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Highly stereoselective synthesis of *C*-(alkynyl)-pseudoglycals from δ-hydroxy-α,β-unsaturated aldehydes☆

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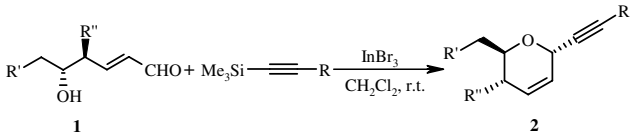
Abstract—An efficient and novel methodology for the synthesis of *C*-(alkynyl)-pseudoglycals from δ-hydroxy-α,β-unsaturated aldehydes has been developed.

Carbohydrates are important constituents of glycoproteins and glycolipids that are involved in numerous biological processes.[1] C-Glycosides[2] have been the subject of considerable interest in carbohydrate, enzymatic and metabolic chemistry, as well as in organic synthesis. They are versatile chiral building blocks for the synthesis of many biologically important natural products such as palytoxin, spongistatin, halichondrin, etc.[3] In addition, they are potential inhibitors of carbohydrate processing enzymes and are stable analogues of glycans involved in important intra- and intercellular processes.[4] In particular, *C*-(alkynyl)-glycosides are attractive due to the presence of a triple bond that can be easily transformed into other chiral molecules and carbohydrate analogues such as ciguatoxin and tautomycin, etc.[5] C-Glycoside analogues have gained considerable attention in the past two decades and to date, numerous methods have been described for their synthesis.[6] In general, 2,3-unsaturated C-glycosides are prepared by C-glycosidation of glycals using different nucleophiles involving Ferrier rearrangement.[7]

The synthesis of optically active compounds has posed challenges directed towards new methodologies with more practical sources. The development of effective C-glycoside syntheses depends on the selective formation of only one anomer as the major reaction product in good to excellent yield. As a part of an ongoing program aimed at developing the synthesis of C-glycoside analogues[8] of complex bioactive glycosides, we report herein a novel and efficient method to access selectively *C*-(alkynyl)-pseudoglycals from δ-hydroxy-α,β-unsaturated aldehydes and alkynyl silanes (Scheme 1). To the best of our knowledge, no synthesis of *C*-(alkynyl)-pseudoglycals from δ-hydroxy-α,β-unsaturated aldehydes has been previously reported. In recent years, indium reagents have emerged as mild and water-tolerant Lewis acids imparting high chemo-, regio- and stereoselectivity in various organic transformations.[9] Compared to conventional Lewis acids, indium halides have advantages of water stability, recyclability and simplicity in operation. Indeed, such Lewis acids are effective catalysts in promoting many fundamental reactions including Diels–Alder reactions, Michael reactions, Friedel–Crafts acylation reactions, Mukaiyama aldol reactions and Sakurai allylation reactions. In addition, indium trihalides are found to be more effective than conventional Lewis acids in promoting the cyanation of ketones, thioacetalization of carbonyl compounds and O-glycosidation under mild conditions.[10]

Initially, we attempted the reaction of δ-hydroxy-enal **1a**[11] with phenyl(trimethylsilyl) acetylene using 5 mol % of indium(III) bromide as a catalyst. Interestingly, the



1 2

Scheme 1.

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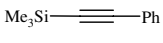
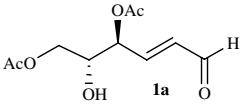
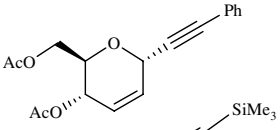
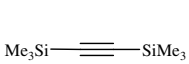
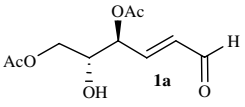
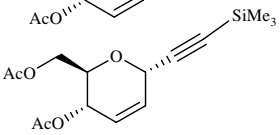
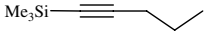
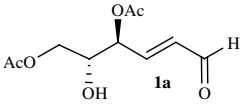
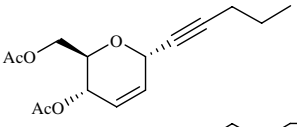
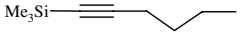
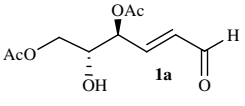
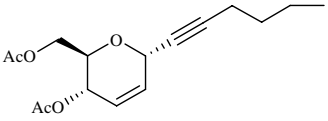
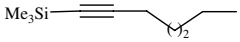
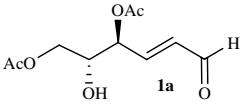
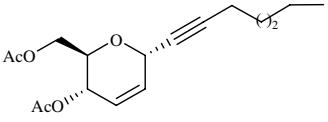
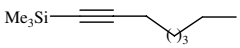
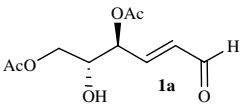
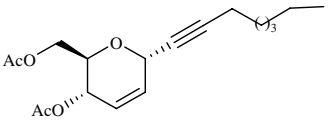
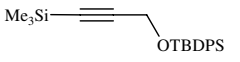
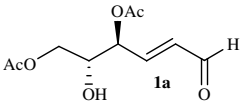
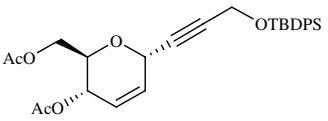
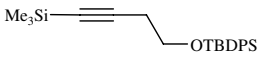
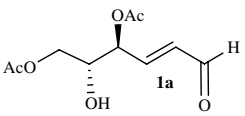
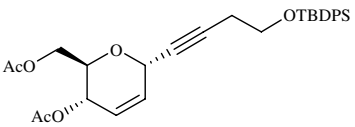
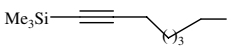
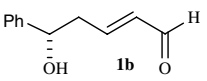
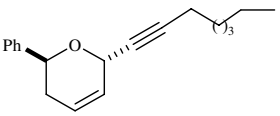
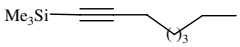
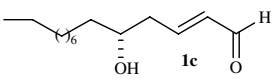
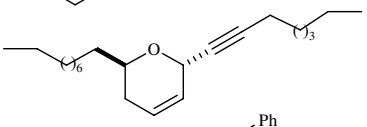
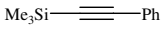
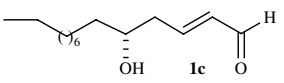
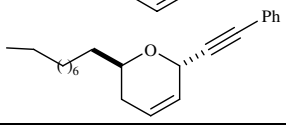
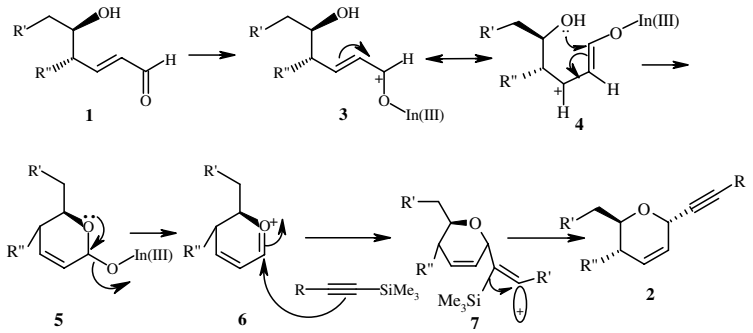
C-(alkynyl)-pseudoglycal product **2a** was isolated in 91% yield, the structure of the product **2a** being verified by ^{1}H NMR spectroscopic data.[12,13] In a similar fashion, various alkynyl silanes including aromatic and aliphatic substituted acetylenes reacted smoothly with aldehyde **1a** under similar reaction conditions to afford the corresponding *C*-(alkynyl)-glycals in good yields (Table 1, entries a–h). No β-anomer was observed in the ^{1}H NMR spectra of the crude products. Encouraged by these results, we turned our attention to other aldehydes. 5-Hydroxy-5-phenyl-(*E*)-2-pentenal **1b**, prepared from benzaldehyde and allyl bromide, reacted efficiently in good yield and with high selectivity (Table 1, entry i). Similarly aldehyde **1c**, prepared from 1-decanal and allyl bromide, reacted smoothly under the reaction conditions with various alkynyl silanes to provide the corresponding *C*-(alkynyl)-glycals in good yields and with high selectivity (Table 1, entries j and k). Again ^{1}H NMR of the crude products indicated that no β-isomer was present. Although aldehydes **1b** and **1c** were used as racemates, optically pure products can be prepared from the enantiopure aldehydes.

Table 1. Formation of *C*-(alkynyl)-pseudoglycals from δ-hydroxy-α,β-unsaturated aldehydes and silyl acetylenes

Entry	Silyl acetylene	δ-(OH)-α,β-unsaturated aldehydes	Time (h)	Product[a] (**2**)	Yield[b] (%)
a			0.5		91
b			1.0		85
c			2.0		90
d			2.0		89
e			3.0		90
f			3.5		85
g			3.5		75
h			1.0		78
i			5.5		70
j			7.0		65
k			7.0		67

[a] All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.



Scheme 2. Possible mechanism for the reaction.

However, *ortho*-hydroxy *trans*-cinnamaldehyde and phenyl (trimethylsilyl) acetylene did not give the desired product under the present reaction conditions. Furthermore, α,β-unsaturated aldehydes not possessing a δ-hydroxyl group did not yield the desired products. It is important to mention that simple unprotected acetylenes, such as phenyl acetylene, did not yield the desired products under the reaction conditions. A possible mechanism is illustrated in Scheme 2 which involves activation of the aldehyde by indium(III) bromide and subsequent formation of the oxonium intermediate **6** in which stereoelectronic and/or steric factors drive the direction of the incoming silyl acetylene. A possible cationic charge would develop on the β-carbon in **7**, which is highly stabilized by the silicon atom.[14] Elimination of the trimethylsilyl group results in the formation of the product **2**. This mechanism better explains the α-stereochemistry of the resultant products than the alternative mechanism where C–C bond formation precedes C–O bond formation. This process is highly regio- and stereoselective affording *C*-(alkynyl)-pseudo-glycals from δ-hydroxy-α,β-unsaturated aldehydes and silyl acetylenes.

There are several advantages in the use of indium tribromide as catalyst for this transformation, which include high yields of products, clean reaction profiles, short reaction times, high selectivity and recoverability of the catalyst. Among various catalysts, indium tribromide was found to be most effective in terms of conversion and selectivity. For example, treatment of aldehyde **1a** with phenyl(trimethylsilyl) acetylene in the presence of 5 mol % of $InBr_3$ or 5 mol % of $InCl_3$ for 1 h afforded 91% and 75% yields, respectively.

This method is simple, convenient and highly stereoselective affording *C*-(alkynyl)-pseudoglycals in good yields from simple δ-hydroxy-α,β-unsaturated aldehydes and alkynyl silanes. In addition, this method is also useful for the direct synthesis of 4-deoxy C-glycoside analogues (Table 1, entries i–k). This method facilitates the introduction of sugar nuclei as a chiral pool as well as alkynyl moiety in one-pot, which makes it an efficient pathway for producing *C*-(alkynyl)-pseudoglycals which can be further modified to give biologically important natural products.

In summary, we have developed an efficient strategy to selectively synthesize simple as well as complex *C*-(alkynyl)-pseudoglycals from simple δ-hydroxy-α,β-unsaturated aldehydes and alkynyl silanes in a highly regio- and stereoselective manner.

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12. General procedure: A mixture of 3-formyl-1-[1-hydroxy-2-methylcarbonyloxy-(1*R*)-ethyl]-(1*S*,2*E*)-2-propenyl acetate **1a** (5 mmol), phenyl (trimethylsilyl) acetylene (5 mmol) and indium tribromide (5 mol %) in dichloromethane (10 mL) was stirred at room temperature. After complete conversion, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×15 mL). The organic layers were dried over anhydrous Na_2SO_4 and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford the pure alkynyl C-glycoside derivative. The aqueous layer was concentrated in vacuo and the catalyst recovered, quantitatively. Spectroscopic data for selected compounds: Compound **2a** (α-anomer): liquid; $[\alpha]_D^{20}$ −105.7 (*c* 1.0 $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.03 (s, 6H), 4.10 (ddd, 1H, $J = 3.0$, 6.5, 12.0 Hz), 4.19 (dd, 1H, $J = 3.0$, 12.0 Hz), 4.21 (dd, 1H, $J = 3.0$, 12.1 Hz), 5.15 (d, 1H, $J = 1.4$ Hz), 5.25 (dd, 1H, $J = 2.2$, 8.8 Hz), 5.78 (dt, 1H, $J = 1.4$, 10.7 Hz), 5.90 (ddd, 1H, $J = 1.4$, 2.2, 10.7 Hz), 7.30–7.20 (m, 3H), 7.40–7.38 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.6, 20.9, 63.0, 64.4, 64.8, 70.0, 84.7, 86.6, 122.2, 125.4, 128.2, 128.6, 129.1, 131.7, 170.1, 170.7; IR (KBr): *v* 3024, 2125, 1745, 1577, 1402, 1219, 1092 cm^{-1}; HRMS calcd for $C_{18}H_{18}O_5$ 314.1154, found 314.1149. Compound **2d**: (α-anomer): liquid; $[\alpha]_D^{25}$ −82.5 (*c* 3.5, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.95 (t, 3H, $J = 6.2$ Hz), 1.30–1.50 (m, 4H), 2.01 (s, 6H), 2.12 (t, 2H, $J = 6.3$ Hz), 4.00 (ddd, 1H, $J = 3.0$, 6.5, 9.0 Hz), 4.18 (dd, 1H, $J = 3.0$, 12.1 Hz), 4.21 (dd, 1H, $J = 3.0$, 12.1 Hz), 4.95 (m, 1H), 5.25 (dd, 1H, $J = 1.9$, 9.0 Hz), 5.60 (dd, 1H, $J = 1.9$, 10.3 Hz), 5.82 (dt, 1H, $J = 2.0$, 10.3 Hz); ^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): δ 13.2, 20.6, 21.2, 21.8, 29.3, 31.7, 63.1, 65.0, 69.7, 76.0, 77.6, 87.4, 124.6, 130.0, 170.1, 170.7; IR (KBr): *v* 2967, 2217, 1731, 1463, 1372, 1238, 1046, 758 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_5$ 294.1467, found 294.1470. Compound **2i** (α-anomer): liquid; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.93 (t, 3H, $J = 6.4$ Hz), 1.22–1.60 (m, 8H), 2.20–2.36 (m, 4H), 4.90 (dd, 1H,$J = 5.2$, 9.8 Hz), 4.95 (d, 1H, $J = 1.5$ Hz), 5.71 (ddd, 1H, $J = 2.3$, 3.7, 10.5 Hz), 5.82 (dtd, 1H, $J = 1.5$, 3.0, 10.5 Hz), 7.22–7.40 (m, 5H); ^{13}C NMR (proton decoupled, 50 MHz, $CDCl_3$): δ 13.7, 21.2, 21.8, 28.7, 29.2, 31.6, 36.2, 65.2, 72.0, 77.1, 85.4, 122.3, 125.6, 128.2, 128.4, 129.3, 131.2; IR (KBr): *v* 2972, 2213, 1453, 1369, 1242, 768 cm^{-1}; HRMS calcd for $C_{19}H_{24}O$ 268.1827, found 268.1822.
13. Our spectral data for products **2a**–**h** (^{1}H NMR, ^{13}C NMR, FTIR, EIMS and optical rotation) were identical with those for the reported compounds.[6g–i,8]
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