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# Synthesis of *C*-2 methylene glycosides from *C*-2 propargyloxymethyl glycals exploiting the alkynophilicity of $AuCl_3$☆

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**Abstract**—*C*-2 Methylene glycosides were synthesized from *C*-2 propargyloxymethyl glycals in a stereoselective manner using a catalytic quantity of $AuCl_3$. The Au-catalyzed reaction was explored using various aglycones. The current protocol enables the preparation of *C*-2 methylene glycosides, tolerates diverse functional groups and is fast, catalytic and mild.


2-*C*-Methylene glycosides are important intermediates for the synthesis of various biologically important small molecules.[1] For example, Matsuda et al. identified[2a] that the 2′-*C*-methylene group of 2′-*C*-methylene nucleosides is essential for the inactivation of the ribonucleotide phosphate reductase enzyme which is involved in tumour progression.[2,3] Booma and Balasubramanian reported the first approach for the synthesis of *C*-2 methylene glycosides from *C*-2-acetoxymethylene glycal based on a Ferrier reaction using $BF_3{\cdot}Et_2O$ as a catalyst.[3a] A subsequent study[3b] employed Nafion-H, Montmorillonite K-10 or $Pd(PPh_3)_4$ to effect similar transformations to obtain *C*-2 methylene glycosides. More recently, Ghosh et al. reported[3c] the $InCl_3$-mediated preparation of these compounds. Our programme to synthesize diverse molecular architectures from carbohydrate precursors led us to synthesize *C*-2 methylene glycosides to exploit their salient features for the development of a diversity oriented synthesis pathway.[4]

We have recently identified that the propargyloxy group behaves as a leaving group when treated with a catalytic amount of $AuCl_3$.[5a] Extrapolation of these observations led to the recognition of a transglycosylation protocol from propargyl glycosides.[5b] In continuation, we disclose in this Letter, the utility of $AuCl_3$ for the preparation of 2-*C*-methylene glycosides from per-*O*-benzylated *C*-2-propargyloxymethyl glycals in the presence of aglycones.

Our efforts started with the preparation of known *C*-2 hydroxymethyl glucal from *C*-2 formyl glucal **1**.[6a] The resulting primary hydroxyl group was easily etherified to obtain enyne **2** using NaH/propargyl bromide in the presence of $nBu_4N^+I^-$ in 87% yield. Enyne **2** was subjected to $AuCl_3$-mediated $S_N2'$ addition in methanol at 0 °C–rt to afford the exomethylene compound **3a** in 63% yield supporting further the behaviour of the propargyloxy group in the presence of $AuCl_3$.[7–9]

The $^1H$ NMR spectrum of **3a** revealed the absence of an acetylenic methine proton at $\delta$ 2.38 ppm and the presence of proton resonances characteristic with an exomethylene group around $\delta$ 5.15–5.31 ppm. The $^{13}C$ NMR spectrum of **3a** also confirmed the presence of an olefin showing a resonance at $\delta$ 110.7 ppm and the DEPT spectrum further confirmed this signal as a $-CH_2$. In addition, the anomeric carbon was identified at $\delta$ 102.4 ppm confirming the product as an α-glucoside and the overall spectroscopic data were in agreement with that reported by Booma et al.[3a,7,9]

To test the general applicability of the methodology, we carried out the $AuCl_3$-mediated $S_N2'$ addition reaction utilizing various aglycones comprising aromatic, aliphatic, alicyclic and carbohydrate-derived alcohols

☆ Some results from this study were presented at the Carbo-XXI symposium held at the University of Delhi, Delhi, November 26–29, 2006.

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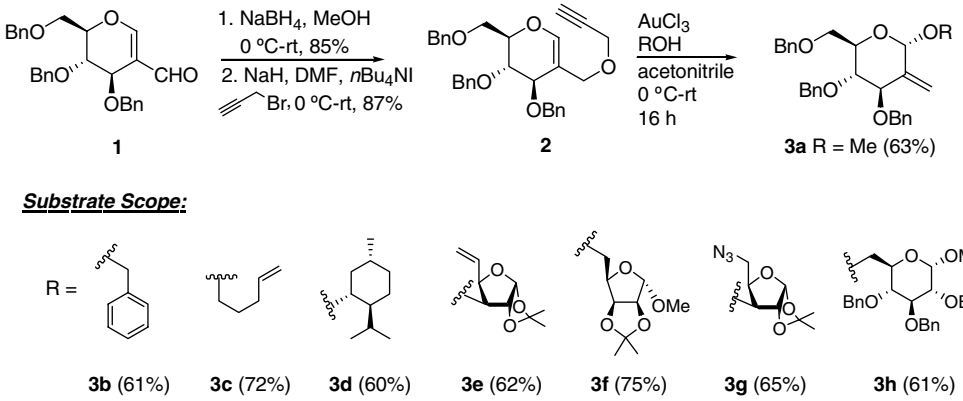
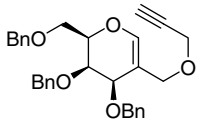
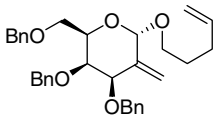
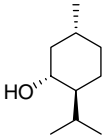
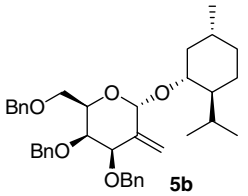
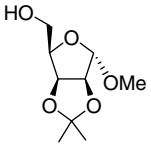
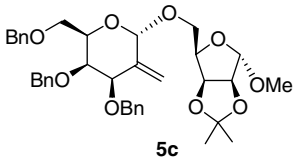
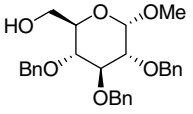
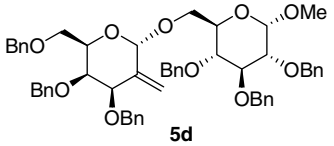
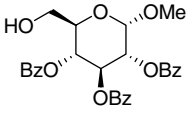
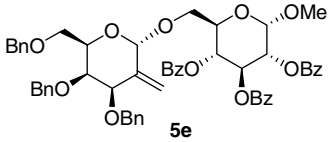
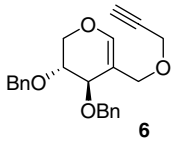
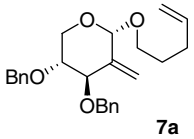



**Scheme 1.** Au-catalyzed synthesis of a range of *C*-2 methylene α-D-glucosides.

**Table 1.** Synthesis of *C*-2 methylene glycosides[a]

| Entry | Substrate | Aglycone | Product | % Yield |
|---|---|---|---|---|
| 1 |  **4** |  |  **5a** | 68 |
| 2 | |  |  **5b** | 60 |
| 3 | |  |  **5c** | 72 |
| 4 | |  |  **5d** | 63 |
| 5 | |  |  **5e** | 61 |
| 6 |  **6** |  |  **7a** | 60 |

[a] All reactions were performed in parallel at 0 °C–rt for 16 h.

(**3b**–**3h**). It is pertinent to mention that the current method tolerates functional groups such as olefins (**3c**, **3e**), isopropylidene (**3e** and **3f**), azide **3g** and ethers **3h** (Scheme 1). The stereoselective formation of α-glycosides can be attributed to the anomeric effect though a thorough mechanistic investigation is pending.

In addition, we have also shown that the per-*O*-benzylated *C*-2-propargyloxymethyl galactal **4** and per-*O*-benzylated *C*-2-propargyloxymethyl xylal **6** also react with aglycones to give the corresponding *C*-2 methylene galactosides and xylosides, respectively, in a stereoselective manner (Table 1). For example, galactal and xylal-derived enynes (**4** and **6**) reacted with pentenyl alcohol to give *C*-2 methylene-containing pentenyl galactoside **5a** and *C*-2 methylene-bearing pentenyl xylopyranoside **7a** in 68% and 60% yields, respectively.[7] It is interesting to note that alicyclic (Table 1, entry 2) and sugar-derived aglycones (Table 1, entries 3–5) also reacted with enyne **4** to give the corresponding galactosides (**5b**–**5e**).[7]

In summary, we have synthesized *C*-2 methylene glycosides from stable propargyloxymethyl glycals exploiting gold catalysis. The current protocol enables the activation of an alkyne group in the presence of various functional groups. Our efforts in utilizing these glycosides possessing an exomethylene group at the *C*-2 position for the preparation of diverse molecular skeletons will be reported in the future.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.144.

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7. All products gave satisfactory $^{1}H$, $^{13}C$, DEPT NMR and MS analysis. See Supplementary data.
8. *General experimental procedure*: To a solution of compound **2** (1 mmol) in anhydrous acetonitrile (5 mL) were added aglycone (2 mmol) and $AuCl_3$ (5 mol% in acetonitrile) at 0 °C and the resulting mixture was stirred at rt for 16 h. The reaction mixture was concentrated in vacuo, the crude residue was redissolved in ethyl acetate and washed with water. The combined organic layers were dried over anhydrous $Na_2SO_4$, concentrated in vacuo and the resulting residue was purified by silica gel column chromatography using light petroleum ether (60–80 °C) and ethyl acetate to afford exomethylene α-glucosides in good yields.
9. *Characterization data of compound* **2**: $[\alpha]_D$ +69.2 ($CHCl_3$, *c* 2.00); $^{1}H$ NMR ($CDCl_3$, 200.13 MHz): 2.38 (t, 1H, $J = 2.39$ Hz), 3.74 (dt, 2H, $J = 3.77$, 5.22 Hz), 3.86 (d, 1H, $J = 11.36$ Hz), 3.90 (dd, 1H, $J = 5.22$, 6.54 Hz), 4.08 (t, 2H, $J = 2.39$ Hz), 4.14–4.32 (m, 3H), 4.53 (s, 2H), 4.64 (s, 2H), 4.67 (ABq, 2H, $J = 11.68$ Hz), 6.51 (s, 1H), 7.22–7.34 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 50.32 MHz): 55.6, 66.9, 67.9, 72.6, 72.8, 73.2, 73.5, 73.9, 74.3, 76.4, 79.7, 108.6, 127.4–128.3, 137.7, 137.8, 138.2, 144.3; calcd mass for $C_{31}H_{32}O_5$: 484.58; found, 507.05 (M+23 for Na).
*Characterization data of compound* **3a**: $[\alpha]_D$ +28.9 ($CHCl_3$, *c* 1.10); $^{1}H$ NMR ($CDCl_3$, 200.13 MHz): 3.38 (s, 3H), 3.61 (t, 1H, $J = 9.42$ Hz), 3.70–3.75 (m, 2H), 3.92 (m, 1H), 4.40–4.90 (m, 7H), 5.06 (s, 1H), 5.16 (dd, 1H, $J = 1.25$, 2.00 Hz), 5.30 (dd, 1H, $J = 1.25$, 2.00 Hz), 7.10–7.42 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 50.32 MHz): 54.4, 68.8, 71.5, 73.4, 73.4, 74.9, 80.0, 81.2, 102.4, 110.7, 127.5–128.4, 138.1, 138.2, 138.3, 142.4; calcd mass for $C_{29}H_{32}O_5$: 460.56; found, 483.04 (M+23 for Na).
*Characterization data of compound* **3b**: $[\alpha]_D$ +37.9 ($CHCl_3$, *c* 1.20); $^{1}H$ NMR ($CDCl_3$, 200.13 MHz): 3.68 (m, 3H), 4.00 (m, 1H), 4.37–4.92 (m, 9H), 5.13 (dd, 1H, $J = 1.31$, 1.99 Hz), 5.26 (s, 1H), 5.30 (dd, 1H, $J = 1.31$, 1.99 Hz), 7.08–7.43 (m, 20H); $^{13}C$ NMR ($CDCl_3$, 50.32 MHz): 68.8, 68.9, 71.8, 73.4, 73.5, 75.0, 80.1, 81.3, 100.8, 110.8, 127.4–128.4, 137.5, 138.2, 138.3, 138.4, 142.3; calcd mass for $C_{35}H_{36}O_5$: 536.67; found, 559.04 (M+23 for Na).
*Characterization data of compound* **3f**: $[\alpha]_D$ +37.2 ($CHCl_3$, *c* 1.20); $^{1}H$ NMR ($CDCl_3$, 200.13 MHz): 1.30, 1.42 (2s, 6H), 3.31 (s, 3H), 3.48–3.91 (m, 5H), 4.08 (m, 2H), 4.41–4.92 (m, 10H), 5.16 (dd, 1H, $J = 1.26$, 1.87 Hz), 5.23 (s, 1H), 5.30 (dd, 1H, $J = 1.26$, 1.87 Hz), 7.12–7.42 (m, 15H); $^{13}C$ NMR ($CDCl_3$, 50.32 MHz): 25.0, 26.1, 54.6, 64.8, 68.7, 71.6, 73.3, 73.4, 74.9, 78.1, 79.7, 80.0, 81.1, 84.9, 101.4, 107.1, 110.7, 112.5, 127.5–128.4, 138.1, 138.2, 138.4, 142.3; calcd mass for $C_{37}H_{44}O_9$: 632.74; found, 655.84 (M+23 for Na).