.74 (1H, dd, J = 9, 4 Hz), 6.9-7.4 (m, 17H). $[\alpha]_D$ +123° (25.0°C, c = 1.472, $CHCl_3$). Anal. Calcd for $C_{29}H_{28}N_2O_5S$: C, 67.42; H, 5.46; N, 5.42; S, 6.21. Found: C, 67.70; H, 5.55; N, 5.09; S, 5.92.

Esterification of Cephalothin (13) to Ester (14) (Table 3)

Cephalothin Methyl Ester (14a) -- When a solution of cephalothin (13) (1.189 g, 3.00 mmol) in dry CH_3OH (12 ml) was treated with pyridine (1.33 ml, 16.5 mmol) and 3 (830 mg, 4.5 mmol) at -6 to -8°C for 1.5 h in a similar way to that described for preparation of **2a**, ester (**14a**) (1.072 g, 87.1%), mp 180-184°C [from CH_2Cl_2-$(C_2H_5)_2O$] was obtained. Ir ($CHCl_3$): 3403, 1791, 1737, 1688, 1642 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.07 (s, 3H), 3.33 and 3.52 (2H, ABq, J = 18 Hz), 3.82 (s, 2H), 4.78 and 5.03 (2H, ABq, J = 8 Hz), 5.80 (1H, dd, J = 9, 5 Hz), 6.70 (1H, d, J = 9 Hz), 6.9-7.3 (m, 3H). $[\alpha]_D$ +28.8° (23.0°C, c = 0.969, $CHCl_3$). Anal. Calcd for $C_{17}H_{18}N_2O_6S_2$: C, 49.74; H, 4.42; N, 6.83; S, 15.62. Found: C, 49.82; N, 4.37; N, 6.82; S, 15.62.

Cephalothin 2,2,2-Trichloroethyl Ester (14b) -- When 13 (1.189 g, 3.00 mmol) and CCl_3CH_2OH (2.0 ml, 21 mmol) were treated with pyridine (1.33 ml, 16.5 mmol) and 3 (747 mg, 4.05 mmol) in a similar way to that described for preparation of **2b** at -8 to -10°C for 1.3 h, ester (**14b**) (1.384 g, 87.4%), mp 118.0-120.5°C, was obtained after SiO_2 chromatography (benzene-ethyl acetate = 8 : 2) followed by crystallization from $(C_2H_5)_2O$. Ir ($CHCl_3$): 3402, 1794, 1744, 1689, 1641 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.07 (s, 3H), 3.37 and 3.55 (2H, ABq, J = 18 Hz), 3.80 (s, 2H), 4.6-5.3 (4H, m), 4.97 (1H, d, J = 5 Hz), 5.83 (1H, dd, J = 9, 5 Hz), 6.60 (1H, d, J = 9 Hz), 6.9-7.3 (m, 3H). $[\alpha]_D$ +13.5° (23.5°C, c = 1.015, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}N_2O_6S_2Cl_3$: C, 40.96; H, 3.25; N, 5.31; S, 12.15; Cl, 20.15. Found: C, 40.91; H, 3.21; N, 5.28; S, 12.07; Cl, 20.05.

Cephalothin Phenylmethyl Ester (14c) When 13 (1.189 g, 3.00 mmol) and phenylmethanol (2.0 ml, 19 mmol) were treated with pyridine (1.33 ml, 16.5 mmol) and 3 (747 mg, 4.05 mmol) in a similar way to that described for preparation of **2b** at -8 to -10°C for 1.3 h, ester (**14c**) (1.337 g, 91.6%), mp 145.5-147.0°C [from $(C_2H_5)_2O$] was obtained. Ir ($CHCl_3$): 3404, 1790, 1738, 1688, 1640 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 2.03 (s, 3H); 3.30 and 3.48 (2H, ABq, J = 18 Hz), 3.80 (s, 2H), 4.88 (1H, d, J = 5 Hz), 4.76 and 5.02 (2H, ABq, J = 14 Hz), 5.20 (s, 2H), 5.78 (1H, dd, J = 9, 5 Hz), 6.62 (1H, d, J = 9 Hz), 6.9-7.3 (m, 3H), 7.37 (s, 5H). $[\alpha]_D$ +5.5° (23.5°C, c = 1.051, $CHCl_3$). Anal. Calcd for $C_{23}H_{22}N_2O_6S_2$: C, 56.77; H, 4.56; N, 5.76; S, 13.18. Found: C, 56.86; H, 4.33; N, 5.68; S, 13.11.

Esterification of Cephalothin (12) with Diphenylmethanol -- When 13 (1.467 g, 3.70 mmol) and diphenylmethanol (819 mg, 4.44 mmol) were treated with a suspension of reagent (**9**), prepared *in situ*, at -10 to -30°C for 3 h as described for preparation of **2d**, cephalothin diphenylmethyl ester (**14d**) (467 mg), its Δ^2-isomer, diphenylmethyl 3-(acetoxy)methyl-7β-(2-thienylacetamido)-2-cephem-3α-carboxylate (**14e**) (482 mg), and a mixture of **14d** and **14e** (64 mg) were obtained as foams (total yield: 48%) on SiO_2 chromatography (benzene-ethyl acetate = 8 : 2) of the crude product. **14d** -- Ir ($CHCl_3$): 3400, 1790, 1738, 1690 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.97 (s, 3H), 3.31 and 3.46 (2H, ABq, J = 18 Hz), 3.80 (s, 2H), 4.6-5.2 (m, 3H),

5.80 (1H, dd, J = 9, 4 Hz), 6.63 (1H, d, J = 9 Hz), 6.8-7.4 (m, 14H). **14e** -- Ir ($CHCl_3$): 3400, 1780, 1740, 1688 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.90 (s, 3H), 3.83 (s, 2H), 4.57 (s, 2H), 5.10 (s, 1H), 5.18 (1H, d, J = 4 Hz), 5.60 (1H, dd, J = 8, 4 Hz), 6.40 (s, 1H), 6.6-7.4 (m, 14H).

tert-Butyl 3-(Acetoxy)methyl-7β-(2-thienylacetamido)-2-cephem-3α-carboxylate (**14f**) -- When **13** (396 mg, 1 mmol) and *tert*-butanol (1.0 ml, 11 mmol) were treated with pyridine (0.44 ml, 5.5 mmol) and **3** (249 mg, 1.35 mmol) at -4 to -8°C for 4 h, at 0°C for 2.5 h, and at 10°C for 1.5 h in a similar way to that described for preparation of **2b**, Δ^2-ester (**14f**) (117 mg, 25.9%), mp 180.5-181.5°C, was obtained on SiO_2 chromatography (benzene-ethyl acetate = 8 : 2) followed by crystallization from CH_2Cl_2-$(C_2H_5)_2O$. Ir ($CHCl_3$): 3410, 1777, 1737, 1687 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 1.47 (s, 9H), 2.05 (s, 3H), 3.82 (s, 2H), 4.51 and 4.69 (2H, ABq, J = 13 Hz), 4.87 (brs, 1H), 5.23 (1H, d, J = 4 Hz), 5.60 (1H, dd, J = 9, 4 Hz), 6.9-7.3 (m, 3H). $[\alpha]_D$ +356° (23.5°C, c = 1.027, $CHCl_3$). Anal. Calcd for $C_{20}H_{24}N_2O_6S_2$: C, 53.08; H, 5.35; N, 6.19; S, 14.17. Found: C, 53.07; H, 5.14; N, 6.03; S, 13.87.

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