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Total Synthesis of Marine Glycosphingolipid Vesparioside B

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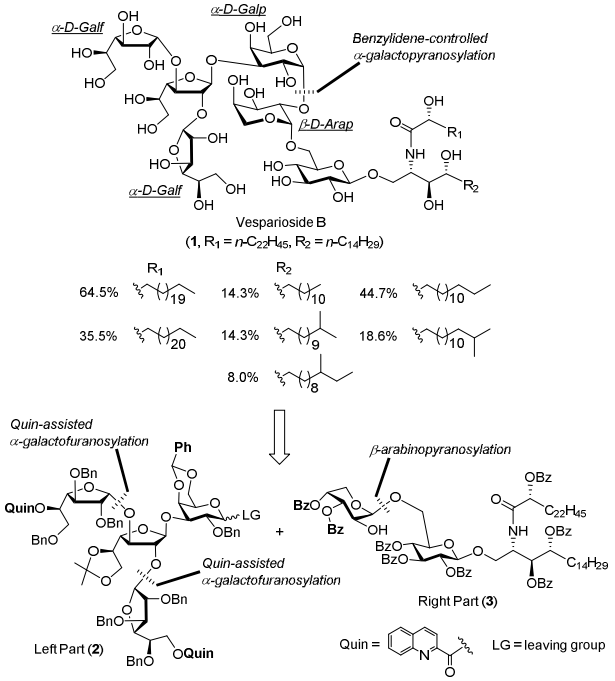
ABSTRACT: The first total synthesis of a major component of marine glycolipid vesparioside B (Scheme 1, **1**, R_1 = *n*-$C_{22}H_{45}$, R_2 = *n*-$C_{14}H_{29}$) has been accomplished through a convergent [4+3] coupling strategy. Key steps included stereoselective installment of a set of challenging 1,2-*cis*-glycoside bonds. A 2-quinolinecarbonyl-assisted α-galactosylation and a novel β-arabinosylation were developed, respectively, to synthesize the α-galactofuranosidic and the β-arabinopyranosidic linkages. Furthermore, a 4,6-*O*-benzylidene-controlled α-galactopyranosylation reaction allowed the efficient connection of the left tetrasaccharide donor **2** with the right disaccharide lipid acceptor **3**, hence leading to the total synthesis of **1**.

INTRODUCTION

Glycosphingolipids (GSLs) from marine sponges often have interesting immunomodulating activities.[1] In 2008, Mangoni and co-workers reported the isolation of vesparioside B (Scheme 1), a novel hexaglycosylated GSL, from Caribbean sponge *Spheciospongia vesparia*.[2] This natural product exists as a mixture of congeners, which differs from the length and the terminus of the alkyl chains of the hydrophobic ceramide part. On the other hand, the hydrophilic part of vesparioside B has been so far the most structurally complex carbohydrate chain of GSLs isolated from marine sponges. The unique structural features of the glycan motif of vesparioside B include: 1) it is rich in furanose, which is rarely found in natural GSLs. 2) it possesses multiple types of 1,2-*cis* glycosidic linkages, including two α-D-galactofuranose (α-D-Gal*f*), one α-D-galactopyranose (α-D-Gal*p*), and one β-D-arabinopyranose (β-D-Ara*p*) moieties. Syntheses of 1,2-*cis* glycosides in a stereoselective manner are usually considered as significantly challenging tasks in carbohydrate chemistry.[3] 3) it contains a 2,3-branched trisaccharide fragment at the non-reducing end and two adjacent 1,2-*cis* glycosidic bonds with high hindrance between the D-Gal*p* and D-Ara*p* units. The presence of these frameworks brings extra difficulties in generating the molecule. We chose vesparioside B as a synthetic target due to the challenge posed by its intricate oligosaccharide architecture. Furthermore, the chemical synthesis may help promote the discovery of its unknown biological activities. In this paper, we describe the total synthesis of the most abundant component of vesparioside B (Scheme 1, **1**, R_1 = *n*-$C_{22}H_{45}$, R_2 = *n*-$C_{14}H_{29}$). In the event, a 2-quinolinecarbonyl-assisted 1,2-*cis*-α-galactofuranosylation strategy and a new 1,2-*cis*-β-arabinopyranosylation method were developed to assemble the α-galactofuranoside and the β-arabinopyranoside scaffolds, respectively.

Scheme 1. Structure and Retrosynthetic Analysis of Vesparioside B



As retrosynthetically showed in Scheme 1, we anticipated that **1** could arise in a highly convergent manner from a [4 + 3] glycosylation between two advanced inter-

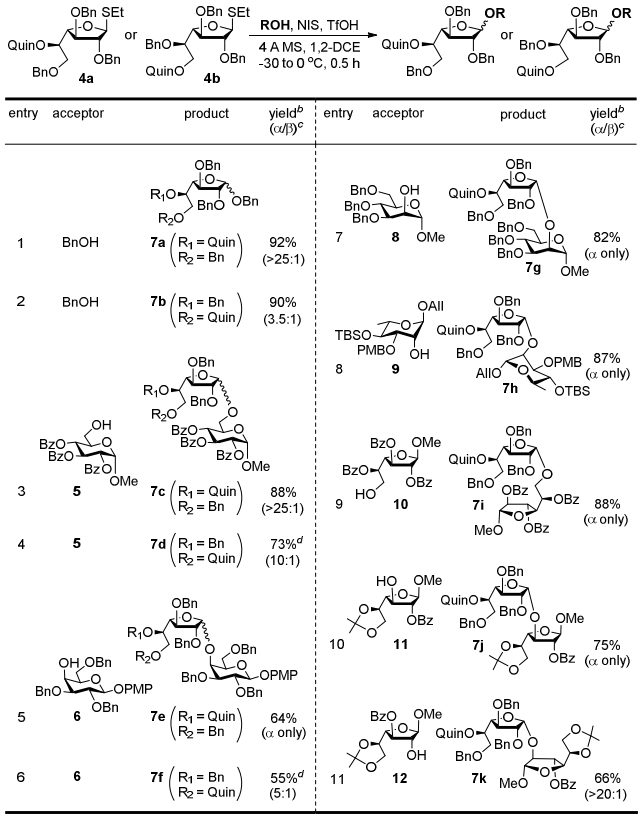
mediates, i.e., the left tetrasaccharide donor **2** and the right disaccharide lipid alcohol **3**. The construction of the critical 1,2-*cis*-α-galactopyranosidic bond linking both portions could in turn rely on a 4,6-*O*-benzylidene-controlled α-selective galactopyranosylation approach. In addition, the key route to compound **2** would involve the stereoselective formation of two challenging 1,2-*cis*-α-galactofuranosyl linkages via a 2-quinolinecarbonyl (Quin)-assisted α-galactofuranosylation approach. On the other hand, the 1,2-*cis*-β-D-arabinopyranosyl unit within compound **3** would be introduced by taking advantage of a 3,4-di-*O*-Bz carrying D-Ara*p* thioglycoside donor.

RESULTS AND DISCUSSION

The total synthesis of **1** commenced with the development of a new method for stereoselective synthesis of 1,2-*cis*-α-galactofuranoside which is found in a number of bacterial and fungal glycoconjugates.[4] In fact, a few strategies have been employed for this in the past.[5,6] Among them, the 2'-carboxybenzyl (CB) glycoside method, developed by Kim and co-workers, has proved to be useful for direct α-galactofuranosylation.[6d,e] Besides, the 2,3-anhydro-D-gulofuranosyl thioglycoside and sulfoxide activators, reported by Lowary et al., have also shown validity in stereocontrolled preparation of α-D-Gal*f*-containing oligosaccharides, but the regioselective opening of the 2,3-epoxide ring structure increases the synthetic steps.[6f,g]

Recently, an elegant hydrogen-bond-mediated aglycone delivery (HAD) strategy was disclosed by Demchenko et al.[7] to stereoselectively synthesize diverse glycosides in particular the 1,2-*cis*-pyranosides including α-gluco-, β-manno-, as well as β-rhamnosides. Key to the high stereoselectivity of this glycosylation method is that the intermolecular hydrogen bonding formed between the donor and acceptor can guide the attack of the acceptor to one specific side of the donor ring.[7a] Based on such a concept, our laboratory developed a reliable Quin-assisted 1,2-*cis*-glycosylation methodology for efficiently preparing β-arabinofuranosides.[8] The Quin functionality, acting as a H-bond acceptor, displays a strong β-stereocontrolling effect in the glycosylation of both D- and L-arabinofuranosyl thioglycoside donors with various acceptors. Here, we sought to extend such Quin-mediated 1,2-*cis*-furanosylation chemistry to the synthesis of the α-linked galactofuranosides. In order to achieve the required α-stereocontrol, the Quin directing group should be incorporated on the α-face of the Gal*f* ring. Thus, the 5- and 6-*O*-Quin substituted Gal*f* ethyl thioglycoside donors **4a**-**b** were synthesized (Table 1, see Supporting Information) and their glycosylation behavior was first evaluated by reaction with simple benzylalcohol, glucose 6-OH, and galactose 4-OH acceptors **5**[9] and **6**[10] under the promotion of *N*-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH) in 1,2-dichloroethane (DCE) at –30 → 0 °C for half an hour. The anomeric configuration of the products was deduced based on the ^{1}H NMR spectroscopy in $CDCl_3$. For the α-anomer, the $^3J_{H1/H2}$ value is 4.0-4.5 Hz, while, for the β-anomer, the $^3J_{H1/H2}$ is 0-2.0 Hz.[6i] As illustrated in Table 1, entries 1-6, the glycosylation of both donors showed α-stereoselectivity in all cases, but the 5-*O*-Quin carrying **4a** is superior to the 6-*O*-Quin carrying analog **4b** as the former generally led to higher levels of chemical yields and α:β ratios than the latter, regardless of the structure of the acceptor (entries 1 vs 2, 3 vs 4, and 5 vs 6, respectively). Next, the reaction of 5-*O*-quinoline-2-carbonylated **4a** was further investigated. We were pleased to find that a broad range of carbohydrate acceptors including D-manno-, L-rhamnopyranosyl, as well as D-galactofuranosyl nucleophiles **8**,[11] **9**,[12] **10**,[13] **11**,[14] and **12** all glycosylated smoothly with **4a**, furnishing the corresponding disaccharide products **7g-k** in good-to-excellent yields either as predominantly or as exclusively α-isomers (Table 1, entries 7-11).

Table 1. Glycosylation of D-Gal*f* thioglycoside Donors 4a-b[a]

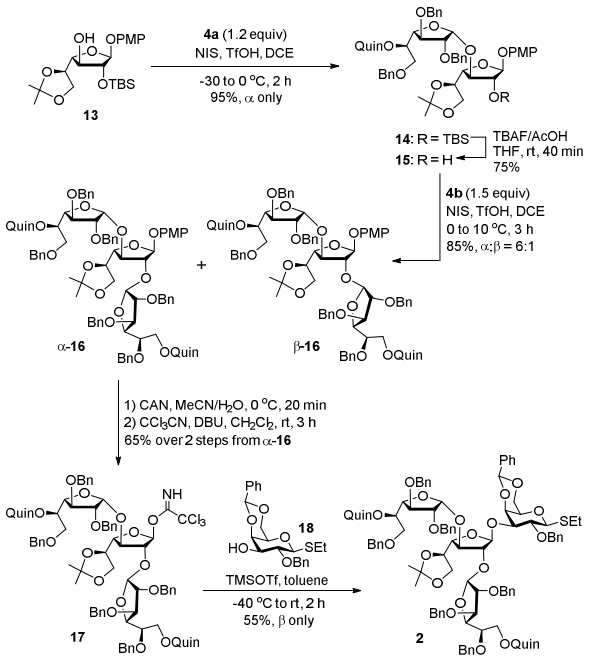


[a] Glycosylations were performed with donor **4a** (1.2 equiv, 7 mM, for entries 1, 3, 5, and 7-11) or **4b** (1.2 equiv, 7 mM, for entries 2, 4, and 6), acceptor (1 equiv), NIS (2 equiv)/TfOH (0.2 equiv), 4 Å molecular sieves (MS) in DCE at –30 → 0 °C for 0.5 h. [b] Yield of the major α-isomer unless otherwise noted. [c] Determined by ^{1}H NMR of the corresponding isomer mixture. [d] Yield of the inseparable mixture of α/β-isomers.

Having established a high-yielding and selective means to the synthesis of 1,2-*cis*-D-galactofuranoside, we

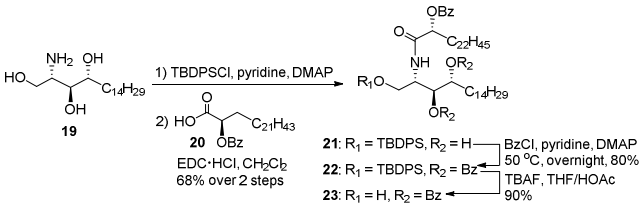
planned to apply it as a key step for creating the left tetrasaccharide sequence **2** (Scheme 2). To this end, the readily available D-galactofuranose derivative **13** (see Supporting Information) was galactofuranosylated with the 5-*O*-Quin equipped building block **4a** under the similar conditions as above to obtain solely the α-galactosyl disaccharide **14** ($J_{H1'/H2'}$ = 4.4 Hz) in excellent yield (95%). Removal of the 2-*O*-TBS group of **14** by treatment with TBAF buffered with HOAc in THF[15] afforded the corresponding glycoside **15** (75% yield). However, the stereoselective assembly of the second α-Gal*f* residue on the C2 position of this (1→3)-linked digalactoside alcohol turned out to be more challenging. Both the newly developed glycosyl donors **4a** and **4b** were examined for the glycosylation with **15** under the promotion of NIS/TfOH (cat.) in DCE. Surprisingly, the 5-*O*-Quin substituted **4a** was labile during the glycosylation since unreacted acceptor **15** and hemiacetal of the donor were notably found at the end of the reaction period by TLC analysis. In contrast, the coupling of the 6-*O*-Quin substituted **4b** with **15** proceeded straightforwardly and the trisaccharide glycoside **16** was accordingly obtained in 85% combined yield as a separable 6:1 α/β mixture in favor of the desired α-isomer.

Scheme 2. Synthesis of the Left Tetrasaccharide Donor 2



Oxidative cleavage of the C1 *p*-methoxyphenyl (PMP) group of pure α-**16** with ceric ammonium nitrate (CAN) in aqueous acetonitrile at 0 °C gave an intermediate hemiacetal (Scheme 2). Activation of the anomeric hydroxyl group through the reaction of trichloroacetonitrile (CCl_3CN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[16] readily gave the trisaccharide trichloroacetimidate **17** as a single β-diastereomer (65% yield, two steps from α-**16**). Then, **17** was subjected to chemoselective glycosylation[17] with the known thiogalactoside alcohol **18**[18] (see Supporting Information). After extensive screening studies, we found that the glycosylation worked well when **17** was coupled with an excess of **18** (**17**/**18**, ca. 1:3) upon activation with catalytic amounts of TMSOTf at −40 °C to room temperature in toluene, delivering the required tetrasaccharide thioglycoside **2** in 55% yield as a single β-isomer ($\delta_{H1'}$ = 5.34 ppm, s) ready for direct condensation with the right fragment. The high selectivity of the coupling is presumably attributed to the shielding of the bottom face of substrate **17** by its 2-*O*-Gal*f* residue, therefore favoring the approach of the nucleophile from the β-face.

Scheme 3. Synthesis of the Ceramide Building Block 23

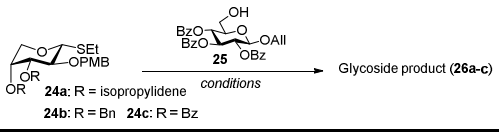


Then, our attention was directed to the synthesis of the disaccharide lipid portion **3**. First, the route to ceramide building block **23** began from commercially available phytosphingosine **19** (Scheme 3). On reaction with 1 equiv of *tert*-butyldiphenylsilyl chloride (TBDPSCl) in pyridine, the primary hydroxyl group of **19** was selectively protected to give a silyl ether. Then, this intermediate was condensed with chiral α-hydroxyl fatty acid **20**[19] in the presence of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC·HCl) to obtain the protected ceramide derivative **21**. Conversion of **21** to the required **23** involved (i) benzoylation of the secondary alcohols of **21** with benzoyl chloride (BzCl), forming **22** (80%), and (ii) desilylation of **22** with TBAF in acidic THF solution, giving rise to the corresponding **23** (90% yield).

The next objective was to explore appropriate conditions for stereoselective construction of 1,2-*cis*-β-D-arabinopyranoside. Previously, during the total synthesis of marine natural product eleutherobin, both Nicolaou and Danishefsky groups have surveyed the glycosylation method for stereoselective attachment of a β-D-Ara*p* unit to the core aglycons. Nicolaou et al.[20] utilized 2-*O*-PMB-3,4-di-*O*-TBS protected D-Ara*p* trichloroacetimidate as donor and found that the glycosylation selectivity greatly depended on the experimental conditions. On the other hand, the glycosylation of the 2-*O*-TBS-3,4-*O*-acetonide protected 1-thioarabinopyranoside, presented by Danishefsky et al,[21] showed slight anomeric selectivity. In our study, we found that the protecting group pattern of the D-arabinopyranosyl donor significantly influenced the anomeric stereochemistry of the glycosylation product. Table 2 summarized the reaction outcomes of D-Ara*p*-derived ethyl thioglycosides **24a-c** having different protecting groups such as an isopropylidene acetal, benzyl ethers, or benzoate esters on the C3 and C4 positions

(Supporting Information) with glucosyl 6-OH substrate **25**.[22] The NIS/TfOH (cat.)-activated coupling of **24a** possessing a 3,4-*O*-acetonide group with **25** displayed poor β-selectivity, affording a 1:2 α/β mixture of disaccharides **26a** in 72% yield (entry 1), which is analogous to the findings reported by Danishefsky et al.[21] Upon switching the promoter system to NIS/AgOTf, no significant improvement was obtained in yield or selectivity (entry 2). A similar result was observed in the reaction of 3,4-di-*O*-Bn protected **24b** (entry 3). To our delight, successful β-D-arabinopyranosylation of **25** was achieved when it was glycosylated with 3,4-di-*O*-benzoylated donor **24c** using NIS/AgOTf (cat.) as activating agent in Et_2O at −17 °C, yielding disaccharide **26c** in 95% yield with a complete 1,2-*cis*-β-selectivity (entry 4). No α-stereoisomer was found even after chromatographic isolation in the glycosylation. The $^3J_{H1/H2}$ coupling constant (J = 3.6 Hz) in ^{1}H NMR spectrum of **26c** clearly indicated the β-anomeric configuration of the 6-*O*-D-Ara*p* residue adopting a $^1C_4$ conformation. Changing the promoter system to NIS/TfOH (cat.) and the solvent to CH_2Cl_2 also led to similar results (entry 5). At present, we are unsure about the origin of the high β-stereoselectivity with the glycosyl substrate **24c**.

Table 2. Glycosylation of D-Ara*p* thioglycoside Donors 24a-c[a]

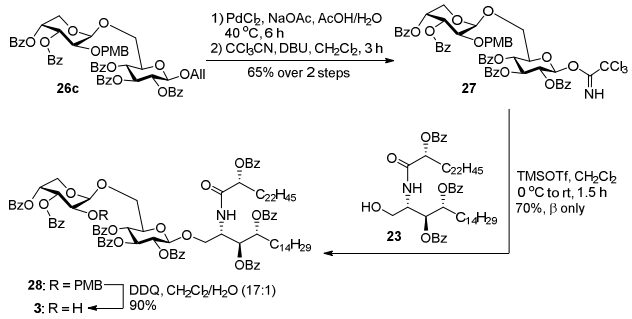


entry	donor	condition	product	yield[b] (α/β)[c]
1	**24a**	NIS, TfOH, Et_2O, -17 °C	**26a**	72% (1:2)
2	**24a**	NIS, AgOTf, Et_2O, -17 °C	**26a**	75% (1:3)
3	**24b**	NIS, AgOTf, Et_2O, -17 °C	**26b**	75% (1:3)
4	**24c**	NIS, AgOTf, Et_2O, -17 °C	**26c**	95%[d] (β only)
5	**24c**	NIS, TfOH, CH_2Cl_2, -17 °C	**26c**	92%[d] (β only)

[a] Glycosylations were carried out with donor **24a-c** (1.2 equiv), acceptor (1 equiv), NIS (2 equiv)/TfOH (0.2 equiv) or AgOTf (0.2 equiv), 4 Å molecular sieves (MS) at −17 °C for 3 h. [b] Yield of the inseparable mixture of α/β-isomers unless otherwise noted. [c] Determined by ^{1}H NMR of the corresponding isomer mixture. [d] Yield of the β-isomer.

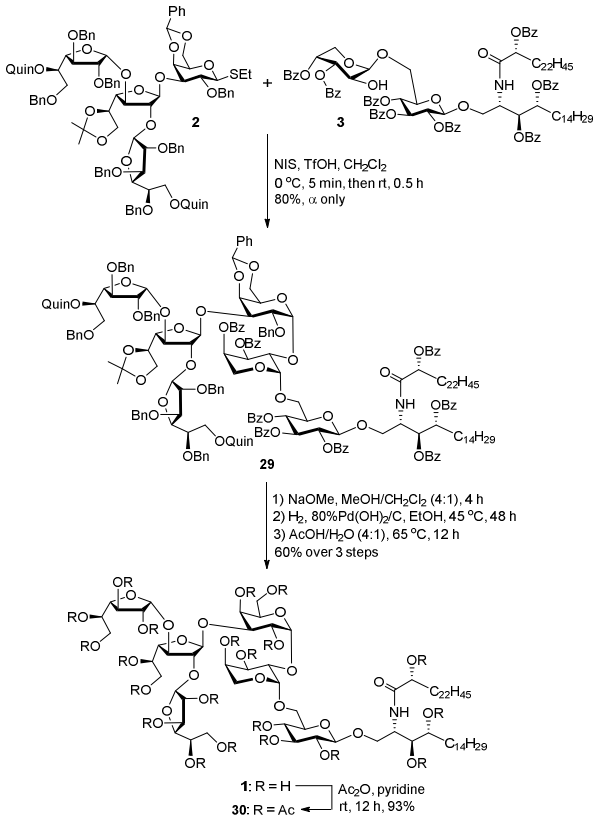
The C1 position of **26c** was then unmasked via a $PdCl_2$-catalyzed deallylation protocol (Scheme 4). As before, the resulting crude hemiacetal was converted easily to disaccharide trichloroacetimidate **27** (65% yield over two steps). Upon activation with TMSOTf, **27** underwent an efficient glycosylation with ceramide acceptor **23** to give disaccharide lipid **28** (70% yield). Exposure of this compound to 3 equiv of DDQ in wet CH_2Cl_2 liberated the 2"-OH to form the alcohol **3** (90% yield), which completed the preparation of the required right part.

Scheme 4. Synthesis of the Right Disaccharide Lipid Acceptor 3



Finally, we aimed for the connection of the key precursors **2** and **3** and elaboration of the resulting product to natural vesparioside B. Scheme 5 shows how the assembly of the α-(1→2)-galactopyranosyl linkage between the left and the right parts was achieved. The C2 hydroxyl group of the β-D-Ara*p* residue in **3** is very crowded since it is *cis* to the bulky aglycone on the neighboring anomeric center. Indeed, owing to the severe hydrolysis of the donor **2**, the NIS/TfOH-mediated coupling of **2** to **3** provided only 16% yield of the desired hexasaccharide lipid **29**. This prompted us to carry out the reaction using an inverse glycosylation protocol,[12,15b,23] i.e., the acceptor **3** was premixed with the NIS/TfOH promoter system in CH_2Cl_2 prior to the slow addition of a CH_2Cl_2 solution of the donor **2** at 0 °C. As a result, decomposition of the donor was effectively suppressed and **29** was obtained in a considerably elevated 80% yield as a single diastereomer.[24] None of the corresponding β-glycoside counterpart was detected by TLC. The α-configuration of the newly formed galactopyranoside bond was unambiguously verified by the expected doublet for anomeric signal of the α-Gal*p* moiety (δ_{H1} = 5.0 ppm, d, $J_{H1/H2}$ = 3.6 Hz). Global deprotection of **29** was performed in the following order (Scheme 5): Zemplén deacylation with NaOMe in MeOH/CH_2Cl_2 (4:1), deprotection of the Bn ethers and the benzylidene acetal by catalytic hydrogenolysis, and finally cleavage of the isopropylidene acetal under acidic conditions. Purification of deprotected glycolipid was completed using chromatography on silica gel with CH_2Cl_2-MeOH (1:2) as eluent to give the target **1** as a white solid in 60% yield over three steps. Synthetic **1** was found to be identical with the natural isolate[2] based on ^{1}H and ^{13}C NMR spectral comparison (see Supporting Information). The free **1** was further acylated with acetic anhydrate (Ac_2O) in pyridine to produce the corresponding peracetylated derivative **30** (93% yield). The NMR data (^{1}H and ^{13}C NMR spectra) and specific rotation of this material are in full agreement with those of the peracetate substance derived from naturally occurring vesparioside B,[2] thereby further confirming the structure of the synthetic molecule.

Scheme 5. Completion of Total Synthesis of Vesparioside B (1)



CONCLUSIONS

In conclusion, we have developed a convergent strategy for the total synthesis of a major congener of structurally unusual vesparioside B. Our synthesis highlights an efficient 4,6-*O*-benzylidene-directed α-galactopyranosylation method for forging the left and the right fragments together to build the whole hexasaccharide glycolipid backbone. Moreover, the difficult-to-obtain 1,2-*cis*-α-galactofuranoside and β-arabinopyranoside were efficiently assembled through the use of 5- or 6-*O*-Quin substituted D-Gal*f* thioglycoside and 3,4-di-*O*-Bz protected D-Ara*p* thioglycoside donors, respectively. These glycosyl donors exhibited excellent glycosylation yields and selectivity. Research is in progress to study the biological function of this natural glycolipid and its analogues.

ASSOCIATED CONTENT

Supporting Information. Experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, and 2D NMR spectra for **2**, α-**16**, β-**16**, **26c**, **28**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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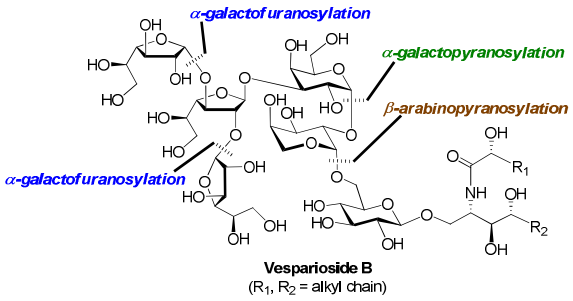
α-galactofuranosylation
α-galactopyranosylation
β-arabinopyranosylation
α-galactofuranosylation
Vesparioside B
(R1, R2 = alkyl chain)

TOC