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Synthetic Studies on 1-Carbacephem Antibiotics: New Synthetic Approach to 3*H*-Carbacephems

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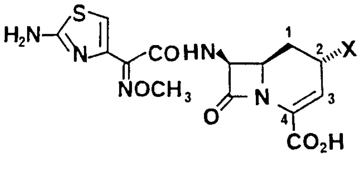
A new synthetic route to 3-*H* (3-unsubstituted) carbacephems was developed starting from readily available dialkyl aminomalonate and using intra-molecular aldol condensation for the construction of the 4,6-fused ring system.

Keywords——1-carbacephem; *cis*-azetidinone; amino malonate; aldol condensation; decarboxylation

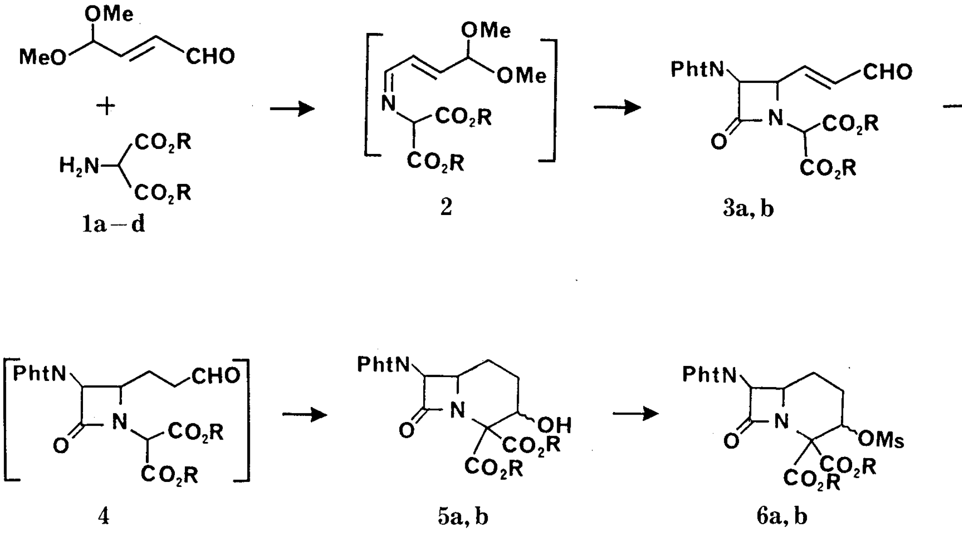
In a previous paper, we reported the synthesis of the 3-*H* (3-unsubstituted) carbacephem nucleus,[1)] the chemical modification at the 2-position and the antimicrobial activities of various 7-acylamino compounds[2)] including KT-3767 and KT-3937, which showed comparable antimicrobial activities to third-generation cephalosporins (Fig. 1). Several methods have recently been developed for the synthesis of carbacephems.[3)] Most of these reported methods have employed internal Wittig cyclization, so that they require long synthetic sequences or starting materials which are not readily available. In this paper, we wish to describe a new synthetic route to the 3-*H* carbacephem nucleus in which dialkyl aminomalonate is used as a starting material and intra-molecular aldol condensation is utilized for the construction of the 4,6-fused ring system.

The Schiff's base (**2**), *i.e.*, the condensate of dialkyl aminomalonate (**1a**—**d**) and 4,4-dimethoxybut-2-enal in the presence of Molecular Sieves-4A in CH_2Cl_2, was reacted with phthaloylglycyl chloride in the presence of triethylamine at room temperature followed by deacetalization (*p*-TsOH, in acetone) to give the *cis*-2-azetidinone (**3a**, **b**). The yields were significantly influenced by the kind of ester of aminomalonate employed [18.1% for the methyl ester (**3a**) and 22.2% for the ethyl ester (**3d**)], while products derived from the *tert*-butyl (**1c**) as well as benzyl (**1d**) ester could not be isolated. When **3a** and **3b** were hydrogenated under ordinary conditions (H_2, 10% Pd–C, in methanol), the products obtained were not the aldehyde (**4**) but the ring-fused compounds, carbacephams (**5a**, **b**), and yields were almost quantitative. In the proton nuclear magnetic resonance (^1H-NMR) spectra, the aldehyde proton and methin proton of the malonate moiety were not observed, so the structures were presumed to be cyclic and were determined after conversion to the mesylates (**6a**, **6b**) by treatment with mesyl chloride in pyridine. This result indicates that the malonate moiety



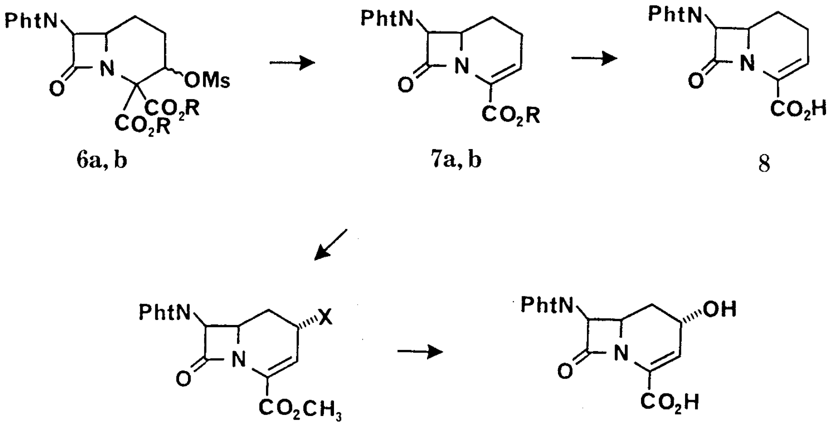
KT3767 : X=H
KT3937 : X=OH

Fig. 1



a : R=Me
b : R=Et
c : R=*tert*-Bu
d : R=Bzl

Chart 1



9 : X=Br
10 : X=OH

Chart 2

contained in **3a** and **3b** was reactive enough to undergo intra-molecular aldol condensation[4] spontaneously under neutral conditions.

The treatment of **6a** and **6b** with even a weak base such as potassium carbonate in aqueous media caused hydrolysis of the phthaloyl moiety. The cleavage of the alkyl group of the ester was eventually carried out by employing an S_N2 type reaction.[5] Reaction of **6a**, **b** with NaI in pyridine at reflux for 3 h afforded decarbalkoxylated products. In the case of **6a**, the products obtained were a mixture of the methyl ester (**7a**) and the carboxylic acid (**8**) in 28% and 31% yields, respectively. On the other hand, **6b** gave only the monoethyl ester (**7b**) in 64% yield under the same conditions. Moreover, **7a** was obtained selectively in 64.6% yield by heating **6a** at reflux with LiI in acetone and **8** was also obtained fom **7a** in 60% yield in a similar manner using pyridine instead of acetone. It seems that the removal of the alkyl group by iodine anion, thermal decarboxylation and demesylation occurred simultaneously and resulted in the formation of the desired 3-*H* carbacephems. This type of cleavage of alkyl esters is not known in the chemistry of the strained Δ^3-cephem system. The conversion of **7b** to **8** was attempted under various conditions, but resulted in decomposition of the carbacephem nucleus.

For the preparation of the 2-α-OH nucleus, the key intermediate of KT-3937, **7a** was converted to the 2-α-bromide (**9**) according to the reported method,[1] followed by hydrolysis with a Lewis acid ($ZnCl_2$) to give desired **10** in 76% yield. The conversion of **10** to the carboxylic acid (**11**) was achieved by the same method (LiI, pyridine, reflux for 3 h, 54% yield). The physical properties of **8** and **11** obtained according to this procedure conformed to the reported data.[1] Since the transformations of **8** and **11** to KT-3767 and KT-3937, respectively, have already been established, this new route to 3-*H* carbacephem nuclei combined with the established following steps provides a novel synthetic route to KT-3767 and KT-3937.

Experimental

^1H-NMR spectra were recorded at 90 MHz on a Varian EM-390 NMR spectrometer and at 100 MHz on a JEOL FX-100 NMR spectrometer using tetramethylsilane (TMS) or dioctyl sodium sulphosuccinate (DSS) as an internal standard. All chemical shifts are reported in δ ppm. Infrared (IR) spectra were taken on a JASCO IR-80B infrared spectrometer. Mass (MS) spectra were recorded on a Hitachi M-80B mass spectrometer. All compounds are racemic, but only one enantiomer is depicted for convenience.

(±) Dimethyl 2-[*cis*-3-Phthalylimido)-4-(3-oxo-1-propenyl) 2-oxo-azetidin-1-yl]malonate (3a)——4,4-Dimethoxy-trans-2-butenal (6.9 g) was added to a suspension of 6.5 g of dimethyl aminomalonate and 20 g of Molecular Sieves 4A in 300 ml of CH_2Cl_2. The mixture was stirred for 18 h, then a solution of 9.9 g of phthaloylglycyl chloride in 50 ml of CH_2Cl_2 and 5.5 ml of triethylamine were added dropwise over 30 min at 0 °C. The reaction mixture was stirred for 3 h at room temperature and washed successively with 0.1 N HCl, H_2O, saturated $NaHCO_3$ solution and brine. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was dissolved in 150 ml of acetone and 2.0 g of *p*-TsOH·H_2O was added. The solution was stirred for 2 h. After addition of 200 ml of AcOEt, the organic layer was separated, washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated. The product obtained was purified by silica gel column chromatography eluting with hexane–AcOEt (1 : 1) to afford **3a** as colorless crystals (3.2 g, 18.1%). mp 150—152 °C. IR (KBr): 1800, 1760, 1755, 1735, 1720, 1700, 1680 cm^{-1}. ^1H-NMR ($CDCl_3$): 9.10 (1H, d), 7.8 (4H, m), 6.97 (1H, dd), 6.18 (1H, dd), 5.79 (1H, d), 5.43 (1H, s), 5.18 (H, dd), 3.87 (3H, s), 3.83 (3H, s). High MS *m/z*: 400.0912 (Calcd for $C_{19}H_{16}N_2O_8$: 400.0906).

The diethyl ester (**3b**) was obtained from diethyl aminomalonate by a procedure similar to that described above (yield 22.2%). IR (KBr): 1800, 1765, 1755, 1740, 1720, 1700, 1685 cm^{-1}. ^1H-NMR ($CDCl_3$): 9.10 (1H, d), 7.8 (4H, m), 6.96 (1H, dd), 6.20 (1H, dd), 5.80 (1H, d), 5.41 (1H, s), 5.23 (1H, dd), 4.35 (2H, q), 4.30 (2H, q), 1.29 (6H, t). High MS *m/z*: 428.1209 (Calcd for $C_{21}H_{20}N_2O_8$: 428.1218).

Dimethyl (6*R,7*S**)-7-Phthalylimido-3-hydroxy-1-azabicyclo[4.2.0]octan-8-oxo-2,2-dicarboxylate (5a)**——Compound **3a** (2.1 g) was subjected to hydrogenation in 80 ml of MeOH for 4 h over a 10% Pd–C catalyst (210 mg) at room temperature under atmospheric pressure. The catalyst was filtered off and washed with MeOH. The combined filtrate and washing was evaporated and the residue was chromatographed on silica gel with hexane–AcOEt (1 : 1) to give **5a** as colorless crystals (1.9 g, 92%). mp 179—181 °C. IR (KBr): 1800, 1785, 1770, 1740 cm^{-1}. ^1H-NMR ($CDCl_3$): 7.82 (4H, m), 5.42 (1H, d), 4.0—4.6 (2H, m), 3.92 (3H, s), 3.87 (3H, s), 1.3—2.3 (4H, m). High MS *m/z*: 402.1053 (Calcd for $C_{19}H_{18}N_2O_8$: 402.1062).

Dimethyl (6*R,7*S**)-3-Methanesulfonyloxy-7-phthalylimido-1-azabicyclo[4.2.0]octan-8-oxo-2,2-dicarboxylate (6a)**——Mesyl chloride (0.1 ml) was added to a solution of 270 mg of **5a** in 6 ml of pyridine under ice-cooling. The reaction mixture was stirred for 4 h at room temperature and evaporated under reduced pressure. After addition of 20 ml of AcOEt to the residue, the solution was washed with H_2O, saturated $NaHCO_3$ and brine, and evaporated to afford **6a** as yellow crystals (320 mg, 99%). mp 206—209 °C. IR (KBr): 1785, 1770, 1759, 1746, 1723 cm^{-1}. ^1H-NMR ($CDCl_3$): 7.8 (4H, m), 5.48 (1H, d), 5.3 (1H, m), 4.4 (1H, m), 3.94 (3H, s), 3.89 (3H, s), 3.21 (3H, s), 1.7—2.8 (4H, m). High MS *m/z*: 480.0826 (Calcd for $C_{20}H_{20}N_2O_{10}S$: 480.0836).

The diethyl ester **6b** was obtained from **5b** (yield 92%). IR (KBr): 1790, 1772, 1760, 1793, 1718 cm^{-1}. ^1H-NMR ($CDCl_3$): 7.8 (4H, m), 5.47 (1H, d), 5.30 (1H, m), 4.2—4.6 (5H, m), 3.20 (3H, s), 1.7—2.6 (4H, m), 1.34 (6H, t). High MS *m/z*: 508.1138 (Calcd for $C_{22}H_{24}N_2O_{10}S$: 508.1149).

Methyl (6*R,7*S**)-7-Phthalylimido-1-azabicyclo[4.2.0]oct-2-en-8-oxo-2-carboxylate (7a)**——A solution of 720 mg of **6a** and 400 mg of LiI in 15 ml of acetone was refluxed for 2 h. After cooling to room temperature, the reaction mixture was diluted with 50 ml of $CHCl_3$, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–AcOEt, 1 : 1) to provide 310 mg of **7a** (64.6%). mp 227—229 °C. IR (KBr): 1795, 1780, 1770, 1730, 1720, 1630 cm^{-1}. ^1H-NMR ($CDCl_3$): 7.8 (4H, m), 6.41 (1H, m), 5.60 (1H, d), 4.0 (1H, m). 3.88 (3H, s), 1.6—2.5 (4H, m). High MS *m/z*: 326.0914 (Calcd for $C_{17}H_{14}N_2O_5$: 326.0902).

Methyl (4*S,6*R**,7*S**)-4-Hydroxy-7-phthalylimido-1-azabicyclo[4.2.0]oct-2-en-8-oxo-2-carboxylate (10)**——A suspension of **7a** (180 mg), *N*-bromosuccinimide (120 mg) and a catalytic amount of azobisisobutyronitrile in 16.2 ml of CCl_4 and 1.8 ml of $CHCl_3$ was refluxed with vigorous stirring for 12 min. After cooling, the reaction mixture was diluted with 15 ml of $CHCl_3$, washed with H_2O and evaported. The yellow solid thus obtained was dissolved in 15 ml of 96% aqueous acetone, and 300 mg of $ZnCl_2$ was added to the solution portionwise over 4 h. After 6 h, the reaction mixture was diluted with 20 ml of $CHCl_3$, washed with water, saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated to give 150 mg of **10** as colorless crystals (76%). mp 213—216 °C. IR (KBr): 1790, 1775, 1760, 1750, 1725 cm^{-1}. NMR ($CDCl_3$): 7.8 (4H, m), 6.45 (1H, d), 5.73 (1H, d), 4.4 (1H, m), 4.0 (1H, m), 3.89 (3H, s), 1.8—2.2 (2H, m). High MS *m/z*: 342.0849 (Calcd for $C_{17}H_{14}N_2O_6$: 342.0851).

The Cleavage of Methyl Esters of Carbacephems (7a, 10)——A suspension of 720 mg of **7a** and 55 mg of LiI in 3.5 ml of pyridine was refluxed for 3 h. After cooling to room temperature, the reaction mixture was concentrated. The residue was triturated in 5 ml of acetone to form precipitates. The precipitates were collected by filtration and washed with ether to afford 8 as the lithium salt (40 mg, 60%). **11** was obtained from **10** by a similar procedure (54%). The physical data of **8** and **11** were identical with those reported.[1]

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