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NEW METHOD FOR THE SYNTHESIS OF GLYCOSYL GLYCERIDES — THE STEREOSELECTIVE REDUCTION OF GLYCOSIDES OF 1-ALKOXY-3-HYDROXYACETONE —

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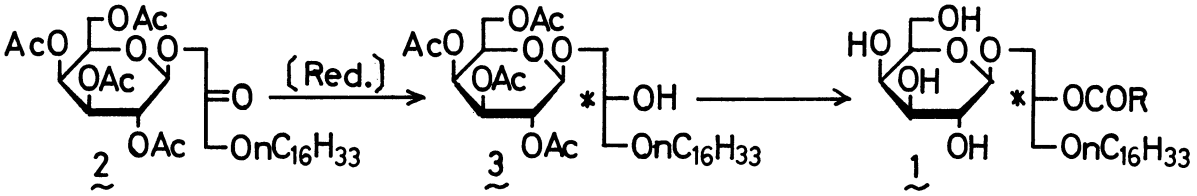
Glycosides of 1-hexadecyloxy-3-hydroxyacetone are prepared from 1-halosugars and 1-O-hexadecyl-2-O-benzylglycerol. The glycosides are converted to the corresponding alcohols, precursors to the synthesis of glycosyl glycerides, by the stereoselective reduction with L-Selectride.

Glycosyl glycerides are widely distributed in plants, bacteria, and animal tissues,[1] and are thought to play a significant role in the photosynthetic apparatus and in myelin, though the precise function is not yet clear. Many methods have already been published for the synthesis of glycosyl glycerides, but, in every case, the optically active glycerol derivatives are used as starting materials.[1),2)] In this communication, we wish to report a new method for the synthesis of optically active glycolipid 1[3] by way of a stereoselective reduction of ketone 2, easily prepared from racemic glycerol derivative, to the corresponding alcohol 3, precursor to the synthesis of glycosyl glyceride.



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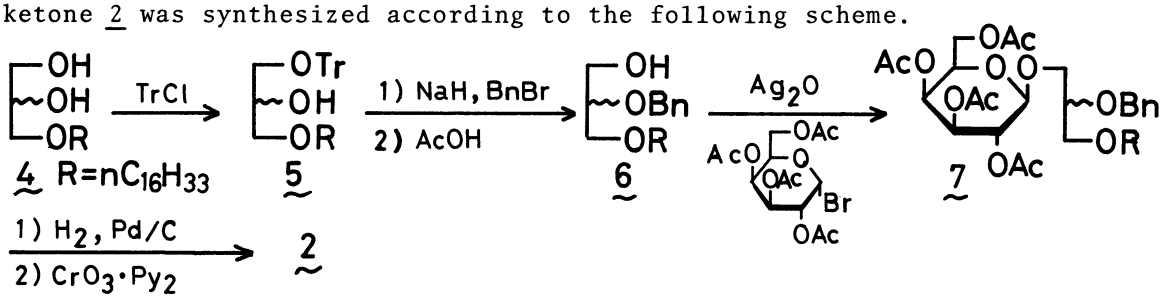
The ketone 2 was synthesized according to the following scheme.



Tritylation of racemic chimyl alcohol 4[4] gave monotrityl ether 5[5] in quantitative yield. Protection of the hydroxyl group of 5 was accomplished by treatment with sodium hydride and benzyl bromide. The resulting benzyl ether[6] was detritylated by refluxing in 80% acetic acid to give the alcohol 6[7] in 79% yield from 5. The alcohol 6 was glycosidated with acetobromogalactose in the presence of

silver oxide and Drierite to give the galactoside 7[8] in 98% yield. (A doublet in the NMR of 7 at δ 4.37 ppm ($J_{1,2}$ = 9Hz) indicates the β-glycoside.) Hydrogenolysis of the galactoside 7 gave the corresponding alcohol[9] in 99% yield and, finally, the alcohol was oxidized to the ketone 2[10] by Collins oxidation in 77% yield.

After screening various reducing agents and solvents on the reduction of the ketone 2, the best result was obtained when the reduction was carried out with L-Selectride ($Li(sec\text{-}Bu)_3BH$) as a reducing agent and THF as a reaction medium. When boron reducing agents are used, the resulting alcohol has R configuration which is identical with natural glycolipid.[3] The results are summarized in Table 1.

Table 1 The reduction of the ketone 2

Reducing Agents	Solvent	Temp.(°C)	Time(hr)	Chem.Yd.(%)	d.e.(%)[a]	Configuration of Alcohol 3
PtO_2/H_2 (1 atm)	EtOH	r.temp.	3.5	73	20	S
"	Benzene	"	17.0	77	17	"
$Li(t\text{-}BuO)_3AlH$	THF	-78	2.5	73	14	"
DIBAL-H	"	"	2.0	52	11	"
B_2H_6	"	0	2.5	77	2	R
$LiBH_4$	"	-78	0.5	86	1	"
$NaBH_4$	EtOH	0	1.0	65	6	"
$Zn(BH_4)_2$	Et_2O	-78	"	83	39	"
L-Selectride	THF	"	"	77	63	"
"	"	-100	"	62	71	"
"	Et_2O	-78	"	50	51	"
"	Toluene	"	"	62	21	"
"	CH_2Cl_2	"	"	76	57	"
N-Selectride	THF	"	"	61	55	"
K-Selectride	"	"	"	53	42	"
$Li(\bigcirc)_3BH$[b]	"	"	"	68	58	"
$Li(sia)_3BH$[b]	"	"	"	57	63	"
"	"	-100	"	64	53	"

a) The diastereomer excess was determined as follows. The alcohol 3 was hydrolyzed to optically active chimyl alcohol, and then subsequently it was acylated with p-nitrobenzoyl chloride to give bis p-nitrobenzoate, whose enantiomer excess was determined based on $[\alpha]_D$ -33.3° (c 1, $CHCl_3$), reported in reference 2.

b) H. C. Brown, J. L. Hubbard, and B. Singaram, J. Org. Chem., 44, 5004 (1979).

A typical experimental procedure is as follows; to a solution of 2 (181 mg, 0.281 mmol) in dry THF (5 ml) was added L-Selectride (0.34 ml of 1.0 M THF solution) at -100 °C under argon. After one hour, 5 ml of phosphate buffer solution and 0.4 ml of 30% hydrogen peroxide solution were added, and the mixture was allowed to warm to room temperature. The product was extracted with ether and the extract was washed with water. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography and the alcohol 3 was isolated in 62% yield,

whose diastereomer excess was determined as 71%.

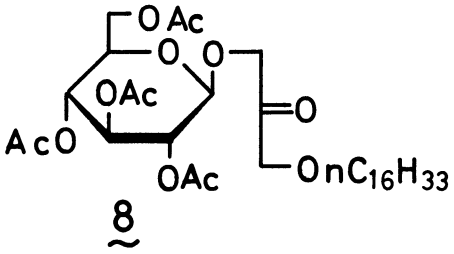
It is anticipated that the stereoselectivity of the reduction would be improved by making the interaction between ketone oxygen and sugar moiety stronger to form a tight complex. Thus, various Lewis acids were added to the reduction system and the results are summarized in Table 2. But, the diastereomer excess was not so remarkably improved by adding one equivalent of Lewis acids such as magnesium, zinc or iron salts.

Table 2 The reduction of the ketone 2 in the presence of Lewis acids (L-Selectride, THF)

Lewis Acids	Temp.(°C)	Time(hr)	Chem.Yd.(%)	d.e.(%)
$MgCl_2$ (1.08 eq.)	-78	1.0	73	72 R
$ZnCl_2$ (1.14)	"	"	90	69 "
" (1.0)	-100	"	62	63 "
" (3.0)	-78	"	96	40 "
$ZnBr_2$ (1.09)	"	"	94	70 "
ZnI_2 (1.09)	"	"	68	69 "
$FeCl_3$ (1.48)	"	"	83	71 "

The alcohol 3 can be converted to glycolipid 1 in two steps by the literature method[11], which is now under way.

Next, this reduction was applied to the other substrates such as glucose derivative 8 and mannose derivative 9.[12] The results are shown in Table 3.



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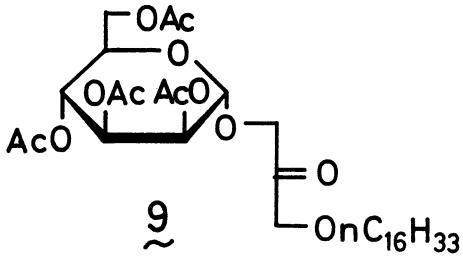

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Table 3 The reduction of the ketone 8 and 9 (L-Selectride, THF, -78 °C, 1hr)

Ketone	Additive	Chem.Yd.(%)	d.e.(%)
8	——	67	58 R
	$ZnCl_2$ (1.0 eq.)	76	60 "
9	——	78	3 S
	$ZnCl_2$ (1.0 eq.)	96	2 "

The glucose derivative 8 gave the almost same result as 2, but the mannose

derivative 9 showed no stereoselectivity. These results suggest that the C-4 acetyl group of sugar moiety does not play an important role on the stereoselectivity and the β-configuration of the anomeric carbon is crucial for high stereoselectivity.

Further experiment concerning the relationship between the structure of sugar moiety and stereoselectivity is now under investigation.

References

1) P. S. Sastry, Advances in Lipid Research, 12, 251 (1974). References are cited therein.
2) R. Gigg, J. Chem. Soc. Perkin I, 1979, 712.
3) a) W. T. Norton and M. Brotz, Biochem. Biophys. Res. Commun., 12, 198 (1963). b) M. G. Rumsby and R. J. Rossiter, J. Neurochem., 15, 1473 (1968).
4) W. J. Baumann and H. K. Mangold, J. Org. Chem., 29, 3055 (1964).
5) mp 46-48°C; IR(KBr) 3450 and 1080 cm^{-1}; NMR($CDCl_3$) δ=0.83 (3H, br.t, J=ca.6Hz), 1.20 (28H, br), 2.42 (1H, d, J=6Hz), 3.0-3.5 (6H, m), 3.73 (1H, m), 6.8-7.3 (15H, m).
6) IR(neat) 1100 cm^{-1}; NMR($CDCl_3$) δ=0.87 (3H, br.t, J=ca.6Hz), 1.23 (28H, br), 3.0-3.7 (7H, m), 4.53 (2H, s), 7.0-7.5 (20H, m).
7) IR(neat) 3400 and 1120 cm^{-1}; NMR($CDCl_3$) δ=0.87 (3H, br.t, J=ca.6Hz), 1.23 (28H, br), 2.18 (1H, br), 3.2-3.8 (7H, m), 4.60 (2H, s), 7.23 (5H, s).
8) IR(neat) 1750, 1220 and 1080 cm^{-1}; NMR($CDCl_3$) δ=0.87 (3H, br.t, J=ca.6Hz), 1.23 (28H, br), 1.90 (3H, s), 1.93 (3H, s), 1.97 (3H, s), 2.07 (3H, s), 3.1-4.1 (10H, m), 4.37 (1H, d, J=9Hz), 4.8-5.3 (3H, m), 7.07 (5H, s).
9) IR(neat) 3500, 1745, 1220 and 1080 cm^{-1}; NMR($CDCl_3$) δ=0.87 (3H, br.t, J=ca.6Hz) 1.23 (28H, br), 1.90 (3H, s), 1.98 (6H, s), 2.08 (3H, s), 2.82 (1H, s), 3.2-4.1 (10H, m), 4.42 (1H, d, J=9Hz), 4.9-5.3 (3H, m).
10) $[\alpha]_D^{21}$ -6.8° (c 1.03, CH_2Cl_2); IR(neat) 1740, 1220 and 1080 cm^{-1}; NMR($CDCl_3$) δ=0.83 (3H, br.t, J=ca.6Hz), 1.20 (28H, br), 1.88 (3H, s), 1.93 (3H, s), 2.00 (3H, s), 2.05(3H, s), 3.32 (2H, t, J=9Hz), 3.6-4.1 (3H, m), 4.00 (2H, s), 4.23 (2H, s), 4.35 (1H, d, J=9Hz), 4.8-5.3 (3H, m).
11) a) H. P. Wherli and Y. Pomeranz, Chem. Phys. Lipids, 3, 357 (1969). b) V. I. Shvets, A. I. Bashkatova, and R. P. Evstigneeva, ibid., 10, 267 (1973).
12) The alcohol 6 was glycosidated with acetobromoglucose or 3,4,6-tri-O-acetyl-1, 2-O-t-butylorthoacetyl-β-D-mannopyranose. They were converted to the ketone 8 and 9 respectively according to the same route as 2.
The physical data of both compounds are as follows.
8: mp 61-63°C; $[\alpha]_D^{20}$ -16.4° (c 1.01, CH_2Cl_2); IR(KBr) 1740, 1220, 1060 and 1040 cm^{-1}; NMR($CDCl_3$) δ=0.87 (3H, br.t, J=ca.6Hz), 1.25 (28H, br), 1.98 (6H, s), 2.05 (6H, s), 3.40 (2H, t, J=9Hz), 4.13 (2H, s), 4.0-4.3 (3H, m), 4.33 (2H, s), 4.50 (1H, d, J=9Hz), 4.9-5.2 (3H, m).
9: $[\alpha]_D^{21}$ +38.1° (c 1.09, CH_2Cl_2); IR(neat) 1740, 1220, 1080 and 1050 cm^{-1}; NMR ($CDCl_3$) δ=0.87 (3H, br.t, J=ca.6Hz), 1.22 (28H, br), 1.92 (3H, s), 1.97 (3H, s), 2.00 (3H, s), 2.07 (3H, s), 3.35 (2H, t, J=9Hz), 3.97 (2H, s), 3.9-4.2(3H, m), 4.27 (2H, s), 4.70 (1H, br.s), 4.9-5.3 (3H, m).

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