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

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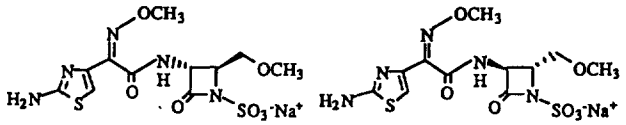
Sodium (3S, 4R)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**2**) was synthesized in fourteen steps from D-aspartic acid. Starting from D-aspartic acid, (3S, 4R)-3-amino-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**12**) was synthesized in ten steps. Acylation of the amino group of **12** with 2-amino-α-(methoxyimino)-4-thiazoleacetic acid, desilylation, sulfonation, and ion exchange afforded sodium (3S, 4R)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**2**). This new β-lactam compound **2** showed low antibacterial activities.

Introduction

In the preceding paper[1], we have described the total synthesis of sodium (3R, 4S)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**1**), which is structurally related to aztreonam[2] and carumonam[3]. In this paper, we wish to report the total synthesis of its antipodal compound, sodium (3S, 4R)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**2**), from D-aspartic acid.



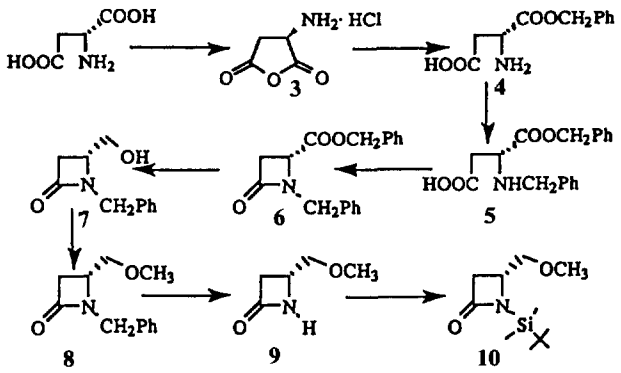
1 **2**

Results and Discussion

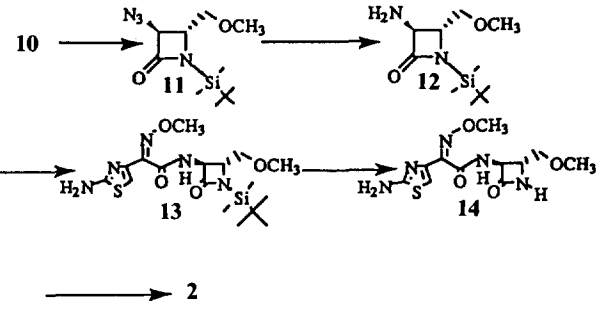
For the manipulation of the (3S, 4R)-configuration in the title compound **2**, D-aspartic acid was chosen as the starting material. Dehydration of D-aspartic acid with PCl_3 afforded D-aspartic anhydride hydrochloride (**3**), which was transformed regioselectively into α-benzyl D-aspartate (**4**) with benzyl alcohol. N-Benzylation of the compound **4** with benzyl bromide produced α-benzyl N-benzyl-D-aspartate (**5**) in 70% yield. Cyclization of this β-amino acid **5** with O-ethyl phosphorodichloridate[4] in CH_3CN (0.01 M) at room temperature afforded (R)-1-benzyl-4-benzyloxycarbonyl-2-azetidinone (**6**) in 90% yield.

Reduction of the benzyloxycarbonyl group of the compound **6** with sodium borohydride and methylation of the resulting hydroxymethyl group with CH_3I in the presence of Ag_2O afforded (R)-1-benzyl-4-methoxymethyl-2-azetidinone (**8**) in 60% overall yield. Due to the reasons discussed in the preceding paper[1], the benzyl group of the compound **8** was removed with lithium in liquid ammonia and reprotected with *t*-butyldimethylsilyl group to give (R)-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**10**) (see Secheme 1).

Introduction of the azido group at the 3-position of the compound **10** with LDA and tosyl azide afforded (3S, 4R)-3-azido-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**11**) in 60% yield. The *trans* configuration between the C-3 and C-4 protons of the compound **11** was confirmed by the coupling constants of 3.0 Hz determined from its 2D-COSY NMR spectral data. The azido group of compound **11** was reduced by hydrogenation over 10% Pd/C and acylated with (Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetic acid in the presence of 1-methanesulfonyloxy-6-trifluoromethylbenzotriazole to produce (3S, 4R)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (**13**) in 60% yield. Desilylation of **13** with tetra-n-butylammonium fluoride, N-sulfonation with sulfur trioxide-pyridine complex and ion exchange with Dowex-50W (Na^+ form) afforded the title compound, sodium (3S, 4R)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (**2**), in 66% yield (see Scheme 2).



Schem 1



Scheme 2

The *in vitro* antibacterial activities of the title compound **2** were also tested against 20 representative strains, but its MIC values were quite high compared to those of cefotaxime.

Experimental

General comments and synthetic procedures of the L-series of the following compounds are described precisely in the preceding paper.[1]

D-Aspartic anhydride hydrochloride (3) was prepared from D-aspartic acid as white solid (85% yield): mp. 142-144℃; IR (KBr) 1820, 1790 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 2.33-3.10 (m, 2H), 3.80-4.37 (m, 1H), 7.90-9.00 (brd, 2H).

α-Benzyl D-aspartate (4) was prepared as white solid from compound **3** and benzyl alcohol (75% yield): mp. 174℃ (lit.[5] 175-176℃); $[\alpha]_D^{26}+0.30°$ (c 0.85, 1 N NaOH); IR (KBr) 3400-2400, 1740 cm^{-1}; ^{1}H-NMR (TFA-d) δ 3.37 (d, J=4.5 Hz, 2H), 4.60 (t J=4 Hz, 1H), 5.20, 5.40 (ABq, J=12 Hz, 2H), 7.30 (s, 5H).

α-Benzyl N-benzyl-D-aspartate (5) was prepared from compound **4**, benzyl bromide and triethylamine as colourless solid (70% yield): mp. 127-129℃; $[\alpha]_D^{26}+30.8°$ (c 0.27, CH_3CN); IR (KBr) 1720 cm^{-1}; ^{1}H-NMR (TFA-d) δ 3.36 (d, J=5 Hz, 2H), 4.34 (t, J=5 Hz, 1H), 4.40 (s, 2H), 5.47, 5.63 (ABq, J=12 Hz, 2H), 7.23 (s, 5H), 7.26 (s, 5H).

(R)-1-Benzyl-4-benzyloxycarbonyl-2-azetidinone (6) was prepared as colorless oil by cyclizing compound **5** with O-ethyl phosphorodichloridate in acetonitrile (90% yield): $[\alpha]_D^{26}+33.7°$ (c 0.71, $CHCl_3$); IR ($CHCl_3$) 1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.90-3.07 (m, 2H), 3.78 (t, J=4 Hz, 1H), 3.90, 4.75 (ABq, J=14 Hz, 2H), 5.03 (s, 2H), 7.16 (s, 5H), 7.26 (s, 5H).

(R)-1-Benzyl-4-hydroxymethyl-2-azetidinone (7) was obtained as white solid from azetidinone **6** (80% yield): mp. 83-85℃; $[\alpha]_D^{26}-33.5°$ (c 2.15, CH_2Cl_2); IR ($CHCl_3$) 3350, 1740 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.70 (d, J=2 Hz, 2H), 3.43-3.82 (brd, 3H), 3.72 (s, 1H), 4.09, 4.58 (ABq, J=14 Hz, 2H), 7.25 (s, 5H).

(R)-1-Benzyl-4-methoxymethyl-2-azetidinone (8) was prepared as yellowish oil by methylation of compound **7** with methyl iodide in the presence of silver oxide (75% yield): $[\alpha]_D^{25}-24.0°$ (c 1.41, $CHCl_3$); IR ($CHCl_3$) 1750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.60-2.80 (m, 2H), 3.03 (s, 3H), 3.20 (brd s, 2H), 3.30-3.67 (m, 1H), 4.33, 4.73 (ABq, J=14 Hz, 2H), 7.03 (s, 5H).

(R)-4-Methoxymethyl-2-azetidinone (9) was prepared as colourless oil by debenzylation of the compound **8** with lithium in liquid ammonia (75% yield): $[\alpha]_D^{25}-7.4°$ (c 0.26, $CHCl_3$); IR ($CHCl_3$) 3370, 1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.66-3.01 (m, 2H), 3.35 (s, 3H), 3.52 (brd s, 2H), 3.41-4.02 (m, 1H), 7.15-7.53 (brd, 1H).

(R)-1-*t*-Butyldimethylsilyl-4-methoxymethyl-2-azetidinone (10) was prepared as colourless oil from compound **9** (quantitative yield): $[\alpha]_D^{25}-16.0°$ (c 1.14, $CHCl_3$); IR ($CHCl_3$) 1775 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.30 (s, 6H), 1.00 (s, 9H), 2.88, 3.06 (dd, J=3 Hz, 5 Hz, 2H), 3.40 (s, 3H), 3.53 (brd s, 2H), 3.40-3.90 (m, 1H).

(3S, 4R)-3-Azido-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (11) was prepared as an oil from compound **10**, LDA and tosyl azide (60% yield): $[\alpha]_D^{27}-60.6°$ (c 0.35, $CHCl_3$); IR ($CHCl_3$) 2250, 1788 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 0.22 (s, 3H), 0.23 (s, 3H), 0.97 (s, 9H), 3.38 (s, 3H), 3.43-3.58 (m, 2H), 3.63-3.80 (m, 1H), 4.43 (d, J=3 Hz, 1H).

(3S, 4R)-3-Amino-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (12) was obtained as an oil from compound **11** by hydrogenation over 10% Pd/C: $[\alpha]_D^{27}-37.9°$ (c 0.29, $CHCl_3$); IR ($CHCl_3$) 3380, 1755 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.23 (s, 6H), 0.93 (s, 9H), 2.10 (s, 2H), 3.34 (s, 3H), 3.49 (brd s, 2H), 3.80-4.05 (m, 1H), 4.55-4.80 (brd, 1H).

(3S, 4R)-3-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-1-*t*-butyldimethylsilyl-4-methoxymethyl-2-azetidinone (13) was prepared as yellowish solid from azetidinone **12** and 2-amino-α-(methoxyimino)-4-thiazoleacetic acid in the presence of FMS (71% yield): mp. 45-47℃; $[\alpha]_D^{25}-16.7°$ (c 4.87, CH_3OH); IR (CH_2Cl_2) 3455, 3325, 1755, 1680 cm^{-1}; ^{1}H-NMR ($CDCl_3$ and DMSO-d_6) δ 0.23 (s, 6H), 1.02 (s, 9H), 3.35 (s, 3H), 3.67 (brd s, 2H), 3.90 (s, 3H), 3.91-4.33 (brd, 1H), 4.80-5.10 (brd, 1H), 6.83 (s, 1H), 8.70-8.90 (brd, 1H).

(3S, 4R)-3-[2-(2-Aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone (14) was prepared as white solid from compound **13** by desilylation with tetrabutylammonium fluoride (83% yield): mp. 125-127℃; $[\alpha]_D^{25}-37.6°$ (c 0.03, CH_3OH); IR (KBr) 3430, 3300, 1782, 1698 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 3.45 (s, 3H), 3.51 (brd s, 2H), 3.55-3.85 (brd, 1H), 3.92 (s, 3H), 4.55-4.85 (brd, 1H), 6.93 (s, 1H), 9.10-9.31 (brd, 1H).

Sodium (3S, 4R)-3-[2-(2-aminothiazol-4-yl)-(Z)-2-methoxyiminoacetamido]-4-methoxymethyl-2-azetidinone-1-sulfonate (2) was prepared as solid from compound **14** by N-sulfornation with sulfur trioxide-pyridine complex followed by ion exchange with Dowex-50W (Na^+ form) (80% yield): IR (KBr) 3440, 3320, 1775, 1705 cm^{-1}; ^{1}H-NMR (DMSO -d_6 and TFA-d) δ 3.58 (s, 3H), 3.73 (brd s, 2H), 3.88 (s, 3H), 3.95-4.15 (brd, 1H), 4.55 (dd, J=3 Hz, 2 Hz, 1H), 6.93 (s, 1H), 9.15-9.40 (brd, 1H).

Antibacterial Activities of the compounds **2** were also tested as described in the preceding paper[1] but the MIC values were very high.

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