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Synthesis of 1,2-Dehydro-1-carbacephalosporin

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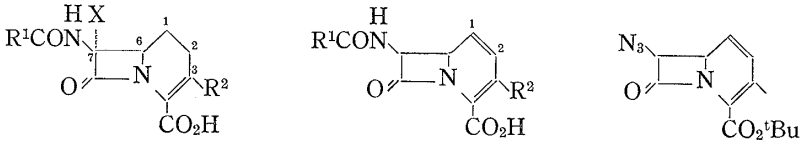
A total synthesis of 1,2-dehydro-1-carbacephalosporin **2** ($R^2=CH_3$) is described. The azido-azetidinone **8**, prepared from the Schiff base **5**, azidoacetyl chloride and triethylamine, was converted to the ylide **13** *via* **10**. Conjugate addition of benzenethiol to **13** followed by an intramolecular Wittig reaction gave the 1-carbacephem derivatives **16**, which were transformed to the sulfoxides **17**. Treatment of **17** with triethylamine yielded the 1,2-dehydro derivative **18**. The carboxylic acid derivatives **19**, and **23**, prepared from **18**, did not show antibacterial activity.

Keywords——1,2-dehydro-1-carba-1-dethiacephalosporin; 1,2-dehydro-1-carbacephem; β-lactam antibiotic; azetidinone; intramolecular Wittig reaction

In the preceding paper,[2] we reported the synthesis and antibacterial activity of various 1-carbacephem antibiotics **1**. None of the 1-carbacephems we prepared, however, exceeded the corresponding 1-thia (cephalosporin) and 1-oxa congeners in biological activity.

In a search for more potent antibiotics of this family, we decided to prepared 1-carbacephems having an extra double bond at C_1—C_2 as represented by the formula **2**, based upon the following considerations.[3] i) The new double bond would introduce additional strain into the β-lactam ring, thus increasing the chemical reactivity of the β-lactam carbonyl toward nucleophiles and hopefully increasing the biological activity; ii) conjugation of the unshared electron pair on the β-lactam nitrogen with the double bond (Δ^3), competitive with the stabilization of the amide C–N bond, would be enhanced by introduction of the new conjugated double bond, thereby weakening the amide C–N bond and conseqluenty increasing the chemical reactivity of the β-lactam.



1 X=H, OCH_3 **2** **3**

Fig. 1

Very recently, Doyle *et al.* reported[4] the preparation of 7-azido-1,2-dehydro-1-carbacephem **3** and unsuccessful attempts to transform it into **2** ($R^2=CH_3$). We now wish to report a successful synthesis of this compound **2** ($R^2=CH_3$) in detail.

The reaction of azidoacetyl chloride and the Schiff base **5**, prepared from cinnamaldehyde and D-amino benzyl ester **4**,[2] in the presence of triethylamine gave the *cis*-azetidinones **6**, **7** and **8** in good combined yield.[5] Formation of the isopropylidene derivative **8** was not prevented even when the reaction was carried out at −50° to −40°. Furthermore, isolation

1) Location: *Fukushima-ku, Osaka 533, Japan.*
2) S. Uyeo and H. Ona, the preceding paper in this Journal.
3) *a*) R.M. Sweet in "Cephalosporins and Penicillins: Chemistry and Biology," ed. by E.H. Flynn, Academic Press, New York, 1972, p. 303; *b*) I. Ernst, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackman, H.R. Pfaendler, and R.B. Woodward, *J. Amer. Chem. Soc.*, **100**, 8214 (1978).
4) T.W. Doyle, T.T. Conway, G. Lim, and B.-Y. Luh, *Can. J. Chem.*, **57**, 227 (1979).
5) T.W. Doyle, B. Belleau, B.-Y. Luh, C.F. Ferrari, and M.P. Cunningham, *Can. J. Chem.*, **55**, 468 (1977).

of pure chiral diastereoisomers **6** and **7** was not achieved. Consequently, the crude product of the cycloaddition reaction was treated with triethylamine to convert it into the single racemic azetidinone **8**. Reduction of **8** with zinc-acetic acid followed by acylation gave the phenylacetamide **9** as a crystalline product. Ozonolysis of **9** in methylene dichloride at −78° and subsequent reduction of the ozonide with zinc-acetic acid afforded the aldehydo-alcohols **10** as a diastereoisomeric mixture. The crude product was then reacted with Wittig reagent **11** in refluxing methylene dichloride, giving the conjugated ketones **12** in good overall yield. Conversion of **12** into the phosphorane **13** was performed by a well established method.[6] Since the double bond in **13** is *trans*, cyclization to the target molecule **14** by intramolecular

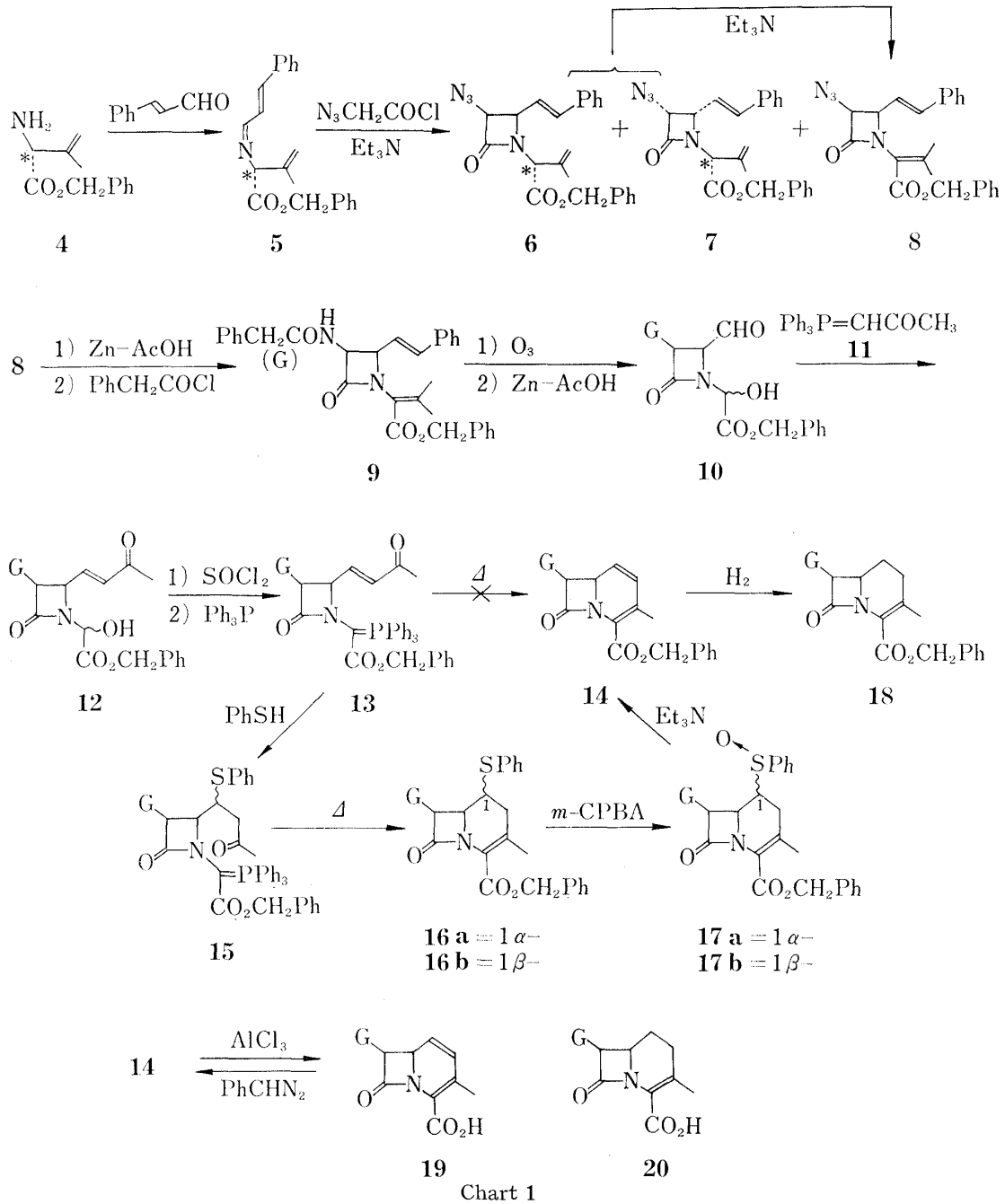


Chart 1

6) *a*) K. Heusler in ref. 3*a* p. 274; *b*) S. Yamamoto, N. Haga, T. Aoki, S. Hayashi, H. Tanida, and W. Nagata, *Heterocycles*, **8**, 283 (1977).

Wittig reaction was unsuccessful. Conjugate addition of benzenethiol to the ylide **13** in tetrahydrofuran in the presence of a catalytic amount of sodium hydride gave the adducts **15** as a diastereoisomeric mixture, which on heating gave an epimeric mixture of 1-carbacephems **16a, b.** We tentatively assign the 1α-benzenethio structure to **16a**, which is produced at a much faster rate than **16b**, which is consequently assigned the 1β-benzenethio structure. The 1β-benzenethio group should have a greater steric interaction with the 7β-phenylacetamido group than the 1α-group, thereby hindering the cyclization reaction. Oxidation of **16a, b**, either as a mixture or a single isomer, with *meta*-chloroperbenzoic acid gave the sulfoxides **17a,b**, which on treatment with triethylamine in dimethylformamide or acetonitrile yielded the desired compound **14** in good yield. In addition to appropriate elemental analysis data and spectral characteristics for the assigned structure, definitive structural proof was provided by the following conversions. Catalytic hydrogenation of **14** gave the dihydro product **18**, which was identical with an authentic sample obtained previously by a different route.[2] Conjugate addition of benzenethiol to **14** yielded an epimeric mixture of **16**. This result suggests that the stereochemistry at C_6 in **14** was unchanged during the elimination reaction in the presence of triethylamine.

As expected, infrared (IR) absorption of the β-lactam carbonyl in **14** appears at 1773 cm^{-1} in chloroform while that in the dihydro derivative **18** appears at 1765 cm^{-1}. Smooth deesterification of **14** with aluminum trichloride and anisole[7] provided the acid **19**, which was reconverted to the ester **14** on treatment with phenyldiazomethane. The acid **19** was found to be as stable as the corresponding dihydro derivative **20** in 5% aqueous sodium bicarbonate.

On the other hand, side-chain cleavage of **14** by the usual method to give the amine **21** and acylation with N-protected D-phenylglycine **22** followed by deblocking afforded the phenylglycylamides **23** as a diastereoisomeric mixture in good overall yield.

To our disappointment, compounds **19** and **23** showed no antibacterial activity at concentrations of 1000 μg/ml against standard microorganisms. In this connection, it should be noted that very recently the benzo-fused carbocyclic β-lactam **24** has been reported to be inactive against Gram-positive and Gram-negative bacteria.[8]

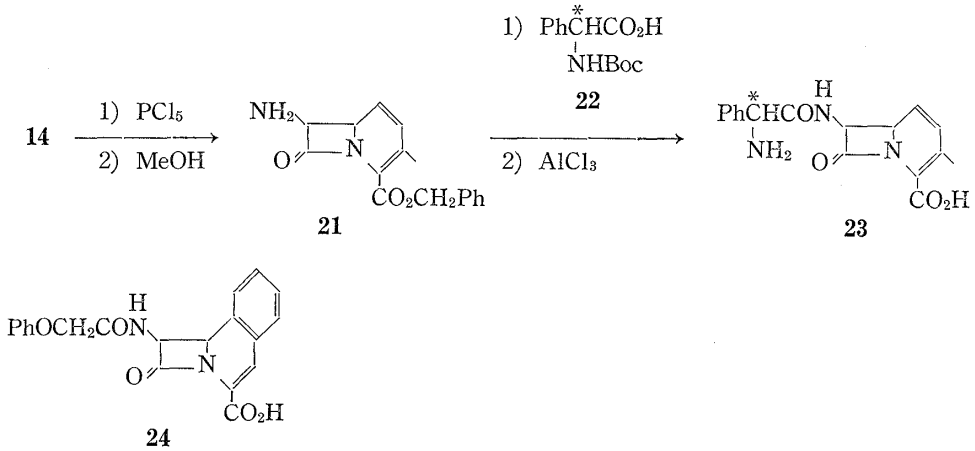


Chart 2

Experimental

All reactions were carried out under a nitrogen atmosphere using dry solvent unless otherwise stated. Melting points were determined on a Yanagimoto apparatus and are uncorrected. IR spectra were obtained on a Hitachi EPI-G3 spectrometer in $CHCl_3$ unless otherwise noted. Ultraviolet (UV) spectra were obtained

7) T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda, and W. Nagata, *Tetrahedron Lett.*, **1979**, 2793.
8) J. Finkelstein, K.G. Holden, and C.D. Perchonock, *Tetrahedron Lett.*, **1978**, 1629.

on a Hitachi EPS-3T spectrometer in 95% EtOH. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60A spectrometer in $CDCl_3$ with TMS as an internal standard. Rotations were determined on a Perkin-Elmer 141 spectrometer in $CHCl_3$. Mass spectra (MS) were obtained on Hitachi RMU8-GN and 6-E spectro-meters. Medium pressure liquid chromatographies were performed on Merck "Lobar®" pre-packed columns packed with LiChroprep® Si 60; size A (240-10 mm, 40—63 μm), size B (310-25 mm, 40—60 μm) and size C (440-37 mm, 63—125 μm).

Benzyl (3β-Phenylacetylamino-4β-styryl)-2-oxoazetidin-1-yl-3-methyl-2-butenoate (9)——(−)Isodehydrovaline benzyl ester hydrochloride (24.5 g, 0.10 mol) was dissolved in a minimum amount of water and the solution was made basic with saturated aqueous $NaHCO_3$, then free amine **4** was extracted with CH_2Cl_2 (×3, total 250 ml). Cinnamaldehyde (13.5 g, 0.102 mol) was added to the extract and the mixture was refluxed with a Dean-Stark trap filled with molecular sieves (4A) for 2 hr. A small amount of the reaction mixture was concentrated and the NMR spectrum of the residue showed complete formation of the Schiff base **5**. NMR δ: 1.79 (3H, d, J=*ca.* 1 Hz), 4.43 (1H, s, =NC<u>H</u>(CO_2–)–), 4.94 (2H, m, =CH_2), 5.11 (2H, s, OC<u>H</u>$_2$Ph), 6.81 and 6.85 (1H, d, J=3.5 Hz and 1H, d, J=5 Hz; –<u>CH</u>=<u>CH</u>Ph), 7.0—7.5 (10H, m, aromatic), 7.81 (1H, dd, J=3.5 and 5 Hz, N=CH–).

The above reaction mixture was cooled at −30°, and Et_3N (20 ml, 1.45 eq) followed by azidoacetyl chloride (13 g, 1.27 eq) were added with vigorous stirring. The mixture was stirred for 1 hr at −30° to −10°, washed with water, dried ($MgSO_4$) and concentrated to *ca.* 200 ml.

The above solution containing **6**, **7** and **8** was treated with Et_3N (20 ml) for 1 hr at room temperature and concentrated to dryness to give crude azido-azetidinone **8**. A small amount of this product was purified by chromatography on a Lobar column (benzene–EtOAc, 9: 1) to give **8** as an oil. IR: 3000 (br w), 2100 (s), 1765 (s), 1720 (m) cm^{-1}; NMR δ: 1.98 (3H, s), 2.20 (3H, s), 4.45—4.85 (2H, m, β-lactam), 5.12 and 5.27 (2H, AB-q, J=12 Hz, OC<u>H</u>$_2$Ph), 6.10 (1H, dd, J=8 and 16 Hz, –C<u>H</u>=CHPh), 6.53 (1H, d, J=16 Hz, =C<u>H</u>Ph), 7.28 (5H, s), 7.37 (5H, s).

A solution of the above crude **8** in 150 ml of CH_2Cl_2 was added dropwise to a mixture of Zn powder (23 g) and acetic acid (25 ml) in 100 ml of CH_2Cl_2 under ice-cooling and the mixture was stirred for 1 hr at room temperature. The mixture was filtered to remove insoluble material, washed with water (×2) and dried ($MgSO_4$). Removal of the solvent by evaporation left an oily residue which was dissolved in ether. Some insoluble material was removed and the ether phase was shaken with 3% hydrochloric acid (×2). The combined aqueous phase and the oily material precipitated under the aqueous phase were extracted with CH_2Cl_2, washed with aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated to give crude amine (38 g).

Phenylacetyl chloride (15 ml, 0.11 mol) was added dropwise to a solution of the above amine and pyridine (8 ml, 0.1 mol) in 150 ml of CH_2Cl_2 at −40° and the mixture was allowed to reach room temperature. After stirring for 1 hr, the mixture was washed with aqueous $NaHCO_3$ and dried ($MgSO_4$). Removal of the solvent and crystallization of the residue from ether gave **9** (21 g, 42% from **4**·HCl). Recrystallization from CCl_4–CH_2Cl_2 gave a pure material, mp 180—181°; $[\alpha]_D^{27}$ 0.0 (c=1.063); IR: 3410 (w), 2990 (w), 1763 (s), 1723 (m), 1683 (m), 1510 (br m), 1497 (m) cm^{-1}; NMR δ: 2.02 (3H, s), 2.18 (3H, s), 3.53 (2H, s, PhC<u>H</u>$_2$CO–), 4.65 (1H, dd, J=5.5 and 8 Hz, β-lactam), 5.20 (2H, br s, CO_2C<u>H</u>$_2$– and 1H, dd, J=5.5 and 8 Hz, β-lactam), 5.94 (1H, dd, J=8 and 16 Hz, –C<u>H</u>=CH–Ph), 6.23 (1H, br d, J=8 Hz, –CONH–), 6.48 (1H, d, J=16 Hz, =C<u>H</u>–Ph), 7.14, 7.26 and 7.38 (15H, three s, aromatic); MS: 494 (M^+), 403 [M^+−91 ($PhCH_2$·)], 385 [M^+−109 (H_2O+$PhCH_2$·)], 375 [M^+−119 ($PhCH_2CO$·)], 259 [M^+−135 ($PhCH_2CO_2$·)]. *Anal.* Calcd for $C_{31}H_{30}N_2O_4$ (499.10): C, 74.60; H, 6.17; N, 5.61. Found: C, 74.55; H, 6.00; N, 5.67.

Benzyl 2{3β-Phenylacetylamino-4β-[3-oxobut-(1E)-en-1-yl]-2-oxoazetidin-1-yl}-2-hydroxyethanoate (12)——Ozone was passed through a solution of **9** (4.946 g, 20.5 mmol) in 205 ml of CH_2Cl_2 under dry ice-acetone cooling until a blue color persisted. Excess ozone was removed by passing dry nitrogen through the reaction mixture.

Acetic acid (61 ml) and Zn powder (61 g) were added to the mixture with vigorous stirring at −30° and the whole was stirred for 50 min at −10°. The filtered reaction mixture was washed with water (×3) and dried ($MgSO_4$). A small portion of the solution was concentrated to give crude **10** (contaminated with benzaldehyde),IR: 3420 (br s w), 3000 (br w), 1775 (s), 1760 (sh s), 1680 (m) cm^{-1}; NMR δ: 3.47 (2H, br s, PhC<u>H</u>$_2$CO), 5.17 (2H, br s, OC<u>H</u>$_2$Ph), 7.0—7.4 (m, aromatic), 9.67 (1H, br d, J=9 Hz, –C<u>H</u>O) others not clear.

The above solution containing **10** and benzaldehyde was treated with the Wittig reagent **11** (6.53 g, 1 equiv) and the mixture was stirred overnight at room temperature then refluxed for 40 min. Removal of the solvent and chromatography of the residue (15.1 g) on a Lobar column (size C, *n*-hexane–$CHCl_3$–EtOAc, 5: 8: 7 and size C, *n*-hexane–EtOAc–EtOH, 20: 10: 3) yielded the desired compound **12** (4.23 g, 48% from **9**). Recrystallization from CCl_4–CH_2Cl_2 gave crystalline **12** as a diastereoisomeric mixture, mp 127—148°; IR: 3500 (br w), 3400 (w), 3000 (w), 1775 (s), 1760 (sh s), 1680 (s) cm^{-1}; NMR δ: 1.98 (3H, s), 3.43 (2H, s, PhC<u>H</u>$_2$CO–), 4.38 and 4.58 (1H, two dd, J=5 and 7 Hz, β-lactam), 5.08 and 5.17 (2H, two s, PhC<u>H</u>$_2$O–), 5.23 and 5.57 (1H, two s, C<u>H</u>OH), 5.33 (1H, br d, J=5 Hz, β-lactam), 6.02 and 6.10 (1H, two d, J=16 Hz, –CH=C<u>H</u>CO–), 6.53 and 6.58 (1H, two dd, J=7 and 16 Hz, –C<u>H</u>=CHCO–), 7.14 and 7.30 (10H, two br s, aromatic). *Anal.* Calcd for $C_{24}H_{24}N_2O_6$ (436.47): C, 66.04; H, 5.54; O, 22.00; N, 6.42. Found: C, 66.23; H, 5.49; O, 21.85; N, 6.54.

Benzyl 7β-Phenylacetylamino-1-benzenethio-3-methyl-1-carba-1-dethia-3-cephem-4-carboxylate (16)——A solution of **12** (2.30 g, 5.24 mmol) in 105 ml of CH_2Cl_2 was treated with $SOCl_2$ (0.58 ml, 1.5 eq) and pyridine (0.63 ml, 1.5 eq) under ice-cooling, and the mixture was stirred for 20 min under the same conditions. The mixture was washed with brine, dried ($MgSO_4$) and concentrated to one-half the original volume. Ph_3P (1.37 g, 1 eq) was added to the solution and the mixture was refluxed for 1.5 hr, washed with aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size C, *n*-hexane–EtOAc–EtOH, 20: 10: 3) gave the ylide **13** (2.39 g, 67%), IR: 3420 (w), 3300 (br w), 3000 (w), 1760 (s), 1680 (s), 1620 (s) cm^{-1}; NMR δ: 1.68 and 2.03 (3H, two br s, $COCH_3$), 3.45 (2H, s, $PhCH_2CO$–), 4.75 and 5.07 (2H, two br s, OCH_2Ph, over-lapped with β-lactam protons), 6.9—7.9 (25H, m, aromatic), other peaks could not be clearly assigned.

A solution of the ylide **13** (2.39 g, 3.51 mmol) in a mixture of 28 ml of THF and 7 ml of CH_2Cl_2 was treated under ice-cooling with a mixture of benzenethiol (0.4 ml, 1.1 eq) and NaH (*ca.* 5 mg) in 1 ml of THF. After stirring for 1 hr under ice-cooling, the solvent was evaporated off under reduced pressure and the product was taken up in 200 ml of EtOAc, washed with 20 ml of cold 5% aqueous NaOH, water and brine, and dried ($MgSO_4$). Removal of the solvent gave crude **14** (2.55 g, 92%) which was dissolved in 35 ml of a mixture of xylene and dioxane (7: 3). This solution was refluxed (bp *ca.* 120°) for 18 hr. Removal of the solvent and chromatography of the residue on a Lobar column (size B, *n*-hexane–$CHCl_3$–EtOAc, 5: 8: 7) gave **16a** (234 mg, 13% from **13**) and **16b** (155 mg, 8.6% from **13**) in this order. Further elution with *n*-hexane–EtOAc–EtOH (20: 10: 3) gave crude **14** (*ca.* 0.5 g, *ca.* 20%), mostyl in the form of the β-isomer. **16a**, mp 217—219° (ether); IR: 3410 (w), 3320 (w), 2990 (w), 1775 (sh s), 1760 (s), 1720 (m), 1680 (m) cm^{-1}; NMR δ: 1.96 (3H, s), 2.2—3.5 (4H, m, $-CH_2-$, $-CHSPh$, β-lactam), 3.55 (2H, s, $PhCH_2CO$), 5.12 (2H, s, OCH_2Ph), 5.57 (1H, dd, J=4.5 and 9 Hz), 7.20 (5H, s), 7.35 (5H, s), 7.2—7.7 (6H, m, –SPh and –NH–). *Anal.* Calcd for $C_{30}H_{28}N_2O_4S$ (512.64): C, 70.29; H, 5.51; N, 5.47; S, 6.26. Found: C, 70.34; H, 5.43; N, 5.42; S, 6.54. **16b**, mp 184—188° (ether); IR: 3410 (w), 2990 (w), 1775 (s), 1725 (m), 1680 (m) cm^{-1}; NMR δ: 1.90 (3H, s), 2.52 (2H, m, $-CH_2-$), 3.52 (2H, s, $PhCH_2CO$), 3.73 (1H, m, $-CHSPh$), 4.06 (1H, dd, J=2.5 and 5 Hz, β-lactam), 5.29 (2H, s, $-OCH_2$-Ph), 5.73 (1H, dd, J=5 and 9.5 Hz), 6.95 (1H, br d, J=9.5 Hz, –NH–), 7.19 (5H, s), 7.29 (5H, s), 7.4 (5H, m). *Anal.* Calcd for $C_{30}H_{28}N_2O_4S$ (512.64): C, 70.29; H, 5.51; N, 5.47; S, 6.26. Found: C, 70.44; H, 5.42; N, 5.52; S, 6.41.

Benzyl 7β-Phenylacetylamino-3-methyl-1,2-dehydro-1-carba-1-dethia-3-cephem-4-carboxylate (14)——A mixture of **16a** (415 mg, 0.81 mmol) and mCPBA (85%, 230 mg, 1.3 eq) in 12 ml of CH_2Cl_2 was stirred for 1.2 hr under ice-cooling. The mixture was diluted with CH_2Cl_2, washed with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent gave crude **17a** (488 mg). IR: 3650 (br w), 3400 (w), 3310 (w), 2980 (w), 1775 (sh s), 1760 (s), 1725 (m), 1680 (m), 1515 (br m), 1495 (m) cm^{-1}; NMR δ: 1.2—4.1 (4H, m, $-CH_2-$, $-CH(SOPh)-$, β-lactam), 1.85 and 1.97 (3H, two s, $-CH_3$), 3.62 (2H, s, $PhCH_2CO$), 5.02 (2H, s, OCH_2Ph), 5.17—5.68 (1H, m, β-lactam), 7.31 (5H, s), 7.38 (5H, s), 7.0—7.9 (6H, m, aromatic and –CONH–).

Similarly, **16b** (630 mg, 1.23 mmol) gave **17b** (672 mg). IR: 3670 (w), 3410 (w), 3260 (br w), 3000 (w), 1785 (s), 1730 (m), 1680 (m), 1510 (br m), 1495 (m) cm^{-1}; NMR δ: 1.2—2.7 (2H, m, $-CH_2-$), 1.91 (3H, s), 3.44 (1H, m, J=2 Hz, $-CH(SOPh)-$), 3.64 (2H, s, $PhCH_2CO$), 4.27 (1H, dd, J=2 and 6 Hz, β-lactam), 5.30 (2H, s, OHC_2Ph), 5.98 (1H, dd, J=6 and 10 Hz), 7.4 (6H, m, aromatic and –NHCO–), 7.62 (5H, s).

A solution of the above **17a** (488 mg) in a mixture of 4.5 ml of DMF and 0.5 ml of Et_3N was heated at 75—80° for 5 hr. Removal of the solvent gave the crude product **14**.

Similarly, a solution of the above **17b** (672 mg) in 6.2 ml of CH_3CN containing 0.68 ml of Et_3N was heated at 75—80° for 1.5 hr to yield, on removal of the solvent, crude **14**. The products from the above two reactions were combined, chromatographed on a Lobar column (size B, $CHCl_3$–EtOAc, 4: 1) and crystallized from ether to give the desired compound **14** (744 mg, 91% from **16**). Recrystallization from CCl_4–CH_2Cl_2 gave a pure material, mp 166—167°; IR: 3675 (br w), 3550 (br w), 3400 (w), 1773 (s), 1710 (m), 1679 (m), 1605 (w), 1495 (m) cm^{-1}; NMR δ: 2.13 (3H, s, $-CH_3$), 3.55 (2H, s, $PhCH_2CO-$), 4.51 (1H, br d, J=4.5 Hz, β-lactam), 5.23 (2H, s, $-OCH_2Ph$), 5.60 (1H, dd, J=4.5 and 7 Hz, β-lactam), 5.68 (1H, br d, J=10 Hz) and 5.89 (br dd, J=1.5 and 10 Hz) ($-CH=CH-$), 7.06 (1H, d, J=7 Hz, $-CONH-$), 7.27 (5H, s), 7.33 (5H, s); UV: 322.5 nm (ε, 5.2×10^3), MS: 402 (M^+), 311 [M^+-91 ($PhCH_2\cdot$)], 284 [$M^++1-199$ ($PhCH_2CO\cdot$)], 228 [$M^++1-175$ (Ph-$CH_2CONHCH{=}CO$)]. *Anal.* Calcd for $C_{24}H_{22}N_2O_4$ (402.46): C, 71.62; H, 5.51; O, 15.90; N, 6.96. Found: C, 71.84; H, 5.49; O, 16.06; N, 6.98.

Hydrogenation of 14——Compound **14** (41 mg, 0.10 mmol) was hydrogenated under atmospheric pressure in a mixture of 1.5 ml of THF and 2.3 ml of EtOAc with pre-reduced 10% Pd-C (10 mg) at room temperature for 30 min. The mixture was filtered through celite, concentrated into dryness and crystallized from ether to give **18** (34 mg, 84%), mp 180—182°, which was identical with an authentic sample (mixed mp determination and comparison of IR and NMR spectra). UV: 267 nm (ε, 1.0×10^4).

Addition of Benzenethiol to 14——A mixture of **14** (20 mg, 0.05 mmol), benzenethiol (6.2 μl, 1.2 eq), 0.1 ml of CH_2Cl_2 and 0.4 ml of THF was treated under ice-cooling with a trace amount of NaH, and the mixture was stirred for 1 hr at the same temperature. The product was taken up in CH_2Cl_2, washed with brine and dried ($MgSO_4$). Removal of the solvent and chromatography of the residue on a Lobar column (size A, *n*-hexane–$CHCl_3$–EtOAc, 5: 8: 7) gave **16a** (*ca.* 3 mg, *ca.* 12%), which was identical with the authentic material

on the basis of TLC and IR spectral comparison, and **16b** (15 mg, 60%), which was similarly identified by TLC, IR and NMR comparison.

7β-Phenylacetylamino-3-methyl-1,2-dehydro-1-carba-1-dethia-3-cephem-4-carboxylic Acid (19)——A solution of **14** (161 mg, 0.4 mmol) in a mixture of 2 ml of anisole, 0.2 ml of CH_3NO_2 and 4 ml of CH_2Cl_2 was treated with $AlCl_3$ (534 mg, 10 equiv) under ice-cooling and the mixture was stirred at room temperature for 2.5 hr. The reaction mixture was diluted with aqueous $NaHCO_3$, washed with CH_2Cl_2, made acidic with dilute hydrochloric acid and extracted with a mixture of CH_2Cl_2 and methyl ethyl ketone (1: 1). The extract was dried ($MgSO_4$), concentrated and crystallized from ether to give the desired compound **19** (70 mg, 56%), mp 125—130°; IR (Nujol): 3375 (w), 3100—2300 (br m), 1770 (s), 1760 (s), 1730 (s), 1710 (s) cm^{-1}; NMR ($CDCl_3+CD_3OD$) δ: 2.23 (3H, s), 3.60 (2H, s, Ph$\underline{CH_2}$CO–), 4.58 (1H, br d, $J=4.5$ Hz, β-lactam), 5.64 (1H, d, $J=4.5$ Hz, β-lactam), 5.84 (br d, $J=10$ Hz) and 6.09 (1H, dd, $J=10$ and 2 Hz, –$\underline{CH}$=$\underline{CH}$–), 7.30 (5H, s); UV: 318 nm (ε, 1.3×10^3).

Reesterification of 19 to 14——The acid **19** (26 mg, 0.083 mmol) was dissolved in a mixture of 7 ml of CH_2Cl_2 and 3 ml of MeOH and treated with excess phenyldiazomethane (freshly prepared from phenylhydrazone and nickel peroxide in ether) at room temperature for 1.5 hr. Removal of the solvent and chromatography of the residue on a Lobar column (size A, $CHCl_3$–EtOAc, 4: 1) gave pure **14** (30 mg, 90%), mp 161—162°, which was identical with the authentic material (mixed mp, TLC and NMR comparison).

Benzyl 7β-Amino-3-methyl-1,2-dehydro-1-carba-1-dethia-3-cephem-4-carboxylate (21)——PCl_5 (125 mg, 2 eq) was added to a solution of **14** (121 mg, 0.3 mmol) in 3 ml of CH_2Cl_2 containing pyridine (73 μl, 3 eq) at −30° and the mixture was stirred at −30° for 1 hr then under ice-cooling for 40 min. The mixture was then cooled to −30° and 1.5 ml of MeOH was added. After stirring for 30 min at −30°, 0.9 ml of water was added and most of the solvent was removed under reduced pressure. The residue was diluted with aqueous $NaHCO_3$, extracted with CH_2Cl_2 (×3), washed with brine and dried ($MgSO_4$). Removal of the solvent and crystallization of the residue from ether gave the amine **21** (70 mg, 82%), mp 137—139°; IR: 3390 (w), 3030 (w), 2995 (w), 2950 (w), 2790 (w), 1765 (s), 1715 (s) cm^{-1}; NMR δ: 1.73 (2H, br s, $-NH_2$), 2.20 (3H, s, $-CH_3$), 4.44 (1H, d, $J=5$ Hz, β-lactam), 4.78 (1H, d, $J=5$ Hz, β-lactam), 5.25 (2H, s, –O$\underline{CH_2}$Ph), 6.09 (2H, s, –CH=CH–), 7.34 (5H, br s). *Anal.* Calcd for $C_{16}H_{16}N_2O_3\cdot1/4H_2O$ (288.82): C, 66.54; H, 5.76; N, 9.70. Found: C, 66.84; H, 5.55; N, 9.64.

7β-[(2*R*)-2-Phenyl-2-amino]acetylamino-3-methyl-1,2-dehydro-1-carba-1-dethia-3-cephem-4-carboxylic Acid (23)——A mixture of the amine **21** (70 mg, 0.246 mmol), N-Boc-phenylglycine **22** (124 mg, 2 eq) and N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (122 mg, 2 eq) in 2.5 ml of THF was stirred at room temperature for 1 hr. The solvent was evaporated off and the residue was chromatographed on a Lobar column (size A, *n*-hexane–EtOAc, 1: 1) to give the amide (125 mg, 98%), mp 62—67° (*n*-hexane–EtOAc); IR: 3415 (w), 2970 (w), 1770 (sh m), 1725 (s), 1685 (s), 1495 (s) cm^{-1}; NMR ($CDCl_3$–CD_3OD) δ: 1.43 (9H, s, *tert*-Bu), 2.16 and 2.21 (3H, two s, $-CH_3$), 4.51 (1H, m, β-lactam), 5.1—6.2 (4H, m, –CH=CH–, PhC$\underline{H}$(NH–)CO–, β-lactam), 5.22 (2H, s, –OC$\underline{H_2}$Ph), 7.33 (10H, s, aromatic), 8.1 (1H, m, –NH–); UV: 322 nm (ε, 1.8×10^3; MS: 429 [M^+ (517)-88], 415 [M^+-1-101 ($CO_2C_4H_9$)], 324 [415-91 ($PhCH_2$)].

A mixture of the above amide (125 mg, 0.24 mmol), $AlCl_3$ (500 mg, 15 eq), 1.25 ml of anisole, 0.125 ml of CH_3NO_2 and 2.5 ml of CH_2Cl_2 was stirred under ice-cooling for 30 min then at room temperature for 2 hr. The mixture was diluted with ice-water, and washed with CH_2Cl_2 (×2), then the aqueous phase was chromatographed on a column packed with HP-20 (high porous polymer, Mitsubishi Daiya-ion HP-20). Elution with a mixture of MeOH and water (9: 11) gave, on removal of the solvent, the desired compound **23** (63 mg, 80%), mp *ca.* 150° (dec.); IR (KBr): 3420 (br s), 3200 (br s), 3030 (s), 2910—2300 (br), 1750 (s), 1690 (s), 1550 (br s); MS: 190 [M^+ (327)-137 (3-methylpicolinic acid)], 162 (190-CO), 147, 93 (β-picoline), 91 ($PhCH_2$).

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