Glycosidation Route to 4″-*epi*-(Methylamino)-4″-Deoxyavermectin B_1 (MK-244, Emamectin Benzoate)

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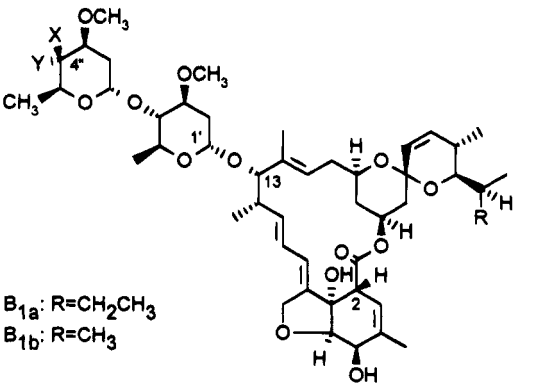
A stereocontrolled glycosidation with phenyl 4-*epi*-[*N*-(allyloxycarbonyl)-methylamino]-4-deoxy-1-thiooleandroside (**10**) and 5-*O*-(allyloxycarbonyl)avermectin B_1 monosaccharide (**12**) using *N*-iodosuccinimide gave *exclusively* the α-anomer **13** in 90% yield. Thiophenyl oleandrose derivative **10** was prepared from methyl oleandroside, which was prepared via methanolysis of avermectins. Deprotection and crystallization as the benzoic acid salt gave 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 (**1a**, MK-244, emamectin benzoate).

Members of the avermectin class of natural products, first isolated[1] from the soil microorganism *Streptomyces avermitilis*, are 16-member lactones possessing a great diversity of functionalities: an L-oleandrose based disaccharide unit, a spiroketal system, a diene, and an acid and base sensitive oxahydrindene ring system. The successful commercialization of two members of the class of avermectins ("abamectin",[1] and "ivermectin"[2]) due to their potent anthelmintic, insecticidal, and acaricidal properties for agricultural and antiparasitic uses in animals and man represents a great advance in pesticidal natural products.

Among a host of analogues prepared from the avermectins is the relatively new class of 4″-aminoavermectins.[3] These amino-saccharide-containing avermectins have been shown to have excellent activity against a variety of insect larvae, spider mites, and aphids, and the use of 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 benzoate (**1a**, MK-244, emamectin benzoate) (Figure 1) as an agricultural insecticide is under investigation.[4]

A synthesis of MK-244 (**1a**) from avermectin B_1 (**5**) could logically proceed by direct displacement of a suitable derivative of the $C_{4''}$-hydroxyl group. Displacement/inversion of equatorial substituents in carbocyclic rings is normally a difficult task; and indeed, attempted displacement of isopropyl 4-*O*-mesyloleandroside (**2**) with sodium benzoate in DMF leads to ring contraction to the furanoside **3** (Figure 2).[5a–f] Ring contraction with triflate derivatives occurs readily in DMF in the absence of other nucleophiles.[5d] However, there are reports of successful



1a: X=$CH_3NH{\cdot}PhCO_2H$, Y=H [MK-244]
1b: X=CH_3NH, Y=H
5: X=H, Y=OH [AVERMECTIN B_1]

Figure 1. Avermectin B1 and MK-244.

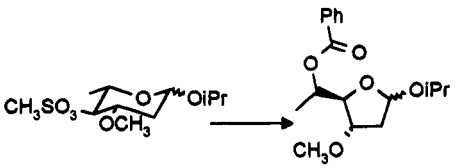


Figure 2. Displacement of oleandrose derivatives.

displacement/inversion reactions with the use of sodium azide in HMPA.[6] In our own experience, the attempted displacement of either the $C_{4''}$-mesylate or -triflate derivative of avermectin B_1 (**5**) with sodium azide in DMF led to epimerization at the C_2 position prior to any displacement/rearrangement.

Syntheses of MK-244 (**1a**) via reductive amination of the 4″-ketone of avermectin B_1 have been reported.[3a,7] An alternative synthesis of 4″-*epi*-aminoavermectins from avermectin B_1 (**5**) (Figure 1) could involve removal of the terminal oleandrose sugar followed by the preparation

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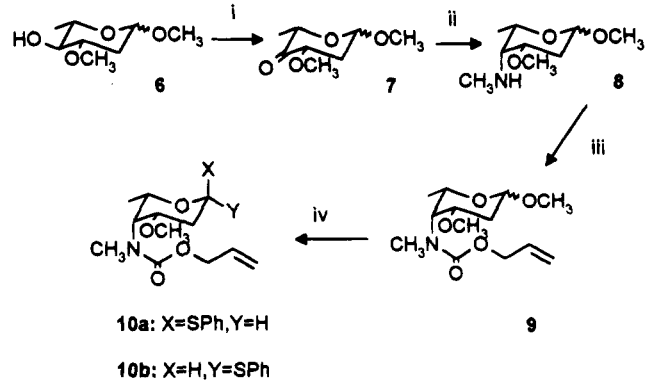
and attachment of a suitable oleandrose derivative. This paper discusses the preparation of MK-244 (**1a**) by such an approach, highlighted by high yielding exclusive α-anomer formation in the coupling of 5-*O*-(allyloxycarbonyl)avermectin B_1 monosaccharide (**12**) with phenyl 4-*epi*-[*N*-(allyloxycarbonyl)methylamino]-4-deoxy-1-thiooleandroside (**10**) by the action of *N*-iodosuccinimide.

Results and Discussion

Among the syntheses of avermectins,[8] stereocontrol of the 1″-anomeric center (refer to Figure 1 for avermectin numbering) in the preparation of the oleandrosyl oleandrose disaccharide unit has been reported. Nicolaou[8a] coupled 4-*O*-TBDMS oleandrosyl fluoride with thiophenyl oleandroside using $AgClO_4/SnCl_2$ to give the disaccharide as the α-anomer in 65% yield. Danishefsky[8b] activated the glycal of oleandrose with *N*-iodosuccinimide in the presence of methyl oleandroside to give a 2′-iododisaccharide with exclusive formation of the α-anomer. More recently, Ley[8d] reported the coupling of an imidazolylcarbonyl oleandroside with acetyloleandroside in the presence of silver perchlorate to give disaccharide in 62% yield with the formation of 11% of the β-anomer; and Mereyala[8e] coupled 2-pyridyl 1-thio-3-*O*-acetyl-oleandroside with methyl oleandroside in the presence of methyl iodide to give predominantly the α-anomer. The direct glycosidation of alcohols with thioglycosides in 2-deoxysugar derivatives using thiophilic reagents generally produces α/β anomeric mixtures with the α-anomer predominating, but not exclusively. Glycosidations using thiosugars containing equatorial 2-amido[9a-d] appendages have long shown excellent stereocontrol due to involvement of a 1,2-acetamido-bridging carbonium intermediate leading to the predominant formation of the β-anomer. In our case, it was anticipated that, should bridging play a role, the axial configuration of the acylamino group would result in a high degree of control in the formation of the α-anomer.

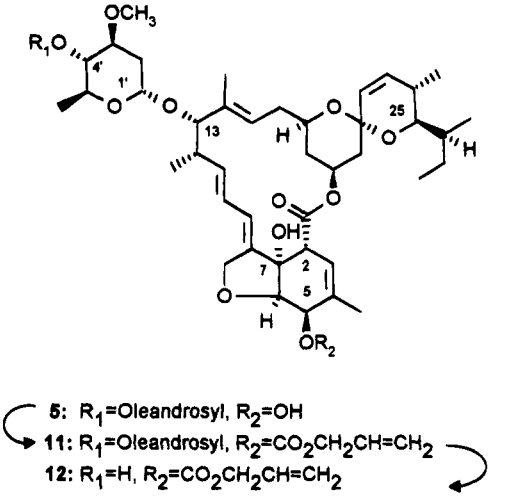
The preparation of our first intermediate (Scheme 1), phenyl 4-*epi*-[*N*-(allyloxycarbonyl)methylamino]-4-deoxy-1-thiooleandroside (**10**), proceeded by the sequence of (1) oxidation of methyl oleandroside (**6**) with PDC[10] to ketone **7** in 90% yield;[5a] (2) reductive amination of **7** with methylamine, acetic acid, and sodium borohydride to give methyl 4−*epi*-(methylamino)oleandroside (**8**) in 80% yield; (3) reaction of **8** with allyl chloroformate to give urethane **9** in 85% yield; and (4) thioacetal formation with thiophenol and $BF_3{\cdot}Et_2O$ to give phenyl 4−*epi*-[N-(allyloxycarbonyl)methylamino]-4-deoxy-1-thiooleandroside (**10**) in 85% yield as a 60:40 mixture of α:β anomers. There are several syntheses of oleandrose[11] available, but acidic methanol solvolysis of avermectins, available to us from the mother liquors after crystallization of avermectin B_1 from fermentation broths, provided a ready source of methyl oleandroside and an independent synthesis of oleandrose was not anticipated for bulk preparations.

Scheme 1. Preparation of Phenyl Thiooleandroside Derivative 10a,b



[a] (i) PDC; (ii) CH_3NH_2, HOAc, $NaBH_4$; (iii) $ClCO_2CH_2CH{=}CH_2$; (iv) $BF_3{\cdot}Et_2O$, HSPh.

Scheme 2. Preparation of Protected Monosaccharide



[a] (i) MTBE, TMEDA, allyl chloroformate; (ii) IPA, H_2SO_4.

Our second intermediate, monosaccharide **12**, was prepared (Scheme 2) as follows: (1) selective protection of the C_5-hydroxyl group of avermectin B_1 (**5**) with allyl chloroformate and TMEDA to give 5-*O*-(allyloxycarbonyl)-avermectin B_1 (**11**) in 97% yield;[7] and (2) solvolytic removal of the terminal oleandrose unit with H_2SO_4 in isopropyl alcohol to give 5-*O*-(allyloxycarbonyl)avermectin B_1 monosaccharide (**12**) in 87% yield.

An initial coupling of (alkoxycarbonyl)amino oleandrose **10** and monosaccharide **12** with *N*-bromosuccinimide[12] in THF (Scheme 3) gave *N*,5-*O*-bis allyloxycarbonyl-4″-*epi*-(methylamino)-4″-deoxyavermectin (**13**) in low conversion and low yields along with a variety of brominated avermectin byproducts. A wide selection of activating reagents are available for the activation of

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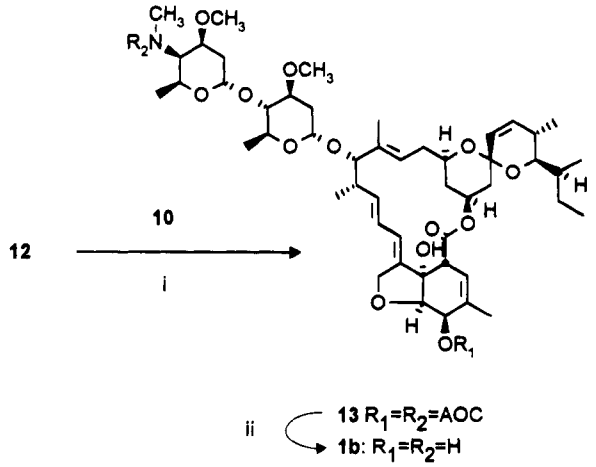
Scheme 3. Coupling and Deprotection



[a] (i) NIS; (ii) $(Ph_3P)_4Pd(0)$, HCO_2H.

1-thioglycosides,[12] but ~90% yield and exclusive α-anomer formation was achieved by activating an excess of **10** with *N*-iodosuccinimide (NIS) in the presence of 2,6-di-*tert*-butylpyridine in *N*-methylpyrrolidinone. Similarly, when the *N*-trifluoroacetamide analogue of **10** was coupled with monosaccharide **12** using NIS, selective α-glycosidation was also achieved in good yield. When either the α or β anomer of phenyl 4-*epi*-[*N*-allyloxycarbonylmethylamino]-4-deoxy-1-thiooleandroside (**10a,b**) was coupled to monosaccharide **12** or α-methyl oleandroside (α-**6**, Scheme 4), only the α,α-disaccharides **13** or **14**, respectively, were produced. However, when phenyl 4-*O*-allyloxycarbonyl-1-thiooleandroside (**16**) (prepared from **15**) was coupled to the α-anomer of methyl α-oleandroside (α-**6**) under identical conditions, a 2:1 mixture of α:β anomers of the disaccharide **17** (Scheme 4) was formed in 40% yield. In addition, methyl 4[4′-*O*-(allyloxycarbonyl)-2′-iodo-α-oleandrosyl]-α-oleandroside (**18**) was formed in 25% yield, presumably via oxidative elimination of the phenylthio group to a glycal, followed by oleandrose addition to an iodonium species similar to Danishefsky's approach to disaccharide coupling. These results suggest the involvement of the axial acetamido group of **10** in the formation of a bridging intermediate[13a–d] leading to chemical and stereocontrol of the reaction pathway.

Deprotection of bisallyloxycarbonyl protected aminoavermectin **13** was achieved using a catalytic amount of $(Ph_3P)_4Pd(0)$ with formic acid in THF to give 4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 (**1b**) in 90% yield. This deprotection occurs in a stepwise sequence with a rapid removal of the 5-*O*-allyloxycarbonyl group (<2 h) followed by a slower removal of the *N*-allyloxycarbonyl-group (48 h). This material was then crystallized as the benzoic acid salt **1a**.

In summary, the synthesis of the agricultural lepidopteran pesticide, emamectin (**1a,** MK-244), via an anomerically specific glycosidation of avermectin B_1 monosaccharide (**12**) with phenyl 4″-*epi*-[*N*-allyloxycarbonylmethylamino]-4-deoxy-4-thiooleandroside (**10**) in 90% yield, was demonstrated.

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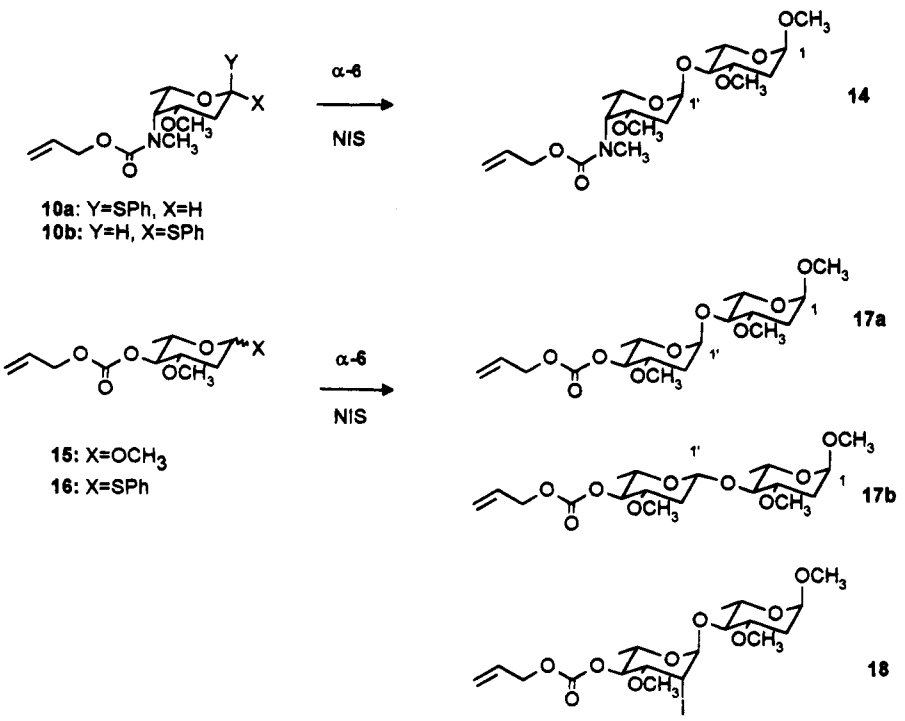
Experimental Section

General. HPLC analyses were performed using a Spectra-Physics SP8700 ternary solvent delivery system; a Vydac C18 protein/peptide column (5 mm particle size, 4.6 × 150 mm); solvent A:B, acetonitrile:water (with 0.1 vol % TFA); 3.0 mL/min at 25 °C with UV detection at 245 nm. TLC analyses were performed on Analtech Uniplate, silica gel GF, 5 × 20 cm, 250 μm. Samples of each product were isolated and purified by column chromatography (E. Merck silica gel 60, 230–400 mesh ASTM using ethyl acetate–hexanes or methanol–methylene chloride mixtures). All reactions were carried out under an atmosphere of N_2 and solvents and reagents were dried where appropriate over 3 Å molecular sieves prior to use. Other solvents and reagents were used as received. Karl Fisher water analyses were carried out on a Metrohm 684 KF coulometer. Infrared spectra were recorded on a Perkin-Elmer 1420 ratio recording infrared spectrophotometer. Melting points were determined using a DuPont 9900 DSC (2 °C/min, under N_2 in an open cup) and are reported as a range from the DSC extrapolated onset temperature to the peak temperature. Proton and carbon-13 spectra were recorded in $CDCl_3$ on a Bruker AM 250 or AM 300 spectrometer. The chemical shifts are reported in ppm relative to residual $CHCl_3$ for proton (δ = 7.27 ppm) and $CDCl_3$ for carbon (δ = 77.0 ppm). All coupling constants are reported in hertz and the following proton multiplicites are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, md = multiple doublet, om = overlapping multiplets, br = broad. Compounds **9a**, **9b**, **10a**, and **10b** are mixtures of rotamers. Only the proton and carbon-13 data for the major rotamer for each structure are reported. High resolution mass spectroscopy studies were performed in the FAB mode. Avermectin B_1 was used as the mixture of B_{1a} and B_{1b} homologues available as "abamectin".

Methyl Oleandroside (6). A solution of predominantly avermectin B_2 (**5,** 560 g, the primary constituent of the mother liquor of avermectin B_1 production) in methanol (7.5 L) with H_2SO_4 (40 g) was aged for 22 h at 50 °C. The mixture was cooled to 25 °C and $NaHCO_3$ (84 g), H_2O (8 L) and toluene (8 L) were added. The phases were separated and the organic phase was extracted with H_2O (10 × 2.5 L). The combined aqueous extracts were loaded onto a column packed with SP207 resin (10 L). The column was eluted with H_2O (20 L), which was discarded, followed by acetonitrile which was collected in 5 L fractions. Evaporation of the appropriate fractions, as detected by TLC (R_f: α-anomer = 0.31; β-anomer = 0.17; 40 vol % hexanes/EtOAc) *in vacuo* gave 184 g of **6** as an amber oil. ^1H NMR (300.13 MHz) α-anomer: δ 4.67 (dd, J = 3.6, 1.3, 1H), 3.54 (dq, J = 9.1, 6.3, 1H), 3.39 (ddd, J = 11.5, 9.1, 4.9, 1H), 3.29 (s, 3H), 3.22 (s, 3H), 3.04 (t, J = 9.1, 1H), 2.84 (br s, OH), 2.17 (ddd, J = 12.7, 4.6, 1.3, 1H), 1.39 (ddd, J = 12.7, 11.5, 3.6, 1H), 1.20 (d, J = 6.3, 3H); β-anomer: δ 4.32 (dd, J = 9.8, 2.0, 1H), 3.43(s, 3H), 3.34 (s, 3H), 3.30–3.05 (om, 2H), 3.05 (t, J = 8.7, 1H), 2.98 (br s, OH), 2.27 (ddd, J = 12.2, 4.4, 2.0, 1H), 1.35 (ddd, J = 12.2, 9.8, 1.5, 1H), 1.29 (d, J = 6.0, 3H). ^{13}C NMR (75.47 MHz) α-anomer: δ 98.2, 78.3, 75.7, 67.3, 56.2, 54.3, 33.8, 17.7; β-anomer: δ 100.5, 80.6, 75.3, 71.5, 56.3, 56.1, 35.0, 17.7. IR (CCl_4): λ_{max} 3600, 3450, 2990, 2940, 2900, 2840, 1450, 1380, 1290, 1210, 1130, 1110, 1080, 1060, 980, 910 cm^{-1}.

Methyl 4-Oxooleandroside (7). Methyl oleandroside (**6,** 7.10 g, 40.4 mmol) in CH_2Cl_2 (200 mL) was treated with 3 Å powered sieves (20 g) and pyridinium dichromate (16.7g, 44.3 mmol) at 2 °C followed by the addition of HOAc (4.0 mL). The mixture was warmed and aged for 2 h at 25 °C. The mixture was treated with Celite (20 g), aged 30 min, and filtered. The solution was evaporated to a dark oil. A solution of the oil in EtOAc (50 mL) was filtered through silica gel 60 (230–400 mesh, 50 g), and the eluent was evaporated to give 7.0 g of **7** as an oil. TLC (R_f: **7,** α-anomer = 0.40; β-anomer = 0.25; 40 vol % hexanes/EtOAc). ^1H NMR (300.13 MHz) α-anomer: δ 4.75 (br d, J = 3.5, 1H), 4.16 (q, J = 6.5, 1H), 4.07 (dd, J = 12.0, 6.6, 1H), 3.34(s, 3H), 3.31 (s, 3H), 2.40 (ddd, J = 12.5, 6.6, 1.5, 1H), 1.91 (ddd, J = 12.5, 12.0, 3.5, 1H), 1.14 (d, J = 6.5, 3H); β-anomer: δ 4.86 (dd, J = 8.6, 3.4, 1H), 4.04 (dq, J =

Scheme 4



6.8, 0.8, 1H), 3.94 (ddd, J = 12.6, 6.8, 0.8, 1H), 3.45 (s, 6H), 2.63 (ddd, J = 12.6, 6.8, 3.4, 1H), 1.94 (dt, J = 12.6, 8.6, 1H), 1.34 (d, J = 6.8, 3H). ^{13}C NMR (75.47 MHz) α-anomer: δ 205.4, 97.9, 78.1, 69.9, 58.2, 55.3, 39.3, 13.7; β-anomer: δ 206.0, 99.7, 78.4, 74.1, 58.1, 56.1, 38.2, 15.4. IR (CCl_4): λ_{max} 3450, 3000, 2950, 2920, 2840, 1740, 1445, 1355, 1205, 1125, 1055, 1000, 915 cm^{-1}.

Methyl 4-*epi*-(Methylamino)-4-deoxyoleandroside (8). Ketone **7** (55.2 g, 317 mmol) in THF (200 mL) was added to a solution of HOAc (50 mL), THF (400 mL), and CH_3NH_2/EtOH (28.6 wt %, 300 g solution) and aged for 3 h. After cooling to 10 °C, $NaBH_4$ (18.0 g, 475 mmol) was added over 15 min and the resulting mixture was aged for 1.5 h at 25 °C. The mixture was cooled to 5 °C, H_2O (600 mL) was added, and the mixture was acidified to pH = 3.5 with H_3PO_4. The mixture was adjusted to pH = 7.5 with 5 N aqueous NaOH, saturated with NaCl(s), and extracted with EtOAc (6 × 75 mL). The extracts were combined and evaporated *in vacuo* to give 6.3 g of **8** as an oil. TLC (R_f: **8**, α/β-anomer = 0.25; 10 vol % MeOH/EtOAc). ^{1}H NMR (300.13 MHz) **8a** α-anomer: δ 4.51 (d, J = 3.3, 1H), 3.60 (q, J = 6.6, 1H), 3.41 (m, 1H), 3.12 (s, 3H), 3.05 (s, 3H), 2.41 (d, J = 3.5, 1H), 2.32 (s, 3H), 1.61–1.44 (om, 2H) 1.04 (d, J = 6.7, 3H), 1.04 (d, J = 6.7, 3H); **8b** β-anomer: 4.04 (dd, J = 9.7, 2.2, 1H), 3.24–3.14 (om, 2H), 3.22 (s, 3H), 3.13 (s, 3H), 2.36–2.29 (om, 1H), 2.33 (s, 3H), 1.69 (ddd, J =12.2, 4.9, 2.4, 1H), 1.30 (m, 1H), 1.09 (d, J = 6.5, 3H). ^{13}C NMR (75.47 MHz) α-anomer: δ 98.0, 74.7, 66.0, 59.6, 54.9, 54.0, 38.0, 30.1, 17.6; β-anomer: 100.5, 78.1, 70.9, 58.6, 55.6, 55.2, 37.9, 31.9, 17.3. HRMS: $[MH]^+$ = 190.1434 (calcd = 190.1443). IR (CCl_4): λ_{max} 3360, 2980, 2940, 2900, 2830, 1630, 1440, 1355, 1300, 1210, 1100, 1050, 1020, 960, 920, 860 cm^{-1}.

Methyl 4-*epi*-[N-(Allyloxycarbonyl)methylamino]-4-deoxyoleandroside (9). Amine **8** (8.4 g, 44.4 mmol) in CH_2Cl_2 (30 mL) was mixed with 1 N aqueous NaOH (50 mL), and allyl chloroformate (7.04 g, 58.4 mmol) in CH_2Cl_2 (20 mL) was added over 30 min. After aging 30 min the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic phases were washed with saturated aqueous NaCl (25 mL). The organic phase was evaporated *in vacuo* to give 12.3 g of **9** as a light amber oil. TLC (R_f: **9**, α-anomer = 0.45; β-anomer = 0.37; 50 vol % hexanes/EtOAc). ^{1}H NMR (300.13 MHz) α-anomer: δ 5.87 (m, 1H), 5.25 (m, 1H), 5.14 (m, 1H), 4.81 (d, J = 3.7, 1H), 4.60–4.47 (om, 3H), 4.03 (dq, J = 6.6, 3.2, 1H), 3.71 (m, 1H), 3.31 (s, 3H), 3.27 (s, 3H), 3.09 (s, 3H), 2.03–1.78 (om, 2H), 1.16 (d, J = 6.6); β-anomer: δ 5.94 (m, 1H), 5.28 (m, 1H), 5.20 (m, 1H), 4.61 (m, 2H), 4.51 (dd, J = 10.2, 2.8, 1H), 4.38 (dd, J = 3.0, 6.2, 1H), 3.69 (qd, J = 6.5, 2.8, 1H), 3.60–3.48 (om, 1H), 3.50 (s, 3H), 3.37 (s, 3H), 3.15 (s, 3H), 2.12 (ddd, J = 12.9, 5.9, 2.5, 1H), 1.75 (m, 1H), 1.27 (d, J = 6.2, 3H). ^{13}C NMR (75.47 MHz) α-anomer: δ 157.5, 133.0, 116.5, 98.6, 72.8, 65.9, 65.0, 56.8, 54.6, 52.4, 33.1, 32.6, 16.8; β-anomer: δ 157.7, 133.1, 116.7, 101.7, 76.3, 71.0, 66.0, 57.2, 56.5, 51.9, 34.6, 33.5, 16.8. HRMS: $[MH]^+$ = 274.1637 (calcd = 274.1654). IR (CCl_4): λ_{max} 2990, 2940, 2905, 2820, 1695, 1450, 1410, 1360, 1325, 1210, 1180, 1150, 1110, 1055, 980, 910 cm^{-1}.

Phenyl 4-*epi*-[N-(allyloxycarbonyl)methylamino]-4-deoxy-1-thiooleandroside (10). A solution of **9** (12.3 g, 45.4 mmol) and thiophenol (5.00 g, 45.4 mmol) in toluene (60 mL) was cooled to 2 °C and BF_3·Et_2O (5.0 mL) was added. The mixture was warmed to 25 °C and aged 2 h. After cooling to 2 °C 5 wt % aqueous NaOH (100 mL) was added, the phases were separated, and the aqueous phase was extracted with toluene (30 mL). The combined organic phases were washed with saturated aqueous NaCl and evaporated *in vacuo* to give 15.1 g of **10** as an amber oil. A sample of the mixture was chromatographed to isolate the individual anomers (silica gel 60, 230–400 mesh; eluting with a 1:4 mixture of EtOAc:hex). TLC (R_f: **10**, α-anomer = 0.65; β-anomer = 0.50; 50 vol % hexanes/EtOAc). HPLC assay: isocratic, solvent A:B 45:55; t_R{min}: 5.54 (β-anomer); 6.64 (α-anomer). ^{1}H NMR (300.13 MHz) α-anomer: δ 7.45 (m, 2H), 7.28 (om, 3H), 5.95 (m, 1H), 5.71 (d, J = 5.8, 1H), 5.23 (m, 1H), 5.19 (m, 1H), 4.69–4.43 (om, 4H), 3.64 (m, 1H), 3.41 (s, 3H), 3.14 (s, 3H), 2.33 (m, 1H), 2.16 (dd, J = 13.3, 5.8, 1H), 1.18 (d, J = 5.8, 1H); β-anomer: δ 7.50 (m, 2H), 7.30 (om, 3H), 5.92 (m, 1H), 5.30 (m, 1H), 5.21 (m, 1H), 4.80 (dd, J = 11.4, 2.4, 1H), 4.62 (m, 2H), 4.53 (dd, J = 5.8, 2.9, 1H), 3.77 (qd, J = 6.1, 2.9, 1H), 3.57 (m, 1H), 3.38 (s, 3H), 3.02 (s, 3H), 2.22 (ddd, J = 12.6, 5.5, 2.4, 1H), 1.89 (m, 1H), 1.28 (d, J = 6.1, 3H). ^{13}C NMR (75.47 MHz) α-anomer: δ 158.0, 134.7, 133.0, 131.3, 128.8, 127.1, 116.6, 84.3, 73.8, 66.5, 66.0, 57.0, 52.7, 33.3, 33.2, 16.7; β-anomer: δ 157.5, 133.1, 132.4, 132.2, 128.8, 127.8, 127.7, 116.7, 82.3, 77.1, 75.1, 66.1, 57.1, 51.7, 34.3, 33.3, 17.3. HRMS α-anomer: $[MH]^+$ = 352.1573 (calcd = 352.1582) ; β-anomer: $[MH]^+$ = 352.1602 (calcd = 352.1582). IR (CCl_4): λ_{max} 2990, 2940, 1695, 1480, 1440, 1325, 1240, 1180, 1150, 1120, 1070, 990 cm^{-1}.

5-*O*-(Allyloxycarbonyl)avermectin B_1 (11). Allyl chloroformate (5.5 mL, 51.6 mmol) in MTBE (15 mL) was added dropwise over 20 min to a solution of avermectin B_1 (**5**, 39.1

g, 44.9 mmol) and TMEDA (5.2 g, 44.9 mmol) in MTBE (200 mL) at −15 °C to give a white precipitate. The reaction mixture was aged for 1.5 h at −10 to −15 °C and then poured into 2% aqueous H_3PO_4 (125 mL). The organic phase was separated and evaporated *in vacuo* to give 52.4 g of **11** as solid. HPLC assay: gradient, solvent A:B 65:35 to 75:25 over 15 min; t_R{min}: **11,** 6.1(B_{1b}); 7.8 (B_{1a}); 80.0 wt %. ^{1}H NMR (400.17 MHz): δ 5.94 (m, 1H), 5.85 (m, 1H), 5.78−5.71 (om, 3H), 5.57 (br s, 1H), 5.55 (dd, *J* = 10.0, 2.7, 1H), 5.42−5.34 (om, 4H), 5.27 (m, 1H), 4.99 (m, 1H), 4.77 (d, *J* = 3.0, 1H), 4.70−4.66 (om, 3H), 4.61 (dd, *J* = 14.3, 2.1, 1H), 4.12 (d, *J* = 6.0, 1H), 3.99 (s, OH), 3.93 (br s, 1H), 3.88−3.80 (om, 2H), 3.77 (dq, *J* = 9.4, 6.3, 1H), 3.62 (m, 1H), 3.51−3.45 (om, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 3.37 (q, *J* = 2.3, 1H), 3.24 (t, *J* = 9.0, 1H), 3.16 (br t, *J* = 9.2, 1H), 2.58 (d, *J* = 1.5, OH), 2.52 (m, 1H), 2.35−2.20 (om, 5H), 2.02 (dd, *J* = 7.4, 1.4, 1H), 1.81 (br s, 3H), 1.81−1.76 (om, 1H), 1.62−1.45 (om, 6H), 1.49 (s, 3H), 1.27 (d, *J* = 6.3, 3H), 1.25 (d, *J* = 6.3, 3H), 1.16 (d, *J* = 6.9, 3H), 0.96−0.87 (om, 10H). ^{13}C NMR (100.61 MHz): δ 173.5, 154.9, 139.3, 138.1, 136.3, 135.2, 133.1, 131.5, 127.8, 124.8, 121.6, 120.4, 118.7, 118.3, 98.5, 95.8, 94.9, 81.9, 80.9, 80.4, 79.4, 78.2, 77.6., 76.1, 74.9, 73.6, 68.8, 68.6, 68.5, 68.4, 68.1, 67.3, 56.5, 56.4, 45.8, 40.5, 39.8, 36.6, 35.2, 34.5, 34.2_6, 34.2_3, 30.6, 27.5, 20.2, 19.7, 18.4, 17.7, 16.4, 15.1, 13.0, 12.1. IR (CCl_4): λ_{max}3500, 3480, 1745, 1715, 1460, 1370, 1290, 1260, 1160, 1100, 1065, 990 cm^{-1}. HRMS: [M + Li]$^+$ = 963.5302 (calcd = 963.5292).

5-*O*-(Allyloxycarbonyl)avermectin B_1 Monosaccharide (12). 5-*O*-(allyloxycarbonyl)avermectin B_1(**11**, 26.9 g, 28.1 mmol) in 1 vol % H_2SO_4/IPA (530 mL) was aged for 40 h at 15 °C. The mixture was quenched with saturated aqueous $NaHCO_3$ (250 mL) and extracted with CH_2Cl_2 (3 × 250 mL). The organic phases were combined and evaporated *in vacuo* to an oil and dissolved in toluene (300 mL). This solution was washed with H_2O (20 x 150 mL) and then concentrated to 28.3 g of **12** as a solid. HPLC assay: isocratic, solvent A:B 70:30; t_R{min}: **12,** 4.43 (B_{1b}); 5.02 (B_{1a}); 70 wt % pure. ^{1}H NMR (400.17 MHz): δ 5.93 (m, 1H), 5.85 (m, 1H), 5.77−5.70 (om, 3H), 5.57 (br s,1H), 5.55 (dd, *J* = 10.0, 2.6, 1H), 5.42−5.35 (om, 3H), 5.26 (m, 1H), 4.98 (br dd, *J* = 10.0, 5.1, 1H), 4.81 (d, *J* = 3.3, 1H), 4.69−4.58 (om, 4H), 4.11 (d, *J* = 6.3, 1H), 3.97 (s, OH), 3.95 (br s, 1H), 3.89−3.83 (om, 2H), 3.55 (m, 1H), 3.48−3.44 (om, 1H), 3.48 (s, 3H), 3.37 (dd, *J* = 4.6, 2.3, 1H), 3.16 (t, *J* = 9.0, 1H), 2.61 (d, *J* = 1.3, OH), 2.52 (m, 1H), 2.31−2.22 (om, 4H), 2.02 (dd, *J* = 7.4, 1.4, 1H), 1.81 (br s, 3H), 1.77−1.76 (om, 1H), 1.62−1.45 (om, 5H), 1.49 (s, 3H), 1.26 (d, *J* = 6.1, 3H), 1.15 (d, *J* = 6.9, 3H), 0.96−0.87 (om, 10H). ^{13}C NMR (100.6 MHz): δ 173.2, 154.7, 139.1, 138.0, 136.1, 135.0, 132.9, 131.4, 127.6, 124.6, 121.5, 120.4, 118.6, 118.1, 95.6, 95.0, 81.7, 80.8, 78.2, 77.4, 76.0, 74.7, 73.4, 68.6, 68.6_3, 68.3_8, 68.2_5, 68.0_2, 56.5, 45.6, 40.4, 39.6, 36.4, 35.0, 34.1, 33.8, 30.4, 27.4, 20.1, 19.5, 17.6, 16.3, 15.0, 12.9, 12.0. IR (CCl_4): λ_{max} 3600, 3480, 2965, 2940, 1740, 1710, 1450, 1370, 1360, 1330, 1300, 1255, 1160, 1100, 1080, 1040, 990 cm^{-1}. HRMS: [M + Li]$^+$ = 819.4525 (calcd = 819.4506).

***N*,5-*O*-Bis(allyloxycarbonyl)-4″-*epi*-(methylamino)-4″-deoxyavermectin B_1 (13).** A solution of monosaccharide **12** (11.8 g, 14.5 mmol), phenyl 4-*epi*-[*N*-(allyloxycarbonyl)methylamino]-4-deoxy-1-thiooleandroside (**10**, 28.7 g, 81.7 mmol) and 2,6-di-*tert*-butylpyridine in *N*-methylpyrrolidinone (75 mL) at 25 °C was treated portionwise with *N*-iodosuccinimide (17.2 g, 76.4 mmol) over 45 min. After a 15 min age, EtOAc (350 mL) and H_2O (100 mL) were added and the mixture was treated with Na_2SO_3 (30 g) and Na_2CO_3 (30 g). The phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic phases were washed with H_2O (3 × 50 mL) and evaporated *in vacuo* to give 66.2 g of **13** as a dark amber oil. Purification by column chromatography gave 16.3 g of **13** as a solid. HPLC assay: isocratic, solvent A:B 77:23; t_R (min) **13**, B_{1b} = 7.7, B_{1a} = 10.7; 88 wt % pure). ^{1}H NMR (400.17 MHz): δ 6.0−5.8 (om, 2H), 5.85 (m, 1H), 5.76 (dd, *J* = 9.9, 1.6, 1H), 5.78−5.71 (om, 2H), 5.57 (br s, 1H), 5.55 (dd, *J* = 10.0, 2.5, 1H), 5.48 (d, *J* = 4.1, 1H), 5.43−5.18 (om, 5H), 5.00 (br dd, *J* = 9.9, 4.0, 1H), 4.77 (d, *J* = 3.4, 1H), 4.71−4.56 (om, 7H), 4.20 (m, 1H), 4.12 (d, *J* = 6.1, 1H), 3.98 (s, OH), 3.93 (br s, 1H), 3.88−3.71 (om, 3H), 3.62 (m, 1H), 3.49 (dd, *J* = 9.8, 1.0, 1H), 3.44 (s, 3H), 3.41(s, 3H), 3.40−3.35 (om, 2H), 3.22 (t, *J* = 9.0, 1H), 3.14 (s, 3H), 2.53 (m, 1H), 2.32−2.21 (om, 4H), 2.11−1.93 (om, 2H), 1.81 (s, 3H), 1.81−1.77 (om, 1H), 1.67−1.46 (om, 6H), 1.49 (s, 3H), 1.24 (d, *J* = 6.2, 3H), 1.20 (d, *J* = 6.6, 3H), 1.16 (d, *J* = 6.9, 3H), 0.96−0.90 (om, 9H), 0.88 (m, 1H). ^{13}C NMR (100.6 MHz): δ 173.5, 157.7, 154.8, 139.3, 138.0, 136.3, 135.2, 133.2, 133.1, 131.5, 127.8, 124.8, 121.6, 120.4, 118.7, 118.3, 116.7, 99.0, 95.8, 95.0, 82.0, 80.9_1, 80.8_8, 79.4, 77.5, 74.9, 73.6, 73.1, 68.8, 68.5_4, 68.5_0, 68.4, 67.2, 66.1, 65.8, 57.0, 56.6, 52.7, 45.8, 40.5, 39.8, 36.6, 35.2, 34.6, 34.3, 33.3, 33.0, 30.6, 27.5, 20.2, 19.7, 18.3, 16.9, 16.4, 15.1, 13.0, 12.1. IR (CCl_4): λ_{max} 3470, 2980, 2940, 1745, 1700, 1455, 1380, 1320, 1310, 1255, 1195, 1160, 1110, 1055, 995, 940 cm^{-1}. HRMS: [M + Li]$^+$ = 1060.5820 (calcd = 1060.5820).

4′-*epi*-(Methylamino)-4″-deoxyavermectin B_1 Benzoate, MK-244 (1a). A solution of protected aminoavermectin **13** (14.4 g, 13.6 mmol), triphenylphosphine (1.57 g, 6.0 mmol), and formic acid (98%, 2.9 mL, 77.0 mmol) in THF (100 mL) at 25 °C was treated with $(Ph_3P)_4Pd(0)$ (0.78 g, 0.7 mmol) and aged 48 h. The mixture was evaporated to half-volume *in vacuo* and partitioned between EtOAc (250 mL) and H_2O containing Na_2SO_3 (10 g) and Na_2CO_3 (10 g). The aqueous layer was further extracted with EtOAc (3 × 100 mL). The combined organic phases were evaporated *in vacuo* to give 15.6 g of **1b** as a solid. HPLC assay: gradient, solvent A:B 40:60 to 45:55 over 15 min; t_R{min}: **1b**, B_{1b} = 10.5, B_{1a} = 14.1; 70 wt % pure. The solid was dissolved into MTBE (45 mL), and benzoic acid (1.5 g, 12.3 mmol) was added. After a 1 h age, hexanes (15 mL) were added and the crystalline slurry was cooled to 2 °C. The mixture was aged 1 h, filtered, washed, and dried *in vacuo* to give 7.9 g of crystalline **1a**, MK-244 (95 wt % pure), mp = (DSC at 10 °C/min) = 137−144 °C. ^{1}H NMR (400.13 MHz): δ 8.10 (m, 2H), 7.53 (m, 1H), 7.43 (m, 2H), 5.87 (m, 1H), 5.75−5.72 (om, 2H), 5.55 (dd, *J* = 9.8, 2.6, 1H), 5.43 (om, 3H), 5.22 (v br, 1H), 5.00 (m, 1H), 4.76 (br d, *J* = 3.0, 1H), 4.69 (m, 2H), 4.30 (br d, *J* = 6.1, 1H), 4.03 (br q, *J* = 6.7, 1H), 3.98 (d, *J* = 6.2, 1H), 3.94 (br s, 1H), 3.88 (m, 2H), 3.82 (dq, *J* = 9.1, 6.2, 1H), 3.74 (ddd, *J* = 11.5, 5.0, 3.8, 1H), 3.58 (m, 1H), 3.48 (dd, *J* = 9.9, 1.3, 1H), 3.42 (s, 3H), 3.40 (s, 3H), 3.30 (q, *J* = 2.2, 1H), 3.23 (dd, *J* = 9.1, 8.7, 1H), 2.87 (br d, *J* = 3.8, 1H), 2.67 (s, 3H), 2.52 (m, 1H), 2.31−2.25 (om, 3H), 2.21 (dd, *J* = 12.7, 5.0, 1H), 2.05−1.90 (om, 2H), 1.87 (br s, 3H), 1.78 (m, 1H), 1.63−1.46 (om, 6H), 1.49 (br s, 3H), 1.34 (d, *J* = 6.7, 3H), 1.23 (d, *J* = 6.2, 3H), 1.16 (d, *J* = 7.0, 3H), 1.11 (d, *J* = 7.1, B_{1b} isomer), 0.96−0.91 (om, 9H), 0.89 (m, 1H). ^{13}C NMR (100.61 MHz): δ 173.7, 170.9, 139.6, 138.0, 137.9, 136.3, 135.7, 132.2, 132.1, 129.9 (2C), 128.1 (2C), 127.79, 124.7, 120.4, 118.3, 118.0, 98.5, 95.7, 95.0, 81.9, 80.8, 80.4, 79.2, 79.1, 74.9, 74.8, 68.42, 68.36, 68.33, 67.7, 67.2, 66.6, 59.9, 56.6, 55.6, 45.7, 40.5, 39.7, 37.1, 36.6, 35.1, 34.5, 34.2, 30.9, 30.6, 27.5, 20.1, 19.9, 18.2, 17.9, 16.4, 15.1, 12.9, 12.0. IR (CCl_4): λ_{max} 3595, 3460, 2995, 2940, 1715, 1455, 1380, 1160, 1120, 990 cm^{-1}. HRMS: [MH]$^+$ = 886.5316 (calcd = 886.5316) for free amine. Anal. Calcd for $C_{56}H_{81}NO_{15}$: C, 66.71; H, 8.10; N, 1.39. Found: C, 66.96; H, 7.82; N, 1.45.

Methyl 4-*O*-[4′-*epi*-[*N*-(Allyloxycarbonyl)methylamino]-α-oleandrosyl]-α-oleandroside (14). A solution of phenyl thiooleandroside **10a** (470 mg, 1.5 mmol), α-methyl oleandroside (α-**6**, 176 mg, 1.00 mmol), 2,6-di-*tert*-butyl pyridine (0.5 mL) in *N*-methylpyrrolidinone (6 mL) at 24 °C was treated with a solution of *N*-iodosuccinimide (350 mg, 1.5 mmol) in NMP (2 mL) dropwise over 30 min. The reddish colored solution was aged 30 min and then quenched into 5 wt % aqueous Na_2SO_3 (30 mL). The mixture was extracted with ethyl acetate (2 × 30 mL) evaporated to an oil (650 mg) and purified by column chromatography to give 238 mg of **14** as a solid foam. TLC (R_f: **14** = 0.35; 50 vol % EtOAc/hexanes). ^{1}H NMR (400.13 MHz): δ 5.99−5.88 (m, 1H), 3.46 (br d, *J* = 4.5, 1H), 5.30 (m, *J* = 28.4, 1H), 5.18 (m, *J* = 10.5, 1H), 4.72 (br d, *J* = 3.6, 1H), 4.60 (m, *J* = 5.4, 2H), 4.56 (dd, *J* = 5.6, 3.1, 1H), 4.20 (dq, *J* = 6.6, 3.1, 1H), 3.74 (ddd, *J* = 9.9, 6.2, 5.6, 1H), 3.64 (dq, *J* = 6.3, 3.9, 1H), 3.58 (ddd, *J* = 11.5, 8.7, 5.0, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.30 (s, 3H), 3.21 (t, *J* = 9.0, 1H), 3.13 (s, 3H), 2.23 (ddd, *J* = 13.0, 5.0, 1.2, 1H), 2.03 (dd, *J* = 13.5, 6.2, 1H), 1.94 (ddd, *J* = 13.5, 9.9, 4.5, 1H), 1.51 (ddd, *J* = 13.0, 11.5, 3.5, 1H), 1.27 (d, *J* = 6.3, 3H), 1.19 (d, *J* = 6.3,

3H). ^{13}C NMR (100.61 MHz): δ 157.7, 133.2, 116.7, 99.0, 98.2, 81.1, 79.3, 73.2, 66.3, 66.0, 65.8, 57.0, 56.5, 54.6, 52.6, 34.5, 33.3, 33.1, 18.4, 16.9. IR (CCl_4): λ_{max} 3460, 3080, 2995, 2940, 2900, 1695, 1645, 1440, 1410, 1380, 1315, 1120, 1070, 990, 925 cm^{-1}. HRMS: $[M + Li]^+$ = 418.2464 (calcd = 418.2440).

Methyl 4-*O*-(Allyloxycarbonyl)oleandroside (15). A solution of methyl oleandroside (**6**, 2.4 g, 13.6 mmol) in MTBE (25 mL) at 5 °C was treated with TMEDA (1.2 mL) and allyl chloroformate (3.0 g, 16.7 mmol). After a 1 h age, the mixture was warmed to 25 °C and then quenched into H_2O (10 mL). The organic phase was washed with H_2O (3 × 10 mL) and then evaporated to give 3.08 g of **15** as an oil. TLC (R_f: **15**, α/β-anomer = 0.35; 25 vol % EtOAc/hexanes). ^1H NMR (250.13 MHz): (mixture of α and β anomers): α-anomer, δ 5.93 (m, 1H), 5.35 (m, 1H), 5.25 (m, 1H), 4.75 (br d, J = 3.7, 1H), 4.64 (m, 2H), 4.44 (t, J = 9.5, 1H), 3.75 (dq, J = 9.8, 6.3, 1H), 3.63 (ddd, J = 11.5, 9.5, 5.2, 1H), 3.33 (s, 3H), 3.31 (s, 3H), 2.26 (ddd, J = 13.2, 5.2, 1.2, 1H), 1.61 (ddd, J = 13.2, 11.5, 3.7, 1H), 1.21 (d, J = 6.3, 3H); β-anomer, δ 5.93 (m, 1H), 5.35 (m, 1H), 5.25 (m, 1H), 4.64 (om, 3H), 4.37 (dd, J = 9.8, 2.0, 1H), 3.50–3.30 (om, 2H), 3.47 (s, 3H), 3.33 (s, 3H), 2.34 (ddd, J = 12.6, 5.1, 2.0, 1H), 1.68–1.50 (om, 1H), 1.27 (d, J = 6.1, 3H). ^{13}C NMR (62.89 MHz): (mixture of α and β anomers) α-anomer, δ 154.7, 131.5, 118.8, 98.1, 80.5, 75.6, 68.5, 65.4, 57.0, 54.6, 34.7, 17.3_8; β-anomer, 154.7, 131.4, 118.7, 100.5, 79.8, 77.8, 69.7, 68.6, 56.6, 56.5, 35.7, 17.4_4. IR (CCl_4): λ_{max} 3060, 2950, 2900, 2800, 1735, 1440, 1350, 1250, 1220, 1120, 1050, 920 cm^{-1}. HRMS: $[MH]^+$ = 261.1321 (calcd = 261.1338).

Phenyl 4-*O*-(Allyloxycarbonyl)-1-thiooleandroside (16). A solution of oleandrose **15** (2.66 g, 10.0 mmol) in toluene (25 mL) at 2 °C was treated with thiophenol (1.07 g, 9.9 mmol) and $BF_3{\cdot}Et_2O$ (1.0 mL). The mixture was warmed to 22 °C, aged for 2 h, cooled to 5 °C and quenched with 5% aqueous NaOH (30 mL) to pH = 7.5. The organic phase was washed with saturated aqueous NaCl (10 mL) and evaporated to an oil (2.89 g). The material was purified by column chromatography (eluent: 15 vol % EtOAc/hexanes) to give 2.26 g of the anomeric mixture **16** as a clear colorless oil. TLC (R_f: **16**, α/β-anomer = 0.45; 25 vol % EtOAc/hexanes). ^1H NMR (250.13 MHz): (mixture of α and β anomers): α-anomer, δ 7.52–7.21 (om, 5H), 6.04–5.86 (om, 1H), 5.62 (brd, J = 5.2, 1H), 5.38 (om, 1H), 5.20 (om, 1H), 4.71–4.63 (om, 2H), 4.51 (ot, 1H), 4.32 (dq, J = 9.7, 6.1, 1H), 3.68 (ddd, J = 11.6, 9.0, 5.0, 1H), 3.40 (s, 3H), 2.55–2.44 (om, 1H), 2.05 (ddd, J = 13.5, 11.6, 5.8, 1H), 1.24 (d, J = 6.1, 3H); β-anomer, δ 7.52–7.21 (om, 5H), 6.04–5.86 (om, 1H), 5.38 (om, 1H), 5.28 (om, 1H), 4.76 (dd, J = 11.9, 1.9, 1H), 4.71–4.63 (om, 2H), 4.47 (ot, 1H), 3.48 (dq, J = 9.7, 6.1, 1H), 3.44–3.36 (om, 1H), 3.36 (s, 3H), 2.55–2.44 (om, 1H), 1.74 (q, J = 11.9, 1H), 1.31 (d, J = 6.1, 3H). ^{13}C NMR (62.89 MHz): δ (mixture of α and β anomers): α-anomer, δ 154.6, 134.7, 131.0, 128.9, 127.1, 118.8, 83.4, 80.4, 76.2, 68.59, 66.6, 57.1, 35.5, 17.3. β-anomer, δ 154.6, 131.7, 131.6, 128.8, 127.5, 118.9, 81.8, 79.4, 79.1, 74.0, 68.6_3, 56.8, 36.0, 17.8. IR (CCl_4): λ_{max} 3040, 2960, 2900, 2860, 2800, 1730, 1570, 1450, 1420, 1350, 1240, 1080, 1060, 970 cm^{-1}. HRMS: $[M]^+$ = 338.1187 (calcd = 338.1187).

Methyl 4-[4′-*O*-(Allyloxycarbonyl)-α-oleandrosyl]-α-oleandroside (17a,b). A solution of phenyl thiooleandroside **16** (338 mg, 1.00 mmol), methyl-α-oleandroside (α-**6**, 176 mg, 1.00 mmol), 2,6-di-*tert*-butylpyridine (0.5 mL) in *N*-methylpyrrolidinone (6 mL) at 24 °C was treated with a solution of *N*-iodosuccinimide (350 mg, 1.5 mmol) in NMP (2 mL) dropwise over 30 min. The reddish colored solution was aged 30 min and then quenched into 5% aqueous Na_2SO_3 (30 mL). The mixture was extracted with ethyl acetate (2 × 30 mL) and evaporated to an oil (300 mg). Column chromatography (eluent: 25 vol % EtOAc/hexanes) gave 97 mg of **17a** and 47 mg of **17b** and 40 mg **18** as oils. TLC (R_f: **18** = 0.45; **17b** = 0.30; **17a** = 0.25; 35 vol % EtOAc/hexanes).

17a. ^1H NMR (400.13 MHz): δ 5.94 (m, 1H), 5.40–533 (om, 2H), 5.27 (m, 1H), 4.73 (br d, J = 3.6, 1H), 4.66 (m, 2H), 4.45 (t, J = 9.5, 1H), 3.89 (dq, J = 9.9, 6.3, 1H), 3.66–3.54 (om, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 3.31 (s, 3H), 3.21 (t, J = 9.1, 1H), 2.27 (om, 2H), 1.63 (ddd, J = 13.1, 11.5, 4.0, 1H), 1.51 (ddd, J = 12.7, 11.1, 3.6, 1H), 1.26 (d, J = 6.3, 3H), 1.20 (d, J = 6.3, 3H). ^{13}C NMR (100.61 MHz): δ 154.7, 131.5, 118.9, 118.8, 98.2_1, 98.2_0, 80.7, 79.3, 75.6, 68.6, 66.3, 66.2, 57.0, 56.3, 54.6, 35.1, 34.5, 18.5, 17.3. IR (CCl_4): λ_{max} 2950, 2900, 2880, 2800, 1730, 1430, 1360, 1340, 1230, 1110, 1085, 1040, 970, 890 cm^{-1}. HRMS: $[M + Li]^+$ = 411.2205 (calcd = 411.2206). Anal. Calcd for $C_{19}H_{32}O_9$: C, 56.4; H, 7.97. Found: C, 56.2; H, 8.26.

17b. ^1H NMR (400.13 MHz): δ 5.93 (m, 1H), 5.35 (m, 1H), 5.26 (m, 1H), 4.71 (br d, J = 2.1, 1H), 4.69 (dd, J = 9.9, 2.0, 1H), 4.65 (m, 2H), 4.44 (t, J = 9.4, 1H), 3.70–3.59 (om, 2H), 3.45–3.35 (om, 2H), 3.40 (s, 3H), 3.35 (s, 3H), 3.29 (s, 3H), 3.17 (t, J = 8.9, 1H), 2.34 (ddd, J = 12.5, 5.2, 2.0, 1H), 2.21 (ddd, J = 13.1, 5.2, 1.6, 1H), 1.61–1.51 (om, 2H), 1.27 (d, J = 6.1, 3H), 1.26 (d, J = 6.1, 3H). ^{13}C NMR (100.61 MHz): δ 154.6, 131.5, 118.9, 100.2, 98.1, 83.6, 79.9, 77.9, 76.9, 69.9, 68.7, 66.4, 57.2, 56.8, 54.5, 36.3, 34.8, 18.3, 17.6. IR (CCl_4): λ_{max} 2960, 2900, 2880, 2800, 1735, 1440, 1365, 1345, 1235, 1090, 1050, 970,960, 890 cm^{-1}. HRMS: $[M + Li]^+$ = 411.2177 (calcd = 411.2206). Anal. Calcd for $C_{19}H_{32}O_9$: C, 56.4; H, 7.97. Found: C, 56.1; H, 7.83.

18. ^1H NMR (400.13 MHz): δ 5.94 (m, 1H), 5.58 (d, J = 1.5, 1H), 5.37 (m, 1H), 5.28 (m, 1H), 4.81 (t, J = 9.4, 1H), 4.74 (br d, J = 3.6, 1H), 4.66 (m, 2H), 4.55 (dd., J = 4.0, 1.5, 1H), 4.00 (dq, J = 9.4, 6.3, 1H), 3.72–3.53 (om, 2H), 3.36 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H), 3.19 (t, J = 9.1, 1H), 2.95 (dd, J = 9.4, 4.0, 1H), 2.27 (ddd, J = 13.0, 5.1, 1.3, 1H), 1.51 (ddd, J = 13.0, 11.5, 3.6, 1H), 1.26 (d, J = 6.3, 3H), 1.25 (d, J = 6.3, 3H). ^{13}C NMR (100.61 MHz): δ 154.5, 131.4, 119.0, 103.0, 98.2, 82.5, 78.7, 78.6, 76.0, 68.8, 67.4, 66.1, 56.5, 56.2, 54.7, 34.3, 32.0, 18.3, 17.4. IR (CCl_4): λ_{max} 2960, 2900, 2880, 2800, 1740, 1430, 1370, 1350, 1250, 1110, 1085, 1040, 970, 890 cm^{-1}. HRMS: $[M + Li]^+$ = 537.1197 (calcd = 537.1173). Anal. Calcd for $C_{19}H_{31}O_9I$: C, 43.03; H, 5.89; I, 23.9. Found C, 43.5; H, 6.00; I, 23.8 (uncorrected for solvent residues).

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Supplementary Material Available: ^1H NMR spectra for compounds **1a**, **7a**, **7b**, **8a**, **8a,b**, **9a**, **9b**, **10a**, **10b**, **11–16**, **17a**, **17b**, and **18** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.