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for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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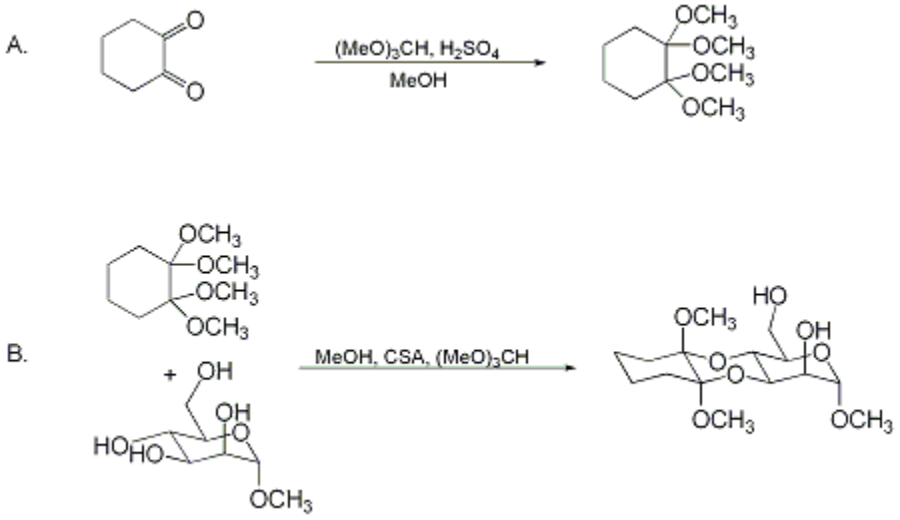
(1'S,2'S)-METHYL-3O,4O-(1',2'-DIMETHOXYCYCLOHEXANE-1',2'-DIYL)-α-D-MANNOPYRANOSIDE

[α-D-Mannopyranoside, methyl 3,4-O-(1,2-dimethoxy- 1,2-cyclohexanediyl)-, [3[S (S)]]-]



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Checked by Karl A. Scheidt and William R. Roush.

1. Procedure

A. 1,1,2,2-Tetramethoxycyclohexane (Note 1). A 500-mL, two-necked flask equipped with a stirrer bead, condenser and heating mantle is flushed with dry argon and then charged with 44.8 g of 1,2-cyclohexanedione (0.400 mol), 100 mL of dry methanol (MeOH) and 160 mL of trimethyl orthoformate (1.46 mol) (Note 2). Stirring is begun and approximately 32 drops of concd sulfuric acid are added to the solution. The resultant black solution is heated under argon at reflux for 5 hr. The heating mantle is removed and the solution is cooled to room temperature. Sodium hydrogen carbonate is carefully added to neutralize the solution (approx 4 g required). Methanol, methyl formate and trimethyl orthoformate are removed by distillation at ambient temperature through a straight path distillation apparatus. The residue is then distilled under reduced pressure to yield 59.5 g of 1,1,2,2-tetramethoxycyclohexane as a colorless liquid (73%) (Note 3), (Note 4).

B. (1'S,2'S)-Methyl-3O,4O-(1',2'-dimethoxycyclohexane-1'2'-diyl)-α-D-mannopyranoside . A 500-mL, two-necked flask equipped with a stirrer bead, condenser and heating mantle is flushed with dry argon and charged with 30 g of methyl-α-D-mannopyranoside (0.15 mol), 300 mL of dry MeOH, 59.5 g of 1,1,2,2-tetramethoxycyclohexane (0.29 mol) and 16.1 g of trimethyl orthoformate (0.15 mol). Camphorsulfonic acid (CSA), 3.48 g, (0.015 mol) is added and the resultant black solution is heated under argon at reflux for 16 hr. The heating mantle is removed and the solution is cooled to room temperature. Sodium bicarbonate is carefully added to neutralize the solution (approx 5 g required) (Note 5). The mixture is transferred to a 1-L, round-bottomed flask, and the solvent is removed under reduced pressure on a rotary evaporator (Note 6). The crude material (Note 7) is purified by column chromatography on silica gel (1.5 Kg of silica gel using a 10-15 cm diameter column; gradient elution 0-5% ethanol in ether) followed by crystallization from ethyl acetate-hexane (Note 8) to yield 20.8-23.2 g of (1'S,2'S)-methyl-3O,4O-(1',2'-dimethoxycyclohexane-1',2'-diyl)-α-D-mannopyranoside as colorless cubes (41-46%) (Note 9).

2. Notes

1. All materials are commercially available from Aldrich Chemical Company, Inc., Acros Organics or Avocado Research Chemicals, Ltd. (Shore Road, Port of Heysham Industrial Park, Heysham, Lancashire, LA3 2XY, England). It is recommended that MeOH be distilled from calcium hydride prior to use.
2. Trimethyl orthoformate acts as a drying agent in both Step A and B. It is therefore advantageous to use an excess of this drying agent to force the reaction to completion.
3. Physical data for purified material are as follows: bp 76°C at 0.8 mm Hg. ^{1}H NMR ($CDCl_3$) δ: 1.31-1.48 (m, 4 H), 1.60-1.75 (m, 4 H), 3.32 (s, 12 H) ; ^{13}C NMR ($CDCl_3$) δ: 21.67, 30.61, 49.25, 102.07 ; IR (neat) cm^{-1}: 2950, 2880, 2840, 1520, 1500, 1480, 1350, 1340, 1200, 1150, 1100, 1050, 960, 870 ; HRMS calcd for $C_{10}H_{20}O_4$ m/z 204.1361, found 204.1363 . Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.60; H, 9.68.
4. The checkers obtained 59.7-64.1 g (73-78%) of 1,1,2,2-tetramethoxycyclohexane.
5. This neutralization step should be performed for at least 20 min. During this period, the reaction turns from an indigo to a light brown color.
6. Concentration of the crude product should be stopped when solids begin to form. The checkers observed that it was difficult to dissolve the crystalline crude product in ether to load the column for chromatographic purification.
7. The crude product consists mainly of the desired product; protection of the cis-2,3-diol occurs only to a minor extent. The major side product from the reaction is the 1,3-dioxolane, which can be slowly converted to the required product under thermodynamic equilibrating conditions; i.e., further treatment of the dioxolane with boiling methanol and a trace of CSA for 4 days produced the required product in 35% yield together with recovery of the dioxolane in 16% yield.
8. The chromatographed product is dissolved in 160 mL of boiling ethyl acetate and then diluted with 150 mL of hexanes. The solution was allowed to cool to room temperature, and then placed in a −20°C freezer overnight. The crystalline product was collected by filtration and washed with cold hexanes.
9. Physical data for purified material are as follows: mp 173°C (EtOAc-hexane); $[\alpha]_D^{25}$ +170° ($CHCl_3$, *c* 0.95); ^{1}H NMR ($CDCl_3$) δ: 1.29-1.43 (m, 2 H), 1.45-1.55 (m, 2 H), 1.62-1.82 (m, 4 H), 2.25 (br, t, 1 H, J = 5.8), 2.89 (s, 1 H), 3.20 (s, 3 H), 3.21 (s, 3 H), 3.35 (s, 3 H), 3.72-3.86 (m, 3 H), 3.92 (br, s, 1 H), 4.14 (dd, 1 H, J = 10.6, 2.9), 4.25 (dd, 1 H, J = 2 × 10.0), 4.72 (d, 1 H, J = 0.9) ; ^{13}C NMR ($CDCl_3$) δ: 21.27 (2 x), 26.88, 26.91, 46.71, 46.82, 54.77, 61.18, 63.64, 68.77, 69.88, 70.73, 98.64, 99.10, 101.59 ; IR (KBr) cm^{-1}: 3500-3400, 3000, 3050, 2820, 1400, 1350, 1340, 1200-1000, 900, 850, 820, 800, 790, 750, 700 ; HRMS calcd for $C_{15}H_{26}O_8$, m/z 334.1628, found 334.1639 . Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.88; H, 7.84. Found: C, 53.77; H, 7.73. The submitters reported mp 168°C (ether); $[\alpha]_D^{25}$ +191° ($CHCl_3$, *c* 0.94).

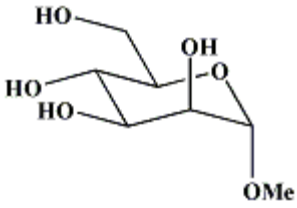
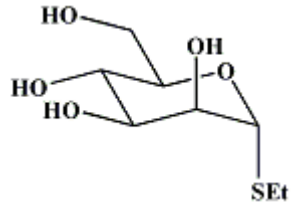
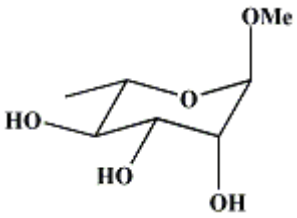
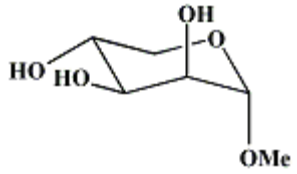
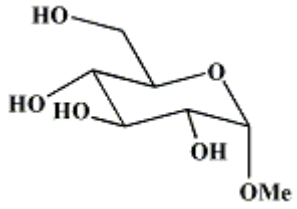
Waste Disposal Information

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

3. Discussion

Until recently, the protection of the trans-hydroxyl groups of sugars has been an inefficient process.[2] This protection has now been simplified by the introduction of the dispiroketal protecting group,[3] and the cyclohexane diacetal (CDA) protecting group.[4] As shown in this report, the CDA protecting group is easily introduced, and the present procedure allows facile protection of the trans-hydroxyl groups of a range of sugars.

SUGAR	*3,4-protected2,3-protected*

	45%	11%
	53%	10%
	74%	8%
	45%	11%
	30%	50%

The ease of selective protection can be explained in terms of maximum anomeric stabilization such that both anomeric methoxy groups of the product are oriented in the axial position with respect to the central dioxane ring. All four sterically demanding alkyl substituents are then placed in the favored equatorial positions. The poor selectivity for the protection of glucose results from the existence of ***two*** pairs of trans-hydroxyl groups in this sugar.

The CDA protecting group has been shown to withstand common sugar derivatization reactions,[4] and is easily removed under acidic conditions.[4] Further, it has proved possible to tune the reactivity of sugars via the introduction of the CDA protecting group, and this in turn has allowed concise syntheses of complex oligosaccharides.[5] [6] [7] [8] [9]

Further research within in our laboratory has illustrated that certain substrates bearing trans-hydroxyl groups can be directly protected using cyclic and acyclic diones, thus alleviating the requirement for prior formation of the tetramethoxydiacetals.[10] [11] For example, butane-2,3-dione has proved particularly useful for the preparation of butane diacetal (BDA) derivatives, which serve as useful alternatives to cyclohexane diacetal (CDA) derivatives.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 552

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

(1'S,2'S)-Methyl-3O,4O-(1',2'-dimethoxycyclohexane-1',2'-diyl)-α-D-mannopyranoside:
α-D-Mannopyranoside, methyl 3,4-O-(1,2-dimethoxy-1,2-cyclohexanediyl)-, [3[S(S)]]- (13); (163125-35-7)

1,1,2,2-Tetramethoxycyclohexane:
Cyclohexane, 1,1,2,2-tetramethoxy- (13);(163125-34-6)

1,2-Cyclohexanedione (8,9); (765-87-7)

Trimethyl orthoformate:
Orthoformic acid, trimethyl ester (8);
Methane, trimethoxy- (9); (149-73-5)

Methyl formate:
Formic acid, methyl ester (8,9); (107-31-3)

Camphorsulfonic acid monohydrate (CSA):
Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (±)- (9); (5872-08-2)