Rhamnosylation Reaction with a Phenyl 1-Thiorhamnoside and a Rhamnosyl Fluoride Which Have $^4C_1$ Conformation

Hidetoshi Yamada* and Tomonari Ikeda
School of Science, Kwansei Gakuin University, Uegahara, Nishinomiya 662-8501

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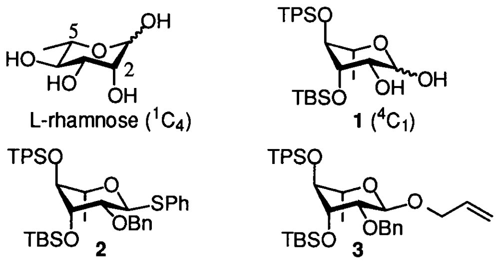
Rhamnosylation reaction with a phenyl 1-thiorhamnoside and a rhamnosyl fluoride that has chair conformation with more axial substituents ($^4C_1$) is described. Flipping of the ring conformation changed the high α-selectivity of the general rhamnosylation reaction. More β-rhamnosides were afforded under several conditions.

The *O*-rhamnosylation reactions generally show high α-selectivity.[1] Steric hindrance of the axial 2-*O*-substituent and the stereoelectronic effect cause the selectivity. We recently reported the chair conformation with more axial substituents of L-rhamnopyranose.[2] Flipping of the natural ring conformation of L-rhamnose was occurred by introduction of TBS [3] for the 3-OH group and TPS for the 4-OH group (**1**). Because both the above-mentioned reasons of the α-selectivity deeply concerned to its ring conformation, we were interested in the change of the diastereoselectivity when the 'flipped' sugars were used as rhamnosyl donors. We disclose here *O*-rhamnosylation reactions with a phenyl 1-thiorhamnoside and a rhamnosyl fluoride that has $^4C_1$ conformation.[4]

Phenyl 1-thio-2-*O*-benzyl-3-*O*-TBS-4-*O*-TPS-α-L-rhamnopyranoside (**2**) was chosen as the glycosyl donor of our preliminary investigations. It was synthesized from an allyl rhamnoside **3** [2] in 99% yield by treatment with PhSTMS and ZnI_2 in 1,2-dichloroethane at 50 °C for 2 h.[5] Only the α-isomer was thermodynamically obtained, and **2** kept the $^4C_1$ conformation.[12]

Figure 1.



L-rhamnose ($^1C_4$)

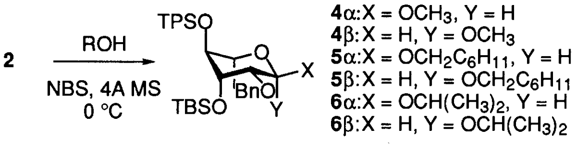
1 ($^4C_1$)

2

3

Reactions of **2** by NBS [6] were achieved with methanol, cyclohexylmethanol, and 2-propanol to give rhamnosides **4**, **5**, and **6**, respectively. Selection of solvents and size of the rhamnosyl acceptors influenced the diastereoselectivity at the anomeric position (Table 1). In dichloromethane, the α-isomer was selectively obtained when the primary alcohols were used as glycosyl donor (entries 1 and 2). In contrast, a reaction with 2-propanol showed β-selectivity (entry 3). In diethyl ether and THF, the β-isomers were preferred (entries 4 - 9). In acetonitrile, none of the case showed the β-selectivity. Increasing size of the alcohol resulted less β-isomer (entries 10 - 12). Derived rhamnosides **4**αβ, **5**αβ, and **6**αβ kept the $^4C_1$ conformation.[12]

Figure 2.



4α:X = OCH_3, Y = H
4β:X = H, Y = OCH_3
5α:X = $OCH_2C_6H_{11}$, Y = H
5β:X = H, Y = $OCH_2C_6H_{11}$
6α:X = $OCH(CH_3)_2$, Y = H
6β:X = H, Y = $OCH(CH_3)_2$

Table 1. Influence of solvent on the rhamnosylation reaction using phenyl 1-thiorhamnoside **2**

Entry	Alcohol	Solvent	Time /min	Yield[a] /%	Product	α:β[b] ratio
1	CH_3OH	CH_2Cl_2	5	68	**4**	87:13
2	$C_6H_{11}CH_2OH$	CH_2Cl_2	120	65	**5**	85:15
3	Me_2CHOH	CH_2Cl_2	10	81	**6**	37:63
4	CH_3OH	Et_2O	30	73	**4**	45:55
5	$C_6H_{11}CH_2OH$	Et_2O	20	73	**5**	50:50
6	Me_2CHOH	Et_2O	60	83	**6**	47:53
7	CH_3OH	THF	60	64	**4**	37:63
8	$C_6H_{11}CH_2OH$	THF	60	68	**5**	47:53
9	Me_2CHOH	THF	120	63	**6**	49:51
10	CH_3OH	CH_3CN	5	71	**4**	50:50
11	$C_6H_{11}CH_2OH$	CH_3CN	10	73	**5**	57:43
12	Me_2CHOH	CH_3CN	10	89	**6**	72:28

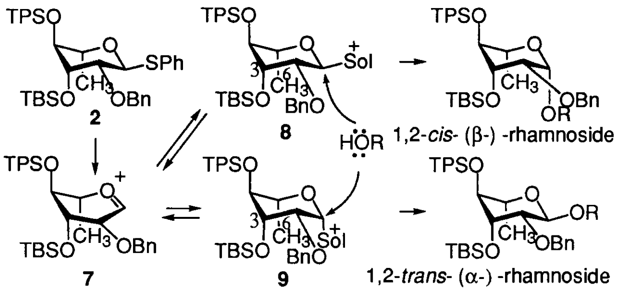
[a] Isolated yield. [b] Ratio determined by HPLC with reflective index detection.

The diastereoselectivity in the ethereal solvents and acetonitrile can be understood considering the reverse anomeric effect [7] and nitrilium-nitrite conjugation (nitrile effect).[8] Generally in *O*-glycosylation, the 1,2-cis- (α-) isomers are selectively obtained in ethereal solvents by the reverse anomeric effect.[7,9] Although **2** is classified into D-*gluco* type around the reaction center, the ratio of 1,2-*trans*- (α-) isomer is higher than in the case of the corresponding glucosylation. The oxonium cation **8** would be more stable than **9** by the reverse anomeric effect. However, an approach of an alcohol from lower face of **8**, the reaction would be slower than the reaction of **9** by a double 1,3-diaxial repulsion due to the oxygen substituent at C-3 and the methyl group of C-6. Therefore, the reaction from the upper face of **9** became relatively increased to give the 1,2-*trans*- (α-) isomer.

Generally in acetonitrile, conjugation from the axial site is more stable when the glycosyl donor is D-*gluco* type to give 1,2-trans- (β-) glucosides.[8,9] In the case with **2**, the conjugation from the axial site **9** would not be as stable as in the case with D-glucose derivatives by the double 1,3-diaxial repulsion. The ratio of the 1,2-*cis*- (β-) isomer, therefore, became relatively higher through **8** when methanol was used as a rhamnosyl acceptor (Table 1, entry 10). Bigger alcohol influenced the 1,3-

diaxial repulsion more than the solvent. Consequently, increasing size of the glycosyl acceptors resulted in more 1,2-*trans*-(α-) isomer through **9** (Table 1, entries 10-12).

Figure 3.



Reactions of the corresponding rhamnosyl fluorides showed a similar tendency. The fluoride **10** was prepared from **2** by treatment with DAST and NBS in dichloromethane at -40 °C.[10] The derived **10** (77% yield) was a 69:31 mixture of α- and β-isomers.[12] Separated each isomer was independently used for rhamnosylation reaction with cyclohexylmethanol under Mukaiyama's conditions[11] ($AgClO_4$, $SnCl_2$, 4A MS, -15 °C, 10 min) to give **5**α and **5**β (Table 2). Because both diastereoisomers **10**α and **10**β showed similar diastereoselectivity, the reaction passed through the same oxonium cation **7**. High α-selective reaction was observed in dichloromethane. In contrast, unusual ratio of the β-isomer was obtained in diethyl ether.

Figure 4.

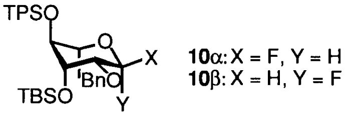


Table 2. Influence of solvent on the reaction using rhamnosyl fluoride **10** with cyclohexylmethanol

Entry	Fluoride	Solvent	Yield[a] /%	α:β[b] ratio
1	**10α**	CH_2Cl_2	70	98:2
2	**10α**	CH_3CN	61	75:25
3	**10α**	Et_2O	84	57:43
4	**10β**	CH_2Cl_2	70	>99:1
5	**10β**	CH_3CN	59	84:16
6	**10β**	Et_2O	80	60:40

[a]Isolated yield. [b]Ratio determined by HPLC with reflective index detection.

In conclusion, during rhamnosylation reactions with rhamnosyl donors that have $^4C_1$ ring conformation, the conformation was maintained. The diastereoselectivity at the anomeric center was different from the case with rhamnosyl donors of normal $^1C_4$ conformation. In some cases, the formation of the β-isomer exceeded the formation of the α-isomer.

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References and Notes

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3 In this paper, the following abbreviations are used; DAST: (diethylamino)sulfur trifluoride, TBS: *tert*-butyldimethylsilyl, TPS: *tert*-butyldiphenylsilyl. Others complied with a standard list of abbreviations on *J. Org. Chem.*, **64**, 21A (1999).

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9 Because we could not find the exactly same reaction conditions in the literature, reactions with phenyl 1-thio-2,3,4,6-tetra-*O*-benzyl-α-D-glucoside (**11**) were also investigated. When **11** was treated with cyclohexylmethanol under the same conditions with the reactions of **2**, the α/β ratios of the resulting glucoside were 80:20 in CH_2Cl_2 (75% yield), 84:16 in Et_2O (61% yield), and 15:85 in CH_3CN (83% yield).

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12 ^1H NMR coupling constants between neighboring protons are following. The value (Hz) was shown in order of H1-H2, H2-H3, H3-H4, and H4-H5 in parenthesis. **2**: (9.2, 2.8, 2.8, and 2.8), **4**α: (6.8, 2.4, 2.4, and 2.4), **4**β: (3.7, 3.4, 4.4, and 2.2), **5**α: (6.8, 2.4, 2.4, and 4.4), **5**β: (3.4, 3.4, 4.4, and 2.4), **6**α: (6.9, 2.7, 2.4, and 3.3), **6**β: (3.6, 3.0, 2.4, and 5.4), **10**α: (6.0, 2.0, 2.0, and 5.6), **10**β: (3.7, 3.2, 4.0, and 4.8).