# Improved Version of the Fischer−Zach Synthesis of Glycals: Vitamin B-12 Catalyzed Reductive Elimination of Glycosyl Bromides

Christopher L. Forbes and Richard W. Franck *

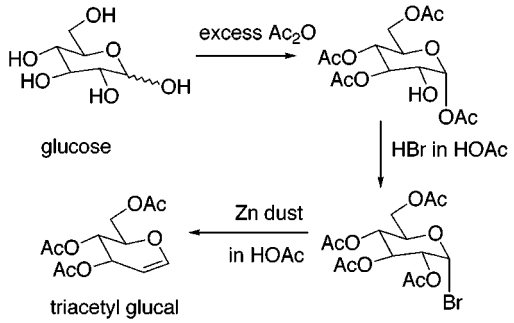
*Department of Chemistry, Hunter College, New York, New York 10021-5024*

*Received September 28, 1998*

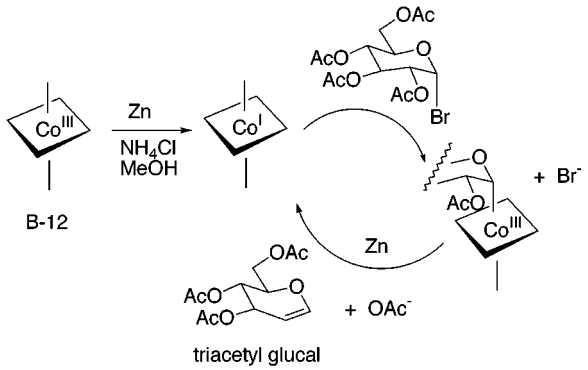
Glycals are unsaturated sugars with a double bond located between C1 and C2. These compounds have a long history of use as building blocks in carbohydrate chemistry, and if anything, their importance has increased, particularly because of their effectiveness as glycosyl donors.[1,2] The first synthesis of glycals was reported by Fischer and Zach, in which 1-bromo-tetracetylglucose was reduced with Zn dust in acetic acid.[3] (Scheme 1).

This historic experiment served as the basis for the modern method described in *Methods in Carbohydrate Chemistry* and recently updated by Koreeda.[4] A minor but annoying technical problem in all versions of the Fischer−Zach method is that extensive washing with sodium bicarbonate is required during workup to neutralize the acetic acid from the reaction medium. The one flaw in the method is that it fails in the furanoid glycal series where the acidic conditions lead to furan derivatives. However, Ireland showed that a Na-naphthalene anion radical reduction served to make furanoid glycals readily available.[5] Over the years, other reducing systems have been used to prepare glycals from 1-bromopyranose materials.[6] By and large, these new methods offer the advantage of avoiding the acidic conditions of the Fischer−Zach procedure. However, none have as yet been widely adopted in place of the original Zn dust method, probably because of a perception that the advantages to be gained are outweighed by problems of special reagent preparation or manipulation. We wish to describe a

**Scheme 1. Fischer−Zach Synthesis of Triacetyl Glucal**




**Scheme 2. B-12 Catalytic Cycle (Adapted from Scheffold) for the Synthesis of Triacetyl Glucal**




modified version of the Fischer−Zach method of forming glycals from glycosyl bromides, which is done in neutral media and therefore avoids the multiple bicarbonate washes for removal of acetic acid, the reaction medium of the original procedure The modification is one described by Scheffold in which vitamin B-12 is used as a catalyst for reductive eliminations.[7] The best precedent for our purposes was the use of B-12 with Zn dust to cleave chloroethyl-O protecting groups.[7c] The vitamin is a source of cobalt(III), which is reduced to Co(I). The Co(I) is assumed to insert into the C−halogen bond, which is fragmented by further reduction. In fact, a mixture of zinc dust and ammonium chloride can be used to carry out the Co(III)−Co(I) transformation. Because the insertion−elimination step reoxidizes the B-12 back to Co(III), only a catalytic amount of vitamin B-12 is necessary for the reaction. (Scheme 2).

Thus, application of the Scheffold protocol, which uses methanol as solvent and ammonium chloride as a buffer along with Zn dust as a reductant, serves admirably in the Fischer−Zach synthesis. The necessary control was run to show that without the vitamin B-12 the Zn dust/methanol combination gave glycal in poor yield. The modification fails with furanoid glycals (as does the original method). Table 1 lists the 1-bromosugar starting materials and yields of glycals formed. Because there is

(1) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. A recent review of glycal chemistry, with particular emphasis on applications of glycosyl transfer in which glycals are the donors, including extensive contributions of the Danishefsky group.

(2) Marzabadi, C. H.; Dios, A.; Geer, A.; Franck, R. W. *J. Org. Chem.* **1998**, *63*, 6673−6679. An article that includes a survey of cycloaddition reactions of glycals.

(3) Fischer, E.; Zach, K. *Sitzungsber. Kl. Preuss. Akad. Wiss.* **1913**, *27*, 311−317.

(4) . (a) Roth, W.; Pigman, W. *Methods in Carbohydrate Chemistry* Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press: New York, 1963; Vol. 2, p 405−408. (b) Shafizadeh, F. *Methods in Carbohydrate Chemistry;* Whistler, R. L., Wolfrom, M. L., Eds., Academic Press: New York, 1963; Vol. 2, p 409−410. (c) Shull, B. K.; Wu, Z.; Koreeda, M. *J. Carbohydr. Chem.* **1996**, *15*, 955−964.

(5) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48−61.

(6) (a) DePouilly, P.; Chenede, A.; Mallet, J.-M.; Sinay, P. *Bull. Soc. Chim. Fr.* **1993**, *130*, 256−265; $SmI_2$. (b) Cavallaro, C. L.; Schwartz, J. J. Org. Chem. 1995, 60, 7056; $(Cp_2TiCl)_2$; this article includes a survey of reductive elimination methods. (c) Spencer, R. P.; Schwartz, J. *Tetrahedron Lett.* **1996,** *37*, 4357−4360; $(Cp_2TiCl)_2$. (d) Furstner, A.; Weidmann, H. *J. Org. Chem.* **1989**, *54*, 2307−2311; K-graphite. Prof. Furstner, Max Planck Institut, Mulheim-Ruhr, <fuerstner@mpi-muelheim.mpg.de> has compiled an exhaustive listing of glycal syntheses via reductive elimination (personal communication from the author).

(7) (a) Scheffold, R.; Rytz, G.; Walder, L. *Modern Synthetic Methods;* Scheffold, R., Salle, O., Eds.; Verlag: Frankfurt, 1983; Vol. 3, 355−440. (b) Scheffold, R.; Abrecht, S.; Orlinski, R.; Ruf, H.-R.; Stamoula, P.; Tinembart, O.; Walder, L.; Weymuth, C. *Pure Appl. Chem.* **1987**, *59*, 363−372. (c) Scheffold, R.; Amble, E. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 629−630. (d) Zhou, D.-L.; Walder, P.; Scheffold, R.; Walder, L. *Helv. Chim. Acta* **1992**, *75* 995−1011.

10.1021/jo981952e CCC: $18.00 
Published on Web 01/26/1999

**Table 1. Reactants, Products, and Yields in the Vitamin B-12 Catalyzed Elimination**

| reactant glycosyl bromide | glycal | yield[a,b] |
|---|---|---|
| tetraacetyl-1-bromo-D-glucose | triacetyl-D-glucal | 94% (60−70%) [98%] |
| tetraacetyl-1-bromo-D-galactose | triacetyl-D-galactal | 93% (66%) [58%] |
| triacetyl-1-bromo-L-rhamnose | diacetyl-L-rhamnal | 45% [71%] |
| tetraacetyl-1-bromo-D-mannose | triacetyl-D-glucal | 95% |

[a] The yields in parenthesis are reported in the *Methods in Carbohydrate Chemistry* procedure (ref 4b). [b] The yields in brackets are reported in the Koreeda procedure (ref 4c).

no difference in yield between the glucose and mannose examples, we conclude that stereoelectronic effects in this series are negligble.

In conclusion, we believe that the Scheffold B-12 modification for Zn dust reductions can be profitably used in almost any case where Zn dust is used in reductive eliminations.

## Experimental Section

The zinc used required successive washings with 1 N HCl, water, and methanol for activation. It was then dried in vacuo for at least 1 h.

Tetra-*O*-acetyl-D-glucopyranosyl bromide was purchased from Sigma Chemicals and was used to prepare tri-*O*-acetyl glucal. The other 1-bromosugars were obtained by means of the classical HBr procedure, which in our hands gave better yields than the alternate TMSBr method. The glycal products were identified by direct comparison with authentic samples.

**Preparation of Tri-*O*-Acetyl Glucal.** A solution of vitamin B-12 (36.7 mg, 0.027 mmol) in 10 mL of anhydrous methanol was purged with $N_2$ for 30 min in a three-necked 50-mL round-bottom flask fitted with a stir bar. Then, the zinc (2.06 g, 31.5 mmol) and ammonium chloride (1.68 g, 31.5 mmol) were added to the solution, which was stirred for 45 min. Afterward, tetra-*O*-acetyl-D-glucopyranosyl bromide (1.07 g, 2.60 mmol) was dissolved in 5 mL of anhydrous methanol and added to the reaction flask. Immediately after addition of the bromide, the dark red solution changed to reddish-yellow in color and then back to the dark red in about 30 s. A TLC was taken after 5 min, which showed that the reaction had gone to completion ($R_f$ = 0.41 in 5:1 petroleum ether/ethyl acetate). The solution was then filtered through a pad of Celite to remove the zinc, and the Celite was rinsed with methanol to ensure that all of the solution was retrieved. The methanol solution was then concentrated via rotary evaporator and vacuum dried to give the crude white and red solid crude product. To isolate pure product, the crude product was dissolved in water (30 mL) and extracted with chloroform (1 × 60 mL and 3 × 30 mL). All of the organic extracts were combined, dried over magnesium sulfate, concentrated via rotary evaporator, and dried under vacuum, at which time a white solid appeared. The NMR of the product was identical to that of a commercial sample of pure tri-O-acetyl glucal. The product was obtained in 94% yield (0.708 g, 2.60 mmol). This procedure was repeated to make tri-*O*-acetyl galactal in 93% yield; the NMR of the galactal also was identical to that of a commercial sample.

**Preparation of 6-Deoxy-3,4 di-*O*-Acetoxy-L-Glucal (L-Rhamnal).** Vitamin B-12 (82.4 mg, 0.06 mmol) was dissolved in 20 mL of dry methanol under inert conditions, followed by the addition of zinc dust (7.89 g, 120.7 mmol) and ammonium chloride (6.48 g, 121.1 mmol). The solution was allowed to stir for 30 min, during which time it took on a deep red-purple color. 6-Deoxy-2,3,4-tri-*O*-acetyl-L-glucosyl bromide (2.0327 g, 6.0 mmol) was then dissolved separately in 25 mL of dry methanol and added to the original reaction flask. The resulting mixture became a yellow-orange color. After 5 min, the contents of the reaction flask were washed through Celite (using methanol) and concentrated under reduced pressure. The reddish solid residue was then dissolved in water (70 mL) and extracted three times with chloroform (70 mL each). The organic layers were collected, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting yellow runny oil was chromatographed on silica gel first pretreated with triethylamine 1% v/v in petroleum ether/ EtOAc 8:1 as a column rinsing solvent and then eluted with petroleum ether/EtOAc 8:1. The isolated product was a pure yellow oil (560 mg, 45%), identical by NMR with a commercial sample.

**Acknowledgment.** This research was supported by NIH grants GM 51216 and RR 03037 (RCMI) and PSC-CUNY funds.

JO981952E