代謝安定型糖鎖を基盤とする
高次生物機能中分子複合糖質アナログ創製

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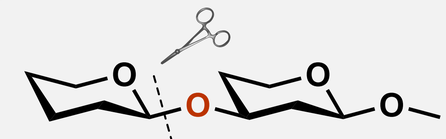
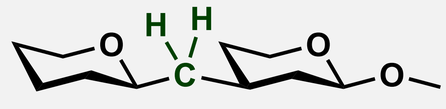
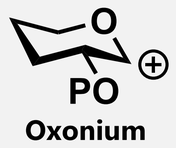
GO HIRAI LAB



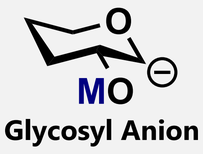
- Metabolism in Cells
- Activity Loss of Original Carbohydrates
- Conformation: *Exo*-Anomeric Effect



- Resistant against Glyco-hydrolases
- Activity Enhancement
- Flexible Conformation



Oxonium
- Facile Generation with LA
- Reaction with Nucleophile

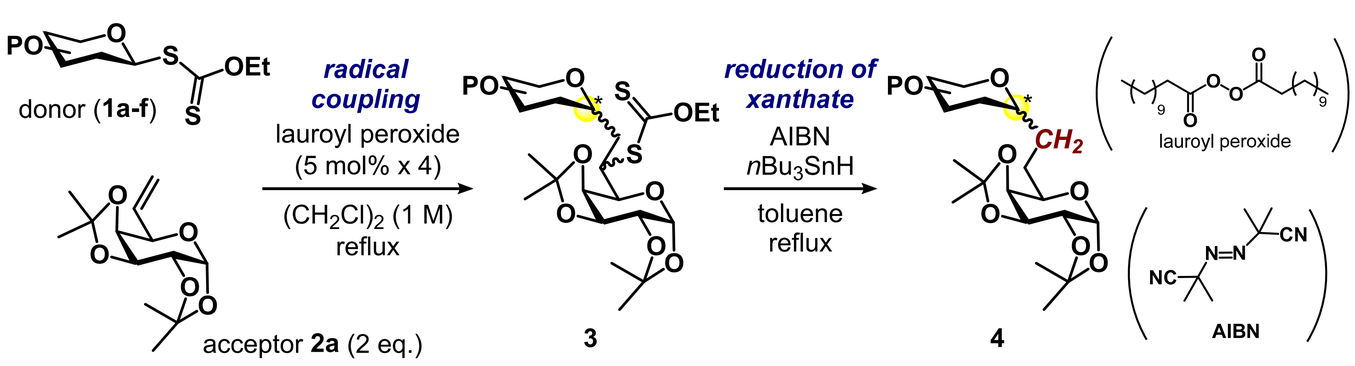


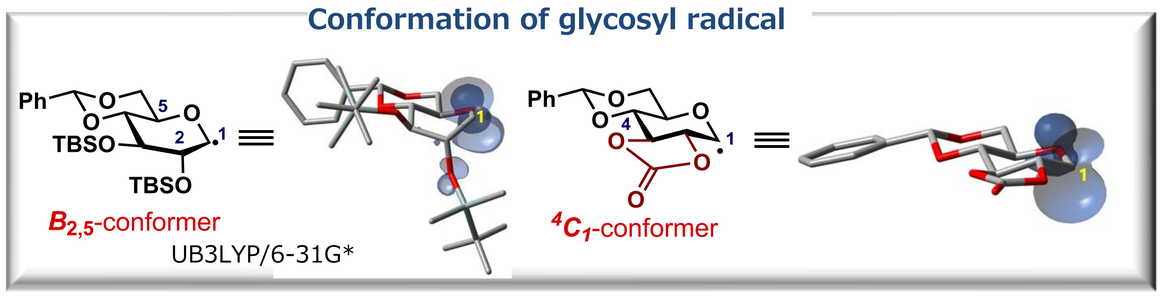
Glycosyl Anion
- Usually Unstable
- Reaction with Electrophile
- β-Elimination

Glycosyl Radical
- Generation with Initiator
- Stereochemical Control: Not Easy

Purpose of Our Project • *Direct Coupling of two sugar units using Glycosyl Radicals* • *Synthesis of Middle Molecular Artificial Glycans with C-Glycosides*

1. Radical Coupling and CH_2-linked Isomaltose Analogue (Hirai, G. *et al. Org. Lett.* **2019**, *21*, 1588-1592)

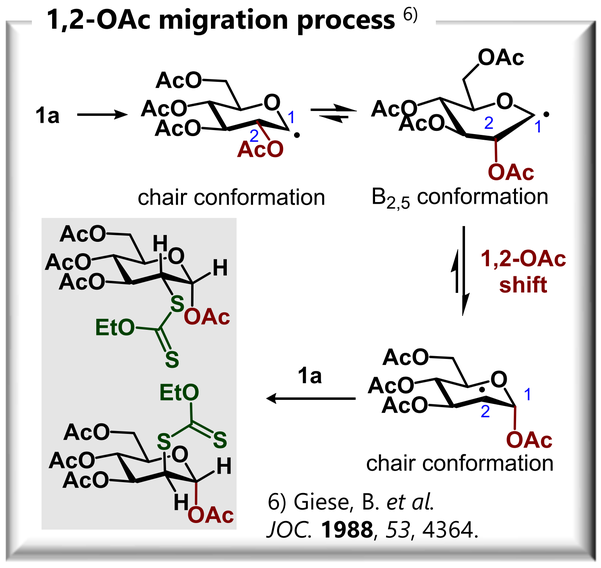




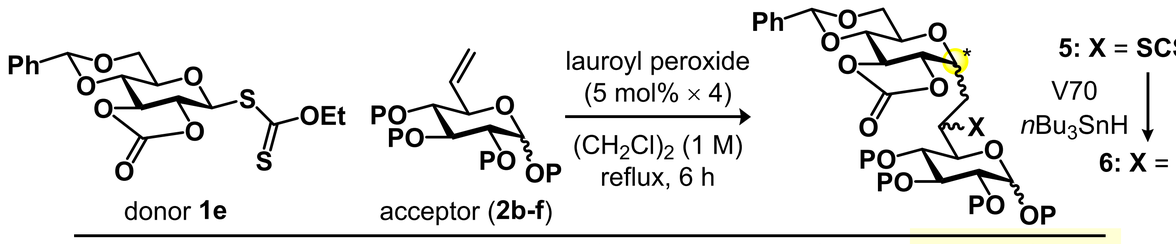
	1 (X = SC(S)OEt)	1a	1b	1c	1d	1e	1f
yields of **3**	n.d.	30%	21%	n.d.	[c]<37%	[c]<17%
recovery of **1**	[a]-	48% (α/β = 5/1)	57% (α/β = 13/1)	88% (α/β = 3/1)	37% (α/β = 2/3)	80% (α/β = 3/10)
recovery of **2a**	33%	63%	57%	90%	49%	60%
[b]yields of **4** (2 steps)	-	30% (α/β = 5/2)	17% (α/β = 4/3)	-	[d]**29% (α/β = 10/1)**	10% (α/β = 10/1)

n.d.: not detected. a) **2-xanthate products** were detected (15%); b) NMR yields; c) trisaccharides were included; d) V70 was used as a radical initiator in reduction of xanthate

1,2-OAc migration process [6)]

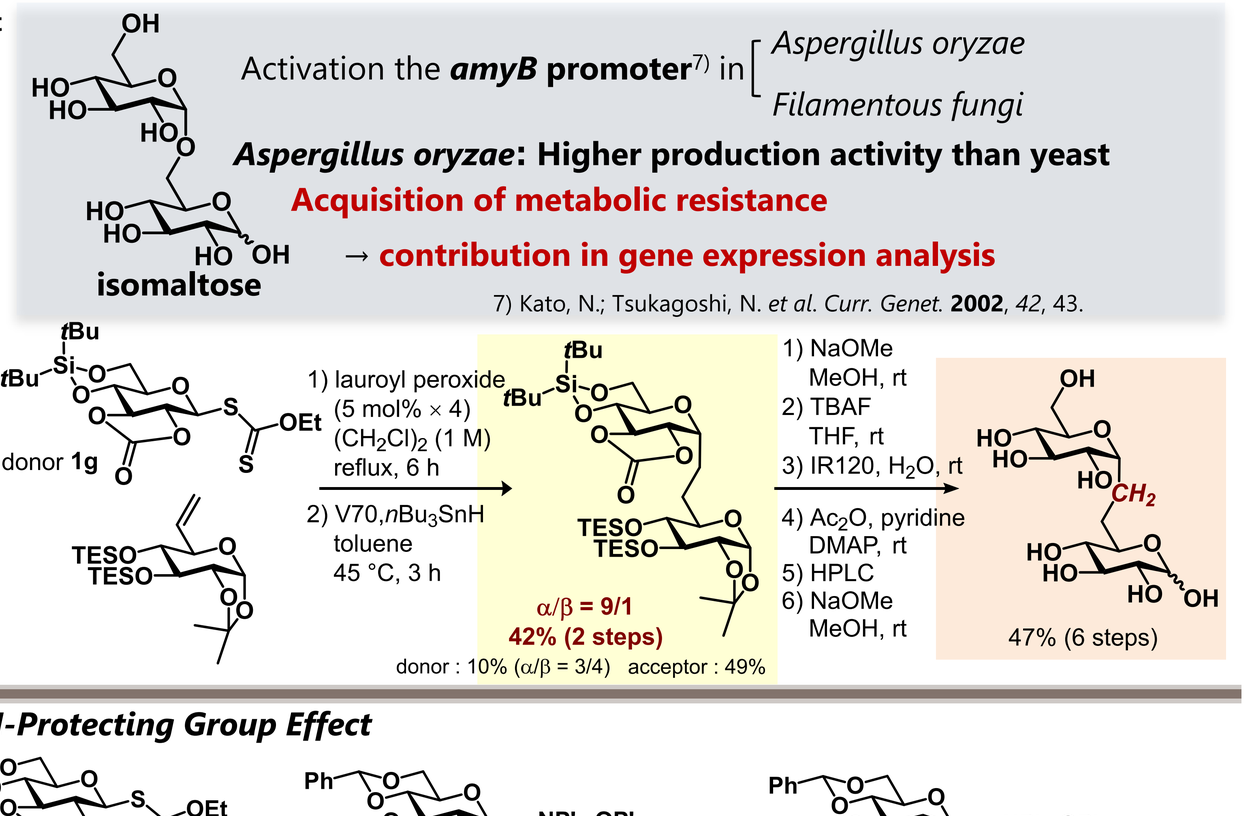


6) Giese, B. *et al. JOC.* **1988**, *53*, 4364.



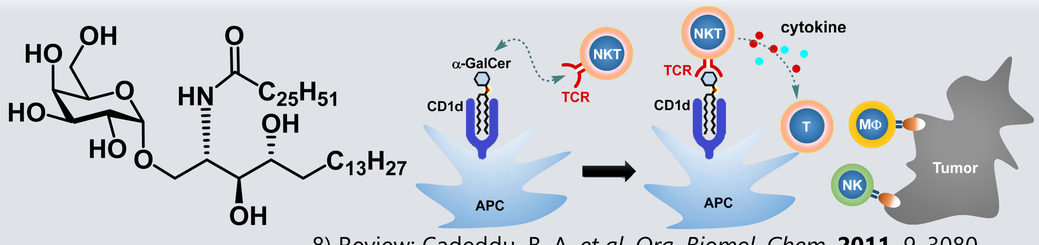
	2b	2c	2d	2e
[a]yields of **5**	n.d.	<13%	<48%	<57%
recovery of **1d**	54% (α/β = 1/5)	33% (α/β = 1/2)	47% (α/β = 5/8)	5% (α/β = 2/5)
recovery of **2**	94%	88%	64%	54%
[b]yields of **6** (2 steps)	-	-	17% (α/β = 7/1)[b)]	**28% (α/β = 7/1)**

n.d.: not detected. a) trisaccharides were included b) isolated yields



2. CH_2-linked α-GalCer and α-GlcCer Analogues

(Hirai, G. *et al. Chem. Commun.* **2020**, *56*, 4712-4715)



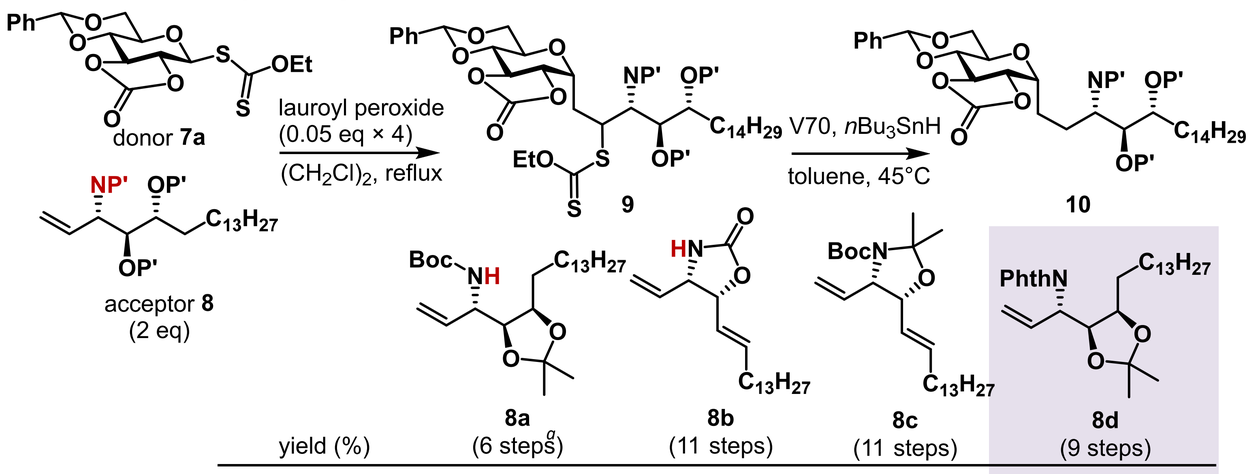
KRN7000[8)]

8) Review; Cadeddu, B. A. *et al. Org. Biomol. Chem.* **2011**, *9*, 3080.
Koezuka, Y., Kirin Brewery Company Ltd *EU Patent WO98/29534.*

Potent anti-cancer effect through activation of NKT-cells

C-glycoside analogues of KRN7000: Tomiyama, H. *et al., JP 2001/354666*, 2002; Franck, W. R. *et al. Angew. Chem. Int. Ed.* **2004**, *43*, 3818; Franck, W. R. *et al. Chem. Res.* **2006**, *39*, 692; Franck, W. R. *et al. Org. Lett.* **2006**, *6*, 4077; Franck, W. R. *et al. J. Exp. Med.* **2003**, *198*, 1631; Wipf, P. *et al. Org. Lett.* **2006**, *8*, 3375; Bittman, R. *et al. Org. Lett.* **2010**, *12*, 2974.

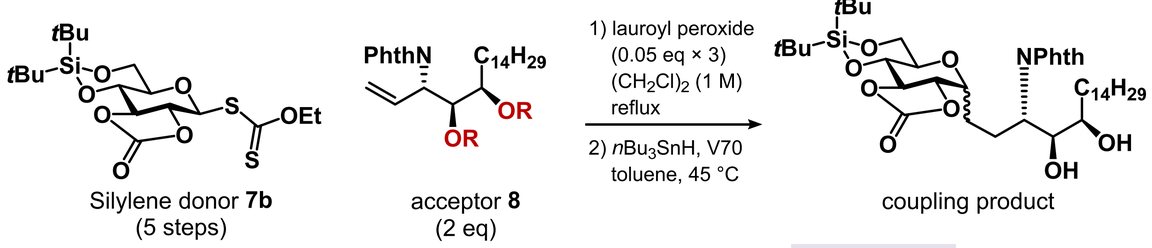
A) N-Protecting Group Effect



yield (%)	8a (6 steps[a)])	8b (11 steps)	8c (11 steps)	8d (9 steps)
1) *C*-glycosylation	n.d.	n.d.	n.d.	18% (brsm 53%)
2) reduction	-	-	-	56
2 steps (α:β)	-	-	-	**10 (6:1)**

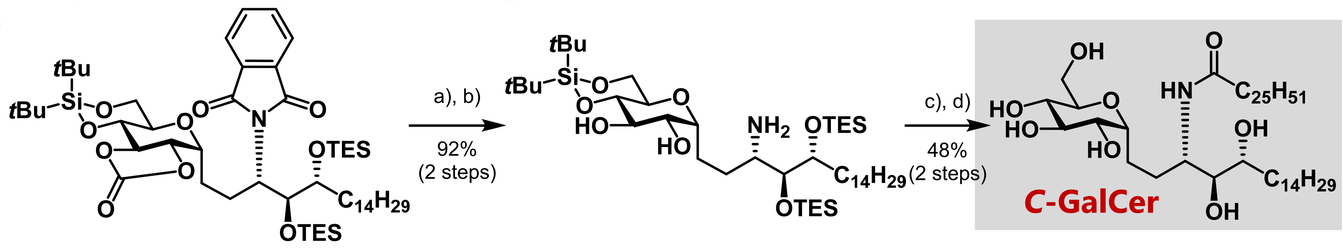
[a] n.d.; not detected. [b] brsm; based on recovered starting material **3a**. [c] Anomeric ratio of **6** was determined by ^{1}H NMR of crude.

B) O-Protecting Group Effect



yield (%)	8d (9 steps)	8e (10 steps)	8f (9 steps)	8g (9 steps)	8h (9 steps)
1) *C*-glycosylation	29 (46% brsm)	32 (53% brsm)	53 (89% brsm)	81 (89% brsm)	48 (65% brsm)
2) reduction	64 (4:1)	52 (5:2)	77 (5:2)	70 (7:2)	62 (4:1)
2 steps (α:β)	19	18	41	**57**	30

C) Synthesis of Glycolipid Analogues



a) MeONa, MeOH, rt; b) ethylenediamine, EtOH, 85 °C; c) $C_{25}H_{51}COSuc$, pyridine, $(CH_2Cl)_2$, rt to 70 °C; d) TBAF, THF, rt