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A METHOD FOR EASY PREPARATION OF OPTICALLY PURE (S)-5-HYDROXY-2-PENTEN-4-OLIDE AND (S)-5-HYDROXYPENTAN-4-OLIDE

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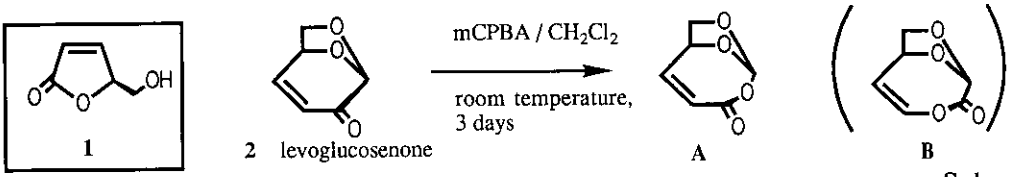
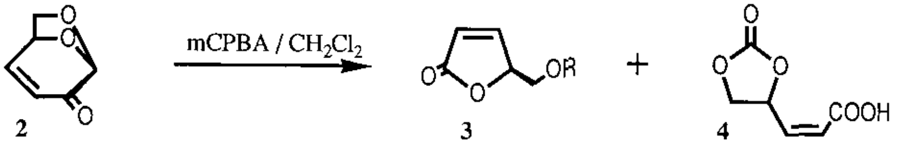
Abstract —— A new method for preparation of (S)-5-hydroxy-2-penten-4-olide **1** and (S)-5-hydroxypentan-4-olide **8** starting from levoglucosenone **2** is described.

(S)-5-Hydroxy-2-penten-4-olide **1** is a very useful chiral source for synthesizing natural products because of its highly functionalized structure containing one chiral center.[1] Despite several syntheses of **1**[2] being known, an efficient method to produce a large quantity has been unknown. In this paper, we report a new method for convenient preparation of **1** from levoglucosenone **2**.[3] As can be seen from Scheme 1, levoglucosenone **2** has an adequate functionalized framework for this purpose with the exception of one carbon atom.



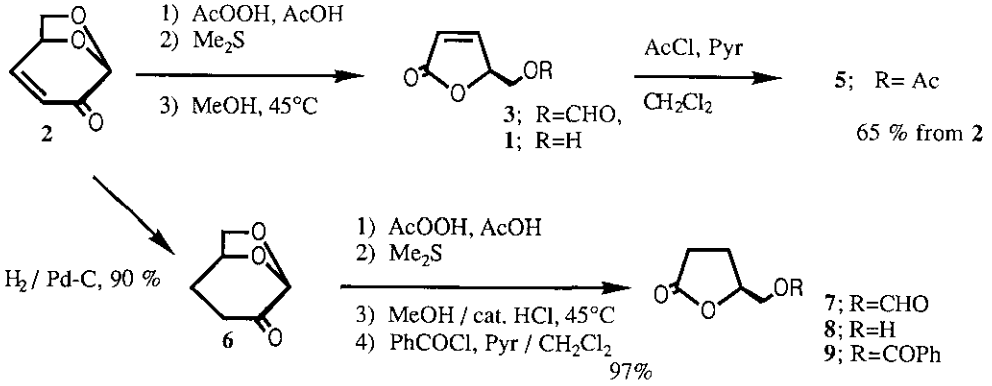
Scheme 1

Shafizadeh et al.[4] has previously reported the Baeyer Villiger oxidation of **2** with mCPBA. They suggested that the oxidation product was not **B** but **A** based on uv and ir spectral data. We noted that this lactone **A** was a good precursor of **1**. We proceeded by investigating the Baeyer Villiger oxidation of **2** carefully and in detail.



Scheme 2

The result showed that the formic ester **3**[5] was the main product (59 %) when Shafizadeh's procedure was used. In addition, carbonate **4**[6] was obtained as a minor product (16 %) (Scheme 2). To avoid a complicated oxidation process, other peracids were examined. The best result was obtained by using peracetic acid, and a new preparation method of the butenolide **1** was established (Scheme 3).



Scheme 3

A typical procedure is as follows: To a solution of levoglucosenone **2** (15 g, 119 mmol) in acetic acid (60 ml), 1.2 molar equivalent peracetic acid (ca. 40 % in acetic acid) was added over 30 min. The mixture was stirred for 2 days at room temperature. Dimethyl sulfide (1.4 ml, 19 mmol) was added to the mixture. After 1 h, the reaction mixture was concentrated *in vacuo*. The residue contained butenolide **1** and a small quantity of formate **3** (about 10%). To the residue methanol (50 ml) was added and the mixture was stirred overnight at 45°C in order to convert the formate **3** into the free (*S*)-5-hydroxy-2-penten-4-olide **1** completely. If necessary, a small amount of HCl could be added to the mixture.

The methanol solution was concentrated *in vacuo* and butenolide **1** was obtained as brown oil.[7] The nmr analysis of this crude **1** showed only a single product. The optical rotation value of the corresponding acetate **5**[8] indicates its high optical purity. The total yield from **2** was 65 %.

This method was also applied to the preparation of (*S*)-5-hydroxypentan-4-olide **8**. The oxidation of the dihydrolevoglucosenone **6**[9] proceeded very fast. The excellent efficiency of this procedure was demonstrated in the high total yield (87 %) of **9** from **2**.[10]

ACKNOWLEDGEMENT

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3. IUPAC name is 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose. Y. Halpern, R. Riffer, and A. Broid, *J. Org. Chem.*, 1973, **38**, 204 ; levoglucosenone **2** is available from Yuki Gosei Kogyo Co.,Ltd.
4. F. Shafizadeh, R. H. Hurneaux, and T. T. Stevenson, *Carbohydr. Res.*, 1979, **71**, 169 .
5. bp 85~90°C/0.5 torr.; n_D=1.4743 (23°C); $[\alpha]_D$ -125° (c 1.18, 23°C, $CHCl_3$); ir (film) ν cm^{-1} 3495, 3105, 2960, 1760, 1725, 1605, 1165, 1110(s); uv λ max(95% EtOH) 208 nm, ε 6300 and 258 nm, ε 210; hrms calcd for $C_6H_6O_4$, 142.0266, found 142.0270; ^{1}H-nmr ($CDCl_3$, 300 MHz): δ 4.49(2H, m), 5.27(1H, m), 6.35(1H, dd, J=2.2, 5.7 Hz), 7.45(1H, dd, J=1.6, 5.7 Hz), 8.15(1H, br s); ^{13}C-nmr ($CDCl_3$, 75 MHz): δ 61.8, 80.2, 123.6, 131.8, 151.9, 160.1. Formate **3** was synthesized by P. Camps, J. Cardellach, J. Font, R. M. Ortuno, and O. Ponsati, *Tetrahedron*, 1982, **38**, 2395.
6. Ir (film)ν cm^{-1} 3400, 1720, 1650(s); ^{1}H-nmr ($CDCl_3$, 300 MHz): δ 4.18(1H, dd, J=7.3, 8.8 Hz), 4.92(1H, dd, J=8.5, 8.8 Hz), 6.03(1H, dddd, J=2.0, 5.8, 7.3, 8.5 Hz), 6.08(1H, dd, J=2.0, 11.4 Hz), 6.63(1H, dd, J=5.8, 11.4 Hz). Me ester of **4**; $[\alpha]_D$ -178°(c 2.26, 23°C, $CHCl_3$); ^{13}C-nmr ($CDCl_3$, 75 MHz): δ

57.1, 75.3, 79.9, 127.9, 151.1, 160.3, 171.2.

7. Ir (film) ν cm^{-1} 3450, 1750, 1600; ^{1}H-nmr (CDCl$_3$, 300 MHz): δ 3.80(1H, dd, J=5.0, 12.2 Hz), 4.00(1H, dd, J=3.8, 12.2 Hz), 5.17(1H, m), 6.22(1H, dd, J=2.1, 5.7 Hz), 7.50(1H, dd, J=1.5, 5.7 Hz).

8. bp 96°C/0.3 torr; $[\alpha]_D$ -126°(c 3.56, 23°C, CHCl$_3$)($[\alpha]_D$ -123.6° (c 3.68, 20°C, CHCl$_3$) was reported in ref.[5]); ir (film) ν cm^{-1} 1740(s), 1600(w), 1230(s); ^{1}H-nmr (CDCl$_3$, 300 MHz): δ 2.08(3H, s), 4.35(2H, m), 5.25(1H, m), 6.23(1H, dd, J=2.1, 5.8 Hz), 7.45(1H, dd, J=1.6, 5.8 Hz) .

9. IUPAC name, 1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hexopyranos-2-ulose. F. Shafizadeh and P. S. Chin, *Carbohydr. Res*., 1977, **58**, 79.

10. Dihydrolevoglucosenone **6** (7.32 g, 57.2 mmol) in acetic acid (25 ml) was treated with 40% peracetic acid (8 ml) below 30°C for 1 h. After the mixture was stirred for 1 h at room temperature, dimethyl sulfide (0.23 ml) was added and the mixture was stirred for an additional 20 min. The solvent was evaporated *in vacuo*. The crude butyrolactone was treated with MeOH (50 ml) and conc. HCl (2 ml) overnight at 45°C. The solvent was evaporated *in vacuo* to provide **8** (6.7 g); ir ν cm^{-1} 3400, 2950, 1770, 1180, 1060; ^{1}H-nmr (CDCl$_3$, 300 MHz): δ 2.1~2.35(2H, m), 2.5~2.7(2H, m), 3.65(1H, dd, J= 4.0, 12.0 Hz), 3.92(1H, dd, J= 3.2, 12.0 Hz). The 5-benzoate **9** (12.2 g, 97.3 % yield) was obtained from **8** (6.7 g), benzoyl chloride (8.85 g) and pyridine (70 ml); mp 60~60.5°C; $[\alpha]_D$ +49.7° (c 1.03, 25°C, EtOH); ir (film) ν cm^{-1} 1780, 1730(sh); ^{1}H-nmr (CDCl$_3$, 300 MHz): δ 2.15 (1H, m), 2.45(1H, m), 2.63(2H, m), 4.44(1H, dd, J=5.3, 12.3 Hz), 4.55(1H, dd, J= 3.2, 12.3 Hz), 4.90(1H, m), 7.45(2H, t, J=7.5 Hz), 7.59(1H, t, J=7.5 Hz), 8.03(2H, d, J=7.5Hz). M. Taniguchi et al. (ref.[1]) synthesized **9** and reported $[\alpha]_D$ +48.2°; mp 59~60.5°C.

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