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The application of phenylmethanethiol and benzenethiol derivatives as odorless organosulfur reagents in the synthesis of thiosugars and thioglycosides

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Abstract—*p*-Octyloxyphenylmethanethiol and *p*-dodecylbenzenethiol were prepared as new odorless organosulfur reagents. Thiosugars and thioglycosides were synthesized using these reagents without encountering any malodorous procedures.

Keywords: Odorless organosulfur reagents; Thiosugars; Thioglycosides; *p*-Octyloxyphenylmethanethiol; *p*-Dodesylbenzenethiol

1. Introduction

Thiosugars, in which the ring oxygen of the monosaccharide is replaced with a sulfur atom, have been utilized in the synthesis of bioactive oligosaccharides as excellent analogs of monosaccharides because of their tolerant reactivity with glycosidases.[1] Naturally occurring thiosugar derivatives, as well as synthesized derivatives, show inhibitory activity against glycosidases, for example, salacinol isolated from *Salacia reticulata* is a potent inhibitor of α-glucosidases.[2] On the other hand, thioglycosides in which the anomeric carbon is linked to a sulfur atom have been often prepared as valid glycosyl donors for use in glycosidation reactions.[3] However, in the preparation of both thiosugars and thioglycosides, malodorous reagents such as phenylmethanethiol and benzenethiol have been unavoidably employed as the reagents for the source of sulfur.

Recently, we have devised odorless thiols and methyl sulfides that are useful in the Corey–Kim oxidation, in the demethylation of methyl ethers or methyl esters, and in the reductive workup procedure of ozonolysis and other sulfur-related reactions, except for the introduction of sulfur groups (BnS, PhS, HS).[4a–g] In addition, we found that the complexes of borane with the odorless sulfides were no less useful reagents than is the borane·dimethyl sulfide complex in the hydroboration and reduction of carbonyl groups.[4h] Therefore, we next tried to develop new odorless organosulfur reagents that are suitable for the preparation of thiosugars and thioglycosides as a part of our study on odorless organic synthesis.

2. Results and discussion

Initially, we tried to modify the structure of odorless *p*-heptylphenylmethanethiol (**4**), but the approach was dropped because of the unsatisfactory overall yield when the reagent was prepared from dibromoxylene.[4a] Since thiols and sulfides having more than 14 tandem-linked carbons do not smell at all due to the increase in molecular weight,[4a] *p*-hexyloxyphenylmethanethiol (**5**) was designed as a new type of odorless thiol by the replacement of one methylene of **4** with an oxygen atom.

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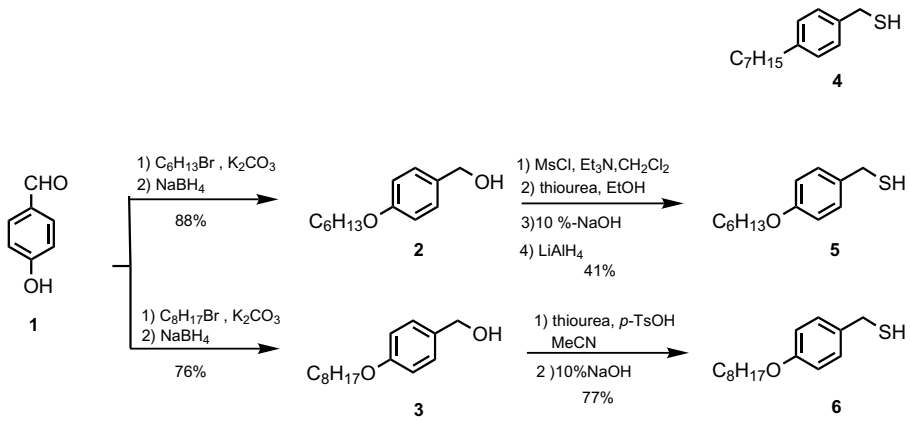


Scheme 1.

O-Alkylation of *p*-hydroxybenzaldehyde (**1**) with bromohexane in the presence of potassium carbonate, followed by reduction with sodium borohydride, gave *p*-hexyloxybenzyl alcohol (**2**), which was converted to **5** in satisfactory yield by the sequence of mesylation, substitution with thiourea, alkaline hydrolysis, and reduction with lithium aluminum hydride. Unfortunately **5** was still slightly malodorous. Accordingly, *p*-octyloxyphenylmethanethiol (**6**), which has two more methylenes than **5**, was synthesized as a new odorless phenylmethanethiol derivative on the basis of our experience of odor tests.[4a] The synthetic route of **6** was quite similar to that of **5**, that is, **1** was treated with bromooctane, followed by reduction with sodium borohydride, to give *p*-octyloxybenzyl alcohol (**3**), which was converted to **6** via the thionium salt in good yield. As expected, **6** was odorless due to its lower volatility (Scheme 1).[4a]

On the other hand, alkylbenzenethiol and its analogs (**10a**–**c**) that have different methylene lengths can be prepared from *p*-alkylphenols (**7a**–**c**) by taking advantage of the Newman–Kwart rearrangement, the O→S rearrangement from **8a**–**c** to **9a**–**c**, in excellent yields (Scheme 2).[4b,5] As expected, the alkylbenzenethiols with longer alkyl chains became less malodorous (Table 1).

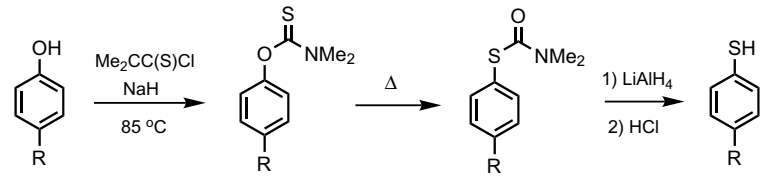
In spite of containing a small amount of analogs having more or less methylenes, dodecylbenzenethiol (**10d**)[6] having five more methylenes in length than **10b** was easily prepared by reduction with lithium aluminum hydride from 4-dodecylbenzenesulfonic acid (**11**), which is available as an inexpensive material used in synthetic detergents.[†] In addition, reduction of dodecylbenzenesufonyl chloride (**12**)[‡] yielded a better result (see Scheme 3).

Having succeeded in the synthesis of odorless benzylmethanethiol (**6**) and benzenethiol (**10b**, **10d**), we applied these reagents to the synthesis of thiosugars and thioglycosides.

Methyl 3,5-di-*O*-benzyl-2-deoxy-D-*erythro*-pentofuranoside (**13**) was treated with **6** to afford the bis(4-octyloxy)benzyl dithioacetal **14a**.[7] The hydroxyl group was mesylated, and the following intramolecular attack of a sulfur atom to the mesylated carbon in the presence of sodium iodide and barium carbonate gave 4-octyloxybenzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-L-*threo*-pentofuranoside (**15a**). It is noteworthy that the combination of bis(4-octyloxy)benzyl dithioacetal **14a** and DMF provided a much better result in this reaction than that of the bisbenzyl dithioacetal **14b** and acetone to afford **15b**.[7] In order to prepare 3,5-di-*O*-benzyl-2-deoxy-5-thio-D-*erythro*-pento-furanoside, the configuration of the hydroxyl group at C-4 should be inverted in advance of nucleophilic substitution on the mesylated carbon. Therefore, the configuration of the secondary alcohol of **14a** was first inverted to afford **16a** by the Mitsunobu reaction with triphenylphosphine, benzoic acid, and DIAD, and following alkaline hydrolysis, gave **16b**. Mesylation of the hydroxyl group of **16b** and successive treatment with sodium iodide and barium carbonate gave 4-octyloxybenzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside (**17**) (Scheme 4). The overall yield from **13** to **17** was six times higher than that reported in the literature.[7]

Thioglycosides (**19a**–**c**) were next prepared using dodecanethiol (**10e**), **10b**, and **10d** as valid glycosyl donors for glycosidation. Per-*O*-acetylated D-glucopyranoside (**18**) was treated with **10e**, **10b**, and **10d**, respectively, in the presence of $BF_3{\cdot}Et_2O$ to afford **19a**–**c**. Here, the thioglycoside (**19c**) thus obtained was used as the glycosyl donor without purification. Glycosylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**20**) with **19a**–**c** in the presence of *N*-iodosuccinimide (NIS) and $BF_3{\cdot}Et_2O$ gave methyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**21**)

[†] Because **11** was purchased as an industrial-grade material, it included analogs with more or less methylenes as contaminants within ca. 5%.
[‡] Compound **12** was purchased from Wako Pure Chemical Industries, Ltd., Japan.

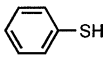
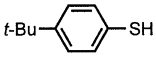
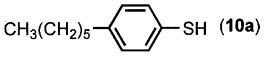
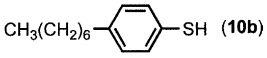
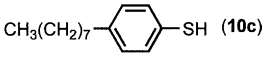
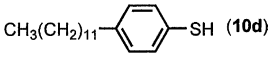


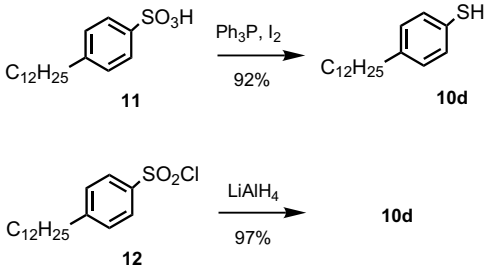
7 8 9 10

a: R = C_6H_{13}	100%	295 °C	81%	96%
b: R = C_7H_{15}	100%	260 °C	74%	80%
c: R = C_8H_{17}	93%	300 °C	84%	88%

Scheme 2.

Table 1. The odor scale of benzenethiols

Entry	Thiols	Carbon length	Odor scale	
			A	B
1		4	5	5
2		6	2	1
3	 (**10a**)	10	0	2
4	 (**10b**)	11	1	0
5	 (**10c**)	12	1	1
6	 (**10d**)	16	0	0



Scheme 3.

in better yields than the reaction with **19d** prepared from benzenethiol and **18** under malodolous conditions.[8] In addition, the glycosylation with alkylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-D-glucopyranoside (**19b**, **19c**) gave only the β-(1→6)-linked glycoside of **21** as same as the reaction with **19d**, while the reaction with dodecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-glycopyranoside (**19a**) gave a mixture of α and β anomers of **21**. Finally, it is noteworthy that all the steps from the preparation of thioglycosides to glycosidation proceeded without the generation of a stench (Scheme 5).

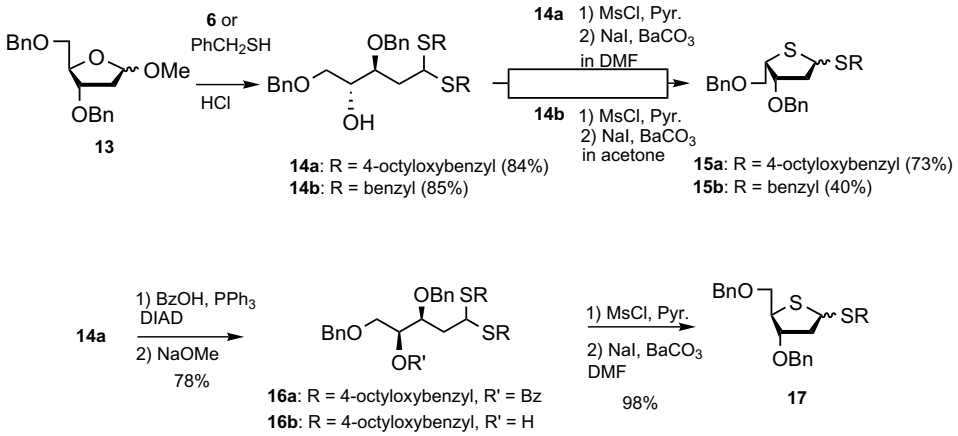
3. Experimental

3.1. General

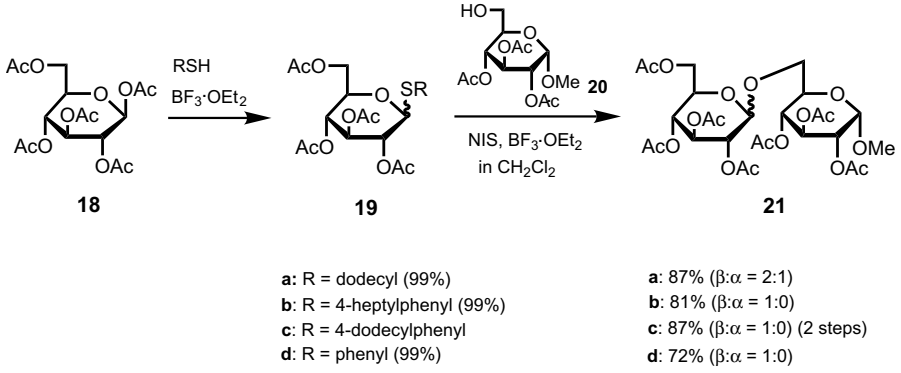
Infrared (IR) spectra were recorded on a JASCO IR-810 or a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer. ^{1}H NMR spectra were obtained on a JEOL JNM-AL300, a Varian XL-300, or a Varian Unity INOVA-400 spectrometer with tetramethylsilane as the internal standard. ^{13}C NMR spectra were obtained on a Varian Unity INOVA-400 spectrometer with $CDCl_3$ as the internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Wako Gel C-200 (silica gel) (100–200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed by using Silica Gel 60N (Kanto Chemical Co., Inc.) as a solid support for the immobile phase. Kieselgel 60 F-254 plates (E. Merck) were used for thin-layer chromatography (TLC). Unless purification with silica gel gave a compound that was deemed pure enough, the compounds were further treated with a recycle-mode HPLC (JAI LC-908) on a GPC column (JAIGEL 1H and 2H). In this case diastereomeric mixtures were also separated by a recycle-mode HPLC (JAI LC-908) on a silica gel column (Kusano Si-10) after the purification mentioned above.

3.2. *p*-Octyloxyphenylmethanol (3)

A mixture of *p*-hydroxybenzaldehyde (**1**, 15.0 g) and K_2CO_3 (33.9 g) in DMF (100 mL) was heated at 90 °C for 1 h, and chilled to room temperature. After adding bromooctane (25.4 mL), the mixture was stirred for 3 h and filtered. The filtrate was condensed in vacuo, diluted with MeOH (100 mL), and treated with $NaBH_4$



Scheme 4.



Scheme 5.

(13.9 g) for 1.5 h. After the reaction, MeOH was evaporated and partitioned between Et_2O and water. The organic layer was successively washed with molar HCl and brine, dried over $MgSO_4$, and evaporated. Crystallization of the residue from *n*-hexane and further purification of its mother liquor by silica gel column chromatography (5:1 hexane–AcOEt) afforded **3** (27.2 g, 94%) as colorless plates: mp 45.5–46.5 °C; IR: 3606, 3446, 3022–2871, 2360, 1612–1583, 1512–1469 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.27 (m, arom 2H), 6.89 (dt, *J* 8.7, 2.5 Hz, arom 2H), 4.61 (s, 2H), 3.95 (t, *J* 6.5 Hz, 2H), 1.77 (quintet, *J* 5.6 Hz, 2H), 1.54 (s, 1H), 1.45 (quintet, *J* 7.1 Hz, 2H), 1.39–1.28 (m, 8H), 0.89 (br t, *J* 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 132, 128.6 (2C), 114.6 (2C), 68, 65, 31, 29.3, 29.25, 29.23, 26, 22.6, 14.1; MS: *m*/*z* 236 (M^+, 23.8), 124 (100), 106 (57); HRMS: Calcd for $C_{15}H_{24}O_2$, *m*/*z* 236.1776; found, *m*/*z* 236.1780. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.04; H, 10.26. Found: C, 76.23; H, 10.24.

3.3. *p*-Octyloxyphenylmethanethiol (6)

p-Octyloxyphenylmethanol (**3**) (250 mg, 1.06 mmol) and *p*-TsOH·H_2O (190 mg) were added to a solution of thiourea (80 mg, 1.1 mmol) in acetonitrile (25 mL), and the reaction mixture was refluxed for 1 h. After adding 10% aq NaOH, the mixture was refluxed for another 4 h, and the reaction solution was acidified with 2.5 M HCl until the pH value reached pH 1. The reaction mixture was extracted with Et_2O, and the organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (5:1 hexane–benzene) to afford **6** (208 mg, 77%). IR ($CHCl_3$): 3021–2856, 2580, 1610–1583, 1512–1434 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dt, *J* 8.79 and 2.51 Hz, arom 2H), 6.83 (dt, *J* 8.8 and 2.6 Hz, arom 2H), 3.93 (t, *J* 6.6 Hz, 2H), 3.71 (d, *J* 7.3 Hz, 2H), 1.76 (quintet, *J* 7.3 Hz, 1H), 1.73 (t, *J* 7.3 Hz, 1H), 1.51–1.27 (m, 10H), 0.89 (br t, *J* 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 133.0, 129.1 (2C), 114.6 (2C), 29.34, 29.30, 29.2, 28.4, 26.0, 22.6, 14.1. MS (20 eV): *m*/*z* 252 (M^+, 5), 219 (69), 151 (8), 107 (100); HRMS: Calcd for $C_{15}H_{24}OS$, *m*/*z* 252.1548 (M^+); found, *m*/*z* 252.1551.

3.4. *O*-*p*-Hexylphenyl *N*,*N*-dimethylthiocarbamate (8a)

A solution of *p*-hexylphenol (**7a**) (1.0 g, 5.6 mmol) in DMF (5.0 mL) and *N*,*N*-dimethylthiocarbamoyl

chloride (832 mg, 6.73 mmol) was successively added to a suspension of NaH (175 mg, 7.29 mmol) in DMF (20 mL) at 0 °C, and the mixture was stirred at 85 °C for 15 h. After the reaction was complete, 2% aq KOH was added to the reaction mixture, which was then extracted with Et_2O. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (4:1 hexane–AcOEt) to afford **8a** (1.5 g, 100%). IR ($CHCl_3$): 3337, 2959, 2932, 2858, 1886, 1597, 1535, 1504, 1466, 1396, 1288, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J 8.4 Hz, 2H), 6.96 (d, J 8.4 Hz, 2H), 3.45 (s, 3H), 3.32 (s, 3H), 2.60 (t, J 7.6 Hz, 2H), 1.56–1.66 (m, 2H), 1.23–1.38 (m, 6H), 0.88 (t, J 6.6 Hz, 3H); MS (70 eV): m/z 265 (M^+, 22), 249 (3), 161 (4), 91 (2), 88 (64), 72 (100); HRMS: Calcd for $C_{15}H_{23}NOS$, m/z 265.1500; found, m/z 265.1486.

3.5. *S*-*p*-Hexylphenyl *N*,*N*-dimethylthiocarbamate (9a)

O-*p*-Hexylphenyl *N*,*N*-dimethylthiocarbamate (**8a**) (1.0 g, 3.8 mmol) was heated at 295 °C for 5.5 h, and the residue was purified by silica gel column chromatography (4:1 hexane–AcOEt) to afford **9a** (810 mg, 81%). IR ($CHCl_3$): 3009, 2932, 2858, 1713, 1663, 1597, 1489, 1466, 1404, 1369, 1261, 1204, 1177, 1092, 1018, 910, 833, 806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, J 8.2 Hz, 2H), 7.18 (d, J 8.3 Hz, 2H), 3.05 (br s, 6H), 2.60 (t, J 7.6 Hz, 2H), 1.55–1.65 (m, 2H), 1.25–1.39 (m, 6H), 0.87 (t, J 6.7, 3H); MS (70 eV): m/z 265 (M^+, 17), 193 (1), 137 (1), 123 (3), 109 (2), 73 (4), 72 (100); HRMS: Calcd for $C_{15}H_{23}NOS$, m/z 206.1500; found, m/z 265.1499.

3.6. *p*-Hexylbenzenethiol (10a)

Lithium aluminum hydride (200 mg, 0.76 mmol) was added to a solution of *S*-*p*-hexylphenyl *N*,*N*-dimethylthiocarbamate (**9a**) (208 mg, 0.78 mmol) in Et_2O (2 mL) at 0 °C, and the reaction mixture was stirred at 65 °C for 3 h. After the reaction was completed, the reaction was quenched with AcOEt and molar HCl, and the mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (6:1 hexane–AcOEt) to afford **10a** (122 mg, 96%). IR ($CHCl_3$): 3032, 2959, 2341, 1682, 1601, 1493, 1466, 1439, 1404, 1377, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J 8.2 Hz, 2H), 7.05 (d, J 8.4 Hz, 2H), 3.39 (s, 1H), 2.54 (t, J 7.6, 2H), 1.53–1.61 (m, 2H), 1.21–1.34 (m, 6H), 0.88 (t, J 6.8 Hz, 3H); MS (70 eV): m/z 194 (M^+, 29), 124 (10), 123 (100); HRMS: Calcd for $C_{12}H_{18}S$, m/z 194.1129; found, m/z 194.1128.

3.7. *O*-*p*-Heptylphenyl *N*,*N*-dimethylthiocarbamate (8b)

IR ($CHCl_3$): 3020, 2932, 2858, 1728, 1601, 1535, 1466, 1396, 1288, 1215, 1173, 1057, 1018, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, J 8.6 Hz, 2H), 6.95 (d, J 8.5 Hz, 2H), 3.45 (s, 3H), 3.33 (s, 3H), 2.60 (t, J 7.3 Hz, 2H), 1.53–1.63 (m, 2H), 1.23–1.36 (m, 8H), 0.87 (t, J 7.0 Hz, 3H); MS (70 eV): m/z 279 (M^+, 22), 107 (8), 72 (100); HRMS: Calcd for $C_{16}H_{25}NOS$, m/z 279.1657; found, m/z 279.1659.

3.8. *S*-*p*-Heptylphenyl *N*,*N*-dimethylthiocarbamate (9b)

IR ($CHCl_3$): 3009, 2932, 2858, 1713, 1655, 1597, 1489, 1466, 1404, 1369, 1261, 1219, 1177, 1092, 1018, 910, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, J 8.4 Hz, 2H), 7.18 (d, J 8.4, 2H), 3.05 (br s, 6H), 2.60 (t, J 7.5 Hz, 2H), 1.57–1.65 (m, 2H), 1.25–1.35 (m, 8H), 0.87 (t, J 7.0 Hz, 3H); MS (70 eV): m/z 279 (M^+, 7), 263 (2), 123 (3), 72 (100); HRMS: Calcd for $C_{16}H_{25}NOS$, m/z 279.1657; found, m/z 279.1659.

3.9. *p*-Heptylbenzenethiol (10b)

IR ($CHCl_3$): 2920, 2858, 1493, 1466, 1103 cm^{-1}; MS (70 eV): m/z 208 (M^+, 28), 125 (5), 124 (10), 123 (100); ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J 8.1 Hz, 2H), 7.05 (d, J 8.1 Hz, 2H), 3.38 (s, 1H), 2.54 (t, J 7.6 Hz, 2H), 1.51–1.62 (m, 2H), 1.22–1.35 (m, 8H), 0.88 (t, J 6.8 Hz, 3H); HRMS: Calcd for $C_{13}H_{20}S$, m/z 294.1474; found, m/z 294.1477.

3.10. *O*-*p*-Octylphenyl dimethylthiocarbamate (8c)

IR ($CHCl_3$): 3020, 2932, 2858, 1597, 1535, 1504, 1466, 1396, 1288, 1242, 1196, 1173, 1142, 1018, 837 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, J 8.6 Hz, 2H), 6.95 (d, J 8.6 Hz, 2H), 3.45 (s, 3H), 3.33 (s, 3H), 2.60 (t, J 7.6 Hz, 2H), 1.54–1.66 (m, 2H), 1.22–1.35 (m, 10H), 0.87 (t, J 6.7 Hz, 3H); MS (70 eV): m/z 293 (M^+, 5), 277 (2), 107 (15), 88 (35), 72 (100); HRMS: Calcd for $C_{17}H_{27}NOS$, m/z 293.1813; found, m/z 293.1797.

3.11. *S*-*p*-Octylphenyl dimethylthiocarbamate (9c)

IR ($CHCl_3$): 3028, 3013, 2928, 2855, 1655, 1466, 1369, 1261, 1092, 1018, 910 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, J 8.2 Hz, 2H), 7.18 (d, J 8.4 Hz, 2H), 3.05 (br s, 6H), 2.60 (t, J 7.6 Hz, 2H), 1.57–1.68 (m, 2H), 1.20–1.38 (m, 10H), 0.87 (t, J 6.8 Hz, 3H); MS (70 eV): m/z 293 (M^+, 13), 277 (5), 123 (4), 72 (100); HRMS: Calcd for $C_{17}H_{27}NOS$, m/z 293.1813; found, m/z 293.1814.

3.12. *p*-Octylbenzenethiol (10c)

IR ($CHCl_3$): 2920, 2855, 1493, 1466, 1119 cm^{-1}; MS (70 eV): *m*/*z* 222 (M^+, 31), 125 (5), 123 (100); ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* 8.4 Hz, 2H), 7.04 (d, *J* 8.0 Hz, 2H), 3.38 (s, 1H), 2.54 (t, *J* 7.6 Hz, 2H), 1.52–1.60 (m, 2H), 1.21–1.31 (m, 10H), 0.87 (t, *J* 6.8 Hz, 3H); HRMS: Calcd for $C_{14}H_{22}S$, *m*/*z* 222.1442; found, *m*/*z* 222.1446; Anal. Calcd for $C_{14}H_{22}S$: C, 75.61; H, 9.97. Found: C, 76.15; H, 10.09.

3.13. *p*-Dodecylbenzenethiol (10d)

Dodecylbenzenesulfonyl chloride (90%, 5.0 g, Wako)[8] was added to a solution of lithium aluminum hydride (1.4 g, 36 mmol) in THF (100 mL) at 0 °C, and the reaction mixture was refluxed for 22 h. After the reaction was completed, the reaction was quenched with molar HCl, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel chromatography (hexane) to afford **10d** (3.9 g, 97% based on the calculation in which the starting material was pure dodesylbenzenesulfonyl chloride).

3.14. 3,4-Di-*O*-benzyl-2-deoxy-D-*erythro*-pentose bis(4-octyloxy)benzyl dithioacetal (14a)

p-Octyloxyphenylmethanethiol **6** (5.8 g, 23 mmol) and concd HCl (2.1 mL) were added to methyl 3,5-di-*O*-benzyl-2-deoxy-α,β-D-*erythro*-pentofuranoside (**13**, 1.5 g, 4.6 mmol), and the reaction mixture was stirred at 40 °C for 18.5 h. After the reaction was complete, satd aq $NaHCO_3$ was added to the reaction mixture, which was the extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (12:1→8:1 hexane–AcOEt) to afford **14a** (3.1 g, 84%) as a colorless oil: $[\alpha]_D^{24}$ −69.44 (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.33–7.26 (arom, 8H), 7.16 (dt, *J* 8.8 and 2.6 Hz, 2H), 7.62–7.04 (m, 2H), 7.02–6.98 (m, 2H), 6.73–6.77 (m, 2H), 4.51 (s, 2H), 4.32 (d, A part of AB J_{AB} 11.4 Hz, 1H), 4.06 (d, B part of AB J_{AB} 11.4 Hz, 1H), 3.88 (t, *J* 6.6 Hz, 2H), 3.85–3.61 (m, 9H), 3.48 (dd, A part of AB J_{AB} 9.6 Hz, *J* 5.9 Hz, 1H), 3.44 (dd, B part of AB J_{AB} 9.6 Hz, *J* 4.2 Hz, 1H), 2.30 (d, *J* 4.2 Hz, 1H), 2.13 (ddd, A part of AB J_{AB} 14.7, *J* 9.9 and 3.9 Hz, 1H), 1.89 (ddd, B part of AB J_{AB} 14.7, *J* 10.9, 2.6 Hz, 1H), 1.81–1.69 (m, 4H), 1.51–1.28 (m, 20H), 0.89 (br t, *J* 6.8, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 158.0, 138.3, 137.8, 130.2 (2C), 130.1 (2C), 130.0, 129.91, 128.5 (2C), 128.2 (2C), 127.83, 127.81, 127.6 (3C), 127.4, 114.4 (2C), 114.3 (2C), 77.2, 73.4, 72.7, 71.8, 70.7, 67.9, 67.8, 46.0, 37.2, 34.3, 33.4, 31.8 (2C), 29.4 (2C), 29.34, 29.31, 29.2 (2C), 26.09, 26.07, 22.6 (2C), 14.0 (2C); FABMS: 823 (M^++Na, 29); HRFABMS: Calcd for $C_{49}H_{68}O_5S_2Na$, *m*/*z* 823.4409 (M^++Na); found, *m*/*z* 252.1551.

3.15. (4-Octyl)benzyl 3,6-di-*O*-benzyl-2-deoxy-1,5-dithio-L-*threo*-pentofuranoside (15a)

Methanesulfonyl chloride (48 μL, 0.63 mmol) was added to a solution of **14a** (204 mg, 0.255 mmol) in pyridine (2 mL), and the reaction mixture was stirred for 4.5 h at room temperature. After the reaction was complete, the reaction was quenched with water and the mixture was extracted with Et_2O. The organic layer was successively washed with molar HCl and brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in DMF (10 mL), to which NaI (372 mg, 2.50 mmol) and $BaCO_3$ (740 mg, 3.75 mmol) were added, and the mixture was stirred at 90 °C for 17.5 h. After the reaction was complete, the mixture was filtered and partitioned between Et_2O and water. The organic layer was successively washed with aq sodium thiosulfate, water, and brine, and then dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (15:1 hexane–AcOEt) to afford **15a** (89.8 mg, 64%) as a mixture of α and β isomers (α:β = 1:2). IR ($CHCl_3$): 3031, 2927, 2858, 1610, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.18 (m, 10H), 6.84–6.78 (m, 2H), 4.59–4.45 (m, 5H), 4.31 (dd, *J* 8.1 and 4.0 Hz, 0.7H, β isomer), 4.26 (dd, *J* 7.3 and 6.2 Hz, 0.3H, α isomer), 4.19–4.15 (m, 0.7H, β isomer), 3.98–3.82 (m, 3.3H), 3.79 (s, 0.7H, b), 3.77 (s, 0.3H, α isomer), 3.69–3.54 (m, 2H), 2.45 (ddd, A part of AB J_{AB} 13.0 Hz, *J* 6.0 and 4.3 Hz, 0.65H, β isomer), 2.32 (ddd, A part of AB J_{AB} 13.5 Hz, *J* 7.3 and 4.8 Hz, 0.35H), 2.23 (ddd, B part of AB J_{AB} 13.5 Hz, *J* 6.8 and 6.2 Hz, 0.35H, α isomer), 1.92 (ddd, B part of AB J_{AB} 13.0 Hz, *J* 8.2 and 3.6 Hz, 0.65H, b), 1.77 (quintet, *J* 7.1 Hz, 2H), 1.44 (quintet, *J* 7.2 Hz, 2H), 1.36–1.22 (m, 10H), 0.89 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): α isomer, δ 158.2, 138.2, 137.9, 130.0 (2C), 129.3, 128.3 (2C), 128.2 (2C), 127.8, 127.7, 127.6 (2C), 127.6 (2C), 114.5 (2C), 80.8 (2C), 73.4, 71.5, 70.4, 50.8, 47.4, 40.3, 36.6, 31.8, 29.3, 29.26, 29.22, 26.0, 22.6, 14.1; β isomer, δ 158.3, 138.1, 138.0, 129.9 (2C), 129.4, 128.4 (2C), 128.3, 127.6 (4C), 127.6 (2C), 114.6 (2C), 80.7 (2C), 73.3, 71.6, 69.5, 68.0, 51.6, 48.7, 41.8, 36.5, 31.8, 31.8, 29.3, 29.26, 29.22, 26.0, 22.6, 14.1. FABMS: *m*/*z* 587 (M^++Na, 2); HRFABMS: Calcd for $C_{34}H_{44}O_3S_2Na$, (M^++Na), *m*/*z* 587.2630; found *m*/*z* 587.2623.

3.16. 4-Benzoyl-3,5-di-*O*-benzyl-2-deoxy-L-*threo*-pentose bis(4-octyloxy)benzyl dithioacetal (16a)

A mixture of triphenylphosphine (151 mg, 0.58 mmol), benzoic acid (71 mg, 0.58 mmol), and diisopropyl azodicarboxylate (DIAD, 0.11 mL, 0.58 mmol) in THF

(1.5 mL) was added dropwise to a solution of **14a** (259 mg, 0.32 mmol) in THF (3.5 mL), and the reaction mixture was stirred for 10 h. After the reaction was complete, THF was evaporated, and the residue was purified by silica gel column chromatography (15:1 hexane–AcOEt) to afford compound **16a** (240 mg, 83%) as a colorless oil: $[\alpha]_D^{22.6}$ −76.25 (*c* 1.07, $CHCl_3$); IR ($CHCl_3$): 3024, 3010, 2927, 2856, 1716, 1608, 1500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.06–8.03 (m, 2H), 7.57–7.54 (m, 1H), 7.45–7.42 (m, 2H), 7.33–7.20 (m, 8H), 7.15–7.12 (m, 2H), 7.06–7.01 (m, 2H), 6.93–6.90 (m, 2H), 6.70–6.64 (m, 2H), 5.38 (ddd, *J* 6.2, 4.9, and 3.7 Hz, 1H), 4.53 (d, A part of AB J_{AB} 12.1 Hz, 1H), 4.47 (d, B part of AB J_{AB} 12.1 Hz, 1H), 4.44 (d, A part of AB J_{AB} 11.4 Hz, 1H), 4.07 (d, B part of AB J_{AB} 11.4 Hz, 1H), 4.06–4.02 (m, 1H), 3.85 (t, *J* 6.7 Hz, 2H), 3.84–3.64 (m, 9H), 3.71 (d, A part of AB J_{AB} 13.2 Hz, 1H), 3.53 (d, B part of AB J_{AB} 13.2, 1H), 2.11 (ddd, A part of AB J_{AB} 14.3 Hz, *J* 10.1, 3.7 Hz, 1H), 1.94 (ddd, A part of AB J_{AB} 14.3 Hz, *J* 11.0 and 2.6 Hz, 1H), 1.77 (quintet, *J* 6.8 Hz, 2H), 1.73 (quintet, *J* 6.6 Hz, 2H), 1.57–0.87 (m, 20H), 0.89 (t, *J* 6.0 Hz, 3H), 0.88 (t, *J* 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 158.1, 138.2, 137.9, 133.0, 130.03 (2C), 130.01, 129.8, 129.7 (2C), 129.5, 128.3 (4C), 128.1 (2C), 127.6 (2C), 127.6 (2C), 127.5 (2C), 127.3 (2C), 114.4 (2C), 114.3 (2C), 75.4, 73.8, 73.3, 73.0, 68.1, 67.9, 67.8, 45.8, 37.3, 34.5, 33.4, 31.8 (2C), 29.4 (2C), 19.32 (2C), 29.31 (2C), 29.2, 26.1, 26.06 (2C), 22.6 (2C). FABMS: *m*/*z* 927 (M^++Na, 1); HRFABMS: Calcd for $C_{56}H_{72}O_6S_2Na$, *m*/*z* 927.4668, (M^++Na); found, *m*/*z* 927.4677.

3.17. 3,5-Di-*O*-benzyl-2-deoxy-L-*threo*-pentose bis(4-octyloxy)benzyl dithioacetal (16b)

NaOMe in MeOH (28%, 0.26 mL, 1.28 mmol) was added to a solution of **16a** (583 mg, 0.64 mmol) in MeOH (2 mL) and $CHCl_3$ (2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 15 h. After the reaction was complete, the mixture was diluted with 5% aq NaH_2PO_4 and extracted with Et_2O. The organic layer was successively washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (8:1→6:1 hexane–AcOEt) to afford **16b** (429 mg, 84%) as a colorless oil: $[\alpha]_D^{27.6}$ −62.15 (*c* 1.39, $CHCl_3$); IR ($CHCl_3$): 3566, 3020, 2850, 1610, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.23 (m, 8H), 7.14–7.12 (m, 2H), 7.09–7.05 (m, 2H), 7.03–7.00 (m, 2H), 6.73–6.68 (m, 4H), 4.48 (s, 2H), 4.25 (d, A part of AB J_{AB} 11.4 Hz, 1H), 4.10 (d, B part of AB J_{AB} 11.4 Hz, 1H), 3.87 (t, *J* 5.7 Hz, 2H), 3.83–3.63 (m, 9H), 3.42 (d, *J* 5.7 Hz, 2H), 2.29 (d, *J* 5.7 Hz, 1H), 2.14 (ddd, A part of AB J_{AB} 14.4 Hz, *J* 9.0 and 4.8 Hz, 1H), 1.94 (ddd, B part of AB J_{AB} 14.4 Hz, *J* 10.1 and 3.7 Hz, 1H), 1.76 (quintet, *J* 6.6 Hz, 2H), 1.65 (quintet, *J* 6.6 Hz, 2H), 1.46–1.29 (m, 20H), 0.89 (t, *J* 6.3 Hz, 3H), 0.88 (t, *J* 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.12, 158.08, 138.3, 137.9, 130.2, 130.1, 129.9, 129.8, 128.4 (2C), 128.2 (2C), 127.8 (2C), 127.7, 127.6 (2C), 127.5 (2C), 114.4 (2C), 114.3 (2C), 76.6, 73.3, 73.2, 71.1, 68.7, 45.7, 37.7, 34.3, 33.7, 31.8 (2C), 29.4 (2C), 29.32, 29.31, 29.2 (2C), 26.1, 26.0, 22.7 (2C), 14.1 (2C). FABMS: *m*/*z* 823 (M^++Na, 27); HRFABMS: Calcd for $C_{49}H_{68}O_5S_2Na$ (M^++Na), *m*/*z* 823.4406; found, *m*/*z* 823.4412.

3.18. *O*-4-Octyloxybenzyl 3,6-di-*O*-benzyl-2-deoxy-1,5-dithio-D-*erythro*-pentofuranoside (17)

Methanesulfonyl chloride (0.35 mL, 4.6 mmol) was added to a solution of **16b** (1.46 g, 1.82 mmol) in pyridine, and the reaction mixture was stirred at room temperature for 1.5 h. After the reaction was complete, the reaction was quenched with water and the mixture was extracted with Et_2O. The organic layer was successively washed with molar HCl and brine, dried over $MgSO_4$, and evaporated. The residue was then dissolved in DMF (85 mL), to which NaI (2.7 g, 11 mmol) and $BaCO_3$ (5.4 g, 27 mmol) were added and stirred at 90 °C for 17 h. After the reaction was complete, the mixture was filtered, and the filtrate was partitioned between Et_2O and water. The organic layer was successively washed with aq sodium thiosulfate, water, and brine, dried over $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (15:1 hexane–AcOEt) to afford **17** (1.01 g, 98%). The isomers (α isomer, 127.0 mg; β isomer, 701.8 mg) were separated by HPLC (5:1 hexane–AcOEt).

3.18.1. α Isomer. Colorless oil: $[\alpha]_D^{21.9}$ +228.5 (*c* 0.62, $CHCl_3$); IR ($CHCl_3$): 2929, 2856, 1608, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (m, 10H), 7.23–7.20 (m, 2H), 6.84–6.80 (m, 2H), 4.55 (d, A part of AB J_{AB} 12.3 Hz, 1H), 4.50 (s, 2H), 4.48 (d, B part of AB J_{AB} 12.3 Hz, 1H), 4.30 (dd, *J* 5.9 and 10 Hz, 1H), 4.40 (q, *J* 5.3 Hz, 2H), 3.92 (t, *J* 6.6 Hz, 2H), 3.82 (q, *J* 5.5 Hz, 1H), 3.79 (s, 1H), 3.52 (dd, A part of AB J_{AB} 9.9 Hz, *J* 8.4 Hz, 1H), 3.47 (dd, B part of AB J_{AB} 9.9 Hz, *J* 6.2 Hz, 1H), 2.43 (ddd, A part of AB J_{AB} 13.5 Hz, *J* 6.9 and 5.1 Hz, 1H), 2.14 (ddd, B part of AB J_{AB} 13.5 Hz, *J* 5.8 and 5.7 Hz, 1H), 1.76 (quintet, *J* 7.0 Hz, 2H), 1.48–1.26 (m, 10H), 0.89 (t, *J* 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 138.0, 137.9, 130.0 (2C), 129.3, 128.4 (2C), 128.3 (2C), 127.7 (2C), 127.64 (2C), 127.6 (2C), 114 (2C), 82.6, 73.1, 71.6, 71.5, 68.0, 53.0, 48.8, 40.9, 36.5, 31.8, 29.3, 29.26, 29.21, 26.0, 22.6, 14.1. FABMS: *m*/*z* 587 (M^++Na, 31); HRFABMS: Calcd for $C_{34}H_{44}O_3S_2Na$ (M^++Na), *m*/*z* 587.2630; found, *m*/*z* 587.2637.

3.18.2. β Isomer. Colorless oil: $[\alpha]_D^{22.3}$ +102.4 (*c* 0.78, $CHCl_3$); IR ($CHCl_3$): 2929, 2856, 1608, 1510 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.25 (m, 10H), 7.22–7.19 (m, 2H), 6.84–6.80 (m, 2H), 4.55–4.46 (m, 5H), 4.24 (dd, *J* 6.4, 3.7 Hz, 1H), 3.92 (t, *J* 6.6 Hz, 2H), 3.77 (dd, *J* 15.0, 13.4 Hz, 2H), 3.67 (ddd, *J* 8.6, 6.2, and 2.6 Hz, 1H), 3.54–3.46 (m, 2H), 2.34 (ddd, A part of AB J_{AB} 13.5 Hz, *J* 5.31 and 3.13 Hz, 1H), 2.00 (ddd, B part of AB J_{AB} 13.5 Hz, *J* 8.9 and 4.4 Hz, 1H), 1.77 (quintet, *J* 6.8 Hz, 2H), 1.44 (quintet, *J* 8.0 Hz, 2H), 1.36–1.18 (m, 8H), 0.89 (t, *J* 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 138.0, 137.9, 129.9 (2C), 129.4, 128.4 (4C), 83.0, 73.0, 71.0, 68.0, 53.1, 49.7, 41.2, 36.4, 31.8, 39.3, 29.3, 29.3, 26.0, 22.6, 14.1. FABMS: *m*/*z* 587 (M^++Na, 73); HRFABMS: Calcd for $C_{34}H_{44}O_3S_2Na$ (M^++Na), *m*/*z* 587.2630; found, *m*/*z* 587.2637.

3.19. Dodecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-D-glucopyranoside (19a)

Dodecanethiol (735 μL, 3.07 mmol) and $BF_3{\cdot}Et_2O$ (1.6 mL, 12.8 mmol) were added to a solution of per-*O*-acetylated D-glucose (1.0 g, 2.6 mmol) in CH_2Cl_2 (5.0 mL), and the reaction mixture was stirred at room temperature for 6 h. After the reaction was complete, the organic solvent was removed in vacuo, and the residue was purified by silica gel chromatography (3:1 hexane–AcOEt) to give **19a** as a mixture of α and β isomers.[9]

3.19.1. α Isomer. IR ($CHCl_3$): 3036, 2928, 2855, 1747, 1601, 1369, 1242, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.65 (d, *J* 5.9 Hz, 1H), 5.37 (t, *J* 9.7 Hz, 1H), 5.05 (dd, *J* 10.2, 9.7 Hz, 1H), 5.02 (dd, *J* 10.2, 5.9 Hz, 1H), 4.43 (ddd, *J* 9.7, 4.7, 2.3 Hz, 1H), 4.30 (dd, A part of AB *J* 12.4, 4.7 Hz, 1H), 4.07 (dd, B part of AB *J* 12.4, 2.3 Hz, 1H), 2.60–2.45 (m, 2H), 2.09 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.64–1.52 (m, 2H), 1.35–1.15 (m, 18H), 0.88 (t, *J* 6.9 Hz, 3H); FABMS: *m*/*z* 538 (M^++Na, 36); HRFABMS: Calcd for $C_{26}H_{44}O_9SNa$, *m*/*z* 555.2604; found, *m*/*z* 555.2610.

3.19.2. β Isomer.[9] IR ($CHCl_3$): 3020, 2928, 2855, 1755, 1601, 1369, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.22 (t, *J* 9.5 Hz, 1H), 5.09 (d, *J* 9.5 Hz, 1H), 5.03 (dd, *J* 10.1, 9.5 Hz, 1H), 4.48 (d, *J* 10.1 Hz, 1H), 4.24 (dd, A part of AB *J* 12.5, 4.9 Hz, 1H), 4.14 (dd, B part of AB *J* 12.5, 2.4 Hz, 1H), 3.70 (ddd, *J* 9.5, 4.9, 2.4 Hz, 1H), 2.73–2.60 (m, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.64–1.51 (m, 2H), 1.33–1.19 (m, 18H), 0.88 (t, *J* 6.9 Hz, 3H); FABMS: *m*/*z* 555 (M^++Na, 14); HRFABMS: Calcd for $C_{26}H_{44}O_9SNa$, *m*/*z* 555.2604; found, *m*/*z* 555.2611.

3.20. 4-Heptylphenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (19b)

Mp 83.5–83.9 °C (hexane and Et_2O); IR ($CHCl_3$): 3032, 3013, 2932, 2858, 1755, 1369, 1246, 1215, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* 8.1 Hz, 2H), 7.12 (d, *J* 8.1 Hz, 2H), 5.21 (t, *J* 9.3 Hz, 1H), 5.04 (t, *J* 9.8 Hz, 1H), 4.96 (dd, *J* 9.8, 9.3 Hz, 1H), 4.65 (d, *J* 10.1 Hz, 1H), 4.20 (d, *J* 4.9 Hz, 1H), 4.19 (d, *J* 2.7 Hz, 1H), 3.71 (ddd, *J* 10.1, 4.9, 2.7 Hz, 1H), 2.59 (t, *J* 7.7 Hz, 2H), 2.09 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.60 (br t, *J* 7.7 Hz, 2H), 1.36–1.22 (m, 8H), 0.88 (br t, *J* 6.9 Hz, 3H); FABMS: *m*/*z* 561 (M^++Na, 90); HRFABMS: Calcd for $C_{27}H_{38}O_9SNa$, *m*/*z* 561.2134; found, *m*/*z* 561.2128.

3.21. Methyl 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (21)

$BF_3{\cdot}Et_2O$ (51 μL, 0.40 mmol) and NIS (90 mg, 0.40 mmol) were added to a mixture of the α isomer of **19a** (61.0 mg, 0.10 mmol), methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**20**) (35.0 mg, 0.10 mmol), and 4 Å molecular sieves (20 mg) in CH_2Cl_2 (2.0 mL), and the reaction mixture was stirred for 5 min at room temperature. After the reaction, satd aq $NaHCO_3$, and satd aq NaS_2O_3 were successively added, and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography (20:1 $CHCl_3$–acetone) to afford **21** (57 mg, 87%).[10]

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