Synthetic Studies on 1,2-Dehydro-1-carbacephem Compounds

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7-Azido-1,2-dehydro-1-carbacephem 13 was efficiently synthesized by employing ketene-imine cycloaddition, intramolecular Horner–Emmons reaction and elimination of a phenylsulfoxide group or an ammonium group. 7-Acylamino 1,2-dehydro-1-carbacephems, 18 and 19, were obtained from 13. Infrared absorption frequencies of the β-lactam carbonyl in 1,2-dehydro-1-carbacephem compounds thus prepared are equal to or higher than those of the corresponding 1-carbacephem compounds. However, 18 and 19 exhibited very poor antibacterial activity.

Keywords β-lactam; carbacephem; 1,2-dehydro-1-carbacephem; ketene-imine cycloaddition; intramolecular Horner–Emmons reaction; infrared absorption; acylation; Michael addition

In the preceding paper[1] we reported the first synthesis of optically active 3-H-1-carbacephem compounds **1** and an examination of their antibacterial activity. In the course of our extensive studies on the synthesis of carbacephem compounds we were interested in 1,2-dehydro-3-H-1-carbacephem compounds **2**. The 1,2-dehydro-1-carbacephem nucleus is considered to have so great a ring strain as to increase the chemical reactivity of the β-lactam carbonyl[2] toward nucleophiles, and this is expected to lead to an increased antibacterial activity. In addition, the 1,2-dehydro ring system is unique to the 1-carbacephem nucleus (it is not available in cephem or 1-oxacephem compounds).

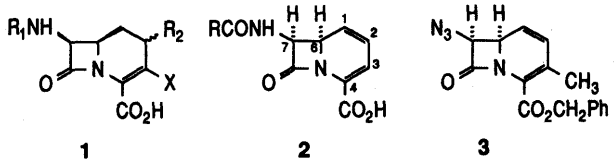


Chart 1

The 1,2-dehydro-1-carbacephem compound **3** was first synthesized by Doyle *et al.*,[3] and after the completion of our work,[4] by Uyeo and Ona.[5] The compounds with limited acyl groups synthesized by Uyeo and Ona have a common 3-CH_3 group which is considered to diminish their antibacterial activities. In the preceding paper the favorable biological features of 3-H-1-carbacephem over the conventional 3-substituted methyl-1-carbacephem compound were demonstrated.[1] We now wish to report the synthesis and antimicrobial activity of 1,2-dehydro-3-H-1-carba-

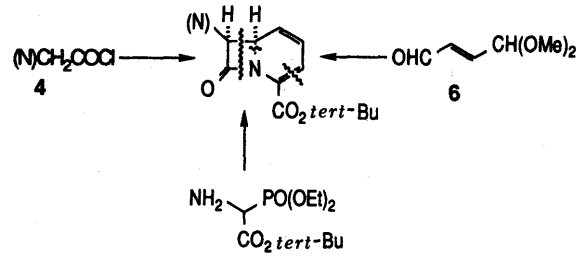


Chart 2

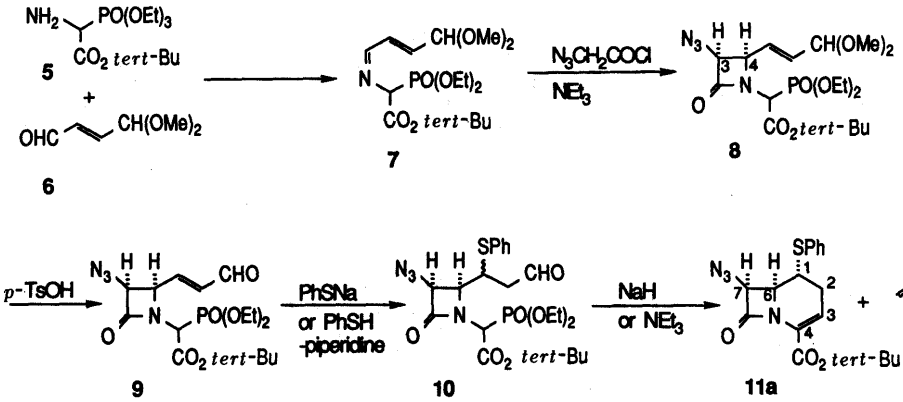


Chart 3

cephem compounds.

1,2-Dehydro-3-H-1-carbacephem was divided into three synthons, namely a C_2 unit with an amine precursor **4** (*e.g.* azidoacetyl chloride or phthalylglycyl chloride), *tert*-butyl diethylphosphonoglycinate **5**, and 4,4-dimethoxy-2-butenal[6] **6**.

Although many methods are known for the preparation of diethylphosphonoglycinate, except for the *tert*-butyl ester, none of them are suitable for a large-scale synthesis. A practical synthesis of *tert*-butyl diethylphosphonoglycinate **5**, which has played a significant role throughout our carbacephem project, was reported in a separate paper.[7]

The aldehyde **6**, prepared from furan in two steps, was condensed with the amine **5** to give the Schiff's base **7** quantitatively. Addition of azidoacetyl chloride to an ice-cold solution of the Schiff's base **7** and triethylamine in benzene–cyclohexane resulted in stereoselective cycloaddition[8] to give the desired 3,4-*cis*-azetidinone **8**. The acetal **8** was readily hydrolyzed to the corresponding aldehyde **9** quantitatively.

Since the double bond of **9** adopts *trans* form, isomerization to the *cis* form was examined. All attempts, however, were unsuccessful. Conjugate addition of sodium thiophenolate[9] or preferably thiophenol with a catalytic amount of piperidine[10] to **9** gave **10** as a diasteromeric mixture. Cyclic olefination of **10** was smoothly effected upon treatment with sodium hydride or triethylamine to afford the bicyclic products **11a** and **11b** as a mixture of C_1-stereoisomers in the ratio of *ca.* 2.5 : 1; these were easily separated by silica gel column chromatography. In both isomers the coupling constant (5.0 Hz) between C_6-H and C_7-H was indicative of the C_6–C_7 *cis*-stereochemistry. The coupling constant between C_1-H and C_6-H was 11.0 Hz for the major isomer and, 3.0 Hz for the minor isomer. On the basis of Dreiding models, the coupling constant of C_1-β-H is expected to be larger than that of C_1-α-H. Thus, the major and minor isomers can be assigned as the 1α-phenylsulfide **11a** and the 1β-phenylsulfide **11b**, respectively. Oxidation of **11a** and **11b** with *m*-chloroperbenzoic acid (MCPBA) or $NaIO_4$ afforded the corresponding sulfoxides **12a** and **12b** almost quantitatively. The sulfoxide **12a** was obtained as a mixture of stereoisomers at the sulfur atom. Pyrolysis of **12a** at 105—110 °C gave the desired 1,2-dehydro-1-carbacephem **13** in moderate yield. The rates of elimination of the two isomers of **12a** were indistinguishable. In the case of the sulfoxide **12b** obtained as a single isomer, the elimination was more smoothly effected upon heating at 70 °C, to give **13** in fairly good yield. Prolonged reaction time decreased the yield of **13**. The objective 1,2-dehydro-1-carbacephem skeleton was thus synthesized through four steps from the aldehyde **9** in 32% overall yield.

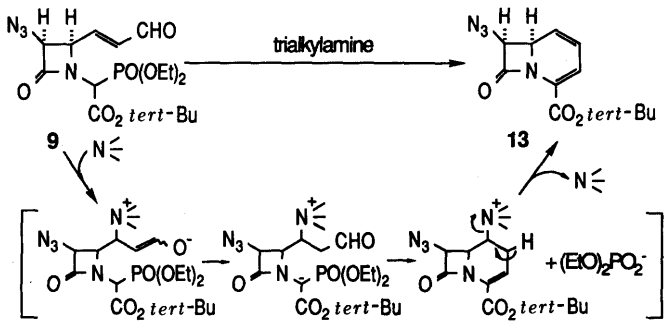


Chart 4

TABLE I. Direct Cyclization of Compound **9**

Base	Solvent	Temp.	Time (h)	Yield (%)
$Me_2NCH_2CH_2OH$	Benzene	r.t.	4	67
$Me_2NCH_2CH_2OH$	AcOEt	r.t.	4	66
$Me_2NCH_2CH_2OH$	DME	r.t.	4	62
DABCO	Benzene	r.t.	5.5	61
DABCO	Benzene	52 °C	2	52
N-Me morpholine	—	52 °C	2	48
Dimethylaminopyridine	Benzene	52 °C	2	45
NEt_3	—	52 °C	2	34
Dicyclohexylamine	—	52 °C	2	12
n-$BuNH_2$	—	52 °C	2	0
EtONa	EtOH	r.t.	3	0
NaH	DME	r.t.	0.4	Trace

r.t. = room temperature.

We also found a notably efficient alternative method for the preparation of the 1,2-dehydro-1-carbacephem **13** directly from the aldehyde **9**. That is, treatment of the aldehyde **9** with trialkylamine surprisingly afforded the 1,2-dehydro-1-carbacephem **13** in fairly good yield. Among various bases examined for this novel type of cyclization (Table I), dimethylethanolamine and diazabicyclooctane gave the most satisfactory results.

A possible reaction mechanism for the cyclization is outlined in Chart 4, *i.e.*, conjugate addition of an amine to the aldehyde **9**, followed by proton shift, Horner–Emmons ring closure and subsequent elimination of amine, results in the formation of the 1,2-dehydro-1-carbacephem compound **13**. Recently dimerization of α,β-unsaturated ketones and nitriles catalyzed by diazabicyclooctane (DABCO) was suggested to involve the conjugate addition of DABCO.[11] In this manner the target compound **13** became readily available. Since **13** can be easily reduced to 7-amino-3-H-1-carbacephem **14**, this method is also efficient as an alternative synthetic method for the useful 3-H-1-carbacephem nucleus. Besides *tert*-butyl ester, trichloroethyl and *p*-nitrobenzyl ester analogues of **13** were similarly obtained from corresponding diethylphosphonoglycinates (Chart 5).

Hydrolysis of the *tert*-butyl ester of **13** with trifluoroacetic acid (TFA) gave the acid **15**, which was reduced to the zwitterionic amine **16a**. Reduction of **13** with hydrogen sulfide and triethylamine followed by hydrolysis of the ester group with TFA also afforded **16b** as the TFA salt. Acylation of **16a** with 2-thienylacetyl chloride gave the corresponding amide **18**. Similarly the amide **19** was ob-

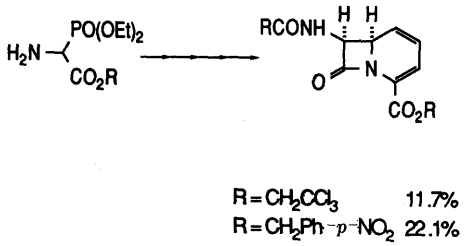


Chart 5

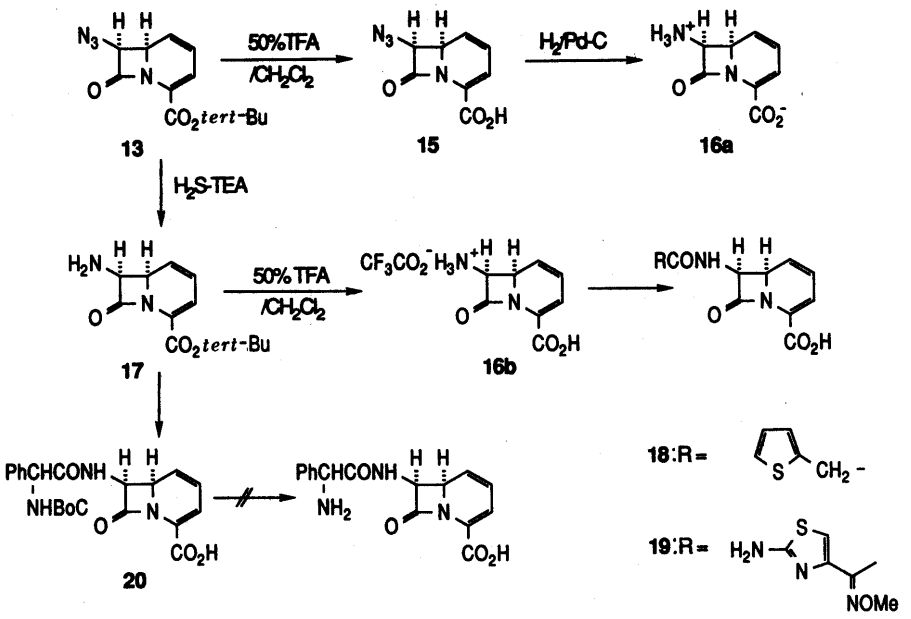
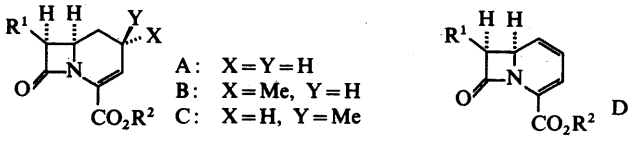


Chart 6

TABLE II. Infrared Absorption Frequencies of β-Lactam Carbonyl



	R^1	N^3		H_2N		$TFA \cdot H_2N$		
	R^2	CO_2 *tert*-Bu	CO_2H	CO_2 *tert*-Bu	CO_2H	CO_2H	CO_2H	CO_2H
A		1790	1760	1775	1770	1780	1775	1760
B		1790	1770	1770		1780		1760
C		1783		1780				
D		1790	1780	1770	1770	1785	1780	1770

tained by acylation of **16b** with 2-(2-chloroacetamidothiazol-4-yl)-2-*syn*-methoxyiminoacetyl chloride followed by deprotection. The amino ester **17** was acylated with Boc-(*R*)-phenylglycine by means of a mixed anhydride method to give the amide **20**, but subsequent deprotection of the Boc group was unsuccessful.

As expected, the infrared (IR) absorption frequencies of the β-lactam carbonyl in 1,2-dehydro-1-carbacephem compounds are equal to or higher than those of the corresponding 1-carbacephem compounds as shown in Table II. However, **18** and **19** exhibited very poor antibacterial activity. The six-membered ring of 1,2-dehydro-1-carbacephem is nearly planar, being quite different from the cephem or 1-carbacephem ring system. This may imply the strict requirement of an appropriate molecular form (besides the reactive β-lactam ring) for the recognition of the β-lactam compound by target enzymes of the microorganism.

Experimental

IR spectra were measured with a JASCO IR-810, proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on Varian T-60 and JEOL GNM PS-100 spectrometers, and mass spectra (MS) were measured with a JEOL JMS-01SG-2. Wako-gel C-200 was used for silica gel chromatography.

Preparation of the Schiff's Base 7 *tert*-Butyl α-amino-diethylphosphonoacetate **5** (1.80 g, 4 mmol) was dissolved in 100 ml of anhydrous CH_2Cl_2 and 4,4-dimethoxy-*trans*-2-butenal **6** (580 mg, 4.4 mmol) dissolved in 20 ml of anhydrous CH_2Cl_2 was added thereto. The mixture was stirred at room temperature for 1 h. After addition of anhydrous $MgSO_4$ (600 mg), the resulting solution was stirred for a further 1 h. The reaction solution was filtered and the filtrate was evaporated under reduced pressure to obtain 1.63 g of an oily product. Yield 100%. NMR ($CDCl_3$) ppm: 8.00 (1H, dd), 6.67 (1H, dd), 4.93 (1H, d), 3.97—4.33 (4H, m), 3.33 (6H, s), 1.50 (9H, s), 1.33 (6H, t). MS *m/z*: 380 ($M^+ + 1$).

***tert*-Butyl (±)-2-[(*cis*-4-(3,3-Dimethoxy-1-propenyl)-3-azido-2-oxoazetidin-1-yl]-2-diethylphosphonoacetate (8)** The Schiff's base **7** (39.2 g, 0.103 mol) was dissolved in 500 ml of anhydrous benzene and 500 ml of anhydrous cyclohexane and 21.2 ml (0.15 mol) of anhydrous triethylamine were added. To the mixture, azidoacetyl chloride (16.8 g, 0.14 mol) dissolved in 750 ml of cyclohexane was added dropwise slowly at 0 °C over about 2 h. The mixture was further stirred at 0 °C for 1 h. Benzene was added, and the reaction solution was washed with saturated $NaHCO_3$ and saturated NaCl. The resulting solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to obtain 45.5 g of a crude product. The product was purified by high performance liquid chromatography (HPLC) (System 500 *n*-hexane : AcOEt = 1 : 2) to obtain 30.9 g (70.7%) of the acetal compound **8**. NMR($CDCl_3$) ppm: 5.83—6.07 (2H, m), 4.50—5.00 (3H, m), 4.23 (4H, m), 3.33 (6H, s), 1.50 (9H, s), 1.37 (6H,

m). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1780, 1745.

***tert*-Butyl (±)-2-[*cis*-4-(3-Oxo-1-propenyl)-3-azido-2-oxoazetidin-1-yl]-2-diethylphosphonoacetate (9)** The acetal compound **8** (520 mg) was dissolved in 10 ml of acetone and 50 mg of *p*-toluenesulfonic acid monohydrate was added thereto. The mixture was stirred at room temperature for 1 h and 45 min. AcOEt was added to the reaction solution and the mixture was washed with 5% $NaHCO_3$ solution and saturated NaCl, then dried over anhydrous Na_2SO_4. The resulting solution was concentrated under reduced pressure to obtain 470 mg (quant.) of the aldehyde compound **9**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1785, 1750, 1700. NMR ($CDCl_3$) ppm: 9.62 (1H, d, J=9 Hz), 7.00 (1H, dd, J=8, 15 Hz), 6.26 (1H, dd, J=7, 15 Hz), 4.84 (1H, d, J=24 Hz), 4.80—5.02 (2H, m), 4.16 (4H, m), 1.46 (9H, s), 1.26 (6H, m). MS *m/z*: 417 (M^++1).

***tert*-Butyl (±)-2-[*cis*-4-(1-Phenylthio-3-oxo-1-propyl)-3-azido-2-oxoacetidin-1-yl]-2-diethylphosphonoacetate (10)** A solution of the aldehyde **9** (9.1 g, 21.9 mmol) in 100 ml of dry benzene was reacted with 2.4 g of thiophenol and 0.1 ml of piperidine. The mixture was stirred at room temperature for 1.5 h, then concentrated under reduced pressure. The residue was chromatographed on silica gel (160 g, *n*-hexane : AcOEt = 1 : 2) to give the thiophenyl compound 8.85 g (70.6%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1780, 1735. MS *m/z*: 526 (M^+).

***tert*-Butyl (5*R**,6*S**,7*S**)-7-Azido-8-oxo-5-phenylthio-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylate (11a) and *tert*-Butyl (5*S**,6*S**,7*S**)-7-Azido-8-oxo-5-phenylthio-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (11b)** A solution of **10** (5.95 g, 11.3 mmol) in 170 ml of anhydrous dimethoxyethane was reacted with 500 mg (12.4 mmol) of 60% NaH under ice-cooling. The mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. Then 100 mg of 60% NaH was added, and the mixture was stirred for a further 1 h at room temperature. AcOEt was added to the reaction solution and the mixture was washed with saturated NH_4Cl and saturated NaCl, then dried over anhydrous Na_2SO_4. The resulting solution was concentrated under reduced pressure to obtain 4.5 g of an oily product which was a mixture of stereoisomers at the 1-position of the desired compound.

The oily product was chromatographed (SiO_2, 160 g; *n*-hexane : AcOEt = 4 : 1) to obtain two isomers.

The less polar isomer **11a**: Yield 2.5 g (59.4%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2130, 1790, 1725, 1640. NMR ($CDCl_3$) ppm: 7.24—7.56 (5H, m), 6.21 (1H, dd, J=3.0, 5.5 Hz), 5.06 (1H, d, J=5 Hz), 3.65 (1H, dd, J=5, 11 Hz), 3.19 (1H, ddd, J=5.5, 11, 11 Hz), 2.74 (1H, ddd, J=5.5, 5.5, 19 Hz), 2.29 (1H, ddd, J=3, 11, 19 Hz), 1.50 (s, 9H). MS *m/z*: 372 (M^+). This isomer was assigned as the 1α-phenylsulfide **11a** in which the configuration of SC_6H_5 is the same as those of 6H and 7H.

The more polar isomer **11b**: Yield 0.94 g (22.3%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1790, 1720, 1630. MS *m/z*: 372 (M^+). NMR ($CDCl_3$) ppm: 7.20—7.52 (5H, m), 6.12 (1H, dd, J=3.5, 4.5 Hz), 4.98 (1H, d, J=5 Hz), 3.99 (1H, dd, J=2.5, 5.0 Hz), 3.82 (1H, m), 2.58—2.70 (2H, m), 1.54 (9H, s). This isomer was assigned as the 1β-phenylsulfide **11b** in which the configuration of SC_6H_5 is opposite to those of 6H and 7H.

***tert*-Butyl (5*R**,6*S**,7*S**)-7-Azido-8-oxo-5-phenylsulfinyl-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylate (12a)** A solution of **11a** (1.14 g, 3.06 mmol) in 80 ml of MeOH and 8 ml of benzene was treated with 1.44 g (6.74 mmol) of $NaIO_4$ in 20 ml of water. The mixture was stirred at room temperature for 60 h. Water was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain 1.16 g (97.5%) of an oily product **12a**. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2130, 1790, 1725, 1640, 1050. NMR ($CDCl_3$) ppm: 7.55 (5H, m), 6.30 (1H, m), 5.27 (0.5H, d, J=5 Hz), 4.78 (0.5H, d, J=5 Hz), 4.07 (1H, dd, J=5, 10 Hz), 2.40—3.00 (2H, m), 1.70—2.13 (1H, m), 1.50 (9H, s).

***tert*-Butyl (5*S**,6*S**,7*S**)-7-Azido-8-oxo-5-phenylsulfinyl-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylate (12b)** A similar procedure was employed to afford 1.0 g of **12b** (93.1%) from **11b** (1.03 g, 2.7 mmol). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2120, 1790, 1720, 1630, 1030.

***tert*-Butyl (6*R**,7*S**)-7-Azido-8-oxo-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylate (13)** Method A: A solution of **12a** (960 mg, 2.47 mmol) in 50 ml of toluene was stirred at 105 to 110 °C for 3.5 h. The solvent was evaporated off *in vacuo* to obtain a crude product, which was subjected to chromatography (SiO_2 50 g, *n*-hexane : AcOEt = 8 : 1) to obtain 330 mg (50.9%) of the desired compound. NMR ($CDCl_3$) ppm: 6.64 (d, 1H, J=6 Hz), 6.24 (ddd, 1H, J=2.5, 6.0, 6.0 Hz), 6.04 (dd, 1H, J=2.0, 10.0 Hz), 5.26 (d, 1H, J=5.0 Hz), 4.64 (m, 1H), 1.50 (s, 9H). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2130, 1790, 1720, 1630.

Method B: A solution of **12b** (895 mg, 2.30 mmol) in 50 ml of CCl_4 was stirred at 70 °C for 1.5 h. The solvent was evaporated off *in vacuo* to obtain a crude product. The product was purified to obtain 449 mg (74.3%) of the desired compound. The properties of the compound coincided with those of the product obtained above.

Method C: A solution of the aldehyde **9** (832 mg, 2.0 mmol) in 4 ml of benzene was treated with 178 mg (2.0 mmol) of dimethylethanolamine. The mixture was stirred at room temperature for 5 h, diluted with 20 ml of AcOEt and washed with saturated NH_4Cl and saturated NaCl. The resulting solution was dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product. This was chromatographed (SiO_2 35 g, *n*-hexane : AcOEt = 3 : 1) to obtain 352 mg (67.2%) of the desired compound. The properties of the compound coincided with those of the product obtained above.

***tert*-Butyl (6*R**,7*S**)-7-Amino-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (14)** A solution of **13** (210 mg) in 17 ml of AcOEt containing 150 mg of 10% Pd–C was stirred at atmospheric pressure in a stream of H_2 gas for 2 h and 45 min. The catalyst was removed by filtration and washed with 40 ml of AcOEt. The filtrate and washings were combined and concentrated under reduced pressure to obtain 1115 mg of the desired compound.

(6*R,7*S**)-7-Azido-8-oxo-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylic acid (15)** A solution of **13** (290 mg, 1.1 mmol) in a mixture of 6 ml of CF_3CO_2H and 6 ml of CH_2Cl_2 was stirred under ice-cooling for 1 h and 40 min and further at room temperature for 30 min. The solvent was removed by distillation under reduced pressure. After addition of AcOEt, the residue was extracted 3 times with 5 ml of 10% K_2CO_3. About 15 ml of the aqueous extract was adjusted to pH 2.5 with 1 N HCl and extracted twice with 10 ml of AcOEt. This extract was dried with Na_2SO_4 and the solvent was evaporated off *in vacuo* to obtain 156 mg (68.4%) of the desired compound as crystals. NMR (CD_3OD) ppm: 6.77 (d, 1H, J=6.0 Hz), 6.33 (m, 1H), 6.13 (dd, 1H, J=2.0, 10.0 Hz), 5.48 (d, 1H, J=5.0 Hz). IR ν_{max}^{KBr} cm^{-1}: 2130, 1780, 1700, 1620. mp 125—126 °C. MS *m/z*: 206 (m^+).

(6*R,7*S**)-7-Ammonio-8-oxo-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylate (16a)** A solution of **15** (39 mg, 0.19 mmol) in 3 ml of EtOH containing 22 mg of 5% Pd–$CaCO_3$ was stirred in a stream of H_2 gas at atmospheric pressure for 5 h and 45 min. The catalyst was removed by filtration and washed with 3 ml of EtOH and 3 ml of water. The filtrate and washings were combined and concentrated under reduced pressure. After addition of 3 ml of AcOEt, the concentrate was extracted with 5 ml of water. The water layer was concentrated to dryness under reduced pressure to obtain 35.4 mg (100%) of the desired compound. IR ν_{max}^{KBr} cm^{-1}: 3430, 1785, 1645, 1615.

The *Rf* value on SiO_2 thin layer chromatography using a mixture of *n*-butanol, acetic acid and water (4 : 1 : 1) and Kieselgel 60 β5719 (product of E. Merck & Co.) was 0.09.

***tert*-Butyl (6*R**,7*S**)-7-Amino-8-oxo-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylate (17)** Triethylamine (0.4 ml) was added to a solution of **13** (250 mg) in 30 ml of CH_2Cl_2, and hydrogen sulfide was bubbled into the mixture for about 3 min. Stirring was carried out at room temperature for 2.5 h, then nitrogen was bubbled into the mixture for 30 min and the solvent was distilled off. The residue was taken up in AcOEt and the mixture was extracted with 10% aqueous citric acid. The extract was adjusted to pH about 7 with K_2CO_3 and extracted with AcOEt. The extract was dried and the solvent was distilled off to obtain 168 mg (74.6%) of the desired compound. IR ν_{max}^{KBr} cm^{-1}: 1770, 1710, 1630. NMR ($CDCl_3$) ppm: 6.60 (d, 1H, J=6 Hz), 6.30 (dd, 1H, J=10, 6, 2.5 Hz), 6.05 (dd, 1H, J=10, 2 Hz), 4.88 (d, 1H, J=5 Hz), 4.58 (m, 1H), 1.58 (s, 9H).

(6*R,7*S**)-2-Carboxy-8-oxo-1-azabicyclo[4.2.0]octa-2,4-diene-7-ammonium trifluoroacetate (16b)** Anisole (40 μl) was added to a solution of **17** (120 mg) in 0.5 ml of 30% CF_3CO_2H in CH_2Cl_2, the mixture was stirred at room temperature for 1.5 h, and the solvent was distilled off. Et_2O was added to the resulting residue and the desired compound 102 mg (68.4%) was obtained by filtration as a powder. IR ν_{max}^{KBr} cm^{-1}: 1800, 1785, 1675, 1620. NMR (D_2O) ppm: 6.62 (d, 1H, J=5.8 Hz), 6.42 (ddd, 1H, J=2.4, 5.8, 9.5 Hz), 6.12 (dd, 1H, J=1.2, 9.7 Hz), 5.22 (d, 1H, J=4.6 Hz), 4.91 (m, 1H).

(6*R,7*S**)-8-Oxo-7-[2-(2-thienyl)acetamido]-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylic Acid (18)** Sodium bicarbonate (76 mg) was added to a solution of **16a** (50 mg) in 2.4 ml of water and 2.4 ml of acetone, then 44 mg of thienylacetyl chloride dissolved in 0.2 ml of acetone was added under ice-cooling. An insoluble product was formed in 5 min, then 2 ml of acetone was added to make the mixture homogenous and the resulting mixture was stirred under ice-cooling for 2 h. The reaction mixture was adjusted to pH 2.0 with 3 ml of 1 N HCl and the solvent was evaporated off *in vacuo* to obtain 60 mg of a crude product. The product was triturated with 1 ml of ether and filtered to obtain 23 mg of the desired product. Yield

27.2%. IR ν_{max}^{KBr} cm^{-1}: 1790, 1780, 1695, 1655, 1630. NMR (CD_3OD) ppm: 7.2—7.3 (m, 1H), 6.93—6.97 (m, 2H), 6.72 (d, 1H, J=5.8 Hz), 6.21 (ddd, 1H, J=2.2, 5.8, 9.8 Hz), 5.89 (dd, 1H, J=1.5, 9.8 Hz), 5.72 (d, 1H, J=4.6 Hz), 4.67—4.73 (m, 1H), 3.80 (s, 2H).

(6*R,7*S**)-7-[2-(2-Amino-4-thiazolyl)-2-*syn*-methoxyiminoacetamido]-1-azabicyclo[4.2.0]octa-2,4-diene-2-carboxylic Acid (19)** Triethylamine (45 μl) was added to a solution of 2-(*N*-chloroacetyl-2-amino-4-thiazolyl)-2-*syn*-methoxyiminoacetic acid (75 mg) in 1.4 ml of CH_2Cl_2, then 56 mg of PCl_5 was added and the mixture was stirred at room temperature for 30 min. After addition of 5 ml of *n*-hexane, the mixture was stirred and the supernatant was removed by decantation. To the residue, 2.7 ml of tetrahydrofuran was added. The mixture was added to a solution of 60 mg of **16b** in 3 ml of 50% aqueous tetrahydrofuran and 120 μl of triethylamine under ice-cooling. The reaction mixture was stirred for about 2.5 h and acidified to a pH of 2 to 3 with 1 N HCl. The solution was extracted with AcOEt. The extract was washed with saturated NaCl, dried and concentrated under reduced pressure. The residue was triturated with ether and 35 mg (39.0%) of N-protected acylated compound was obtained by filtration as a powder. IR ν_{max}^{KBr} cm^{-1}: 1765, 1700—1710, 1690, 1660, 1550. NMR (CD_3OD) ppm: 7.50 (s, 1H), 6.8 (m, 1H), 6.1—6.4 (m, 2H), 5.9 (m, 1H), 4.3 (s, 2H), 4.0 (s, 3H).

The above product (15 mg) was dissolved in 0.3 ml of dimethylacetamide and 5.3 mg of thiourea was added. The mixture was stirred at room temperature for about 18 h. Ether was added to the mixture and the supernatant was removed by decantation. The residue was subjected to chromatography (HP-20 6 ml, H_2O:MeOH=4:1—1:1) to obtain 10.2 mg (77.2%) of the desired compound. IR ν_{max}^{KBr} cm^{-1}: 1770, 1650—1670, 1630, 1540. NMR (D_2O) ppm: 7.05 (s, 1H), 6.64 (d, 1H, J=5.4 Hz), 6.25 (m, 1H), 6.06 (d, 1H), 5.85 (d, 1H, J=4.6 Hz), 4.01 (s, 3H).

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