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Total Synthesis of Sodium (3R, 4S)-3-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate from L-Aspartic Acid

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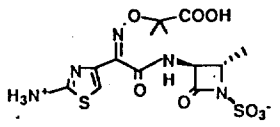
A new monocyclic β-lactam analogue, sodium (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**3**) was synthesized from L-aspartic acid. Starting from L-aspartic acid, (S)-1-benzyl-4-benzyloxycarbonyl-2-azetidinone (**7**) was synthesized in four steps by following the established procedures and converted into (3R, 4S)-3-amino-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**13**) in six steps. Acylation of the amino group of **13** with 2-amino-α-(methoxyimino)-4-thiazoleacetic acid, desilylation, and sulfonation with sulfur trioxide-pyridine complex followed by ion exchange afforded sodium (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**3**). Antibacterial activities of this β-lactam compound **3** were, however, found to be quite low compared to cefotaxime.

Introduction

Since the discovery of penicillins in 1929[1] and cephalosphorins in 1949[2], numerous classical β-lactam compounds have been introduced as antibiotics. After 1976, however, new types of β-lactam compounds, so-called nonclassical β-lactams, have been isolated from the natural sources. These are carbapenems,[3] clavulanic acids,[4] nocardicins,[5] and monobactams.[6] Of these, nocardicins contain characteristic oximino group and monobactams N-sulfonate functionality, which are very rare in nature.



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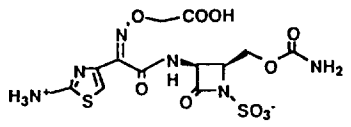

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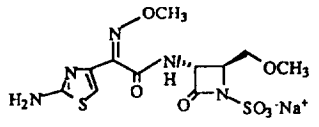


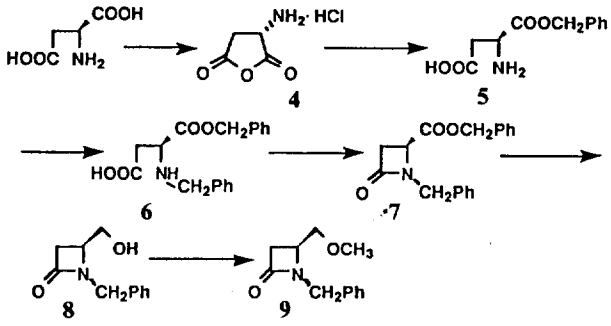
3

Recently, new monocyclic β-lactam antibiotics such as aztreonam (**1**)[7] and carumonam (**2**)[8] which have characteristic structural features of nocardicins and monobactams, have been introduced. These new antibiotics are known to have strong antibacterial activities against gram-negative and positive bacteria, and high stability to β-lactamase.

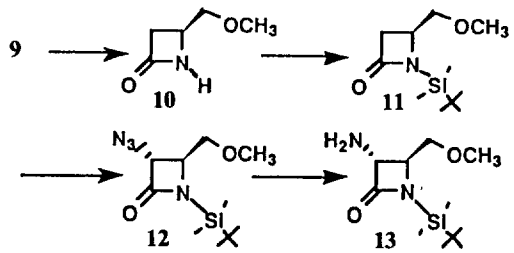
In connection with our ongoing research on the β-lactam chemistry, we now wish to report the total synthesis and antibacterial activities of sodium (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**3**), a monocyclic β-lactam analogue structurally related to aztreonam and carumonam.

Results and Discussion

The (3R, 4S)-configuration of the title compound **3** can be derived from naturally occurring L-aspartic acid. We have already reported[9] that the alcoholysis of L-aspartic anhydride hydrohalides produces α-esters regioselectively. Thus, treatment of L-aspartic acid with phosphorus trichloride afforded L-aspartic anhydride hydrochloride (**4**) and alcoholysis of this salt with benzyl alcohol produced α-benzyl L-aspartate (**5**) in high yield. N-Benzylation of the compound **5** with benzyl bromide and cyclization of the resulting α-benzyl N-benzyl-L-aspartate (**6**) with O-ethyl phosphorodichloridate[10] and triethylamine in acetonitrile (0.01 M) at room temperature afforded (S)-1-benzyl-4-benzyloxycarbonyl-2-azetidinone (**7**) in 95% yield. The formation of the β-lactam **7** was confirmed by the lactam carbonyl absorption band appeared at $\nu = 1750$ cm^{-1} in its IR spectrum. Reduction of the benzyloxycarbonyl group with excess sodium borohydride and methylation of the resulting hydroxymethyl group with methyl iodide in the presence of silver oxide produced (S)-1-benzyl-4-methoxymethyl-2-azetidinone (**9**) in 60% overall yield (see



Scheme 1



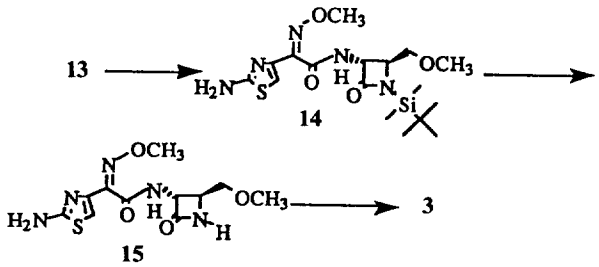
Scheme 2

Scheme 1).

To introduce the amino group at the 3 position, the compound **9** was treated with LDA followed by tosyl azide or bromine azide, but the 3-azido derivative could only be obtained in trace amounts, probably due to the acidic benzylic protons. Therefore, the N-benzyl group of the compound **9** was removed by lithium in liquid ammonia and reprotected with *t*-butyldimethylsilyl group to afford (S)-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**11**) in 73% overall yield. Treatment of the compound **11** with LDA and tosyl azide[11] at −78℃ then afforded (3R, 4S)-3-azido-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**12**) in 57% yield. The *trans* configuration between the C-3 and C-4 protons of the compound **12** was verified by the coupling constants of 2.92 Hz[12] obtained from its 2D-COSY NMR spectral data. The azido group of the compound **12** was then reduced to the amino group by the hydrogenation over 10% Pd/C (see Scheme 2).

Condensation of (3R, 4S)-3-amino-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**13**) and (Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid with the aid of 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS)[13] as a coupling reagent afforded (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**14**) in 72% yield. Removal of *t*-butyldimethylsilyl group of the compound **14** with tetra-*n*-butylammonium fluoride and treatment of the resulting (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone (**15**) with sulfur trioxide-pyridine complex[14] at −50℃ followed by ion exchange resin (Dowex-50 W, Na^+ form)[15] at room temperature afforded the desired product, sodium (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**3**) in 81% yield (see Scheme 3).

The *in vitro* antibacterial activities of the product **3** were



Scheme 3

determined against twenty strains by conventional agar dilution procedures. However, the minimum inhibitory concentration (MICs) of the compound **3** were so high compared to those of cefotaxime that this compound is found not to possess any significant antibacterial activities.

Experimental

General. Proton NMR spectra were recorded either on Varian EM 360A (60 MHz), Varian VXR-200S (200 MHz) or Bruker AC-300P (300 MHz) NMR spectrometer with tetramethylsilane as an internal standard. Chemical shifts are given in ppm units downfield from TMS. Infrared spectra were recorded on a Perkin Elmer 710B IR spectrophotometer and optical rotations were measured on a Jasco DIP-181 digital polarimeter. Melting points were measured on an Electrothermal melting point apparatus and are not corrected. Parr hydrogenation apparatus was used for the hydrogenation and silica gel 60 (70-230 mesh, Merck) was used for column chromatography.

L-Aspartic anhydride hydrochloride (4). To a stirred solution of L-aspartic acid (26.6 g, 200 mmol) in dry THF (200 m*l*), was added dropwise 17.8 m*l* (200 mmol) of PCl_3 and the mixture was stirred vigorously at rt for 3 hr. The solid material was collected by filtration, washed twice with petroleum ether and dried *in vacuo*; which gave 27.6 g of **4** (91% yield): mp. 136-138℃ (lit.[9c] mp. 139-140℃), IR (KBr) 3200-2400, 1810, 1750, 1730 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.47-3.31 (m, 2H), 3.90-4.37 (m, 1H), 8.17-8.83 (brd, 3H).

α-Benzyl L-aspartate (5). A solution of **4** (15.2 g, 100 mmol) in benzyl alcohol (200 m*l*) was stirred at rt for 12 hr. The reaction mixture was treated with 13.9 m*l* (100 mmol) of triethylamine followed by diethyl ether and filtered. Recrystallization from distilled water afforded 19.6 g of white crystalline **5** (88% yield): mp. 174-175℃ (lit.[16] mp. 174-175℃); $[\alpha]_D^{26}$-1.2° (c 0.83, 1 N NaOH); IR (KBr) 3350-2400, 1740 cm^{-1}; ^{1}H-NMR (TFA-d) δ 3.08 (d, J=5 Hz, 2H), 4.38 (t, J=5 Hz, 1H), 5.27 (s, 2H), 7.42 (s, 5H).

α-Benzyl N-benzyl-L-aspartate (6). A solution of **5** (12.0 g, 54 mmol), 16.6 m*l* (199 mmol) of triethylamine and 7.0 m*l* (59 mmol) of benzyl bromide in 75% aqueous methanol (200 m*l*) was stirred at rt for 15 hr. The solvent was evaporated *in vacuo* and the residue was acidified with 0.1 N HCl solution. The white precipitates were collected by filtration and recrystallized from 50% aqueous methanol; which afforded 11.0 g of white crystalline **6** (65% yield): mp. 127-129℃ (lit.[9b] mp. 127-130℃); $[\alpha]_D^{26}$-36.7° (c 0.30, CH_3CN); IR (KBr) 3100-2500, 1740 cm^{-1}; ^{1}H-NMR (TFA-d) δ 3.39 (d, J=5 Hz, 2H), 4.49 (t, J=5 Hz, 1H), 4.58 (s, 2H), 5.30, 5.50

(ABq, J=12 Hz, 2H), 7.46 (s, 5H), 7.49 (s, 5H).

(S)-1-Benzyl-4-benzyloxycarbonyl-2-azetidinone (7). To a solution of **6** (0.63 g, 2 mmol) in 400 m*l* of dry acetonitrile, was added 0.28 m*l* (4.4 mmol) of O-ethyl phosphorodichloridate and the mixture was stirred at rt for 1 hr. Triethylamine (0.61 m*l*, 4.4 mmol) was then added and the mixture stirred for additional 2 hr. After solvent removal, the residue was dissolved in CH_2Cl_2 (70 m*l*), washed once with 5% aqueous HCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue afforded 0.56 g of oily **7** (95% yield): $[\alpha]_D^{26}$-39.0° (c 1.88, $CHCl_3$); IR ($CHCl_3$) 1750, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.05-3.23 (m, 2H), 3.94 (t, J=4 Hz, 1H), 4.12, 4.73 (ABq, J=14 Hz, 2H), 5.12 (s, 2H), 7.27 (s, 5H), 7.37 (s, 5H).

(S)-1-Benzyl-4-hydroxymethyl-2-azetidinone (8). To a 0℃ solution of azetidinone **7** (1.0 g, 3.39 mmol) in THF (300 m*l*) was added sodium borohydride (1.28 g, 10 eq in 30 m*l* of distilled water) over a period of 20 min and stirred for 20 min. The reaction mixture was allowed to warm to rt and stirred for 6 hr. The solvent was removed *in vacuo* and the residue was extracted twice with chloroform. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue gave 0.52 g of white crystalline **8** (80% yield): mp. 83-85℃; $[\alpha]_D^{26}$+21.3° (c 0.34, CH_2Cl_2); IR ($CHCl_3$) 3375, 1745 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.83 (d, J=2 Hz, 2H), 3.48 (s, 1H), 3.43-3.84 (brd, 3H), 4.19, 4.62 (ABq, J=14Hz, 2H), 7.32 (s, 5H).

(S)-1-Benzyl-4-methoxymethyl-2-azetidinone (9). A solution of azetidinone **8** (0.67 g, 3.5 mmol), 0.81 g (3.5 mmol) of Ag_2O and 5 m*l* of CH_3I in dry DMF (10 m*l*) was stirred at rt for 45 hr. Distilled water was added and the mixture was extracted with chloroform three times. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue afforded 0.54 g of oily **9** (75% yield): $[\alpha]_D^{25}$+43.8° (c 1.68, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.63-2.83 (m, 2H), 3.17 (s, 3H), 3.33 (brd s, 2H), 3.35-3.72 (m, 1H), 4.13, 4.48 (ABq, J=14 Hz, 2H), 7.20 (s, 5H).

(S)-4-Methoxymethyl-2-azetidinone (10). To a −78 ℃ solution of 0.50 g of lithium in liquid ammonia was added a solution of azetidinone **9** (2.46 g, 12 mmol) in 30 m*l* of THF and 3 m*l* of *t*-butanol and the mixture stirred at −78℃ for 5 min. The extra lithium in the reaction mixture was quenched with 3.85 g (6 eq) of NH_4Cl and the solvent was evaporated. Column chromatography of the residue afforded 1.01 g of oily azetidinone **10** (73% yield): $[\alpha]_D^{25}$+46.6° (c 1.74, $CHCl_3$); IR ($CHCl_3$) 3360, 1750 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 2.65-3.00 (m, 2H), 3.37 (s, 3H), 3.52 (brd s, 2H), 3.45-4.00 (m, 1H), 6.93-7.50 (brd, 1H).

(S)-1-*t*-Butyldimethylsilyl-4-methoxymethyl-2-azetidinone (11). To a 0℃ solution of azetidinone **10** (1.05 g, 9.13 mmol) in CH_2Cl_2 (20 m*l*) was added diisopropylethylamine (1.60 m*l*, 9.13 mmol) followed by *t*-butyldimethylsilyl chloride (1.38 g, 1.0 eq in 5 m*l* of CH_2Cl_2). The reaction mixture was stirred at 0℃ for 20 min, at rt for 4 hr and then concentrated *in vacuo*. Column chromatography of the residue gave 2.07 g (quantitative) of azetidinone **11**:$[\delta]_D^{25}$+ 46.6° (c 1.63, $CHCl_3$); IR ($CHCl_3$) 1755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.18 (s, 6H), 0.87 (s, 9H), 2.69 (dd, J=4 Hz, 1 Hz, 1H), 3.07 (dd, J=4 Hz, 1 Hz, 1H), 3.36 (s, 3H), 3.40 (d, J=1 Hz, 2H), 3.60-3.67 (m, 1H).

(3R, 4S)-3-Azido-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (12). A solution of of diisopropylamine (1.2 m*l*) and 5.0 m*l* of *n*-butyllithium (1.6 M solution in dry THF) was stirred at −78℃ for 30 min and then azetidinone **11** (1.53 g, 6.68 mmol in 10 m*l* of dry THF) was added in portions. The reaction mixture was stirred at the same temperature for 2 hr and allowed to warm to −50℃. Tosyl azide (1.32 g, 1.0 eq) was added and the mixture was stirred at −50℃ for 1 hr. Chlorotrimethylsilane (1.7 m*l*, 2 eq) was added and the mixture was heated to 50℃, stirred for 5 hr and then cooled to rt. The resulting suspension was filtered and the filtrate was concentrated *in vacuo*. The residue was dissolved in dichloromethane and washed with distilled water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography of the residue afforded 1.03 g of oily azetidinone **12** (57% yield): $[\alpha]_D^{27}$+19.5° (c 0.17, $CHCl_3$); IR ($CHCl_3$) 2160, 1750 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.19 (s, 3H), 0.88 (s, 9H), 3.30 (s, 3H), 3.44 (d, J=1Hz, 2H), 3.47-3.53 (m, 1H), 4.37 (d, J=2.92Hz, 1H).

(3R, 4S)-3-Amino-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (13). A solution of azetidinone **12** (0.80 g, 2.96 mmol) in dry ethyl acetate was hydrogenated under hydrogen pressure of 30 psi in the presence of 10% Pd/C. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The oily azetidinone **13** was used for the next reaction without further purification: $[\alpha]_D^{27}$+2.9° (c 0.65, $CHCl_3$); IR ($CHCl_3$) 3400, 1745 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.22 (s, 6H), 0.92 (s, 9H), 2.05 (s, 2H), 3.33 (s, 3H), 3.52 (d, J=2Hz, 2H), 3.73-4.00 (m, 1H), 4.57-4.77 (brd, 1H).

(3R, 4S)-3-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (14). To a 0℃ solution of 2-amino-α-(methoxyimino)-4-thiazoleacetic acid (0.37 g, 1.1 eq) in dry DMFW as added 0.26 m*l* (1.1 eq) of triethylamine followed by 0.52 g (1.1 eq) of 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole (FMS) and the mixture was stirred at 0℃ for 30 min. A solution of azetidinone **13** (0.41 g, 1.68 mmol) in 5 m*l* of dry DMF was added and the mixture was allowed to warm to rt and stirred for 1.5 hr. The solution was concentrated *in vacuo* and the residue was dissolved in ethyl acetate, washed with 5% aqueous $NaHCO_3$ and brine. Solvent removal and crystallization from diethyl ether/*n*-hexane afforded 0.52 g of **14** (72% yield): mp. 55-58℃; $[\alpha]_D^{25}$+2.6° (c 1.31, CH_3OH); IR (CH_2Cl_2) 3445, 3325, 1770, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$ and DMSO-d_6) δ 0.23 (s, 6H), 0.90 (s, 9H), 3.35 (s, 3H), 3.63 (brd s, 2H), 3.93 (s, 3H), 4.00-4.37 (m, 1H), 4.75-5.10 (brd, 1H), 6.83 (s, 1H), 8.33-8.67 (brd, 1H).

(3R, 4S)-3-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone (15). To a −78℃ solution of azetidinone **14** (0.37 g, 0.87 mmol) in dry THF was added slowly 1.4 m*l* (1.6 eq) of 1 M solution of tetra-*n*-butylammonium fluoride in THF and the mixture was stirred at −78℃ for 1.5 hr. The reaction mixture was diluted with ethyl acetate and washed with distilled water. Usual work-up and crystallization from dichloromethane/petroleum ether afforded 0.23 g of **15** (83% yield); mp. 149-152℃; $[\alpha]_D^{25}$+57.1° (c 0.08, CH_3OH); IR (KBr) 3420, 3310, 1765, 1695 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.25 (s, 3H), 3.60 (brd s, 2H), 3.83 (s, 3H), 3.92-4.22 (m, 1H), 4.45-4.80 (brd, 1H), 6.82 (s, 1H), 9.13-9.47 (brd, 1H).

Sodium (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (3). To a −50℃ solution of azetidinone **15** (0.19 g, 0.61 mmol) in dry DMF was added 0.15 g (1.5 eq) of sulfur trioxide-pyridine complex and the reaction mixture was allowed to warm to 0℃ and stirred for 1 hr. Dowex-50W (Na^+ form, 2.85 g) was added and the mixture was stirred at rt for 2 hr. After filtration, the filtrate was concentrated *in vacuo* and the residue was dissolved in water and washed with dichloromethane three times. Concentration of the aqueous layer resulted in the crystallization of 0.21 g of **3** (81% yield); IR (KBr) 3430, 3310, 1760, 1680 cm^{-1}; ^1H-NMR (DMSO-d_6 and TFA-d) δ 3.22 (s, 3H), 3.47 (d, J=2Hz, 2H), 3.80 (s, 3H), 3.85-3.95 (m, 1H), 4.49 (dd, J=3Hz, 2Hz, 1H), 6.80 (s, 1H), 8.80-9.05 (brd, 1H).

Determination of Antibacterial Activities. Minimum inhibitory concentrations (MICs) of the compound **3** were determined by the standard two-fold agar dilution method (Hoechst 345). Mueller Hinton Agar was used as medium against twenty standard strains. Final inoculum size was 10^7 colony-forming units and the lowest concentration inhibiting the visible growth after 18 hr incubation at 37℃ was expressed as the MIC values. The determined MIC values of the compound **3**, however, were very high compared to those of cefotaxime.

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