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A FACILE SYNTHETIC APPROACH TO THE FRAGMENT D OF ANTIBIOTIC NOSIHEPTIDE, 2-[1-AMINO-3-CARBOXY-3-HYDROXY-(1S,3S)-PROPYL]-THIAZOLE-4-CARBOXYLIC ACID

Masaharu IWAKAWA, Yasunobu KOBAYASHI, Shun-ichi IKUTA, and Juji YOSHIMURA*
Laboratory of Chemistry for Natural Products, Faculty of Science,
Tokyo Institute of Technology, Nagatsuta, Midoriku, Yokohama 227

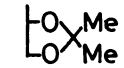
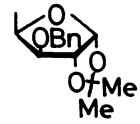
The lactam corresponding to fragment D of a polypeptide antibiotic nosiheptide was prepared *via* oxidation of the corresponding thiazolidine-4-carboxylate obtained by the condensation of 2-azido-2,3-dideoxy-D-*threo*-pentoalduronate with L-cysteine methyl ester.

Among the acid hydrolysates of a polypeptide antibiotic nosiheptide was found fragment D (1), a new thiazole-4-carboxylic acid having a γ-amino acid moiety.[1] Although the absolute configuration of 1 was determined to be 2-[1-amino-3-carboxy-3-hydroxy-(1S,3S)-propyl]-thiazole-4-carboxylic acid by the X-ray crystallographical study on the whole molecule of nosiheptide,[2] optical rotation and ^{13}C-NMR data[1] indicated that the isolated product is a mixture of diastereomers due to the epimerization during hydrolysis. In this paper we would like to report a simple approach toward the total synthesis of optically pure 1.

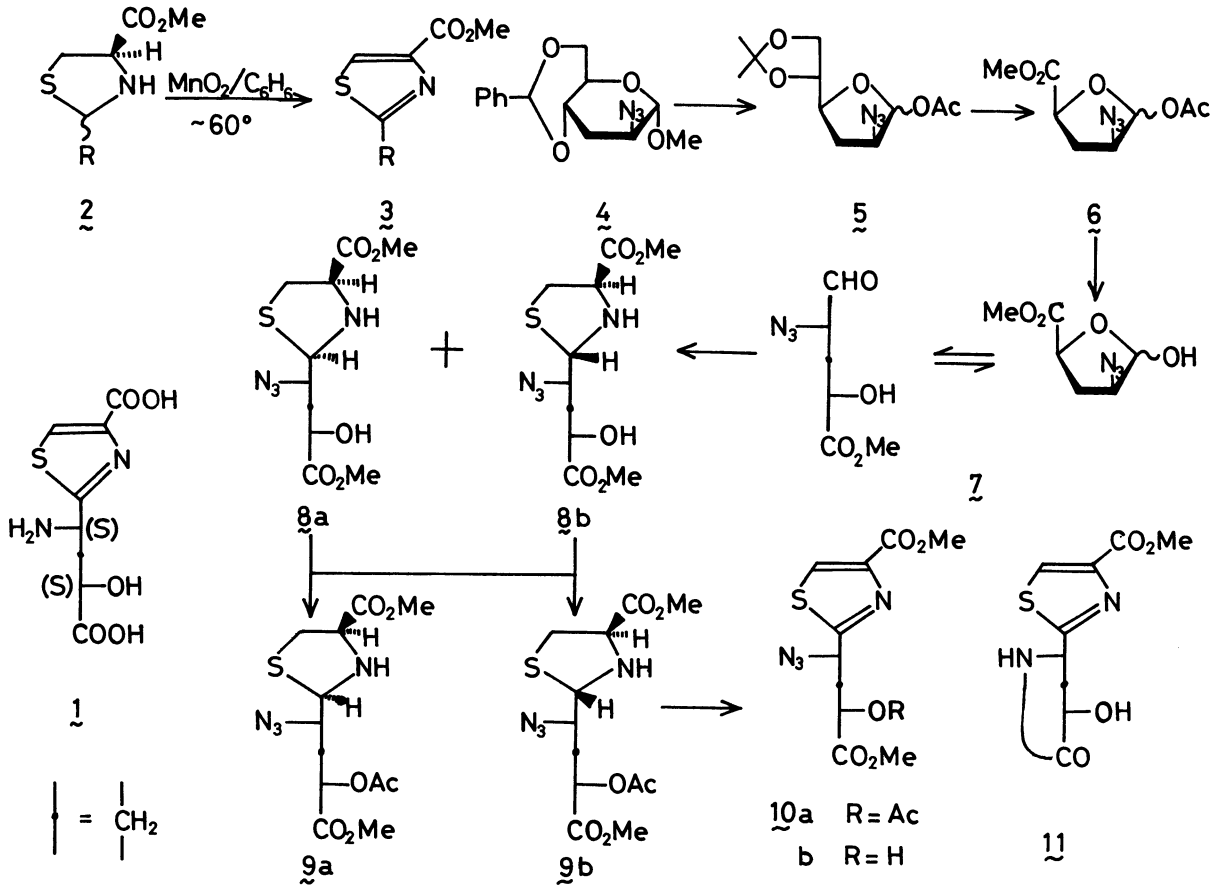
Hantzsch's method, condensation of thioamides with α-halogenocarbonyl compounds, has been well known as a general method for a preparation of 2-substituted-thiazole-4-carboxylic acids,[3] but is not suitable for our approach, since the preparation of optically active thioamide is supposed to be complicate. In biosynthetic pathways *N*-acylcysteine moiety in a polypeptide chain is cyclized to 2-substituted-Δ^2-thiazoline-4-carboxylate and successively dehydrogenated to afford 2-substituted-thiazole-4-carboxylate (3).[4] The latter conversion was effected by active manganese dioxide.[5] This sequence was actually followed for the synthesis of the peptide moiety of bleomycin.[6] Besides, aldoses are known to give 2-substituted-thiazolidine-4-carboxylic acids when they are treated with L-cysteine.[7] Thus the corresponding methyl thiazolidine-4-carboxylate (2)[8] obtained from L-cysteine methyl ester and an aldose having desired configuration and substituents would be ideal precursors for such thiazole derivative as 1, if a simple method for the conversion of thiazolidine into thiazole is available. The above mentioned active manganese dioxide has been also known as an oxidizing agent to convert disubstituted amines into Schiff's bases.[9] Therefore, it is reasonable to assume that this reagent would convert thiazolidines into thiazolines and then into thiazoles, though this type of transformation is unprecedented. When 2a-d were treated with active manganese dioxide prepared by Goldman's proceduce[10] in benzene at 60°C, the corresponding 3a-d were obtained in moderated yields as shown in Table 1. Thus the critical step for our approach toward the synthesis of 1 was established.

The precursor for the γ-amino acid moiety, methyl 2-azido-2,3-dideoxy-D-*threo*-pentofuranuronate (7), was prepared from D-glucose as follows. Methyl 2-azido-4,6-O-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside (4)[11] was converted into

Table 1 Conversion of 2 into 3.

Compound 2 R		Yield[a] (%)	Mp (°C)	$[\alpha]_D$[b]	Reaction Time	Yield[a] of 3 (%)	Mp (°C) (Bp)	$[\alpha]_D$[b]
a H		82	—	-122°	6h	60	73-75[c]	—
b Et		94	—	-114°	3h	30	(150-170/ 22 Torr)	—
c 		80	—	-112°	6h	60	78.5-79	+55.6°
d 	(2R)	45	121-123	-55°	6h	55	98-100	-122°
	(2S)	38	102-104	-175°	6h	20		

a) Yields are based on consumed starting materials. b) In dichloromethane at 15±5°C. c) Mp 72-75°C (ref. 4).



the corresponding furanose derivative (5: 91% yield) by the successive treatment with 75% acetic acid, acetic anhydride containing a catalytic amount of conc. sulfuric

acid, sodium methoxide in dry methanol, acetone-cupper(II) sulfate with a trace of *p*-toluenesulfonic acid, and acetic anhydride in pyridine. Selective hydrolysis of 5 with 75% acetic acid at room temperature followed by a modified Lemieux's oxidation[12] and esterification with diazomethane afforded methyl 1-O-acetyl-2-azido-2,3-dideoxy-D-*threo*-pentofuranos-5-uronate (6: 67%).

Deacetylation of 6 with sodium methoxide in methanol and condensation of the product (7) with L-cysteine methyl ester afforded a mixture of the thiazolidine-4-carboxylates (8). Chromatographic separation of the mixture on a silica gel column afforded (2R)-epimer (8a: 47%) and crystalline (2S)-epimer (8b: 25%). The chirality at C-2 of thiazolidine ring was tentatively assigned on a basis of ^{1}H-NMR data.[13] Selective acetylation[7] of 8a in a mixture of acetic anhydride, acetic acid, and 60% perchloric acid afforded a mixture of O-acetyl derivatives (9a: 40% and 9b: 49%), among which 9b was identical with that obtained by the treatment of 8b with acetic anhydride and pyridine. Treatment of 9a and 9b with activated manganese dioxide in benzene for 2 h at 60°C afforded thiazole derivative (10a) in 54% and 34% yield, respectively. The presence of a thiazole ring was supported by IR (3120 cm^{-1}) and ^{1}H-NMR spectrum (δ 8.20, H-5)[3]. This syrupy 10a was transformed into crystalline 10b (88%) on O-deacetylation. Reduction of azido group of 10b was performed with carefully washed Raney nickel in methanol and crystalline lactam (11: 72%) was successfully obtained as crystals from ethanol-hexane mixture. Thus a chiral synthesis of a fragment D derivative could be achieved from D-glucose. Physical data of new compounds were presented in the last.[14]

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14) (2R)-2d: NMR (δ): 1.34, 1.51 (each s, 6 H, 2xCMe), 2.79 (t, 1 H, $J_{5a,5b}$=10, $J_{5a,4}$=10, H-5a), 3.26 (dd, 1 H, $J_{5b,4}$=6.5, H-5b), 3.79 (s, 3 H, OMe), 3.78 (dd, 1 H, H-4), 4.14 (d, 1 H, $J_{1',2'}$=4.0, H-2'), 4.62, 4.72 (ABq, 2 H, J=12.0, CH_2Ph), 4.46 (dd, 1 H, $J_{2,1'}$=6.0, H-1'), 4.62 (d, 1 H, $J_{3',4'}$=4.0, H-3'), 4.78

(d, 1 H, H-2), 5.98 (d, 1 H, H-4'), 7.34 (s, 5 H, Ph). (2S)-2d: NMR (δ): 1.32, 1.51 (each s, 6 H, 2xCMe), 2.79 (dd, 1 H, $J_{5a,5b}$=10.0, $J_{5a,4}$=8.5, H-5a), 3.24 (dd, 1 H, $J_{5b,4}$=6.0, H-5b), 3.76 (s, 3 H, OMe), 3.97 (dd, 1 H, H-4), 4.00 (d, 1 H, $J_{1',2'}$=3.5, H-2'), 4.14 (dd, 1 H, $J_{1',2}$=9.5, H-1'), 4.54, 4.60 (ABq, 2 H, J=12.0, CH_2Ph), 4.57 (d, 1 H, $J_{3',4'}$=4.0, H-3'), 4.98 (d, 1 H, H-2), 5.94 (d, 1 H, H-4'), 7.34 (m, 5 H, Ph).

3b: NMR (δ): 1.40 (t, 3 H, $J_{1',2'}$=7.0, H-2'), 3.10 (q, 2 H, H-1'), 3.94 (s, 3 H, OMe), 8.06 (s, 1 H, H-5).

3c: NMR (δ): 1.49, 1.61 (each s, 6 H, 2xCMe), 3.98 (s, 3 H, OMe), 4.10 (dd, 1 H, $J_{2'a,2'b}$=9.0, $J_{1',2'b}$=5.0, H-2'b), 4.48 (dd, 1 H, $J_{1',2'a}$=7.0, H-2'a), 5.42 (dd, 1 H, H-1'), 8.18 (s, 1 H, H-5).

3d: IR (cm^{-1}): 1735 (ester), 3100 (thiazole), NMR (δ): 1.35, 1.53 (each s, 6 H, 2xCMe), 3.99 (s, 3 H, OMe), 4.23, 4.37 (ABq, 2 H, J=12.0, CH_2Ph), 4.31 (d, 1 H, $J_{1',2'}$=3.0, H-2'), 4.69 (d, 1 H, $J_{3',4'}$=3.5, H-3'), 5.69 (d, 1 H, H-1'), 6.08 (d, 1 H, H-4'), 6.91-7.31 (m, 5 H, Ph), 8.23 (s, 1 H, H-5).

4: $[\alpha]_D^{14}$ +84.0° (c 1.3, $CHCl_3$), IR (cm^{-1}); 2100 (N_3), NMR (δ): 2.12 (m, 2 H, H-3a,3b), 3.37 (s, 3 H, OMe), 3.6-4.0 (m, 4 H, H-2,4,6a,6b), 4.20 (m, 1 H, H-5), 4.53 (d, 1 H, $J_{1,2}$=1.0, H-1), 5.52 (s, 1 H, CHPh), 7.36 (m, 5 H, Ph).

5: bp 170-200°C/15 Torr, $[\alpha]_D^{25}$ +53.0° (c 0.65, CH_2Cl_2), IR (cm^{-1}); 2100 (N_3), 1740 (ester), NMR (δ): 1.34, 1.41 (each s, 6 H, 2xCMe), 2.04 (s, 3 H, OAc), 1.92-2.72 (m, 2 H, H-3a,3b), 3.60-4.32 (m, 5 H, H-2,4,5,6a,6b), 6.09 (s, 1 H, H-1).

6: bp 195-200°C/17 Torr, $[\alpha]_D^{21}$ +75.8° (c 1.01, CH_2Cl_2), IR (cm^{-1}): 2120 (N_3), 1750 (ester), NMR (δ): 2.07 (s, 3 H, OAc), 2.34 (oct, 1 H, $J_{3a,3b}$=14.0, $J_{2,3a}$=2.0, $J_{3a,4}$=4.0, H-3a), 2.66 (oct, 1 H, $J_{2,3b}$=6.0, $J_{3b,4}$=9.0, H-3b), 3.78 (s, 3 H, OMe), 4.12 (dd, 1 H, H-2), 4.76 (dd, 1 H, H-4), 6.23 (s, 1 H, H-1).

8a: $[\alpha]_D^{23}$ -147.5° (c 1.08, CH_2Cl_2), NMR (δ): 1.86 (m, 2 H, H-2'a,2'b), 2.98 (dd, 1 H, $J_{5a,5b}$=10.5, $J_{4,5b}$=7.5, H-5b), 3.34 (dd, 1 H, $J_{4,5a}$=6.5, H-5a), 3.7 (m, 1 H, H-1'), 3.80 (s, 6 H, 2xOMe), 4.14 (m, 1 H, H-4), 4.37 (dd, 1 H, $J_{2'a,3'}$= 5.5, $J_{2'b,3'}$=8.0, H-3'), 4.74 (d, 1 H, $J_{1',2}$=7.8, H-2).

8b: mp 84-85°C, $[\alpha]_D^{26}$ -15.6° (c 0.78, CH_2Cl_2), NMR (δ): 2.08 (m, 2 H, H-2'a, 2'b), 2.92 (t, 1 H, $J_{5a,5b}$=$J_{4,5b}$=10.0, H-5b), 3.36 (dd, 1 H, $J_{4,5a}$=6.5, H-5a), 3.88 (s, 6 H, 2xOMe), 3.7-4.0 (m, 2 H, H-4,1'), 4.48 (dd, 1 H, $J_{2'a,3'}$=5.0, $J_{2'b,3'}$=9.0, H-3'), 4.68 (d, 1 H, $J_{1',2}$=6.0, H-2).

10a: $[\alpha]_D^{21}$ -47.8° (c 1.32, CH_2Cl_2), NMR (δ): 2.16 (s, 3 H, OAc), 2.48 (m, 2 H, H-2'a,2'b), 3.76 (s, 3 H, OMe), 3.96 (s, 3 H, COOMe on thiazole), 5.08 (dd, 1 H, $J_{2'a,3'}$=5.0, $J_{2'b,3'}$=9.5, H-3'), 5.28 (dd, 1 H, $J_{1',2'a}$=9.5, $J_{1',2'b}$= 4.5, H-1'), 8.22 (s, 1 H, H-5).

10b: mp 89-91°C, $[\alpha]_D^{20}$ -62.8° (c 0.48, EtOH), NMR (δ): 2.36 (m, 2 H, H-2'a, 2'b), 3.85 (s, 3 H, OMe), 4.01 (s, 3 H, COOMe on thiazole), 4.54 (dd, 1 H, $J_{2'a,3'}$=8.0, $J_{2'b,3'}$=5.5, H-3'), 5.30 (dd, 1 H, $J_{1',2'a}$=6.0, $J_{1',2'b}$=8.0, H-1'), 8.31 (s, 1 H, H-5).

11: mp 160-163.5°C, $[\alpha]_D^{15}$ -111.5° (c 0.3, 20% EtOH in CH_2Cl_2), NMR (δ): 1.98 (dt, 1 H, $J_{2'a,2'b}$=13.0, H-2'a), 3.02 (dt, 1 H, H-2'b), 3.90 (s, 3 H, OMe), 4.38 (t, 1 H, $J_{2'a,3'}$=$J_{2'b,3'}$=8.0, H-3'), 5.00 (t, 1 H, $J_{1',2'a}$=$J_{1',2'b}$=8.0, H-1'), 8.34 (s, 1 H, H-5).

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