SYNTHESIS OF A USEFUL CHIRAL BUILDING BLOCK, (*S*)-5-ACETOXY-2-PENTEN-4-OLIDE FROM D-GLUCOSE

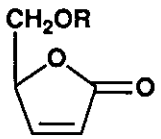
Ichiro Honda[a,b], Makoto Shibagaki[a,*], Koshi Koseki[a], Hideyuki Kuno[a], Kyoko Takahashi[a], and Hajime Matsushita[a]

[a]Life Science Research Laboratory, Japan Tobacco Inc., 6-2, Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan
[b]Present address; Faculty of Agriculture, Utsunomiya University, 350 Mine-machi, Utsunomiya, Tochigi 321, Japan

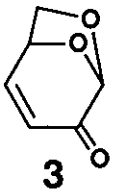
Abstract---A new method for preparation of (*S*)-5-acetoxy-2-penten-4-olide starting from D-glucose with 5 steps is described.

Many useful chiral compounds have been synthesized starting from sugars and their derivatives.[1] Recently, we established a simple method for preparing levoglucosenone(**3**),[2] which is a unique chiral 1,6-anhydrosugar, starting from D-galactose. In our laboratory, several useful chiral compounds were synthesized using **3** as a starting material. For example, D-altrose, D-altrosan and D-allosan,[3] (+)-*trans*-whisky lactone, (+)-*trans*-cognac lactone and (+)-eldanolide,[4] and some nucleotides[5] were prepared from **3**. (*S*)-5-Hydroxy-2-penten-4-olide(**2**)[6] was also synthesized from **3**.

In this paper, we report a new method for preparing the acetyl derivative of **2**, (*S*)-5-acetoxy-2-penten-4-olide(**1**), starting from D-glucose (**5**) with 5 steps.



1 R=Ac
2 R=H



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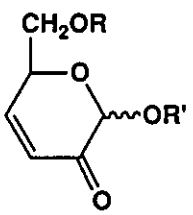
The above compounds(**1** and **2**) have used as useful chiral building blocks. For example, (+)-*trans*-burseran,[7] (-)-isostegan,[7] (+)-steganacin,[8] (-)-verrucarinolactone,[9] and prostacyclin analogues[10] were prepared using **1** or **2**. The synthetic methods of production of **1** and **2** have been described in several reports.[11] However, it has been difficult to prepare **1** or **2** on a large scale, because the starting materials used in previous methods are relatively expensive. In order to overcome the problem, D-glucose(**5**) was selected as a starting material. In this study, 3,4-dideoxy-D-*glycelo*-hex-3-enopyran-2-uloside(**4**) was used in the synthesis of **2**, by a similar method as has been described in our previous paper.[6] As **4** was synthesized in good yield from **5**, a new economical method for synthesizing **1** was established.



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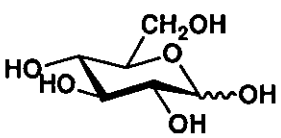

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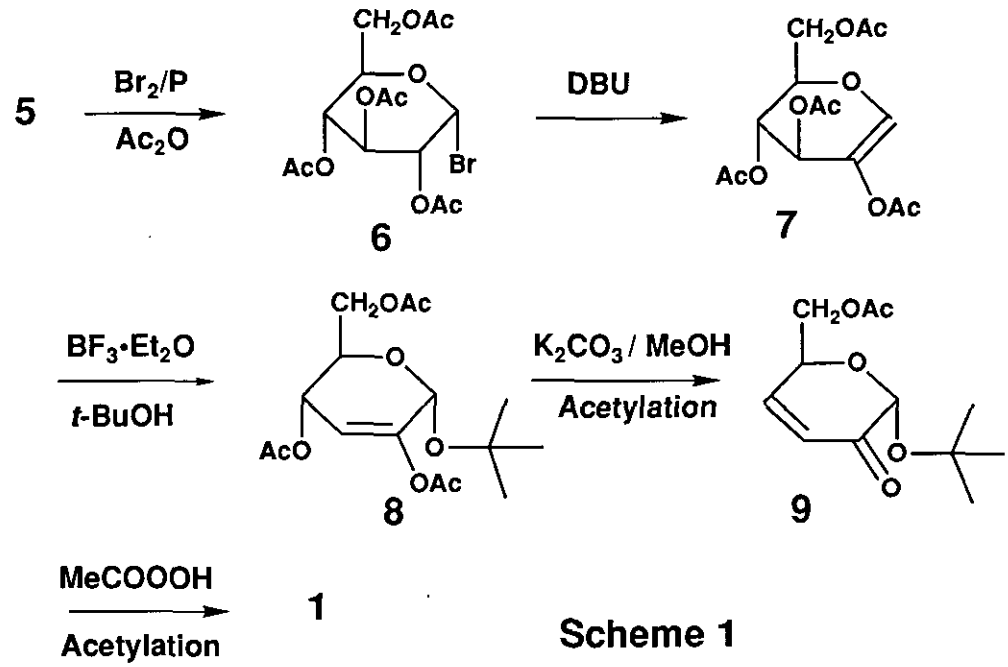
D-Glucose(**5**) was converted to the α-bromo-tetra-*O*-acetate(**6**) in 80% yield, using bromine and phosphorus in acetic anhydride(Scheme 1).[12] Treatment of **6** with DBU (1,8-diazabicyclo[5.4.0]-7-undecene), afforded 2-acetoxy-tri-*O*-acetyl glucal(**7**) almost quantitatively.[13] A Ferrier reaction was applied to **7** using *t*-butyl alcohol and boron trifluoride etherate,[14] and the *t*-butyl α-glucoside(**8**) was produced in 87% yield. Basic treatment of **8** with potassium carbonate in methanol gave the enone derivative(**9**)[15] in 67% yield. Under the Baeyer Villiger oxidation of **9** as reported previously,[5] and subsequent

acetylation, **1** was obtained in 70% yield. The specific rotation was identical with the value reported in previous paper.[5]



Scheme 1

In conclusion, optically pure **1** was obtained in 34% yield in 5 steps from D-glucose.

EXPERIMENTAL

All mp and bps were uncorrected. ^{1}H-Nmr spectra were recorded at 300 MHz with TMS as an internal standard using a Brucker AC-300P spectrometer. Optical rotation was measured on a Jasco DIP-370 polarimeter.

2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide(**6**)

Acetic anhydride(200 ml, 2.1 mol) and perchloric acid(1.2 ml, 60%) were stirred in a 500 ml round bottomed flask equipped with a mechanical stirrer. To this solution, 50 g(0.28 mol) of D-glucose(**5**) (dried over phosphorus pentoxide for one day) was gradually added while keeping the temperature between 30-40°C. It was then cooled down to 20°C by iced water, and red phosphorus(15 g, 480 mmol) and bromine(29 ml, 560 mmol) were slowly added maintaining the temperature below 20°C. Then water(18 ml, 1 mol) was

carefully added while keeping the mixture below 30°C. After this, the reaction mixture was stirred for 3 h, and chloroform(300 ml) was added and filtered. The filtrate was poured into 500 ml of crushed ice, and the organic layer was separated, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate and concentrated *in vacuo*. The residue(110 g) was crystallized by scratching with a glass rod. Recrystallization from ether gave 91 g(80% yield) of white crystals of **6**; ^{1}H-nmr ($CDCl_3$) δ 2.04(3H, s), 2.06(3H, s), 2.10(3H, s), 2.11(3H, s), 4.13(1H, m), 4.25-4.40(2H, m), 4.84(1H, dd, *J*=4.0, 10.0 Hz), 5.17(1H, t, *J*=10 Hz), 5.56(1H, t, *J*=10 Hz), 6.61(1H, d, *J*=4.0 Hz); mp 89-90°C; $[\alpha]_D^{27}$ +198° (c 0.99, $CHCl_3$), in good agreement with values reported in the literature.[12]

3,4,6-Tri-*O*-acetyl-2-acetoxy-D-glucal(**7**)

A solution of **6**(16 g, 40 mmol) in 1,2-dichloroethane(40 ml) was cooled in a carbon tertachloride-dry ice bath under argon. In order to avoid a lightening effect, this reaction flask was covered with aluminum foil. To this solution, DBU (8 ml, 56 mmol) was slowly added keeping the temperature below -10°C. The solution was then stirred for 1 h below -10°C and 1.5 h at room temperature. Then it was diluted with dichloromethane(400 ml), washed with aqueous hydrogen chloride (5%, 200 ml), saturated sodium bicarbonate and brine, and dried over magnesium sulfate. The solvent was evaporated *in vacuo* to give crystalline **7**(13 g, 98% yield). Recrystallization from ether/hexane gave white needles of **7**; ^{1}H-nmr ($CDCl_3$) δ 2.07(3H, s), 2.10-2.12(9H), 4.23(1H, dd, *J*=2.8, 11.4 Hz), 4.3-4.5(2H), 5.24(1H, dd, *J*=4.4, 5.6 Hz), 5.56(1H, d, *J*=2.8 Hz), 6.64(1H, s); mp 61-62°C; $[\alpha]_D^{27}$ -32.5°(c 1.01, $CHCl_3$), in good agreement with values reported in the literature.[14]

t-Butyl 2,4,6-tri-*O*-acetyl-3-deoxy-α-D-*erythro*-hex-2-enopyranoside(**8**)

To a solution of **7**(10 g, 30 mmol) and *t*-butyl alcohol(10 ml) in dichloromethane(20 ml), boron trifluoride etherate(1.5 ml) was added

gradually at room temperature. After stirring for 2 days, 1 ml of boron trifluoride etherate was added, and the reaction mixture was stirred for one more day. Then it was diluted with 200 ml of dichloromethane, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate and concentrated to give crystalline **8**(9.1 g, 87% yield). Recrystallization from ether/hexane afforded white crystals of **8**; ^{1}H-nmr ($CDCl_3$) δ 1.26(9H, s), 2.07(3H, s), 2.09(3H, s), 2.15(3H, s), 4.15-4.30(3H, m), 5.32(1H, s), 5.42(1H, m), 5.69(1H, d, J=2.2 Hz); mp 62-63°C; $[\alpha]_D^{27}$ +80.5°(c 0.99, $CHCl_3$), in good agreement with values reported in the literature.[13,16]

t-Butyl 6-*O*-acetyl-3,4-dideoxy-α-D-*glycelo*-hex-3-enopyran-2-uloside(**9**)

A solution of **8**(3.44 g, 10 mmol) in methanol(50 ml) was cooled in a carbon tetrachloride-dry ice bath under argon. One equivalent of potassium carbonate(1.38 g, 10 mmol) was added in portions to this solution and stirring was maintained for 1 h. Then the reaction mixture was quenched with Dowex-50 (H^+), allowed to warm up to room temperature and filtered. After evaporation of the filtrate, the residue was dissolved in ether, washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and evaporated. This product was acetylated with acetic anhydride(1 ml, 10 mmol), pyridine(1 ml) and dimethylaminopyridine (catalytic) in dichloromethane(20 ml) for 1 h. The reaction mixture was poured into ice-water, and extracted with 50 ml of chloroform. The extract was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and evaporated. After purification by silica gel column chromatography (hexane:ethyl acetate = 5:1), 1.59 g(67%) of **9** was obtained; ^{1}H-nmr ($CDCl_3$) δ 1.31(9H, s), 2.10(3H, s), 4.21(1H, dd, *J*=4.5, 11.5 Hz), 4.36(1H, dd, *J*=5.7, 11.5 Hz), 4.85(1H, m), 5.14(1H, s), 6.17(1H, dd, *J*=2.7, 11.5 Hz), 6.94(1H, dd, *J*=1.7, 10.5 Hz); $[\alpha]_D^{27}$ +6.5°(c 1.13, $CHCl_3$), in good agreement with values reported in the literature.[15]

(*S*)-5-Acetoxy-2-penten-4-olide(**1**)

Compound (**9**)(1.22 g, 5 mmol) was dissolved in aqueous peracetic acid(40% solution, 2 ml) at room temperature. After stirring for 12 h, dimethyl sulfide(1.4 ml, 19 mmol) was gradually added keeping the solution below 20°C. After evaporation, the residue was acetylated with acetic anhydride (0.5 ml, 5 mmol), pyridine(0.5 ml) and dimethylaminopyridine(catalytic) in dichloromethane for 1.5 h. The reaction mixture was poured into ice-water, and extracted with 50 ml of chloroform. The extract was washed with saturated sodium bicarbonate and brine, dried over magnesium sulfate, filtered and evaporated. After purification by silica gel column chromatography (hexane:ethyl acetate = 3:2), 550 mg(70%) of **1** was obtained; ^{1}H-nmr ($CDCl_3$) δ 2.07(3H, s), 4.35(2H, m), 5.25(1H, m), 6.23(1H, dd, J=2.0, 5.7 Hz), 7.45(1H, dd, J=1.6, 5.7 Hz); bp 105-110°C (0.2 Torr); $[\alpha]_D^{29}$ -124.9°(c 1.56, $CHCl_3$), in good agreement with values reported in the literature.[6]

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