



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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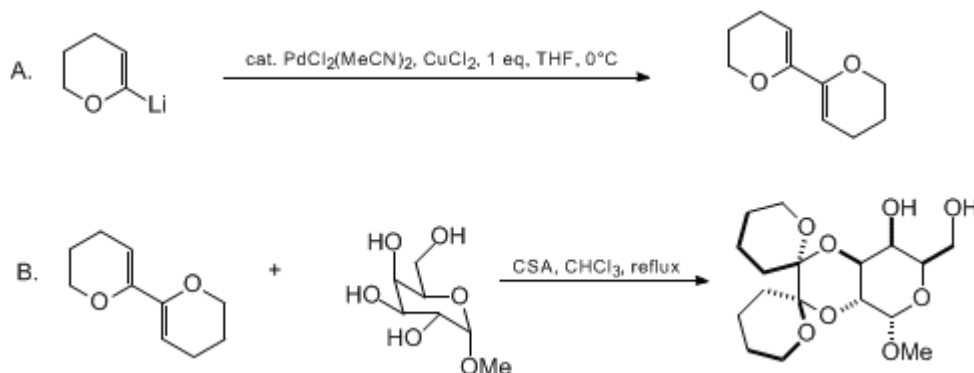
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Organic Syntheses, Coll. Vol. 10, p.552 (2004); Vol. 77, p.212 (2000).

METHYL 2,3-O-(6,6'-OCTAHYDRO-6,6'-BI-2H-PYRAN-2,2'-DIYL)- α -D-GALACTOPYRANOSIDE

[α -D-Galactopyranoside, methyl, 2,3-O-(octahydro[2,2'-bi-2H-pyran]-2,2'-diyl-, [2(2R,2'R)-]]



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Checked by Laurent Ducry, Leïla Abrous, and Amos B. Smith, III.

1. Procedure

Caution! tert-Butyllithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009].

A. 6,6'-Bi(3,4-dihydro-2H-pyran) (Bis-DHP) (Note 1). A 500-mL, two-necked flask (Flask A) equipped with a magnetic stirrer is flushed with dry *argon* and then charged with 30 mL of dry distilled 3,4-dihydro-2H-pyran (329 mmol) and 60 mL of dry tetrahydrofuran (THF) (Note 2). Stirring is begun and the solution is cooled to -78°C by means of external cooling. An inert *argon* atmosphere is maintained throughout the reaction. *tert*-Butyllithium in pentanes (200 mL of a 1.7 M solution, 340 mmol) is added dropwise under *argon* and the resultant cloudy mixture is stirred at 0°C (ice/water bath) for 1 hr. Meanwhile, another 1-L flask (Flask B) equipped with a magnetic stirrer is flushed with dry *argon* (an inert *argon* atmosphere is again maintained throughout the reaction) and then charged with 2.0 g of palladium(II) chloride bis(acetonitrile) complex (2.2 mol%, 7.4 mmol), 46.3 g of copper(II) chloride (344 mmol) and 300 mL of dry THF. Stirring is initiated and the slurry is cooled to 0°C by means of external cooling. When the slurry has reached 0°C , the clear pale yellow solution from Flask A is added via cannula to cooled Flask B at 0°C . The orange brown slurry becomes black and the resultant mixture is stirred at 0°C for 1 hr. An aqueous saturated ammonium chloride / concentrated ammonium hydroxide solution (4:1, pH 10) is added to quench the reaction and the solution is extracted with ether (3×200 mL). The combined ether extracts are dried over magnesium sulfate (MgSO_4), filtered and concentrated under reduced pressure to give a yellow solid. This is purified by column chromatography on silica gel (Merck 9385, 6 cm \times 20 cm) eluting with 1% triethylamine / 5% ether / 94% petroleum ether to yield 15.0 g of 6,6'-bi(3,4-dihydro-2H-pyran) (Bis-DHP) as a white crystalline solid (55%) (Note 3) and (Note 4).

B. Methyl 2,3-O-(6,6'-octahydro-6,6'-bi-2H-pyran-2,2'-diyl)- α -D-galactopyranoside. A 100-mL, two-necked flask equipped with a magnetic stirrer, condenser and heating mantle is flushed with dry *argon* and then charged with 2.8 g of methyl α -D-galactopyranoside (14.4 mmol), 50 mL of dry chloroform and 5.0 g of Bis-DHP (30.1 mmol) (Note 5) and (Note 6). The solution is maintained under an *argon* atmosphere and 0.14 g of DL-camphorsulfonic acid (0.6 mmol) is added. The mixture is heated under reflux for 1.5 hr. After this time, 4.6 mL of anhydrous ethylene glycol (83.3 mmol) (Note 7) is added and heating is continued for a further 0.5 hr. The heating mantle is removed and the solution cooled to room temperature. The resultant solution is diluted with 100 mL of dichloromethane, made basic by the addition of potassium carbonate (approximately 0.5 g required), filtered and concentrated under reduced pressure. The crude material is purified by column chromatography on silica gel (Merck 9385, 6 cm \times 30 cm) eluting with 80-100% ethyl acetate/petroleum ether to yield 3.3 g of methyl 2,3-O-(6,6'-octahydro-6,6'-bi-2H-pyran-2,2'-diyl)- α -D-galactopyranoside

as an off-white foam (64%) (Note 8).

2. Notes

1. 6,6'-Bi(3,4-dihydro-2H-pyran), 98% (Bis-DHP) is commercially available from Aldrich Chemical Company, Inc., P.O. Box 355, Milwaukee, WI 53201, USA. Catalog # 34,973-9.

2. Because of the sensitivity of the reagents toward moisture, both procedures A and B should be carried out in oven-dried glassware under dry and inert conditions.

3. Pure bis(dihydropyran) is a white and relatively stable crystalline solid. As would be expected for an enol ether, it is sensitive to hydrolysis and is best stored for a long time under an inert atmosphere at -10°C .

4. Physical data for purified material are as follows: mp $49-50^{\circ}\text{C}$ (petroleum ether); $^1\text{H NMR}$ (270 MHz, CDCl_3) δ : 1.78-1.87 (m, 4 H), 2.08-2.14 (m, 4 H), 4.01-4.05 (m, 4 H), 5.16 (t, 2 H, $J = 3.8$); $^{13}\text{C NMR}$ (68 MHz, CDCl_3) δ : 20.2, 22.4, 66.2, 96.8, 147.6; m/z (EI) 166 (M^+), 138, 111, 83, 55. Anal. calcd for $\text{C}_{10}\text{H}_{14}\text{O}_2$: C, 72.26; H, 8.49. Found C, 72.24; H, 8.56.

5. The checkers have found that the chloroform must be distilled prior to use to obtain an optimum yield.

6. Although toluene can be used for these reactions, boiling chloroform is preferred. The use of more polar solvents such as dimethylformamide (DMF) or acetonitrile fail to give any products, presumably because of the competitive decomposition of the bis-(dihydropyran). When the solubility of the starting material in boiling chloroform is poor, reaction yields can be improved by applying ultrasound.

7. By-products from this reaction include protection of the primary hydroxyl group and incorporation of only one Bis-DHP ring. These products are less stable than the desired product and may be deprotected on reaction with ethylene glycol making purification of the reaction mixture much more efficient.

8. Physical data for dispiroketal (dispoke) protected material are as follows: $[\alpha]_{\text{D}}^{23} -19.0$ (c 1.05 in CHCl_3); $^1\text{H NMR}$ (270 MHz, CDCl_3) δ : 1.42-1.62 (m, 8 H), 1.65-1.85 (m, 4 H), 2.59 (br s, 1 H), 2.84 (br s, 1 H), 3.42 (s, 3 H), 3.55-3.75 (m, 4 H), 3.80-4.00 (m, 3 H), 4.05-4.15 (m, 2 H), 4.23 (dd, 1 H, $J = 10.3, 3.4$), 4.85 (d, 1 H, $J = 3.4$); m/z (EI) 360 (M^+), 200, 167 ($\text{C}_{10}\text{H}_{15}\text{O}_2^+$), 149, 111, 100. Anal. calcd for $\text{C}_{17}\text{H}_{28}\text{O}_8$: C, 56.65; H, 7.83. Found C, 56.42; H, 8.01.

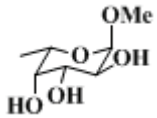
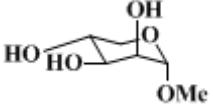
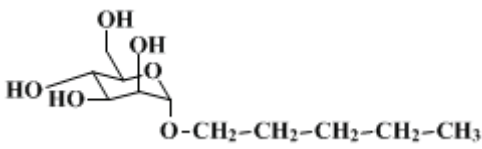
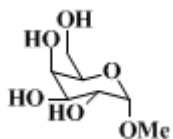
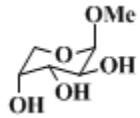
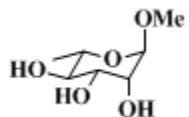
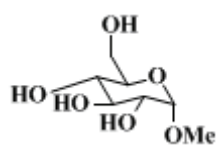
Waste Disposal Information

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

3. Discussion

Until recently, the protection of the trans-hydroxyl groups of sugars has been an inefficient process.³ This protection has now been simplified by the introduction of the dispiroketal (dispoke) group^{4,5} and the cyclohexane diacetal (CDA) protecting group.⁶ Regiocontrol, in the form of protection of the diequatorial vicinal diol pairs over axial-equatorial or diaxial systems occurs as a result of the stabilizing influence of multiple anomeric effects. Thus a general method for the protection of the diequatorial vicinal diols in a wide range of monosaccharides has been developed (Table 1). In only a few cases when steric interactions are of a lesser magnitude is some cis-diol protection noticed. O-Methyl, S-ethyl or O-pentenyl groups are tolerated at the C-1 carbon of the sugar with the more lipophilic groups enhancing the yields of dispiroketal protection. This reflects the greater solubility of these derivatives in chloroform.

TABLE I
PROTECTION FOR DIEQUATORIAL VICINAL DIOLS

Sugar	3,4-Protection	2,3-Protection
	0%	76%
	62%	0%
	45%	0%
	0%	64%
	40%	58%
	47%	32%
	26%	42%

For protection of glucose derivatives, which possess two sets of 1,2-trans diequatorial diols, protection is best achieved by way of **chiral** bis(dihydropyrans).⁷ In this way, complete regioselectivity can be achieved as a result of chirality "matching" of the C-2, C-3 diol pairs with that of the bis(dihydropyran).

The dispiroketal group is stable toward a variety of reaction conditions, including mild acid, and is compatible with glycosidic coupling reactions regardless of whether it is present on the donor or acceptor moiety.⁵ When applied to sugar chemistry, the dispiro moiety can be employed as both a protecting group and a handle for tuning the reactivity of the sugar. This has allowed the concise syntheses of complex oligosaccharides to be achieved.⁸ Finally, the facile cleavage of the dispiroketal unit can be accomplished with 95% **trifluoroacetic acid** at room temperature.⁵

References and Notes

1. Present addresses: S. V. Ley: University Chemical Laboratories, Lensfield Road, Cambridge, CB2 1EW, UK;
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Appendix

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

Methyl 2,3-O-(6,6'-octahydro-6,6'-bi-2H-pyran-2,2'-diyl)- α -D-galactopyranoside:

α -D-Galactopyranoside, methyl, 2,3-O-(octahydro[2,2'-bi-2H-pyran]-2,2'-diyl-, [2(2R,2'R)]- (13); (144102-32-9)

6,6'-Bi(3,4-dihydro-2H-pyran) [Bis-DHP]:

6,6'-Bi-2H-pyran, 3,3',4,4'-tetrahydro- (12); (109669-49-0)

3,4-Dihydro-2H-pyran:

2H-Pyran, 3,4-dihydro- (8,9); (110-87-2)

tert-Butyllithium:

Lithium, tert-butyl- (8);

Lithium, (1,1-dimethylethyl)- (9); (594-19-4)

Palladium(II) chloride bisacetonitrile: ALDRICH:

Bis(acetonitrile)dichloropalladium(II):

Palladium, bis(acetonitrile)dichloro- (8,9); (14592-56-4)

Copper(II) chloride:

Copper chloride (8,9); (7447-39-4)

Methyl α -D-galactopyranoside:

α -D-Galactopyranoside, methyl (8,9); (3396-99-4)

(\pm)-Camphorsulfonic acid:

Boranesulfonic acid, 2-oxo-, (\pm)- (8);

Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (\pm)- (9); (5872-08-2)