Bioorganic & Medicinal Chemistry 21 (2013) 6554–6564

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and anti-tumor activity of carbohydrate analogues of the tetrahydrofuran containing acetogenins

Stewart Bachan [a], K. A. Tony [a], Akira Kawamura [a], Diego Montenegro [a], Anjali Joshi [b], Himanshu Garg [b], David R. Mootoo [a,*]

[a] Department of Chemistry, Hunter College, 695 Park Avenue, New York, NY 10065, USA
[b] Center of Excellence for Infectious Disease, Department of Biomedical Sciences, Texas Tech University Health Sciences Center, El Paso, TX 79905, USA

ARTICLE INFO

Article history:
Received 8 June 2013
Revised 6 August 2013
Accepted 15 August 2013
Available online 29 August 2013

Keywords:
Carbohydrate
Lipid
Metathesis
Mimetic
Dynamic light scattering

ABSTRACT

The tetrahydrofuran (THF) containing annonaceous acetogenins (AAs) are attractive candidates for drug development because of their potent cytotoxicity against a wide range of tumors and their relatively simple and robust structures. Replacement of the THF segment with a sugar residue may deliver analogues with improved tumor selectivity and pharmacokinetics and are therefore attractive for drug development. As a first test to the feasibility of such structures, a set of such monosaccharide analogues was synthesized and assayed against four human tumor cell lines, cervical (HeLa), breast (MDA-MB231), T-cell leukemia (Jurkat) and prostate (PC-3). Certain analogues showed low micromolar activity that was comparable to a structurally similar, naturally occurring mono-THF acetogenin. A preliminary examination of the structure–activity profile of these carbohydrate analogues suggests that they have a similar mechanism of action as their THF congeners.

1. Introduction

The tetrahydrofuran (THF)-containing annonaceous acetogenins (AAs) are noted for their potent cytotoxicity against a variety of tumor cell lines.[1–3] There is considerable interest in their development as clinical agents.[4,5] Their cytotoxic activity is believed to be connected to their interaction with the reduced nicotinamide adenine dinucleotide (NADH): ubiquinone oxidoreductase (complex I), a membrane-bound protein of the mitochondrial electron-transport system.[6] Several reviews on structure activity relationships (SARs) for the THF-containing AAs have been published.[7–10] The AAs generally contain one or more tetrahydrofuran (THF) rings, although a small number contain a tetrahydropyran (THP), and are classified into two major structural subgroups depending on the number and arrangement of the THFs: the mono-THF and the adjacently linked bis-THF acetogenins (Fig. 1). A relatively small number of structures with non-adjacently connected bis-THF or THF–THP motifs comprise a third subgroup. The central ether segment is generally flanked at each terminus by a carbinol center, giving rise to a central polar core. One of the carbinol carbons is connected to a methylated γ-lactone ring by a polymethylene spacer, which may contain one or more hydroxyl groups, and the other carbinol center is linked to a long hydrophobic chain. SAR studies suggest that the butenolide moiety

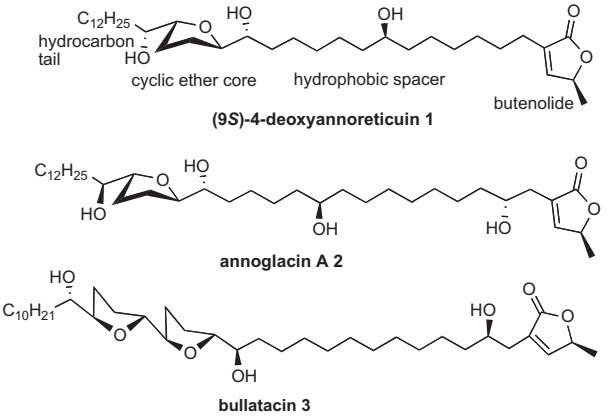


Figure 1. Representative mono- and bis-THF acetogenins.

contributes significantly to anti-tumor activity as analogues in which the alkene is reduced are generally much less active. The cyclic ether core is also important for activity but the high potency observed for frameworks with a diverse arrangement and numbers of the THF rings, suggests that a broad range of core structures that meet a critical volume and polarity requirement may be tolerated. The length and degree of hydroxylation of the hydrocarbon chains are also important, with too long or short chains and a high degree

* Corresponding author. Tel.: +1 212 772 4356; fax: +1 212 772 5332.
E-mail address: dmootoo@hunter.cuny.edu (D.R. Mootoo).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.08.027

of hydroxylation leading to reduced activity. These SARs are consistent with a cytotoxicity model in which the cyclic ether core sits at the membrane–water interface in the mitochondria and the lipid chains stabilizes a conformation that presents the butenolide to a binding domain on complex I. Interestingly, the structural requirements for activity against complex I appears to be less stringent than the SARs for anti-tumor activity, suggesting that anti-tumor activity may be linked to other mechanisms of action.[11,12] Although individual THF containing AAs show very high selectivity against certain tumors cell lines, their potent activity against mitochondrial ATP production suggests that in general they may be too cytotoxic for clinical application.

Against this backdrop we are interested in analogues of the THF acetogenins in which the cyclic ether core is replaced with a carbohydrate residue. Given the wide variations of the cyclic ether core among highly potent analogues, we speculated that a carbohydrate could be used as a mimic of the cyclic ether core. The structures so generated are to be distinguished from the glycosylated AAs examined by Hocquemiller and co-workers, in which alcohols on natural acetogenins are glycosylated.[13] In the analogues in the present study, the carbohydrate motif is imprinted in the acetogenin framework and may be less likely to interfere with binding to the cellular target. Like the Hocquemiller molecules, their carbohydrate-likeness has important implications for drug design. First, the carbohydrate motif may allow for targeting of tumors that overexpress cell surface lectins or carbohydrate transporters.[14,15] Second, the hydrophilicity of the carbohydrate may help overcome potential problems with low water solubility and non-specific cellular uptake. Third, the easy access to diverse carbohydrates allows for a wide variety of analogues for drug optimization studies. Herein we describe the synthesis and evaluation of the anti-tumor activity of a preliminary set of these new carbohydrate-like AAs.

2. Results and discussion

2.1. Analog design

An α-mannopyranose sugar scaffold was selected because of the relatively simple synthetic chemistry required for the modification of this template (Fig. 2). To mimic the frameworks of the natural AAs, the hydrocarbon chains were appended as an *O*-glycoside at C1 and as a 6-*C*-extended sugar. Structures **4**–**7** in which one or more hydroxyl groups were removed from the sugar ring were prepared, to evaluate whether increasing the density of hydroxyl groups leads to reduced activity, as observed in the naturally occurring THF AAs. The β-galactose **8** derived analog was also of interest to probe how the relative positioning of the two hydrocarbon branches on the sugar scaffold might impact on activity. Finally, to interrogate whether the anti-tumor activity of the new analogues was due to a similar mechanism of action as the natural AAs, structures **9**–**11**, with a reduced butenolide and without the butenolide or the hydrocarbon tail, were prepared.

2.2. Synthesis

A modular plan in which a fixed butenolide alkene **17** and different carbohydrate alkene partners **18**–**23** were connected through an olefin cross metathesis (CM) was conceived. The carbohydrate alkenes were prepared via established carbohydrate transformations from known precursors **12**–**16** (Table 1).

The fully oxygenated mannose-derived alkenes **18** and **23** were prepared from penta-*O*-acetylated mannose **12** (Scheme 1). Thus, treatment of **12** with 9-decenol and $BF_3{\cdot}OEt_2$ gave the 9-decenyl-α-glycoside, which was subjected to standard procedures for acetate hydrolysis and *O*-isopropylidene formation, to give the

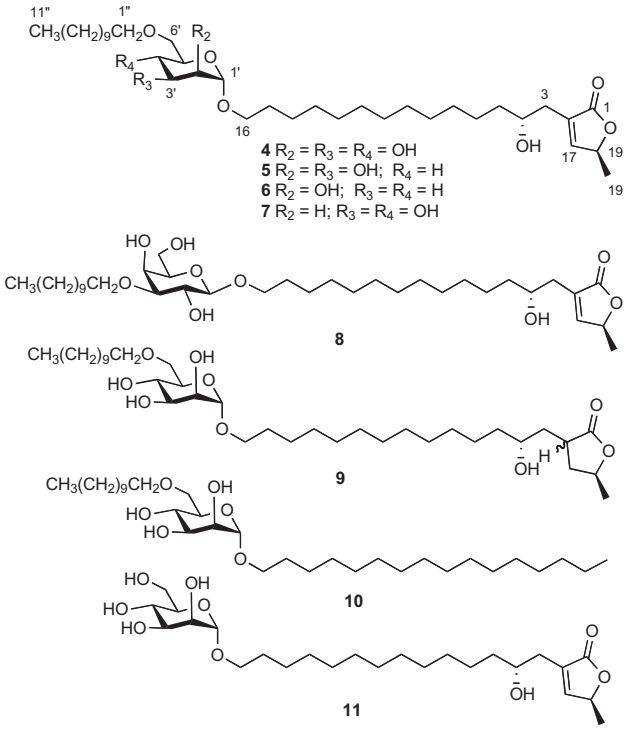


Figure 2. Sugar mimics of mono-THF acetogenins.

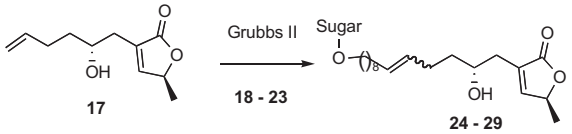
2,3,4,6-di-*O*-isopropylidene **23**. Selective removal of the 4,6-*O*-isopropylidene in **23** and sequential formation of the pivalate and ethoxyethyl acetal on the diol **30**, provided **31**. Ester cleavage on **31**, O-alkylation of the resulting alcohol with 1-bromo-undecane, and hydrolysis of the ethoxyethyl acetal protecting group, afforded **18**.

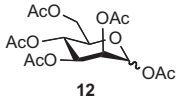
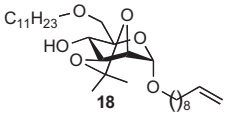
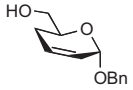
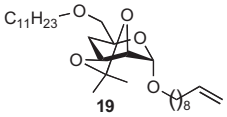
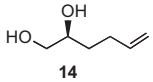
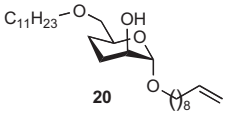
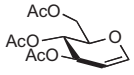
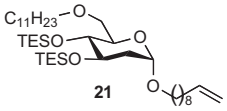
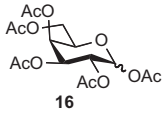
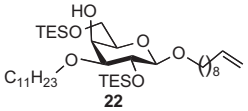
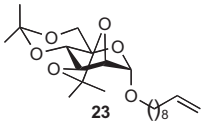
For the 4-deoxy pyranoside alkene **19**, the 2,3-eno-pyranoside **13**[16] was converted via an O-alkylation-alkene dihydroxylation sequence to the 4-deoxy-pyranoside **32**. Hydrogenolysis of **32** and acetylation of the product provided the 1,2,3-tri-*O*-acetyl derivative, which was subjected to the aforementioned glycosidation procedure with 9-decenol. This reaction afforded a single α-glycoside **33**, which after ester hydrolysis and isopropylidination of the derived diol led to the 2,3-*O*-isopropylidene **19**.

The synthesis of the 3,4-dideoxy pyranoside **20** started from the D-glyceraldehyde-derived, alkene **14**.[17] Selective Bu_2SnO-mediated O-alkylation of the primary alcohol in **14** afforded **34**. The hydroxyalkene **34** was next transformed to the *E* α,β-unsaturated ester **35**, through a straightforward sequence of reactions: O-benzylation, ozonolyis of the alkene and reaction of the derived aldehyde with methyl(triphenylphosphoranylidene)acetate. Asymmetric dihydroxylation on **35** using AD-mix α,[18] followed by isopropylidenation of the resultant diol afforded methyl ester **36**. Basic hydrolysis on **36** and Suárez fragmentation on the resulting acid with iodosobenzene diacetate and iodine provided a mixture of acetates **37**.[19] Hydrogenolysis of **37**, treatment of the product with aqueous TFA and standard acetylation of the resulting material led to a mixture of di-*O*-acetates **38**α/β (ca. ratio 100/1). Application of the glycosidation and acetate hydrolysis procedures on **38**α, as previously described, provided **20**.

The 2-deoxy-pyranoside **21** was prepared from commercially available tri-*O*-acetyl-D-glucal **15**. Thus, $Ph_3P{\cdot}HBr$ catalyzed glycosidation of **15** with 9-decenol, followed by ester hydrolysis on the product, provided triol **39** as a single α-glycoside.[20,21] Standard alcohol protecting group processing on **39** and *O*-alkylation as described earlier, provided **40**, and then **21**.

Table 1
Cross metathesis reactions



Carbohydrate precursor	Carbohydrate alkene for CM	CM product (% yield)	Target analog
 12	 18	**24** (64)[a]	**4**
 13	 19	**25** (20)[a]	**5**
 14	 20	**26** (38)[b]	**6**
 15	 21	**27** (24)[a]	**7**
 16	 22	**28** (16)[b]	**8**
12	 23	**29** (50)[a]	**11**

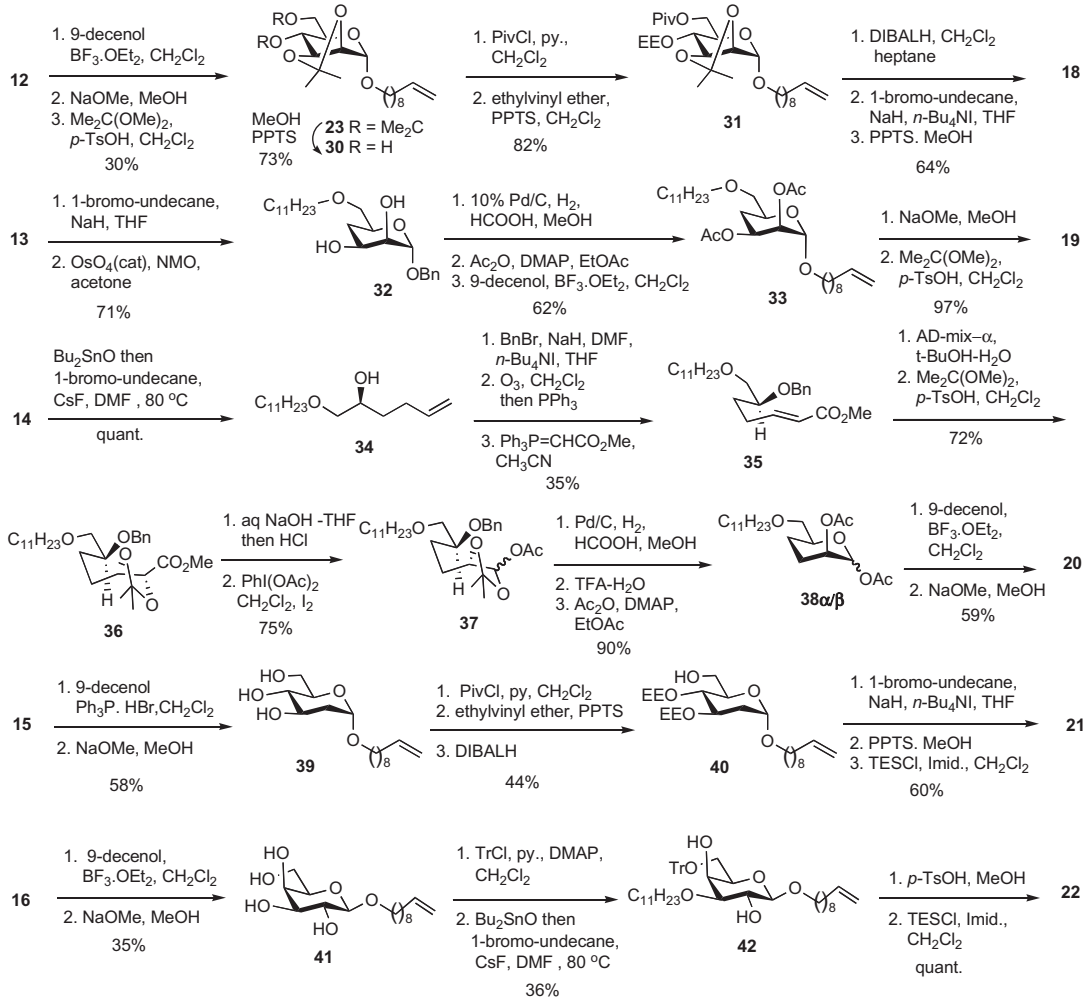
[a] CM performed with 3–4 mol equiv of carbohydrate alkene.
[b] CM performed with 3 mol equiv of **17**

The galactose-derived alkene **22** was obtained from penta-*O*-acetyl-α-D-galactopyranose **16**. The standard glycosidation of **18** with 9-decenol and deacetylation of the product gave 9-decenyl-β-D-galactopyranoside **41** as the exclusive product. Selective tritylation of the primary alcohol in **41** and Bu_2SnO mediated alkylation of the resulting triol with undecylbromide afforded **42**.[22] Removal of the trityl ether and treatment of the resulting triol with excess TESCl and imidazole gave the 2,6-di-O-silylated derivative **22**.

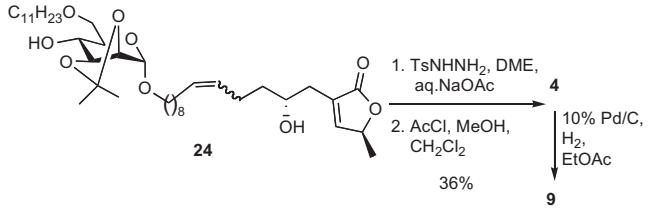
CM reactions were performed with three to four molar equivalents of either butenolide **17**[23,24] or the respective carbohydrate alkene partner **18–23** using 10 mol % Grubbs 2nd generation catalyst (Table 1).[25,26] In general, it was more practical to use the carbohydrate alkene (vs the butenolide alkene), as the limiting reactant reagent for two reasons. First, the carbohydrate alkene was more easily accessible than the butenolide partner. Second, the major side product, when the carbohydrate was in excess, was the homodimer of the carbohydrate alkene, which was more easily separated by chromatography from the desired heterodimer, than was the butenolide homodimer, the side product obtained when the butenolide alkene was in excess. The reaction yields of the CM heterodimer ranged from 16% to 64% based on the limiting alkene. Yields were generally lower when sugar alkenes with more than one free hydroxyl group were used. However, the reaction conditions were not optimized with respect to the catalyst, reactant ratio, concentration and temperature.[25,26] Selective reduction of the isolated alkene in the CM products **24–29** was performed using diimide generated from tosylhydrazide and sodium acetate (Scheme 2).[27] The reduction products were subjected to cleavage of their acetal or silyether protecting groups by treatment with 3% acetyl chloride in methanol and dichloromethane, leading to the final products **4–8**, and **11**. Standard hydrogenation of **4** provided **9** as an inseparable diastereomeric mixture of α-substituted γ-lactones.

2.3. Cytotoxicity measurements

The cytotoxicity of **4–11** against four human tumor cell lines, Jurkat (T cell leukemia), HeLa (cervical), MDA-MB231 (breast) and PC-3 (prostate) was determined using the CellTiter-Glo® luminescent cell viability assay after 48 h of treatment with the test compounds (Table 2). The structurally related naturally occurring mono-THF acetogenin, (9*S*)-4-deoxyannoreticuin **1** was used as a positive control. All of the sugar analogues with both the hydrocarbon spacer-butenolide and the hydrocarbon tail (i.e., **4–8**) showed activity at less than 100 μM. The 6-O-alkylated α-glycosides **4–7**, showed low micromolar activity comparable to the THF congener **1**. The removal of one or more of the secondary alcohols from the sugar core did not have a marked effect on activity. The 3-O-alkylated-β-galactose analog **8** was noticeably less active, suggesting that the relative positioning of the hydrocarbon appendages on the sugar ring, or the presence or absence of the free primary alcohol on the sugar core may have a more significant



Scheme 1. Synthesis of carbohydrate alkenes for CM reactions



Scheme 2. Representative transformations on CM products.

Table 2
IC_{50} (mM) data for more active acetogenin analogues

Compound	Jurkat	HeLa	MDA MB231	PC-3
4	10.11 ± 0.84	15.17 ± 0.98	21.18 ± 3.30	32.56 ± 0.76
5	19.66 ± 3.55	23.31 ± 1.07	36.71 ± 4.88	52.83 ± 1.21
6	10.69 ± 1.02	13.93 ± 1.25	21.75 ± 2.95	28.73 ± 0.80
7	13.29 ± 2.72	16.30 ± 1.21	16.81 ± 3.51	44.04 ± 0.96
8	78.17 ± 7.68	50.32 ± 9.07	73.55 ± 14.49	ND*
1	17.79 ± 1.56	20.99 ± 2.71	34.16 ± 1.83	43.05 ± 2.40

* Not determined

impact on activity. A wider structure activity study is needed to assess the relative effect of these variables. Analogues with a hydrogenated or missing butenolide residue, or without the hydrocarbon tail (**9**–**11**), were inactive. These data suggested that both the hydrocarbon tail and the hydrophobic spacer-butenolide segments on the cyclic oxygenated core were critical for activity. This significant loss in activity on hydrogenation of the butenolide or its removal is as observed for the THF containing AAs and suggests that both the THF and sugar derived compounds have a similar mechanism of action.[28,29] The observation that the relative sensitivity of the different cell lines (i.e. Jurkat > HeLa > MDA MB231 > PC-3) for the active sugar analogues was the same as for the THF AA **1**, reinforces this notion.

2.4. Dynamic light scattering measurements

Dynamic light scattering measurements on the fully hydroxylated sugar analog **4** and the THF congener **1** were compared to get insight on how the sugar modification impacts on solution properties in the active concentration range (1–100 μM).[30] Both **1** and **4** exhibited similar particle distribution, ranging from 40 to ~200 nm at lower concentrations, 1 and 10 μM (see Supplementary data). However at 100 μM, while the sugar analog **4** behaved similarly, the THF analog **1** showed a noticeably broader particle distribution ranging from 40 to ~1000 nm, indicating the presence of large aggregates (Fig. 3). The apparently higher solubility of **4** compared to **1** at 100 μM is as expected for the more hydrophilic sugar derivative and has implications for formulations with higher drug dosing.

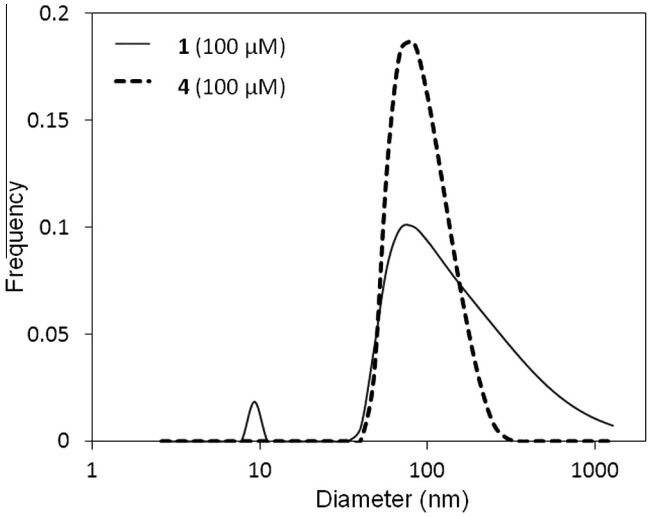


Figure 3. Dynamic light scattering analysis of **1** (solid line) and **4** (dashed line) at 100 μM. The *X*-axis (in log scale) is the particle diameter size; *Y*-axis is the frequency.

3. Conclusion

Together the cytotoxicity data on these novel sugar AA supports our hypothesis that in the case of the mono-THF AAs, the THF ring can be replaced with a cyclic sugar residue without loss in anti-tumor activity. The preliminary SAR data suggests that these sugar analogues have a similar mechanism of action to the THF congeners, but rigorous mechanistic studies including the binding of the new sugar AAs to complex I are needed to strengthen this speculation. It has been observed in the THF containing AAs that subtle variations in the length of the hydrophobic chains can lead to marked increase in anti-tumor activity. Therefore, it may be possible to increase the anti-tumor activity of these sugar containing AAs through similar changes. An intriguing question is whether varying the substitution pattern on the sugar entity can also lead to increased tumor potency and, or selectivity. Studies along these lines are in progress.

4. Experimental

4.1. Synthesis

4.1.1. General

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe and septa technique. Solvents were purified by standard procedures or used from commercial sources as appropriate. Thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel HF_{254} aluminum sheets. Chromatograms were observed under UV (short and long wavelength) light, and were visualized by heating plates that were dipped in a solution of ammonium(VI) molybdate tetrahydrate (12.5 g) and cerium(IV) sulfate tetrahydrate (5.0 g) in 10% aqueous sulfuric acid (500 mL). Flash column chromatography (FCC) was performed using silica gel 60 (230–400 mesh) and employed a stepwise solvent polarity gradient, correlated with TLC mobility. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker 500 MHz spectrometer, in $CDCl_3$. Chemical shifts are relative to the deuterated solvent peak and are in parts per million (ppm). Assignments for selected nuclei were determined from ^{1}H COSY experiments. High resolution mass spectrometry was performed on Ultima Micromass Q-TOF or Agilent G6550 Q-TOF mass spectrometers.

4.1.2. 9-Decenyl 2,3-*O*-isopropylidene-6-undecyl-α-D-mannopyranoside (18)

A 1 M solution of DIBAL-H in heptane (7.3 mL, 7.3 mmol) was added at −78 °C to a solution of **31** (1.30 g, 2.53 mmol) in DCM (15 mL). The reaction mixture was allowed to warm to rt. After 3 h the reaction was quenched with saturated aqueous Rochelle's salt and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue afforded **31** (966 mg); R_f = 0.55 (15% EtOAc/petroleum ether). To a solution of this material (966 mg, 2.24 mmol) in THF were added a 60% dispersion of NaH in mineral oil (180 mg, 4.5 mmol), Bu_4NI (82 mg, 0.20 mmol), and $C_{11}H_{23}Br$ (0.8 mL, 4.5 mmol). The reaction mixture was stirred for 12 h and then quenched with water and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was treated with PPTS (100 mg, 0.40 mmol) in MeOH (15 mL) for 1 h, and the reaction was quenched with Et_3N. Removal of the solvent in vacuo, and FCC of the residue afforded **18** (828 mg, 64% from **31**). R_f = 0.50 (15% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 6.8 Hz), 1.27 (bs, 22H), 1.38 (s, 3H), 1.55 (s, 3H), 1.60 (m, 8H), 2.06 (m, 2H), 2.99 (bs, 1H, OH), 3.44 (m, 1H), 3.50 (m, 2H), 3.65 (m, 1H), 3.73 (m, 4H), 4.17 (m, 2H), 4.96 (m, 3H), 5.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3 (two lines), 28.1, 29.1, 29.3, 29.5 (two lines), 29.6, 29.7, 29.8 (three lines), 32.1, 34.0, 68.0 (two lines), 71.6, 71.9, 72.3, 75.5, 78.1, 97.3, 109.6, 114.3, 139.4. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{30}H_{60}NO_6$, 530.4415, found 530.4419.

4.1.3. 9-Decenyl 2,3-*O*-isopropylidene-6-*O*-undecyl-4-deoxy-α-D-lyxo-pyranoside (19)

To a solution **33** (419 mg, 0.78 mmol) in MeOH (5 mL) was added NaOMe (50 mg). The reaction was stirred for 30 min and then adjusted to pH ~6 with 1 M HCl in MeOH. The mixture was then concentrated in vacuo and the crude residue was taken up in DCM (20 mL). 2,2-DMP (5 mL) and *p*TsOH (50 mg) was added, the reaction stirred for 1 h, then quenched with Et_3N. Evaporation of the volatiles under reduced pressure and FCC of the residue afforded **19** (371 mg, 97% from **33**). R_f = 0.42 (10% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, J = 6.8 Hz), 1.23–1.38 (m, 26H), 1.31 (s, 3H, buried under m), 1.49 (s, 3H), 1.52 (m, 5H), 1.88 (m, 1H), 2.01 (m, 2H), 3.42 (m, 4H), 3.50 (m, 1H), 3.70 (m, 1H), 3.82 (m, 1H), 3.92 (d, 1H, J = 5.6 Hz), 4.33 (m, 1H), 4.91 (m, 2H), 4.99 (s, 1H), 5.77 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3, 26.4 (two lines), 28.3, 29.1, 29.3, 29.5, 29.6 (two lines), 29.8, 29.9, 30.8, 32.1, 34.0, 65.7, 67.7, 71.0, 71.9, 73.5, 73.8, 97.7, 109.0, 114.3, 139.4. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{30}H_{60}NO_5$, 514.4466, found 514.4468.

4.1.4. 9-Decenyl 3,4-dideoxy-6-*O*-undecyl-α-D-threo-pyranoside (20)

To a solution of **38**α (500 mg, 1.30 mmol) in DCM (10 mL) was added 9-decen-1-ol (1.0 mL, 5.7 mmol) and $BF_3{\cdot}OEt_2$ (0.1 mL, 0.8 mmol). The reaction was stirred for 3 h, then quenched with $NaHCO_3$ and extracted with EtOAc. The organic fraction was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was taken up in MeOH (5 mL) and treated with NaOMe (50 mg). The reaction was stirred for 30 min and then neutralized with 1 M HCl in MeOH. Removal of the solvent in vacuo and FCC of the residue gave **20** (334 mg, 59% from **38**α). R_f = 0.4 (20% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.9 Hz), 1.26 (m, 26H), 1.58 (m, 4H), 1.67 (m, 1H), 1.75 (m, 1H), 1.99 (m, 2H), 2.04 (m, 2H), 3.41 (dd, 1H, J = 6.5, 12.5 Hz), 3.44 (m, 4H), 3.62 (m, 1H), 3.63 (m, 1H), 3.95 (m, 1H), 4.68 (s, 1H), 4.95 (m, 2H), 5.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 21.8, 22.9, 25.3, 26.3, 26.4, 29.1, 29.3, 29.5, 29.6 (two lines), 29.7, 29.8, 29.9, 32.1 34.0, 66.1, 67.7, 67.9, 71.9, 74.0, 99.8, 114.3, 139.4. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{27}H_{56}NO_4$, 458.4204, found 458.4204.

4.1.5. 9-Decenyl 3,4-di-*O*-triethylsilyl-6-*O*-undecyl-2-deoxy-α-D-arabinopyranoside (21)

To a solution of **40** (1.05 g, 2.36 mmol) in dry DMF (30 mL) was added NaH as a 60% dispersion in mineral oil (283 mg, 7.1 mmol), $C_{11}H_{23}Br$ (1.6 mL, 7.1 mmol) and Bu_4NI (87 mg, 0.24 mmol). The reaction was stirred for 2 h, quenched with water and extracted with ether. The organic fraction was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was taken up in MeOH (15 mL) and treated with PPTS (100 mg). The reaction was stirred for 1 h and then the solvent was removed in vacuo. FCC of the residue gave 9-undecenyl 2-deoxy-6-*O*-undecyl-α-D-*arabino*-pyranoside (668 mg); R_f = 0.24 (30% EtOAc/petroleum ether). To a solution of this material (668 mg, 1.45 mmol) in dry DCM (5 mL) was added TESCl (0.5 mL, 3.05 mmol) and imidazole (112 mg, 1.65 mmol). The reaction was stirred for 2 h, then quenched with water and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue afforded **21** (953 mg, 60% from **40**). R_f = 0.56 (5% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.63 (m, 12H), 0.85 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.9 Hz, 9H), 0.96 (t, J = 7.9 Hz, 9H), 1.20–1.40 (m, 26H), 1.57 (m, 5H), 2.01 (m, 3H), 3.27 (m, 1H), 3.42 (m, 3H), 3.56 (m, 4H), 3.91 (m, 1H), 4.81 (d, 1H, J = 2.1 Hz), 4.90 (d, 1H, J = 10.2 Hz), 4.97 (d, 1H, J = 17.1 Hz), 5.79 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 5.5, 5.6, 7.2, 7.3, 14.3, 22.9, 26.4, 29.1, 29.3, 29.5, 29.6 (three lines), 29.8 (three lines), 29.9, 32.1, 34.0, 39.1, 67.3, 70.2, 71.3, 71.9, 72.0, 73.5, 97.2, 114.3, 139.4. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{39}H_{84}NO_5Si_2$ 702.5883, found 702.5878.

4.1.6. 9-Decenyl 2,6-di-*O*-(triethylsilyl)-3-*O*-undecyl-β-D-galactopyranoside (22)

To a solution of **42** (560 mg, 0.78 mmol) in MeOH (20 mL) was added *p*TsOH (150 mg). The reaction was stirred for 12 h and then quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic extract was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave 9-decenyl 3-*O*-undecyl-α-D-galactopyranoside (370 mg). R_f = 0.6 (80% EtOAc/petroleum ether). To a sample of this material (225 mg, 0.48 mmol) in DCM (10 mL) was added imidazole (162 mg, 2.40 mmol) and TESCl (0.25 mL, 1.5 mmol). The reaction was stirred for 2 h, then quenched with water and extracted with ether. The organic fraction was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave **22** (360 mg, quant. from **42**). R_f = 0.4 (5% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.66 (m, 12H), 0.90 (t, 3H, J = 7.0 Hz), 0.93 (t, 9H, J = 7.8 Hz), 0.94 (t, 9H, J = 7.8 Hz), 1.29 (m, 26H), 1.62 (m, 4H), 2.05 (m, 2H), 2.40 (bs, 1H, OH), 3.19 (dd, 1H, J = 3.4, 9.0 Hz), 3.44 (m, 2H), 3.50 (m, 1H), 3.61 (m, 2H), 3.83 (m, 2H), 3.93 (dd, 1H, J = 6.5, 10.3 Hz), 4.05 (bs, 1H), 4.18 (d, 1H, J = 7.6 Hz), 4.96 (bd, J = 10.1 Hz, 1H), 5.02 (bd, 1H, J = 17.1 Hz), 5.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 4.5, 5.2, 6.9, 7.1, 14.3, 22.9, 26.2, 26.3, 29.1, 29.3, 29.5, 29.6 (two lines), 29.7 (two lines), 29.8 (two lines), 30.2, 32.1, 34.0, 62.1, 65.7, 70.0, 70.3, 72.1, 74.7, 82.7, 103.1, 114.3, 139.4. HRMS (ESI) calcd for $(M+Na)^+$ $C_{39}H_{80}NaO_6Si_2$, 723.5386, found 723.5380.

4.1.7. 9-Decenyl 2, 3, 4, 6-di-*O*-isopropylidene-6-undecyl-α-D-mannopyranoside (23)

To a solution of penta-*O*-acetylated mannose **12** (5.41 g, 13.9 mmol) in DCM (45 mL) were added 9-decen-1-ol (3.5 mL, 21.0 mmol) and $BF_3{\cdot}OEt_2$ (5.7 mL, 59.0 mmol). The reaction mixture was stirred for 24 h and then quenched with saturated aqueous $NaHCO_3$ solution. The mixture was extracted with DCM, dried, and concentrated in vacuo. FCC of the residue gave the decenyl glycoside (2.4 g): R_f = 0.32 (25% EtOAc/petroleum ether). This material was treated with NaOMe (0.3 g, 5.6 mmol) in MeOH (25 mL). The reaction was stirred for 1 h and then adjusted to pH 6 with 1 M HCl in MeOH. The mixture was concentrated in vacuo to give the crude tetraol, which was dissolved in DCM (25 mL) and treated with 2,2-DMP (10 mL, 82.0 mmol) and *p*-TsOH (100 mg, 0.5 mmol). The reaction mixture was stirred for 1 h, then quenched with saturated aqueous $NaHCO_3$ solution, and processed as described in the previous step. FCC of the residue gave **23** (1.7 g, 30% from **12**): R_f = 0.7 (10% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.15 (bs, 10H), 1.28 (s, 3H), 1.36 (s, 3H), 1.45 (s, 3H), 1.48 (s, 3H), 1.51 (m, 2H), 1.97 (m, 2H), 3.32 (m, 1H), 3.50 (m, 1H), 3.60 (m, 1H), 3.66 (m, 2H), 3.79 (dd, 1H, J = 5.7, 10.7 Hz), 4.09 (m, 2H), 4.87 (m, 3H), 5.73 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 19.1, 26.3 (two lines), 28.4, 29.1, 29.2 (two lines), 29.5 (two lines), 29.6, 34.0, 61.4, 62.3, 68.1, 73.0, 75.1, 76.4, 97.9, 99.9, 109.6, 114.3, 139.4. HRMS (ESI) calcd for $(M+Na)^+$ $C_{22}H_{38}NaO_6$, 421.2561, found 421.256.

4.1.8. 9-Decenyl 2,3-*O*-isopropylidene-α-D-*manno*-pyranoside (30)

To a solution of **23** (1.7 g, 4.3 mmol) in MeOH (15 mL) was added PPTS (640 mg, 2.1 mmol). The reaction mixture was stirred for 13 h and then quenched with Et_3N. The mixture was concentrated in vacuo. FCC of the residue gave **30** (1.11 g, 73%). R_f = 0.14 (30% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.32 (bs, 10H), 1.39 (s, 3H), 1.55 (s, 3H), 1.60 (m, 2H), 2.07 (m, 2H), 2.57 (d, 1H, J = 4.9 Hz, OH), 3.46 (m, 1H), 3.73 (m, 3H), 3.76 (m, 2H), 3.86 (m, 2H), 4.95 (m, 2H), 5.02 (s, 1H), 5.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 28.0, 29.1, 29.2, 29.5, 29.6, 34.0, 62.9, 68.2, 69.7, 70.2, 75.7, 78.2, 97.5, 109.8, 114.4, 139.4. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{19}H_{38}NO_6$, 376.2694, found 376.2697.

4.1.9. 9-Decenyl 4-*O*-(1-ethoxyethyl)-2,3-*O*-isopropylidene-6-*O*-pivaloyl-α-D-*manno*-pyranoside (31)

To a solution of diol **30** (1.11 g, 3.1 mmol) in DCM (20 mL) was added pyridine (2.5 mL, 31.0 mmol) and pivaloyl chloride (0.46 mL, 3.4 mmol). The reaction mixture was stirred for 4 h and then concentrated in vacuo. FCC of the residue gave the pivaloate ester of the primary alcohol (1.13 g), R_f = 0.4 (20% EtOAc/petroleum ether). Ethyl vinyl ether (9 mL, 94.0 mmol) and PPTS (100 mg) were added to a solution of this material (1.13 g, 2.56 mmol) in DCM (3 mL). The reaction mixture was stirred for 1 h and then quenched with Et_3N. Removal of the volatiles in vacuo and FCC of the residue gave the derived 4-*O*-ethoxyethyl ether (1.30 g, 82% from **30**), R_f = 0.85 (20% EtOAc/petroleum ether). ^{1}H NMR δ ($CDCl_3$) 1.15–1.37 (m, 28H), 1.48, 1.49 (both s, 3H), 1.52 (m, 2H), 2.02 (m, 2H), 3.32–3.58 (m, 3H), 3.62–3.78 (, 3H), 4.07 (m, 2H), 4.16, 4.23 (both t, 1H, J = 7.6 Hz), 4.38, 4.47 (both dd, 1H, J = 2.5, 12.6 Hz), 4.82–5.02 (m, 4H), 5.78 (m, 1H). ^{13}C NMR δ ($CDCl_3$) 15.3, 15.6, 20.4, 21.0, 26.4, 26.6, 28.2 (two lines), 29.1, 29.3, 29.5, 29.6 (two lines), 29.9 (two lines), 34.0, 61.2, 62.1, 63.5, 64.1, 66.9, 67.0, 67.7, 67.8, 73.3, 73.5, 76.0 (two lines), 78.5, 78.9, 96.8, 96.9, 109.4, 109.5, 114.4, 139.4, 178.4, 178.5. HRMS (ESI) calcd for $(M+Na)^+$ $C_{28}H_{50}NaO_8$, 537.3398, found 537.3396.

4.1.10. Benzyl 6-*O*-undecyl-4-deoxy-α-D-lyxo-pyranoside (32)

To a solution of **13**[16] (125 mg, 0.57 mmol) in dry DMF (5 mL) was added NaH as a 60% dispersion in mineral oil (70 mg, 1.70 mmol). The mixture was stirred for 15 min and then $C_{11}H_{23}Br$ (0.25 mL, 1.14 mmol) was added at rt. The reaction was stirred for a further 18 h, then quenched with water and extracted with ether. The organic phase was washed with water, dried (Na_2SO_4), filtered, and concentrated in vacuo. To a solution of the residue in acetone (6 mL) was added OsO_4 as a 2.5 wt % in *t*-BuOH (0.30 mL, 0.02 mmol) and a 50 wt % solution of *N*-methyl morpholine-*N*-oxide in water (0.40 mL, mg, 1.93 mmol). The reaction was stirred for 18 h, then quenched with $NaHSO_3$ (100 mg). The resulting slurry was stirred for 10 min, then filtered through a bed of Celite. The filtrate was evaporated under reduced pressure, and the residue taken up in EtOAc and washed with water and brine. The

organic phase was dried (Na_2SO_4) filtered and concentrated in vacuo. FCC of the residue gave **32** (165 mg, 71%, from **13**). R_f = 0.42 (70% EtOAc/petroleum ether). ^{1}H NMR δ ($CDCl_3$) 0.88 (t, 3H, J = 6.8 Hz), 1.26 (m, 16H), 1.60 (m, 3H), 1.80 (m, 1H), 2.12 (d, 1H, J = 8.5 Hz, OH), 2.18 (d, 1H, J = 7.1 Hz, OH), 3.48 (m, 4H), 3.79 (bs, 1H), 3.98 (m, 1H), 4.07 (m, 1H), 4.50 (apparent d, 1H, J = 11.9 Hz), 4.73 (apparent d, 1H, J = 11.9 Hz), 4.99 (s, 1H), 7.33 (m, 5H). ^{13}C NMR δ ($CDCl_3$) 14.3, 22.9, 26.3, 29.5, 29.7, 29.8 (two lines), 31.4, 32.1, 65.8, 67.6, 69.2, 69.4, 72.0, 73.4, 99.5, 128.0, 128.1, 128.6, 137.4. HRMS (ESI) calcd for $(M+Na)^+$ $C_{24}H_{40}NaO_5$, 431.2768, found 431.2766.

4.1.11. 9-Decenyl 4-deoxy-2,3-di-*O*-acetyl-6-*O*-undecyl-α-D-*lyxo*-pyranoside (33)

To a solution of diol **32** (516 mg, 1.26 mmol) in methanol (10 mL) was added HCOOH (0.2 mL) and 10% wt Pd/C (150 mg). The mixture was stirred under a hydrogen atmosphere (balloon) for 20 h. The reaction was then purged with nitrogen and filtered through a bed of Celite. The filtrate was concentrated in vacuo. The crude residue was dissolved in EtOAc (25 mL) and treated with Ac_2O (5 mL) and DMAP (50 mg). The mixture was stirred for 30 min and then quenched with MeOH (1 mL). The mixture was diluted with EtOAc and washed successively with aqueous 1 N HCl and saturated aqueous $NaHCO_3$. The organic fraction was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave the 1,2,3-tri-*O*-acetyl derivative (501 mg). To a solution of this material (501 mg, 1.1 mmol), in DCM (25 mL) was added 9-decen-1-ol (0.1 mL, 5.6 mmol) and $BF_3{\cdot}OEt_2$ (0.45 mL, 3.3 mmol). The reaction was stirred for 6 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave **33** (419 mg, 62% from **32**). R_f = 0.38 (15% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.8 Hz), 1.26–1.39 (m, 26H), 1.57 (m, 4H), 1.81 (m, 2H), 2.02 (s, 3H), 2.1 (m, 1H), 2.13 (s, 3H), 3.39 (m, 1H), 3.45 (m, 3H), 3.52 (m, 1H), 3.68 (m, 1H), 4.01 (m, 1H), 4.82 (s, 1H), 4.94 (m, 2H), 5.07 (s, 1H), 5.28 (m, 1H), 5.81 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 21.2 (two lines), 22.9, 26.3 (two lines), 28.6, 29.1, 29.3, 29.5 (two lines), 29.6 (two lines), 29.7, 29.8 (two lines), 32.1, 34.0, 67.2, 67.4, 68.1, 68.4, 98.3, 114.3, 139.4, 170.2, 170.5.

4.1.12. (*S*)-1-(Undecyloxy)hex-5-en-2-ol (34)

To a solution of diol **14**[17] (2.34 g, 16.7 mmol) in MeOH (30 mL) was added Bu_2SnO (4.32 g, 17.4 mmol). The reaction was heated to reflux for 3 h and then toluene (40 mL) was added. The mixture was heated at reflux for 2 h with a Dean–Stark trap for removal of the toluene–water azeotrope. The solvent was then removed in vacuo and the residue taken up in dry DMF (30 mL). $C_{11}H_{23}Br$ (10 mL, 56.0 mmol) and CsF (8.4 g, 55.0 mmol) were then introduced and the reaction heated at 80 °C for 15 h. The mixture was then diluted with water and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave **34** (4.51 g, quant.). R_f = 0.30 (10% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz), 1.28 (m, 16H), 1.50 (m, 4H), 2.17 (m, 1H), 2.24 (m, 1H), 2.38 (d, 1H, J = 3.0 Hz, OH), 3.27 (dd, 1H, J = 8.0, 9.4 Hz), 3.47 (m, 3H), 3.81 (m, 1H), 4.95 (bd, J = 10.2 Hz, 1H), 5.04 (bd, J = 18.8 Hz, 1H), 5.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3, 29.5, 29.6, 29.8 (three lines), 29.9, 32.1, 32.4, 69.9, 71.7, 75.1, 115.0, 138.5. HRMS (ESI) calcd for $(M+H)^+$ $C_{17}H_{35}O_2$, 271.2632, found 271.2633.

4.1.13. (*S*, *E*)-Methyl-6-(benzyloxy)-7-undecyloxy-hept-2-enoate (35)

To a solution of **34** (1.95 g, 7.22 mmol) in DMF (20 mL) at 0 °C, was added a 60% dispersion of NaH in mineral oil (576 mg, 14.4 mmol), *n*-Bu_4NI (265 mg, 0.7 mmol) and BnBr (2.2 mL, 18.0 mmol). The reaction was stirred for 16 h at rt, then quenched with water and extracted with ether. The organic fraction was washed with water, dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave the derived benzyl ether. This material was dissolved in DCM (25 mL) and the solution cooled to −78 °C. Ozone was bubbled through the solution for 15 min. The mixture was then purged with N_2, treated with PPh_3 (3.78 g, 14.0 mmol) for 1 h and concentrated in vacuo. FCC of the residue gave the crude aldehyde derivative (2.32 g). To a solution of this product (2.32 g, ca. 6.4 mmol) in CH_3CN (30 mL) was added methyl(triphenylphosphoranylidene)acetate (3.2 g, 9.6 mmol). The mixture was heated at reflux for 15 h, cooled to rt and then filtered through a bed of Celite. The filtrated was concentrated in vacuo. FCC of the residue gave **35** (1.04 g, 35% from **34**). R_f = 0.86 (20% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, J = 6.9 Hz), 1.23–1.31 (m, 18H), 1.66 (m, 2H), 2.22 (m, 1H), 2.30 (m, 1H), 3.41 (m, 3H), 3.51 (m, 2H), 3.69 (s, 3H), 4.59 (ABq, 2H, J = 11.7 Hz, $\Delta\delta$ = 0.17 ppm), 5.77 (dt, 1H, J = 1.5, 15.7 Hz), 6.93 (dt, 1H, J = 6.9, 15.7 Hz), 7.25 (m, 1H), 7.31 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3, 28.4, 29.5, 29.7, 29.8, 29.9, 30.7, 32.1, 51.6, 71.9, 72.3, 73.4, 77.2, 121.2, 127.8, 128.0, 128.5, 138.8, 149.4, 167.2. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{26}H_{46}NO_4$, 436.3421, found 436.3421.

4.1.14. (4*R*,5*S*)-Methyl 5-((*S*)-3-(benzyloxy)-4-(undecyloxy)butyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (36)

A mixture of **35** (1.04 g, 2.49 mmol), AD mix-α (3.0 g) and 1:1 *t*-BuOH/water (100 mL) was stirred at 0 °C for 16 h. The reaction was quenched with Na_2SO_3 (1 g) and the mixture filtered. The filtrate was extracted with EtOAc and the organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was dissolved in DCM (10 mL) and treated with 2,2-DMP (10 mL) and *p*-TsOH (50 mg, 0.3 mmol) for 30 min. Et_3N was then added and the mixture concentrated in vacuo. FCC of the residue gave ester **36** (875 mg, 72% from **35**). R_f = 0.62 (10% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.82 (t, 3H, J = 6.9 Hz), 1.15–1.25 (m, 16H), 1.37 (s, 3H), 1.39 (s, 3H), 1.50 (m, 4H), 1.62 (m, 1H), 1.79 (m, 1H), 3.38 (m, 3H), 3.46 (dd, 1H, J = 5.5, 9.5 Hz), 3.55 (m, 1H), 3.67 (s, 3H), 4.05 (m, 2H), 4.55 (ABq, 2H, J = 11.4 Hz, $\Delta\delta$ = 0.14 ppm), 7.52 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 25.9, 26.4, 27.2, 27.9, 29.3, 29.5, 29.7, 29.8, 29.9, 32.1, 52.5, 71.8, 72.2, 73.6, 77.7, 79.0, 79.1, 11.1, 127.7, 128.1, 128.5, 139.1, 171.5. HRMS (ESI) calcd for $(M+Na)^+$ $C_{29}H_{48}NaO_6$, 515.3343, found 515.3345.

4.1.15. (*S*)-5-((*S*)-3-(benzyloxy)-4-(undecyloxy)butyl)-2,2-dimethyl-1,3-dioxolan-4-yl acetate (37)

1 M aqueous KOH (0.3 mL) was added to mixture of **36** (42 mg, 0.085 mmol) in THF (1.5 mL) and water (0.5 mL). The reaction mixture was stirred at rt for 30 min, then adjusted to pH 5 by the addition of 1 M HCl, diluted with brine and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave the derived acid (40 mg, 98%). R_f = 0.10 (30% (EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 6.9 Hz), 1.27 (m, 16H), 1.44 (s, 3H), 1.48 (s, 3H), 1.59 (m, 2H), 1.74 (m, 2H), 1.89 (m, 2H), 3.46 (m, 2H), 3.49 (d, 1H, J = 4.6 Hz) 3.55 (dd, 1H, J = 5.8, 10.1 Hz), 3.64 (m, 1H), 4.15 (m, 3H), 4.66 (ABq, 2H, $\Delta\delta$ = 0.13 ppm, J = 11.7 Hz), 7.29 (m, 1H), 7.36 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 25.8, 26.3, 27.3, 27.9, 29.3, 29.5, 29.7, 29.8, 29.9, 32.1, 71.9, 72.2, 73.6, 78.5, 79.1, 111.4, 127.7, 128.0, 128.5, 138.9, 172.5.

To a sample of the material from the previous step (40 mg, 0.084 mmol) in dry DCM (2 mL), was added iodosobenzene diacetate (41 mg, 0.13 mmol) and iodine (15 mg, 0.06 mmol). The reaction was stirred at rt for 1 h and then quenched with 10% aqueous $Na_2S_2O_3$. The product was extracted with EtOAc and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC

of the residue gave **37** (31 mg, 76% from **36**). R_f = 0.10 (30% (EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, J = 6.9 Hz), 1.18–1.35 (m, 16H), 1.40–1.70 (m, 6H), 2.02, 2.04 (both s, 3H, resp ratio, ca. 1:5), 3.40 (m, 3H), 3.48 (m, 1H), 3.59 (m, 1H), 4.16 (m, 1H), 451 (m, 1H), 4.65 (m, 1H), 5.92, 6.10 (both d, 1H, resp. ratio ca. 5:1, J = 2.3, 3.3 Hz), 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$, major isomer) δ 14.3, 22.9, 26.4, 27.0, 27.6, 28.0, 28.9, 29.6, 29.7, 29.9 (two lines), 32.1, 71.9, 72.2, 73.6, 77.6, 82.1, 99.1, 112.5, 127.7, 128.0, 128.5, 139.0, 170.7. HRMS (ESI) calcd for $(M+Na)^+$ $C_{29}H_{48}NaO_6$, 515.3343, found 515.3346.

4.1.16. 1,2-Di-*O*-acetyl-3,4-dideoxy-6-*O*-undecyl –α/β-D-threo-pyranoside (38α/β)

A mixture of **37** (733 mg, 1.49 mmol), MeOH (10 mL), 10% Pd/C (100 mg) and HCOOH (0.2 mL) was stirred over a hydrogen atmosphere (balloon) for 24 h. The mixture was then purged with nitrogen and filtered through a bed of Celite. The solvent was removed in vacuo and the crude residue was further treated with 1:1 v/v mixture of TFA/H_2O (2 mL). The reaction was stirred for 18 h and then quenched with saturated aqueous $NaHCO_3$. The product was extracted with EtOAc and the organic phase dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was subjected to the acetylation procedure described in the preparation of **33**. FCC of the crude product gave **38**α (510 mg, 89% from **37**) and **38**β (8 mg, 1% from **37**). For **38**α: R_f = 0.73 (20% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz), 1.25–1.35 (m, 16H), 1.57 (m, 3H), 1.75 (m, 1H), 1.95 (m, 1H), 2.04 (m, 1H), 2.13 (s, 6H), 3.48 (dd, 1H, J = 5.1, 12.7 Hz), 3.47 (m, 2H), 3.52 (m, 1H), 4.02 (m, 1H), 4.75 (bs, 1H), 6.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 21.2, 21.3, 22.3, 22.9, 26.2, 29.5, 29.6, 29.8, 32.1, 66.7, 70.3, 72.0, 73.6, 91.2, 169.1, 170.7. HRMS (ESI) calcd for $(M+Na)^+$ $C_{23}H_{40}NaO_8$, 467.2615 found 467.2617. For **38**α: R_f = 0.60 (20% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz), 1.25–1.37 (m, 16H), 1.55–1.73 (m, 4H), 1.85 (m, 1H), 2.15 (m, 1H), 2.11 (s, 3H), 2.17 (s, 3H), 3.48 (m, 3H), 3.60 (dd, 1H, J = 5.6, 10.2 Hz), 3.88 (m, 1H), 5.10 (bs, 1H), 5.80 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 21.2, 21.4, 22.5, 22.9, 26.3, 29.6, 29.8 (two lines), 32.1, 34.3, 66.6, 72.0, 73.2, 76.3, 93.1, 169.2, 170.7 HRMS (ESI) calcd for $(M+Na)^+$ $C_{23}H_{40}NaO_8$, 467.2615, found 467.2617.

4.1.17. 9-Decenyl 2-deoxy-α-D-arabinopyranoside (39)

To a solution of commercially available **15** (2.50 g, 9.19 mmol) in dry DCM (45 mL) was added 9-decen-1-ol (1.80 mL, 10.1 mmol) and triphenylphosphine hydrobromide (472 mg, 1.40 mmol). On complete disappearance of **15** by TLC, the mixture was concentrated in vacuo. The residue was then taken up in dry MeOH (30 mL) and NaOMe (100 mg) was added to the solution. The reaction mixture was stirred for 1 h, then neutralized with 1 M HCl in MeOH and filtered. The filtrate was concentrated in vacuo and the residue subjected to FCC to provide **39** (1.60 g, 58% from **15**). R_f = 0.2 (80% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.31–1.42 (m, 10H), 1.57 (m, 2H), 1.67 (dt, 1H, J = 3.5, 12.8 Hz), 1.90 (bs, 3H, OH), 2.07 (m, 2H), 2.16 (dd, 1H, J = 3.8, 12.8 Hz), 3.35 (m, 1H), 3.51 (t, 1H, J = 9.4 Hz), 3.61 (m, 2H), 3.87 (m, 2H), 4.03 (m, 1H), 4.91 (bs, 1H), 4.98 (m, 2H), 5.83 (m, 1H). ^{13}H NMR ($CDCl_3$) δ 26.4, 29.1, 29.3, 29.6 (two lines), 29.7, 34.0, 37.6, 62.6, 67.7, 69.4, 71.2, 72.8, 97.6, 114.4, 139.5. HRMS (ESI) calcd for $(M+Na)^+$ $C_{16}H_{30}NaO_5$, 325.1985, found 325.1988.

4.1.18. 9-Decenyl 2-deoxy-3,4-di-*O*-(1-ethoxyethyl)-α-D-arabinopyranoside (40)

To a solution of **39** (1.60 g, 5.30 mmol) in dry DCM (50 mL) was added pyridine (4.3 mL, 53 mmol) and PivCl (0.7 mL, 5.8 mmol). The reaction was stirred for 3 h, then diluted with water and extracted with EtOAc. The organic layer was washed with 1 M HCl, saturated aqueous $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue gave the 6-*O*-pivaloyl derivative (910 mg). R_f = 0.23 (30% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 9H), 1.27–1.35 (m, 10H), 1.56 (m, 2H), 1.62 (dt, J = 3.5, 12.7 Hz, 1H), 2.02 (m, 2H), 2.13 (dd, 1H, J = 5.1, 12.9 Hz), 2.35 (m, 1H), 3.09 (m, 1H), 3.14 (d, 1H, J = 3.7 Hz), 3.32 (m, 1H), 3.58 (m, 1H), 3.66 (bd, 1H, J = 9.8 Hz), 3.97 (m, 1H), 4.10 (dd, 1H, J = 1.9, 12.3 Hz), 4.62 (dd, 1H, J = 3.7, 12.9 Hz), 4.88 (d, 1H, J = 3.0 Hz), 4.91 (d, 1H, J = 10.2 Hz), 4.97 (d, 1H, J = 17.2 Hz), 5.78 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 26.4, 27.4, 29.1, 29.2, 29.6 (two lines), 29.7, 34.0, 37.3, 63.7, 67.7, 68.8, 70.6, 72.4, 97.6, 114.3, 139.4, 180.3.

To a mixture of the material from the previous step (910 mg, 2.35 mmol), ethyl vinyl ether (20 mL) and DCM (10 mL) was added PPTS (200 mg). The reaction was stirred for 30 min, quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was with taken up in dry THF (45 mL) and treated with LAH (447 mg, 12 mmol). The reaction was stirred for 3 h then quenched at 0 °C with saturated aqueous Rochelle's salt (3 mL) and 2 N NaOH (3 mL). After stirring for 2 h, the mixture was diluted with water and extracted with EtOAc. The organic fraction was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue afforded **40** (1.05 g, 44% from **39**), R_f = 0.32 (30% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.17–1.22 (m, 22H), 1.58 (m, 2H), 1.65 (m, 1H), 2.10–2.26 (m, 4H), 3.30–4.18 (m, 11H), 4.62–5.02 (m, 5H), 5.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 15.3, 15.5 (two lines), 15.6 (two lines), 20.2, 20.3, 20.4, 20.6, 20.7, 20.9, 21.2, 21.7, 26.4, 29.1, 29.3, 29.6, 29.7, 34.0, 36.1, 36.4, 36.8, 37.5, 37.6, 60.2, 60.8, 61.0 61.2, 61.7, 62.1, 62.2, (two lines) 62.6, 62.7 (two lines), 62.8, 63.4, 63.7, 67.5, 67.6 (three lines), 71.2, 71.3, 71.5, 71.7 (two lines), 71.9, 72.1, 73.2, 73.8, 74.3, 74.5, 75.1, 75.7, 76.0, 78.8, 81.4, 97.3, 97.4, 97.5 (two lines), 97.6 (two lines), 101.1, 101.2, 101.4 (two lines), 102.6, 98.3, 114.3, 139.4. HRMS (ESI) calcd for $(M+Na)^+$ $C_{24}H_{46}NaO_7$, 469.3136, found 469.3136.

4.1.19. 9-Decenyl β-D-galactopyranoside (41)

To a solution of commercially available penta-*O*-acetyl-α-D-galactopyranose **16** (3.0 g, 7.7 mmol) in DCM (30 mL) was added 9-decen-1-ol (5.5 mL, 31 mmol) and $BF_3.OEt_2$ (3.0 mL, 23 mmol). The reaction was stirred at rt for 24, then quenched with saturated aqueous $NaHCO_3$ and extracted with DCM. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. FCC of the residue afforded 9-decenyl tetra-*O*-acetyl-α-D-galactopyranoside (1.3 g, 35%); R_f = 0.40 (30% EtOAc/petroleum ether). To a sample of this product (2.9 g, 6.0 mmol) in dry MeOH was added NaOMe (96 mg, 1.8 mmol). The solution was stirred for 30 min, then neutralized with 1 M HCl in MeOH and concentrated in vacuo. FCC of the residue gave **41** (1.9 g, quant.), R_f = 0.20 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$) δ 1.31 (bs, 12H), 1.38 (m, 2H), 1.64 (m, 2H), 2.05 (q, 2H, J = 6.9 Hz), 2.15 (bs, 1H), 3.38 (bs, 1H), 3.55 (m, 2H), 3.65 (m, 2H), 3.87 (m, 3H), 4.07 (bs, 1H), 4.17 (bs, 1H), 4.27 (d, 1H, J = 7.2 Hz), 4.37 (bs, 1H), 4.95 (bd, J = 10 .2 Hz, 1H), 5.00 (bd, J = 16.8 Hz, 1H), 5.83 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 26.1, 29.1, 29.3, 29.6, 29.7, 29.8, 34.0, 61.7, 69.1, 70.6, 71.5, 73.7, 74.3, 103.4, 114.4, 139.3.

4.1.20. 9-Decenyl 6-*O*-triphenylmethyl-3-*O*-undecyl-β-D-galactopyranoside (42)

To a solution of **41** (1.9 g, 6.0 mmol) in DCM (30 mL) was added pyridine (1.5 mL, 18 mmol), DMAP (73 mg, 0.6 mmol) and trityl chloride (1.8 g, 6.6 mmol). The reaction was stirred for 12 h at which time the solvent was removed in vacuo. FCC of the residue afforded 9-decenyl 6-*O*-trityl-α-D-galactopyranoside (1.8 g, 54%). R_f = 0.5 (40% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 1.30–1.38 (m, 12H), 1.64 (m, 2H), 2.05 (q, 2H, J = 7.1 Hz), 2.30 (d, 1H,

J = 4.4 Hz, OH), 2.41 (s, 1H, OH), 2.59 (d, 1H, J = 5.9 Hz, OH), 3.40 (dd, 1H, J = 5.6, 10.0 Hz), 3.48 (dd, 1H, J = 5.6, 10.0 Hz), 3.55 (m, 1H), 3.60 (m, 3H), 3.93 (m, 1H), 4.06 (t, 1H, J = 3.4 Hz), 4.24 (d, 1H, J = 7.1 Hz), 4.95 (bd, 1H, J = 10 .1 Hz), 5.00 (bd, 1H, J = 10 .1 Hz), 5.81 (m, 1H), 7.26 (m, 3H), 7.33 (bt, 6H, J = 7.8 Hz), 7.48 (bd, 6H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 26.2, 29.1, 29.2, 29.5, 29.6, 29.8, 34.0, 62.7, 69.2, 70.2, 72.6, 73.6, 73.7, 87.2, 103.1, 114.3, 127.4, 128.1, 128.8, 139.4, 143.8.

To a portion of the material from the previous step (668 mg, 1.19 mmol) in MeOH (20 mL) was added Bu_2SnO (308 mg, 1.20 mmol). The mixture was heated at reflux for 3 h in MeOH and then at reflux in toluene (20 mL). The solvent was removed in vacuo and the residue taken up in dry DMF (10 mL). CsF (606 mg, 4.00 mmol) and $C_{11}H_{23}Br$ (0.70 mL, 4.10 mmol) were introduced, the mixture stirred at 80 °C for 15 h and then cooled to rt, diluted with water and extracted with EtOAc. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue gave **42** (560 mg, 66%). R_f = 0.8 (30% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.1 Hz), 1.25–1.42 (m, 26 H), 1.67 (m, 4H), 2.05 (m, 2H), 2.32 (m, 2H), 3.28 (dd, 1H, J = 3.3, 9.4 Hz), 3.39 (dd, 1H, J = 5.5, 9.4 Hz), 3.5 (dd, 1H, J = 6.1, 9.3 Hz), 3.54–3.62 (m, 3H), 3.68 (m, 2H), 3.95 (m, 1H), 4.05 (bs, 1H), 4.26 (d, 1H, J = 7.8 Hz), 4.97 (m, 2H), 5.82 (m, 1H), 7.18–7.29 (m, 9H), 7.42 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3, 29.1, 29.3, 29.5, 29.6, 29.7, 29.8 (two lines), 30.1, 32.1, 34.0, 63.2, 66.5, 70.0, 70.4, 71.1, 74.0, 81.4, 87.0, 103.1, 114.3, 127.3, 128.1, 128.9, 139.4, 144.1. HRMS (ESI) calcd for $(M+Na)^+$ $C_{46}H_{66}NaO_6$, 737.4752, found 737.4757.

4.1.21. General procedure for CM reactions: Mannose–butenolide CM product (24)

A solution of **18** (155 mg, 0.3 mmol) and butenolide **17**[23,24] (20 mg, 0.1 mmol) in DCM (8 mL) was degassed using N_2 for 30 min and then Grubb's II catalyst (9 mg, 0.01 mmol) was added. The reaction was stirred for 18 h and then concentrated in vacuo. FCC of the residue gave **24** (44 mg, 63% from **17**). R_f = 0.14 (20% EtOAc/petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.1 Hz), 1.25–1.35 (m, 26 H), 1.36 (s, 3H), 1.46 (d, 3H, J = 7.0 Hz), 1.54 (s, 3H), 1.59 (m, 6H), 1.93–2.56 (m, 6H), 3.38 (m, 2H), 3.50 (m, 1H), 3.58 (m, 1H), 3.67 (m, 1H), 3.74 (1H), 3.85 (m, 3H), 4.10, 4.11 (d, 1H, J = 7.0), 4.20 (t, 1H, J = 6.7 Hz), 5.00 (s, 1H), 5.08 (m, 1H), 5.35–5.59 (m, 2H), 7.18, 7.19 (both s, 1H, ca ratio 3:1). ^{13}C NMR ($CDCl_3$) (major isomer) δ 14.3, 19.3, 22.9, 26.3 (two lines), 26.6, 28.3, 29.1, 29.3 (two lines), 29.5, 29.6, 29.6 (two lines), 29.7 (two lines), 29.8, 29.9, 30.3, 32.1, 32.7, 32.8, 32.9, 33.5, 37.3, 63.0, 68.0, 68.5, 69.9, 71.8, 75.5, 76.1, 78.2, 78.9, 97.3, 109.4, 125.2, 129.5, 131.7, 135.5, 152.0, 174.8. HRMS (ESI) calcd for $(M+Na)^+$ $C_{39}H_{68}NaO_9$, 703.4756, found 703.4750.

4.1.22. General procedures for processing of CM products: 6-*O*-undecyl-mannose-acetogenin analog (4)

To a solution of **24** (44 mg, 0.065 mmol) and $TsNHNH_2$ (363 mg, 1.95 mmol) in DME (12 mL) at reflux, was added a solution of NaOAc (426 mg, 2.60 mmol) in H_2O (12 mL), over a 4 h period. The mixture was then cooled, diluted with EtOAc, and washed with 1 M HCl and saturated aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude residue was taken up in DCM (5 mL) and treated with 3% AcCl in MeOH (0.5 mL). The reaction was stirred for 1 h and then quenched with solid $NaHCO_3$. The mixture filtered and concentrated in vacuo. FCC of the residue afforded **4** (15 mg, 36%, two steps). R_f = 0.3 (80% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (6, 3H, J = 7.1 Hz, CH_3-11″), 1.26 (m, 34H, $(CH_2)_{17}$), 1.44 (d, 3H, J = 6.8 Hz, CH_3-19), 1.48 (m, 2H, CH_2-5), 1.57 (m, 4H, CH_2-15, CH_2-2″), 2.18 (bs, 1H, OH), 2.28 (bs, 1H, OH), 2.42 (dd, 1H, J = 8.3, 15.1 Hz, H-3a), 2.51 (bs, partially buried, 1H, OH), 2.55 (m, 1H, H-3b), 3.41 (m, 1H, H-16a), 3.51 (t, 1H, J = 9.6 Hz, H-4′), 3.62 (m, 1H, H-5′), 3.65 (m, 2H, H-1″a, H-16b), 3.73 (m, 1H, H-1″b), 3.78 (m, 1H, H-6′a), 3.87 (m, 2H, H-4, 6′b), 3.94 (dd, 1H, J = 3.2, 9.0 Hz, H-3′), 3.96 (bs, 1H, H-2′), 4.82 (s, 1H, H-1′), 5.07 (bq, 1H, J = 6.8 Hz, H-18), 7.20 (s, 1H, H-17). ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 22.9, 25.8 (two lines), 26.2, 26.3, 29.4, 29.5, 29.5, 29.6 (four lines), 29.7 (three lines), 29.8 (two lines), 30.6, 32.1, 33.6, 37.6, 62.3, 68.1, 70.3, 71.3, 71.6, 71.8, 73.5, 76.1, 78.2, 99.6, 131.4, 152.0, 174.9. HRMS (ESI) calcd for $(M+HCOO)^-$ $C_{37}H_{67}O_{11}$, 687.4689, found 687.4678.

4.1.23. 4-Deoxy-6-*O*-undecyl-lyxose-pyranoside-acetogenin analog (5)

CM on **19** (358 mg, 0.72 mmol) and butenolide **17** (47 mg, 0.24 mmol) following the procedure described for **24**, gave **25** (31 mg, 20%, Supplementary data). Processing of **25** (31 mg, 0.046 mmol) as described for **4**, provided **5** (16 mg, 38%). R_f = 0.13 (60% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.1 Hz), 1.28 (m, 34H), 1.45 (d, 3H, J = 6.80 Hz), 1.48 (m, 2H), 1.55 (m, 5H), 1.79 (m, 1H), 2.41 (dd, 1H, J = 8.2, 15.1 Hz), 2.55 (bd, J = 15.1 Hz), 3.35–3.50 (m, 5H), 3.66 (m, 1H), 3.72 (bs, 1H), 3.86 (m, 2H), 4.02(m, 1H), 4.85 (s, 1H), 5.08 (q, 1H, J = 6.80 Hz), 7.18 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 22.9, 25.8, 26.3, 29.5, 29.6 (three lines), 29.6 (two lines), 29.7 (three lines), 29.8, 29.9 (two lines), 31.5, 32.1, 33.6, 37.7, 65.9, 67.3, 68.0, 69.5, 70.2, 72.0, 73.5, 78.2, 100.3, 131.4, 152.0, 174.9. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{35}H_{68}NO_8$, 630.4939, found 630.4928.

4.1.24. 3,4-Dideoxy-6-*O*-undecyl-threose-acetogenin analog (6)

CM on **20** (27 mg, 0.061 mol) and butenolide **17** (39 mg, 0.2 mmol) following the procedure described for **24**, gave **26** (14 mg, 38%, Supplementary data). Diimide reduction on **26** (14 mg, 0.023 mmol) as described for **4**, provided **6** (12 mg, 84%); R_f = 0.15 (35% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, J = 6.9 Hz), 1.23 (m, 34H), 1.41 (d, 3H, J = 6.8 Hz), 1.46 (m, 2H), 1.57 (m 5H), 1.64 (m, 1H), 1.73 (m, 1H), 1.97 (m, 1H), 2.05 (bs, partially buried, 1H), 2.23 (bs, 1H), 2.38 (dd, 1H, J = 8.3, 15.2 Hz), 2.52 (bd, 1H, J = 15.2 Hz), 3.36 (dd, 1H, J = 4.3, 10.4 Hz), 3.43 (m, 4H), 3.60 (bs, 1H), 3.69 (m, 1H), 3.82 (m, 1H), 3.91 (m, 1H), 4.61 (s, 1H), 5.04 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 21.8, 22.9, 25.2, 25.8, 26.3, 26.4, 29.5, 29.6 (two lines), 29.7 (two lines), 29.8, 29.9, 32.1, 33.5, 37.6, 66.1, 67.7, 67.9, 70.2, 71.9, 73.9, 78.2, 99.8, 131.4, 152.0, 174.8. HRMS (ESI) calcd for $(M+Na)^+$ $C_{35}H_{64}NaO_7$, 619.4544, found 619.4543.

4.1.25. 2-Deoxy-6-*O*-undecyl-arabinose-acetogenin analog (7)

CM on **21** (426 mg, 0.62 mmol) and butenolide **17** (41 mg, 0.21 mmol) following the procedure described for **24**, gave **27** (43 mg, 24%, Supplementary data). Processing of **27** (43 mg, 0.05 mmol) as described for **4**, provided **7** (12 mg, 40%); R_f = 0.26 (60% EtOAc/petroleum ether); ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 3H), 1.28 (m, 34H), 1.41 (d, 3H, J = 6.8 Hz), 1.45 (m, 2H), 1.55 (m, 4H), 1.64 (dt, 1H, J = 3.6, 12.6 Hz), 2.08 (dd, 1H, J = 5.1, 12.8 Hz), 2.30 (bs, 1H), 2.37 (dd, 1H, J = 8.4, 15.2 Hz), 2.40 (bs, partially buried, 1H), 2.49 (bd, 1H, J = 15.2 Hz), 3.15 (bs, 1H), 3.31 (m, 1H), 3.47 (m, 3H), 3.58 (m, 2H), 3.67 (m, 2H), 3.82 (m, 1H), 3.96 (m, 1H), 4.85 (d, 1H, J = 3.2 Hz), 5.04 (q, 1H, J = 6.8 Hz), 7.16 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 22.9, 25.7, 26.2, 26.4, 29.5 (two lines), 29.6, 29.7 (three lines), 29.8, 29.9, 32.1, 33.6, 37.1, 37.6, 67.7, 69.0, 69.2, 70.2, 72.2, 72.3, 75.5, 78.2, 97.6, 131.4, 152.0, 174.8. HRMS (ESI) calcd for $(M+Na)^+$ $C_{36}H_{66}NaO_8$, 649.4650, found 649.4648.

4.1.26. 3-*O*-Undecyl-galactose-acetogenin analog (8)

CM on **22** (158 mg, 0.2 mmol) and butenolide **17** (14 mg, 0.07 mmol) following the procedure described for **24**, gave **28** (11 mg, 16%, Supplementary data). Processing of **28** (11 mg,

0.011 mmol) as described for **4**, provided **8** (6 mg, 86%). R_f = 0.15 (60% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, J = 7.1 Hz), 1.31 (m, 34H), 1.44 (d, 3H, J = 6.9 Hz), 1.47 (m, 2H), 1.63 (m, 4H), 2.14 (bd, 1H, J = 5.0 Hz), 2.25 (bd, 1H, J = 4.6 Hz), 2.33 (bd, 1H, J = 1.8 Hz), 2.40 (dd, 1H, J = 8.8, 15.5 Hz), 2.55 (bd, 1H, J = 15.5 Hz), 3.31 (dd, 1H, J = 3.5, 9.5 Hz), 3.55 (m, 2H), 3.61 (m, 1H), 3.68 (m, 2H), 3.86 (m, 2H), 3.93 (m, 1H), 4.01 (m, 1H), 4.05 (bs, 1H), 4.27 (d, 1H, J = 7.8 Hz), 5.09 (m, 1H), 7.10 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 19.3, 22.9, 25.7, 26.1, 26.2, 29.5, (two lines), 29.6 (two lines), 29.7 (three lines), 29.8, 30.1, 30.2, 32.1, 33.5, 37.6, 62.8, 66.9, 70.2, 70.3, 70.5, 71.0, 74.5, 78.2, 81.1, 103.2, 131.4, 152.0, 174.8. HRMS (ESI) calcd for $(M+Na)^+$ $C_{35}H_{64}NaO_9$, 665.4599, found 665.4581.

4.1.27. Dihydro 6-*O*-undecyl-mannose acetogenin analog (9)

Compound **4** (6 mg, 0.01 mmol) was stirred in MeOH (2 mL) with Pd/C (15 mg) over a 24 h period in a hydrogen atmosphere. The reaction mixture was filtered though a bed of Celite and concentrated in vacuo. FCC of the residue gave **9** (6 mg, 99%). R_f = 0.3 (80% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 3H, J = 6.9 Hz), 1.23 (m, 34H), 1.41 (d, 3H, J = 6.2 Hz), 1.43–1.62 (m, 6H), 1.65, 1.91, 2.50, 2.90 (3 m, 6H), 2.10 (bs, 1H), 3.37 (m, 1H), 3.49 (t, 1H, J = 9.4 Hz), 3.56 – 3.91 (m, 9H), 4.37, 4.51 (2 m, 1H), 4.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 21.0, 22.9, 24.4, 25.4, 25.7, 26.2, 26.3, 29.4 (two lines), 29.5 (two lines), 29.6 (two lines), 29.7 (two lines), 29.8 (two lines), 29.9, 30.6, 32.1, 35.6, 36.2, 37.9, 38.2, 38.4, 39.6, 39.9, 40.0, 62.3, 66.8, 68.0, 70.6, 71.3, 71.5, 71.8, 73.5, 76.1, 76.8, 79.9, 99.6, 180.3, 180.4. HRMS (ESI) calcd for $(M+Na)^+$ $C_{35}H_{66}NaO_9$, 653.4599, found 653.4601.

4.1.28. Hexadecyl 6-*O*-undecyl-α-D-mannopyranoside (10)

To a solution of **12** (1.85 g, 4.7 mmol) in DCM (30 mL) was added $BF_3{\cdot}OEt_2$ (1.8 mL, 14.2 mmol) and 1-hexandecanol (3.4 g, 14.2 mmol). The mixture was stirred at reflux for 20 h, quenched with $NaHCO_3$ and extracted with DCM. The organic phase was dried (Na_2SO_4) filtered and concentrated in vacuo. FCC of the residue gave hexadecyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (1.6 g, 85%). Using a similar sequence of alcohol protecting group reactions, as described for the synthesis of **30** from **12**, this material (1.6 g, 2.8 mmol) was converted to hexadecyl 2,3-*O*-isopropylidene-α-D-mannopyranoside: (500 mg, 53%, three steps). R_f = 0.16 (30% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 6.9 Hz), 1.28 (m, 28H), 1.38 (s, 3H), 1.55 (s, 3H), 1.60 (m, 2H), 2.14 (t, 1H, J = 6.3 Hz), 2.71 (d, 1H, J = 4.8 Hz), 3.44 (m, 1H), 3.67 (m, 1H), 3.76 (m, 2H), 3.86 (m, 2H), 4.17 (m, 1H), 4.20 (m, 1H), 5.01 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.2, 26.3, 28.0, 29.5, 29.6, 29.7, 29.8 (two lines), 29.9 (two lines), 32.1, 62.8, 68.2, 69.7, 70.1, 75.7, 78.2, 97.4, 109.8.

Undecylation on hexadecyl 2,3-*O*-isopropylidene-α-D-mannopyranoside (500 mg, mmol) following the alkylation procedure described in the synthesis of **18**, provided hexadecyl 2,3-*O*-isopropylidene-6-*O*-undecyl-α-D-mannopyranoside (190 mg, 40% br sm). A mixture of this material (190 mg, 0.31 mmol), *p*-TsOH (150 mg, 0.78 mmol) and 1:1 MeOH/DCM (10 mL) was stirred for 2 h at rt, then quenched with $NaHCO_3$ and extracted with DCM. The organic phase was dried (Na_2SO_4) filtered and concentrated *in vacuo*. FCC of the residue provided **10** (171 mg, 98%). R_f = 0.4 (15% EtOAc/Petroleum ether). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, 6H, J = 6.9 Hz), 1.23 (m, 42H), 1.54 (m, 4H), 2.14 (bs, 1H), 2.40 (bs, 1H), 2.47 (bs, 1H), 3.35 (m, 1H), 3.52 (t, 1H, J = 9.4 Hz), 3.55 (m, 1H), 3.60 (m, 2H), 3.68 (m, 1H), 3.75 (dd, 1H, J = 3.8, 11.7 Hz), 3.83 (dd, 1H, J = 2.4, 11.7 Hz), 3.90 (m, 2H), 4.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 26.3 (two lines), 29.5 (two lines), 29.6 (two lines), 29.7 (two lines), 29.8 (three lines), 29.9 (two lines), 30.6, 32.1 (two lines), 62.3, 68.1, 71.3, 71.5, 71.8, 73.5, 76.0, 99.6. HRMS (ESI) calcd for $(M+NH_4)^+$ $C_{33}H_{70}NO_6$, 576.5198, found 576.5198.

4.1.29. Mannose–acetogenin analog (11)

CM on **23** (283 mg, 0.71 mmol) and butenolide **17** (47 mg, 0.24 mmol) following the procedure described for **24**, gave **29** (134 mg, 50%, Supplementary data), R_f = 0.20 (30% EtOAc/petroleum ether. Processing of **29** (67 mg, 1.2 mmol) as described for **4**, provided **11** (40 mg, 69%). R_f = 0.32 (10% MeOH/DCM). ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 18H), 1.35 (d, J = 6.8 Hz, 3H), 1.40 (m, 2H), 1.46 (m, 2H), 2.33 (dd, J = 8.2, 15.2 Hz, 1H), 2.44 (bd, J = 13.5 Hz, 1H), 2.79 (m, 1H), 3.32 (m, 1H), 3.45 (d, J = 9.6 Hz, 1H), 3.56 (m, 1H), 3.70 (bd, J = 11 Hz, 1H), 3.76 (m, 1H), 3.87 (m, 3H), 4.25 (bs, 1H), 4.62 (bs, 1H), 4.77 (s, 1H), 4.80 (bs, 1H), 4.99 (m, 1H), 7.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.2, 25.8, 29.5 (two lines), 29.6 (two lines), 29.7, 33.4, 37.5, 61.2, 66.5, 68.0, 70.2, 71.2, 71.8, 72.3, 78.3, 100.2, 131.3, 152.2, 175.0. HRMS (ESI) calcd for $(M+Na)^+$ $C_{25}H_{44}NaO_9$, 511.2878, found 511.2871.

4.2. Cytotoxicity assays and IC_{50}'s

Human cervical cancer cell line HeLa, breast cancer cell line MDA-MB231 and prostate cancer cell line PC-3 were cultured in Dulbecco's modified Eagles Medium supplemented with 10% FBS and penicillin streptomycin (5000 U/ml). T cell leukemia cell line Jurkat, was maintained in RPMI media supplemented with 10% FBS and penicillin streptomycin (5000 U/ml). Stock solutions of compounds were made in DMSO at a concentration of 20 mM. Serial dilutions of the test compounds were prepared in media at 37 °C before addition to cells.

Cytotoxicity was determined on various cell lines by incubating with serial dilutions of the test compounds for 48 h. Cell viability was determined using Cell titer Glo assay (Promega Corp. Madison, WI) as per the manufacturer's instructions. This assay is based on the measurement of ATP produced by healthy viable cells. Data were normalized to no compound control and expressed as percent viability. Dose response curves obtained from cytotoxicity assays using serial dilution of the compounds were fit using the Sigma plot analysis software. Each experiment was repeated thrice and the average IC_{50} was calculated along with standard deviation.

4.3. Dynamic light scattering measurements

Dynamic light scattering was measured using the PD2000DLS (PDDLS/Cool Batch 90T from Precision Detectors) instrument used in batch mode at 25 °C. Compounds **1** and **4** were dissolved in DMSO to obtain 10 mM stock solutions, which were further diluted to obtain 1 mM and 100 mM solutions in DMSO. 1 μl of each DMSO solution was added to 99 μl of Millipore water (1:100 dilution). 30 μl of the mixture was transferred into a glass microcuvette and immediately subjected to the measurement. In each experiment total acquisition time was 15 ms, for a total of 10 scans, which was repeated 5 times. The data was processed with SigmaPlot™.

Acknowledgements

This publication was made possible by a Research Centers in Minority Institutions Program grant from the National Institute of Health Disparities (MD007599) of the National Institutes of Health (NIH). Support from a Clinical Translational Science Center award (TR000457) from the NIH and the PSC-CUNY Research Program are also acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.08.027.

References and notes

1. Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z. M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275–306.
2. Alali, F. Q.; Liu, X. X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504–540.
3. Bermejo, A.; Figadere, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269–303.
4. McLaughlin, J. L. *J. Nat. Prod.* **2008**, *71*, 1311–1321.
5. Liaw, C.-C.; Wu, T.-Y.; Chang, F.-R.; Wu, Y.-C. *Planta Med.* **2010**, *76*, 1390–1404.
6. Londerhausen, M.; Leicht, W.; Lieb, F.; Moeschler, H.; Weiss, H. *Pestic. Sci.* **1991**, *33*, 427–438.
7. Zafra-Polo, M. C.; Gonzalez, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253–271.
8. Miyoshi, H.; Ohshima, M.; Shimada, H.; Akagi, T.; Iwamura, H.; McLaughlin, J. L. *Biochim. Biophys. Acta* **1998**, *1365*, 443–452.
9. Hopp, D. C.; Zeng, L.; Gu, Z.; McLaughlin, J. L. *J. Nat. Prod.* **1996**, *59*, 97–99.
10. Kojima, N.; Tanaka, T. *Molecules* **2009**, *14*, 3621–3661.
11. Hendrich, A. B.; Michalak, K. *Curr. Drug Targets* **2003**, *4*, 23–30.
12. Freitas, I. *J. Photochem. Photobiol.* **1990**, *7*, 359–361.
13. Queiroz, E. F.; Roblot, F.; Duret, P.; Figadère, B.; Gouyette, A.; Laprévote, O.; Serani, L.; Hocquemiller, R. *J. Med. Chem.* **2000**, *43*, 1604–1610.
14. Gorelik, E.; Galili, U.; Raz, A. *Cancer Metastasis Rev.* **2001**, *20*, 245–277.
15. Calvo, M. B.; Figueroa, A.; Pulido, E. G.; Campelo, R. G.; Aparicio, L. A. *Int. J. Endocrinol.* **2010**, 1–14.
16. Krohn, K.; Shuklov, I. *J. Carbohydr. Chem.* **2006**, *25*, 331–343.
17. Bradshaw, J. S.; Huszthy, P.; McDaniel, C. W.; Zhu, C. Y.; Dalley, N. K.; Izatt, R. M. *J. Org. Chem.* **1990**, *55*, 3129–3137.
18. Jacobsen, E. N.; Mark, I.; Mungall, W. S.; Schrcider, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968–1970.
19. De Armas, P.; Francisco, C. G.; Suárez, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 772–774.
20. Ferrier, R. J. *Top. Curr. Chem.* **2001**, *215*, 153–175.
21. Pierwocha, A. W.; Walczak, K. *Carbohydr. Res.* **2008**, *343*, 2680–2686.
22. Goncalves, A. G.; Noseda, M. D.; Duarteb, M. E. R.; Grindley, T. B. *Carbohydr. Res.* **2005**, *340*, 2245–2250.
23. Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396–10399.
24. Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014–12015.
25. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
26. Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.
27. Wang, F.; Kawamura, A.; Mootoo, D. R. *Bioorg. Med. Chem.* **2008**, *16*, 8413–8418.
28. Hui, Y.-H.; Rupprecht, J. K.; Liu, Y. M.; Anderson, J. E.; Smith, D. L.; Chang, C.-J.; McLaughlin, J. L. *J. Nat. Prod.* **1989**, *52*, 463–477.
29. Sasaki, S.; Maruta, K.; Naito, H.; Maemura, R.; Kawahara, E.; Maeda, M. *Chem. Pharm. Bull.* **1998**, *46*, 154–158.
30. Berne, B. J.; Pecora, R. *Dynamic Light Scattering*; Wiley: New York, 1976.