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Stereoselective total synthesis of acremomannolipin A and its anomer, the potent calcium signal modulators with a novel glycolipid structure: role of the stereochemistry at the anomeric center on the activity

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ABSTRACT

A full account of stereoselective total synthesis of a novel glycolipid, acremomannolipin A (**1**), the potent calcium signal modulator isolated from *Acremonium strictum*, by employing the stereoselective β-mannosylation of 4,6-*O*-benzylidene-protected mannosyl sulfoxide with D-mannitol as the key reaction is described. The α-anomer (*epi*-**1**) of **1** was also synthesized selectively. The calcium modulating activity was reduced upon inversion of the configuration at the anomeric center, indicating that the β-configuration of the mannose moiety is preferable for the activity.

1. Introduction

Acremonium Link ex Fries 1821 belongs to a very large group of white or pink molds with wet heads of conidia produced one-by-one from the tips of straight hyphae or lateral nipples. They are extremely common in man's environment, are found in soil, decaying vegetation, and food stuffs.[1] It is not commonly associated with human diseases, but has been identified as a pathogen in cases of mycetoma, keratomycosis, postoperative endophthalmitis, onychomycosis, and meningitis.[2] The genus is well known for producing numerous important enzymes including alkaline protease,[3] isopenicillin *N* synthetase,[4] glucooligosaccharide oxidase,[5] protease,[6] ascorbate oxidase,[7] phenol oxidase,[8] and β-glucanases.[9] Xenovulene A, a novel GABA-benzodiazepine receptor binding compound;[10] acremonol and acremodiol, two new fungal bislactones;[11] acremostatins A, B, and C, three new lipoaminopeptides;[12] UCS 1025 A and B, new antitumor antibiotics;[13] polyketide-derived antibiotics;[14] Acremostrictin, a new antibacterial tricyclic lactone;[15] and Acremolin[16] are some new secondary metabolites isolated from the genus belonging to *Acremonium*.

Recently, we identified a novel glycolipid, acremomannolipin A[17] (**1**), from a species of the same genus, *Acremonium strictum*, as a potential calcium signal modulator, which might be involved in the MAPK-related and/or calcineurin-mediated processes in higher organisms[18] using a newly developed chemical–genetic method.[19] The activity was so potent as to exert the effect at a concentration of 200 nM. Calcium signaling pathways are known to be widely proliferated throughout the cell and participate in all basic cellular functions.[20] As the ability to manipulate Ca^{2+} signaling pathways would provide a powerful tool for applications in therapeutic and biotechnological settings, **1** is an attractive target from a biological standpoint. Besides the stimulating biological properties, the structure of **1** is quite unique, in which the D-mannopyranose is connected to D-mannitol through a β-glycosidic linkage, and all the hydroxyls in the mannose are highly masked as peresters. Thus the sugar moiety is hydrophobic, whereas the mannitol part exhibits the highly hydrophilic property. All of these features have posed significant challenges for the total synthesis of **1** (Fig. 1).

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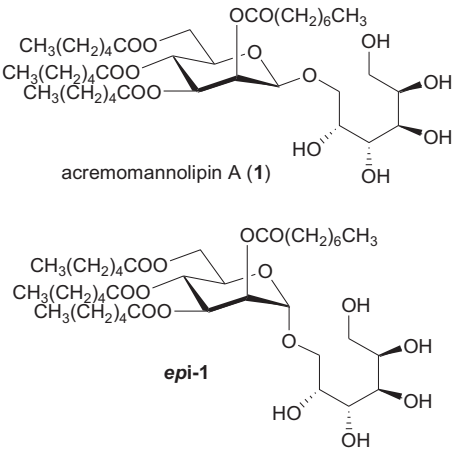
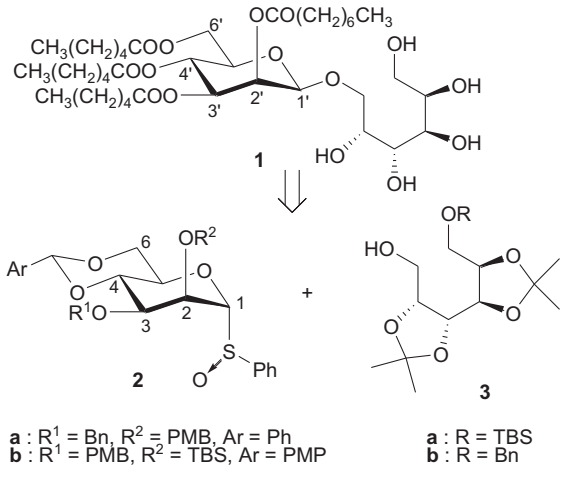


Fig. 1. Acremomannolipin A (**1**) and the α-anomer (*epi*-**1**).

On the other hand, the β-mannopyranosidic bond had long been considered as one of the most difficult classes of glycosidic linkage to be prepared until 1996 when Crich and Sun[21] developed the innovative approach to the stereoselective β-mannosylation. Thereafter other new approaches were also developed.[22] Crich reported that a rigid bicyclic structure involving the mannose moiety by introducing a cyclic acetal at 4,6-hydroxyls in the mannose (Scheme 1) was essential for the mannosyl donor to permit selective β-mannosylation with a mannosyl acceptor. We recently applied the protocol to the synthesis of **1** and accomplished the first stereoselective total synthesis of **1**, which was published as a communication.[23] In this paper, a full account of the processes is described. Although the stereoselectivity of the coupling reaction in the work was quite satisfactory (β/α=ca. 30/1), modification of the protecting groups in the present study made the coupling reaction more stereospecific and gave the desired β-isomer exclusively. The α-anomer (*epi*-**1**) was also synthesized, and its calcium modulation activity was evaluated to examine the effect of the stereochemistry at the anomeric center of the mannose on the activity.



Scheme 1. Retrosynthetic analysis of acremomannolipin A (**1**).

2. Results and discussion

2.1. Synthesis of acremomannolipin A (1): part I

The retrosynthetic analysis of **1** is shown in Scheme 1. It is well recognized that selection of appropriate protecting groups is critical in the synthetic glyco-chemistry. Thus, we carefully designed the donor and the acceptor in the glycosidation reaction by extracting appropriate protecting groups for the totally ten hydroxyls in the reactants.

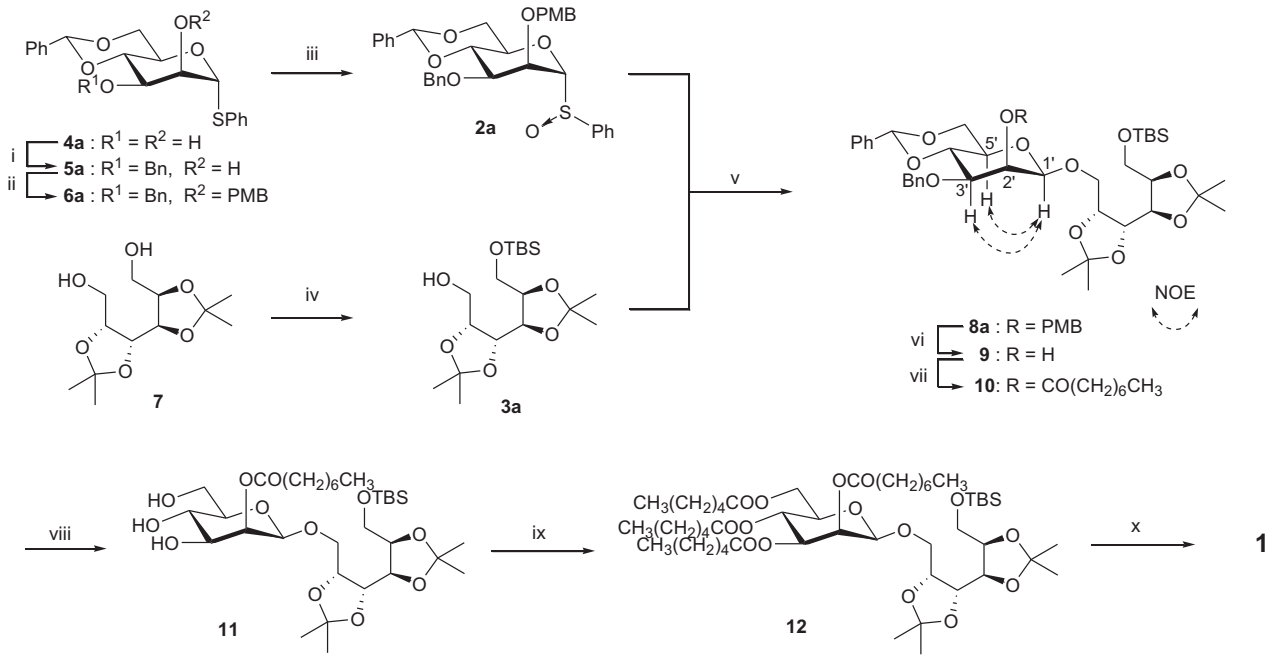
As the first trial, phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside *S*-oxide (**2a**), in which the protecting groups at C3, C4, and C6 were designed as those, which were removable simultaneously without affecting the ester moiety at C2, was chosen as a mannosyl donor for the coupling reaction. Accordingly the protecting group of its acceptor was deductively determined as *tert*-butyldimethylsilyl (TBS) group, which survives conditions for deprotecting C3, C4, C6 hydroxyls after the coupling reaction, and 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol (**3a**), was designed as a mannosyl acceptor. Thus diol, phenyl 4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (**4a**), was readily prepared from D-mannose in four steps according to the literature.[24] The C3 hydroxyl in **4a** was selectively benzylated via stannylene acetal, and the C2 hydroxyl in the resulting benzyl ether, phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside[25] (**5a**), was subsequently protected with *p*-methoxybenzyl chloride (PMBCl) to give phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-1-thio-α-D-mannopyranoside (**6a**) in 78% yield. The perprotected mannose derivative **6a** was then oxidized with *meta*-chloroperoxybenzoic acid (*m*CPBA) to give exclusively the corresponding mannosyl sulfoxide **2a** in good yield. The absolute configuration at the *S*-chiral center was determined to be *R* according to the literature.[26]

On the other hand, the mannosyl acceptor (**3a**) was prepared by mono-silylation of 2,3:4,5-di-*O*-isopropylidene-D-mannitol (**7**), which was derived from D-mannitol in three steps according to the literature[27] (Scheme 2). The selective mono-silylation of **7** was successfully conducted by the slow addition of an equimolar amount of *tert*-butyldimethylsilyl chloride (TBSCl) to an alcoholate prepared by treatment of the starting material (**7**) with sodium hydride, giving **3a** in 88% yield. When the reaction was carried out in the presence of imidazole and DMAP, concomitant formation of bis-silylated compound (11%) was observed while the starting material (**7**) still remained.

With donor **2a** and acceptor **3a** in hand, these two reactants were subjected to the coupling reaction according to Crich's method. Thus, compound **2a** was activated with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) at −78 °C in CH_2Cl_2, and the generated mannosyl triflate was treated with **3a** to give the desired β-isomer, 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-β-D-mannopyranoside (**8a**), in 71% isolated yield. Formation of a trace amount of undesirable α-isomer (δ_H 5.61, benzylidene proton) was detected by inspection of the ^1H NMR spectrum of the crude mixture (β/α ratio, ca. 30/1).

The product showed a sodium adduct ion $[M+Na]^+$ at *m*/*z* 859 in the fast atom bombardment (FAB) mass spectrum. A signal at δ_H 4.58 due to the anomeric proton had a small coupling constant ($J_{1',2'}$=nearly zero) characteristic of β-mannosides. The β-stereochemistry at the anomeric center was finally confirmed by NOE correlations among the signals due to C1′-H, C3′-H, and C5′-H as shown in Scheme 2.

Selective removal of the PMB group at C2′ in **8a** was successfully conducted by DDQ to give 2-*O*-deprotected β-D-mannopyranoside (**9**) in 91% yield, which was then treated with octanoyl chloride to afford the corresponding octanoyl ester (**10**) in 98% yield. Simultaneous hydrogenolysis of both the benzyl at C3′ and the benzylidene moiety at C4′ and C6′ in **10** over palladium on carbon gave the desired 3,4,6-unprotected β-D-mannoside (**11**), which was then derived to the corresponding tetraester (**12**) by

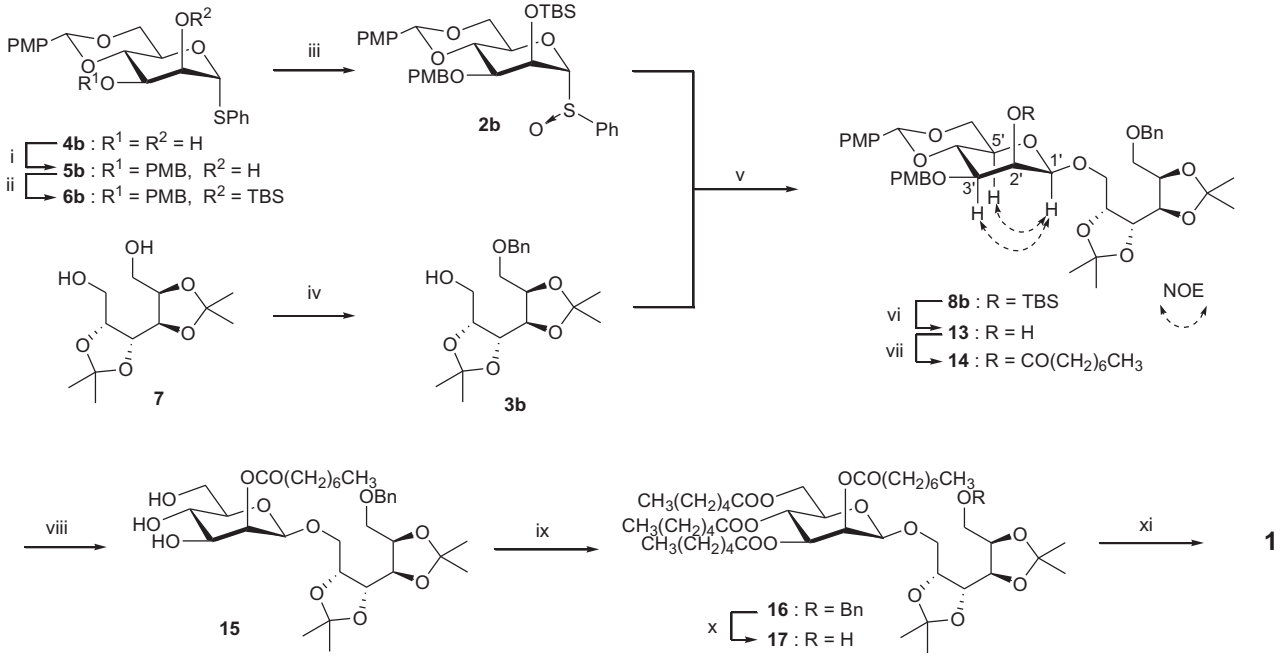


Scheme 2. Reagents and conditions: (i) Bu_2SnO, toluene, reflux, then BnBr, CsF, $^{i}Bu_4NBr$, reflux (85%); (ii) PMBCl, NaH, $^{i}Bu_4NI$, DMF, rt (78%); (iii) *m*CPBA, CH_2Cl_2, 0 °C (83%); (iv) TBSCl, NaH, DMF, 0 °C (88%); (v) Tf_2O, DTBMP, CH_2Cl_2, −78 °C (71%); (vi) DDQ, CH_2Cl_2, H_2O, rt (91%); (vii) $CH_3(CH_2)_6COCl$, Py, DMAP, CH_2Cl_2, rt (98%); (viii) H_2, Pd–C, AcOEt, rt (88%); (ix) $[CH_3(CH_2)_4CO]_2O$, Py, DMAP, CH_2Cl_2, rt (93%); (x) 90% TFA aq, 0 °C (94%).

treating with hexanoic anhydride in 82% yield in two steps. The suspected migration of the octanoyl group from the 2′-oxygen to the 3′-hydroxy group was not observed in the reaction. Finally, the two acetonide moieties and the TBS group in **12** were simultaneously removed under acidic conditions without affecting ester moieties to afford the target acremomannolipin A (**1**) in 94% yield. The physical and spectroscopic properties of the synthesized specimen were completely in accord with those of natural acremomannolipin A.[17]

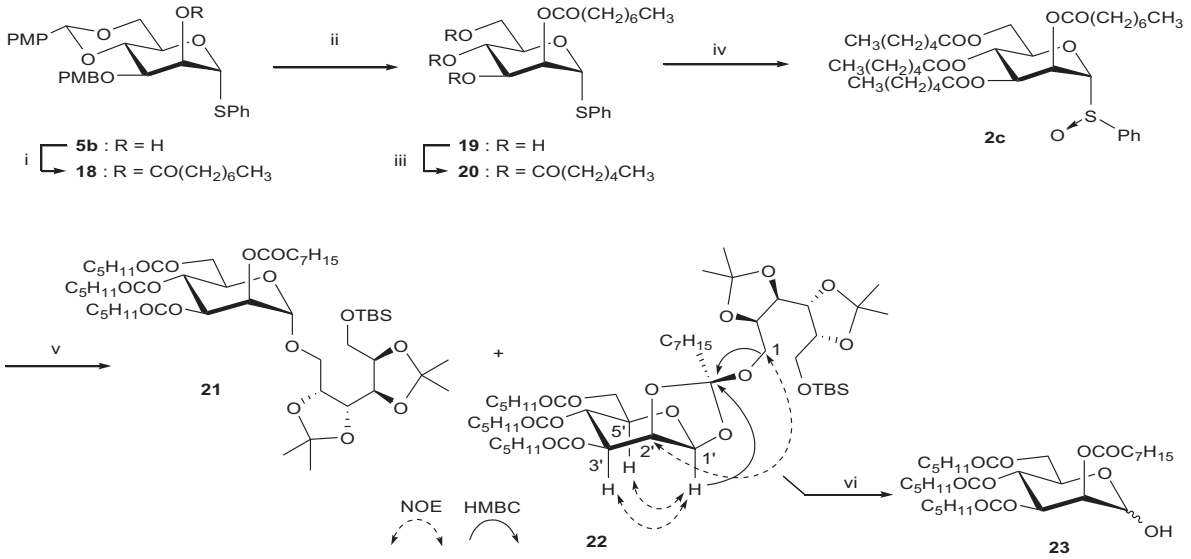
2.2. Synthesis of acremomannolipin A (1): part 2

When the protecting groups of the four hydroxyls at C4′ and C6′, C3′ and C2′ in the mannosyl donor were substituted by *para*methoxybenzylidene, PMB, and TBS, respectively, as shown in Scheme 3, the β-selectivity of the coupling reaction improved, and the desired β-mannoside (**8b**) being provided exclusively. Thus, newly protected mannopyranoside *S*-oxide, phenyl 3-*O*-*p*-methoxybenzyl-4,6-*O*-*p*-methoxybenzylidene-2-*O*-



Scheme 3. Reagents and conditions: (i) Bu_2SnO, toluene, reflux, then PMBCl, CsF, $^{i}Bu_4NBr$, reflux (69%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt (84%); (iii) *m*CPBA, CH_2Cl_2, 0 °C (71%); (iv) BnBr, NaH, DMF, 0 °C (78%); (v) Tf_2O, DTBMP, CH_2Cl_2, −78 °C (65%); (vi) TBAF, THF, rt (86%); (vii) $CH_3(CH_2)_6COCl$, Py, DMAP, CH_2Cl_2, rt (quant.); (viii) DDQ, CH_2Cl_2, H_2O, rt (56%); (ix) $[CH_3(CH_2)_4CO]_2O$, Py, DMAP, CH_2Cl_2, rt (96%); (x) H_2, Pd–C, AcOH, MeOH, rt (78%). (xi) 90% TFA aq, 0 °C (92%).

(*tert*-butyldimethylsilyl)-1-thio-α-D-mannopyranoside *S*-oxide (**2b**), was prepared via a similar process to that for the preparation of **2a** starting from phenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-mannopyranoside[24] (**4b**) in 41% overall yields. The newly prepared mannosyl donor (**2b**) was subjected to the coupling reaction with 6-*O*-benzyl-2,3:4,5-di-*O*-isopropylidene-D-mannitol (**3b**) to give the corresponding coupled product, 6-*O*-benzyl-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 2-*O*-(*tert*-butyldimethylsilyl)-3-*O*-*p*-methoxybenzyl-4,6-*O*-*p*-methoxybenzylidene-β-D-mannopyranoside (**8b**), in 65% isolated yield. In this reaction, the signal due to the benzylidene proton of the α-anomer (δ_H ca. 5.57) was not detected even by the careful inspection of the ^{1}H NMR spectrum of the crude mixture measured at 800 MHz. The NMR spectroscopic properties of **8b** were in good accord with those of **8a**, and the relative stereochemistry of **8b** was also confirmed by NOE experiments. The increased selectivity would be attributed to a steric hindrance by the bulky TBS moiety, which disturbed the oxacarbenium ion formation leading to the α-mannoside.[21] Removal of the silyl group at C2′ with TBAF, and subsequent acylation of the revived hydroxyl with octanoyl chloride gave 2-*O*-octanoyl β-D-mannoside (**14**) in 86% yield via two steps. The *p*-methoxybenzyl and *p*-methoxybenzylidene moieties of **14** were simultaneously removed by action of DDQ to give 3,4,6-free β-D-mannoside (**15**), which was then derived to the corresponding tetraester (**16**) by treating with hexanoic anhydride in 82% yield in two steps. Unexpectedly, two isopropylidene acetal moieties of compound **16** resisted to the acidic hydrogenolysis, and the corresponding bisacetonide (**17**) was obtained as the main product, which was finally converted to acremomannolipin A (**1**) by the treatment with 90% TFA in 92% yield (Scheme 3).



Scheme 4. Reagents and conditions: (i) $CH_3(CH_2)_6COCl$, Py, DMAP, CH_2Cl_2, rt (99%) (ii) DDQ, CH_2Cl_2, H_2O, rt (89%); (iii) $[CH_3(CH_2)_4CO]_2O$, Py, DMAP, CH_2Cl_2, rt (82%); (iv) *m*CPBA, CH_2Cl_2, 0 °C (89%, major/minor=5/1); (v) **3a**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C (**21a**: 21%, **22a**: 20%); (vi) TMSOTf, CH_2Cl_2, −78 °C (quant.).

2.3. Synthesis of α-anomer of acremomannolipin A (*epi*-1)

We next turned our attention to the synthesis of the α-anomer of acremomannolipin A (*epi*-**1**) in order to examine the effect of the stereochemistry at the anomeric center on the calcium signal modulating activity.

Neighboring-group participation of *O*-acyl moieties at the C2 position is known to be one of the most powerful tools for controlling the stereoselectivity in the glycosidation of pyranoses.[28] Meanwhile, 4,6-*O*-cyclic acetal moieties in the mannosyl donors, such as **2a** and **2b** are known to be unpreferable for the α-mannoside formation.[21] Thus, we first schemed introduction of an acyl group at the 2-position of the mannose, and designed a mannosyl donor bearing all the acyl groups necessary for the preparation of *epi*-**1** (Scheme 4).

Starting from thiomannopyranoside **5b**, octanoylation at C2-hydroxyl and subsequent oxidative removal of both *p*-methoxybenzylidene and PMB moieties of the resulting octanoate, phenyl 3-*O*-*p*-methoxybenzyl-4,6-*O*-*p*-methoxybenzylidene-2-*O*-octanoyl-1-thio-α-D-mannopyranoside (**18**), by action of DDQ gave the corresponding monoester (**19**) in good yield. Esterification of the three free hydroxyls in **19** with hexanoic anhydride gave phenyl 3,4,6-tri-*O*-hexanoyl-2-*O*-octanoyl-1-thio-α-D-mannopyranoside (**20**), which was then oxidized with *m*CPBA to give the desired mannosyl donor **2c** as a ca. 5/1 diastereomeric mixture at the sulfur atom. These diastereomers were readily separated with each other on column chromatography, which was conducted to remove other side products, and the major diastereoisomer thus obtained was treated with **3a** at −78 °C in the presence of DTBMP for 1 h. In the reaction, the desired coupled product, 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 3,4,6-tri-*O*-hexanoyl-2-*O*-octanoyl-α-D-mannopyranoside (**21**), was obtained, however in poor yield (21%). Formation of a nearly equal amount (20%) of an undesired orthoester (**22**) was detected as a side product. The FAB mass spectrum of α-mannoside **21** showed a peak at *m*/*z* 981 corresponding to the sodium adduct-ion $[M+Na]^+$, supporting the mannoside formation as shown in Scheme 4. Upfield shifts of signals due to C3′ and C5′ carbons caused by the γ-*gauche* effect with the α-oriented oxygen was observed in the ^{13}C NMR spectrum of **21**, suggesting the formation of an α-mannosidic linkage. Although no critical correlations, which indicate the β-orientation of the anomeric proton H-1′, was detected in NOESY spectrum, the larger coupling constant (ca. $J_{1',2'}$=2.0 Hz) of H-1′ compared to that of **8a** (ca. $J_{1',2'}$=nearly zero) suggested the equatorial orientation of the anomeric proton.

The orthoester **22** had the same molecular weight as **21**, showing the sodium adduct-ion $[M+Na]^+$ at *m*/*z* 981 in the FAB mass spectrum. The orthoester structure was determined on the

basis of the ^{13}C NMR spectral properties, which involves a singlet (δ_C 125.4) characteristic of the orthester's quaternary carbon and three singlets due to ester carbonyls (δ_C 172.1, 173.1 and 173.4). HMBC correlations were observed between the C1 methylene protons (δ_H 3.44 and δ_H 3.62) and the quaternary carbon, and also between the signals due to the anomeric proton shown in Scheme 4. ROESY correlations of the anomeric proton (H-1′) with both H-3′ and H-5′ indicated the α-configuration of the anomeric proton. Another NOE correlation between H-2′ and the methylene protons (H-1) of the mannitol chain suggested the *exo* orientation of the mannitol moiety.

Attempted conversion of the orthoester **22** to **21** under the coupling conditions was unsuccessful even by the prolonged reaction time. As orthoesters are known to be often intermediates to the corresponding glycosides,[28,29] TMSOTf-mediated conversion[29] of **22** to **21** was also attempted in vain, a ca. 10/1 mixture of 3,4,6-tri-*O*-hexanoyl-2-*O*-octanoyl-1-α- and β-D-mannopyranose (**23**) being obtained (Scheme 4).

In order to access the α-epimer more effectively, the mannosylation was then envisioned with 2-*O*-benzylated mannosyl donor, phenyl 2-*O*-benzyl-3,4,6-tri-*O*-hexanoyl-1-thio-α-D-mannopyranoside *S*-oxide (**2d**), which would avoid the orthoester formation.

As illustrated in Scheme 5, the donor **2d** was obtained starting from glycoside **5b** in four steps in 72% overall yield. Thus, benzylation of **5b** and subsequent DDQ oxidation of the resulting per-protected mannoside, phenyl 3-*O*-*p*-methoxybenzyl-4,6-*O*-*p*-methoxybenzylidene-2-*O*-benzyl-1-thio-α-D-mannopyranoside (**24**), gave 2-benzyl thiomannoside (**25**), which was then treated with hexanoic anhydride to give 3,4,6-tri-*O*-hexanoyl-mannoside (**26**). Finally, the mannoside **26** was subjected to *m*CPBA oxidation to provide the desired mannosyl donor (**2d**) in good yield.

identical with those of the specimen obtained in Scheme 4. Finally the two acetonide moieties and the TBS group in compound **21** were simultaneously removed by action of aqueous TFA to give the target (*epi*-**1**) in 70% yield. The NMR spectroscopic properties of acremomannolipin A (**1**) and *epi*-**1** were summarized in Table 1. The signals due to at C-3′ and C-5′of *epi*-**1** also characteristically shifted up-field in comparison with those of **1**.

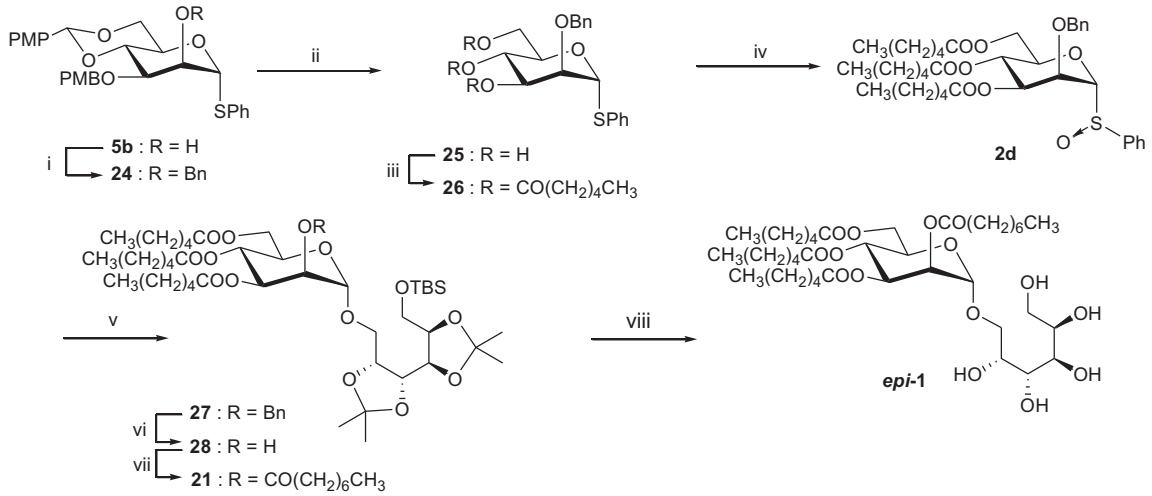
2.4. Evaluation of 1′-*epi*-acremomannolipin A (*epi*-1)

The potency of the calcium signal modulating activity of 1′-*epi*-acremomannolipin A (*epi*-**1**) was examined and compared with that of acremomannolipin A (**1**).

Disruption of the calcineurin gene (*ppb1*$^+$) in fission yeast resulted in a Cl^--sensitive growth defect, thus calcineurin gene deletion cells (Δ*ppb1*) grew in the yeast extract peptone dextrose (YPD) medium, but failed to grow in a YPD medium containing 0.12 M $MgCl_2$ [see filter paper disc a containing DMSO (control) in Fig. 2]. When a solution of acremomannolipin A (**1**) in DMSO was added onto filter paper discs e, f, g, Δ*ppb1* cells grew well around the discs. On the basis of the effect of **1** on the growth of Δ*ppb1* cells in the presence of $MgCl_2$, the activity of homolog *epi*-**1** was evaluated by comparison of the size of colonies around the discs.

By addition of *epi*-**1** onto filter paper discs b, c, and d, which contains 10 μM, 50 μM, and 100 μM of *epi*-***1***, respectively, colonies were observed around the discs b, c, and d, but the size of these colonies were smaller than those around the discs e, f, and g, which contained **1**, showing that the activity of *epi*-**1** was inferior to that of **1**. Thus, the β-mannoside linkage of **1** is found not essential for outset of the activity, but preferable for the activity.

In conclusion, the first stereoselective total synthesis of a novel glycolipid acremomannolipin A (**1**), isolated from *A. strictum* as the



Scheme 5. Reagents and conditions: (i) BnBr, NaH, DMF, rt (86%); (ii) DDQ, CH_2Cl_2, H_2O, rt (95%); (iii) $[CH_3(CH_2)_4CO]_2O$, Py, DMAP, CH_2Cl_2, rt (90%); (iv) *m*CPBA, CH_2Cl_2, 0 °C (98%, major/minor=23/1); (v) **3a**, Tf_2O, DTBMP, CH_2Cl_2, −78 °C (54%); (vi) H_2, Pd−C, AcOEt, rt (59%); (vii) $CH_3(CH_2)_6COCl$, Py, DMAP, CH_2Cl_2, rt (quant.); (viii) 90% TFA aq, 0 °C (70%).

With the mannosyl donor **2d** in hand, coupling reaction with the acceptor **3a** was conducted under the same conditions used for the mannosylation with **2c** to give the desired α-mannoside, 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 2-*O*-benzyl-3,4,6-tri-*O*-hexanoyl-α-D-mannopyranoside (**27**), in 54% yield. Formation of a small amount of β-isomer (α/β=ca. 23/1) was detected. Hydrogenolysis of the benzyl moiety in **27** and subsequent octanoylation of the corresponding 2-*O*-deprotected mannoside (**28**) with octanoyl chloride quantitatively gave the desired tetraester **21**, spectral properties of which were completely

potent calcium signal modulator, has been established by employing the stereoselective β-mannosylation of 4,6-*O*-benzylidene-protected mannosyl sulfoxide (**2a**) with a D-mannitol derivative (**3a**) as the key reaction. Modification of the protective groups of the mannosyl donor (**2b**) improved the stereoselectivity of the coupling reaction, and gave the corresponding β-isomer (**8b**) exclusively. The α-anomer (*epi*-**1**) of **1** was also selectively synthesized by employing appropriately protected mannosyl donor (**2d**) with an acceptor (**3a**). Upon inversion of the configuration at the anomeric center, the calcium modulating activity was reduced,

Table 1
^{1}H and ^{13}C NMR spectral data of acremomannolipin A (**1**) and 1′-*epi*-acremomannolipin A (*epi*-**1**) in CD_3OD

Positions	Acremomannolipin A (**1**) (800 MHz)	(200 MHz)	1′-*epi*-Acremomannolipin A (*epi*-**1**) (700 MHz)	(175 MHz)
	δ_H (*J* Hz)	δ_C	δ_H (*J* Hz)	δ_C
1	4.13 dd (10.6, 2.8)	73.7	3.74 dd (10.0, 2.0)	71.2
	3.69 dd (10.6, 6.6)		3.89 dd (10.0, 5.8)	
2	3.78 ddd (8.6, 6.6, 2.8)	71.7	3.85 ddd (8.6, 5.8, 2.0)	71.06
3	3.72 dd (8.6, 0.9)	71.1	3.81 d (8.6)*	71.14
4	3.75 dd (8.2, 0.9)	71.2	3.81 d (8.6)*	71.14
5	3.66 ddd (8.2, 6.0, 3.6)	73.0	3.70 ddd (8.6, 6.0, 3.6)	73.0
6	3.61 dd (11.2, 6.0)	65.2	3.64 dd (11.0, 6.0)	65.2
	3.79 dd (11.2, 3.6)		3.82 dd (11.0, 3.6)	
1′	4.92 d (0.8)	100.6	4.86 d (1.8)	99.2
2′	5.51 dd (3.2, 0.8)	70.5	5.34 dd (3.0, 1.8)	70.6
3′	5.16 dd (10.0, 3.2)	72.7	5.36 dd (10.0, 3.0),	70.9
4′	5.30 dd (10.0, 10.0)	66.8	5.37 dd (10.0, 10.0)	66.8
5′	3.83 ddd (10.0, 4.2, 2.2)	73.5	4.18 ddd (10.0, 4.0, 2.0)	66.9
6′	4.28 dd (12.2, 4.2)	63.1	4.13 dd (12.4, 2.0)	63.1
	4.14 dd (12.2, 2.2)		4.26 dd (12.4, 4.0)	

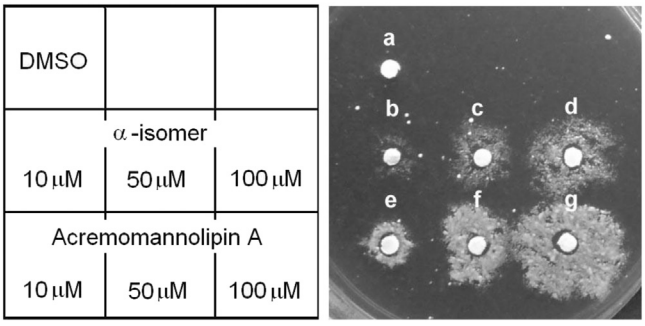


Fig. 2. Suppression of the Cl^--sensitive growth defect of calcineurin deletion cells by acremomannolipin A (**1**) and *epi*-**1**. Calcineurin deletion (Δ*ppb1*) cells were spread onto the YPD medium containing 0.12 M $MgCl_2$. Filter paper a contains 5 μL of DMSO (control). Cells were grown at 27 °C for 3 days.

and the β-configuration of the mannose moiety was found preferable for the activity. Further studies on the structure–activity relationships of this novel compound **1** and calcium signal modulating activity are in progress.

3. Experimental

3.1. General

Mps were determined on an AS ONE ATM-02 melting point apparatus, and mps are uncorrected. IR spectra were measured on a Shimadzu IRAffinity-1 spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 400 (400 MHz ^{1}H, 100 MHz ^{13}C), a JEOL JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C), JEOL JNM-ECA 700 (700 MHz ^{1}H, 175 MHz ^{13}C), or a JEOL JNM-ECA 800 (800 MHz ^{1}H, 200 MHz ^{13}C) spectrometer. Chemical shifts (δ) and coupling constants (*J*) are given in parts per million and hertz, respectively. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-700T spectrometer. Optical rotations were determined with a JASCO P-2200 polarimeter. Column chromatography was effected over Fuji Silysia silica gel BW-200. All the organic extracts were dried over anhydrous sodium sulfate prior to evaporation.

*3.1.1. Phenyl 3-O-benzyl-4,6-O-benzylidene-2-O-p-methoxybenzyl-1-thio-α-D-mannopyranoside (**6a**).* To a suspension of sodium hydride (NaH, 60% in liquid paraffin, 1.27 g, 31.8 mmol) in dimethylformamide (DMF, 110 mL) was added a solution of phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside[25] (**5a**, 7.17 g, 15.9 mmol) in DMF (50 mL), and the mixture was stirred for 30 min at room temperature. Then, *p*-methoxybenzyl chloride (PMBCl, 4.3 mL, 31.8 mmol) and tetrabutylammonium iodide (11.8 g, 31.8 mmol) were added, and the resulting mixture was stirred at room temperature for 18 h. Under cooling with ice-water, the reaction mixture was diluted with water and extracted with EtOAc. The extract was successively washed with water and brine, and concentrated in vacuo. The residue (16.5 g) was purified by means of column chromatography (*n*-hexane–EtOAc, 15/1) to give title compound **6a** (3.34 g, 78%) as a colorless oil. $[\alpha]_D^{24}$ +97.8 (*c* 1.03, $CHCl_3$). IR (neat) cm^{-1}: 1612, 1512, 1250, 1099, 1030. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H, OC*H*$_3$), 3.88 (dd, *J*=9.2, 9.2 Hz, 1H, H-4), 3.95 (dd, *J*=9.2, 3.2 Hz, 1H, H-3), 4.03 (dd, *J*=3.2, 1.2 Hz, 1H, H-2), 4.21 (dd, *J*=10.0, 4.0 Hz, 1H, H-6a), 4.28 (ddd, *J*=9.2, 9.2, 4.0 Hz, 1H, H-5), 4.30 (dd, *J*=10.0, 9.2 Hz, 1H, H-6b), 4.64/4.81 (each d, *J*=12.4 Hz, 1H, C*H*$_2$Ph), 4.66 (s, 2H, OC*H*$_2$C$_6$H$_4$OCH$_3$), 5.45 (d, *J*=1.2 Hz, 1H, H-1), 5.64 (s, 1H, C*H*Ph), 6.84 (d, *J*=8.8 Hz, 2H, Ar), 7.26–7.41 (m, 15H, Ar), 7.51 (dd, *J*=7.6, 1.6 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.3 (q), 65.4 (d), 68.5 (t), 72.7 (t), 73.0 (t), 76.2 (d), 77.5 (d), 79.1 (d), 87.2 (d), 101.5 (d), 113.8 (d, 2C), 126.1 (d, 2C), 127.57 (d, 2C), 127.61 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.8 (d), 129.1 (d, 2C), 129.7 (s), 129.8 (d, 2C), 131.6 (d, 2C), 133.8 (s), 137.6 (s), 138.4 (s), 159.4 (s). FABMS *m/z* (%): 593 ([M+Na]$^+$, 11), 121 (100). FABHRMS calcd for $C_{34}H_{34}O_6SNa$ [M+Na]$^+$: 593.1974; found: 593.1995.

*3.1.2. Phenyl 3-O-benzyl-4,6-O-benzylidene-2-O-p-methoxybenzyl-1-thio-α-D-mannopyranoside S-oxide (**2a**).* To a solution of **6a** (3.34 g, 5.85 mmol) in dichloromethane (CH_2Cl_2, 59 mL) was added *m*-chloroperbenzoic acid (*m*CPBA, 1.62 g, 7.02 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. After the reaction was quenched with aqueous sodium thiosulfate–sodium hydrogen carbonate, the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, and concentrated in vacuo. The residue (3.87 g) was purified by means of column chromatography (*n*-hexane–EtOAc, 8/1) to give a single diastereomer of title compound **2a** (2.85 g, 83%) as a colorless solid. Mp 128 °C. $[\alpha]_D^{25}$ −60.9 (*c* 1.02, $CHCl_3$). IR (neat) cm^{-1}: 1612, 1512, 1250, 1107, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75 (dd, *J*=10.0, 10.0 Hz, 1H, H-4), 3.79 (s, 3H, OC*H*$_3$), 4.09 (ddd, *J*=10.0, 10.0, 4.8 Hz, 1H, H-5), 4.21 (dd, *J*=10.0, 4.8 Hz, 1H, H-6a), 4.27 (dd, *J*=10.0, 3.2 Hz, 1H, H-3), 4.31 (dd, *J*=10.0, 10.0 Hz, 1H, H-6b), 4.38 (dd, *J*=3.2, 0.9 Hz, 1H, H-2), 4.47 (d, *J*=0.9 Hz, 1H, H-1), 4.51 (s, 2H, OC*H*$_2$C$_6$H$_4$OCH$_3$), 4.64/4.81 (each d, *J*=12.0 Hz, 1H, C*H*$_2$Ph), 5.63 (s, 1H, C*H*Ph), 6.78 (d, *J*=8.8 Hz, 2H, Ar), 7.13 (d, *J*=8.8 Hz, 2H, Ar), 7.30–7.54 (m, 15H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.2 (q), 68.2 (t), 70.0 (d), 72.2 (d), 73.1 (t), 73.2 (t), 76.3 (d), 78.0 (d), 97.7 (d), 101.6 (d), 113.8 (d, 2C), 124.3 (d, 2C), 126.1 (d, 2C), 127.6 (d), 127.7 (d, 2C), 128.2 (d, 2C), 128.3 (d,

2C), 129.0 (d), 129.3 (d), 129.4 (d, 2C), 130.0 (d, 2C), 131.6 (s), 137.3 (s), 138.3 (s), 141.6 (s), 159.4 (s). FABMS *m*/*z* (%): 609 ([M+Na]$^+$, 7), 121 (100). FABHRMS calcd for $C_{34}H_{34}O_7SNa$ [M+Na]$^+$ 609.1923; found: 609.1906.

*3.1.3. 6-O-(tert-Butyldimethylsilyl)-2,3:4,5-di-O-isopropylidene-D-mannitol (**3a**).* To a suspension of NaH (60% in liquid paraffin, 84.0 mg, 2.10 mmol) in DMF (9.0 mL) was added a solution of 2,3:4,5-di-*O*-isopropylidene-D-mannitol[27] (**7**) (500 mg, 1.91 mmol) in DMF (10.0 mL), and the mixture was stirred for 30 min at room temperature. At 0 °C, *tert*-butyldimethylsilyl chloride (316 mg, 2.10 mmol) was added portionwise and the resulting mixture was stirred at room temperature for 14 h. Under cooling with ice-water, the reaction mixture was diluted with water and extracted with EtOAc. The extract was washed successively with water and brine, and concentrated in vacuo. The residue (788 mg) was purified by means of column chromatography (*n*-hexane–EtOAc, 7/1) to give title compound **3a** (631 mg, 88%) as a colorless solid. Mp 57–58 °C. $[\alpha]_D^{23}$ +5.52 (*c* 0.98, $CHCl_3$). IR (neat) cm^{-1}: 3503, 1462, 1377, 1254, 1215, 1088, 1045. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 0.084/0.087 [each s, 3H, Si(C*H*$_3$)$_2$], 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], 1.38/1.40/1.48/1.53 [each s, 3H, C(C*H*$_3$)$_2$], 2.42 (dd, *J*=6.0 Hz, 1H, OH), 3.67 (dd, *J*=10.3, 4.0 Hz, 1H, H-1a), 3.65–3.73 (m, 2H, H-1b and H-6a), 3.80 (dd, *J*=10.3, 9.2 Hz, 1H, H-6b), 4.23 (ddd, *J*=9.2, 5.1, 4.0 Hz, 1H, H-5), 4.27 (ddd, *J*=6.0, 6.0, 4.6 Hz, 1H, H-2), 4.40 (dd, *J*=6.0, 4.6 Hz, 1H, H-3), 4.41 (dd, *J*=6.0, 5.1 Hz, 1H, H-4). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: −5.6 (q), −5.4 (q), 18.3 (s), 25.1 (q), 25.5 (q), 25.9 (q, 3C), 27.4 (q), 27.5 (q), 61.9 (t), 62.0 (t), 75.0 (d), 75.1 (d), 76.9 (d), 77.3 (d), 108.6 (s), 108.8 (s). FABMS *m*/*z* (%): 377 ([M+H]$^+$, 24), 73 (100). FABHRMS calcd for $C_{18}H_{37}O_6Si$ [M+H]$^+$: 377.2359; found: 377.2379.

*3.1.4. Coupling reaction of mannosyl S-oxides **2a** with protected mannitol **3a**.* Under argon atmosphere, to a mixture of **2a** (1.00 g, 1.70 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 700 mg, 3.41 mmol), and CH_2Cl_2 (17 mL) was added trifluoromethanesulfonic anhydride (Tf_2O, 0.30 mL, 1.87 mmol) at −78 °C, and the mixture was stirred at −78 °C for 10 min. At that temperature, a solution of **3a** (770 mg, 2.05 mmol) in CH_2Cl_2 (17 mL) was added and the resulting mixture was stirred at −78 °C for another 1 h. After addition of aqueous sodium hydrogen carbonate to the reaction mixture at −78 °C, the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, and concentrated in vacuo. The residue (2.52 g) was purified by means of column chromatography (*n*-hexane–EtOAc, 10/1) to give 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*p*-methoxybenzyl-β-D-mannopyranoside (**8a**, 1.01 g, 71%) as a colorless oil. $[\alpha]_D^{24}$ −35.6 (*c* 1.08, $CHCl_3$). IR (neat) cm^{-1}: 1512, 1377, 1250, 1215, 1092, 1049. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 0.07/0.08 [each s, 3H, Si(C*H*$_3$)$_2$], 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], 1.36/1.39/1.46/1.50 [each s, 3H, C(C*H*$_3$)$_2$], 3.31 (ddd, *J*=10.4, 9.8, 4.6 Hz, 1H, H-5′), 3.56 (dd, *J*=9.8, 2.9 Hz, 1H, H-3′), 3.60 (dd, *J*=10.3, 3.7 Hz, 1H, H-6a), 3.65 (dd, *J*=10.3, 6.6 Hz, 1H, H-1a), 3.76 (dd, *J*=10.3, 7.8 Hz, 1H, H-6b), 3.80 (s, 3H, OC*H*$_3$), 3.90 (dd, *J*=10.4, 10.4 Hz, 1H, H-6′a), 3.97 (d, *J*=2.9 Hz, 1H, H-2′), 4.00 (dd, *J*=10.3, 4.3 Hz, 1H, H-1b), 4.17 (dd, *J*=9.8, 9.8 Hz, 1H, H-4′), 4.24 (ddd, *J*=7.8, 6.0, 3.7 Hz, 1H, H-5), 4.26 (dd, *J*=6.0, 5.8 Hz, 1H, H-4), 4.31 (dd, *J*=10.4, 4.6 Hz, 1H, H-6′b), 4.44 (dd, *J*=6.0, 5.8 Hz, 1H, H-3), 4.45 (ddd, *J*=6.6, 6.0, 4.3 Hz, 1H, H-2), 4.54/4.64 (each d, *J*=12.6 Hz, 1H, OC*H*$_2$Ph), 4.58 (s, 1H, H-1′), 4.79/4.87 (each d, *J*=11.8 Hz, 1H, OC*H*$_2$C$_6$H$_4$OCH$_3$), 5.61 (s, 1H, C*H*Ph), 6.84 (d, *J*=8.6 Hz, 2H, Ar), 7.25–7.39 (m, 10H, Ar), 7.49 (dd, *J*=8.0, 1.7 Hz, 2H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: −5.5 (q), −5.4 (q), 18.3 (s), 25.46 (q), 25.51 (q), 25.9 (q, 3C), 27.6 (q), 27.8 (q), 55.2 (q), 62.2 (t), 67.6 (d), 68.6 (t), 68.7 (t), 72.2 (t), 74.4 (t), 74.9 (d), 75.1 (d), 75.4 (d), 76.2 (d), 76.9 (d), 77.8 (d), 78.6 (d), 101.4 (d), 102.1 (d), 108.5 (s), 108.8 (s), 113.5 (d, 2C), 126.0 (d, 2C), 127.46 (d, 2C), 127.49 (d), 128.16 (d, 2C), 128.24 (d, 2C), 128.8 (d), 130.1 (d, 2C), 130.5 (s), 137.5 (s), 138.3 (s), 159.1 (s). FABMS *m*/*z* (%): 859 ([M+Na]$^+$, 10), 73 (100). FABHRMS calcd for $C_{46}H_{64}O_{12}SiNa$ [M+Na]$^+$: 859.4065; found: 859.4042.

*3.1.5. 6-O-(tert-Butyldimethylsilyl)-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3-O-benzyl-4,6-O-benzylidene-β-D-mannopyranoside (**9**).* To a mixture of **8a** (447 mg, 0.533 mmol), CH_2Cl_2 (4.6 mL), and H_2O (200 μL) was added 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 177 mg, 0.747 mmol), and the mixture was stirred at room temperature for 1 h. After addition of aqueous sodium hydrogen carbonate, the resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, and concentrated in vacuo. The residue (505 mg) was purified by means of column chromatography (*n*-hexane–EtOAc, 5/1) to give title compound **9** (348 mg, 91% yield) as a colorless oil. $[\alpha]_D^{24}$ −4.90 (*c* 1.03, $CHCl_3$). IR (neat) cm^{-1}: 3503, 1381, 1254, 1215, 1165, 1045. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.08/0.09 [each s, 3H, Si(C*H*$_3$)$_2$], 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], 1.37/1.38/1.47/1.49 [each s, 3H, C(C*H*$_3$)$_2$], 2.56 (brs, 1H, OH), 3.34 (ddd, *J*=9.6, 9.6, 4.8 Hz, 1H, H-5′), 3.62 (dd, *J*=9.6, 3.6 Hz, 1H, H-3′), 3.63 (dd, *J*=9.2, 6.0 Hz, 1H, H-6a), 3.64 (dd, *J*=9.2, 3.2 Hz, 1H, H-6b), 3.78 (dd, *J*=10.4, 7.6 Hz, 1H, H-1a), 3.87 (dd, *J*=10.4, 9.6 Hz, 1H, H-6′a), 3.99 (dd, *J*=10.4, 4.8 Hz, 1H, H-1b), 4.14 (dd, *J*=9.6, 9.6 Hz, 1H, H-4′), 4.16 (d, *J*=3.6, 0.9 Hz, 1H, H-2′), 4.25 (dd, *J*=6.0, 6.0 Hz, 1H, H-4), 4.29 (ddd, *J*=6.0, 6.0, 3.2 Hz, 1H, H-5), 4.33 (dd, *J*=10.4, 4.8 Hz, 1H, H-6′b), 4.40 (ddd, *J*=7.6, 6.0, 4.8 Hz, 1H, H-2), 4.42 (ddd, *J*=6.0, 6.0 Hz, 1H, H-3), 4.60 (d, *J*=0.9 Hz, 1H, H-1′), 4.78/4.85 (each d, *J*=12.4 Hz, 1H, OC*H*$_2$Ph), 5.61 (s, 1H, C*H*Ph), 7.29–7.41 (m, 8H, Ar), 7.50 (dd, *J*=7.6, 1.6 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: −5.5 (q), −5.4 (q), 18.3 (s), 25.4 (q, 2C), 25.9 (q, 3C), 27.5 (q), 27.8 (q), 62.3 (t), 67.0 (d), 68.4 (t), 68.6 (t), 69.7 (d), 72.4 (t), 75.1 (d), 75.2 (d), 75.9 (d), 76.58 (d), 76.9 (d), 78.4 (d), 100.3 (d), 101.5 (d), 108.5 (s), 108.8 (s), 126.0 (d, 2C), 127.79 (d), 127.83 (d, 2C), 128.2 (d, 2C), 128.4 (d, 2C), 128.9 (d), 137.4 (s), 138.0 (s). FABMS *m*/*z* (%): 739 ([M+Na]$^+$, 5), 73 (100). FABHRMS calcd for $C_{38}H_{56}O_{11}SiNa$ [M+Na]$^+$: 739.3490; found: 739.3499.

*3.1.6. 6-O-(tert-Butyldimethylsilyl)-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3-O-benzyl-4,6-O-benzylidene-2-O-octanoyl-β-D-mannopyranoside (**10**).* To a mixture of **9** (348 mg, 0.486 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 119 mg, 0.972 mmol), pyridine (0.12 mL, 1.46 mmol), and CH_2Cl_2 (4.9 mL) was added *n*-octanoyl chloride (0.25 mL, 1.46 mmol) at room temperature. After being stirred at room temperature for 20 h, the reaction mixture was diluted with water, and the resulting mixture was extracted with CH_2Cl_2. The extract was successively washed with aqueous sodium hydrogen carbonate, water and brine, and concentrated in vacuo. The residue (673 mg) was purified by means of column chromatography (*n*-hexane–EtOAc, 15/1) to give title compound **10** (403 mg, 98%) as a colorless oil. $[\alpha]_D^{24}$ −36.4 (*c* 1.02, $CHCl_3$). IR (neat) cm^{-1}: 1744, 1381, 1250, 1215, 1157, 1096, 1049. ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 0.07/0.08 [each s, 3H, Si(C*H*$_3$)$_2$], 0.87 [t, *J*=6.8 Hz, 3H, CO(CH$_2$)$_6$C*H*$_3$], 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], 1.25–1.37 [m, 8H, CO(CH$_2$)$_2$(C*H*$_2$)$_4$CH$_3$], 1.37 [s, 6H, C(C*H*$_3$)$_2$], 1.46/1.47 [each s, 3H, C(C*H*$_3$)$_2$], 1.66 [ddt, *J*=7.6, 7.6, 7.6 Hz, 2H, COCH$_2$C*H*$_2$(CH$_2$)$_6$C*H*$_3$], 2.42/2.46 [each dt, *J*=15.6, 7.6 Hz, 1H, COC*H*$_2$(CH$_2$)$_6$CH$_3$], 3.37 (ddd, *J*=10.0, 9.6, 4.8 Hz, 1H, H-5′), 3.56 (dd, *J*=10.4, 3.6 Hz, 1H, H-6a), 3.60 (dd, *J*=10.4, 5.6 Hz, 1H, H-1a), 3.71 (dd, *J*=9.6, 3.6 Hz, 1H, H-3′), 3.73 (dd, *J*=10.4, 8.0 Hz, 1H, H-6b), 3.87 (dd, *J*=10.4, 10.0 Hz, 1H, H-6′a), 3.94 (dd, *J*=10.4, 6.0 Hz, 1H, H-1b), 3.96 (dd, *J*=9.6, 9.6 Hz, 1H, H-4′), 4.16 (ddd, *J*=8.0, 5.6, 3.6 Hz, 1H, H-5), 4.27 (dd, *J*=7.6, 5.6 Hz, 1H, H-4), 4.34 (dd, *J*=10.4, 4.8 Hz, 1H, H-6′b), 4.36 (ddd, *J*=6.0, 5.6, 5.6 Hz, 1H, H-2), 4.42 (dd, *J*=7.6, 5.6 Hz, 1H, H-3), 4.61/4.73 (each d, *J*=12.4 Hz, 1H, OC*H*$_2$Ph), 4.71 (d, *J*=0.9 Hz, 1H, H-1′), 5.61 (s, 1H, C*H*Ph), 5.67 (dd, *J*=3.6, 0.9 Hz, 1H, H-2′), 7.27–7.41 (m, 8H, Ar), 7.50 (dd, *J*=8.0, 1.6 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: −5.6 (q), −5.4 (q), 14.1 (q), 18.3 (s), 22.6 (t), 24.9 (t), 25.4 (q), 25.6 (q), 25.9 (q,

3C), 27.6 (q), 27.9 (q), 28.98 (t), 29.03 (t), 31.7 (t), 34.1 (t), 62.2 (t), 67.4 (d), 68.29 (t), 68.33 (d), 68.5 (t), 71.5 (t), 75.1 (d), 75.2 (d), 75.7 (d), 75.8 (d), 76.9 (d), 78.0 (d), 99.5 (d), 101.5 (d), 108.4 (s), 108.7 (s), 126.1 (d, 2C), 127.66 (d), 127.70 (d, 2C), 128.2 (d, 2C), 128.3 (d, 2C), 128.9 (d), 137.3 (s), 137.7 (s), 173.0 (s). FABMS *m/z* (%): 865 ([M+Na]$^+$, 4), 91 (100). FABHRMS calcd for $C_{46}H_{70}O_{12}SiNa$ [M+Na]$^+$: 865.4534; found: 865.4561.

*3.1.7. 6-O-(tert-Butyldimethylsilyl)-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 2-O-octanoyl-β-D-mannopyranoside (**11**).* Under balloon pressure of hydrogen, a solution of **10** (885 mg, 1.05 mmol) in EtOAc (10 mL) was hydrogenated over 10% palladium on carbon (90 mg) at room temperature until the uptake of hydrogen ceased. The catalyst was filtered off and washed with MeOH. The combined filtrate and washings were condensed in vacuo. The residue (735 mg) was purified by means of column chromatography ($CHCl_3$–MeOH, 30/1) to give title compound **11** (614 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ −13.5 (*c* 1.04, $CHCl_3$). IR (neat) cm^{-1}: 3418, 1744, 1466, 1381, 1254, 1219, 1165, 1080. ^{1}H NMR (400 MHz, CD_3OD) δ: 0.085/0.090 [each s, 3H, Si(C*H*$_3$)$_2$], 0.90 [t, *J*=6.8 Hz, 3H, CO(CH$_2$)$_6$C*H*$_3$], 0.91 [s, 9H, SiC(C*H*$_3$)$_3$], 1.26–1.38 [m, 8H, CO(CH$_2$)$_2$(C*H*$_2$)$_4$CH$_3$], 1.32/1.35/1.417/1.422 [each s, 3H, C(C*H*$_3$)$_2$], 1.62 [ddt, *J*=7.6, 7.6, 7.6 Hz, 2H, COCH$_2$C*H*$_2$(CH$_2$)$_6$CH$_3$], 2.35/2.41 [each dt, *J*=16.4, 7.6 Hz, 1H, COC*H*$_2$(CH$_2$)$_6$CH$_3$], 3.27 (ddd, *J*=9.6, 6.4, 2.0 Hz, 1H, H-5′), 3.46 (dd, *J*=9.6, 9.6 Hz, 1H, H-4′), 3.57 (dd, *J*=10.4, 5.2 Hz, 1H, H-1a), 3.59 (dd, *J*=10.8, 4.4 Hz, 1H, H-6a), 3.63 (dd, *J*=9.6, 3.2 Hz, 1H, H-3′), 3.68 (dd, *J*=12.0, 6.4 Hz, 1H, H-6′a), 3.75 (dd, *J*=10.8, 6.8 Hz, 1H, H-6b), 3.91 (dd, *J*=12.0, 2.0 Hz, 1H, H-6′b), 4.01 (dd, *J*=10.4, 7.6 Hz, 1H, H-1b), 4.21 (ddd, *J*=6.8, 6.8, 4.4 Hz, 1H, H-5), 4.33 (ddd, *J*=7.6, 5.6, 5.2 Hz, 1H, H-2), 4.37 (dd, *J*=6.8, 6.8 Hz, 1H, H-4), 4.43 (dd, *J*=6.8, 5.6 Hz, 1H, H-3),4.70 (s, 1H, H-1′), 5.34 (d, *J*=3.2 Hz, 1H, H-2′). ^{13}C NMR (100 MHz, CD_3OD) δ: −5.3 (q), −5.2 (q), 14.4 (q), 19.2 (s), 23.7 (t), 25.6 (q), 25.87 (q), 25.93 (t), 26.5 (q, 3C), 27.9 (q), 28.0 (q), 30.2 (t, 2C), 32.9 (t), 35.1 (t), 63.1 (t), 63.7 (t), 69.0 (d), 69.2 (t), 72.8 (d), 73.7 (d), 76.3 (d), 76.6 (d), 76.9 (d), 78.4 (d), 78.8 (d), 100.5 (d), 109.5 (s), 109.7 (s), 174.9 (s). FABMS *m/z* (%): 687 ([M+Na]$^+$, 61), 73 (100). FABHRMS calcd for $C_{32}H_{60}O_{12}SiNa$ [M+Na]$^+$: 687.3752; found: 687.3757.

*3.1.8. 6-O-(tert-Butyldimethylsilyl)-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-β-D-mannopyranoside (**12**).* To a mixture of **11** (151 mg, 0.227 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 111 mg, 0.908 mmol), pyridine (0.07 mL, 0.908 mmol), and CH_2Cl_2 (2.3 mL) was added hexanoic anhydride (0.21 mL, 0.908 mmol) at room temperature, and the mixture was stirred for 30 min at room temperature. The reaction was quenched by the addition of water, and the resulting mixture was extracted with CH_2Cl_2. The extract was successively washed with aqueous sodium bicarbonate, water and brine, and condensed in vacuo. The residue (262 mg) was purified by means of column chromatography (*n*-hexane–EtOAc, 15/1) to give title compound **12** (202 mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ −13.9 (*c* 1.04, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1377, 1250, 1219, 1165, 1096, 1072. ^{1}H NMR (800 MHz, $CDCl_3$) δ: 0.06/0.07 [each s, 3H, Si(C*H*$_3$)$_2$], 0.879/0.881/0.885/0.90 (each t, *J*=6.9 Hz, 3H, acyl C*H*$_3$), 0.886 [s, 9H, SiC(C*H*$_3$)$_3$], 1.22–1.36 (m, 20H, acyl C*H*$_2$), 1.35/1.37/1.45/1.47 [each s, 3H, C(C*H*$_3$)$_2$], 1.52–1.60 (m, 4H, acyl C*H*$_2$), 1.61–1.67 (m, 4H, acyl C*H*$_2$), 2.17/2.21 (each ddd, *J*=15.8, 8.2, 7.1 Hz, 1H, COC*H*$_2$), 2.23/2.28 (each dt, *J*=15.6, 7.5 Hz, 1H, COC*H*$_2$), 2.30/2.34 (each dt, *J*=15.9, 7.5 Hz, 1H, COC*H*$_2$), 2.39/2.44 (each dt, *J*=15.8, 7.8 Hz, 1H, COC*H*$_2$), 3.54 (dd, *J*=10.6, 3.9 Hz, 1H, H-6a), 3.58 (dd, *J*=10.6, 6.0 Hz, 1H, H-1a), 3.65 (ddd, *J*=9.9, 5.7, 2.5 Hz, 1H, H-5′), 3.71 (dd, *J*=10.6, 8.3 Hz, 1H, H-6b), 3.95 (dd, *J*=10.6, 6.9 Hz, 1H, H-1b), 4.13 (ddd, *J*=8.3, 5.7, 3.9 Hz, 1H, H-5), 4.16 (dd, *J*=12.1, 2.5 Hz, 1H, H-6′a), 4.23 (dd, *J*=12.1, 5.7 Hz, 1H, H-6′b), 4.26 (dd, *J*=8.0, 5.7 Hz, 1H, H-4), 4.35 (ddd, *J*=6.9, 6.0, 5.7 Hz, 1H, H-2), 4.41 (dd, *J*=8.0, 5.7 Hz, 1H, H-3), 4.77 (d, *J*=0.7 Hz, 1H, H-1′), 5.05 (dd, *J*=10.0, 3.2 Hz, 1H, H-3′), 5.25 (dd, *J*=10.0, 9.9 Hz, 1H, H-4′), 5.49 (dd, *J*=3.2, 0.7 Hz, 1H, H-2′). ^{13}C NMR (200 MHz, $CDCl_3$) δ: −5.6 (q), −5.5 (q), 13.81 (q), 13.83 (q), 13.9 (q), 14.1 (q), 18.3 (s), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 24.2 (t), 24.4 (t), 24.5 (t), 25.0 (t), 25.3 (q), 25.5 (q), 25.9 (q, 3C), 27.6 (q), 28.0 (q), 29.00 (t), 29.05 (t), 31.2 (t, 2C), 31.3 (t), 31.7 (t), 33.9 (t), 33.96 (t), 34.01 (t), 34.03 (t), 62.2 (t), 62.5 (t), 65.7 (d), 68.2 (t), 68.5 (d), 71.1 (d), 72.6 (d), 75.1 (d), 75.2 (d), 75.7 (d), 76.8 (d), 98.4 (d), 108.4 (s), 108.8 (s), 172.2 (s), 172.6 (s), 172.8 (s), 173.4 (s). FABMS *m/z* (%): 981 ([M+Na]$^+$, 5) 99 (100). FABHRMS calcd for $C_{50}H_{90}O_{15}SiNa$ [M+Na]$^+$: 981.5947; found: 981.5930.

*3.1.9. D-Mannitol-1-yl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-β-D-mannopyranoside=acremomannolipin A (**1**).* A solution of **12** (30.0 mg, 0.0313) in 90% trifluoroacetic acid aq (1.0 mL) was stirred at 0 °C for 30 min. The reaction mixture was concentrated in vacuo and co-evaporated with MeOH. The residue (26.6 mg) was purified by means of column chromatography ($CHCl_3$–MeOH, 100/1) to give title compound **1** (22.4 mg, 94%).

In a similar manner, hydrolysis of **17** (26.0 mg, 0.0308 mmol) gave title compound **1** (21.7 mg, 92%).

A colorless amorphous. $[\alpha]_D^{23}$ −32.9 (*c* 1.00, MeOH). IR (neat) cm^{-1}: 3383, 1748, 1246, 1165, 1099, 1069. ^{1}H NMR (700 MHz, CD_3OD) δ: 0.90 (t, *J*=7.2 Hz, 6H, acyl CH_3), 0.91/0.92 (each t, *J*=7.2 Hz, 3H, acyl CH_3), 1.25–1.42 (m, 20H, acyl CH_2), 1.53–1.59 (m, 4H, acyl CH_2), 1.62–1.70 (m, 4H, acyl CH_2), 2.19/2.21 (each dt, *J*=15.3, 7.4 Hz, 1H, COC*H*$_2$), 2.27/2.31 (each dt, *J*=15.8, 7.4 Hz, 1H, COC*H*$_2$), 2.34/2.37 (each dt, *J*=15.6, 7.4 Hz, 1H, COC*H*$_2$), 2.40/2.47 (each dt, *J*=15.4, 7.4 Hz, 1H, COC*H*$_2$), 3.61 (dd, *J*=11.2, 6.0 Hz, 1H, H-6a), 3.66 (ddd, *J*=8.2, 6.0, 3.6 Hz, 1H, H-5), 3.69 (dd, *J*=10.6, 6.6 Hz, 1H, H-1a), 3.72 (dd, *J*=8.6, 1.0 Hz, 1H, H-3), 3.75 (dd, *J*=8.2, 1.0 Hz, 1H, H-4), 3.78 (ddd, *J*=8.6, 6.6, 2.4 Hz, 1H, H-2), 3.79 (dd, *J*=11.2, 3.6 Hz, 1H, H-6b), 3.83 (ddd, *J*=10.0, 4.2, 2.2 Hz, 1H, H-5′), 4.13 (dd, *J*=10.6, 2.4 Hz, 1H, H-1b), 4.15 (dd, *J*=12.2, 2.2 Hz, 1H, H-6′a), 4.28 (dd, *J*=12.2, 4.2 Hz, 1H, H-6′b), 4.92 (d, *J*=0.8 Hz, 1H, H-1′), 5.16 (dd, *J*=10.0, 3.2 Hz, 1H, H-3′), 5.30 (dd, *J*=10.0, 10.0 Hz, 1H, H-4′), 5.51 (dd, *J*=3.2, 0.8 Hz, 1H, H-2′). ^{13}C NMR (175 MHz, CD_3OD) δ: 14.2 (q, 2C), 14.3 (q), 14.5 (q), 23.35 (t), 23.37 (t), 23.4 (t), 23.8 (t), 25.5 (t), 25.59 (t), 25.62 (t), 26.3 (t), 30.2 (t), 30.3 (t), 32.3 (t), 32.4 (t), 32.5 (t), 33.0 (t), 34.85 (t), 34.93 (t), 35.0 (t), 35.2 (t), 63.0 (t), 65.2 (t), 66.8 (d), 70.5 (d), 71.1 (d), 71.2 (d), 71.7 (d), 72.7 (d), 73.0 (d), 73.5 (d), 73.7 (t), 100.6 (d), 173.8 (s), 173.9 (s),174.8 (s), 175.0 (s). FABMS *m/z* (%): 787 ([M+Na]$^+$, 25), 57 (100). FABHRMS calcd for $C_{38}H_{68}O_{15}Na$ [M+Na]$^+$: 787.4456; found: 787.4434.

*3.1.10. Phenyl 3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-1-thio-α-D-mannopyranoside (**5b**).* A mixture of phenyl 4,6-*O*-*p*-methoxybenzylidene-1-thio-α-D-mannopyranoside[24] (**4b**, 11.2 g, 28.7 mmol), dibutyltin (IV) oxide (10.5 g, 29.2 mmol), and toluene (191 mL) was refluxed for 1 h. The water formed during the reaction was azeotropically removed by using a Dean–Stark apparatus. After the reaction mixture was cooled, tetrabutylammonium bromide (9.80 g, 30.4 mmol), cesium fluoride (4.44 g, 29.2 mmol), and *p*-methoxybenzyl chloride (4.1 mL, 30.1 mmol) were successively added to the mixture, which was heated under reflux for 2 h. After being cooled, the reaction mixture was poured into aqueous sodium hydrogen carbonate, and diluted with EtOAc. The deposited precipitates were filtered through Celite and washed with EtOAc. The combined filtrate and washings separated into two phases, and the aqueous layer was extracted with EtOAc. The combined EtOAc layer was washed with brine, and concentrated in vacuo. The residue (17.8 g) was purified by means of column chromatography (*n*-hexane–EtOAc, 5/1) to give title compound **5** (10.1 g, 69%) as a colorless amorphous. $[\alpha]_D^{24}$ +202.5 (*c* 1.03, $CHCl_3$). IR (neat) cm^{-1}: 3445, 1612, 1585, 1250, 1096, 1030. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.82 (s, 1H, OH), 3.815 (s, 3H, OC*H*$_3$), 3.822 (s, 3H, OC*H*$_3$), 3.83 (dd, *J*=9.6, 9.6 Hz, 1H, H-4), 3.93 (dd, *J*=9.6, 3.2 Hz, 1H, H-3), 4.13 (dd,

J=10.4, 9.6 Hz, 1H, H-6a), 4.18 (dd, J=10.4, 4.8 Hz, 1H, H-6b), 4.24 (d, J=3.2 Hz, 1H, H-2), 4.31 (ddd, J=9.6, 9.6, 4.8 Hz, 1H, H-5), 4.66/4.81 (each d, J=11.2 Hz, 1H, OCH_2C$_6$H$_4$OCH$_3$), 5.57 (s, 1H, OCHC$_6$H$_4$OCH$_3$), 5.58 (s, 1H, H-1), 6.88 (d, J=8.4 Hz, 2H, Ar), 6.91 (d, J=8.4 Hz, 2H, Ar), 7.27–7.33 (m, 5H, Ar), 7.42–7.46 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.21 (q), 55.23 (q), 64.6 (d), 68.4 (t), 71.3 (d), 72.8 (t), 75.4 (d), 78.9 (d), 87.8 (d), 101.6 (d), 113.5 (d, 2C), 113.9 (d, 2C), 127.4 (d, 2C), 127.6 (d), 129.1 (d, 2C), 129.6 (d, 2C), 129.8 (d), 130.0 (d), 131.6 (s, 2C), 133.3 (s), 159.5 (s), 160.0 (s). FABMS m/z (%): 533 ([M+Na]$^+$, 7), 55 (100). FABHRMS calcd for $C_{28}H_{30}O_7SNa$ [M+Na]$^+$: 533.1610; found: 533.1617.

*3.1.11. Phenyl 2-O-(tert-butyldimethylsilyl)-3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-1-thio-α-D-mannopyranoside (**6b**).* To a mixture of **5b** (9.11 g, 17.8 mmol), 2,6-lutidine (5.2 mL, 44.6 mmol), and CH_2Cl_2 (18 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (6.1 mL, 26.8 mmol), and the mixture was stirred at room temperature for 2 h. After the reaction was quenched with water, the resulting mixture was extracted with CH_2Cl_2. The extract was washed successively with aqueous sodium hydrogen carbonate and brine, and concentrated in vacuo. The residue (12.4 g) was purified by means of column chromatography (n-hexane–EtOAc, 30/1) to give title compound **6b** (9.34 g, 84%) as a colorless oil. $[\alpha]_D^{24}$ +95.0 (c 1.07, $CHCl_3$). IR (neat) cm^{-1}: 1612, 1516, 1250, 1099, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.03/0.07 [each s, 3H, Si(CH_3)$_2$], 0.89 [s, 9H, SiC(CH_3)$_3$], 3.81 (s, 6H, OCH$_3$), 3.82 (dd, J=10.0, 10.0 Hz, 1H, H-4), 3.84 (dd, J=10.0, 2.8 Hz, 1H, H-3), 4.166 (dd, J=10.0, 10.0 Hz, 1H, H-6a), 4.173 (dd, J=10.0, 4.4 Hz, 1H, H-6b), 4.25 (dd, J=2.8, 1.6 Hz, 1H, H-2), 4.26 (dd, J=10.0, 10.0, 4.4 Hz, 1H, H-5), 4.64/4.74 (d, J=11.6 Hz, 1H, OCH_2C$_6$H$_4$OCH$_3$), 5.31 (d, J=1.6 Hz, 1H, H-1), 5.58 (s, 1H, OCHC$_6$H$_4$OCH$_3$), 6.86 (d, J=8.8 Hz, 2H, Ar), 6.90 (d, J=8.8 Hz, 2H, Ar), 7.27–7.33 (m, 3H, Ar), 7.289 (d, J=8.8 Hz, 2H, Ar), 7.295 (d, J=8.8 Hz, 2H, Ar), 7.43 (d, J=8.8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.0 (q), −4.4 (q), 18.2 (s), 25.8 (q, 3C), 55.2 (q), 55.3 (q), 65.6 (d), 68.6 (t), 72.6 (t), 72.8 (d), 75.5 (d), 79.1 (d), 90.3 (d), 101.5 (d), 113.5 (d, 2C), 113.6 (d, 2C), 127.4 (d, 2C), 127.6 (d), 129.1 (d, 2C), 129.5 (d, 2C), 130.2 (d), 130.5 (d), 131.9 (s, 2C), 133.8 (s), 159.1 (s), 159.9 (s). FABMS m/z (%): 647 ([M+Na]$^+$, 3), 121 (100). FABHRMS calcd for $C_{34}H_{44}O_7SiSNa$ [M+Na]$^+$: 647.2475; found: 647.2461.

*3.1.12. Phenyl 2-O-(tert-butyldimethylsilyl)-3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-1-thio-α-D-mannopyranoside S-oxide (**2b**).* Following the method used for the preparation of **2a**, **6b** (9.34 g, 15.0 mmol) was oxidized with *m*CPBA (3.23 g, 15.0 mmol). Work-up and column chromatography (n-hexane–EtOAc, 6/1) gave title compound **2b** (6.78 g, 71%) as a colorless oil. $[\alpha]_D^{25}$ −57.4 (c 1.06, $CHCl_3$). IR (neat) cm^{-1}: 1612, 1516, 1250, 1115, 1099, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ: −0.12/0.00 [each s, 3H, Si(CH_3)$_2$], 0.81 [s, 9H, SiC(CH_3)$_3$], 3.71 (dd, J=10.0, 10.0 Hz, 1H, H-4), 3.82 (s, 6H, OCH_3), 4.03–4.09 (m, 1H, H-5), 4.15–4.19 (m, 3H, H-3, H-6a and H-6b), 4.31 (d, J=1.2 Hz, 1H, H-1), 4.63 (dd, J=2.4, 1.2 Hz, 1H, H-2), 4.67/4.78 (each d, J=11.6 Hz, 1H, OCH_2C$_6$H$_4$OCH$_3$), 5.58 (s, 1H, OCHC$_6$H$_4$OCH$_3$), 6.87 (d, J=8.8 Hz, 2H, Ar), 6.90 (d, J=8.8 Hz, 2H, Ar), 7.31 (d, J=8.8 Hz, 2H, Ar), 7.41 (d, J=8.8 Hz, 2H, Ar), 7.52–7.60 (m, 5H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.4 (q), −4.5 (q), 18.0 (s), 25.7 (q, 3C), 55.2 (q), 55.3 (q), 67.4 (d), 68.2 (t), 70.4 (d), 73.0 (t), 75.7 (d), 78.1 (d), 100.6 (d), 101.6 (d), 113.5 (d, 2C), 113.6 (d, 2C), 124.4 (d, 2C), 127.4 (d, 2C), 129.4 (d, 2C), 129.7 (d, 2C), 129.9 (d), 130.5 (s), 131.6 (s), 141.8 (s), 159.2 (s), 160.0 (s). FABMS m/z (%): 663 ([M+Na]$^+$, 13), 73 (100). FABHRMS calcd for $C_{34}H_{44}O_8SiSNa$ [M+Na]$^+$: 663.2424; found: 663.2449.

*3.1.13. 6-O-Benzyl-2,3:4,5-di-O-isopropylidene-D-mannitol (**3b**).* To a suspension of NaH (60% in liquid paraffin, 50.4 mg, 1.26 mmol) in DMF (7.0 mL) was added a solution of 2,3:4,5-di-*O*-isopropylidene-D-mannitol[27] (**7**) (300 mg, 1.14 mmol) in DMF (6.0 mL), and the mixture was stirred for 30 min at room temperature. At 0 °C, benzyl bromide (0.15 mL, 1.26 mmol) was added dropwise, and the resulting mixture was stirred at room temperature for 20 h. Under cooling with ice-water, the reaction mixture was diluted with water, and the resulting mixture was extracted with EtOAc. The extract was washed with and brine, and concentrated in vacuo. The residue (799 mg) was purified by means of column chromatography (n-hexane–EtOAc, 5/1) to give title compound **3b** (316 mg, 78%) as a colorless solid. Mp 48–50 °C. $[\alpha]_D^{24}$ −5.2 (c 1.07, $CHCl_3$). IR (neat) cm^{-1}: 3418, 1381, 1246, 1215, 1088, 1045. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33/1.38/1.48/1.50 [each s, 3H, C(CH_3)$_2$], 2.41 (t, J=6.4 Hz, 1H, OH), 3.55 (dd, J=9.2, 4.8 Hz, 1H, H-6a), 3.60–3.69 (m, 3H, H-1a, H-1b and H-6b), 4.16 (ddd, J=6.4, 6.4, 6.4 Hz, 1H, H-5), 4.22 (dd, J=6.0, 6.0 Hz, 1H, H-4), 4.36–4.42 (m, 2H, H-2 and H-3), 4.49/4.58 (each d, J=11.6 Hz, 1H, OCH_2Ph), 7.29–7.38 (m, 5H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.2 (q), 25.5 (q), 27.4 (q), 27.5 (q), 61.8 (t), 68.6 (t), 73.7 (t), 74.9 (d), 75.0 (d), 75.3 (d), 77.4 (d), 108.6 (s), 109.0 (s), 128.0 (d, 3C), 128.5 (d, 2C), 137.4 (s). FABMS m/z (%): 375 ([M+Na]$^+$, 22), 91 (100). FABHRMS calcd for $C_{19}H_{28}O_6Na$ [M+Na]$^+$: 375.1784; found: 375.1794.

*3.1.14. Coupling reaction of mannosyl S-oxides **2b** with protected mannitol **3b**.* Following the method used for the coupling reaction of **2a** and **3a**, **2b** (1.04 g, 1.63 mmol) was coupled with **3b** (688 mg, 1.96 mmol) in the presence of DTBMP (668 mg, 3.26 mmol) and Tf_2O (0.29 mL, 1.79 mmol). Work-up and column chromatography (n-hexane–EtOAc, 8/1) gave 6-*O*-benzyl-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 2-*O*-(*tert*-butyldimethylsilyl)-3-*O*-*p*-methoxybenzyl-4,6-*O*-*p*-methoxybenzylidene-β-D-mannopyranoside (**8b**, 920 mg, 65%) as a colorless oil. $[\alpha]_D^{23}$ −26.9 (c 1.02, $CHCl_3$). IR (neat) cm^{-1}: 1612, 1516, 1381, 1250, 1096, 1038. ^{1}H NMR (800 MHz, $CDCl_3$) δ: 0.06/0.09 [each s, 3H, Si(CH_3)$_2$], 0.90 [s, 9H, SiC(CH_3)$_3$], 1.33/1.35/1.45/1.47 [each s, 3H, C(CH_3)$_2$], 3.21 (ddd, J=9.8, 9.8, 4.8 Hz, 1H, H-5′), 3.43 (dd, J=9.8, 2.8 Hz, 1H, H-3′), 3.51 (dd, J=9.6, 5.5 Hz, 1H, H-6a), 3.61 (dd, J=9.6, 7.3 Hz, 1H, H-6b), 3.68 (dd, J=10.4, 6.8 Hz, 1H, H-1a), 3.80 (s, 3H, OCH_3), 3.81 (dd, J=10.3, 9.8 Hz, 1H, H-6′a), 3.82 (s, 3H, OCH_3), 3.96 (dd, J=10.4, 5.8 Hz, 1H, H-1b), 4.02 (dd, J=9.8, 9.8 Hz, 1H, H-4′), 4.06 (dd, J=2.8, 0.4 Hz, 1H, H-2′), 4.19 (dd, J=6.0, 5.5 Hz, 1H, H-4), 4.216 (dd, J=6.0, 5.5 Hz, 1H, H-3), 4.223 (dd, J=10.3, 4.8 Hz, 1H, H-6′b), 4.32 (ddd, J=7.3, 6.0, 5.5 Hz, 1H, H-5), 4.35 (ddd, J=6.8, 6.0, 5.8 Hz, 1H, H-2), 4.38 (d, J=0.4 Hz, 1H, H-1′), 4.49/4.54 (d, J=11.6 Hz, 1H, OCH_2Ph), 4.64/4.68 (d, J=12.0 Hz, 1H, OCH_2C$_6$H$_4$OCH$_3$), 5.55 (s, 1H, CHC$_6$H$_4$OCH$_3$), 6.85/6.90/7.27/7.42 (each d, J=8.8 Hz, 2H, Ar), 7.28–7.30 (m, 3H, Ar), 7.33–7.35 (m, 2H, Ar). ^{13}C NMR (200 MHz, $CDCl_3$) δ: −4.6 (q), −4.4 (q), 18.5 (s), 25.4 (q), 25.5 (q), 25.9 (q, 3C), 27.4 (q), 27.5 (q), 55.2 (q), 55.3 (q), 67.6 (d), 67.8 (t), 68.7 (t), 69.3 (t), 71.2 (d), 71.9 (t), 73.5 (t), 74.7 (d), 74.8 (d), 75.56 (d), 75.59 (d), 77.1 (d), 78.7 (d), 101.1 (d), 101.4 (d), 108.7 (s), 108.9 (s), 113.5 (d, 2C), 113.6 (d, 2C), 127.4 (d, 2C), 127.9 (d), 128.0 (d, 2C), 128.5 (d, 2C), 129.4 (d, 2C), 130.2 (s), 130.5 (s), 137.8 (s), 159.1 (s), 159.9 (s). FABMS m/z (%): 889 ([M+Na]$^+$, 3), 121 (100). FABHRMS calcd for $C_{47}H_{66}O_{13}SiNa$ [M+Na]$^+$: 889.4170; found: 889.4173.

*3.1.15. 6-O-Benzyl-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-β-D-mannopyranoside (**13**).* To a solution of **8b** (534 mg, 0.616 mmol) in tetrahydrofuran (5.0 mL) was added 1 M solution of tetrabutylammonium fluoride (TBAF) in THF (12.3 mL, 12.3 mmol) at room temperature, and the reaction mixture was stirred for 5 h. After the reaction mixture was diluted with water, the resulting mixture was extracted with EtOAc. The extract was washed with brine, and concentrated in vacuo. The residue was purified by means of column chromatography (n-hexane–EtOAc, 2/1) to give title compound **13** (481 mg, 86% yield) as a colorless amorphous. $[\alpha]_D^{24}$ +0.71 (c 1.02, $CHCl_3$). IR (neat) cm^{-1}: 3503, 1612, 1516, 1381, 1250, 1215,

1172, 1092, 1038. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34/1.37/1.459/1.462 [each s, 3H, C(CH_3)$_2$], 2.65 (br s, 1H, OH), 3.26 (ddd, J=9.6, 9.6, 4.8 Hz, 1H, H-5′), 3.48 (dd, J=9.6, 4.8 Hz, 1H, H-6a), 3.56 (dd, J=9.6, 3.2 Hz, 1H, H-3′), 3.58 (dd, J=9.6, 6.4 Hz, 1H, H-6b), 3.61 (dd, J=10.4, 7.2 Hz, 1H, H-1a), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.83 (dd, J=10.0, 9.6 Hz, 1H, H-6′a), 3.96 (dd, J=10.4, 6.4 Hz, 1H, H-1b), 4.05 (d, J=3.2 Hz, 1H, H-2′), 4.08 (dd, J=9.6, 9.6 Hz, 1H, H-4′), 4.22 (dd, J=7.2, 5.6 Hz, 1H, H-4), 4.25 (dd, J=7.2, 6.0 Hz, 1H, H-3), 4.28 (dd, J=10.0, 4.8 Hz, 1H, H-6′b), 4.33 (ddd, J=6.4, 5.6, 4.8 Hz, 1H, H-5), 4.46–4.50 (m, 1H, H-2), 4.48/4.56 (each d, J=11.6 Hz, 1H, OCH_2Ph), 4.49 (s, 1H, H-1′), 4.68/4.76 (each d, J=12.0 Hz, 1H, O$CH_2C_6H_4OCH_3$), 5.55 (s, 1H, O$CHC_6H_4OCH_3$), 6.86 (d, J=8.4 Hz, 2H, Ar), 6.91 (d, J=8.4 Hz, 2H, Ar), 7.28–7.36 (m, 7H, Ar), 7.42 (d, J=8.4 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.4 (q, 2C), 27.6 (q), 27.8 (q), 55.2 (q), 55.3 (q), 66.9 (d), 67.9 (t), 68.5 (t), 69.0 (t), 69.7 (d), 72.1 (t), 73.6 (t), 75.1 (d), 75.2 (d), 75.3 (d), 75.5 (d), 76.1 (d), 78.3 (d), 100.1 (d), 101.5 (d), 108.6 (s), 108.8 (s), 113.6 (d, 2C), 113.8 (d, 2C), 127.3 (d, 2C), 127.9 (d), 128.1 (d, 2C), 128.5 (d, 2C), 129.5 (d, 2C), 129.9 (s), 130.0 (s), 137.6 (s), 159.3 (s), 160.0 (s). FABMS m/z (%): 775 ([M+Na]$^+$, 4), 57 (100). FABHRMS calcd for $C_{41}H_{52}O_{13}Na$ [M+Na]$^+$: 775.3306; found: 775.3306.

*3.1.16. 6-O-Benzyl-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-2-O-octanoyl-β-D-mannopyranoside (**14**).* Following the method used for the esterification of **10**, **13** (373 mg, 0.496 mmol) was esterified with octanoyl chloride (0.13 mL, 0.744 mmol). Work-up and column chromatography (n-hexane–EtOAc, 8/1) gave quantitatively title compound **14** (436 mg) as a colorless oil. $[\alpha]_D^{25}$ −34.3 (c 0.98, $CHCl_3$). IR (neat) cm^{-1}: 1744, 1516, 1373, 1250, 1092, 1045. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, J=6.8 Hz, 3H, CO(CH$_2$)$_6$CH_3), 1.24–1.32 (m, 8H, CO(CH$_2$)$_2$(CH_2)$_4$CH$_3$), 1.34/1.37/1.44/1.46 [each s, 3H, C(CH_3)$_2$], 1.63 (tt, J=7.2, 7.2 Hz, 2H, COCH$_2$CH_2(CH_2)$_4$CH$_3$), 2.43 (t, J=7.2 Hz, 2H, COCH_2(CH_2)$_5$CH$_3$), 3.27 (ddd, J=10.0, 10.0, 4.8 Hz, 1H, H-5′), 3.44 (dd, J=9.6, 4.8 Hz, 1H, H-6a), 3.56 (dd, J=10.4, 4.8 Hz, 1H, H-1a), 3.57 (dd, J=9.6, 7.6 Hz, 1H, H-6b), 3.62 (dd, J=10.0, 3.6 Hz, 1H, H-3′), 3.79 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.82 (dd, J=10.4, 10.0 Hz, 1H, H-6′), 3.898 (dd, J=10.0, 10.0 Hz, 1H, H-4′), 3.900 (dd, J=10.4, 7.6 Hz, 1H, H-1b), 4.22 (dd, J=7.6, 5.6 Hz, 1H, H-4), 4.25 (dd, J=5.6, 5.2 Hz, 1H, H-3), 4.27 (dd, J=7.6, 7.6, 4.8 Hz, 1H, H-5), 4.28 (dd, J=10.4, 4.8 Hz, 1H, H-6′b), 4.37 (ddd, J=7.6, 5.2, 4.8 Hz, 1H, H-2), 4.48/4.53 (each d, J=12.0 Hz, 1H, OCH_2Ph), 4.56 (d, J=0.8 Hz, 1H, H-1′), 4.53/4.66 (each d, J=12.0 Hz, 1H, O$CH_2C_6H_4OCH_3$), 5.54 (s, 1H, O$CHC_6H_4OCH_3$), 5.61 (dd, J=3.6, 0.8 Hz, 1H, H-2′), 6.84 (d, J=8.8 Hz, 2H, Ar), 6.91 (d, J=8.8 Hz, 2H, Ar), 7.27–7.36 (m, 7H, Ar), 7.41 (d, J=8.8 Hz, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1 (q), 22.6 (t), 24.9 (t), 25.5 (q), 25.6 (q), 27.7 (q), 27.9 (q), 29.0 (t, 2C), 31.7 (t), 34.1 (t), 55.2 (q), 55.3 (q), 67.3 (d), 67.8 (t), 68.3 (d), 68.4 (t), 69.1 (t), 71.2 (t), 73.6 (t), 75.0 (d), 75.16 (d), 75.24 (d, 2C), 75.3 (d), 77.8 (d), 99.2 (d), 101.5 (d), 108.6 (s), 108.7 (s), 113.5 (d, 2C), 113.7 (d, 2C), 127.4 (d, 2C), 127.86 (d), 127.94 (d, 2C), 128.5 (d, 2C), 129.4 (d, 2C), 129.76 (s), 129.84 (s), 137.7 (s), 159.3 (s), 160.0 (s), 173.2 (s). FABMS m/z (%): 901 ([M+Na]$^+$, 9), 121 (100). FABHRMS calcd for $C_{49}H_{66}O_{14}Na$ [M+Na]$^+$: 901.4350; found: 901.4349.

*3.1.17. 6-O-Benzyl-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 2-O-octanoyl-β-D-mannopyranoside (**15**).* Following the method used for the de-O-p-methoxybenzylation of **8a**, **14** (429 mg, 0.488 mmol) was treated with DDQ (231 mg, 0.977 mmol) in a mixture of CH_2Cl_2 (4.8 mL) and H_2O (0.2 mL). Work-up and column chromatography ($CHCl_3$–MeOH, 30/1) gave title compound **15** (176 mg, 56%) as a colorless oil. $[\alpha]_D^{24}$ −14.5 (c 1.05, $CHCl_3$). IR (neat) cm^{-1}: 3445, 1744, 1373, 1246, 1219, 1165, 1076. ^{1}H NMR (400 MHz, CD_3OD) δ: 0.80 (t, J=7.2 Hz, 3H, CO(CH$_2$)$_6$CH_3), 1.14–1.26 (m, 8H, CO(CH$_2$)$_2$(CH_2)$_4$CH$_3$), 1.20/1.26/1.305/1.314 [each s, 3H, C(CH_3)$_2$], 1.51 (ddt, J=7.6, 7.6, 7.6 Hz, 2H, COCH$_2$CH_2(CH_2)$_4$CH$_3$), 2.27/2.31 (each dt, J=16.0, 7.6 Hz, 1H, COCH_2(CH_2)$_5$CH$_3$), 3.14 (ddd, J=9.6, 6.4, 2.4 Hz, 1H, H-5′), 3.33 (dd, J=10.0, 4.8 Hz, 1H, H-6a), 3.37 (dd, J=9.6, 9.6 Hz, 1H, H-4′), 3.45 (dd, J=10.8, 4.4 Hz, 1H, H-1a), 3.50 (dd, J=10.0, 7.2 Hz, 1H, H-6b), 3.51 (dd, J=9.6, 2.8 Hz, 1H, H-3′), 3.59 (dd, J=12.0, 6.4 Hz, 1H, H-6′a), 3.81 (dd, J=12.0, 2.4 Hz, 1H, H-6′b), 3.87 (dd, J=10.8, 7.2 Hz, 1H, H-1b), 4.15 (ddd, J=7.2, 4.8, 4.8 Hz, 1H, H-5), 4.16 (dd, J=5.6, 4.8 Hz, 1H, H-4), 4.26 (dd, J=6.8, 5.6 Hz, 1H, H-3), 4.31 (ddd, J=7.2, 6.8, 4.4 Hz, 1H, H-2), 4.39/4.44 (each d, J=11.6 Hz, 1H, OCH_2Ph), 4.53 (s, 1H, H-1′), 5.24 (d, J=2.8 Hz, 1H, H-2′), 7.17–7.26 (m, 5H, Ar). ^{13}C NMR (100 MHz, CD_3OD) δ: 14.4 (q), 23.7 (t), 25.76 (q), 25.84 (q), 25.9 (t), 28.0 (q, 2C), 30.2 (t, 2C), 32.9 (t), 35.1 (t), 63.1 (t), 68.9 (d), 69.0 (t), 70.3 (t), 72.8 (d), 73.6 (d), 74.4 (t), 76.4 (d), 76.6 (d), 76.65 (d), 76.71 (d), 78.7 (d), 100.2 (d), 109.6 (s), 109.7 (s), 128.9 (d), 129.2 (d, 2C), 129.5 (d, 2C), 139.3 (s), 175.0 (s). FABMS m/z (%): 663 ([M+Na]$^+$, 16), 91 (100). FABHRMS calcd for $C_{33}H_{52}O_{12}Na$ [M+Na]$^+$: 663.3356; found: 663.3382.

*3.1.18. 6-O-Benzyl-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-β-D-mannopyranoside (**16**).* Following the method used for the esterification of **12**, **15** (149 mg, 0.233 mmol) was treated with hexanoic anhydride (0.21 mL, 0.932 mmol). Work-up and column chromatography (n-hexane–EtOAc, 8/1) gave title compound **16** (188 mg, 87%) as a colorless oil. $[\alpha]_D^{24}$ −20.3 (c 1.02, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1373, 1246, 1219, 1161, 1099. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.88/0.894 (each t, J=6.8 Hz, 3H, CH_3), 0.885 (t, J=6.8 Hz, 6H, acyl CH_3), 1.23–1.35 (m, 20H, acyl CH_2), 1.34/1.35/1.44/1.45 [each s, 3H, C(CH_3)$_2$], 1.51–1.66 (m, 8H, acyl CH_2), 2.17/2.22/2.23/2.29/2.30/2.34/2.40/2.45 (each dt, J=15.6, 7.6 Hz, 1H, COCH_2), 3.42 (dd, J=9.6, 4.8 Hz, 1H, H-6a), 3.54 (dd, J=10.4, 5.2 Hz, 1H, H-1a), 3.55 (dd, J=9.6, 8.4 Hz, 1H, H-6b), 3.57 (ddd, J=10.0, 5.6, 2.4 Hz, 1H, H-5′), 3.91 (dd, J=10.4, 7.2 Hz, 1H, H-1b), 4.15 (dd, J=12.0, 2.4 Hz, 1H, H-6′a), 4.212 (dd, J=12.0, 5.6 Hz, 1H, H-6′b), 4.19–4.27 (m, 3H, H-3, H-4 and H-5), 4.37 (ddd, J=7.6, 5.2, 5.2 Hz, 1H, H-2), 4.46/4.53 (each d, J=12.0 Hz, 1H, OCH_2Ph), 4.64 (d, J=0.8 Hz, 1H, H-1′), 5.02 (dd, J=10.0, 3.2 Hz, 1H, H-3′), 5.24 (dd, J=10.0, 10.0 Hz, 1H, H-4′), 5.49 (dd, J=3.2, 0.8 Hz, 1H, H-2′), 7.27–7.38 (m, 5H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.80 (q), 13.82 (q), 13.9 (q), 14.0 (q), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 24.2 (t), 24.4 (t), 24.5 (t), 25.0 (t), 25.3 (q), 25.6 (q), 27.7 (q), 27.9 (q), 28.99 (t), 29.02 (t), 31.2 (t, 2C), 31.3 (t), 31.7 (t), 33.93 (t), 33.94 (t), 34.00 (t), 34.02 (t), 62.4 (t), 65.7 (d), 67.8 (t), 68.4 (d), 69.0 (t), 71.0 (d), 72.6 (d), 73.5 (t), 75.0 (d), 75.2 (d, 2C), 75.3 (d), 98.2 (d), 108.6 (s), 108.7 (s), 127.8 (d), 128.0 (d, 2C), 128.5 (d, 2C), 137.7 (s), 172.2 (s), 172.6 (s), 173.0 (s), 173.4 (s). FABMS m/z (%): 957 ([M+Na]$^+$, 5), 73 (100). FABHRMS calcd for $C_{51}H_{82}O_{15}Na$ [M+Na]$^+$: 957.5551; found: 957.5539.

*3.1.19. 2,3:4,5-Di-O-isopropylidene-D-mannitol-1-yl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-β-D-mannopyranoside (**17**).* Following the method used for the hydrogenation of **11**, a solution of **16** (30.0 mg, 0.0321 mmol) in a mixture of acetic acid (0.2 mL) and MeOH (1.0 mL) was treated with 10% palladium on carbon (5.0 mg) until uptake of hydrogen ceased. Work-up and column chromatography (n-hexane–EtOAc, 5/1) gave title compound **17** (21.1 mg, 78%) as a colorless oil. $[\alpha]_D^{24}$ −27.9 (c 1.02, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1377, 1246, 1219, 1165, 1099. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.881/0.883/0.89/0.90 (each t, J=6.8 Hz, 3H, acyl CH_3), 1.26–1.38 (m, 20H, acyl CH_2), 1.37/1.38/1.48/1.51 [each s, 3H, C(CH_3)$_2$], 1.52–1.67 (m, 8H, acyl CH_2), 2.17/2.22/2.23/2.29/2.31/2.35/2.41/2.46 (each dt, J=16.0, 7.6 Hz, 1H, COCH_2), 3.58 (dd, J=12.0, 4.8 Hz, 1H, H-6a), 3.63 (dd, J=10.0, 4.0 Hz, 1H, H-1a), 3.64 (dd, J=12.0, 5.6 Hz, 1H, H-6b), 3.66 (ddd, J=10.0, 5.6, 2.8 Hz, 1H, H-5′), 4.01 (dd, J=10.0, 7.2 Hz, 1H, H-1b), 4.17 (dd, J=12.4, 2.8 Hz, 1H, H-6′a), 4.216 (ddd, J=6.0, 5.6, 4.8 Hz, 1H, H-5), 4.223 (dd, J=12.4, 5.6 Hz, 1H, H-6′b), 4.28 (dd, J=6.0, 6.0 Hz, 1H, H-3), 4.34 (ddd, J=7.2, 6.0, 4.0 Hz, 1H, H-2), 4.37 (dd, J=6.0, 6.0 Hz, 1H, H-4), 4.72 (s, 1H, H-1′), 5.05 (dd, J=10.0,

3.2 Hz, 1H, H-3′), 5.26 (dd, *J*=10.0, 10.0 Hz, 1H, H-4′), 5.49 (dd, *J*=3.2 Hz, 1H, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8 (q, 2C), 13.9 (q), 14.1 (q), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 24.2 (t), 24.4 (t), 24.5 (t), 24.56 (t), 24.63 (q), 25.0 (q), 25.1 (q), 25.5 (q), 28.97 (t), 29.03 (t), 31.2 (t, 2C), 31.3 (t), 31.7 (t), 33.89 (t), 33.94 (t), 34.0 (t), 34.1 (t), 61.8 (t), 62.3 (t), 65.5 (d), 68.1 (t), 68.5 (d), 70.9 (d), 72.7 (d), 74.8 (d, 2C), 75.1 (d), 77.1 (d), 98.6 (d), 108.6 (s), 109.1 (s), 172.2 (s), 172.6 (s), 173.1 (s), 173.4 (s). FABMS *m*/*z* (%): 867 ([M+Na]$^+$, 76), 99 (100). FABHRMS calcd for $C_{44}H_{76}O_{15}Na$ [M+Na]$^+$: 867.5082; found: 867.5079.

*3.1.20. Phenyl 3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-2-O-octanoyl-1-thio-α-D-mannopyranoside (**18**).* Following the method used for the esterification of **10**, **5b** (300 mg, 0.588 mmol) was treated with octanoyl chloride (0.15 mL, 0.882 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 30/1) gave quantitatively title compound **18** (369 mg, 99%) as a colorless oil. $[\alpha]_D^{25}$ +86.2 (*c* 1.04, $CHCl_3$). IR (neat) cm^{-1}: 1740, 1516, 1250, 1173, 1099, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87 [t, *J*=7.2 Hz, 3H, $CO(CH_2)_6CH_3$], 1.23–1.35 [m, 8H, $CO(CH_2)_2(CH_2)_4CH_3$], 1.64 [tt, *J*=7.2, 7.2 Hz, 2H, $COCH_2CH_2(CH_2)_6CH_3$], 2.40 [t, *J*=7.2 Hz, 2H, $COCH_2(CH_2)_6CH_3$], 3.80 (s, 3H, OCH_3), 3.827 (s, 3H, OCH_3), 3.831 (dd, *J*=10.0, 9.6 Hz, 1H, H-6a), 3.98 (dd, *J*=9.6, 3.2 Hz, 1H, H-3), 4.08 (dd, *J*=9.6, 9.6 Hz, 1H, H-4), 4.20 (dd, *J*=10.0, 4.8 Hz, 1H, H-6b), 4.34 (ddd, *J*=9.6, 9.6, 4.8 Hz, 1H, H-5), 4.59/4.65 (each d, *J*=11.6 Hz, 1H, OCH_2Ph), 5.44 (d, *J*=0.8 Hz, 1H, H-1), 5.59 (s, 1H, CHAr), 5.60 (dd, *J*=3.2, 0.8 Hz, 1H, H-2), 6.86/6.91 (each d, *J*=8.8 Hz, 2H, Ar), 7.26–7.34 (m, 5H, Ar), 7.42–7.46 (m, 4H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.0 (q), 22.6 (t), 24.9 (t), 28.9 (t), 29.0 (t), 31.6 (t), 34.2 (t), 55.2 (q), 55.3 (q), 65.2 (d), 68.4 (t), 71.0 (d), 71.9 (t), 73.7 (d), 78.4 (d), 87.2 (d), 101.6 (d), 113.5 (d, 2C), 113.8 (d, 2C), 127.4 (d, 2C), 127.9 (d), 129.2 (d, 2C), 129.5 (d, 2C), 129.7 (s), 129.9 (s), 132.1 (d, 2C), 133.1 (s), 159.3 (s), 160.0 (s), 172.9 (s). FABMS *m*/*z* (%): 637 ([M+H]$^+$, 10), 121 (100). FABHRMS calcd for $C_{36}H_{45}O_8S$ [M+H]$^+$: 637.2835; found: 637.2862.

*3.1.21. Phenyl 2-O-octanoyl-1-thio-α-D-mannopyranoside (**19**).* Following the method used for the de-*O*-*p*-methoxybenzylation of **8a**, **18** (353 mg, 0.554 mmol) was treated with DDQ (525 mg, 2.21 mmol). Work-up and column chromatography ($CHCl_3$–MeOH, 50/1) gave title compound **19** (153 mg, 69%) as a colorless oil. $[\alpha]_D^{24}$ +114.4 (*c* 1.01, $CHCl_3$). IR (neat) cm^{-1}: 3383, 1740, 1585, 1161, 1107, 1072. ^{1}H NMR (400 MHz, CD_3OD) δ: 0.88 [t, *J*=6.8 Hz, 3H, $CO(CH_2)_6CH_3$], 1.25–1.37 [m, 8H, $CO(CH_2)_2(CH_2)_4CH_3$], 1.61 [tt, *J*=7.2, 7.2 Hz, 2H, $COCH_2CH_2(CH_2)_6CH_3$], 2.36/2.40 [each dt, *J*=16.0, 7.2 Hz, 2H, $COCH_2(CH_2)_6CH_3$], 3.72 (dd, *J*=9.6, 9.6 Hz, 1H, H-4), 3.75 (dd, *J*=12.0, 5.6 Hz, 1H, H-6a), 3.84 (dd, *J*=12.0, 2.4 Hz, 1H, H-6b), 3.85 (dd, *J*=9.6, 3.2 Hz, 1H, H-3), 4.04 (ddd, *J*=9.6, 5.6, 2.4 Hz, 1H, H-5), 5.24 (dd, *J*=3.2, 1.6 Hz, 1H, H-2), 5.41 (d, *J*=1.6 Hz, 1H, H-1), 7.26–7.34 (m, 3H, Ar), 7.51–7.55 (m, 2H, Ar). ^{13}C NMR (100 MHz, CD_3OD) δ: 14.4 (q), 23.7 (t), 25.9 (t), 30.07 (t), 30.10 (t), 32.8 (t), 34.9 (t), 62.5 (t), 69.0 (d), 71.4 (d), 75.4 (d), 75.9 (d), 87.8 (d), 128.8 (d), 130.2 (d, 2C), 133.3 (d, 2C), 135.3 (s), 175.0 (s). FABMS *m*/*z* (%): 421 ([M+Na]$^+$, 56), 57 (100). FABHRMS calcd for $C_{20}H_{30}O_6SNa$ [M+Na]$^+$: 421.1661; found: 421.1678.

*3.1.22. Phenyl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-1-thio-α-D-mannopyranoside (**20**).* Following the method used for the esterification of **12**, **19** (142 mg, 0.358 mmol) was treated with hexanoic anhydride (0.33 mL, 1.43 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 30/1) gave title compound **20** (223 mg, 90%) as a colorless oil. $[\alpha]_D^{25}$ +71.9 (*c* 1.07, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1227, 1161, 1103. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86–0.91 (m, 12H, acyl CH_3), 1.25–1.33 (m, 20H, acyl CH_2), 153–1.68 (m, 8H, acyl CH_2), 2.21–2.41 (m, 8H, $COCH_2$), 4.13 (dd, *J*=12.4, 1.6 Hz, 1H, H-6a), 4.26 (dd, *J*=12.4, 5.6 Hz, 1H, H-6b), 4.54 (ddd, *J*=10.0, 5.6, 1.6 Hz, 1H, H-5), 5.32 (dd, *J*=10.0, 3.2 Hz, 1H, H-3), 5.37 (dd, *J*=10.0, 10.0 Hz, 1H, H-4), 5.47 (d, *J*=1.2 Hz, 1H, H-1), 5.52 (dd, *J*=3.2, 1.2 Hz, 1H, H-2), 7.28–7.33 (m, 3H, Ar), 7.47–7.50 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.78 (q, 2C), 13.84 (q), 14.0 (q), 22.21 (t, 2C), 22.2 (t), 22.5 (t), 24.3 (t), 24.4 (t), 24.5 (t), 24.9 (t), 28.9 (t), 29.0 (t), 31.1 (t), 31.2 (t), 31.3 (t), 31.6 (t), 33.89 (t), 33.94 (t), 34.0 (t), 34.1 (t), 62.2 (t), 65.9 (d), 69.3 (d), 69.7 (d), 70.7 (d), 85.8 (d), 128.0 (d), 129.1 (d, 2C), 131.9 (d, 2C), 132.8 (s), 172.3 (s), 172.5 (s), 172.6 (s), 173.3 (s). FABMS *m*/*z* (%): 715 ([M+Na]$^+$, 4), 73 (100). FABHRMS calcd for $C_{38}H_{60}O_9SNa$ [M+Na]$^+$: 715.3856; found: 715.3867.

*3.1.23. Phenyl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-1-thio-α-D-mannopyranoside S-oxide (**2c**).* Following the method used for the preparation of **2a**, **20** (210 mg, 0.303 mmol) was oxidized with *m*CPBA (71.8 mg, 0.334 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 10/1) gave title compound **2c** (160 mg, 74%) and its diastereomer (32.1 mg, 15%).

Compound **2c**: A colorless oil. $[\alpha]_D^{25}$ −56.3 (*c* 1.08, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1227, 1161, 1111, 1045. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.87/0.88/0.90/0.91 (each t, *J*=7.0 Hz, 3H, acyl CH_3), 1.21–1.36 (m, 20H, acyl CH_2), 1.53–1.68 (m, 8H, acyl CH_2), 2.19/2.219/2.221/2.27/2.28/2.31/2.35/2.37 (each dt, *J*=15.8, 7.6 Hz, 1H, $COCH_2$), 4.18 (dd, *J*=12.4, 2.2 Hz, 1H, H-6a), 4.24 (dd, *J*=12.4, 5.5 Hz, 1H, H-6b), 4.55 (d, *J*=1.6 Hz, 1H, H-1), 4.59 (ddd, *J*=9.8, 5.5, 2.2 Hz, 1H, H-5), 5.38 (dd, *J*=9.8, 9.8 Hz, 1H, H-4), 5.66 (dd, *J*=3.6, 1.6 Hz, 1H, H-2), 5.74 (dd, *J*=9.8, 3.6 Hz, 1H, H-3), 7.55–7.72 (m, 5H, Ar). ^{13}C NMR (175 MHz, $CDCl_3$) δ: 13.8 (q, 2C), 13.9 (q), 14.0 (q), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 24.35 (t), 24.45 (t), 24.49 (t), 24.8 (t), 28.8 (t), 29.0 (t), 31.17 (t), 31.20 (t), 31.3 (t), 31.6 (t), 33.9 (t), 33.97 (t), 34.00 (t), 34.02 (t), 62.3 (t), 65.3 (d), 65.8 (d), 69.3 (d), 74.8 (d), 94.9 (d), 124.4 (d, 2C), 129.5 (d, 2C), 131.8 (d), 140.1 (s), 172.1 (s), 172.2 (s), 172.3 (s), 173.2 (s). FABMS *m*/*z* (%): 731 ([M+Na]$^+$, 8), 73 (100). FABHRMS calcd for $C_{38}H_{60}O_{10}SNa$ [M+Na]$^+$: 731.3805; found: 731.3799.

Minor isomer: A colorless oil. $[\alpha]_D^{24}$ +125.9 (*c* 1.18, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1242, 1227, 1161, 1142, 1107, 1045. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87/0.89/0.895/0.897 (each t, *J*=6.8 Hz, 3H, acyl CH_3), 1.22–1.37 (m, 20H, acyl CH_2), 1.54–1.63 (m, 8H, acyl CH_2), 2.22/2.25/2.276/2.281/2.31/2.32/2.34/2.36 (each dt, *J*=15.8, 7.6 Hz, 1H, $COCH_2$), 4.07 (dd, *J*=12.4, 2.0 Hz, 1H, H-6a), 4.19 (dd, *J*=12.4, 5.2 Hz, 1H, H-6b), 4.47 (d, *J*=1.6 Hz, 1H, H-1), 4.75 (ddd, *J*=10.0, 5.2, 2.0 Hz, 1H, H-5), 5.42 (dd, *J*=10.0, 10.0 Hz, 1H, H-4), 5.59–5.62 (m, 2H, H-2 and H-3), 7.57–7.61 (m, 3H, Ar), 7.73–7.75 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.76 (q, 2C), 13.81 (q), 13.9 (q), 22.17 (t, 2C), 22.22 (t), 22.5 (t), 24.3 (t, 2C), 24.4 (t), 24.7 (t), 28.8 (t), 28.9 (t), 31.08 (t), 31.11 (t), 31.2 (t), 31.5 (t), 33.8 (t, 2C), 33.9 (t, 2C), 62.0 (t), 64.9 (d), 67.6 (d), 69.3 (d), 74.7 (d), 93.9 (d), 125.0 (d, 2C), 129.4 (d, 2C), 131.9 (d), 139.8 (s), 172.2 (s), 172.4 (s, 2C), 173.2 (s). FABMS *m*/*z* (%): 731 ([M+Na]$^+$, 19), 583 (100). FABHRMS calcd for $C_{38}H_{60}O_{10}SNa$ [M+Na]$^+$: 731.3805; found: 731.3804.

*3.1.24. Coupling reaction of mannosyl S-oxide **2c** with protected mannitol **3a**.* Following the method used for the preparation of **8a**, **2c** (100 mg, 0.141 mmol) was coupled with **3a** (63.6 mg, 0.169 mmol) in the presence of DTBMP (57.9 mg, 0.282 mmol) and Tf_2O (25 μL, 0.155 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 20/1) gave 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 3,4,6-tri-*O*-hexanoyl-2-*O*-octanoyl-α-D-mannopyranoside (**21**, 28.6 mg, 21%) and 1,2-*O*-[6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yloctylidene]-3,4,6-tri-*O*-hexanoyl-β-D-mannopyranose (**22**, 27.4 mg, 20%).

Compound **21**: A colorless oil. $[\alpha]_D^{24}$ +21.2 (*c* 0.83, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1250, 1219, 1165, 1092. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.090/0.093 [each s, 3H, $Si(CH_3)_2$], 0.87–0.91 (m, 12H, acyl CH_3), 0.91 [s, 9H, $SiC(CH_3)_3$], 1.21–1.35 (m, 20H, acyl CH_2), 1.36/1.38/1.46/1.47 [each s, 3H, $C(CH_3)_2$], 1.54/1.57 (each ddt, *J*=7.6, 7.6, 7.6 Hz, 2H,

acyl CH_2), 1.64 (ddt, J=7.6, 7.6, 7.6 Hz, 4H, acyl CH_2), 2.18/2.21/2.24/2.28/2.34/2.369/2.374/2.40 (each dt, J=15.6, 7.6 Hz, 1H, COCH_2), 3.64 (dd, J=9.8, 5.6 Hz, 1H, H-1a), 3.68 (dd, J=10.4, 4.0 Hz, 1H, H-6a), 3.73 (dd, J=9.8, 6.2 Hz, 1H, H-1b), 3.81 (dd, J=10.4, 8.6 Hz, 1H, H-6b), 4.06 (ddd, J=9.8, 5.0, 2.2 Hz, 1H, H-5′), 4.11 (dd, J=12.4, 2.2 Hz, 1H, H-6′a), 4.22 (ddd, J=8.6, 6.2, 4.0 Hz, 1H, H-5), 4.25 (dd, J=12.4, 5.0 Hz, 1H, H-6′b), 4.28 (dd, J=6.2, 6.2 Hz, 1H, H-4), 4.39 (ddd, J=6.2, 6.2, 5.6 Hz, 1H, H-2), 4.43 (dd, J=6.2, 6.2 Hz, 1H, H-3), 4.83 (d, J=1.6 Hz, 1H, H-1′), 5.24 (dd, J=2.2, 1.6 Hz, 1H, H-2′), 5.32–5.35 (m, 2H, H-3′ and H-4′). ^{13}C NMR (175 MHz, $CDCl_3$) δ: −5.6 (q), −5.4 (q), 13.8 (q, 2C), 13.9 (q), 14.0 (q), 18.3 (s), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 24.38 (t), 24.42 (t), 24.5 (t), 25.0 (t), 25.4 (q, 2C), 25.9 (q, 3C), 27.4 (q), 27.9 (q), 28.9 (t), 29.0 (t), 31.2 (t, 2C), 31.3 (t), 31.7 (t), 34.00 (t), 34.03 (t, 2C), 34.1 (t), 62.0 (t), 62.1 (t), 65.6 (d), 67.6 (t), 68.8 (d), 68.9 (d), 69.2 (d), 75.0 (d), 75.1 (d), 75.5 (d), 77.0 (d), 97.8 (d), 108.6 (s), 108.8 (s), 172.3 (s, 2C), 172.7 (s), 173.4 (s). FABMS m/z (%): 981 ([M+Na]$^+$, 10), 73 (100). FABHRMS calcd for $C_{50}H_{90}O_{15}SiNa$ [M+Na]$^+$: 981.5947; found: 981.5952.

Compound **22**: A colorless oil. $[\alpha]_D^{26}$ −2.21 (c 1.69, $CHCl_3$). IR (neat) cm^{-1}: 1748, 1250, 1219, 1165, 1096, 1045. ^{1}H NMR (700 MHz, $CDCl_3$) δ: 0.07/0.08 [each s, 3H, Si(CH_3)$_2$], 0.87–0.92 (m, 12H, acyl CH_3), 0.89 [s, 9H, SiC(CH_3)$_3$], 1.24–1.35 (m, 20H, acyl CH_2), 1.36/1.37/1.456/1.465 [each s, 3H, C(CH_3)$_2$], 1.48–1.54 (m, 2H, acyl CH_2), 1.55–1.64 (m, 6H, acyl CH_2), 1.95/2.00 (each ddd, J=13.8, 10.6, 5.8 Hz, 1H, CCH_2), 2.24/2.28/2.30/2.32/2.34/2.37 (each dt, J=15.6, 7.6 Hz, 1H, COCH_2), 3.44 (dd, J=9.2, 4.6 Hz, 1H, H-1a), 3.57 (dd, J=10.4, 4.0 Hz, 1H, H-6a), 3.62 (dd, J=9.2, 7.4 Hz, 1H, H-1b), 3.64 (ddd, J=9.8, 4.6, 2.4 Hz, 1H, H-5′), 3.75 (dd, J=10.4, 8.0 Hz, 1H, H-6b), 4.11 (dd, J=12.2, 2.4 Hz, 1H, H-6′a), 4.13 (ddd, J=8.0, 5.8, 4.0 Hz, 1H, H-5), 4.21 (dd, J=12.2, 4.6 Hz, 1H, H-6′b), 4.32 (dd, J=7.6, 5.8 Hz, 1H, H-4), 4.34 (ddd, J=7.4, 5.6, 4.6 Hz, 1H, H-2), 4.42 (dd, J=7.6, 5.6 Hz, 1H, H-3), 4.58 (dd, J=4.0, 2.6 Hz, 1H, H-2′), 5.13 (dd, J=9.8, 4.0 Hz, 1H, H-3′), 5.30 (dd, J=9.8, 9.8 Hz, 1H, H-4′), 5.47 (d, J=2.6 Hz, 1H, H-1′). ^{13}C NMR (175 MHz, $CDCl_3$) δ: −5.6 (q), −5.4 (q), 13.83 (q), 13.84 (q), 13.9 (q), 14.1 (q), 18.3 (s), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 23.7 (t), 24.4 (t), 24.5 (t, 2C), 25.4 (q), 25.5 (q), 25.9 (q, 3C), 27.6 (q), 27.7 (q), 29.2 (t), 29.6 (t), 31.16 (t), 31.18 (t), 31.3 (t), 31.9 (t), 33.96 (t), 33.99 (t), 34.01 (t), 38.2 (t), 61.0 (t), 62.0 (t), 62.2 (t), 65.0 (d), 70.4 (d), 71.4 (d), 75.1 (d), 75.2 (d), 75.3 (d), 76.6 (d), 77.1 (d), 97.2 (d), 108.4 (s), 108.6 (s), 125.4 (s), 172.1 (s), 173.1 (s), 173.4 (s). FABMS m/z (%): 981 ([M+Na]$^+$, 6), 73 (100). FABHRMS calcd for $C_{50}H_{90}O_{15}SiNa$ [M+Na]$^+$: 981.5947; found: 981.5963.

*3.1.25. 3,4,6-Tri-O-hexanoyl-2-O-octanoyl-α-D-mannopyranoside (**23**).* To a solution of **22** (20.0 mg, 0.0208 mmol) in CH_2Cl_2 (0.5 mL) was added trimethylsilyl trifluoromethanesulfonate (TMSOTf, 4 μL, 0.0208 mmol) at −78 °C, and the mixture was stirred at −78 °C for 1.5 h. After addition of triethylamine, the resulting mixture was successively washed with 1 N hydrochloric acid, aqueous sodium bicarbonate, and brine, and concentrated in vacuo. The residue was purified by means of column chromatography (n-hexane–EtOAc, 10/1) to give title compound **23** (12.5 mg, quant. α:β=ca. 10:1) as a colorless oil. $[\alpha]_D^{22}$ +4.4 (c 1.05, $CHCl_3$). IR (neat) cm^{-1}: 3445, 1748, 1462, 1242, 1161, 1107, 1080. ^{1}H NMR (800 MHz, $CDCl_3$) δ: 0.86–0.92 (m, 12H, acyl CH_3), 1.21–1.40 (m, 20H, acyl CH_2), 1.52–1.68 (m, 8H, acyl CH_2), 2.15–2.46 (m, 8H, COCH_2), 3.18 (d, J=3.9 Hz, 0.9H, α-OH), 3.43 (d, J=9.6 Hz, 0.1H, β-OH), 3.71 (ddd, J=10.1, 5.5, 2.3 Hz, 0.1H, β-H-5), 4.10–4.24 (m, 2H, β-H-6a, and β-H-6b), 4.17 (dd, J=11.7, 2.3 Hz, 0.9H, α-H-6a), 4.21 (dd, J=11.7, 4.8 Hz, 0.9H, α-H-6b), 4.23 (ddd, J=10.1, 4.8, 2.3 Hz, 0.9H, α-H-5), 5.00 (dd, J=9.6, 1.2 Hz, 0.1H, β-H-1), 5.09 (dd, J=10.1, 3.4 Hz, 0.1H, β-H-3), 5.23 (dd, J=3.9, 1.8 Hz, 0.9H, α-H-1), 5.25 (dd, J=10.1, 10.1 Hz, 0.1H, β-H-4), 5.29 (dd, J=3.5, 1.8 Hz, 0.9H, α-H-2), 5.34 (dd, J=10.1, 10.1 Hz, 0.9H, α-H-4), 5.42 (dd, J=3.4, 1.2 Hz, 0.1H, β-H-2), 5.43 (dd, J=10.1, 3.5 Hz, 0.9H, α-H-3). ^{13}C NMR (200 MHz, $CDCl_3$) δ: 13.8 (q, 2C), 13.9 (q), 14.0 (q), 22.2 (t, 2C), 22.3 (t), 22.6 (t), 24.2 (t, 0.1C), 24.3 (t, 0.9C), 24.42 (t, 0.1C), 24.45 (t, 0.9C), 24.48 (t, 0.1C), 24.5 (t, 0.9C), 24.9 (t, 0.9C), 25.0 (t, 0.1C), 28.9 (t), 29.0 (t), 31.18 (t), 31.20 (t), 31.3 (t), 31.7 (t), 33.9 (t, 0.1C), 33.99 (t, 0.1C), 34.02 (t, 0.9C), 34.03 (t), 34.05 (t, 0.9C), 34.12 (t, 0.1C), 34.2 (t, 0.9C), 62.25 (t, 0.1C), 62.33 (t, 0.9C), 65.2 (d, 0.1C), 65.8 (d, 0.9C), 68.6 (d, 0.9C), 68.8 (d, 0.9C), 69.7 (d, 0.9C), 70.0 (d, 0.1C), 71.0 (d, 0.1C), 72.7 (d, 0.1C), 92.3 (d, 0.9C), 92.9 (d, 0.1C), 172.3 (s, 0.1C), 172.4 (s, 0.9C), 172.61 (s, 0.9C), 172.64 (s, 0.1C), 172.8 (s, 0.9C), 173.4 (s, 0.1C), 173.48 (s, 0.1C), 173.51 (s, 0.9C). FABMS m/z (%): 623 ([M+Na]$^+$, 39), 99 (100). FABHRMS calcd for $C_{32}H_{56}O_{10}Na$ [M+Na]$^+$: 623.3771; found: 623.3765.

*3.1.26. Phenyl 3-O-p-methoxybenzyl-4,6-O-p-methoxybenzylidene-2-O-benzyl-1-thio-α-D-mannopyranoside (**24**).* To a suspension of NaH (60% in liquid paraffin, 28.2 mg, 1.17 mmol) in DMF (3.0 mL) was added a solution of **5b** (300 mg, 0.588 mmol) in DMF (3.0 mL), and the mixture was stirred for 10 min at room temperature. Then benzyl bromide (0.14 mL, 1.17 mmol) was added, and the resulting mixture was stirred at room temperature for 4 h. Under cooling with ice-water, the reaction mixture was diluted with water, and extracted with EtOAc. The extract was washed with brine, and concentrated in vacuo. The residue was purified by means of column chromatography (n-hexane–EtOAc, 20/1) to give title compound **24** (305 mg, 86%) as a colorless oil. $[\alpha]_D^{24}$ +99.6 (c 1.05, $CHCl_3$). IR (neat) cm^{-1}: 1612, 1516, 1250, 1099, 1034. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.81 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (dd, J=10.0, 10.0 Hz, 1H, H-6a), 3.94 (dd, J=9.6, 3.2 Hz, 1H, H-3), 3.99 (dd, J=3.2, 1.2 Hz, 1H, H-2), 4.19 (dd, J=10.0, 4.0 Hz, 1H, H-6b), 4.23–4.30 (m, 2H, H-4 and H-5), 4.58/4.73 (each d, 1H, OCH_2Ar), 4.71 (s, 2H, OCH_2Ar), 5.49 (d, J=1.2 Hz, 1H, H-1), 5.60 (s, 1H, CHAr), 7.86/7.90/7.44 (each d, J=8.8 Hz, 2H, Ar), 7.25–7.38 (m, 12H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 55.3 (q, 2C), 65.5 (d), 68.5 (t), 72.7 (t), 73.0 (t), 75.8 (d), 78.1 (d), 78.9 (d), 87.1 (d), 101.5 (d), 113.5 (d, 2C), 113.8 (d, 2C), 127.4 (d, 2C), 127.6 (d), 127.8 (d), 128.1 (d, 2C), 128.4 (d, 2C), 129.1 (d, 2C), 129.3 (d, 2C), 130.1 (s), 130.4 (s), 131.6 (d, 2C), 133.8 (s), 137.8 (s), 159.2 (s), 160.0 (s). FABMS m/z (%): 601 ([M+H]$^+$, 3), 121 (100). FABHRMS calcd for $C_{35}H_{37}O_7S$ [M+H]$^+$: 601.2260; found: 601.2277.

*3.1.27. Phenyl 2-O-benzyl-1-thio-α-D-mannopyranoside (**25**).* Following the method used for the de-O-p-methoxybenzylation of **8a**, **24** (230 mg, 0.381 mmol) was treated with DDQ (360 mg, 1.53 mmol). Work-up and column chromatography ($CHCl_3$–MeOH, 50/1) gave title compound **25** (131 mg, 95%) as a colorless oil. $[\alpha]_D^{25}$ +84.8 (c 1.05, $CHCl_3$). IR (neat) cm^{-1}: 3406, 1103, 1072. ^{1}H NMR (400 MHz, CD_3OD) δ: 3.73 (dd, J=12.0, 6.0 Hz, 1H, H-6a), 3.74 (dd, J=9.2, 9.2 Hz, 1H, H-4), 3.75 (dd, J=9.2, 3.2 Hz, 1H, H-3), 3.82 (dd, J=12.0, 2.4 Hz, 1H, H-6b), 3.94 (dd, J=3.2, 1.2 Hz, 1H, H-2), 3.98 (ddd, J=9.2, 6.0, 2.4 Hz, 1H, H-5), 4.64/4.69 (each d, J=12.0 Hz, 1H, CH_2Ph), 5.45 (d, J=1.2 Hz, 1H, H-1), 7.23–7.32 (m, 6H, Ar), 7.37–7.39 (m, 2H, Ar), 7.42–7.45 (m, 2H, Ar). ^{13}C NMR (100 MHz, CD_3OD) δ: 62.7 (t), 69.1 (d), 73.1 (d), 73.8 (t), 75.8 (d), 81.3 (d), 87.7 (d), 128.6 (d), 128.8 (d), 129.3 (d, 2C), 129.4 (d, 2C), 130.1 (d, 2C), 133.1 (d, 2C), 135.8 (s), 139.5 (s). FABMS m/z (%): 385 ([M+Na]$^+$, 40), 91 (100). FABHRMS calcd for $C_{19}H_{22}O_5SNa$ [M+Na]$^+$: 385.1086; found: 385.1114.

*3.1.28. Phenyl 2-O-benzyl-3,4,6-tri-O-hexanoyl-1-thio-α-D-mannopyranoside (**26**).* Following the method used for the esterification of **12**, **25** (100 mg, 0.275 mmol) was treated with hexanoic anhydride (0.25 mL, 1.10 mmol). Work-up and column chromatography (n-hexane–EtOAc, 30/1) gave title compound **26** (165 mg, 90%) as a colorless oil. $[\alpha]_D^{24}$ +53.9 (c 0.95, $CHCl_3$). IR (neat) cm^{-1}: 1744, 1242, 1165, 1099. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87/0.885/0.893 (each t, J=6.8 Hz, 3H, CO(CH$_2$)$_4$CH_3), 1.22–1.34 [m, 12H, CO(CH$_2$)$_2$(CH_2)$_2$CH$_3$], 1.53–1.63 [m, 6H, COCH$_2$CH_2(CH$_2$)$_2$CH$_3$], 2.20/2.258/2.259/2.27/2.30/2.31 [each dt, J=15.2, 7.6 Hz, 1H, COCH_2(CH$_2$)$_3$CH$_3$], 4.11 (dd, J=3.2, 1.6 Hz, 1H, H-2), 4.14 (dd, J=12.0,

2.4 Hz, 1H, H-6a), 4.24 (dd, *J*=12.0, 5.6 Hz, 1H, H-6b), 4.45 (ddd, *J*=10.0, 5.6, 2.4 Hz, 1H, H-5), 4.55/4.67 (each d, *J*=12.4 Hz, 1H, C*H*$_2$Ph), 5.20 (dd, *J*=10.0, 3.2 Hz, 1H, H-3), 5.49 (dd, *J*=10.0, 10.0 Hz, 1H, H-4), 5.58 (d, *J*=1.6 Hz, 1H, H-1), 7.27–7.33 (m, 8H, Ar), 7.44–7.47 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8 (q, 2C), 13.9 (q), 22.3 (t, 3C), 24.4 (t), 24.46 (t), 24.54 (t), 31.2 (t, 2C), 31.3 (t), 34.0 (t), 34.10 (t), 34.12 (t), 62.5 (t), 66.3 (d), 69.9 (d), 71.2 (d), 72.5 (t), 76.8 (d), 85.4 (d), 127.6 (d), 127.8 (d, 2C), 127.9 (d), 128.4 (d, 2C), 129.1 (d, 2C), 131.5 (d, 2C), 133.7 (s), 137.4 (s), 172.4 (s), 173.0 (s), 173.4 (s). FABMS *m*/*z* (%): 679 ([M+Na]$^+$, 7), 135 (100). FABHRMS calcd for $C_{37}H_{52}O_8SNa$ [M+Na]$^+$: 679.3281; found: 679.3294.

*3.1.29. Phenyl 2-O-benzyl-3,4,6-tri-O-hexanoyl-1-thio-α-D-mannopyranoside S-oxide (**2d**).* Following the method used for the preparation of **2a**, **26** (128 mg, 0.195 mmol) was oxidized with *m*CPBA (46.2 mg, 0.215 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 10/1) gave title compound **2d** (121 mg, 92%) and its diastereomer (8.5 mg, 6%).

Compound **2d**: A colorless oil. $[\alpha]_D^{25}$ −46.0 (*c* 1.15, $CHCl_3$). IR (neat) cm^{-1}: 1744, 1242, 1165, 1111, 1042. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.875/0.89/0.90 [each t, *J*=7.2 Hz, 3H, CO(CH$_2$)$_4$C*H*$_3$], 1.20–1.33 [m, 12H, CO(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$], 1.50–1.67 [m, 6H, COCH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$], 2.17/2.22/2.26/2.31 [each dt, *J*=15.6, 7.6 Hz, 1H, COC*H*$_2$(CH$_2$)$_3$CH$_3$], 2.34 [t, *J*=7.6 Hz, 2H, COC*H*$_2$(CH$_2$)$_3$CH$_3$], 4.16 (dd, *J*=12.4, 2.4 Hz, 1H, H-6a), 4.22 (dd, *J*=12.4, 5.6 Hz, 1H, H-6b), 4.29/4.40 (each d, *J*=12.0 Hz, 1H, C*H*$_2$Ph), 4.32 (dd, *J*=3.6, 1.6 Hz, 1H, H-2), 4.42 (ddd, *J*=9.6, 5.6, 2.4 Hz, 1H, H-5), 4.56 (d, *J*=1.6 Hz, 1H, H-1), 5.46 (dd, *J*=9.6, 9.6 Hz, 1H, H-4), 5.57 (dd, *J*=9.6, 3.6 Hz, 1H, H-3), 7.04–7.06 (m, 2H, Ar), 7.23–7.25 (m, 3H, Ar), 7.53–7.56 (m, 3H, Ar), 7.62–7.65 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.82 (q, 2C), 13.9 (q), 22.2 (t, 2C), 22.3 (t), 24.42 (t), 24.43 (t), 24.5 (t), 31.20 (t), 31.22 (t), 31.24 (t), 33.97 (t), 34.03 (t), 34.1 (t), 62.4 (t), 65.6 (d), 70.8 (d), 71.3 (d), 72.5 (t), 74.9 (d), 95.3 (d), 124.4 (d, 2C), 127.9 (d), 128.0 (d, 2C), 128.3 (d, 2C), 129.4 (d, 2C), 131.5 (d), 136.8 (s), 140.8 (s), 172.3 (s), 172.5 (s), 173.3 (s). FABMS *m*/*z* (%): 695 ([M+Na]$^+$, 7), 91 (100). FABHRMS calcd for $C_{37}H_{52}O_9SNa$ [M+Na]$^+$: 695.3230; found: 695.3254.

Minor isomer: A colorless oil. $[\alpha]_D^{24}$ +103.4 (*c* 0.84, $CHCl_3$). IR (neat) cm^{-1}: 1744, 1242, 1165, 1099, 1042. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.87/0.89/0.90 [each t, *J*=7.2 Hz, 3H, CO(CH$_2$)$_4$C*H*$_3$], 1.20–1.44 [m, 12H, CO(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$], 1.53–1.67 [m, 6H, COCH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$], 2.231/2.26/2.28/2.29/2.30/2.34 [each dt, *J*=15.6, 7.6 Hz, 1H, COC*H*$_2$(CH$_2$)$_3$CH$_3$], 4.11 (dd, *J*=12.4, 2.4 Hz, 1H, H-6a), 4.20 (dd, *J*=12.4, 5.6 Hz, 1H, H-6b), 4.21 (dd, *J*=4.4, 3.2 Hz, 1H, H-2), 4.44 (d, *J*=4.4 Hz, 1H, H-1), 4.47/4.52 (each d, *J*=11.6 Hz, 1H, OC*H*$_2$Ph), 4.51 (ddd, *J*=8.4, 5.6, 2.4 Hz, 1H, H-5), 5.29 (dd, *J*=8.4, 7.2 Hz, 1H, H-4), 5.40 (dd, *J*=7.2, 3.2 Hz, 1H, H-3), 7.14–7.16 (m, 2H, Ar), 7.26–7.29 (m, 3H, Ar), 7.52–7.55 (m, 3H, Ar), 7.64–7.68 (m, 2H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.86 (q, 2C), 13.89 (q), 22.26 (t, 2C), 22.29 (t), 24.4 (t), 24.48 (t), 24.49 (t), 31.16 (t), 31.22 (t), 31.24 (t), 33.9 (t), 34.0 (t, 2C), 62.0 (t), 66.5 (d), 70.0 (d), 71.3 (d), 72.5 (t), 74.6 (d), 93.3 (d), 125.2 (d, 2C), 128.2 (d), 128.3 (d, 2C), 128.5 (d, 2C), 129.3 (d, 2C), 131.6 (d), 136.5 (s), 140.2 (s), 172.2 (s), 172.7 (s), 173.3 (s). FABMS *m*/*z* (%): 695 ([M+Na]$^+$, 11), 91 (100). FABHRMS calcd for $C_{37}H_{52}O_9SNa$ [M+Na]$^+$: 695.3230; found: 695.3222.

*3.1.30. Coupling reaction of mannosyl S-oxide **2d** with protected mannitol **3a**.* Following the method used for the preparation of **8a**, **2d** (100 mg, 0.149 mmol) was coupled with **3a** (67.3 mg, 0.179 mmol) in the presence of DTBMP (61.0 mg, 0.297 mmol) and Tf_2O (27 μL, 0.163 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 15/1) gave 6-*O*-(*tert*-butyldimethylsilyl)-2,3:4,5-di-*O*-isopropylidene-D-mannitol-1-yl 2-*O*-benzyl-3,4,6-tri-*O*-hexanoyl-α-D-mannopyranoside (**27**, 74.3 mg, 54%) as a colorless oil. $[\alpha]_D^{25}$ +27.2 (*c* 1.07, $CHCl_3$). IR (neat) cm^{-1}: 1744, 1246, 1215, 1169, 1096, 1049. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.075/0.084 [each s, 3H, Si(C*H*$_3$)$_2$], 0.877/0.882/0.89 [each t, *J*=7.2 Hz, 3H, CO(CH$_2$)$_4$C*H*$_3$], 0.90 [s, 9H, SiC(C*H*$_3$)$_3$], 1.22–1.33 [m, 12H, CO(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$], 1.35/1.38 [each s, 3H, C(C*H*$_3$)$_2$], 1.46 [s, 6H, C(C*H*$_3$)$_2$], 1.52–1.65 [m, 6H, COCH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$], 2.21/2.23/2.24/2.28/2.32/2.36 [each dt, *J*=15.8, 7.7 Hz, 1H, COC*H*$_2$(CH$_2$)$_3$CH$_3$], 3.58 (dd, *J*=10.0, 5.7 Hz, 1H, H-1a), 3.65 (dd, *J*=10.3, 4.0 Hz, 1H, H-6a), 3.72 (dd, *J*=10.0, 5.7 Hz, 1H, H-1b), 3.79 (dd, *J*=10.3, 8.6 Hz, 1H, H-6b), 3.85 (dd, *J*=3.4, 1.7 Hz, 1H, H-2′), 3.97 (ddd, *J*=10.0, 5.2, 2.3 Hz, 1H, H-5′), 4.12 (dd, *J*=12.3, 2.3 Hz, 1H, H-6′a), 4.18 (ddd, *J*=8.6, 5.5, 4.0 Hz, 1H, H-5), 4.23 (dd, *J*=12.3, 5.2 Hz, 1H, H-6′b), 4.24 (dd, *J*=6.0, 5.5 Hz, 1H, H-4), 4.36 (ddd, *J*=6.0, 5.7, 5.7 Hz, 1H, H-2), 4.41 (dd, *J*=6.0, 6.0 Hz, 1H, H-3), 4.60/4.63 (each d, *J*=12.1 Hz, 1H, C*H*$_2$Ph), 4.87 (d, *J*=1.7 Hz, 1H, H-1′), 5.22 (dd, *J*=10.0, 3.4 Hz, 1H, H-3′), 5.46 (dd, *J*=10.0, 10.0 Hz, 1H, H-4′), 7.26–7.33 (m, 5H, Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: −5.6 (q), −5.4 (q), 13.86 (q, 2C), 13.90 (q), 18.3 (s), 22.3 (t, 3C), 24.4 (t), 24.5 (t, 2C), 25.4 (q), 25.6 (q), 25.9 (q, 3C), 27.6 (q), 27.8 (q), 31.3 (t, 3C), 34.0 (t), 34.1 (t), 34.2 (t), 62.0 (t), 62.4 (t), 66.0 (d), 67.1 (t), 69.0 (d), 71.2 (d), 73.2 (t), 75.1 (d), 75.2 (d), 75.4 (d), 75.5 (d), 77.0 (d), 98.1 (d), 108.6 (s), 108.7 (s), 127.7 (d, 2C), 127.8 (d), 128.4 (d, 2C), 137.7 (s), 172.3 (s), 172.7 (s), 173.5 (s). FABMS *m*/*z* (%): 945 ([M+Na]$^+$, 7), 91 (100). FABHRMS calcd for $C_{49}H_{82}O_{14}SiNa$ [M+Na]$^+$: 945.5372; found: 945.5343.

*3.1.31. 6-O-(tert-Butyldimethylsilyl)-2,3:4,5-di-O-isopropylidene-D-mannitol-1-yl 3,4,6-tri-O-hexanoyl-α-D-mannopyranoside (**28**).* Following the method used for the hydrogenation of **11**, a solution of **27** (36.0 mg, 0.0390 mmol) in EtOAc (0.5 mL) was treated with 10% palladium on carbon (5.0 mg) until uptake of hydrogen ceased. Work-up and column chromatography (*n*-hexane–EtOAc, 5/1) gave title compound **28** (19.2 mg, 59%) as a colorless oil. $[\alpha]_D^{25}$ +44.0 (*c* 1.60, $CHCl_3$). IR (neat) cm^{-1}: 3460, 1744, 1250, 1219, 1169, 1096, 1069. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.087/0.092 [each s, 3H, Si(C*H*$_3$)$_2$], 0.89 [t, *J*=7.2 Hz, 9H, CO(CH$_2$)$_4$C*H*$_3$], 0.91 [s, 9H, SiC(C*H*$_3$)$_3$], 1.23–1.35 [m, 12H, CO(CH$_2$)$_2$(C*H*$_2$)$_2$CH$_3$], 1.37/1.39/1.46/1.48 [each s, 3H, C(C*H*$_3$)$_2$], 1.53–1.66 [m, 6H, COCH$_2$C*H*$_2$(CH$_2$)$_2$CH$_3$], 2.17 (br s, 1H, OH), 2.23/2.280/2.281/2.32/2.33/2.37 [each dt, *J*=15.6, 7.6 Hz, 1H, COC*H*$_2$(CH$_2$)$_3$CH$_3$], 3.63 (dd, *J*=9.6, 5.6 Hz, 1H, H-1a), 3.65 (dd, *J*=10.4, 4.0 Hz, 1H, H-6a), 3.75 (dd, *J*=9.6, 5.2 Hz, 1H, H-1b), 3.80 (dd, *J*=10.4, 8.8 Hz, 1H, H-6b), 4.01–4.04 (m, 2H, H-2′ and H-5′), 4.11 (dd, *J*=12.4, 2.4 Hz, 1H, H-6′a), 4.19 (ddd, *J*=8.8, 6.0, 4.0 Hz, 1H, H-5), 4.25 (dd, *J*=12.4, 4.4 Hz, 1H, H-6′b), 4.27 (dd, *J*=6.4, 6.0 Hz, 1H, H-4), 4.38 (ddd, *J*=6.0, 5.6, 5.2 Hz, 1H, H-2), 4.41 (dd, *J*=6.4, 6.0 Hz, 1H, H-3), 4.90 (d, *J*=1.6 Hz, 1H, H-1′), 5.26 (dd, *J*=10.0, 3.2 Hz, 1H, H-3′), 5.36 (dd, *J*=10.0, 10.0 Hz, 1H, H-4′). ^{13}C NMR (100 MHz, $CDCl_3$) δ: −5.6 (q), −5.4 (q), 13.8 (q, 2C), 13.9 (q), 18.4 (s), 22.2 (t, 2C), 22.3 (t), 24.4 (t), 24.47 (t), 24.55 (t), 25.3 (q), 25.5 (q), 25.9 (q, 3C), 27.6 (q), 27.8 (q), 31.2 (t, 2C), 31.3 (t), 34.0 (t), 34.1 (t), 34.2 (t), 62.0 (t), 62.1 (t), 65.6 (d), 67.4 (t), 68.7 (d), 69.3 (d), 71.4 (d), 75.0 (d), 75.2 (d), 75.6 (d), 77.0 (d), 99.5 (d), 108.6 (s), 108.8 (s), 172.36 (s), 172.43 (s), 173.5 (s). FABMS *m*/*z* (%): 855 ([M+Na]$^+$, 4), 99 (100). FABHRMS calcd for $C_{42}H_{76}O_{14}SiNa$ [M+Na]$^+$: 855.4902; found: 855.4893.

*3.1.32. Octanoylation of C2′-OH in compound **28**.* Following the method used for the esterification of **10**, **28** (5.9 mg, 0.00708 mmol) was treated with octanoyl chloride (3.6 μL, 0.0212 mmol). Work-up and column chromatography (*n*-hexane–EtOAc, 15/1) gave quantitatively title compound **21a** (6.6 mg, 97%). The NMR spectroscopic properties of **21a** were in good accord with those of a specimen obtained by the coupling reaction between mannosyl *S*-oxides **2c** and protected mannitol **3a**.

*3.1.33. D-Mannitol-1-yl 3,4,6-tri-O-hexanoyl-2-O-octanoyl-α-D-mannopyranoside [1′-epi-acremomannolipin A (epi-**1**)].* Following the method used for the preparation of **1**, hydrolysis of **21** (8.3 mg, 0.0865 mmol) gave title compound *epi*-**1** (4.6 mg, 70%) as a colorless amorphous. $[\alpha]_D^{23}$ +17.5 (*c* 0.45, $CHCl_3$). IR (neat) cm^{-1}: 3383,

1748, 1246, 1161, 1103. ^{1}H NMR (700 MHz, CD_3OD) δ: 0.901/0.902/0.91/0.93 (each t, J=7.2 Hz, 3H, acyl CH_3), 1.24–1.39 (m, 20H, acyl CH_2), 1.52–1.60 (m, 4H, acyl CH_2), 1.63–1.70 (m, 4H, acyl CH_2), 2.19/2.22/2.27/2.31/2.34/2.37/2.39/2.45 (each dt, J=15.8, 7.4 Hz, 1H, COCH_2), 3.64 (dd, J=11.0, 6.0 Hz, 1H, H-6a), 3.70 (ddd, J=8.6, 6.0, 3.6 Hz, 1H, H-5), 3.74 (dd, J=10.0, 2.0 Hz, 1H, H-1a), 3.81 (d, J=8.6 Hz, 2H, H-3 and H-4), 3.82 (dd, J=11.0, 3.6 Hz, 1H, H-6b), 3.85 (ddd, J=8.6, 5.8, 2.0 Hz, 1H, H-2), 3.89 (dd, J=10.0, 5.8 Hz, 1H, H-1b), 4.13 (dd, J=12.4, 2.0 Hz, 1H, H-6′a), 4.18 (ddd, J=10.0, 4.0, 2.0 Hz, 1H, H-5′), 4.26 (dd, J=12.4, 4.0 Hz, 1H, H-6′b), 4.86 (d, J=1.8 Hz, 1H, H-1′), 5.34 (dd, J=3.0, 1.8 Hz, 1H, H-2′), 5.36 (dd, J=10.0, 3.0 Hz, 1H, H-3′), 5.37 (dd, J=10.0, 10.0 Hz, 1H, H-4′). ^{13}C NMR (175 MHz, CD_3OD) δ: 14.2 (q, 2C), 14.3 (q), 14.4 (q), 23.35 (t), 23.37 (t), 23.4 (t), 23.7 (t), 25.5 (t), 25.62 (t), 25.63 (t), 26.3 (t), 30.16 (t), 30.21 (t), 32.36 (t, 2C), 32.44 (t), 32.9 (t), 34.9 (t), 34.99 (t), 35.03 (t), 35.2 (t), 63.1 (t), 65.2 (t), 66.8 (d), 69.9 (d), 70.6 (d), 70.9 (d), 71.06 (d), 71.14 (d, 2C), 71.2 (t), 73.0 (d), 99.2 (d), 173.8 (s), 174.06 (s), 174.12 (s), 175.05 (s). FABMS m/z (%): 787 ([M+Na]$^+$, 9), 73 (100). FABHRMS calcd for $C_{38}H_{68}O_{15}Na$ [M+Na]$^+$: 787.4456; found: 787.4433.

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