

Titanium tetrachloride mediated reductive ring opening of *C*-aryl pseudoglycals

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Abstract

A facile reductive ring opening of *C*-aryl pseudoglycals is reported for the first time. The combination of titanium tetrachloride (Lewis acid) and triethylsilane (reducing agent) at $-78\text{ }^{\circ}\text{C}$ in dichloromethane is a mild and efficient reagent system for this transformation. The reagent system was successfully tested on various *C*-aryl pseudoglycal substrates to yield the corresponding ring opened products containing two asymmetric hydroxyls and a *cis*-double bond.

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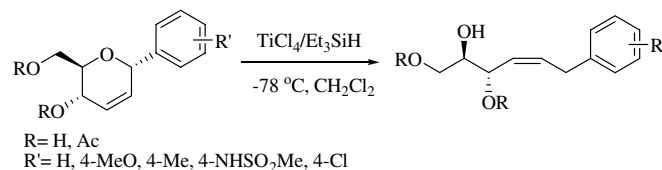
Keywords: Titanium tetrachloride; Aryl pseudoglycal; Reductive ring opening; Triethylsilane

C-Aryl glycosides are valuable scaffolds due to their presence in natural products with important medicinal and therapeutic properties.^{1,2} Furthermore, these compounds have great importance in synthetic organic chemistry as chiral building blocks, due to their rigid structures and inherent stereochemical diversity.^{3–5} In particular, *C*-aryl glycopyranosides with a double bond in the 2,3-position (pseudoglycals) are highly useful synthetic intermediates, since this unsaturation can be further functionalized.⁶ *C*-Aryl pseudoglycals can undergo a reductive ring opening reaction to provide enantiopure acyclic triols, which may serve as useful intermediates for the synthesis of biologically active compounds. Thus, in continuation of our work on silane reductions,^{7,8} we became interested in reductive ring opening of *C*-aryl pseudoglycals.

The commonly used methods for reductive ring opening of cyclic ethers are hydrogenation under high pressure,^{9,10} dissolving metal reductions,^{11–15} scandium(III) triflate/triethylsilane¹⁶ and others.^{17,18} All these methods have their own advantages as well as limitations depending on the nature of the substrate and reaction conditions.¹⁹ There-

fore, the development of mild and efficient methods for this transformation is important. We report herein on a mild method for the reductive ring opening of *C*-aryl pseudoglycals using titanium(IV) chloride/triethylsilane (Scheme 1).

Initially, we examined the ring opening of phenyl pseudoglycal **1a**, which was prepared from tri-*O*-acetyl-D-glucal and phenyl boronic acid in the presence of palladium(II) acetate,^{20,21} by employing various Lewis acids in combination with triethylsilane. Table 1 shows the results of this study for optimized conditions. Among the Lewis acids screened, ZnCl_2 , MoCl_5 , $\text{B}(\text{C}_6\text{F}_5)_3$, and TiCl_4 , only titanium(IV) chloride provided the acyclic product in 20% yield (reaction profile was not clean, multiple spots were observed by TLC). To optimize further the reaction conditions with TiCl_4 , the same reaction was carried out at $-78\text{ }^{\circ}\text{C}$ for 1.5 h, which afforded the desired product



Scheme 1. Reductive ring opening of *C*-aryl pseudoglycals.

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Table 1
Reactivity of various Lewis acids in reductive ring opening of phenyl pseudoglycol **1a** with Et₃SiH^a

Entry	Lewis acid	Conditions	Time (h)	Yield ^b (%)
1	ZnCl ₂ (1 equiv)	CH ₂ Cl ₂ /rt	24	0
2	MoCl ₅ (1 equiv)	CH ₂ Cl ₂ /rt	24	0
3	B(C ₆ F ₅) ₃ (1 equiv)	CH ₂ Cl ₂ /rt	24	0
4	TiCl ₄ (1 equiv)	CH ₂ Cl ₂ /rt	2.5	20
5	TiCl ₄ (2 equiv)	CH ₂ Cl ₂ /–78 °C	1.5	80

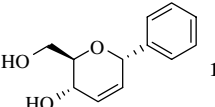
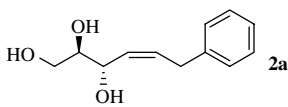
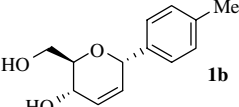
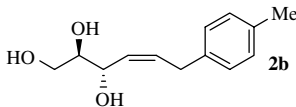
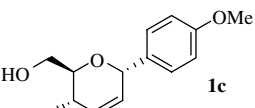
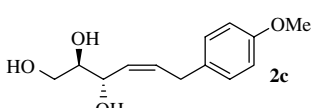
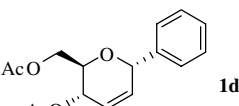
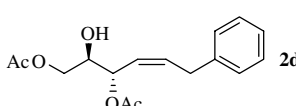
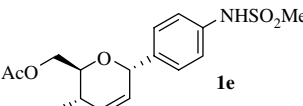
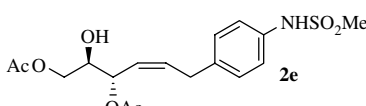
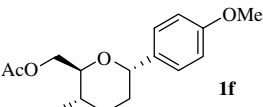
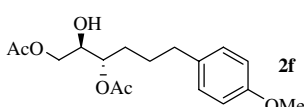
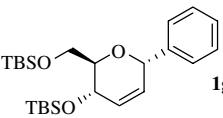
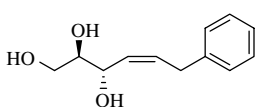
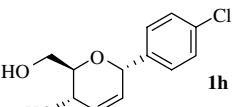
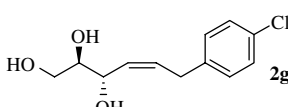
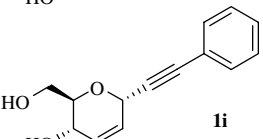
^a 3 equiv of Et₃SiH was used.

^b Isolated yield.

in 80% yield (Table 1, entry 5). A combination of TiCl₄ with reducing agents such as NaBH₄ and polymethylhydrosiloxane (PMHS) was not effective for this reaction. It was found that the combination of 2 equiv of titanium tetrachloride and 3 equiv of triethylsilane gave the best results.

To determine the generality of the above reagent system, several other C-aryl pseudoglycols were prepared and subjected to the reductive ring opening reaction. Almost all the substrates gave the corresponding acyclic product in good yield and the results are displayed in Table 2. The

Table 2
Reductive ring opening of C-aryl pseudoglycols using TiCl₄–Et₃SiH

Entry	C-Aryl pseudoglycol	Time (h)	Product	Yield ^a (%)
1	 1a	1.5	 2a	80
2	 1b	1.5	 2b	78
3	 1c	1	 2c	85
4	 1d	2	 2d	76
5	 1e	2	 2e	74
6	 1f	2.5	 2f	73
7	 1g	2	 2a	75
8	 1h	6	 2g	32
9	 1i	6	No reaction	

^a Isolated yield after column chromatography.

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