รายงานวิจัยฉบับสมบูรณ์

โครงการ

Diastereoselective Synthesis of Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors for Type 2 Diabetes Drug Candidates by a Novel Glycosyl *N*-Methyl Acetohydroxamate

โดย
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สนับสนุนโดยสำนักงานคณะกรรมการการอุดมศึกษา และสำนักงานกองทุนสนับสนุนการวิจัย

บทคัดย่อ

สารประกอบกลุ่มไทโอไกลโคไซด์เป็นสารประกอบคาร์โบไฮเดรตที่มีความสำคัญเนื่องจากแสดงฤทธิ์ในการยับยั้งโปรตีน sodium/glucose cotransporter 2 (SGLT2) และยังสามารถใช้เป็นสารลดแรงตึงผิวชนิดไม่มีประจุ, สารเลียนแบบน้ำตาลธรรมชาติ และเป็นสารตั้งต้นในการสังเคราะห์ทางคาร์โบไฮเดรตชนิดต่างๆ งานวิจัยก่อนหน้านี้รายงานว่าการสังเคราะห์ไทโอไกลโคไซด์ด้วยสารตั้งต้นชนิดน้ำตาล 1-hydroxy และไทออล ในสภาวะที่ใช้ตัวทำละลายอินทรีย์ มีกรดบรอนสเตดหรือกรดลิวอิสเป็นตัวเร่งปฏิกิริยา จะให้ผลิตภัณฑ์ที่ต้องการในปริมาณน้อยแต่ให้ผลิตภัณฑ์ข้างเคียงชนิดน้ำตาลเปิดวง dithioacetal ในปริมาณมาก ซึ่งสารประกอบน้ำตาลเปิดวง dithioacetal นั้นเกิดจากปฏิกิริยาต่อเนื่องของการแตกออกพันธะ endocyclic ของไทโอไกลโคไซด์ ในงานวิจัยนี้ คณะผู้วิจัยรายงานการพัฒนาปฏิกิริยาไกลโคซิลเลชันแบบกำจัดน้ำออก (dehydrative glycosylation) โดยทำปฏิกิริยาในน้ำและใช้ตัวเร่งปฏิกิริยาแบบ Bronsted acid–surfactant combined catalyst (BASC) ปฏิกิริยาไกลโคซิลเลชันระหว่างสารตั้งต้นชนิดน้ำตาล 1-hydroxy furanose/pyranose และไทออลชนิดปฐมภมิ, ทุติยภูมิ, ตติยภูมิของแอลิฟาติก/แอโรมาติก ให้ไทโอไกลโคไซด์ในปริมาณปานกลางจนถึงสูง เมื่อใช้ตัวเร่งปฏิกิริยาเป็น dodecyl benzenesulfonic acid (DBSA) และกระตุ้นด้วยรังสีไมโครเวฟ การใช้รังสีไมโครเวฟช่วยกระตุ้นปฏิกิริยาทำให้ใช้ระยะเวลาในการทำปฏิกิริยาที่สั้นลงและให้ผลิตภัณฑ์ในปริมาณสูงขึ้น ที่สำคัญการสังเคราะห์ที่ใช้น้ำเป็นตัวทำละลายไม่ก่อให้เกิดผลิตภัณฑ์ข้างเคียงชนิดน้ำตาลเปิดวง dithioacetal ดังเช่นสังเคราะห์ในตัวทำละลายอินทรีย์ที่มีรายงานมาก่อนหน้านี้ จึงกล่าวได้ว่าการสังเคราะห์ที่พัฒนาขึ้นนั้น เป็นการสังเคราะห์ไทโอไกลโคไซด์ที่ไม่ยุ่งยาก, ทำได้รวดเร็ว, ไม่จำเป็นต้องทำในสภาวะปราศจากน้ำ (anhydrous conditions) นอกจากนี้งานวิจัยนี้ยังเป็นตัวอย่างที่แสดงถึงผลผลิตภัณฑ์ที่ได้แตกต่างกันเมื่อทำปฏิกิริยาเคมีโดยใช้ตัวทำละลายเป็นน้ำและตัวทำละลายอินทรีย์

คำสำคัญ ไทโอไกลโคไซด์, ตัวเร่งปฏิกิริยาผสมระหว่างกรดบรอนสเตดและสารลดแรงตึงผิว, น้ำตาลเปิดวงชนิดไดไทโอแอซีแทล, สารยับยั้งโปรตีนชนิดนำส่งร่วมของโซเดียม/กลูโคส แบบที่ 2

Abstract

Thioglycoside is an important class of sugar since it exhibited sodium/glucose cotransporter 2 (SGLT2) inhibition activity and can be used as non-ionic biosurfactants, biomimetic glycosides, and building blocks for carbohydrate synthesis. Previously, Bronsted- or Lewis acid-catalyzed dehydrative glycosylations between 1-hydroxy sugar and thiol were reported to yield open-chain dithioacetal sugar as the major product, instead of the desired thioglycoside. The dithioacetal sugar is a by-product derived through endocyclic bond cleavage of the thioglycoside. Herein, we report dehydrative glycosylation in water mediated by Bronsted acid–surfactant combined catalyst (BASC). Glycosylations between 1-hydroxy furanosyl/pyranosyl sugars and primary, secondary, tertiary aliphatic/aromatic thiols in the presence of dodecyl benzenesulfonic acid (DBSA) provided thioglycoside products in moderate to good yields. Microwave irradiation led to the improvement of the yields and shortening the reaction time. Remarkably, the open-chain dithioacetal sugar was not detected under DBSA-mediated glycosylation in water. This method is a simple, convenient, and rapid approach to produce a library of thioglycoside without the requirement of anhydrous conditions. Moreover, this work represents a showcase of complement reactivity profiles of glycosylation in organic solvents and water.

Keywords Thioglycoside, Bronsted acid–surfactant combined catalyst, Open-chain dithioacetal sugar, Sodium/glucose cotransporter 2 (SGLT2) inhibitor

บทสรุปสำหรับผู้บริหาร

ผู้วิจัยวางแผนในการสังเคราะห์แบบ diastereoselective ของสารสารยับยั้งโปรตีน sodium/glucose cotransporter 2 (SGLT2) ซึ่งเป็นแนวทางในการรักษาโรคเบาหวานชนิดที่ 2 เริ่มจากการใช้สารตั้งต้นชนิด glycosyl *N*-methyl acetohydroxamate ในตัวทำละลายอินทรีย์ แต่ไม่ประสบความสำเร็จเนื่องจากสารตั้งต้นมีความว่องไว ปฏิกิริยาต่ำมาก แม้ว่าจะกระตุ้นด้วยตัวเร่งปฏิกิริยาแบบกรดบรอนสเตดหรือกรดลิวอิส ก็ไม่เกิดผลิตภัณฑ์ตามต้องการ ผู้วิจัยจึงเปลี่ยนแนวทางการสังเคราะห์โดยหันมาใช้สารตั้งต้นชนิดน้ำตาล 1-hydroxy แทน โดยวางแผนการสังเคราะห์สารยับยั้งโปรตีน SGLT2 ชนิดไทโอไกลโคไซด์ ด้วยปฏิกิริยาไกลโคซิลเลชันแบบกำจัดน้ำออก (dehydrative glycosylation) โดยใช้สารลดแรงตึงผิวในน้ำเป็นตัวทำละลาย นับว่าเป็นแนวทางการสังเคราะห์แบบใหม่ที่เป็นมิตรกับสิ่งแวดล้อมเมื่อเทียบกับการสังเคราะห์ในตัวทำละลายอินทรีย์แบบเดิม นอกจากนั้นสารประกอบไทโอไกลโคไซด์ที่สังเคราะห์ขึ้น ยังนำไปประยุกต์ใช้ได้อย่างหลากหลายเช่น เป็นสารตั้งต้นในการสังเคราะห์สารประกอบคาร์โบไฮเดรต, เป็นสารเลียนแบบน้ำตาลธรรมชาติ และเป็นสารลดแรงตึงผิวชนิดไม่มีประจุ โดยงานวิจัยนี้คณะผู้วิจัยเลือกใช้ dodecylbenzenesulfonic acid (DBSA) ซึ่งเป็นสารลดแรงตึงผิวที่มีฤทธิ์เป็นกรด หาซื้อได้ง่ายและราคาถูก DBSA สามารถก่อตัวเป็นไมเซลล์ในตัวทำละลายที่เป็นน้ำ จึงเพิ่มประสิทธิภาพการละลายของสารประกอบอินทรีย์ได้ ผู้วิจัยใช้สารตั้งต้นน้ำตาลฟิวราโนไซด์และไพราโนไซด์ชนิด 1-hydroxy กับไทออลชนิดแอลิฟาติก, แอโรมาติกและเฮทเทอโรไซคลิก พบว่าเมื่อกระตุ้นปฏิกิริยาด้วยรังสีไมโครเวฟ ทำให้ลดระยะเวลาในการสังเคราะห์และได้ปริมาณผลิตภัณฑ์ไทโอไกลโคไซด์เพิ่มขึ้นด้วย นอกจากนั้น ผู้วิจัยได้ศึกษาอุณหภูมิและปริมาณ DBSA ที่เหมาะสมต่อการสังเคราะห์และพบว่า เมื่อใช้ DBSA ปริมาณ 100 mol% ที่อุณหภูมิ 80 องศาเซลเซียส สามารถสังเคราะห์ไทโอฟิวราโนไซด์ได้ทั้งชนิดที่เป็นอะลิฟาติกและอะโรเมติก โดยให้ diastereoselectivity เป็นแบบ β อีกทั้งการสังเคราะห์ที่พัฒนาขึ้นนั้น ไม่พบผลิตภัณฑ์ข้างเคียงชนิดน้ำตาลเปิดวง dithioacetal ซึ่งเกิดจากการเปิดวงน้ำตาลของไทโอไกลโคไซด์ โดยสรุปวิธีการสังเคราะห์ที่พัฒนาขึ้นนี้สามารถทำได้ง่าย สะดวก และไม่จำเป็นต้องใช้สภาวะที่ปราศจากน้ำ (anhydrous conditions) เหมือนวิธีที่รายงานมาก่อนหน้า

Introduction

Glycals and *exo*-glycals are essential classes of building blocks in organic synthesis especially in the field of carbohydrate chemistry.[1] They both contain nucleophilic enol ether functional groups which are amenable for stereoselective installation of glycosidic linkages for targeted carbohydrates.[2] Numerous hydrolytically stable *C*-glycosides which contained unique biological activities have been prepared from glycals and *exo*-glycals.[3] Generally, epoxidation of glycals followed by ring-opening with suitable nucleophiles produces *C*-glycosides.[2c, 4] Alternatively, stereoselective hydrogenation of *exo*-glycal to yield *C*-glycoside is also a reliable method for the preparation of alkyl *C*-glycosides.[5] Ramberg-Bäcklund olefination of glycosyl sulfone derived from the oxidation of thioglycosides represents another versatile approach for the synthesis of alkyl *C*-glycosides (Figure 1).[3a, 6]

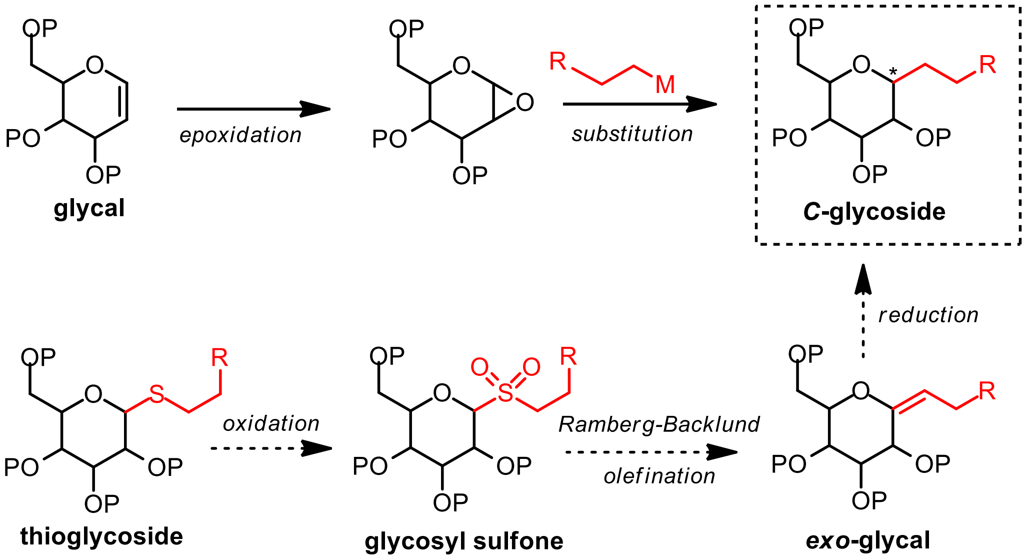


Figure 1. Synthesis of alkyl *C*-glycoside *via* glycal and *exo*-glycal; P = protecting group, R = alkyl group.

On a course of our synthesis of alkyl *C*-glycosides *via* Ramberg-Bäcklund olefination,[7] we first set to generate a library of alkyl thiofuranosides by Fischer glycosylation using a perbenzylated 1-hydroxy sugar as an armed glycosyl donor (Figure 2).[8] The Fischer glycosylation is a hemiacetal-to-acetal transformation that is often a starting point in the preparation of monomers in oligosaccharide syntheses or construction of complex natural products. This method possesses several advantages as follows: 1) 1-hydroxy sugar donor is highly stable, 2) it does not require anhydrous conditions thus it is capable to scale up, and 3) the condensation produces water as the only by-product which abided to the green chemistry concept. Dehydrative glycosylation between the 1-hydroxy sugar **1**

(2,3,5-tri-*O*-benzyl-L-arabinofuranoside) and 1-dodecanethiol in the presence of catalytic HCl was first carried out (Figure 2). Analysis of the crude mixture indicated that 1-dodecyl thiofuranoside **1a** was obtained as a minor product along with the open-chain dithioacetal sugar **1b** as a major product. The dithioacetal sugar **1b** was thought to derive from protonation of the ring-oxygen (O4) of the 1-dodecyl thiofuranoside **1a**, followed by endocyclic C1-O4 bond cleavage to form a thionium intermediate. The second addition of 1-dodecanethiol to this thionium intermediate gave the dithioacetal sugar **1b** as the major product.

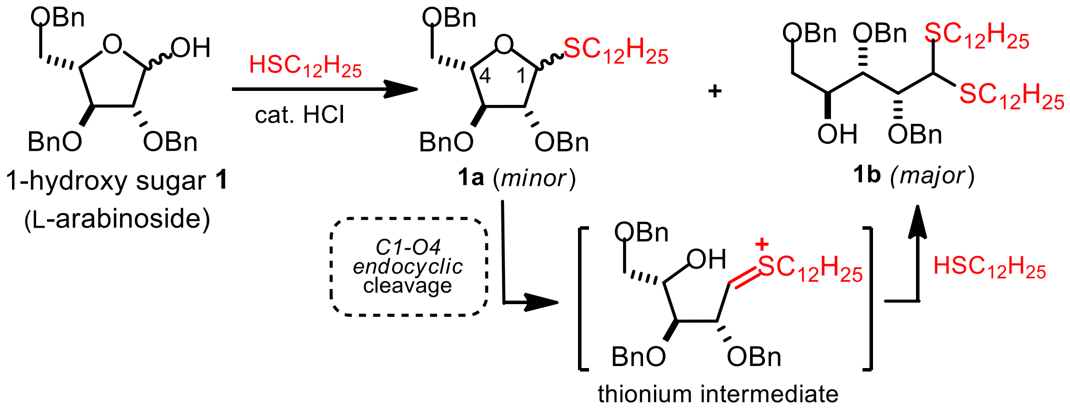


Figure 2. Preliminary results on the Fischer glycosylation of 1-hydroxy sugar **1** yielded dithioacetal sugar **1b** as the major product.

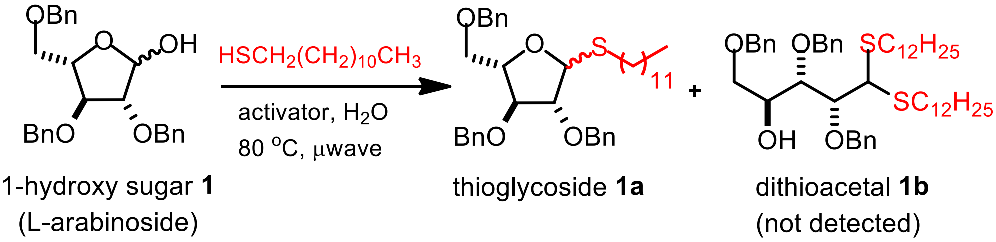
The endocyclic bond cleavage of glycosides was recognized since 1967 by Clayton and co-workers from the observation of anomerization and ring contraction during the hydrolysis of methyl thiopyranosides with dilute acids.[9] Previous reports have well-documented the challenges of dehydrative glycosylation between armed pyranosyl/furanosyl donors and reactive nucleophiles, especially the combination of furanosyl donors and highly nucleophilic thiols.[10] For examples; dithioacetal sugars were obtained during the dehydrative glycosylation of 1-hydroxy sugars under catalysis by Bronsted acids such as trifluoroacetic acid,[11] HCl,[12] and HBr.[13] Products derived from the endocyclic bond cleavage were also observed under Lewis acid-catalysis such as $SnCl_4$,[14] $BF_3.OEt_2$,[4a, 15] $B(OMe)_3$,[15] and Me_2BBr.[16] Additionally, thiol nucleophiles can undergo oxidation to generate disulfide side-product under Lewis acid-catalysis.[17] To circumvent these challenges, other activators were recently developed to activate the 1-hydroxy sugars such as sulfoxonium triflate reagents[18] and cyclic phosphonium anhydrides.[19] Less reactive glycosyl donors such as peracylated 1-hydroxy sugars have been used as a glycosyl donor. However, the peracylated 1-hydroxy sugar must be converted to a more reactive glycosyl halide first, then followed by substitution of an acceptor. Strictly anhydrous conditions were required for these processes to prevent hydrolysis of the glycosyl halide intermediates.[20] Lastly, the armed perbenzylated 1-hydroxy sugar donors could be converted to other glycosyl donors such as glycosyl trichloroacetimidates[21] or glycosyl halides[12c] but at the cost of extra reaction steps. On the other hand, such endocyclic bond cleavage can be synthetically utilized such as in a strategy for the preparation of thiofuranosides by ring contraction of thiopyranosides[22] or 1,2-*cis* aminoglycosidic bond formation through endocyclic cleavage-mediated anomerization by Manabe and Ito group.[10c, 23,24] Moreover, the formation of dithioacetal sugar derived through endocyclic bond cleavage has been used as a conventional method to protect the aldehyde/ketone functional group of aldose/ketose sugars.[25] Nevertheless, a direct synthesis of perbenzylated thioglycosides from 1-hydroxy sugars is still highly desirable, and there is no current methodology that allows such transformation without the substantial formation of the dithioacetal sugar side products.

Water has become one of the most promising “green solvents” for modern organic synthesis since it is environmentally friendly, cheap, and often provides unique reactivity profiles that complement similar reactions performed in organic solvents.[26] The growing interest in using water as reaction media motivates us to explore chemical glycosylation in water. Glycosylation reactions in water alone or mixture of organic solvent/water[27] have been demonstrated recently for both unprotected and protected sugar substrates.[28] For the rather hydrophobic protected sugars, their solubility in water can be enhanced by the aid of surfactants.[26] Several surfactant systems such as the Lewis acid–surfactant combined catalysts (LASC) or the Bronsted acid–surfactant combined catalysts (BASC) introduced by Kobayashi and co-workers,[29] and the designer surfactants by Lipshutz and co-workers have been proven as powerful tools for performing chemical synthesis in water without additional co-solvents.[26b] We envisage that the hydrophobicity of both protected 1-hydroxy sugars and aliphatic thiols would make them suitable candidates for performing glycosylation in water that can be assisted by the presence of a surfactant. Herein, we report the study of dehydrative glycosylation in water between 1-hydroxy sugars and thiols in the presence of LASC, BASC, and designer surfactants.

Results and Discussion

Lewis acid–surfactant combined catalyst (LASC) was first considered as a surfactant for this study.[29] Several water-tolerant Lewis acids have been successfully employed as catalysts for nucleophilic addition to carbonyl compounds in water such as $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, $Pr(OTf)_3$, and $Cu(OTf)_2$.[30] The combination of water-tolerant Lewis acids and anionic surfactants yielded LASC that gains both catalytic activity and solubility in water.[31] The dehydrative glycosylation between the 1-hydroxy sugar **1** and 1-dodecanethiol in the presence of LASC was investigated and the results were shown in Table 1.

Table 1. Dehydrative glycosylation in water mediated by Lewis acid–surfactant combined catalyst (LASC)



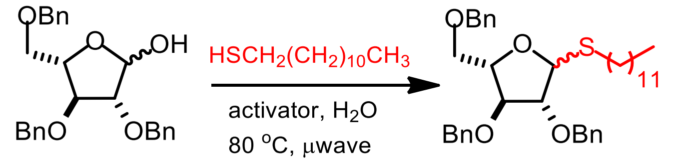
Entry[a]	Activator	Conversion[b]	1a (yield)[b,c]	1a (α/β)[d]
1	$Sc(DBS)_3$[e]	<5%	trace	ND
2	$Yb(DBS)_3$[e]	<5%	trace	ND
3	$Sc(OTf)_3$/DBSA[f]	ND	59%	50:50
4	$Yb(OTf)_3$/DBSA[f]	ND	63%	44:56
5	$La(OTf)_3$/DBSA[f]	68%	67% (99%)	39:61
6	$Gd(OTf)_3$/DBSA[f]	73%	64% (88%)	41:59
7	$Nd(OTf)_3$/DBSA[f]	77%	64% (83%)	40:60
8	$Pr(OTf)_3$/DBSA[f]	66%	56% (85%)	42:58
9	$Cu(OTf)_2$/DBSA[f]	ND	15%	40:60

[a] Standard conditions: 1-dodecanethiol (1.2 equiv), H_2O, 80 °C by microwave irradiation (µwave), 5 h; [donor] = 0.50 M. [b] Conversions and yields were determined from isolated product and recovered 1-hydroxy sugar after column chromatography. [c] Yield in parenthesis is based on recovered starting materials. [d] Selectivities (α/β) were obtained as determined by ^1H NMR integration. [e] LASC catalyst (10 mol%). [f] Lewis acid (10 mol%)/DBSA (100 mol%). DBS = dodecylbenzenesulfonate, DBSA = dodecylbenznesulfonic acid, ND = not determined.

The dehydrative glycosylation reactions were carried out in water at 80 °C under microwave irradiation with catalytic $Sc(DBS)_3$ (scandium tris(dodecylbenzenesulfonate)) and $Yb(DBS)_3$ (ytterbium tris(dodecylbenzenesulfonate)) (entries 1–2).[32] Both LASCs gave only trace amount of the desired thioglycoside **1a** accompanied with the unreacted 1-hydroxy sugar **1**. Increasing the catalyst loading, reaction time, and temperature showed no improvement of the product yields. Cooperative catalyst system between LASC and Bronsted acid have previously been shown to enhance the rate of several chemical reactions in water.[33] We reasoned that the addition of a Bronsted acid may accelerate the reaction by promoting the leaving ability of the OH group. The glycosylation reactions were then performed with a combination of water-tolerant Lewis acids and DBSA (entries 3–8).[34] Significant improvements of the yield were indeed observed for all reactions to a range of 56–67% yields with the formation of both α- and β-anomers in comparable amounts. When the combination of $Cu(OTf)_2$/DBSA was used, the product **1a** was obtained in only 15% yield (entry 9). Importantly, in all cases the crude reaction mixtures contained only the unreacted 1-hydroxy sugar **1** and the thioglycoside product **1a** without a trace of the dithioacetal sugar **1b** commonly observed as the major by-product.

The results from Table 1 suggested that Bronsted acid plays a crucial role for the dehydrative glycosylation of 1-hydroxy sugars.[35] Next, the Bronsted acid–surfactant combined catalyst (BASC) was investigated for the same glycosylation (Table 2). Perfluoro-octanesulfonic acid (PFOS), perfluoro-octanoic acid (PFOA), and dodecyl benzenesulfonic acid (DBSA) were applied to the reaction under microwave irradiation at 80 °C (entries 1–3). The PFOS-mediated glycosylation gave a distinct two-layer heterogeneous mixture and afforded only 48% conversion with low yield (entry 1). On the other hand, the PFOA and DBSA surfactants provided well-dispersed white turbid emulsions during the course of the reaction. Gratifyingly, both high conversions and yields of the thioglycoside **1a** were obtained from the PFOA- and DBSA-mediated glycosylation (entries 2 and 3). Regarding to the anomeric selectivity, DBSA (α/β = 7:93) provided higher β selectivity compared to PFOA (α/β = 29:71). Thus, the DBSA was preferable over PFOA as the activator for this study since it provided higher selectivity and the health and environmental concern from the persistency of PFOA in the environment.[36]

Table 2. Dehydrative glycosylation in water mediated by Bronsted acid–surfactant combined catalyst (BASC) and Bronsted acid alone



1-hydroxy sugar **1** thioglycoside **1a**

Entry[a]	**Activator**	**Temp**	**Conversion**[b]	**1a (yield)**[b,c]	**1a (α/β)**[d]
1	PFOS	80 °C	48%	18% (37%)	30:70
2	PFOA	80 °C	78%	71% (91%)	29:71
3	**DBSA**	**80 °C**	**73%**	**72% (99%)**	**7:93**
4	DBSA	40 °C	44%	44% (99%)	8:92
5	DBSA	60 °C	58%	57% (99%)	8:92
6	DBSA	100 °C	80%	64% (80%)	6:94
7	TPGS-750-M/*p*-TsOH	80 °C	ND	56%	10:90
8	*p*-TsOH	80 °C	ND	17%	20:80
9	*p*-$HOC_6H_4SO_3H$	80 °C	ND	27%	12:88

[a] Standard conditions: 1-dodecanethiol (1.2 equiv), BASC or Bronsted acid (100 mol%), H_2O, heated by microwave irradiation (µwave), 5 h; [donor] = 0.50 M. [b] Conversions and yields were determined from isolated product and recovered 1-hydroxy sugar by column chromatography. [c] Yield in parenthesis is based on recovered starting materials. [d] Selectivities (α/β) were obtained as determined by ^1H NMR integration. PFOS = perfluoro-octanesulfonic acid, PFOA = perfluoro-octanoic acid, TPGS-750-M = DL-α-tocopherol methoxypolyethylene glycol succinate, ND = not determined.

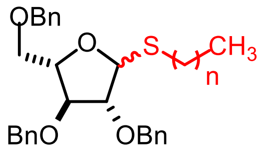
The DBSA-mediated glycosylations were examined at different temperatures to probe the effect on the yield and selectivity of the product. Lowering the temperature to 40 °C and 60 °C gave inferior yields and conversion (entries 4 and 5). Increasing the temperature to 100 °C caused some decomposition as evidenced by the formation of a brown tar-like syrup, which resulted in a lower yield (entry 6). Efforts to reduce the amount of DBSA from 1 equivalent to catalytic amount resulted in lower yield and a less dispersion of both substrates (1-hydroxy sugar **1** and 1-dodecanethiol) was noticed. Next, the use of Lipshutz's designer surfactant, TPGS-750-M, was evaluated.[37] A combination of TPGS-750-M and *p*-toluenesulfonic acid (*p*-TsOH) also provided the same product **1a** with good β selectivity, albeit in somewhat lower yield when compared with DBSA (entry 7). Finally, performing the reactions with Bronsted acid alone (*p*-TsOH and *p*-hydroxybenzenesulfonic acid) gave the product **1a** in only low yield (entries 8 and 9) which emphasized the necessity of surfactant in the reactions. It is noteworthy that for the DBSA-mediated thioglycosylation, the ratios of the α and β thioglycosides **1a** remain almost the same over the whole temperature range examined (40, 60, 80, and 100 °C; entries 3–6). Moreover, the glycosylations at 80 °C with different Bronsted acids (entries 1–3, 7–9) gave different α/β selectivities, ranging from 6:94 to 30:70, thus the product formations were not in equilibrium otherwise the same selectivity would have been observed. This implies that the selectivity of the formation of α and β thioglycosides **1a** should be under kinetic control. The results from Table 2 revealed that DBSA is a suitable Bronsted acid–surfactant combined catalyst in performing the dehydrative glycosylation in water.

The scope of nucleophile: aliphatic, aromatic, and heterocyclic thiols were next investigated for the DBSA-mediated glycosylation of the1-hydroxy sugar **1** in water (Table 3). Primary alkyl thioglycosides **1a**, **2**–**6** with different chain length (C12, C8, C10, C14, C15, and C18) were obtained under the standard conditions in moderate to good yields (58–72%), with decent α/β selectivities (7:93 to 19:81). Delightfully, the formation of the dithioacetal sugar by-product was not observed in all reactions.

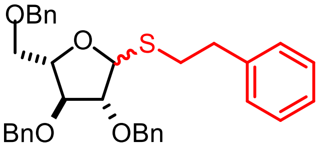
Table 3. The scope of thiol nucleophiles in the DBSA-mediated dehydrative glycosylation of 1-hydroxy sugar **1** in water[a,b]

1-hydroxy sugar **1**
(L-arabinoside, α/β =53:47)

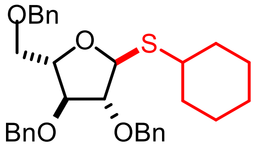
thiogycoside **1a**, **2-14**
Yield (α/β)



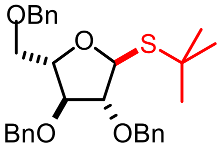
1a; n=11, 72% (7:93)
2; n= 7, 71% (14:86)
3; n= 9, 67% (14:86)
4; n=13, 65% (19:81)
5; n=14, 58% (8:92)
6; n=17, 63% (9:91)



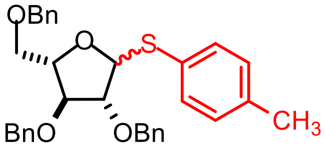
7; 42% (38:62)



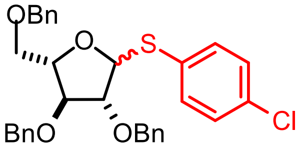
8; 45% (100:0)



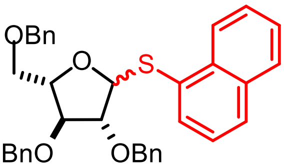
9; 24% (100:0)



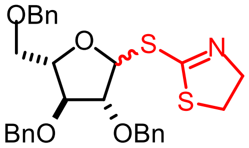
10; 41% (16:84)



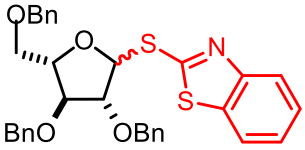
11; 43% (14:86)



12; 47% (86:14)



13; no product formation



14; no product formation

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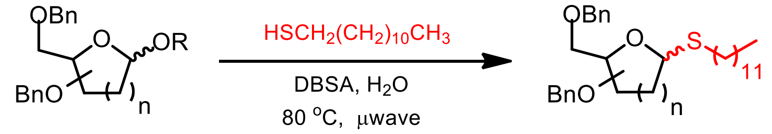
[a] Standard conditions: thiol (1.2 equiv), DBSA (100 mol%), H_2O, heated by microwave irradiation (µwave), 5 h; [donor] = 0.50 M. [b] Isolated yield by column chromatography and selectivities (α/β) were obtained as determined by ^{1}H NMR integration.

The glycosylation of 1-hydroxy sugar **1** with 2-phenyl ethanethiol yielded the expected thioglycoside **7** in moderate yield (42%) and selectivity (α/β = 38:62). Thioglycosides **8** and **9** deriving from secondary aliphatic thiol (cyclohexanethiol) and tertiary aliphatic thiol (*tert*-butylthiol) were obtained in moderate to low yields of 45% and 24%, respectively with only α anomers were detected. Steric hindrance and water solubility of *tert*-butylthiol could be the reasons for the lower yield of the thioglycoside **9**. In addition, aromatic thiols bearing both electron-donating and withdrawing groups were tested. Gratifyingly, thioglycosides **10**, **11**, and **12** were all obtained in moderate yields. In general, β selectivities were observed in the glycosylation of 1-hydroxy L-arabinofuranoside **1** and thiols. However, bulky thiol nucleophiles seem to favor the formation of α-products (**8**, **9**, and **12**), which can be rationalized by the preferred attack of these bulky nucleophiles to the less hindrance face of the oxocarbenium ion deriving from the 1-hydroxy sugar donor. When heterocyclic thiols including 2-mercaptothiazoline and 2-mercaptobenzothiazole were examined as potential nucleophiles, thioglycosides **13** and **14** were not formed and the 1-hydroxy sugar **1** was fully recovered.[38] Crystal structures of 2-mercaptothiazoline and 2-mercaptobenzothiazole revealed that both heterocyclic thiols prefer to exist as the thiocarbonyl tautomer instead of the thiol form, thus reducing its nucleophilicity.[39] It is important to note that this newly developed protocol required only slightly excess (1.2 equivalents) of the thiol to obtain decent to good yields of the thioglycosides. Conversely, traditional Fischer glycosylation often requires a large excess of the acceptor, often as a solvent, to drive the equilibrium forward. [40] The use of the malodorous thiol acceptor in large excess amounts or as a solvent hampers the full synthetic potential of Fischer glycosylation.

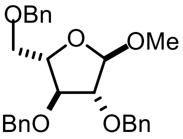
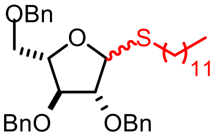
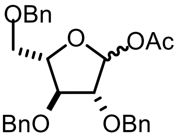
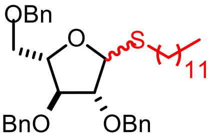
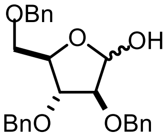
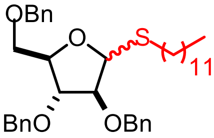
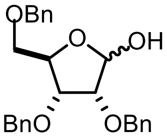
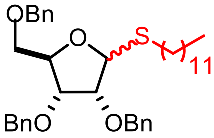
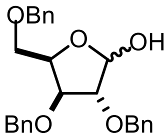
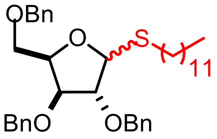
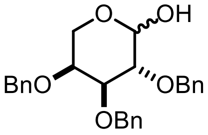
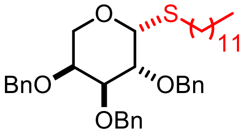
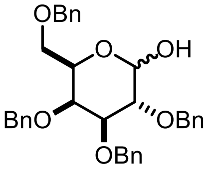
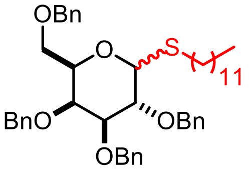
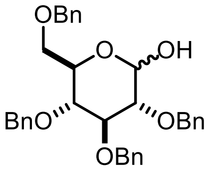
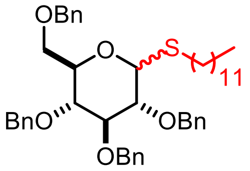
Lastly, to test the compatibility with various glycosyl donors, the glycosylation reactions between 1-dodecanethiol and different glycosyl donors were examined (Table 4). A comparison among L-arabinofuranosyl donors with different leaving groups at the anomeric position, methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside (**15**) and acetyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**) was also made to probe the effect of leaving group (entries 1 and 2). The thioglycoside **1a** was obtained in low yield (10%) for the glycosyl donor **15** and moderate yield (60%) for the glycosyl donor **16**. Thus, 1-hydroxy and 1-acetoxy sugars are more suitable glycosyl donors than 1-methoxy sugars for the presently developed DBSA-mediated dehydrative glycosylation in water.

Table 4. The scope of furanosyl/pyranosyl donors in the DBSA-mediated dehydrative glycosylation with 1-dodecanethiol in water[a, b]



glycosyl donor **15-22**

thioglycoside **1a**, **17a-22a**

Entry	Glycosyl Donor (α/β)	Product/Yield (α/β)
1	 **15** (100:0) L-arabinofuranoside	 **1a**; 10% (9:91)
2	 **16** (59:41) L-arabinofuranoside	 **1a**; 60% (10:90)
3	 **17** (22:78) D-arabinofuranoside	 **17a**; 66% (16:84)
4	 **18** (50:50) D-ribofuranoside	 **18a**; 73% (17:83)
5	 **19** (50:50) D-xylofuranoside	 **19a**; 75% (69:31)
6	 **20** (37:63) L-arabinopyranoside	 **20a**; 60% (0:100)
7	 **21** (66:34) D-galactopyranoside	 **21a**; 32% (65:35)
8	 **22** (50:50) D-glucopyranoside	 **22a**; 45% (64:36)

[a] Standard conditions: thiol (1.2 equiv), DBSA (100 mol%), H_2O, heated by microwave irradiation (µwave), 5 h; [donor] = 0.50 M. [b] Isolated yield by column chromatography and selectivities (α/β) were determined by ^1H NMR integration.

The glycosylation of 1-dodecanethiol by other perbenzylated 1-hydroxy furanosyl donors, namely D-arabinofuranoside (**17**), D-ribofuranoside (**18**), and D-xylofuranoside (**19**) provided the thioglycosides **17a**, **18a**, and **19a** in 66% (α/β = 16:84), 73% (α/β = 17:83), and 75% (α/β = 69:31) yield, respectively (entries 3–5). Finally, 1-hydroxy pyranosyl sugars such as L-arabinopyranoside (**20**), D-galactopyranoside (**21**), and D-glucopyranoside (**22**) were also acceptable donors to yield the corresponding thioglycosides **20a**, **21a**, and **22a** in 60% (α/β = 0:100), 32% (α/β= 65:35), and 45% (α/β= 64:36) yield, respectively (entries 6–8).

Under the Bronsted acid–surfactant combined catalytic system in this study, we hypothesized that the emulsion droplet is generated by DBSA during the course of the reaction as shown in Figure 3.

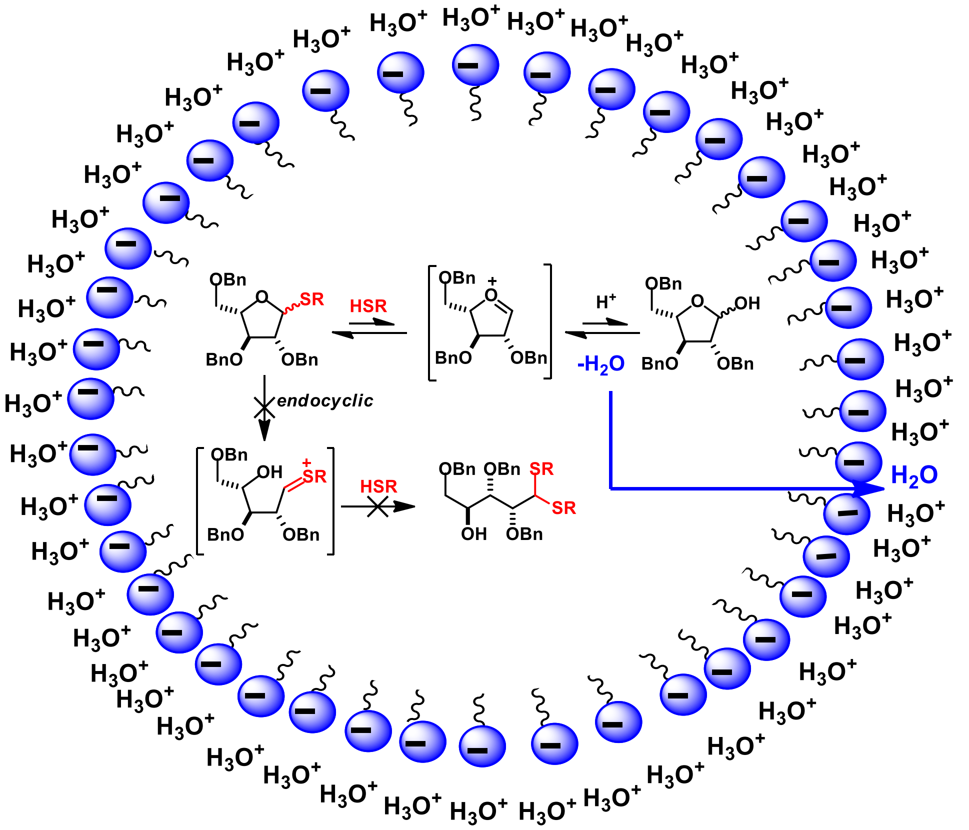


Figure 3. The proposed mechanism of dehydrative glycosylation in water mediated by DBSA

The perbenzylated 1-hydroxy sugar is encapsulated within the droplet and undergoes protonation at the surface of the emulsion droplets. The anionic surface of the DBSA accumulates a high concentration of hydronium ion thus increases the rate of dehydration.[41] At the same time, the hydrophobic thiol was also encapsulated, making the local concentrations of both reactants very high. Next, dehydration followed by the addition of the thiol provides the desired thioglycoside.[42] Inside the droplet, the equilibrium of the dehydration should favor the oxocarbenium side when compared to the reaction outside the droplet that contain a large excess of water. The initially formed thioglycoside product, whose hydrophobicity is increased significantly compared to the 1-hydroxy sugar precursor, is permanently shielded inside the hydrophobic pocket thus having little chance to be protonated by the acid outside the droplet. As a result, the endocyclic bond cleavage is diminished and consequently, the dithioacetal sugar is not generated as usually observed when the glycosylation was performed under conventional organic solvent conditions.[43]

Conclusion

A large selection of thioglycosides was successfully synthesized by a dehydrative glycosylation between 1-hydroxy sugars and thiols in water. The reactions were performed in the presence of DBSA as a Bronsted acid–surfactant combined catalyst (BASC). The glycosylation reactions between 1-hydroxy furanosyl and pyranosyl sugars (both D- and L-sugars) and only slight excess of primary, secondary, tertiary aliphatic and aromatic thiols provided the expected thioglycoside products as a mixture of α and β anomers in moderate to good yields and selectivity. The moderate anomer selectivity is generally not a concern for many applications of the thioglycosides such as bio-surfactant or further transformation *via* the Ramberg-Bäcklund reaction. The use of readily available perbenzylated 1-hydroxy sugars as the glycosyl donor and the ability to perform the reaction in water are the major advantages of the present methodology. In addition, the present DBSA-mediated glycosylation of 1-hydroxy sugars did not yield the open-chain dithioacetal sugars by-product as often observed when similar glycosylation was performed in organic solvents. By taking advantage of the hydrophobic environment inside the emulsion droplet, this work represents a unique chemoselectivity preference for the formation of thioglycoside over dithioacetal sugar. Moreover, this method also offers a convenient and rapid approach to generate a library of thioglycosides, which are not only valuable as synthetic intermediates and thioglycosyl donors for oligomerization,[44] but also present their own importance as bioactive thioglycosides,[45] non-ionic biosurfactants for solubilization and reconstitution of membrane protein,[46] and biomimetic glycosides.[47] The thioglycosides are currently being used as precursors for the synthesis of alkyl *C*-glycosides in our laboratory.

Experimental Section

All chemicals and solvents were purchased from Acros, Merck, Sigma-Aldrich, TCI, or RCI Lab Scan. Solvents were dried with 3 Å molecular sieves for anhydrous reactions. Reaction monitoring by TLC were performed on silica gel 60 F254 0.2 mm pre-coated aluminium plates and purchased from Merck. Preparative thin layer chromatography was 0.5 mm thickness coated by silica gel 60 GF254 from Merck. Chemical spots on TLC were observed by visualization under 254 nm UV light or stained with *p*-anisaldehyde staining solution. Silica gel 60 (70–230 mesh) from Merck was used in purification by column chromatography. Solvents for NMR experiments were purchased from Cambridge Isotope Laboratories or Euriso-top. Milli-Q water was obtained from ultrapure water system with Millipak® 40 filter unit 0.22 μm, Millipore (USA). Reactions were irradiated over CEM Discover Labmate microwave reactor at 218 psi. Functional group determinations were confirmed by infrared (IR) spectroscopy on Nicolet 6700 instrument. Chemical structure characterization was conducted by nuclear magnetic resonance (NMR) spectrometer on Bruker Avance 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C NMR. Exact masses of all products were determined by high resolution mass spectroscopy (HRMS) operating on a SpiralTOF™ MALDI TOF Mass Spectrometer Revolutionary (Scientific and Technological Research Equipment Centre (STREC), Chulalongkorn University).

General procedure for DBSA-mediate glycosylation of 1-hydroxy sugar in water

In a typical procedure, 1-hydroxy sugar (0.24 mmol) and thiol (0.29 mmol, 1.2 equivalents) were added in a microwave vessel followed by a stock solution of DBSA (0.24 mmol, 0.5 mL, 1 equivalent). The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography. After 5 h, the reaction was quenched by adding saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate: hexanes.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (1a)

The glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **1a** was obtained as a yellow syrup (105 mg, 72%, α/β = 7:93). β-Anomer: $[\alpha]_D^{25}$ −50.0° (c 0.25, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34–7.23 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.66–4.44 (m, 6H), 4.17–4.11 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.69–2.60 (m, 2H), 1.62–1.57 (m, 2H), 1.51–1.21 (m, 18H), 0.88 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 32.0, 30.9, 30.0, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.2, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3484.

Octyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (2)

The glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-octanethiol (50 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **2** was obtained as a yellow syrup (94 mg, 71%, α/β = 14:86). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.22 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.63–4.46 (m, 6H), 4.17–4.12 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.7, 6.4 Hz, 2H), 2.65 (dt, *J* = 8.4, 4.1 Hz, 2H), 1.64–1.58 (m, 2H), 1.38–1.20 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.3, 137.9, 137.6, 128.5, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 31.9, 30.9, 30.0, 29.6, 29.6, 29.4, 29.3, 29.1, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{34}H_{44}O_4SNa$ [M+Na$^+$] 571.2858, found 571.2859.

Decyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (3)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-decanethiol (61 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **3** was obtained as a yellow syrup (91 mg, 67%, α/β = 14:86). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.23 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.64–4.44 (m, 6H), 4.17–4.14 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.71 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.68–3.57 (m, 1H), 2.65 (dt, *J* = 8.4, 4.1 Hz, 2H), 1.64–1.58 (m, 2H), 1.40–1.18 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 31.8, 30.9, 30.0, 29.7, 29.3, 29.2, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{36}H_{48}O_4SNa$ [M+Na$^+$] 599.3171, found 599.3161.

Tetradecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (4)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-tetradecanethiol (79 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.41). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **4** was obtained as a yellow syrup (99 mg, 65%, α/β = 19:81). β-Anomer: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.22 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.64–4.42 (m, 6H), 4.18–4.10 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.6 Hz, 1H), 2.65 (td, *J* = 7.4, 1.9 Hz, 2H), 1.64–1.58 (m, 2H), 1.38–1.19 (m, 22H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ_C 138.3, 137.9, 137.6, 128.4, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 32.00, 30.9, 30.0, 29.8, 29.7, 29.7, 29.7, 29.6, 29.4, 29.3, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{40}H_{56}O_4SNa$ [M+Na$^+$] 655.3797, found 655.3788.

Pentadecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (5)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-pentadecanethiol (83 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.42). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **5** was obtained as a yellow syrup (90 mg, 58%, α/β = 8:92). β-Anomer: ^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.19 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.65–4.45 (m, 6H), 4.18–4.10 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.65 (td, *J* = 7.3, 1.9 Hz, 2H), 1.64–1.60 (m, 2H), 1.38–1.19 (m, 24H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 31.9, 30.9, 30.0, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{41}H_{58}O_4SNa$ [M+Na$^+$] 669.3953, found 669.3957.

Octadecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (6)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-octadecanethiol (83 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.48). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **6** was obtained as a yellow syrup (104 mg, 63%, α/β = 9:91). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.23 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.63–4.46 (m, 6H), 4.18–4.11 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.65 (td, *J* = 7.4, 2.0 Hz, 2H), 1.64–1.58 (m, 2H), 1.38–1.22 (m, 30H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 136.1, 135.8, 135.5, 126.3, 126.3, 126.2, 125.8, 125.7, 125.6, 125.5, 125.4, 85.0, 82.2, 81.7, 79.9, 71.2, 70.2, 69.8, 69.3, 29.8, 28.8, 27.8, 27.6, 27.6, 27.5, 27.4, 27.3, 27.2, 27.1, 26.9, 20.6, 12.0. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{44}H_{64}O_4SNa$ [M+Na$^+$] 711.4423, found 711.4414.

2-Phenylethyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (7)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 2-phenylethanethiol (34 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **7** was obtained as a yellow syrup (54 mg, 42%, α/β = 38:62). Mixture of α and β-anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45–7.06 (m, 20H), 5.37 (d, *J* = 5.0 Hz, 0.6 H, β-anomeric proton), 5.33 (d, *J* = 2.4 Hz, 0.4H, α-anomeric proton), 4.64–4.39 (m, 6H), 4.29 (q, J = 4.9 Hz, 0.4H), 4.19–4.11 (m, 1.2H), 4.04 (t, *J* = 4.0 Hz, 0.6H), 3.97 (t, *J* = 4.9 Hz, 0.8H), 3.74–3.58 (m, 2H), 2.96–2.89 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 138.0, 137.8, 137.7, 137.4, 128.6, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 126.3, 126.3, 88.8, 87.7, 87.2, 84.3, 83.7, 82.1, 80.0, 73.4, 73.4, 72.4, 72.2, 72.0, 71.9, 71.4, 69.2, 36.6, 36.4, 32.6, 32.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{34}H_{36}O_4SNa$ [M+Na$^+$] 563.2232, found 563.2285.

Cyclohexyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (8)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), cyclohexanethiol (35 μL, 0.29

mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **8** was obtained as a yellow syrup (56 mg, 45%, α/β = 100:0). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42–7.13 (m, 15H), 5.45 (d, *J* = 2.4 Hz, 1H, α-anomeric proton), 4.73–4.37 (m, 6H), 4.31–4.29 (m, 1H), 3.97 (dd, *J* = 7.8, 2.6 Hz, 2H), 3.75–3.46 (m, 2H), 2.90 (ddd, *J* = 10.4, 6.7, 3.7 Hz, 1H), 2.13–1.84 (m, 2H), 1.82–1.49 (m, 2H), 1.48–1.10 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 89.2, 86.5, 83.6, 80.7, 73.3, 72.2, 72.0, 69.2, 45.3, 37.4, 30.8, 25.8. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{32}H_{38}O_4SNa$ [M+Na$^+$] 541.2388, found 541.2384.

tert-Butyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (9)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), *tert*-butylthiol (34 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **9** was obtained as a yellow syrup (28 mg, 24%, α/β = 100:0). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42–7.15 (m, 15H), 5.53 (d, *J* = 2.9 Hz, 1H, α-anomeric proton), 4.65–4.38 (m, 6H), 4.31–4.27 (m, 1H), 4.00–3.95 (m, 2H), 3.66–3.60 (m, 2H), 1.40 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.8, 137.7, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 89.5, 86.0, 83.5, 79.8, 73.3, 72.2, 72.1, 69.3, 31.5. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{30}H_{36}O_4SNa$ [M+Na$^+$] 515.2232, found 515.2239.

4-Methylphenyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (10)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 4-methylbenzenethiol (36 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.36). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **10** was obtained as a yellow syrup (52 mg, 41%, α/β= 16:84). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50–7.15 (m, 17H), 7.09 (d, *J* = 7.8 Hz, 2H), 5.60 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.69–4.48 (m, 6H), 4.25 (t, *J* = 4.2 Hz, 1H), 4.21–4.16 (m, 1H), 4.09 (t, *J* = 3.7 Hz, 1H), 3.77 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.69 (dd, *J* = 10.1, 7.0 Hz, 1H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.8, 137.4, 137.0, 131.6, 129.7, 128.4, 128.4, 128.3, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 90.4, 84.3, 83.5, 82.4, 73.4, 72.5, 71.9, 71.1, 21.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{33}H_{34}O_4SNa$ [M+Na$^+$] 549.2075, found 549.2092.

4-Chlorophenyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (11)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 4-chlorobenzenethiol (34 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **11** was obtained as a yellow syrup (57 mg, 43%, α/β = 14:86). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50–7.13 (m, 19H), 5.62 (d, *J* = 4.8 Hz, 1H, anomeric proton), 4.67–4.42 (m, 6H), 4.30–4.24 (m, 1H), 4.23–4.13 (m, 1H), 4.09 (t, *J* = 3.7 Hz, 1H), 3.74 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.66 (dd, *J* = 10.0, 6.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 137.7, 137.2, 132.3, 129.0, 128.5, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 89.8, 84.3, 83.2, 82.6, 73.4, 72.6, 71.9, 70.9. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{32}H_{31}ClO_4SNa$ [M+Na$^+$] 569.1529, found 569.1531.

1-Naphthyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (12)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-naphthalenethiol (40 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.30). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **12** was obtained as a yellow solid (64 mg, 47%, α/β = 86:14). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.52–8.40 (m, 1H), 7.89–7.73 (m, 3H), 7.59–7.37 (m, 3H), 7.33–7.24 (m, 15H), 5.60 (d, *J* = 2.5 Hz, 1H), 4.69–4.39 (m, 6H), 4.24 (t, *J* = 3.0 Hz, 1H), 4.04 (dd, *J* = 6.8, 3.3 Hz, 1H), 3.67–3.60 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 137.8, 137.4, 131.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 126.6, 126.2, 125.7, 125.5, 90.6, 88.8, 83.8, 80.9, 73.3, 72.3, 72.2, 69.2. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{36}H_{34}O_4SNa$ [M+Na$^+$] 585.2075, found 585.2066.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-D-arabinofuranoside (17a)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-D-arabinofuranoside **17** (α/β = 22:78, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29

mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **17a** was obtained as a yellow syrup (96 mg, 66%, α/β = 16:84). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.21 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.68–4.35 (m, 6H), 4.18–4.11 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.68 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.67–2.61 (m, 2H), 1.64–1.55 (m, 2H), 1.43–1.18 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 87.2, 84.4, 83.9, 82.9, 73.4, 72.4, 71.9, 71.4, 31.9, 31.3, 30.9, 30.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3466.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-D-ribofuranoside (18a)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-D-ribofuranoside **18** (α/β = 53:47, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **18a** was obtained as a yellow syrup (105 mg, 73%, α/β = 17:83). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34–7.24 (m, 15H), 5.21 (d, *J* = 4.0 Hz, 1H, anomeric proton), 4.66–4.49 (m, 6H), 4.27–4.25 (m, 1H), 4.01 (t, *J* = 5.4 Hz, 1H), 3.86 (t, *J* = 4.5, 1H), 3.60–3.56 (m, 2H), 2.67–2.58 (m, 2H), 1.64–1.55 (m, 2H), 1.30–1.25 (m, 18H), 0.89 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.3, 137.8, 137.7, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 86.3, 81.7, 81.0, 78.3, 73.5, 73.4, 72.3, 70.9, 31.9, 31.2, 31.0, 30.1, 29.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3463.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-D-xylofuranoside (19a)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-D-xylofuranoside **19** (α/β = 50:50, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **19a** was obtained as a yellow syrup (105 mg, 73%, α/β = 69:31). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.37–7.25 (m, 15H), 5.54 (d, *J* = 5.1 Hz, 1H, anomeric proton), 4.65–4.42 (m, 6H), 4.14 (dd, *J* = 5.2, 2.8 Hz, 1H), 4.08 (dd, *J* = 5.1, 2.8 Hz, 1H), 3.99 (t, *J* = 3.9, 1H), 3.77–3.63 (m, 2H), 2.68–2.62 (m, 2H), 1.66–1.57 (m, 2H), 1.30–1.25 (m, 18H), 0.88 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 138.3, 138.0, 137.6, 128.5, 128.4, 128.4, 128.3, 127.9, 127.9, 127.9, 127.8, 127.6, 127.6, 87.3, 84.1, 82.2, 80.9, 73.4, 72.8, 72.2, 68.1, 31.9, 31.7, 30.8, 30.0, 29.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3463.

Dodecyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-arabinopyranoside (20a)

Glycosylation was carried out as described in the general procedure by using 2,3,5-tri-*O*-benzyl-L-arabinopyranoside **20** (α/β = 37:63, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiopyranoside **20a** was obtained as a yellow syrup (86 mg, 60%, α/β = 0:100). β-Anomer: **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.28–7.16 (m, 15H), 5.13 (d, *J* = 3.8 Hz, 1H, anomeric proton), 4.67–4.41 (m, 6H), 3.93 (dd, *J* = 7.7, 3.9 Hz, 1H), 3.87 (dd, *J* = 11.7, 2.7 Hz, 1H), 3.73 (dt, *J* = 5.6, 2.8 Hz, 1H), 3.69–3.51 (m, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 1.69–1.59 (m, 2H), 1.31–1.13 (s, 18H), 0.80 (q, *J* = 7.4, 6.8 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 137.6, 137.4, 137.3, 127.4, 127.3, 127.0, 126.8, 126.7, 126.7, 126.6, 126.6, 82.7, 76.2, 75.1, 72.5, 72.0, 72.0, 70.7, 61.3, 38.3, 30.9, 29.5, 28.8, 28.7, 28.6, 28.6, 28.6, 28.5, 28.5, 28.3, 28.2, 28.2, 27.9, 27.5, 21.7, 13.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3485.

Dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-galactopyranoside (21a)

Glycosylation was carried out as described in the general procedure by using 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside **21** (α/β = 66:34, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.32). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiopyranoside **21a** was obtained as a yellow syrup (56 mg, 32%, α/β = 65:35). Mixture of α and β-anomer: **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.49–7.06 (m, 20H), 5.46 (d, *J* = 5.5 Hz, 0.5H, α-anomeric proton), 4.96–4.38 (m, 8H), 4.42 (d, *J* = 9.2 Hz, 0.5H, β-anomeric proton), 4.34–4.19 (m, 1H), 3.94 (dd, *J* = 9.2, 2.8 Hz, 0.5H), 3.80 (dd, *J* = 9.8, 2.9 Hz, 0.5H), 3.66–3.37 (m, 4H), 2.80–2.61 (m, 1H), 2.60–2.35 (m, 1H), 1.73 – 1.44 (m, 2H), 1.38 – 1.21 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, CDCl$_3$) δ_C 137.6, 137.4, 137.3, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.6, 127.6, 127.6, 127.5, 127.3, 127.4, 85.6, 84.1, 83.7, 79.6, 78.6, 76.7, 76.5, 76.3, 75.3, 74.8, 74.4, 73.7, 73.6, 73.3, 73.4, 72.8, 72.5, 69.7, 69.1, 68.9, 32.2, 31.9, 30.7, 29.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.0, 26.4, 23.4, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{46}H_{60}O_4SNa$ [M+Na$^+$] 747.4059, found 747.4084.

Dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-glucopyranoside (22a)

Glycosylation was carried out as described in the general procedure by using 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **22** (α/β = 50:50, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (hexanes: ethyl acetate = 4:1; *p*-anisaldehyde, R_f = 0.32). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate: hexanes from 0:1 to 3:7 as eluent. Thiopyranoside **22a** was obtained as a yellow syrup (78 mg, 45%, α/β = 64:36). Mixture of α and β-anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45–7.07 (m, 20H), 5.37 (d, *J* = 4.9 Hz, 0.5H, α-anomeric proton), 5.20–4.51 (m, 7.5H), 4.45 (dt, *J* = 11.6 , 5.3 Hz, 2H), 4.19 (d, *J* = 9.9 Hz, 0.5H, β-anomeric proton), 3.90–3.51 (m, 4H), 3.50–3.33 (m, 0.5H), 2.62–2.38 (m, 2H), 1.71–1.49 (m, 2H), 1.37–1.21 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ_C 138.8, 138.6, 138.4, 138.3, 138.1, 138.1, 138.0, 138.0, 128.4, 128.4, 128.4, 128.1, 128.0, 128.0, 127.8, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 86.7, 85.3, 83.5, 82.6, 81.9, 79.7, 79.2, 78.1, 77.6, 75.7, 75.7, 75.5, 75.0, 73.5, 72.4, 72.1, 70.5, 69.6, 69.2, 68.7, 31.9, 30.9, 30.0, 29.8, 29.7, 29.6, 29.6, 29.4, 29.3, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{46}H_{60}O_4SNa$ [M+Na$^+$] 747.4059, found 747.4035.

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Supporting Information

Surfactant-Mediated Thioglycosylation of 1-Hydroxy Sugar in Water

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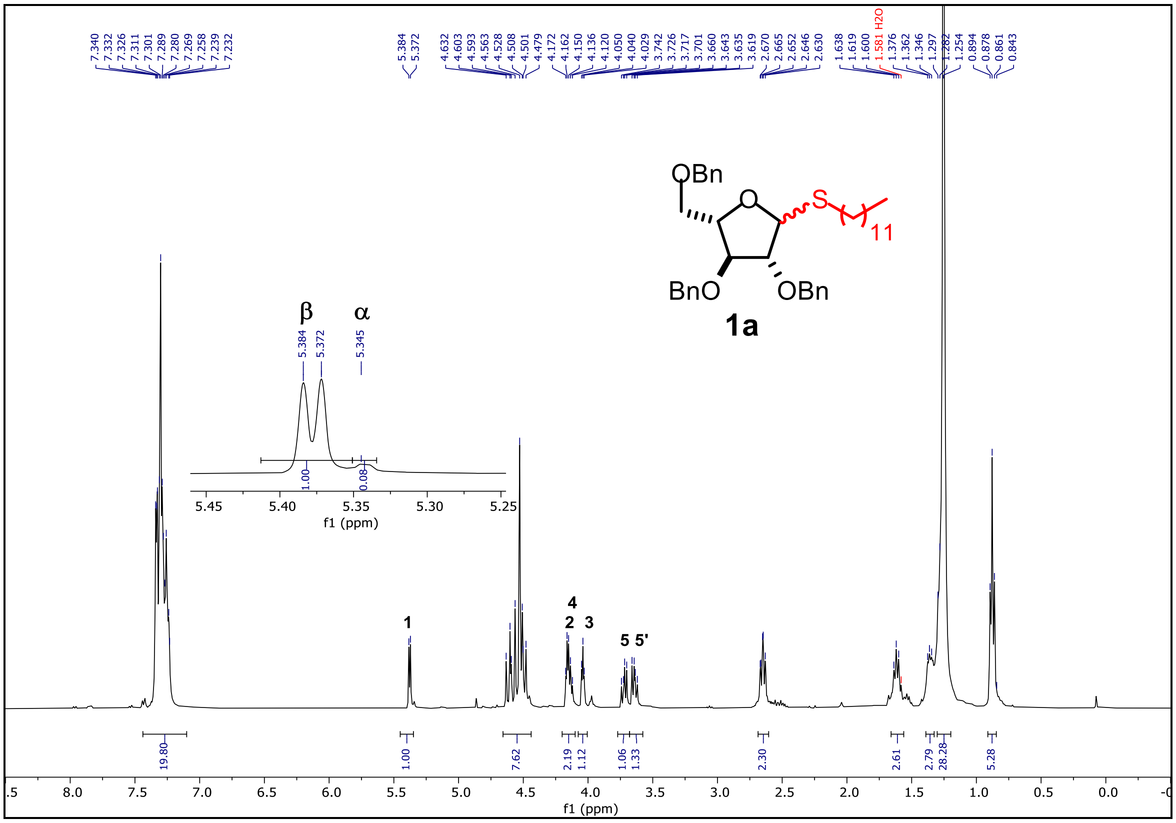


Figure S1. ^{1}H NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**1a**) (400 MHz, $CDCl_3$).

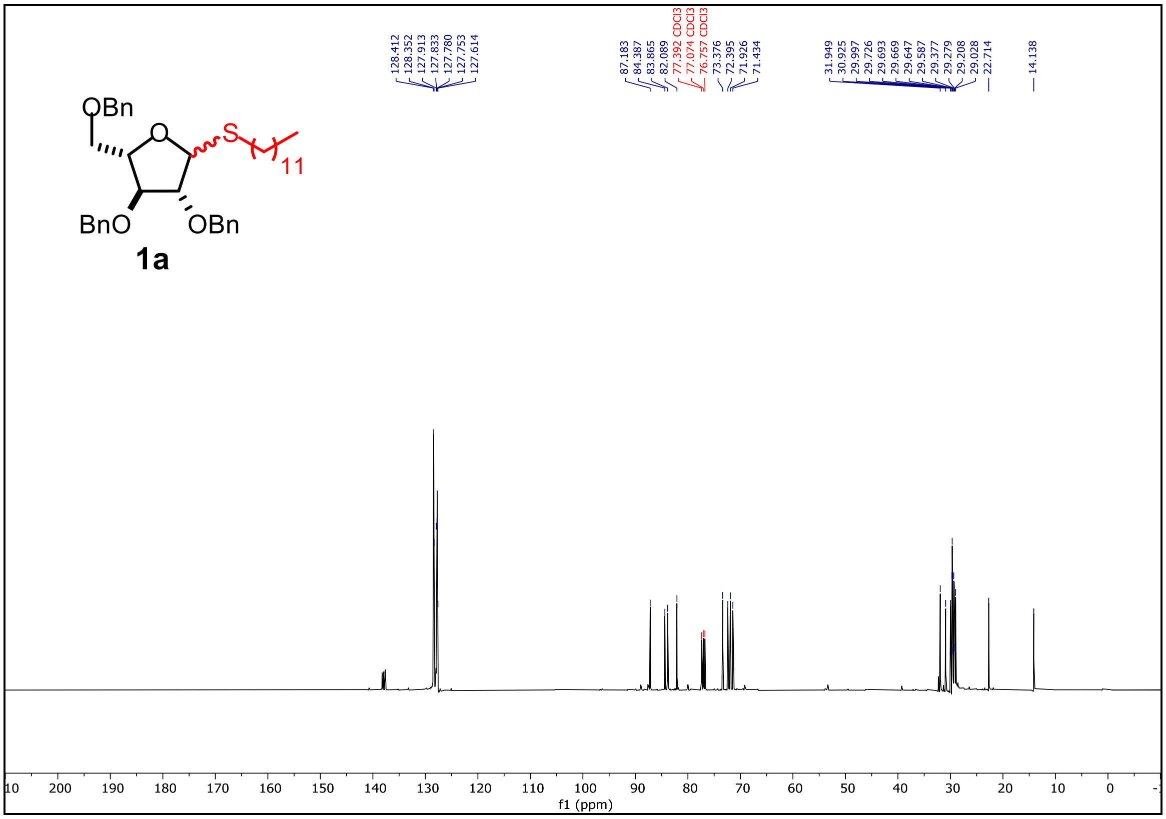
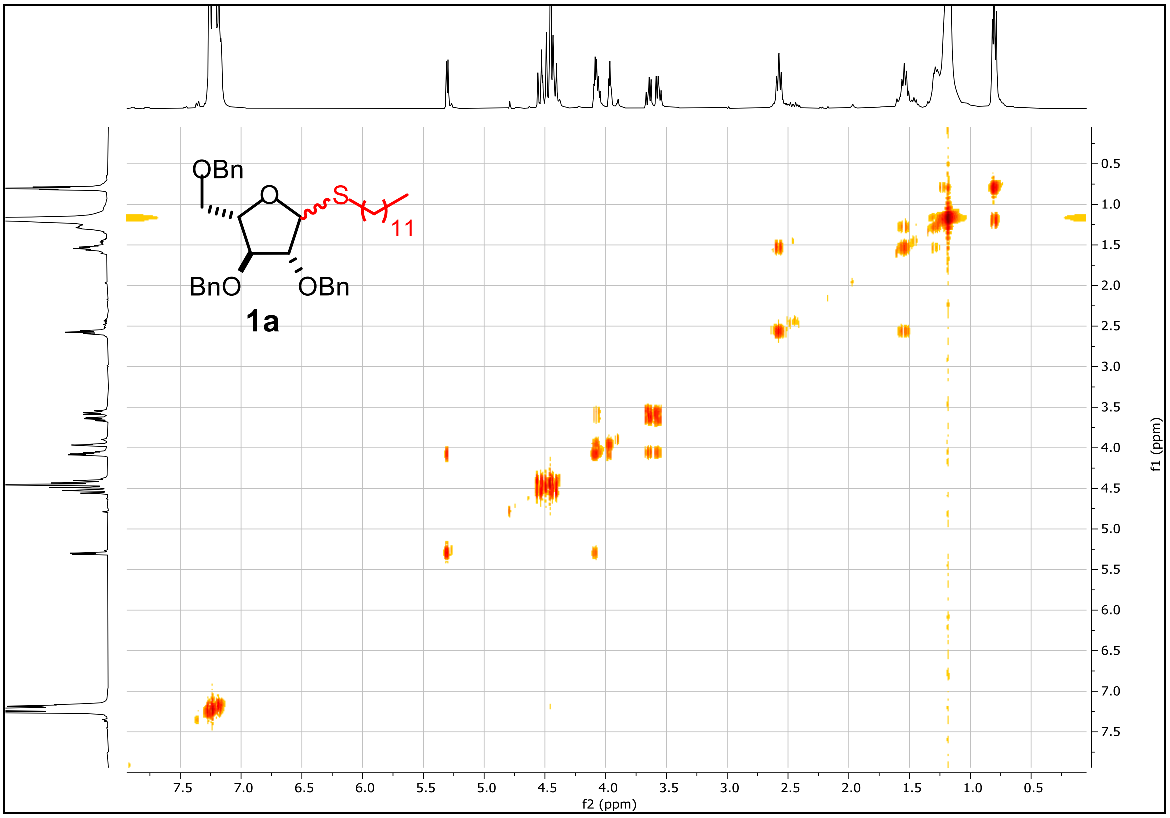


Figure S2. ^{13}C NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**1a**) (101 MHz, $CDCl_3$).



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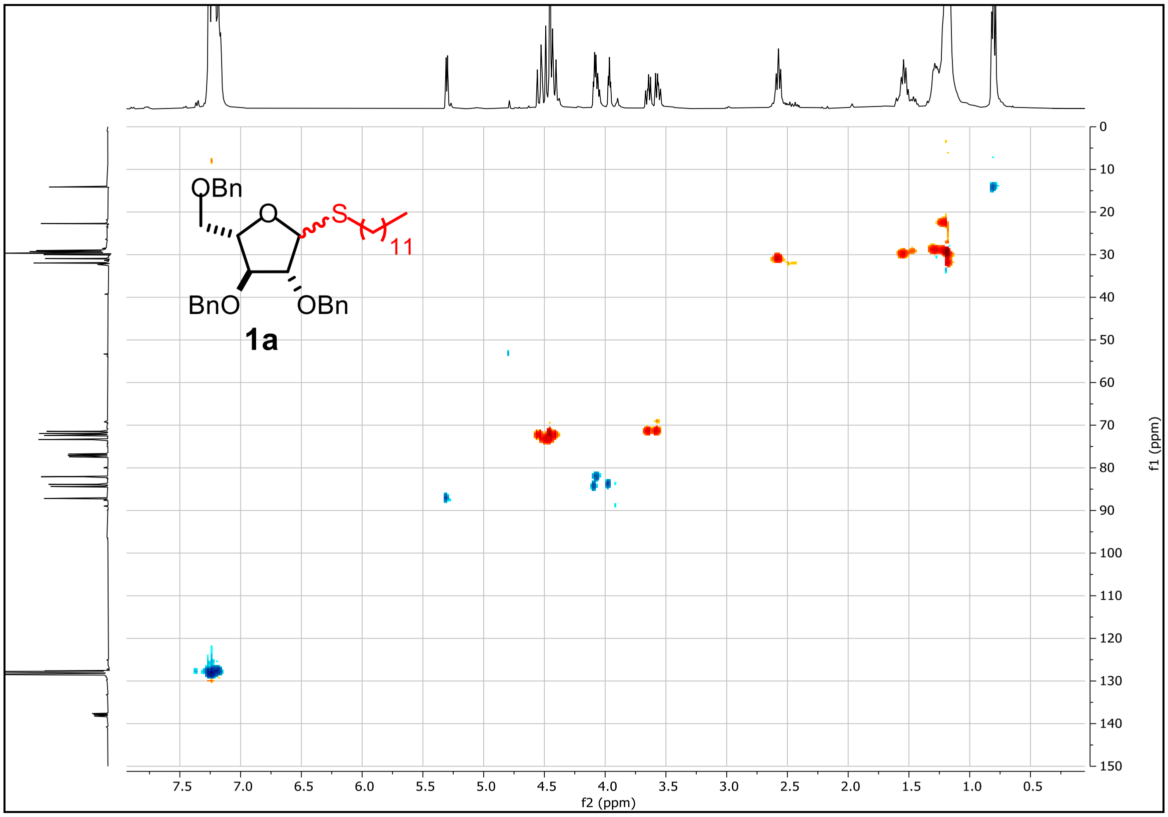

Figure S4. HSQC spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**1a**) (400 MHz, $CDCl_3$).

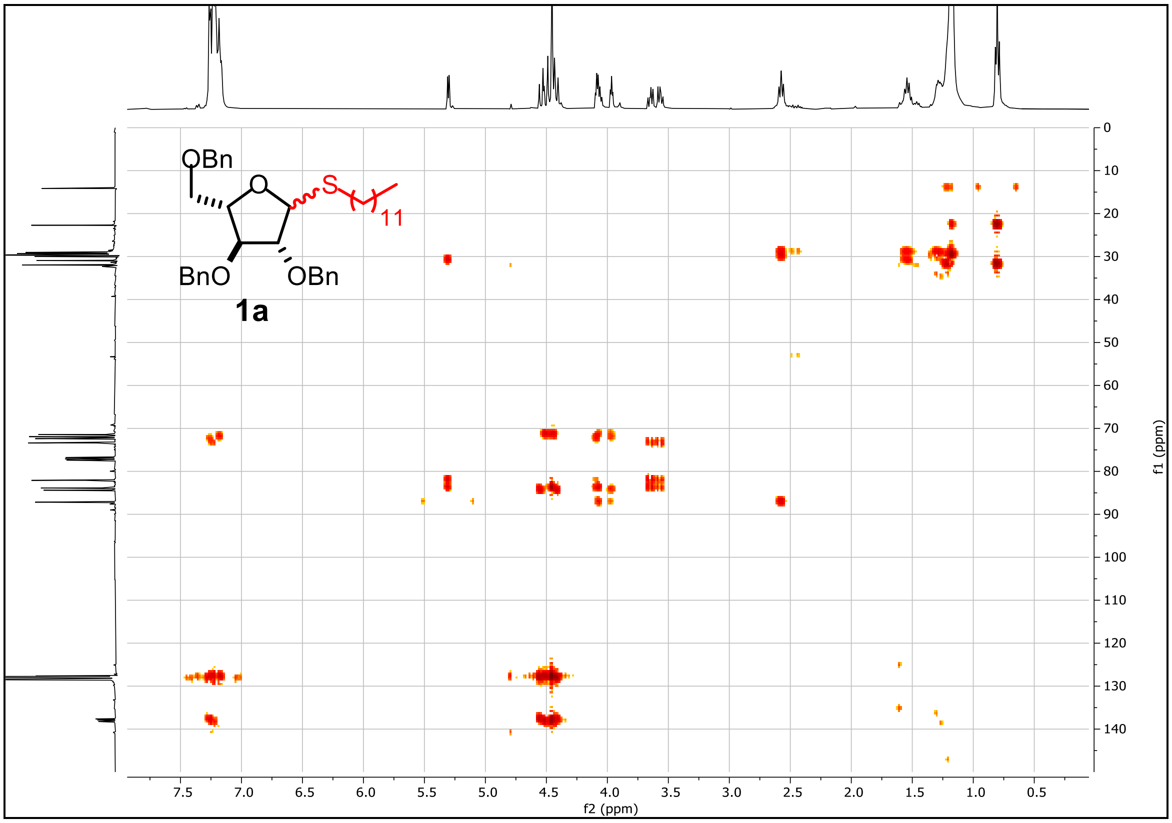

Figure S5. HMBC spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**1a**) (400 MHz, $CDCl_3$).

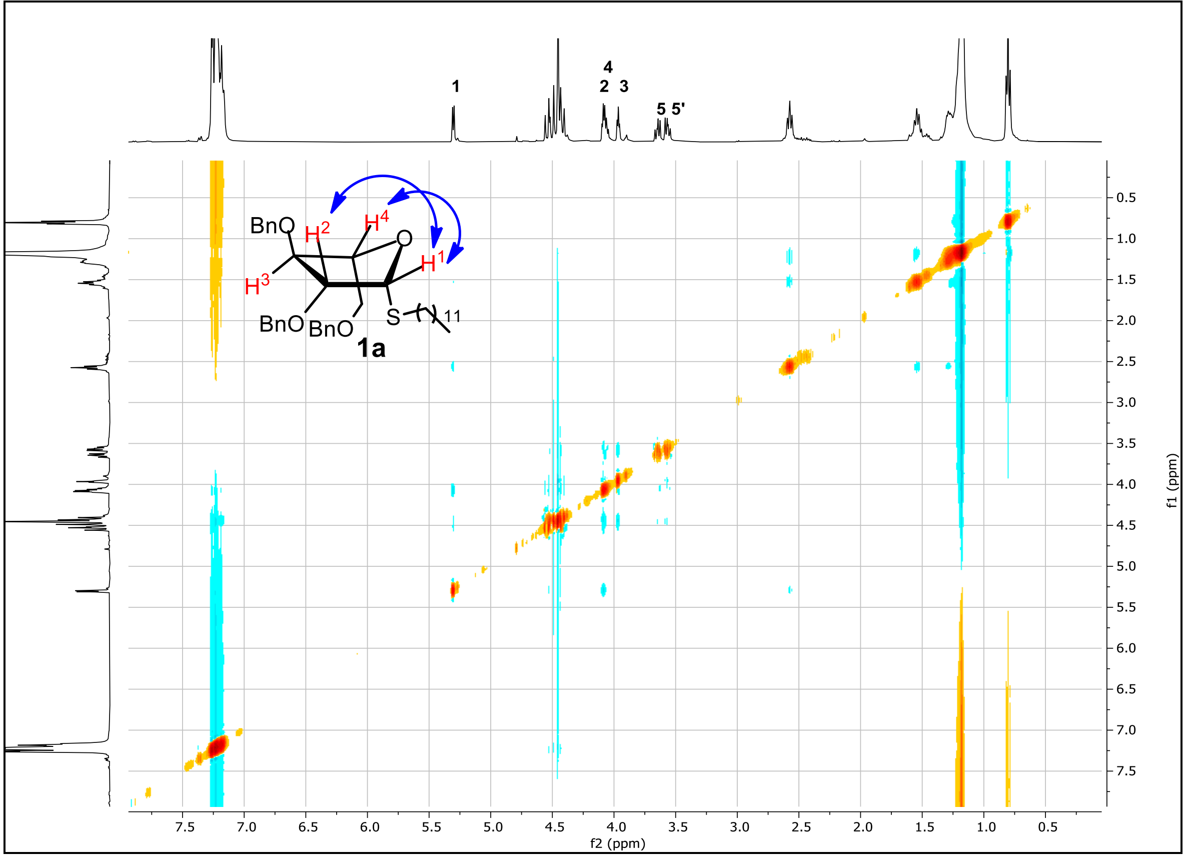

Figure S6. NOESY spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**1a**) (400 MHz, $CDCl_3$).

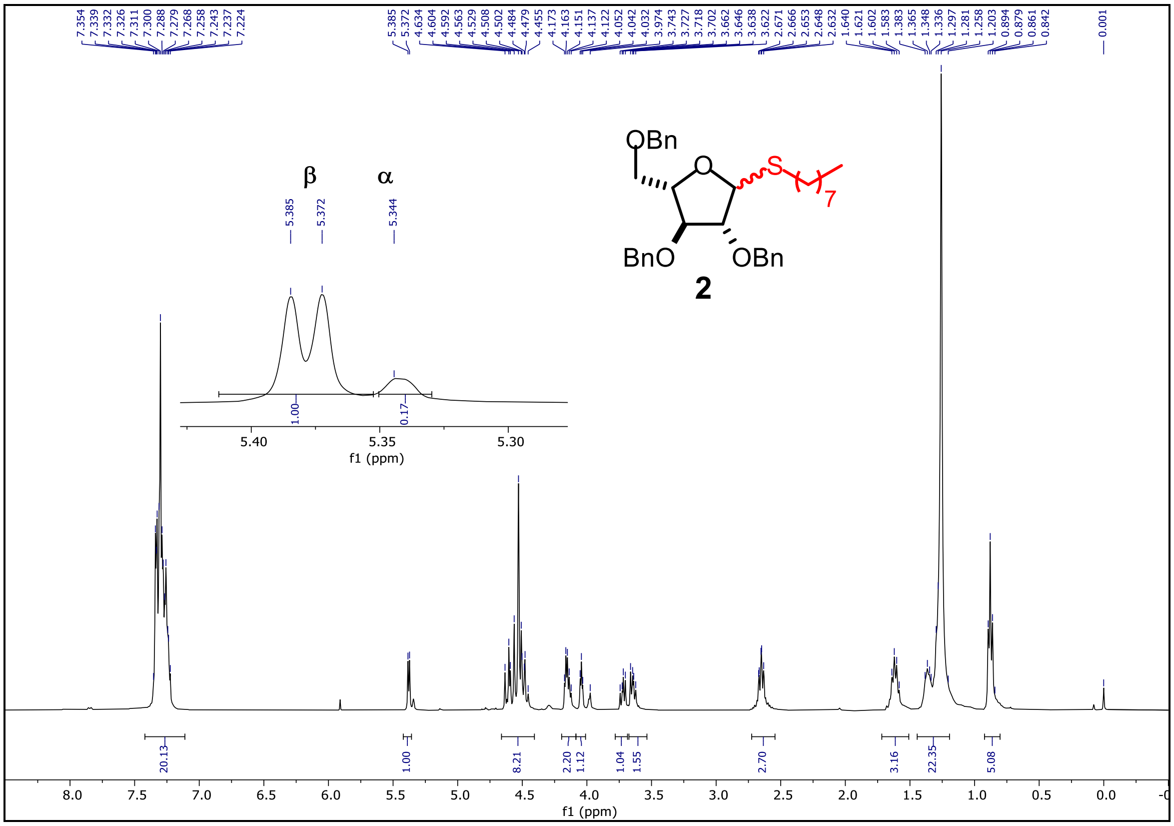

Figure S7. ^{1}H NMR spectrum of octyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**2**) (400 MHz, CDCl$_3$).

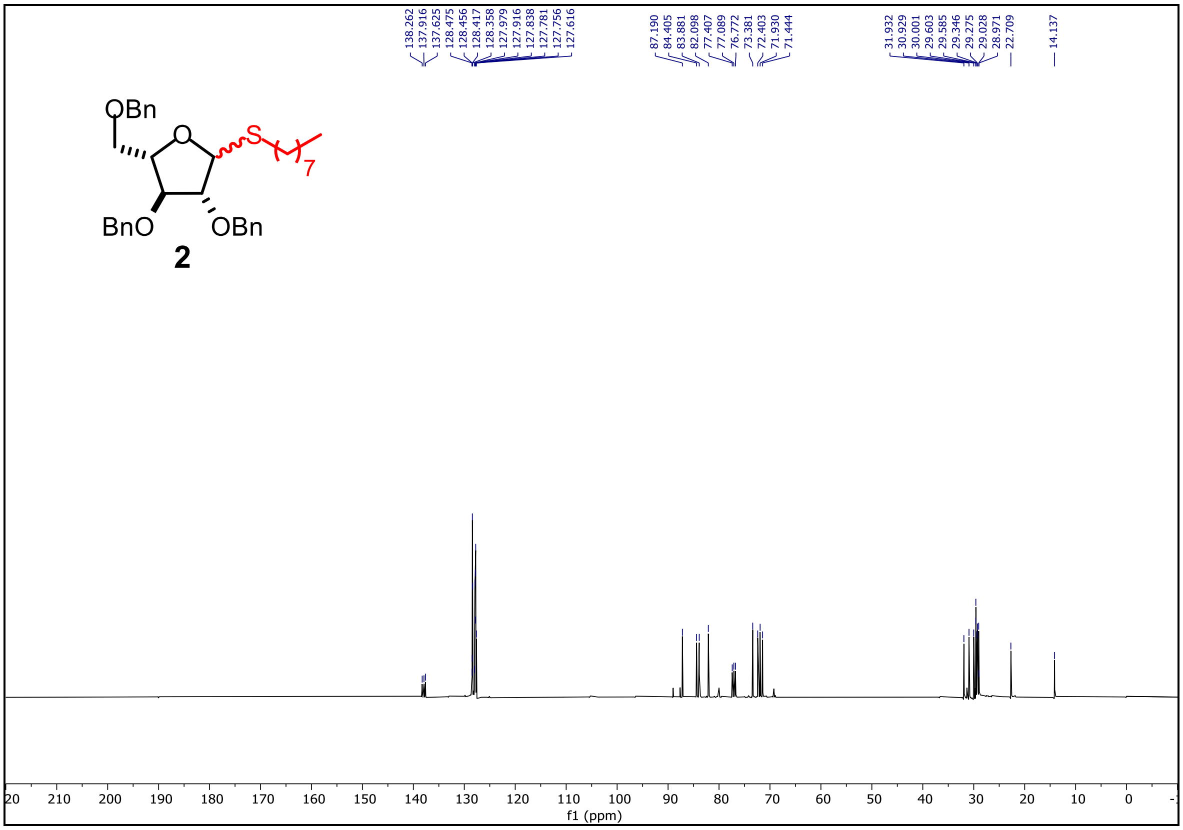

Figure S8. ^{13}C NMR spectrum of octyl 2,3,5-tri-*O*-benzyl-α,**β**-L-thioarabinofuranoside (**2**) (101 MHz, CDCl$_3$).

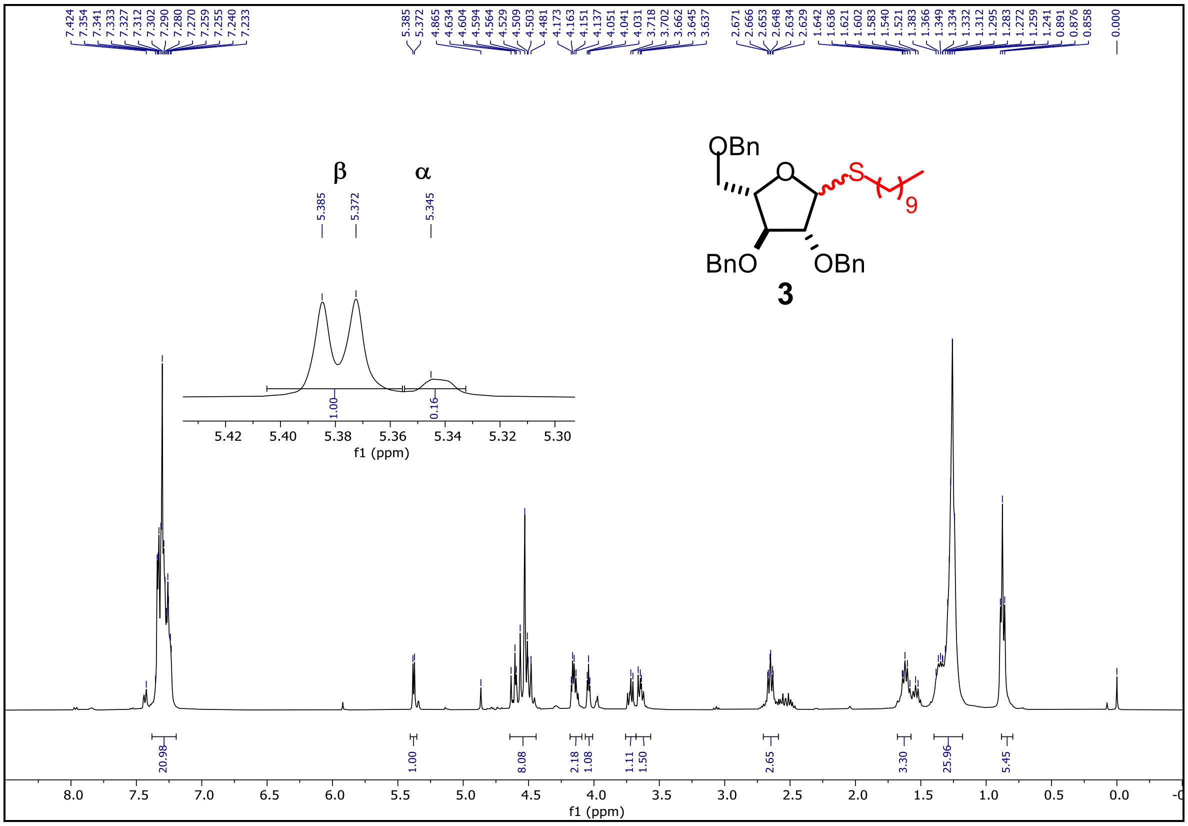

Figure S9. ^{1}H NMR spectrum of decyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**3**) (400 MHz, CDCl$_3$).

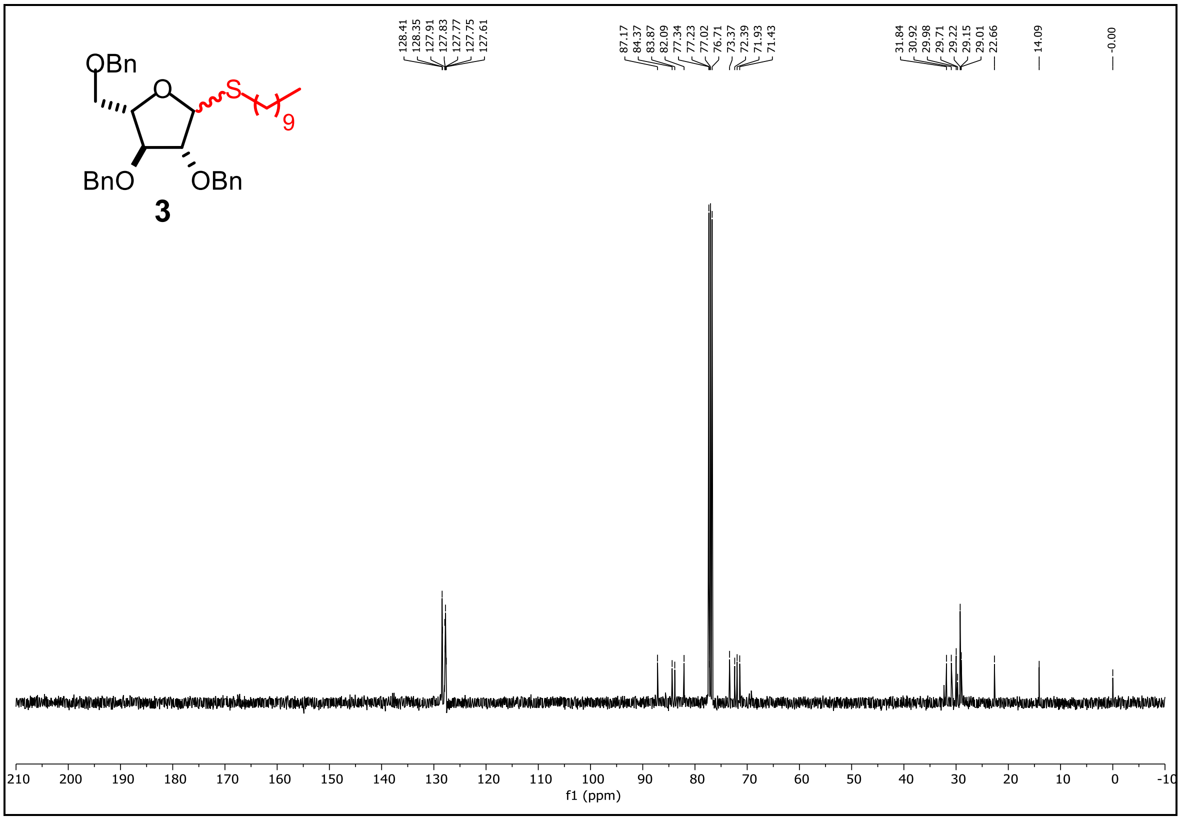

Figure S10. ^{13}C NMR spectrum of decyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**3**) (101 MHz, CDCl$_3$).

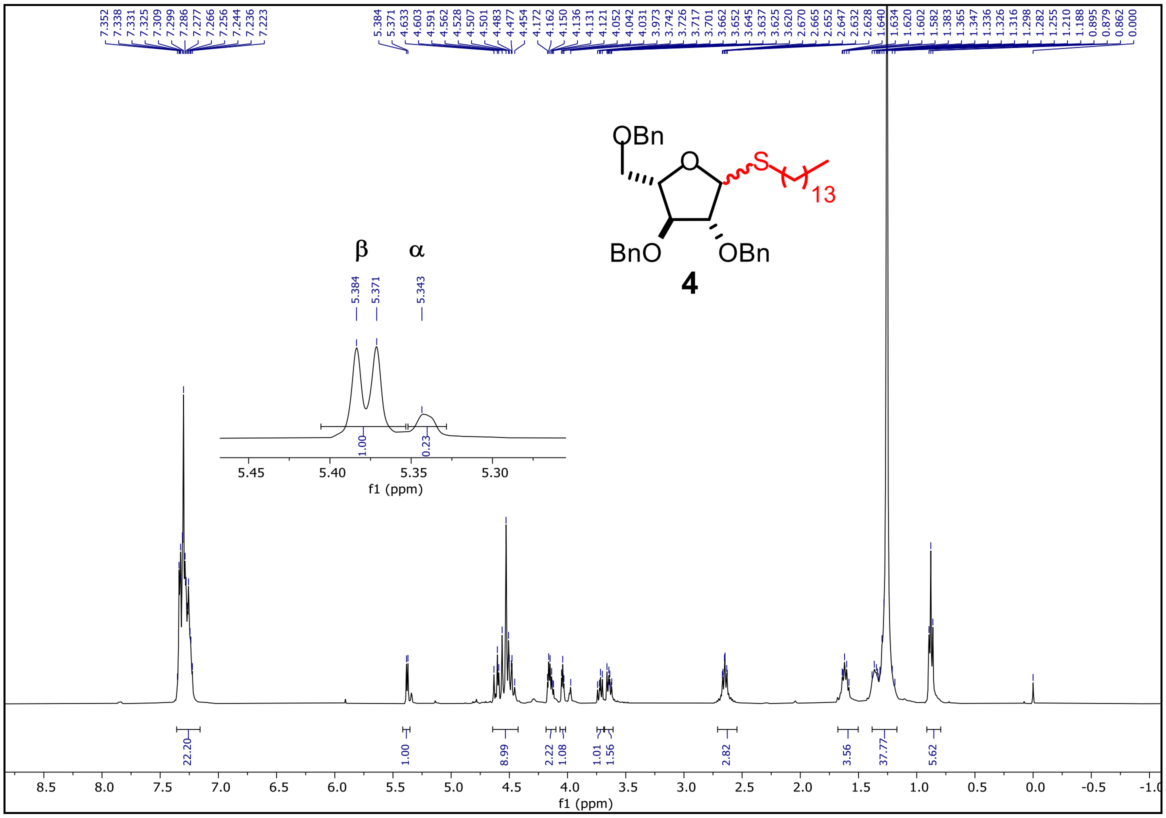

Figure S11. ^{1}H NMR spectrum of tetradecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**4**) (400 MHz, $CDCl_3$).

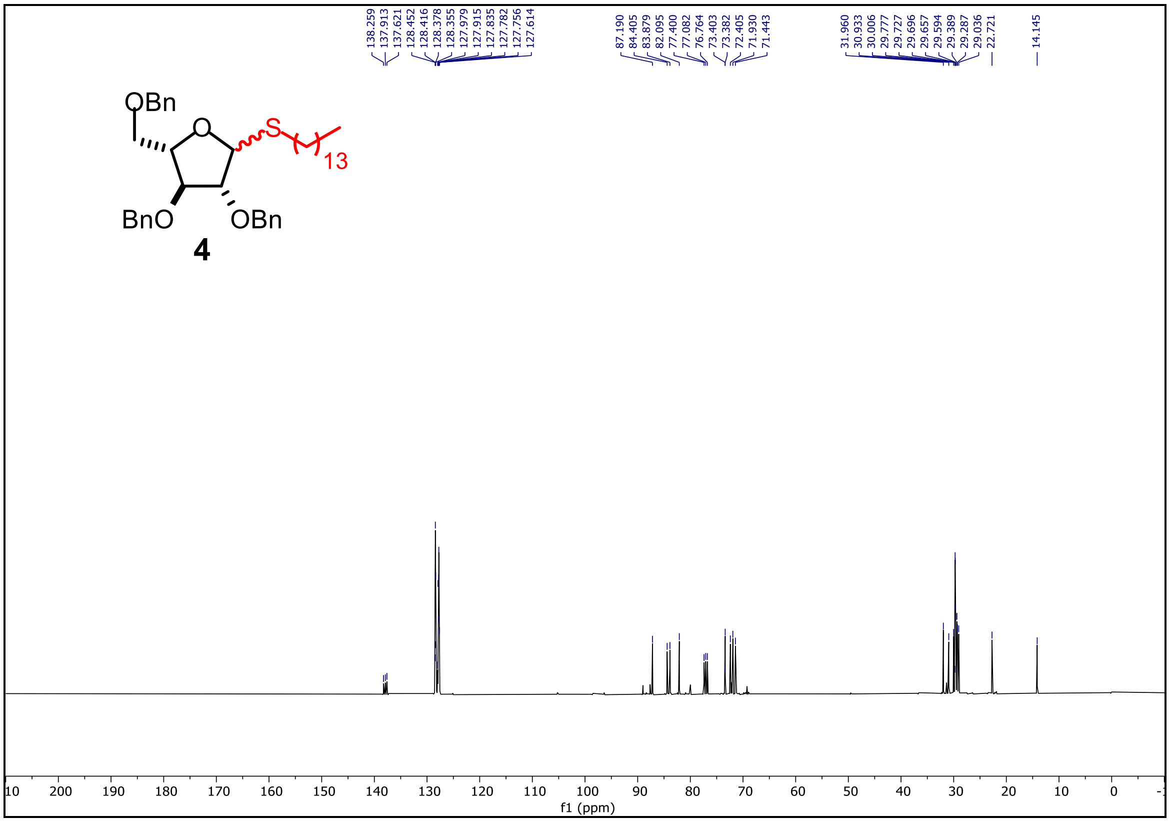

Figure S12. ^{13}C NMR spectrum of tetradecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**4**) (101 MHz, $CDCl_3$).

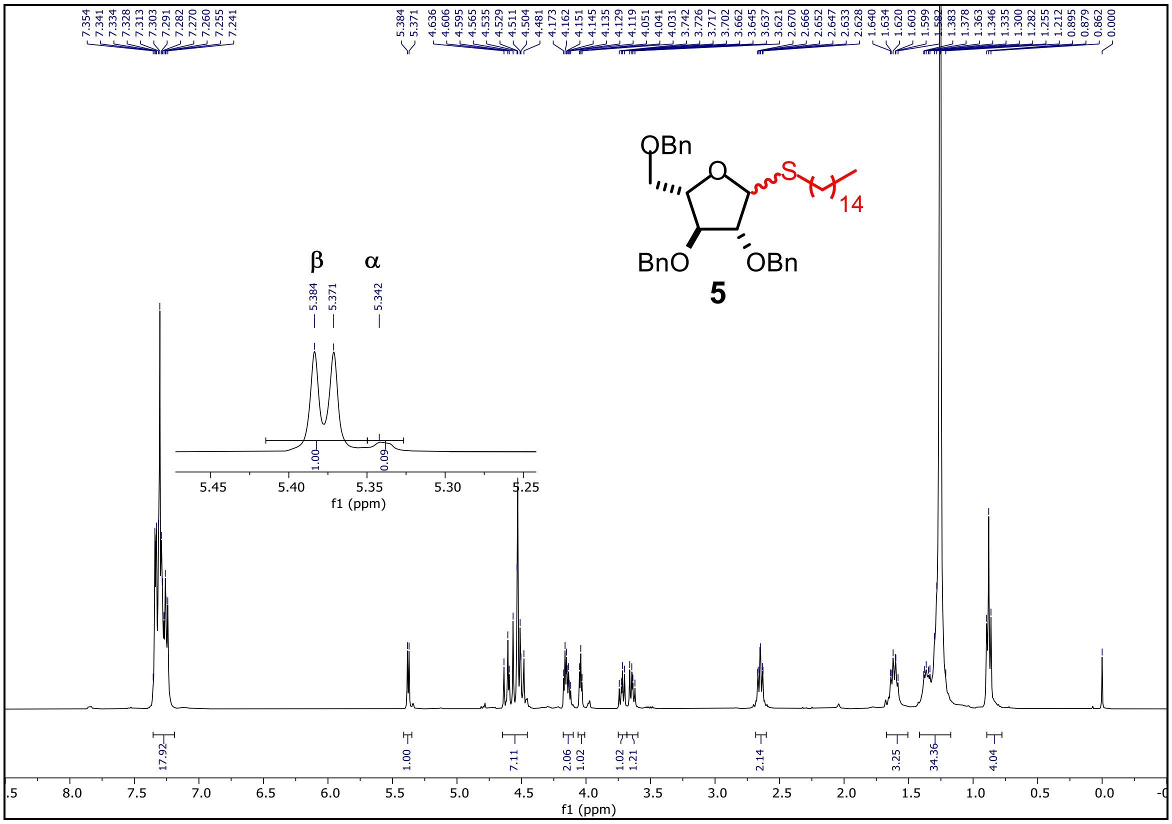

Figure S13. ^{1}H NMR spectrum of pentadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**5**) (400 MHz, $CDCl_3$).

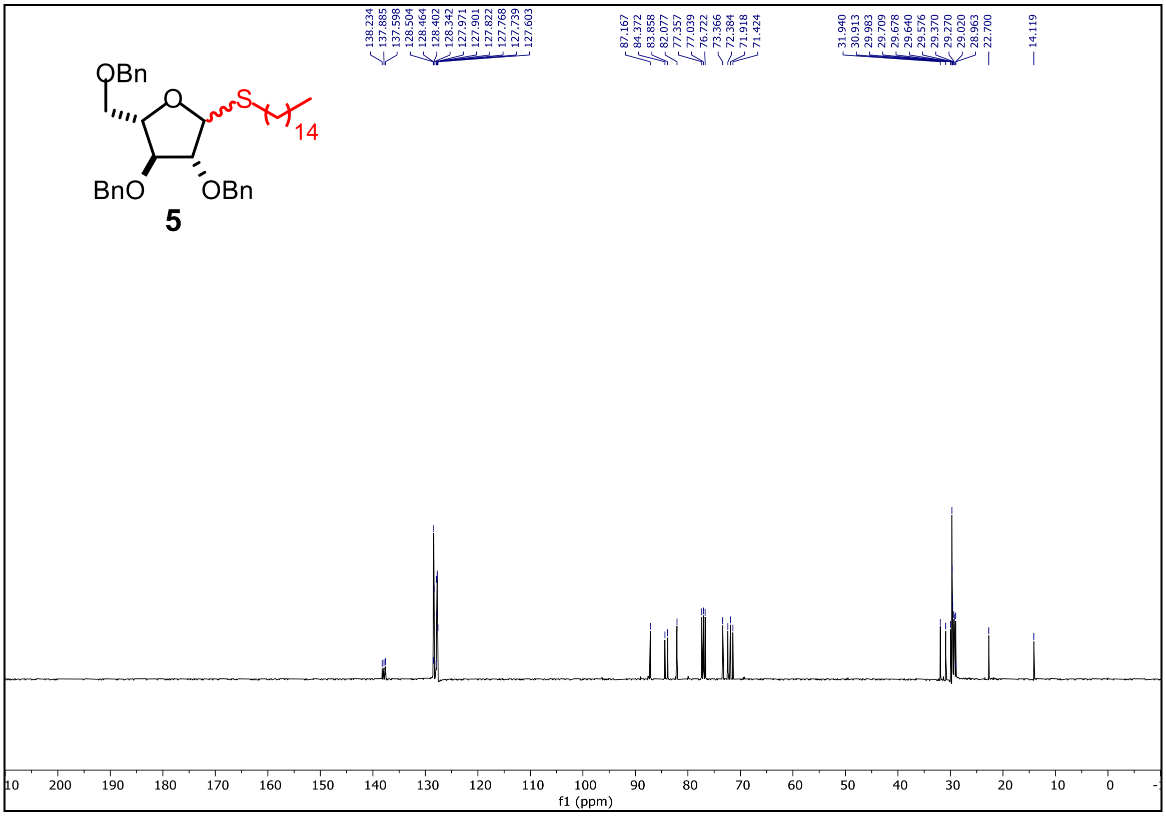

Figure S14. ^{13}C NMR spectrum of pentadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**5**) (101 MHz, $CDCl_3$).

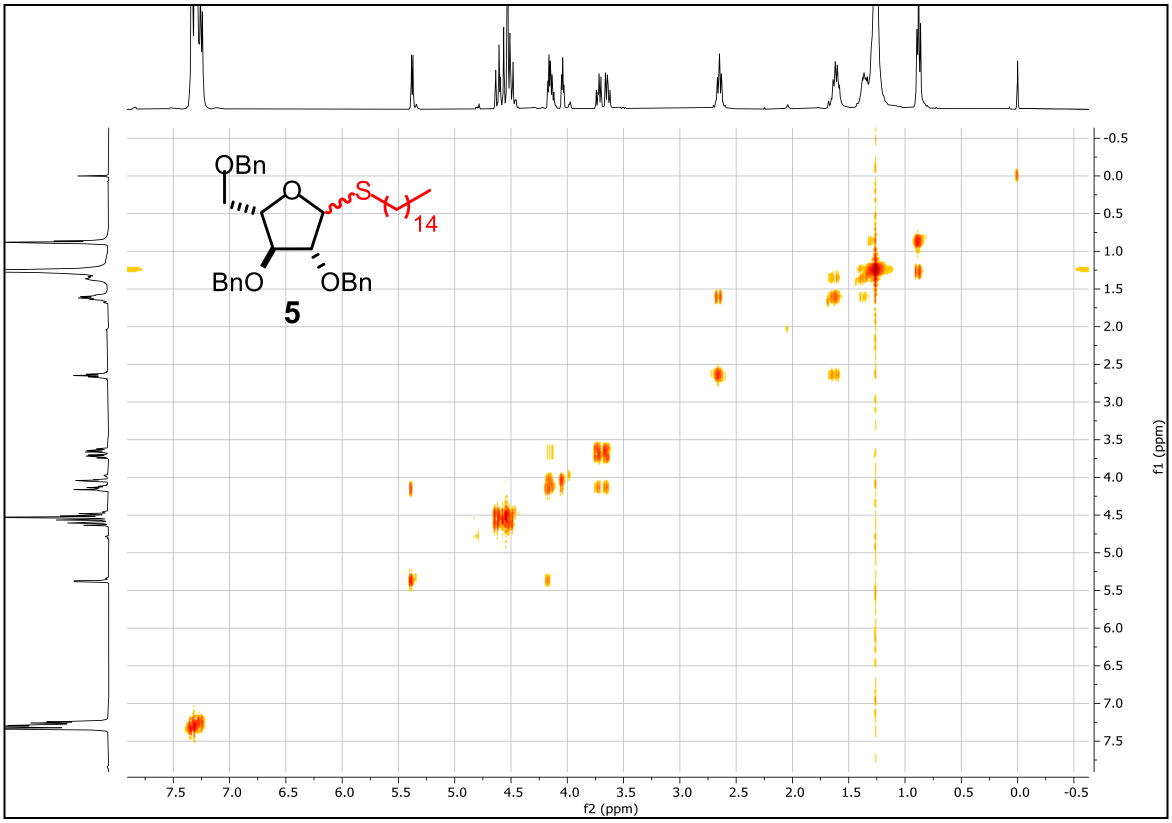

Figure S15. COSY spectrum of pentadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**5**) (400 MHz, CDCl$_3$).

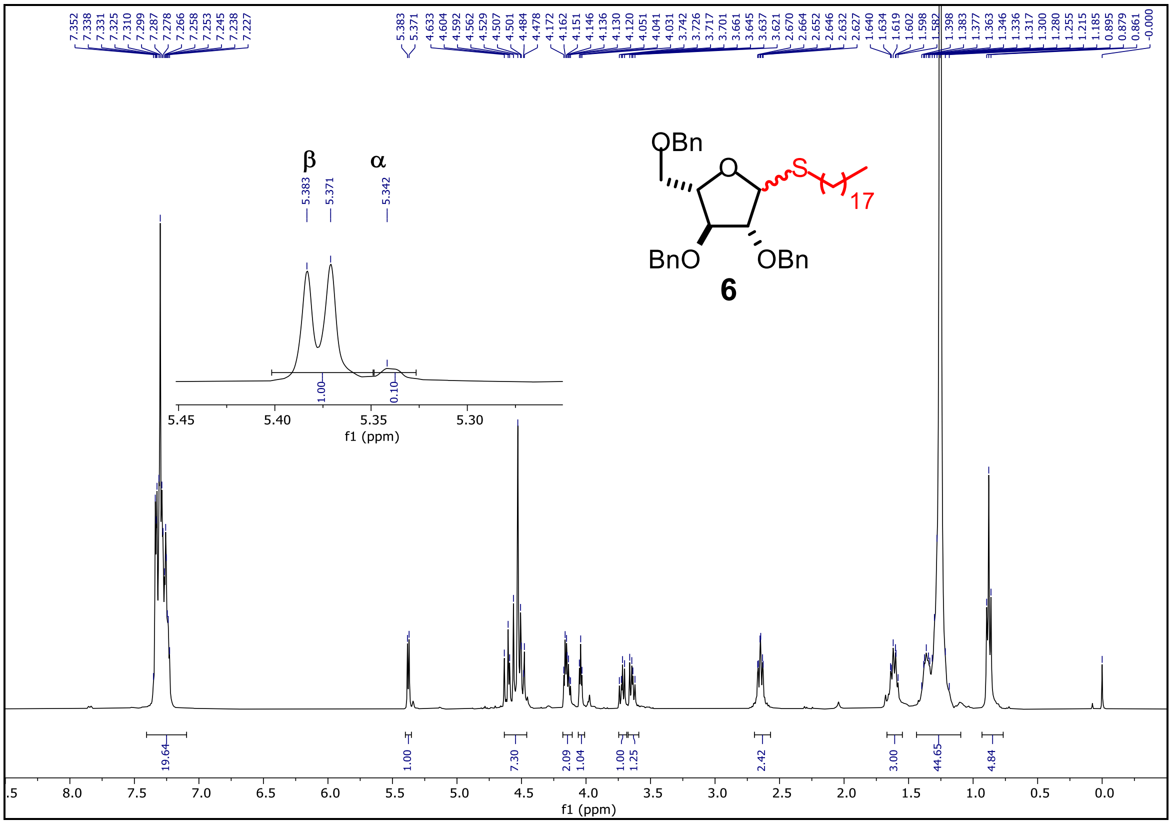

Figure S16. ^{1}H NMR spectrum of octadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**6**) (400 MHz, $CDCl_3$).

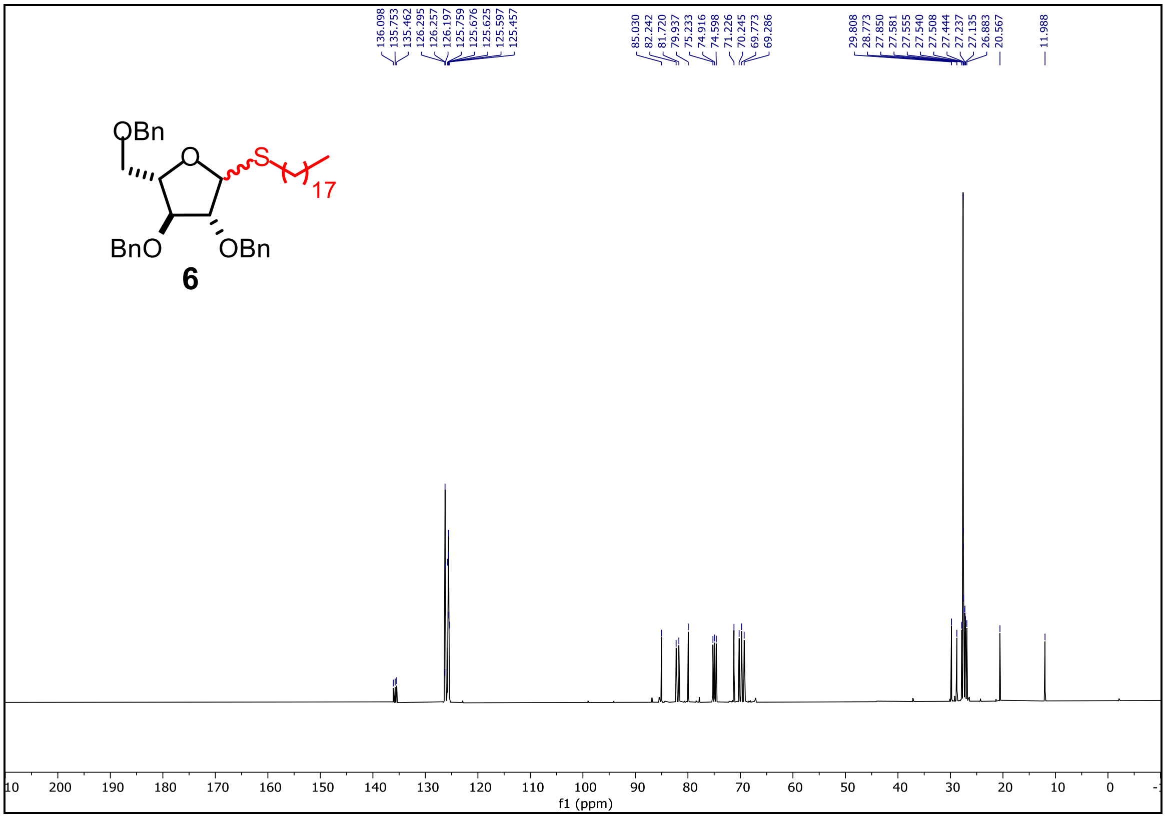

Figure S17. ^{13}C NMR spectrum of octadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**6**) (101 MHz, $CDCl_3$).

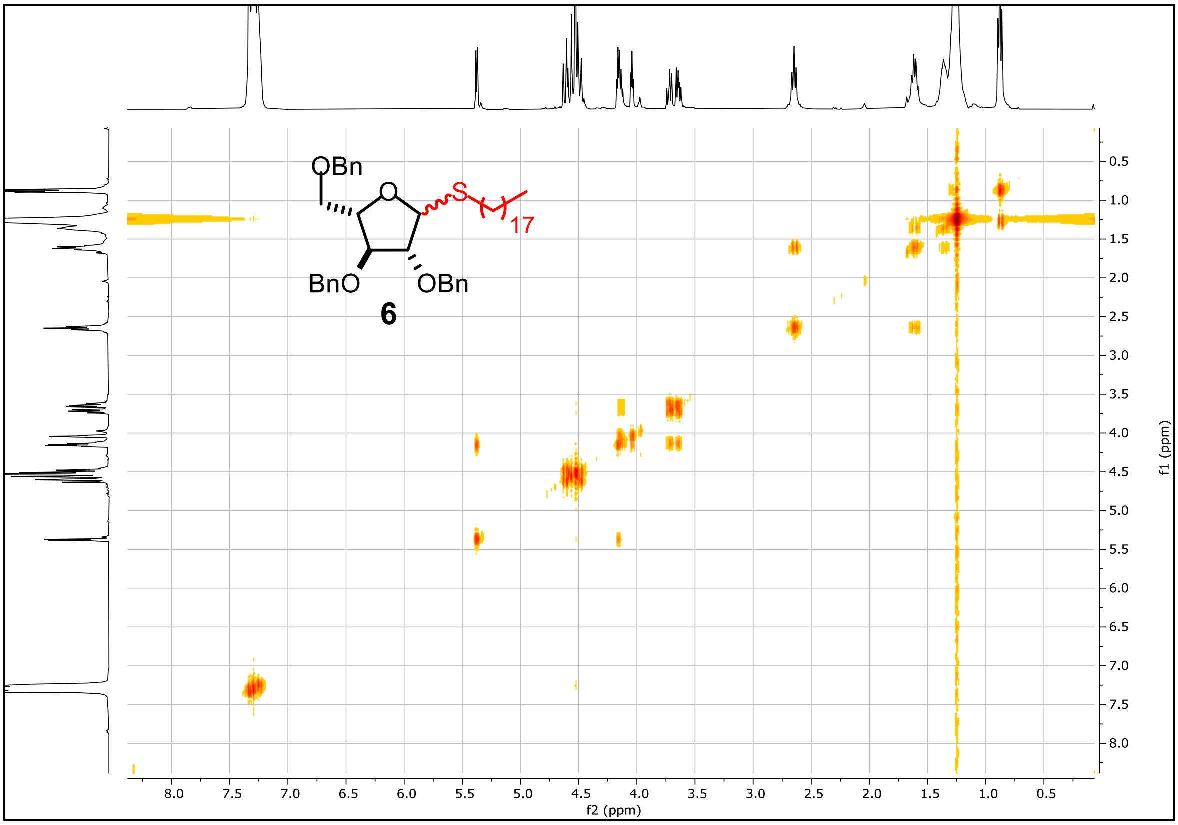

Figure S18. COSY spectrum of octadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**6**) (400 MHz, CDCl$_3$).

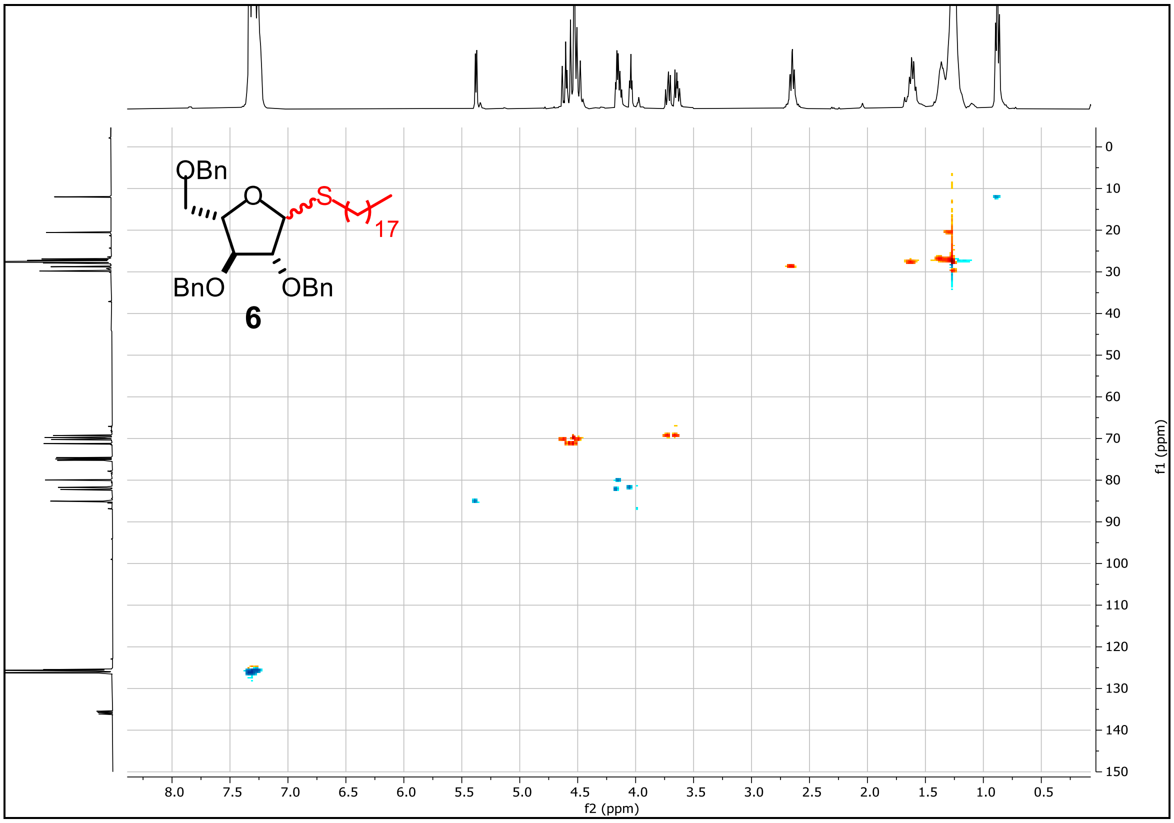

Figure S19. HSQC spectrum of octadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**6**) (400 MHz, CDCl$_3$).

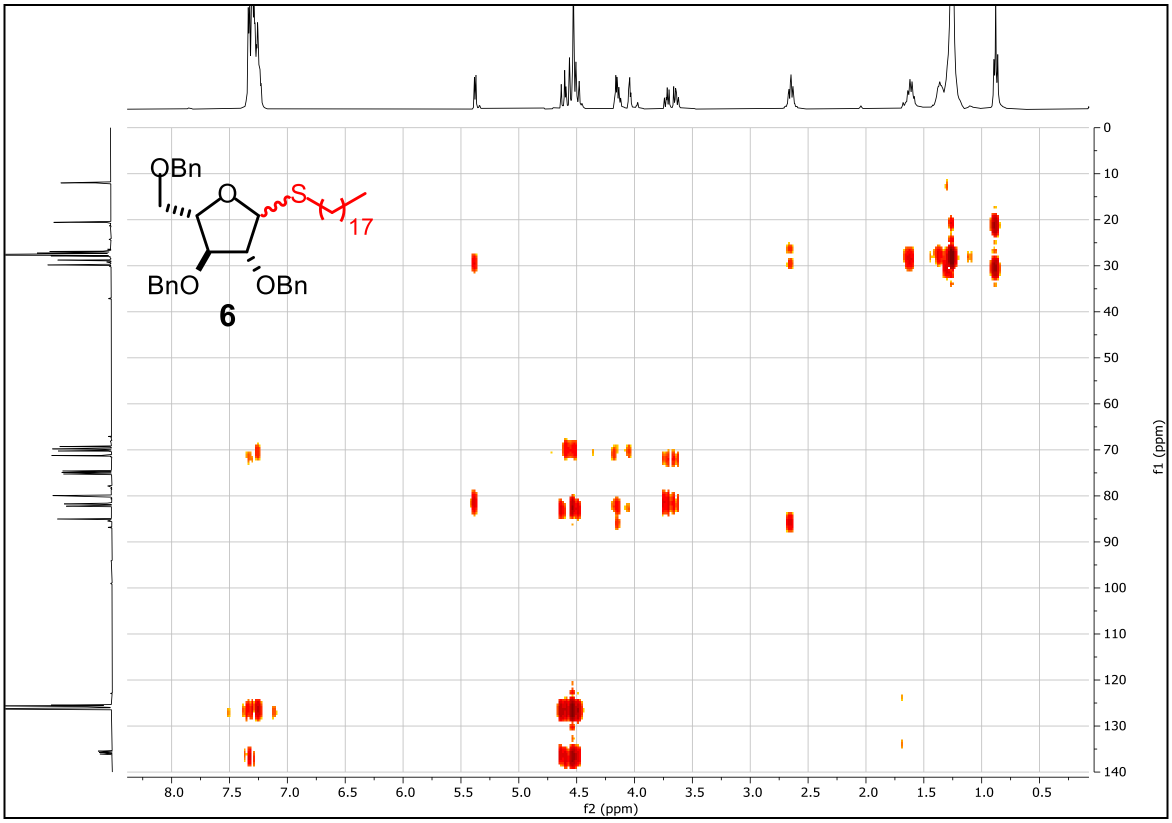

Figure S20. HMBC spectrum of octadecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**6**) (400 MHz, $CDCl_3$).

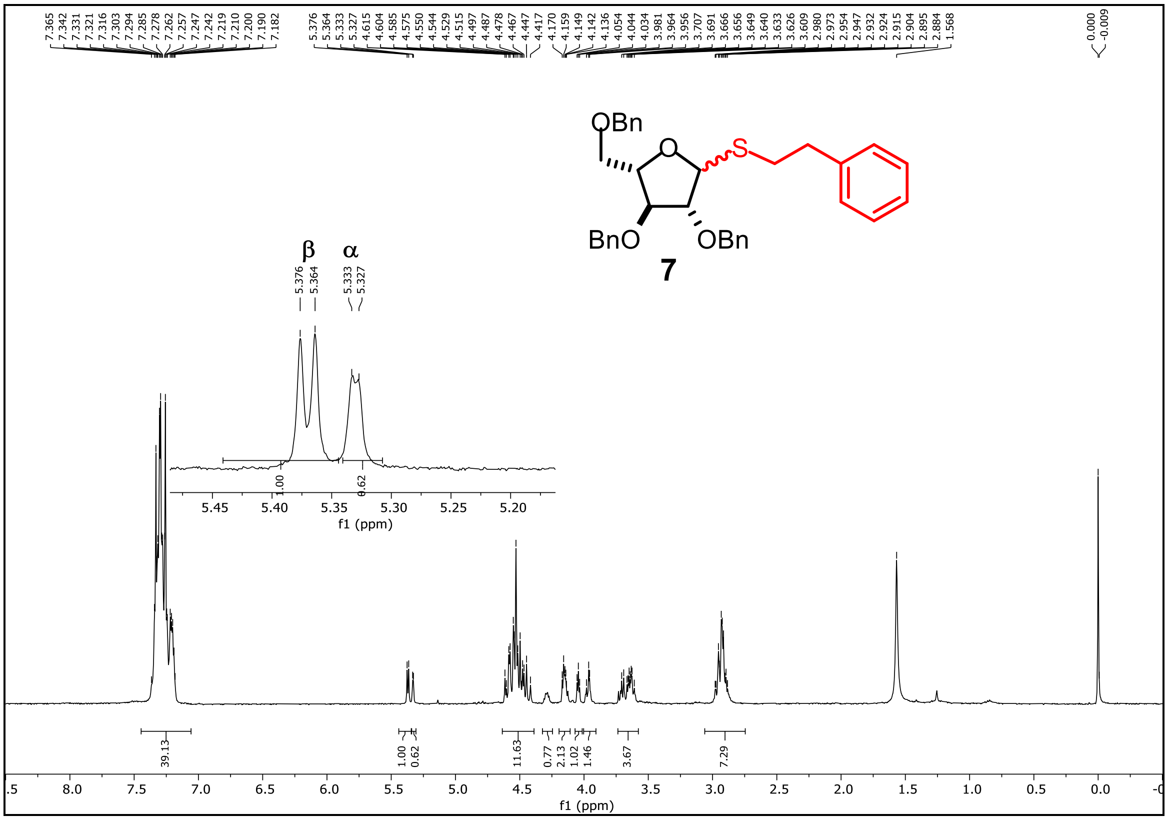

Figure S21. ^{1}H spectrum of 2-phenylethyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**7**) (400 MHz, $CDCl_3$).

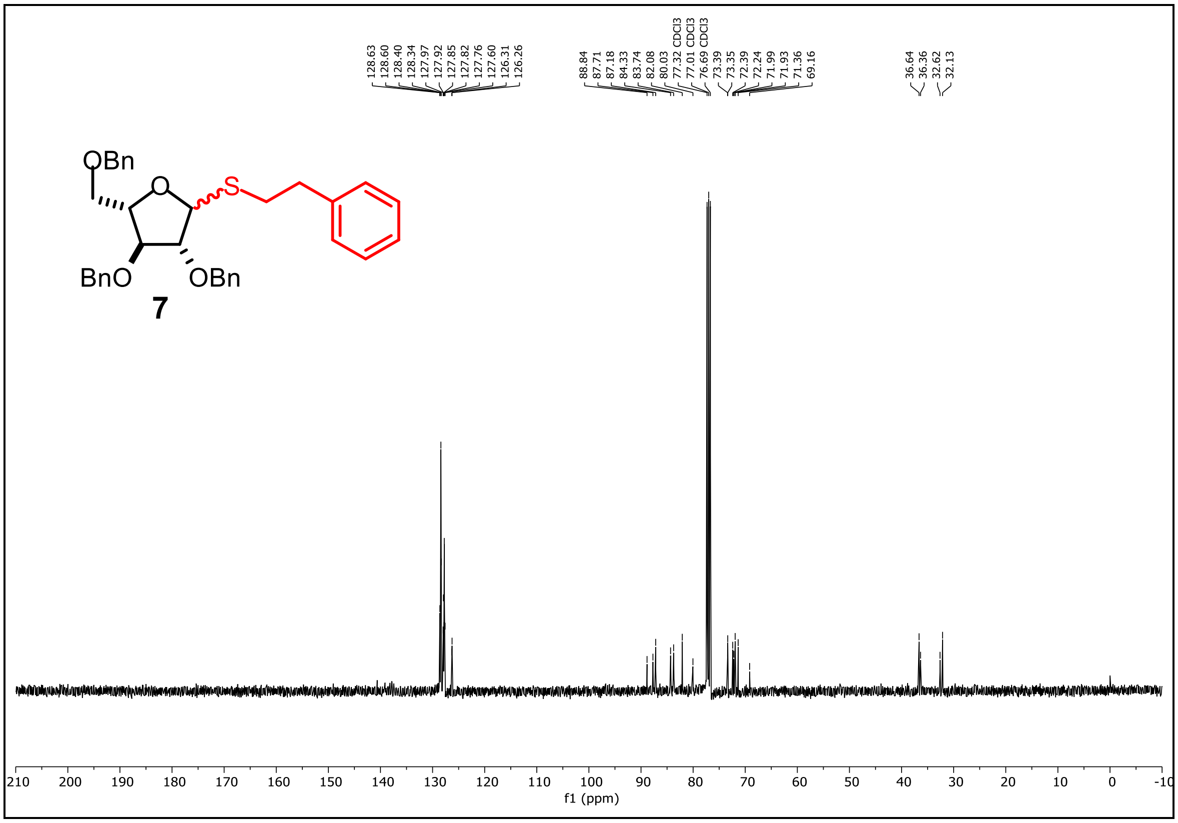

Figure S22. ^{13}C spectrum of 2-phenylethyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**7**) (101 MHz, $CDCl_3$).

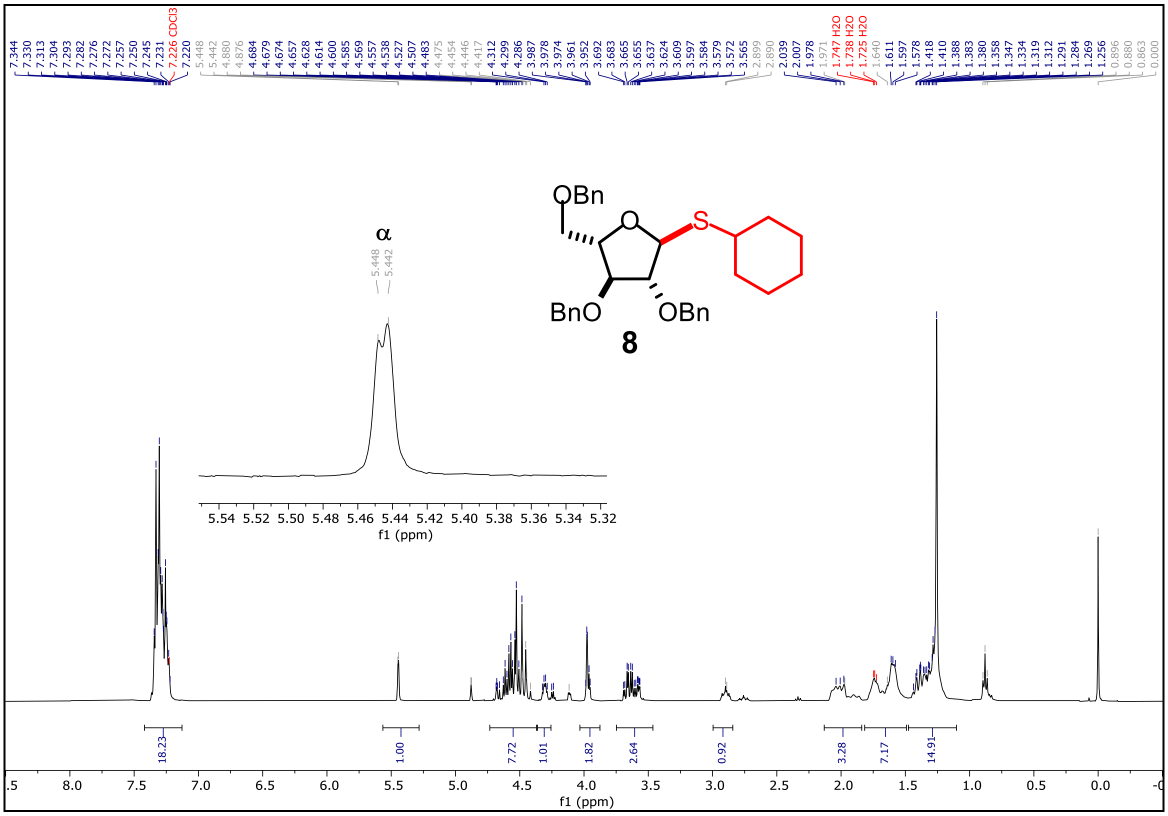

Figure S23. ^{1}H spectrum of cyclohexyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**8**) (400 MHz, $CDCl_3$).

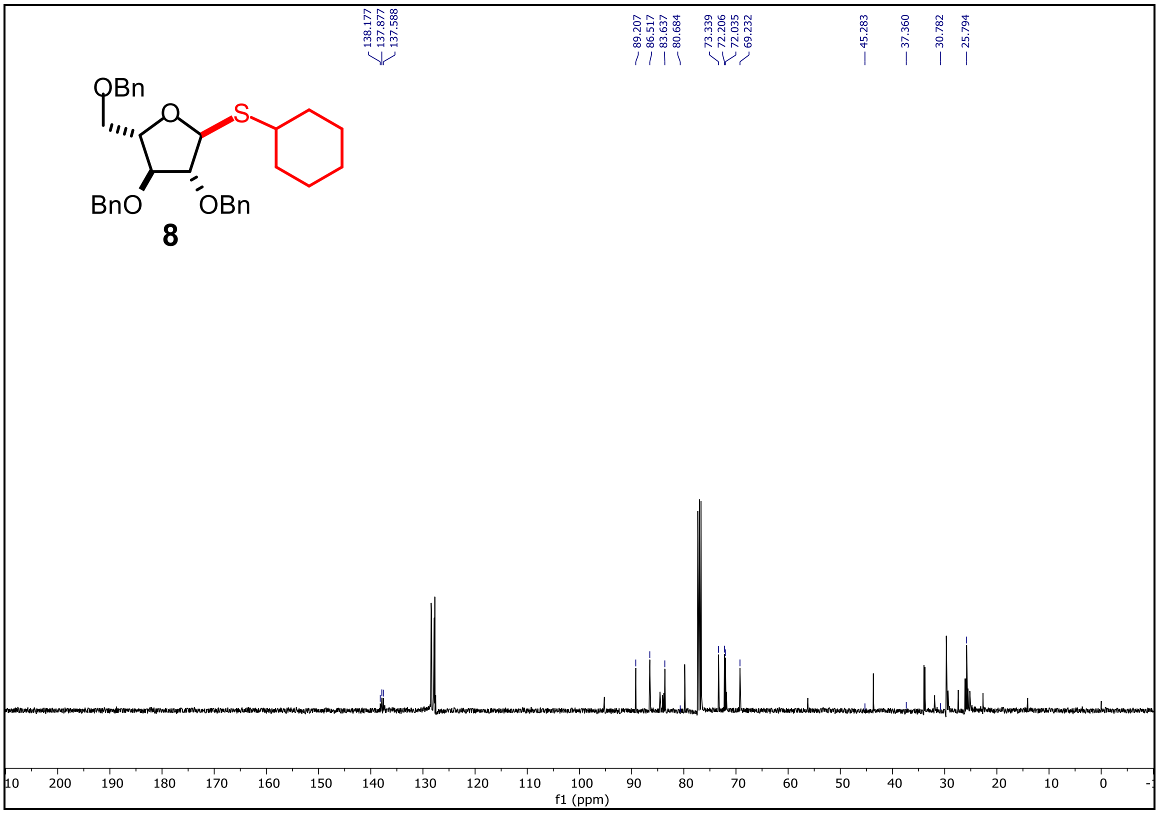

Figure S24. ^{13}C spectrum of cyclohexyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**8**) (101 MHz, $CDCl_3$).

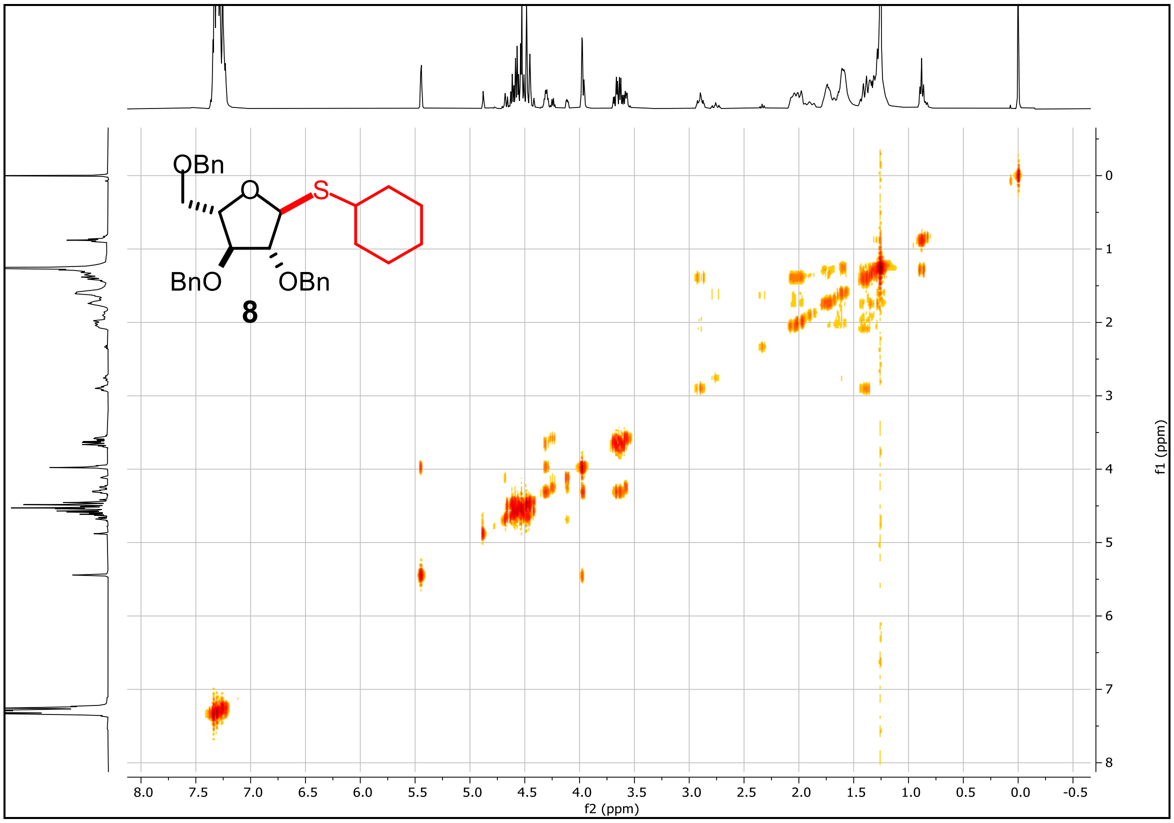

Figure S25. COSY spectrum of cyclohexyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**8**) (400 MHz, $CDCl_3$).

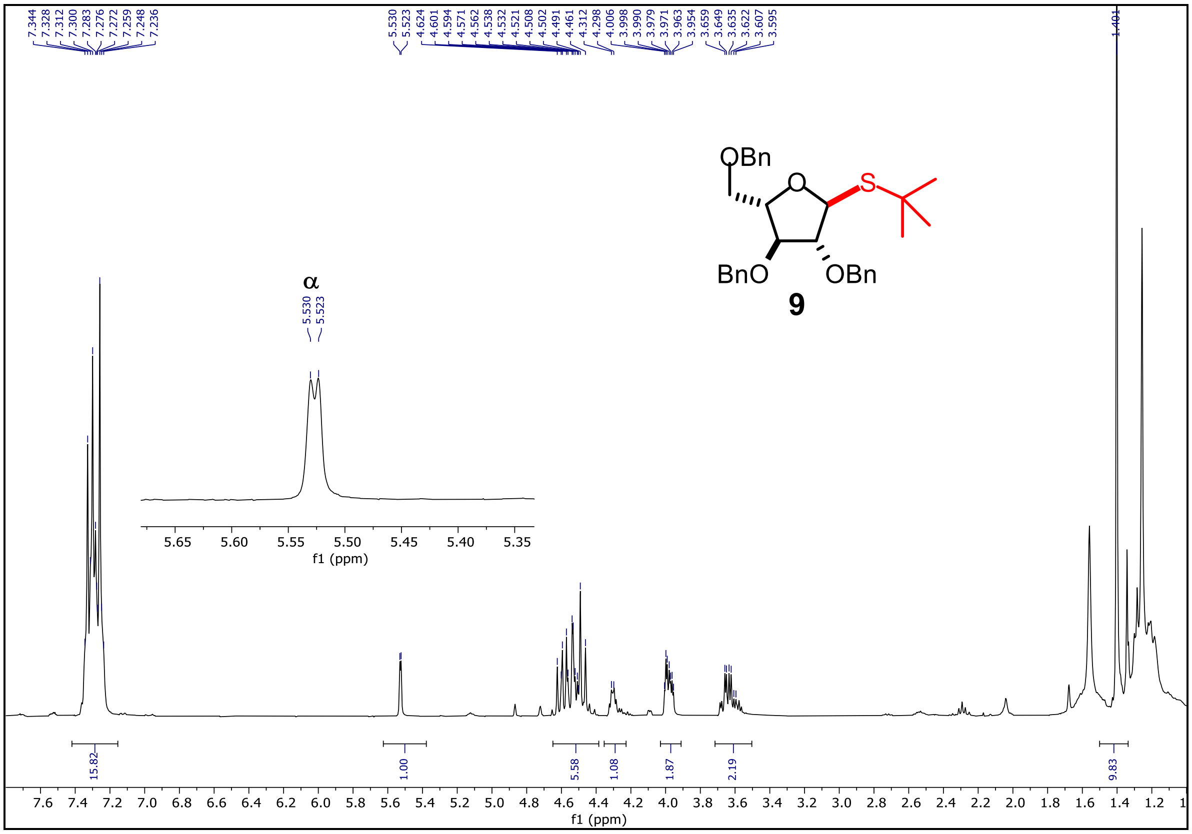

Figure S26. ^{1}H spectrum of *tert*-butyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**9**) (400 MHz, $CDCl_3$).

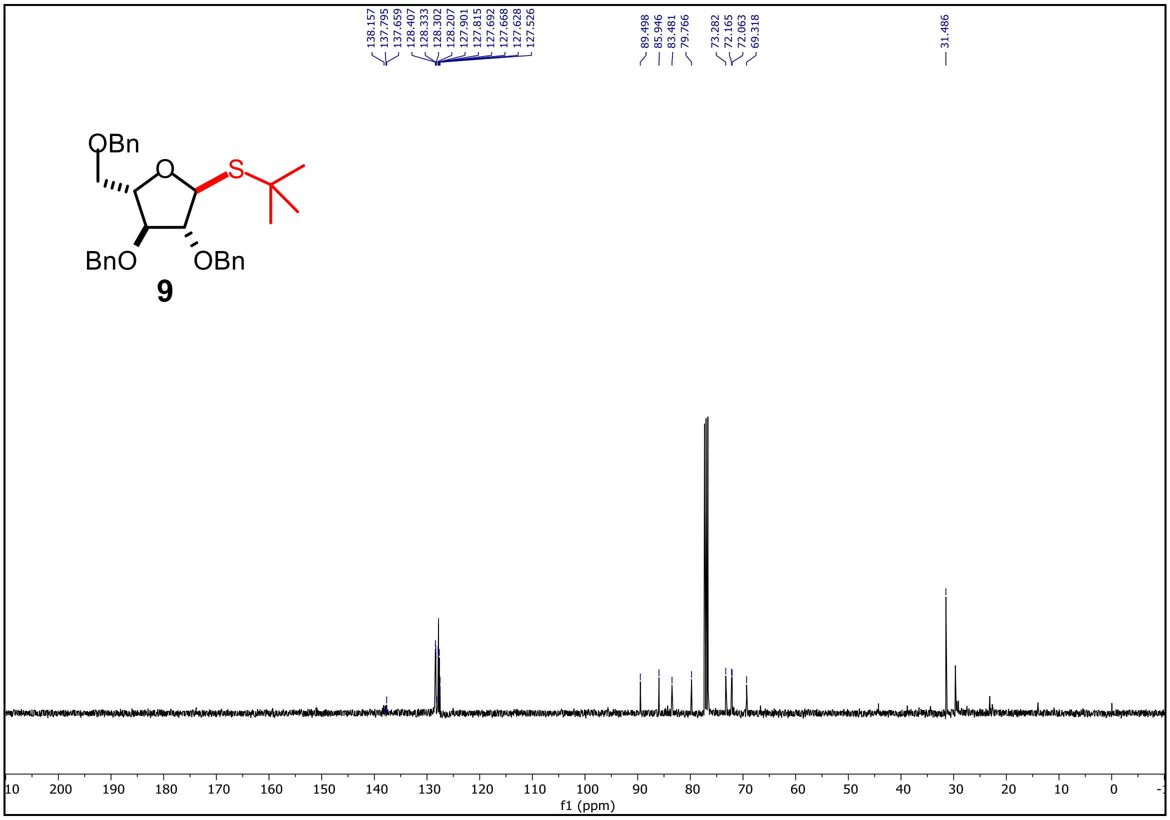

Figure S27. ^{13}C spectrum of *tert*-butyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**9**) (101 MHz, $CDCl_3$).

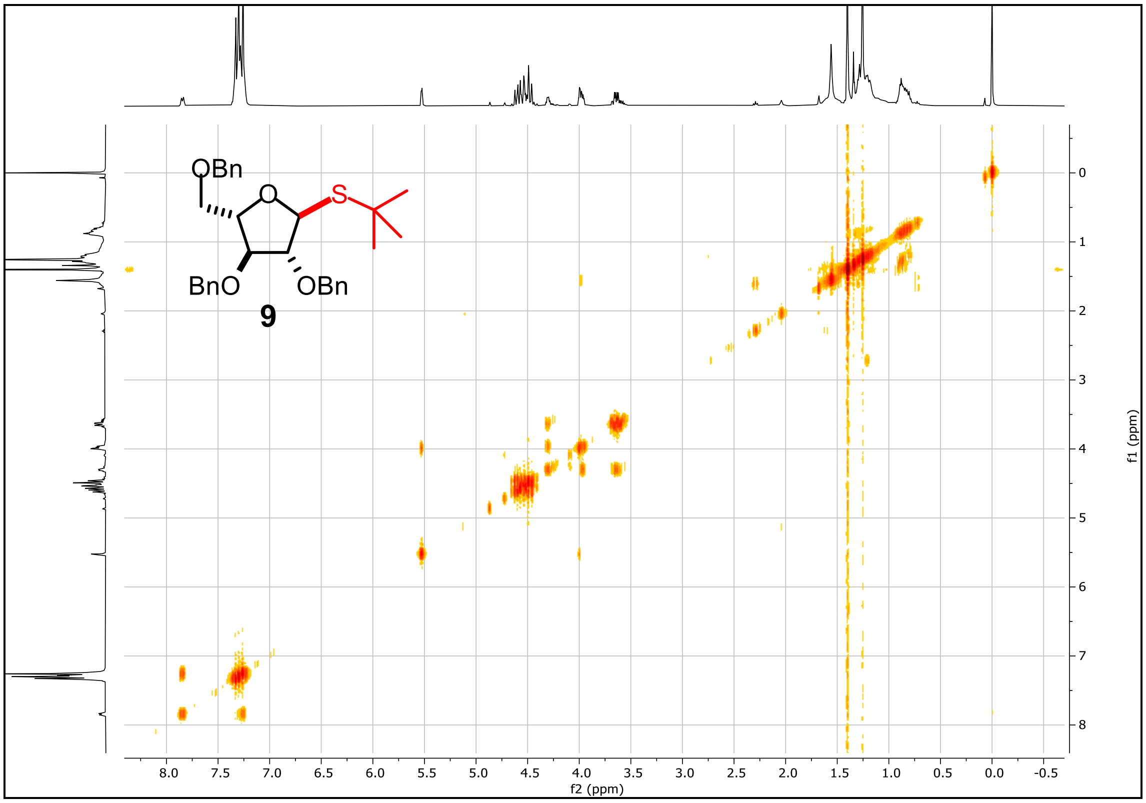

Figure S28. COSY spectrum of *tert*-butyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**9**) (400 MHz, $CDCl_3$).

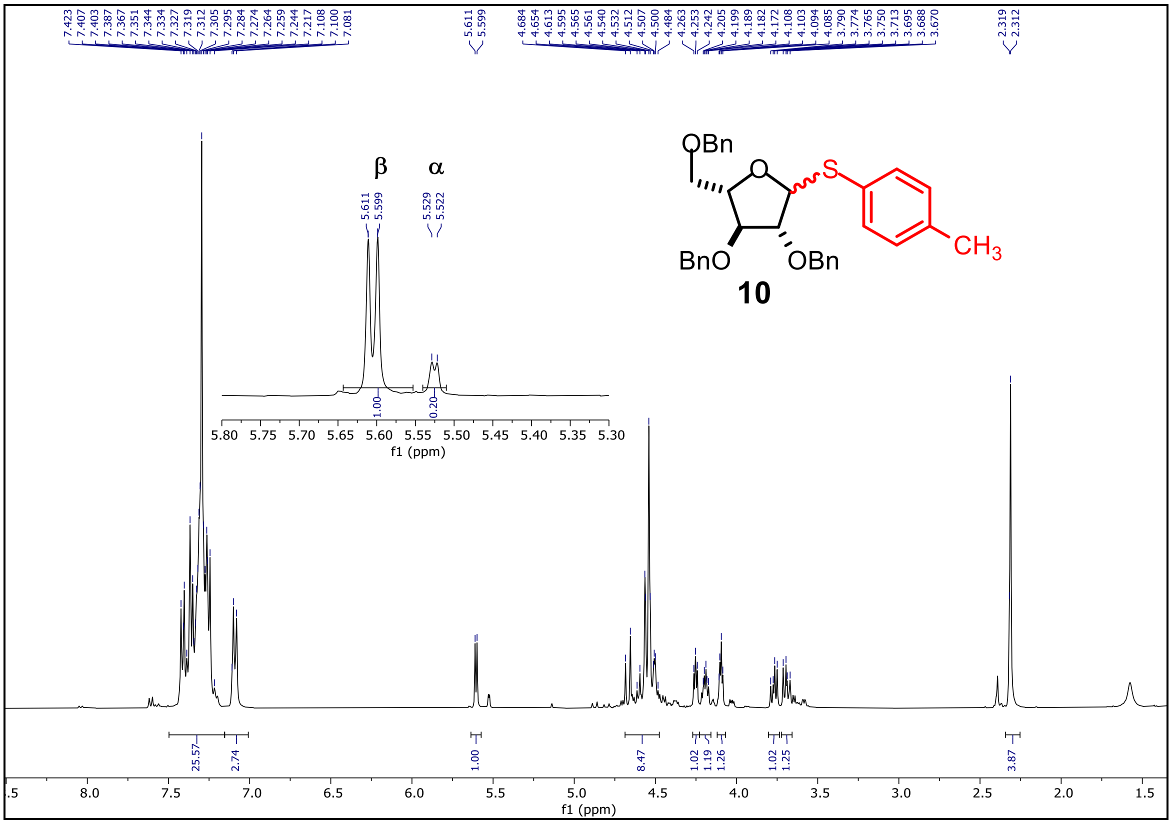

Figure S29. ^{1}H spectrum of 4-methylphenyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**10**) (400 MHz, CDCl$_3$).

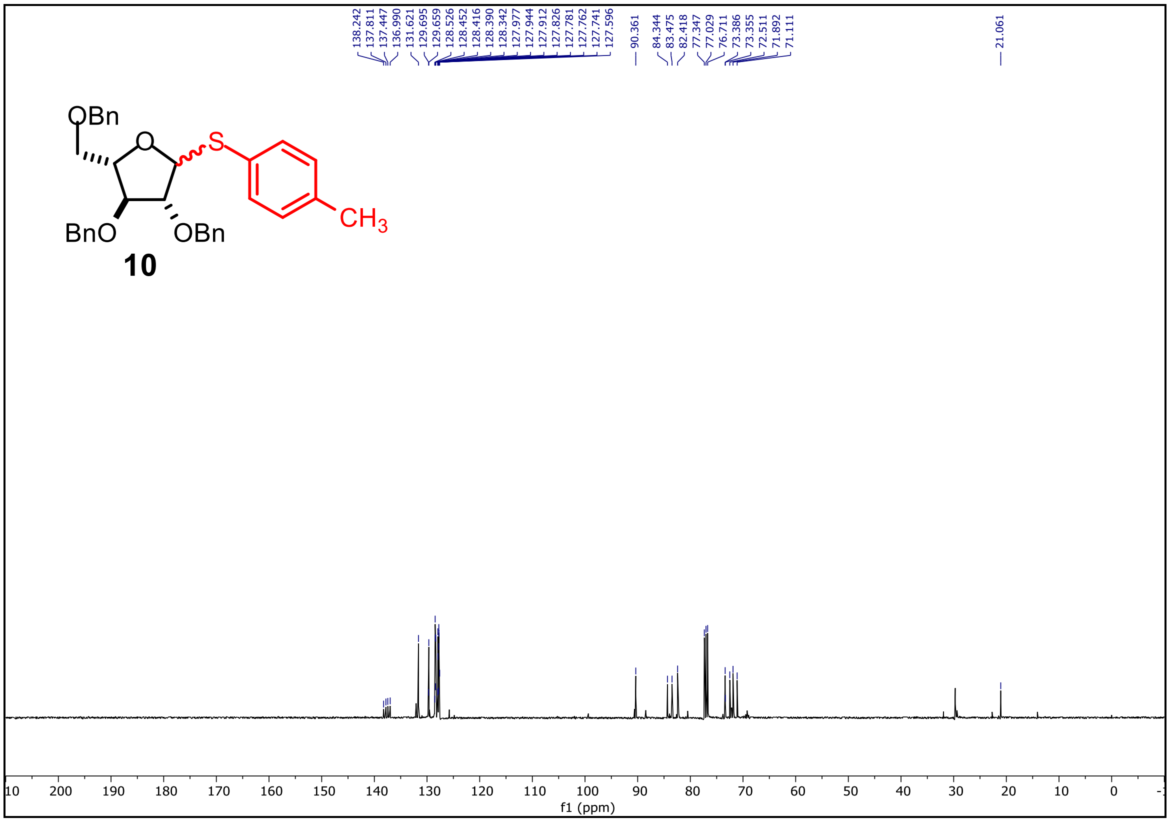

Figure S30. ^{13}C spectrum of 4-methylphenyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**10**) (101 MHz, CDCl$_3$).

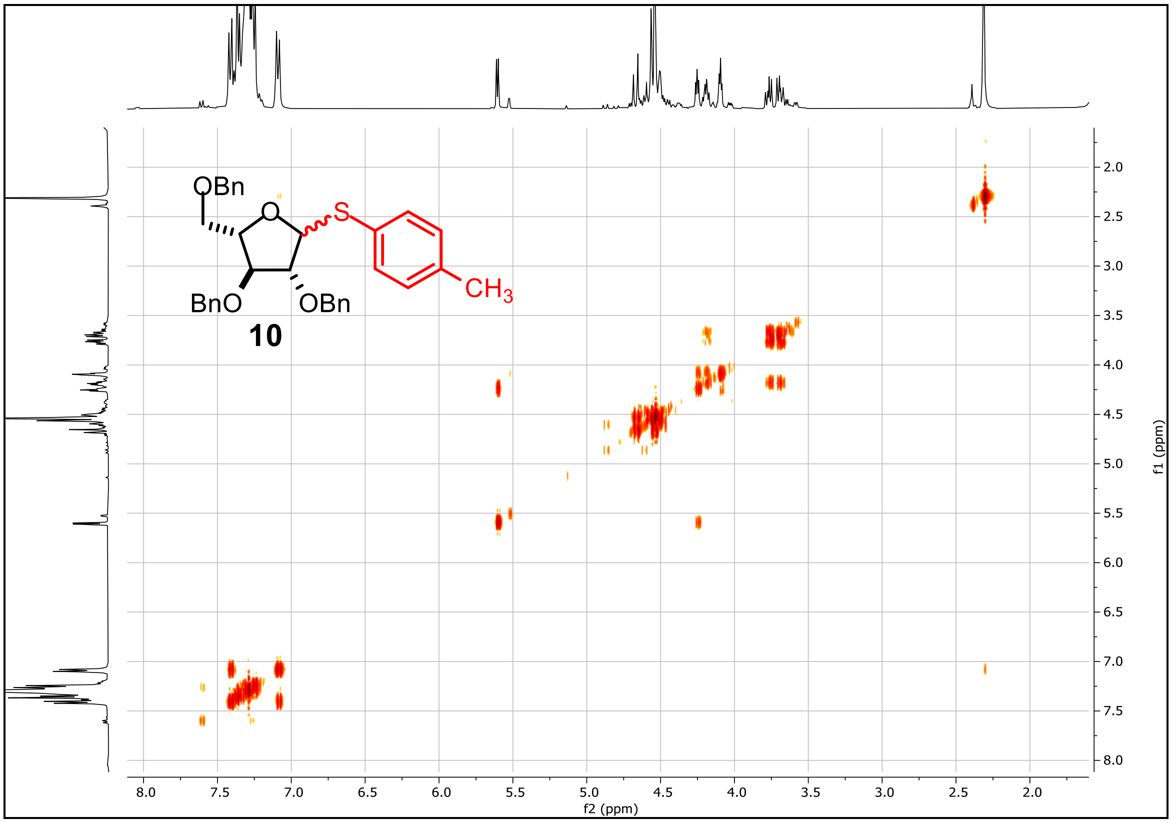

Figure S31. COSY spectrum of 4-methylphenyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**10**) (400 MHz, $CDCl_3$).

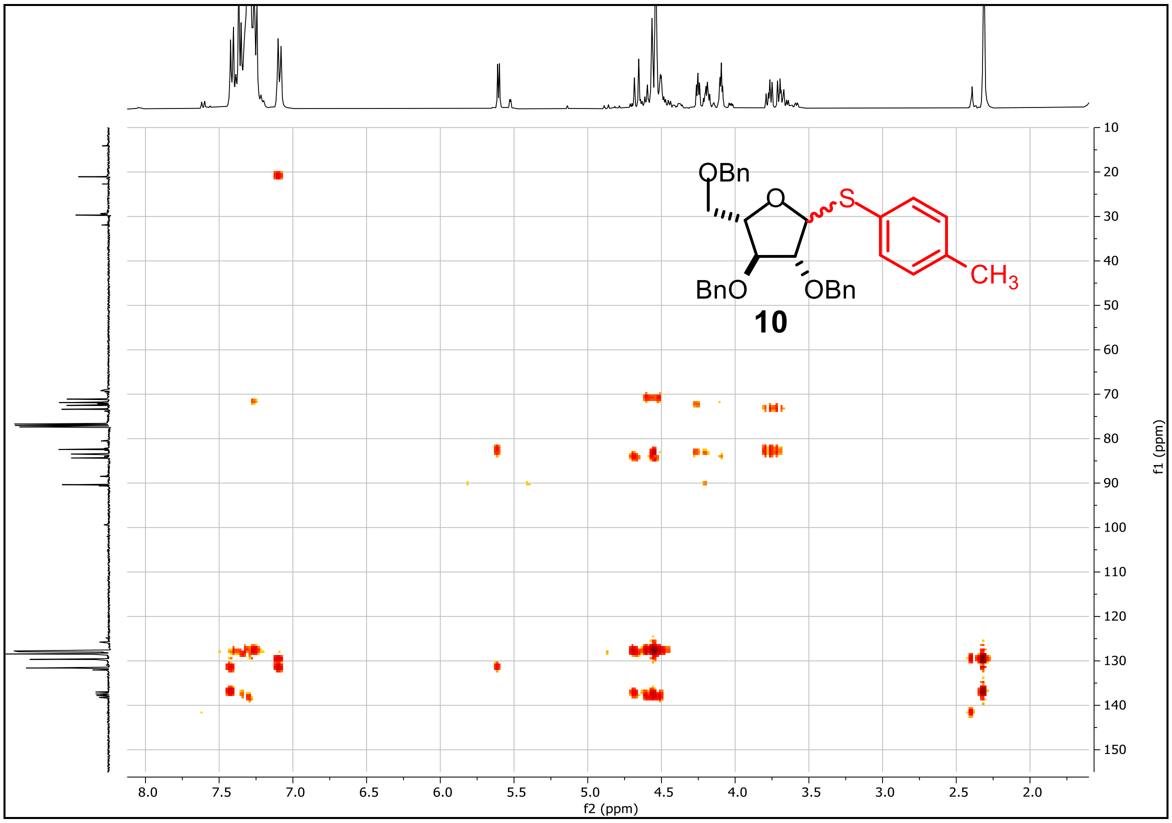

Figure S32. HMBC spectrum of 4-methylphenyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**10**) (400 MHz, $CDCl_3$).

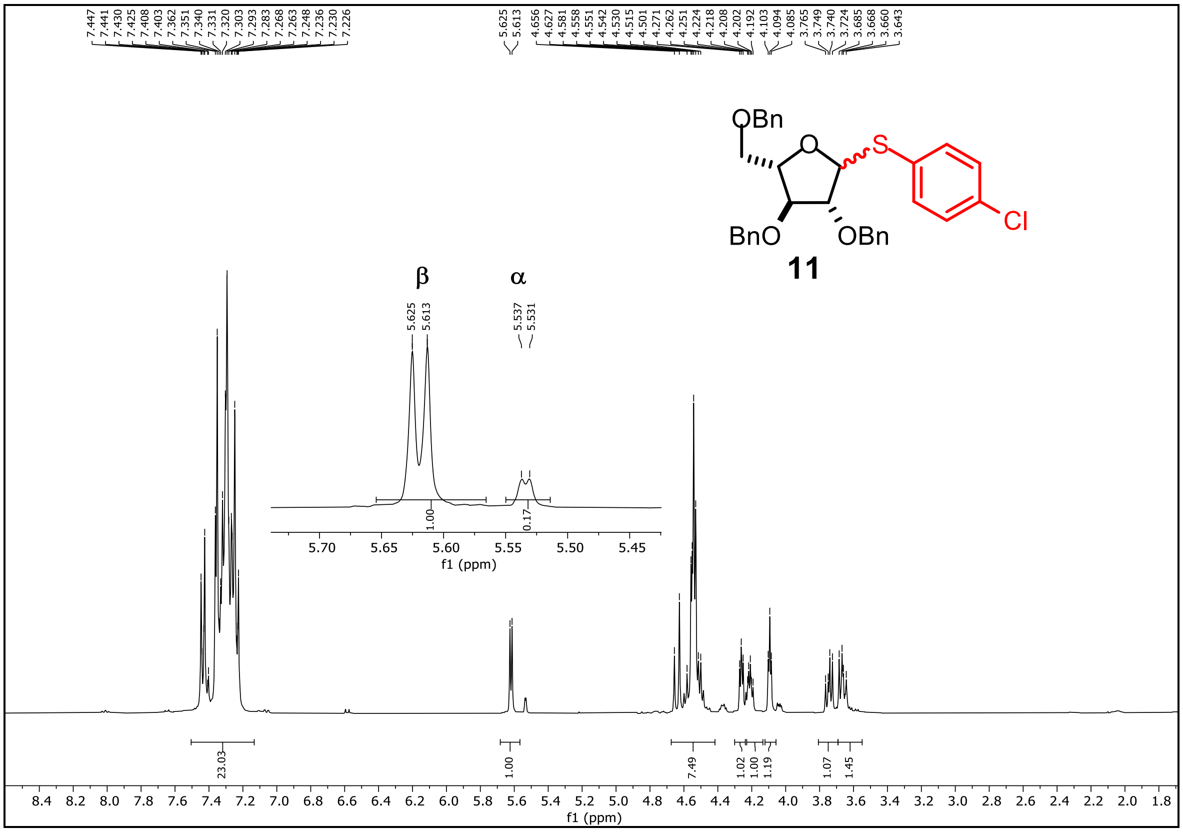

Figure S33. ^{1}H spectrum of 4-chlorophenyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**11**) (400 MHz, CDCl$_3$).

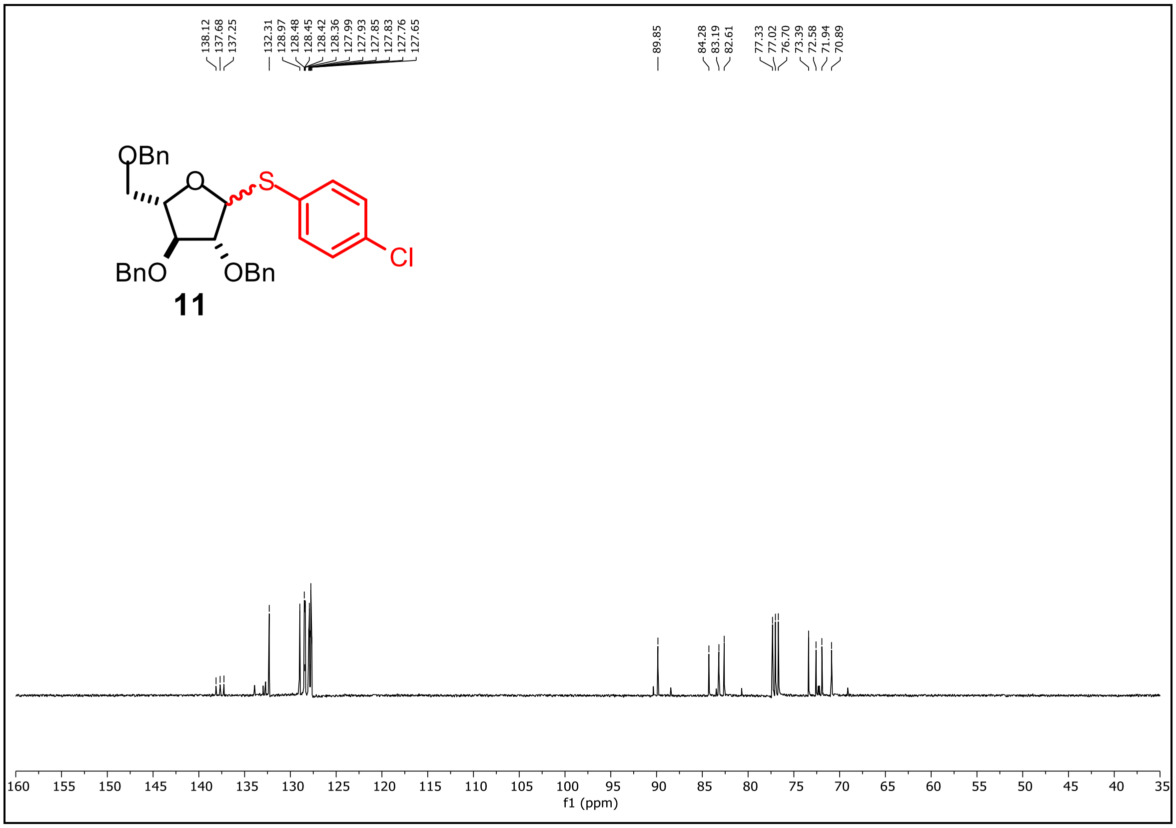

Figure S34. ^{13}C spectrum of 4-chlorophenyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-L-arabinofuranoside (**11**) (101 MHz, CDCl$_3$).

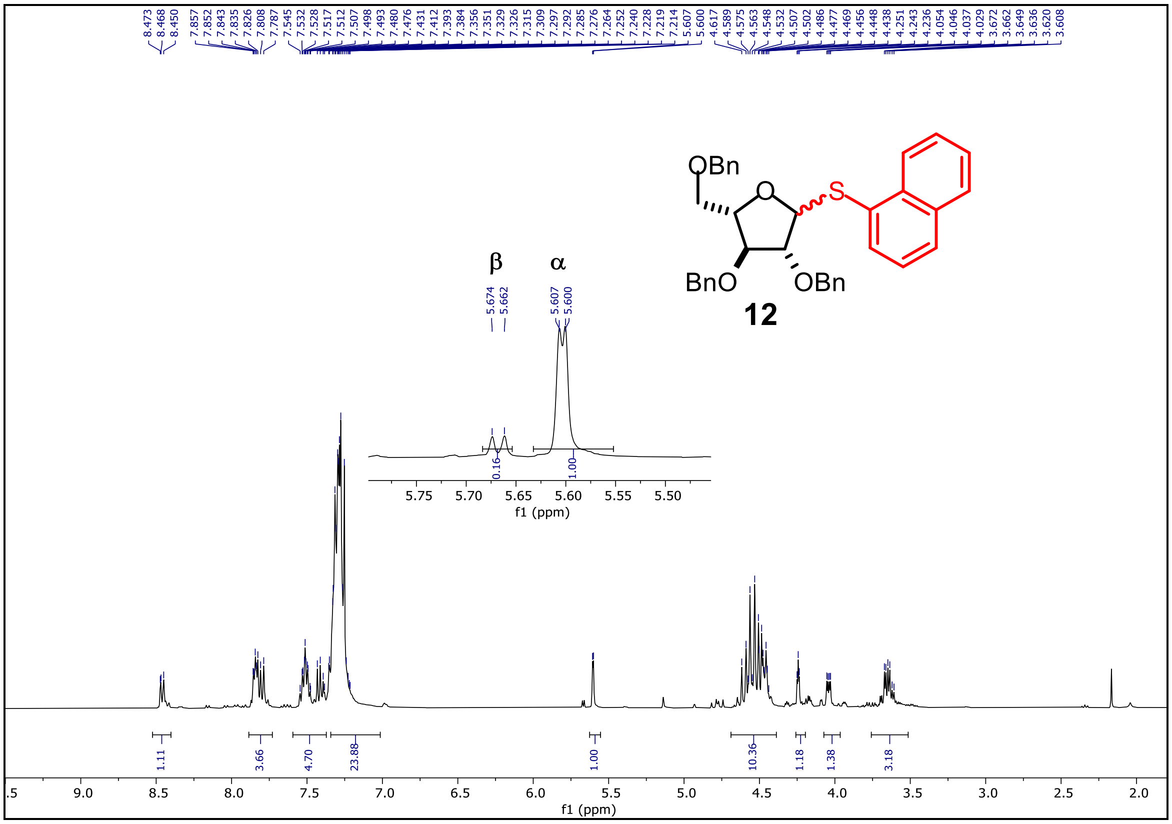

Figure S35. ^{1}H spectrum of 1-naphthyl 2,3,5-tri-*O*-benzyl-1-thio-**α**,β-L-arabinofuranoside (**12**) (400 MHz, CDCl$_3$).

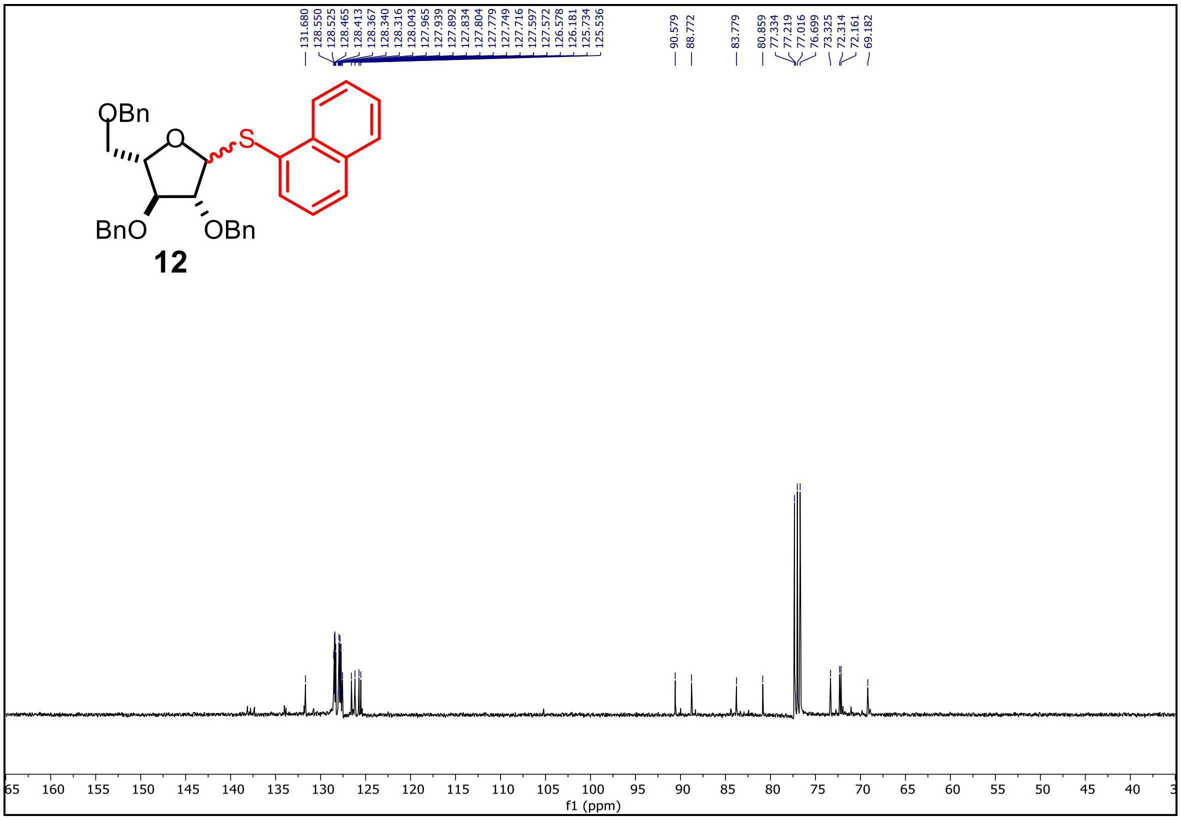

Figure S36. ^{13}C spectrum of 1-naphthyl 2,3,5-tri-*O*-benzyl-1-thio-**α**,β-L-arabinofuranoside (**12**) (101 MHz, CDCl$_3$).

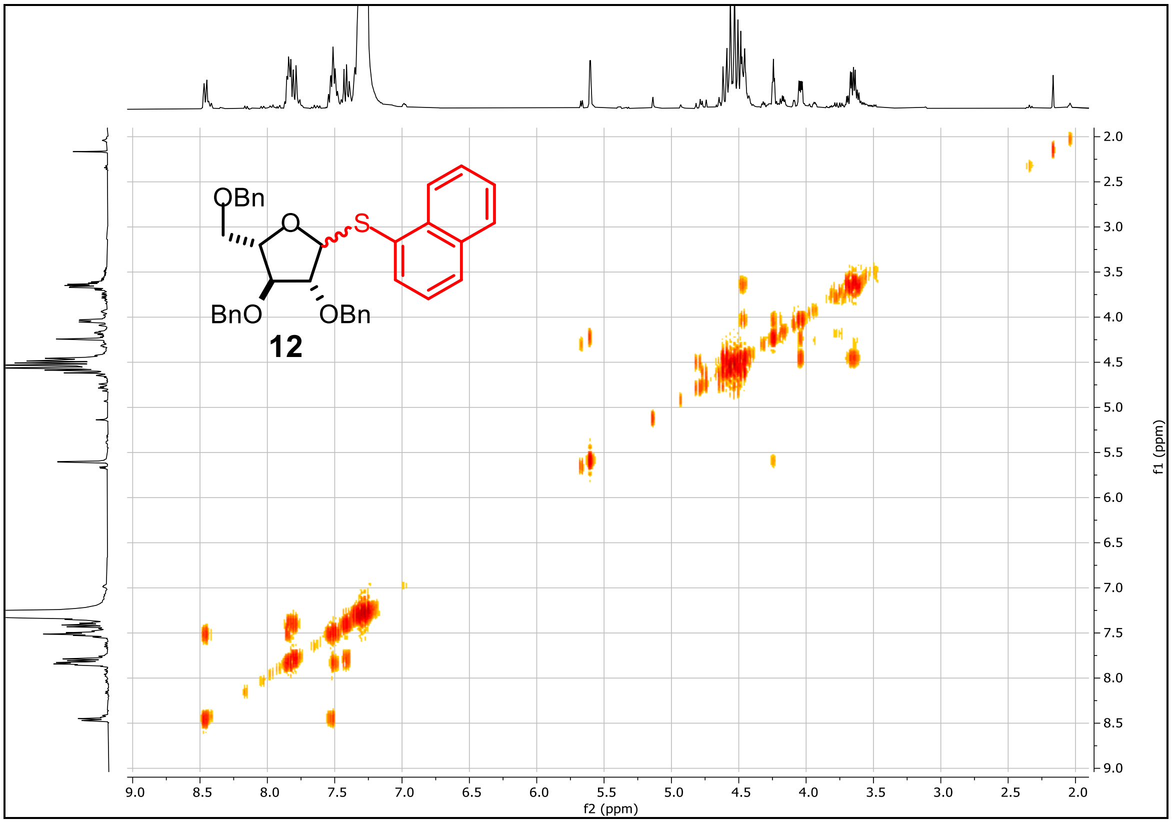

Figure S37. COSY spectrum of 1-naphthyl 2,3,5-tri-*O*-benzyl-1-thio-α,β-L-arabinofuranoside (**12**) (400 MHz, $CDCl_3$).

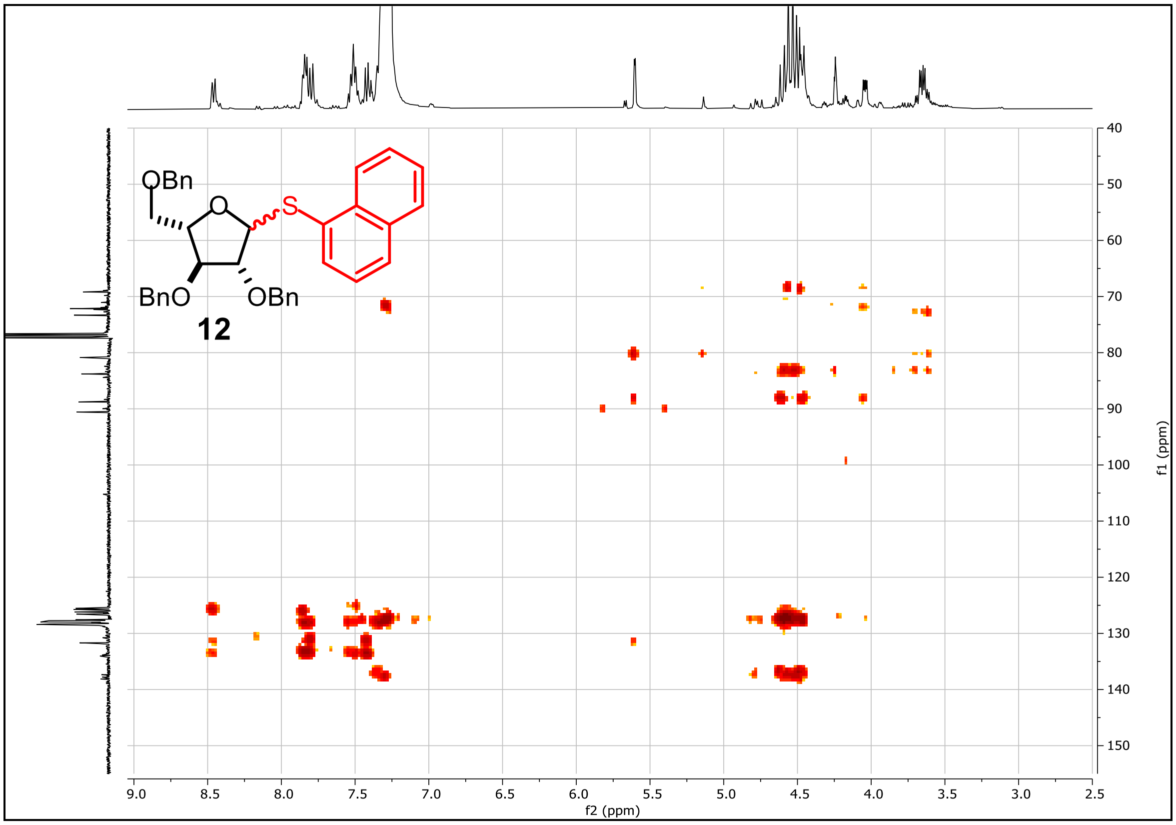

Figure S38. HMBC spectrum of 1-naphthyl 2,3,5-tri-*O*-benzyl-1-thio-α,β-L-arabinofuranoside (**12**) (400 MHz, $CDCl_3$).

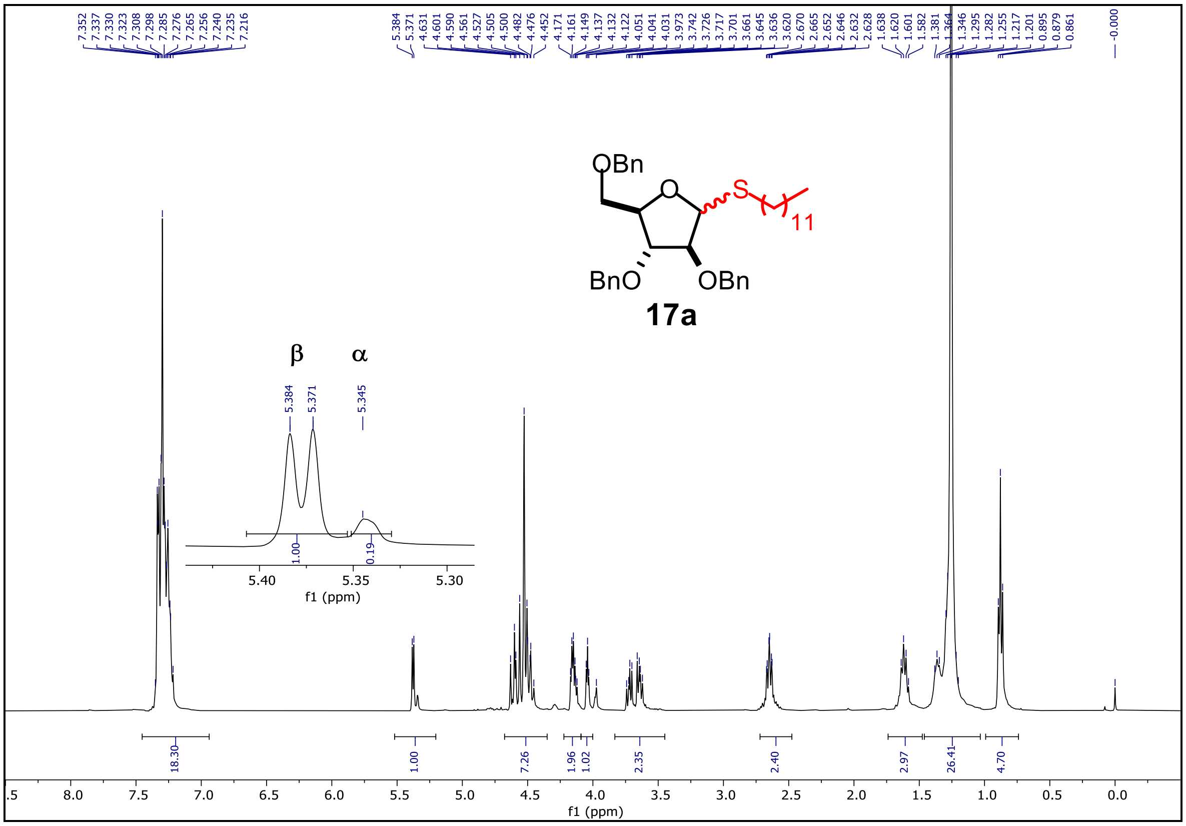

Figure S39. ^{1}H NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-D-arabinofuranoside (**17a**) (400 MHz, CDCl$_3$).

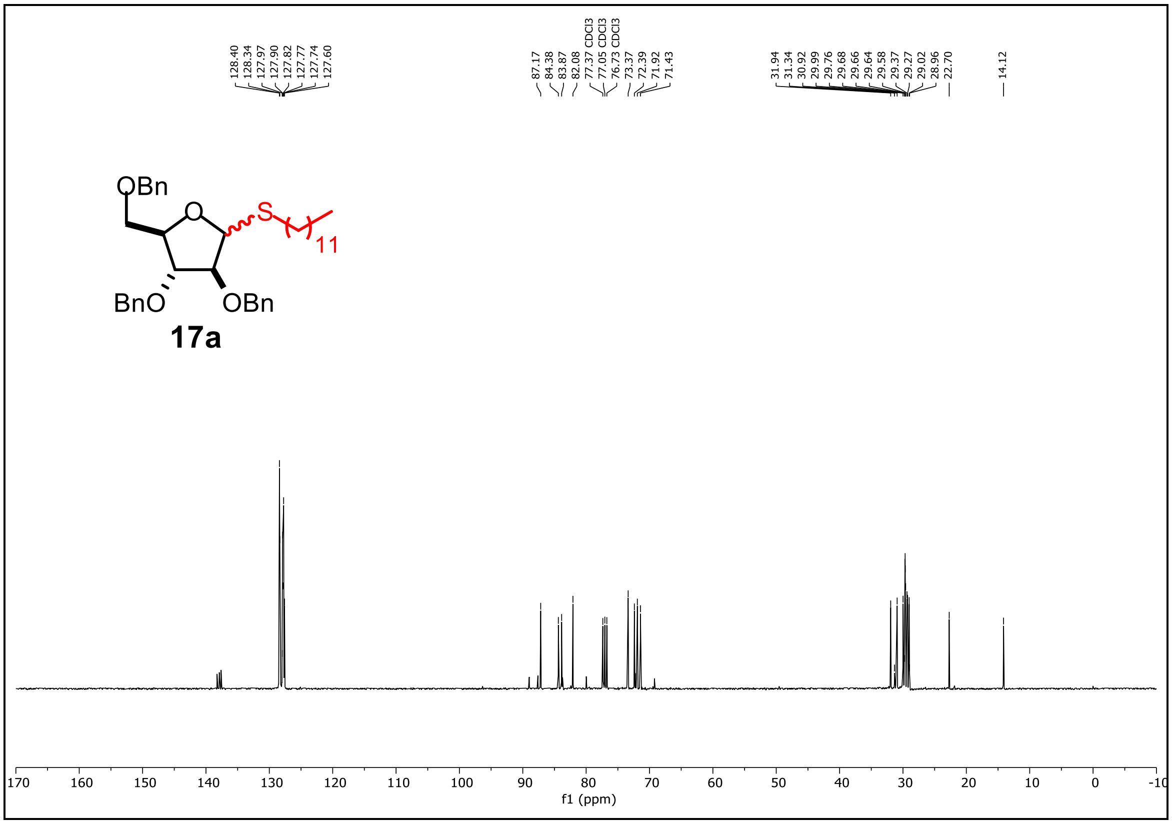

Figure S40. ^{13}C NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-D-arabinofuranoside (**17a**) (101 MHz, CDCl$_3$).

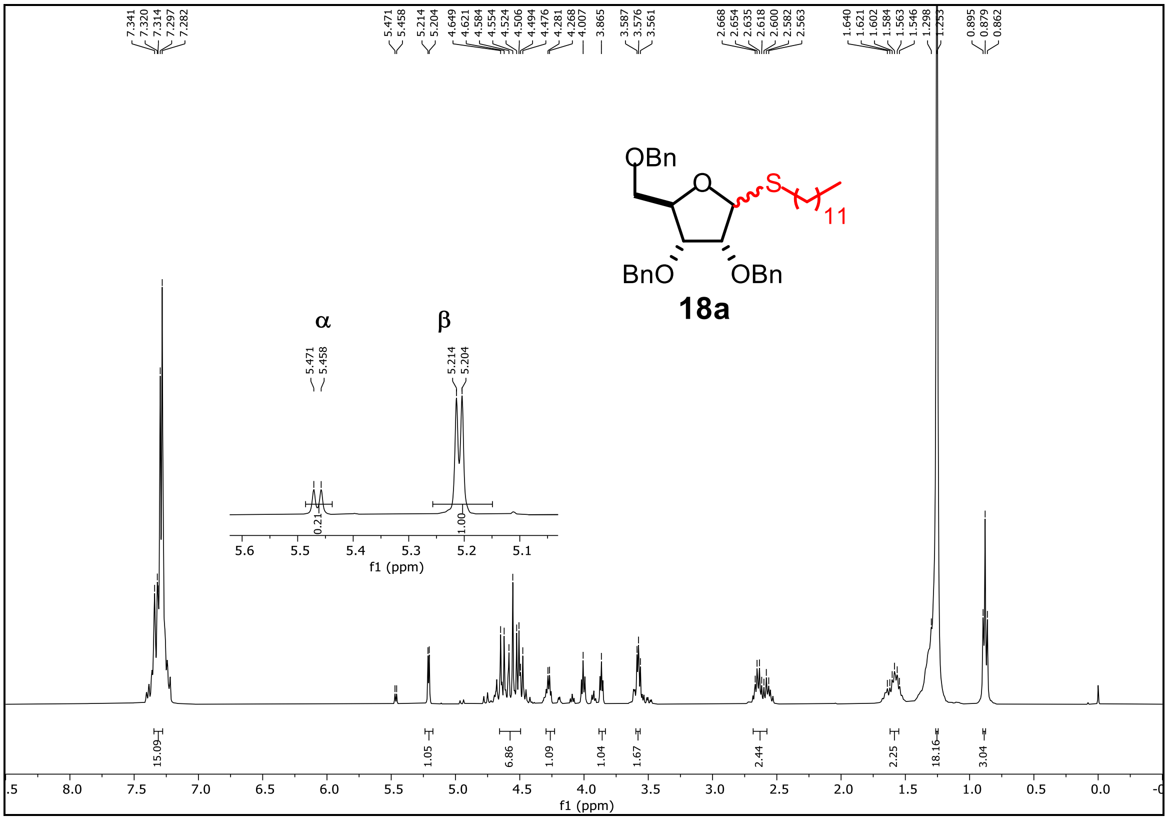

Figure S41. ^{1}H NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-D-ribofuranoside (**18a**) (400 MHz, CDCl$_3$).[1, 2]

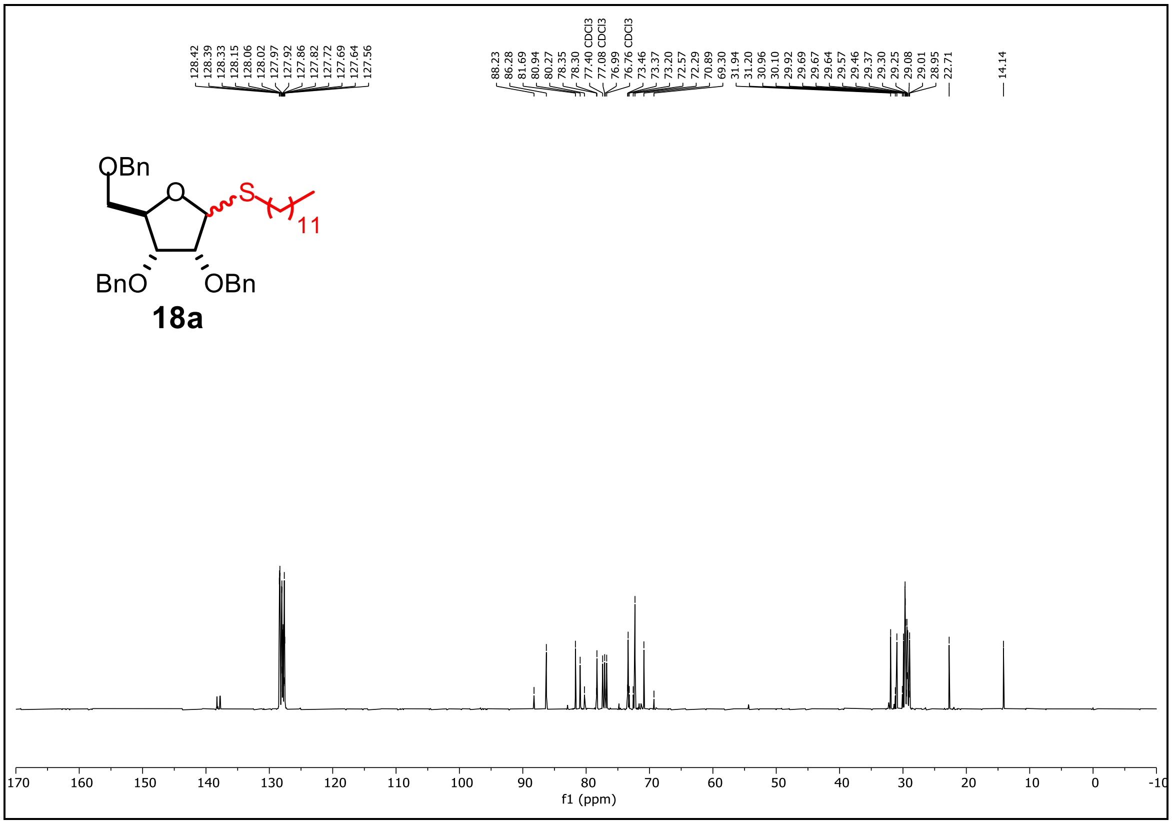

Figure S42. ^{13}C NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,**β**-D-ribofuranoside (**18a**) (101 MHz, CDCl$_3$).

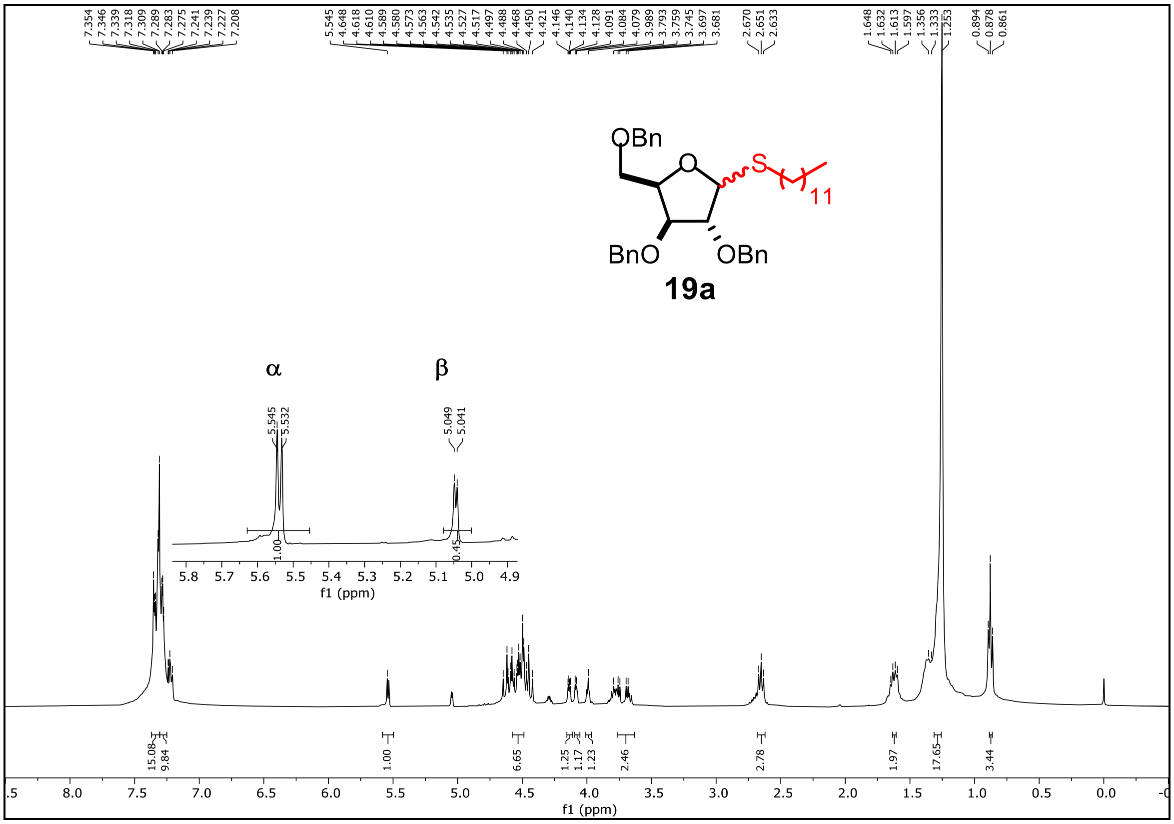

Figure S43. ^{1}H NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,β-D-xylofuranoside (**19a**) (400 MHz, $CDCl_3$).[3]

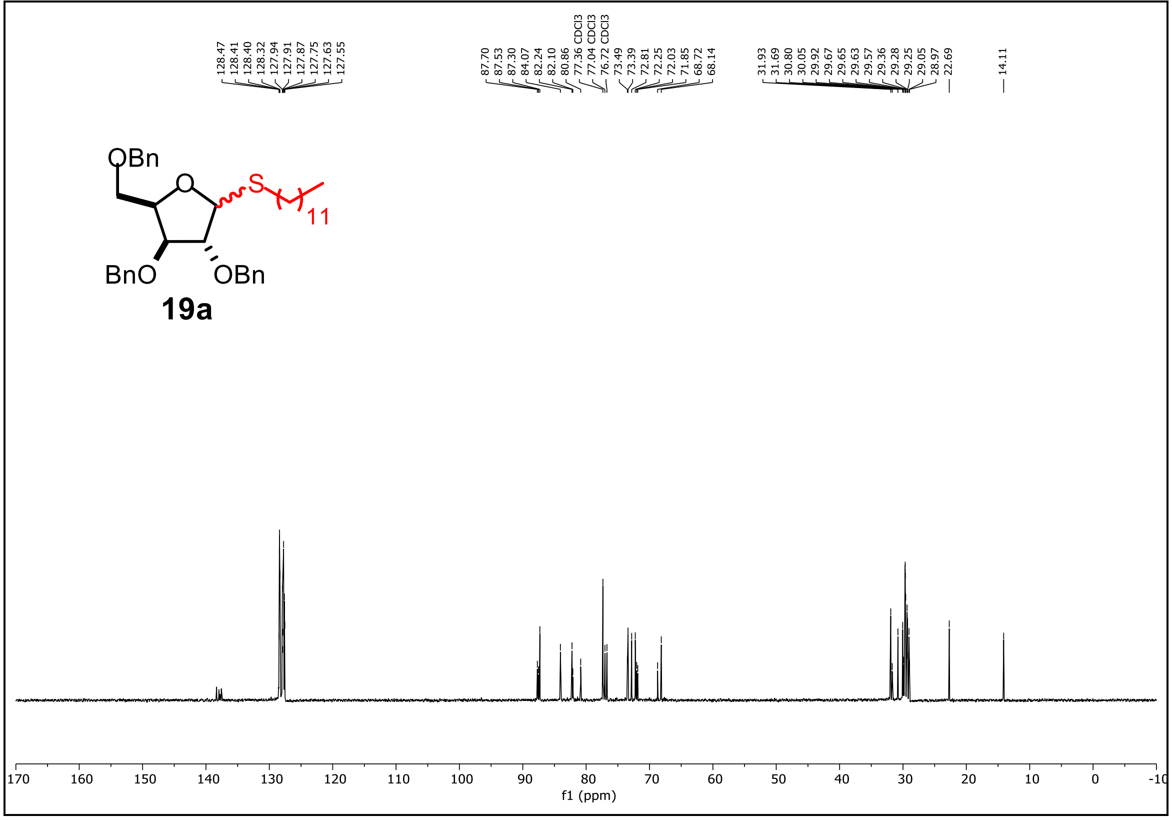

Figure S44. ^{13}C NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α,β-D-xylofuranoside (**19a**) (101 MHz, $CDCl_3$).

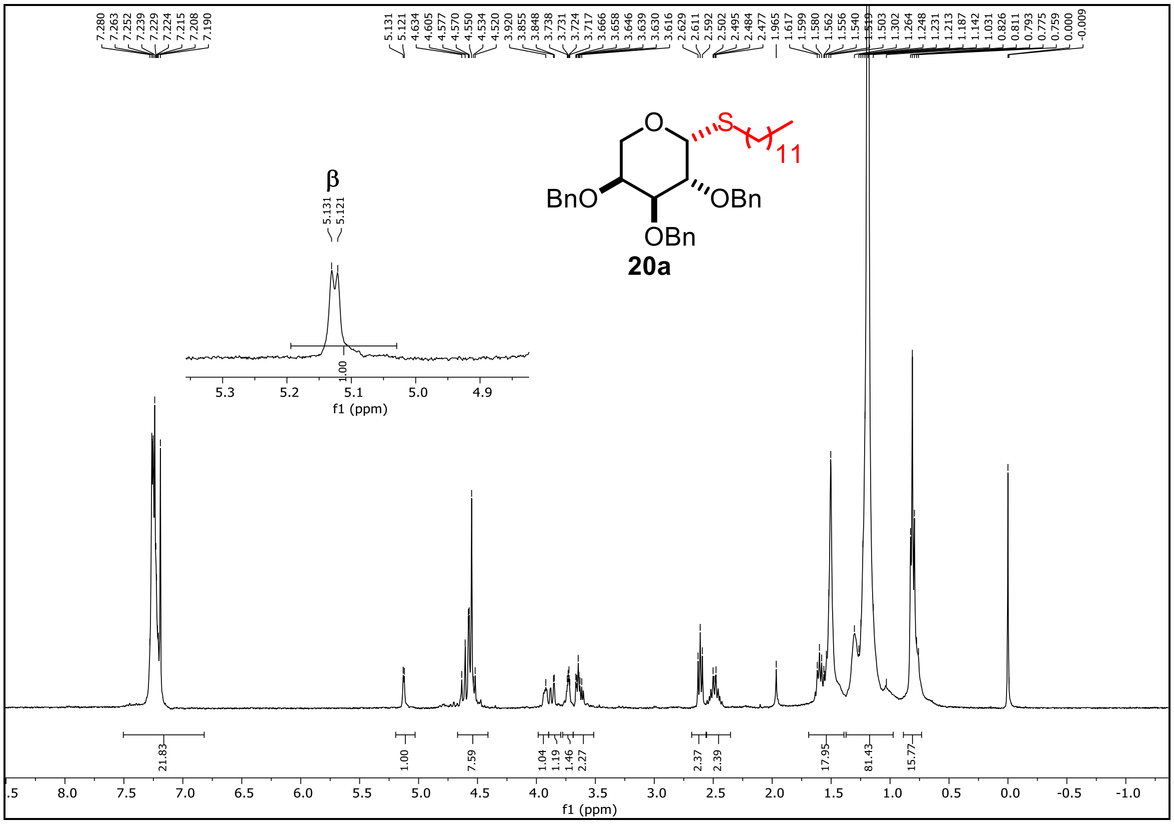

Figure S45. ^{1}H NMR spectrum of dodecyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-arabinopyranoside (**20a**) (400 MHz, $CDCl_3$).[4]

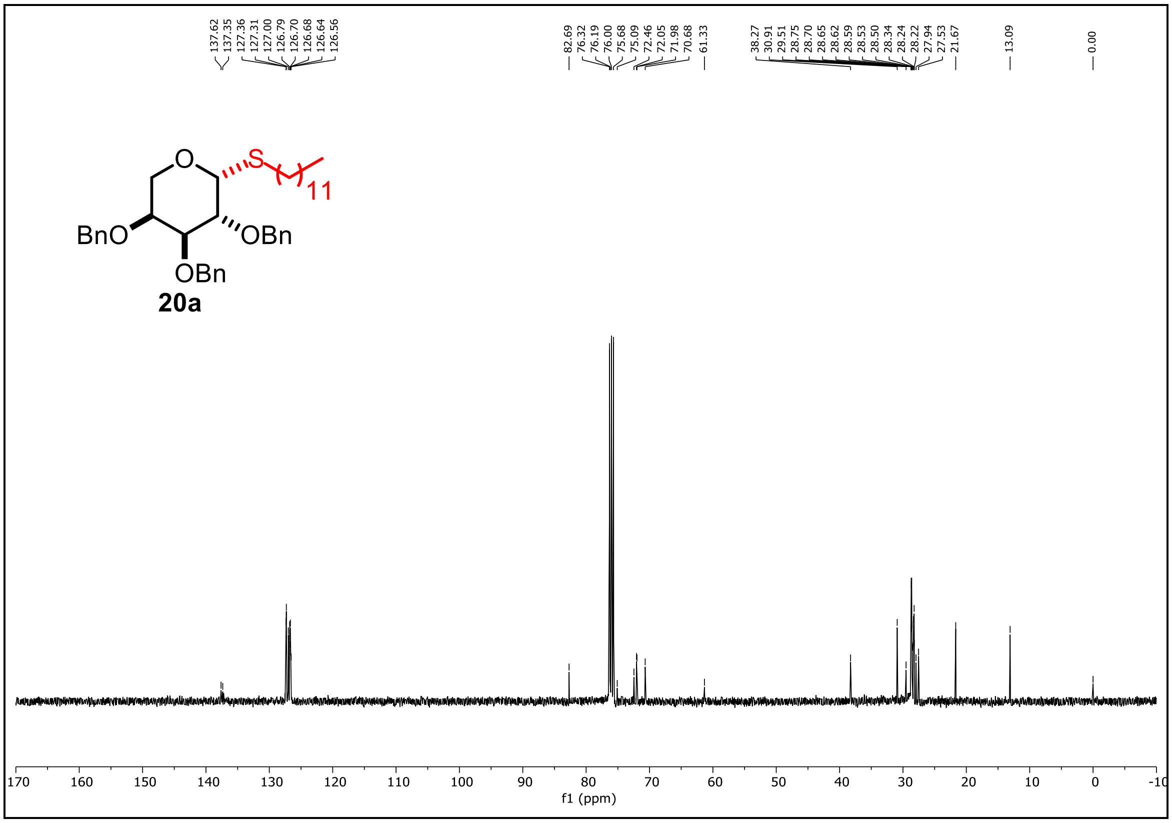

Figure S46. ^{13}C NMR spectrum of dodecyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-arabinopyranoside (**20a**) (101 MHz, $CDCl_3$).

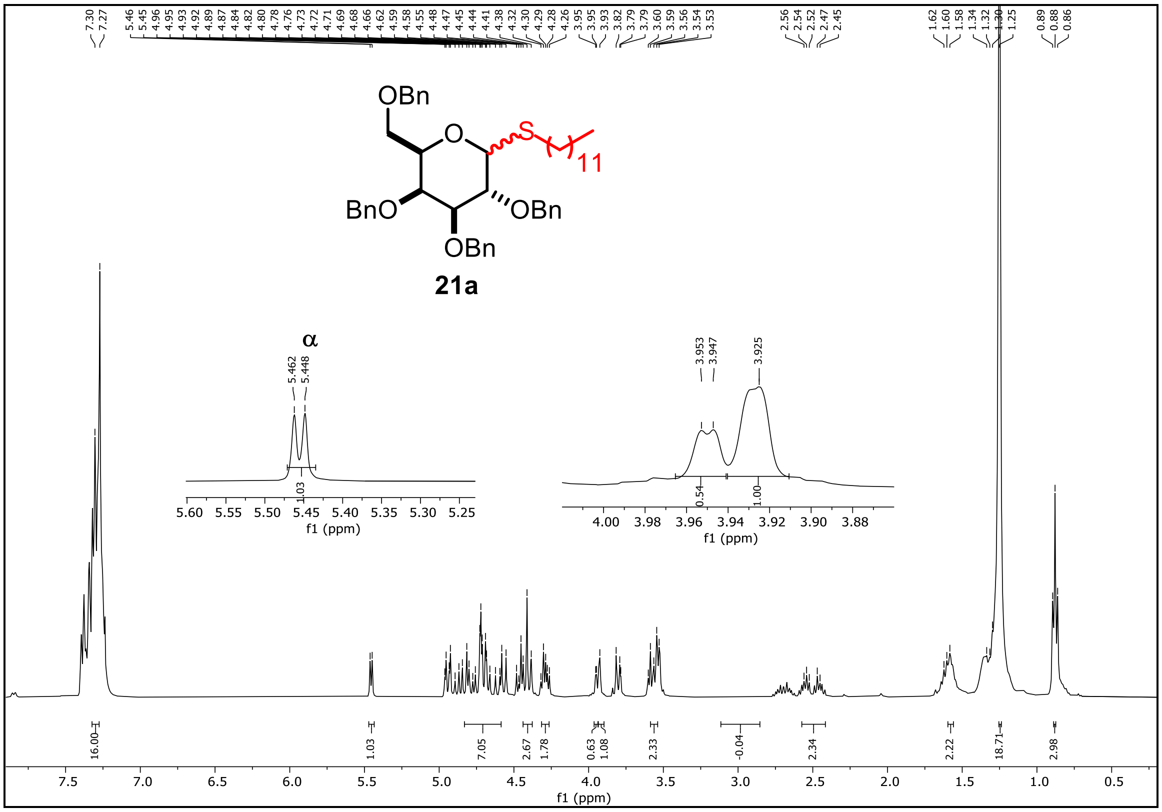

Figure S47. ^{1}H NMR spectrum of dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-**α**,β-D-galactopyranoside (**21a**) (400 MHz, $CDCl_3$).[5]

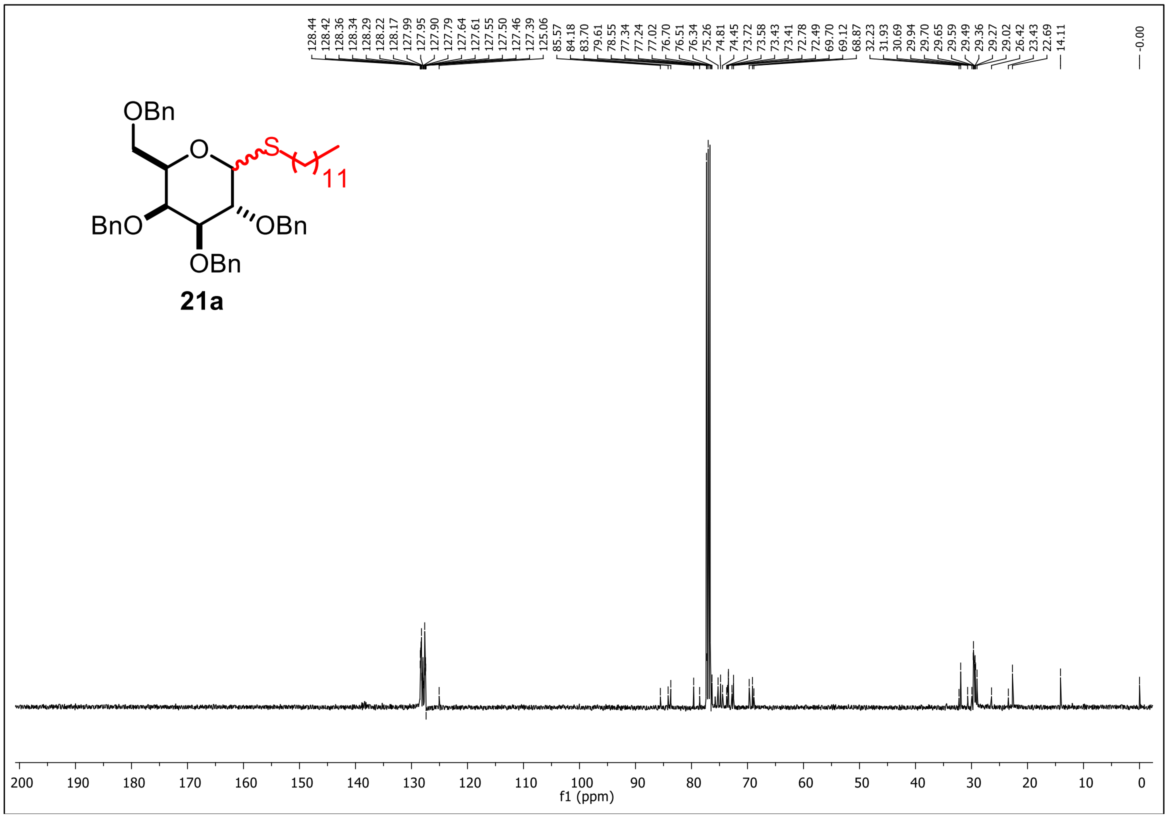

Figure S48. ^{13}C NMR spectrum of dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-**α**,β-D-galactopyranoside (**21a**) (101 MHz, $CDCl_3$).

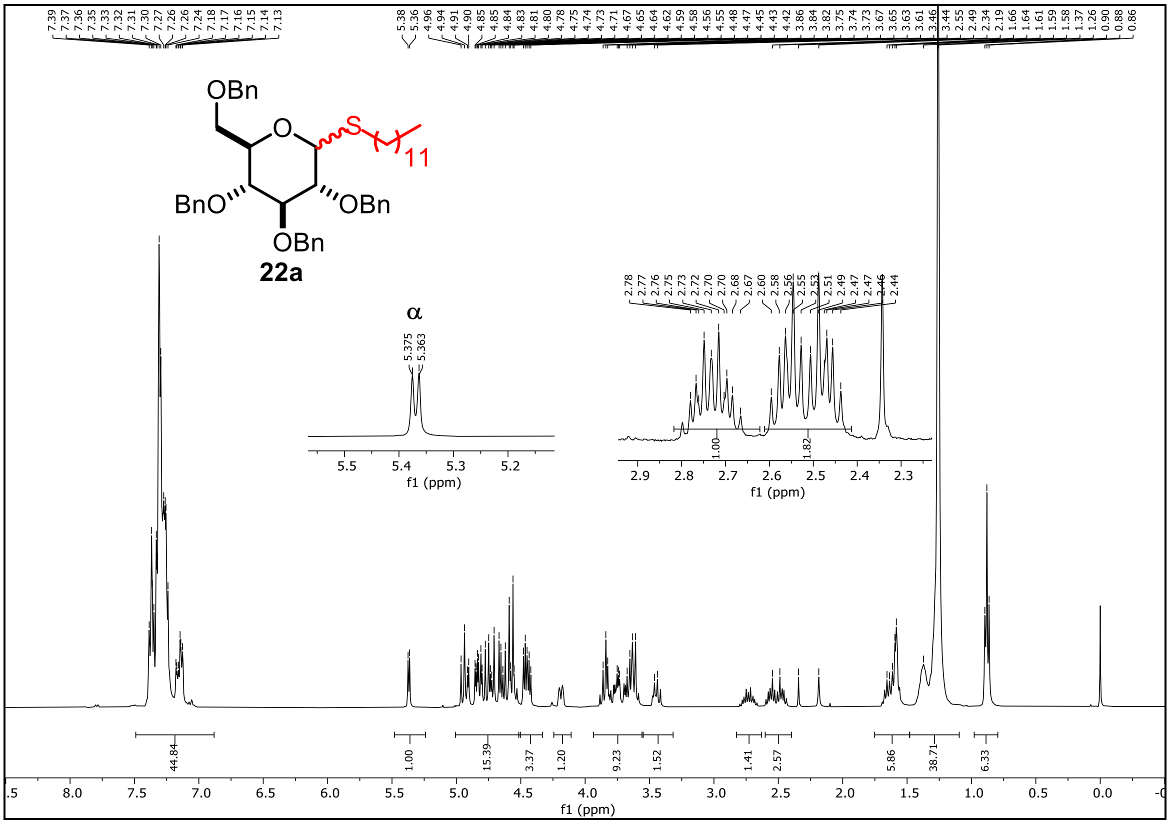

Figure S49. ^{1}H NMR spectrum of dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-**α**,β-D-glucopyranoside (**22a**) (400 MHz, $CDCl_3$).[6]

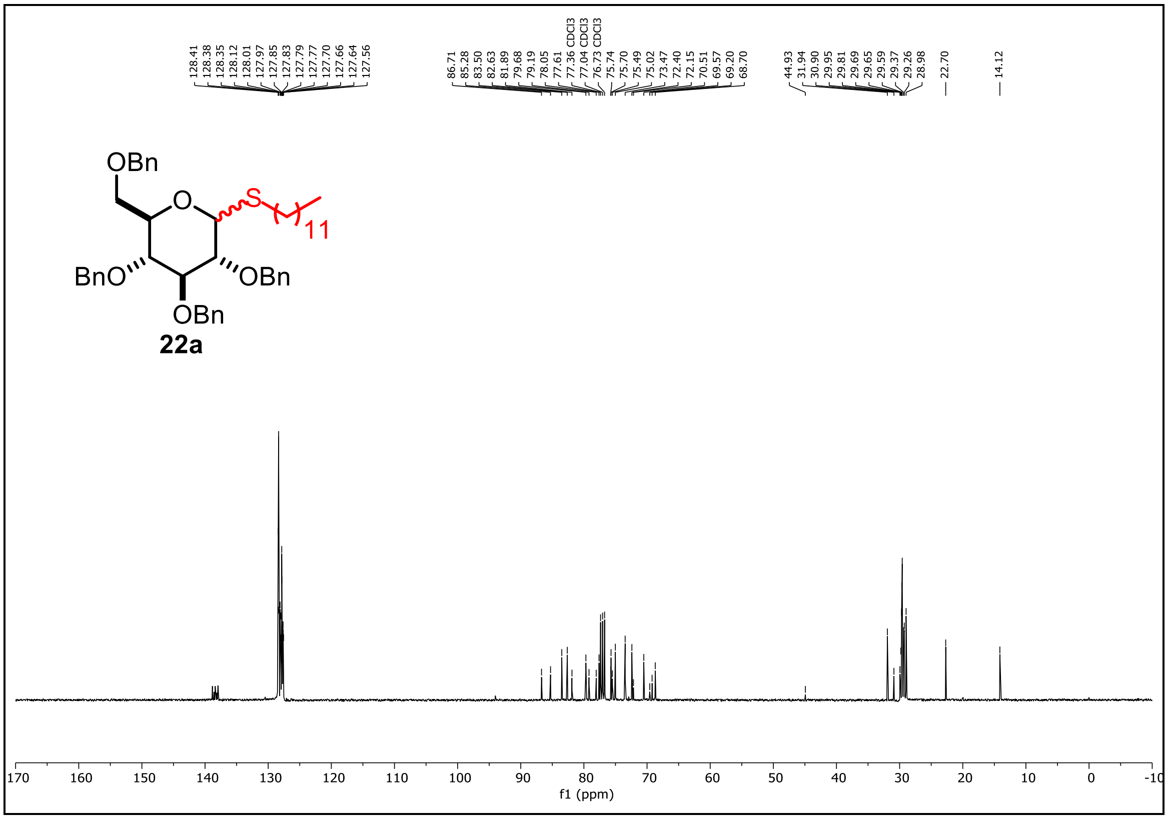

Figure S50. ^{13}C NMR spectrum of dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-**α**,β-D-glucopyranoside (**22a**) (101 MHz, $CDCl_3$).

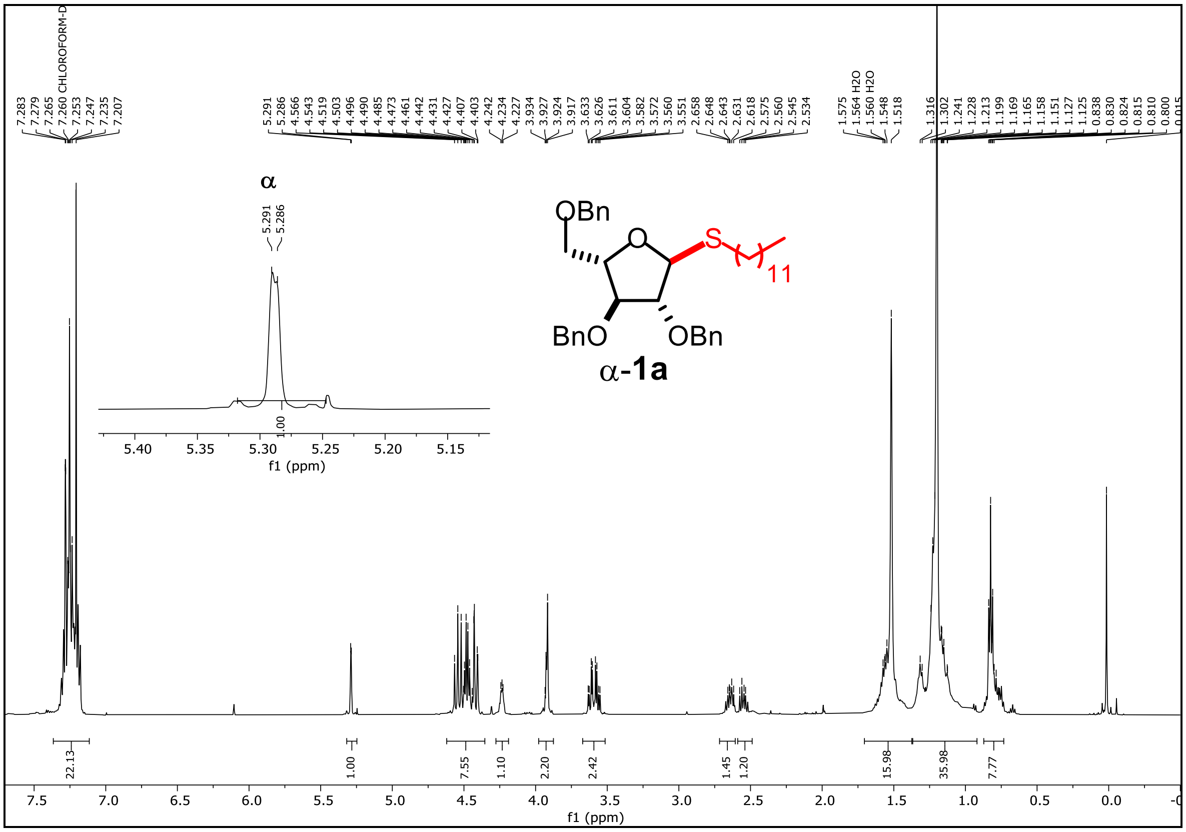

Figure S51. ^{1}H NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**1a**) (500 MHz, $CDCl_3$).

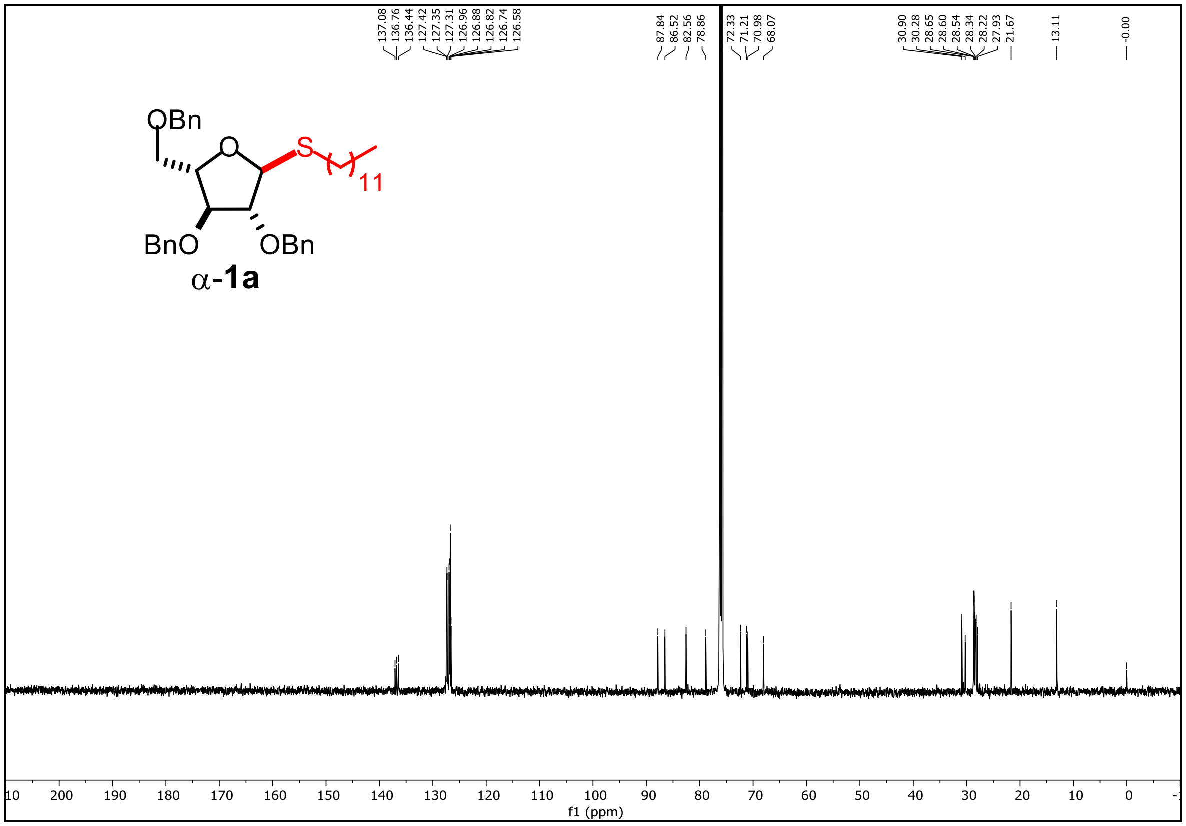

Figure S52. ^{13}C NMR spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**1a**) (126 MHz, $CDCl_3$).

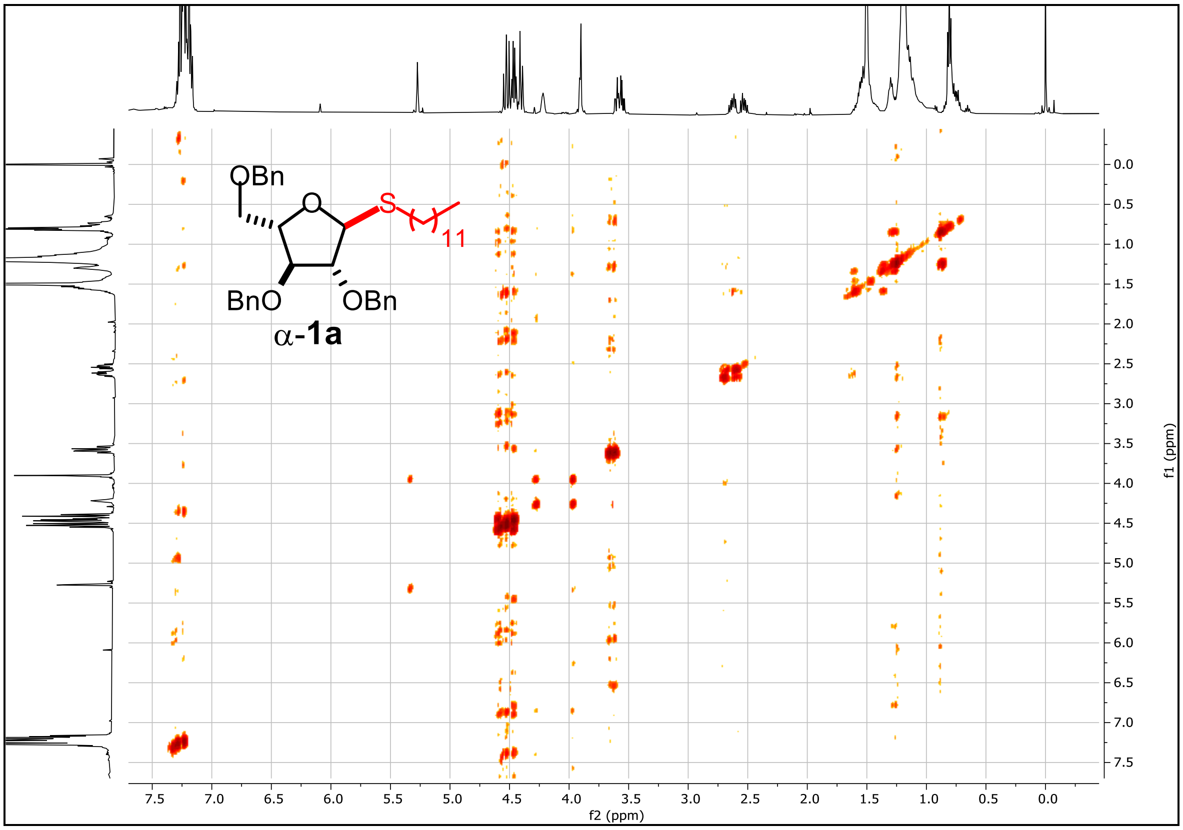

Figure S53. COSY spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**1a**) (500 MHz, $CDCl_3$).

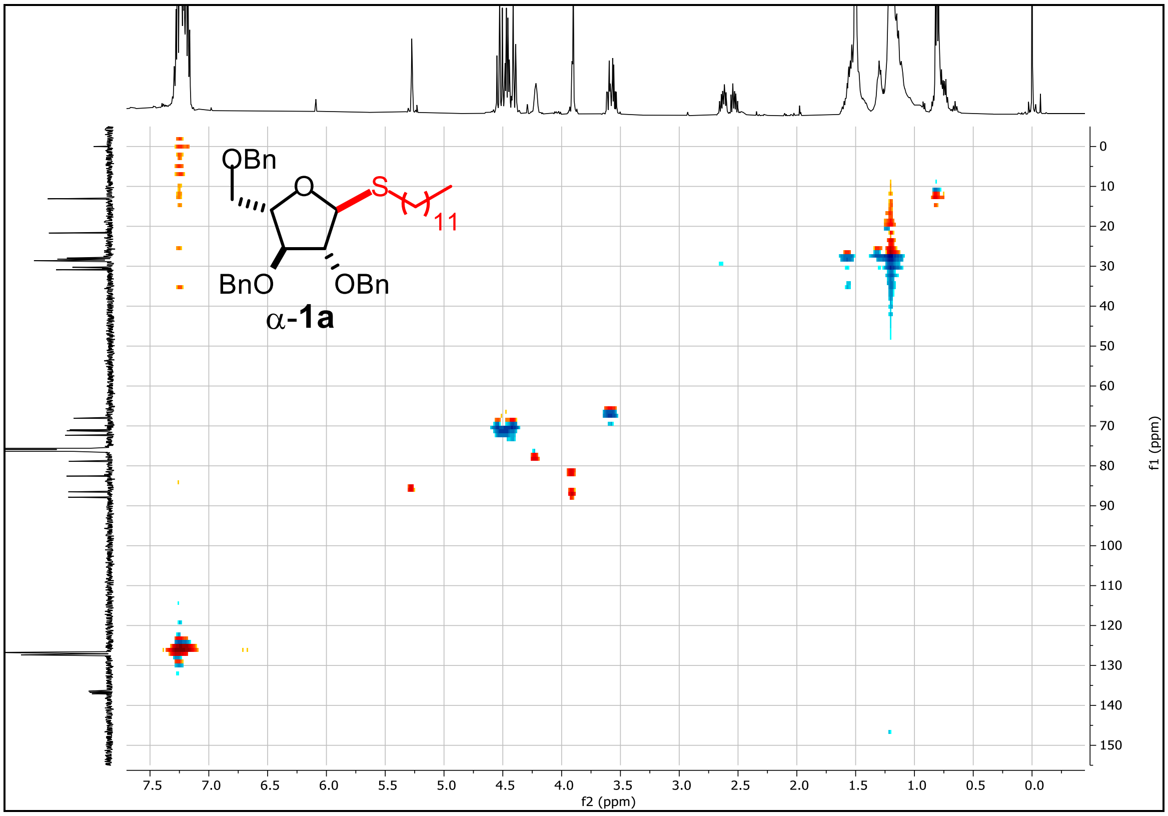

Figure S54. HSQC spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**1a**) (500 MHz, $CDCl_3$).

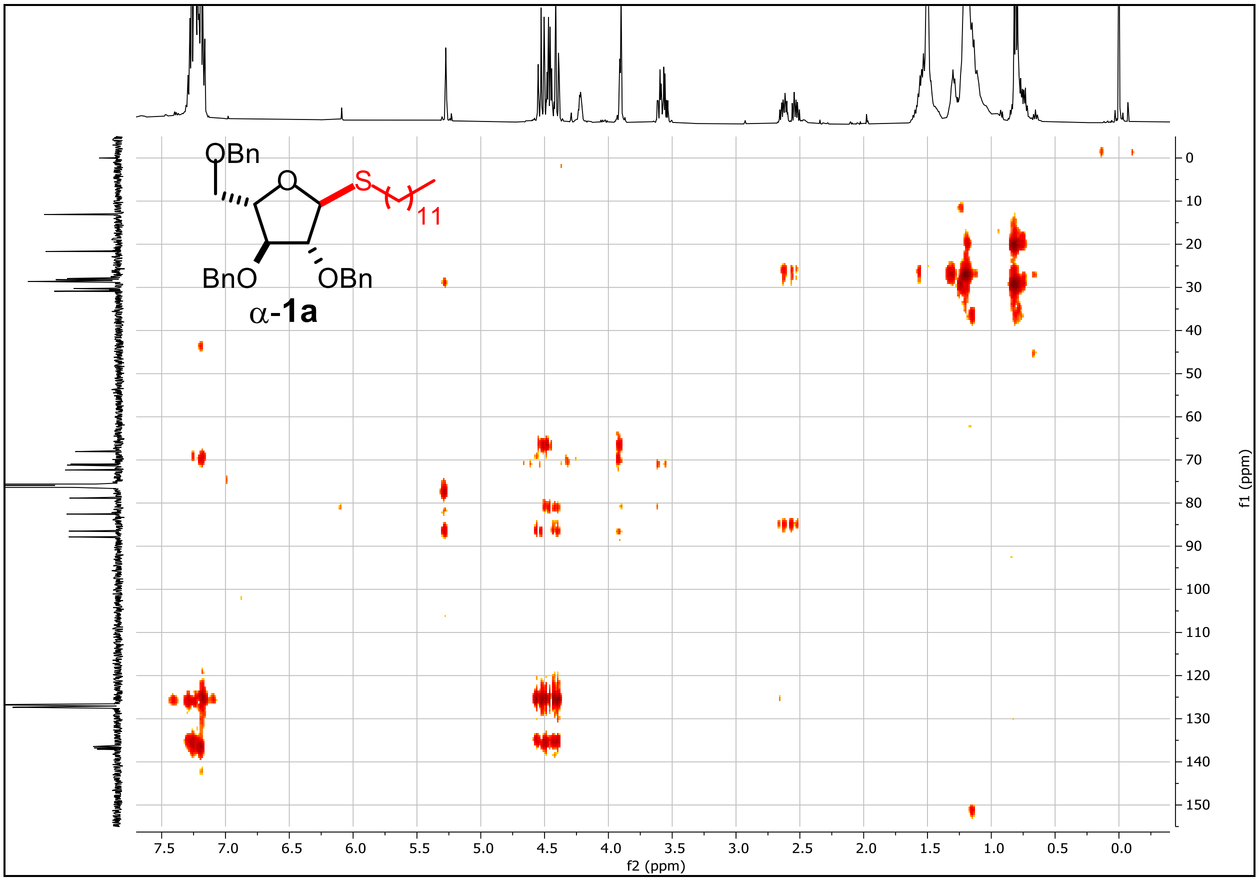

Figure S55. HMBC spectrum of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (**1a**) (500 MHz, $CDCl_3$).

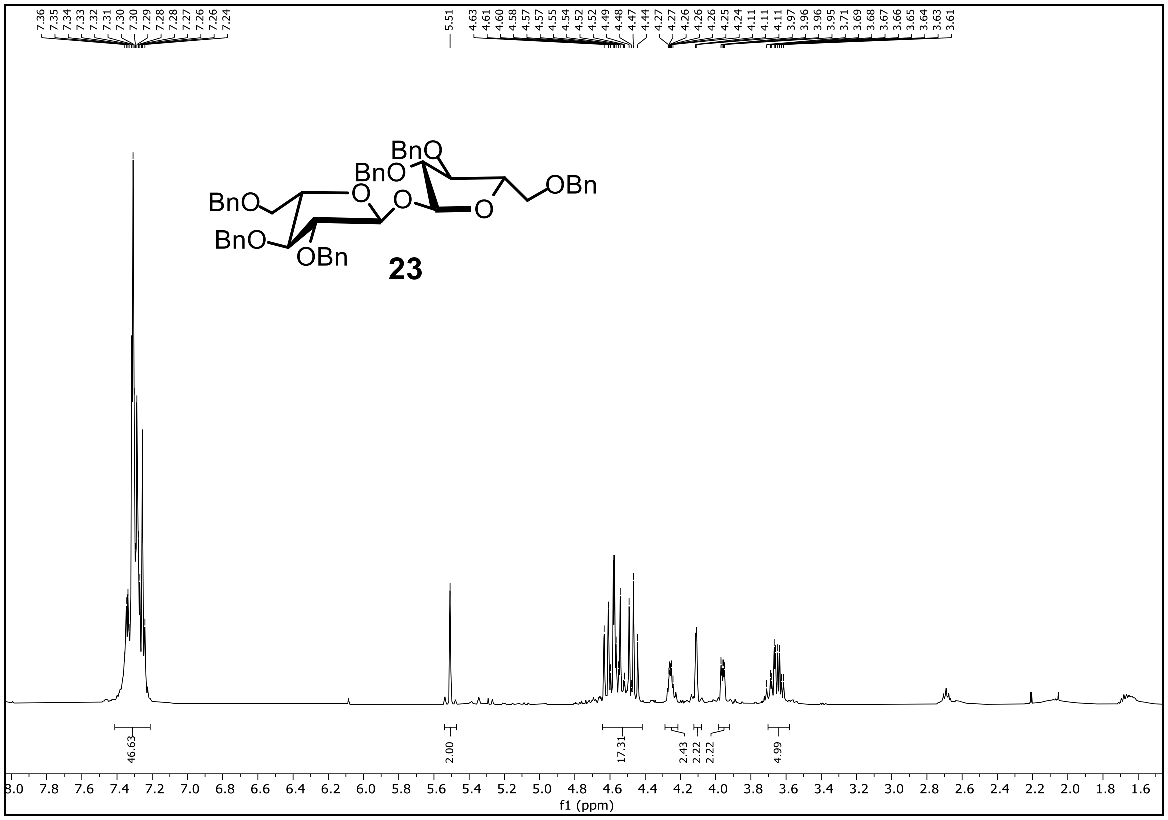

Figure S56. ^{1}H NMR spectrum of 2,3,5,2’,3’,5’-hexa-*O*-benzyl-α,α- L-arabinofuranoside (**23**) (500 MHz, CDCl$_3$).

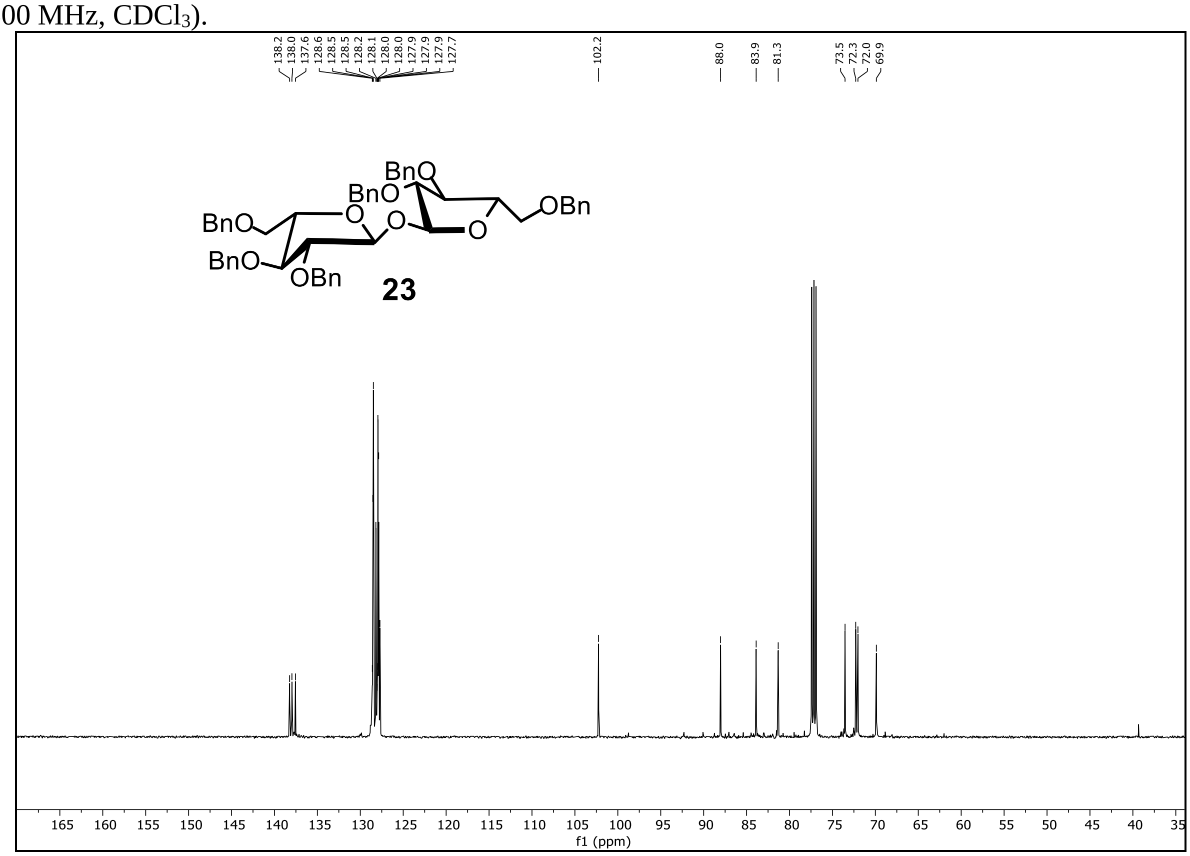

Figure S57. ^{13}C NMR spectrum of 2,3,5,2’,3’,5’-hexa-*O*-benzyl-α,α- L-arabinofuranoside (**23**) (126 MHz, CDCl$_3$).

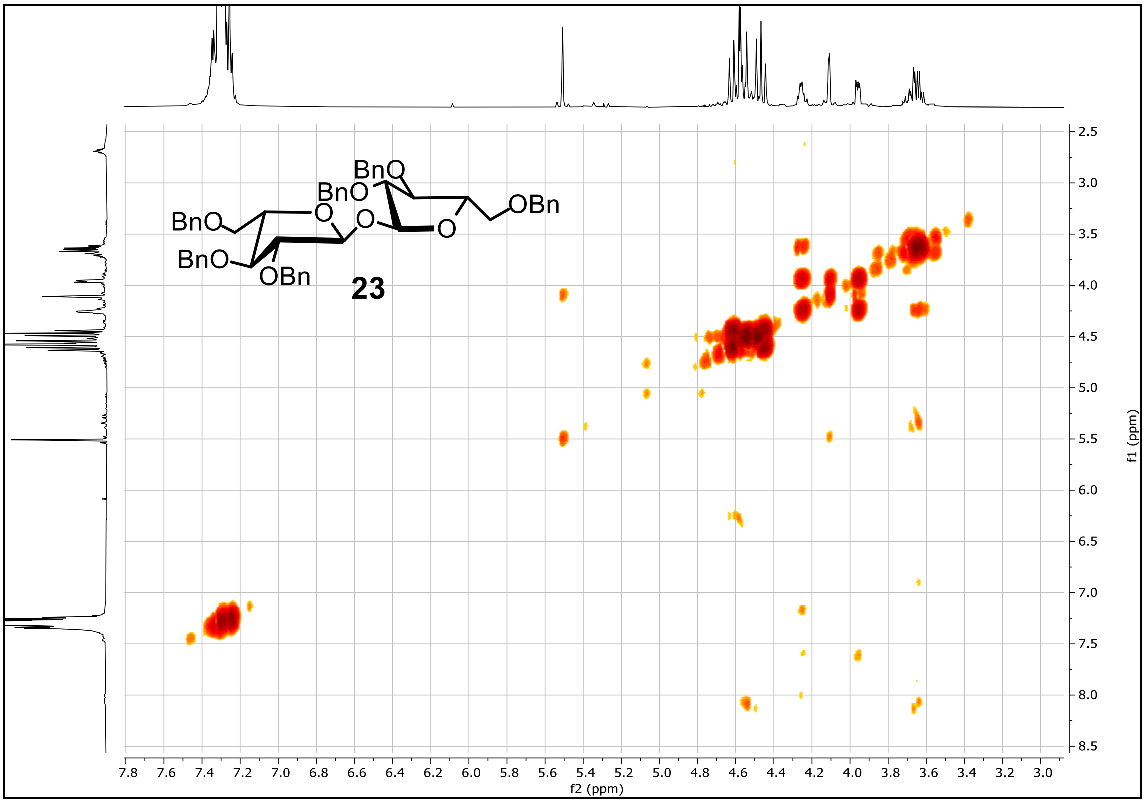

Figure S58. COSY spectrum of 2,3,5,2’,3’,5’-hexa-*O*-benzyl-α,α-L-arabinofuranoside (**23**) (500 MHz, CDCl$_3$).

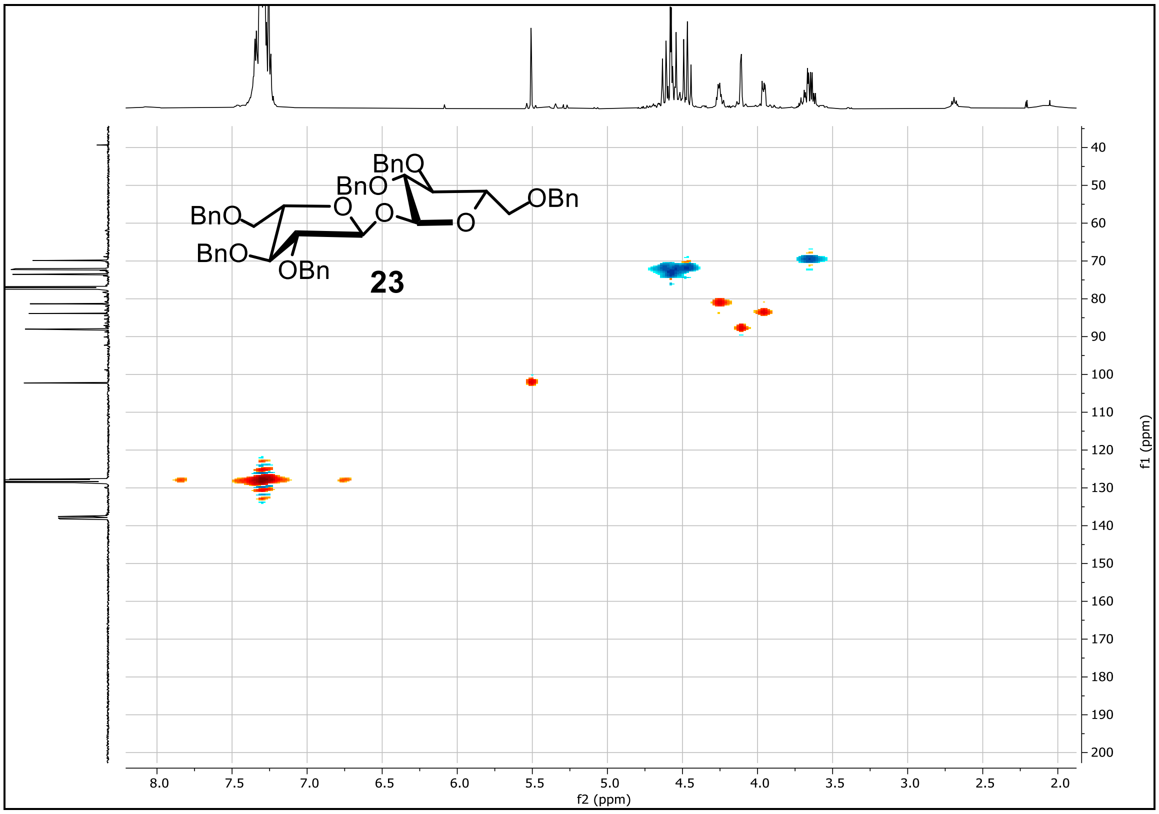

Figure S59. HSQC spectrum of 2,3,5,2’,3’,5’-hexa-*O*-benzyl-α,α-L-arabinofuranoside (**23**) (500 MHz, CDCl$_3$).

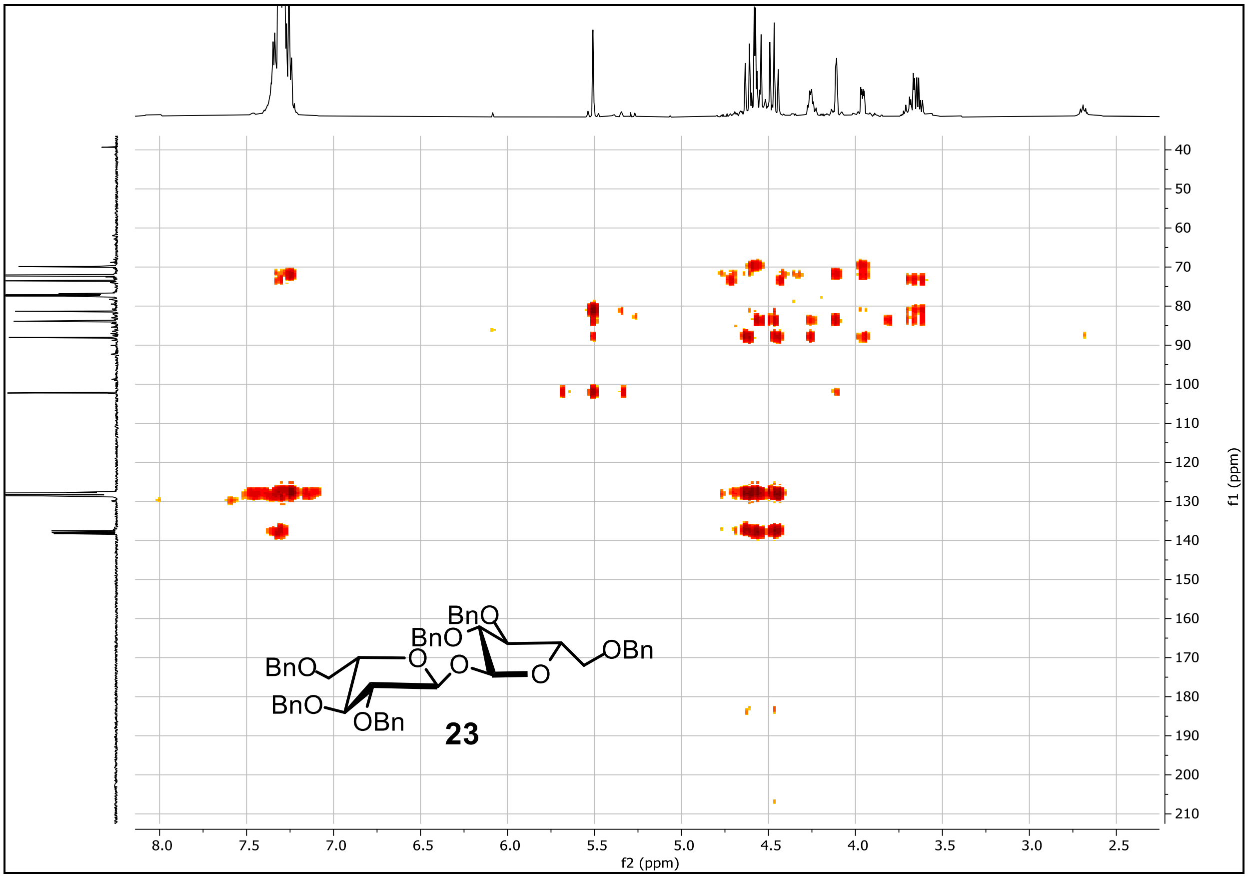

Figure S60. HMBC spectrum of 2,3,5,2’,3’,5’-hexa-*O*-benzyl-α,α-L-arabinofuranoside (**23**) (500 MHz, $CDCl_3$).

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1. Ratthachag, T.; Buntasana, S.; Vilaivan, T.; **Padungros, P.**, Surfactant-Mediated Thioglycosylation of 1-Hydroxy Sugar in Water. *The Journal of Organic Chemistry* (manuscript under review, submitted on 27 Febuary 2020)

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Surfactant-Mediated Thioglycosylation of 1-Hydroxy Sugar in Water

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Surfactant-Mediated Thioglycosylation of 1-Hydroxy Sugar in Water

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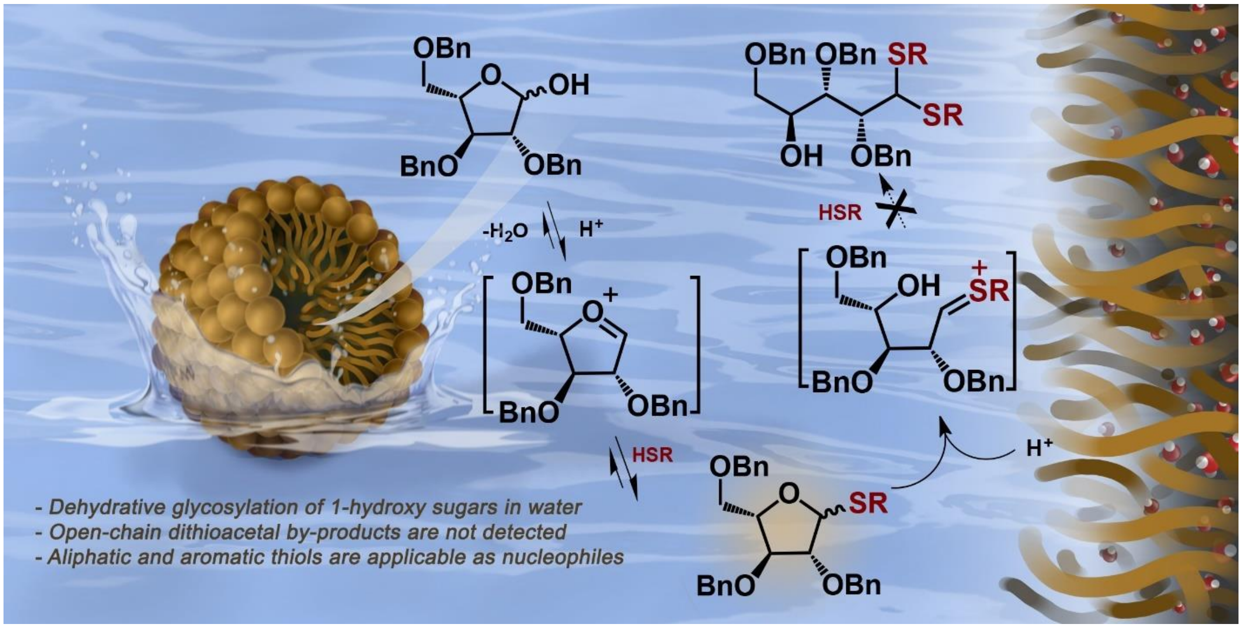
Graphical Abstract



- Dehydrative glycosylation of 1-hydroxy sugars in water
- Open-chain dithioacetal by-products are not detected
- Aliphatic and aromatic thiols are applicable as nucleophiles

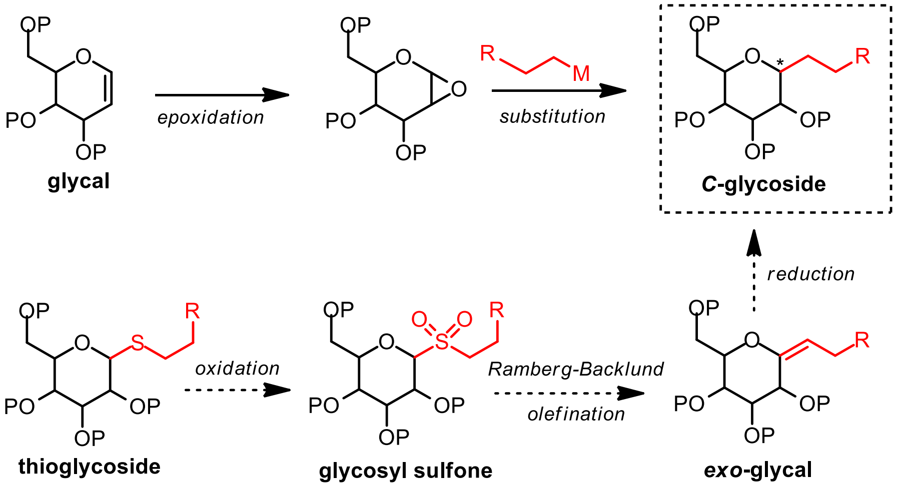
Abstract

Thioglycoside is an important class of sugar since it can be used as non-ionic biosurfactants, biomimetic glycosides, and building blocks for carbohydrate synthesis. Previously, Bronsted- or Lewis acid-catalyzed dehydrative glycosylations between 1-hydroxy sugar and thiol were reported to yield open-chain dithioacetal sugar as the major product, instead of the desired thioglycoside. The dithioacetal sugar is a by-product derived through endocyclic bond cleavage of the thioglycoside. Herein, we report dehydrative glycosylation in water mediated by Bronsted acid─surfactant combined catalyst (BASC). Glycosylations between 1-hydroxy furanosyl/pyranosyl sugars and primary, secondary, tertiary aliphatic/aromatic thiols in the presence of dodecyl benzenesulfonic acid (DBSA) provided thioglycoside products in moderate to good yields. Microwave irradiation led to the improvement of the yields and shortening the reaction time. Remarkably, the open-chain dithioacetal sugar was not detected under DBSA-mediated glycosylation in water. This method is a simple, convenient, and rapid approach to produce a library of thioglycoside without the requirement of anhydrous conditions. Moreover, this work represents a showcase of complement reactivity profiles of glycosylation in organic solvents and water.

Introduction

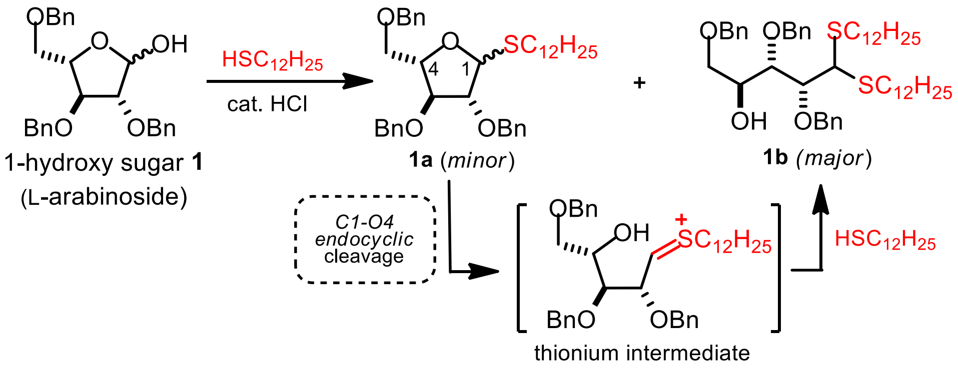
Glycals and *exo*-glycals are essential classes of building blocks in organic synthesis especially in the field of carbohydrate chemistry.[1] They both contain nucleophilic enol ether functional groups which are amenable for stereoselective installation of glycosidic linkages for targeted carbohydrates.[2] Numerous hydrolytically stable *C*-glycosides which contained unique biological activities have been prepared from glycals and *exo*-glycals.[3] Generally, epoxidation of glycals followed by ring-opening with suitable nucleophiles produces *C*-glycosides (Scheme 1).[2c, 4] Alternatively, stereoselective hydrogenation of *exo*-glycal to yield *C*-glycoside is also a reliable method for the preparation of alkyl *C*-glycosides.[5] Ramberg-Bäcklund olefination of glycosyl sulfone derived from the oxidation of thioglycosides represents another versatile approach for the synthesis of alkyl *C*-glycosides.[3f, 6]

Scheme 1. Synthesis of alkyl *C*-glycoside *via* glycal and *exo*-glycal (P = protecting group, R = alkyl group)



On a course of our synthesis of alkyl *C*-glycosides *via* Ramberg-Bäcklund olefination,[7] we first set to generate a library of alkyl thiofuranosides by Fischer glycosylation using a perbenzylated 1-hydroxy sugar as an armed glycosyl donor (Scheme 2).[8] The Fischer glycosylation is a hemiacetal-to-acetal transformation that is often a starting point in the preparation of monomers in oligosaccharide syntheses or construction of complex natural products.[9] This method possesses several advantages as follows: 1) 1-hydroxy sugar donor is highly stable, 2) it does not require anhydrous conditions thus it is capable to scale up, and 3) the condensation produces water as the only by-product which abided to the green chemistry concept. Dehydrative glycosylation between the 1-hydroxy sugar **1** (2,3,5-tri-*O*-benzyl-L-arabinofuranoside) and 1-dodecanethiol in the presence of catalytic HCl was first carried out. Analysis of the crude mixture indicated that 1-dodecyl thiofuranoside **1a** was obtained as a minor product along with the open-chain dithioacetal sugar **1b** as a major product. The dithioacetal sugar **1b** was thought to derive from protonation of the ring-oxygen (O4) of the 1-dodecyl thiofuranoside **1a**, followed by endocyclic C1-O4 bond cleavage to form a thionium intermediate. The second addition of 1-dodecanethiol to this thionium intermediate gave the dithioacetal sugar **1b** as the major product.

Scheme 2. Preliminary results on the Fischer glycosylation of 1-hydroxy sugar **1** yielded dithioacetal sugar **1b** as the major product



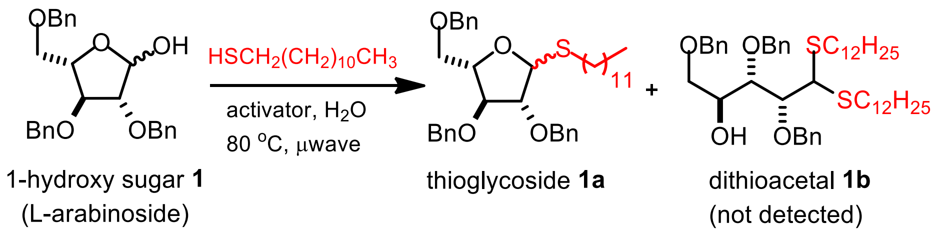
The endocyclic bond cleavage of glycosides was recognized since 1967 by Clayton and co-workers from the observation of anomerization and ring contraction during the hydrolysis of methyl thiopyranosides with dilute acids.[10] Previous reports have well-documented the challenges of dehydrative glycosylation between armed pyranosyl/furanosyl donors and reactive nucleophiles, especially the combination of furanosyl donors and highly nucleophilic thiols.[11] For examples; dithioacetal sugars were obtained during the dehydrative glycosylation of 1-hydroxy sugars under catalysis by Bronsted acids such as trifluoroacetic acid,[12] HCl,[13] and HBr.[14] Products derived from the endocyclic bond cleavage were also observed under Lewis acid-catalysis such as SnCl$_4$,[15] BF$_3$·OEt$_2$,[4a, 16] B(OMe)$_3$,[16] and Me$_2$BBr.[17] Additionally, thiol nucleophiles can undergo oxidation to generate disulfide side-product under Lewis acid-catalysis.[18] To circumvent these challenges, other activators were recently developed to activate the 1-hydroxy sugars such as sulfoxonium triflate reagents[19] and cyclic phosphonium anhydrides.[20] Less reactive glycosyl donors such as peracylated 1-hydroxy sugars have been used as a glycosyl donor. However, the peracylated 1-hydroxy sugar must be converted to a more reactive glycosyl halide first, then followed by substitution of an acceptor. Strictly anhydrous conditions were required for these processes to prevent hydrolysis of the glycosyl halide intermediates.[21] Lastly, the armed perbenzylated 1-hydroxy sugar donors could be converted to other glycosyl donors such as glycosyl trichloroacetimidates[22] or glycosyl halides[13e] but at the cost of extra reaction steps. On the other hand, such endocyclic bond cleavage can be synthetically utilized such as in a strategy for the preparation of thiofuranosides by ring contraction of thiopyranosides[23] or 1,2-*cis* aminoglycosidic bond formation through endocyclic cleavage-mediated anomerization by Manabe and Ito group.[11c, 24,25] Moreover, the formation of dithioacetal sugar derived through endocyclic bond cleavage has been used as a conventional method to protect the aldehyde/ketone functional group of aldose/ketose sugars.[26] Nevertheless, a direct synthesis of perbenzylated thioglycosides from 1-hydroxy sugars is still highly desirable, and there is no current methodology that allows such transformation without the substantial formation of the dithioacetal sugar side products.

Water has become one of the most promising “green solvents” for modern organic synthesis since it is environmentally friendly, cheap, and often provides unique reactivity profiles that complement similar reactions performed in organic solvents.[27] The growing interest in using water as reaction media motivates us to explore chemical glycosylation in water. Glycosylation reactions in water alone or mixture of organic solvent/water[28] have been demonstrated recently for both unprotected and protected sugar substrates.[29] For the rather hydrophobic protected sugars, their solubility in water can be enhanced by the aid of surfactants.[27] Several surfactant systems such as the Lewis acid–surfactant combined catalysts (LASC) or the Bronsted acid─surfactant combined catalysts (BASC) introduced by Kobayashi and co-workers,[30] and the designer nonionic surfactants by Lipshutz and co-workers have been proven as powerful tools for performing chemical synthesis in water without additional co-solvents.[27b] We envisage that the hydrophobicity of both protected 1-hydroxy sugars and aliphatic thiols would make them suitable candidates for performing glycosylation in water that can be assisted by the presence of a surfactant. Herein, we report the study of dehydrative glycosylation in water between 1-hydroxy sugars and thiols in the presence of LASC, BASC, and designer surfactants.

Results and Discussion

Lewis acid–surfactant combined catalyst (LASC) was first considered as a surfactant for this study.[30] Several water-tolerant Lewis acids have been successfully employed as catalysts for nucleophilic addition to carbonyl compounds in water such as $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, $Pr(OTf)_3$, and $Cu(OTf)_2$.[31] The combination of water-tolerant Lewis acids and anionic surfactants yielded LASC that gains both catalytic activity and solubility in water.[32] The dehydrative glycosylation between the 1-hydroxy sugar **1** and 1-dodecanethiol in the presence of LASC was investigated and the results were shown in Table 1.

Table 1. Dehydrative thioglycosylation in water mediated by Lewis acid–surfactant combined catalyst (LASC)



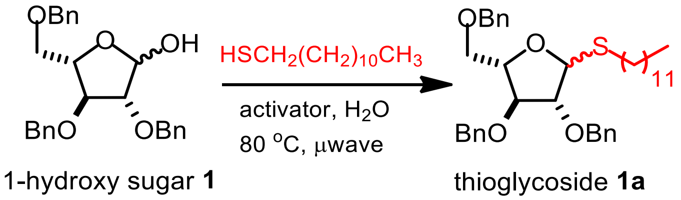
Entry[a]	**Activator/Surfactant**	**Conversion**[b]	**1a (yield)** [b,c]	**1a (α/β)**[d]
1	$Sc(DBS)_3$[e]	<5%	trace	ND
2	$Yb(DBS)_3$[e]	<5%	trace	ND
3	$Sc(OTf)_3$/DBSA[f]	ND	59% (ND)	50:50
4	$Yb(OTf)_3$/DBSA[f]	ND	63% (ND)	44:56
5	$La(OTf)_3$/DBSA[f]	68%	67% (99%)	39:61
6	$Gd(OTf)_3$/DBSA[f]	73%	64% (88%)	41:59
7	$Nd(OTf)_3$/DBSA[f]	77%	64% (83%)	40:60
8	$Pr(OTf)_3$/DBSA[f]	66%	56% (85%)	42:58
9	$Cu(OTf)_2$/DBSA[f]	ND	15% (ND)	40:60

[a] Standard conditions: 1-dodecanethiol (1.2 equiv), H_2O, 80 °C by microwave irradiation (µwave), 5 h; [donor] = 0.50 M. [b] Conversions and yields were determined from isolated product and recovered 1-hydroxy sugar after column chromatography. [c] Yield in parenthesis is based on recovered starting materials (brsm). [d] Selectivities (α/β) were obtained as determined by ^1H NMR integration. [e] LASC catalyst (10 mol%). [f] Lewis acid (10 mol%)/DBSA (1 equiv). DBS = dodecylbenzenesulfonate, DBSA = dodecylbenznesulfonic acid, ND = not determined.

The dehydrative glycosylation reactions were carried out in water at 80 °C under microwave irradiation with catalytic $Sc(DBS)_3$ (scandium tris(dodecylbenzenesulfonate)) and $Yb(DBS)_3$ (ytterbium tris(dodecylbenzenesulfonate)) (Table 1,entries 1–2).[33] Both LASCs gave only trace amount of the desired thioglycoside **1a** accompanied with the unreacted 1-hydroxy sugar **1**. Increasing the catalyst loading, reaction time, and temperature showed no improvement of the product yields. Cooperative catalyst system between LASC and Bronsted acid have previously been shown to enhance the rate of several chemical reactions in water.[34] We reasoned that the addition of a Bronsted acid may accelerate the reaction by promoting the leaving ability of the OH group. The glycosylation reactions were then performed with a combination of water-tolerant Lewis acids and DBSA (entries 3–8).[35] Significant improvements of the yield were indeed observed for all reactions to a range of 56–67% yields with the formation of both α- and β-anomers in comparable amounts. When the combination of $Cu(OTf)_2$/DBSA was used, the product **1a** was obtained in only 15% yield (entry 9). Importantly, in all cases the crude reaction mixtures contained only the unreacted 1-hydroxy sugar **1** and the thioglycoside product **1a** without a trace of the dithioacetal sugar **1b** commonly observed as the major by-product.

The results from Table 1 suggested that Bronsted acid plays a crucial role for the dehydrative glycosylation of 1-hydroxy sugars.[36] Next, the Bronsted acid–surfactant combined catalyst (BASC) was investigated for the same glycosylation (Table 2). Perfluoro-octanesulfonic acid (PFOS), perfluoro-octanoic acid (PFOA), and dodecyl benzenesulfonic acid (DBSA) were applied to the reaction under microwave irradiation at 80 °C (Table 2, entries 1–3). The PFOS-mediated glycosylation gave a distinct two-layer heterogeneous mixture and afforded only 48% conversion with low yield (entry 1). On the other hand, the PFOA and DBSA surfactants provided well-dispersed white turbid emulsions during the course of the reaction. Gratifyingly, both high conversions and yields of the thioglycoside **1a** were obtained from the PFOA- and DBSA-mediated glycosylation (entries 2 and 3). Regarding to the anomeric selectivity, DBSA (α/β = 7:93) provided higher β selectivity compared to PFOA (α/β = 29:71). Thus, the DBSA was preferable over PFOA as the activator for this study since it provided higher selectivity and the health and environmental concern from the persistency of PFOA in the environment.[37]

Table 2. Dehydrative thioglycosylation in water mediated by Bronsted acid–surfactant combined catalyst (BASC), Bronsted acid/ nonionic surfactant, and Bronsted acid alone



Entry[a]	Activator/Surfactant	Temp	Conversion[b]	1a (yield)[b,c]	1a (α/β)[d]
1	PFOS (1 equiv)	80 °C	48%	18% (37%)	30:70
2	PFOA (1 equiv)	80 °C	78%	71% (91%)	29:71
3	**DBSA** (1 equiv)	**80 °C**	**73%**	**72% (99%)**	**7:93**
4	DBSA (1 equiv)	40 °C	44%	44% (99%)	8:92
5	DBSA (1 equiv)	60 °C	58%	57% (99%)	8:92
6	DBSA (1 equiv)	100 °C	80%	64% (80%)	6:94
7	CSA (0.1 equiv)/Nok	80 °C	20%	2% (10%)	0:100
8	*p*-TsOH (0.1 equiv)/Nok	80 °C	31%	18% (58%)	0:100
9	*p*-TsOH (0.1 equiv)/Coolade	80 °C	ND	15% (ND)	0:100
10	CSA (0.1 equiv)/TPGS-750-M	80 °C	15%	8% (53%)	0:100
11	*p*-TsOH (0.1 equiv)/TPGS-750-M	80 °C	40%	33% (83%)	0:100
12	*p*-TsOH (1 equiv)/TPGS-750-M	80 °C	ND	56% (ND)	10:90
13	***p*-TsOH (1 equiv)/TPGS-750-M**	**120 °C**	**ND**	**79% (ND)**	**24:76**
14	*p*-TsOH (1 equiv)	80 °C	ND	17% (ND)	20:80
15	*p*-$HOC_6H_4SO_3H$ (1 equiv)	80 °C	ND	27% (ND)	12:88

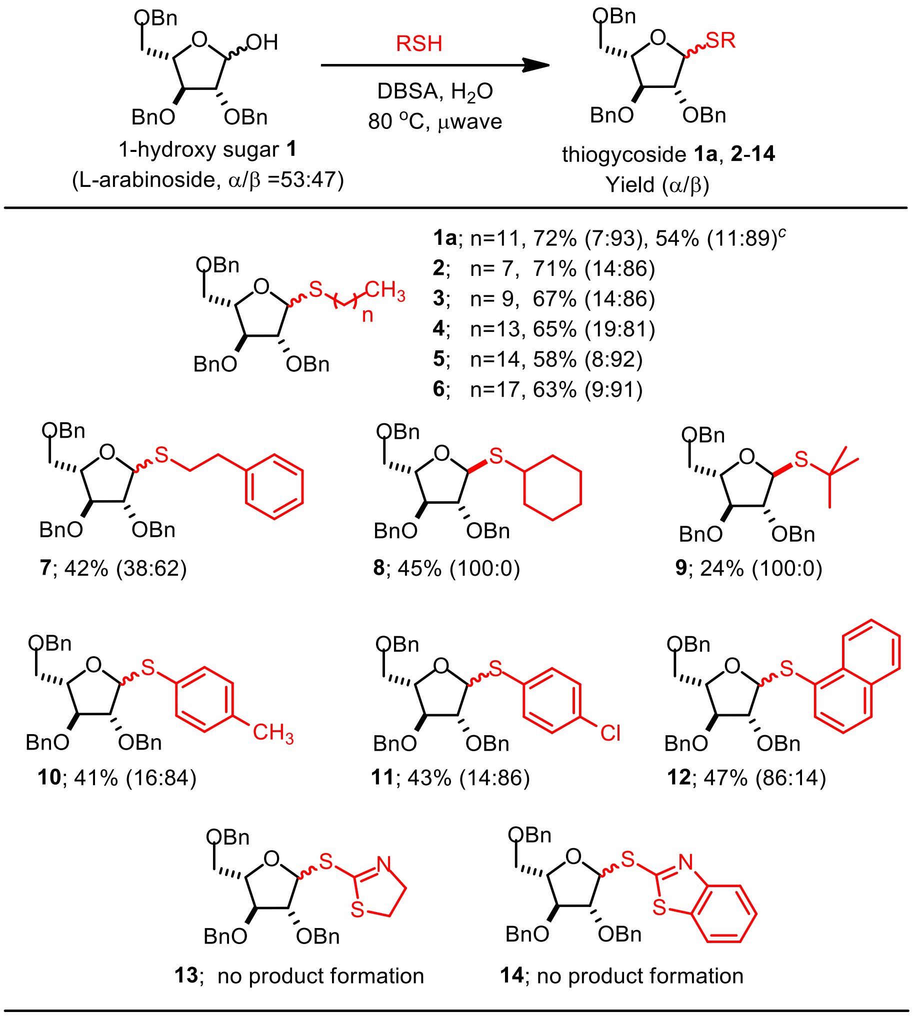
[a] Standard conditions: 1-dodecanethiol (1.2 equiv), BASC or Bronsted acid (0.1 or 1 equiv), H_2O, heated by microwave irradiation (μwave), 5 h; [donor] = 0.50 M; 2% w/w of nonionic surfactants were used for entries 7–13. [b] Conversions and yields were determined from isolated product and recovered 1-hydroxy sugar by column chromatography. [c] Yield in parenthesis is based on recovered starting materials (brsm). [d] Selectivities (α/β) were obtained as determined by ^1H NMR integration. PFOS = perfluoro-octanesulfonic acid, PFOA = perfluoro-octanoic acid, ND = not determined.

The DBSA-mediated glycosylations were examined at different temperatures to probe the effect on the yield and selectivity of the product. Lowering the temperature to 40 °C and 60 °C gave inferior yields and conversion (entries 4 and 5). Increasing the temperature to 100 °C caused some decomposition as evidenced by the formation of a brown tar-like syrup, which resulted in a lower yield (entry 6). Efforts to reduce the amount of DBSA from 1 equivalent to catalytic amount resulted in lower yield and a less dispersion of both substrates (1-hydroxy sugar **1** and 1-dodecanethiol) was noticed.

Designer nonionic surfactants from Lipshutz's groups have been proven as a suitable medium for many synthetically useful organic reactions in water.[27] We were captivated by its potential and decided to evaluate these nonionic surfactants in our study. Combinations of Lipshutz's designer surfactants and lipophilic sulfonic acids as a source of Bronsted acid were next investigated. A mixture of 1-hydroxysugar **1** and 1-dodecanethiol was treated with 10 mol% of camphorsulfonic acid (CSA) or *p*-toluenesulfonic acid (*p*-TsOH) with Nok surfactant (SPGS-550-M)[38] yielded the thioglycoside **1a** only in trace amount (2% yield, α/β = 0:100; entry 7) and 18% yield (α/β = 0:100; entry 8). The combination of 10 mol% of *p*-TsOH and Coolade surfactant[39] also resulted in a poor yield of the thioglycoside **1a** (15%, α/β = 0:100; entry 9). Next, TPGS-750-M surfactant[40] was examined (entries 10–13).[40] The combination of catalytic CSA or *p*-TsOH with TPGS-750-M still resulted in poor yield (8%, α/β = 0:100; entry 10 and 33%, α/β = 0:100; entry 11). However, increasing the amount of *p*-TsOH to 1 equivalent in the presence of TPGS-750-M provided a higher yield of product **1a** (56%, α/β = 10:90; entry 12). When the reaction temperature was raised to 120 °C, a considerable improvement was observed and the product **1a** was obtained in 79% yield with moderate selectivity (α/β = 24:76, entry 13) along with decomposition by-products. Such ester-based nonionic surfactants might not be suitable for this particular reaction since the conditions involved prolonged heating under acidic conditions which may cause a partial hydrolysis of the ester linkages.[27a] Finally, performing the reactions with the Bronsted acid alone (*p*-TsOH and *p*-hydroxybenzenesulfonic acid) gave the product **1a** in only low yields (entries 14 and 15) even at a full equivalent, which conclusively emphasized the necessity of surfactant in the reactions. It is noteworthy that in the DBSA-mediated thioglycosylation, the ratios of the α and β thioglycosides **1a** remain almost the same over the whole temperature ranges examined (40, 60, 80, and 100 °C; entries 3–6). Moreover, the glycosylations at 80 °C with different Bronsted acids (entries 1–3, 12, 14–15) gave different α/β selectivities, ranging from 7:93 to 30:70, thus the α and β thioglycosides **1a** were not in equilibrium otherwise the same selectivity would have been observed. This implies that the selectivity for the formation of α and β thioglycosides **1a** should be under kinetic control. The results from Table 2 revealed that two conditions, namely DBSA (entry 3) and *p*-TsOH (1 equiv)/TPGS-750-M (entry 13), are capable of promoting the dehydrative thioglycosylation to form the thioglycosides **1a** in comparable yields. Nevertheless, DBSA was chosen as a Bronsted acid–surfactant combined catalyst for further studies since it is less expensive and does not require additional acids.

The scope of nucleophile: aliphatic, aromatic, and heterocyclic thiols were next investigated for the DBSA-mediated glycosylation of the 1-hydroxy sugar **1** in water under microwave irradiation (Table 3). Primary alkyl thioglycosides **1a**, **2**–**6** with different chain length (C12, C8, C10, C14, C15, and C18) were obtained under the standard conditions in moderate to good yields (58–72%), with decent α/β selectivities (7:93 to 19:81). The superior results of the microwave heating were confirmed by performing the DBSA-mediated thioglycosylation experiment by heating in an oil bath at 80 °C in a sealed tube for 48 hours, which gave the desired alkyl thioglycoside **1a** in lower yield (54%, α/β = 11:89).[c] Delightfully, the formation of the dithioacetal sugar by-product was not observed in all reactions.

Table 3. The scope of thiol nucleophiles in the DBSA-mediated dehydrative thioglycosylation of 1-hydroxy sugar **1** in water[a,b]

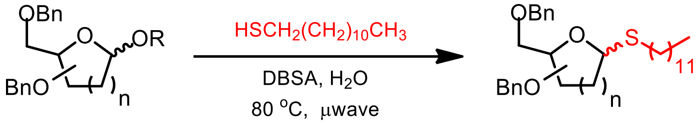


[a] Standard conditions: thiol (1.2 equiv), DBSA (1 equiv), H_2O, 80 °C by microwave irradiation (μwave), 5 h; [donor] = 0.50 M. [b] Isolated yield by column chromatography and selectivities (α/β) were obtained as determined by ^1H NMR integration. [c] Reaction was performed under standard conditions in a sealed tube and heating with an oil bath at 80 °C for 48 hours.

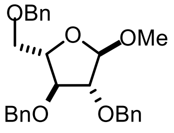
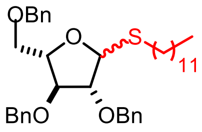
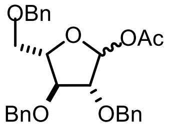
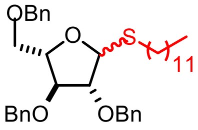
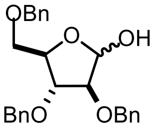
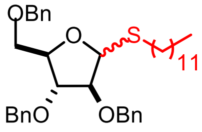
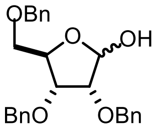
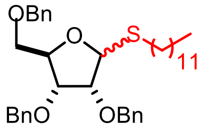
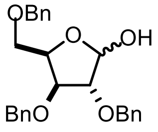
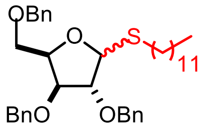
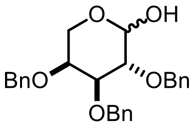
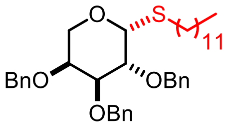
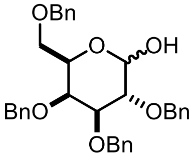
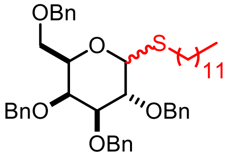
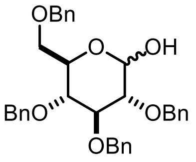
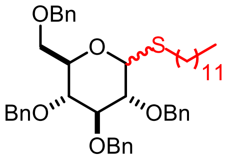
The glycosylation of 1-hydroxy sugar **1** with 2-phenyl ethanethiol yielded the expected thioglycoside **7** in moderate yield (42%) and selectivity (α/β = 38:62). Thioglycosides **8** and **9** deriving from secondary aliphatic thiol (cyclohexanethiol) and tertiary aliphatic thiol (*tert*-butylthiol) were obtained in moderate to low yields of 45% and 24%, respectively with only α anomers were detected. Steric hindrance and water solubility of *tert*-butylthiol could be the reasons for the lower yield of the thioglycoside **9**. In addition, aromatic thiols bearing both electron-donating and withdrawing groups were tested. Gratifyingly, thioglycosides **10**, **11**, and **12** were all obtained in moderate yields. In general, β selectivities were observed in the glycosylation of 1-hydroxy L-arabinofuranoside **1** and thiols. However, bulky thiol nucleophiles seem to favor the formation of α-products (**8**, **9**, and **12**). When heterocyclic thiols including 2-mercaptothiazoline and 2-mercaptobenzothiazole were examined as potential nucleophiles, thioglycosides **13** and **14** were not formed and the 1-hydroxy sugar **1** was fully recovered.[41] Crystal structures of 2-mercaptothiazoline and 2-mercaptobenzothiazole revealed that both heterocyclic thiols prefer to exist as the thiocarbonyl tautomer instead of the thiol form, thus reducing its nucleophilicity.[42] It is important to note that this newly developed protocol required only slightly excess (1.2 equivalents) of the thiol to obtain decent to good yields of the thioglycosides. Conversely, traditional Fischer glycosylation often requires a large excess of the acceptor, often as a solvent, to drive the equilibrium forward.[43] The use of the malodorous thiol acceptor in large excess amounts or as a solvent hampers the full synthetic potential of Fischer glycosylation.

To test the compatibility with various glycosyl donors, the glycosylation reactions between 1-dodecanethiol and different glycosyl donors were examined (Table 4). A comparison among L-arabinofuranosyl donors with different leaving groups at the anomeric position, methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside (**15**) and acetyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside (**16**) was also made to probe the effect of leaving group (Table 4, entries 1 and 2). The thioglycoside **1a** was obtained in low yield (10%) for the glycosyl donor **15** and moderate yield (60%) for the glycosyl donor **16**. Thus, 1-hydroxy and 1-acetoxy sugars are more suitable glycosyl donors than 1-methoxy sugars for the presently developed DBSA-mediated dehydrative thioglycosylation in water.

Table 4. The scope of furanosyl/pyranosyl donors in the DBSA-mediated dehydrative thioglycosylation with 1-dodecanethiol in water[a, b]



glycosyl donor **15-22** → thioglycoside **1a**, **17a-22a**

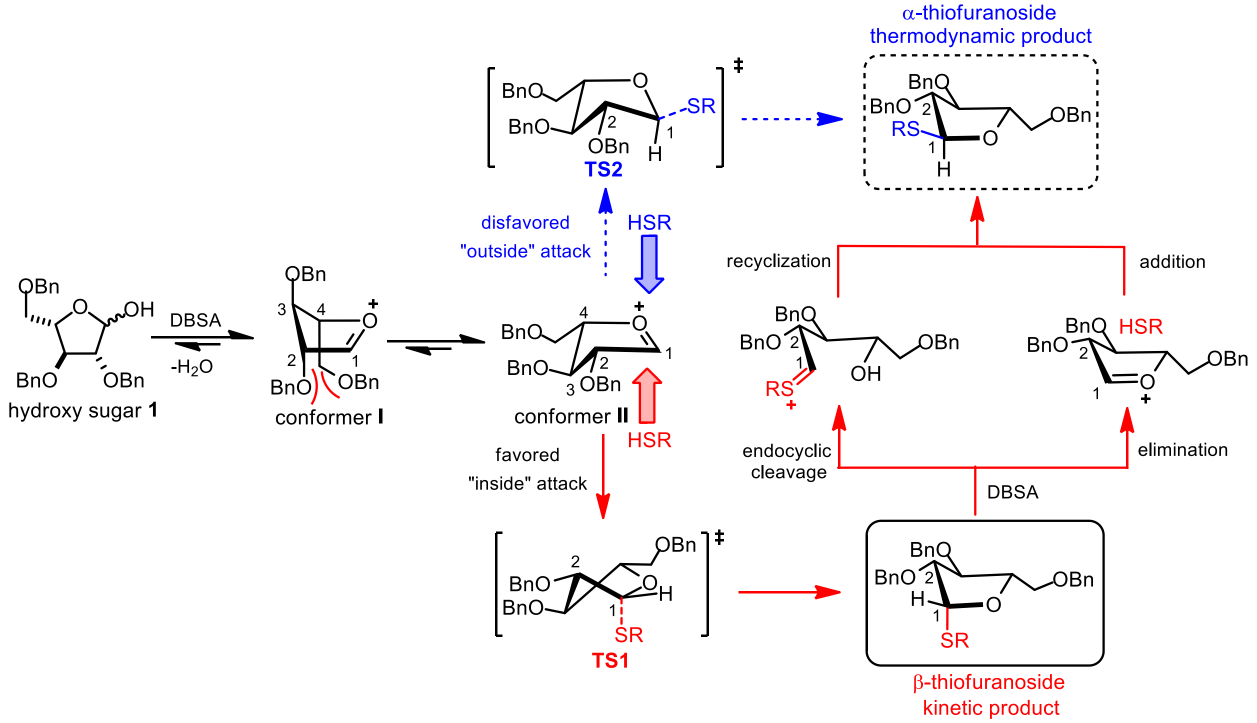
Entry	Glycosyl Donor (α/β)	Product/Yield (α/β)
1	 **15** (100:0) L-arabinofuranoside	 **1a**; 10% (9:91)
2	 **16** (59:41) L-arabinofuranoside	 **1a**; 60% (10:90)
3	 **17** (22:78) D-arabinofuranoside	 **17a**; 66% (16:84)
4	 **18** (50:50) D-ribofuranoside	 **18a**; 73% (17:83)
5	 **19** (50:50) D-xylofuranoside	 **19a**; 73% (69:31)
6	 **20** (37:63) L-arabinopyranoside	 **20a**; 60% (0:100)
7	 **21** (66:34) D-galactopyranoside	 **21a**; 32% (65:35)
8	 **22** (50:50) D-glucopyranoside	 **22a**; 45% (64:36)

[a] Standard conditions: thiol (1.2 equiv), DBSA (1 equiv), H_2O, 80 °C by microwave irradiation (µwave), 5 h; [donor] = 0.50 M. [b] Isolated yield by column chromatography and selectivities (α/β) were determined by ^{1}H NMR integration.

The glycosylation of 1-dodecanethiol by other perbenzylated 1-hydroxy furanosyl donors, namely D-arabinofuranoside (**17**), D-ribofuranoside (**18**), and D-xylofuranoside (**19**) provided the thioglycosides **17a**, **18a**, and **19a** in 66% (α/β = 16:84), 73% (α/β = 17:83), and 73% (α/β = 69:31) yield, respectively (entries 3–5). Finally, 1-hydroxy pyranosyl sugars such as L-arabinopyranoside (**20**), D-galactopyranoside (**21**), and D-glucopyranoside (**22**) were also acceptable donors to yield the corresponding thioglycosides **20a**, **21a**, and **22a** in 60% (α/β = 0:100), 32% (α/β = 65:35), and 45% (α/β = 64:36) yield, respectively (entries 6–8).

Under the Bronsted acid–surfactant combined catalytic system in this study, we hypothesize that the emulsion droplet is generated by DBSA during the course of the reaction. The perbenzylated 1-hydroxy sugar is encapsulated within the droplet and undergoes protonation at the surface of the emulsion droplets. The anionic surface of the DBSA accumulates a high concentration of hydronium ion thus increases the rate of dehydration.[44] At the same time, the lipophilic thiol is also encapsulated, making the local concentrations of both reactants very high. Next, dehydration followed by the addition of the thiol provides the desired thioglycoside.[45] Inside the droplet, the equilibrium of the dehydration should favor the oxocarbenium side when compared to the reaction outside the droplet that contains a large excess of water. We hypothesize that the oxocarbenium intermediate could be stabilized by either the sulfur atom of the encapsulated thiol or by the small amount of water within the hydrophobic pocket called hydrophobic hydration.[44] For example, the hydrophobic interior of sodium dodecylsulfate (SDS) micelle was previously reported to stabilize the oxocarbenium intermediate generated during a Prins cyclization in water.[46] It should be noted that the second protonation of the initially formed thioglycoside product to yield a thionium intermediate is also possible at the acidic surface of the droplets. Since the majority of the lipophilic thiol would be trapped inside the droplet thus the chance to undergo a second addition to the thionium intermediate is minimized. As a result, the dithioacetal sugar was not generated as usually observed when the glycosylation was performed under conventional organic solvent conditions.[47] With regards to stereoselectivity, we propose that the five-membered ring oxocarbenium intermediate adopts an envelope conformation whereas a carbon at position 3 (C3) is placed on the top (^{3}E conformer) or at the bottom (E_3 conformer) of the envelope and the oxocarbenium moiety aligns on the plane as depicted in Scheme 3.

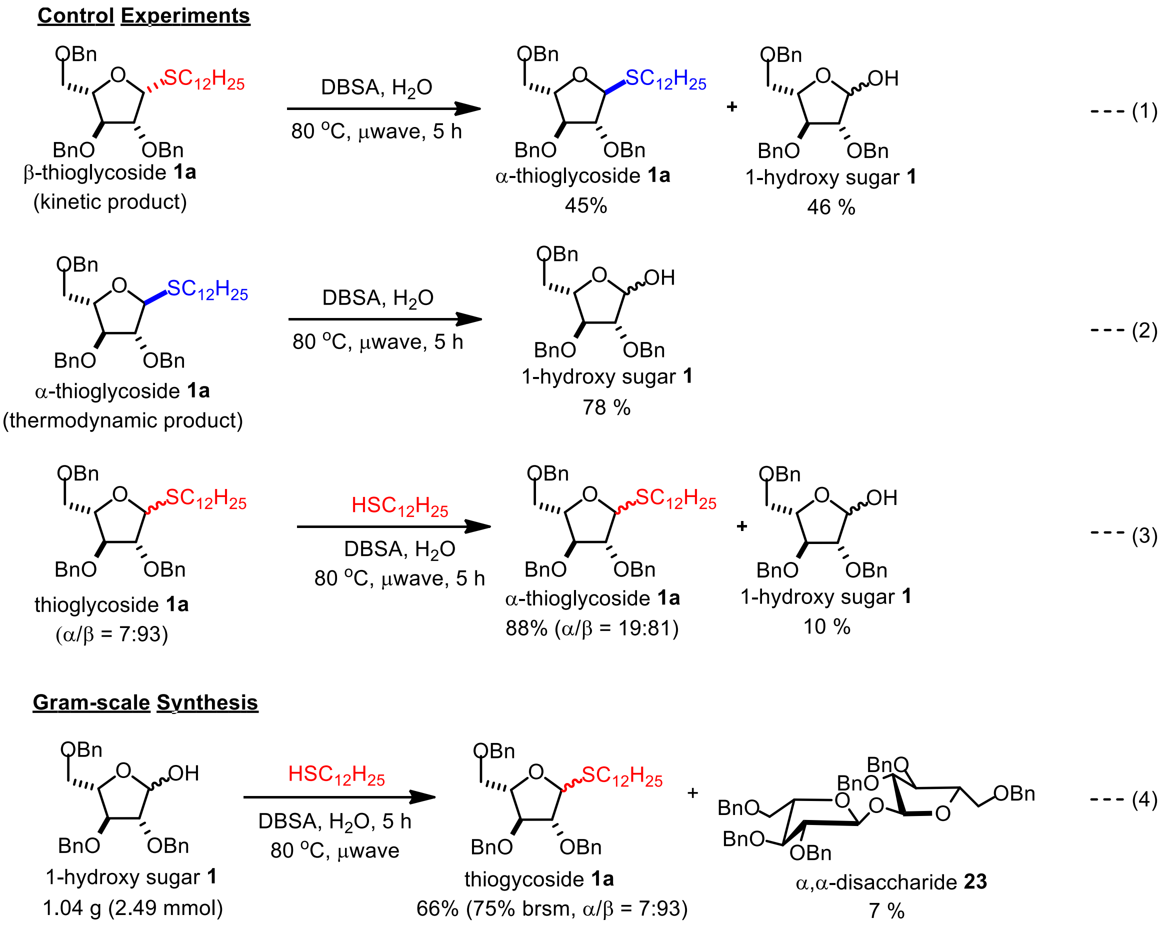
Scheme 3. Proposed mechanism of dehydrative thioglycosylation of **1a** in water mediated by DBSA



Under equilibration, conformer **II** (E_3) is favor over conformer **I** (^3E) since it contains all pseudoequatorial substituents, which is in contrary to all pseudoaxial orientations in the conformer **I**. Destabilization of the conformer **I** is caused by a *syn*-butanol interaction between the benzyloxy group at C2 and the benzyloxymethyl substituent at C4 of the furanose ring.[48] Based on this conformational analysis, the stereochemical outcome could be explained by Woerpel's model.[49] The nucleophilic addition would be possible from either side of the conformer **II**. However, the thiol attack "inside" the envelope in which the substituents on both C1 and C2 are in a staggered relationship should lead to the lower energy transition state (**TS1**) compared to the "outside" attack pathway. The "inside" attack according to **TS1** would yield β-thiofuranoside as a kinetic product. Conversely, the "outside" attack leading to the α-thiofuranoside product would result in the higher energy transition state (**TS2**) caused by an eclipsed conformer of C1 and C2.

Control experiments and gram-scale synthesis were next examined (Scheme 4). It is important to note that the kinetic product (β-thiofuranoside) is amenable to an epimerization to yield the thermodynamically more stable α-thiofuranoside *via* an endocyclic bond cleavage/recyclization or reversible elimination/addition of the thiol.[50] Isomerization of the pure β-thioglycoside **1a** was investigated by heating under microwave irradiation in the presence of DBSA (1 equiv) at 80 °C (Scheme 4, equation 1). The starting material was completely consumed and the α-thioglycoside **1a** was isolated in 45% yield with exclusive α-selectivity along with 46% yield of the 1-hydroxy sugar **1** resulting from the competing hydrolysis reaction.

Scheme 4. Control experiments and gram-scale synthesis of 1-dodecyl thioglycoside **1a**



When the pure α-thioglycoside **1a** was subjected to the same conditions, only the hydrolysis product, 1-hydroxy sugar **1**, was obtained in 78% yield without the formation of the β-thioglycoside **1a** (equation 2). These results supported the hypothesis that the β-thioglycoside is the kinetic product and could be epimerized to the thermodynamic α-thioglycoside upon prolonged heating. The finding was well aligned with the preference of α-thioglycoside formation when bulky thiol nucleophiles were used (Table 3, products **8**, **9**, and **12**), in such cases the epimerization of the β-thioglycoside would be highly favorable. Next, treatment of the thioglycoside **1a** (α/β = 7:93) with 1.2 equivalents of 1-dodecanethiol under the same conditions resulted in a recovery of the thioglycoside **1a** in 88% yield with a partial epimerization (α/β = 19:81) along with the hydrolysis product **1** in only 10% yield (equation 3). The presence of 1-dodoecanethiol in the reaction clearly suppressed the hydrolysis (compared to 46% yield of hydrolysis product from equation 1) as well as the epimerization of the β-thioglycoside **1a** to the more stable α-thioglycoside. The epimerization could proceed through the thionium intermediate or reversible elimination/addition of the thiol to the oxocarbenium intermediate (Scheme 3). The latter pathway would be consistent with the suppression of epimerization by the excess thiol.

Lastly, the practicality of the developed method was demonstrated through a gram-scale synthesis of the dodecyl thioglycoside **1a** (equation 4). The DBSA-mediated thioglycosylation of 1-hydroxy sugar **1** (1.04 g, 2.49 mmol) proceeded smoothly under the standard condition to provide the thioglycoside **1a** in 66% yield (75% brsm yield) with α/β = 7:93 after column chromatography. Interestingly, we were able to isolate the α,α-disaccharide **23**[51] derived from dimerization of hydroxy sugar **1** as a side-product in 7% yield. None of the open-chain dithioacetal sugar could be isolated from this larger scale reaction.

Conclusion

A large selection of thioglycosides was successfully synthesized by a dehydrative thioglycosylation between 1-hydroxy sugars and thiols in water. The reactions were performed in the presence of DBSA as a Bronsted acid–surfactant combined catalyst (BASC). The glycosylation reactions between 1-hydroxy furanosyl and pyranosyl sugars (both D- and L-sugars) and only slight excess of primary, secondary, tertiary aliphatic and aromatic thiols provided the expected thioglycoside products as a mixture of α and β anomers in moderate to good yields and selectivity. The moderate anomer selectivity is generally not a concern for many applications of the thioglycosides such as bio-surfactant or further transformation *via* the Ramberg-Bäcklund reaction. The use of readily available perbenzylated 1-hydroxy sugars as the glycosyl donor and the ability to perform the reaction in water are the major advantages of the present methodology. In addition, the present DBSA-mediated glycosylation of 1-hydroxy sugars did not yield the open-chain dithioacetal sugars by-product as often observed when similar glycosylation was performed in organic solvents. By taking advantage of the hydrophobic environment inside the emulsion droplet, this work represents a unique chemoselectivity preference for the formation of thioglycoside over dithioacetal sugar. Moreover, this method also offers a convenient and rapid approach to generate a library of thioglycosides, which are not only valuable as synthetic intermediates and thioglycosyl donors for oligomerization,[52] but also present their own importance as bioactive thioglycosides,[53] non-ionic biosurfactants for solubilization and reconstitution of membrane protein,[54] and biomimetic glycosides.[55] The thioglycosides are currently being used as precursors for the synthesis of alkyl *C*-glycosides in our laboratory.

Experimental Section

All chemicals and solvents were purchased from Acros, Merck, Sigma-Aldrich, TCI, or RCI Lab Scan. Solvents were dried with 3 Å molecular sieves for anhydrous reactions. Reaction monitoring by TLC were performed on silica gel 60 F254 0.2 mm pre-coated aluminium plates and purchased from Merck. Preparative thin layer chromatography was 0.5 mm thickness coated by silica gel 60 GF254 from Merck. Chemical spots on TLC were observed by visualization under 254 nm UV light or stained with *p*-anisaldehyde staining solution. Silica gel 60 (70–230 mesh) from Merck was used in purification by column chromatography. Solvents for NMR experiments were purchased from Cambridge Isotope Laboratories or Euriso-top. Milli-Q water was obtained from ultrapure water system with Millipak® 40 filter unit 0.22 μm, Millipore (USA). Microwave irradiation was carried out in a sealed vessel at 218 psi employing a CEM microwave reactor, model Discover Labmate. Functional group determinations were confirmed by infrared (IR) spectroscopy on a Nicolet 6700 instrument. Chemical structure characterization was conducted by nuclear magnetic resonance (NMR) spectrometer on a Bruker Avance 400 NMR spectrometer operating at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C{^{1}H} NMR or a JEOL JNM-ECZ500R/S1 spectrometer operating at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C{^{1}H} NMR. Exact masses of all products were determined by high resolution mass spectrometry (HRMS) on a JEOL SpiralTOF™ MALDI-TOF Mass Spectrometer or a Bruker Daltonics-micrOTOF-QII-ESI-Qq-TOF Mass Spectrometer.

General procedure A: DBSA-mediated glycosylation of 1-hydroxy sugar in water

In a typical procedure, 1-hydroxy sugar (0.24 mmol) and thiol (0.29 mmol, 1.2 equivalents) were added in a microwave vessel followed by an aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL, 1 equivalent). The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography. After 5 h, the reaction was quenched by adding saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (1a)

The glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **1a** was obtained as a yellow syrup (105 mg, 72%, α/β = 7:93).

β-Anomer: **$[\alpha]_D^{25}$** –50.0° (c 0.25, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34–7.23 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.66–4.44 (m, 6H), 4.17–4.11 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.69–2.60 (m, 2H), 1.62–1.57 (m, 2H), 1.51–1.21 (m, 18H), 0.88 (t, *J* = 6.6 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 32.0, 30.9, 30.0, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.2, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3484.

Octyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (2)

The glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-octanethiol (50 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **2** was obtained as a yellow syrup (94 mg, 71%, α/β = 14:86). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.22 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.63–4.46 (m, 6H), 4.17–4.12 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.7, 6.4 Hz, 2H), 2.65 (dt, *J* = 8.4, 4.1 Hz, 2H), 1.64–1.58 (m, 2H), 1.38–1.20 (m, 10H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.3, 137.9, 137.6, 128.5, 128.5, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 31.9, 30.9, 30.0, 29.6, 29.6, 29.4, 29.3, 29.1, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{34}H_{44}O_4SNa$ [M+Na$^+$] 571.2858, found 571.2859.

Decyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (3)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-decanethiol (61 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **3** was obtained as a yellow syrup (91 mg, 67%, α/β = 14:86). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.23 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.64–4.44 (m, 6H), 4.17–4.14 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.71 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.68–3.57 (m, 1H), 2.65 (dt, *J* = 8.4, 4.1 Hz, 2H), 1.64–1.58 (m, 2H), 1.40–1.18 (m, 14H), 0.87 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.4, 128.4, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 31.8, 30.9, 30.0, 29.7, 29.3, 29.2, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{36}H_{48}O_4SNa$ [M+Na$^+$] 599.3171, found 599.3161.

Tetradecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (4)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-tetradecanethiol (79 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.41). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **4** was obtained as a yellow syrup (99 mg, 65%, α/β = 19:81). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.22 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.64–4.42 (m, 6H), 4.18–4.10 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.3 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.6 Hz, 1H), 2.65 (td, *J* = 7.4, 1.9 Hz, 2H), 1.64–1.58 (m, 2H), 1.38–1.19 (m, 22H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.3, 137.9, 137.6, 128.4, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 32.00, 30.9, 30.0, 29.8, 29.7, 29.7, 29.7, 29.6, 29.4, 29.3, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{40}H_{56}O_4SNa$ [M+Na$^+$] 655.3797, found 655.3788.

Pentadecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (5)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-pentadecanethiol (83 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.42). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **5** was obtained as a yellow syrup (90 mg, 58%, α/β = 8:92). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.19 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.65–4.45 (m, 6H), 4.18–4.10 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.65 (td, *J* = 7.3, 1.9 Hz, 2H), 1.64–1.60 (m, 2H), 1.38–1.19 (m, 24H), 0.87 (t, *J* = 7.0 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.5, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 87.2, 84.4, 83.9, 82.1, 73.4, 72.4, 71.9, 71.4, 31.9, 30.9, 30.0, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{41}H_{58}O_4SNa$ [M+Na$^+$] 669.3953, found 669.3957.

Octadecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (6)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-octadecanethiol (83 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.48). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **6** was obtained as a yellow syrup (104 mg, 63%, α/β = 9:91). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.23 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.63–4.46 (m, 6H), 4.18–4.11 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.72 (dd, *J* = 9.9, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.65 (td, *J* = 7.4, 2.0 Hz, 2H), 1.64–1.58 (m, 2H), 1.38–1.22 (m, 30H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 136.1, 135.8, 135.5, 126.3, 126.3, 126.2, 125.8, 125.7, 125.6, 125.5, 125.4, 85.0, 82.2, 81.7, 79.9, 71.2, 70.2, 69.8, 69.3, 29.8, 28.8, 27.8, 27.6, 27.6, 27.5, 27.4, 27.3, 27.2, 27.1, 26.9, 20.6, 12.0. **HRMS** (MALDI-TOF): *m/z* calcd for $C_{44}H_{64}O_4SNa$ [M+Na$^+$] 711.4423, found 711.4414.

2-Phenylethyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (7)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 2-phenylethanethiol (34 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **7** was obtained as a yellow syrup (54 mg, 42%, α/β = 38:62). Mixture of α and β-anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45–7.06 (m, 20H), 5.37 (d, *J* = 5.0 Hz, 0.6 H, β-anomeric proton), 5.33 (d, *J* = 2.4 Hz, 0.4H, α-anomeric proton), 4.64–4.39 (m, 6H), 4.29 (q, J = 4.9 Hz, 0.4H), 4.19–4.11 (m, 1.2H), 4.04 (t, *J* = 4.0 Hz, 0.6H), 3.97 (t, *J* = 4.9 Hz, 0.8H), 3.74–3.58 (m, 2H), 2.96–2.89 (m, 4H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 138.0, 137.8, 137.7, 137.4, 128.6, 128.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 126.3, 126.3, 88.8, 87.7, 87.2, 84.3, 83.7, 82.1, 80.0, 73.4, 73.4, 72.4, 72.2, 72.0, 71.9, 71.4, 69.2, 36.6, 36.4, 32.6, 32.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{34}H_{36}O_4SNa$ [M+Na$^+$] 563.2232, found 563.2285.

Cyclohexyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (8)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), cyclohexanethiol (35 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **8** was obtained as a yellow syrup (56 mg, 45%, α/β = 100:0). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42–7.13 (m, 15H), 5.45 (d, *J* = 2.4 Hz, 1H, α-anomeric proton), 4.73–4.37 (m, 6H), 4.31–4.29 (m, 1H), 3.97 (dd, *J* = 7.8, 2.6 Hz, 2H), 3.75–3.46 (m, 2H), 2.90 (ddd, *J* = 10.4, 6.7, 3.7 Hz, 1H), 2.13–1.84 (m, 2H), 1.82–1.49 (m, 2H), 1.48–1.10 (m, 6H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 89.2, 86.5, 83.6, 80.7, 73.3, 72.2, 72.0, 69.2, 45.3, 37.4, 30.8, 25.8. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{32}H_{38}O_4SNa$ [M+Na$^+$] 541.2388, found 541.2384.

tert-Butyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside (9)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), *tert*-butylthiol (34 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **9** was obtained as a yellow syrup (28 mg, 24%, α/β = 100:0). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.42–7.15 (m, 15H), 5.53 (d, *J* = 2.9 Hz, 1H, α-anomeric proton), 4.65–4.38 (m, 6H), 4.31–4.27 (m, 1H), 4.00–3.95 (m, 2H), 3.66–3.60 (m, 2H), 1.40 (s, 9H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.8, 137.7, 128.4, 128.3, 128.3, 128.2, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 89.5, 86.0, 83.5, 79.8, 73.3, 72.2, 72.1, 69.3, 31.5. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{30}H_{36}O_4SNa$ [M+Na$^+$] 515.2232, found 515.2239.

4-Methylphenyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (10)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 4-methylbenzenethiol (36 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.36). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **10** was obtained as a yellow syrup (52 mg, 41%, α/β = 16:84). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50–7.15 (m, 17H), 7.09 (d, *J* = 7.8 Hz, 2H), 5.60 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.69–4.48 (m, 6H), 4.25 (t, *J* = 4.2 Hz, 1H), 4.21–4.16 (m, 1H), 4.09 (t, *J* = 3.7 Hz, 1H), 3.77 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.69 (dd, *J* = 10.1, 7.0 Hz, 1H), 2.31 (s, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.8, 137.4, 137.0, 131.6, 129.7, 128.4, 128.4, 128.3, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 90.4, 84.3, 83.5, 82.4, 73.4, 72.5, 71.9, 71.1, 21.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{33}H_{34}O_4SNa$ [M+Na$^+$] 549.2075, found 549.2092.

4-Chlorophenyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (11)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 4-chlorobenzenethiol (34 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.35). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **11** was obtained as a yellow syrup (57 mg, 43%, α/β = 14:86). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.50–7.13 (m, 19H), 5.62 (d, *J* = 4.8 Hz, 1H, anomeric proton), 4.67–4.42 (m, 6H), 4.30–4.24 (m, 1H), 4.23–4.13 (m, 1H), 4.09 (t, *J* = 3.7 Hz, 1H), 3.74 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.66 (dd, *J* = 10.0, 6.8 Hz, 1H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 137.7, 137.2, 132.3, 129.0, 128.5, 128.4, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.8, 127.6, 89.8, 84.3, 83.2, 82.6, 73.4, 72.6, 71.9, 70.9. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{32}H_{31}ClO_4SNa$ [M+Na$^+$] 569.1529, found 569.1531.

1-Naphthyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (12)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 100 mg, 0.24 mmol), 1-naphthalenethiol (40 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.30). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **12** was obtained as a yellow solid (64 mg, 47%, α/β = 86:14). α-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 8.52–8.40 (m, 1H), 7.89–7.73 (m, 3H), 7.59–7.37 (m, 3H), 7.33–7.24 (m, 15H), 5.60 (d, *J* = 2.5 Hz, 1H), 4.69–4.39 (m, 6H), 4.24 (t, *J* = 3.0 Hz, 1H), 4.04 (dd, *J* = 6.8, 3.3 Hz, 1H), 3.67–3.60 (m, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.1, 137.8, 137.4, 131.7, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 126.6, 126.2, 125.7, 125.5, 90.6, 88.8, 83.8, 80.9, 73.3, 72.3, 72.2, 69.2. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{36}H_{34}O_4SNa$ [M+Na$^+$] 585.2075, found 585.2066.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-D-arabinofuranoside (17a)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-D-arabinofuranoside **17** (α/β = 22:78, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **17a** was obtained as a yellow syrup (96 mg, 66%, α/β = 16:84). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.35–7.21 (m, 15H), 5.38 (d, *J* = 4.9 Hz, 1H, anomeric proton), 4.68–4.35 (m, 6H), 4.18–4.11 (m, 2H), 4.04 (t, *J* = 4.0 Hz, 1H), 3.68 (dd, *J* = 9.8, 6.4 Hz, 1H), 3.64 (dd, *J* = 9.9, 6.5 Hz, 1H), 2.67–2.61 (m, 2H), 1.64–1.55 (m, 2H), 1.43–1.18 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.2, 137.9, 137.6, 128.4, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 87.2, 84.4, 83.9, 82.9, 73.4, 72.4, 71.9, 71.4, 31.9, 31.3, 30.9, 30.0, 29.8, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3466.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-D-ribofuranoside (18a)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-D-ribofuranoside **18** (α/β = 53:47, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **18a** was obtained as a yellow syrup (105 mg, 73%, α/β = 17:83). β-Anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.34–7.24 (m, 15H), 5.21 (d, *J* = 4.0 Hz, 1H, anomeric proton), 4.66–4.49 (m, 6H), 4.27–4.25 (m, 1H), 4.01 (t, *J* = 5.4 Hz, 1H), 3.86 (t, *J* = 4.5, 1H), 3.60–3.56 (m, 2H), 2.67–2.58 (m, 2H), 1.64–1.55 (m, 2H), 1.30–1.25 (m, 18H), 0.89 (t, *J* = 6.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ_C 138.3, 137.8, 137.7, 128.4, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.7, 127.6, 127.6, 86.3, 81.7, 81.0, 78.3, 73.5, 73.4, 72.3, 70.9, 31.9, 31.2, 31.0, 30.1, 29.9, 29.7, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3463.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-D-xylofuranoside (19a)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-D-xylofuranoside **19** (α/β = 50:50, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R$_f$ = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiofuranoside **19a** was obtained as a yellow syrup (105 mg, 73%, α/β = 69:31). α-Anomer: **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.37–7.25 (m, 15H), 5.54 (d, *J* = 5.1 Hz, 1H, anomeric proton), 4.65–4.42 (m, 6H), 4.14 (dd, *J* = 5.2, 2.8 Hz, 1H), 4.08 (dd, *J* = 5.1, 2.8 Hz, 1H), 3.99 (t, *J* = 3.9, 1H), 3.77–3.63 (m, 2H), 2.68–2.62 (m, 2H), 1.66–1.57 (m, 2H), 1.30–1.25 (m, 18H), 0.88 (t, *J* = 6.4 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ_C 138.3, 138.0, 137.6, 128.5, 128.4, 128.4, 128.3, 127.9, 127.9, 127.9, 127.8, 127.6, 127.6, 87.3, 84.1, 82.2, 80.9, 73.4, 72.8, 72.2, 68.1, 31.9, 31.7, 30.8, 30.0, 29.9, 29.7, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 29.0, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3463.

Dodecyl 2,3,4-tri-*O*-benzyl-1-thio-β-L-arabinopyranoside (20a)

Glycosylation was carried out as described in the general procedure A by using 2,3,5-tri-*O*-benzyl-L-arabinopyranoside **20** (α/β = 37:63, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R$_f$ = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiopyranoside **20a** was obtained as a yellow syrup (86 mg, 60%, α/β = 0:100). β-Anomer: **^{1}H NMR** (400 MHz, CDCl$_3$) δ_H 7.28–7.16 (m, 15H), 5.13 (d, *J* = 3.8 Hz, 1H, anomeric proton), 4.67–4.41 (m, 6H), 3.93 (dd, *J* = 7.7, 3.9 Hz, 1H), 3.87 (dd, *J* = 11.7, 2.7 Hz, 1H), 3.73 (dt, *J* = 5.6, 2.8 Hz, 1H), 3.69–3.51 (m, 2H), 2.61 (t, *J* = 7.4 Hz, 2H), 1.69–1.59 (m, 2H), 1.31–1.13 (s, 18H), 0.80 (q, *J* = 7.4, 6.8 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, CDCl$_3$) δ_C 137.6, 137.4, 137.3, 127.4, 127.3, 127.0, 126.8, 126.7, 126.7, 126.6, 126.6, 82.7, 76.2, 75.1, 72.5, 72.0, 72.0, 70.7, 61.3, 38.3, 30.9, 29.5, 28.8, 28.7, 28.6, 28.6, 28.6, 28.5, 28.5, 28.3, 28.2, 28.2, 27.9, 27.5, 21.7, 13.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3485.

Dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-galactopyranoside (21a)

Glycosylation was carried out as described in the general procedure A by using 2,3,4,6-tetra-*O*-benzyl-D-galactopyranoside **21** (α/β = 66:34, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.32). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiopyranoside **21a** was obtained as a yellow syrup (56 mg, 32%, α/β = 65:35). Mixture of α and β-anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.49–7.06 (m, 20H), 5.46 (d, *J* = 5.5 Hz, 0.5H, α-anomeric proton), 4.96–4.38 (m, 8H), 4.42 (d, *J* = 9.2 Hz, 0.5H, β-anomeric proton), 4.34–4.19 (m, 1H), 3.94 (dd, *J* = 9.2, 2.8 Hz, 0.5H), 3.80 (dd, *J* = 9.8, 2.9 Hz, 0.5H), 3.66–3.37 (m, 4H), 2.80–2.61 (m, 1H), 2.60–2.35 (m, 1H), 1.73 – 1.44 (m, 2H), 1.38 – 1.21 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 137.6, 137.4, 137.3, 128.4, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.9, 127.8, 127.6, 127.6, 127.6, 127.5, 127.3, 127.4, 85.6, 84.1, 83.7, 79.6, 78.6, 76.7, 76.5, 76.3, 75.3, 74.8, 74.4, 73.7, 73.6, 73.3, 73.4, 72.8, 72.5, 69.7, 69.1, 68.9, 32.2, 31.9, 30.7, 29.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.0, 26.4, 23.4, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{46}H_{60}O_5SNa$ [M+Na$^+$] 747.4059, found 747.4084.

Dodecyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-glucopyranoside (22a)

Glycosylation was carried out as described in the general procedure A by using 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside **22** (α/β = 50:50, 100 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), and aqueous solution of 0.5 M DBSA (0.24 mmol, 0.5 mL). The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.32). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Thiopyranoside **22a** was obtained as a yellow syrup (78 mg, 45%, α/β = 64:36). Mixture of α and β-anomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 7.45–7.07 (m, 20H), 5.37 (d, *J* = 4.9 Hz, 0.5H, α-anomeric proton), 5.20–4.51 (m, 7.5H), 4.45 (dt, *J* = 11.6 , 5.3 Hz, 2H), 4.19 (d, *J* = 9.9 Hz, 0.5H, β-anomeric proton), 3.90–3.51 (m, 4H), 3.50–3.33 (m, 0.5H), 2.62–2.38 (m, 2H), 1.71–1.49 (m, 2H), 1.37–1.21 (m, 18H), 0.88 (t, *J* = 6.7 Hz, 3H). **^{13}C{^{1}H} NMR** (101 MHz, $CDCl_3$) δ_C 138.8, 138.6, 138.4, 138.3, 138.1, 138.1, 138.0, 138.0, 128.4, 128.4, 128.4, 128.1, 128.0, 128.0, 127.8, 127.8, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 86.7, 85.3, 83.5, 82.6, 81.9, 79.7, 79.2, 78.1, 77.6, 75.7, 75.7, 75.5, 75.0, 73.5, 72.4, 72.1, 70.5, 69.6, 69.2, 68.7, 31.9, 30.9, 30.0, 29.8, 29.7, 29.6, 29.6, 29.4, 29.3, 29.0, 22.7, 14.1. **HRMS** (MALDI-TOF): *m*/*z* calcd for $C_{46}H_{60}O_5SNa$ [M+Na$^+$] 747.4059, found 747.4035.

Control Experiment *Scheme 4, Equation 1*

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-β-L-arabinofuranoside **1a** (α/β = 0:100, 56 mg, 0.09 mmol) was added in a microwave vessel followed by aqueous solution of 0.5 M DBSA (0.09 mmol, 0.18 mL, 1 equivalent). The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. Then the reaction was carried out as described in the general procedure A and monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.50). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 1:19 to 3:7 as eluent. Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside **1a** was obtained as a yellow syrup (25 mg, 45%, α/β = 100:0) and 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** was obtained as white solid (18 mg, 46%). Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside **1a**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.45–7.14 (m, 15H), 5.34 (d, *J* = 2.3 Hz, 1H, anomeric proton), 4.67–4.42 (m, 6H), 4.30–4.25 (m, 1H), 3.93 (2H), 3.62 (dd, *J* = 10.9, 3.7 Hz, 2H), 2.62 (d, *J* = 6.7 Hz, 2H), 1.74–1.49 (m, 2H), 1.46–1.10 (m, 18H), 0.84 (s, 3H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 137.1, 136.8, 136.4, 127.4, 127.4, 127.3, 127.0, 126.9, 126.8, 126.7, 126.6, 87.8, 86.5, 82.6, 78.9, 72.3, 71.2, 71.0, 68.1, 30.9, 30.3, 28.6, 28.6, 28.5, 28.3, 28.2, 27.9, 21.7, 13.1. **HRMS** (ESI-QTOF): *m/z* calcd for $C_{38}H_{52}O_4SNa$ [M+Na$^+$] 627.3484, found 627.3481.

Control Experiment *Scheme 4, Equation 2*

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-α-L-arabinofuranoside **1a** (α/β = 100:0, 7.5 mg, 0.01 mmol) was added in a microwave vessel followed by aqueous solution of 0.5 M DBSA (0.02 mmol, 0.04 mL, 2 equivalent). The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. Then the reaction was carried out as described in the general procedure A and monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.15). The crude mixture was purified by column chromatography using ethyl acetate:hexanes = 3:7 as eluent to remove DBSA. The yield of 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** was determined by ^{1}H NMR integration as 78%.

Control Experiment *Scheme 4, Equation 3*

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside **1a** (α/β = 7:93, 167 mg, 0.28 mmol) and 1-dodecanethiol (0.08 mL, 0.33 mmol, 1.2 equivalents) were added in a microwave vessel followed by aqueous solution of 0.5 M DBSA (0.28 mmol, 0.56 mL, 1 equivalent). The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. Then the reaction was carried out as described in the general procedure A and monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 0:1 to 3:7 as eluent. Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside **1a** was recovered as yellow syrup (147 mg, 88%, α/β = 19:81) and 2,3,5-tri-*O*-benzyl-L-arabinofuranoside **1** was obtained as white solid (12 mg, 10%).

Gram-scale synthesis of dodecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (1a) *Scheme 4, Equation 4*

2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 1.04 g, 2.49 mmol) and 1-dodecanethiol (0.71 mL, 2.98 mmol, 1.2 equivalents) were added in a microwave vessel followed by aqueous solution of 0.75 M DBSA (2.50 mmol, 3.35 mL, 1 equivalent). The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography. After 5 h, the reaction was quenched by adding saturated $NaHCO_3$ solution (15 mL), extracted with ethyl acetate (5 × 20 mL), and washed with brine (15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes from 1:19 to 3:7 as eluent. Thiofuranoside **1a** was obtained as a yellow syrup (988 mg, 66%, α/β = 7:93), α,α-disaccharide (**23**) was obtained as colorless syrup (70 mg, 7%), and 1-hydroxy sugar **1** was recovered as a white solid (125 mg, 12%). The coupling was 88% conversion and 75% yield based on recovered starting materials. 2,3,5,2',3',5'-Hexa-*O*-benzyl-α,α-L-arabinofuranoside (**23**)[51]: **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.49–7.14 (m, 30H), 5.51 (s, 2H, 2 anomeric protons), 4.64–4.46 (m, 12H), 4.26 (dt, J = 8.3, 3.0 Hz, 2H), 4.13–4.08 (m, 2H), 3.96 (dd, J = 7.1, 3.3 Hz, 2H), 3.65 (qd, J = 10.8, 4.7 Hz, 4H). **^{13}C{^{1}H} NMR** (126 MHz, $CDCl_3$) δ_C 138.2, 138.0, 137.6, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 102.2, 88.0, 83.9, 81.3, 73.5, 72.3, 72.0, 69.9, 32.0, 31.7, 29.8, 29.8, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 22.8, 22.8, 14.3. **HRMS** (ESI-QTOF): *m*/*z* calcd for $C_{52}H_{54}O_9Na$ [M+Na$^+$] 845.3666, found 845.3659.

General procedure B: Bronsted acid/nonionic surfactant-mediated glycosylation of 1-hydroxy sugar in water

In a typical procedure, all nonionic surfactants (TPGS-750-M, Nok, and Coolade) were prepared as 2% w/w aqueous solution. 1-Hydroxy sugar (0.24 mmol), thiol (0.29 mmol, 1.2 equivalents), and Bronsted acid (0.1 or 1.0 equivalent) were added in a microwave vessel followed by 2% w/w nonionic surfactant and final concentration was adjusted to 0.5 M based on 1-hydroxy sugar. The reaction mixture was placed in the microwave reactor and irradiated at 80 °C for 5 h. The reaction was monitored by thin-layer chromatography. After 5 h, the reaction was quenched by adding saturated $NaHCO_3$ solution (2.5 mL), extracted with ethyl acetate (5 × 2.5 mL), and washed with brine (3 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness in a rotary evaporator. The crude product was purified by column chromatography on silica gel using gradient elution with ethyl acetate:hexanes.

Dodecyl 2,3,5-tri-*O*-benzyl-1-thio-L-arabinofuranoside (1a) *Table 2 entry 13*

The glycosylation was carried out as described in the general procedure B except the vessel was irradiated under microwave at 120 °C. 2,3,5-Tri-*O*-benzyl-L-arabinofuranoside **1** (α/β = 53:47, 101 mg, 0.24 mmol), 1-dodecanethiol (70 μL, 0.29 mmol), *p*-TsOH·H_2O (41 mg, 0.24

mmol) and 2% w/w aqueous solution of TPGS-750-M (0.50 mL) were combined in a vessel and irradiated under microwave at 120 °C for 5 h. The reaction was monitored by TLC (ethyl acetate:hexanes = 1:4; *p*-anisaldehyde, R_f = 0.40). The crude mixture was purified by column chromatography using gradient elution with ethyl acetate:hexanes from 1:19 to 3:7 as eluent. Thiofuranoside **1a** was obtained as a yellow syrup (115 mg, 79%, α/β = 24:76).

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C3_008_OF: SYNTHESIS OF THIOFURANOSIDE BY DEHYDRATIVE GLYCOSYLATION IN MICELLAR MEDIA

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Abstract: Chemical synthesis uses organic solvents as reaction media and produces a vast amount of organic waste. Increasing environmental concerns led us to consider replacing organic solvents with water as reaction media. Herein, we report dehydrative glycosylation of perbenzylated-L-arabinose with aliphatic, aromatic, and heterocyclic thiols in aqueous media to afford thiofuranosides. Dehydration was mediated by Brønsted acid-surfactant, dodecylbenzenesulfonic acid (DBSA) in water. Microwave irradiation led to improvement of yields and shorter reaction times. Other reaction parameters such as temperature and the amount of acid used were also optimized. Aliphatic, aromatic, and heterocyclic thiofuranosides were prepared from 2,3,5-tri-*O*-benzyl-L-arabinofuranose in moderate yields (22–72%). From this study we conclude that the hydrophobicity of the substrates is an important factor in the success of this reaction. The addition of Lewis acid to increase the yield, and mechanistic studies are under way.

Introduction: Strict environmental concerns have demanded that clean reaction processes should use water instead of harmful organic solvents such as ethyl acetate, dichloromethane, methanol, and tetrahydrofuran in accordance with the 12 green chemistry principles.[1] In particular, there are various advantages of using water as a solvent. First, in comparison with other organic solvents, water is cheap and safe. In addition, water has a large heat capacity allowing for easy control of the reaction temperature.[2-3] Consequently, chemists pursue these concepts and try to carry out the chemical reactions in water. The first study of Diels-Alder reaction in green solvent was reported by Breslow and co-workers in the early 1980s.[4] It revealed that the Diels-Alder reaction could be accelerated by hydrophobic interactions of poor water soluble starting materials in water. Moreover, the rate of reaction was a hundred times faster than in protic and aprotic organic solvents. Since then, there have been a large number of studies of organic reactions in aqueous media. Nonetheless, the challenge is that most organic compounds are insoluble in water. Moreover, many sensitive functional groups will decompose in aqueous media. An alternative method to improve these obstacles is to add a surfactant so that it forms a micellar system.[5–7] Dodecylbenzenesulfonic acid (DBSA) has a structure as shown in Figure 1, and has been widely used as a surfactant in aqueous solution.[8–12] Dodecylbenzenesulfonic acid and polymer supported sulfonic acid were reported by Kobayashi and co-workers in 2002.[13] Furthermore, they studied DBSA-catalyzed dehydrative glycosylation of D-ribofuranose and various alcohols in 2006.[14]

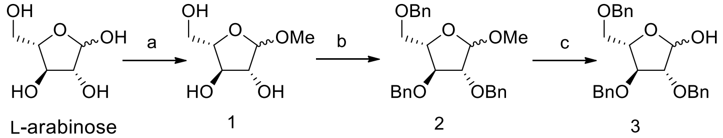
Thiofuranoside is the precursor to synthesis of decaprenolphophoarabinose (DPA), antitubercular agent. It can inhibit arabinosyl trasferases and arabinan biosynthesis, which are vital process for bacterial survival.[15] In this work, we report a green method to synthesize thiofuranosides from L-arabinose and various thiols in micellar conditions promoted by DBSA.

Figure 1. Illustration of dehydrative glycosylation between L-arabinose and thiols in the presence of dodecylbenzenesulfonic acid (DBSA)

Methodology:

Material: All chemicals and reagents were purchased from commercial sources and used without further purification. Stock solutions of DBSA surfactant were prepared using MilliQ water to provide the desired concentration for each reaction. NMR spectra were recorded at 400 MHz for ^{1}H experiments and 100 MHz for ^{13}C experiments using $CDCl_3$ as NMR solvent. Tetrachloroethane was used as an internal standard for calculating the NMR yields of reactions.

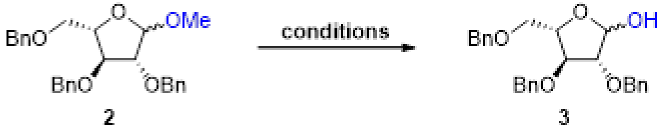
Preparation of 2,3,5-tri-O-benzyl-L-arabinofuranose (3): L-arabinose was used as a precursor for the preparation of 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**3**).[16] Methyl L-arabinofuranoside (**1**) was synthesized by dissolving commercially available L-arabinose in anhydrous methanol followed by dropwise addition of propionyl chloride. The *in situ* generated HCl in MeOH acted as a catalyst to accelerate MeOH substitution at anomeric position of L-arabinose (Scheme 1). The reaction mixture was stirred for 4 h at room temperature. It should be noted that longer reaction times led to the formation of >10% of methyl L-arabinopyranoside side products.



Scheme 1. Synthesis of **3**; (a) propionyl chloride, anhydrous MeOH, rt, 4h (b) NaH, BnBr, TBAI, DMF, 0 °C to rt, o/n, 40% yield (over 2 steps) ; (c) CH_3COOH, H_2O, µwave, 150 °C, 2 h, 90% yield.

The next step was to protect the alcohol groups as benzyl ethers using BnBr, NaH as base and catalytic amount of tetrabutylammonium iodide (TBAI). The desired product **2** was obtained in 40% yield over 2 steps.[17] Finally, the anomeric methoxy group was deprotected under acidic conditions.[18] Surprisingly, the cleavage was not straightforward as we expected due to high stability of the furanose (**2**). Several conditions were examined (Table 1, entries 1–11) and found that the best conditions were performed by microwave irradiation at 150 °C for 2 h (entry 11). It gave the desired product **3** in 90% yield. The investigation of this deprotection was presented in Table 1. 2,3,5-Tri-O-benzyl-L-arabinofuranose (**3**) was synthesized according to the following procedure: compound **2** (500 mg, 1.15 mmol) and a 1:4 mixture of acetic acid and MilliQ water (2.5 mL) were added in the microwave vessel. The reaction mixture was irradiated by microwave at 150 °C for 2 hours. It was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 × 3.0 mL), and washed once with brine (3.0 mL). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes 0:1 to 1:0 eluent. 2,3,5-Tri-*O*-benzyl-L-arabinofuranose (**3**) was obtained as a pale yellow solid as isomeric mixture of α:β (379 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 3.48–3.63 (m, 2H), 3.93 (s,1H), 3.99–4.03 (m, 1H), 4.07–4.11 (m, 1H), 4.14–4.18 (m, 1H), 4.41–4.69 (m, 6H), 5.28–5.43 (m, 1H, anomeric proton), 7.18–7.42 (m,15H).

Table 1. Optimization for the hydrolysis of methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**2**).



Entry	Conditions	Temperature (ºC)	Time (h)	Yield (%)
1	CH_3COOH, 1.0 M H_2SO_4 (2:1)	70	72	trace[a]
2	CH_3COOH, 2.0 M H_2SO_4, THF (2:1:1)	100	48	trace[a]
3	0.1M HCl, dioxane (1:1)	60	48	NR
4	0.1M DBSA, H_2O (1:1)	80	48	NR
5	CH_3COOH:H_2O (1:4)	115	24	30
6	0.1M HCl, dioxane (1:1)	70, μwave	1	30
7	CH_3COOH:H_2O (1:4)	115, μwave	0.45	55
8	CH_3COOH:H_2O (1:4)	115, μwave	1	60
9	CH_3COOH:H_2O (1:4)	125, μwave	2	65
10	CH_3COOH:H_2O (1:4)	130, μwave	2	72
11	CH_3COOH:H_2O (1:4)	150, μwave	2	90

[a]It was detected by TLC. μwave = microwave, NR = No reaction

General Procedure for the Synthesis of Thiofuranosides: 2,3,5-Tri-*O*-benzyl-L-arabinofuranose (**3**) (100 mg, 0.24 mmol) and 1-dodecanethiol (70 μL, 0.29 mmol) were added in a microwave vessel followed by a stock solution of 0.5 M DBSA (0.5 mL). It was stirred in a microwave reactor at 80 ºC for 5 h. The reaction was monitored by thin-layer chromatography (25% ethyl acetate in hexanes eluent, *p*-anisaldehyde, R_f = 0.5). After the reaction reached to the completion, it was quenched with saturated $NaHCO_3$ solution (1.5 mL), extracted with ethyl acetate (3 × 2.5 mL), and washed with brine (3.0 mL). The combined organic layer was dried using anhydrous $MgSO_4$ and concentrated to dryness in a rotatory evaporator. The crude product was purified by column chromatography on silica gel using gradient ethyl acetate:hexanes 0:1 to 3:7 eluent. Dodecylthio 2,3,5-tri-*O*-benzyl-L-arabinofuranose (**4**) was obtained as a yellow syrup (105 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.88 (t, J = 6.5 Hz, 3H), 1.15–1.45 (m, 18H), 1.65–1.73 (m, 2H), 2.50–2.76 (m, 2H), 3.44–3.77 (m, 2H), 3.98 (s, 1H), 4.04 (d, J = 3.8 Hz, 1H), 4.11–4.19 (m, 1H), 4.40–4.70 (m, 6H), 5.30–5.42 (m, 1H, anomeric proton), 7.14–7.42 (m, 15H).

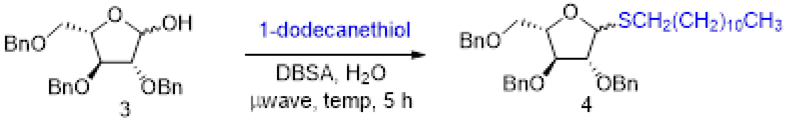
Results and Discussion: We first chose to examine dehydrative glycosylation of **3** with 1-dodecanethiol in the DBSA micellar conditions. Both precursors are relatively hydrophobic molecules thus they were selected as model substrates. In order to find the optimal reaction conditions, the amount of surfactant used, the reaction time and temperature were varied and the results are summarized in Table 2.

Initially, we started with 10 mol% of DBSA at 80 °C to afford a mixture of anomeric products (**4**), albeit in poor 36% yield (entry 1). From TLC monitoring, some starting material was not consumed and was recovered after column chromatography. We therefore calculated the product yield in term of brsm (based on recovered starting material) in order to elucidate the accuracy yield. When the amount of surfactant used was increased to stoichiometric levels, the product was obtained in significantly higher yield (entries 2–7). Employing excess DBSA (entry 8) resulted in a viscous solution which was difficult to stir. The reaction temperature also affected the yield of the desired product. When the temperature was lowered from 80 ºC to 40 ºC and 60 ºC, % yield decreased from 72 to 44 and 57, respectively (entries 9–10). On the other hand, when the temperature was raised to 100 ºC or 120 ºC, either a lower yield was obtained (entry 11) or the reaction mixture decomposed within 1 h (entry 12). Additionally, the product was obtained in 54% yield from conventional heating (entry 13), but the reaction time was much longer (28 h vs 5 h). It was absolutely clear that without DBSA, the product was not formed (entry 14). Hence, the optimal reaction conditions were 100 mol% DBSA at 80 ºC under microwave irradiation (entry 7).

Figure 2 represents TLCs and reaction vessels of the dehydrative glycosylation. It showed that a milky suspension of 10 mol% DBSA at 80 ºC (Table 2, entry 1) gave low yield (Figure 2a). In contrast, high yield of the product was afforded from a pale-yellow suspension with 100 mol% DBSA at 80 ºC

(Table 2, entry 7) (Figure 2b). In addition, the reaction mixture decomposed within 1 h of microwave irradiation and changed to a black-brown solution (Figure 2c) at 120 °C (Table 2, entry 12).

Table 2. Optimization of dehydrative glycosylation



Entry	DBSA (mol %)	Temperature (°C)	Yield (%)
1	10	80	36 (40 brms)
2	20	80	56 (75 brms)
2	30	80	51 (98 brms)
4	40	80	50 (77 brms)
5	50	80	54 (78 brsm)
6	80	80	65 (93 brsm)
7	100	80	72 (99 brsm)
8	200	80	69 (95 brsm)
9	100	40	44 (99 brsm)
10	100	60	57 (99 brsm)
11	100	100	64 (80 brsm)
12	100	120	decomposition[a]
13	100	80	54[b] (84 brsm)
14	0	80	NR

[a]The reaction mixture decomposed at 120 °C within 1 h. [b]The product was obtained under conventional heating for 28 h. µwave = microwave, brsm = based on recovered starting material, NR = No reaction

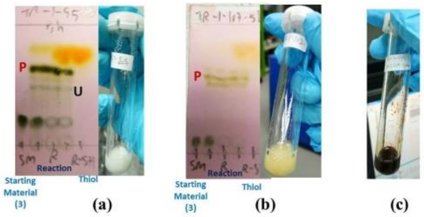


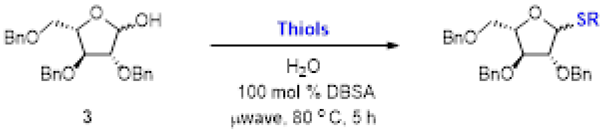
Figure 2. TLCs and reaction mixture vessels. (a) 10 mol% DBSA, 80 °C (Table 1, entry 1). (b) 100 mol% DBSA, 80 °C (Table 1, entry 7). (c) 100 mol% DBSA, 120 °C (Table 1, entry 12).

Next, the scope of the *S*-nucleophile was investigated as shown in Table 3. The desired products from the primary and secondary aliphatic thiols (**5**, **6**, **8**, and **15**) were obtained in the moderate yields. Nevertheless, the product (**7**) was obtained in low yield for tertiary aliphatic thiol. In case of less reactive nucleophile such as aromatic and heterocyclic thiols, the products (**10**, **11**, **12**–**14**) were obtained in the low yield. 2-Thiazoline-2-thiol gave only trace amount of products (**9**) and the yields of the products were calculated by NMR. We next attempted to improve the yield of the reaction by addition of a Lewis acid.

Generally, Lewis acids are not used in aqueous media as most are unstable in water. However, lanthanide trifluoromethanesulfonates (lanthanide triflates) such as $La(OTf)_3$, $Yb(OTf)_3$, $Eu(OTf)_3$, $Gd(OTf)_3$, and $Sc(OTf)_3$ Lewis acids were reported to be stable in aqueous solution,[19–20] and so we attempted the glycosylation of compound **3** with 1-dodecanethiol in the presence of $Sc(OTf)_3$.The results are summarized in Table 3. We found that the effect of the Lewis acid was dependent on the structure of the thiol acceptor. In case of 1-dodecanethiol, the addition of Lewis acid led to reduction of yields of compound **5**. Whereas with 1-octadecanethiol nucleophile, addition of $Sc(OTf)_3$ improved the yields of **8**. In view of these results, we are currently investigating the effect of Lewis acids in the DBSA-mediated synthesis of thioglycosylations in aqueous solutions.

We propose that the reaction begins by protonation of the anomeric hydroxyl group to form an oxocarbenium ion. The hydrophobic micelle core repels water and expulses it out of the micelle. Lastly, the thiol nucleophile attacks the oxocarbenium ion and the acid is regenerated as shown in Figure 3.

Table 3. Synthesis of thiofuranosides by dehydrative glycosylation



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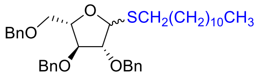
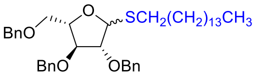
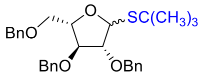


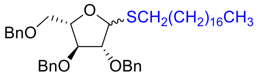
5 (α:β = 1:1, 72% yield)
(α:β = 1:1, 59% yield)[a]
(α:β = 1:1, 48% yield)[b]
(α:β = 1:1, 40% yield)[c]



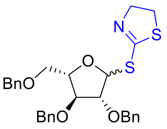
6 (51% yield)



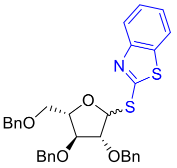
7 (α:β = 2:1, 24% yield)[a,d]



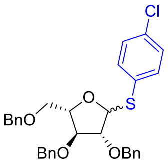
8 (α:β = 4:1, 62% yield)[a]
(α:β = 4:1, 57% yield)



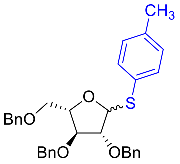
9 (Trace)[a]



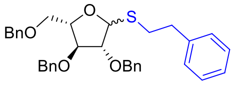
10 (α:β = 1:5, 22% yield)[a,d]



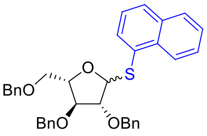
11 (α:β = 1:1, 43% yield)[a]



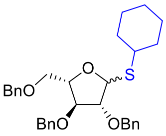
12 (α:β = 1:5, 41% yield)



13 (α:β = 1:2, 42% yield)[a]



14 (α:β = 7:1, 43% yield)[a]



15 (45% yield)[a]

[a] 10 mol% $Sc(OTf)_3$, [b] 10 mol% $Sc(OTf)_3$ and 50 mol% DBSA, [c] 10 mol% $Sc(OTf)_3$ and 30 mol% DBSA, [d] % conversion from ^1H NMR calculation

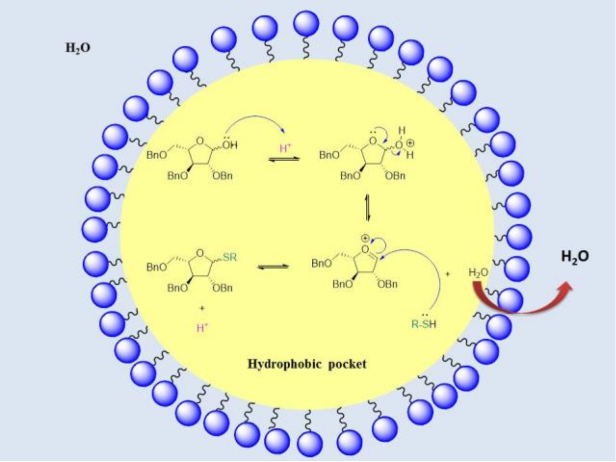


Figure 3. A proposed mechanism for the DBSA mediated synthesis of thiofuranoside in aqueous solutions.

Conclusion: A novel and environmentally friendly method for the synthesis of various thiofuranosides from L-arabinose precursor was developed. The use of water as the solvent avoids the use of toxic and hazardous organic solvents. The reaction conditions were optimized and it was found that the reaction tolerated a wide variety of thiols, including alkyl, aryl, and heterocyclic thiols. Performing the reaction in a microwave reactor significantly increased the yields and reduced the reaction times. We are currently investigating whether the yields can be further improved in the presence of a Lewis acid such as $Sc(OTf)_3$.

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