SYNTHESIS OF (2S, 4S)-2-HYDROXY-4-HYDROXYMETHYL-4-BUTANOLIDE, A HUNGER SUBSTANCE

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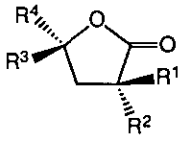
Abstract --- (2S,4S)-2-Hydroxy-4-hydroxymethyl-4-butanolide (**1a**), which is a hunger substance, was synthesized stereoselectively starting from D-γ-ribono-1,4-lactone (**2**).

It is well known that some blood factors such as glucose, free fatty acids, insulin, glucagon, and some peptides act as feeding modulating substances.[1] They stimulate the neuron in lateral hypothalamic area (LHA) and ventromedial hypothalamic nucleus (VMH) to induce hunger and satiety. In search of other humoral factors related to hunger and satiety, Oomura et al. have found that 2-hydroxy-4-hydroxymethyl-4-butanolide (**1**) is responsible for the elicitation of the food intake of rats.[2] Okukado et al. have revealed that the steric structure of natural **1** is (2S,4S)-form (**1a**), since **1a** was the most physiologically active among four synthetic isomers (**1a**, **1b**, **1c**, and **1d**) of **1**.[3]

Hunger substance (**1a**) can be expected as regards application to agricultural or medicinal substances in future. Since it is impractical to obtain **1a** from natural sources because of its paucity, an efficient procedure for preparation of **1a** is highly desirable. Two reports have been published concerning the preparation of **1a** so far. One of them has to be done under a condition with difficult

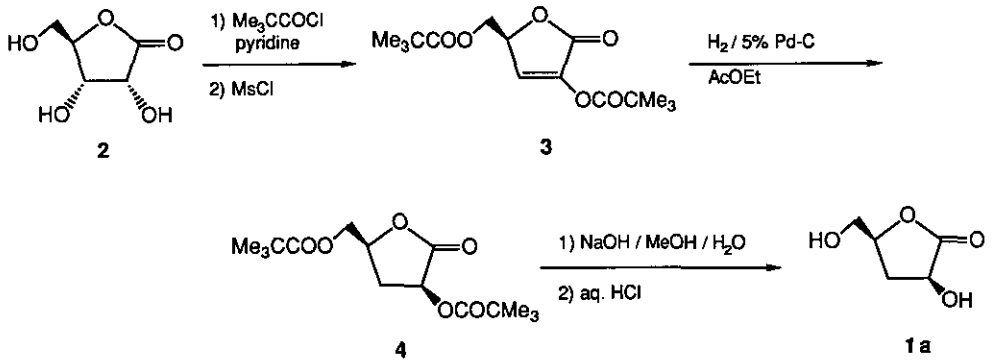


1 **a**: R^1=OH, R^2=H, R^3=CH_2OH, R^4=H
b: R^1=H, R^2=OH, R^3=CH_2OH, R^4=H
c: R^1=OH, R^2=H, R^3=H, R^4=CH_2OH
d: R^1=H, R^2=OH, R^3=H, R^4=CH_2OH

control of the reaction to avoid any colored by-products.[4] The other preparation of **1a** requires many steps and in very low yield.[3]

In this paper, we report a method that gives **1a** in higher yield by easier operations than the precedented methods.

As shown in Scheme 1, our synthesis of **1a** is simple and straightforward. We selected D-γ-ribono-1,4-lactone (**2**) as a starting material. Regioselective 2,5-O-protection of **2** with pivaloyl chloride in pyridine, and subsequent 3-O-mesylation followed by β-elimination with mesyl chloride gave **3** in 62.8% yield in a one-pot operation.[5] Hydrogenation of **3** over 5% palladium on carbon as a catalyst in ethyl acetate gave **4** stereoselectively in 94.9% yield.[6] Treatment of **4** with an aqueous sodium hydroxide in methanol subsequent diluted hydrochloric acid acidification gave (2S,4S)-2-hydroxy-4-hydroxymethyl-4-butanolide (**1a**) in 97.6% yield (total yield from **2** was 58.2%).



Scheme 1

In conclusion, starting from D-γ-ribono-1,4-lactone (**2**), we developed a useful method for the preparation of (2S,4S)-2-hydroxy-4-hydroxymethyl-4-butanolide (**1a**). This has enabled the mass production of **1a** for the purpose of feeding mechanism studies, the application to agricultural or medicinal substances in future, and so on.

EXPERIMENTAL

Spectral Measurements.

All bps and mps were uncorrected. Ir spectra were measured on a Jasco FT/IR-5000 spectrophotometer. ^{1}H-Nmr spectra were recorded at 300 MHz and ^{13}C-nmr spectra at 75 MHz, with TMS as an internal standard on a Brucker AC-300P spectrometer. Optical rotation was measured on a Jasco DIP-370 polarimeter.

(S)-2,5-Dipivaloyloxy-2-penten-4-olide (3).

To a stirred and ice-cooled solution of 1.00 g (6.75 mmol) of D-γ-ribono-1,4-lactone (**2**) in 16.0 ml of dry pyridine was added dropwise 2.04 g (16.9 mmol) of pivaloyl chloride under an nitrogen atmosphere followed by stirring for 0.5 h at room temperature. To the reaction mixture was added dropwise 3.09 g (27.0 mmol) of mesyl chloride at 0 °C under an nitrogen atmosphere followed by stirring for 3 h at room temperature. The reaction mixture was poured into cold water and extracted with ether. The organic layer was washed with successive, 1 mol dm^{-1} hydrochloric acid, saturated sodium hydrogen carbonate solution, water, saturated copper sulfate solution, and water. It was dried over anhydrous magnesium sulfate and then the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane / ethyl acetate = 6/1; v/v) to afford 1.26 g (62.8%) of pure (S)-2,5-dipivaloyloxy-2-penten-4-olide (**3**) as white powder.[5] This was recrystallized from *n*-hexane-ether.; mp 66.0-67.5°C; $[\alpha]_D^{26}$ -32.6° (c 0.31, $CHCl_3$); ir (KBr) 3106(w), 2976(m), 2940(w), 2916(w), 2876(w), 1783(s), 1760(s), 1727(s), 1667(m), 1481(m), 1446(w), 1404(w), 1377(w), 1367(w), 1344(w), 1280(m), 1210(w), 1162(m), 1114(s), 1075(m), 1035(w), 998(w), 980(w), 934(m), 899(m), 855(w), 822(w), 789(w), 764(m), 739(w), 659(w), 578(w), and 503(m) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 7.14 (1H, d, $J_{3,4}$=2.0 Hz, H-3), 5.22 (1H, dt, $J_{4,5}$=$J_{4,5'}$=4.1 Hz, $J_{3,4}$=2.0 Hz, H-4), 4.37 (2H, d, $J_{4,5}$=$J_{4,5'}$=4.1 Hz, H-5 and H-5'), 1.33 (9H, s, *t*-butyl), 1.18 (9H, s, *t*-butyl); Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found C, 60.38; H, 7.55.

(2S,4S)-2,5-Dipivaloyloxy-4-pentanolide (4).

A vigorously shaken solution of 298 mg (1.00 mmol) of (S)-2,5-dipivaloyloxy-2-penten-4-olide (**3**) in 20.0 ml of ethyl acetate was hydrogenated at atmospheric pressure over 30 mg of 5% palladium on active carbon at room temperature. The catalyst was removed by filtration through Celite, and then the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane / ethyl acetate = 5/1; v/v) to afford 285 mg (94.9%) of pure (2S,4S)-2,5-dipivaloyloxy-4-pentanolide (**4**) as white powder.[6] This was recrystallized from *n*-hexane-ether.; mp 78.0-80.0°C; $[\alpha]_D^{25}$ +45.9° (c 0.31, $CHCl_3$); ir (KBr) 2964(m), 2938(m), 2916(w), 2878(w), 1796(s), 1721(s), 1483(m), 1458(m), 1417(w), 1400(w),

1373(m), 1288(s), 1197(s), 1154(s), 1108(m), 1087(m), 1065(m), 1035(w), 1013(m), 980(m), 948(m), 924(m), 895(w), 833(w), 797(w), 783(w), 770(m), 702(m), 652(m), 621(w), 584(w), 563(m), and 462(m) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 5.50 (1H, dd, $J_{2,3}$=10.0 Hz, $J_{2,3'}$=9.0 Hz, H-2), 4.73-4.65 (1H, m, H-4), 4.38 (1H, dd, $J_{5,5'}$=12.3 Hz, $J_{4,5}$=3.3 Hz, H-5), 4.20 (1H, dd, $J_{5,5'}$=12.3 Hz, $J_{4,5'}$=5.6 Hz, H-5'), 2.77 (1H, ddd, $J_{3,3'}$=12.8 Hz, $J_{2,3'}$=9.0 Hz, $J_{3',4}$=6.1 Hz, H-3'), 2.03 (1H, ddd, $J_{3,3'}$=12.8 Hz, $J_{2,3}$=10.0 Hz, $J_{3,4}$=10.0 Hz, H-3), 1.26 (9H, s, *t*-butyl), 1.23 (9H, s, *t*-butyl); Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found C, 59.98; H, 8.24.

(2S,4S)-2,5-Dihydroxy-4-pentanolide ((2S,4S)-2-hydroxy-4-hydroxymethyl-4-butanolide, **1a**).

A solution of 10.55 g (35.13 mmol) of (2S,4S)-2,5-dipivaloyloxy-4-pentanolide (**4**) in 53.7 ml of an aqueous sodium hydroxide solution and 53.7 ml of methanol was stirred overnight at room temperature. The mixture was acidified with a diluted hydrochloric acid, and then the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: ethyl acetate) to afford 4.53 g (97.6%) of pure (2S,4S)-2,5-dihydroxy-4-pentanolide ((2S,4S)-2-hydroxy-4-hydroxymethyl-4-butanolide, **1a**) as a colorless oil; $[\alpha]_D^{28}$ +23.5° (c 3.61, MeOH)(lit.,[3] $[\alpha]_D^{20}$ +23.2°, c 3.61, MeOH); ir (film) 3380(br), 2942(m), 1773(s), 1638(w), 1454(m), 1423(m), 1332(m), 1288(m), 1205(s), 1131(s), 1054(s), 994(s), 959(m), 922(w), 901(m), 874(w), 803(m), 733(m), 710(m), 652(m), and 619(m) cm^{-1}; ^{1}H-nmr (CD_3OD) δ: 4.55 (1H, dd, $J_{2,3}$=10.6 Hz, $J_{2,3'}$=8.5 Hz, H-2), 4.50-4.42 (1H, m, H-4), 3.80 (1H, dd, $J_{5,5'}$=12.7 Hz, $J_{4,5}$=2.9 Hz, H-5), 3.59 (1H, dd, $J_{5,5'}$=12.7 Hz, $J_{4,5'}$=5.0 Hz, H-5'), 2.53 (1H, ddd, $J_{3,3'}$=12.7 Hz, $J_{2,3'}$=8.5 Hz, $J_{3',4}$=5.7 Hz, H-3'), 1.99 (1H, ddd, $J_{3,3'}$=12.3 Hz, $J_{2,3}$=10.6 Hz, $J_{3,4}$=10.6 Hz, H-3); ^{13}C-nmr (CD_3OD) δ: 179.9, 79.4, 70.1, 64.6, and 34.4; Hrms calcd for $C_5H_8O_4$ 132.0423, found 132.0428.

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REFERENCES AND NOTES

1. (a) Y. Oomura, "Hunger", ed by D. Novin, W. Wyrwicka, and G. A. Bray, Raven, New York, 1976, p. 145; (b) J. R. Martin and D. Novin, Physiol. Behav., 1977, **19**, 461; (c) S. C. Woods E. C. Lotter, L. D. Mckay, and D. Porte, Jr., Nature (London), 1979, **282**, 503; (d) W. J. Freed, M. J. Perlow, and R. J. Wyatt, Science, 1979, **206**, 850; (e) J. Knoll, Physiol. Behav., 1979, **23**, 497; (f) T. Tsuda, Y. Kishino, and T. Katsunuma, Physiol. Behav., 1982, **29**, 519.

2. (a) T. Sakata, Y. Oomura, M. Fukushima, K. Tsutsui, and K. Hashimoto, Brain Res. Bull., (Suppl. 4), 1980, **5**, 23; (b) Y. Oomura and K. Hattori, Gendai-Kagaku, **1982**, 140; (c) N. Shimizu, Y. Oomura, and T. Sakata, Am. J. Physiol., 1984, **246**, 542; (d) Y. Oomura and N. Shimizu, Kagaku to Seibutsu, 1984, **22**, 228; (e) T. Sakata, K. Fujimoto, K. Terada, and K. Arase, Physiol. Behav., 1985, **34**, 969; (f) Y. Oomura and H. Nishimura, Kagaku, 1987, **42**, 440.

3. O. Uchikawa, N. Okukado, T. Sakata, K. Arase, and K. Terada, Bull. Chem. Soc. Jpn., 1988, **61**, 2025.

4. **1a** was prepared from acetylated aldonolactones by simultaneous elimination and hydrogenation in the presence of catalytic palladium and triethylamine by Bock et al. A good quality catlalyst and high pressure (100 atm) were required since slow hydrogenation leads to colored by-products because the unsaturated lactone undergoes further elimination. These conditions make this method difficult.; K. Bock, I. Lundt, and C. Pedersen, Acta Chem. Scand. B, 1981, **35**, 155.

5. This step gave 2,3,5-O-tripivaloyl-D-γ-ribono-1,4-lactone (18.7% yield) and 3-pivaloyloxy-5-methylene-2(5H)-furanone (9.1% yield) as by-products. Cleavage of the 2,3,5-O-pivaloyl groups of the by-product may regenerate starting material **2**.

6. This step gave (4S)-4-hydroxymethyl-4-butanolide as a by-product (1.5% yield). The diastereomer of **4**, (2R,4S)-2-pivaloyloxy-4-pivaloyloxymethyl-4-butanolide which would be given by hydrogen addition from the same face to the 4-pivaloyloxymethyl group on the lactone ring, was not obtained.

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