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SYNTHESIS AND ABSOLUTE CONFIGURATION OF 6-*O*-PHOSPHOCHOLINE-α-D-GLUCOPYRANOSYL GLYCEROLIPID ISOLATED FROM HTLV-I-INFECTED CELL LINES

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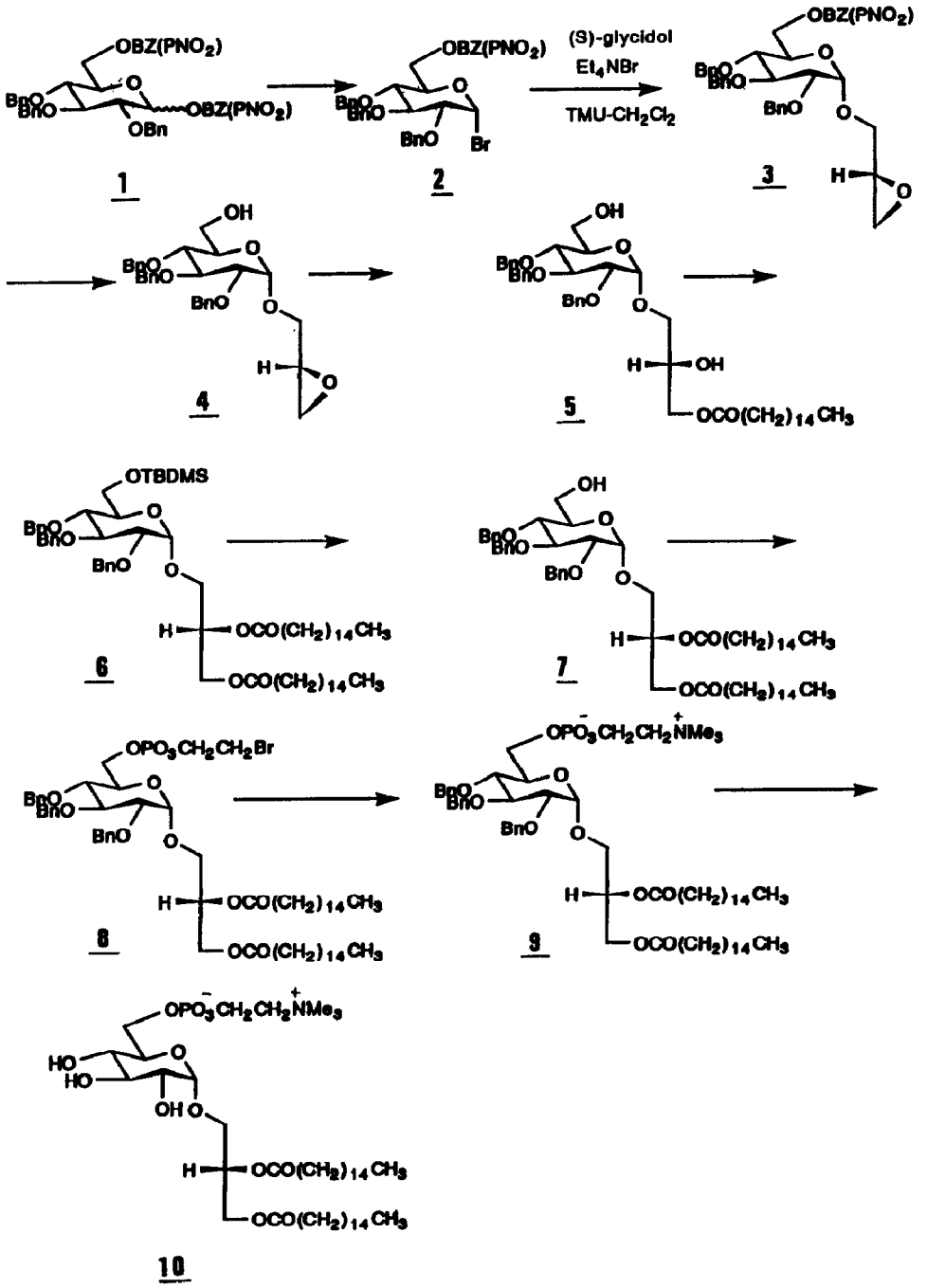
Summary: Syntheses of both stereoisomers of α-D-glucopyranosylglycerolipids enabled us to confirm the structure and the (2*S*)-configuration of a new glycoglycerolipid isolated from HTLV-I infected T-cell lines.

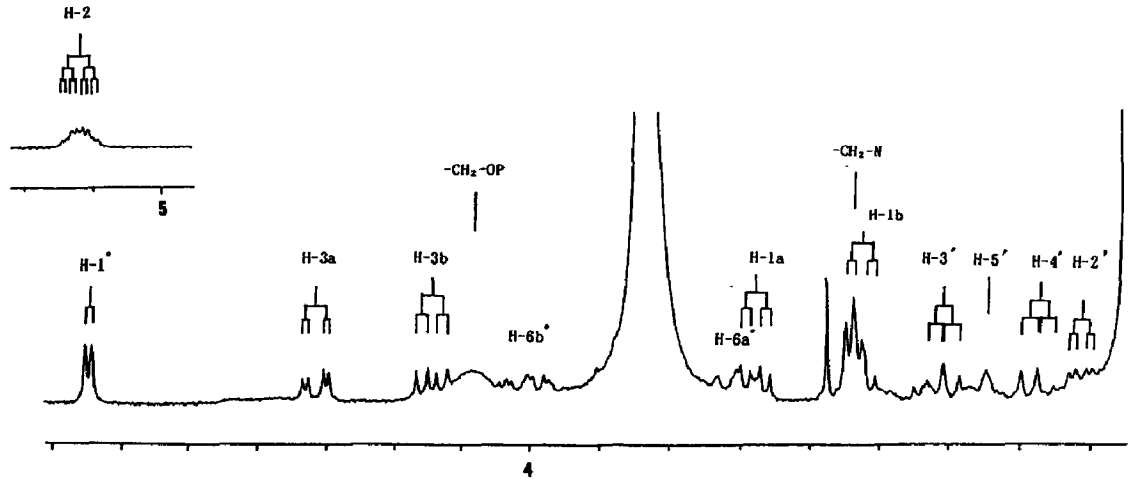
In recent efforts to investigate alterations of the glycolipid composition due to HTLV-I virus (human T lymphotropic virus type I) infections, a new glucosyl glycerolipid with a 6-*O*-phosphocholine group was isolated from the culture of HTLV-I-infected human helper T-cells.[1] By FT-IR, NMR and MS studies, the structure was assigned as 1,2-di-*O*-palmitoyl-3-*O*-(6-*O*-phosphocholine-α-D-glucopyranosyl)-glycerol (**10**, SCHEME).[1] In this study, we wish to confirm the absolute structure involving the configuration at C-2 of the glyceride moiety by the stereoselective synthesis,

Our synthetic approach was initiated towards the (2*S*)-isomer since α-D-glucopyranosyl glycerides known todays[2] commonly bear a (2*S*)-configuration at the glyceride moiety. As starting materials, 6-*O*-*p*-nitrobenzoyl-α-D-glucopyranosyl bromide (**2**)[3] and commercially available (*S*)-glycidol were employed for constructing sugar and glyceride bones, respectively. The coupling between **2** and (*S*)-glycidol according to halide ion catalyzed method[3,4] was attempted in several conditions changing bases for the acid capture in which the use of tetramethylurea in CH_2Cl_2 gave the best result. Consequently, 3-*O*-α-D-glucopyranosyl glycidol **3** was obtained in 85% yield from **2**. De-benzoylation of **3** with sodium methoxide in methanol followed by epoxide opening with cessium palmitate in DMF gave **5** in


OBZ(PNO2)
BnO
BnO
OBn
OBZ(PNO2)
1
OBZ(PNO2)
BnO
BnO
BnO
Br
2
(S)-glycidol
Et4NBr
TMU-CH2Cl2
OBZ(PNO2)
BnO
BnO
BnO
H
O
3
OH
BnO
BnO
BnO
H
O
4
OH
BnO
BnO
BnO
H
OH
OCO(CH2)14CH3
5
OTBDMS
BnO
BnO
BnO
H
OCO(CH2)14CH3
OCO(CH2)14CH3
6
OH
BnO
BnO
BnO
H
OCO(CH2)14CH3
OCO(CH2)14CH3
7
OPO3CH2CH2Br
BnO
BnO
BnO
H
OCO(CH2)14CH3
OCO(CH2)14CH3
8
OPO3CH2CH2NMe3
BnO
BnO
BnO
H
OCO(CH2)14CH3
OCO(CH2)14CH3
9
OPO3CH2CH2NMe3
HO
HO
OH
H
OCO(CH2)14CH3
OCO(CH2)14CH3
10

70% yield. Treatment of **5** in pyridine with an equimolar amount of *tert*-butyldimethylsilyl chloride (TBDMSCl)[5] and then with palmitoyl chloride gave **6** in 75% yield. After the de-silylation with trifluoroacetic acid in methanol, a phosphocholine group was introduced at 6'-OH according to reported methods[6]: Treatment of **7** with bromoethylphosphoric acid dichloride in trichloroethylene gave **8** in 80% yield, and Me_3N in DMF-$CHCl_3$-*iso*PrOH was next treated to afford **9** in 45% yield. Catalytic hydrogenation with $Pd(OH)_2$ in CH_3OH-H_2O-CH_3COOH (10:1:1) proceeded quantitatively to give a desired glucopyranosyl glycerolipid **10** with a (*2S*)-configuration at the glycerol moiety as waxy solid [FAB-MS (positive); 896 (M+1), $[\alpha]_D^{22}$ +24.9 ° (c 0.06, $CHCl_3$-CH_3OH)].

^{1}H-NMR spectrum of **10** (400 MHz, DMSO-d_6, 60 ℃, Table) completely matched with that of the glucosyl glyceride isolated from HTLV-I-infected cell lines. Thus, both the structure and the (*2S*)-configuration of the lipid could be confirmed to be the same as **10**. The result was further checked by the synthesis of the (*2R*)-isomer starting from (*R*)-glycidol instead of (*S*)-glycidol. As the result, the NMR spectrum of the (*2R*)-isomer revealed different ^{1}H-chemical shifts from those of **10** and the natural product particularly in ^{1}H-signals of the glycerol moiety (Table).



Partial 400 MHz ^{1}H-NMR Spectrum of **10** (DMSO-d_6, 60°).

Table ^{1}H-NMR Chemical Shifts (ppm) of a Glucosylglycerolipid Isolated from HTLV-Infected Cell Lines, and Synthesized (*2S*)- and (*2R*)-Isomers (400 MHz, DMSO-d6 at 60 ℃).

	H-1' ←	H-2'	H-3'	H-4'	H-5'	H-6a'	H-6b' →	H-1a ←	H-1b	H-2	H-3a	H-3b →
			Sugar moiety						Glycerol moiety			
Natural	4.66	3.21	-------[a]		3.35	4.00	3.70	3.68	3.53	5.11	4.32	4.14
(2S)-Isomer	4.65	3.21	3.41	3.28	3.34	4.00	3.70	3.68	3.53	5.11	4.32	4.14
(2R)-Isomer	4.62	--[a]	3.39	3.25	3.36	3.97	3.74	3.65	3.46[b]	5.06[b]	4.25[b]	4.08[b]

a: Not assigned due to the overlapping of signals.
b: Clear difference was observed compared with natural isomer.

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