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Synthesis of carbohydrate analogues of the THF-acetogenin 4-deoxyannonmontacin and their cytotoxicity against human prostate cancer cell lines

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ABSTRACT

The THF containing acetogenin 4-deoxyannonmontacin (4-DAN) has attracted interest for its potent cytotoxicity against a broad range of human tumor cell lines, and relatively simple structure. Herein is described the synthesis and cytotoxicity of C-10 epimers of 4-DAN and analogues thereof comprising carbohydrate and thiophene substitutes for the THF and butenolide moieties respectively. The key synthetic ploy was the union of THF and butenolide segments or their substitutes, via an alkene cross metathesis. The different analogues showed cytotoxicity in the low micromolar to nanomolar range against the human prostate cancer cell lines LNCaP and PC3. A relatively simple mannose-linked thiophene analog was found to be similar in activity to 4-DAN.

1. Introduction

The tetrahydrofuran containing annonaceous acetogenins (THF-AGEs), are naturally occurring, cytotoxic agents that are active against a broad range of human cancer cell lines, including multi-drug resistant (MDR) strains, often in the picomolar range and lower [1–4]. However, their equally potent toxicity to normal cells presents a hurdle to clinical applications. To this end, diverse and easily accessible analogues are of interest for a clearer understanding of their anti-tumor activity and as therapeutic leads [1–5]. In this context the mono-THF-AGE 4-deoxyannonomontacin (4-DAN) **1a** is an attractive template for drug discovery because of its potent activity and relative simple structure [6]. In addition, the C-10 carbinol is a convenient handle for conjugation of tumor vectors or imaging agents (Fig. 1) [7,8]. Accordingly, we sought a scalable synthesis of analogues of 4-DAN [9]. To simplify the synthesis, a mixture of C-10 epimers was targeted (i.e **1a/b**), as our earlier studies suggested that changing the configuration at the analogous position in the very closely related THF-AGE 4-deoxyreticuin did not affect cytotoxicity [10].

We were also interested in substituting the THF and butenolide segments in 4-DAN with carbohydrate and thiophene residues respectively. Carbohydrate moieties may act as vectors for receptors on certain tumors, and reduce overall hydrophobicity, both of which are relevant to increasing tumor selectivity. Our earlier studies supported such carbohydrate analogues, which are structurally distinct from the acetogenin-sugar conjugates that have been reported by other laboratories [11,12]. Data from the Kojima group validated the use of thiophene-carboxamide moieties as surrogates for the butenolide [13]. However, introduction of both of sugar and thiophene substitutes on a single framework has not been examined. Herein we present a more systematic evaluation of these THF and butenolide replacements by synthesis of **1a/b - 4a/b** and evaluation of their cytotoxicity against androgen dependent and androgen independent human prostate cell lines, LNCaP and PC3 respectively.

2. Results and discussion

Retrosynthesis. Our synthesis plan followed a convergent strategy in which THF and butenolide components, (or their substitutes) were coupled via an alkene cross metathesis (CM), similar to that used in our earlier syntheses[14,15].

Synthesis of THF and carbohydrate segments. We first devised a more streamlined synthesis of the THF segment compared to our synthesis of the THF segment in 4-deoxyreticuin [9]. Accordingly, AD-mix β mediated dihydroxylation on the known *E*-hepta-4-decen-1-ol **5** [16,17], (obtainable in two steps from tridecanal), afforded the derived triol, which was transformed to the isopropylidene derivative **6** (Scheme 1). The enantiomeric purity of **6** was determined to be greater than 95% by

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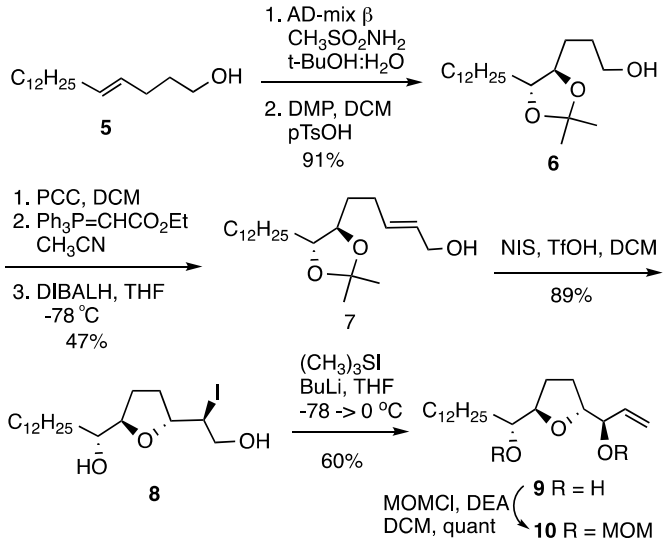
^{1}HNMR analysis of the (*R*)-MPTA ester. Chain extension on **6** through an alcohol oxidation-stabilized Wittig olefination-ester reduction sequence provided alkenol **7** in 47% overall yield from **6**. In the key step in the synthesis, **7** was treated with NIS and TfOH in dichloromethane. In agreement with our earlier observations on the iodoetherification of related *O*-isopropyidene alkenes, this reaction gave a high yield (89%), of the *trans*-THF isomer **8** [10,18–20]. The *cis* product was not observed. The stereochemistry of **8** was confirmed by X-ray analysis (Fig. 2) [21]. Exposure of **8** to dimethylsulfoniuom methylide effected *in situ* epoxide formation followed by ring opening to provide alkene THF-alkene **9** [22]. The NMR data for **9** was essentially identical to that for a sample we obtained from a different synthetic route, and very similar to data from another laboratory [12,13]. Alcohol protection in **9** using MOMCl and diisopropylethylamine afforded **10**.

The sugar alkene segment **13** was prepared via routine alcohol protecting group operations on 2,3-O-isopropylidene allyl α-D-mannopyranoside **11**, which was obtained in three steps from D-mannose (Scheme 2) [23]. Thus, selective silylation of the primary alcohol in **11** provided **12**. Subsequent protection of the secondary alcohol in **12** as the methoxymethyl ether, desilylation of the product and alkylation of the resulting primary alcohol with 1-bromo-undecane afforded **13**.

Synthesis of butenolide and thiophene segments. The synthesis of the butenolide alkene and substitutes thereof for the CM reactions, started with epoxide **14**, obtained from methyl 1-undecenoate (Scheme 3) [24]. The CuI promoted reaction of **14** with 4-penten-1-ylmagnesium bromide and silylation of the resulting alcohol afforded **15**. Following an established protocol, a two-step aldol-elimination sequence on **15** and aldehyde **16** afforded butenolide-alkene **17** [25]. LAH reduction of ester **15** provided alcohol **18**, which was transformed to thiophene alkene **21** via a straightforward three-step sequence: (i) mesylation of **18** to **19**; (ii) aminolysis of **19** to **20;** (iii) EDCI mediated amidation of **20** and 2-thiophene carboxylic acid.



Scheme 1. Synthesis of THF alkene.

CM reactions. The CM of THF-alkene **9** and 1.5 equivalents of butenolide alkene **17** was performed in CH_2Cl_2, at room temperature, in the presence of 20 mol% Grubbs II catalyst (Scheme 4). The THF-butenolide CM product **22** was obtained in 54% yield. For the THF- thiophene analog **2-a/b** the MOM-protected alkene **10** performed better than **9** as

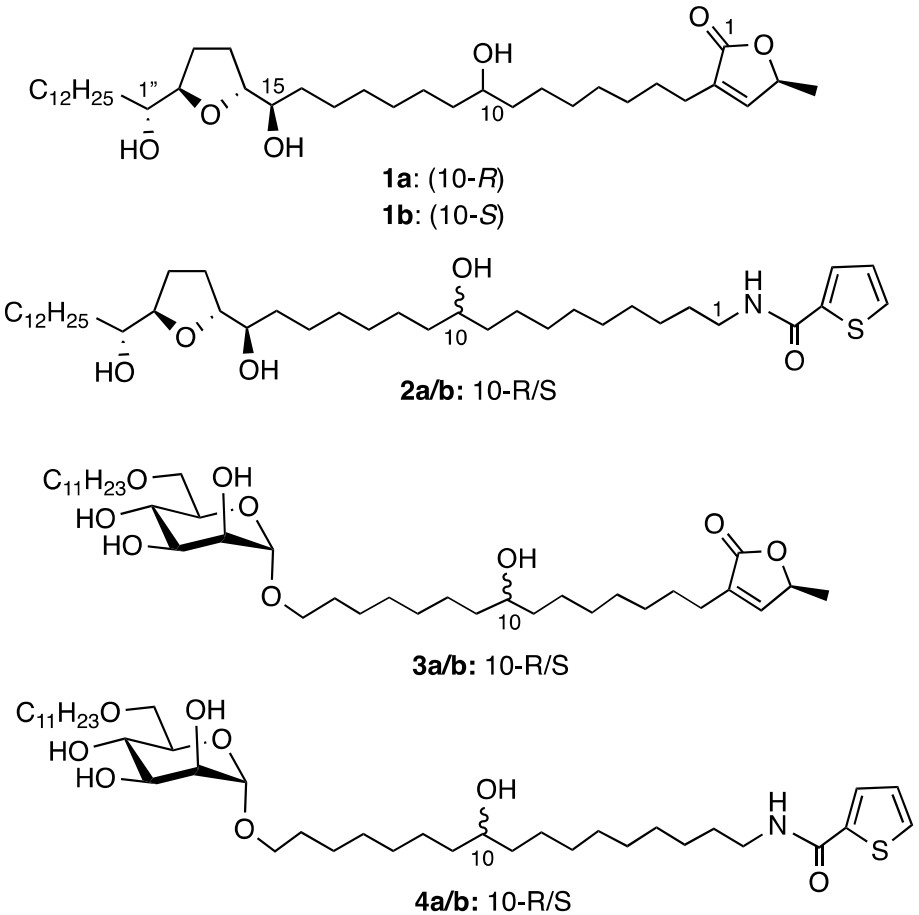


Fig. 1. Analogues of 4-DAN.

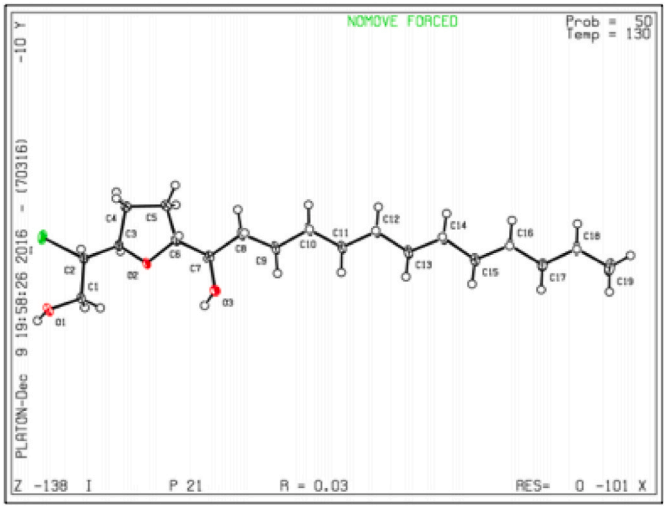
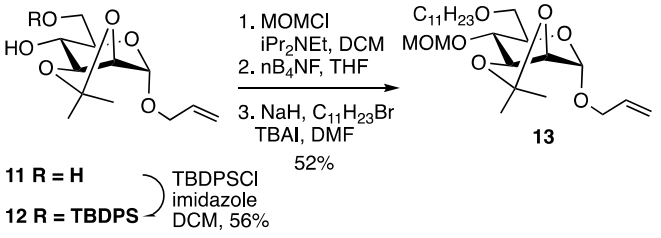
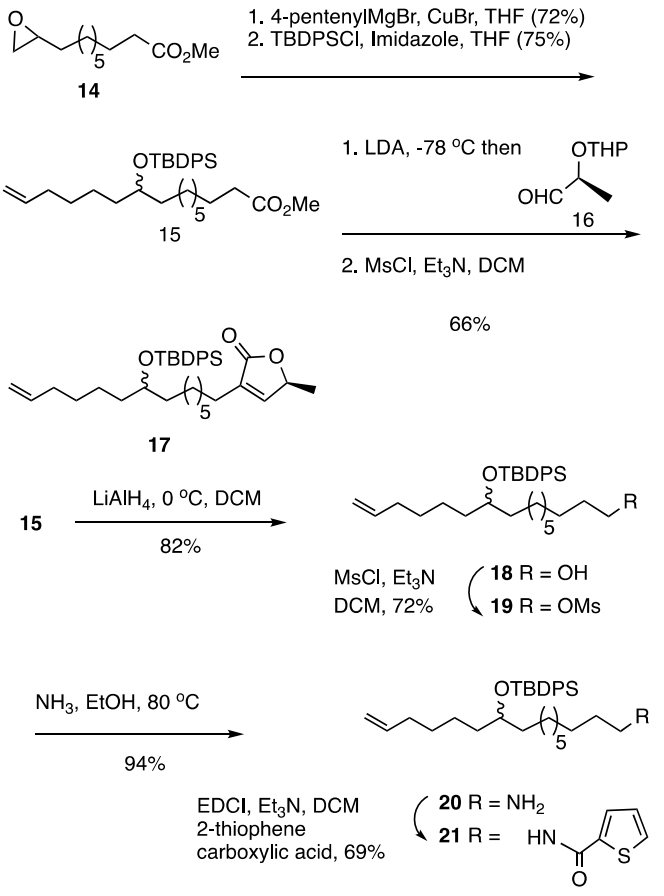


Fig. 2. X-Ray structure of iodo-THF **8**.



Scheme 2. Synthesis of carbohydrate alkene.



Scheme 3. Synthesis of butenolide and thiophene alkenes.

the THF-alkene component. Thus, reaction of **10** and 3 equivalents of **21** provided the THF-thiophene CM product **23** in 90% yield based on recovered **10**. Similarly, CMs using two equivalents of carbohydrate alkene **13** and **17** or **21** in the presence of Grubbs I catalyst at 40 °C afforded the sugar-butenolide and sugar-thiophene CM products, **24** and **25** in 74 and 70% yield respectively.

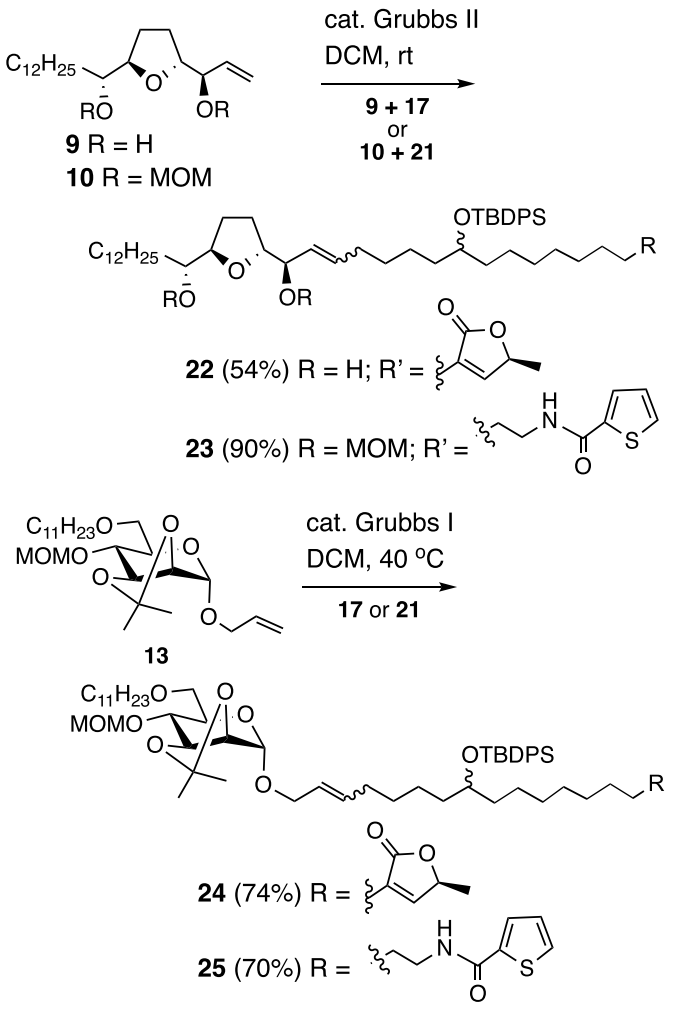
Transformation of CM products to target compounds. Alkene reduction on **22** using diimide, followed by acid catalyzed removal of alcohol protecting groups provided a mixture of C-10 epimers of 4-DAN, **1-a/b** (Scheme 5). Not surprisingly, given the remoteness of the epimeric carbon, this mixture was chromatographically inseparable, and the ^{1}H and ^{13}C NMR data for both epimers were very similar and essentially identical to the natural epimer, 4-DAN (Table 1). This synthesis which involves the late stage union of THF and butenolide precursors, available in nine and five steps respectively from inexpensive precursors, compares favorably to the previous total synthesis of 4-DAN that requires 17 and 10 step -sequences to analogous THF and butenolide precursors [7]. For either of the individual C-10 epimers, the present synthesis can be easily modified by starting with the requisite enantiomer of **14**, which can be obtained by resolution of **rac-14**, or asymmetric epoxidation of the alkene precursor [10,26,27].

Following the two-step reaction sequence on **22**, CM products **23** and **24** were transformed to **2-a/b** and **3-a/b** respectively. Palladium mediated hydrogenation of **25**, followed by removal of the silyl ether protecting group provided **4-a/b**. The final products, as for **1-a/b** were obtained as inseparable mixtures of epimers at the remote secondary carbinol.

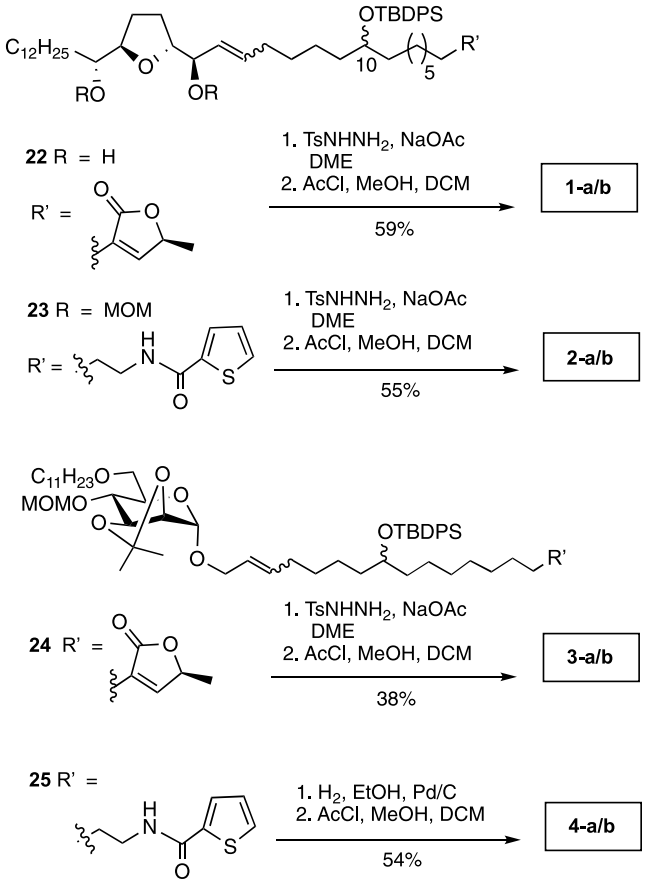
Cytotoxicity studies. The cytotoxicity of **1-a/b**, **2-a/b**, **3-a/b** and **4-a/b** against two human prostate cell lines, LNCaP (androgen dependent) and PC-3 (androgen independent) was determined by the XTT cell viability assay after 48 h of treatment with the test compounds (Table 2). The assays indicate androgen independent PC-3 cells were slightly more sensitive than LNCaP cells towards these compounds. The parent analog **1-a/b** showed low micromolar to nanomolar range activity against both cell lines. Replacement of the butenolide segment with the thiophene moiety (cf **2-a/b**), or the THF residue with the mannose residue (cf **3-a/b**), led to an appreciable reduction in potency. Surprisingly, when both modifications were implemented (cf **4-a/b**), the activity was very similar to that of the parent analog. These data suggests that the potency of **4-a/b** may be due to a synergistic effect of these individual modifications, rather than on predominantly one of the two changes. In the absence of mechanistic data it is unclear whether the mode of action of this novel analog is the same as the naturally occurring class of THF containing acetogenins. The IC_{50} values obtained with the test compounds are comparable to those for the commonly used chemotherapeutic Doxorubicin, which had IC_{50} values of 0.71 and 2.3 μM against LNCaP and PC-3 cells respectively. Thus, these are interesting lead compounds for *in vivo* studies.

3. Conclusion

In summary, a modular synthesis of 4-DAN, employing an alkene CM as the key segment coupling reaction was achieved. The synthetic strategy was applied to analogues of 4-DAN in which the THF and butenolide segments were replaced with mannose and thiophene moieties respectively. The final compounds were screened against LNCaP and PC-3 prostate cancer cell lines. The most active was a mannose-thiophene congener which showed very similar activity to the naturally occurring parent THF-butenolide. Given its potency and relatively simple synthesis, this mannose-thiophene is an attractive candidate for further biological studies. Mechanistic studies and tumor targeting strategies on this lead mannose derivative are in progress and will be reported in due course.



Scheme 4. Cross metathesis reactions.



Scheme 5. Transformation of CM products to target compounds.

4. Experimental section

4.1. General methods

Moisture and oxygen sensitive reactions were performed under an argon atmosphere. Solvents were purified by standard procedures or used directly from commercial sources. Thin layer chromatography (TLC) was done on 0.25 mm thick precoated silica gel HF254 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. Hexanes used for FCC had a boiling point in the 40–60 °C range. ^{1}H and ^{13}C NMR spectra were obtained on Bruker 400, 500 and 600 MHz instruments. Chemical shifts are quoted in ppm relative to tetramethysilane (δ_H 0.00) and coupling constants (J) are given in Hertz. First order approximations are employed throughout. High resolution mass spectrometry was performed on an Agilent 6520 Q-TOF instrument. X-ray diffraction data were collected on a Bruker X8 Kappa Apex II diffractometer. Crystal data, data collection and refinement parameters are summarized in Table S1.1. The structure was solved using direct methods and standard difference map techniques and was refined by full-matrix least-squares procedures on F2 with SHELXTL (Version 2014/7). The absolute configuration was established by anomalous dispersion effects.

Table 1
Selected NMR data for naturally occurring 4-DAN (**1a**) and **1-a/b**.

Carbon #	1a		1-a/b	
	^{1}H (δ ppm)	^{13}C (δ ppm)	^{1}H (δ ppm)	^{13}C (δ ppm)
1	–	174.0	–	174.2
2	–	134.3	–	134.5
3	2.26 t (7.0)	25.1	2.26 tt (1.5, 7.5)	25.3
4	1.53 (m)	27.4	1.55 (m)	27.6
10	3.58 m	71.9	3.56 m	72.1
17, 22	3.40 q (5.5)	74.0	3.40 q (6.5)	74.2
18, 21	3.80 q (7.5)	82.7, 82.6	3.79 q (6.5)	82.7, 82.8
19a,19b	1.69 m, 1.98 m	28.7	1.66 m, 1.97 m	28.9
20a,20b	1.69 m, 1.98 m	28.7	1.66 m, 1.97 m	28.9
34	0.88 t (7.5)	14.1	0.87 t (7.6)	14.4
35	6.99 t (1.5)	148.9	6.99 q (1.5, 6.5)	149.1
36	5.00 qq (7.2)	77.4	4.99 bq (6.7)	77.7
37	1.41 d (6.5)	19.2	1.42 d (6.8)	19.4

Table 2
Cytotoxicity (IC_{50}, μM) of **1-a/b**, **2-a/b**, **3-a/b**, **4-a/b**.

Test Comp.	LNCaP (μM)	PC-3 (μM)
1-**a/b**	0.27	0.075
2-**a/b**	1.9	1.5
3-**a/b**	3.4	4.5
4-**a/b**	0.48	0.061
Doxorubicin	0.71	2.3

4.2. THF-butenolide (1-a/b)

A solution of sodium acetate (0.62 g, 3 mmol) in water (12 mL) was added via a syringe pump, over 4 h, to a mixture of **22** (86 mg, 0.10 mmol), *p*-toluenesulfonylhydrazide (1.25 g, 3 mmol) and DME (10 mL) at reflux. After cooling to rt, the reaction mixture was concentrated under reduced pressure, diluted with water and extracted with EtOAc. The organic extract was washed with 2 M HCl, and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue afforded the 15,16-dihydro derivative of **22** (74 mg, 86%) as a pale yellow oil: *Rf* = 0.68 (2% acetone/dichloromethane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (m, 4H), 7.29–7.45 (m, 6H), 6.94 (s, 1H), 4.95 (m, 1H), 3.76 (m, 2H), 3.66 (m, 1H), 3.36 (m, 2H), 2.21 (m, 2H), 1.96 (m, 4H), 1.85 (br s, 2H), 1.36 (d, partially buried, J = 6.8 Hz, 3H), 1.34 (m, 10H), 1.25 (m, 36H), 1.00 (s, 9H), 0.85 (t, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 149.0, 136.1, 135.0, 134.5, 129.5, 127.5, 82.8, 82.7, 77.7, 74.2, 73.4, 36.5, 36.4, 33.7 (2 signals), 32.1, 31.8, 29.9 (2 signals), 29.8 (3 signals), 29.6, 29.4, 29.3, 28.9, 27.5, 27.3, 25.8, 25.8, 25.4, 25.0, 22.9 (2 signals), 19.6, 19.4, 14.3, 11.7. HRMS (ESI) *m/z* calcd for $C_{53}H_{86}O_6SiNa$ $(M + Na)^+$ 869.6091; found 869.6068.

A mixture of 5% AcCl in MeOH (0.5 mL) was added at rt to a solution of the product from the previous step (30 mg, 0.035 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at this temperature for 4 h, then adjusted to pH 6 with a saturated solution of K_2CO_3 in methanol. The mixture was filtered and concentrated *in vacuo*. FCC of the residue afforded **1-a/b** (15 mg, 68%) as a white wax: *Rf* = 0.20 (60% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) 6.99 (q, J = 1.5 Hz, 1H), 4.99 (qq, J = 1.5, 6.5 Hz, 1H), 3.79 (q, J = 6.5 Hz, 2H), 3.56 (m, 1H), 3.40 (q, J = 6.5 Hz, 2H), 2.26 (tt, J = 1.5, 7.5 Hz, 2H), 1.97 (m, 2H), 1.66 (m, 2H), 1.55 (m, 2H), 1.42 (d, partially buried, J = 6.8 Hz, 3H), 1.55–1.25 (m, 44H), 0.87 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 149.1, 134.5, 82.8, 82.8, 77.7, 74.3, 74.2, 72.2, 37.7, 37.6, 33.7, 33.6, 32.1, 29.9 (4 signals), 29.8 (2 signals), 29.6, 29.5, 29.3, 29.0, 27.6, 25.8, 25.7, 25.4, 22.9, 19.4, 14.4. HRMS (ESI) *m/z* calcd for $C_{37}H_{69}O_6$ $(M + H)^+$ 609.5094; found 609.5087.

4.3. THF-Thiophene (2-a/b)

A solution of sodium acetate (100 mg, 1.2 mmol) in water (1.3 mL) was added via a syringe pump, over 4 h, to a mixture of **23** (15 mg, 0.015 mmol) and *p*-toluenesulfonylhydrazide (200 mg, 1.06 mmol) in DME (1.3 mL) at reflux. The reaction was then processed as described for **1-a/b** to give the dihydro derivative of **23** (14 mg, 93%) as a yellow gum: *Rf* = 0.45 (25% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 8.0 Hz, 4H), 7.35 (m, 8H), 7.01 (t, J = 3.8 Hz, 1H), 5.91 (br s, 1H), 4.76 (m, 2H), 4.59 (m, 2H), 3.88 (m, 2H), 3.62 (m, 1H), 3.37 (m, 4H), 3.30 (s, 3H), 3.29 (s, 3H), 1.84–1.00 (m, 60H), 0.98 (s, 9H), 0.81 (t, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 139.4, 136.1, 135.1, 129.8, 129.5, 128.0, 127.7, 127.5, 96.9, 81.7, 79.9, 73.4, 55.9, 40.3, 36.5, 32.1, 31.5, 30.0 (two peaks), 29.9 (two peaks), 29.8, 29.7, 29.6, 29.5 (two peaks), 28.7, 27.3, 27.1, 25.7, 25.1, 22.9, 19.6, 14.3.

The product from the previous step (14 mg, 0.014 mmol) was dissolved in CH_2Cl_2 (1 mL) and treated with 5% AcCl in MeOH (0.4 mL) at rt for 4 h. At that time an additional portion of 5% AcCl in MeOH (0.2 mL) was added and stirring continued for an additional 1 h. The reaction was then processed as described for **1-a/b** to give **2-a/b** (5.5 mg, 59%) as a white powder: *Rf* = 0.40 (60% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, J = 3.7 Hz 1H), 7.42 (d, J = 4.9 Hz, 1H), 7.03 (dd, J = 3.7, 4.9 Hz, 1H), 5.96 (br s, 1H), 3.76 (m, 2H), 3.54 (m, 1H), 3.38 (m, 4H), 2.00–1.10 (m, 54H), 0.84 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 161.9, 139.1, 129.7, 127.8, 127.6, 82.7, 82.6, 74.1, 74.0, 72.0, 59.0, 40.1, 37.5, 33.5, 32.0, 29.7, 29.6 29.5, 29.4, 29.2, 28.8, 26.7, 25.6, 22.7, 14.2. HRMS (ESI) *m/z* calcd for $C_{39}H_{72}NO_5S$ $(M + H)^+$ 666.5131; found 666.5127.

4.4. Mannose-Butenolide (3-a/b)

A solution of sodium acetate (1.50 g, 18.8 mmol) in water (25 mL) was added via a syringe pump, over 4 h, to a mixture of **24** (388 mg, 0.40 mmol) and *p*-toluenesulfonylhydrazide (2.70 g, 14.5 mmol) in DME (25 mL) at reflux. The reaction was then processed as described for **1-a/b** to give the dihydro derivative of **24** (246 mg, 63%) as a yellow gum: *Rf* = 0.50 (2% acetone/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.60 (m, 4H), 7.33 (m, 6H), 6.88 (bs, 1H), 4.99 (s, 1H), 4.97 (m, 1H), 4.71 (ABq, J = 6.2 Hz, $\Delta\delta$ = 0.21 ppm, 2H), 4.12 (t, J = 6.0 Hz, 1H), 4.02 (m, 1H), 3.62 (m, 5H), 3.52 (m, 1H), 3.43 (m, 1H), 3.34 (m, 2H), 3.32 (s, 3H), 2.22 (m, 2H), 1.50–1.00 (m, 52H), 0.95 (s, 9H), 0.80 (t, J = 7.2 Hz, 3H). HRMS (ESI) *m/z* calcd for $C_{58}H_{92}O_{10}SiNa$ $(M + Na)^+$ 1001.6514, found 1001.6500.

A portion of the product from the previous step (30 mg, 0.031 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with 5% AcCl in MeOH (0.4 mL) at rt for 4 h. Additional 5% AcCl in MeOH (0.4 mL) was then introduced and stirring continued for 4 h. The reaction was then processed as described for **1-a/b** to give **3-a/b** (12 mg, 60%) as a white powder: *Rf* = 0.40 (5% MeOH/DCM). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.96 (s, 1H), 4.97 (m, 1H), 4.80 (s, 1H), 3.93 (dd, J = 1.4, 3.2 Hz, 1H), 3.85 (dd. J = 3.0, 9.1 Hz, 1H), 3.81–3.66 (m, 5H), 3.60 (m, 1H), 3.52 (m, 1H), 3.43 (m, 1H), 2.25 (m, 2H), 2.18 (bs, 4H, OH), 1.45–1.20 (m, 42H), 1.37 (partially buried d, J = 6.8 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) 174.2, 149.2, 134.5, 99.7, 77.5, 72.4, 72.2, 71.9, 70.8, 70.7, 69.5, 68.0, 37.7, 32.1, 29.8 (4 signals), 29.7, 29.6, 29.5, 29.4, 29.3, 27.6, 26.3, 26.2, 25.8, 25.7, 25.4, 22.9, 19.4, 14.3. HRMS (ESI) *m/z* calcd for $C_{37}H_{69}O_9$ $(M + H)^+$ 657.4942, found 657.4930.

4.5. Mannose-Thiophene (4-a/b)

A solution of **25** (245 mg, 0.23 mmol) in EtOH (10 mL) and Pd/C (150 mg, 10% wt) was purged with N_2 for 30 min. Then, the mixture was stirred under a hydrogen atmosphere (balloon) for 12 h. Additional Pd/C was then added (50 mg, 10% wt) and stirring continued for 24 h. The reaction was then purged with N_2 and filtered through a bed of Celite to yield the dihydro derivative of **25** (200 mg, 82%) as a clear oil: *Rf* = 0.53 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.64 (m, 4H), 7.43 (m, 1H), 7.38 (m, 1H), 7.34 (m, 6H), 7.04 (m, 1H), 5.92 (br s, 1H), 5.00 (s, 1H), 4.86 (apparent d, J = 6.3 Hz, 1H), 4.66 (apparent d, J = 6.3 Hz, 1H), 4.18 (t, J = 5.4 Hz, 1H), 4.07 (d, J = 5.4 Hz, 1H), 3.68 (m, 6H), 3.58 (m, 1H), 3.49 (m, 1H), 3.38 (m, 7H), 1.56 (m, 6H), 1.55 (s, 3H), 1.37 (m, 4H), 1.32 (partially buried s, 3H), 1.09–1.26 (m, 36H), 1.02 (s, 9H), 0.85 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 600 MHz) δ 162.0, 139.4, 136.2, 135.0, 129.9, 129.8, 129.6, 128.0, 127.9, 127.8, 127.6, 109.5, 97.1, 96.5, 78.7, 76.3, 73.4, 72.0, 69.9, 68.4, 67.8, 56.2, 40.3, 36.5, 32.1, 30.0, 29.9 (2 signals), 29.8 (2 signals), 29.7 (2 signals), 29.6 (2 signals), 29.5, 28.1, 27.3, 27.2, 26.8, 26.6, 26.4 (2 signals), 25.1, 22.9, 22.6, 19.6, 14.3.

A portion of the product from the previous step (42 mg, 0.041 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with 5% AcCl in MeOH (0.4 mL). Additional 5% AcCl in MeOH (0.2 mL) was then introduced and stirring continued for 8h. The reaction was then processed as described for **1-a/b** to give **4-a/b** (19 mg, 66%) as a white amorphous solid. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.42 (d, J = 3.6 Hz, 1H), 7.38 (d, J = 4.9 Hz, 1H), 6.99 (dd, J = 4.9 Hz, J = 3.8 Hz, 1H), 5.94 (br s, 1H), 3.84 (dd, J = 1.5, 3.2 Hz, 1H), 3.76 (dd, J = 2.7, 9.1 Hz, 1H), 3.72–3.58 (m, 5H), 3.51 (m, 1H), 3.43 (m, 2H), 3.35 (m, 3H), 2.28 (bs, 4H, OH), 1.58 (m, 5H), 1.38–1.18 (m, 41H), 0.81 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 600 MHz) δ 162.1, 139.3, 129.9, 128.1, 127.8, 99.8, 72.3, 72.2, 71.9, 71.8, 70.8, 70.6, 69.7, 68..0, 40.3, 37.6 (2 signals), 32.1, 29.8 (2 signals), 29.7 (2 signals), 29.6, 29.5, 29.4, 27.1, 6.3, 26.2, 25.8, 25.7, 22.9, 14.3. HRMS (ESI) *m/z* calcd for $C_{39}H_{71}NO_8SNa$ $(M + Na)^+$ 736.4793, found 736.4782.

4.6. 3-((4R,5R)-5-dodecyl-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol [6]

Methanesulfonamide (2.0 g, 45.3 mmol), AD-mix β (18.5 g, 0.023 mol) in 1:1 (v/v) water:t-BuOH (100 mL) was stirred for 1 h until the mixture was homogeneous. The mixture was cooled to 0 °C for 30 min at which time an orange precipitate was formed. A solution of **5** [14,15] (6.16 g, 0.24 mmol) in *t*-BuOH (17 mL) was next added and the mixture was stirred at 0 °C for 48 h. The reaction was then quenched with Na_2SO_3, filtered and extracted with EtOAc. The organic phase was concentrated *in vacuo* and the residue recrystallized from ethyl acetate to give the derived triol (6.71 g, 96%) as a white amorphous solid: MP: 66–69 °C; *Rf* = 0.15 (75% EtOAc/hexanes);. α_D^{25} $[\alpha]_D^{25}$ = 15.3 (c 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.72 (m, 2H), 3.47 (m, 2H), 3.08 (br s, 1H), 2.33 (br s, 1H), 2.30 (br s, 1H), 1.77 (m, 2H), 1.58–1.42 (m, 4H), 1.28 (br s, 20H), 0.90 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 74.9, 74.6, 63.2, 33.8, 32.1, 31.1, 29.9 (2 signals), 29.8 (2 signals), 29.6, 29.2, 25.9, 22.9, 14.3. HRMS (ESI): *m/z* $[C_{17}H_{36}O_3Na]^+$ calcd for 311.2555; found 311.2562.

To a solution of the product from the previous step (8.55 g, 29.7 mmol) in CH_2Cl_2 (58 mL) was added 2,2-dimethoxypropane (4.32 mL, 35.1 mmol) and *p*-TsOH (0.56 g, 2.93 mmol). The mixture was stirred for 1 h, then quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue (10–15% EtOAc/hexanes) afforded **6** (9.23 g, 94%) as a clear oil: *Rf* = 0.36 (35% acetone/hexanes). The enantiomeric purity of **6** was determined to be greater than 95% by Mosher ester analysis (*vide infra*). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.65 (m, 2H), 3.59 (m, 2H), 2.24 (br s, 1H), 1.71 (m, 2H), 1.56–1.20 (m, 22H), 1.37 (s, partially buried, 6H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 108.2, 81.2, 81.1, 62.9, 32.9, 32.1, 29.9 (2 signals), 29.8 (3 signals), 29.7 (2 signals), 29.5, 27.5, 27.4, 26.3, 22.8, 14.3. HRMS (ESI): *m/z* $[C_{20}H_{40}O_3Na]^+$ calcd for 351.2875, found 351.2869.

4.7. (R)-MTPA ester of **6**

To a stirred solution of **6** (35 mg, 0.11 mmol) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (46 mg, 0.20 mmol) in CH_2Cl_2 (5 mL), DMAP (*ca* 2 mg) and DCC (42 mg, 0.20 mmol) were added. The reaction was stirred at rt for 1 h at which time the mixture was diluted with ethyl ether. The resulting suspension was filtered over Celite and the filtrate was washed with brine and water. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude mixture was purified by FFC to give the **6-(*R*)-MTPA** (50 mg, 84%) as a white solid**:** *Rf* = 0.78 (30% acetone/hexanes). ^{1}H NMR (C_6D_6, 500 MHz) δ 7.68 (m, 2H), 7.09–6.96 (m, 3H), 4.10 (m, 1H), 4.05 (m, 1H), 3.49 (m 1H), 3.42 (s, 3H), 3.41 (partially buried m, 1H), 1.65–1.55 (m, 6H), 1.29 (s, 3H), 1.28 (s, 3H), 1.26 (m, 20H), 0.91 (t, *J* = 5.7 Hz, 3H). ^{13}C NMR (C_6D_6, 125 MHz) δ 166.9, 133.5, 130.1, 130.0, 129.2, 129.0, 128.8, 128.7, 127.9, 125.6, 123.7, 108.5, 81.6, 81.0, 66.4, 55.7, 33.5, 32.7, 30.6, 30.5 (2 signals), 30.4 (2 signals), 30.2, 29.5, 28.0, 27.9, 27.1, 26.1 (2 signals), 26.0, 23.5, 14.7, 1.7. HRMS (ESI): *m/z* $[C_{30}H_{47}F_3O_5Na]^+$ calcd for 567.3268; found 567.3249.

4.8. (R)-MTPA ester of ***rac*-6**

Osmium tetroxide in *t*-butanol (2.5% wt, 0.35 mL, 0.03 mmol) was added to a solution of **5** (50 mg, 0.20 mmol) in a 1:1 mixture of water acetone (2 mL) at rt. Then, 50% w/w solution of *N*-methylmorpholine-N-oxide in water (0.04 mL, 0.20 mmol) was introduced and the reaction mixture was stirred for 2 h, at which time Na_2SO_3 (17 mg, 0.06 mmol) was added and stirring continued for an additional 1 h. The mixture was then diluted with water and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue provided the triol derivative (50 mg, 87%) as a clear gum: *Rf* = 0.15 (75% EtOAc/hexanes). This product was transformed in two steps, as described for optically active **6**, to the ***R***-MTPA-ester of (+/−)-**6**: *Rf* = 0.78 (30% acetone/hexanes). ^{1}H NMR (C_6D_6, 400 MHz) δ 7.66 (m, 2H), 7.05 (m, 3H), 4.07 (m, 2H), 3.89 (m, 1H), 3.50 (m, 1H), 3.47 (m, 1H), 3.38 (m, 3H), 3.33 (m, 3H), 1.55 (m, 2H), 1.40 (br s, 16H), 0.8 (m, 2H), 0.7 (m, 2H), 0.4 (m, 3H). ^{13}C NMR (C_6D_6, 100 MHz) δ 165.4, 165.3, 132.0, 128.6, 128.5, 128.5, 127.7, 127.5, 127.4, 127.1, 127.0, 126.9, 126.7, 126.6, 126.1, 124.5, 121.7, 107.0, 84.1, 83.8, 80.1, 79.5, 64.9, 64.9, 60.9, 55.7, 54.1 (2 signals), 51.1, 48.9, 32.0, 31.3, 31.2, 30.2, 29.0 (2 signals), 28.9 (3 signals), 28.6, 28.0, 26.5, 26.4, 25.5, 25.3, 25.2, 24.6 (3 signals), 24.5, 23.6 (2 signals), 21.9, 13.2, 12.6.

4.9. (E)-5-((4R,5R)-5-dodecyl-2,2-dimethyl-1,3-dioxolan-4-yl)pent-2-en-1-ol (7)

A suspension of powdered, freshly activated molecular sieves (7 g), Fluorosil (7 g), Celite (7 g), CH_3COONa (2.54 g, 31.2 mmol), PCC (6.61 g, 31 mmol) and **6** (6.84 g, 20.8 mmol) in CH_2Cl_2 (19 mL) was stirred under nitrogen for 1 h. At that time, the mixture was diluted with ether and filtered over Fluorosil. The filtrate was concentrated under reduced pressure and the residue subjected to FCC to give the derived aldehyde (4.42 g, 65%) as a yellow oil: *Rf* = 0.45 (15% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (s, 1H), 3.54 (m, 2H), 2.57 (m, 2H), 1.90 (m, 1H), 1.68 (m, 1H), 1.46 (m, 2H), 1.34–1.19 (m, 20H), 1.34 (s, partially buried, 6H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.1, 108.4, 81.0, 80.0, 40.7, 33.0, 32.1, 29.9 (2 signals), 29.8, 29.7, 27.5, 27.4, 26.3, 25.3, 22.9, 14.3.

To a solution of the product from the previous step (5.06 g, 15.5 mmol) in CH_3CN (150 mL) was added methyl (triphenylphosphoranylidene) acetate (15.5 g, 46.5 mmol). The mixture was heated at reflux for 1.5 h, then filtered over Celite. The filtrate was concentrated under reduced pressure and the residue purified by FCC to give the unsaturated ester derivative (4.67 g, 79%) as a clear oil: *Rf* = 0.85 (15% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.94 (m, 1H), 5.81 (m, 1H), 3.68 (s, 3H), 3.55 (m, 2H), 2.36 (m, 1H), 2.25 (m, 1H), 1.76 (m, 2H), 1.45 (m, 2H), 1.32–1.10 (m, 20H), 1.32 (s, partially buried 6H), 0.82 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.2, 148.8, 121.4, 108.2, 81.0, 80.2, 51.6, 33.1, 32.1, 31.4, 29.9, 29.8 (3 signals), 29.7, 29.5, 29.0, 27.5, 27.4, 26.3, 22.9, 14.3. HRMS (ESI): *m/z* $[C_{23}H_{42}O_4Na]^+$ calcd for 405.2981; found 405.2985.

To a portion of the product from the previous step (450 mg, 1.18 mmol) in CH_2Cl_2 (10 mL) was added a 1.2 M DIBAL-H in toluene (2.3 mL, 2.76 mmol) at −78 °C under nitrogen. The mixture was warmed to rt, stirred at this temperature for an additional 1.5 h, poured into a saturated aqueous solution of Rochelle's salt (10 mL), and extracted with CH_2Cl_2. The organic phase was washed with brine, dried ($NaSO_4$) and filtered and evaporated under reduced pressure. FCC of the residue (20% EtOAc/hexanes) afforded **7** (405 mg, 97%) as a clear gum: *Rf* = 0.53 (25% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.66 (m, 2H), 4.06 (m, 2H), 3.57 (m, 2H), 2.23 (m, 1H), 2.10 (m, 1H), 1.69 (s, 1H), 1.56 (m, 4H), 1.32 (s, partially buried, 6H), 1.18 (m, 20H), 0.81 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 132.5, 129.6, 108.1, 81.2, 81.1, 63.9, 33.1, 32.6, 32.1, 30.0, 29.9, 29.8 (2 signals), 29.7, 29.5, 29.0, 27.5 (2 signals), 26.4, 22.9, 14.3. HRMS (ESI): *m/z* $[C_{22}H_{42}O_3Na]^+$ calcd for 377.3032; found 377.3026.

4.10. (R)-1-((2R,5R)-5-((S)-2-hydroxy-1-iodoethyl)tetrahydrofuran-2-yl)tridecan-1-ol (8)

To a solution of compound **7** (390 mg, 1.10 mmol) in CH_3CN (100 mL) was added NIS (100 mg, 4.40 mmol) and AgOTf (6 mg, 0.02 mmol). The mixture was stirred at rt for 3 h, then diluted with 10% aqueous $Na_2S_2O_3$ and extracted with EtOAc. The organic phase was dried

(Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue afforded **8** (430 mg, 89%) as white needles: MP: 47–49 °C; *Rf* = 0.33 (25% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.23 (m, 1H), 4.11 (m, 1H), 4.00 (m, 1H), 3.95 (m, 2H), 3.46 (m, 1H), 2.85 (t, *J* = 13.1 Hz, 1H), 2.41 (m, 1H), 2.10 (m, 2H), 1.99–1.73 (m, 2H), 1.42 (m, 2H), 1.28 (s, 20H), 0.85 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 84.1, 83.1, 74.0, 68.0, 39.3, 34.3, 33.9, 32.1, 29.9 (2 signals), 29.8 (2 signals), 29.6, 28.2, 25.8, 22.9, 14.4. HRMS (ESI): *m/z* $[C_{19}H_{37}IO_3Na]^+$ calcd for 463.1685; found 463.1681.

4.11. (R)-1-((2R,5R)-5-((R)-1-hydroxyallyl)tetrahydrofuran-2-yl) tridecan-1-ol (9)

To a solution of Me_3SI (2.23 g, 10.4 mmol) in THF (11 mL) at −78 °C was added a 2.5 M solution *n*-BuLi in THF (3.6 mL, 9.0 mmol) under N_2. The mixture was warmed to rt, maintained at this temperature for 1 h, then recooled to −78 °C. A solution of **8** (500 mg, 1.14 mmol) in THF (12 mL) was then introduced and the mixture stirred at −78 °C for 2 h. A second portion of sulfonium ylide was then prepared in THF (11 mL) from Me_3SI (1.88 g, 9.1 mmol) and *n*-BuLi (2.9 mL, 7.3 mmol) at −78 °C, then warmed to rt and added to the original reaction mixture at −78 °C. The mixture was allowed to warm to rt, and stirred for an additional 2 h at this temperature. The reaction was then quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. FCC of the residue gave **9** (220 mg, 60%) as a clear oil: *Rf* = 0.57 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.76 (m, 1H), 5.34 (dd, *J* = 1.4, 17.2 Hz, 1H), 5.17 (dd, *J* = 1.3, 10.5 Hz, 1H), 3.92 (t, *J* = 6.2 Hz, 1H), 3.82 (m, 2H), 3.38 (m, 1H), 2.93 (bs, 1H, OH), 2.67 (bs, 1H, OH), 1.93 (m, 2H), 1.64 (m, 2H), 1.42 (m, 1H), 1.34 (m, 3H), 1.21 (m, 18H), 0.74 (t, *J* = 6.9 Hz, 3H).^{13}C NMR ($CDCl_3$, 125 MHz) δ 136.8, 117.4, 83.1, 82.4, 75.8, 74.2, 33.5, 32.1, 29.9 (2 signals), 29.8 (4 signals), 29.5, 28.7, 28.6, 25.8, 22.9, 14.3. HRMS (ESI): *m/z* $[C_{20}H_{38}O_3Na]^+$ calcd for 349.2719; found 349.2715.

4.12. (2R,5R)-2-((R)-1-(methoxymethoxy)allyl)-5-((R)-1-(methoxymethoxy)tridecyl)-tetrahydrofuran (10)

MOMCl (0.14 mL, 1.84 mmol) was added to a mixture of **9** (150 mg, 0.46 mmol) and DIPEA (0.41 mL, 2.3 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The solution was allowed to warm to rt, stirred at this temperature for 16 h, then poured into water and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), concentrated *in vacuo* and purified by FCC (10% EtOAc/hexanes) to afford **10** (190 mg, 95%) as a clear oil: *Rf* = 0.5 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.71 (m, 1H), 5.28 (m, 1H), 5.24 (m, 1H), 4.82 (m, 1H), 4.65 (m, 4H), 3.99 (m, 3H), 3.37 (d, *J* = 2.8 Hz, 6H), 1.89 (m, 2H), 1.66 (m, 2H), 1.39 (m, 4H), 1.23 (m, 20H), 0.86 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 135.0, 118.9, 96.9, 94.2, 81.8, 81.1, 79.7, 79.4, 55.9, 55.5, 32.1, 31.3, 30.0, 29.9 (2 signals), 29.8, 29.6, 28.3, 28.2, 25.8, 22.9, 14.3. HRMS (ESI): *m/z* $[C_{24}H_{46}O_5Na]^+$ calcd for 437.3243; found 437.3238.

4.13. Propen-1-yl-6-O-tert-butyldiphenylsilyl-4-O-methoxyethyl-2,3-O-isopropylidene-α-D-mannopyranoside (12)

A mixture of **11** (2.19 g, 8.41 mmol), TBDPSCl (2.37 mL, 9.25 mmol) and imidazole (1.14 g, 16.8 mmol) in anhydrous THF (80 mL) was stirred overnight at rt. The mixture was concentrated under reduced pressure, diluted with water and extracted with ether. The combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. FCC of the residue afforded recovered **11** (630 mg) and **12** (1.7 g, 56% brsm) as a clear oil: *Rf* = 0.40 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (m, 4H), 7.44 (m, 6H), 5.90 (m, 1H), 5.28 (m, 1H), 5.22 (m, 1H), 5.06 (s, 1H), 4.18 (m, 3H), 3.99 (m, 1H), 3.95 (m, 2H), 3.91 (m, 1H), 3.88 (m, 1H), 2.75 (m, 1H), 1.53 (s, 3H), 1.27 (s, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 500 MHz) δ 135.8, 135.7, 133.6, 133.0, 130.0 (2 signals), 127.9 (2 signals), 118.1, 109.7, 96.3, 78.3, 75.5, 71.0, 69.6, 68.0, 64.8, 28.1, 27.0, 26.3, 19.4. HRMS (ESI) calcd for $C_{28}H_{38}O_6SiNa$ $(M + Na)^+$ 521.2335, found 521.2329.

4.14. Propen-1-yl-3,4-O-isopropyledene-4-O-methoxymethyl-6-O-undecyl-α-D-manno-pyranoside (13)

MOMCl (0.87 mL, 11.5 mmol) was added to a solution **12** (1.86 g, 3.72 mmol) and DIPEA (2.67 mL, 15.3 mmol) in anhydrous DCM (25 mL) at 0 °C. The mixture was stirred at rt for 16 h, then diluted with water and extracted with DCM. The organic phase was dried (Na_2SO_4), concentrated *in vacuo*. FCC of the residue afforded the 4-*O*-methoxymethyl derivative (1.77 mg, 88%) as a clear oil: *Rf* = 0.60 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (m, 4H), 7.40 (m, 6H), 5.93 (m, 1H), 5.30 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.22 (dd, *J* = 1.2, 10.4 Hz, 1H), 5.13 (s, 1H), 4.77 (ABq, *J* = 6.4 Hz, $\Delta\delta$ = 0.21, 2H), 4.27 (m, 2H), 4.23 (m, 1H), 4.02 (dd, *J* = 6.4, 10.0 Hz, 1H), 3.90 (dd, *J* = 1.9, 9.6 Hz, 1H), 9.85 (dd, *J* = 5.4, 11.0 Hz, 1H), 3.72 (m, 2H), 3.22 (s, 3H), 1.55 (s, 3H), 1.38 (s, 3H), 1.08 (s, 9H).

A mixture of the product from the previous step (140 mg, 0.26 mmol), TBAF (1 M in THF, 0.60 mL, 0.60 mmol) and THF (2 mL) was stirred for 16 h at rt. The solvent was then evaporated *in vacuo*. FCC of the residue provided the desilylated derivative (75 mg, 95%) as a gum: *Rf* = 0.30 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.94 (m, 1H), 5.35 (dd, *J* = 2.2, 17.2 Hz, 1H), 5.25 (dd, *J* = 1.2, 10.2 Hz, 1H), 5.12 (s, 1H), 4.84 (ABq, *J* = 6.9 Hz, $\Delta\delta$ = 0.25, 2H), 4.27 (dd, *J* = 5.7, 7.5 Hz, 1H), 4.17 (m, 2H), 4.03 (dd, *J* = 7.2, 12.8 Hz, 1H), 3.85 (m, 1H), 3.76 (dd, *J* = 7.4, 10.2 Hz, 1H), 3.65 (m, 1H), 3.45 (s, 3H), 2.35 (t, *J* = 6.9 Hz, 1H), 1.38 (s, 3H), 1.29 (s, 3H).

A 60% suspension of NaH in mineral oil (54 mg, 1.35 mmol) was added to a mixture of the material from the previous step (75 mg, 0.25 mmol) and TBAI (14 mg, 0.04 mmol) in DMF (1 mL) at 0 °C, under nitrogen. The mixture was then warmed to rt over 30 min, then cooled to 0 °C, after which undecyl bromide (0.18 mL, 0.74 mmol) was added. The reaction was stirred at rt for 16 h, then cooled to 0 °C, quenched with MeOH (0.5 mL) and diluted with water. The mixture was extracted with ethyl ether and the organic phase washed with brine, dried (Na_2SO_4) and evaporated *in vacuo*. FCC of the residue afforded **13** (71 mg, 62%) as a gum: *Rf* = 0.60 (10% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.87 (m, 1H), 5.26 (m, 1H), 5.17 (m, 1H), 5.65 (s, 1H), 4.86 (d, *J* = 5.3 Hz, 1H), 4.65 (d, *J* = 5.2 Hz, 1H), 4.19 (m, 1H), 4.11 (m, 1H), 3.98 (m, 1H), 3.66 (m, 3H), 3.57 (m, 1H), 3.48 (m, 1H), 3.42 (m, 4H), 1.55 (m, 4H), 1.50 (s, 3H), 1.31 (partially buried s, 3H), 1.30–1.22 (m, 21H), 0.86 (t, *J* = 5.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.6, 117.8, 109.3, 96.3, 96.2, 78.4, 75.9, 73.2, 71.8, 69.7, 68.3, 67.9, 56.0, 31.9, 29.8, 29.7, 29.6, 29.5, 29.3, 27.9, 26.4, 26.2, 22.7, 14.2. HRMS (ESI) calcd for $C_{25}H_{47}O_7$ $(M + H)^+$ 458.3244, found 458.3243.

4.15. Methyl (R/S)-10-((tert-butyldiphenylsilyl)oxy)hexadec-15-enoate (15)

An approximately 1 M solution of 4-pentenylmagnesium bromide in THF was prepared by dropwise addition of 4-pentenyl bromide (24 mL, 0.21 mol) to a suspension of magnesium (4.8 g, 0.20 mmol) in anhydrous THF (200 mL). To a suspension of CuBr (I) (3.70 g, 0.26 mol) in THF (300 mL) at 0 °C was added a portion of the 1 M solution of 4-pentenylmagnesium bromide (150 mL, 0.13 mol) over 5 min. A solution of **14** [24] (10.6 g, 49.5 mmol) in anhydrous THF (60 mL) was then introduced, dropwise over 5 min. The reaction was stirred at 0 °C for 10 min, then saturated aqueous NH_4Cl was added and the mixture extracted with ethyl ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue gave the derived alcohol (10.2 g, 72%) as a clear oil: *Rf* = 0.15 (10% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.77 (m, 1H), 4.92 (m, 1H), 4.91 (m, 1H), 3.63 (s, 3H), 3.53 (br s, 1H), 2.26 (m, 2H), 2.03 (m, 2H), 1.34–1.26 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.6, 139.1,

114.6, 72.1, 51.7, 37.6, 37.5, 34.3, 29.8, 29.6, 29.4, 29.3 (2 signals), 29.1, 25.8, 25.3, 25.1.

A mixture of the product from the previous step (7.31 g, 0.025 mol), TBDPSCl (6.24 mL, 0.024 mol) and imidazole (8.33 g, 0.12 mol) in anhydrous THF (200 mL) was heated at reflux under nitrogen for 4 h. The mixture was then diluted with water, extracted with ethyl ether and washed with brine. The organic phase was dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The residue was purified by FCC to afford **15** (9.37 g, 75%) as a colorless oil: *Rf* = 0.75 (10% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (m, J = 7.6 Hz, 4H), 7.36 (m, 6H), 5.72 (m, 1H), 4.89 (m, 1H), 4.87 (m, 1H), 3.67 (m, partially buried, 1H), 3.64 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.91 (m, 2H), 1.08–1.25 (m, 20H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.4, 139.1, 136.0, 134.8, 129.4, 127.4, 114.2, 73.2, 51.5, 36.3, 36.1, 34.1, 33.7, 29.6, 29.4, 29.2, 29.1, 29.0, 27.1, 25.0, 24.8, 24.4, 19.4. HRMS (ESI): *m/z* $[C_{33}H_{51}O_3Si]^+$ calcd for 523.3602, found 523.3585.

4.16. (5S)-3-((R/S)8-((tert-butyldiphenylsilyl)oxy)tetradec-13-en-1-yl)-5-methylfuran-2(5H)-one (17)

To a solution of diisopropylamine (9.8 mL, 0.07 mmol) in anhydrous THF (120 mL) at −78 °C was added *n*-BuLi (21.7 mL, 2.3 M in hexane, 0.05 mol). The mixture was warmed to 0 °C and stirred at this temperature for 10 min, then re-cooled to −78 °C. A solution of **15** (5.2 g, 0.01 mol) in anhydrous THF (60 mL) was then added and the mixture maintained at −78 °C for 1 h, at which time a solution of **16** [22] (4.7 g, 0.03 mmol) in anhydrous THF (30 mL) was added dropwise over 30 min. After stirring at −78 °C for an additional 45 min, the reaction was diluted with saturated aqueous NH_4Cl and extracted with ethyl ether. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure and the residue taken up in a mixture methanol (40 mL) and 2-propanol (4 mL). Th solution was adjusted to pH 4 by addition of $TsOH{\cdot}H_2O$ (0.25 g), stirred at rt for 20 h, then concentrated under reduced pressure. FCC of the residue afforded recovered **15** (1.5 g), and a more polar material as a yellow oil (3.6 g): R*f* = 0.25 (20% EtOAc/hexanes),

To a portion of the product (3.3 g) from the previous step in CH_2Cl_2 (100 mL) was added Et_3N (4.1 mL, 0.03 mol) and MsCl (0.9 mL, 0.01 mol) at 0 °C. After stirring at rt for 14 h, the reaction was diluted with saturated aqueous NH_4Cl and extracted with ethyl ether. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. FCC of the residue afforded **17** (2.34 g, 66% based on recovered **15**) as a colorless oil: R*f* = 0.45 ((20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65–7.63 (m, 4H), 7.42–7.31 (m, 6H), 6.94 (s, 1H), 5.76–5.67 (m, 1H), 4.96 (m, 1H), 4.87 (m, 1H), 4.83 (m, 1H), 3.67 (m, 1H), 2.22 (m, 2H), 1.91 (m, 2H), 1.16 (m, 3H), 1.07–1.15 (m, 18H), 1.03 (s, (H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 149.0, 139.2, 136.1, 135.0, 130.0, 129.5, 127.9, 127.5, 114.3, 77.3, 36.4, 36.3, 33.9, 29.7, 29.4, 29.3, 29.1, 27.5, 27.3, 26.7, 25.3, 25.0, 24.6, 19.6, 19.4. HRMS (ESI): *m/z* $[C_{35}H_{51}O_3Si]^+$ calcd for 546.3529; found 546.3529.

4.17. (R/S)-10-((tert-butyldiphenylsilyl)oxy)hexadec-15-en-1-ol (18)

LAH (0.10 g, 2.7 mmol) was slowly added to a solution of **15** (0.92 g, 1.8 mmol) in CH_2Cl_2 (18 mL) at 0 °C. The mixture was warmed to rt and stirred for an additional 1 h. Then, slowly water (10 mL), NaOH (1 mL, 1 M), and anhydrous Na_2SO_4 were sequentially added. The mixture was stirred for 30 min and the resulting suspension filtered over Celite. The filtrate was concentrated *in vacuo*. FCC of the residue provided **18** (0.71 g, 82%) as a clear oil: *Rf* = 0.20 (10% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (m, 4H), 7.34 (m, 6H), 5.72 (m, 1H), 4.92 (m, 1H), 4.88 (m, 1H), 4.10 (m, 1H), 3.68 (m, 1H), 3.62 (m, 2H), 1.92 (m, 2H), 1.54 (m, 4H), 1.38–1.17 (m, 8H), 1.02 (s, 9H). HRMS (ESI): *m/z* $[C_{32}H_{50}O_2SiNa]^+$ calcd for 517.3478; found 517.3472.

4.18. (R/S)-10-((tert-butyldiphenylsilyl)oxy)hexadec-15-en-1-yl methanesulfonate (19)

To a solution of **18** (1.00 g, 2.02 mmol) at 0 °C in CH_2Cl_2 (30 mL) was added Et_3N (0.35 mL, 2.57 mmol) and MsCl (0.19 mL, 2.57 mmol). The mixture was warmed to rt and stirred for 16 h, then diluted with water and extracted with ethyl ether. The organic phase was washed with brine, dried (Na_2SO_4), filtered and evaporated *in vacuo*. FCC of the residue afforded **19** (0.84 g, 72%) as a yellow oil: *Rf* = 0.5 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (m, 4H), 7.41–7.32 (m, 6H), 5.72 (m, 1H), 4.91 (m, 1H), 4.88 (m, 1H), 4.20 (t, J = 6.6 Hz, 2H), 3.67 (m, 1H), 2.98 (s, 3H), 1.91 (m, 2H), 1.72 (m, 2H), 1.40–1.06 (m, 20H), 1.02 (br s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.3, 136.1, 129.6, 127.6, 114.4, 73.4, 70.4, 37.6, 36.5, 36.3, 34.0, 29.9, 29.8, 29.6, 29.5, 29.3, 29.2, 29.1, 27.3, 25.6, 25.1, 24.6, 19.6. HRMS (ESI): *m/z* $[C_{33}H_{52}O_4SSiNa]^+$ calcd for 595.3253; found 595.3246.

4.19. (R/S)-10-((tert-butyldiphenylsilyl)oxy)hexadec-15-en-1-amine (20)

A mixture of **19** (0.65 g, 1.13 mmol) and a saturated solution of ammonia in ethanol (150 mL) in a sealed high-pressure tube was heated at 80 °C for 4 h. The volatiles were then removed *in vacuo* and the residue purified by FCC to give **20** (0.48 g, 86%) as a yellow oil: *Rf* = 0.32 (20% $MeOH/CH_2Cl_2$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.63 (m, 4H), 7.36 (m, 6H), 5.70 (m, 1H), 4.88 (m, 1H), 4.85 (m, 1H), 4.10 (m, 1H), 3.10 (m, 2H), 1.90 (m, 2H), 1.45 (m, 2H), 1.35 (m, 4H), 1.16 (m, 16H), 1.06 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.2, 136.1, 134.9, 129.5, 127.5, 114.3, 73.3, 40.1, 39.4, 36.4, 36.3, 33.9, 29.8, 29.7, 29.6, 29.2, 29.1, 27.8, 27.2, 26.7, 25.0, 24.5, 19.6.

4.20. N-((R/S)-10-((tert-Butyldiphenylsilyl)oxy)hexadec-15-en-1-yl) thiophene-2-carboxamide (21)

EDCI (0.30 g, 1.58 mmol), Et_3N (0.29 mL, 2.10 mmol) and DMAP (13 mg, 0.10 mmol) were added sequentially to a mixture of **20** (0.26 g, 0.53 mmol) and 2-thiophene carboxylic acid (0.10 g, 0.78 mmol) in anhydrous CH_2Cl_2 (26 mL). The reaction was stirred for 16 h, then diluted with water and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered and evaporated under reduced pressure. FCC of the residue provided **21** (0.22 g, 69%) as a yellow oil: *Rf* = 0.7 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.65 (m, 4H), 7.45 (m, 2H), 7.42 (m, 6H), 7.04 (d, J = 6.0 Hz, 1H), 5.90 (br s, 1H), 5.71 (m, 1H), 4.90 (m, 1H), 4.88 (m, 1H), 3.67 (m, 1H), 3.40 (m, 2H), 1.90 (m, 2H), 1.57 (m, 4H), 1.36 (m, 6H), 1.15 (m, 12H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 139.3, 136.2, 135.0, 129.8, 129.6, 128.0, 127.8, 127.6, 114.4, 73.4, 40.3, 36.5, 36.3, 33.9, 30.0, 29.9, 29.7, 29.7, 29.5, 29.2, 27.3, 27.2, 25.0, 24.6, 19.6. HRMS (ESI): *m/z* $[C_{37}H_{53}NO_2SSiNa]^+$ calcd for 626.3458; found 626.3456.

4.21. (5S)-3-((15R)-(8R/S)-((tert-butyldiphenylsilyl)oxy)-15-hydroxy-15-((2R,5R)-5-((R)-1-hydroxytridecyl)tetrahydrofuran-2-yl)pentadec-13-en-1-yl)-5-methylfuran-2(5H)-one (22)

A mixture of **9** (0.10 g, 0.30 mmol) and **17** (0.28 g, 0.51 mmol) in CH_2Cl_2 (2 mL) was purged with nitrogen for 30 min. Grubbs 2nd generation catalyst (25 mg, 0.03 mmol) was then introduced and the mixture stirred for 16 h at rt, after which DMSO (0.05 mL) was added and stirring continued for 30 min. The mixture was then concentrated *in vacuo*. FCC of the residue (40% EtOAc/hexanes) afforded **22** (136 mg, 54%) as a clear oil: *Rf* = 0.65 (40% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (m, 4H), 7.40–7.30 (m, 6H), 6.94 (s, 1H), 5.67 (m, 1H), 5.30 (m, 1H) 4.96 (m, 1H), 3.84–3.77 (m, 3H), 3.80 (m, 1H), 3.38 (m, 1H), 2.47 (br s, 1H), 2.28 (br s, partially buried, 1H), 2.21 (m, 2H), 1.90 (m, 4H), 1.63 (m, 2H), 1.45 (m, 3H), 1.33 (m, 10H), 1.22–1.14 (m, 30H), 1.00 (s, 9H), 0.85 (t, J = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 149.0, 136.1, 134.9, 134.5, 129.6, 128.3, 127.6, 82.9, 82.7, 77.7, 75.9, 74.2, 73.3, 36.4, 36.3, 33.8, 32.5, 32.5, 32.1, 29.9 (4 signals), 29.8 (3 signals), 29.6, 29.4, 29.3, 28.7, 27.6, 27.3, 25.8, 25.4, 25.0, 24.6, 22.9, 19.6, 19.4, 14.3. HRMS (ESI): *m/z* $[C_{53}H_{84}O_6SiNa]^+$ calcd for 867.5935, found 867.5909.

4.22. *N-((17R)-(10R/S)-((tert-butyldiphenylsilyl)oxy)-17-(methoxymethoxy)-17-((2R,5R)-5-((R)-1-(methoxymethoxy)tridecyl) tetrahydrofuran-2-yl)heptadec-15-en-1-yl)thiophene-2-carboxamide* ***(23)***

A mixture of **10** (22 mg, 0.053 mmol) and **21** (86 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was purged with nitrogen for 30 min. Grubbs 2nd generation catalyst (25 mg, 0.03 mmol) was then introduced and the mixture stirred for 3 h at rt. At that time, additional Grubbs 2nd generation catalyst (5 mg, 0.006 mmol) was added and stirring continued for 20 h at rt. The reaction was then processed as described for **22.**, to give unreacted **10** (15 mg) and **23** (15 mg, 90% brsm) as a yellow gum: *Rf* = 0.45 (25% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.60 (m, 4H), 7.45–7.30 (m, 12H), 7.03 (t, *J* = 4.0 Hz, 1H), 6.04 (br s, 1H), 5.58 (m, 1H), 5.16 (m, 1H), 4.82 (apparent d, *J* = 6.9 Hz, 1H), 4.64 (m, 3H), 4.51 (apparent d, *J* = 6.6 Hz, 1H), 3.94 (m, 2H), 3.82 (m, 1H), 3.62 (m, 1H), 3.45 (m, 1H), 3.38 (m, partially buried, 2H), 3.37 (s, 3H), 3.34 (s, 3H), 1.88–1.00 (m, 50H), 0.99 (s, 9H), 0.83 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 139.2, 136.7, 136.0, 134.7 (2 signals), 129.9, 129.5, 128.1, 127.9, 127.7, 127.5, 126.0, 96.8, 93.1, 81.5, 81.1, 79.6, 78.7, 73.0, 55.9, 55.3, 40.1, 36.2, 36.1, 32.5, 32.0, 31.1, 29.9, 29.8, 29.6, 29.5, 29.4, 29.2, 28.5, 28.1, 27.1, 25.8, 24.9, 24.5, 22.9, 19.5, 14.4. HRMS (ESI): *m/z* $[C_{59}H_{95}NO_7SiNa]^+$ calcd for 1012.6490, found 1012.6489.

4.23. *(5S)-3-((E)-8R/S-((tert-butyldiphenylsilyl)oxy)-15-(((4S,6R,7R,7aS)-7-(methoxy-methoxy)-2,2-dimethyl-6-((undecyloxy) methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)pentadec-13-en-1-yl)-5-methylfuran-2(5H)-one* ***(24)***

A mixture of **13** (255 mg, 0.56 mmol) and **17** (680 mg, 1.25 mmol) in CH_2Cl_2 (15 mL) was purged with nitrogen for 30 min. Grubbs I catalyst (65 mg, 0.084 mmol) was then introduced and the mixture stirred for 3h at 40 °C. The reaction was then processed as described for **22.** FCC of the crude product gave recovered **13** (8 mg) and **24** (388 mg, 74% brsm, E:Z ~4:1), as a light yellow oil. *Rf* = 0.33 (10% acetone/hexanes). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 (m, 4H), 7.42 (m, 6H), 6.99 (s, 1H), 5.75 (m, 1H), 5.52 (m, 1H), 5.12 (s, 1H), 5.02 (m, 1H), 4.90 (apparent d, *J* = 6.3 Hz, 1H), 4.70 (apparent d, *J* = 6.3 Hz, 1H), 4.25–4.15 (m, 3H), 3.96 (m, 1H), 3.72 (m, 4H), 3.62 (m, 1H), 3.55 (m, 1H), 3.45 (m, 4H), 2.26 (m, 2H), 1.96 (m, 2H), 1.70–1.20 (m, 45H), 1.07 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 173.8, 136.0, 135.8, 134.8, 134.7, 134.4, 129.5, 129.3, 127.4 (2 signals), 109.3, 96.3, 95.9, 78.5, 77.4, 73.3 (2 signals) 73.2, 71.8, 69.7, 68.3, 36.3, 36.2, 32.2, 31.9, 29.8, 29.6 (2 signals), 29.3, 29.2, 29.1 (2 signals), 27.9, 27.4, 27.1 (2 signals), 26.4, 26.2, 25.2, 24.9, 24.6, 22.7, 19.4, 19.2 (2 signals), 14.1. HRMS (ESI) calcd for $C_{58}H_{93}O_{10}Si$ $(M + H)^+$ 976.6460, found 976.6454.

4.24. *N-(10R/S-((tert-butyldiphenylsilyl)oxy)-17-(((4S,6R,7R,7aS)-7-(methoxymethoxy)-2,2-dimethyl-6-((undecyloxy)methyl)tetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-yl)oxy)-2-methylheptadec-15-en-1-yl) thiophene-2-carboxamide* ***(25)***

A mixture of **13** (160 mg, 0.35 mmol) and **21** (560 mg, 0.93 mmol), in CH_2Cl_2 (10 mL) was purged with nitrogen for 30 min. Grubbs I catalyst (43 mg, 0.05 mmol) was then introduced and the mixture stirred for 6 h at 40 °C. The reaction was then processed as described for **22** to provide **25** (251 mg, 70%) as a pale yellow oil. *Rf* = 0.53 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.64 (m, 4H), 7.40 (dd, *J* = 1.1, 3.7 Hz, 1H), 7.43 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.34 (m, 6H), 7.04 (dd, *J* = 3.7, 5.0 Hz, 1H), 5.92 (bs, 1H), 5.63 (m, 1H), 5.45 (m, 1H), 5.05 (br s, 1H), 4.85 (apparent d, *J* = 6.3 Hz, 1H), 4.65 (apparent d, *J* = 6.3 Hz, 1H), 4.18 (m, 1H), 4.10 (m, 2H), 3.86 (m, 1H), 3.66 (m, 3H), 3.58 (m, 1H), 3.48 (m, 1H), 3.39 (m, 6H), 1.91 (m, 2H), 1.55 (m, 4H), 1.47 (s, 3H), 1.40–1.05 (m, 37H), 1.02 (s, 9H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.0, 139.3, 136.1 (2 signals), 135.0, 134.9, 129.8, 129.6 (2 signals), 128.0, 127.7, 127.6, 125.1, 109.4, 96.5, 96.0, 78.6, 76.2, 73.4, 73.3, 72.0, 69.9, 68.4, 67.8, 56.1, 40.2, 36.5, 35.3, 32.4, 32.1, 29.9 (2 signals), 29.8, 29.7 (2 signals), 29.6, 29.5 (2 signals), 29.2, 28.0, 27.3, 27.1, 26.6, 26.4, 25.0, 24.7, 22.9, 19.6, 14.3. HRMS (ESI) calcd for $C_{60}H_{95}NO_9SSiNa$ $(M + Na)^+$ 1056.6389, found 1056.6389.

5. Cytotoxicity measurements

Cell number optimization: Serial dilutions of cells in culture media were plated in triplicate from 100 to 100000 in a 96 well plate. Cells were incubated at 37 °C in a CO_2 incubator for 72 h. Activated solution of XTT reagent was made by adding 0.1 ml of activation reagent to 5 ml of XTT reagent. 50 μL of activated XTT reagent was added per well. The plate was incubated for 2 h and absorbance from wells was measured at 475 nM. Background was measured at 660 nM. Background subtraction was made, and absorbance was plotted against cell number. Optimum cell number was determined based on the linear range of XTT standard curve.

IC_{50} determination: Serial dilutions of compounds to be tested were made in culture media from 1nM to 1mM concentration. Determined cell number from the standard graph were plated in 96 well plate in triplicate per each dilution of the compounds. The cells were allowed to attach overnight by incubation at 37 °C in a CO_2 incubator. The media from the well was removed and media with serial dilutions of the compounds was added to the cells. The cells were incubated with the compound for 48 h at 37 °C in CO_2 incubator. Activated XTT reagent was added to the wells and incubated for 2 h. Absorbance from the wells was measured at 475 nM and background at 660 nM. Background subtraction was made, and all the data was plotted in prism and IC_{50} values were determined.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carres.2022.108671.

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