Pergamon

Tetrahedron Letters, Vol. 35, No. 31, pp. 5673-5676, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01131-1

Allyl *C*-Glycosidations of Totally Unprotected Glycals and Allyltrimethylsilane with Trimethylsilyl Trifluoromethanesulfonate (TMSOTf)

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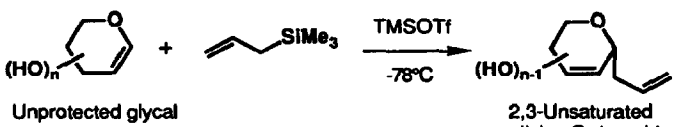
Abstract: Allyl *C*-glycosidations of the totally unprotected glycals, L-rhamnal (**1**), D-glucal (**2**), D-galactal (**3**) and D-fucal (**4**), with allyltrimethylsilane (**5**) using TMSOTf proceeded much more effectively than those of the corresponding acetylated glycals **10~13** to furnish the unprotected and 2,3-unsaturated allyl α-*C*-glycosides **6~9** in high yields, respectively.

While remarkable progress has been made in glycoside synthesis, the development of simple, selective, efficient and practical glycosidation methods is still a central problem not only in carbohydrate chemistry but also in synthetic organic chemistry.[1,2] In this context, the use of unprotected sugar as a glycosyl donor in the glycosidation reaction has undoubtedly considerable advantages. Recently, we have disclosed the synthesis of aryl *C*-glycosides by the glycosidations of unprotected methyl glycosides and unprotected 1-hydroxy sugars.[3,4] *C*-Glycosides as well as *O*- and *N*-glycosides are the subject of considerable interest in organic chemisrty and biochemistry.[5] In connection with this project, we have investigated the allyl *C*-glycosidations[2] of unprotected sugars. In this communication, we report that the allyl *C*-glycosidations of the totally unprotected glycals, L-rhamnal (**1**), D-glucal (**2**), D-galactal (**3**) and D-fucal (**4**), with allyltrimethylsilane (**5**) using TMSOTf (trimethylsilyl trifluoromethanesulfonate) proceeded effectively at low temperature in a fashion similar to the carbon-Ferrier reaction[6,7] to give stereoselectively the corresponding unprotected and 2,3-unsaturated allyl α-*C*-glycosides **6~9** in high yields, respectively (Scheme 1).



Unprotected glycal

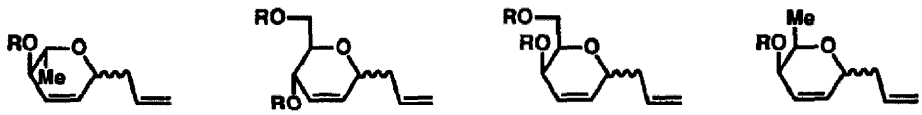
2,3-Unsaturated allyl α-*C*-glycoside

Scheme 1

During our initial attempts to find a suitable activator, we tested several acid activators such as TMSOTf, TBSOTf (TBSOTf=*t*-butyldimethylsilyl trifluoromethanesulfonate), $BF_3{\cdot}Et_2O$, Tf_2O, TfOH and CSA (CSA=DL-10-camphorsulfonic acid) for the glycosidation of the unprotected L-rhamnal (**1**) and allyltrimethylsilane (**5**). In order to avoid the self *O*-glycosidation of **1**, these reactions were carried out at the low temperature of -78°C. From the results shown in Table 1, it was found that TMSOTf was in sharp contrast with the other activators and worked effectively. Thus, the unprotected glycal **1** was smoothly coupled with **5** by using 1.0 equiv. of TMSOTf in CH_2Cl_2 (0.1M for **1**) at -78°C for 0.5h to afford only the unprotected and 2,3-unsaturated allyl α-*C*-glycoside **6**[8,9] in 94% yield. Since self coupling products from the *O*-glycosidation of **1** were not detected during the reaction at any stage, the present method depended on the faster trapping of **5** than a hydroxyl group of the glycosyl donor **1**.

To enhance the synthetic utility of this reaction, the *C*-glycosidations of several other unprotected glycals, D-glucal (**2**), D-galactal (**3**) and D-fucal (**4**), with **5** were next examined. The results summarized in Table 2 as entries 3, 5 and 7 showed that although the yield of the glycosidation of **4** was not very high, the glycosidations of **2** and **3** proceeded under similar conditions to give the allyl *C*-glycosides **7**[8] and **8**[8], respectively, in high yields. Remarkably, the stereoselectivity of these glycosidations was quite α-specific in all cases.[9] In the glycosidations of **2**~**4**, the use of MeCN as a co-solvent and the low concentration of the glycals in the solvent were crucial factors to get high yields of the desired allyl *C*-glycosides because of their low solubility in CH_2Cl_2 at low temperature.

Our next attention was to compare the unprotected glycals **1**~**4** and the corresponding acetylated glycals **10**~**13** from view point of yield and stereoselectivity in their allyl *C*-glycosidations with **5** by TMSOTf. Although acetylated glycals were frequently used as suitable glycosyl donors in the carbon-Ferrier reaction,[7] the allyl *C*-glycosidations of the acetylated glycals **10**~**13** using TMSOTf have never been reported. The results of the *C*-glycosidations of **10**~**13** under similar conditions as those for **1**~**4**, respectively, are summarized in Table 2 as entries 2, 4, 6 and 8. Notably, it was found that the allyl *C*-glycosidations of the totally unprotected glycals **2**-**4** with **5** proceeded much more effectively than those of the acetylated glycals **11**~**13** to give high yields of the allyl *C*-glycosides **7**, **8** and **9**[8], respectively. Furthermore, the stereoselectivity of the glycosidations of **1** and **2** was higher than that of the corresponding acetylated glycals **10** and **11**.



6: R=H (α)
14: R=Ac (α/β=9.9/1)

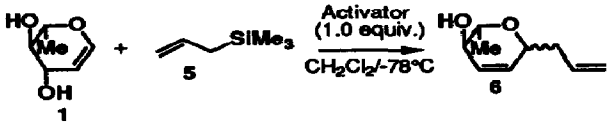
7: R=H (α)
15: R=Ac (α/β=37/1)

8: R=H (α)
16: R=Ac (α)

9: R=H (α)
17: R=Ac (α)

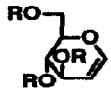
A representative experimental procedure is described for the reaction of **1** and **5**: To a mixture of L-rhamnal **1** (28.8 mg, 0.221 mmol) and allyltrimethylsilane (0.0703 ml, 0.443 mmol) in dry CH_2Cl_2 (2.2 ml) was added trimethylsilyl trifluoromethanesulfonate (0.0428 ml, 0.221 mmol) dropwise at -78°C under argon. The reaction mixture was stirred at the same temperature for 0.5 h and quenched with sat. $NaHCO_3$ (aq.). The mixture was then extracted with ethyl acetate and the extracts were washed with brine, dried over anhydrous

Table 1 Allyl *C*-glycosidations of unprotected glycal **1** and **5**[a)]



Entry	Activator	t / h	Yield / %[b)]	α/β Ratio[c)]
1	TMSOTf	0.5	94	>99/1
2	TBSOTf	0.5	46	>99/1
3	BF_3·Et_2O	0.5	trace	-
4	Tf_2O	0.5	0	-
5	TfOH	0.5	73	35/1
6	CSA	0.5	0	-

Table 2 Allyl *C*-glycosidations of several glycals and **5**[a)]

Entry	Glycal		Solvent / (M for glycal)	t / h	products	Yield / %[b)]	α/β Ratio[c)]
1		**1**: R=H	CH_2Cl_2 (0.1)	0.5	**6**	94	>99/1
2		**10**: R=Ac			**14**	95	9.9/1
3		**2**: R=H	CH_2Cl_2[2]-MeCN[1] (0.05)	0.5	**7**	91	>99/1
4		**11**: R=Ac			**15**	63	37/1
5		**3**: R=H	CH_2Cl_2[2]-MeCN[1] (0.02)	1	**8**	90	>99/1
6		**12**: R=Ac			**16**	19	>99/1
7		**4**: R=H	CH_2Cl_2[2]-MeCN[1] (0.02)	2	**9**	66	>99/1
8		**13**: R=Ac			**17**	20	>99/1

a) All reactions were carried out by use of 2.0 equiv. of **5** to the glycal.
b) Isolated yields after purification by column chromatography.
c) α/β Ratios were determined by ^{1}H-NMR (270 MHz) spectroscopy.

Na_2SO_4 and concentrated to a crude syrup which was chromatographed on silica gel with 3:2 hexane-ethyl acetate to afford the unprotected and 2,3-unsaturated allyl α-*C*-glycoside **6** (32.1 mg, 94.0%) as a sole product.

In conclusion, the ally *C*-glycosidations of the unprotected glycals with allyltrimethylsilane using TMSOTf exhibit two significant advantages. The first one is the higher reactivity of such glycosyl donors compared to the *O*-acethylated derivatives. The second advantage is the extremely high α-stereoselectivity of the present glycosidation reactions.

Acknowledgment: We are grateful to the Institute of Microbial Chemistry for the generous support of our program.

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8. All new compounds were purified by silica-gel column chromatography and were fully characterized by spectoscopic means. Significant ^{1}H-NMR spectra [270MHz, $CDCl_3$, δ (TMS), J(Hz)] are the following. **6**: 1.27 (3H, d, J=6.2, H-6), 1.73 (1H, d, J=8.4, OH), 2.31 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 2.42 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 3.65-3.75 (1H, m, H-4), 3.77 (1H, dq, J=6.2 and 4.6, H-5), 4.20 (1H, m, H-1), 5.05-5.2 (2H, m, H-3'), 5.75-5.95 (3H, m, H-2, 3 and 2'); **7**: 2.06 (2H, br s, OHx2), 2.31 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 2.47 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 3.55 (1H, ddd, J=7.9, 5.9 and 4.3, H-5), 3.77 (1H, dd, J=11.7 and 5.9, H-6), 3.83 (1H, dd, J=11.7 and 4.3, H-6), 4.10 (1H, br d, J=7.9, H-4), 4.24 (1H, m, H-1), 5.05-5.2 (2H, m, H-3'), 5.75-5.95 (3H, m, H-2, 3 and 2'); **8**: 2.06 (2H, br s, OHx2), 2.28 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 2.46 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 3.75-3.95 (4H, m, H-4, 5 and 6), 4.32 (1H, m, H-1), 5.12 (1H, br d, J=10.2, H-3'), 5.19 (1H, br d, J=17.2, H-3'), 5.84 (1H, ddt, J=17.2, 10.2 and 6.8, H-2'), 5.94 (1H, dd, J=10.2 and 3.2, H-2), 6.05 (1H, ddd, J=10.2, 5.4 and 2.0, H-3); **9**: 1.26 (3H, d, J=6.2, H-6), 1.55 (1H, br s, OH), 2.27 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 2.44 (1H, br ddd, J=13.8, 6.8 and 6.8, H-1'), 3.68 (1H, br dd, J=5.4 and 2.1, H-4), 3.92 (1H, dq, J=6.2 and 2.1, H-5), 4.23 (1H, m, H-1), 5.10 (1H, br d, J=10.1, H-3'), 5.12 (1H, br d, J=17.3, H-3'), 5.86 (1H, ddt, J=17.3, 10.1 and 6.8, H-2'), 5.89 (1H, dd, J=10.2 and 3.2, H-2), 6.04 (1H, ddd, J=10.2, 5.4 and 2.0, H-3).
9. In the unprotected allyl *C*-glycosides, the configurations of the anomeric positions were confirmed by ^{1}H-NMR analyses of the corresponding acetylated glycosides which were obtained by standard acetylation (Ac_2O, Py, 4-DMAP) and already reported including the results of their stereochemical assignments in refs. 7a, 7f and 7g.

(*Received in Japan* 11 *April* 1994; *accepted* 23 *May* 1994)