International Summit on
Past and Present Research Systems of Green Chemistry
August 25-27, 2014 Philadelphia, USA

Recent structure activity relationship studies (SAR) on natural occurring sulfonium salts as potent α-glucosidase inhibitors

Weijia Xie
China Pharmaceutical University
2014-08-25

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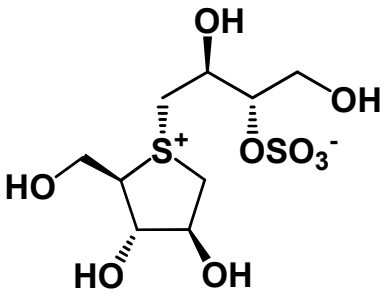
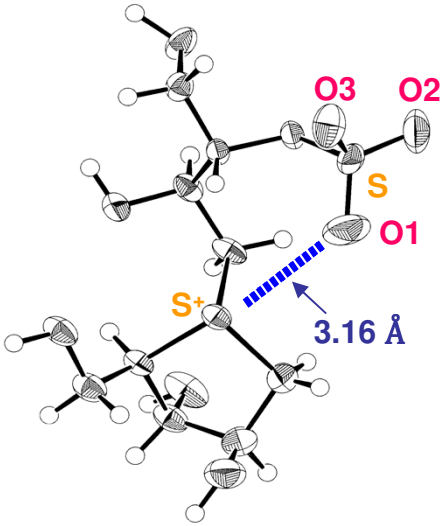
1. Introduction
2. Synthetic and Biological Studies on Neoponkoranol and its Epimers
3. Structure Modification and Biological Evaluation of Neosalacinol
4. Total Synthesis of Neokotalanol

Introduction



Salacinol (1)



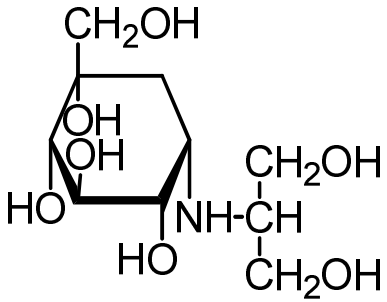
Perspective view of 1

Isolation and Structure Determination: from an antidiabetic Ayurvedic traditional medicine, *Salacia reticulata*

. Yoshikawa, O. Muraoka, and co-workers
a. Tetrahedron Lett., **38**, 8367 (1997).
b. *Bioorg. Med. Chem.*, **10**, 1547 (2002).

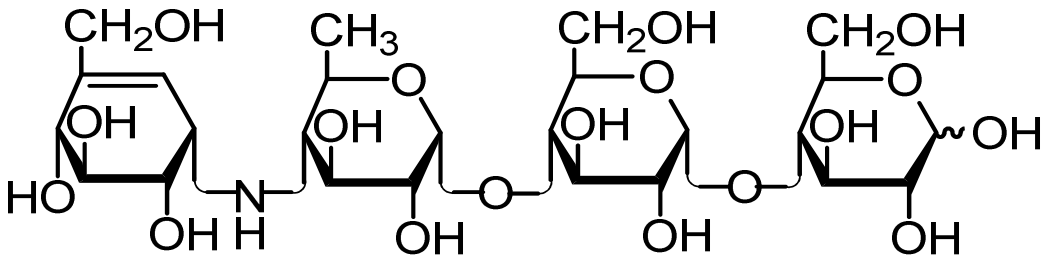
IC_{50} Values (μM, *in vitro*)

Maltase	Sucrase	Isomaltase
5.2	1.6	1.3



Voglibose

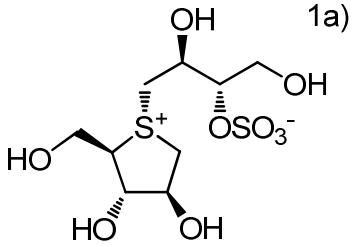
1.2	0.2	2.1



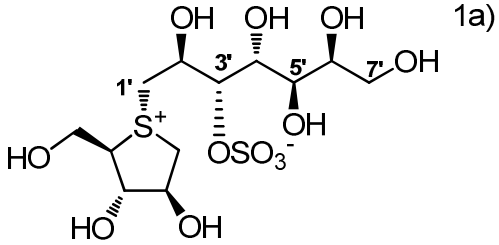
Acarbose

2.0	1.7	155

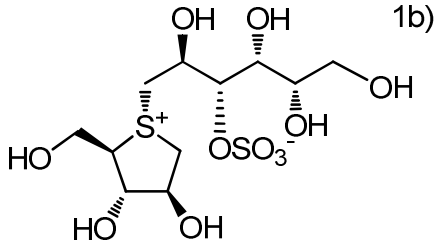
Introduction



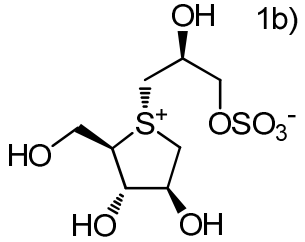
salacinol (**1**) : R = OSO_3^-



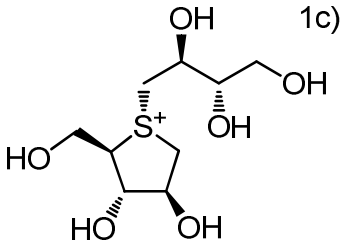
kotalanol (**2**) : R = OSO_3^-



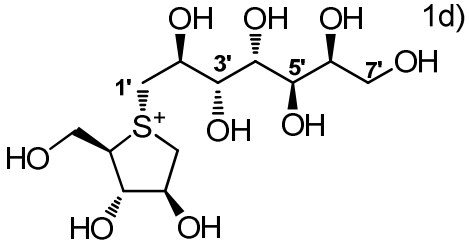
ponkoranol (**3**) : R = OSO_3^-



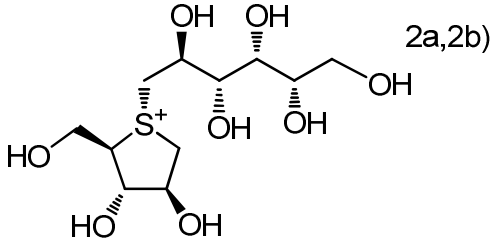
salaprinol (**4**) : R = OSO_3^-



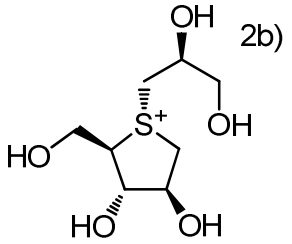
neosalacinol (**5**) : R = OH



neokotalanol (**6**) : R = OH



neoponkoranol (**7**): R = OH



neosalaprinol (**8**) : R = OH

1. a) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339-1340; b) Yoshikawa, M.; Xu, F.; Nakamura, S.; Wang, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Heterocycles* **2008**, *75*, 1397-1405; c) Minami, Y.; Kuriyama, C.; Ikeda, K.; Kato, A.; Takebayashi, K.; Adachi, I.; Fleet, W. J. G.; Kettawan, A.; Okamoto, T.; Asano, N. *Bioorg. Med. Chem.* **2008**, *16*, 2734-2740; d) Ozaki, S.; Oe, H.; Kitamura, S. *J. Nat. Prod.* **2008**, *71*, 981-984.
2. (a) Eskandari, R.; Kuntz, D. A.; Rose, D. R.; Pinto, B. M. *Org. Lett.*, **2010,** *12*, 1632-1635; (b) Xie, W.; Tanabe, G.; Akaki, J.; Morikawa, T.; Ninomiya, K.; Minematsu, T.; Yoshikawa, M.; Wu, X.; Muraoka, O. *Bioorg. Med. Chem.*, **2011**, *19*, 2015-2022.

Important Structural Determinants for the Inhibitory Activity

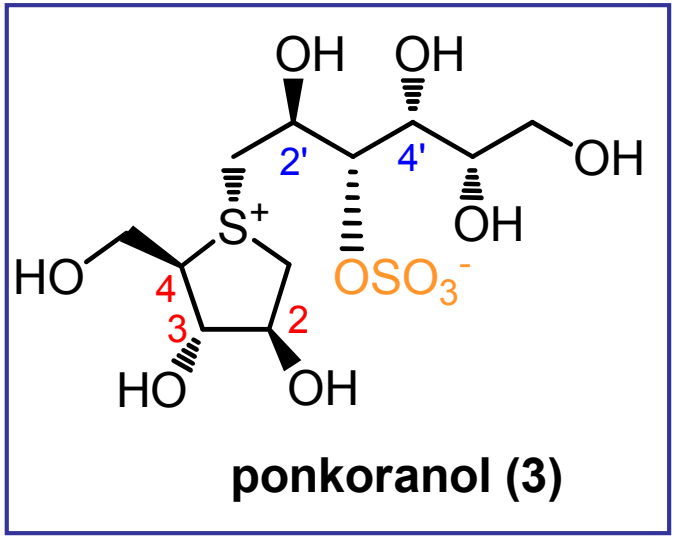
(a) **2*S*, 3*S*, 4*R* configurations of the thiosugar moiety are important.**

(b) **The α-orientation of the side chain is essential for the inhibition.**

(c) **Polyhydroxylated side chain longer than four carbons does not enhance the inhibitory activity significantly.**

(d) **Cooperative role of 2'*S*-OH and 4'-OH is critical for strong inhibitions. Furthermore, it is of prime importance that *R* configuration of OH at C4' is imperative to inhibitors bearing the side chain more than four carbons.**

(e) **Sulfate moiety might not contribute to inhibitory activity.**



ponkoranol (3)

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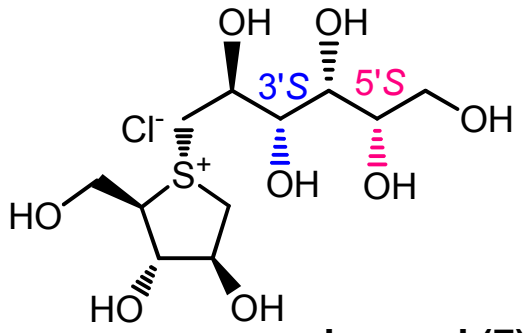
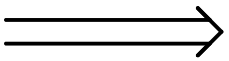
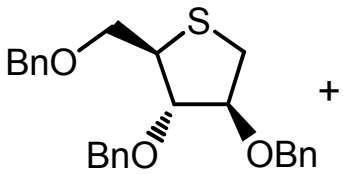
Synthetic and Biological Studies on Neoponkoranol and Its Epimers



neoponkoranol (7)





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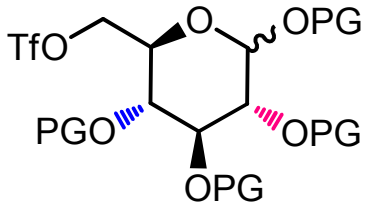
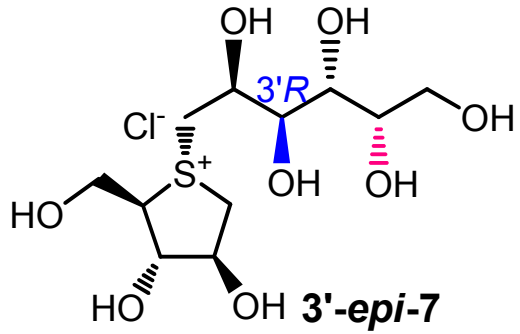
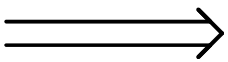
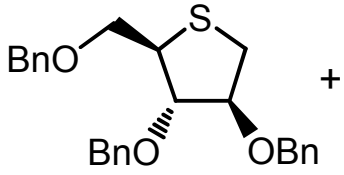


derived from D-glucose



3'-*epi*-7





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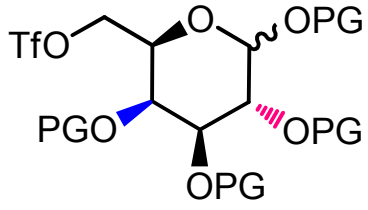
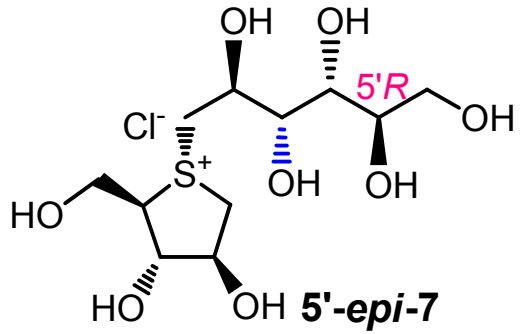
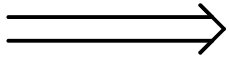
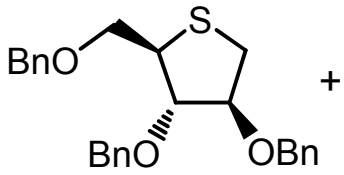


derived from D-galactose



5'-*epi*-7





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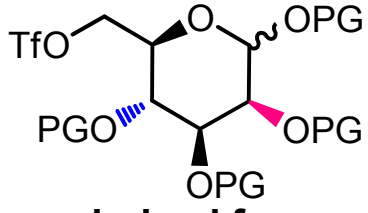
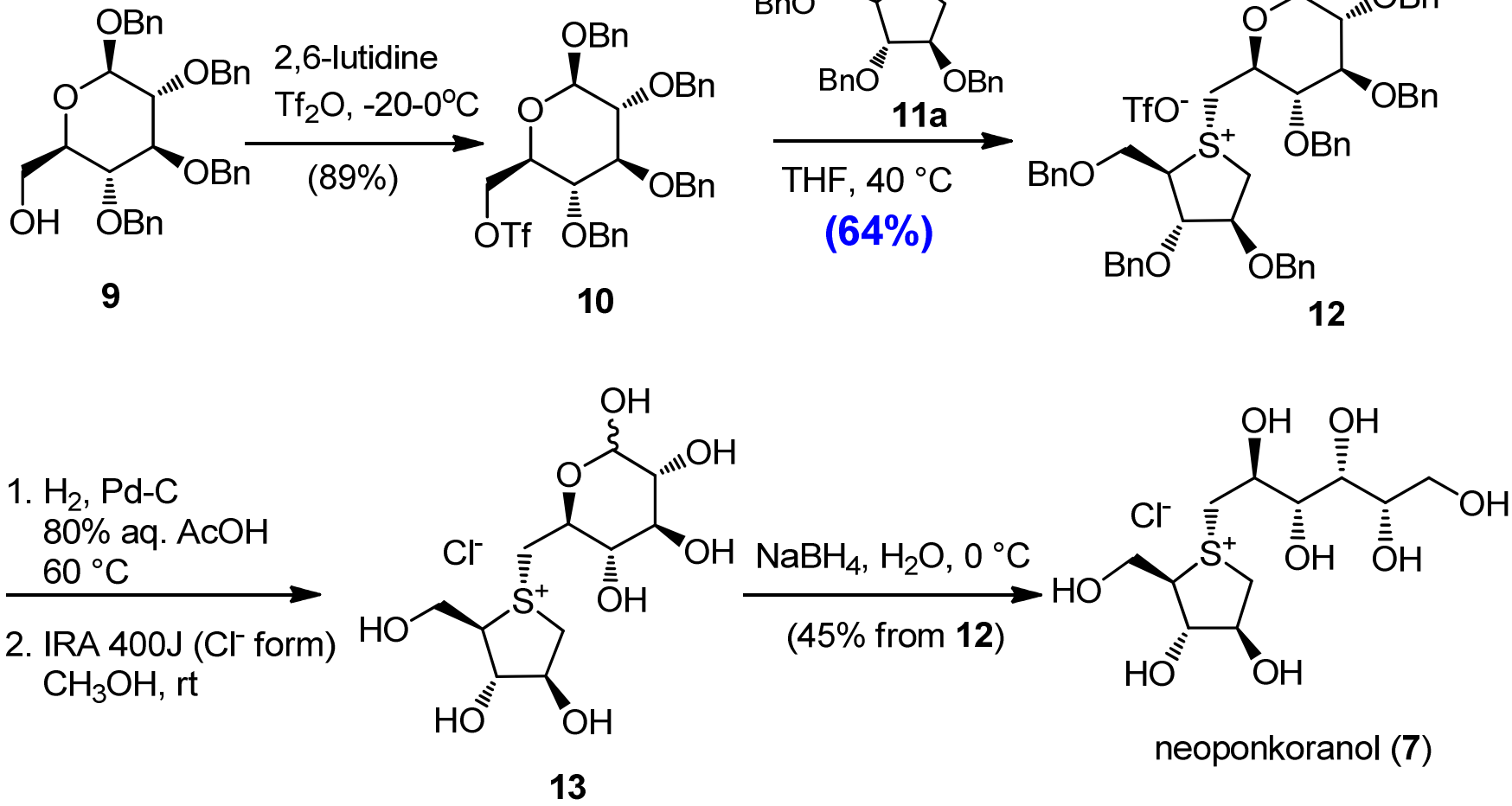
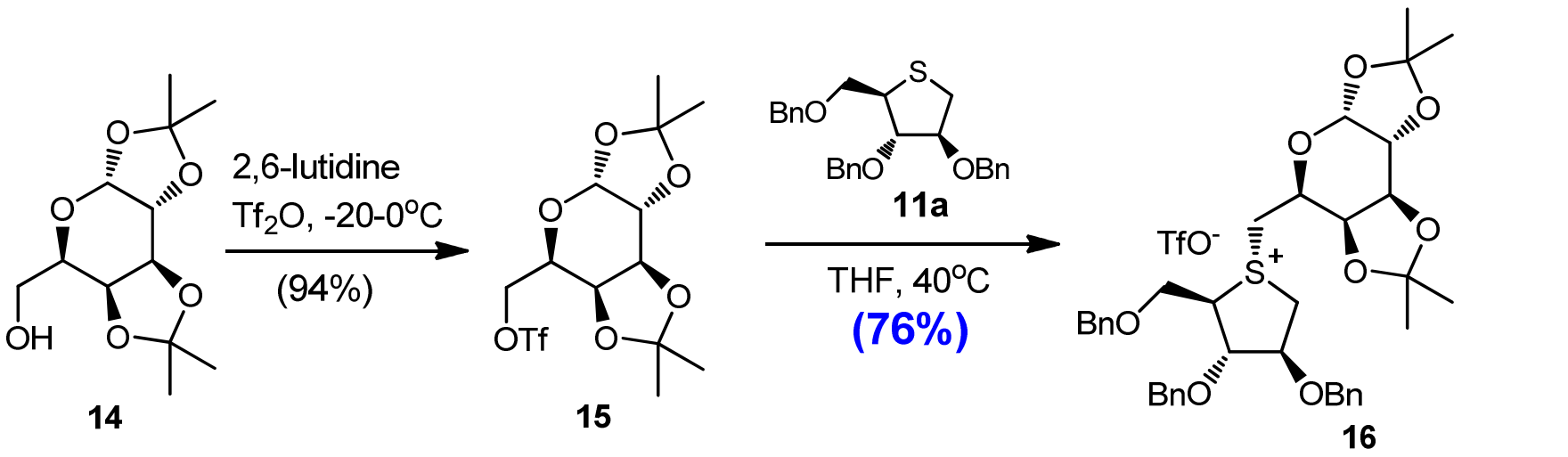


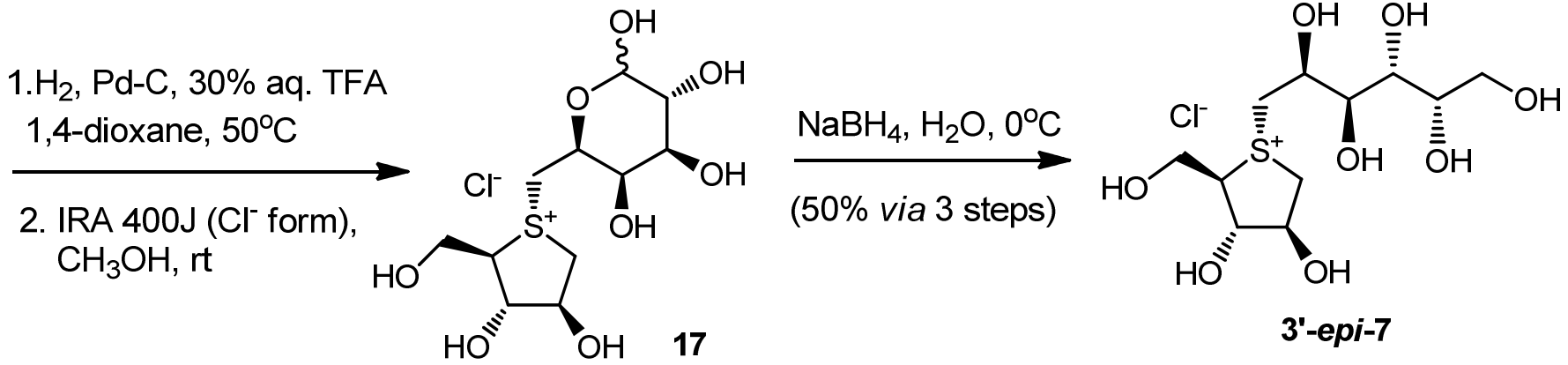
derived from D-mannose

Synthesis of Neoponkoranol

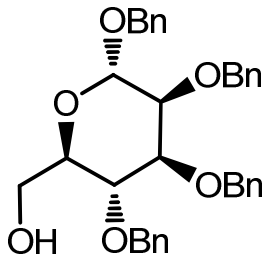


Synthesis of 3'-*epi*-Neoponkoranol





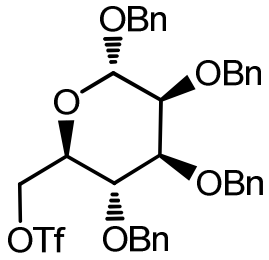
Synthesis of 5'-*epi*-Neoponkoranol



18

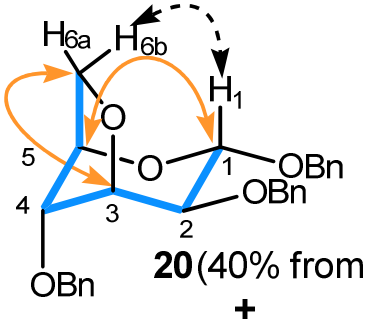
2,6-lutidine,
Tf_2O, -20-0°C

80%



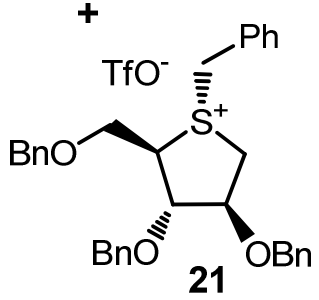
19

Thiosugar (**11a**),
THF, 0°C



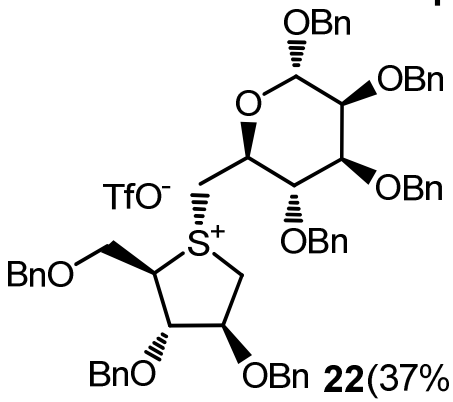
20(40% from **19**)

+



21

+



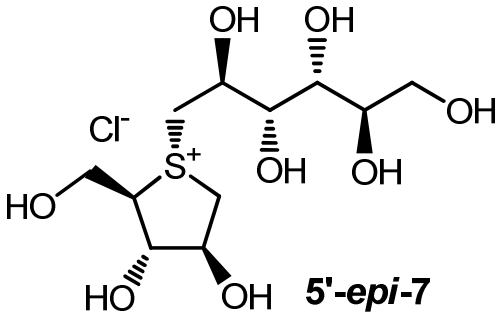
22(37% from **19**)

(48% from **11**)

COSY
HMBC
NOE

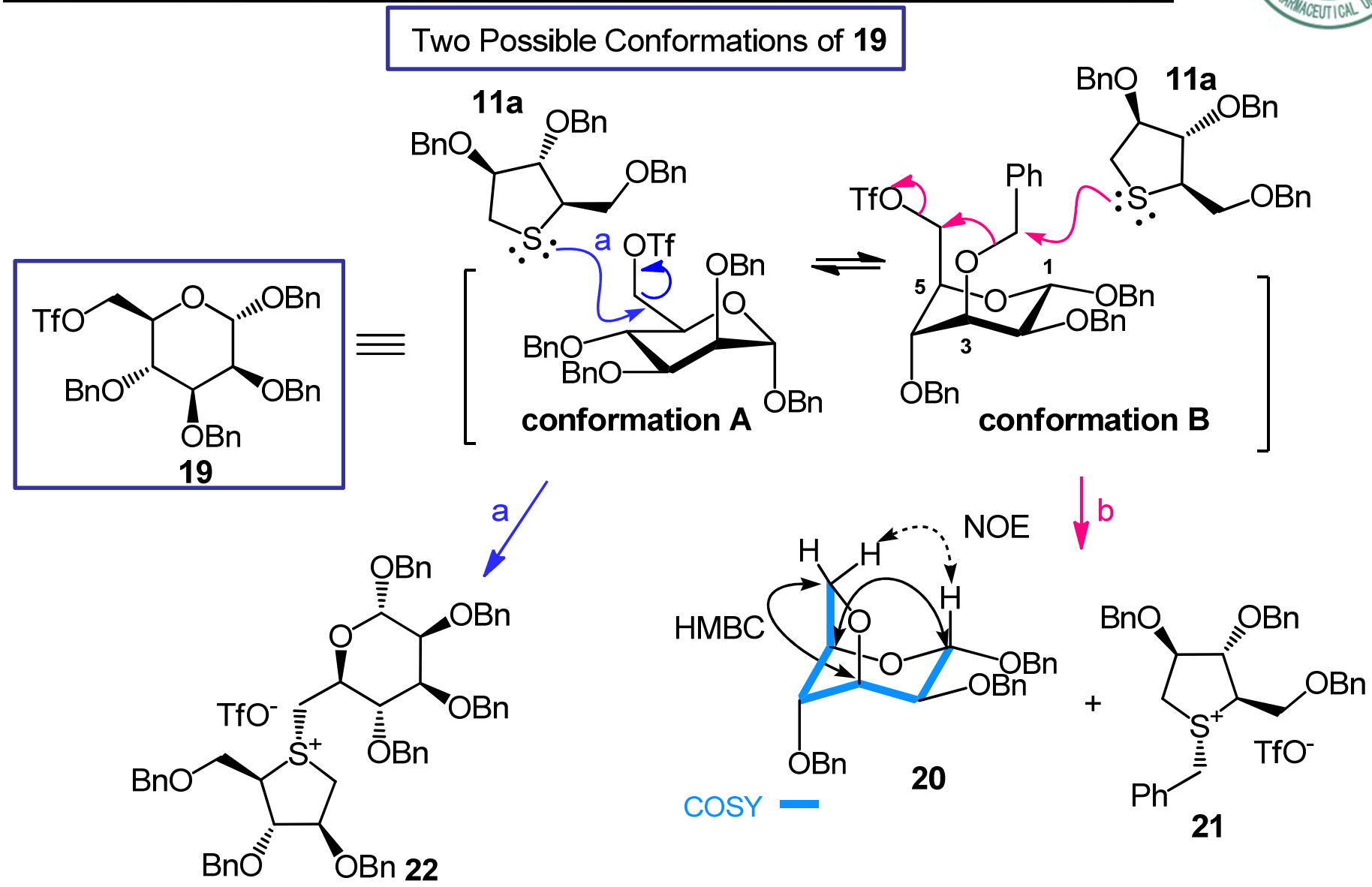
1) H_2, Pd-C, 80% aq.
AcOH, 60°C

2) IRA 400J (Cl^- form),
CH_3OH, rt
3) $NaBH_4$, H_2O, 0°C.

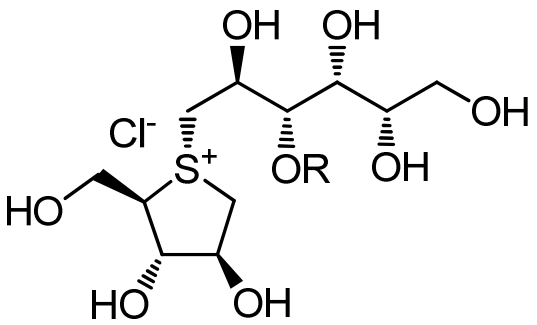


5'-*epi*-7

Plausible Coupling Reaction Mechanism of Triflate (19) with Thiosugar (11a)

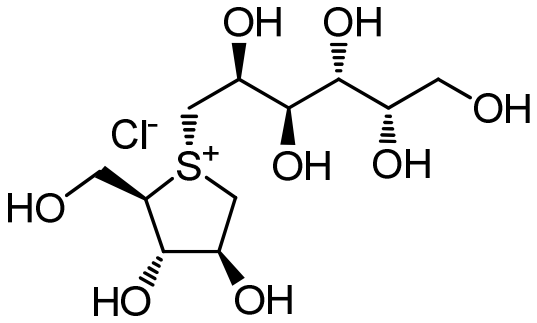


α-Glucosidase Inhibitory Activities of Neoponkoranol and Its Analogs

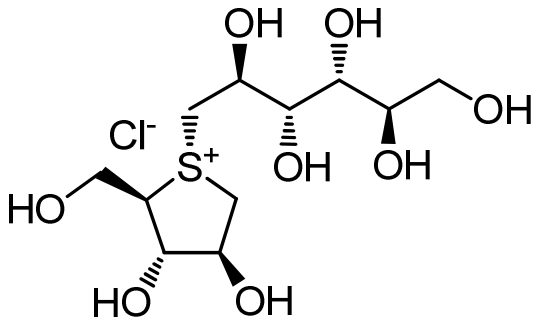


ponkoranol (3) : R = SO_3^-

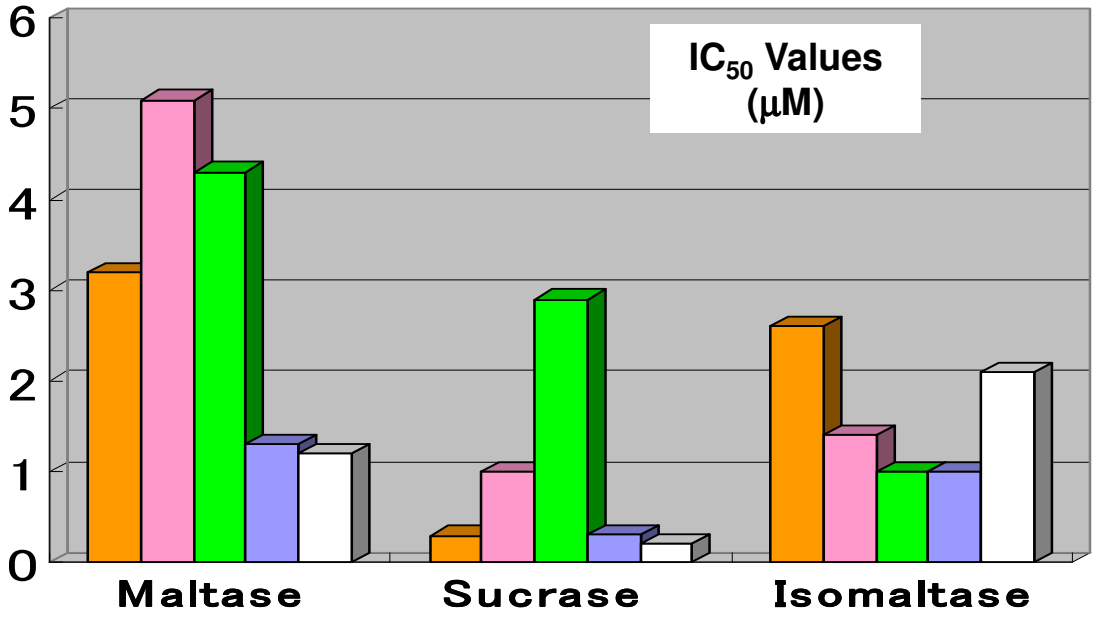
neoponkoranol (7) : R = H

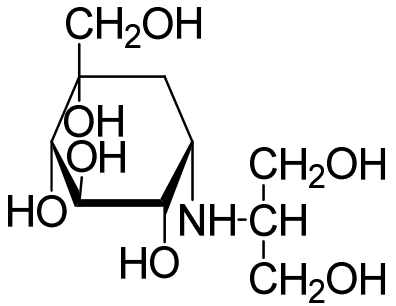


3'-*epi*-7



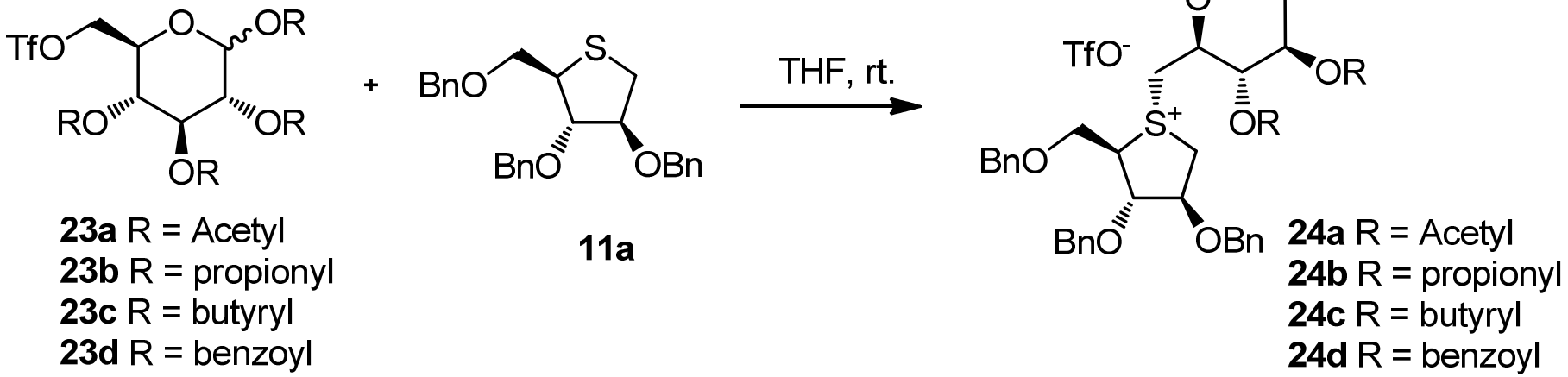
5'-*epi*-7





Voglibose

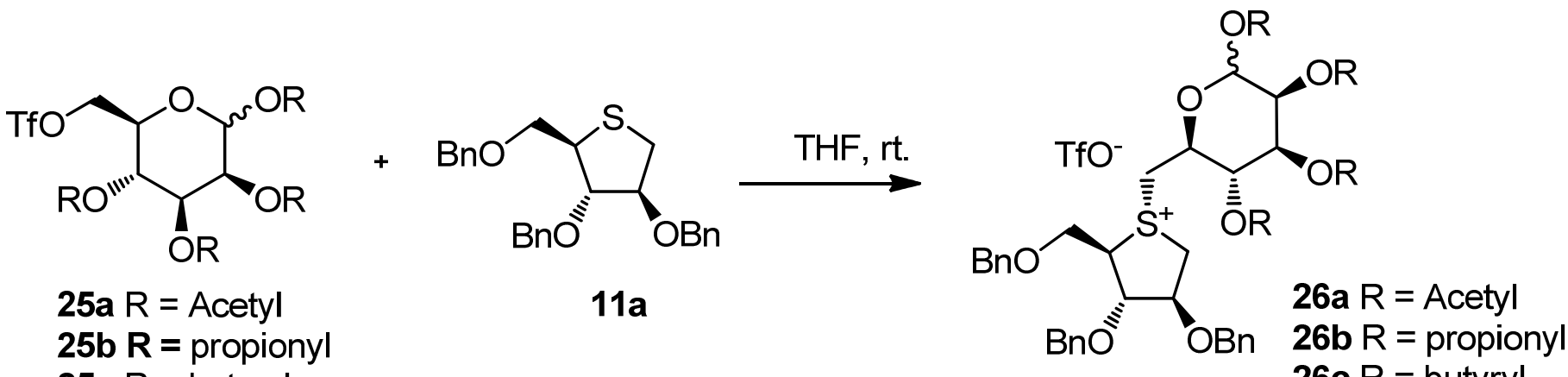
Synthetic studies on Neoponkoranol and Its 5'-Epimer



23a R = Acetyl
23b R = propionyl
23c R = butyryl
23d R = benzoyl

11a

24a R = Acetyl
24b R = propionyl
24c R = butyryl
24d R = benzoyl



25a R = Acetyl
25b R = propionyl
25c R = butyryl
25d R = benzoyl

11a

26a R = Acetyl
26b R = propionyl
26c R = butyryl
26d R = benzoyl

Synthetic studies on Neoponkoranol and Its 5'-Epimer

Table1. Yields of coupling reaction[a] between different triflates and thiosugar (**11a**)

Entry	Protecting groups	Yields[b] of the coupled products	
		D-glucose-derived	D-mannose-derived
1	Benzyl	64%[c]	37%[c]
2	Acetyl	76%[d]	71%[d]
3	Propionyl	80%[d]	75%[d]
4	Butyryl	84%[d]	84%[d]
5	Benzoyl	88%[d]	85%[d]

[a] All reactions were performed in 1.0 mmol scale in anhydrous solvents.
[b] Isolated yield after column chromatography.
[c] **Xie, W.**; Tanabe, G.; Akaki, J.; Morikawa, T.; Ninomiya, K.; Minematsu, T.; Yoshikawa, M.; Wu, X.; Muraoka, O. *Bioorg. Med. Chem.*, **2011**, *19*, 2015-2022.
[d] Liu, D.; **Xie, W.***; Liu, L.; Yao, H.; Xu, J.; Tanabe, G.; Muraoka, O.; Wu, X. *Tetrahedron Lett.* **2013**, *54*, (47), 6333-6336.

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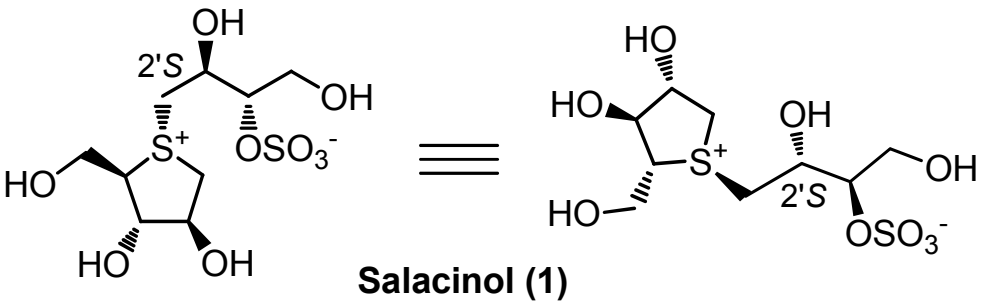
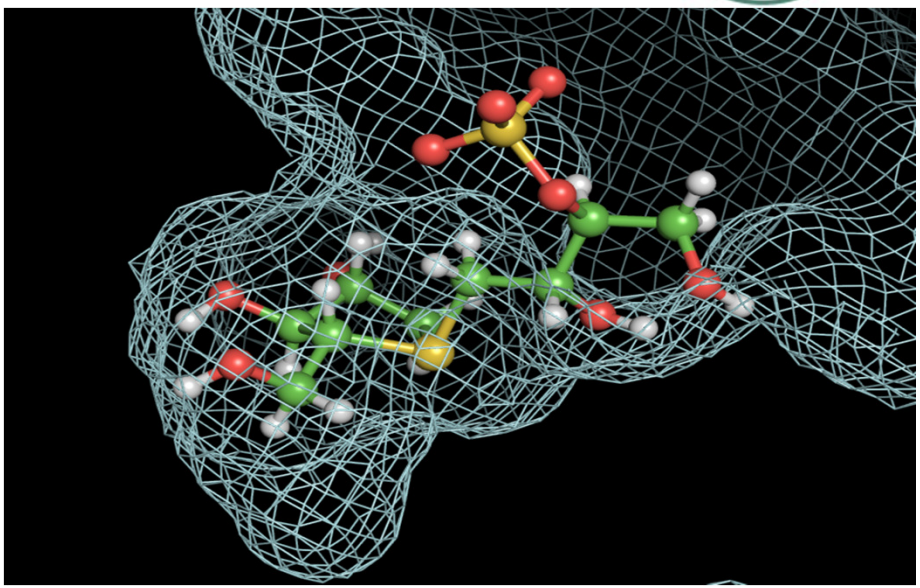
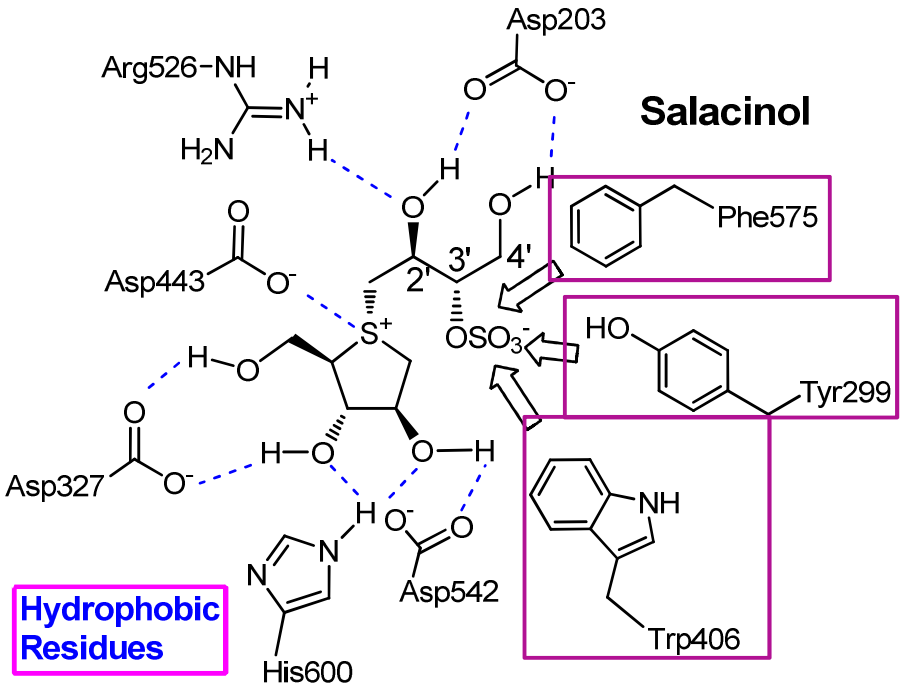
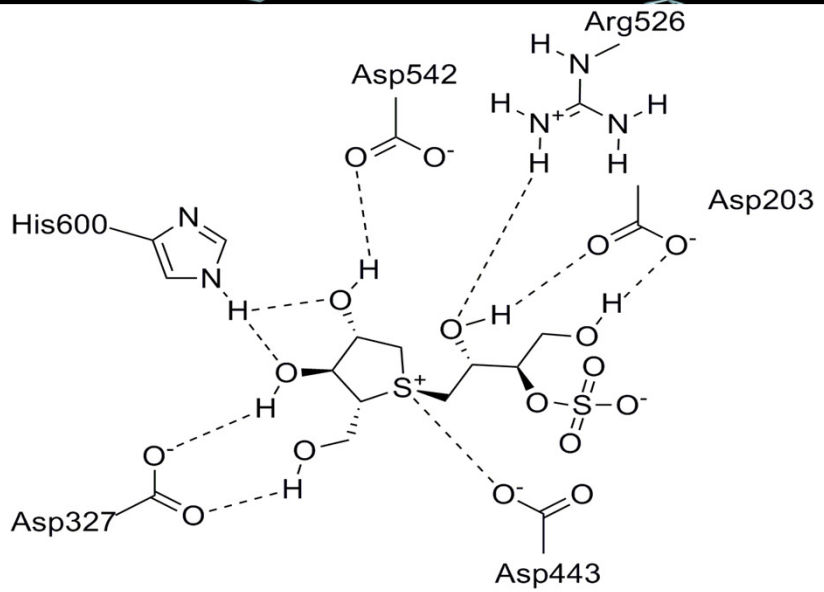


Salacinol (1)

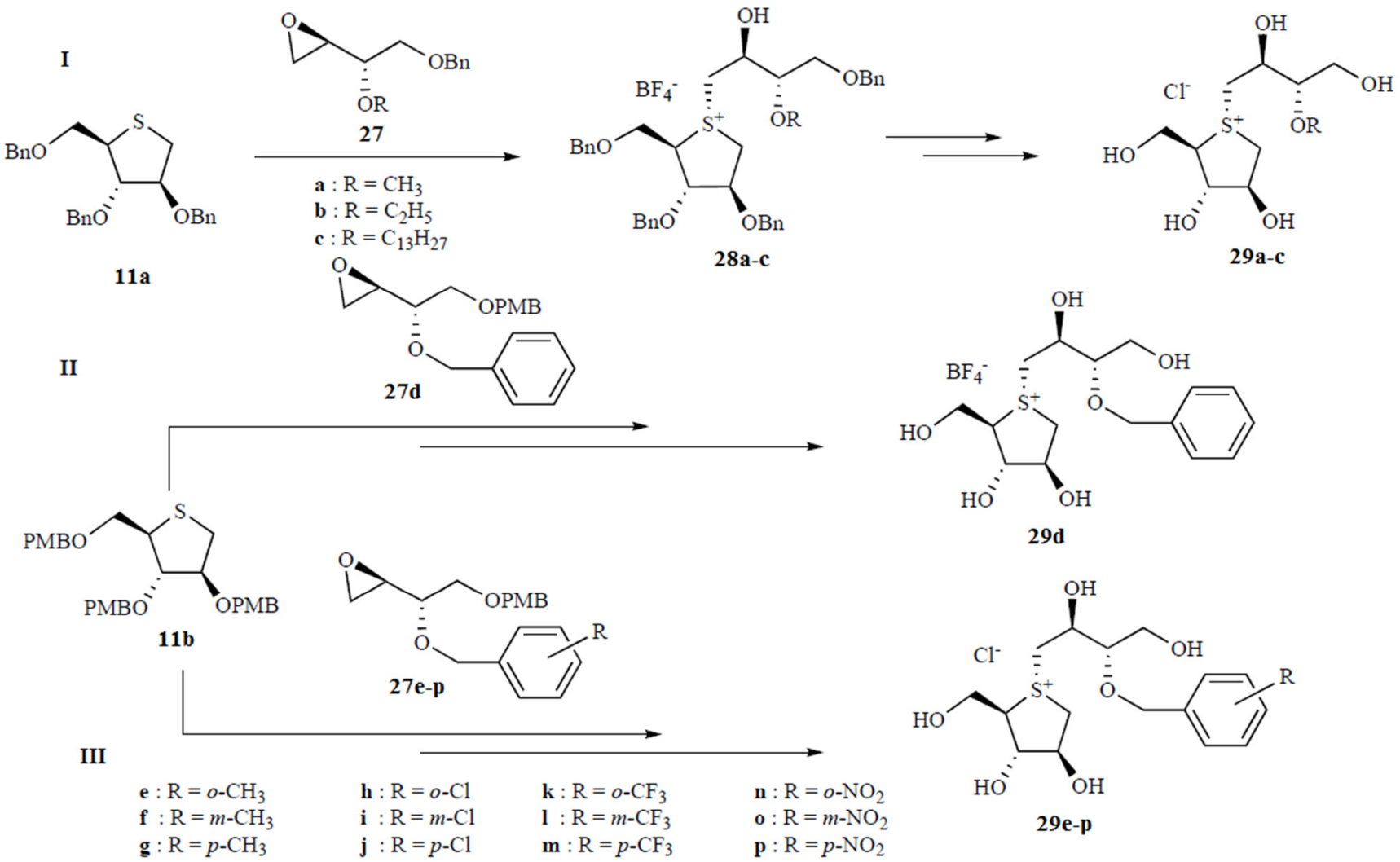
1. S. Nakamura, O. Muraoka, I. Nakanishi, *et al*. *Bioorg. Med. Chem Lett*., **2010**, *20*, 4420.







Structure Modification of Neosalacinol



Background of the project

Table 2. IC_{50} Values (mM) of thiosugar sulfonium salts and related compounds against disaccharidases

Entry	Compound	Maltase	Sucrase	Isomaltase
1	29a (R = H)	0.32	0.44	0.14
2	29b (R = CH_3)	0.46	5.3	0.39
3	29c (R = CH_3)	1.3	1.0	0.95
4	29d (R = C_2H_5)	0.32	0.44	0.14
5	29e (R = *o*-CH_3)	0.66	0.41	0.48
6	29f (R = *m*-CH_3)	0.84	1.3	0.35
7	29g (R = *p*-CH_3)	0.86	1.1	0.68
8	29h (R = *o*-Cl)	0.31	0.09	0.26
9	29i (R = *m*-Cl)	0.53	0.80	0.31
10	29j (R= *p*-Cl)	0.89	0.72	0.48
11	29k (R = *o*-CF_3)	0.33	0.15	0.19
12	29l (R = *m*-CF_3)	0.98	0.82	0.25
13	29m (R = *p*-CF_3)	0.98	0.72	0.38
14	29n (R = *o*-NO_2)	0.13	0.042	0.21
15	29o (R = *m*-NO_2)	0.94	0.49	0.23
16	29p (R = *p*-NO_2)	0.68	0.38	0.23
17	Voglibose	1.2	0.2	2.1
18	Acarbose	2.0	1.7	155

Background of the project

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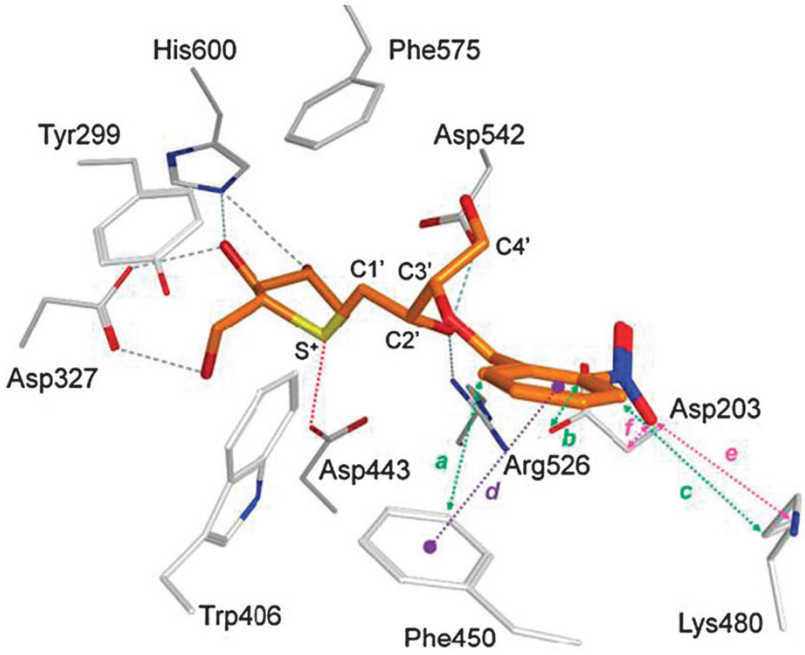
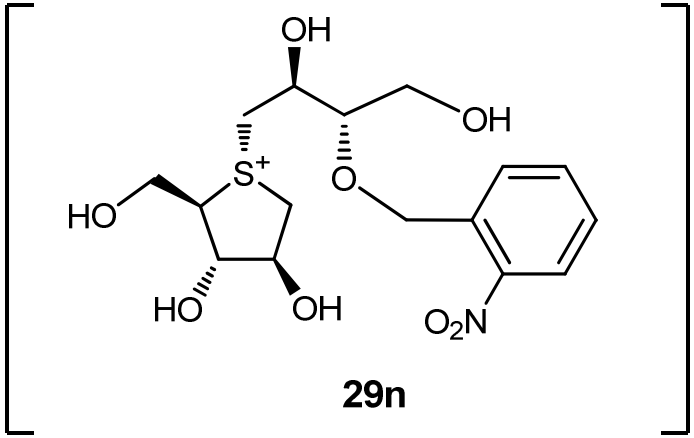
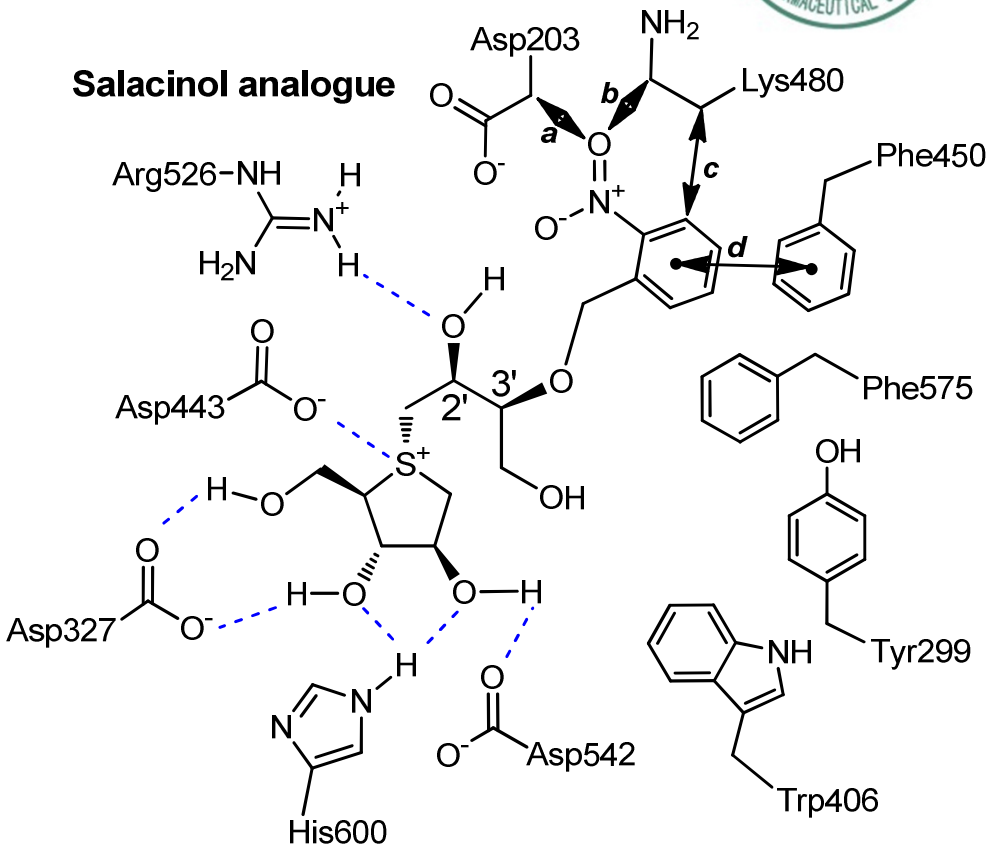
Molecular Docking of 29n with hNtMGAM active site





29n

Salacinol analogue



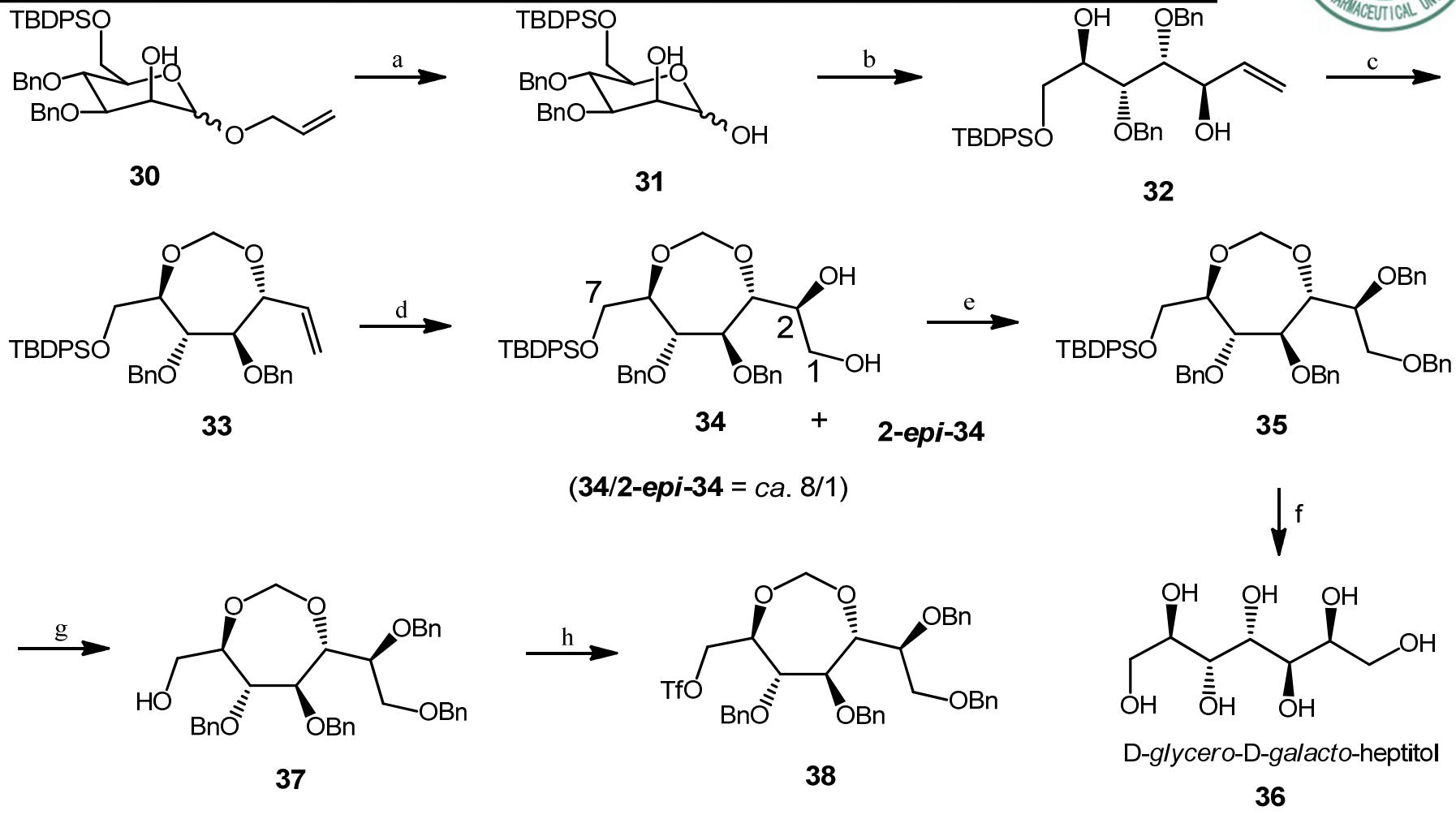
inhibitory potency>>Salacinol (40 folds)

Reference: Tanabe, G.; Nakamura, S.; **Xie, W.**; Tsuchiya, S.; Akaki, J.; Morikawa, T.; Yoshikawa, M.; Muraoka, O. *Chem. Commun.* **2012**, 8646–8648.)

1. Introduction
2. Synthetic and Biological Studies on Neoponkoranol and its Epimers
3. Structure Modification and Biological Evaluation of Neosalacinol
4. Total Synthesis of Neokotalanol

Total Synthesis of Neokotalanol (I)

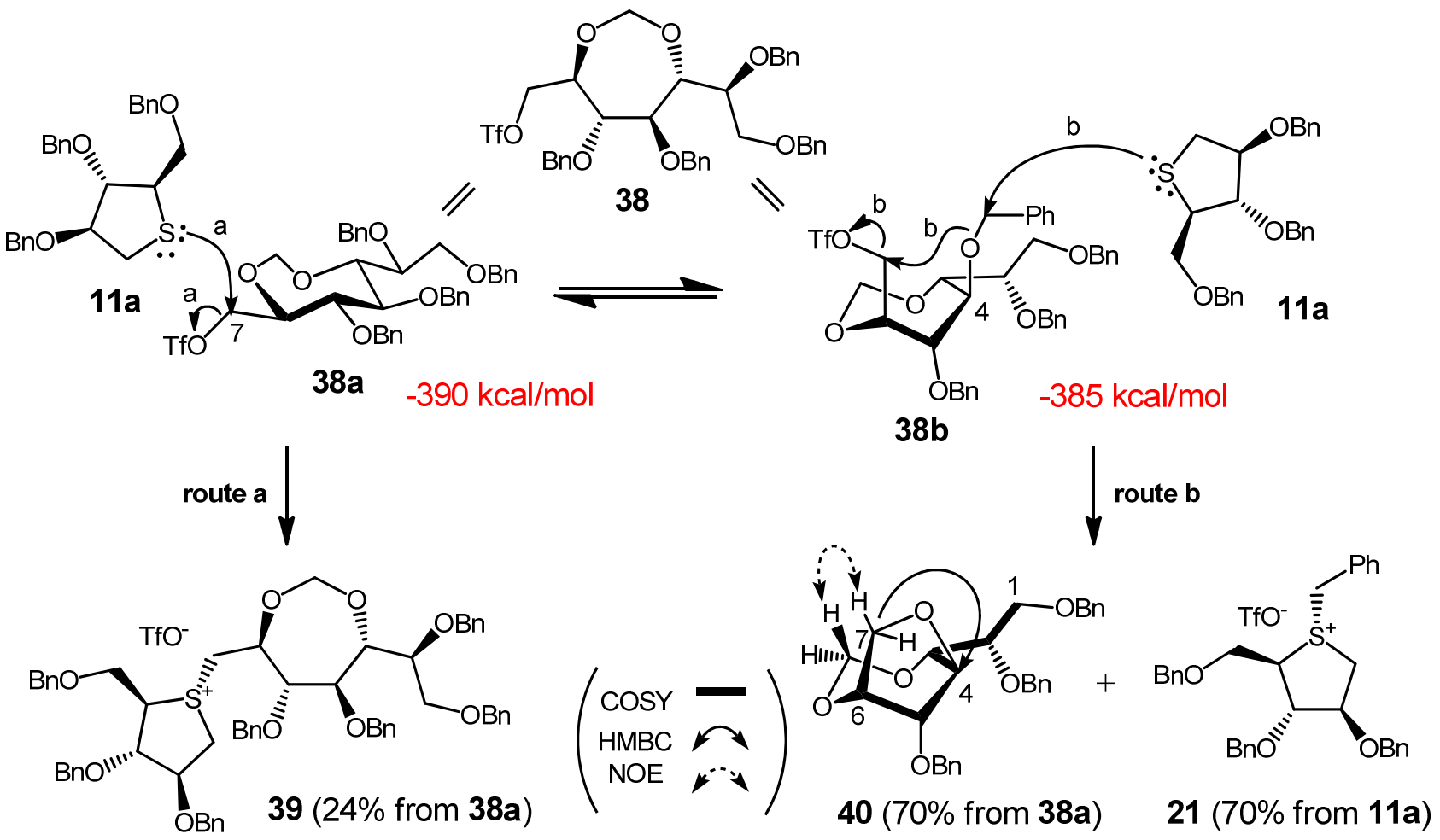
Preparation of Side Chain Moiety



Reagents and conditions: (a) $(Ph_3P)_3RhCl$, $^{i}Pr_2NEt$, EtOH, reflux, then HgO, $HgCl_2$, acetone/H_2O, 9/1, rt, 90% ; (b) Ph_3PCH_3Br, nBuLi THF, 0 °C, then 45 °C, 74%; (c) CH_2Br_2, $tBu_4N^+Br^-$, 50% aqueous NaOH, 60 °C, 54%; (d) AD-mix-β, tBuOH, H_2O, 0°C, 74%; (e) BnBr, NaH, DMF, 0°C-rt, 53%; (f) BCl_3, CH_2Cl_2 -78°C-0°C; (g) TBAF, THF-H_2O, 0°C-rt, 86%; (h) Tf_2O, 2,6-lutidine, -20-0°C, 83%.

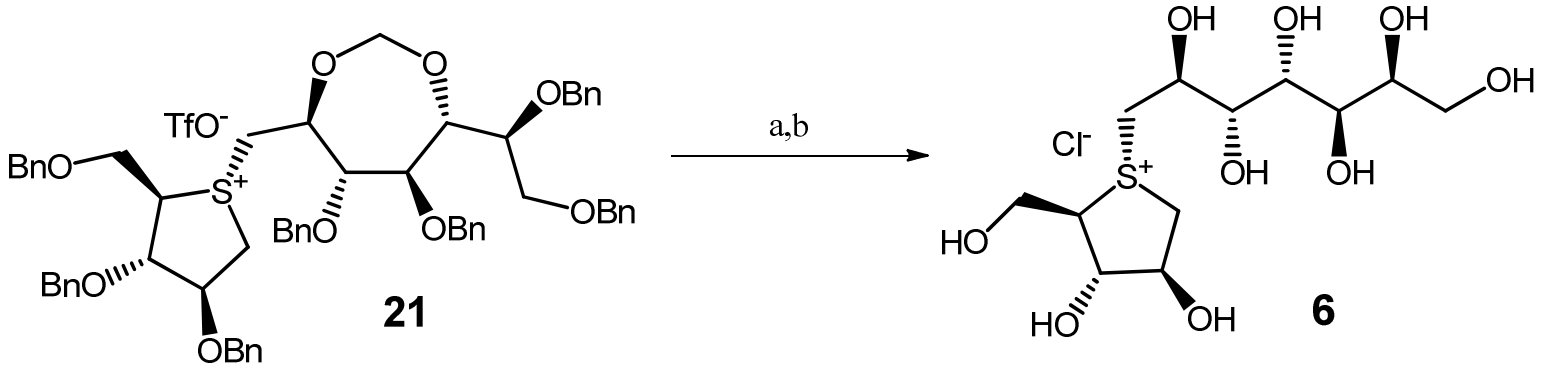
Total Synthesis of Neokotalanol (II)

Coupling Reaction Between Side Chain and Thiosugar



Total Synthesis of Neokotalanol (III)

Deprotection of Sulfonium Salt (21)



Reagents and conditions: (a) BCl_3, CH_2Cl_2, -78 °C; (b) IRA 400J (Cl^- form), MeOH, rt, 60% from **21**.

Reference: **Xie, W.**; Tanabe, G.;Tsutsui, N.;Wu. X.; Muraoka, O.* *Chin. J. Nat. Med.11*(6), 676, **2013**.

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