Short Synthesis of (3*S*,4*R*)- and (3*R*,4*R*)-3-Hydroxy-4-hydroxymethyl-4-butanolides, Two Lactones from Levoglucosenone

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Two lactones, (3*S*,4*R*)- and (3*R*,4*R*)-3-hydroxy-4-hydroxymethyl-4-butanolides, were easily and stereoselectively synthesized in good yield from levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose).

Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose **1**)[1] is a pyrolytic product of cellulose,[2] which is quite useful as a chiral source for synthesizing organic compounds, owing to its highly functionalized structure containing one chiral center.[3]

This paper describes the synthesis of two γ-lactones, (3*S*,4*R*)- and (3*R*,4*R*)-3-hydroxy-4-hydroxymethyl-4-butanolides (**3** and **8**), which are of physiological interest. Oomura and Sakata et al. showed that **3** and **8** function as satiety-modulating substances in the lateral hypothalamic area (LHA) and ventromedial hypothalamic nucleus (VMH) and to suppress food intake by rats.[4,5] Marquez et al. indicated for the 3-*O*-tetradecanoyl derivative of **3** to have the conformation of a constrained analogue of diacylglycerol, and, accordingly, to function as a potent inhibitor ($K_i = 5.3$ μM, M=mol dm^{-3}) in the binding of [20-^{3}H]-12,13-bis(*O*-butyryl)phorbol to protein kinase C (PK-C).[6] Lactones **3** and **8** might have applications as medicinal or agricultural substances in the future, and the development of efficient methods for their preparation would be desirable. The previous syntheses of **3** or **8** are not always efficient, involving steps of low selectivities, conversion of multi-steps or difficult procedures.[7—9] In our previous paper,[3a] the Baeyer–Villiger oxidation of **1** with peracetic acid was shown to give γ-lactone, (*S*)-5-hydroxy-2-penten-4-olide very selectively. The present methods for obtaining **3** and **8** from **1** are related to that result and are easy, with high stereoselectivity and good overall yield.

As shown in Scheme 1, the synthesis of **3** is very simple. The base-catalyzed hydration of **1** with catalytic triethylamine in water gave 1,6-anhydro-3-deoxy-β-D-*erythro*-hexopyranos-2-ulose (**2**) stereoselectively in 75.6% yield.[10] The regioselective Baeyer–Villiger oxidation of **2** with peracetic acid in acetic acid, followed by a treatment with concd hydrochloric acid in methanol, afforded **3** in 85.1% yield (64.3% overall yield in two steps from **1**).

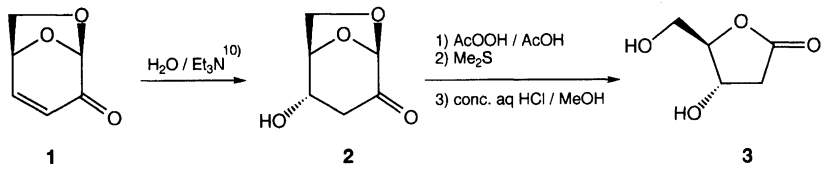
Lactone **8**, the C-3 epimer of **3**, was thus synthesized from **1** via 1,6-anhydro-3-deoxy-β-D-*threo*-hexopyranos-2-ulose (**7**) which was the C-4 epimer of **2**, as shown in Scheme 2. The starting compound **1** was first converted to 1,6:3,4-dianhydro-β-D-talopyranose (**5**) by a known procedure in three steps in 66.2% overall yield.[2,3e—g] The oxidation of the hydroxyl group of **5** with a Swern oxidant gave 1,6:3,4-dianhydro-β-D-*lyxo*-hexopyranos-2-ulose (in 87.9% yield), which was isolated as monohydrate **6**. The treatment of **6** with sodium triethyl(phenylseleno)borate(1-)[11] brought about a regioselective cleavage of the oxirane ring to furnish β-ketol **7** in 80.6% yield. The regioselective Baeyer–Villiger oxidation of **7** with peracetic acid in acetic acid, followed by a treatment with concd hydrochloric acid in methanol, gave **8** in 90.5% yield (42.3% overall yield in five steps from **1**).

In summary, starting from levoglucosenone (**1**), novel methods for the preparation of (3*S*,4*R*)- and (3*R*,4*R*)-3-hydroxy-4-hydroxymethyl-4-butanolide (**3** and **8**) stereoselectively in a few steps in good yield were developed. By these methods, **3** and **8** can be easily obtained and effectively used in various physiological studies.

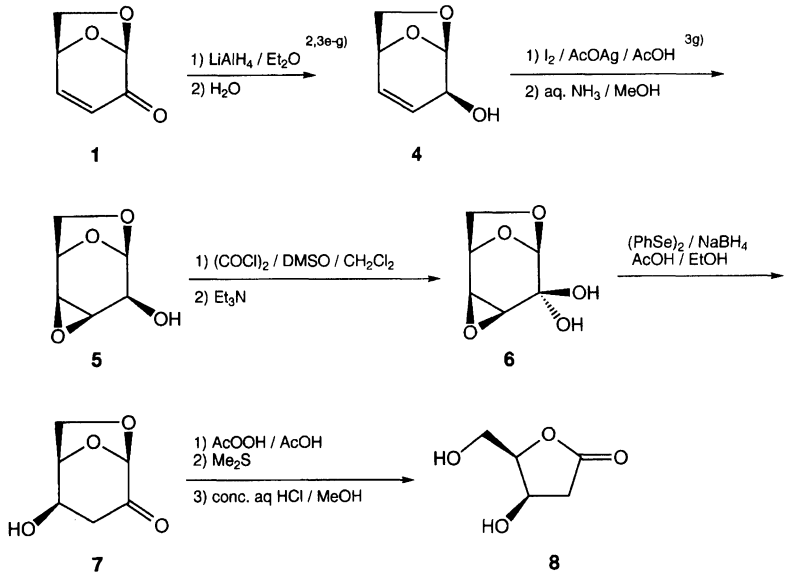
Experimental

Spectral Measurements. All 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 the internal standard, on a Brucker AC-300P spectrometer. The optical rotation was measured on a JASCO DIP-370 polarimeter.

(3*S*,4*R*)-3-Hydroxy-4-hydroxymethyl-4-butanolide (3). To a stirred and water-cooled solution of 2.65 g (18.4



Scheme 1.



Scheme 2.

mmol) of **2**[10] in 32.0 cm^3 of acetic acid was slowly added dropwise 12.0 cm^3 of 40% peracetic acid in acetic acid under an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. To a stirred and water-cooled mixture was slowly added 9.00 cm^3 (123 mmol) of dimethyl sulfide. The mixture was stirred for 1 h at room temperature, and then evaporated under reduced pressure. To the residue were added 69.0 cm^3 of methanol and 2.8 cm^3 of concd hydrochloric acid. The mixture was stirred at room temperature overnight under an argon atmosphere, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=1/4; v/v) to afford 2.07 g (85.1%) of **3** as an oil. Compound **3** was identified by comparing its ^{1}H NMR spectra data and ^{13}C NMR spectra data with those of the literature.[9d] $[\alpha]_D^{24}$ −4.5° (*c* 1.44, C_2H_5OH) [lit,[9d] $[\alpha]_D$ −1.5°, *c* 1, C_2H_5OH].

1,6 : 3,4-Dianhydro-β-D-*lyxo*-hexopyranos-2-ulose Monohydrate (6). To a stirred solution of 1.05 cm^3 (12.2 mmol) of oxalyl chloride in 70.0 cm^3 of dry dichloromethane was slowly added a solution of 1.86 cm^3 (26.3 mmol) of dimethyl sulfoxide in 17.0 cm^3 of dry dichloromethane at −70 °C under an argon atmosphere. After stirring the reaction mixture for 2 min, a solution of 1.68 g (11.7 mmol) of **5**[3g] in 35.0 cm^3 of dry dichloromethane was slowly added to it, followed by stirring at −70 °C for 15 min under an argon atmosphere. Then, 8.16 cm^3 (57.5 mmol) of triethylamine was slowly added to the reaction mixture. It was stirred for 5 min. The temperature was allowed to rise to room temperature. The mixture was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=1/3; v/v) to afford 1.64 g (87.9%) of 1,6 : 3,4-dianhydro-β-D-*lyxo*-hexopyranos-2-ulose. This was recrystallized as monohydrate **6** from hexane–ethyl acetate. Mp 106—110 °C; $[\alpha]_D^{26}$ −48.2° *c* 0.20, $CHCl_3$) [lit,[12] mp 110—112 °C; $[\alpha]_D^{20}$ −41°, *c* 1, $CHCl_3$]; IR (KBr) 3388 (br), 3360 (m), 2944 (m), 2914 (w), 2506 (m), 2442 (m), 1620 (w), 1439 (w), 1381 (w), 1344 (w), 1320 (w), 1270 (w), 1245 (m), 1191 (m), 1156 (m), 1116 (s), 1083 (s), 1006 (s), 973 (m), 934 (s), 913 (s), 872 (s), 803 (m), 777 (m), 652 (m), 590 (w), 524 (w), 478 (m), and 445 cm^{-1} (w); ^{1}H NMR ($CDCl_3/CD_3OD$=2 : 1; v/v) δ=5.04 and 4.94 (1H, br, H-1), 4.86 and 4.85 (1H, dd, $J_{5,6'}$=4.8 Hz, $J_{5,4}$=4.6 Hz, H-5), 3.99 and 3.97 (1H, d, $J_{6,6'}$=6.6 Hz, H-6), 3.72 and 3.71 (1H, dd, $J_{4,5}$=4.6 Hz, $J_{4,3}$=4.5 Hz, H-4), 3.56 (1H, dd, $J_{6',6}$=6.6 Hz, $J_{6',5}$=4.8 Hz, H-6'), 3.23 and 3.16 (1H, dd, $J_{3,4}$=4.5 Hz, $J_{3,1}$=2.0 Hz, H-3). Found: C, 44.87; H, 5.17%. Calcd for $C_6H_8O_5$: C, 45.01; H, 5.04%.

1,6-Anhydro-3-deoxy-β-D-*threo*-hexopyranos-2-ulose (7). To a stirred solution of 469 mg (1.50 mmol) of diphenyl diselenide in 7.5 cm^3 of dry ethanol was slowly added 113 mg (3.00 mmol) of sodium borohydride at room temperature. After 5 min, 11.6 mm^3 of acetic acid was added to the reaction mixture at 0 °C under an argon atmosphere. A solution of 160 mg (1.00 mmol) of **6** in 8.0 ml of dry ethanol was then added dropwise to the mixture. Stirring was continued at the same temperature for 2 h under an argon atmosphere. The reaction mixture was diluted with 78.0 cm^3 of ethyl acetate, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=1/2; v/v) to afford 116 mg (80.6%) of **7**. This was recrystallized from hexane–diethyl ether. Mp 49.0—50.5 °C; $[\alpha]_D^{26}$ −218.0° (*c* 1.0, $CHCl_3$) [lit,[13] $[\alpha]_D^{20}$ −158.1°, *c* 1, $CHCl_3$];

IR (KBr) 3468 (s), 2984 (m), 2922 (m), 1746 (s), 1491 (m), 1427 (m), 1367 (m), 1340 (m), 1313 (m), 1247 (m), 1199 (w), 1110 (s), 1069 (s), 1036 (w), 1011 (m), 982 (m), 961 (s), 922 (m), 893 (m), 874 (s), 820 (w), 793 (m), 748 (w), 596 (m), 545 (m), 530 (m), 480 (m), and 437 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ=5.06 (1H, br, H-1), 4.59 (1H, ddbr, $J_{5,6'}$=4.9 Hz, $J_{5,4}$=4.0 Hz, H-5), 4.42—4.34 (1H, m, H-4), 4.37 (1H, dd, $J_{6,6'}$=8.0 Hz, $J_{6,5}$=0.7 Hz, H-6), 3.90 (1H, ddd, $J_{6',6}$=8.0 Hz, $J_{6',5}$=4.9 Hz, $J_{6',4}$=0.5 Hz, H-6'), 2.77 (1H, dddd, $J_{3,3'}$=15.8 Hz, $J_{3,4}$=6.8 Hz, $J_{3,5}$=1.6 Hz, $J_{3,1}$=1.2 Hz, H-3), 2.67 (1H, d, $J_{4\text{-OH},4}$=4.4 Hz, 4-OH), and 2.52 (1H, dd, $J_{3',3}$=15.8 Hz, $J_{3',4}$=9.8 Hz, H-3'). Found: C, 49.57; H, 5.58%. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.59%.

(3*R*,4*R*)-3-Hydroxy-4-hydroxymethyl-4-butanolide (8). To a stirred and water-cooled solution of 1.58 g (11.0 mmol) of **7** in 20.0 cm^3 of acetic acid was slowly added dropwise 7.0 cm^3 of 40% peracetic acid in acetic acid under an argon atmosphere. The reaction mixture was stirred for 1 h at room temperature under an argon atmosphere. To a stirred and water-cooled mixture was slowly added 5.0 cm^3 of dimethyl sulfide. The mixture was stirred for 1 h at room temperature, and then evaporated under reduced pressure. To the residue was added 40.0 cm^3 of methanol and 1.6 cm^3 of concd hydrochloric acid. The mixture was stirred at room temperature overnight under an argon atmosphere, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate=1/5; v/v) to afford 1.31 g (90.5%) of **8** as an oil. The obtained compound **8** was identified by comparing its ^1H NMR spectra data and ^{13}C NMR spectra data with those of the literature.[9d] $[\alpha]_D^{24}$ +67.3° (*c* 1.01, CH_3OH) [lit,[9d] $[\alpha]_D^{20}$ +49.3°, *c* 0.56, CH_3OH].

References

1) This compound is available from Yuki Gosei Kogyo Co., Ltd., Hirakawa-cho CH BLDG. 3-24 Hirakawa-cho 2 chome, Chiyoda-ku, Tokyo 102, Japan.

2) F. Shafizadeh and P. P. S. Chin, *Carbohydr. Res.*, **58**, 79 (1977), and references cited therein.

3) a) K. Koseki, T. Ebata, H. Kawakami, H. Matsushita, Y. Naoi, and K. Itoh, *Heterocycles*, **31**, 423 (1990); b) H. Kawakami, T. Ebata, K. Koseki, H. Matsushita, Y. Naoi, and K. Itoh, *Chem. Lett.*, **1990**, 1459; c) T. Ebata, K. Matsumoto, H. Yoshikoshi, K. Koseki, H. Kawakami, and H. Matsushita, *Heterocycles*, **31**, 1585 (1990); d) H. Kawakami, T. Ebata, K. Koseki, K. Matsumoto, H. Matsushita, Y. Naoi, and K. Itoh, *Heterocycles*, **31**, 2041 (1990); e) K. Matsumoto, T. Ebata, K. Koseki, H. Kawakami, and H. Matsushita, *Bull. Chem. Soc. Jpn.*, **64**, 2309 (1991); f) K. Matsumoto, T. Ebata, K. Koseki, H. Kawakami, and H. Matsushita, *Heterocycles*, **32**, 2225 (1991); g) K. Matsumoto, T. Ebata, K. Koseki, K. Okano, H. Kawakami, and H. Matsushita, *Heterocycles*, **34**, 1935 (1992); h) K. Matsumoto, T. Ebata, K. Koseki, K. Okano, H. Kawakami, and H. Matsushita, *Carbohydr. Res.*, **246**, 345 (1993); i) "Levoglucosenone and Levoglucosans, Chemistry and Applications," ed by Z. J. Witczak, ATL Press, Inc., USA (1994), pp. 3—118, and references cited therein.

4) Y. Oomura, in "Sotennenbutsu to Seirikassei," ed by H. Imura, T. Goto, K. Nakajima, and K. Muraji, University of Tokyo Press, Tokyo (1984), pp. 287—314, and references cited therein.

5) T. Sakata, *Brain Res. Bull.*, **25**, 969 (1990).

6) K. Teng, V. E. Marquez, G. W. A. Milne, J. J. Barchi, Jr., M. G. Kazanietz, N. E. Lewin, P. M. Blumberg, and E. Abushanab, *J. Am. Chem. Soc.*, **114**, 1059 (1992).

7) Conventional methods for the preparation of **3** only have been reported in: a) Y. Kita, H. Yasuda, O. Tamura, F. Itoh, Y. Yuan Ke, and Y. Tamura, *Tetrahedron Lett.*, **26**, 5777 (1985); b) N. Baggett, J. G. Buchanan, M. Y. Futal, C. H. Lauchut, K. J. MuCullough, and J. W. Weher, *J. Chem. Soc., Chem. Commun.*, **1985**, 1826.

8) Conventional methods for the preparation of **8** only have been reported in: a) J. Humphlett, *Carbohydr. Res.*, **4**, 157 (1967); b) G. A. Danilova, V. I. Mel'nikova, and K. K. Pivnitsky, *Tetrahedron Lett.*, **27**, 2489 (1986).

9) Conventional methods for the preparation of **3** and **8** have been reported in: a) K. Bock, I. Lundt, and C. Pedersen, *Carbohydr. Res.*, **90**, 17 (1981); b) B. Rague, Y. Chapleur, and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, **1982**, 2063; c) F. J. López-Herrera, M. V. Fernández, and S. G. Claros, *Tetrahedron*, **46**, 7165 (1990); d) M. V. Fernández, P. Durante-Lanes, and F. J. López-Herrera, *Tetrahedron*, **46**, 7911 (1990).

10) F. Shafizadeh, R. H. Furneaux, and T. T. Stevenson, *Carbohydr. Res.*, **71**, 169 (1979).

11) a) M. Miyashita, T. Suzuki, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **111**, 3728 (1989); b) S. Takano, Y. Shimazaki, Y. Sekiguchi, and K. Ogasawara, *Synthesis*, **1989**, 539.

12) K. Heyns, R. -W. Rennecke, and P. Köll, *Chem. Ber.*, **108**, 3645 (1975).

13) R. -W. Rennecke, K. Eberstein, and P. Köll, *Chem. Ber.*, **108**, 3652 (1975).