Organic Syntheses

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.

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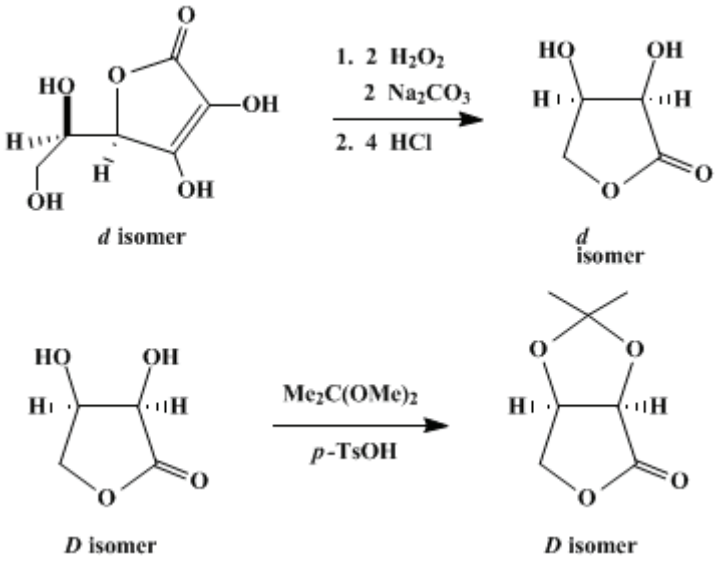
2,3-*O*-ISOPROPYLIDENE-D-ERYTHRONOLACTONE

[Furo[3,4-*d*]-1,3-dioxol-4(3*aH*)-one, dihydro-2,2-dimethyl-(3*aR*-*cis*)-]



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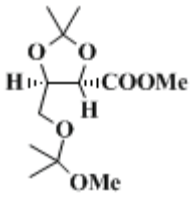
1. Procedure

A 1-L, three-necked, round-bottomed flask fitted with a thermometer, addition funnel, and an air motor-driven paddle stirrer is charged with 35.2 g (0.20 mol) of erythorbic acid (Note 1) and 500 mL of deionized water. The solution is stirred with ice bath cooling (Note 2), and 42.4 g (0.40 mol) of anhydrous, powdered sodium carbonate (Note 3) is added in small portions (Note 4). The resulting yellow solution (Note 5) is stirred with ice-bath cooling while 44 mL (0.45 mmol) of 31.3% by weight aqueous hydrogen peroxide (Note 6) is added dropwise over a 10-min period. The internal temperature rises from 6 to 19°C (Note 7). The solution, containing a few solid particles, is stirred for 5 min with ice bath cooling, during which time the internal temperature continues to rise to 27°C. The flask is now immersed in a water bath that is heated to 42°C. The solution is stirred for 30 min, during which time the internal temperature reaches a maximum of 42°C (Note 8). Norit A (8 g) is added in portions over 10 min to decompose the excess peroxide and the mixture is heated on a steam bath with continued stirring for 30 min, at which point gas evolution has essentially ceased and a negative starch–iodide test is observed. The internal temperature reaches and is kept at 75–78°C. The hot mixture is filtered with suction on a Celite pad into a 2-L, three-necked, round-bottomed flask and the filtercake is washed, in several small portions, with a total of 100 mL of deionized water. The combined filtrate and washes are acidified to pH 1 by the *cautious* (Note 9) addition of 150 mL (0.90 mol) of 6 *N* aqueous hydrochloric acid, in portions, with swirling. The acidic solution is concentrated with a rotary evaporator at 50° C/water aspirator pressure. The residue is dried at 50°C/0.2 mm to give 84.6 g of a pale-yellow solid residue containing D-erythronolactone, oxalic acid, and sodium chloride (Note 10) and (Note 11). To this material is added 175 mL of acetone (Note 13) and the mixture is swirled to loosen the solids caked on the sides of the flask. A 50-g portion of anhydrous, powdered magnesium sulfate (Note 14) is now added and the mixture is stirred by means of an air motor-driven paddle stirrer as 350 mL (2.85 mol) of 2,2-dimethoxypropane (Note 15) is added in one portion. To the stirred mixture is added 0.42 g (0.0022 mol) of *p*-toluenesulfonic acid monohydrate at room temperature. The slurry is blanketed with nitrogen and stirred at room temperature for 18 hr. In a 2-L, three-necked, round-bottomed flask fitted with a thermometer and an air motor-driven paddle stirrer, a mixture of 500 mL of anhydrous ether and 61.3 mL (0.44 mol) of triethylamine (Note 16) is cooled in an ice bath to 5°C. The reaction mixture is

decanted into this solution. The residual solids are rinsed with 60 mL of ether, which is also decanted into the triethylamine solution. After being stirred for a few minutes (Note 17), the mixture is filtered with suction on a 600-mL, coarse, sintered-glass funnel. The solids are washed thoroughly with a total of 300 mL of anhydrous ether by slurrying three times on the funnel with the vacuum turned off; the vacuum is then applied to draw the wash ether through the funnel. The filtrate and washes are combined and concentrated with a rotary evaporator at water aspirator pressure, and the residue is dried at 45°C/0.5 mm to give 34.3 g of a pale-yellow solid (Note 18). This material is dissolved in approximately 150 mL of 1 : 1 hexanes : ethyl acetate and the solution (Note 19) is adsorbed on a column of 200 g of silica gel (Note 20) packed in 1 : 1 hexanes : ethyl acetate. The column is eluted with a total volume of 2 L of 1 : 1 hexanes : ethyl acetate (Note 21). The eluate is concentrated with a rotary evaporator at aspirator pressure and the solid residue is dried under high vacuum to afford 27.3 g of a colorless solid. This material, contained in a 1-L, one-necked, round-bottomed flask, is treated with 150 mL of anhydrous ether and the mixture is refluxed on a steam bath for 5 min to dissolve all the solid. The solution is removed from the steam bath and treated with 225 mL of hexanes. An immediate precipitate results. The mixture is refrigerated (0°C) for 3.5 hr and then filtered with suction. The solid is washed with a total of 100 mL of hexanes, in small portions, and then dried under high vacuum at 20° C. There is obtained 23.6 g (74.7%) of 2,3-*O*-isopropylidene-D-erythronolactone as a white solid, mp 65.5–66°C, $[\alpha]_D^{25}$ −113.8° (*c* 1.11 H_2O) (Note 22),(Note 23),(Note 24),(Note 25).

2. Notes

1. Erythorbic acid is the same compound as D-isoascorbic acid, available from the Aldrich Chemical Company, Inc. This substance is also known as *araboascorbic acid*.
2. The internal temperature is 6°C initially.
3. Sodium carbonate was obtained from the Fisher Scientific Company.
4. Vigorous evolution of carbon dioxide is observed. The internal temperature rises to 8°C.
5. A few particles of undissolved sodium carbonate may remain.
6. Aqueous hydrogen peroxide was obtained from the Fisher Scientific Company. The lot analysis given on the bottle is used to calculate the volume of hydrogen peroxide solution required. Approximately 10% molar excess of peroxide appears to be required to provide a clean product.
7. The oxidation is quite exothermic. Attempts to increase the concentrations of the reactants led to an exotherm that was difficult to control and was complicated by the precipitation of solids, which hampered stirring.
8. A small amount of gas evolution is noted during this period.
9. Evolution of carbon dioxide is vigorous.
10. It is essential that all the water be removed at this point and that a constant weight of approximately 84 g be obtained.
11. If desired, D-erythronolactone can be isolated at this point by treatment of the residue with boiling ethyl acetate. On this scale, the solid is triturated at reflux with 325 mL of ethyl acetate for 5 min. The solution is decanted and the trituration is repeated with 130 mL of ethyl acetate. The combined solutions are cooled to 5°C and filtered. The solid is washed in portions with a total of 400 mL of cold ethyl acetate. After air drying, there is obtained 15.4 g (77.0%) of D-erythronolactone as a white solid, mp 97.5–99.5°C, $[\alpha]_D^{25}$ −72.8° (H_2O, *c* 0.498) (Note 12).
12. The physical properties of D-erythronolactone are as follows: Lit.[2] mp 104–105°C, $[\alpha]_D^{20}$ −73.2° (H_2O, *c* 0.533).
13. Acetone was obtained from Fisher Scientific Company.
14. The drying agent is added to remove any residual moisture and to facilitate the subsequent filtration.
15. 2,2-Dimethoxypropane was obtained from the Aldrich Chemical Company, Inc.
16. Triethylamine was obtained from Eastman Chemical Products, Inc.
17. The mixture is alkaline to pH paper.
18. TLC analysis of the crude product (1 : 3 hexane : ethyl acetate, EM Silica Gel 60 F-254 plates) reveals the desired acetonide lactone to be the major component (R_f 0.6) with one minor, less polar impurity and several minor, more polar impurities. The ^{1}H NMR and IR spectra of a pure sample of the less polar impurity (an oil) were compatible with the following structure: ^{1}H NMR (100 MHz, $CDCl_3$) δ: 1.31 (2 s, 6 H, $(CH_3)_2C$), 1.39 (s, 3 H, C_2-CH_3), 1.59 (s, 3 H, C_2-CH_3), 3.20 (s, 3 H, OCH_3), 3.41 (dd, 1 H, J = 6, 10.5, CH_2O), 3.57 (dd, 1 H, J = 4.5, 10.5, CH_2O), 3.76 (s, 3 H, CO_2CH_3), 4.49 (m, 1 H, H_5), 4.67 (d, 1 H, $J_{4,5}$ = 7, H_4); IR ($CHCl_3$) cm^{-1}: 1760, 1735 (ester C=O).



19. A small amount of insoluble material is present.
20. EM Silica Gel 60, 0.063–0.2 mm was used. The column dimensions are approximately 1.75 in. × 14 in.
21. TLC is utilized to ensure that all of the desired product is eluted from the column. This procedure removes the minor, polar impurities present in the crude product that appear at or near the origin of the TLC plate.
22. This material is homogeneous on TLC analysis; ^{1}H NMR (100 MHz, $CDCl_3$) δ: 1.37 (s, 3 H, C_2-CH_3), 1.46 (s, 3 H, C_2-CH_3), 4.42 (d, 2 H, $J_{6,6a}$ = 2, H_6), 4.75 (d, 1 H, $J_{3a,6a}$ = 6, H_{3a}), 4.89 (dt, 1 H, $J_{3a,6a}$ = 6, $J_{6,6a}$ = 2, H_{6a}); IR ($CHCl_3$) cm^{-1}: 1786 (γ-lactone C=O).
23. The physical properties are as follows: lit.[3] mp 68–68.5°C, $[\alpha]_D^{20}$ −112° (H_2O, *c* 1.5).
24. The reaction sequence has been run on a 176-g (1.0-mol) scale with no loss in yield.
25. The checkers obtained 22.5 g (71.1%) of product as a white solid, mp 68.0–68.5°C, $[\alpha]_D^{20}$ −123.4° (H_2O, *c* 0.96). It is important that crystallization from the ether–hexane mixture be carried out at 0°C. In one run in which crystallization was carried out at 8°C, the checkers obtained only 15.3 g (48.4%) of product, mp 65.5–66.0°C.

3. Discussion

2,3-*O*-Isopropylidene-D-erythronolactone and the corresponding lactol, 2,3-*O*-isopropylidene-D-erythrose, are useful chiral synthons in the total synthesis of certain natural products such as the leukotrienes[4] and pyrrolizidine alkaloids.[5] The lactol is readily available from the lactone, in excellent yield, by reduction with diisobutylaluminum hydride.[4,5,6] 2,3-*O*-Isopropylidene-L-erythrose has been employed as the starting material in an enantioselective synthesis of (+)-15*S*-prostaglandin A_2.[7] Optically pure, selectively protected, polyfunctional C_4-units such as these have great potential in synthesis if readily available, in substantial quantity, from inexpensive members of the pool of chiral starting materials.[8]

D-Erythronolactone and/or its isopropylidene derivative have been prepared starting from L-rhamnose,[9] D-ribose,[10] D-ribonolactone,[3] potassium D-glucuronate,[11] D-glucose,[12] and erythorbic acid,[2] by optical resolution of racemic erythronolactone,[13] and asymmetric total synthesis.[14] 2,3-*O*-Isopropylidene-D-erythrose has been obtained from D-arabinose by a route that does not involve the intermediacy of the lactone.[15] All of these processes suffer from either relatively low overall yields or the requirement of a large number of individual stages. The procedure described here, which is based on a similar oxidative degradation of L-ascorbic acid (vitamin C) to L-threonic acid,[16] is undoubtedly the most expeditious route to the acetonide of D-erythronolactone available. In addition, the starting material, erythorbic acid, is an inexpensive and readily available substance, commonly used as a food preservative. It is pertinent to note that recently L-ascorbic acid has itself found synthetic utility as a precursor to (*R*)-glycerol acetonide, an important C_3 chiral synthon.[17]

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

silica gel

H_2O

hexanes

erythorbic acid

(+)-15S-prostaglandin A_2

(R)-glycerol acetonide

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

Oxalic acid (144-62-7)

nitrogen (7727-37-9)

carbon dioxide (124-38-9)

d-ARABINOSE (28697-53-2)

acetone (67-64-1)

Norit A (7782-42-5)

hydrogen peroxide (7722-84-1)

d-Glucose (492-62-6)

magnesium sulfate (7487-88-9)

hexane (110-54-3)

triethylamine (121-44-8)

diisobutylaluminum hydride (1191-15-7)

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

L-ascorbic acid

ERYTHRONOLACTONE,
D-Erythronolactone

D-isoascorbic acid

D-ribose (50-69-1)

D-ribonolactone (5336-08-3)

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

2,3-O-isopropylidene-D-erythronolactone,
Furo[3,4-d]-1,3-dioxol-4(3aH)-one, dihydro-2,2-dimethyl-(3aR-cis)- (25581-41-3)

2,3-O-isopropylidene-D-erythrose

2,3-O-Isopropylidene-L-erythrose

L-rhamnose

potassium D-glucuronate

L-threonic acid