A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

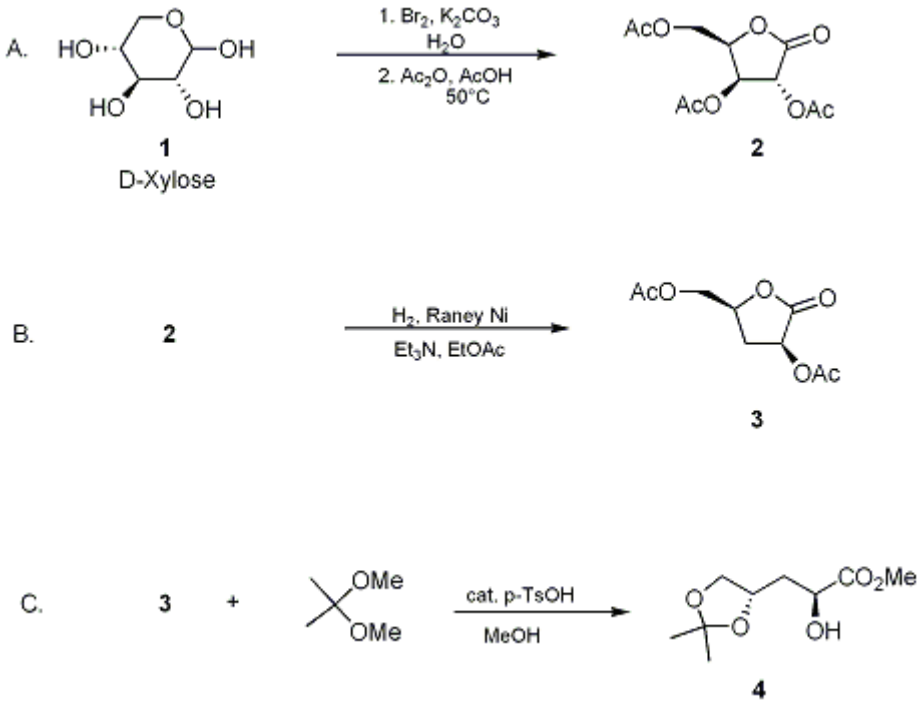
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.072.0048

Organic Syntheses, Coll. Vol. 9, p.717 (1998); Vol. 72, p.48 (1995).

(2S,4S)-2,4,5-TRIHYDROXYPENTANOIC ACID 4,5-ACETONIDE METHYL ESTER

[D-erythro-Pentonic acid, 3-deoxy-4,5-O-(1-methylethylidene)-, methyl ester]



Submitted by Ruen Chu Sun and Masami Okabe[1].
Checked by Timothy C. Gahman and Larry E. Overman.

1. Procedure

A. *Tri-O-acetyl-D-xylono-1,4-lactone* **2**. a) Bromine oxidation. A 250-mL, three-necked, round-bottomed reaction flask equipped with a magnetic stirrer, thermometer, and an addition funnel is charged with 30.0 g (0.20 mol) of D-xylose and 80 mL of water. After the clear aqueous solution is cooled with an ice-water bath, 34.0 g (0.23 mol) of potassium carbonate is added in portions, keeping the temperature below 20°C. After the mixture is cooled to below 5°C, 12 mL (0.22 mol) of bromine is added dropwise over 90 min, keeping the temperature of the reaction mixture below 10°C (Note 1). The orange solution is stirred at that temperature for 30 min, then at room temperature overnight. The reaction is quenched by careful addition of 88% formic acid (2.5 mL) to afford a colorless solution (Note 2). The solution is concentrated at 50°C on a rotary evaporator and 20 mL of acetic acid is added. The mixture is concentrated again at 50°C to remove any residual water (Note 3).

b) Acetylation. The residual white semi-solid is transferred to a 500-mL, three-necked, round-bottomed reaction flask with the aid of warm acetic acid (40 mL). The flask is equipped with a mechanical stirrer, thermometer, and an addition funnel. After the suspension is warmed to 50°C, 180 mL (1.9 mol) of acetic anhydride is added dropwise over 90 min, keeping the temperature between 50–55°C. After the mixture is stirred at that temperature overnight and then cooled to room temperature, 200 mL of water is added. The mixture is extracted with 200 mL of dichloromethane (CH_2Cl_2). The organic layer is washed with 200 mL of water. The combined aqueous layers are back-extracted with 100 mL of CH_2Cl_2. The combined organic layers are placed in a 1-L Erlenmeyer flask. After the solution is cooled with an ice-water bath, 200 mL of 2 N sodium hydroxide is added and the mixture is stirred for 30 min. The aqueous layer is separated and back-extracted with 50 mL of CH_2Cl_2. The combined organic layers are washed with 200 mL of brine, dried over sodium sulfate, and concentrated

under reduced pressure. The residue (54 g) is suspended in 50 mL of ethyl acetate. To the stirred suspension, 70 mL of hexane is added dropwise. After stirring at room temperature for 1 hr, the mixture is cooled with an ice-water bath for 30 min. The precipitate is filtered and washed with a cold 1:2 ethyl acetate/hexane mixture (2 × 60 mL) to yield 39.3–40.7 g (71.6–74.2%) of **2** as light beige crystals, mp 96–97°C (lit.[2] mp 94–95°C) (Note 4).

B. *Di-O-acetyl-3-deoxy-D-arabino-1,4-lactone* **3** (Note 5). A 300-mL, bench-top, high-pressure reactor (Note 6) is charged with 9.83 g (35.8 mmol) of **2**, 1 g of Raney nickel (Note 7), and 65 mL of ethyl acetate. After 7.5 mL (73 mmol) of triethylamine is added, the pressure in the bomb is immediately raised to 1000 psi with hydrogen. After the mixture is *stirred vigorously* (see (Note 6)) at room temperature (15°C) for 3 hr, the temperature is adjusted to 30°C, and the stirring is continued for 24 hr. The pressure is released, and the bomb is flushed with nitrogen. The catalyst is removed by filtration and washed with ethyl acetate (*CAUTION! Fire hazard!* See (Note 7)). The combined filtrate and washes are washed with 75 mL of water. The aqueous layer is back-extracted with 25 mL of ethyl acetate. The combined organic layers are then washed with 75 mL of 1 N hydrochloric acid. The aqueous layer is back-extracted again with 25 mL of ethyl acetate and this extract is combined with the original organic layer. After washing with 75-mL portions of saturated sodium bicarbonate solution, and brine, the organic layer is dried over sodium sulfate and the solvent is removed to give ca. 6.5 g of crude product (Note 8). The crude product is dissolved in 7 mL of warm ethyl acetate. Cooling to room temperature with stirring results in crystallization of **3**. Hexane (13 mL) is added dropwise to the slurry. After the mixture is stirred at room temperature for 1 hr, it is stored in a refrigerator overnight. The precipitate is filtered and washed with a cold 1:4 ethyl acetate/hexane mixture (6 mL) to yield 5.8 g (75%) of **3** as a white solid, mp 68–70°C (lit.[2] mp 69–71°C) (Note 9).

C. *(2S,4S)-2,4,5-Trihydroxypentanoic acid 4,5-acetonide methyl ester* **4**. A 100-mL, round-bottomed reaction flask equipped with a magnetic stirrer, reflux condenser, and an argon inlet tube is charged with 5.4 g (25 mmol) of the diacetate **3**, 0.5 g (2.5 mmol) of p-toluenesulfonic acid monohydrate, and 5 mL of methanol. After the mixture is refluxed for 3 hr and cooled to room temperature, 18 mL (140 mmol) of 2,2-dimethoxypropane is added. After 3 hr of stirring, sodium acetate (powder, 0.41 g, 5 mmol) is added and the mixture is stirred for 20 min to quench the reaction. Ethyl acetate (50 mL) and saturated sodium bicarbonate solution (50 mL) are added to the reaction mixture. The organic layer is removed and the aqueous layer is back-extracted twice with 25-mL portions of ethyl acetate. The combined organic layers are washed with 25 mL of brine, dried over sodium sulfate, and concentrated to afford 5.5 g of a colorless oil. Distillation through a short path distillation apparatus (with no forerun) gives 4.6 g of **4** (90% yield) as a colorless oil, bp 71–78°C (0.1 mm) (Note 10).

GC analysis of the product on a capillary column shows the diastereomeric purity to be 98.9% (Note 11). Enantiomeric integrity is confirmed after conversion to the corresponding p-phenylbenzoate by HPLC analysis on a chiral column (Note 12).

2. Notes

1. Since the reaction is exothermic at the beginning, one must avoid the accumulation of bromine in the reaction mixture.
2. A negative potassium iodide-starch test is obtained.
3. To remove the last traces of water and acetic acid the checkers found it most convenient to place the residue on a high vacuum line overnight.
4. The elemental analysis and the spectral properties of the product **2** are as follows: Anal. Calcd for $C_{11}H_{14}O_8$: C, 48.18; H, 5.15. Found: C, 47.97; H, 5.01. IR (KBr) cm^{-1}: 1805, 1792, 1750; ^1H NMR ($CDCl_3$) δ: 2.13 (s, 3 H), 2.14 (s, 3 H), 2.19 (s, 3 H), 4.27 (dd, 1 H, J = 12.8 and 2.9), 4.39 (dd, 1 H, J = 12.8 and 2.9), 5.00 (dt, 1 H, J = 7.7 and 2.9), 5.62 (t, 1 H, J = 7.8), 5.69 (d, 1 H, J = 7.9).
5. This is a modification of the procedure described by Bock, Lundt, and Pedersen.[2]
6. The checkers used a Parr model 4022 stirred pressure reactor. Rapid stirring is essential to ensure that hydrogenation takes place more rapidly than elimination; otherwise a number of side reactions, e.g., deoxygenation at C(5), occur. Deoxygenation was observed by the checkers if the stirring rate was less than maximum or if the reactor was filled to a higher level, e.g., when the reaction was conducted on

twice the scale described. Using industrial hydrogenation equipment with stirring at 500 rpm, the submitters report that this step can be conducted on a 1-mol scale with identical yield.

7. *Caution! The catalyst is extremely pyrophoric when exposed to the air in a dry condition; it should be kept wet with solvent at all times*. The catalyst (Raney 2800 Grade Active Nickel Catalyst in Water) is purchased from Davison Chemical, and is weighed out while it is wet. The catalyst is washed by suspension in methanol and decanted to remove water. It is further washed with ethyl acetate prior to use. The checkers obtained similar results with Raney nickel (50% slurry in water) catalyst purchased from Aldrich Chemical Company, Inc.

8. The crude diacetate contains a small amount of the epimeric acetate, as detected by NMR (m, 4.88 ppm, $CDCl_3$), that can be produced by isomerization of **3** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (CH_2Cl_2).

9. The elemental analysis and the spectral properties of product **3** are as follows: Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.11, H. 5.59. IR (KBr) cm^{-1}: 1791, 1745; ^1H NMR ($CDCl_3$) δ: 2.07 (dt, 1 H, J = 12.8 and 10.3), 2.12 (s, 3 H), 2.18 (s, 3 H), 2.78 (ddd, 1 H, J = 12.8, 8.8, and 6.0), 4.19 (dd, 1 H, J = 12.5 and 5.8), 4.38 (dd, 1 H, J = 12.5 and 3.1), 4.68 (m, 1 H), 5.51 (dd, 1 H, J = 10.3 and 8.8).

10. The elemental analysis and the spectral properties of product **4** are as follows: Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.83; H, 7.96; $[\alpha]_D$ +3.0° (MeOH, *c* 1.0). IR (neat) cm^{-1}: 3455, 1742, 1378, 1368; ^1H NMR ($CDCl_3$) δ: 1.37 (s, 3 H), 1.43 (s, 3 H), 1.81 (ddd, 1 H, J = 13.9, 9.3, and 4.5), 2.11 (ddd, 1 H, J = 13.9, 8.4, and 3.1), 3.01 (d, 1 H, J = 5.9), 3.60 (dd, 1 H, J = 8.2 and 6.8), 3.80 (s, 3 H), 4.11 (dd, 1 H, J = 8.2 and 6.0), 4.32 (m, 1 H), 4.39 (m, 1 H).

11. The retention time of **4** is 5.1 min, and that of the (2R,4S)-isomer is 4.7 min (on an OV-101, 12.5-m capillary column: 100°C to 140°C at 4°C/min). ^1H NMR ($CDCl_3$) of the (2R,4S)-isomer δ: 1.34 (s, 3 H), 1.40 (s, 3 H), 2.05 (t, 2 H, J = 6.1), 3.15 (d, 1 H, J = 3.8), 3.64 (dd, 1 H, J = 8.2 and 6.7), 3.80 (s, 3 H), 4.10 (dd, 1 H, J = 8.2 and 6.1), 4.31 (m, 1 H), 4.35 (m, 1 H).

12. A small amount of **4** is treated with p-phenylbenzoyl chloride (1.2 equiv) and triethylamine (2 equiv) in CH_2Cl_2 at room temperature overnight. After aqueous workup, the crude product is purified by chromatography on silica gel, eluting with 15% ethyl acetate in hexane. The fractions containing the product are combined and concentrated. The residue is dissolved in 5% 2-methyl-1-propanol/heptane (ca. 1 mg/2 mL). The corresponding diastereomeric mixture is prepared via isomerization of **3** with DBU, and the (2R,4R)-isomer (enantiomer) is prepared from L-xylose. HPLC analysis of the solution on Chiralcel OC 250 mm × 5 mm (purchased from Daicel Chemical), eluting with 5% 2-methyl-1-propanol in heptane (1 mL/min), reveals no detectable amount of the enantiomer [0.24% of the (2R,4S)-isomer was detected]. The retention times of the (2S,4S)-, (2R,4R)-, and (2R,4S)-isomers are 33.2, 45.3, and 54.0 min, respectively. Alternatively a Chiracel OD column can be employed.

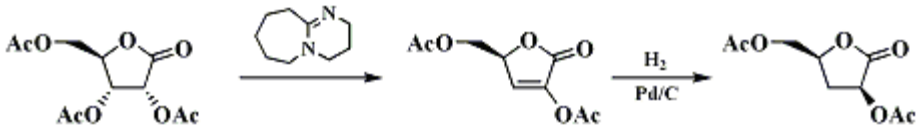
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure for the preparation of (2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl ester is a slight modification of a method previously reported by the submitters.[3] The hydrogenation step is based on the method of Bock, Lundt, and Pedersen,[2] in which the 3-acetoxy group is eliminated and the resulting unsaturated lactone is simultaneously reduced with high stereoselectivity to afford di-O-acetyl-3-deoxy-D-arabino-1,4-lactone. A cleaner reaction was achieved by using Raney-Ni (instead of using palladium on carbon). When platinum catalysts are employed, the corresponding 2,3-dideoxy sugar lactones are obtained.[4]

A two-step sequence to prepare di-O-acetyl-3-deoxy-D-arabino-1,4-lactone from tri-O-acetyl-D-ribono-1,4-lactone has also been reported, but in a low yield of 46% because of the difficulty of controlling the elimination of the 3-acetoxy group, since the 2,3-unsaturated lactone also undergoes further elimination.[5] Furthermore, partial racemization of the enolizable 2,3-unsaturated lactone could occur during treatment with DBU.[6]



The ready availability of the selectively protected 2,4,5-trihydroxypentanoic acid derivatives of defined stereochemistry, such as (2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl ester described here, coupled with Mitsunobu inversion,[3,7] provide chiral synthons with the promise of broad utility.

References and Notes

1. Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ 07110. The authors would like to thank Mr. Ted Carbone and Mr. Louis Portland for their technical assistance in the high-pressure hydrogenation.
2. Bock, K.; Lundt, I.; Pedersen, C. *Acta Chem. Scand., Ser. B* **1981**, *B35*, 155.
3. Okabe, M.; Sun, R.-C.; Zenchoff, G. B. *J. Org. Chem.* **1991**, *56*, 4392.
4. Katsuki, J.; Inanaga, J. *Tetrahedron Lett.* **1991**, *32*, 4963.
5. Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. I* **1984**, 1315.
6. Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161.
7. Mitsunobu, O. *Synthesis* **1981**, 1.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

brine

(2S,4S)-2,4,5-Trihydroxypentanoic acid 4,5-acetonide methyl ester

Di-O-acetyl-3-deoxy-D-arabino-1,4-lactone

D-erythro-Pentonic acid, 3-deoxy-4,5-O-(1-methylethylidene)-, methyl ester

(2S,4S)-2,4,5-trihydroxypentanoic acid 4,5-acetonide methyl

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

acetic anhydride (108-24-7)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

formic acid (64-18-6)

nitrogen (7727-37-9)

platinum (7440-06-4)

nickel,
Raney nickel (7440-02-0)

palladium on carbon (7440-05-3)

dichloromethane (75-09-2)

2-methyl-1-propanol (78-83-1)

heptane (142-82-5)

hexane (110-54-3)

triethylamine (121-44-8)

d-xylose

2,2-dimethoxypropane (77-76-9)

p-toluenesulfonic acid monohydrate (6192-52-5)

1,8-diazabicyclo[5.4.0]undec-7-ene (6674-22-2)

Tri-O-acetyl-D-xylono-1,4-lactone

p-phenylbenzoate

p-phenylbenzoyl chloride (14002-51-8)

L-xylose (5328-37-0)

tri-O-acetyl-D-ribono-1,4-lactone