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$Yb(OTf)_3$-catalyzed *C*-glycosylation: highly stereoselective synthesis of *C*-pseudoglycals

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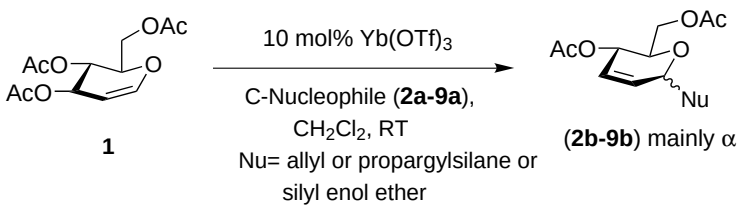
Abstract—A variety of functionalized *C*-pseudoglycals (pseudoglycal *C*-glycosides or *C*-hex-2-enopyranosides) have been obtained in excellent yields and stereoselectivity from the $Yb(OTf)_3$-catalyzed reaction of tri-*O*-acetyl glucal with silylated nucleophiles such as allyl and propargyl silanes and silyl enol ethers. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of *C*-glycosides[1] has been the subject of intense study for various reasons: (1) the discovery of naturally occurring *C*-nucleosides with important pharmacological properties[2] gave impetus to synthetic efforts for preparing active carbohydrate analogs; (2) the synthesis of biologically significant macromolecules such as palytoxin,[3] spongistatin[4] and halichondrin[5] requires *C*-glycosides as chiral building blocks; (3) *C*-glycosides are potential inhibitors of carbohydrate processing enzymes and they are stable analogues of glycans involved in important intra- and intercellular processes.[6] Among these *C*-glycosides, *C*-pseudoglycals, i.e glycals possessing the double bond between C(2) and C(3), represent a very important class of compounds because the double bond may be easily modified, for instance, by hydroxylation, hydrogenation, epoxidation and aminohydroxylation.

For the *C*-glycosylation of glycals with carbon nucleophiles furnishing *C*-pseudoglycals, a strong Lewis acid such as $BF_3{\cdot}OEt_2$[7] or $TiCl_4$[8] is generally required as an activator. Other reagents such as DDQ,[9] $AlCl_3$,[10] TMSOTf,[10] montmorillonite,[11] and $InCl_3$[12] are also known to promote *C*-glycosylation of glycals. A two-step process involving Tebbe methylenation and thermal Claisen rearrangement to produce *C*-β-pseudoglycals is a recent addition.[13] However, many of these procedures have limitations in terms of yields, stereoselectivities, reaction temperatures, compatibility with other functional groups present in the molecule and amounts of catalyst or reagent used. Therefore, there is still a great demand to find a potentially general method for this transformation. Recently, we reported an expeditious approach to the synthesis of *O*- and *S*-pseudoglycals by $Yb(OTf)_3$-catalyzed Ferrier glycosylation.[14] The continued interest of our research group in the synthesis of *C*-glycosides[1] has prompted us to explore the same catalyst in *C*-glycosylation as well. We now report our findings on the synthesis of *C*-pseudoglycals starting from tri-*O*-acetyl glucal and silylated species as acceptors in the presence of catalytic amounts of $Yb(OTf)_3$ (Scheme 1). Our results are summarized in Table 1.



Scheme 1.

Keywords: glycal; pseudoglycal; *C*-glycosides; ytterbium triflate; catalysis.

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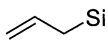
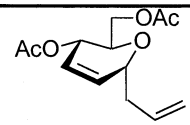
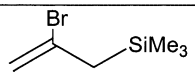
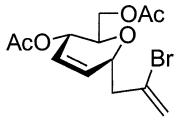
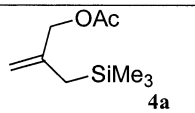
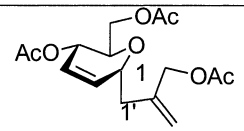
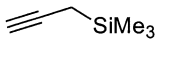
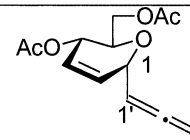
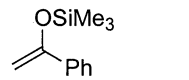
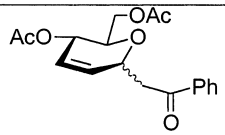
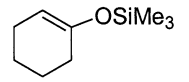
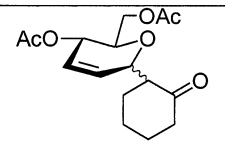
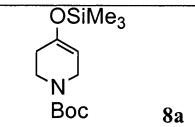
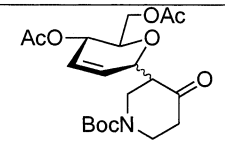
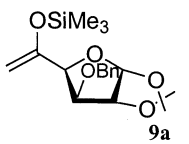
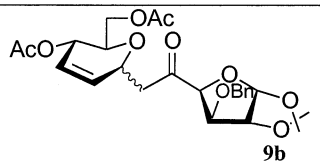
Table 1. Glycosidation of **1** with silylated nucleophiles in the presence of 10 mol% of $Yb(OTf)_3$

Entry	Acceptor	Glycoside	Time (h)	Yield (%) [a]	α/β [b]
1	 **2a**	 **2b**	3	94	α
2	 **3a**	 **3b**	4	89	α
3	 **4a**	 **4b**	4	89	α
4	 **5a**	 **5b**	16	92	α
5	 **6a**	 **6b**	10	90	8:1
6	 **7a**	 **7b**	12	89	11:1
7	 **8a**	 **8b**	15	84	8:1
8	 **9a**	 **9b**	12	88	5:1

(a) Isolated yields after column chromatography (b) α/β ratios were determined by NMR (250 MHz) analysis and / or isolation of pure isomers.

In a test case, 1 equiv. of **1** was treated with 1.2 equiv. of allyl trimethylsilane **2a** (entry 1, Table 1) and 10 mol% of $Yb(OTf)_3$ to furnish exclusively the known *C*-allyl α-glycoside **2b**[7b] in 92% yield. Encouraged by these findings, a cross section of silylated nucleophiles was chosen to react with **1** in the presence of 10 mol% $Yb(OTf)_3$. Substituted allylsilanes such as 2-bromoallylsilane **3a** (entry 2, Table 1) and 2-acetoxymethylallylsilane **4a** (entry 3, Table 1) smoothly afforded the corresponding *C*-α-glycosides **3b** and **4b**[15] in 88 and 90% yield, respectively. The reaction of propargylsilane **5a** (entry 4, Table 1) with **1** at 0°C for 16 h provided *C*-α-allenylglycoside **5b**,[16] which is a useful precursor for our ongoing program of enzyme inhibitor synthesis.

We focused our attention further on the reactivity of silyl enol ethers with **1** under the same conditions. In order to check this, commercially available silyl enol ether **6a** (entry 5, Table 1) was reacted with **1** to produce the corresponding *C*-α-glycoside **6b**[7a] as the major product. Silyl enol ether **7a** (entry 6, Table 1) also behaved identically to give *C*-glycoside **7b** in 86% yield. The success of *C*-glycosylation of **1** with silyl enol ether **8a** furnishing **8b** (entry 7, Table 1) is notable, since this indicates that similar Boc-protected aminoacid derivatives will be suitable substrates for these reaction conditions, thereby allowing access to *C*-glycosyl amino acids, which have become objects of synthetic interest.[17] The general applicability of this

protocol was further exemplified by the synthesis of a (1-5)-linked *C*-disaccharide derivative **9b** from **9a** (entry 8, Table 1) in 86% yield.

In summary, $Yb(OTf)_3$ has been demonstrated as an efficient catalyst for highly stereoselective *C*-glycosylations to produce a variety of functionalized *C*-pseudoglycals, which are useful intermediates for various applications. In addition, the catalyst recovered from the reaction mixture can be reused without serious loss of activity.[18] The non-hazardous and low toxic nature of lanthanoids should also be emphasized.

General procedure: To a mixture of tri-*O*-acetyl glucal **1** (1 equiv.) and nucleophile (1.2 equiv.) in CH_2Cl_2 was added $Yb(OTf)_3$ (10 mol%) at room temperature[19] and stirred. The contents were stirred for the required time (Table 1) and the reaction was monitored by TLC. Water (20 ml) was added to the reaction mixture and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography with mixtures of petroleum ether/ethyl acetate to furnish the products.

Acknowledgements

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15. Compound **4b**α: $[\alpha]_D^{21}$ +14.1 ($c=1.1$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 2.05 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, $COCH_3$), 2.27 (dd, $J_{1'a,1}=5.0$ Hz, $J_{1'a,1'b}=14.7$ Hz, 1 H, 1′-H_a), 2.47 (dd, $J_{1'b,1}=8.8$ Hz, $J_{1'b,1'a}=14.7$ Hz, 1 H, 1′-H_b), 3.93 (ddd, $J_{5,6a}=3.4$ Hz, $J_{5,6b}=6.3$ Hz, $J_{5,4}=9.9$ Hz, 1 H, 5-H), 4.14 (dd, $J_{6a,5}=3.4$ Hz, $J_{6a,6b}=11.9$ Hz, 1 H, 6-H_a), 4.21 (dd, $J_{6b,5}=6.3$ Hz, $J_{6b,6a}=11.9$ Hz, 1 H, 6-H_b), 4.38 (ddd, $J_{1,2}=2.4$ Hz, $J_{1,1'a}=5.0$ Hz, $J_{1,1b}=8.8$ Hz, 1 H, 1-H), 4.58 (d, $J_{3'a,3'b}=13.4$ Hz, 1 H, 3′-H_a), 4.59 (d, $J_{3'b,3'a}=13.4$ Hz, 1 H, 3′-H_b), 5.06 (s, 1 H, 4′-H_a, terminal methylene), 5.11 (dd, $J_{4,3}=2.3$ Hz, $J_{4,5}=9.9$ Hz, 1 H, 4-H), 5.16 (s, 1 H, 4′-H_b, terminal methylene), 5.80 (dd, $J_{3,4}=2.3$ Hz, $J_{3,2}=10.4$ Hz, 1 H, 3-H), 5.91 (dd, $J_{2,1}=2.4$ Hz, $J_{2,3}=10.4$ Hz, 1 H, 2-H). ^{13}C NMR ($CDCl_3$, 150 MHz): 20.7, 20.8, 21.0, 36.9, 62.7, 64.8, 66.6, 69.6, 70.4, 115.4, 123.9, 132.7, 140.1, 170.3, 170.5, 170.7. MS (EI): 326 (M^+), 267 ($M^+-C_2H_3O_2$).
16. Compound **5b**α: $[\alpha]_D^{21}$ +86.9 ($c=1$, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz): δ 2.05 (s, 3 H, $COCH_3$), 2.06 (s, 3 H, $COCH_3$), 3.88 (ddd, $J_{5,6a}=2.9$ Hz, $J_{5,6b}=5.4$ Hz, $J_{5,4}=8.4$ Hz, 1 H, 5-H), 4.14 (dd, $J_{6a,5}=2.9$ Hz, $J_{6a,6b}=12.1$ Hz, 1 H, 6-H_a), 4.17 (dd, $J_{6b,5}=5.4$ Hz, $J_{6b,6a}=12.1$ Hz, 1 H, 6-H_b), 4.81 (dd, $J_{1,2}=2.6$ Hz, $J_{1,1'}=5.2$ Hz, 1 H, 1-H), 4.83 (m, 2H, 3′-H_a and 3′-H_b), 5.21 (dd, $J_{4,3}=2.1$ Hz, $J_{4,5}=8.4$ Hz, 1 H, 4-H), 5.25 (m, 1 H, 1′-H), 5.78 (dd, $J_{3,4}=2.1$ Hz, $J_{3,2}=10.4$ Hz, 1 H, 3-H), 5.88 (dd, $J_{2,1}=2.6$ Hz, $J_{2,3}=10.4$ Hz, 1 H, 2-H). ^{13}C NMR ($CDCl_3$, 150 MHz): 20.7, 21.0, 63.1, 65.0, 68.8, 70.5, 77.2, 89.4, 125.1, 130.7, 170.3, 170.8, 209.1. MS (EI): 253 (MH^+), 213 ($M^+-C_3H_4$). Anal. calcd for $C_{13}H_{16}O_5$ (252.26): C, 61.89; H, 6.39. Found: C, 61.62; H, 6.12.
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18. For example, essentially the same result was obtained in the glycosylation of **1** with allyltrimethylsilane (entry 1, Table 1) (81%, 4 h, α) and 1-phenyl-1-(trimethylsily-

loxy)ethylene (entry 5, Table 1) (10 h, 79%, $\alpha/\beta = 7:1$) by using the catalyst recovered from the aqueous layer, which was dried under vacuo for 24 h before use. For the reusability of lanthanoid triflates as catalysts, see: (a) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett*. **1992**, *33*, 6815; (b) Kobayashi, S.; Hachiya, I. *Tetrahedron Lett*. **1992**, *33*, 1625; (c) Kobayashi, S. *Chem. Lett*. **1991**, 2187.

19. In the case of propargylsilane (entry 4, Table 1) the reaction mixture was stirred at 0°C.