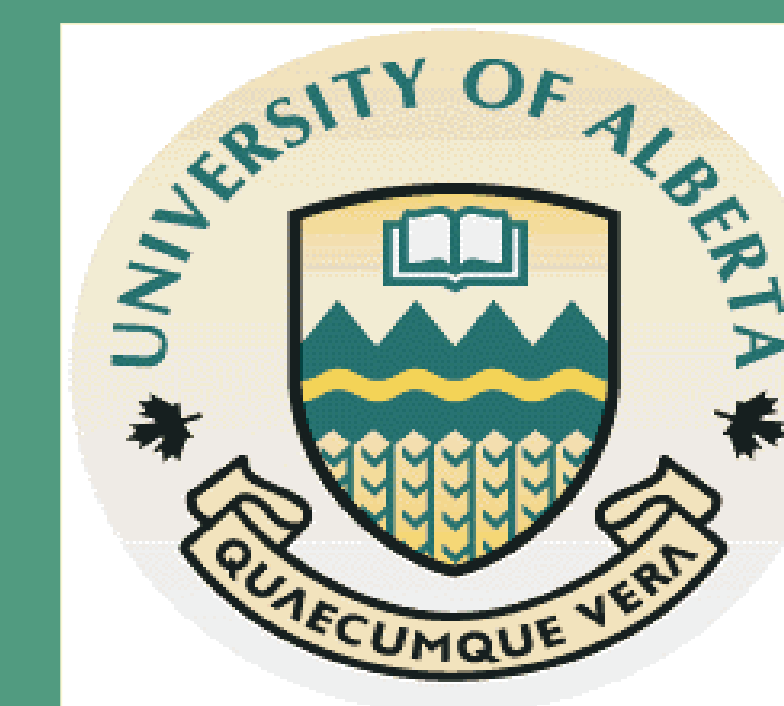
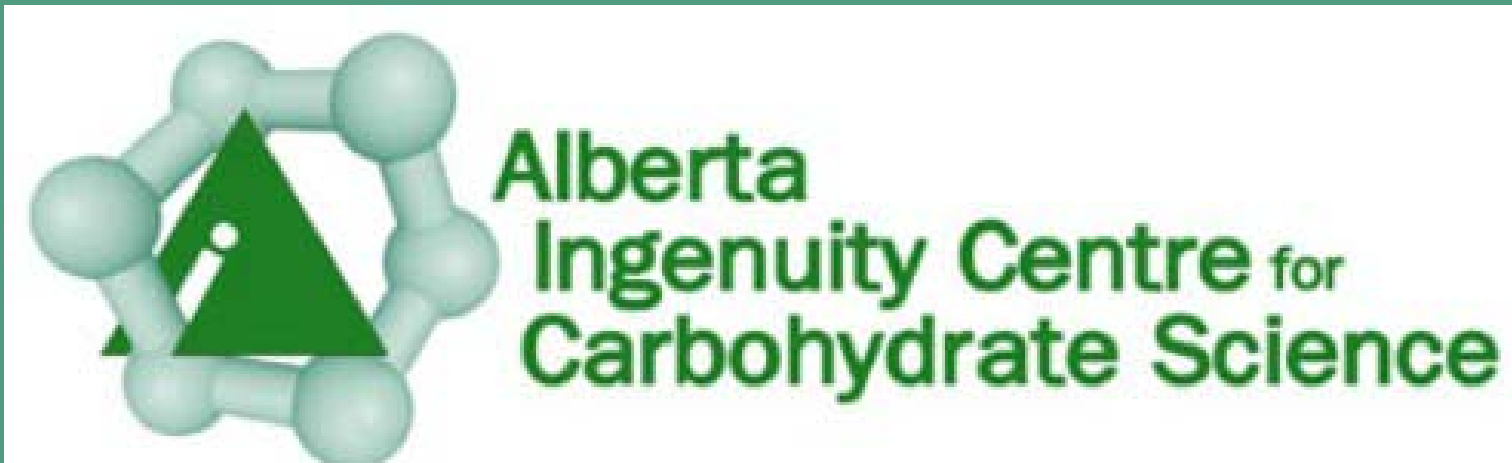


Towards the Total Synthesis of SB_{1a}, a Carbohydrate Hapten Associated with Human Hepatocellular Carcinoma

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Introduction

Every year, over 16,000 new cases of primary liver cancer are diagnosed in the United States. Worldwide, the numbers are even higher: areas of Africa and Asia have incidence rates ten times as high as those in America and appear to be increasing.

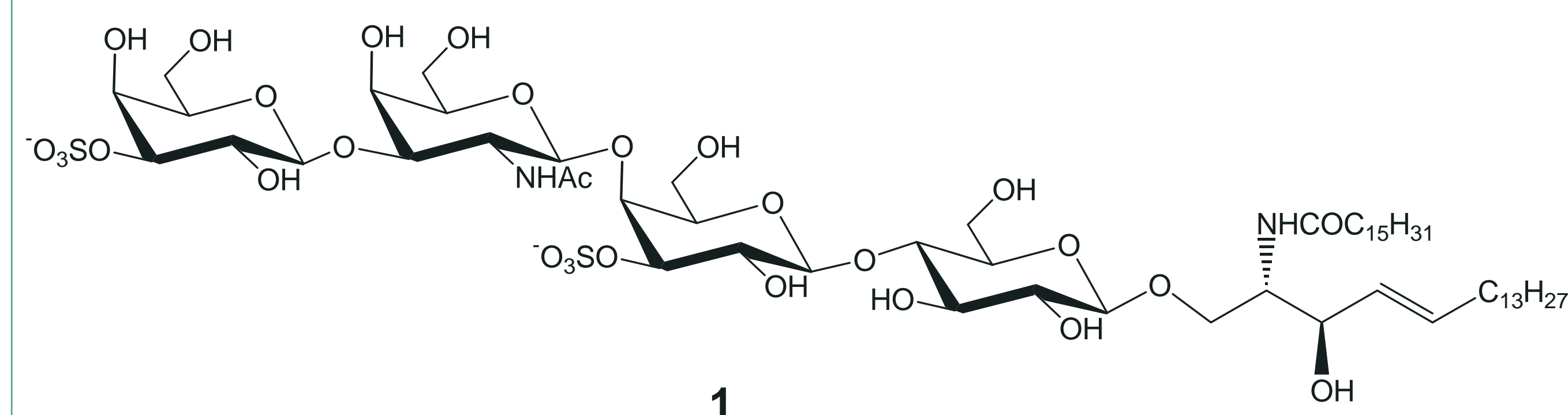
Hepatocellular carcinoma (HCC) accounts for over 80% of primary liver cancers. It affects men twice as often as women, and usually presents after age fifty. Exact causes for hepatocellular carcinoma are unknown, but contributing factors include chronic liver disease, viral hepatitis (especially hepatitis B and C) and cirrhosis.¹



Hepatocellular cancer, CT scan

Abberant cell-surface glycosylation is often closely associated with tumor progression and malignancy. In most cases, carbohydrate antigens may be rather specific to a certain type of tumor and are not overexpressed or recognized by the immune system in normal tissues. Therefore, carbohydrate antigens have mesmerized scientists in relevant fields because of their potential applications in tumor immunotherapy.²

SB_{1a} (**1**), a glycosphingolipid with a disulfated tetrasaccharide moiety, is one of the most important cancer-associated carbohydrate antigens of HCC. The normal human liver contains essentially no detectable amount of SB_{1a}. However, studies have shown that a remarkable accumulation of SB_{1a} exists, not only in the cultured human HCC cell lines, but also in glycolipid fractions extracted from HCC tissues.

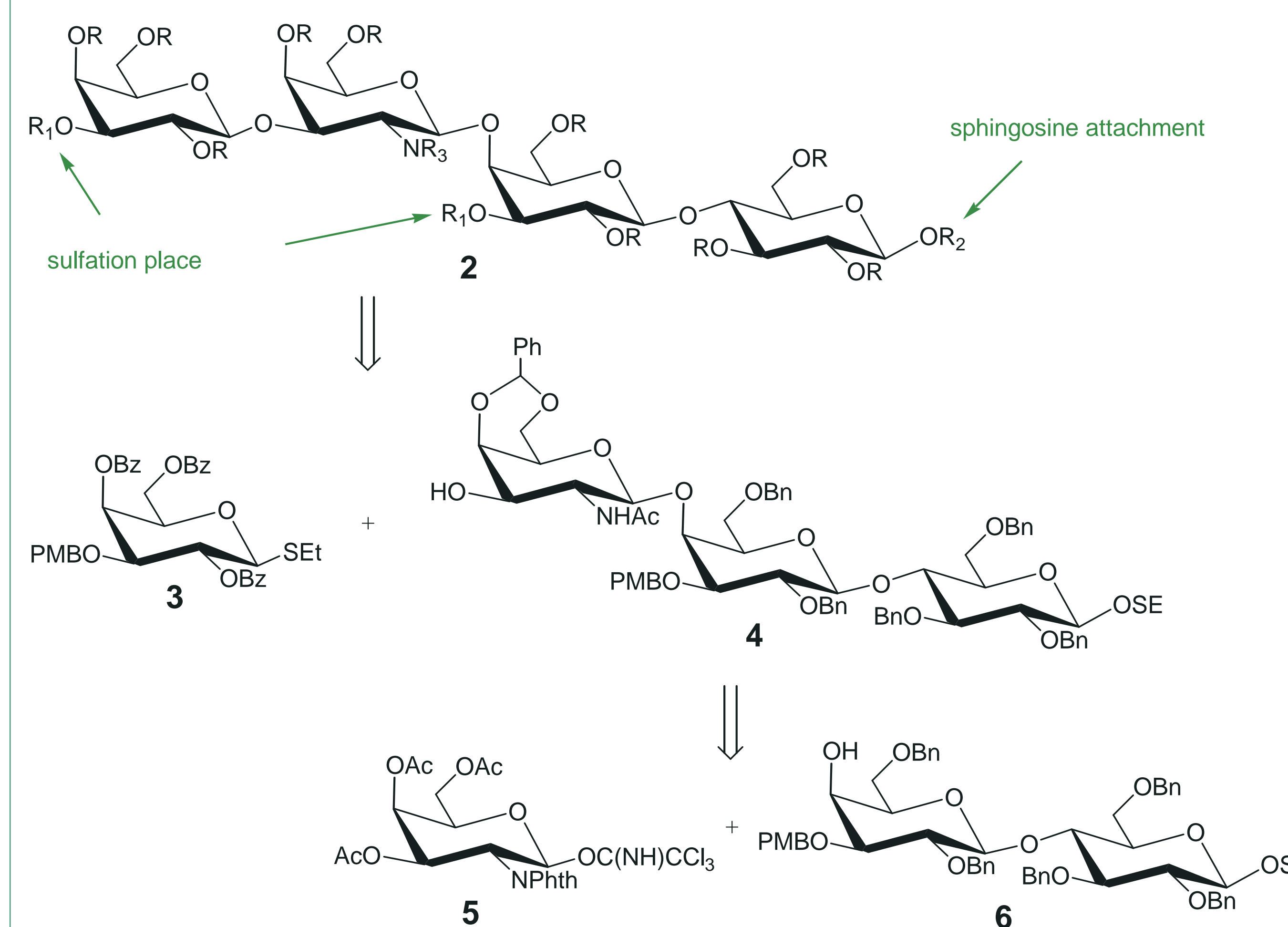


Target

In order to elucidate the functions of SB_{1a} in detail, especially its mechanism involved in onset, progression, and metastasis of HCC, and hence pursue optimal carbohydrate-based anticancer vaccines for HCC, total chemical synthesis of SB_{1a} is of primary importance.

Retrosynthetic Analysis

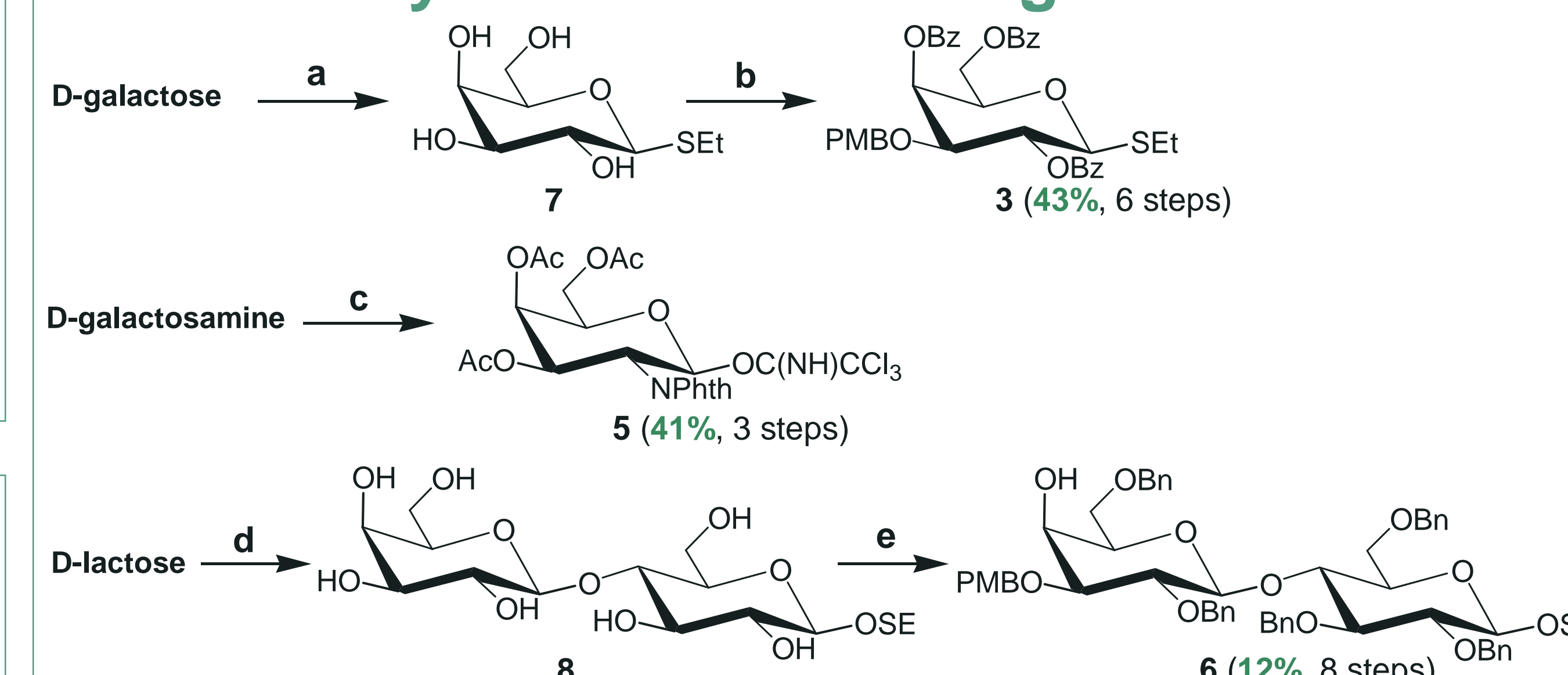
From various existing methodologies for the preparation of oligosaccharides we have chosen the stepwise approach that was proven to be the most efficient in studies performed earlier on the synthesis of SB_{1a} analogue.³ Therefore a protected tetrasaccharide **2** was designed as a key intermediate compound on the way to the target molecule.



Bn = Benzyl; Bz = benzoate; Phth = phthalimido; PMB = *p*-methoxybenzyl; SE = 2-trimethylsilylethyl

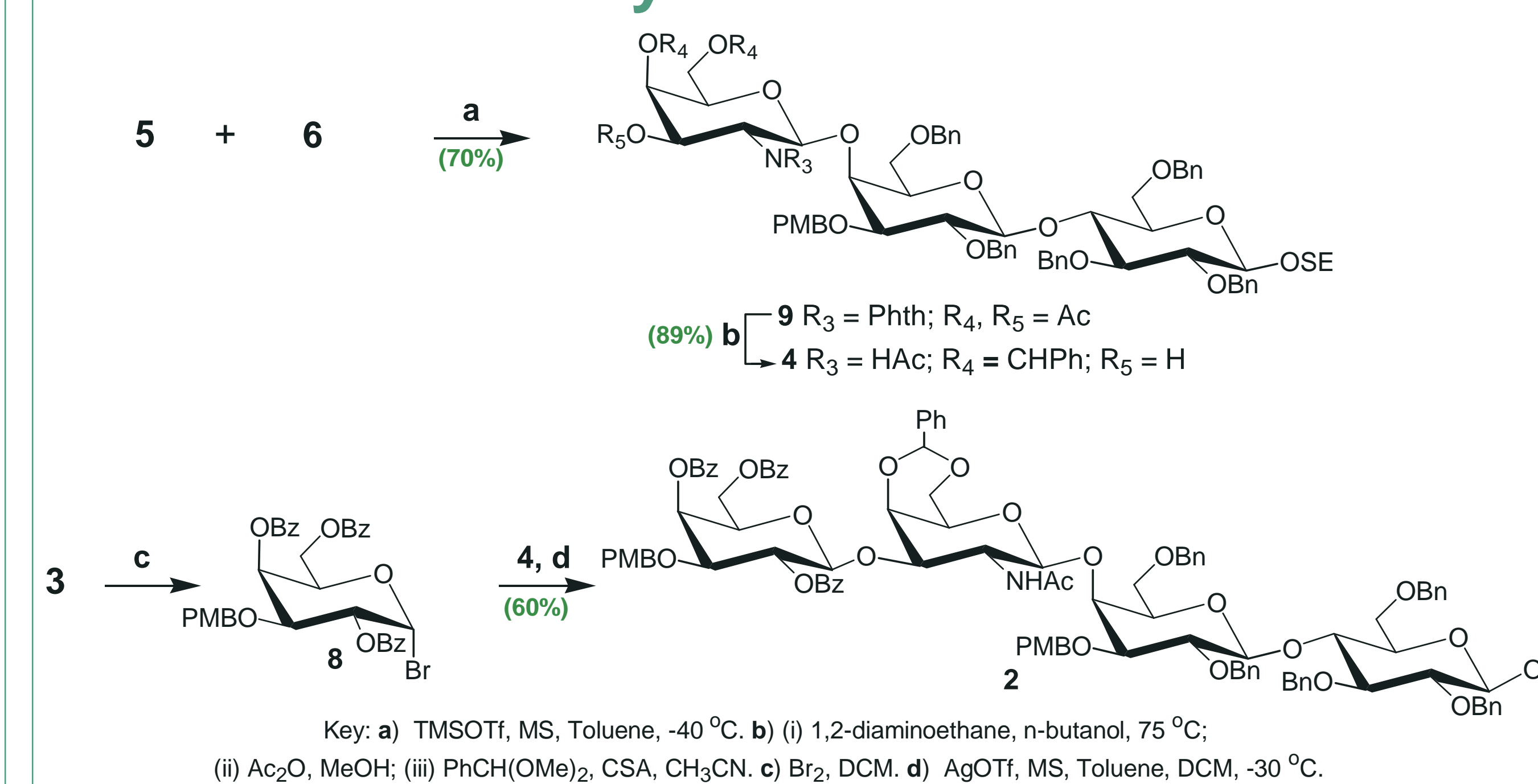
The assembly of the tetrasaccharide **2** can be accomplished using three building blocks: galactosyl donor **3**, galactosamino donor **5** and lactosyl acceptor **6**. The reducing end is protected with 2-trimethylsilylethyl group that can be selectively removed to allow sphingosine introduction via trichloroacetimidate procedure. Hydroxyls at positions C-3' and C-3''' are selectively protected with PMB groups to allow sulfation in the corresponding positions.

Synthesis of Building Blocks



Key: a) (i) Ac₂O, Py, DMAP; (ii) BF₃·Et₂O, EtSH, DCM; (iii) MeONa, MeOH. b) (i) Bu₂SnO, MeOH; (ii) PMBCl, CsF, DMF; (iii) BzCl, Py, DMAP. c) (i) MeONa, MeOH; (ii) Phthalic anhydride, Et₃N, MeOH; (iii) Ac₂O, Py, DMAP; (iv) NH₂-NH₂·OAc, DMF; (v) trichloroacetimidate, DBU, DCM. d) (i) Ac₂O; (ii) HBr, HOAc; (iii) 2-trimethylsilylethanol, HgO, HgBr₂, CaSO₄, DCM; (iv) MeONa, MeOH. e) (i) Me₂C(OMe)₂, acetone, *p*-TsOH; (ii) BnBr, NaH, DMF; (iii) 80% AcOH, 70°C; (iv) PMBCl, (Bu₄N)Br, Toluene.

Assembly of Tetrasaccharide



Key: a) TMSOTf, MS, Toluene, -40 °C. b) (i) 1,2-diaminoethane, *n*-butanol, 75 °C; (ii) Ac₂O, MeOH; (iii) PhCH(OMe)₂, CSA, CH₃CN. c) Br₂, DCM. d) AgOTf, MS, Toluene, DCM, -30 °C.

Future Work

- 1) Replacement of PMB groups at positions C-3' and C-3''' of **2** with chloroacetate protecting group.
- 2) Deprotection of benzyl ethers together with benzylidene acetal and reprotection with acyl protecting groups to ensure β-selectivity of sphingosine introduction.
- 3) Incorporation of a sphingosine moiety at the reducing end of molecule.
- 4) Selective deprotection of chloroacetates and sulfation.
- 5) One-step final deprotection of target molecule **1**.

References

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- 3) Li, Q., Li, H., Li, Q., Lou, Q.-H., Su, B., Cai, M.-S., Li, Z.-J. (2002) *Carbohydr. Res.* 337, 1929.

Acknowledgement

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