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α -SELECTIVE THERMAL GLYCOSIDATION OF RHAMNOSYL AND MANNOSYL CHLORIDES

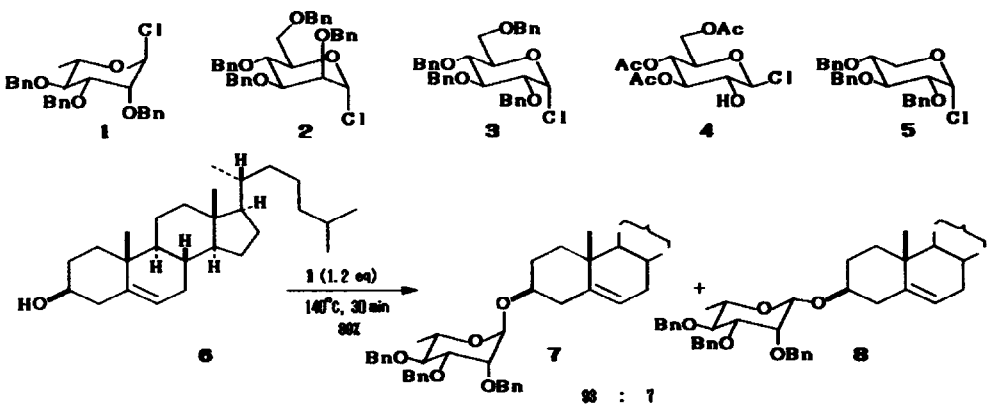
Mugio NISHIZAWA,* Yukiko KAN, Waka SHIMOMOTO, and Hidetoshi YAMADA

Faculty of Pharmaceutical Sciences, Tokushima Bunri University
Yamashiro-Cho, Tokushima 770, Japan

Abstract: Stereoselective thermal glycosylation of a variety of alcohols with 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl chloride and 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl chloride have achieved to give α-glycosides in high selectivity.

In the previous communications we have described a thermal glycosidation procedure of alcohols with glucosyl or xylosyl chlorides, 3, 4, or 5, without using any metal salt.[1,2] The procedure was operationally very simple but non-stereoselective. When this procedure was applied with 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl chloride (1) and 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl chloride (2), highly α-selective glycosidation resulted particularly with sterically much hindered alcohols based on a steric as well as stereoelectronic effects of C-2 axially oriented oxygen functionalities.[3]

The results are summarized in Table I. A typical experimental example is shown by the rhamnosylation of cholesterol using neither metal salt nor any other addendum. A dried mixture of cholesterol (6) (54.7 mg, 0.14mmol) and rhamnosyl chloride 1 (77.0 mg, 0.18 mmol, 1.2 equiv) was heated at 140° C for 30 min under an argon atmosphere.[1] The material was dissolved in



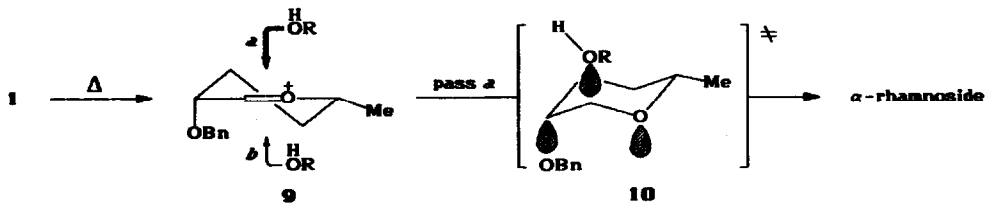
dichloromethane and which was directly subjected to silica gel column chromatography with a mixture of hexane and ethyl acetate (10:1) as an eluant to give rise to a mixture of α- and β-rhamnosides (100.5 mg, 89% yield). Upon HPLC analysis using a 4.6 × 250 mm column with a mixture of hexane and ethyl acetate (30:1) at flow rate of 1.5 mL/min, the α/β ratio was established to be 93:7. The major isomer, $[\alpha]_D^{14}$ -41.4° (*c* 0.80, $CHCl_3$), with Rt 10.3 min showed anomeric carbon NMR signal at 96.0 ppm with a J_{CH} = 166 Hz and a doublet anomeric proton NMR signal at 4.81 ppm with J = 1.7 Hz, and which was assigned to α-rhamnoside 7. The minor isomer, $[\alpha]_D^{14}$+18.2° (*c* 0.26, $CHCl_3$), with Rt 11.6 min showed those signals at 99.3 ppm with J_{CH} = 151 Hz (^{13}C NMR) and 4.47 ppm as a broad singlet (^1H NMR), and was assigned to be β-rhamnoside 8.[4]

When the same operation was carried out in the presence of *N,N,N',N'*-tetramethylurea (TMU, 1.2 equiv) as an acid scavenger, rhamnosylation of cholesterol occurred in analogous yield but the stereoselectivity decreased to 88:12 (run 2).[5]

Although thermal condensations of 1 with sterically less hindered alcohols such as geraniol, decanol, or methanol gave rhamnosides with low stereoselectivities (run 12, 13, and 14), sterically much hindered alcohols such as dihydrolanosterol (12), methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (13), allyl 3,4,6-tri-*O*-benzyl-α-D- and β-D-glucopyranosides (14a and 14b, respectively), allyl 2,3-di-*O*-benzyl-α-L-rhamnopyranoside (15), cholesteryl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (16), and 1-methylcyclohexanol, afforded α-rhamnosides essentially complete stereoselectivity in moderate to good yields (run 4, 5, 6, 7, 8, 9, 10, and 11). Rhamnosylation of cholestanol (11) occurred very high yield (99.5%) with moderate stereoselectivity (run 3).[6]

Thermal condensation of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl chloride (2) with cholesterol (6) and methyl glucoside 13 were also examined, and highly α-selective glycosidations were achieved again (run 15 and 16).[7]

During the disaccharide synthesis (run 5, 6, 7, 8, 9 and 10), the stereochemistry of preexisting glycosidic linkages were not changed at all under the thermal glycosidation condition. Thus the observed stereoselectivity is a result of kinetic control, and thermodynamic equilibrium between α and β glycosides may not exist. To the thermally generated cationic intermediate 9, nucleophile (ROH) will attack through pass *a*, since pass *b* has a severe steric repulsion with the neighboring axial substituent. Now a late transition state 10 can be imagined, which maintains three orbitals of trans antiperiplanar relationship as

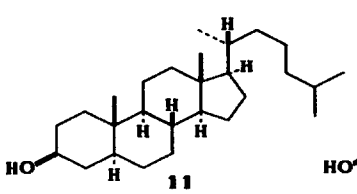


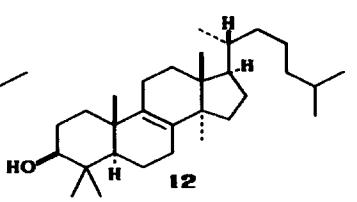
illustrated.[3] Thus the preferential formation of α-rhamnoside is reasonable not only from a steric reason but also from a stereoelectronic effects. The case of glucosyl chloride or xylosyl chloride,[2] neither steric nor stereoelectronic demand exists and thus lead to a comparable amounts of both stereoisomers.

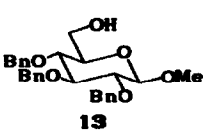
Table I. α-Selective thermal glycosidation.

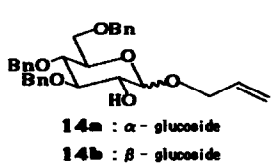
run	alcohol	donor	equiv	temp (° C)	time (min)	yield(%)	α/β ratio
1	cholesterol (6)	1	1.2	140	30	89	93:7
2	cholesterol (6)[a]	1	1.2	140	30	89	88:12
3	cholestanol (11)	1	1.2	140	30	99.5	87:13
4	dihydrolanosterol (12)	1	1.2	140	60	48	100:0
5	methyl glucoside 13	1	1.2	140	30	55	100:0
6	allyl glucoside 14a	1	1.2	140	60	56	100:0
7	allyl glucoside 14b	1	1.2	140	30	65	100:0
8	allyl glucoside 14b[a]	1	1.2	140	30	75	100:0
9	allyl rhamnoside 15	1	1.2	140	30	60	100:0
10	cholesteryl glucoside 16	1	1.2	140	45	74	100:0
11	1-methylcyclohexanol	1	1.2	140	30	21	100:0
12	geraniol	1	1.2	90	60	66	70:30
13	decanol	1	1.2	140	30	74	82:18
14	methanol[b]	1	--	25	120	88	43:57
15	cholesterol (6)	2	1.2	140	45	79	87:13
16	methyl glucoside 13	2	1.2	140	30	80	100:0

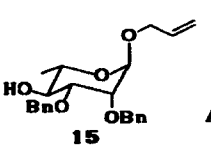
[a]Thermal reaction was carried out in the presence of TMU (1.2 equiv). [b]Large excess of methanol was employed.

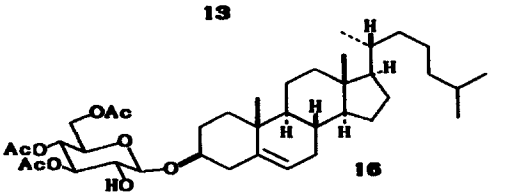












Therefore, the thermal glycosidation described here does not use any hazardous (or expensive) metal salt or even solvent, and is simple, safety, clean, and economical enough for practical use.

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1. M. Nishizawa, Y. Kan, and H. Yamada, *Tetrahedron Lett.*, 29, 4597 (1988).
2. M. Nishizawa, Y. Kan, and H. Yamada, *Chem. Pharm. Bull.*, 37, 565 (1989).
3. P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry" Ed. J. E. Baldwin, Organic Chemistry Series Vol 1, pp 18, 1983.
4. R. Kasai, M. Okihara, J. Asakawa, and O. Tanaka, *Tetrahedron*, 35, 1427 (1979).
5. Thermal rhamnosidation in the presence of tetramethylurea gave analogous to even lower yield in most cases.
6. Optical rotation value and ^{13}C NMR (in $CDCl_3$) chemical shift value (C-H coupling constant) of anomeric carbon of each α isomer were: run 3, $[\alpha]_D^{16}$-19.2° (*c* 0.58, $CHCl_3$), 95.7 ppm (169 Hz); run 4, $[\alpha]_D^{16}$+0.3° (*c* 1.70, $CHCl_3$), 100.7 ppm (166 Hz); run 5, $[\alpha]_D^{16}$-12.9° (*c* 2.05, $CHCl_3$), 98.4 ppm (167 Hz); run 6, $[\alpha]_D^{14}$-1.6° (*c* 2.55, $CHCl_3$), 98.7 ppm (170 Hz); run 7, $[\alpha]_D^{13}$+32.0° (*c* 3.18, $CHCl_3$), 97.5 ppm (169 Hz); run 9, $[\alpha]_D^{15}$-13.4° (*c* 3.52, $CHCl_3$), 97.0 ppm (167 Hz); run 10, $[\alpha]_D^{15}$ -19.0° (*c* 5.22, $CHCl_3$), 98.3ppm (172 Hz); run 11, $[\alpha]_D^{16}$-46.9° (*c* 0.32, $CHCl_3$), 91.9 ppm (164 Hz); run 12, $[\alpha]_D^{15}$-20.8° (*c* 1.47, $CHCl_3$), 96.9 ppm (167 Hz); run 13, $[\alpha]_D^{13}$-22.6° (*c* 0.40, $CHCl_3$), 98.0 ppm (169 Hz); run 14, $[\alpha]_D^{13}$-26.6° (*c* 1.16, $CHCl_3$), 99.1 ppm (169 Hz); run 15, $[\alpha]_D^{16}$+25.8° (*c* 0.60, $CHCl_3$), 95.8 ppm (163 Hz); run 16, $[\alpha]_D^{13}$+15.2° (*c* 3.33, $CHCl_3$), 98.2 ppm (169 Hz), and of each β isomer were: run 3, $[\alpha]_D^{13}$+22.6° (*c* 0.10, $CHCl_3$); run 12, $[\alpha]_D^{15}$+56.9° (*c* 0.58, $CHCl_3$), 99.5 ppm (154 Hz); run 13, $[\alpha]_D^{15}$-75.7° (*c* 0.05, $CHCl_3$), 101.7 ppm (155 Hz); run 14, $[\alpha]_D^{13}$+80.3° (*c* 1.41, $CHCl_3$), 102.6 ppm (150 Hz); run 15, $[\alpha]_D^{14}$-25.5° (*c* 0.12, $CHCl_3$).
7. Recently related α-selective glycosidation of mannosyl fluoride in the presence of $CpZrCl_2$-$AgBF_4$ was reported, see K. Suzuki, H. Maeta, T. Suzuki, and T. Matsumoto, *Tetrahedron Lett.*, 30, 6879 (1989).

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