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Note

β-Selective O-rhamnosylation with a rhamnosyl trichloroacetimidate that has the $^4C_1$ conformation

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Abstract

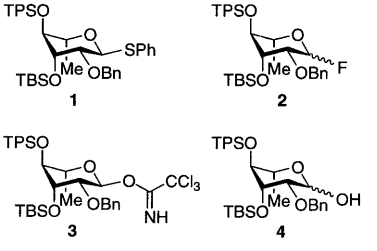
A β-selective rhamnosylation reaction was accomplished by using 2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-4-*O*-*tert*-butyldiphenylsilyl-α-L-rhamnopyranosyl trichloroacetimidate and a catalytic amount of 9-borabicylco[3.3.1]nonyl trifluoromethanesulfonate. The rhamnosyl donor has the $^4C_1$ ring conformation to change the general high α-selectivity of the rhamnosylation reactions. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: β-Selective O-rhamnosylation; $^4C_1$ Conformation; Trichloroacetimidate

1. Introduction

The glycosylation reaction using trichloroacetimidate as a leaving group has been a most useful procedure for the chemical formation of the O-glycosylic bond. The diastereoselectivity of the reaction has been controlled by both the S_N2-type reaction and by solvent-dependent control through an oxocarbenium ion intermediate when the glycosyl donor is the D-gluco type [1]. Even by this method, however, it has been difficult to invert the high α-selectivity of the D-manno type glycosyl donors [2]. The steric hindrance of the axial 2-O-substituent and the thermodynamic anomeric effect strongly assist in the formation of the α isomers.

We recently reported a rhamnosylation reaction with a thiorhamnoside **1** and a rhamnosyl fluoride **2** that have the $^4C_1$ conformation [3]. Flipping of the natural ring conformation of L-rhamnose changed the glycosyl donor into D-gluco type around the reaction center and caused a decrease of the original high α-selectivity. Sometimes the formation of the β isomer slightly exceeded the formation of the α isomer. In the present contribution we describe a β-selective rhamnosylation reaction with a rhamnosyl trichloroacetimidate **3** that has the $^4C_1$ conformation.



2. Results and discussion

The rhamnosyl donor **3** was prepared from the corresponding lactol **4** [4] by treatment

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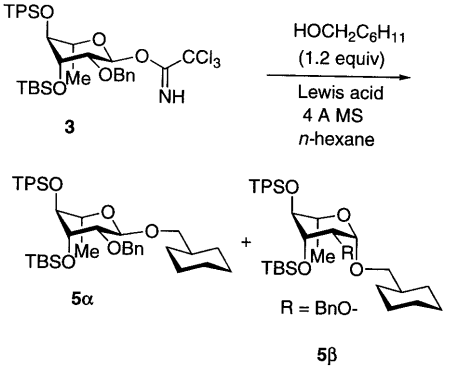
Table 1
Influence of Lewis acid on the rhamnosylation reaction using trichloroacetimidate **3**

Entry	Lewis acid (equiv)	Temperature (°C)	Time (h)	Yield [a] (%)	**5**α:**5**β [b]
1	$MgBr_2{\cdot}Et_2O$ (5.0)	rt	16	55	72:28
2	$AlCl_3$ (0.5)	−40	60	61	60:40
3	$BF_3{\cdot}OEt_2$ (0.1)	−78	0.5	97	43:57
4	TMSOTf (0.05)	−78	1.17	70	51:49
5	TESOTf (0.05)	−78	0.17	72	46:54
6	TBSOTf (0.05)	−78	0.17	72	41:59
7	TIPSOTf (0.05)	−78	0.25	72	32:68

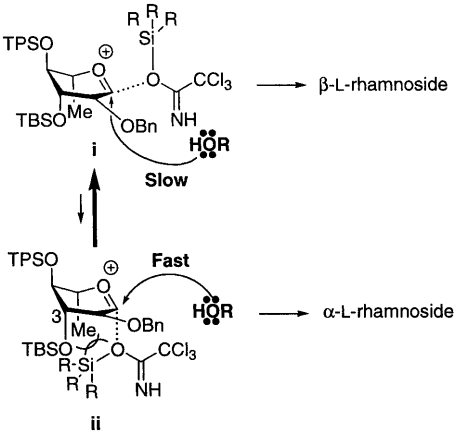
[a] Isolated yield.
[b] Ratio was determined by HPLC using a YMC R-SIL-5 column (4.6 × 250 mm) with 100:1 *n*-hexane–EtOAc. Detection was by refractive index.

with diazabicyclo[5.4.0]undec-7-ene (DBU)[1] and CCl_3CN in dichloromethane at room temperature [5]. Only the α isomer was obtained as the thermodynamic product [6], and the resulting trichloroacetimidate kept the $^4C_1$ conformation. The ^{1}H NMR coupling constants between the neighboring protons on the pyranoside ring of **3** were H-1–H-2: 6.9 Hz, H-2–H-3: 2.4 Hz, H-3–H-4: 2.4 Hz, and H-4–H-5: 5.7 Hz. The reaction of **3** with various Lewis acids is summarized in Table 1. Cyclohexylmethanol (1.2 equivalents of **3**) was used as a glycosyl acceptor. Each reaction was carried out in hexane. The S_N2-type glycosylation was observed by the combination of the glycosyl trichloroacetimidates and nonpolar solvents [1,2c,7]. Moreover, during some preliminary reactions of **3** with $BF_3{\cdot}OEt_2$ or TMSOTf in dichloromethane, diethyl ether, or *n*-hexane, the highest β-selectivity was observed in *n*-hexane in either case. With $MgBr_2{\cdot}Et_2O$ or $AlCl_3$ the reaction was slow, and the α isomer **5**α was preferred (entries 1 and 2). With $BF_3{\cdot}OEt_2$ the β isomer **5**β was slightly preferred to the α isomer (entry 3). Activation with TMSOTf afforded a 1:1 mixture. When using silyl trifluoromethanesulfonates (triflates) as the Lewis acid, increasing size of the silyl triflate resulted in more β-selectivity (entries 4–7). Thus, utilization of TIPSOTf provided a β-selective reaction to give a 32:68 mixture of the **5**α and **5**β anomers (Scheme 1).

From the result of the reactions with silyl triflates, we considered the following possible mechanism for the reaction (Scheme 2). Because the reaction was carried out in *n*-hexane, solvent effects would be diminished. One of the oxocarbenium ion intermediates **i**



Scheme 1.



Scheme 2.

[1] In this paper, the following abbreviations are used; TBS: *tert*-butyldimethylsilyl, TES: triethylsilyl, TIPS: triisopropylsilyl, and TPS: *tert*-butyldiphenylsilyl. Others comply with a standard list of abbreviations published in the *ACS Style Guide*, 2nd edition, American Chemical Society, Washington, DC, 1997, pp. 107–141.

would have an equilibrium giving **ii**. The intermediate **i** would be more stable than **ii** by the double 1,3-diaxial repulsion with the oxygen substituent at C-3 and the C-6 methyl group of **ii**. Meanwhile, the reaction with an alcohol would be faster at **ii** than at **i** by steric repulsion. Using a bigger Lewis acid as an activator, the steric repulsion of **ii** would be increased. Therefore, the equilibrium would be biased to **i** to obtain the β rhamnoside, although the reaction rate with the alcohol is slower. When the smaller TMSOTf was used as catalyst, the ratio of **ii** was relatively increased.

On the basis of the above consideration, we investigated the rhamnosylation reaction with an alternative large Lewis acid, 9-borabicylco[3.3.1]nonyl trifluoromethanesulfonate (9-BBNOTf), as a catalyst. Treatment of **3** with 9-BBNOTf at −78 °C afforded a 32:68 mixture of **5**α and **5**β in 86% yield. A lower reaction temperature gave more β selectivity. Thus, when the reaction was carried out at −95 °C, the α:β ratio was 27:73 (73% yield). In order to attempt a lower reaction temperature, *n*-pentane was used as the solvent. In this case, however, the diastereoselectivity was almost the same as in the case of *n*-hexane. Treatment of **3** with 9-BBNOTf in *n*-pentane at −78 °C afforded a 32:68 mixture of **5**α and **5**β (86% yield). When the reaction was carried out at −129 °C, the α:β ratio was 30:70 (94% yield).

In conclusion, a β-selective rhamnosylation reaction proceeded with the rhamnosyl trichloroacetimidate that has the $^4C_1$ conformation when the reaction was carried out at low temperature with 9-BBNOTf as a catalyst in *n*-hexane. When using silyl triflates as the Lewis acid, increasing size of the triflate afforded more β isomer.

3. Experimental

General methods.—The reactions were carried under a positive pressure of argon. *n*-Hexane and *n*-pentane used as solvents for the reactions. These solvents were distilled from CaH_2. High-performance liquid chromatography (HPLC) was performed on a Shimazu LC-10AD instrument with a Hitachi L-7490 refractive index detector using a YMC R-SIL-5 column (4.6 × 250 mm). Optical rotations were determined on a JASCO DIP-370 in the indicated solvent. IR spectra were determined using a JASCO FT-IR-5300 spectrophotometer and reported as ν_{max} values. NMR spectra were determined on JEOL α-400 or Varian Unity 300 instruments. Chemical shifts are reported in δ units downfield from tetramethylsilane (Me_4Si). The ^{1}H NMR data were indicated by chemical shift with the number of the protons, coupling pattern, coupling constants, and assignment in parentheses. Splitting patterns are designated as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, and br: broad. The ^{13}C NMR data were indicated by chemical shift with the type of carbon in parentheses. HRMS was determined on a JEOL AX-500 spectrometer.

2-O-*Benzyl-3*-O-tert-*butyldimethylsilyl-4*-O-tert-*butyldiphenylsilyl*-α-L-*rhamnopyranosyl trichloroacetimidate* (**3**).—Trichloroacetonitrile (43.4 μL, 0.430 mmol) and DBU (6.4 μL, 0.043 mmol) were added to a solution of 2-*O*-benzyl-3-*O*-*tert*-butyldimethylsilyl-4-*O*-*tert*-butyldiphenylsilyl-α-L-rhamnopyranose (**4**) [4] in CH_2Cl_2 (3 mL) at rt. The reaction mixture was stirred for 2 h, then diluted with CH_2Cl_2. The mixture was filtered through a cotton–Celite pad and evaporated to give the crude trichloroacetimidate **3**. The crude product was directly used for the following rhamnosylation reactions.

Data for **3**: $[\alpha]_D^{20}$ −52.2° (*c* 1.61, $CHCl_3$); FTIR (film) 3340 (C=NH), 3070 (Ar), 3050 (Ar), 3020 (Ar), 2970 (–CH_2–), 2895 (–CH_2–), 2860 (–CH_2–), 1670 (C=NH), 1470 (C=NH), 1100 (R–O–R′) cm^{-1}; ^{1}H NMR (300 MHz in $CDCl_3$) δ −0.25 (3 H, s), −0.08 (3 H, s), 0.74 (9 H, s), 1.02 (9 H, s), 1.06 (3 H, d, *J* 7.2 Hz; H-6), 3.62 (1 H, br dd, *J* 5.7, 2.4 Hz; H-4), 3.91 (1 H, qd, *J* 7.2, 5.7 Hz; H-5), 4.00 (1 H, dd, *J* 6.9, 2.4 Hz; H-2), 4.00 (1 H, dd, *J* 2.4, 2.4 Hz; H-3), 4.63 (1 H, d, *J* 12.0 Hz; C*H*HPh), 4.72 (1 H, d, *J* 12.0 Hz; CH*H*Ph), 6.20 (1 H, d, *J* 6.9 Hz; H-1), 7.24–7.48 (11 H, m; Ar), 7.57–7.63 (4 H, m; Ar), 8.60 (1 H, br s; NH); ^{13}C NMR (100 MHz in $CDCl_3$) δ −5.4 (CH_3), −4.6 (CH_3), 18.0 (C), 18.9 (CH_3; C-6), 19.2 (C), 25.7 (3 × CH_3), 26.9

($3 \times CH_3$), 72.3 (CH_2), 73.4 (CH), 73.7 (CH), 75.8 (CH), 77.3 (CH), 94.2 (C; CCl_3), 98.3 (CH; C-1), 127.6 (CH), 127.7 ($2 \times$ CH), 127.8 ($2 \times$ CH), 127.9 ($2 \times$ CH), 128.3 ($2 \times$ CH), 129.9 (CH), 130.0 (CH), 133.2 (C), 135.7 (C), 135.8 ($2 \times$ CH), 135.9 ($2 \times$ CH), 138.0 (C), 161.4 (C; C=NH).

Typical method of the rhamnosylation reaction.—To a solution of **3** (124.5 mg, 0.078 mmol) in hexane (3 mL) was added 4 Å MS (300 mg), and the mixture was cooled to −95 °C. To the mixture was successively added cyclohexylmethanol (11.5 μL, 0.094 mmol) and 0.5 M solution of 9-BBNOTf in hexane (15.6 μL, 0.008 mmol). After stirring for 30 min at −95 °C, aq $NaHCO_3$ was added to the reaction mixture. The mixture was filtered through a cotton–Celite pad and washed with brine. Drying over $MgSO_4$, evaporation, and chromatography on silica gel (2 g, eluting with 50:1 *n*-hexane–EtOAc) afforded a mixture of **5**α and **5**β (39.8 mg, 73% yield). The mixture was separated by HPLC (eluant: 100:1 *n*-hexane–EtOAc, flow rate: 3.5 mL/min).

Data for **5**α: $[\alpha]_D^{21}$ −52.7° (*c* 0.46, $CHCl_3$); FTIR (film) 3070 (Ar), 3050 (Ar), 3020 (Ar), 2930 (–CH_2–), 2860 (–CH_2–), 1105 (R–O–R′) cm^{-1}; ^1H NMR (400 MHz in $CDCl_3$ at 50 °C) δ −0.26 (3 H, s), −0.10 (3 H, s), 0.74 (9 H, s), 0.99 (1 H, m), 1.03 (9 H, s), 1.09 (3 H, d, *J* 6.8 Hz; H-6), 1.14–1.33 (4 H, m), 1.60–1.88 (6 H, m), 3.39 (1 H, dd, *J* 9.5, 6.8 Hz; –OC*H*HC_6H_{11}), 3.60 (1 H, dd, *J* 4.4, 2.4 Hz; H-4), 3.64 (1 H, dd, *J* 9.5, 6.4 Hz; –OC*H*HC_6H_{11}), 3.70 (1 H, dd, *J* 6.6, 2.4 Hz; H-2), 3.89 (1 H, qd, *J* 6.8, 4.4 Hz; H-5), 3.95 (1 H, dd, *J* 2.4, 2.4 Hz; H-2), 4.64 (1 H, d, *J* 12.0 Hz; C*H*HPh), 4.76 (1 H, d, *J* 12.0 Hz; C*H*HPh), 4.79 (1 H, d, *J* 6.8 Hz; H-1), 7.23–7.44 (11 H, m; Ar), 7.61–7.64 (4 H, m; Ar); ^{13}C NMR (100 MHz in $CDCl_3$) δ −5.4 (CH_3), −4.7 (CH_3), 18.1 (C), 18.6 (CH_3; C-6), 19.2 (C), 25.8 ($3 \times CH_3$), 25.9 (CH_2), 25.9 (CH_2), 26.7 (CH_2), 26.9 ($3 \times CH_3$), 29.9 (CH_2), 30.2 (CH_2), 38.1 (CH), 72.5 (CH_2), 72.8 (CH), 74.0 (CH), 74.4 (CH_2), 76.8 (CH), 76.9 (CH), 98.8 (CH; C-1), 127.3 (CH), 127.7 ($2 \times$ CH), 127.8 ($2 \times$ CH), 127.8 ($2 \times$ CH), 128.1 ($2 \times$ CH), 129.7 (CH), 129.8 (CH), 133.4 (C), 133.5 (C), 135.8 ($2 \times$ CH), 135.9 ($2 \times$ CH), 138.8 (C); HRMS (FAB) calcd for $C_{42}H_{62}O_5Si_2Na$ 725.4033. Found: 725.4056.

Data for **5**β: $[\alpha]_D^{21}$ +14.8° (*c* 1.56, $CHCl_3$); FTIR (film) 3070 (Ar), 3020 (Ar), 2930 (–CH_2–), 2860 (–CH_2–), 1110 (R–O–R′) cm^{-1}; ^1H NMR (400 MHz in $CDCl_3$) δ −0.19 (3 H, s), −0.03 (3 H, s), 0.76 (9 H, s), 1.02 (9 H, s), 0.86–1.27 (6 H, m), 1.22 (3 H, d, *J* 7.3 Hz; H-6), 1.55–1.79 (5 H, m), 3.04 (1 H, dd, *J* 9.3, 6.3 Hz; –OC*H*HC_6H_{11}), 3.67 (1 H, dd, *J* 8.8, 6.3 Hz; –OC*H*HC_6H_{11}), 3.76 (1 H, br, qd, *J* 7.3, 2.4 Hz; H-5), 3.80 (1 H, dd, *J* 4.4, 2.4 Hz; H-4), 3.86 (1 H, dd, *J* 3.4, 3.4 Hz; H-2), 3.91 (1 H, dd, *J* 4.4, 3.4 Hz; H-3), 4.55 (1 H, d, *J* 12.2 Hz; C*H*HPh), 4.67 (1 H, d, *J* 12.2 Hz; C*H*HPh), 4.83 (1 H, d, *J* 3.4 Hz; H-1), 7.23–7.42 (11 H, m; Ar), 7.62–7.66 (4 H, m; Ar); ^{13}C NMR (100 MHz in $CDCl_3$) δ −5.3 (CH_3), −4.4 (CH_3), 18.2 (C), 19.3 (C), 20.0 (CH_3; C-6), 25.8 ($3 \times CH_3$), 25.9 (CH_2), 25.9 (CH_2), 26.6 (CH_2), 27.0 ($3 \times CH_3$), 30.1 (CH_2), 30.2 (CH_2), 38.2 (CH), 71.1 (CH_2), 71.6 (CH), 73.9 (CH), 74.9 (CH_2), 75.2 (CH), 77.2 (CH), 98.5 (CH, C-1), 127.3 (CH), 127.5 ($2 \times$ CH), 127.6 ($2 \times$ CH), 127.7 ($2 \times$ CH), 128.1 ($2 \times$ CH), 129.6 (CH), 129.8 (CH), 133.4 (C), 134.0 (C), 135.7 ($2 \times$ CH), 135.8 ($2 \times$ CH), 138.9 (C); HRMS (FAB) calcd for $C_{42}H_{62}O_5Si_2Na$ 725.4033. Found: 725.4020.

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