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Synthesis of new, potent avermectin-like insecticidal agents

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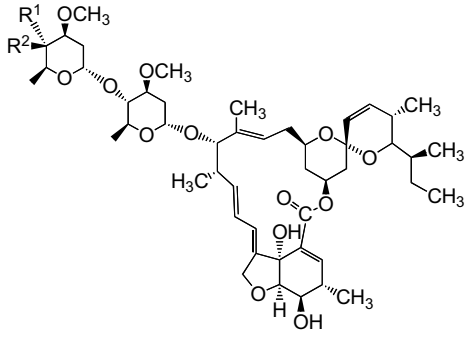
Abstract—4′-Modified avermectin derivatives were designed and synthesized. Some of the new synthetic compounds showed excellent in vivo bioactivity against cabbage larvae when compared to commercially available avermectin B_{1a}. In this synthesis, uncommon thioglycosyl sugar donors, prepared from the hydrolysis of natural antibiotics, proved compatible with sugar-macrolide synthesis in the presence of *N*-iodosuccinimide (NIS) or I_2 in *N*-methylpyrrolidone at room temperature.

Keywords: Antibiotics; Glycosylation; Pesticide; Thioglycoside

1. Introduction

The avermectins are a family of macrocyclic lactones that have a disaccharide on C-13 of the macrocycle and are isolated as natural fermentation products of *Streptomyces avermitilis*. They have been shown to possess broad-spectrum activity against helminthes and arthropods with relatively low toxicity in both humans and animals.[1] Among them, avermectin B_{1a} (**1**, AVM, Fig. 1), is an important and widely used agricultural pesticide in China now.[2] Although compound **1** is extremely effective against mites, it is much less effective against insects, especially the cabbage looper, the core earworm, and the southern armyworm.[3] Extensive investigation of the synthesis and biological evaluation of avermectin derivatives has been undertaken to obtain compounds with improved insecticidal activity.[4] From these efforts, a major breakthrough came with the discovery of 4″-aminoavermectins.[5] These amino sugar-containing avermectins showed excellent activity against a variety of insect larvae, spider mites, and aphids. The use of 4″-*epi*-(methylamino)-4″-deoxyavermectin B_{1a} benzoate (**2**, MK-244, Fig. 1) as an agricultural insecticide has achieved commercial success.[6] This specific example, when taken together with the success of other analogs,[7] demonstrates that synthetic modifications at the terminal sugar of AVM offers derivatives having potent and improved bioactivity. Here, we report the synthesis and preliminary insecticide activities of new avermectin analogues.



1 R^1 = OH, R^2 = H
2 R^1 = H, R^2 = MeNH·HCO_2Ph

Figure 1. Structures of AVM (**1**) and MK-244 (**2**).

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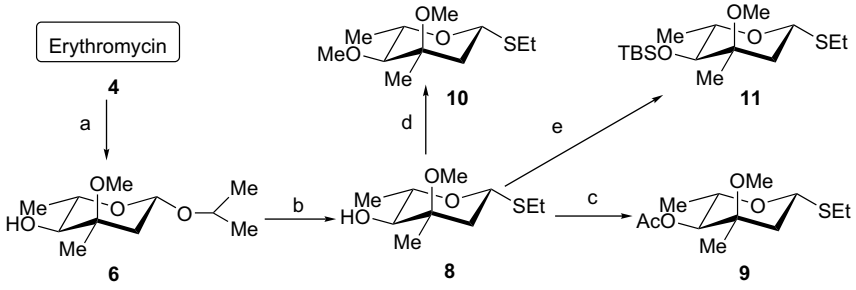
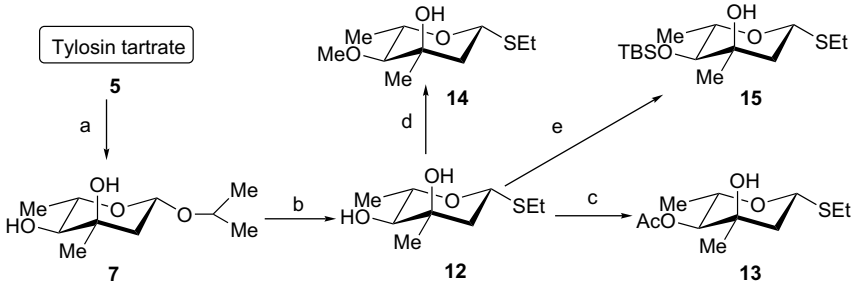
2. Results and discussion

Our previous investigation[8] showed that the macrolactone **3** was highly unstable and decomposed quickly in the presence of a catalytic amount of TMSOTf and $BF_3{\cdot}Et_2O$ in CH_2Cl_2. This means a number of Schmidt's glycosyl donors[9] may not be applicable in the synthesis of AVM analogues under standard glycosylation conditions. This situation prompted us to work carefully with thioglycoside donors in our project. We found that glycosylation of a thioglycoside with macrolactone **3** in anhydrous *N*-methylpyrrolidone using NIS or iodine as catalyst afforded the best yield of desired compounds. We believe that the active sugar intermediate, which is recognized as an oxacarbenium ion, might be stabilized by *N*-methylpyrrolidone, and this would be helpful for the high yielding glycosylation that follows. Moreover, our interest in AVM complex natural products led us to design a new series of AVM analogues in which the 4′-hydroxyl of the oleandrosyl unit was replaced with uncommon sugar derivatives. Realizing that an L-sugar might give better pesticide activity, we next prepared these uncommon L-sugar derivatives from erythromycin **4** and tylosin **5** via simple acid hydrolysis (Schemes 1 and 2). Thus, 2-deoxysugar derivatives, L-cladinoside **6** and L-mycaroside **7**, were prepared from H_2SO_4-catalyzed hydrolysis of **4** and **5** in 2-propanol, respectively. Modified Helfrich reaction of **6** (or **7**) with thioethanol in anhydrous CH_2Cl_2 in the presence of $BF_3{\cdot}Et_2O$ gave thioglycoside **8** (or **12**) in good yield. Acetylation of **8** (or **12**) with acetic anhydride in pyridine gave the 4-*O*-acetyl donor **9** (or **13**). Methylation of **8** with MeI and NaH in DMF afforded methylated donor **10**, while the corresponding reaction of **12** gave a more complex result. Alternatively, methylation of **12** with MeI in DMF using Ag_2O as base gave the 4-O-methylated donor **14** in a yield of 58%. The *tert*-OH-3 in both **13** and **14** were inactive and remained in the free form. On the other hand, silylation of **8** (or **12**) with *tert*-butylchlorodimethylsilane and imidazole furnished the 4-O-silylated donor **11** (or **15**).

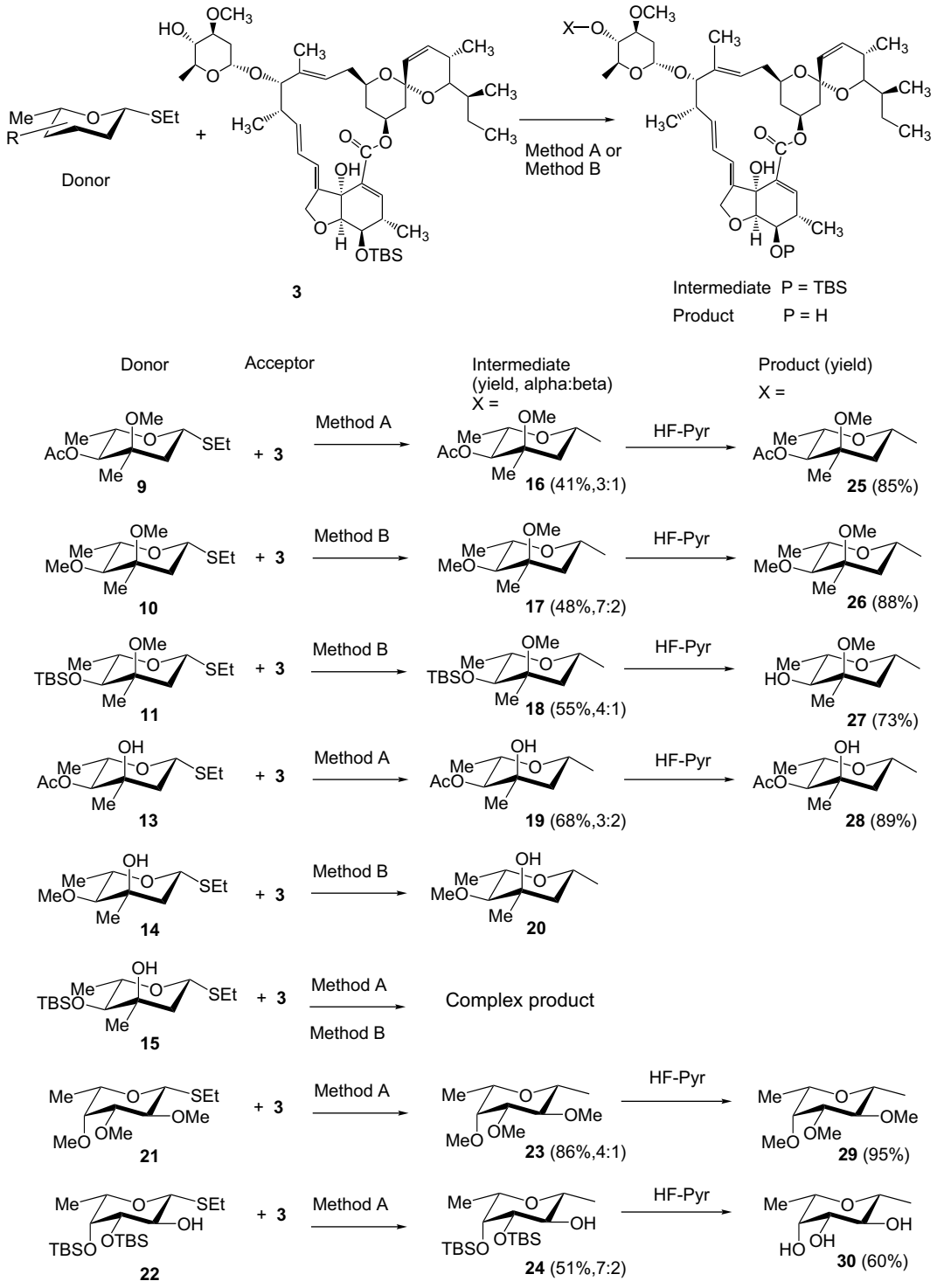
Coupling of **9** and **3** in the presence of NIS in anhydrous *N*-methylpyrrolidone under a N_2 atmosphere gave 41% yield of **16** as a α,β mixture in a ratio of 3:1 (Scheme 3). The separation of the α and β anomers was found to be fairly difficult, and only a very small amount of the α anomer was isolated and used for physical data analysis. The α-linkage was determined based on 2D NMR data (H-1: 5.24 ppm, $J_{H1,H2a} = J_{H1,H2e} = 4.5$ Hz, C-1: 97.42 ppm, $J_{C1,H1}$ 169 Hz). The analogous reaction between **13** and **3** was also carried out under these conditions to give a good yield of **19** (68%) as an α,β mixture with a ratio of 3:2. For L-cladinoside donor **10** and **11**, iodine was determined to be a better catalyst.[10] Condensation of **10** and **3** in *N*-methylpyrrolidone using iodine as catalyst afforded **17** (48%, α:β = 7:2), while **11** and **3** generated **18** under the same conditions with 55% overall yield and 4:1 α,β ratio. Surprisingly, L-mycaroside donor **14** produced a very low



Scheme 1. Preparation of uncommon sugar donors from erythromycin. Reagents: (a) H_2SO_4, 2-propanol, 75%; (b) EtSH, $BF_3{\cdot}Et_2O$, 81%; (c) Ac_2O, Pyr; (d) MeI, NaH, DMF, 84%; (e) TBSCl, Im, DMF, 78%.



Scheme 2. Preparation of uncommon sugar donors from tylosin tartrate. Reagents: (a) H_2SO_4, 2-propanol, 89%; (b) EtSH, $BF_3{\cdot}Et_2O$, 72%; (c) Ac_2O, Pyr; (d) MeI, Ag_2O, DMF, 58%; (e) TBSCl, Im, DMF, 50%.



Scheme 3. Coupling of uncommon sugars to the AVM macrolactone: method A: NIS, *N*-methylpyrrolidone; method B: I_2, *N*-methylpyrrolidone.

yield of product **20** (16%) in the iodine-catalyzed glycosylation, while **15** gave no desired product at all. When using NIS as catalyst, both **14** and **15** failed to couple with AVM derivative **3** under the above-mentioned reaction conditions. Although we currently have no idea as to what happened in the reaction, we speculate through observation that the rapid consumption of **14** and **15** was a critical factor in this fruitless glycosylation. Impressively, when L-fucosyl donor **21** and **22** reacted with **3** in *N*-methylpyrrolidone using NIS as catalyst, **23** and **24** was isolated in very good yield and stereoselectivity (for **23**, 86%, $\alpha:\beta = 4:1$; for **24**, 51%, $\alpha:\beta = 7:2$), respectively. Finally, a global removal of the *tert*-butyldimethylsilyl (TBS) group from intermediates **16**–**24**, using the hydrogen

Table 1. Bioactivities of compounds **25**–**30** to cabbage larvae

Compound	Microgram per larva	Total number	Dead number	Mortality (%)
25 (95% of α)	1.65	29	21	72
26 (α:β = 7:2)	1.65	28	24	85
27 (α:β = 4:1)	1.65	30	28	93
28 (97% of α)	1.65	28	17	61
29 (95% of α)	1.65	30	28	93
30 (α:β = 7:2)	1.65	30	11	37
1 (90% of α)	1.65	30	16	53
2 (95% of α)	1.65	29	26	90
Acetone	—	20	1	5

fluoride–pyridine complex,[11] afforded the corresponding desired products **25**–**30**. It is noteworthy that cleavage of TBS with tetra-*n*-butylammonium fluoride, using published methods,[12] failed.

Bioactivity was evaluated in preliminary studies using the cabbage leaf dip bioassay described by Zhao et al.[13] The fourth instar larvae were tested with compounds **25**–**30** (α,β mixture) in acetone solution, and mortality was assessed three days after treatment. The results showed potency at microgram levels as summarized in Table 1. Since compounds **27** and **29** appeared more potent, their toxicities in animals were then examined in ICR mice using standard methods. The LD_{50}s were determined to be 17.5 and 87.5 mg/kg, respectively. We also observed that **27** and **29** presented bioactivities as early as 6 h after the first dosage, while the same phenomena were noted in two days for **1** and **2**.

In conclusion, novel AVM analogues have been designed and synthesized. The key step is to attach uncommon sugar units, prepared from natural erythromycin and tylosin, to the 4′-position of AVM macrolactone. The use of partially methylated thioglycosides as donors, and NIS or I_2 as catalyst in *N*-methylpyrrolidone at rt, provided acceptable yields of target AVM analogues, which show excellent bioactivity against cabbage larvae. The method described here should be valuable in the synthesis of other sugar-containing macrolide antibiotics.[14]

3. Experimental

3.1. General

Optical rotations were determined at 20 °C with a Perkin–Elmer Model 241-Mc automatic polarimeter at $\lambda = 254$ nm. ^1H, ^{13}C, ^1H–^1H COSY, and HMQC NMR spectra were recorded with ARX 600 spectrometers for solutions in $CDCl_3$. Chemical shifts are given in parts per million downfield from internal Me_4Si. Mass spectra were measured using MALDI-TOFMS with dihydroxybenzoic acid (DHB) as the matrix. Thin-layer chromatography (TLC) was performed on silica gel HF_{254} with detection by charring with 30% (v/v) H_2SO_4 in MeOH or in some cases by a UV detector.

3.2. Ethyl 1-thio-L-cladinoside (8)

To a solution of 2-propanol (400 mL) and concentrated H_2SO_4 (6 mL) was added erythromycin (**4**, 20 g, 27.2 mmol) portion by portion in 20 min. The mixture was stirred at 5 °C for 1 h, then at rt for 40 h, at the end of which time, the mixture was neutralized with aqueous $NaHCO_3$ and evaporated in vacuum to remove 2-propanol. The water phase was then extracted with EtOAc (300 mL × 2). The combined organic phase was dried over anhyd Na_2SO_4 and concentrated under vacuum to give a red solid. Purification of this crude product on a silica gel column with 2:7 EtOAc–petroleum ether as eluent gave 2-propyl L-cladinoside **6** (4.5 g, 75%) as a yellowish oil (α,β mixture, 1:1):^1H NMR for β isomer: δ 1.14–1.30 (m, 12H), 1.40 (dd, 1H, *J* 9.7, 14.4 Hz), 2.13 (br s, 1H), 2.19 (dd, 1H, *J* 1.6, 14.4 Hz), 2.97 (d, 1H, *J* 9.4 Hz), 3.25 (s, 3H), 3.56–3.59 (m, 1H), 3.93–4.01 (m, 1H), 4.65 (dd, 1H, *J* 1.6, 9.7 Hz). MALDI-TOFMS: Calcd for $C_{11}H_{22}O_4$, 218; Found: 219 $(M+H)^+$. To a solution of **6** (2.2 g, 10 mmol) in CH_2Cl_2 (10 mL) was added thioethanol (0.92 mL, 12 mmol) and $BF_3{\cdot}Et_2O$ (3 mL, 12 mmol) at 0 °C. The mixture was stirred under these conditions for 30 min, neutralized with aq $NaHCO_3$, and extracted with CH_2Cl_2 (80 mL × 2). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated to dryness, and purified on a silica gel column with 3:1 petroleum ether–EtOAc as the eluent to give **8** (1.8 g, 81%) as a yellowish oil (α,β mixture, 2:5): ^1H NMR for β isomer: δ 1.24–1.30 (m, 9H), 1.54 (dd, 1H, *J* 14.2, 12.0 Hz), 2.23 (dd, 1H, *J* 14.2, 1.7 Hz), 2.25 (br s, 1H), 2.65–2.70 (m, 2H), 2.97 (d, 1H, *J* 9.5 Hz), 3.27 (s, 3H), 3.57–3.58 (m, 1H), 4.70 (dd, 1H, *J* 12.0, 1.7 Hz). MALDI-TOFMS: Calcd for $C_{10}H_{20}O_3S$, 220; Found: 243 $(M+Na)^+$. Anal. Calcd for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15. Found: C, 54.60; H, 9.03.

3.3. Ethyl 4-*O*-acetyl-1-thio-L-cladinoside (9)

To a solution of compounds **8** (1.65 g, 7.5 mmol) in pyridine (5 mL) was added Ac_2O (2 mL) at 0 °C, and stirred at rt for 8 h, then evaporated to dryness under reduced pressure. Purification by column chromatograph using 4:1 petroleum ether–EtOAc as eluent gave compound **9** (1.9 g, 97%) as a yellowish oil (α,β mixture, 2:5): ^1H NMR for β isomer: δ 1.12–1.14 (m, 6H), 1.27–1.31 (m, 3H), 1.65 (dd, 1H, *J* 11.7, 14.4 Hz), 2.13 (s, 3H), 2.22 (d, 1H, *J* 14.4 Hz), 2.70–2.74 (m, 2H), 3.27 (s, 3H), 3.93–3.99 (m, 1H), 4.66 (d, 1H, *J* 9.7 Hz), 4.82 (d, 1H, 11.7 Hz). MALDI-TOFMS: Calcd for $C_{12}H_{22}O_4S$, 262; Found: 285 $(M+Na)^+$. Anal. Calcd for $C_{12}H_{22}O_4S$: C, 54.93; H, 8.45. Found: C, 55.02; H, 8.51.

3.4. Ethyl 4-*O*-methyl-1-thio-L-cladinoside (10)

A solution of **8** (200 mg, 0.91 mmol) in DMF (2 mL) was cooled to 0 °C, then NaH (74 mg, 60%, 1.9 mmol) was added under a N_2 atmosphere. After stirring for 15 min under these conditions, CH_3I (0.38 mL, 4.6 mmol) was added to the mixture with stirring in a water-ice bath for 1 h. The reaction was then quenched with ice-water (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic phase was dried, concentrated, and purified on a silica gel column with 6:1 petroleum ether–EtOAc as eluent to give **10** (180 mg, 84%) as a colorless oil (α,β mixture, 2:5): ^{1}H NMR for β isomer: δ 1.30–1.25 (m, 9H), 1.52 (t, 1H, *J* 12.2 Hz), 2.16 (d, 1H, *J* 12.2 Hz), 2.76–2.66 (m, 3H), 3.26 (s, 3H), 3.52 (s, 3H), 3.82–3.86 (m, 1H), 4.77 (d, 1H, *J* 12.2 Hz). Anal. Calcd for $C_{11}H_{22}O_3S$: C, 56.37; H, 9.46. Found: C, 56.28; H, 9.39.

3.5. Ethyl 4-*O*-*tert*-butyldimethylsilyl-1-thio-L-cladinoside (11)

A solution of **8** (350 mg, 1.59 mmol) and imidazole (442 mg, 6.5 mmol) in DMF (4 mL) was cooled to 0 °C, then TBSCl (285 mg, 1.9 mmol) was added under a N_2 atmosphere. The mixture was stirred at rt for 6 h, then quenched with ice-water (20 mL) and extracted with EtOAc (30 mL × 2). The combined organic phase was dried, concentrated, and purified on a silica gel column with 15:1 petroleum ether–EtOAc as eluent to give **11** (414 mg, 78%) as a colorless oil (α,β mixture, 2:5): ^{1}H NMR for β isomer: δ −0.05, 0.10 (2s, 6H), 0.93 (s, 9H), 1.29–1.25 (m, 9H), 1.55 (dd, 1H, *J* 10.1, 13.7 Hz), 2.19 (d, 1H, *J* 13.7 Hz), 2.65–2.70 (m, 2H), 2.78 (d, 1H, *J* 7.1 Hz), 3.30 (s, 3H), 3.85–3.90 (m, 1H), 4.78 (d, 1H, *J* 10.1 Hz). Anal. Calcd for $C_{16}H_{34}O_3SSi$: C, 57.43; H, 10.24. Found: C, 57.55; H, 10.23.

3.6. Ethyl 1-thio-L-mycaroside (12)

Tylosin tartarte **5** (21 g, 19.7 mmol) was added to a solution of 2-propanol (400 mL) and H_2SO_4 (4 mL) in 30 min at rt. After the same procedure as described in the preparation of **6**, 3.6 g of 2-propyl mycaroside **7** was obtained as a yellowish oil (89%, α,β mixture, 1:1): ^{1}H NMR for β isomer: δ 1.30–1.14 (m, 12H), 1.61 (dd, 1H, *J* 9.6, 13.8 Hz), 1.95 (dd, 1H, *J* 2.1, 13.8 Hz), 2.23 (br s, 2H), 3.06 (d, 1H, *J* 9.4 Hz), 3.58–3.62 (m, 1H), 3.96–3.99 (m, 1H), 4.85 (dd, 1H, *J* 9.6, 2.1 Hz). MALDI-TOFMS: Calcd for $C_{10}H_{20}O_4$, 204; Found: 222.4 $(M+NH_4)^+$, 243.3 $(M+K)^+$. Using the same procedure as described in the preparation of **8** from **6**, compound **12** was obtained as α,β mixture in a total yield of 72% (α,β mixture, 2:5): ^{1}H NMR for β isomer: δ 1.13–1.17 (m, 6H), 1.30 (t, 3H, *J* 7.6 Hz), 1.82 (dd, 1H, *J* 11.7, 12.8 Hz), 2.00 (dd, 1H, *J* 1.8, 12.8 Hz), 2.25 (br s, 2H), 2.68–2.73 (m, 2H), 3.07 (d, 1H, *J* 9.4 Hz), 3.58–3.61 (m, 1H), 4.90 (dd, 1H, *J* 11.7, 1.8 Hz). Anal. Calcd for $C_9H_{18}O_3S$: C, 52.40; H, 8.79. Found: C, 52.35; H, 8.73.

3.7. Ethyl 4-*O*-acetyl-1-thio-L-mycaroside (13)

Acetylation of **12** (1.6 g, 7.75 mmol) as described in the preparation of **9** from **8** quantitatively gave **13** (1.92 g, α,β mixture) as yellowish oil: ^{1}H NMR for β isomer: δ 1.15–1.17 (m, 6H), 1.30 (t, 3H, *J* 7.9 Hz), 1.81 (t, 1H, *J* 12.0 Hz), 2.04 (d, 1H, *J* 14.3 Hz), 2.15 (s, 3H), 2.60–2.74 (m, 3H), 3.83–3.86 (m, 1H), 4.63 (d, 1H, *J* 9.8 Hz), 4.95 (d, 1H, *J* 12.0 Hz). Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12. Found: C, 53.13; H, 8.17.

3.8. Ethyl 4-*O*-methyl-1-thio-L-mycaroside (14)

To a pre-cooled (0 °C) solution of compounds **12** (260 mg, 1.26 mmol) in CH_2Cl_2 (3 mL) was added freshly prepared Ag_2O (530 mg, 2.27 mmol) in a dark room under a N_2 atmosphere. The mixture was stirred under these conditions for 30 min, then CH_3I was added (0.40 mL, 6.3 mmol). Another 30 min later, the reaction mixture was warmed up to rt and was kept stirring for 24 h. The suspension was filtered off and the filtrate was concentrated to dryness. Purification by column chromatograph using 4:1 petroleum ether–EtOAc as eluent gave compound **14** (160 mg, 58%) as a light yellowish oil: ^{1}H NMR for β isomer: δ 1.26–1.31 (m, 9H), 1.68 (dd, 1H, *J* 11.8, 13.9 Hz), 2.00 (dd, 1H, *J* 13.9, 1.7 Hz), 2.30 (br s, 1H), 2.65–2.73 (m, 3H), 3.55 (s, 3H), 3.61–3.65 (m, 1H), 4.89 (dd, 1H, *J* 11.8, 1.7 Hz). Anal. Calcd for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15. Found: C, 54.57; H, 9.21.

3.9. Ethyl 4-*O*-*tert*-butyldimethylsilyl-1-thio-L-mycaroside (15)

A solution of **12** (350 mg, 1.7 mmol) was treated as described in the preparation of **11** from **8** to give **15** (272 mg, α,β mixture, 50%) as a colorless oil: ^{1}H NMR for β isomer: δ 0.05, 0.07 (2s, 6H), 0.95 (s, 9H), 1.24–1.32 (m, 9H), 1.75 (dd, 1H, *J* 11.0, 13.5 Hz), 1.98 (dd, 1H, *J* 13.5, 2.0 Hz), 2.25 (br s, 1H), 2.60–2.75 (m, 3H), 3.60–3.63 (m, 1H), 4.93 (dd, 1H, *J* 11.0, 2.0 Hz). Anal. Calcd for $C_{15}H_{32}O_3SSi$: C, 56.20; H, 10.06. Found: C, 56.27; H, 10.11.

3.10. 4-*O*-Acetylcladinosyl intermediate 16

Method A: To a mixture of AVM derivative **3** (198 mg, 0.235 mmol) and donor **9** (158 mg, 0.6 mmol) in *N*-methylpyrrolidinone (3 mL) at rt was added NIS (120 mg, 0.6 mmol) under N_2 protection. The mixture was stirred at rt for 0.5 h, and to it was added excess

of aq $Na_2S_2O_6$ in one portion. It was then extracted with EtOAc (30 mL × 2), and the combined organic phase was washed with brine and water and dried over Na_2SO_4. Removal of the solvent afforded a syrupy material that was chromatographed using 13:7 EtOAc–petroleum ether as eluent to give **16** (100 mg, 41%, α:β = 3:1) as an amorphous solid: ^{1}H NMR for α isomer: δ 0.14 (s, 6H), 0.88–0.95 (m, 18H), 1.10–1.12 (m, 8H), 1.26–1.29 (m, 4H), 1.47–1.49 (m, 4H), 1.55–1.65 (m, 3H), 1.79 (s, 3H), 2.00–2.04 (m, 4H), 2.15 (s, 3H), 2.25–2.30 (m, 3H), 2.36 (s, 1H), 2.45–2.47 (m, 1H), 3.24 (t, 1H, *J* 9.1 Hz), 3.30 (s, 3H), 3.36–3.42 (m, 2H), 3.45 (s, 3H), 3.49 (d, 1H, *J* 10.5 Hz), 3.61–3.64 (m, 1H), 3.82–3.88 (m, 3H), 3.93 (s, 1H), 4.06–4.13 (m, 1H), 4.35–4.39 (m, 1H), 4.43 (br s, 1H), 4.58 (dd, 1H, *J* 1.7, 14.4 Hz), 4.63–4.72 (m, 2H), 4.80 (d, 1H, *J* 3.2 Hz), 4.99–5.00 (m, 1H), 5.24 (d, 1H, *J* 4.5 Hz), 5.33 (s, 1H), 5.34–5.40 (m, 2H), 5.55 (dd, 1H, *J* 9.9, 2.4 Hz), 5.72–5.74 (m, 2H), 5.78 (br d, 1H, *J* 9.6 Hz), 5.81–5.83 (m, 1H). Selected ^{13}C NMR: −4.40, 12.21, 13.13, 15.32, 16.56, 17.34, 18.42, 20.21, 21.11, 21.47, 26.06, 27.71, 30.76, 34.47, 35.40, 46.00, 49.86, 56.59, 62.84, 68.58, 68.65, 69.70, 73.45, 76.99, 78.90, 79.75, 94.96, 95.97, 97.42, 117.48, 118.50, 119.59, 128.03, 128.39, 129.20, 135.28, 136.34, 137.80, 137.82, 140.44, 170.96, 174.24. MALDI-TOFMS: Calcd for $C_{57}H_{90}O_{15}Si$, 1042.6; Found: 1065.5 $(M+Na)^+$.

3.11. 4-*O*-Methylcladinosyl intermediate 17

Method B: To a solution of AVM lactone **3** (400 mg, 0.47 mmol) and donor **10** (160 mg, 0.68 mmol) in *N*-methylpyrrolidinone (2 mL) was added I_2 (160 mg, 0.63 mmol) and stirred at 0 °C over 30 min under a N_2 atmosphere. At the end of this time, the mixture was diluted with EtOAc (30 mL) and treated with aq $Na_2S_2O_6$. The organic phase was separated and the aq phase was further extracted with EtOAc (20 mL × 2). The combined organic phase was washed with brine and water and dried over Na_2SO_4. Purification of the concentrated residue by silica gel column chromatography gave **17** (230 mg, 48%, α:β 7:2) as a white solid: Selected ^{1}H NMR resonances for the α isomer: δ 0.14 (s, 6H), 0.88–0.97 (m, 18H), 1.12–1.13 (m, 4H), 1.24–1.32 (m, 10H), 1.49–1.58 (m, 10H), 1.77–1.79 (m, 4H), 2.20–2.21 (m, 1H), 2.27–2.30 (m, 4H), 2.51 (m, 1H), 2.68 (d, 1H, *J* 9.5 Hz), 3.26–3.28 (m, 4H), 3.40–3.42 (m, 4H), 3.47–3.57 (m, 2H), 3.53 (s, 3H), 3.65–3.70 (m, 1H), 3.81–3.87 (m, 1H), 3.93 (s, 1H), 4.07 (s, 1H), 4.23–4.25 (m, 1H), 4.44 (s, 1H), 4.58 (dd, 1H, *J* 14.3, 2.2 Hz), 4.68 (dd, 1H, *J* 14.4, 2.2 Hz), 4.78 (d, 1H, *J* 3.2 Hz), 4.95–5.05 (m, 1H), 5.23 (d, 1H, *J* 4.6 Hz), 5.33–5.36 (m, 2H), 5.55 (dd, 1H, *J* 9.9, 2.5 Hz), 5.72–5.76 (m, 3H), 5.81–5.82 (m, 1H). MALDI-TOFMS: Calcd for $C_{56}H_{90}O_{14}Si$, 1014.6; Found: 1037.4 $(M+Na)^+$.

3.12. 4-*O*-*tert*-Butyldimethylsilylcladinosyl intermediate 18

Compound **18**, prepared from **3** (110 mg, 0.13 mmol) and **11** (67 mg, 0.2 mmol) by method B as described in the preparation of **17**, was isolated as a foam (80 mg, 55%, α:β 4:1): Selected ^{1}H NMR for α isomer: δ 0.03, 0.07 (2s, 6H), 0.14 (s, 6H), 0.85–0.97 (m, 27H), 1.15–1.26 (m, 14H), 1.53–1.60 (m, 10H), 1.81–1.87 (m, 4H), 2.20–2.21 (m, 1H), 2.27–2.30 (m, 4H), 2.51 (m, 1H), 2.68 (d, 1H, *J* 9.5 Hz), 3.26–3.40 (m, 5H), 3.47–3.57 (m, 2H), 3.53 (s, 3H), 3.63–3.66 (m, 1H), 3.81–3.87 (m, 1H), 3.93 (s, 1H), 4.09 (s, 1H), 4.23–4.25 (m, 1H), 4.44 (s, 1H), 4.58 (dd, 1H, *J* 12.4, 3.2 Hz), 4.68 (dd, 1H, *J* 12.4, 3.2 Hz), 4.77 (d, 1H, *J* 3.2 Hz), 4.97–5.01 (m, 1H), 5.23 (d, 1H, *J* 4.6 Hz), 5.30–5.35 (m, 2H), 5.57 (dd, 1H, *J* 10.5, 2.0 Hz), 5.72–5.75 (m, 3H), 5.82–5.84 (m, 1H). MALDI-TOFMS: Calcd for $C_{61}H_{102}O_{14}Si_2$, 1114.68; Found: 1137.5 $(M+Na)^+$.

3.13. 4-*O*-Acetylmycarosyl intermediate 19

Compound **19**, prepared from **3** (490 mg, 0.58 mmol) and **13** (460 mg, 1.85 mmol) by method A as described in the preparation of **16**, was isolated as a white solid (406 mg, 68%): ^{1}H NMR for α isomer: δ 0.08 (s, 6H), 0.85–0.94 (m, 18H), 1.10–1.16 (m, 9H), 1.25–1.29 (m, 5H), 1.45–1.48 (m, 5H), 1.54–1.60 (m, 4H), 1.90–2.02 (m, 4H), 2.10–2.18 (m, 3H), 2.24–2.31 (m, 4H), 2.49–2.51 (m, 2H), 3.25 (t, 1H, *J* 9.7 Hz), 3.38–3.48 (m, 5H), 3.61–3.65 (m, 1H), 3.81–3.91 (m, 4H), 4.04 (s, 1H), 4.16–4.19 (m, 1H), 4.32 (d, 1H, *J* 2.8 Hz), 4.57–4.68 (m, 3H), 4.78 (d, 1H, *J* 3.2 Hz), 4.95–5.00 (m, 2H), 5.32–5.37 (m, 3H), 5.54 (d, 1H, *J* 9.9 Hz), 5.68–5.76 (m, 3H), 5.82–5.80 (m, 1H). MALDI-TOFMS: Calcd for $C_{56}H_{88}O_{15}Si$, 1028.59; Found: 1047 $[M+NH_4^+]$.

3.14. 2,3,4-Tri-*O*-methyl-1-thio-α-L-fucopyranoside (21)

Compound **21** was prepared from ethyl 1-thio-α-L-fucopyranoside[15] as described in the making of **10** from **3**: $[\alpha]_D^{20}$ −78 (*c* 1, $CHCl_3$); ^{1}H NMR: δ 1.24 (t, 3H, *J* 6.8 Hz, CH_3), 1.28 (d, 3H, *J* 6.0 Hz, H-6), 2.64–2.73 (m, 2H, SCH_2), 3.15 (dd, 1H, *J* 3.0, 9.5 Hz, H-3), 3.26 (t, 1H, *J* 9.5 Hz, H-2), 3.37 (d, 1H, *J* 3.0 Hz, H-4), 3.43–3.47 (m, 1H, H-5), 3.50, 3.55, 3.57 (3s, 9H, $3CH_3$), 4.22 (d, 1H, *J* 9.5 Hz). MALDI-TOFMS: Calcd for $C_{11}H_{22}O_4S$, 250.12; Found: 273 $(M+Na)^+$.

3.15. 2,3,4-Tri-*O*-methyl-L-fucopyranosyl AVM intermediate 23

Compound **23** (α:β = 4:1), prepared from **3** (290 mg, 0.34 mmol) and **21** (213 mg, 0.85 mmol) by method A as described in the preparation of **16**, was isolated as a white solid (305 mg, 86%). For the α isomer: (95–97%

purity); ^{1}H NMR: δ 0.13–0.14 (m, 6H, C(CH_3)$_2$), 0.89–0.95 (m, 18H), 1.14 (d, 3H, J 7.3 Hz, CH_3-12a), 1.23–1.25 (m, 9H), 1.45–1.60 (m, 6H, CH_3-14a, H-20a, H-16a, H-2^{I}a, CH_2-27), 1.74–1.79 (m, 4H, H-18e, CH_3-4a), 2.00–2.05 (m, 1H, H-20e), 2.23–2.30 (m, 4H, H-2^{I}e, H-24, H-26, H-16e), 2.49–2.53 (m, 1H, H-12), 3.34–3.39 (m, 2H, H-2, H-4^I), 3.42 (s, 3H, OCH_3), 3.45–3.51 (m, 3H, H-3^I, H-3^{II}, H-25), 3.53–3.60 (t, 9H, FUCOSE-OCH_3), 3.66 (dd, 1H, J 8.1, 10.1 Hz, H-2^{II}), 3.76–3.98 (m, 6H, H-6, H-17, H-13, H-5^I, H-4^{II}, H-5^{II}), 4.06 (s, 1H, 7-OH), 4.43–4.44 (m, 1H, H-5), 4.58, 4.66 (2dd, 2H, J 14.0, 2.2 Hz, H-8a), 4.73 (d, 1H, J 3.4 Hz, H-1^I), 4.97–5.01 (m, 1H, H-3), 5.31–5.36 (m, 2H, H-19, H-15), 5.57 (dd, 1H, J 2.5, 9.9 Hz, H-23), 5.60 (d, 1H, J 4.00 Hz, H-1^{II}), 5.68–5.71 (m, 2H, H-10, H-11), 5.78 (dd, 1H, H-22), 5.80–5.83 (m, 1H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$): −4.60, −4.87 (–Si(CH_3)$_2$–), 12.02 (C-28), 12.96 (C-26a), 15.10 (C-14a), 16.38 (C-24a), 16.46 (C-6^{II}), 18.42 (C-6^I), 18.48 (–C(CH)$_3$), 20.01 (C-4a), 20.07 (C-12a), 25.88 (–C(CH)$_3$), 27.48 (C-27), 30.55 (C-24), 34.29 (C-16), 34.50 (C-26), 35.17 (C-2^I), 36.52 (C-18), 39.70 (C-12), 40.47 (C-20), 45.77 (C-2), 56.02 (2^I-OCH_3), 57.98, 58.57, 61.68 (FUCOSE-OCH_3), 66.49 (C-5^I), 66.94 (C-5^{II}), 67.93 (C-8a), 68.34 (C-19), 68.41 (C-6), 69.51 (C-5), 74.84 (C-25), 77.62 (C-2^{II}), 79.02 (C-3^I), 79.23 (C-4^{II}), 79.26 (C-4^I), 80.04 (C-3^{II}), 80.11 (C-17), 80.26 (C-7), 95.31 (C-1^I), 95.77 (C-21), 96.95 (C-1^{II}), 117.24 (C-15), 118.37 (C-3), 119.34 (C-9), 124.82 (C-10, C-23), 135.34 (C-14), 136.20 (C-22), 137.52 (C-4, C-11), 140.18 (C-8), 174.00 (C-1). MALDI-TOFMS: Calcd for $C_{56}H_{90}O_{15}Si$, 1030.6; Found: 1054 [M+Na]$^+$; 1070 [M+K]$^+$.

3.16. 3,4-Di-*O*-*tert*-butyldimethylsilyl-α-L-fucopyranosyl AVM intermediate 24

Compound **24** (α:β = 7:2), prepared from **3** (95 mg, 0.11 mmol) and **22** (240 mg, 0.55 mmol) by method A as described in the preparation of **16**, was isolated as a white solid (70 mg, 51%): Selected ^{1}H NMR for the α isomer: δ 0.03–0.08 (2s, 9H), 0.11–0.13 (m, 9H), 0.85–0.97 (m, 37H), 1.16–1.25 (m, 9H), 1.45–1.60 (m, 6H), 1.74–1.79 (m, 4H), 2.23–2.30 (m, 7H), 2.49–2.53 (m, 2H), 3.34–3.39 (m, 2H), 3.42 (s, 3H), 3.45–3.51 (m, 3H), 3.64 (dd, 1H, J 7.1, 9.4 Hz), 3.75–4.00 (m, 6H), 4.05 (s, 1H), 4.43–4.44 (m, 1H, H-5), 4.59 (dd, 1H, J 12.1, 3.7 Hz), 4.67 (dd, 1H, J 12.1, 2.5 Hz), 4.69 (d, 1H, J 3.9 Hz), 4.97–5.01 (m, 1H, H-3), 5.30–5.35 (m, 2H), 5.55 (dd, 1H, J 2.5, 9.9 Hz), 5.65 (d, 1H, J 4.0 Hz), 5.68–5.70 (m, 2H), 5.76 (dd, 1H, J 9.9, 4.3 Hz), 5.80–5.83 (m, 1H, H-9). MALDI-TOFMS: Calcd for $C_{65}H_{112}O_{15}Si_3$, 1216.7; Found: 1240 [M+Na]$^+$.

3.17. General procedure for the desilylation of intermediates 16–19 and 23–24

The intermediate (**16**–**19** and **23**–**24**, 1 mmol) was dissolved in pyridine (3 mL) and acetonitrile (10 mL). To the solution was added HF/Pyr (15 mL, 70%) with stirring at 0 °C for 20 h, at the end of which time TLC indicated the completion of the reaction. The mixture was evaporated to dryness under reduced pressure. Purification of the residue on a silica gel column using EtOAc as eluent afforded corresponding product **25**–**30**. All these products were white foams.

For the α isomer of **25** (about 95% purity): ^{1}H NMR: δ 0.85–0.95 (m, 10H), 1.10–1.20 (m, 8H), 1.24–1.26 (m, 6H), 1.46–1.64 (m, 8H), 1.76 (m, 1H), 1.88 (br s, 3H), 2.00–2.05 (m, 1H), 2.15 (s, 3H), 2.20–2.31 (m, 4H), 2.35–2.37 (d, 1H, J 3.3 Hz), 2.47–2.53 (m, 1H), 3.21–3.30 (m, 5H), 3.43–3.50 (m, 4H), 3.60–3.65 (m, 1H), 3.81–3.98 (m, 5H), 4.30 (d, 1H), 4.35–4.40 (m, 1H), 4.67–4.69 (m, 2H), 4.72 (d, 1H, J 10 Hz), 4.79 (d, 1H, J 3.0 Hz), 4.94–4.98 (m, 1H), 5.24 (d, 1H, J 4.4 Hz), 5.40–5.43 (m, 2H), 5.54–5.57 (dd, 1H, J 2.5, 9.9 Hz), 5.72–5.78 (m, 3H), 5.85–5.88 (m, 1H); MALDI-TOFMS: Calcd for $C_{51}H_{76}O_{15}$, 928.52 [M]; Found: 951.42 [M+Na]$^+$; 967.39 [M+K]$^+$.

For **26** (about 95% purity): Selected ^{1}H NMR for the α isomer: δ 0.78–0.90 (m, 14H), 1.16 (d, 1H, J 7.1 Hz), 1.20 (d, 3H, J 6.7 Hz), 1.25 (d, 3H, J 6.0 Hz), 1.43–1.59 (m, 8H), 1.75–1.80 (m, 4H), 2.01 (dd, 1H, J 12.8, 4.2 Hz), 2.15–2.35 (m, 5H), 2.49–2.52 (m, 1H), 3.14, 3.21 (2t, 2H, J 9.2 Hz), 3.30–3.40 (m, 11H), 3.44–3.46 (m, 4H), 3.58–3.78 (m, 2H), 3.82–3.87 (m, 2H), 3.94, 4.10, 4,43 (3s, 3H), 4.58 (d, 1H, J 14.7 Hz), 4.68 (d, 1H, J 14.7 Hz), 4.75 (d, 1H, J 3.3 Hz), 5.00–5.38 (m, 4H), 5.56–5.75 (m, 4H), 5.83–5.85 (m, 1H). MALDI-TOFMS: Calcd for $C_{50}H_{76}O_{14}$, 900.52; Found: 923.5 [M+Na]$^+$.

For **27** (about 95% purity): Selected ^{1}H NMR for α isomer: δ 0.84–0.92 (m, 14H), 1.16–1.25 (m, 7H), 1.43–1.62 (m, 10H), 1.75–1.80 (m, 4H), 2.10 (dd, 1H, J 13.5, 2.5 Hz), 2.15–2.35 (m, 7H), 2.49–2.52 (m, 1H), 3.14–3.25 (m, 2H), 3.30–3.40 (m, 5H), 3.44–3.46 (m, 2H), 3.60–3.75 (m, 4H), 3.82–3.87 (m, 2H), 3.94, 4.10, 4.43 (3s, 3H), 4.58 (d, 1H, J 14.5 Hz), 4.68 (d, 1H, J 14.5 Hz), 4.77 (d, 1H, J 3.0 Hz), 5.02–5.38 (m, 4H), 5.55–5.83 (m, 5H). MALDI-TOFMS: Calcd for $C_{49}H_{74}O_{14}$, 886.5; Found: 889.4 [M+Na]$^+$.

For the α isomer of **28** (about 97% purity); ^{1}H NMR: δ 0.85–0.95 (m, 10H), 1.15–1.24 (m, 14H), 1.45–1.65 (m, 8H), 1.75 (m, 1H), 1.88 (br s, 3H), 2.03–2.05 (m, 1H), 2.17 (s, 3H), 2.24–2.30 (m, 5H), 2.32–2.35 (d, 1H, J 3.3 Hz), 2.45–2.47 (m, 1H), 3.21–3.30 (m, 2H), 3.45–3.60 (m, 5H), 3.80–4.00 (m, 5H), 4.30 (d, 1H), 4.35–4.37 (m, 1H), 4.67–4.69 (m, 2H), 4.77 (d, 1H, J 10 Hz), 4.79 (d, 1H, J 3.0 Hz), 4.96–4.98 (m, 1H), 5.24 (d, 1H, J 4.4 Hz), 5.40–5.43 (m, 2H), 5.55–5.57 (dd, 1H, J 2.5, 9.9 Hz), 5.75–5.78 (m, 3H), 5.85–5.88 (m, 1H); MALDI-TOFMS: Calcd for $C_{50}H_{74}O_{15}$, 914.5; Found: 936.5 [M+Na]$^+$.

For the α isomer of **29** (about 95% purity); ^{1}H NMR: δ 0.85–0.95 (m, 10H), 1.14 (d, 3H, J 6.4 Hz), 1.24–1.26 (m,

6H), 1.45–1.50 (m, 4H), 1.58–1.64 (m, 4H), 1.76 (m, 1H), 1.88 (br s, 3H), 2.00–2.05 (m, 1H), 2.23–2.29 (m, 4H), 2.36 (d, 1H, *J* 7.3 Hz), 2.47–2.53 (m, 1H), 3.28–3.30 (m, 1H), 3.35–3.41 (m, 1H), 3.42 (s, 3H), 3.46–3.50 (m, 2H), 3.53–3.60 (3s, 9H), 3.64 (dd, 1H, *J* 10.1, 2.9 Hz), 3.78–4.00 (m, 7H), 4.20–4.23 (m, 1H), 4.30 (t, 1H, *J* 9.7 Hz), 4.68–4.74 (m, 3H), 4.94–4.96 (m, 1H), 5.37–5.43 (m, 2H), 5.55 (dd, 1H, *J* 2.5, 9.9 Hz), 5.60 (d, 1H, *J* 4.0 Hz), 5.71 (t, 2H), 5.77 (dd, 1H, *J* 3.1, 9.7 Hz), 5.85–5.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 12.02 (C-28), 12.96 (C-26a), 15.07 (C-14a), 16.38 (C-24a), 16.47 (C-6^{II}), 18.50 (C-6^{I}), 19.97 (C-4a), 20.00 (C-12a), 27.50 (C-27), 30.58 (C-24), 34.26 (C-16), 34.50 (C-26), 35.17 (C-2^{I}), 36.60 (C-18), 39.83 (C-12), 40.49 (C-20), 45.72 (C-2), 56.07, 57.99, 58.87, 61.70, 66.51 (C-5^{I}), 66.97 (C-5^{II}), 66.74 (C-5), 68.15 (C-19), 68.33 (C-8a), 68.48 (C-17), 74.89 (C-25), 77.62 (C-2^{II}), 79.02 (C-3^{I}), 79.05 (C-4^{II}), 79.25 (C-4^{I}), 79.26 (C-6), 80.11 (C-3^{II}), 80.41 (C-7), 82.57 (C-13), 95.31 (C-1^{I}), 95.77 (C-21), 96.96 (C-1^{II}), 118.06 (C-15), 118.37 (C-3), 120.43 (C-9), 124.76 (C-10), 127.78 (C-23), 135.31 (C-14), 136.30 (C-22), 137.98 (C-4), 138.04 (C-11), 139.59 (C-8), 173.72 (C-1); MALDI-TOFMS: Calcd for $C_{50}H_{76}O_{15}$, 916.52; Found: 939.70 $[M+Na]^+$, 955.70 $[M+K]^+$.

For **30** (about 92% purity): Selected ^{1}H NMR: δ 0.85–0.95 (m, 10H), 1.14 (d, 3H, *J* 6.3 Hz), 1.25–1.30 (m, 6H), 1.45–1.50 (m, 4H), 1.60–1.70 (m, 4H), 1.76–1.88 (m, 4H), 2.05–2.07 (m, 1H), 2.20–2.30 (m, 7H), 2.35 (d, 1H, *J* 7.7 Hz), 2.47–2.53 (m, 1H), 3.28–3.30 (m, 1H), 3.35–3.41 (m, 1H), 3.46–3.50 (m, 2H), 3.62–3.66 (m, 4H), 3.75–4.00 (m, 7H), 4.20–4.23 (m, 1H), 4.31 (t, 1H, *J* 9.5 Hz), 4.68–4.74 (m, 3H), 4.96–4.98 (m, 1H), 5.35–5.44 (m, 2H), 5.57 (dd, 1H, *J* 2.5, 9.9 Hz), 5.60 (d, 1H, *J* 4.0 Hz), 5.72 (t, 2H, *J* 9.3 Hz), 5.78 (dd, 1H, *J* 3.1, 9.7 Hz), 5.85–5.88 (m, 1H). MALDI-TOFMS: Calcd for $C_{47}H_{70}O_{15}$, 874.47; Found: 897.3 $[M+Na]^+$.

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