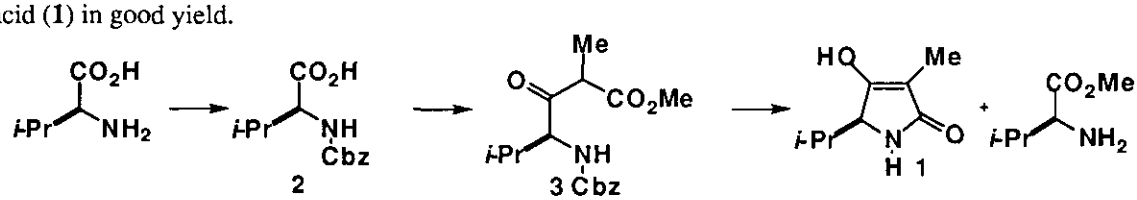
2(3*H*)-AND 2(5*H*)-FURANONES. VIII.[1] PREPARATION AND α NUCLEOPHILICITY OF (*S*)-γ-ISOPROPYL-α-METHYL-β-TETRAMIC ACID

Naoki Toyooka,* Morihiro Nishio, Hiroyuki Shinoda, and Takefumi Momose

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan

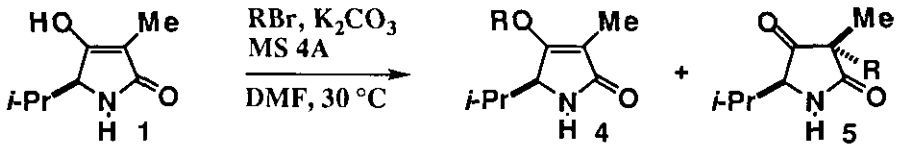
Abstract - An efficient preparation of (*S*)-γ-isopropyl-α-methyl-β-tetramic acid has been established, and the α nucleophilicity of the acid has been also examined.

In the preceding paper,[1] we reported the chirality transfer on the tetronic acid templates using the alkylation or the Michael reaction at the α-position. β-Tetramic acid nucleus, the nitrogen homologue of tetronic acid, has been found in the biologically active natural products, such as tirandamycin, erthroskyrine, tenuazonic acid, ikarugamycin, and althiomycin, therefore, numerous efforts to prepare this ring system have been reported. However, no example of the fundamental study on the alkylation of this acid has been reported. In this Note, we wish to report an efficient preparation of (*S*)-γ-isopropyl-α-methyl-β-tetramic acid (**1**) and the chirality transfer on the acid using the alkylation or Michael reaction at the α-position. The first method[2] for the preparation of the acid is the Dieckmann cyclization of the amide ester. This method, however, is not applicable to the preparation of optically active tetramic acid because of racemization at the γ-position.[3] The second method[4] is the condensation of amino acid with meldrum's acid to give a γ-substituted β-tetramic acid. This condensation is an excellent method for the preparation of optically active β-tetramic acid, however, not applicable to the preparation of α,γ-disubstituted tetramic acid. The third method[5] is the cyclization of amino β-keto ester. This method seems to be applicable to wide variety of optically active mono- or disubstituted β-tetramic acids. Therefore, we applied the third method for the preparation of **1**. Protection of amino group in L-valine with carbobenzyloxy chloride (CbzCl) afforded the carboxylic acid (**2**). Construction of the β-keto ester moiety was performed by the sequence of activation of the carboxyl with carbonyldiimidazole (CDI) followed by the substitution of the resulting imidazolide with lithium enolate of methyl propionate to give the β-keto ester (**3**). Finally, hydrogenolysis of **3** and spontaneous cyclization of the resulting amino ester furnished the desired tetramic acid (**1**) in good yield.



First, we examined the alkylation of **1** and the results were summarized in Table 1.

Table 1: Alkylation of γ-isopropyl-α-methyl-β-tetramic acid



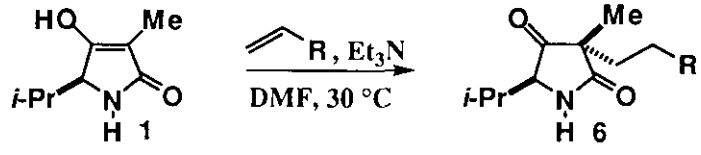
R	Time (h)	Yield (%)[a]		Diastereomeric excess
		4	**5**	(% de)[b]
allyl	15	7(**4a**)	84(**5a**)	95
benzyl	15	6(**4b**)	90(**5b**)	>99

a: Yields of **4** and **5** were isolated ones, respectively. b: The diastereomeric excess (% de) was determined by the integration of the C5-methine proton in the ^{1}H NMR spectrum of the crude products.

The alkylation of **1** with allyl or benzyl bromide proceeded in better regio- and stereoselectivity than corresponding tetronic acid under the same reaction condition.[1] The stereochemistry of the quaternary carbon center on the major alkylated products (**5a**) and (**5b**) were anticipated to be *S* according to the result from the alkylation of α,γ-disubstituted tetronic acid.[1]

Next, we examined the Michael reaction of **1** and the results were summarized in Table 2.

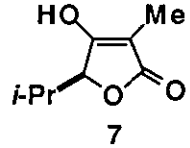
Table 2: Michael reaction of γ-isopropyl-α-methyl-β-tetramic acid



entry	R	Time (h)	Yield (%)[a]	Diastereomeric excess
			6	(% de)[b]
1	CHO	3	81(**6a**)	>99
2	COMe	15	99(**6b**)	>99
3	CO_2Me	72	92(**6c**)	>99
4	CN	72	88(**6d**)	96

a: Yields of **6a-d** were isolated ones, respectively. b: The diastereomeric excess (% de) was determined by the integration of the C5-methine proton in the ^{1}H NMR spectrum of the crude products.

In contrast to the reactivity at the α-position of tetronic acids toward the Michael acceptor,[1] it was noteworthy that the Michael reaction of **1** with methyl acrylate or acrylonitrile proceeded smoothly to give the adduct in high yield (entry 3 or 4). The AM1 calculations {HOMO for tetramic acid (**1**); -9.554 eV, for tetronic acid (**7**); -9.873 eV} suggested higher reactivity of **1** than **7** on the Michael reaction at the α-position.



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In summary, we demonstrated that the alkylation and the Michael reaction of **1** proceeded in good regio- and stereoselective manner to give the products bearing the chiral quaternary carbon center. These products would serve as chiral building blocks for the synthesis of natural products having a quaternary carbon center.

EXPERIMENTAL

IR spectra were measured with a Perkin-Elmer 1600 series FTIR spectrophotometer. ^{1}H NMR spectra were recorded at 270 MHz on a JEOL JNM-GSX 270 instrument with tetramethylsilane as an internal standard. MS spectra and high resolution MS spectra (HRMS) were measured on a JEOL JMS D-200 spectrometer. Optical rotations were measured on a JASCO DIP-140 instrument. Chromatography was performed on a silica gel column (Merck Kieselgel 60 or Fuji-Davision BW-200) unless otherwise stated. The extracts were dried over $MgSO_4$ unless otherwise specified.

(3*S*)-3-Methyl-2-[(*N*-phenylmethoxycarbonyl)amino]butanoic acid (2) To a stirred solution of L-valine (10 g, 85.5 mmol) in 5% $NaHCO_3$ solution (500 mL) was added benzyl chloroformate (CbzCl) (12.2 mL, 85.5 mmol), and the resulting solution was stirred at rt for 20 h. The aqueous solution was washed with Et_2O (150 mL), and the aqueous layer was acidified with 20% HCl. The aqueous layer was extracted with CH_2Cl_2 (150 mL x 3), and the organic extracts were combined, dried, and evaporated to give a colorless solid (18 g, mp 47.5-50 °C), which was used directly in the next step.

Methyl (3*S*)-2,5-dimethyl-3-oxo-4-[(*N*-phenylmethoxycarbonyl)amino]hexanoate (3) To a stirred solution of LDA [prepared from *i*-Pr_2NH (3.9 mL, 27.5 mmol) and *n*-BuLi (17.1 mL, 10% in hexane)] was added methyl propionate (2.6 mL, 26.7 mmol) at -78 °C, and the resulting solution was stirred at -78 °C for 30 min. To the reaction mixture was added imidazolide [prepared from **2** (2.03 g, 8.09 mmol) and CDI (1.44 g, 8.9 mmol) in THF (10 mL) at rt for 2 h] at -78 °C, and the stirring was continued for 30 min. The reaction was quenched with 10% HCl (20 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (40 mL x 3), and the organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was purified by column chromatography (hexane:EtOAc=7:1) to afford **3** (1.24 g, 48%) as a colorless oil. IR (neat) 3355, 1744, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 and 1.01 (each 1.5H, each d, each J = 6.6 Hz), 0.81 and 1.04 (each 1.5H, each d, each J = 6.6 Hz), 1.33 and 1.38.(each 1.5H, each d, each J = 7.1 Hz), 2.15-2.34 (1H, m), 3.69-3.71 (each 1.5H, each s), 4.47-4.60 (1H, m), 7.35 (5H, s); HRMS Calcd for $C_{17}H_{23}NO_5$: 321.1574. Found: 321.1563.

(5*S*)-3-Methyl-5-(2-propyl)pyrrolidine-2,4-dione (1) To a stirred solution of **3** (1.86 g, 5.79 mmol) in MeOH (14 mL) was added $Pd(OH)_2$ (20 mg), and the resulting suspension was stirred at rt under a hydrogen atmosphere for 1 h. The catalyst was filtered through a Celite pad, and washed with MeOH (10 mL x 2). The filtrate and washings were combined and evaporated to give **1** (883.7 mg, 98%) as a colorless solid. Further purification by recrystallization from EtOH-Et_2O afforded the analytical sample (603.4 mg) as a colorless solid (mp 185-186 °C). IR (KBr) 3234, 2963, 2870, 1660, 1640, 1291, 1264, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.73 (3H, d, J = 6.8 Hz), 0.96 (3H, d, J = 6.8 Hz), 1.63 (3H, s), 2.05-

2.18 (1H, m), 3.84 (1H, d, J = 3.2 Hz); Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.73; H, 8.18; N, 8.78; $[\alpha]^{26}_D$ -41.2° (c 1.15, MeOH).

General procedure for the alkylation of tetramic acid (1) To a stirred solution of **1** (2.0 mmol) in DMF (4 mL) were added K_2CO_3 (138.2 mg, 2 mmol) and molecular sieves 4A (20 mg), and the resulting suspension was stirred at rt for 30 min. To the suspension was added alkyl halide (1.2 mmol), and the stirring was continued at 30 °C. To the suspension was added benzene (60 mL), and the insoluble material was removed by filtration. The filtrate was washed with H_2O (10 mL x 2), and the organic layer was dried and evaporated to give a pale yellow oil, which was purified by column chromatography (hexane:acetone=40:1-5:1) to afford the alkylated products.

(5*S*)-3-Methyl-4-(2-propenyloxy)-5-(2-propyl)-3-pyrrolin-2-one (4a) IR (neat) 3854, 3237, 2963, 1681, 1323 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.76 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.8 Hz), 1.91 (3H, s), 2.08-2.14 (1H, m), 3.87 (1H, br), 4.78 (2H, t, J = 5.5 Hz), 5.30 (1H, dd, J = 10.5, 1.2 Hz), 5.38 (1H, dd, J = 17.3, 1.2 Hz), 5.90-6.04 (1H, m), 6.41 (1H, br); HRMS Calcd for $C_{11}H_{17}NO_2$: 195.1257. Found: 195.1255; $[\alpha]^{26}_D$ -18.2° (c 0.45, $CHCl_3$).

(3*S*,5*S*)-3-Methyl-3-(2-propenyl)-5-(2-propyl)pyrrolidine-2,4-dione (5a) IR (neat) 3854, 1766, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.8 Hz), 1.19 (3H, s), 2.14-2.28 (1H, m), 2.31-2.49 (2H, br m), 3.70 (1H, d, J = 3.7 Hz), 5.09 (1H, d, J = 9.8 Hz), 5.10 (1H, d, J = 18.1 Hz), 5.59-5.75 (2H, m), 8.00 (1H, br); HRMS Calcd for $C_{11}H_{17}NO_2$: 195.1257. Found: 195.1262; $[\alpha]^{26}_D$ -28.9° (c 1.40, $CHCl_3$).

(5*S*)-3-Methyl-4-phenylmethoxy-5-(2-propyl)-3-pyrrolin-2-one (4b) IR (neat) 3629, 2966, 1654, 1321 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (3H, d, J = 6.6 Hz), 1.01 (3H, d, J = 7.1 Hz), 1.96 (3H, s), 2.10-2.17 (1H, m), 3.89 (1H, br), 5.25 and 5.33 (2H, ABq, J = 11.5 Hz), 5.83 (1H, br), 7.34-7.43 (5H, m); HRMS Calcd for $C_{15}H_{19}NO_2$: 245.1414. Found: 245.1401; $[\alpha]^{26}_D$ -9.4° (c 1.22, $CHCl_3$).

(3*S*,5*S*)-3-Methyl-3-phenylmethyl-5-(2-propyl)pyrrolidine-2,4-dione (5b) IR (neat) 3212, 1766, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80 (3H, d, J = 6.8 Hz), 0.93 (3H, d, J = 6.8 Hz), 1.28 (3H, s), 2.03-2.10 (1H, m), 2.92 (1H, d, J = 3.7 Hz), 2.91 and 3.04 (2H, ABq, J = 12.9 Hz), 7.09-7.30 (5H, m), 7.70 (1H, br); HRMS Calcd for $C_{15}H_{19}NO_2$: 245.1414. Found: 245.1404; $[\alpha]^{26}_D$ -35.7° (c 1.22, $CHCl_3$).

General procedure for the Michael reaction of tetramic acid (1) To a stirred solution of **1** (1.0 mmol) in DMF (2 mL) were added Et_3N (0.14 mL, 1 mmol) and α,β-unsaturated compound (2 mmol) at 0 °C, and the resulting solution was stirred at 30 °C. To the solution were added benzene (60 mL) and H_2O (10 mL), and the organic layer was separated, dried, and evaporated to give a pale yellow oil, which was purified by column chromatography (hexane:acetone=5:1~3:1) to afford the products.

(3*S*,5*S*)-3-Formylethyl-3-methyl-5-(2-propyl)pyrrolidine-2,4-dione (6a) IR (neat) 3222, 2966, 1764, 1694, 1388 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.8 Hz), 1.21 (3H, s), 2.00 (2H, t, J = 7.5 Hz), 2.12-2.24 (1H, m), 2.47-2.56 (2H, m), 3.85 (1H, d, J = 4.2 Hz), 7.85 (1H, br), 9.70 (1H, br s); HRMS Calcd for $C_{11}H_{17}NO_3$: 211.1207. Found: 211.1196; $[\alpha]^{26}_D$ -58.5° (c 1.80, $CHCl_3$).

(3*S*,5*S*)-3-Methyl-3-(3-oxobutyl)-5-(2-propyl)pyrrolidine-2,4-dione (6b) IR (neat) 3228, 1764, 1698, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, d, each *J* = 6.6 Hz), 1.06 (3H, d, *J* = 7.0 Hz), 1.19 (3H, s), 1.95 (2H, dd, *J* = 7.8, 7.6 Hz), 2.13 (3H, s), 2.10-2.24 (1H, m), 3.89 (1H, d, *J* = 3.9 Hz), 8.16 (1H, br); HRMS Calcd for $C_{12}H_{19}NO_3$: 225.1365. Found: 225.1376; $[\alpha]^{26}_D$ -55.7° (*c* 1.06, $CHCl_3$).

(3*S*,5*S*)-3-Methyl-3-(methoxypropanoyl)-5-(2-propyl)pyrrolidine-2,4-dione (6c) IR (neat) 3822, 3282, 2796, 1735, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3H, d, *J* = 6.9 Hz), 1.05 (3H, d, *J* = 6.9 Hz), 1.20 (3H, s), 2.01 (2H, t, *J* = 8.1 Hz), 2.12-2.23 (1H, m), 2.24-2.44 (2H, m), 3.65 (3H, s), 3.85 (1H, d, *J* = 3.9 Hz), 7.74 (1H, br); HRMS Calcd for $C_{12}H_{19}NO_4$: 241.1314. Found: 241.1332; $[\alpha]^{26}_D$ -50.2° (*c* 1.40, $CHCl_3$).

(3*S*,5*S*)-3-Cyanoethyl-3-methyl-5-(2-propyl)pyrrolidine-2,4-dione (6d) IR (neat) 3222, 2967, 1765, 1698, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, *J* = 6.7 Hz), 1.07 (3H, d, *J* = 6.7 Hz), 1.24 (3H, s), 1.94-2.09 (2H, m), 2.11-2.23 (1H, m), 2.43 (2H, t, *J* = 7.5 Hz), 3.92 (1H, d, *J* = 4.7 Hz), 7.92 (1H, br); HRMS Calcd for $C_{11}H_{16}N_2O_3$: 208.1210. Found: 208.1210; $[\alpha]^{26}_D$ -50.8° (*c* 1.07, $CHCl_3$).

ACKNOWLEDGMENT

This work was financially supported in part by a Grant-in-Aid for Scientific Research (No. 02771652) from the Ministry of Education, Science, Sports, and Culture, Japan.

REFERENCES AND NOTES

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Received, 25th January, 1999