

Total Synthesis of Marine Glycosphingolipid Vesparioside B

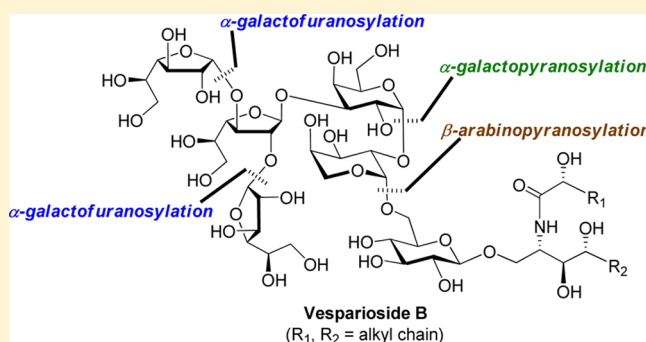
Peng-Cheng Gao,^{†,‡} San-Yong Zhu,^{†,§} Hui Cao,[†] and Jin-Song Yang^{*,†,‡}

[†]Department of Chemistry of Medicinal Natural Products, and Key Laboratory of Drug Targeting, Ministry of Education, West China School of Pharmacy, Sichuan University, Chengdu 610041, China

[‡]State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

S Supporting Information

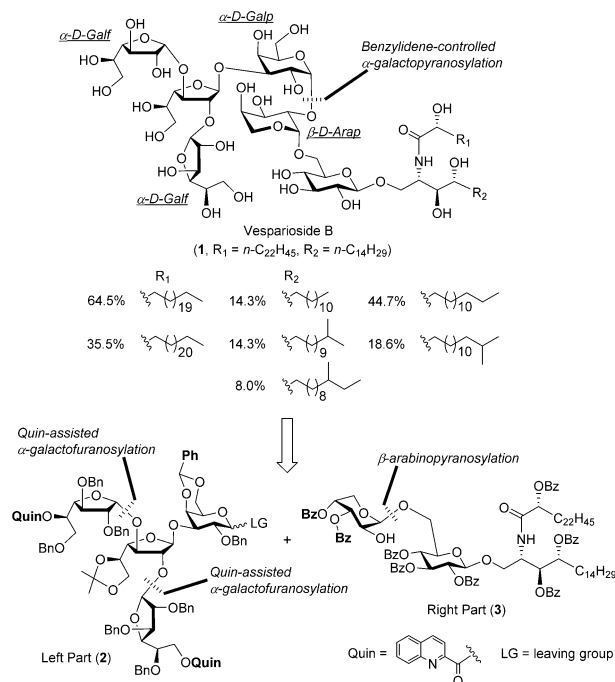
ABSTRACT: The first total synthesis of a major component of marine glycolipid vesparioside B (Scheme 1, 1, R₁ = *n*-C₂₂H₄₅, R₂ = *n*-C₁₄H₂₉) has been accomplished through a convergent [4 + 3] coupling strategy. Key steps included stereoselective installment of a set of challenging 1,2-*cis*-glycoside 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. Structure and Retrosynthetic Analysis of Vesparioside B



(Scheme 1), a novel hexaglycosylated GSL, from Caribbean sponge *Sphaciospongia 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 the following: (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-Galp), one α -D-galactopyranose (α -D-Galp), and one β -D-arabinopyranose (β -D-Arap) 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-Galp and D-Arap 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, R₁ = *n*-C₂₂H₄₅, R₂ = *n*-C₁₄H₂₉). In the event, a 2-quinolinecarbonyl-assisted 1,2-*cis*- α -galactofuranosylation strategy and a new 1,2-*cis*- β -arabinopyranosylation method were

Received: December 2, 2015

Published: January 19, 2016

developed to assemble the α -galactofuranoside and the β -arabinopyranoside scaffolds, respectively.

As retrosynthetically shown in Scheme 1, we anticipated that **1** could arise in a highly convergent manner from a [4 + 3] glycosylation between two advanced intermediates, 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-Arap 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-Galf-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-, and β -rhamnosides. The 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} On the basis of 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. To achieve the required α -stereocontrol, the Quin directing group should be incorporated on the α -face of the Galf ring. Thus, the 5- and 6-*O*-Quin-substituted Galf ethyl thioglycoside donors **4a,b** were synthesized (Table 1, see Supporting Information) and their glycosylation behavior was first evaluated by reaction with simple benzyl alcohol, glucose 6-OH, and galactose 4-OH acceptors **5**⁹ and **6**¹⁰ under the promotion from *N*-iodosuccinimide (NIS) and catalytic trifluoromethanesulfonic acid (TfOH) in 1,2-dichloroethane (DCE) at $-30 \rightarrow 0$ °C for 0.5 h. The anomeric configuration of the products was deduced based on the ¹H NMR spectroscopy in CDCl₃. 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 analogue **4b** as

Table 1. Glycosylation of D-Galf Thioglycoside Donors **4a,b**^a

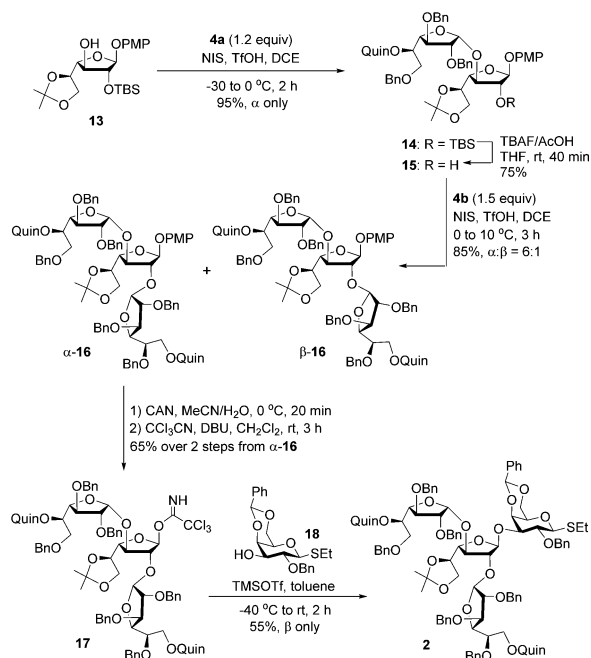
| Donor 4a | | | | Donor 4b | | | |
|----------|-----------------|--|---|----------|----------------------------|-----------------------|---|
| entry | acceptor | product | yield ^b (α/β) ^c | entry | acceptor | product | yield ^b (α/β) ^c |
| 1 | BnOH | 7a (R ₁ = Quin, R ₂ = Bn) | 92% (>25:1) | 7 | 8 (OMe) | 7g (OMe) | 82% (α only) |
| 2 | BnOH | 7b (R ₁ = Bn, R ₂ = Quin) | 90% (3.5:1) | 8 | 9 (TBSO, PMBO, All) | 7h (All, OTBS) | 87% (α only) |
| 3 | 5 (OMe) | 7c (R ₁ = Quin, R ₂ = Bn) | 88% (>25:1) | 9 | 10 (BzO, MeO) | 7i (MeO) | 88% (α only) |
| 4 | 5 | 7d (R ₁ = Bn, R ₂ = Quin) | 73% ^d (10:1) | 10 | 11 (HO, OMe) | 7j (OMe) | 75% (α only) |
| 5 | 6 (OPMP) | 7e (R ₁ = Quin, R ₂ = Bn) | 64% (α only) | 11 | 12 (BzO, MeO) | 7k (MeO) | 66% (>20:1) |
| 6 | 6 | 7f (R ₁ = Bn, R ₂ = Quin) | 55% ^d (5:1) | | | | |

^aGlycosylations 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 $-30 \rightarrow 0$ °C for 0.5 h. ^bYield of the major α -isomer unless otherwise noted. ^cDetermined by ¹H NMR of the corresponding isomer mixture. ^dYield of the inseparable mixture of α/β -isomers.

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, and 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).

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 conditions similar to those 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 THF¹⁵ afforded the corresponding glycoside **15** (75% yield). However, the stereoselective assembly of the second α -Galf residue on the C2 position of this (1 \rightarrow 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

Scheme 2. Synthesis of the Left Tetrasaccharide Donor 2

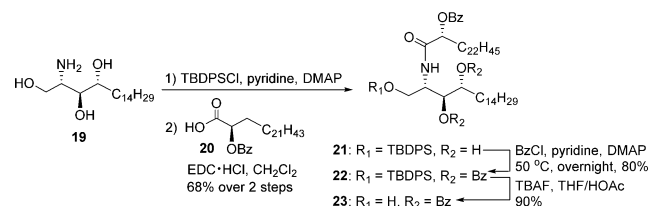


promotion from NIS/TfOH (cat.) in DCE. Surprisingly, the 5-*O*-Quin-substituted **4a** was labile during the glycosylation because unreacted acceptor **15** and hemiacetal of the donor were notably found at the end of the reaction period by TLC analysis. In contrast, the coupling of the 6-*O*-Quin-substituted **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.

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 (CCl₃CN) 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 glycosylation¹⁷ 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 ($\delta_{\text{H}1'} = 5.34$ 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*-GalF residue, therefore favoring the approach of the nucleophile from the β -face.

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 (TBDPSCI) 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-(dimethylamino)propyl)-*N'*-ethylcarbodiimide hydrochloride (EDC·HCl) to obtain the protected ceramide derivative **21**.

Scheme 3. Synthesis of the Ceramide Building Block 23



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-Arap unit to the core aglycons. Nicolaou et al.²⁰ utilized 2-*O*-PMB-3,4-di-*O*-TBS-protected D-Arap 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-Arap-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

Table 2. Glycosylation of D-Arap Thioglycoside Donors **24a**–**c**^a

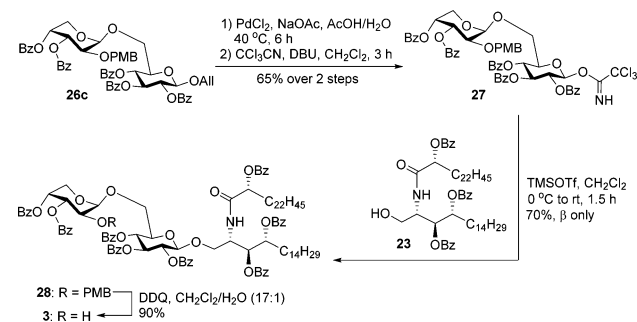
| entry | donor | condition | product | yield ^b (α/β) ^c |
|-------|------------|---|------------|--|
| 1 | 24a | NIS, TfOH, Et ₂ O, -17 °C | 26a | 72% (1:2) |
| 2 | 24a | NIS, AgOTf, Et ₂ O, -17 °C | 26a | 75% (1:3) |
| 3 | 24b | NIS, AgOTf, Et ₂ O, -17 °C | 26b | 75% (1:3) |
| 4 | 24c | NIS, AgOTf, Et ₂ O, -17 °C | 26c | 95% ^d (β only) |
| 5 | 24c | NIS, TfOH, CH ₂ Cl ₂ , -17 °C | 26c | 92% ^d (β only) |

^aGlycosylations 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. ^bYield of the inseparable mixture of α/β -isomers unless otherwise noted. ^cDetermined by ¹H NMR of the corresponding isomer mixture. ^dYield of the β -isomer.

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 Et₂O 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 ¹H NMR spectrum of **26c** clearly indicated the β -anomeric configuration of the 6-*O*-D-Arap residue adopting a ¹C₄ conformation. Changing the promoter system to NIS/TfOH (cat.) and the solvent to CH₂Cl₂ 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**.

The C1 position of **26c** was then unmasked via a PdCl₂-catalyzed deallylation protocol (Scheme 4). As previously, the

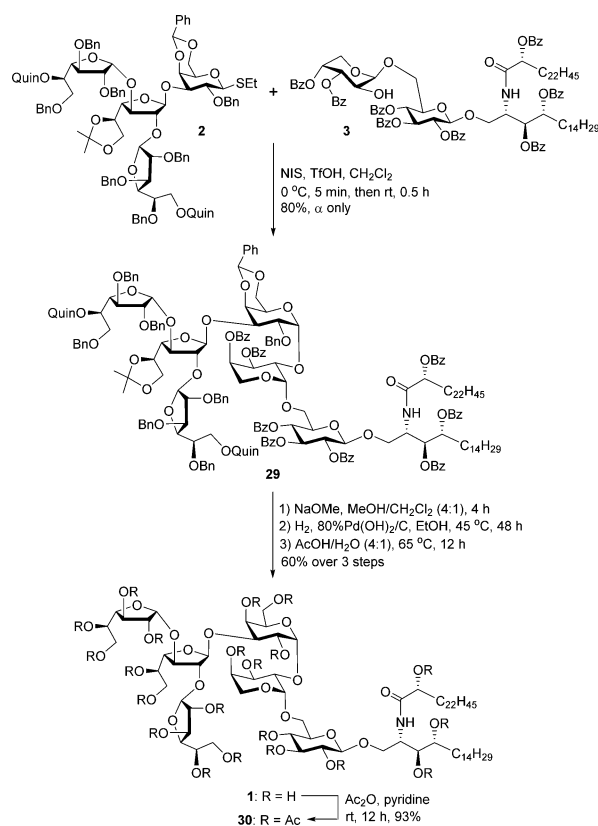
Scheme 4. Synthesis of the Right Disaccharide Lipid Acceptor 3



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 CH₂Cl₂ liberated the 2''-OH to form the alcohol **3** (90% yield), which completed the preparation of the required right part.

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 \rightarrow 2)-galactopyranosyl linkage between the left and the right parts was achieved. The C2 hydroxyl group of the β -D-Arap 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 CH₂Cl₂ prior to the slow addition of a CH₂Cl₂ 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

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



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 -Galp 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/CH₂Cl₂ (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 CH₂Cl₂-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 isolate² based on ¹H and ¹³C NMR spectral comparison (see Supporting Information). The free **1** was further acylated with acetic anhydride (Ac₂O) in pyridine to produce the corresponding peracetylated derivative **30** (93% yield). The NMR data (¹H and ¹³C 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.

CONCLUSIONS

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-Galf

thioglycoside and 3,4-di-O-Bz-protected D-Arap 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

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b12589.

Experimental details, ¹H and ¹³C NMR spectra for all new compounds, and 2D NMR spectra for **2**, α -**16**, β -**16**, **26c**, **28**, and **29** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*yjs@scu.edu.cn

Present Address

§651 W. Hancock St., Apt. 205, Detroit, MI 48201, USA.

Author Contributions

[†]These authors contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the NSFC (21372166, 21172156, 21321061), the 973 program (2010CB833202), and the Ministry of Education (20100181110082) of China.

■ REFERENCES

- (1) (a) Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A. *J. Am. Chem. Soc.* **1997**, *119*, 12465–12470. (b) Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A.; Maffia, P. *Tetrahedron* **1996**, *52*, 1573–1578. (c) Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771–2784. (d) Costantino, V.; D'Esposito, M.; Fattorusso, E.; Mangoni, A.; Basilico, N.; Parapini, S.; Taramelli, D. *J. Med. Chem.* **2005**, *48*, 7411–7417. (e) Crul, M.; Mathôt, R. A. A.; Giaccone, G.; Punt, C. J. A.; Rosing, H.; Hillebrand, M. J. X.; Ando, Y.; Nishi, N.; Tanaka, H.; Schellens, J. H. M.; Beijnen, J. H. *Cancer Chemother. Pharmacol.* **2002**, *49*, 287–293.
- (2) Costantino, V.; Fattorusso, E.; Imperatore, C.; Mangoni, A. *J. Org. Chem.* **2008**, *73*, 6158–6165.
- (3) For reviews on stereocontrolled synthesis of 1,2-*cis*-glycosides, see: (a) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687–2704. (b) Demchenko, A. V. *Synlett* **2003**, 1225–1240.
- (4) (a) Peltier, P.; Euzen, R.; Daniellou, R.; Nugier-Chauvin, C.; Ferrières, V. *Carbohydr. Res.* **2008**, *343*, 1897–1923. (b) Stenutz, R.; Weintraub, A.; Widmalm, G. *FEMS Microbiol. Rev.* **2006**, *30*, 382–403. (c) Perepelov, A. V.; Li, D.; Liu, B.; Senchenkova, S. y. N.; Guo, D.; Shashkov, A. S.; Feng, L.; Knirel, Y. A.; Wang, L. *Innate Immun.* **2011**, *17*, 164–173. (d) Perepelov, A. V.; Liu, B.; Senchenkova, S. y. N.; Shashkov, A. S.; Feng, L.; Knirel, Y. A.; Wang, L. *Carbohydr. Res.* **2011**, *346*, 373–376. (e) Zdorovenko, E. L.; Valueva, O. A.; Varbanets, L. D.; Shubchinskiy, V. V.; Shashkov, A. S.; Knirel, Y. A. *Carbohydr. Res.* **2010**, *345*, 1812–1815. (f) Tefsen, B.; Ram, A. F.; van Die, I.; Routier, F. H. *Glycobiology* **2012**, *22*, 456–469.
- (5) For reviews on stereoselective synthesis of 1,2-*cis*- α -galactofuranoside, see: Richards, M. R.; Lowary, T. L. *ChemBioChem* **2009**, *10*, 1920–1938. (d) Liang, X.-Y.; Deng, L.-M.; Yang, J.-S. *Youji Huaxue* **2013**, *33*, 245–258.
- (6) (a) Gelin, M.; Ferrières, V.; Plusquellec, D. *Carbohydr. Lett.* **1997**, *2*, 381–388. (b) Gelin, M.; Ferrières, V.; Plusquellec, D. *Eur. J. Org. Chem.* **2000**, 1423–1431. (c) Gandolfi-Donadio, L.; Gola, G.; de

- Lederkremer, R. M.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2006**, *341*, 2487–2497. (d) Lee, Y. J.; Lee, B.-Y.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2006**, *8*, 3971–3974. (e) Baek, J. Y.; Joo, Y. J.; Kim, K. S. *Tetrahedron Lett.* **2008**, *49*, 4734–4737. (f) Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9658–9671. (g) Bai, Y.; Lowary, T. L. *J. Org. Chem.* **2006**, *71*, 9672–9680. (h) Ghosh, S.; Misra, A. K. *Tetrahedron: Asymmetry* **2010**, *21*, 2755–2761. (i) Gola, G.; Tilve, M. J.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2011**, *346*, 1495–1502. (j) Tilve, M. J.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2011**, *346*, 2838–2848. (k) Tilve, M. J.; Gallo-Rodriguez, C. *Carbohydr. Res.* **2014**, 397, 7–17.
- (7) (a) Yasomane, J. P.; Demchenko, A. V. *J. Am. Chem. Soc.* **2012**, *134*, 20097–20102. (b) Yasomane, J. P.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2014**, *53*, 10453–10456. (c) Pistorio, S. G.; Yasomane, J. P.; Demchenko, A. V. *Org. Lett.* **2014**, *16*, 716–719. (d) Yasomane, J. P.; Demchenko, A. V. *Chem. - Eur. J.* **2015**, *21*, 6572–6581. (e) Kayastha, A. K.; Jia, X.-G.; Yasomane, J. P.; Demchenko, A. V. *Org. Lett.* **2015**, *17*, 4448–4451.
 - (8) Liu, Q.-W.; Bin, H.-C.; Yang, J.-S. *Org. Lett.* **2013**, *15*, 3974–3977.
 - (9) Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9152–9155.
 - (10) Huang, J.-S.; Huang, W.; Meng, X.; Wang, X.; Gao, P.-C.; Yang, J.-S. *Angew. Chem., Int. Ed.* **2015**, *54*, 10894–10898.
 - (11) Glinschert, A.; Oscarson, S. *Carbohydr. Res.* **2015**, *414*, 65–71.
 - (12) Xie, L.; Zhu, S.-Y.; Shen, X.-Q.; He, L.-L.; Yang, J.-S. *J. Org. Chem.* **2010**, *75*, 5764–5767.
 - (13) Mariño, K.; Marino, C.; de Lederkremer, R. M. *Anal. Biochem.* **2002**, *301*, 325–328.
 - (14) Baldoni, L.; Marino, C. *J. Org. Chem.* **2009**, *74*, 1994–2003.
 - (15) (a) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 13095–13096. (b) Zhu, S.-Y.; Huang, J.-S.; Zheng, S.-S.; Zhu, K.; Yang, J.-S. *Org. Lett.* **2013**, *15*, 4154–4157. TBAF buffered with HOAc has been tested as the best choice for the removal of the TBS group. The utility of TBAF in THF led to partial hydrolysis of the Quin group.
 - (16) Schmidt, R. R.; Jung, K.-H. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Dekker: New York, 1997; p 283.
 - (17) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095–1121.
 - (18) Garegg, P. J.; Kvarnström, I.; Niklasson, A.; Niklasson, G.; Svensson, S. C. T. *J. Carbohydr. Chem.* **1993**, *12*, 933–953.
 - (19) Iwayama, Y.; Ando, H.; Ishida, H.; Kiso, M. *Chem. - Eur. J.* **2009**, *15*, 4637–4648.
 - (20) Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; van Delft, F. L.; Vourloumis, D.; Xu, J.-Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674–8680.
 - (21) Chen, X.-T.; Bhattacharya, S.-K.; Zhou, B.-S.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563–6579.
 - (22) Kishida, M.; Akita, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2625–2630.
 - (23) For examples of the use of inverse glycosylation protocol in the synthesis of glycosides, see: (a) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 1990, 694–696. (b) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem. - Eur. J.* **2003**, *9*, 320–326. (c) Fürstner, A.; Jeanjean, F.; Razon, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2097–2101.
 - (24) For examples of the 4,6-O-benzylidene acetal directed α -galactopyranosylation, see: (a) Yule, J. E.; Wong, T. C.; Gandhi, S. S.; Qiu, D.-X.; Riopel, M. A.; Koganty, R. R. *Tetrahedron Lett.* **1995**, *36*, 6839–6842. (b) Chen, L.-Q.; Kong, F.-Z. *Tetrahedron Lett.* **2003**, *44*, 3691–3695. (c) Crich, D.; Yao, Q.-J. *J. Am. Chem. Soc.* **2004**, *126*, 8232–8236. (d) Mogemark, M.; Elofsson, M.; Kihlberg, J. *J. Org. Chem.* **2003**, *68*, 7281–7288. (e) Crich, D.; de la Mora, M.; Vinod, A. U. *J. Org. Chem.* **2003**, *68*, 8142–8148. (f) Tanaka, H.; Takeuchi, R.; Jimbo, M.; Kuniya, N.; Takahashi, T. *Chem. - Eur. J.* **2013**, *19*, 3177–3187.