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

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Abstract

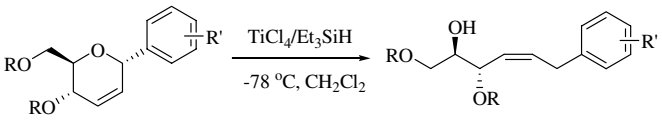
A facile reductive ring opening of *C*-aryl pseudoglycals is reported for the first time. The combination of titanium tetrachloride (Lewis acid) and triethylsilane (reducing agent) at −78 °C in dichloromethane is a mild and efficient reagent system for this transformation. The reagent system was successfully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

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/triethylsilane[16] 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] Therefore, 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, $ZnCl_2$, $MoCl_5$, $B(C_6F_5)_3$, 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 °C for 1.5 h, which afforded the desired product



R= H, Ac
R'= H, 4-MeO, 4-Me, 4-$NHSO_2Me$, 4-Cl

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 pseudoglycal **1a** with Et_3SiH[a]

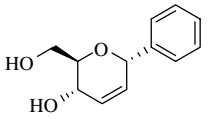
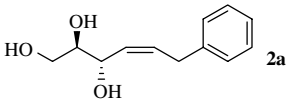
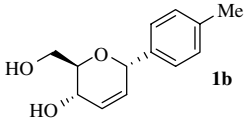
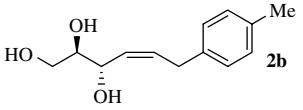
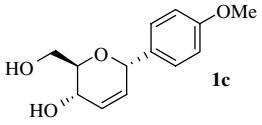
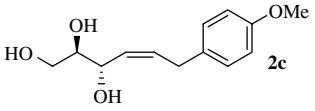
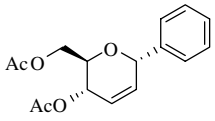
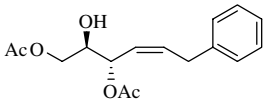
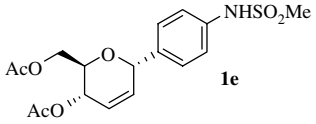
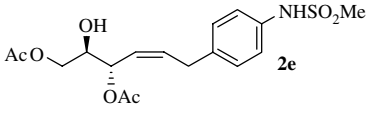
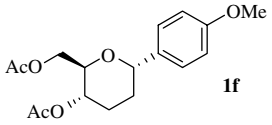
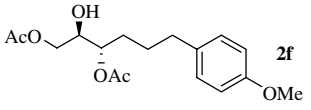
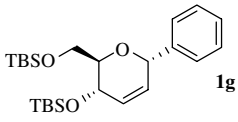
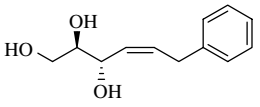
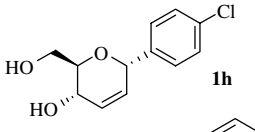
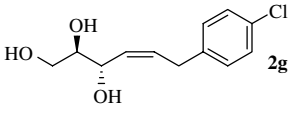
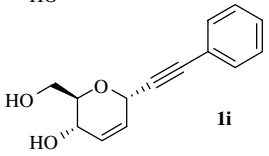
Entry	Lewis acid	Conditions	Time (h)	Yield[b] (%)
1	$ZnCl_2$ (1 equiv)	CH_2Cl_2/rt	24	0
2	$MoCl_5$ (1 equiv)	CH_2Cl_2/rt	24	0
3	$B(C_6F_5)_3$ (1 equiv)	CH_2Cl_2/rt	24	0
4	$TiCl_4$ (1 equiv)	CH_2Cl_2/rt	2.5	20
5	$TiCl_4$ (2 equiv)	CH_2Cl_2/−78 °C	1.5	80

[a] 3 equiv of Et_3SiH was used.
[b] Isolated yield.

in 80% yield (Table 1, entry 5). A combination of $TiCl_4$ with reducing agents such as $NaBH_4$ 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 pseudoglycals 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 pseudoglycals using $TiCl_4$–Et_3SiH

Entry	*C*-Aryl pseudoglycal	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.

acetylated pseudoglycals **1d** and **1e** underwent smooth ring opening to give products **2d** and **2e**, respectively, (Table 2, entries 4 and 5). The reaction of aryl substituted tetrahydropyran **1f** (without unsaturation in the ring) was also successful (Table 2, entry 6). However, *tert*-butyldimethylsilyl ethers were cleaved under the present reaction conditions and afforded the acyclic product as triol **2a** (Table 2, entry 7). The reaction of pseudoglycal **1h** containing an electron-withdrawing group provided the triol **2g** in lower yield (Table 2, entry 8).[22] Finally, attempts towards the reductive ring opening of *C*-alkynyl pseudoglycal **1i** were unsuccessful (Table 2, entry 9). All the obtained products were fully characterized from IR, ^{1}H, ^{13}C NMR, and HRMS spectral data. The geometry of the alkene was confirmed as *cis* from COSY spectra.

In summary, we report the reductive ring opening of *C*-aryl pseudoglycals using triethylsilane in the presence of titanium tetrachloride under mild reaction conditions. The reaction proceeded smoothly to provide acyclic products having two asymmetric centers (hydroxyl groups) and a *cis*-olefin functionality. These products could be important intermediates in the synthesis of various biologically active compounds including sphingolipid analogues and work in this direction is currently underway.

General experimental procedure for reductive ring opening of C-aryl pseudoglycals: To a stirred solution of *C*-aryl pseudoglycal (1 mmol) in anhydrous dichloromethane (10 mL) were added triethylsilane (0.48 mL, 3 mmol) and titanium tetrachloride (0.22 mL, 2 mmol) at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred at the same temperature for a given time (see Table 2). After completion of the reaction (monitored by TLC), the reaction mixture was diluted with dichloromethane (10 mL) and water (5 mL). After separating the dichloromethane layer, the water layer was extracted with dichloromethane (2 × 10 mL). The combined extract was washed with brine (5 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude was purified by column chromatography over silica gel to give the corresponding product.[23]

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22. The progress of the reaction was found to be slow for substrate **1h** compared to others. Even at room temperature with longer reaction time, no further progress of the reaction was observed.
23. Characterisation data for the products: (**2a**): White solid, mp = 81–83 °C; $[\alpha]_D^{20}$ −3.0 (*c* 1, $CHCl_3$); IR (KBr): *v* 3367, 3025, 2924, 1649, 1053, 864, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.36–7.15 (m, 5H), 5.83 (dt, *J* = 10.6, 7.8 Hz, 1H), 5.59 (t, *J* = 10.6 Hz, 1H), 4.69 (dd, *J* = 8.3, 3.9 Hz, 1H), 3.83–3.72 (m, 3H) 3.55–3.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 140.0 (C), 133.3 (CH), 128.86 (CH), 128.83 (CH), 128.4 (CH), 126.5 (CH), 74.0 (CH), 69.7 (CH), 63.5 (CH_2), 34.2 (CH_2); ESI (MS): *m/z* 231 (M+Na); HRMS (ESI) Calcd for $C_{12}H_{16}O_3Na$: 231.0997 $[M+Na]^+$, found: 231.1004 $[M+Na]^+$; (**2b**): White solid, mp = 84–86 °C; $[\alpha]_D^{20}$ −1.1 (*c* 1, $CHCl_3$); IR (KBr): *v* 3424, 2924, 2854, 2362, 1744, 1632, 1459, 760 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.09–6.99 (m, 4H), 5.76 (dt, *J* = 10.8, 7.5 Hz, 1H), 5.55 (t, *J* = 10.8 Hz, 1H), 4.65 (dd, *J* = 8.5, 3.8 Hz, 1H), 3.78–3.67 (m, 3H), 3.47–3.28 (m, 2H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 134.5 (C), 133.6 (C), 131.4 (CH), 127.1 (CH), 126.2 (CH), 125.9 (CH), 71.5 (CH), 67.3 (CH), 61.1 (CH_2), 31.4 (CH_2), 27.4 (CH_3); ESI (MS): *m/z* 245 (M+Na); HRMS (ESI) Calcd for $C_{13}H_{18}O_3Na$: 245.1153 $[M+Na]^+$, found: 245.1156 $[M+Na]^+$; (**2c**): White solid, mp = 79–81 °C; $[\alpha]_D^{20}$ −4.7 (*c* 0.5, $CHCl_3$); IR (KBr): *v* 3357, 2925, 1613, 1512, 1249, 1035, 817 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.02 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 5.81 (distorted dt, *J* = 9.3, 7.8 Hz, 1H), 5.50 (t, *J* = 9.6 Hz, 1H), 4.65–4.63 (m, 1H), 3.72 (s, 3H), 3.71–3.63 (m, 3H), 3.43–3.27 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): *δ* 158.1 (C), 131.7 (CH), 129.5 (CH), 129.2 (C), 128.3 (CH), 114.0 (CH), 73.7 (CH), 69.5 (CH), 63.3 (CH_2), 55.1 (CH_3), 33.2 (CH_2); ESI (MS): *m/z* 261 (M+Na); HRMS (ESI) Calcd for $C_{13}H_{18}O_4Na$: 261.1102 $[M+Na]^+$, found: 261.1115 $[M+Na]^+$; (**2d**): Viscous liquid, $[\alpha]_D^{20}$ +8.7 (*c* 1, $CHCl_3$); IR (KBr): *v* 3461, 1738, 1372, 1234, 1040, 745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.32–7.18 (m, 5H), 5.92 (distorted dt, *J* = 10.8, 7.8 Hz, 1H), 5.74 (dd, *J* = 9.3, 5.1 Hz, 1H), 5.55 (t, *J* = 10.8 Hz, 1H), 4.18–4.16 (m, 2H), 4.04–3.99 (m, 1H), 3.67–3.45 (m, 2H), 2.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 171.3 (C), 170.2 (C), 139.8 (C), 136.1 (CH), 128.8 (CH), 128.6 (CH), 126.4 (CH), 124.0 (CH), 71.4 (CH), 70.5 (CH), 64.9 (CH_2), 34.5 (CH_2), 21.2 (CH_3), 20.9 (CH_3); ESI (MS): *m/z* 315 (M+Na); HRMS(ESI) Calcd for $C_{16}H_{20}O_5Na$: 315.1208 $[M+Na]^+$, found: 315.1203 $[M+Na]^+$. (**2e**): Viscous liquid; $[\alpha]_D^{20}$ +8.4 (*c* 0.5, $CHCl_3$); IR

(KBr): ν 3452, 2924, 1729, 1633, 1233, 1151, 972, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.19–7.10 (m, 4H), 5.99–5.90 (m, 1H), 5.56 (distorted dt, $J = 10.8$, 7.2 Hz, 1H), 5.32 (dd, $J = 11.1$, 7.2 Hz, 1H), 4.18–4.12 (m, 2H), 4.02–3.97 (m, 1H), 3.38–3.34 (m, 2H), 2.97 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2 (C), 170.1 (C), 136.7 (C), 135.5 (CH), 130.0 (CH), 125.8 (CH), 121.6 (C), 121.5 (CH), 75.0 (CH), 71.4 (CH), 65.1 (CH_2), 39.4 (CH_3), 38.2 (CH_2), 21.4 (CH_3), 21.0 (CH_3); ESI (MS): m/z 408 (M+Na); HRMS (ESI) Calcd for $C_{17}H_{23}NO_7NaS$: 408.1092 $[M+Na]^+$, found: 408.1079 $[M+Na]^+$. (**2f**): Viscous liquid; $[\alpha]_D^{20}$ +1.5 (c 0.5, $CHCl_3$); IR (KBr): ν 3452, 2924, 2853, 1736, 1610, 1511, 1241, 1034, 829 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.04 (d, $J = 8.4$ Hz, 2H), 6.79 (d, $J = 8.7$ Hz, 2H), 4.99–4.86 (m, 1H), 4.17–4.01 (m, 2H), 3.85 (bs, 1H), 3.75 (s, 3H), 2.58–2.46 (m, 2H), 2.04 (s, 3H), 2.06 (s, 3H), 1.69–1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5 (C), 171.1 (C), 158.0 (C), 134.0 (C), 129.4 (CH), 114.0 (CH), 74.5 (CH), 71.5 (CH), 65.4 (CH_2), 55.4 (CH_3), 34.8 (CH_2), 29.9 (CH_2), 27.5 (CH_2), 21.2 (CH_3), 21.1 (CH_3); ESI (MS): m/z 347$(M+Na)^+$; HRMS (ESI) Calcd for $C_{17}H_{24}O_6Na$: 347.1470 $[M+Na]^+$, found: 347.1461 $[M+Na]^+$. (**2g**): White solid, mp = 78–81 °C; $[\alpha]_D^{20}$ +8.0 (c 0.1, $CHCl_3$); IR (KBr): ν 3439, 2926, 2857, 1614, 1459, 1106, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, $J = 8.1$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 5.78 (dt, $J = 11.1$, 8.4 Hz, 1H), 5.58 (t, $J = 10.8$ Hz, 1H), 4.65 (dd, $J = 8.4$, 4.8 Hz, 1H), 3.83–3.71 (m, 3H), 3.50–3.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4 (C), 132.8 (C, CH), 129.8 (CH), 129.3 (CH), 128.9 (CH), 73.9 (CH), 69.7 (CH), 63.5 (CH_2), 33.6 (CH_2); ESI (MS): m/z 242 (M^+); HRMS (ESI) Calcd for $C_{12}H_{15}O_3NaCl$: 265.0607 $[M+Na]^+$, found: 265.0610 $[M+Na]^+$.