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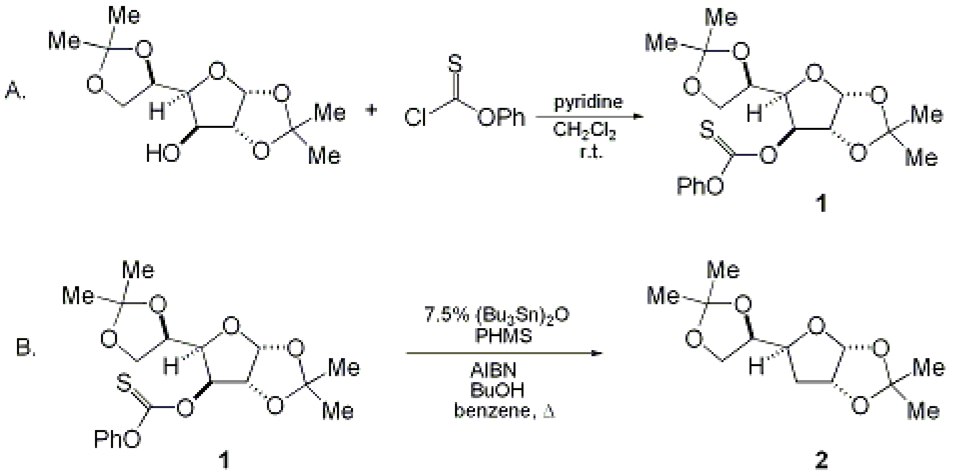
# TRIBUTYLSTANNANE ($Bu_3SnH$)-CATALYZED BARTON-McCOMBIE DEOXYGENATION OF ALCOHOLS: 3-DEOXY-1,2:5,6-BIS-O-(1-METHYLETHYLIDENE)-α-D-RIBO-HEXOFURANOSE

### [ α-D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)- ]



Submitted by Jordi Tormo and Gregory C. Fu[1] .
Checked by Jan W. Thuring and Andrew B. Holmes.

## 1. Procedure

*A. 1,2:5,6-Bis-O-(1-methylethylidene)-O-phenyl carbonothioate-α-D-glucofuranose* (**1**). All glassware is oven-dried. A 250-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar and an argon inlet. Under a gentle flow of argon, the flask is charged with 100 mL of anhydrous dichloromethane ($CH_2Cl_2$) (Note 1) and 12.6 g (48.2 mmol) of 1,2:5,6-di-O-isopropylidene-D-glucose (Note 2). The flask is immersed in an ice bath, stirring is started, and 7.34 mL (53.1 mmol) of phenyl chlorothionoformate (Note 3) and 4.63 mL (57.9 mmol) of pyridine (Note 4) are added by syringe. After 30 min, the ice bath is removed, and the resulting mixture is stirred at room temperature for 14 hr. Then, in order to destroy the excess phenyl chlorothionoformate , 5 mL of anhydrous methanol (MeOH) (Note 5) is added via syringe, and the mixture is stirred at room temperature for 15 min. The resulting solution is washed with 100 mL of aqueous hydrochloric acid (HCl) (1 N) and 100 mL of brine, dried over anhydrous sodium sulfate ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude product (20.5 g; yellow oil) is triturated by the addition of hexane (50 mL), scratched with a spatula and stirred for 30 min at 0°C. The cream-colored solid is collected by filtration of the cold suspension and washed with a minimal amount (5-10 mL) of hexane to give 15.2 g of **1**. Recrystallization from hexane (50 mL) affords the product as white crystals (13.9 g; 74%). The mother liquors are combined and evaporated to dryness to give a residue that is recrystallized from hexane (10 mL) to give a second crop of **1** (1.50 g; 8%) (Notes 6, 7 and 8).

*B. 3-Deoxy-1,2:5,6-bis-O-(1-methylethylidene)-α-D-ribo-hexofuranose* (**2**). All glassware is oven-dried. A 250-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar and a reflux condenser with an argon inlet. Under a gentle flow of argon , the flask is charged with 15 mL of anhydrous benzene (Note 9) and 13.0 g (32.7 mmol) of **1** . To this mixture are added via cannula a solution of 0.620 mL (1.21 mmol) of bis(tributyltin) oxide [$(Bu_3Sn)_2O$] (Note 10), 0.800 g (4.90 mmol) of 2,2'-azobis(isobutyronitrile) (AIBN) (Note 11), 9.81 g (164 mmol) of poly(methylhydrosiloxane) (PMHS) (Note 12), and 16.4 mL (180 mmol) of 1-butanol (Note 13) in 20 mL of anhydrous benzene . The resulting mixture is heated at reflux for 3 hr, after which time a solution of 0.620 mL (1.21 mmol) of $(Bu_3Sn)_2O$ and 0.800 g (4.90 mmol) of AIBN in 9 mL of anhydrous benzene is added via cannula. The reaction mixture is heated at reflux for an additional 3 hr. The solution is allowed to cool to room temperature, and then transferred to a 1-L, one-necked, round-bottomed flask. Benzene and excess 1-butanol are removed under water pump vacuum, and the resulting residue is redissolved in 100 mL of THF (Note 14) . To this solution is added SLOWLY (Note 15) 400 mL of aqueous sodium hydroxide (NaOH) (2 N). The resulting mixture is stirred at room temperature for 15 hr. The layers are separated, and the aqueous layer is extracted twice with 100 mL of diethyl ether . The combined organic layers are washed with 100 mL of aqueous HCl (1 N) and 100 mL of brine, dried over anhydrous $Na_2SO_4$ , filtered, and concentrated under reduced pressure. The resulting residue is purified by chromatography (Note 16) to give 6.2-6.4 g (76-80%) of **2** as a pale-yellow oil (Notes 17 and 18).

## 2. Notes

1. Laboratory grade dichloromethane was first distilled and then was further purified and dried by distillation from calcium hydride . The submitters used solvent supplied by EM Science.
2. 1,2:5,6-Di-O-isopropylidene-D-glucose (diacetone-D-glucose; Aldrich Chemical Company, Inc., 98%) was used without purification.
3. Phenyl chlorothionoformate (Aldrich Chemical Company, Inc., 99%) was used without purification.
4. Pyridine (Aldrich Chemical Company, Inc.) was purified by distillation from calcium hydride .
5. Methanol was used as supplied by Merck & Company, Inc. or Mallinckrodt Inc.
6. Both crops were pure as judged by elemental analysis. The combined yield ranged from 15.4-17.3 g (82-90%). The checkers found the recrystallization procedure to be more convenient (albeit in slightly lower yield) than isolation by chromatography. The residue can alternatively be purified by flash column chromatography with 30 g of silica (Merck 9385 Kieselgel 60, 230-400 ASTM) per g of residue, eluting with a gradient of 0 → 50% EtOAc/hexane to afford 18.0 g (94%; the checkers obtained 91% on half scale) of **1** as a colorless solid, mp 108-110°C (Notes 7 and 8).
7. TLC analyses ($R_f = 0.47$, in EtOAc/hexane 7:3; the submitters observed $R_f = 0.49$ in EtOAc/hexane 4:1) were performed on 0.25-mm Merck 60 $F_{254}$ silica gel plates (the submitters used 0.25-mm silica gel 60 plates supplied by EM Reagents) that were stained with a solution of phosphomolybdic acid in 95% ethanol .
8. Compound **1** ($[\alpha]_D{}^{18}$ −44.9° ($CHCl_3$, *c* 0.6), lit.[2] $[\alpha]_D{}^{18}$ −43° ($CHCl_3$)) has the following spectral data: $^1H$ NMR (250 MHz, $CDCl_3$) δ: 1.35 (s, 3 H), 1.38 (s, 3 H), 1.45 (s, 3 H), 1.56 (s, 3 H), 4.04-4.15 (m, 2 H), 4.31 (m, 2 H), 4.78 (d, 1 H, J = 4), 5.65 (d, 1 H, J = 2), 5.97 (d, 1 H, J = 4), 7.12 (d, 2 H, J = 8), 7.31 (t, 1 H, J = 8), 7.44 (t, 2 H, J = 7) ; $^{13}C$ NMR (62.5 MHz, $CDCl_3$) δ: 25.7, 26.7, 27.1, 27.3, 67.5, 72.7, 80.1, 83.3, 85.5, 105.4, 109.9, 112.9, 122.1, 127.2, 130.0, 153.7, 194.1 ; IR (KBr pellet) $cm^{-1}$: 2987, 1164, 1082, 948, 917 . HRMS (FAB) m/z Calcd for $C_{19}H_{24}O_7S$: 396.1243. Found: 396.1243 . Anal. Calcd for $C_{19}H_{24}O_7S$: C, 57.6; H, 6.1. Found: C, 57.5; H, 6.1.
9. Benzene (Aldrich Chemical Company, Inc. or EM Science) was purified by distillation from sodium benzophenone ketyl . *CAUTION: Benzene is harmful as a vapor and by skin absorption, and it should always be handled in a well-ventilated hood. Chronic exposure may cause fatal blood disease.*
10. $(Bu_3Sn)_2O$ (Aldrich Chemical Company, Inc. or Gelest) was distilled [bp 140-142°C (0.1 mm)] before its use.
11. 2,2'-Azobis(isobutyronitrile) (98%; Aldrich Chemical Company, Inc.) was used without purification.
12. Poly(methylhydrosiloxane) (Fluka Chemical, Corp.) was degassed overnight under full vacuum at 25°C (≈0.1 mm) prior to use.
13. Anhydrous 1-butanol (99.8%; Aldrich Chemical Company, Inc.) was used without purification.
14. Tetrahydrofuran (Merck or EM Science) was used without purification.
15. The addition of base should be slow, as the aqueous NaOH (2 N) cleaves the siloxanes and ionizes the phenol that is generated in the reaction. The reaction is vigorous.
16. Flash column chromatography is performed with 30 g of silica (Merck 9385 Kieselgel 60, 230-400 ASTM) per gram of residue, eluting with a gradient of 0 → 50% EtOAc/hexane .
17. TLC analyses ($R_f = 0.32$, in hexane:EtOAc 7:3; the submitters observed $R_f = 0.33$ in hexane :EtOAc 4:1) were performed on 0.25-mm Merck 60 $F_{254}$ silica gel plates (the submitters used 0.25-mm silica gel 60 plates supplied by EM Reagents) that were stained with a solution of phosphomolybdic acid in 95% ethanol .
18. Compound **2** ($[\alpha]_D{}^{20}$ −8.1° ($CHCl_3$, *c* 2.4), lit.[3] $[\alpha]_D{}^{18}$ −8.5° ($CHCl_3$, *c* 1.5)) has the following

spectral data: $^1$H NMR (250 MHz, $CDCl_3$) δ: 1.32 (s, 3 H), 1.36 (s, 3 H), 1.43 (s, 3 H), 1.51 (s, 3 H), 1.77 (m, 1 H), 2.19 (dd, 1 H, J = 4, 14), 3.82 (m, 1 H), 4.12 (m, 3 H), 4.75 (t, 1 H, J = 4), 5.81 (d, 1 H, J = 4) ; $^{13}$C NMR (62.5 MHz, $CDCl_3$) δ: 25.5, 26.5, 26.8, 27.1, 35.6, 67.6, 77.2, 79.0, 80.8, 106.0, 110.0, 111.7 ; IR (neat) $cm^{-1}$: 1064, 957, 941 . HRMS (FAB) m/z Calcd for $C_{12}H_{20}O_5$: 244.1311. Found: 244.1312 . Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.0; H, 8.2. Found: C, 59.0; H, 8.3.

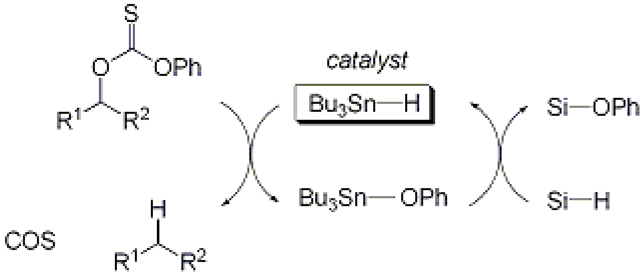
## Waste Disposal Information

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

## 3. Discussion

The Barton-McCombie protocol for the deoxygenation of alcohols [4,5] is an extremely useful method that has found widespread application in synthetic organic chemistry.[6] This radical-mediated process typically employs 1.5-3 equiv of $Bu_3SnH$[7] as the reducing agent. Because some tributyltin-containing compounds are toxic,[8] and product isolation from large quantities of organotin residues can be difficult,[9] the development of alternative reducing agents to $Bu_3SnH$ has been an active area of investigation. Indeed, it has been established that silicon hydrides[10] and dialkyl phosphites[11] can serve as substitutes for $Bu_3SnH$ in many instances. Despite these facts, $Bu_3SnH$ continues to be the reagent most commonly used for effecting this reduction.[12]

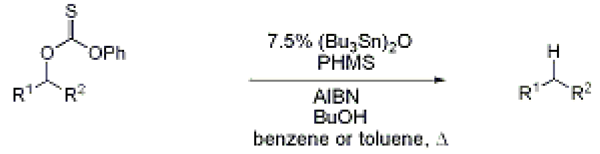
Given this, the development of a reaction variant in which $Bu_3SnH$ is employed as a *catalyst*, while a non-toxic second metal hydride serves as the stoichiometric reductant, has significant practical advantages. The procedure reported here uses 15 mol% $Bu_3SnH$ [generated in situ from $(Bu_3Sn)_2O$[13]] in conjunction with poly(methylhydrosiloxane) (PMHS) [14,15] (for the proposed catalytic cycle, see the figure below).[16]

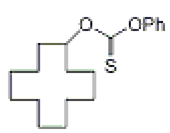
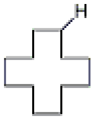
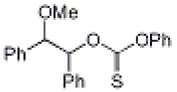
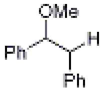
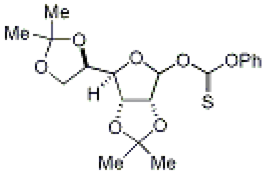
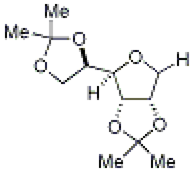
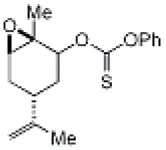
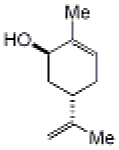


Additional applications of this method to the deoxygenation of secondary alcohols are provided in the Table.

Table

TABLE



| Substrate | Product | Isolated Yield (%) |
|---|---|---|
|  |  | 66 |
|  |  | 70 |
|  |  | 63 |
|  |  | 68 |

## References and Notes

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11. Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1993**, *58*, 6838-6842.

**12.** This statement is based on a search of the Beilstein Crossfire database.
**13.** Prices from Aldrich Chemical Company, Inc., per mole of tin are as follows: $(Bu_3Sn)_2O$: \$38; $Bu_3SnH$: \$250. Unlike $Bu_3SnH$, $(Bu_3Sn)_2O$ is not sensitive to light, $O_2$, or adventitious impurities.
**14.** Prices from Aldrich Chemical Company, Inc., per mole of hydride are as follows: PMHS: \$6; $Bu_3SnH$: \$250.
**15.** $D_{50}$ of PMHS: 80 g/kg: Klyaschitskaya, A. L.; Krasovskii, G. N.; Fridlyand, S. A. *Gig. Sanit.* **1970**, *35*, 28-31; *Chem. Abs.* **1970**, *72*, 124864r.
**16.** Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949-6950. The $Bu_3SnH$-catalyzed deoxygenation of dithiocarbonates requires more vigorous reaction conditions.

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

Tributylstannane :
Stannane, tributyl- (8,9); (688-73-3)

3-Deoxy-1,2:5,6-bis-O-(methylethylidene)-α-D-ribo-hexofuranose:
D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-isopropylidene, α- (8);
α-D-ribo-Hexofuranose, 3-deoxy-1,2:5,6-bis-O-(1-methylethylidene)- (9); (4613-62-1)

1,2:5,6-Bis-O-(1-methylethylidene)-, O-phenyl carbonothioate-α-D-glucofuranose:
Glucofuranose, 1,2:5,6-di-O-isopropylidene, O-phenyl thiocarbonate, α-D- (8);
α-D-Glucofuranose, 1,2:5,6-bis-O-(1-methylethylidene)-, O-phenyl thiocarbonate (9); (19189-62-9)

1,2:5,6-Di-O-isopropylidene-D-glucose:
Glucofuranose 1,2:5,6-di-O-isopropylidene-α-D- (8);
α-D-Glucofuranose, 1,2:5,6-bis-O-(1-methylethylidene)- (9); (582-52-5)

Phenyl chlorothionoformate:
Formic acid, chlorothio-, O-phenyl ester (8);
Carbonochloridothioic acid, O-phenyl ester (9); (1005-56-7)

Pyridine (8,9); (110-86-1)

Benzene: CANCER SUSPECT AGENT (8,9); (71-43-2)

Bis(tributyltin) oxide:
Distannoxane, hexabutyl- (8,9); (56-35-9)

Azobisisobutyronitrile:
Propionitrile, 2,2'-azobis[2-methyl- (8);
Propanenitrile, 2,2'-azobis[2-methyl- (9); (78-67-1)

Poly(methylhydrosiloxane): PMHS:
Poly[oxy(methylsilylene)] (8,9); (9004-73-3)

1-Butanol:
Butyl alcohol (8);
1-Butanol (9); (71-36-3)