SYNTHESIS OF N-ETHOXYCARBONYLMETHYL GEISSMAN-WAISS LACTONE: UNUSUAL EPIMERIZATION OF α, β-UNSATURATED γ-LACTONE

Masakazu Tanaka, Takeshi Murakami, Hiroshi Suemune, and Kiyoshi Sakai*

Faculty of Pharmaceutical Sciences, Kyushu University, Fukuoka 812, Japan

Abstract- N-Ethoxycarbonylmethyl Geissman-Waiss lactone ((±)-**2**) was easily synthesized from bis-lactone (**3**), and an unexpected epimerization of γ-butenolactone was observed in the process of asymmetric synthesis of **2**.

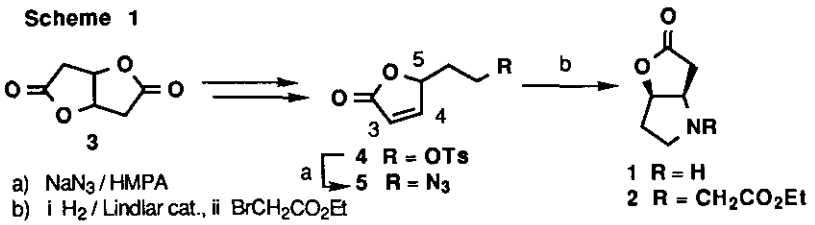
2-Oxa-6-azabicyclo[3.3.0]octan-3-one (Geissman-Waiss lactone **1**) and its N-ethoxycarbonylmethyl derivative (**2**) were first prepared by Geissman and Waiss from β-alanine[1] as a racemic form, and were useful synthons for the synthesis of some pyrrolizidine alkaloids such as retronecine, heliotridine and platynecine.[2a-c] The biological activities of pyrrolizidine alkaloids, which possess hepatotoxic, and in certain cases, antitumor and carcinogenic activities, have made Geissman-Waiss lactone an attractive synthetic target. [2d-h]

As a part of our synthetic studies on biologically active lactones from bis-lactone (**3**),[3] we have achieved the synthesis of Geissman-Waiss lactone derivative (**2**).

Readily prepared bis-lactone (**3**) was converted into the γ-(2-tosyloxyethyl)-α,β-unsaturated γ-lactone (**4**) by the methods previously reported.[3b] Treatment of **4** with NaN_3 in HMPA at room temperature afforded the azide (**5**) in 50% yield. The structure of **5** was confirmed by the signal of δ 3.56 (2H, m, $-CH_2N_3$), 5.17 (1H, m, 5-H), 6.16 (1H, dd, J = 5.6, 2.1 Hz, 3-H), 7.52 (1H, dd, J = 5.6, 1.5 Hz, 4-H) in the ^1H nmr spectrum, and the absorption bands at 2100 ($-N_3$) and 1750 cm^{-1} in the ir spectrum. Reduction of the azide function in **5** with H_2/10% Pd-C/MeOH afforded the undesired saturated amine, suggesting difficulty in the selective reduction of the azide function in preference to the olefinic function. However, this problem was overcome by using Corey's procedure.[4] Treatment of azide (**5**) with Lindlar catalyst in ethanol under hydrogen atmosphere, followed by

alkylation with ethyl bromoacetate, provided the desired N-ethoxycarbonylmethyl Geissman-Waiss lactone (**2**) in 30% yield. The spectroscopic data (ir, ^{1}H nmr, and ms) of **2** were identical with those reported.[2f] (Scheme 1)

Scheme 1



The above successful result for the synthesis of racemic Geissman-Waiss lactone derivative (**2**) prompted us to study the synthesis of **2** in optically active form. Previously we had developed the synthetic procedure of optically active γ-(2-hydroxyethyl)-2,5-dihydro-2-furanone ((-)-**9**) using enantioselective Pseudomonas fluorescens lipase (PFL)-catalyzed hydrolysis of the diacetate ((±)-**6**) as a key step.[3c] (Scheme 2)

Scheme 2

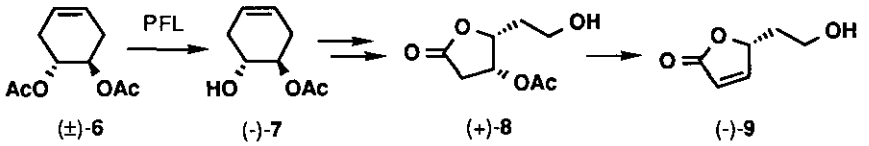
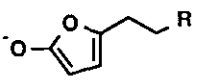


Figure 1



We reexamined the synthesis of **9** extensively, and the newly obtained **9** from optically pure (-)-**7** showed a different specific rotation value $[\alpha]_D^{25}$ -16° from the previous case $[\alpha]_D^{21}$ -46.4°(>99%ee from (+)-MTPA ester).[3c] The decrease of enantiomeric excess (e.e.) was also confirmed by Mosher's method,[5] which shows the newly obtained **9** was only 34%ee. The ^{1}H nmr spectrum of MTPA ester indicated the presence of two diastereotopic protons (δ: 6.03, 6.06) in the ratio of 33 to 67. These findings suggest that racemization of **9** occurs under the reaction conditions employed in elimination of the acetate (**8**). In the previous case,[3c] compound (**8**) was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.5 eq.) for 8 h at 0°C. On the other hand, prolonged reaction time and higher temperature (room temperature) were required for completion of reaction in the present case. This unexpected racemization may be caused by base-catalyzed facile aromatization of α,β-unsaturated lactone as shown in Figure 1. This troublesome problem has been resolved by shortening the reaction time to 1-2 h at 0°C. Thus re-prepared α,β-unsaturated γ-lactone (**9**) showed a specific rotation value of -46° (>99%ee), the same value as the case reported in our previous paper.[3c] However, attempts to convert the optically active **9** to optically active **2**, according to the procedure of the above-described racemic synthesis, were

unsuccessful. Compounds (**4**, **5** and **2**) obtained in this way were racemic ($[\alpha]_D$ 0°), because the employed reaction conditions again allow facile racemization of γ-substituted α,β-unsaturated lactone.

EXPERIMENTAL

General Methods. Ir spectra were measured with a JASCO A-202 spectrometer, and ^1H nmr and ^{13}C nmr spectra were recorded on a JEOL JNM-GX-270 or JEOL JNM-FX-100 spectrometer. Mass spectra (ms) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter at the sodium line. For column chromatography, silica gel (Merck, Kieselgel 60, 70-230) was used. Thin layer chromatography (tlc) was performed on Silica gel F_{254} plates (Merck).

5-(2-Azidoethyl)-2,5-dihydro-2-furanone ((±)-**5**). A mixture of **4** (600 mg, 2.26 mmol) and NaN_3 (280 mg, 4.31 mmol) in HMPA (20 ml) was stirred at room temperature for 1 h. The reaction mixture was diluted with H_2O (150 ml), and extracted with benzene. The benzene extract was washed with brine, and dried over $MgSO_4$, then concentrated in vacuo to afford an oily residue, which was purified by silica gel column chromatography. The fraction eluted with 20 % AcOEt in hexane afforded **5** (170 mg, 50 %) as a colorless oil. Ir (neat): 2100, 1750, 1160 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.77-1.90 (2H, m), 3.56 (2H, m), 5.17 (1H, m), 6.16 (1H, dd, J = 5.6, 2.1 Hz), 7.52 (1H, dd, J = 5.6, 1.5 Hz). Ms m/z: 125 (M^+-N_2).

(1RS, 5RS)-2-Oxa-6-aza-6-(ethoxycarbonylmethyl)bicyclo[3.3.0]octan-3-one ((±)-**2**). A suspension of **5** (129 mg, 0.843 mmol) and Lindlar catalyst (55 mg) in EtOH (5 ml) was stirred at room temperature under H_2 atmosphere. After 2 h, Lindlar catalyst was filtered off. A solution of ethyl bromoacetate (140 mg, 0.843 mmol) in EtOH (5 ml) was added to the above filtrate, and refluxed for 14 h. Removal of the solvents in vacuo and silica gel column chromatographic purification (elution with 30 % AcOEt in hexane) of the residue afforded **2** (66 mg, 30 %) as colorless needles. Ir (Nujol): 1770, 1735, 1160, 1180 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.28 (3H, t, J = 7.3 Hz), 2.05-2.35 (2H, m), 2.53 (1H, dd, J = 2.3, 18.0 Hz), 2.62 (1H, dd, J = 5.6, 18.0 Hz), 2.78 (1H, q, J = 7.9 Hz), 3.22 (1H, dt, J = 3.6, 7.9 Hz), 3.33 (1H, d, J = 17.2 Hz), 3.50 (1H, d, J = 17.2 Hz), 3.67 (1H, dt, J = 2.3, 5.6 Hz), 4.18 (2H, q, 7.3 Hz), 5.00 (1H, dt, J = 2.3, 6.6 Hz). ^{13}C Nmr ($CDCl_3$) δ: 14.2, 31.2, 34.5, 51.5, 52.2, 60.6, 61.9, 84.0, 170.2, 175.9. Ms m/z: 213(M^+), 140, 42.

(R)-5-(2-Hydroxyethyl)-2,5-dihydro-2-furanone ((-)-**9**). Compound (+)-**8** (240 mg, 1.27 mmol) in THF (7 ml) and benzene (14 ml) was stirred in the presence of DBU (193 mg, 1.27 mmol) at 0°C. After 2 h, the

reaction mixture was diluted with 5% HCl, and extracted with AcOEt. The AcOEt extract was washed with 5% $NaHCO_3$ aq, brine, and dried over $MgSO_4$. The solvent was removed in vacuo to afford an oily residue, which was subject to silica gel column chromatography. The fraction eluted with 60% AcOEt in hexane afforded (-)-**9** (87 mg, 53%) as a colorless oil. $[\alpha]_D^{25}$ -46° (c = 1.09, $CHCl_3$). Ir (neat): 3400, 1740, 1600, 1050 cm^{-1}. ^1H Nmr ($CDCl_3$) δ: 1.75 (1H, s), 1.77-2.24 (2H, m), 3.83 (2H, t, J = 5.2 Hz), 5.26 (1H, m), 6.10 (1H, dd, J = 2.0, 5.8 Hz), 7.58 (1H, dd, J = 1.5, 5.8 Hz). Ms m/z: 128 (M^+), 110, 83, 82, 55, 31. Under the reaction conditions, DBU (2.5 eq.), room temperature for 10 h, the obtained **9** showed $[\alpha]_D^{25}$ -16° (c = 1.00, $CHCl_3$).

This paper is dedicated to Prof. Masatomo Hamana on the occasion of his 75th birthday.

REFERENCES AND NOTES

1. T. A. Geissman and A. C. Waiss Jr., J. Org. Chem., **1962**, 27, 139.

2. (a) K. Narasaka, T. Sakakura, T. Uchimaru, K. Morimoto, and T. Mukaiyama, Chemistry Lett., **1982**, 455. (b) K. Narasaka, T. Sakakura, T. Uchimaru, and D. G. Vuong, J. Am. Chem. Soc., **1984**, 106, 2954. (c) H. Rüeger and M. Benn, Heterocycles, **1982**, 19, 23. (d) H. Rüeger and M. Benn, Heterocycles, **1983**, 20, 1331. (e) S. Saito, S. Matsumoto, S. Sato, M. Inaba, and T. Moriwake, Heterocycles, **1986**, 24, 2785. (f) H. Niwa, O. Okamoto, Y. Miyachi, Y. Uosaki, and K. Yamada, J. Org. Chem., **1987**, 52, 2941. (g) N. Ikota and A. Hanaki, Heterocycles, **1988**, 27, 2535. (h) Y. Nagao, W. M. Dai, M. Ochiai, and M. Shiro, J. Org. Chem., **1989**, 54, 5211.

3. (a) M. Hizuka, N. Hayashi, T. Kamashita, H. Suemune, and K. Sakai, Chem. Pharm. Bull., **1988**, 36, 1550. (b) M. Hizuka, C. Fang, H. Suemune, and K. Sakai, Chem. Pharm. Bull., **1989**, 37, 1185. (c) H. Suemune, M. Hizuka, T. Kamashita, and K. Sakai, Chem. Pharm. Bull., **1989**, 37, 1379.

4. E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, Synthesis, **1975**, 590.

5. J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., **1969**, 34, 2543.

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