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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.

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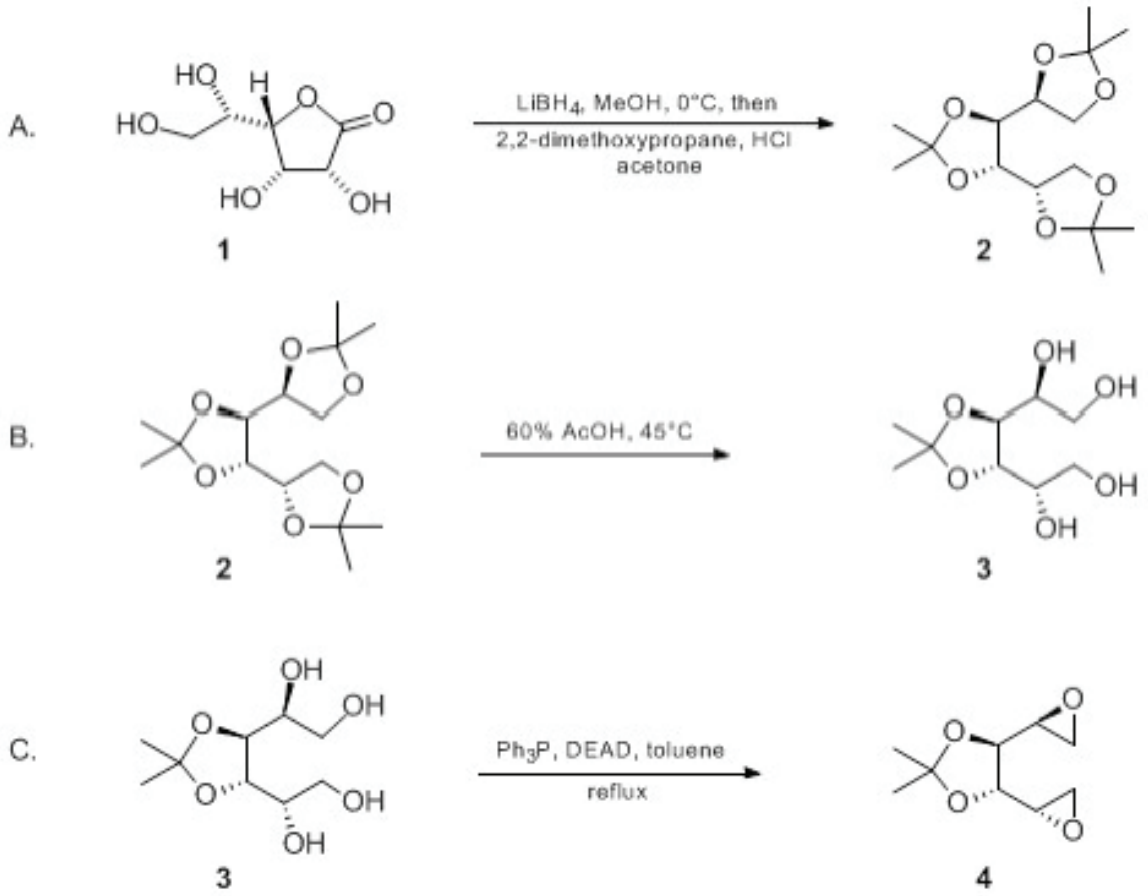
SYNTHESIS OF 1,2:5,6-DIANHYDRO-3,4-O-ISOPROPYLIDENE-L-MANNITOL



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Checked by Peter A. Orahovats, Jason S. Newcom, and William R. Roush.

1. Procedure

A. 1,2:3,4:5,6-Tri-O-isopropylidene-L-mannitol (**2**). A 2-L, two-necked, round-bottomed flask equipped with a powder funnel and a magnetic stirbar is charged with L-mannonic acid γ-lactone (20 g, 0.11 mol) (Note 1) and 300 mL of methanol. The resulting suspension is cooled in an ice bath and lithium borohydride (4.12 g, 0.193 mol) is added in several portions via the powder funnel (Note 2) over 30 min. *Caution! Extensive*

foaming due to hydrogen gas evolution. After the addition is complete, the ice bath is removed and the mixture is stirred for an additional 30 min. The reaction mixture is then recooled in an ice-bath and quenched by the addition of 4N HCl in dioxane (Note 3) until the mixture stops bubbling (1-2 mL). The mixture is then transferred to a 2-L, single-necked, round-bottomed flask and the solvent is concentrated at reduced pressure until a glassy solid is obtained (Note 4). The round-bottomed flask is fitted with a three-way stopcock to which a nitrogen-filled balloon is attached. The solid is then suspended in 100 mL of acetone and 2,2-dimethoxypropane (78 mL, 0.66 mol) (Note 5) is added in one portion. Next, 4N HCl in dioxane (82.5 mL, 0.33 mol) is added slowly with stirring. The reaction mixture is stirred at ambient temperature for 16 h, during which time it becomes bright red in color. If TLC analysis indicates the reaction is not complete (Note 6), then an additional portion of 2,2-dimethoxypropane (13 mL, 0.11 mol) is added and stirring is continued for an additional 6 h. The solvent volume is then reduced by 80% at reduced pressure and the reaction mixture is slowly poured into 400 mL of saturated sodium bicarbonate solution. The product precipitates from solution, and after 10-12 h the solid is collected on a Büchner funnel and air-dried (Note 7). The waxy solid is dissolved in 350 mL of absolute ethanol and cooled to −78 °C to give 23.1-24.3 g (69%) of the product as a white solid. A second crop of crystals is collected (5.7-5.9 g) and combined to give a final yield of 29.0-30.0 g (86-87%) (Notes 8, 9).

B. 3,4-O-Isopropylidene-L-mannitol (**3**). A 2-L, single-necked, round-bottomed flask equipped with a magnetic stirbar is charged with 1,2:3,4:5,6-tri-*O*-isopropylidene-L-mannitol (2) (20 g, 0.066 mol) and 300 mL of 60% acetic acid. The flask is attached to a rotary evaporator (at atmospheric pressure) and the reaction mixture is stirred at 45 °C for ca. 1.5 h. At that point, monitoring by TLC indicates that the reaction has progressed approximately halfway to completion. The pressure in the rotary evaporator is then reduced to 1 mmHg (by attaching it to a vacuum pump in a hood), and the bath temperature is reduced to 40 °C. Under these conditions, full removal of the solvent is achieved in ca. 60 min to yield a highly viscous slurry. This residue is taken up in 200 mL of dichloromethane, stirred for 10 min, and any precipitate is removed by filtration through Celite (Note 11). The filtrate is concentrated at reduced pressure, and the residue is crystallized from 120 mL of diethyl ether and dried at 1 mmHg to give 9.8 g

(67%) of the product as a white solid. The filtrate is concentrated to a volume of 50 mL and a second crop of 1.1 g (7%) is collected by filtration and combined to give a final yield of 10.9 g (74%) (Notes 12, 13).

C. 1,2:5,6-Dianhydro-3,4-O-isopropylidene-L-mannitol (**4**). A 1-L, two-necked, round-bottomed flask equipped with a nitrogen inlet, addition funnel, and a magnetic stirbar is charged with 3,4-*O*-isopropylidene-L-mannitol (14.5 g, 0.065 mol), 160 mL of dry toluene (Note 14), and triphenylphosphine (42.9 g, 0.163 mol). The stirred suspension is cooled under a nitrogen atmosphere in an ice bath while diethyl azodicarboxylate (25.9 mL, 0.163 mol) (Note 15) is added dropwise over 20 min. During the addition the reaction mixture becomes homogeneous. After the addition is complete, the ice bath is replaced with an oil bath, the addition funnel is replaced with a reflux condenser, and the reaction mixture is heated at reflux with continued stirring for 1-2 h (Note 16). The resulting pink reaction mixture is allowed to cool to room temperature, applied directly to a dry silica gel column, and eluted with 30-50% ether/hexane to give 9.4 g (78%) of the desired product as a volatile oil (Note 17).

2. Notes

1. L-Mannonic acid γ-lactone was purchased from Sigma Chemical Company, St. Louis, MO.

2. If the lithium borohydride sticks to the spatula or powder funnel, additional methanol can be used to wash the material into the reaction mixture without affecting the yield. On this reaction scale, an additional 25-50 mL of methanol could be used. Using 2.0M $LiBH_4$ in THF instead of solid $LiBH_4$ complicates the following step resulting in lower yields.

3. 4N HCl in dioxane was purchased from Aldrich Chemical Company, Inc.

4. Caution should be used evaporating the solvent, as the residue tends to foam upon concentration. Concentration is carried out by rotary evaporation and then for 30 min at high vacuum (1 mmHg) while warming with a heat gun to remove all of the methanol.

5. Purchased from Aldrich Chemical Company, Inc. and used as received.

6. The reaction was monitored using TLC with 60% ether/hexane as the eluent. The desired product has $R_f = 0.95$ and the undesired diacetonide has $R_f = 0.25$. Visualization was done using *p*-anisaldehyde.

7. The checkers found that best results were obtained when the trisacetonide was allowed to precipitate from the sodium bicarbonate solution over 10-12 h.

8. The checkers found that it was necessary to cool the crystallization solution to −78 °C to induce crystallization.

9. The physical and spectral properties are as follows: mp 72-74 °C; $[\alpha]_D = -13.4$ ($CHCl_3$, c 1.2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.4 (s, 6 H), 1.45 (s, 6 H), 1.5 (s, 6 H), 4.05 (m, 4 H), 4.15 (m, 2 H), 4.25 (m, 2 H); CIMS (NH_3) *m/z*: 303 ($M+H^+$, 100%).

10. The reaction was monitored using TLC with 5% MeOH/CH_2C_2 as the eluent. The desired monoacetonide 3 has a $R_f = 0.25$. It was desirable to run the reaction to the point where most of the higher R_f components were consumed. This will produce some unwanted L-mannitol that can be filtered off as described above.

11. The L-mannitol recovered in this manner could be recycled if desired.

12. The checkers found that further hydrolysis of mannitol diacetonide can occur during the removal of solvent, and that removal of all acetic acid from the product was problematic. Residual acetic acid in the product complicates the next step. The procedure described reduces these problems.

13. The physical and spectral properties are as follows: mp 83-86 °C; $[\alpha]_D = -26.4$ (H_2O, c 3); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.25 (s, 6 H), 3.35 (m, 2 H), 3.5 (m, 4 H), 3.85 (m, 2 H), 4.45 (t, *J* = 5.9 Hz, 2 H), 5.1 (d, *J* = 4.4 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 29.1, 64.8, 74.7, 80.9, 110.1; CIMS (NH_3) *m/z*: 240 ($M+NH_4^+$, 100%); Anal. calcd. for $C_9H_{14}O_4$: C, 48.64; H, 8.16. Found: C, 48.54; H, 8.16.

14. The toluene used was from a freshly opened bottle obtained from EM Science.

15. Neat DEAD was unavailable from commercial sources at the time the procedure was being checked. Therefore, the checkers used a commercially available 40% solution of DEAD in toluene with results comparable to that described in the original procedure.

16. The reaction was initially monitored using 10% MeOH/CH_2Cl_2 to follow the disappearance of tetraol **3**. The appearance of the diepoxide **4** is monitored using 50% ether/hexane.

17. The physical and spectral properties are as follows: $[\alpha]_D$ = + 0.38 ($CHCl_3$, c 0.8); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 6 H), 3.77 (dd, 2 H, *J* = 2.9, 1.4), 2.65 (dd, 2 H, *J* = 5.2, 3.0), 2.80 (t, 2 H, *J* = 9.5), 3.10 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.6, 27.9, 46.3, 52.6, 79.5, 111.5; CIMS (NH_3 m/z: 204 ($M+NH_4^+$, 100%); Anal calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.78; H, 7.52.

3. Discussion

Preparing the title compound from L-mannitol using methodology developed for the D-isomer[2] would be prohibitively expensive. Our approach uses a much less expensive, commercially available starting material. Current synthetic approaches to the D-isomer involve selective conversion of the two primary hydroxyl groups of 3,4-*O*-isopropylidene-D-mannitol into good leaving groups followed by base treatment to facilitate epoxide formation. We found prolonged exposure of the epoxide to base reduces the reaction's overall yield. To overcome this liability we used a one-pot conversion of 3,4-*O*-isopropylidene-L-mannitol to the title compound using Mitsunobu-based technology. This approach was found to be more reproducible and consistently gave yields in the 60-80% range.

The title compound is a key C_6 building block. Several labs have prepared novel α-amino acids, biological probes and other interesting compounds using the D-diepoxide as a key intermediate.[3] An efficient route to the L-enantiomer provides a pathway to compounds with the opposite configuration, one not readily available from commercial sources, and a valuable probe of stereochemistry in biological systems and reaction mechanism.

1. Astrazeneca, Inc., B312, CNS Discovery, 1800 Concord Pike, Wilmington, DE, USA 19850-5437

2. Johnson and Johnson Pharmaceutical Research and Development, LLC, Welsh and McKean Roads, P.O. Box 776, Spring House, PA 19477-0776.

3. (a) Wiggins, L.F. *J. Chem. Soc.* **1946**, 384. (b) Le Merrer, Y.; Dureault, A.; Greck, C.; Micas-Languin, D.; Gravier, C.; Depezay, J. *Heterocycles*, **1987**, *25*, 541. (c) Ghosh, A.K.; McKee, S.P.; Thompson, W.J. *Tetrahedron Lett*. **1991**, *32(41)*, 5729.

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

1,2:3,4:5,6-Tri-O-isopropylidene-L-mannitol: L-Mannitol,1,2:3,4:5,6-tris-O-(1-methylethylidene)-; (153059-35-9).

L-Mannonic acid γ-lactone: L-Mannonic acid, γ-lactone; (22430-23-5).

Lithium borohydride: Borate(−1), tetrahydro-, lithium; (16949-15-8).

2,2-Dimethoxypropane: Propane, 2,2-dimethoxy-; (77-76-9).

3,4-O-Isopropylidene-L-mannitol: L-Mannitol, 3,4-O-(1-methylethylidene)-; (153059-36-0)

1,2:5,6-Dianhydro- 3,4-O-isopropylidene-L-mannitol: L-Mannitol,1,2:5,6-dianhydro- 3,4-O-(1-methylethylidene)-; (153059-37-1).

Triphenylphosphine: Phosphine, triphenyl-; (603-35-0).

Diethyl azodicarboxylate: Azodicarboxylic acid diethyl ester; (1972-58-3)

01271

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
Mercury-300 "Zn"

PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 3.333 sec
Width 4500.5 Hz
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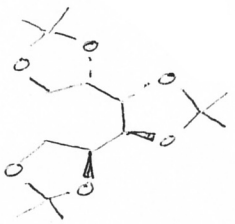
OBSERVE H1, 300.0732273 MHz
DATA PROCESSING
Line broadening 0.2 Hz
FT size 32768
Total time 0 min, 55 sec



0127FCCa

Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature
INOVA-400 "Zr"

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Acq. time 2.666 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.9649450 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 42 sec