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ORIGINAL PAPER

Design and synthesis of new cephalosporin antibiotics

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Abstract Cephalosporins are important antibiotics. We synthesized new cephalosporin analogs containing novel side chains of methyl, propyl, benzyl, and phenoxy groups. Four synthetic methods with N-alkylation and N-acylation at position C-7 and esterification at position C-4 of 7-aminodesacetoxycephalosporanic acid are reported here.

Keywords Cephalosporin · Antibiotics · Alkylation · Esterification · Side chains

Introduction

Cephalosporins are β-lactam antibiotics for treatment of infectious diseases. Chemical manipulation of cephalosporin has led to development of important marketed antibiotics [1–3]. Considerable interest has focused on modification of the substituent at C-3 position and side chains at position C-4 and C-7 of the cephem nucleus to obtain a variety of cephalosporin analogs with enhanced antibacterial activity. Alteration at C-3 position of the cephem nucleus has been carried out with methyl [4], propenyl [5], and imidazo[1,2-*b*]pyridazinium-1-ylmethyl [6]. Modification at position C-7 of the cephem nucleus has been undertaken with thiophene-2-acetamido [7], 2-amino-2-phenoxyacetyl [8], and benzylacetyl groups [9]. Replacement at position C-4 of the cephem nucleus has been carried out by *tert*-butyl [9], ethyl [10], and acetoxymethyl ester groups [11].

In this work, we designed and synthesized novel cephalosporins with new side chains. N-Alkylation and N-acylation of 7-aminodesacetoxycephalosporin (7-ADCA) at position C-7 were performed with methyl, propyl, benzyl, and phenoxy groups as amino and amido side-chain moieties. Esterification of C-4 carboxylic acid was carried out with methyl, propyl, and benzyl groups. We developed four synthetic methods to achieve these formations. These methods are simple and convenient for parallel synthesis, which can be used for building compound libraries.

Results and discussion

Synthesis of cephalosporin secondary amino derivatives from 7-ADCA was carried out with propyl iodide in the presence of sodium bicarbonate (Scheme 1). The amino group at C-7 and the carboxyl group at C-4 of 7-ADCA become strong nucleophiles under basic conditions. C-4 carboxylate nucleophile conducted S_N2 reaction with propyl iodide to yield 7-ADCA ester. Simultaneously, C-7 primary amine nucleophile attacked propyl iodide through an S_N2 reaction to form the secondary amine **2**. This is an effective and convenient procedure for simultaneous N-alkylation at C-7 position and esterification on the C-4 carboxyl group of 7-ADCA with sodium bicarbonate as base.

Treatment of 7-ADCA and sodium bicarbonate with two equivalents of propyl iodide in dimethylformamide (DMF) formed a carboxylate propyl ester crude product. The residue was purified by silica gel column chromatography with EtOAc/*n*-hexane as eluent to yield carboxylate propyl ester **2**. Only monoalkyl product **2** was obtained in this reaction condition. Other polyalkyl products were not

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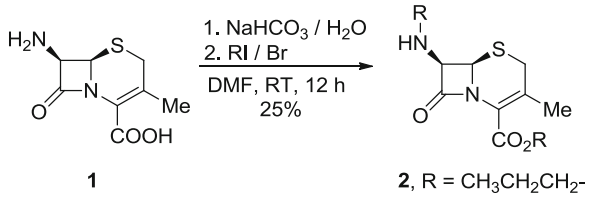
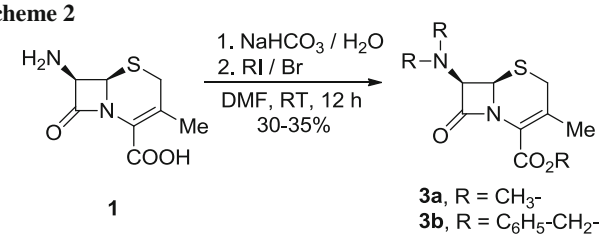
Scheme 1



Scheme 2



observed. Product **2** was identified by ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and high resolution mass spectrometry.

Synthesis of cephalosporin tertiary amino derivatives from 7-ADCA was carried out with methyl iodide and benzyl bromide in the presence of sodium bicarbonate (Scheme 2). The amino group at C-7 and carboxyl group at C-4 of 7-ADCA are more nucleophilic under basic conditions. C-4 carboxyl nucleophile attacked alkyl halides to form 7-ADCA esters. At the same time, two protons at C-7 primary amine were both replaced by alkyl groups to obtain tertiary amine products **3a** and **3b**. Treatment of 7-ADCA and sodium bicarbonate with 3 equivalents of methyl iodide or benzyl bromide in DMF yielded final products **3a** and **3b**. In ^{1}H NMR spectra, for product **3a**, the 6-proton singlet peak representing two methyl groups attached to the amino group was found at 2.48 ppm. The 3-proton singlet of methyl group attached to the carboxyl group appeared at 3.79 ppm. For compound **3b**, the ^{1}H NMR spectra showed that two benzyl groups connected to the amino group.

C-7 N-acylation and C-4 carboxyl esterification of 7-ADCA to form cephalosporin amide esters can be achieved in two steps (Scheme 3). The first step is carbamate formation. 7-ADCA was dissolved in water containing five equivalents of sodium bicarbonate. The reaction was completed by using microwave synthesizer irradiation at 70 °C for 2 h. The concentrated aqueous solution was then lyophilized overnight to obtain 7-ADCA carbamate **4**, which was characterized by ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry.

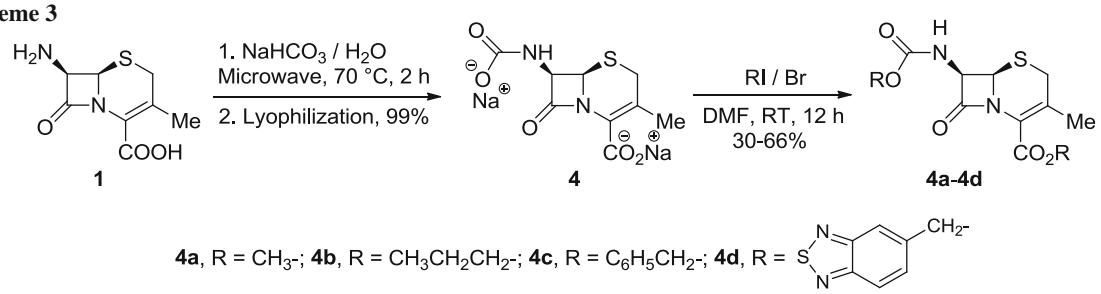
Synthesis of cephalosporin amide esters was achieved through S_N2 reactions in parallel between carbamate salt **4** with various aliphatic, aromatic, and heterocyclic bromides in DMF (Scheme 3). After treatment of **4** in DMF with methyl iodide at room temperature for 3 h, water was added to the reaction mixture and extracted with diethyl ether. The organic solvent was removed and the residue was purified by silica gel column chromatography with EtOAc/*n*-hexane as eluent to yield complete formation of methyl carbamate methyl ester **4a**, propyl carbamate propyl ester **4b**, benzyl carbamate benzyl ester **4c**, and benzothiazole methyl carbamate benzothiazole methyl ester **4d**. In ^{1}H NMR spectra, for product **4a**, the 3-proton singlet peak of methyl group attached to C-7 carbamate appears at 3.85 ppm. The 3-proton singlet peak of methyl group attached to C-4 carboxyl group centers at 3.75 ppm. Products **4b**, **4c**, and **4d** were identified by ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry.

Synthesis of cephalosporin with C-7 phenoxyacetyl amide and C-4 propyl ester proceeded in three steps (Scheme 4). The first step was N-acylation at C-7 to obtain phenoxyacetyl amido 7-ADCA carboxylic acid. The second step was to make potassium salt of carboxylic acid. The third step was to make carboxylate ester by S_N2 reaction between potassium salt and propyl iodide. To a cooled aqueous solution of 7-ADCA containing sodium bicarbonate, phenoxyacetyl chloride in acetone was added. The clear aqueous solution was acidified with cold sulfuric acid solution and extracted with methyl isobutyl ketone (MIBK). The extracted solution was mixed with potassium 2-ethylhexanoate in 1-butanol. The resulting precipitated white solid was collected by filtration to give product 7-ADCA phenoxyacetyl potassium salt **6** in 60 % yield. To **6** in DMF, propyl iodide was added and stirred at room temperature for 12 h. The solvent was removed and the residue was purified by column chromatography with EtOH/*n*-hexane to get product **7a** in 69 % yield. The carboxyl benzyl ester **7b** was obtained with the same procedures by using benzyl bromide in the last step S_N2 reaction.

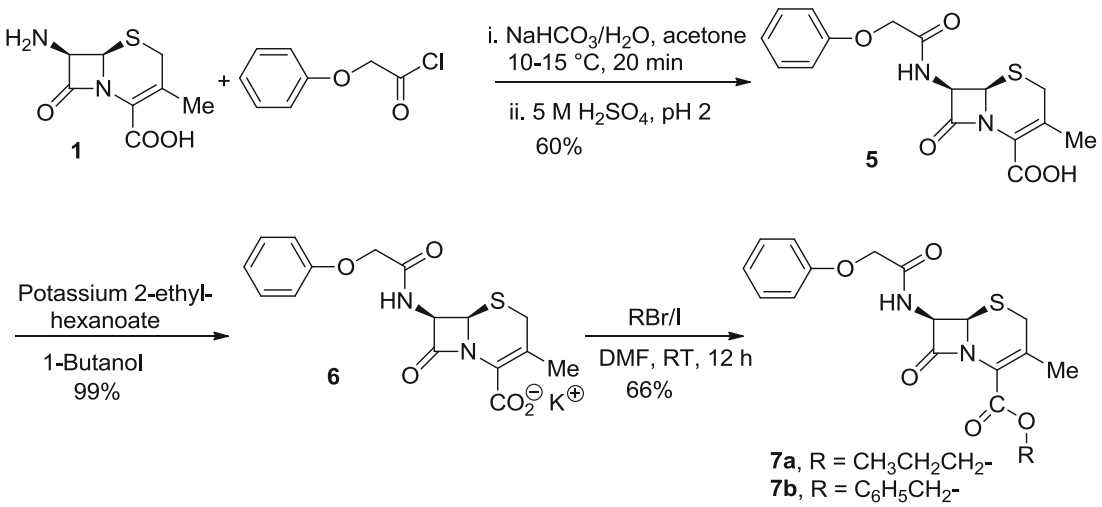
Phenoxyacetyl amide esters **7a** and **7b** were identified by ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrometry. In ^{1}H NMR spectra, for product **7a**, complex patterns of benzene ring protons were found at 7.20 ppm and 2-proton singlet peak of methylene was visible at 4.57 ppm. The 2-proton of methylene in propyl group attached to carboxyl group appears at 4.25 ppm as multiple peaks. These findings confirm the presence of phenoxyacetyl and propyl side chains. For product **7b**, ^{1}H NMR signals indicated the presence of phenoxyacetyl and benzyl side chains.

Over the past six decades, numerous modifications of side chains of cephalosporin have been undertaken and many cephalosporins synthesized [1, 2], leading to the marketing of several antibiotics [3, 5]. According to our SciFinder search, the side chains selected in this work are

Scheme 3



Scheme 4



novel and nine cephalosporin analogs reported herein are new. These compounds were deposited into the NIH Molecular Library Small Molecule Repository. They were screened, and their biological results were deposited into PubChem.

Conclusions

Novel amino and amide side chains at C-7 position of cephalosporin nucleus and ester side chains at C-4 position were designed. Nine new cephalosporin analogs were synthesized. Synthetic methods for N-alkylation and N-acylation and esterification of carboxyl moiety of cephalosporin nucleus were developed in this work.

Experimental

Column chromatography was carried out by employing silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed on a silica gel W/UV254 Uniplate™. Anhydrous organic solvents were purchased. Melting points were determined using a Barnstead International MET-TEMP® capillary melting point apparatus, model 1001D-120VAC. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400-MHz spectrometer (400 and 100 MHz, respectively), or a 500-MHz spectrometer (500 and 125.5 MHz, respectively). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass spectrometry (HRMS) spectra were obtained on a double-focusing mass spectrometer.

The biological activity of the compounds can be found in PubChem by using their compound identification numbers: 247935 (**2**), 25011655 (**3a**), 24816504 (**3b**), 24789294 (**4a**), 24789354 (**4b**), 25011056 (**4c**), 25011654 (**4d**), 25011659 (**7a**), and 25011657 (**7b**).

Propyl (6R,7R)-3-methyl-8-oxo-7-(propylamino)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
(**2**, $C_{14}H_{22}N_2O_3S$)
7-ADCA (**1**, 215 mg, 1.0 mmol) was dissolved in 10 cm^3 of water containing 250 mg of sodium bicarbonate (3.0 mmol, 3.0 equiv.). The yellow mixture solution was treated with 2 equivalents of propyl iodide in DMF and

stirred at room temperature for 12 h. Water was added to the reaction mixture and extracted with diethyl ether (3×50 cm^3). The organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (1:2 EtOAc/*n*-hexane) to obtain carboxylate propyl ester **2** as colorless semisolid (25 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.24$ (s, 1H), 4.92 (d, $J = 4.6$ Hz, 1H), 4.56 (d, $J = 4.6$ Hz, 1H), 4.24–4.12 (m, 2H), 3.51 (d, $J = 18.2$ Hz, 1H), 3.19 (d, $J = 18.2$ Hz, 1H), 2.78–2.67 (m, 2H), 2.10 (s, 3H), 1.74–1.69 (m, 2H), 1.55–1.51 (m, 2H), 0.98–0.92 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.66$, 123.04, 69.70, 67.16, 58.37, 51.04, 29.93, 23.57, 21.88, 19.99, 11.52, 10.45 ppm; HRMS (FAB): *m/z* calcd. for $C_{14}H_{23}N_2O_3S$ $[M+H]^+$ 299.1429, found 299.1436.

Methyl (6R,7R)-7-(dimethylamino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
(**3a**, $C_{11}H_{16}N_2O_3S$)
7-ADCA (**1**, 215 mg, 1.0 mmol) was dissolved in 10 cm^3 of water containing 420 mg of sodium bicarbonate (5.0 mmol, 5.0 equiv.). The yellow mixture solution was treated with three equivalents of methyl iodide in DMF and stirred at room temperature for 12 h. Water was added to the reaction mixture and extracted with diethyl ether (3×50 cm^3). The organic layer was washed with water and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (1:3 EtOAc/*n*-hexane) to yield the complete formation of carboxylate methyl ester **3a** as a colorless semisolid (30 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.84$ (d, $J = 4.4$ Hz, 1H), 4.03 (d, $J = 4.5$ Hz, 1H), 3.85 (s, 3H), 3.48 (d, $J = 18.4$ Hz, 1H), 3.21 (d, $J = 18.4$ Hz, 1H), 2.45 (s, 6H), 2.12 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.51$, 162.85, 130.68, 122.68, 75.42, 57.22, 52.31, 44.75, 30.81, 19.96 ppm; HRMS (FAB): *m/z* calcd. for $C_{11}H_{17}N_2O_3S$ $[M+H]^+$ 257.0960, found 257.0969.

Benzyl (6R,7R)-7-(dibenzylamino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
(**3b**, $C_{29}H_{28}N_2O_3S$)
7-ADCA (**1**, 215 mg, 1.0 mmol) was dissolved in 10 cm^3 of water containing 420 mg of sodium bicarbonate (5.0 mmol, 5.0 equiv.). The yellow mixture solution was treated with three equivalents of benzyl bromide in DMF and stirred at room temperature for 12 h. Water was added to the reaction mixture and extracted with diethyl ether (3×50 cm^3). The organic layer was washed with water and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (1:3 EtOAc/*n*-hexane) to yield the complete formation of carboxylate benzyl ester **3b** as a colorless semisolid (35 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$–7.44 (m, 15H), 5.34–5.23 (m, 2H), 4.77 (d, $J = 4.6$ Hz, 1H), 4.70 (d, $J = 4.6$ Hz, 1H), 3.93–4.04 (m, 4H), 3.46 (d, $J = 18.4$ Hz, 1H), 3.18 (d, $J = 18.4$ Hz, 1H), 2.09 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.30$, 162.36, 138.22, 135.27, 129.13, 129.05, 128.86, 128.64, 128.43, 128.40, 127.29, 71.82, 67.59, 58.66, 56.42, 30.64, 20.06 ppm; HRMS (FAB): *m/z* calcd. for $C_{29}H_{29}N_2O_3S$ $[M+H]^+$ 485.1899, found 485.1902.

Sodium (6R,7R)-7-(carboxylatoamino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
*(**4**, $C_9H_8N_2Na_2O_5S$)*
7-ADCA (215 mg, 1.0 mmol) was dissolved in 10 cm^3 of water containing 300 mg of sodium bicarbonate (3.5 mmol, 3.5 equiv.). The reaction was carried out in microwave at 70 °C for 2 h. The concentrated aqueous solution was then lyophilized overnight to obtain 300 mg (99 %) yellow powder **4**. M.p.: 218–220 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.28$ (d, $J = 4.6$ Hz, 1H), 4.94 (d, $J = 4.6$ Hz, 1H), 3.52 (d, $J = 17.9$ Hz, 1H), 3.12 (d, $J = 18.0$ Hz, 1H), 1.81 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.36$, 169.25, 166.98, 163.03, 160.59, 126.43, 121.69, 61.47, 58.20, 28.16, 18.43 ppm; HRMS (FAB): *m/z* calcd. for $C_9H_9N_2Na_2O_5S$ $[M+H]^+$ 303.0027, found 303.0031.

*General procedure for carbamate esters **4a–4d***

Methyl (6R,7R)-7-(methoxycarbonylamino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**4a**, $C_{11}H_{14}N_2O_5S$)
To a suspension of 90 mg **4** (0.3 mmol) in 5 cm^3 DMF was added 0.4 cm^3 methyl iodide (0.6 mmol). The reaction mixture was stirred at room temperature for 3 h. Water was added to the reaction mixture and extracted with diethyl ether (3×10 cm^3). The organic layer was washed with water and then dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (1:2 EtOAc/*n*-hexane) to yield the complete formation of the methyl carbamate methyl ester **4a** as colorless semisolid (50 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.63$ (m, 1H), 5.41 (d, $J = 5.6$ Hz, 1H), 4.99 (d, $J = 4.8$ Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.53 (d, $J = 18.0$ Hz, 1H), 3.24 (d, $J = 18.2$ Hz, 1H), 2.17 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.49$, 162.61, 156.11, 130.69, 122.44, 75.41, 57.21, 52.41, 44.73, 30.80, 30.13, 20.01 ppm; HRMS (FAB): *m/z* calcd. for $C_{11}H_{18}N_3O_5S$ $[M+NH_4]^+$ 304.0967, found 304.0990.

Propyl (6R,7R)-3-methyl-8-oxo-7-(propyloxy-carbonylamino)-5-thia-1-azabicyclo[4.2.0] oct-2-ene-2-carboxylate (**4b**, $C_{15}H_{22}N_2O_5S$)
Colorless semisolid (55 %); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 5.62$ (dd, $J = 4.7$, 9.6 Hz, 1H), 5.33 (d, $J = 9.6$ Hz, 1H), 4.97 (d, $J = 4.7$ Hz, 1H), 4.24–4.14 (m, 2H), 4.10–4.05 (m, 2H), 3.52 (d, $J = 18.2$ Hz, 1H), 3.23 (d, $J = 18.2$ Hz, 1H), 2.14 (s, 3H), 1.71–1.54 (m, 4H), 0.96–0.92 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 163.70$, 161.28, 154.75, 129.85, 121.70, 66.66, 66.55, 66.28, 59.88, 56.24, 51.95, 29.06, 21.15, 20.84, 19.04, 9.45, 9.24 ppm; HRMS (FAB): *m/z* calcd. for $C_{15}H_{23}N_2O_5S$ $[M+H]^+$ 343.1327, found 343.1338.

Benzyl (6R,7R)-7-(benzyloxycarbonylamino)-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**4c**, $C_{23}H_{22}N_2O_5S$)
Colorless semisolid (49 %); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$–7.35 (m, 10H), 5.62 (d, $J = 4.5$ Hz, 1H), 5.56 (d, $J = 9.6$ Hz, 1H), 5.28 (s, 2H), 5.16 (s, 2H), 4.96 (d, $J = 4.6$ Hz, 1H), 3.52 (d, $J = 18.5$ Hz, 1H), 3.22 (d, $J = 18.5$ Hz, 1H), 2.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.64$, 162.05, 155.47, 135.66, 135.12, 131.87, 128.80, 128.69, 128.63, 128.59, 128.48, 128.25, 122.46, 67.77, 67.64, 60.98, 57.24, 30.16, 20.13 ppm; HRMS (FAB): *m/z* calcd. for $C_{23}H_{23}N_2O_5S$ $[M+H]^+$ 439.1327, found 439.1336.

Benzo[c][1,2,5]thiadiazol-5-ylmethyl (6R,7R)-7-[(benzo[c]-[1,2,5]thiazol-5-ylmethoxy)carbonylamino]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**4d**, $C_{25}H_{21}N_4O_5S_3$)
Yellow semisolid (66 %); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04$ (d, $J = 6.8$ Hz, 2H), 8.00 (d, $J = 4.2$ Hz, 2H), 7.67 (dd, $J = 1.6$, 9.0 Hz, 1H), 7.59 (dd, $J = 1.6$, 9.0 Hz, 1H), 5.44 (d, $J = 2.6$ Hz, 2H), 4.93 (d, $J = 4.6$ Hz, 1H), 4.66 (d, $J = 4.6$ Hz, 1H), 4.18 (s, 2H), 3.56 (d, $J = 18.5$ Hz, 1H), 3.29 (d, $J = 18.5$ Hz, 1H), 2.21 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.53$, 160.71, 154.17, 153.46, 136.53, 135.59, 131.93, 128.85, 128.26, 121.02, 120.79, 119.74, 118.97, 106.60, 105.33, 66.64, 66.14, 65.78, 59.95, 56.16, 48.39, 29.21, 29.50, 22.88, 19.22 ppm; HRMS (FAB): *m/z* calcd. for $C_{23}H_{17}N_6O_5S_3$ $[M-H]^-$ 553.0579, found 553.0680.

Potassium (6R,7R)-3-methyl-8-oxo-7-(2-phen-oxyacetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
(**6**, $C_{16}H_{15}KN_2O_5S$)
To a cooled and stirred solution of 3.0 g 7-ADCA in 60 cm^3 water containing 6.0 g of sodium bicarbonate, phenoxyacetyl chloride in 5 cm^3 of acetone was added in 1 min. The resulting mixture was stirred vigorously during 20 min while the temperature was kept at 10–15 °C. The clear solution was extracted twice with 15 cm^3 portion of MIBK. The organic extracts were discarded. The clear aqueous solution was cooled to 10–15 °C and acidified to pH 2 with cold 5 M sulfuric acid solution. The acidified solution was extracted with MIBK twice. The extracted solution was mixed with 10 cm^3 solution of potassium 2-ethylhexanoate in 1-butanol. After stirring for 5 min, a white solid was precipitated and collected by filtration. Washing the white solid with dry acetone and drying in vacuo yielded 2.0 g product **6** (60 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$–7.25 (m, 2H), 7.00–6.87 (m, 2H), 5.54 (d, $J = 1.6$, 1H), 4.98 (d, $J = 1.6$ Hz, 1H), 4.45 (s, 2H), 3.46 (d, $J = 18.5$ Hz, 1H), 3.11 (d, $J = 18.5$ Hz, 1H), 1.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.88$, 163.98, 162.28, 157.08, 131.27, 129.83, 129.75, 122.36, 114.85, 67.43, 67.18, 58.39, 56.93, 30.32, 21. 09 ppm; HRMS (FAB): *m/z* calcd. for $C_{16}H_{16}KN_2O_5S$ $[M+H]^+$ 387.0418, found 387.0419.

Propyl (6R,7R)-3-methyl-8-oxo-7-(2-phenoxyacetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
(**7a**, $C_{19}H_{21}N_2O_5S$)
To 386 mg 7-ADCA phenoxy potassium salt (**6**, 1.0 mmol) in 10 cm^3 DMF, 0.5 cm^3 propyl iodide (3 mmol) was added and stirred at room temperature for 12 h. Solvent was removed and extracted with CH_2Cl_2 (3 × 50 cm^3). The organic layer was dried over sodium sulfate and concentrated. The residue was purified by column chromatography with EtOH/*n*-hexane (1:1) to get 222 mg (69 %) white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.31$ (m, 2H), 7.04 (t, 1H), 6.94 (m, 2H), 5.86 (dd, $J = 1.6$, 9.0 Hz, 1H), 5.02 (s, 1H), 4.57 (s, 2H), 4.24 (m, 2H), 3.51 (d, $J = 18.5$ Hz, 1H), 3.21 (d, $J = 18.5$ Hz, 1H), 2.15 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.84$, 163.93, 162.25, 157.01, 131.25, 129.81, 129.73, 122.33, 114.81, 67.33, 67.14, 58.36, 56.91, 30.14, 21.89, 20.02, 10.49 ppm; HRMS (FAB): *m/z* calcd. for $C_{19}H_{22}N_2O_5S$ $[M+H]^+$ 391.1338, found 391.1331.

Benzyl (6R,7R)-3-methyl-8-oxo-7-(2-phenoxyacetamido)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate
(**7b**, $C_{23}H_{21}N_2O_5S$)
To 386 mg 7-ADCA phenoxy potassium salt (**6**, 1.0 mmol) in 10 cm^3 DMF, 510 mg benzyl bromide (3 mmol) was added and stirred at room temperature for 12 h. Solvent was removed and the residue was dissolved in 150 cm^3 CH_2Cl_2. The organic layer was washed with water several times, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography with EtOH/*n*-hexane (1:1) to get 268 mg white solid. Yield: 66 %; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.33$ (m, 9H), 7.04 (t, 1H), 6.95 (m, 2H), 5.86 (dd, $J = 1.6$, 9.0 Hz, 1H), 5.29 (s, 2H), 5.00 (s, 1H), 4.57 (s, 2H), 3.52 (d, $J = 18.2$ Hz, 1H), 3.21 (d, $J = 18.5$ Hz, 1H), 2.15 (s,

3H), 1.75 (m, 2H), 0.98 (t, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 168.85$, 164.06, 162.01, 157.04, 129.83, 128.72, 128.62, 128.52, 122.35, 114.83, 67.66, 67.16, 58.41, 56.96, 30.22, 20.12 ppm; HRMS (FAB): *m*/*z* calcd. for $C_{23}H_{22}N_2O_5S$ $[M+H]^+$ 439.1338, found 439.1335.

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