Tetrahedron 64 (2008) 10649–10663

Contents lists available at ScienceDirect

Tetrahedron

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

Synthesis and evaluation of the bioactivity of simplified analogs of the seco-pseudopterosins; progress toward determining a pharmacophore☆

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ARTICLE INFO

Article history:
Received 21 July 2008
Received in revised form 29 August 2008
Accepted 3 September 2008
Available online 18 September 2008

Keywords:
Pseudopterosins
Seco-pseudopterosins
Structural analogs
Total synthesis
Minimal pharmacophore
Marine natural products
Phagocytosis
Anti-inflammatory activity
Adenosine receptors

ABSTRACT

The pseudopterosins are marine natural products that display significant anti-inflammatory and wound healing properties. We describe the synthesis of six structural analogs of the seco-pseudopterosin-like core that are devoid of all but one of the stereocenters found in the carbocyclic core of the natural products. Our targets were selected in an attempt to identify the minimal pharmacophore for the pseudopterosins and their seco analogs. A deliberate effort was made to utilize a conservative synthetic approach based upon the use of well-established reactions, which enabled us to develop routes that proved to be efficient, practical, and easy to implement. The results of several bioassays, including an assessment of the ability to inhibit phagocytosis and to competitively bind to the adenosine receptor A_{2A}, demonstrate that greatly simplified structural analogs of the pseudopterosins and their seco forms are capable of maintaining several of the important bioactivities that characterize the natural products, and do so with comparable efficacy. Those systems bearing two rather than one oxygen atom appended directly to the aromatic ring are the more effective binding agents. This observation may provide a significant clue regarding the key structural features of the minimal pharmacophore.

1. Introduction

The pseudopterosin class of diterpene glycosides display potent anti-inflammatory and wound healing properties. Pseudopterosin A (PsA, **1**, Fig. 1), for example, inhibits phorbol myristate acetate (PMA) induced inflammation in mice;[2] induces the release of calcium from an intracellular store; prevents the release of prostaglandins and leukotrienes from zymosan stimulated murine macrophages; and inhibits the degranulation of human polymorphonuclear leukocytes.[3,4] These effects may be related to the reduction in release of pro-inflammatory mediators produced during inflammation and injury.

Despite the many reports of pseudopterosin synthesis and the existence of the simplified skeleton that is inherent to the seco-pseudopterosins,[5,6] there has been no systematic effort to delineate a rudimentary structure–activity relationship for these systems. Our efforts to identify the pharmacophore focus upon a two-pronged approach, one of which calls for making structural modifications to the natural product and the other calling for the total synthesis of simple structures in an effort to determine the *minimal* pharmacophore needed to express activity. The first approach has thus far led to the identification of a new pseudopterosin, *iso*-PsE (Fig. 1),[7] as well as the synthesis and evaluation of aspects of the bioactivity for the first C-glycoside analog of a pseudopterosin. Among other notable findings, we have established that the pseudopterosins are most likely not prodrugs that simply deliver the aglycon to the active site(s).[8]

Analysis of the pseudopterosin structure reveals a somewhat flattened tricyclic diterpene substructure (the hexahydrophenalene unit) that is appended to a sugar through an electron rich aromatic

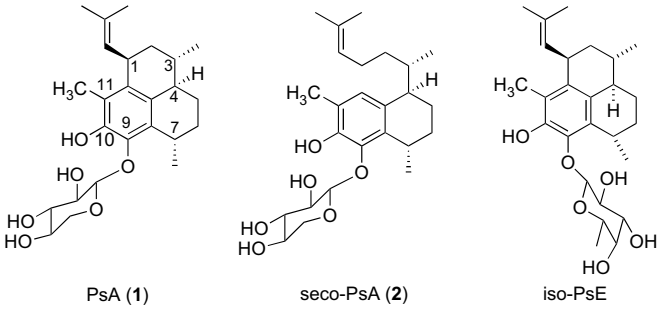

Figure 1. Structures of pseudopterosin A, seco-pseudopterosin A, *iso*-PsE.

☆ See Ref. 1.

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doi:10.1016/j.tet.2008.09.025

3a, **3b**, **3c** **4a**, **4b**, **4c**

Sugar = a-series: D-xylose; b-series: L-arabinose; c-series: L-fucose

Figure 2. Phase 1 and phase 2 target structures.

ring. The tricyclic core exhibits an isobutenyl side chain and two methyl groups. We elected to synthesize structures that were devoid of the stereocenters at C-1, C-3, and C-7, which appear in the natural product. To avoid the stereochemical issues at C-1, we chose to delete the bond connecting that center to the aromatic ring. To avoid stereochemical complications at C-3 and C-7, we chose structures where the methyl appendages were deleted. These decisions promised to greatly diminish the synthetic challenges and allow us to address the importance of these subunits in the expression of bioactivity.

In this paper, we highlight (a) the development of conceptually conservative, but efficient and easily scalable synthetic sequences leading to the construction of simplified analogs of the natural substances, and (b) an assessment and comparison of their activity with the naturally occurring substances. We elected to synthesize systems possessing the seco-pseudopterosin-like core that were devoid of all but one of the stereocenters found in the natural products (viz., C-4) except for those centers found on the sugar. We chose to accomplish this in two phases, the first being to assemble structures **3a**–**c** containing a sugar at C-9 while devoid of the C-10 OH and C-11 methyl groups on the aromatic ring (phase 1), the second being to synthesize structures **4a**–**c**, each bearing a sugar at C-9 as well as an OH unit appended to C-10 (phase 2) (Fig. 2).

2. Results and discussion

2.1. Construction of the phase 1 targets 3a–c

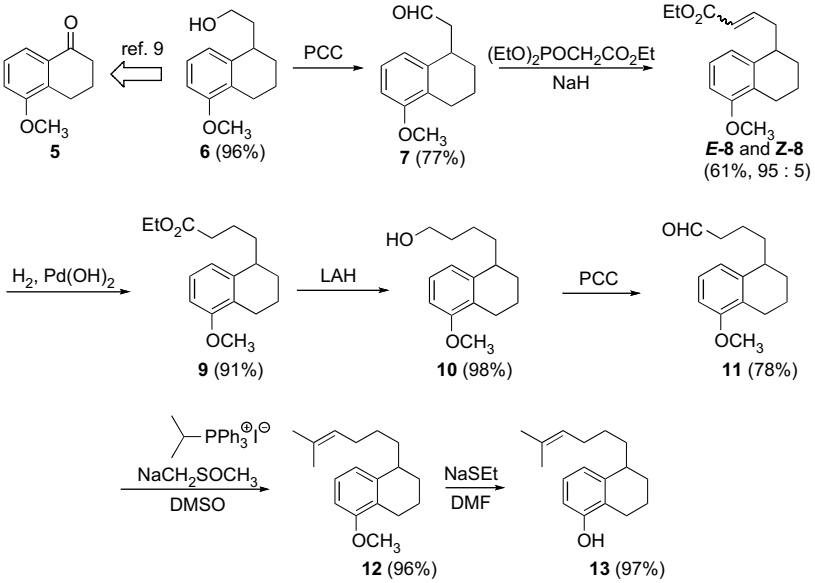
Construction of the aglycon **13** proceeded via the pathway illustrated in Scheme 1. The sequence began with the known alcohol **6**, a substance that was obtained from the commercially available 5-methoxy-1-tetralone (**5**) in three steps.[9] Oxidation state alteration was accomplished using PCC[10] to afford aldehyde **7** (77%). A Horner–Emmons reaction gave a 95:5 mixture of enoates ***E*-8** and ***Z*-8** in 61% yield. Following hydrogenation to provide ester **9**, an oxidation state change was accomplished by treating ester **9** with LAH to provide alcohol **10** (98%). Oxidation of **10** with PCC provided aldehyde **11**, thus setting the stage for a Wittig olefination to install the remaining three carbons.

After considerable experimentation, it was discovered that the most effective base/solvent system for the Wittig reaction was dimsylsodium in DMSO. Thus, dimsylsodium was prepared from NaH and DMSO, and *iso*propyl-triphenylphosphonium iodide was added to give a clear red solution of the corresponding ylide. The addition of aldehyde **11** to the ylide, in DMSO, gave an excellent 96% yield of alkene **12** after chromatographic purification. We selected TMSI,[11] LiI/collidine/Δ,[12] BBr_3,[13] and NaSEt[14] as possible reagents for the requisite aryl methyl ether cleavage. Surprisingly, the only reagent to successfully perform the transformation was NaSEt, providing the desired phenol **13** in 97% chromatographed yield. The stage was now set for glycosylation and global sugar deprotection.

2.2. Glycosylation

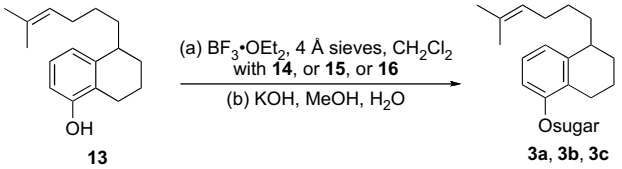
We selected D-xylose, L-arabinose, and L-fucose as the sugar units to append to the aglycon since they are the most common systems found in the pseudopterosins and seco-pseudopterosins. In each instance, the known peracetylated trichloroacetimidates, 2,3,4-tri-*O*-acetyl-D-xylopyranose-1-trichloroacetimidate (**14**), 2,3,4-tri-*O*-acetyl-L-arabinopyranose-1-trichloroacetimidate (**15**), and 2,3,4-tri-*O*-acetyl-L-fucopyranose-1-trichloroacetimidate (**16**), were used in the coupling reaction.[15] The results are illustrated in Table 1.

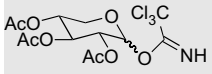
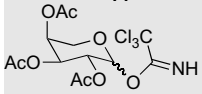
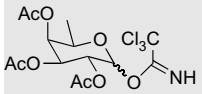
Phenol **13** and the xylose-derived trichloroacetimidate **14** were combined in dichloromethane and powdered 4 Å molecular sieves were added. The mixture was allowed to stir for 20 min at room temperature, and then chilled in a dry ice/*i*-PrOH bath and $BF_3 \cdot OEt_2$ was added, as described by McDonald and Pletcher,[16] to give the desired xylopyranoside in 78% chromatographed yield. Removal of the acetate groups was achieved as described by Carpino (KOH, aqueous MeOH, room temperature) providing a 70% yield of the target xylopyranoside **3a**.[5b,17] Employing identical chemistry, phenol **13** was coupled with arabinopyranoside trichloroacetimidate **15**



Scheme 1. Synthesis of phase 1 aglycon **13**.

Table 1
Glycosylation of the phase 1 aglycon; formation of target structures **3a-c**



Acetimidate	Yield (%)		Product
	Step a	Step b	
 **14**	78	70	β-D-Xylopyranoside **3a**
 **15**	77	71	β-L-Arabinopyranoside **3b**
 **16**	98	66	β-L-Fucopyranoside **3c**

to afford the anticipated arabinopyranoside (77%). Deprotection (KOH, aqueous MeOH, room temperature) then gave the target arabinopyranoside **3b**. Similarly, the coupling of phenol **13** with the fucopyranoside trichloroacetimidate **16** led to the fucopyranoside triacetate (98%). Acetate hydrolysis (KOH, aqueous MeOH, room temperature) then provided the desired fucopyranoside **3c** in 66% chromatographed yield.

Though not elegant, the pathway leading to structures **3a**–**c** proved to be efficient, practical, and easy to implement. From commercially available 5-methoxy-1-tetralone (**5**), xylopyranoside **3a** is available in 15% overall yield over 12 steps; arabinopyranoside **3b** is constructed in 15% overall yield over 12 steps; and fucopyranoside **3c** is available in 18% yield over 12 steps. In toto 120–400 mg of the final products were prepared and readied for bioassay.

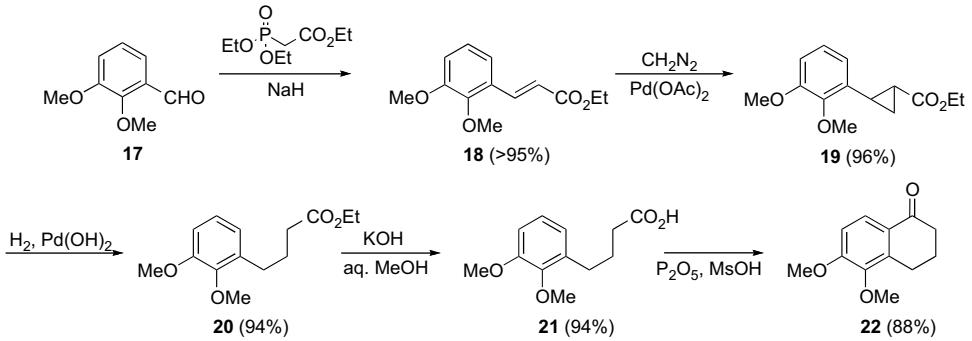
2.3. Phase 2 targets: the development of an efficient synthetic pathway

The chemistry illustrated in Scheme 1 promised to be transferable to the synthesis of the phase 2 target structures if a suitable quantity of 5,6-dimethoxy-α-tetralone (**22**) could be prepared. An intramolecular Friedel–Crafts acylation has been employed in the majority of reported syntheses of 5,6-dimethoxy-α-tetralone (**22**);[18] however, the synthesis of the requisite 4-(2,3-dimethoxyphenyl)-butyric acid (**21**) is usually the issue standing between the method and utility. Consequently, we designed a short, efficient synthesis of 4-(2,3-dimethoxyphenyl)-butyric acid (**21**) using only readily available, commercial materials and parlayed it into the target 5,6-dimethoxy-α-tetralone (**22**). Scheme 2 highlights the route.

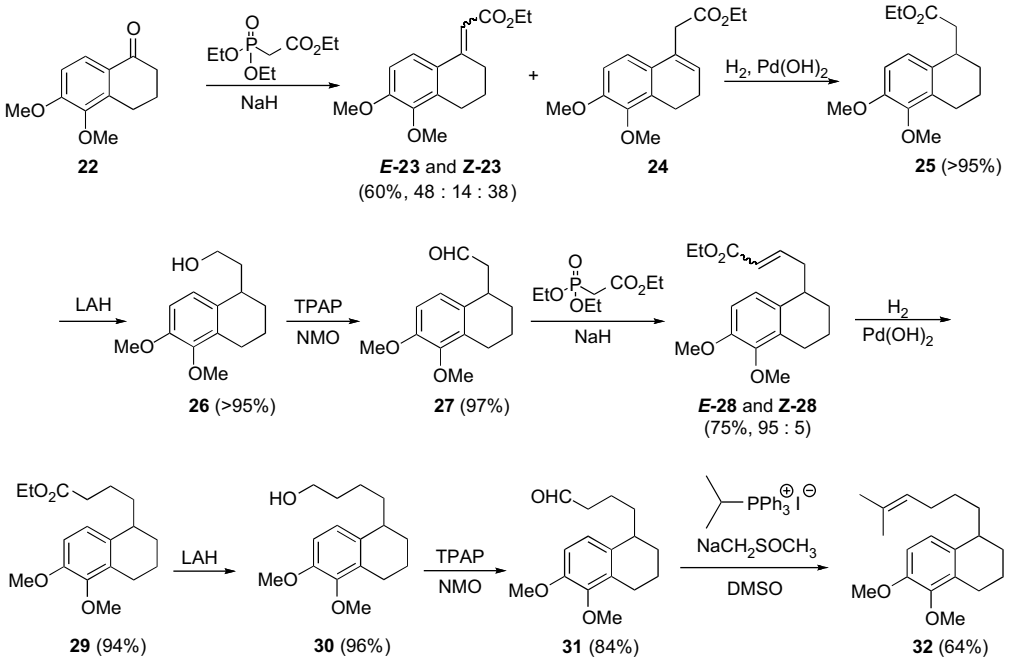
The route to **20** was suggested by a report of Tanis et al.[19] wherein a high yield scaleable preparation of a related trimethoxyaryl butyrate was achieved via a $Pd(OAc)_2$ mediated cyclopropanation of a cinnamate ester with diazomethane. Toward this end, 2,3-dimethoxybenzaldehyde (**17**) was converted to the cinnamate ester **18** (>95%) via a Horner–Emmons reaction, and the cinnamate was smoothly converted to the cyclopropanated ester **19** in 96% yield upon treatment with CH_2N_2 and $Pd(OAc)_2$. Cyclopropane hydrogenolysis with H_2 (50 psi) and Pearlman's catalyst, $Pd(OH)_2$, led to the aryl butyrate **20** (94%), which was easily hydrolyzed (KOH, aqueous MeOH) to give the 4-aryl butyric acid **21** (94%). The Friedel–Crafts acylation to give the desired tetralone **22** was achieved with Eaton's reagent (P_2O_5, MsOH)[20] in an 88% yield. Overall, the sequence requires five steps, utilizes only commercially available reagents, is easily scaled up, and affords the desired tetralone **22** in 74% overall yield.

With a substantial supply of **22** in hand, we proceeded to prepare the desired phase 2 aglycon dimethyl ether **32** in the manner portrayed in Scheme 3. The reaction of **22** with the sodium salt of triethyl phosphonoacetate gave a 48:14:38 mixture of ***E*-23**/***Z*-23**/**24** in 60% yield. Hydrogenation gave ester **25** (>95%) and LAH reduction led to alcohol **26** (>95%), setting the stage for an oxidation and second Horner–Emmons addition.

At this juncture, we elected to examine the aldehyde forming paradigm in greater detail; while the PCC oxidation had previously afforded good yields, it exhibited enough variability to be worrisome. The Ley TPAP/NMO oxidation,[21] with its generality, simple procedure, and work-up, appeared to be an ideal alternative to PCC. Application of the TPAP/NMO oxidation to alcohol **26** provided an excellent 97% yield of aldehyde **27**, validating the choice. A second Horner–Emmons addition then transformed aldehyde **27** to a 95:5 mixture of ***E*-28** and ***Z*-28** in 75% yield. The completion of the sequence required another reduction, ester to aldehyde conversion, and a final Wittig reaction. Reduction of the mixture of ***E*-28** and ***Z*-28** with $H_2/Pd(OH)_2$ provided ester **29** in 94% yield, which when followed by LAH reduction afforded a 96% yield of alcohol **30**. A second application of the Ley TPAP/NMO oxidation then gave aldehyde **31** (84%) that was subsequently treated with *iso*-propylidene triphenylphosphorane to yield the target phase 2 aglycon dimethyl ether **32** (64%). As was the case for the chemistry shown in Scheme 1, the chemistry leading to **32** is reasonably efficient providing gram quantities of material in 21% overall yield over nine steps from tetralone **22**.



Scheme 2. An improved synthesis of 5,6-dimethoxy-α-tetralone **22**.



Scheme 3. Synthesis of the phase 2 aglycon dimethyl ether **32**.

At this point, the completion of the syntheses of phase 2 targets required bis-methyl ether deprotection and a differentiation of the hydroxyl groups in order to permit regiospecific glycosylation.[5a,b] Toward that end, and as shown in Scheme 4, catechol dimethyl ether **32** was deprotected with excess NaSEt in hot DMF to give the oxygen sensitive catechol **33** in 70% chromatographed yield. Rapid protection was needed in order to avoid quinone formation. When treated with 0.95 equiv of TBDMSOTf and *i*-Pr_2NEt in DMF at 0 °C, it was converted to the mono-protected product that has been assigned the structure **34** in 79% yield. Overall, we have achieved the synthesis of a selectively mono-protected catechol **34** in a total of 11 linear steps and 12% overall yield from tetralone **22**.

As shown in Table 2, mono-protected catechol **34** was treated with the xylopyranoside derived trichloroacetimidate **14** and $BF_3{\cdot}OEt_2$ to provide the desired β-xylopyranoside in a 64% chromatographed yield.[16] Treatment of it with methanolic NaOMe at 40 °C for 2 h afforded global deprotection and lead to a 57% yield of the target xylopyranoside **4a**. A similar coupling with arabinopyranoside trichloroacetimidate **15** afforded the arabinopyranoside triacetate (55%), which led to the desired arabinopyranoside **4b** (88%) after deprotection. Likewise, **34** was coupled with the fucose-derived trichloroacetimidate **16** to provide the protected fucopyranoside in an 88% purified yield. Deprotection with NaOMe (MeOH, 40 °C) then gave the third phase 2 target structure, fucopyranoside **4c**, in an 84% chromatographed yield.

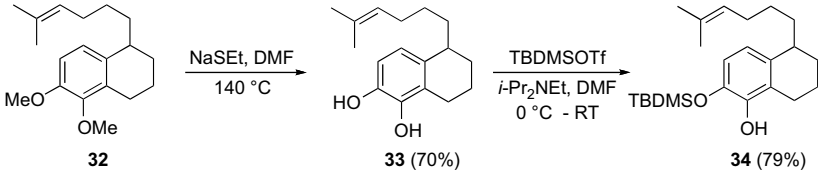
We achieved the synthesis of >100 mg quantities of each of our phase 2 targets in 13 steps from tetralone **22** in 4.4%, 5.8%, and 10.8% yields. With sufficient quantities of all six targeted pyranosides **3**–**c** and **4a**–**4c**, we were positioned to assess whether these compounds might exhibit anti-inflammatory/wound healing activity.

2.4. Biological evaluation

Moya and Jacobs have investigated the ciliate *Tetrahymena thermophila* as a pharmacological model to study the cellular anti-inflammatory mechanism of action of PsA (**1**).[22] PsA (**1**) has exhibited a myriad of activities including (1) the inhibition of phorbol myristate acetate (PMA) induced inflammation in mice;[2] (2) the prevention of the release of prostaglandins and leukotrienes from zymosan stimulated murine macrophages; and (3) the inhibition of degranulation of human polymorphonuclear leukocytes.[3] It has also been postulated that the natural role of pseudopterosins in *Pseudopterogorgia elisabethae* is that of protection of cell injury by inhibiting an inducible oxidative burst.[4] Its mechanism to block cellular degranulation and release of pro-inflammatory mediators is unresolved. Moya and Jacobs have produced data indicating that PsA (**1**) has a selective affinity for a site that is responsible for inhibiting phagosome formation in *T. thermophila*.[22] Furthermore, PsA (**1**) also induces a local and discrete release of calcium from an intracellular store. The authors surmise that these effects may be related to the reduction in release of pro-inflammatory mediators produced during inflammation and injury.

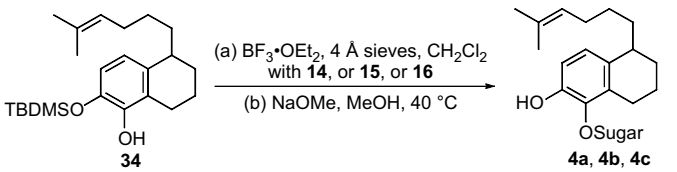
T. thermophila cells were used to examine the effect of **3a**–**c** on phagosome formation. The assay was performed by exposing the cells to each test compound, and after a 10 min exposure, the cells were then fixed and scored for phagocytic activity. Results are plotted in a semi-log response graph in which the *x*-axis represents the concentration of the compound and the *y*-axis represents the activity, measured as percent inhibition of phagocytosis.

In Figure 3, we show the inhibition of phagocytosis activity for xylopyranoside **3a**, arabinopyranoside **3b**, and fucopyranoside **3c** in



Scheme 4. Completion of the phase 2 aglycon assembly.

Table 2
Glycosylation of the phase 2 aglycon; formation of target structures **4a–c**



Acetimidate	Yield (%)		Product
	Step a	Step b	
14	64	57	β-D-Xylopyranoside **4a**
15	55	88	β-L-Arabinopyranoside **4b**
16	88	84	β-L-Fucopyranoside **4c**

the *T. thermophila* assay. As shown, our stripped-down bicyclic analogs exhibit reasonable inhibition of phagocytosis with potencies, measured as ED_{50} values, of 8 μM for **3a**, 15 μM for **3b**, and 10 μM for **3c**. Thus even these much-simplified structures are capable of inhibiting phagocytosis of the same magnitude as that of pseudopterosin A (ED_{50}=5.4 μM, historical data, not shown).

Similarly, structures **4a–c** inhibited phagocytosis. Each was screened at a concentration of 5 μM and produced an inhibition in phagocytosis of 17.5%, 1.8%, and 17.7%, respectively.

Since the pseudopterosins have demonstrable wound healing properties, and because the involvement of adenosine receptors has been implicated in wound healing,[23] we elected to assess the ability of all six of the synthetic analogs, **3a–c** and **4a–c**, to serve as competitive binding agents toward the adenosine receptors, A_1, A_{2A}, A_{2B}, and A_3 of cultured human embryonic kidney cells (HEK-293).[24]

A single concentration of 5 μM was used in the initial screens. Dose-dependent analyses were then conducted on those compounds that were shown to successfully compete for binding toward a given receptor. In this manner, we identified structure **3c** for its ability to bind to the A_3 receptor. When examined in greater detail, however, the dose response analysis showed less than 50% inhibition at the highest concentration tested and afforded an IC_{50} value of >25 μM.

Structures **4b** and **4c** were identified as candidates for additional screening toward the A_{2A} receptor. In contrast to the structures bearing a single oxygen on the aromatic ring, those more electron rich systems with *two oxygen atoms appended to the aromatic ring*, viz., **4b** and **4c**, are effective competitive binding agents, and display a dose-dependent response. For example, the arabinopyranoside **4b** binds to the A_{2A} receptor in a cooperative manner with a Hill coefficient, n(H), of 1. It competitively inhibited the binding of NECA to the receptor with an IC_{50} equal to 14 μM and a binding constant, K_i, of 12 μM. The fucopyranoside **4c** binds the A_{2A} receptor with a Hill coefficient of 0.9, and an IC_{50} equal to 10 μM and a K_i value of 8.3 μM. These values are remarkably close to those recorded for the naturally occurring pseudopterosins A (**1**) and *iso*-PsE each of which display an IC_{50} value of 13.

2.5. Concluding remarks

The results described herein demonstrate that greatly simplified structural analogs of the pseudopterosins and their seco forms are capable of maintaining several of the important bioactivities that characterize the natural products, and do so with comparable efficacy. That the more electron rich systems, **4b** and **4c** are more effective than **3a** and **3b** as competitive adenosine binding agents

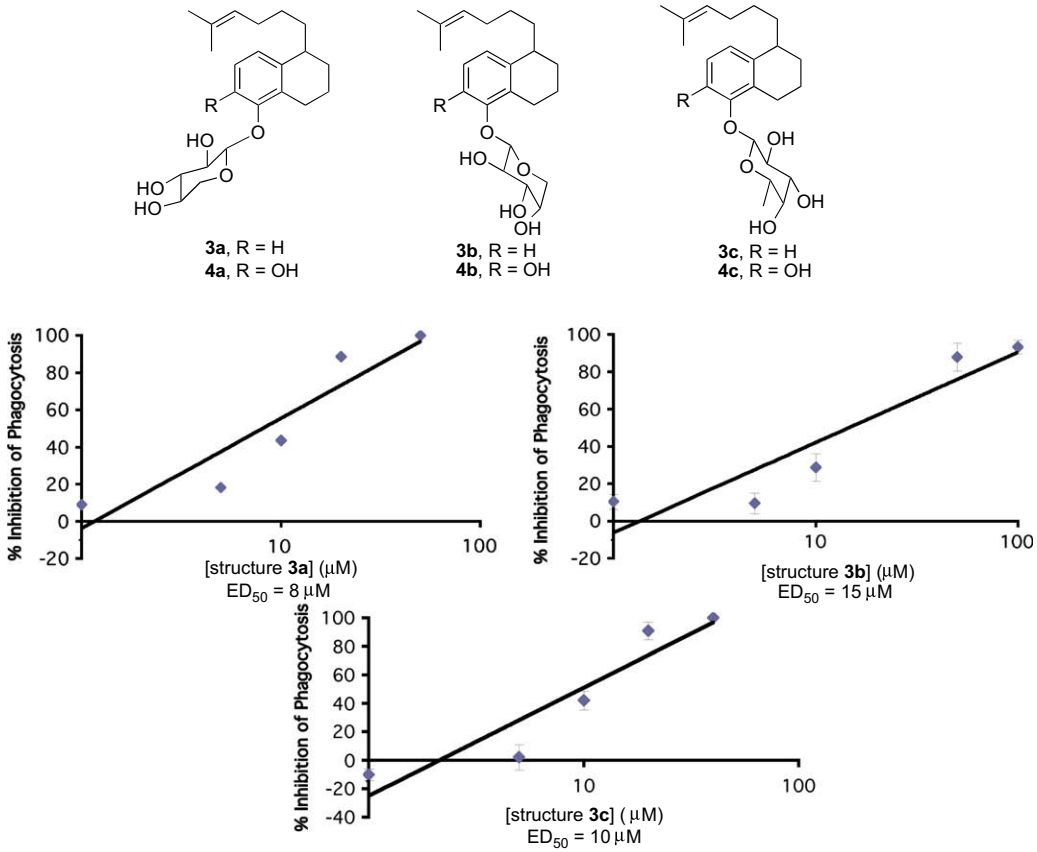


Figure 3. Xylopyranoside **3a**, arabinopyranoside **3b**, and fucopyranoside **3c** inhibit phagocytic activity in *T. thermophila* in a specific and dose-dependent manner. The ED_{50} value for **3a** (top left), **3b** (top right), and **3c** (bottom) is equal to 8, 15, and 10 μM, respectively.

are potentially significant. We suspect that oxidizability may play a critical role in the expression of bioactivity by the pseudopterosins and their seco analogs. Clearly, the more electron rich systems ought to be easier to oxidize. Experiments designed to probe the validity of these thoughts are underway at this time.

3. Experimental

3.1. General

All reactions were performed in flame-dried glassware under an inert atmosphere of dry nitrogen or argon. Solvents and reagents were reagent grade and used without purification unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether were dried by distillation from sodium/benzophenone ketyl. Methylene chloride, acetonitrile, pyridine, and $BF_3 \cdot OEt_2$ were dried and distilled from calcium hydride. Methanol was dried and distilled from magnesium metal. Dimethylsulfoxide (DMSO) was dried and distilled from sodium hydride. Commercially available reagents were acquired from the suppliers mentioned and were used without further purification unless otherwise mentioned. Hydrogenations and hydrogenolysis reactions were performed utilizing a Parr shaker. Solids were purified chromatographically and by recrystallization.

3.2. Preparation of 2-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanal (7)

To a mixture of 2-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanol (**6**) (5.15 g, 0.025 mol),[9] 4 Å molecular sieves (5.87 g), Celite® (21.30 g), and sodium acetate (2.70 g, 0.033 mol) in 225 mL of CH_2Cl_2 was added PCC (pyridinium chlorochromate, 7.10 g, 0.033 mol) at room temperature. After stirring at room temperature for 2 h, an additional portion of 4 Å molecular sieves (0.88 g), Celite® (3.20 g), sodium acetate (410 mg, 4.94 mmol), and PCC (1.07 g, 0.005 mol) were added, and the mixture was allowed to stir at room temperature overnight. After addition of Et_2O (125 mL), the mixture was filtered through silica gel (250 g). The chromium salt/silica was washed with (3×125 mL) Et_2O. The combined filtrates were concentrated in vacuo to provide 3.95 g (0.019 mol, 77%) of 2-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanal (**7**) as a clear, colorless oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.49. IR (neat): 3004, 2929, 2837, 1720, 1581, 1464, 1251, 1105, 1068, 910, 777, 731 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.55 (m, 1H, C2–H), 1.62 (m, 1H, C3–H), 1.78 (m, 1H, C2–H), 1.89 (m, 1H, C3–H), 2.58 (m, 1H, C9–H), 2.64–2.82 (3H, C4/9–H), 3.46 (m, 1H, C1–H), 3.82 (s, 3H, –OCH_3), 6.68 (d, J=8.4 Hz, 1H, C8–H), 6.74 (d, J=8.4 Hz, 1H, C6–H), 7.12 (t, J=8.4 Hz, 1H, C7–H), 9.83 (s, 1H, –CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.3, 157.4, 140.4, 126.3, 126.2, 120.5, 107.4, 55.4, 51.2, 32.4, 28.2, 23.1, 19.1. EIMS (+): 204 (M^+, 48), 176 (30), 175 (30), 161 (base), 160 (base), 145 (36), 128 (35), 115 (60), 91 (53), 77 (25). HRMS (EI, +): calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1147.

3.3. Preparation of *E*- (*E*-8) and *Z*-ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (*Z*-8)

To NaH (1.39 g, 0.035 mol, 1.8 equiv, 60% in oil) covered with toluene (18 mL), cooled in an ice-water bath under argon, was added triethyl phosphonoacetate (7.80 g, 0.035 mol, 1.8 equiv) over 30 min. After the addition was complete, the mixture was placed in an oil bath and the temperature was raised to 50 °C (internal). The mixture was allowed to stir for 1 h at 50 °C, and then was cooled to room temperature, followed by cooling in an ice-water bath. To this cooled solution of sodio triethyl phosphonoacetate was added a solution of 2-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-ethanal (**7**) (3.95 g, 0.019 mol) in toluene (18 mL) over 30 min. After the addition was complete, the ice-water bath was removed, the mixture was warmed to room temperature, and then was warmed in an oil bath to reflux and maintained at reflux for 4 h. The mixture was cooled to room temperature and was then poured into ice-water (75 mL) in a separatory funnel. The organic phase was separated and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude products as an orange-brown oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.66, 0.55.

The crude products were purified by chromatography using the flash technique (70 mm OD; 300 g 230–400 mesh silica gel, packed hexanes/Et_2O 98:2; run hexanes/Et_2O 95:5, 500 mL; hexanes/Et_2O 90:10, 500 mL; hexanes/Et_2O 80:20, 750 mL, 50 mL fractions) to afford 3.23 g (0.012 mol; 61%) of a mixture of *Z*-ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (***Z*-8**)/*E*-ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (***E*-8**) as a pale yellow oil. A 0.50 g sample of the mixture was separated by chromatography using the flash technique (50 mm OD; 150 g 230–400 mesh silica gel, packed hexanes/Et_2O 98:2; run hexanes/Et_2O 95:5, 500 mL; hexanes/Et_2O 90:10, 500 mL; hexanes/Et_2O 80:20, 750 mL, 50 mL fractions) to afford 30 mg (0.11 mmol) of the *Z*-enoate ***Z*-8**. IR (neat): 2933, 2839, 1716, 1651, 1583, 1464, 1307, 1253, 1171, 1099, 1047, 779, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.62–1.92 (4H, C2/3–H), 2.60 (m, 2H, C9–H), 2.70 (m, 1H, C4–H), 2.98 (m, 1H, C4–H), 3.09 (m, 1H, C1–H), 3.81 (s, 3H, OCH_3), 4.18 (q, J=7.2 Hz, 2H, OCH_2CH$_3$), 5.84 (d, J=10.9 Hz, 1H, C11–H), 6.28 (m, 1H, C10–H), 6.67 (d, J=8.0 Hz, 1H, C6–H), 6.86 (d, J=8.0 Hz, 1H, C8–H), 7.14 (t, J=8.0 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 157.4, 148.0, 141.1, 126.2, 126.1, 122.9, 120.8, 107.3, 60.4, 55.4, 39.7, 37.2, 27.0, 23.2, 18.9, 14.5. EIMS (+): 274 (M^+, 14), 229 (6), 200 (10), 1661 (base), 145 (18), 128 (30), 115 (28). HRMS (EI, +): calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1578.

Fractions 37–45 were combined to afford 470 mg (1.72 mmol) of the *E*-enoate ***E*-8**. ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.62–1.80 (2H, C2/3–H), 1.86 (m, 2H, C2/3–H), 2.40–2.75 (4H, C4/9–H), 2.94 (m, 1H, C1–H), 4.19 (q, J=7.2 Hz, 2H, OCH_2CH$_3$), 5.86 (d, J=16.2 Hz, 1H, C11–H), 6.67 (d, J=8.0 Hz, 1H, C8–H), 6.82 (d, J=8.0 Hz, 1H, C6–H), 7.01 (m, 1H, C10–H), 7.14 (t, J=8.0 Hz, 1H, C7–H).

3.4. Preparation of ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanoate (9)

A solution of *E*- and *Z*-ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (***E*-8**, ***Z*-8**) (300 mg, 1.08 mmol) in 40 mL of methanol was hydrogenated under 56 psi of hydrogen over 59 mg of $Pd(OH)_2$ (20% on carbon). After 18 h, argon was bubbled through the solution for 15 min. The catalyst was removed by filtration through Celite® moistened with CH_2Cl_2 and was washed with CH_2Cl_2 (5×10 mL). Concentration of the combined filtrates in vacuo provided 280 mg (1.03 mmol; 95%) of ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanoate (**9**) as a pale yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.64. IR (neat): 2933, 2863, 1733, 1581, 1464, 1249, 1172, 1101, 1070, 1033, 777, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=7.2 Hz, 3H, OCH$_2$CH_3), 1.35 (m, 2H, C2/3–H), 1.60–1.82 (6H, C2/3/9/10–H), 2.34 (m, 2H, C11–H), 2.55 (m, 1H, C1–H), 2.68 (m, 1H, C4–H), 2.76 (m, 1H, C4–H), 3.80 (s, 3H, O–CH_3), 4.19 (q, J=7.2 Hz, 2H, OCH_2CH$_3$), 6.65 (d, J=8.0 Hz, 1H, C8–H), 6.78 (d, J=8.0 Hz, 1H, C6–H), 7.10 (t, J=8.0 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 157.3, 142.6, 126.0, 125.9, 121.0, 106.9, 60.4, 55.4, 37.6, 36.3, 34.9, 26.7, 23.3, 23.1, 18.9, 14.4. EIMS (+): 276 (M^+, 25), 230 (6), 213 (7), 174 (11), 161 (base), 115 (13), 91 (13). HRMS (EI, +): calcd for $C_{17}H_{24}O_3$ 276.1725, found 276.1731.

3.5. Preparation of 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butan-1-ol (10)

A stirring suspension of $LiAlH_4$ (490 mg, 12.9 mmol, 1.2 equiv) in 11 mL of Et_2O was cooled in an ice-water bath to 0 °C. To this

suspension was added a solution of the ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanoate (**9**) (2.98 g, 0.011 mol) in 18 mL of Et_2O dropwise via cannula. An additional 2 mL of Et_2O was added to the flask and transferred after the initial addition was complete. The gray reaction mixture was allowed to slowly warm to room temperature. Stirring was continued at room temperature for an additional 13 h. The reaction mixture was cooled to 0 °C and 0.50 mL of water, 0.50 mL 15% NaOH, and 1.50 mL of water were added sequentially dropwise. Following these additions, the reaction mixture was allowed to warm to room temperature at which time a white precipitate formed. The reaction mixture was filtered through a pad of Celite® and the filter cake was washed alternately with three portions each of Et_2O (15 mL) and CH_2Cl_2 (15 mL), and dried (Na_2SO_4). Concentration in vacuo provided 2.49 g (0.011 mol, 98%) of 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butan-1-ol (**10**) as a clear, colorless oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.14. IR (neat): 3363, 2931, 2859, 1581, 1463, 1436, 1340, 1249, 1097, 1074, 775, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.34–1.84 (11H, C2/3/9/10/11–H, –OH), 2.56 (m, 1H, C4–H), 2.68 (m, 1H, C4–H), 2.74 (m, 1H, C1–H), 3.66 (br q, J=5.2 Hz, 2H, C12–H), 3.81 (s, 3H, OCH_3), 6.65 (d, J=7.6 Hz, 1H, C8–H), 6.79 (d, J=7.6 Hz, 1H, C6–H), 7.10 (t, J=7.6 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 142.9, 125.9, 125.7, 121.1, 106.8, 62.9, 55.3, 37.8, 36.7, 33.1, 26.8, 23.8, 23.3, 18.9. EIMS (+): 234 (M^+, 26), 175 (7), 162 (28), 161 (base). HRMS (EI, +): calcd for $C_{15}H_{22}O_2$ 234.1619, found 234.1617.

3.6. Preparation of 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanal (11)

To a mixture of 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butan-1-ol (**10**) (2.49 g, 0.011 mol), 4 Å molecular sieves (2.50 g), Celite® (9.05 g), and sodium acetate (1.15 g, 0.014 mol) in 200 mL of CH_2Cl_2 was added PCC (pyridinium chlorochromate, 3.02 g, 0.014 mol) at room temperature. After stirring at room temperature for 2 h, an additional portion of 4 Å molecular sieves (0.25 g), Celite® (1.00 g), sodium acetate (115 mg, 1.4 mmol), and PCC (300 mg, 1.4 mmol) were added and the mixture was allowed to stir at room temperature overnight. After addition of Et_2O (100 mL), the mixture was filtered through silica gel (150 g). The chromium salt/silica gel was washed with ether (3×100 mL) and the combined filtrates were concentrated in vacuo to provide the crude product as a yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.52.

The crude product was purified by chromatography using the flash technique (50 mm OD; 100 g 230–400 mesh silica gel, packed petroleum ether/Et_2O 95:5; run petroleum ether/Et_2O 90:10, 30 mL fractions) to afford 1.93 g (0.0083 mol, 78%) of 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanal (**11**) as a colorless oil. IR (neat): 2931, 2861, 2836, 1722, 1581, 1464, 1438, 1340, 1249, 1105, 1074, 777, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.86 (8H, C2/3/9/10–H), 2.44 (m, 2H, C11–H), 2.56 (m, 1H, C4–H), 2.68 (m, 1H, C4–H), 2.79 (m, 1H, C1–H), 3.81 (s, 3H, OCH_3), 6.66 (d, J=8.0 Hz, 1H, C8–H), 6.77 (d, J=8.0 Hz, 1H, C6–H), 7.10 (t, J=8.0 Hz, 1H, C7–H), 9.78 (t, J=2.0 Hz, 1H, –CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.6, 157.2, 142.2, 125.9, 125.8, 120.9, 106.9, 55.3, 44.1, 37.6, 36.2, 26.8, 23.2, 20.1, 18.9. EIMS (+): 232 (M^+, 28), 204 (8), 175 (8), 161 (base). HRMS (EI, +): calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1467.

3.7. Preparation of 5-methoxy-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (12)

Sodium hydride (200 mg, 4.5 mmol, 2.1 equiv, 60% in oil) was placed in a three-necked round bottom flask under argon and washed three times with petroleum ether to remove the mineral oil. To the NaH was added dimethylsulfoxide (DMSO, 25 mL). The mixture was heated to 75 °C (internal) and held for 45 min, until the evolution of hydrogen ceased. A portion of the warmed dimsylsodium solution (2.25 mL) was transferred via syringe to a 25 mL round bottom flask containing DMSO (2.00 mL) at room temperature under argon. The resulting diluted dimsylsodium solution was added dropwise via cannula to isopropyl-triphenylphosphonium iodide (1.95 g, 0.0045 mol, 2.1 equiv) in 10 mL of DMSO creating a bright red solution that was allowed to stir at room temperature for 45 min. To the red solution was then added via cannula a solution of 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanal (**11**) (500 mg, 2.14 mmol) in 1 mL of DMSO. The reaction mixture, which turned orange, then yellow over 1 h, was stirred overnight at room temperature and quenched with water (3 mL). The mixture was diluted with aqueous NH_4Cl (15 mL) and then extracted with Et_2O (4×20 mL). The combined organic layers were washed with water (15 mL) and dried (Na_2SO_4). Concentration in vacuo gave the crude product as a yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.82.

The crude product was purified by chromatography using the flash technique (50 mm OD; 100 g 230–400 mesh silica gel, packed pentane; run pentane/Et_2O 95:5, 20 mL fractions) to afford 533 mg (2.05 mmol, 96%) of 5-methoxy-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (**12**) as a clear, colorless oil. IR (neat): 2929, 2858, 1581, 1464, 1437, 1252, 1101, 1070, 908, 775, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35–1.82 (8H, C2/3/9/10–H), 1.55 (s, 3H, C15–H), 1.69 (s, 3H, C14–H), 1.98 (m, 2H, C11–H), 2.55 (m, 1H, C4–H), 2.70 (m, 1H, C4–H), 2.75 (m, 1H, C1–H), 3.81 (s, 3H, OCH_3), 5.13 (br t, J=7.0 Hz, 1H, C12–H), 6.54 (d, J=7.6 Hz, 1H, C8–H), 6.79 (d, J=7.6 Hz, 1H, C6–H), 7.10 (t, J=7.6 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 143.2, 131.5, 125.9, 125.8, 124.9, 121.2, 106.7, 55.3, 37.8, 36.6, 28.4, 27.9, 26.9, 25.9, 23.4, 19.0, 17.9. EIMS (+): 258 (M^+, 33), 187 (54), 174 (base), 161 (97). HRMS (EI, +): calcd for $C_{18}H_{26}O$ 258.1983, found 258.1981.

3.8. Preparation of 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-ol (13)

A solution of 5-methoxy-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (**12**) (290 mg, 1.11 mmol) in 10 mL DMF was degassed by sparging with Ar for 30 min and then NaSEt (1.86 g, 0.022 mol, 20 equiv) was added in one portion. The resulting solution was then heated to reflux for 4.5 h under Ar. The mixture was cooled and an additional portion of NaSEt (470 mg, 5.5 mmol, 5 equiv) was added. The solution was brought back to reflux and was maintained at reflux overnight. After the mixture was cooled to room temperature, water (10 mL) was added and the reaction mixture was acidified with 1.0 M HCl. Ether (10 mL) was added, the layers were separated, and the aqueous phase was extracted with ether (3×10 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as a yellow oil. TLC (pentane/Et_2O 75:25, UV, PMA): R_f=0.52.

The crude product was purified by chromatography using the flash technique (25 mm OD; 20 g 230–400 mesh silica gel, packed hexanes/Et_2O 95:5; run hexanes/Et_2O 90:10, 8 mL fractions) to afford 263 mg (1.08 mmol; 97%) of 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-ol (**13**) as a light yellow oil. IR (neat): 3371, 2927, 2856, 1581, 1462, 1377, 1322, 1271, 1240, 881, 781, 717 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.90 (8H, C2/3/9/10–H), 1.61 (s, 3H, C15–H), 1.69 (s, 3H, C14–H), 1.99 (m, 2H, C11–H), 2.56 (m, 1H, C4–H), 2.64 (m, 1H, C4–H), 2.72 (m, 1H, C1–H), 4.60 (s, 1H, OH), 5.14 (br t, J=7.0 Hz, 1H, C12–H), 6.60 (d, J=8.0 Hz, 1H, C8–H), 6.77 (d, J=8.0 Hz, 1H, C6–H), 7.02 (t, J=8.0 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 143.6, 131.8, 126.1, 124.9, 123.4, 121.4, 111.8, 37.7, 36.5, 28.4, 27.9, 26.9, 25.9, 23.0, 19.0, 17.9. EIMS (+): 244 (M^+, 53), 173 (45), 160 (base), 147 (86), 131 (11), 107 (12), 91 (11). HRMS (EI, +): calcd for $C_{17}H_{24}O$ 244.1827, found 244.1824.

3.9. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside

As described by McDonald and Pletcher,[16] 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-ol (**13**) (155 mg, 0.632 mmol, 2 equiv) and 2,3,4-tri-*O*-acetyl-D-xylopyranose-1-trichloroacetimidate (**14**) (133 mg, 0.316 mmol) were combined and azeotropically dried via rotary evaporation with anhydrous toluene (3×5 mL). To the dried starting materials were added dichloromethane (4 mL) and activated, powdered 4 Å molecular sieves (0.317 g). The mixture was stirred at room temperature for 20 min, and then was cooled in a dry ice/isopropanol bath and distilled $BF_3 \cdot OEt_2$ (three drops) was added over 10 min. The mixture was stirred for 30 min, and then was quenched by the addition of saturated aqueous $NaHCO_3$ (5 mL) and the mixture was warmed to room temperature. The mixture was diluted with dichloromethane (10 mL), the organic phase was separated, and filtered through a pad of anhydrous sodium sulfate and Celite®. The filter cake was rinsed with dichloromethane (15 mL), and the combined filtrates were concentrated in vacuo to afford the crude material as a clear viscous yellow oil. TLC (pentane/Et_2O 60:40, UV, PMA): R_f=0.32.

The crude product was purified using the flash technique (15 mm OD; 25 g 230–400 mesh silica gel) with 70:30 pentane/ether as the eluent. The first 10 fractions afforded 102 mg (0.416 mmol; 66%) of recovered phenol. Fractions 11–19 gave 124 mg (0.246 mmol, 78%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside as a clear pale yellow glass. IR (neat): 2865, 1750, 1581, 1373, 1228, 1045, 904, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.90 (8H, C2/3/9/10–H), 1.61 (s, 3H, C15–H), 1.69 (s, 3H, C14–H), 1.99 (m, 2H, C11–H), 2.10 (s, 3H, OAc), 2.12 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.43 (m, 1H, C4–H), 2.59 (m, 1H, C4–H), 2.72 (m, 1H, C1–H), 3.53 (m, 1H, C20–H), 4.21 (dm, *J*=12.3 Hz, 1H, C20–H), 5.02 (m, 1H, C19–H), 5.08–5.26 (4H, C12/16/17/18–H), 6.82 (d, *J*=8.0 Hz, 1H, C8–H), 6.90 (dm, *J*=8.0 Hz, 1H, C6–H), 7.08 (t, *J*=8.0 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 170.1, 169.6, 169.5, 163.9, 154.3, 154.2, 143.8, 143.7, 131.6, 127.2, 127.1, 125.9, 124.8, 123.5, 123.5, 111.3, 111.8, 98.3, 70.7, 70.7, 70.1, 68.6, 61.8, 61.7, 37.7, 37.7, 36.5, 36.5, 28.3, 27.8, 27.8, 26.8, 26.6, 25.9, 23.4, 21.0, 20.9, 18.9, 18.7, 17.9. ESI-MS (TOF, +): 525 (M^++Na, base), 503 (M^++H, 30), 383 (14), 323 (52), 259 (64). HRMS (ESI/TOF, +): calcd for $C_{28}H_{38}O_8$+Na 525.2458, found 525.2457.

3.10. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-D-xylopyranoside (3a)

According to the procedure of Carpino,[5b,17] 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (265 mg, 0.527 mmol) was dissolved in methanol (20 mL) and water (16.9 mL) was added to produce a white solid in suspension. To this mixture was added 1 N aqueous KOH (3.14 mL, 3.14 mmol, 6 equiv). The mixture was stirred for 2 h at room temperature, and then the solvent was removed in vacuo and the residue was diluted with brine (50 mL). The solution and precipitate were extracted with chloroform (3×100 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo afforded 139 mg (0.369 mmol, 70%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-D-xylopyranoside (**3a**) as a white solid, mp 144.6–149.8 °C. TLC (hexanes/EtOAc 50:50, UV, PMA): R_f=0.13. IR (neat): 3423 (br), 2933, 2840, 1580, 1460, 1242, 1045, 906, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15–1.80 (8H, C2/3/9/10–H), 1.58 (s, 3H, C15–H), 1.67 (s, 3H, C14–H), 1.98 (m, 2H, C11–H), 2.46–2.76 (3H, C1/4–H), 3.29 (br t, *J*=8.7 Hz, 1H, C20–H), 3.60–3.84 (3H, C18/19/20–H), 3.95 (m, 1H, C17–H), 4.35 (br, 3H, OH), 4.84 (dm, *J*=7.4 Hz, 1H, C16–H), 5.12 (br t, *J*=6.8 Hz, 1H, C12–H), 6.77 (d, *J*=8.0 Hz, 1H, C8–H), 6.84 (t, *J*=8.0 Hz, 1H, C6–H), 7.02 (m, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 154.5, 143.6, 143.6, 131.6, 127.3, 127.2, 126.0, 125.9, 124.9, 123.6, 123.6, 112.1, 112.1, 111.9, 111.9, 101.4, 101.4, 76.0, 73.3, 73.2, 69.9, 69.9, 65.4, 37.8, 37.7, 36.6, 36.6, 28.4, 28.4, 27.9, 26.8, 26.0, 23.7, 23.6, 19.0, 18.9, 17.9. ESI-MS (TOF, +): 399 (M^++Na, base), 377 (M^++H, 5), 371 (4), 359 (3). HRMS (ESI/TOF, +): calcd for $C_{22}H_{32}O_5$+Na 399.2141, found 399.2155.

3.11. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-arabinopyranoside

The procedure was identical to that described for the reaction of structures **13** and **14**; hence, only those items that differ from that procedure are provided in the following: 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-ol (**13**, 452 mg, 1.85 mmol, 2 equiv) and 2,3,4-tri-*O*-acetyl-L-arabinopyranose-1-trichloroacetimidate (**15**, 389 mg, 0.925 mmol); dichloromethane (8 mL) and activated, powdered 4 Å molecular sieves (0.929 g); $BF_3 \cdot OEt_2$ (five drops); $NaHCO_3$ (20 mL); dichloromethane (25 mL). The filter cake was rinsed with dichloromethane (50 mL), and the combined filtrates were concentrated in vacuo to afford the crude material as a clear viscous yellow oil. TLC (pentane/Et_2O 60:40, UV, PMA): R_f=0.32.

The crude product was purified by chromatography using the flash technique (30 mm OD; 30 g 230–400 mesh silica gel, packed pentane/Et_2O 75:25; compound was applied on silica gel (5 g); run pentane/Et_2O 70:30, 10 mL fractions) to afford 304 mg (1.24 mmol, 67% of recovered phenol) and 358 mg (0.712 mmol, 77%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*alic>-acetyl-β-L-arabinopyranoside as an amorphous solid. IR (neat): 3104, 2800, 1745, 1576, 1458, 1371, 1213, 1047, 1022, 912, 779, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.15–1.84 (8H, C2/3/9/10–H), 1.59 (s, 3H, C15–H), 1.67 (s, 3H, C14–H), 1.84–2.19 (4H, C11/14–H), 2.07 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.44 (m, 1H, C4–H), 2.60 (m, 1H, C4–H), 2.70 (m, 1H, C1–H), 3.74 (dm, *J*=12.8 Hz, 1H, C20–H), 4.09 (dm, *J*=12.8 Hz, 1H, C20–H), 5.07 (m, 1H, C17–H), 5.11 (m, 1H, C12–H), 5.16 (dd, *J*=8.8, 3.2 Hz, 1H, C18–H), 5.31 (m, 1H, C19–H), 5.42 (m, 1H, C16–H), 6.80 (d, *J*=8.0 Hz, 1H, C8–H), 6.88 (m, 1H, C7–H), 7.06 (t, *J*=8.0 Hz, 1H, C6–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.4, 169.6, 169.6, 164.0, 163.9, 154.4, 154.4, 143.8, 143.7, 131.6, 127.1, 127.1, 125.9, 125.8, 124.8, 123.5, 123.4, 111.2, 111.1, 98.7, 98.6, 70.0, 69.2, 69.2, 67.4, 67.4, 62.8, 62.8, 53.6, 37.7, 37.7, 36.6, 36.5, 28.3, 28.3, 27.9, 27.8, 26.9, 26.7, 25.9, 23.5, 23.4, 21.1, 21.0, 20.9, 19.0, 18.8, 17.9. ESI-MS (TOF, +): 525 (M^++Na, base), 497 (6), 443 (3). HRMS (ESI/TOF, +): calcd for $C_{28}H_{38}O_8$+Na 525.2458, found 525.2463.

3.12. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-L-arabinopyranoside (3b)

According to the procedure of Carpino,[5b,17] 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-arabinopyranoside (471 mg, 0.937 mmol) was dissolved in methanol (25 mL) and water (19.4 mL) was added to produce a white solid in suspension. To this mixture was added 1 N aqueous KOH (5.58 mL, 5.58 mmol, 6 equiv). The mixture was stirred for 2 h at room temperature, and then the solvent was removed in vacuo and the residue was diluted with brine (75 mL). The solution and precipitate was extracted with chloroform (3×150 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a clear, pale yellow glass. TLC (hexanes/EtOAc 50:50, UV, PMA): R_f=0.11.

The crude product was purified by chromatography using the flash technique (15 mm OD; 14 g 230–400 mesh silica gel, packed CH_2Cl_2/MeOH 98:2; run CH_2Cl_2/MeOH 95:5, 10 mL fractions) to

afford 251 mg (0.665 mmol, 71%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-L-arabinopyranoside (**3b**) as a cream colored solid. Mp 106.3–109.1 °C. IR (neat): 3423 (br), 2933, 2840, 1580, 1460, 1242, 1045, 906, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.70 (8H, C2/3/9/10–H), 1.63 (s, 3H, C15–H), 1.72 (s, 3H, C14–H), 2.00 (m, 2H, C11–H), 2.58 (m, 1H, C1–H), 2.65 (br s, 2H, C4–H), 3.40 (br d, *J*=12.1 Hz, 1H, C20–H), 3.75 (br d, *J*=8.6 Hz, 1H, C19–H), 3.93 (br d, *J*=12.1 Hz, 1H, C20–H), 3.98 (m, 1H, C17–H), 4.07 (br t, *J*=8.0 Hz, 1H, C18–H), 4.30–5.30 (br, 3H, OH), 4.67 (d, *J*=7.1 Hz, 1H, C16–H), 5.15 (br t, *J*=6.9 Hz, 1H, C12–H), 6.79 (d, *J*=8.0 Hz, 1H, C8–H), 6.86 (d, *J*=8.0 Hz, 1H, C6–H), 7.00 (t, *J*=8.0 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 154.9, 143.4, 131.5, 131.4, 127.4, 125.8, 124.8, 123.5, 112.6, 112.5, 102.3, 73.3, 71.2, 68.7, 66.2, 53.6, 37.7, 37.6, 36.6, 36.5, 28.3, 27.8, 26.8, 26.7, 25.9, 23.5, 18.9, 17.9. ESI-MS (TOF, +): 775 ($2M^+$+Na, 20), 399 (M^++Na, base). HRMS (ESI/TOF, +): calcd for $C_{22}H_{32}O_5$+Na 399.2141, found 399.2151.

3.13. Preparation of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-fucopyranoside

The procedure was identical to that described for the reaction of structures **13** and **14**; hence, only those items that differ from that procedure are provided in the following: 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-ol (**13**) (394 mg, 1.61 mmol, 2 equiv) and 2,3,4-tri-*O*-acetyl-L-fucopyranose-1-trichloroacetimidate (**16**) (350 mg, 0.805 mmol); dichloromethane (6 mL); 4 Å molecular sieves (0.809 g); $BF_3{\cdot}OEt_2$ (five drops); $NaHCO_3$ (5 mL); dichloromethane (10 mL). The filter cake was rinsed with dichloromethane (15 mL), and the combined filtrates were concentrated in vacuo to afford the crude material as a clear viscous yellow oil. TLC (pentane/Et_2O 60:40, UV, PMA): R_f=0.27.

The crude product was purified by chromatography using the flash technique (30 mm OD; 40 g 230–400 mesh silica gel, packed pentane/Et_2O 75:25; compound was applied on silica gel (5 g); run pentane/Et_2O 70:30 (0.1 L), 60:40 (0.4 L), 10 mL fractions) to afford 162 mg (0.662 mmol, 82% of recovered phenol) and 408 mg (0.790 mmol, 98%) of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-fucopyranoside as a white amorphous solid. IR (neat): 2933, 2859, 1749, 1579, 1459, 1369, 1218, 1064, 910, 827, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, *J*=6.3 Hz, 3H, C21–H), 1.30–1.80 (8H, C2/3/9/10–H), 1.58 (s, 3H, C15–H), 1.67 (s, 3H, C14–H), 1.94–2.10 (4H, C11/14–H), 2.00 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.19 (s, 3H, OAc), 2.40 (m, 1H, C4–H), 2.70 (m, 1H, C4–H), 2.75 (m, 1H, C1–H), 3.96 (br q, *J*=6.3 Hz, 1H, C20H), 5.00 (d, *J*=8.0 Hz, C17–H), 5.10–5.16 (2H, C12/18–H), 5.29 (m, 1H, C19H), 5.50 (m, 1H, C16–H), 6.80 (m, 1H, C8–H), 6.87 (m, 1H, C7–H), 7.06 (t, *J*=8.0 Hz, 1H, C6–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.4, 169.6, 169.5, 154.6, 154.5, 143.6, 143.5, 131.4, 127.0, 126.9, 125.7, 124.7, 123.4, 123.3, 123.2, 111.1, 110.9, 99.1, 99.0, 92.0, 88.4, 71.4, 71.3, 70.2, 69.4, 68.7, 68.6, 37.6, 36.5, 36.4, 28.3, 28.2, 27.7, 27.6, 26.8, 26.6, 25.8, 23.3, 23.3, 20.9, 20.8, 18.9, 18.7, 17.8, 16.2. ESI-MS (TOF, +): 539 (M^++Na, base), 455 (10), 273 (12), 153 (23). HRMS (ESI/TOF, +): calcd for $C_{29}H_{40}O_8$+Na 539.2620, found 539.2636.

3.14. Preparation of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-L-fucopyranoside (3c)

According to the procedure of Carpino,[5b,17] 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (718 mg, 1.39 mmol) was dissolved in methanol (52 mL) and water (43.7 mL) was added to produce a white solid in suspension. To this mixture was added 1 N aqueous KOH (8.27 mL, 8.27 mmol, 6 equiv). The mixture was stirred for 2 h at room temperature, and then the solvent was removed in vacuo and the residue was diluted with brine (115 mL). The solution and precipitate were extracted with chloroform (3×200 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo afforded 420 mg (1.08 mmol, 77%) of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-L-fucopyranoside (**3c**) as a white solid. TLC (hexanes/EtOAc 50:50, UV, PMA): R_f=0.03.

The crude product was purified by chromatography using the flash technique (15 mm OD; 14 g 230–400 mesh silica gel, packed CH_2Cl_2/MeOH 98:2; run CH_2Cl_2/MeOH 97:3, 10 mL fractions) to afford 356 mg (0.911 mmol, 66%) of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-1-yloxy)-β-L-fucopyranoside (**3c**) as a white solid. Mp 87.7–90.1 °C. IR (neat): 3392 (br), 2931, 2859, 1579, 1439, 1243, 1168, 1080, 908, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (d, *J*=6.4 Hz, 3H, C21–H), 1.30–1.75 (8H, C2/3/9/20–H), 1.61 (s, 3H, C15–H), 1.70 (s, 3H, C14–H), 2.00 (m, 2H, C11–H), 2.55 (m, 1H, C1–H), 2.65 (m, 2H, C4–H), 3.50 (br q, *J*=6.4 Hz, 1H, C20–H), 3.70 (br d, *J*=13.2 Hz, 1H, C18–H), 3.77 (br s, 1H, C19–H), 4.03 (dd, *J*=1.32, 13.0 Hz, 1H, C17–H), 4.13 (br s, 1H, OH), 4.60 (br s, 1H, OH), 4.69 (dm, *J*=7.7 Hz, 1H, C16–H), 5.13 (m, 1H, C12–H), 6.80 (m, 1H, C6–H), 6.88 (dm, *J*=7.83 Hz, 1H, C8–H), 7.01 (t, *J*=7.83 Hz, 1H, C7–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 143.4, 131.6, 127.4, 127.3, 125.8, 124.9, 123.4, 123.3, 112.6, 112.3, 102.2, 101.9, 74.2, 71.9, 71.1, 70.9, 37.8, 37.7, 36.7, 36.6, 28.4, 27.9, 27.8, 26.8, 26.7, 26.0, 23.6, 18.9, 17.9, 16.5. ESI-MS (TOF, +): 413 (M^++Na, base), 125 (7). HRMS (ESI/TOF, +): calcd for $C_{23}H_{34}O_5$+Na 413.2304, found 413.2310.

3.15. Preparation of *E*-ethyl 3-(2,3-dimethoxyphenyl)-prop-2-enoate (18)

The procedure was identical to that reported for the preparation of structures ***E*-8** and ***Z*-8**. Hence, only those items that differ from that procedure are recorded in the following: NaH (1.63 g, 0.0406 mol, 1.4 equiv, 60% in oil) covered with toluene (25 mL); triethyl phosphonoacetate (9.12 g, 0.0406 mol, 1.4 equiv); 2,3-dimethoxybenzaldehyde (**17**, 5.00 g, 0.0301 mol) in toluene (25 mL); ice-water (75 mL). Filtration and concentration in vacuo afforded the crude product as an orange-brown oil. TLC (hexanes/EtOAc 80:20, UV, cerium molybdate stain): R_f=0.38.

The crude products were purified by chromatography using the flash technique (50 mm OD; 100 g 230–400 mesh silica gel, packed hexanes/Et_2O 95:5; run hexanes/Et_2O 90:10, 50 mL fractions) to afford 7.03 g (0.0298 mol, >95%) of *E*-ethyl 3-(2,3-dimethoxyphenyl)prop-2-enoate (**18**) as a pale yellow oil. Spectral data matched that reported by Rapoport et al.[25]

3.16. Preparation of ethyl 2-(2,3-dimethoxyphenyl)-cyclopropanecarboxylate (19)

Into a flask containing a solution of *E*-ethyl 3-(2,3-dimethoxyphenyl)prop-2-enoate (**18**) (6.88 g, 0.0291 mol) dissolved in a mixture of Et_2O (160 mL) and CH_2Cl_2 (50 mL) containing $Pd(OAc)_2$ (50 mg, 0.22 mmol), cooled in an ice-water bath, was distilled diazomethane (58 mmol, 2 equiv). Diazomethane was prepared by the addition of Diazald® (15 g, 0.058 mol, 2 equiv) as a solution in Et_2O (140 mL) to a solution of 50% aqueous KOH (43 mL), Et_2O (84 mL), and diethylene glycol diethyl ether (150 mL) warmed to 75 °C. The rate of addition of the Diazald® solution was adjusted to achieve a slow distillation of diazomethane. The mixture was allowed to stir for 15 min after the distillation was complete. Then, a solution of acetic acid in ether (1 N) was added drop by drop until the diazomethane color had dissipated. The mixture was then filtered through Celite®, the filter cake was rinsed with Et_2O (150 mL), and the combined filtrates were concentrated in vacuo. The pale

yellow residual oil was dissolved in Et_2O (0.35 L), washed with satd aqueous $NaHCO_3$ (2×0.25 L), and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude cyclopropyl ester **19** (6.12 g, 0.0279 mol, 96%) as a clear, pale yellow oil. This material was deemed to be of sufficient purity to proceed directly to the hydrogenolysis step. TLC (hexanes/EtOAc 80:20, UV, I_2): R_f=0.33. IR (neat): 2981, 2938, 2904, 2834, 1722, 1581, 1477, 1405, 1328, 1276, 1178, 1076, 1008, 912, 782, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.34 (m, 1H, C9–H), 1.6 (m, 1H, C9–H), 1.85 (m, 1H, C8–H), 2.80 (m, 1H, C7–H), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.18 (m, 2H, OCH_2CH_3), 6.45 (dd, J=8.0 Hz, 1.6, 1H, C4–H), 6.77 (dd, J=8.0, 1.6 Hz, 1H, C6–H), 6.97 (t, J=8.0 Hz, 1H, C5–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 152.9, 148.1, 134.0, 124.1, 117.0, 110.6, 61.0, 60.7, 55.8, 23.5, 20.8, 16.0, 14.4. ESI-MS (TOF, +): 273 (M^+, 25), 251 (10), 205 (base), 190 (35). HRMS (ESI/TOF, +): calcd for $C_{14}H_{18}O_4$+Na 273.1103, found 273.1127.

3.17. Preparation of ethyl 4-(2,3-dimethoxyphenyl)-butanoate (20)

To a solution of ethyl 2-(2,3-dimethoxyphenyl)cyclopropane carboxylate (**19**) (7.33 g, 0.0293 mol) in MeOH (125 mL) was added $Pd(OH)_2$ (20% on carbon, 1.15 g). The mixture was sparged with nitrogen for 10 min, and then was hydrogenolyzed on a Parr apparatus with a starting pressure of 52 psi of H_2 for 18 h. The catalyst was removed by filtration through a pad of Celite®, the filter cake was rinsed with CH_2Cl_2 (0.4 L), and the combined filtrates were concentrated in vacuo to provide ethyl 4-(2,3-dimethoxyphenyl) butanoate (**20**) as a clear, colorless oil (6.97 g, 0.0275 mol, 94%). This material was judged to be of sufficient purity to proceed to the hydrolysis step without further purification. Spectral data matched with that reported by Rama Rao et al.[18a] TLC (hexanes/EtOAc 80:20, UV, cerium molybdate stain): R_f=0.43.

3.18. Preparation of 4-(2,3-dimethoxyphenyl)-butanoic acid (24)[26]

To a solution of ethyl 4-(2,3-dimethoxyphenyl)butanoate (**20**) (3.98 g, 0.0158 mol) in a mixture of MeOH (60 mL) and water (2 mL) was added powdered KOH (1.91 g, 0.0341 mol, 2.16 equiv). The mixture was stirred until the KOH dissolved, and then was heated to reflux and maintained at reflux for 1 h. At this juncture, TLC indicated the reaction was complete by disappearance of the starting material, and the mixture was then cooled to room temperature. Methanol was removed by rotary evaporation and the residue was diluted with water (100 mL). The pH of the solution was adjusted to ca. 1 with 1 N aqueous HCl. The mixture was transferred to a separatory funnel with Et_2O (150 mL) and the aqueous layer was saturated with salt. The organic layer was separated, the aqueous phase was extracted with Et_2O (2×150 mL), and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo gave the crude acid **21** (3.33 g, 0.0149 mol, 94%) as a clear, colorless oil. This material was judged to be of sufficient purity to proceed to the cyclization step without any further purification. Spectral data matched with that reported by Rama Rao et al.[18a] TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.03.

3.19. Preparation of 5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (22)

To 4-(2,3-dimethoxyphenyl)butanoic acid (**21**) (3.66 g, 0.0163 mol) was added Eaton's reagent (43.7 mL, 65.55 g) and the mixture was allowed to stir for 12 h under argon. As the reaction proceeded, the solution became dark yellow-orange color, and at the end of the 12 h period was poured over ice (150 g). The ice was allowed to melt and the mixture was transferred to a separatory funnel with CH_2Cl_2 (150 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2×75 mL). The combined organic phases were washed with satd aqueous $NaHCO_3$ (2×300 mL) and dried (Na_2SO_4). Filtration and concentration in vacuo provided the crude tetralone **22** as a dark brown sticky solid.

The crude product was purified by chromatography using the flash technique (50 mm OD; 150 g 230–400 mesh silica gel, packed hexanes/Et_2O 80:20; run hexanes/Et_2O 80:20 (0.25 L), 70:30 (0.5 L), 65:35 (1 L), 50 mL fractions) to afford 2.95 g (0.0143 mol, 88%) of 5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-one (**22**) as a white solid. Spectral data matched with that reported by Rama Rao et al.[18a] TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.21. Mp 94.1–95.8 °C.

3.20. Preparation of *E*- and *Z*-ethyl 2-(5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)ethanoate (*E*-23, *Z*-23) and ethyl 2-(5,6-dimethoxy-3,4-dihydronaphthalen-1-yl)ethanoate (24)

The procedure was identical to that reported for the preparation of structures *E*-**8** and ***Z*-8**. Hence, only those items that differ from that procedure are recorded in the following: NaH (390 mg, 9.9 mmol, 1.8 equiv, 60% in oil) covered with toluene (11 mL); triethyl phosphonoacetate (2.21 g, 0.00986 mol, 1.8 equiv); 5,6-dimethoxy-1-tetralone (**25**) (1.13 g, 0.00548 mol) in toluene (11 mL); ice-water (30 mL) in a separatory funnel. The organic phase was separated and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude products as a yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.43, 0.35, 0.33.

The crude products were purified by chromatography using the flash technique (50 mm OD; 100 g 230–400 mesh silica gel, packed hexanes/Et_2O 95:5; run hexanes/Et_2O 90:10, 150 mL; hexanes/Et_2O 85:15, 1.3 L; hexanes/Et_2O 80:20, 350 mL; hexanes/Et_2O 70:30, 300 mL, 20 mL fractions) to afford 909 mg (3.29 mmol, 60%) of a 14:48:38 mixture of *Z*-ethyl 2-(5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)ethanoate (***Z*-23**)/*E*-ethyl 2-(5,6-dimethoxy-3,4-dihydronaphthalen-1(2*H*)-ylidene)ethanoate (***E*-23**)/ethyl 2-(5,6-dimethoxy-3,4-dihydronaphthalen-1-yl)ethanoate (**24**) as a clear, colorless oil. IR (neat): 2937, 2837, 1711, 1593, 1491, 1273, 1155, 1086, 1020, 808 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (m, 3H, OCH_2CH_3), 1.82 (m, 0.38H), 1.94 (m, 0.62H), 2.24 (m, 0.62H), 2.42 (m, 0.62H), 3.83 (m, 2H), 3.14 (br t, J=6.2 Hz, 0.38H), 3.39 (s, 0.76H), 3.75–3.95 (10H), 4.10–4.25 (2H), 5.71 (br s, 0.48H, ***E*-23** C9–H), 5.85 (br t, J=4.6 Hz, 0.38H, **24** C2–H), 6.24 (br s, 0.14H, ***Z*-23** C9–H), 6.70–6.95 (1.52H), 7.42–7.50 (0.48H). EIMS (+): 276 (M^+, base). HRMS (EI, +): calcd for $C_{16}H_{20}O_4$ 276.1361, found 276.1358.

3.21. Preparation of ethyl 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanoate (25)

A solution of ***E*-23**, ***Z*-23**, and **24** (362 mg, 1.31 mmol) in 60 mL of methanol was hydrogenated under 47 psi of hydrogen over 0.072 g of $Pd(OH)_2$ (20% on carbon). After 18 h, argon was bubbled through the solution for 15 min. The catalyst was removed by filtration through Celite® with CH_2Cl_2 and the filter cake was rinsed with CH_2Cl_2 (5×10 mL). Concentration of the combined filtrates in vacuo provided 363 mg (1.30 mmol, >95%) of ethyl 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanoate (**25**) as a pale yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.33. IR (neat): 2931, 2850, 1730, 1489, 1452, 1419, 1273, 1161, 1078, 1031, 802 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, J=7.0 Hz, 3H, OCH_2CH_3), 1.63 (m, 1H, C3–H), 1.70–1.90 (3H, C2/3–H), 2.49 (dd, J=15.2, 9.8 Hz, 1H, C4–H), 2.62–2.78 (2H, C9–H), 2.83 (dt, J=15.2, 5.7 Hz, 1H, C4–H), 3.32 (m, 1H, C1–H), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.16 (q, J=7.0 Hz, 2H, OCH_2CH_3), 6.74 (d, J=8.6 Hz, 1H, C7–H), 6.89 (d, J=8.6 Hz, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 150.7,

146.6, 132.8, 131.7, 123.7, 110.3, 60.5, 60.0, 55.9, 42.3, 34.3, 28.1, 23.6, 19.1, 14.4. EIMS (+): 278 (M^+, 29), 204 (9), 191 (base), 160 (9). HRMS (EI, +): calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1530.

3.22. Preparation of 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanol (26)

The procedure was identical to that reported for the preparation of structure **10**. Hence, only those items that differ from that procedure are recorded. Since reductions using lithium aluminum hydride can be dangerous, please follow the *detailed procedure* given for the preparation of structure **10**, making substitutions for the quantities used according to the following: $LiAlH_4$ (170 mg, 4.4 mmol, 1.2 equiv) in 5 mL of Et_2O; ethyl 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanoate (**25**) (1010 mg, 3.64 mmol) in 10 mL of Et_2O dropwise via cannula. An additional 3 mL of Et_2O was added to the flask and transferred after the initial addition was complete. The gray reaction mixture was allowed to slowly warm to room temperature. Stirring continued at room temperature for an additional 13 h. The reaction mixture was cooled to 0 °C and 0.20 mL of water, 0.20 mL of 15% NaOH, and 0.39 mL of water were added sequentially; washed alternately with three portions each of Et_2O (10 mL) and CH_2Cl_2 (10 mL). Concentration in vacuo provided 858 mg (3.60 mmol, >95%) of 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanol (**26**) as a pale yellow oil. TLC (hexanes/Et_2O 40:60, UV, vanillin): R_f=0.21. IR (neat): 3432 (br), 2933, 2860, 1488, 1452, 1274, 1220, 1049, 1001, 802, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.6–1.9 (5H, C2/3/9–H), 1.95 (m, 1H, C9–H), 2.70 (m, 1H, C4–H), 2.80 (dt, J=17.8, 6.7 Hz, 1H, C4–H), 2.92 (m, 1H, C1–H), 3.78 (m, 2H, C10–H), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.75 (d, J=8.3 Hz, 1H, C7–H), 6.91 (d, J=8.3 Hz, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 146.1, 134.1, 131.1, 123.1, 109.8, 60.6, 59.8, 55.6, 39.6, 33.5, 27.3, 23.4, 18.9. EIMS (+): 236 (M^+, 26), 191 (base), 160 (13), 115 (8). HRMS (EI, +): calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1414.

3.23. Preparation of 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanal (27)

To 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanol (**26**) (310 mg, 1.29 mmol) in CH_2Cl_2 (30 mL) were added sequentially *N*-methylmorpholine-*N*-oxide (230 mg, 1.94 mmol, 1.5 equiv), powdered, anhydrous 4 Å molecular sieves (0.65 g), and tetrapropylammonium perruthenate (TPAP, 46 mg, 0.13 mmol, 10 mol %). The mixture was allowed to stir for 50 min at room temperature, at which point TLC analysis indicated the reaction was complete. The reaction mixture was filtered through a plug of silica gel. The plug was rinsed with ether and the combined filtrates were concentrated in vacuo to provide 300 mg (1.25 mmol, 97%) of the crude aldehyde **27** as a clear, pale yellow oil. The material was not further purified and was used 'as is'. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.26. IR (neat): 2937, 2834, 2721, 1722, 1602, 1489, 1454, 1421, 1277, 1222, 1095, 910, 802, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (m, 1H, C2–H), 1.78 (m, 2H, C2/3–H), 1.91 (m, 1H, C3–H), 2.60–2.85 (4H, C4/9–H), 3.40 (m, 1H, C1–H), 3.74 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 6.75 (d, J=8.4 Hz, 1H, C7–H), 6.84 (d, J=8.4 Hz, 1H, C8–H), 9.83 (t, J=2.3 Hz, 1H, –CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.2, 150.5, 132.2, 131.6, 123.4, 118.8, 110.2, 59.8, 55.7, 51.2, 31.8, 28.5, 23.3, 19.2. EIMS (+): 234 (M^+, 55), 191 (base), 176 (7), 160 (14), 115 (9). HRMS (EI, +): calcd for $C_{14}H_{18}O_3$ 234.1255, found 234.1251.

3.24. Preparation of *E*- and *Z*-ethyl 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (28)

The procedure was identical to that reported for the preparation of structures ***E*-8** and ***Z*-8**. Hence, only those items that differ from that procedure are recorded in the following: NaH (390 mg, 9.6 mmol, 1.8 equiv, 60% in oil) covered with toluene (15 mL); triethyl phosphonoacetate (2.16 g, 0.0096 mol, 1.8 equiv); 2-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethanal (**27**) (1.25 g, 0.00530 mol) in toluene (15 mL) over 30 min; ice-water (50 mL). The organic phase was separated and dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude products as a yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.45, 0.40.

The crude products were purified by chromatography using the flash technique (40 mm OD; 100 g 230–400 mesh silica gel, packed hexanes/Et_2O 98:2; run hexanes/Et_2O 95:5, 200 mL; hexanes/Et_2O 90:10, 200 mL; hexanes/Et_2O 80:20, 600 mL, 25 mL fractions) to afford 1.23 g (0.00398 mol, 75%) of a 5:95 mixture (by ^1H NMR) of *Z*-ethyl 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (***Z*-28**)/*E*-ethyl 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (***E*-28**) as a clear, colorless oil. IR (neat): 2870, 2823, 1708, 1608, 1491, 1450, 1419, 1276, 1220, 1180, 1091, 1039, 908, 802, 734, 701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.6–1.82 (4H, C2/3–H), 2.42 (m, 1H, C9–H), 2.58–2.76 (2H, C4/9–H), 2.80 (m, 1H, C4–H), 2.93 (m, 1H, C1–H), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.19 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.85 (dm, J=15.5 Hz, 1H, C11–H), 6.75 (d, J=8.6 Hz, 1H, C7–H), 6.89 (d, J=8.6 Hz, 1H, C8–H), 6.99 (m, 1H, C10–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 150.3, 147.6, 146.3, 132.7, 131.4, 123.5, 122.7, 109.9, 60.0, 59.6, 55.5, 39.5, 36.4, 27.2, 23.3, 18.9, 14.2. EIMS (+): 304 (M^+, 7), 191 (base), 176 (4), 160 (8). HRMS (EI, +): calcd for $C_{18}H_{24}O_4$ 304.1674, found 304.1680.

3.25. Preparation of ethyl 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanoate (29)

A solution of *E*- and *Z*-ethyl 4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)but-2-enoate (***E*-28**/***Z*-28**) (1.66 g, 0.00544 mol) in 75 mL of methanol was hydrogenated under 50 psi of hydrogen over 0.25 g of $Pd(OH)_2$ (20% on carbon). After 18 h, argon was bubbled through the solution for 15 min. The catalyst was removed by filtration through Celite® moistened with CH_2Cl_2 and was washed with CH_2Cl_2 (5×15 mL). Concentration of the combined filtrates in vacuo provided 1.57 g (0.00511 mol, 94%) of ethyl 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanoate (**29**) as a pale yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.47. IR (neat): 2987, 2933, 2834, 1734, 1491, 1452, 1276, 1224, 1176, 1087, 1057, 802, 727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, J=7.1 Hz, 3H, OCH_2CH_3), 1.45–1.83 (8H, C2/3/9/20–H), 2.34 (m, 2H, C11–H), 2.64–2.92 (3H, C1/4–H), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.12 (q, J=7.1 Hz, 2H, OCH_2CH_3), 6.74 (d, J=8.4 Hz, 1H, C7–H), 6.87 (d, J=8.4 Hz, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.8, 150.3, 146.4, 134.5, 131.5, 123.8, 110.0, 60.3, 59.9, 55.8, 37.0, 34.6, 34.5, 27.1, 23.6, 22.9, 19.2, 14.4. EIMS (+): 306 (M^+, 24), 261 (5), 191 (base). HRMS (EI, +): calcd for $C_{18}H_{26}O_4$ 306.1831, found 306.1838.

3.26. Preparation of 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butan-1-ol (30)

The procedure was identical to that used in the preparation of structure **10**; only differences in the quantities of materials are reported here. $LiAlH_4$ (230 mg, 5.9 mmol, 1.2 equiv) in 10 mL of Et_2O; ethyl 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-butanoate (**29**) (1.51 g, 0.0049 mol) in 15 mL of Et_2O. An additional 2 mL of Et_2O was added to the flask and transferred after the initial addition was complete. Quenching at 0 °C with 0.20 mL of water, 0.20 mL 15% NaOH, and 0.59 mL of water; filter cake was washed alternately with three portions each of Et_2O (15 mL) and CH_2Cl_2 (15 mL) and dried (Na_2SO_4). Concentration in vacuo provided 1.25 g (0.0047 mol, 96%) of 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butan-1-ol (**30**) as a colorless oil. TLC (hexanes/EtOAc

80:20, UV, vanillin): R_f=0.14. IR (neat): 3388, 2931, 2856, 1488, 1450, 1419, 1276, 1221, 1060, 1030, 1008, 802, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.85 (10H, C2/3/9/10/11–H), 2.55–2.62 (3H, C4–H, OH), 2.70 (m, 1H, C1–H), 3.68 (br q, J=5.1 Hz, 2H, C12–H), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.74 (d, J=8.4 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 146.4, 134.9, 131.5, 123.8, 109.9, 62.9, 59.9, 55.8, 37.2, 36.9, 33.1, 27.2, 23.7, 23.6, 19.2. EIMS (+): 264 (M^+, 21), 191 (base). HRMS (EI, +): calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1719.

3.27. Preparation of 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanal (31)

To 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butan-1-ol (**30**) (1.25 g, 0.00472 mol) in CH_2Cl_2 (80 mL) were added sequentially *N*-methylmorpholine-*N*-oxide (830 mg, 7.10 mmol, 1.5 equiv), powdered, anhydrous 4 Å molecular sieves (2.36 g), and tetrapropylammonium perruthenate (TPAP, 170 mg, 0.47 mmol, 10 mol %). The mixture was allowed to stir for 50 min at room temperature, at which point TLC analysis indicated the reaction was complete. The reaction mixture was filtered through a plug of silica gel. The plug was rinsed with ether and the combined filtrates were concentrated in vacuo to provide 1.05 g (0.00396 mol, 84%) of the crude aldehyde (**31**) as a clear, pale yellow oil. A sample of this material was purified, but the bulk of the material was carried on 'as is'. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.26.

A 228 mg sample of the crude product was purified by chromatography using the flash technique (15 mm OD; 6 g 230–400 mesh silica gel, packed petroleum Et_2O/Et_2O 95:5; run petroleum Et_2O/Et_2O 90:10, 7 mL fractions) to afford 165 mg (0.628 mmol, 72% of the crude sample) of 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanal (**31**) as a colorless oil. IR (neat): 3014, 2933, 2832, 2717, 1726, 1604, 1491, 1450, 1419, 1277, 1224, 1064, 894, 804, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.55–1.84 (8H, C2/3/9/10–H), 2.43 (m, 2H, C4–H), 2.60–2.84 (3H, C1/11–H), 3.83 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.74 (d, J=8.4 Hz, 1H, C7–H), 6.86 (d, J=8.4 Hz, 1H, C8–H), 9.78 (t, J=1.5 Hz, 1H, –CHO). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7, 150.3, 146.4, 134.2, 131.5, 123.7, 109.9, 59.9, 55.8, 44.2, 37.0, 36.4, 27.1, 23.6, 19.9, 19.2. EIMS (+): 262 (M^+, 23), 191 (base). HRMS (EI, +): calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1563.

3.28. Preparation of 5,6-dimethoxy-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (32)

Sodium hydride (200 mg, 4.5 mmol, 2.1 equiv, 60% in oil) was placed in a three-necked round bottom flask under argon and washed three times with petroleum ether to remove the mineral oil. To the NaH was added dimethylsulfoxide (DMSO, 25 mL). The mixture was heated to 75 °C (internal) and held for 45 min, until the evolution of hydrogen ceased. A portion of the warmed dimsylsodium solution (1.60 mL) was transferred via syringe to a 25 mL round bottom flask containing DMSO (2.00 mL) at room temperature under argon. The resulting diluted dimsylsodium solution was added dropwise via cannula to isopropyl-triphenylphosphonium iodide (1.38 g, 0.0032 mol, 2.1 equiv) in 7 mL of DMSO creating a bright red solution that was allowed to stir at room temperature for 45 min. To the red solution was then added via cannula a solution of 4-(5,6-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)butanal (**31**) (400 mg, 1.5 mmol) in 3.5 mL of DMSO. The reaction mixture, which turned orange, then yellow over 1 h, was stirred overnight at room temperature and quenched with water (5 mL). The mixture was diluted with aqueous NH_4Cl (15 mL) and then extracted with Et_2O (3×15 mL). The combined organic layers were washed with water (25 mL) and dried (Na_2SO_4). Concentration in vacuo gave the crude product **32** as a yellow oil. TLC (hexanes/EtOAc 80:20, UV, vanillin): R_f=0.60.

The crude product **32** was purified by chromatography using the flash technique (40 mm OD; 50 g 230–400 mesh silica gel, packed pentane; run pentane/Et_2O 98:2, 20 mL fractions) to afford 284 mg (0.96 mmol, 64%) of 5,6-dimethoxy-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (**32**) as a colorless oil. IR (neat): 2929, 2856, 1602, 1489, 1452, 1327, 1276, 1222, 1095, 800, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.70 (6H, C2/3/9–H), 1.56 (s, 3H, C15–H), 1.60 (s, 3H, C14–H), 1.78 (m, 2H, C10–H), 2.00 (m, 2H, C11–H), 2.55–2.70 (2H, C1/4–H), 2.76 (dt, J=16.1 Hz, 6.7, 1H, C4–H), 3.79 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 5.13 (br t, J=6.7 Hz, 1H, C12–H), 6.74 (d, J=8.6 Hz, 1H, C7–H), 6.89 (d, J=8.6 Hz, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 146.3, 135.0, 131.5, 131.4, 124.9, 123.9, 109.8, 59.9, 55.8, 37.1, 36.8, 28.4, 27.7, 27.3, 25.9, 23.7, 19.3, 17.8. EIMS (+): 288 (M^+, 34), 257 (3), 217 (41), 204 (42), 191 (base). HRMS (EI, +): calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2079.

3.29. Preparation of 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol (33)

A solution of 5,6-dimethoxy-1-(5-methylhex-4-enyl)-1,2,3,4-tetrahydronaphthalene (**32**) (55 mg, 0.19 mmol) in 10 mL DMF was degassed by sparging with Ar for 30 min, and then NaSEt (400 mg, 4.8 mmol, 25 equiv) was added in one portion. The resulting solution was then heated to reflux for 4.5 h under Ar. The mixture was cooled and an additional portion of NaSEt (240 mg, 2.9 mmol, 15 equiv) was added. The solution was brought back to reflux and was maintained at reflux overnight. After the mixture was cooled to room temperature, water (10 mL) was added and the reaction mixture was acidified with 1.0 M HCl. Ether (10 mL) was added, the layers were separated, and the aqueous phase was extracted with ether (3×10 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as a yellow oil. TLC (hexanes/EtOAc 80:20, UV, PMA): R_f=0.17.

The crude product was purified by chromatography using the flash technique (15 mm OD; 10 g 230–400 mesh silica gel, packed hexanes/Et_2O 95:5; run hexanes/Et_2O 90:10, 40 mL; hexanes/Et_2O 85:15, 300 mL, 8 mL fractions) to afford 35 mg (0.13 mmol, 70%) of 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol (**33**) as a light yellow oil. IR (neat): 3435 (br), 2931, 2858, 1494, 1452, 1290, 1255, 1191, 906, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.30–1.90 (8H, C2/3/9/10–H), 1.62 (s, 3H, C15–H), 1.70 (s, 3H, C14–H), 2.00 (m, 2H, C11–H), 2.55–2.77 (3H, C1/4–H), 5.15 (m, 1H, C12–H), 5.25 (br s, 1H, OH), 5.35 (br s, 1H, OH), 6.64 (d, J=8.3 Hz, 1H, C7–H), 6.69 (d, J=8.3 Hz, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.2, 140.5, 135.3, 131.6, 124.9, 124.2, 120.5, 112.7, 37.2, 36.7, 28.4, 27.8, 27.0, 25.9, 23.3, 18.9, 17.9. EIMS (+): 260 (M^+, 47), 189 (45), 163 (base). HRMS (EI, +): calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1774.

3.30. Preparation of 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol-2-*tert*-butyldimethylsilyl ether (34)

To a solution of **33** (400 mg, 1.54 mmol) in DMF (anhydrous, 4 mL) cooled in an ice-water bath under argon were added sequentially TBDMSOTf (441 mg, 1.67 mmol, 1.08 equiv, 384 mL) and *i*-Pr_2NEt (270 mg, 2.09 mmol, 1.35 equiv, 364 mL). The mixture was allowed to stir for 30 min at 0 °C, and TLC at that point indicated that the reaction was incomplete. An additional 0.3 equiv of TBSOTf (122 mg, 0.46 mmol, 0.106 mL) and 0.37 equiv of *i*-Pr_2NEt (74 mg, 0.57 mmol, 0.099 mL) were then added and stirring was allowed to continue for an additional 35 min. The pale yellow reaction mixture was diluted with EtOAc (15 mL), cast into a separatory funnel, and washed with water (2×10 mL), brine (15 mL), and the organic phase was dried (Na_2SO_4). Filtration and concentration in vacuo afforded the crude product as a viscous, yellow oil. TLC (hexanes/EtOAc 80:20, UV, PMA): R_f=0.88.

The crude product was purified by chromatography using the flash technique (50 mm OD; 40 g 230–400 mesh silica gel, packed hexanes; run hexanes (100 mL), hexanes/CH_2Cl_2 (98:2, 100 mL), hexanes/CH_2Cl_2 (96:4, 75 mL), hexanes/CH_2Cl_2 (94:6, 80 mL), hexanes/CH_2Cl_2 (92:8, 80 mL), hexanes/CH_2Cl_2 (90:10, 750 mL)) to afford 456 mg (1.21 mmol, 79%) of 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol-2-*tert*-butyldimethylsilyl ether (**34**) as a clear, colorless oil. IR (neat): 3542 (br), 2929, 2858, 1491, 1462, 1282, 1255, 1232, 976, 873, 833, 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.25 (s, 3H, Si–CH_3), 0.26 (s, 3H, Si–CH_3), 1.00 (s, 9H, Si–*t*-Bu), 1.30–1.95 (8H, C2/3/9/10–H), 1.57 (s, 3H, C15–H), 1.69 (S, 3H, C14–H), 2.00 (m, 2H, C11–H), 2.55–2.77 (3H, C1/4–H), 5.13 (m, 1H, C12–H), 6.57 (d, J=8.3 Hz, 1H, C7–H), 6.62 (d, J=8.3 Hz, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 139.3, 135.9, 131.6, 125.0, 124.1, 119.3, 114.6, 37.3, 36.7, 28.5, 28.3, 27.9, 27.3, 26.0, 23.5, 19.0, 18.4, 18.0, −4.0, −4.1. EIMS (+): 374 (M^+, 45), 317 (77), 277 (27), 261 (23), 219 (base), 179 (49). HRMS (EI, +): calcd for $C_{23}H_{38}O_2Si$ 374.2641, found 374.2674.

3.31. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside

The procedure was identical to that described for the reaction of structures **13** and **14**; hence, only those items that differ from that procedure are provided in the following: 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol-2-*tert*-butyldimethylsilyl ether (**34**) (133 mg, 0.355 mmol) and 2,3,4-tri-*O*-acetyl-D-xylopyranose-1-trichloroacetimidate (**14**) (179 mg, 0.426 mmol, 1.2 equiv); 4 Å molecular sieves (0.587 g); $BF_3{\cdot}OEt_2$ (four drops); $NaHCO_3$ (5 mL). The mixture was diluted with dichloromethane (15 mL), the organic phase was separated, and filtered through a pad of anhydrous sodium sulfate and Celite®. The filter cake was rinsed with dichloromethane (15 mL) and the combined filtrates were concentrated in vacuo to afford the crude material as a clear viscous yellow oil. TLC (pentane/Et_2O 60:40, UV, PMA): R_f=0.30.

The crude product was purified by chromatography using the flash technique (30 mm OD; 40 g 230–400 mesh silica gel, packed pentane/Et_2O 75:25; compound was applied on silica gel (7.5 g); run pentane/Et_2O 70:30, 125 mL, 10 mL fractions; pentane/Et_2O 60:40, 500 mL, 10 mL fractions) to afford 54 mg (0.144 mmol, 40% of recovered phenol) and 143 mg (0.227 mmol, 64%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside as a clear pale yellow glass. IR (neat): 2931, 2858, 1756, 1486, 1369, 1246, 1216, 1070, 1037, 836, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.20 (6H, Si–CH_3), 1.01 (s, 9H, Si–*t*-Bu), 1.30–1.90 (8H, C2/3/9/10–H), 1.60 (s, 3H, C15–H), 1.68 (s, 3H, C14–H), 1.99 (m, 2H, C11–H), 2.03 (s, 3H, OAc), 2.04 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.50–2.85 (m, 3H, C1/4–H), 3.24 (m, 1H, C20–H), 4.07 (dm, J=12.3 Hz, 1H, C20–H), 4.98 (m, 1H, C12–H), 5.14 (m, 1H, C19–H), 5.15–5.26 (2H, C17/18–H), 5.42 (m, 1H, C16–H), 6.63 (d, J=8.3 Hz, 1H, C7–H), 6.82 (m, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 170.0, 169.6, 145.0, 144.9, 142.7, 142.6, 135.7, 135.6, 133.0, 132.9, 131.4, 125.0, 124.9, 124.8, 124.7, 124.6, 117.6, 117.5, 99.2, 99.0, 72.2, 72.1, 71.9, 71.8, 69.3, 62.7, 62.7, 37.3, 37.1, 36.7, 36.5, 28.5, 28.3, 27.8, 27.7, 27.1, 26.1, 26.0, 25.9, 24.6, 24.5, 21.0, 20.9, 20.8, 19.3, 19.1, 18.5, 17.9, −3.8, −3.9, −4.0. ESI-MS (TOF, +): 655 (M^++Na, base), 633 (M^++H, 15), 259 (14). HRMS (ESI/TOF, +): calcd for $C_{28}H_{38}O_8$+Na 655.3278, found 655.3289.

3.32. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-β-D-xylopyranoside (4a)

To a solution of (5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-D-xylopyranoside (282 mg, 0.446 mmol) in methanol (35 mL) was added 0.5 M NaOMe in MeOH (8.91 mL, 4.45 mmol, 10 equiv). The mixture was placed in a 40 °C oil bath and was allowed to stir, under argon, for 2 h. The mixture was allowed to cool to room temperature, and then the methanol was removed in vacuo and the residue was dissolved in water (85 mL). The pH was adjusted to ca. pH=6 with 0.1 N aqueous HCl to produce a cloudy aqueous phase. The mixture was transferred to a separatory funnel with $CHCl_3$ (100 mL), the aqueous phase was saturated with salt, and the organic phase was separated. The aqueous layer was extracted with $CHCl_3$ (2×100 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo gave the crude product as a yellow, glassy, semi-solid. TLC (hexanes/EtOAc 50:50, UV, PMA): R_f=0.08.

The crude product was purified using the flash technique (15 mm OD; 10 g 230–400 mesh silica gel, packed CH_2Cl_2; run CH_2Cl_2 50 mL; CH_2Cl_2/MeOH, 98:2, 75 mL; CH_2Cl_2/MeOH, 97:3, 500 mL) to afford 100 mg (0.255 mmol, 57%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-β-D-xylopyranoside (**4a**) as a clear pale yellow glass. IR (neat): 3367 (br), 2925, 2858, 1606, 1486, 1452, 1265, 1039, 815, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.87 (8H, C2/3/9/10–H), 1.60 (s, 3H, C15–H), 1.69 (s, 3H, C14–H), 1.97 (m, 2H, C11–H), 2.42–2.85 (4H, C1/4–H, OH), 3.12 (br t, J=8.7 Hz, 1H, C20–H), 3.60 (m, 1H, C20–H), 3.65–3.85 (3H, C18/19–H, OH), 3.95 (m, 1H, C17–H), 4.46 (m, 1H, C16–H), 4.80 (br, 1H, OH), 5.12 (br t, J=6.8 Hz, 1H, C12–H), 5.70 (br, 2H, OH), 6.67 (d, J=8.0 Hz, 1H, C7–H), 6.79 (m, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.9, 146.7, 145.9, 142.4, 142.3, 134.7, 131.7, 131.6, 131.5, 126.3, 124.9, 124.8, 114.2, 106.0, 105.9, 77.5, 76.7, 74.1, 69.6, 66.0, 53.6, 50.7, 37.1, 36.8, 28.5, 28.4, 27.8, 27.0, 25.9, 24.3, 19.1, 17.9, 14.9. ESI-MS (TOF, +): 415 (M^++Na, base), 387 (11). HRMS (ESI/TOF, +): calcd for $C_{22}H_{32}O6$+Na 415.2091, found 415.2109.

3.33. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-arabinopyranoside

The procedure was identical to that described for the reaction of structures **13** and **14**; hence, only those items that differ from that procedure are provided in the following: 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol-2-*tert*-butyldimethylsilyl ether (**34**) (150 mg, 0.40 mmol) and 2,3,4-tri-*O*-acetyl-L-arabinopyranose-1-trichloroacetimidate (**15**) (202 mg, 0.48 mmol, 1.2 equiv); dichloromethane (5 mL); 4 Å molecular sieves (482 mg); $BF_3{\cdot}OEt_2$ (four drops); saturated aqueous $NaHCO_3$ (20 mL); diluted with dichloromethane (25 mL). The filter cake was rinsed with dichloromethane (50 mL), and the combined filtrates were concentrated in vacuo to afford the crude material as a clear, viscous yellow oil. TLC (pentane/Et_2O 60:40, UV, PMA): R_f=0.32.

The crude product was purified by chromatography using the flash technique (30 mm OD; 30 g 230–400 mesh silica gel, packed pentane/Et_2O 75:25; compound was applied on silica gel (5 g); run pentane/Et_2O 70:30, 100 mL; pentane/Et_2O 60:40, 400 mL; 10 mL fractions) to afford 39 mg (0.104 mmol, 26% of recovered phenol). Fractions 18–25 gave 139 mg (0.22 mmol, 55%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-arabinopyranoside as a clear, colorless glass. IR (neat): 2931, 2858, 1749, 1602, 1489, 1369, 1297, 1247, 1218, 1091, 1047, 974, 782, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 6H, Si–CH_3), 0.99 (s, 9H, Si–*t*-Bu), 1.25–1.92 (8H, C2/3/9/10/11–H), 1.59 (s, 3H, C15–H), 1.68 (s, 3H, C14–H), 1.96 (m, 2H, C11–H), 2.04 (s, 3H, –OAc), 2.05 (s, 3H, –OAc), 2.06 (s, 3H, OAc), 2.50–3.00 (m, 3H, C1/4–H), 3.53 (br d, J=12.9 Hz, 1H, C20–H), 4.00 (dm, J=12.9 Hz, 1H, C20–H), 5.05 (m, 1H, C17–H), 5.14 (m, 1H, C12–H), 5.18 (m, 1H, C18–H), 5.24 (m, 1H, C19–H), 5.43 (m, 1H, C16–H), 6.64 (d, J=8.4 Hz, 1H, C9–H), 6.81 (m, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 170.3, 169.6, 145.2, 145.1, 143.1, 143.0, 135.7, 135.6, 132.7, 132.6, 131.5, 124.9, 124.6, 117.8, 117.7, 99.5, 99.3, 70.4, 70.3, 70.0, 67.9,

67.8, 63.6, 63.4, 37.3, 37.2, 36.8, 36.6, 28.5, 28.4, 27.8, 27.7, 27.2, 27.1, 26.1, 26.0, 24.6, 24.5, 21.1, 21.0, 20.9, 19.3, 18.5, 17.9, −3.8, −3.9, −4.0, −4.1. ESI-MS (TOF, +): 655 (M^++Na, base), 633 (M^++H, 6). HRMS (ESI/TOF, +): calcd for $C_{34}H_{52}O_9Si$+Na 655.3278, found 655.3301.

3.34. Preparation of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-β-L-arabinopyranoside (4b)

To a solution of (5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-arabinopyranoside (188 mg, 0.297 mmol) in methanol (25 mL) was added 0.5 M NaOMe in MeOH (5.94 mL, 2.97 mmol, 10 equiv). The mixture was placed in a 40 °C oil bath and was allowed to stir, under argon, for 2 h. The mixture was allowed to cool to room temperature, and then methanol was removed in vacuo and the residue was dissolved in water (60 mL). The pH was adjusted to ca. pH=6 with 0.1 N aqueous HCl to produce a cloudy aqueous phase. The mixture was transferred to a separatory funnel with $CHCl_3$ (75 mL), the aqueous phase was saturated with salt, and the organic phase was separated. The aqueous layer was extracted with $CHCl_3$ (2×75 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo gave the crude product as a yellow, glassy, semi-solid. TLC (hexanes/EtOAc 50:50, UV, PMA): R_f=0.06.

The crude product was purified using the flash technique (15 mm OD; 10 g 230–400 mesh silica gel, packed CH_2Cl_2; run CH_2Cl_2 50 mL; CH_2Cl_2/MeOH, 98:2, 75 mL; CH_2Cl_2/MeOH, 97:3, 500 mL) to afford 103 mg (0.262 mmol, 88%) of 2-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-β-L-arabinopyranoside (**4b**) as a clear pale yellow glass. IR (neat): 3384 (br), 3054, 2927, 1606, 1486, 1450, 1265, 1068, 1018, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25–1.77 (8H, C2/3/9/10–H), 1.60 (s, 3H, C15–H), 1.69 (s, 3H, C14–H), 2.20–2.70 (3H, C1/11–H), 2.80 (m, C4–H), 3.35 (m, 1H, C20–H), 3.80 (m, 1H, C19–H), 3.85 (br, 1H, –OH), 3.95–4.15 (2H, C17/20–H), 4.11 (br t, *J*=8.0 Hz, 1H, C18–H), 4.40 (d, *J*=7.1 Hz, 1H, C16–H), 4.86 (br, 1H, –OH), 5.12 (br t, *J*=6.9 Hz, 1H, C12–H), 5.35 (br, 1H, –OH), 5.67 (br, 1H, –OH), 6.67 (br d, *J*=8.0 Hz, 1H, C7–H), 6.80 (m, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 147.7, 146.6, 142.1, 134.4, 131.5, 126.4, 126.3, 124.9, 114.3, 106.2, 106.1, 73.5, 72.2, 69.0, 67.1, 37.2, 37.1, 36.9, 36.8, 28.5, 28.4, 27.9, 27.8, 27.2, 27.0, 26.0, 24.3, 19.3, 19.0, 17.9. ESI-MS (TOF, +): 415 ($2M^+$+Na, base), 387 (9). HRMS (ESI/TOF, +): calcd for $C_{22}H_{32}O6$+Na 415.2091, found 415.2109.

3.35. Preparation of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-fucopyranoside

The procedure was identical to that described for the reaction of structures **13** and **14**; hence, only those items that differ from that procedure are provided in the following: 5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalene-1,2-diol-2-*tert*-butyldimethylsilyl ether (**34**) (92 mg, 0.246 mmol) and 2,3,4-tri-*O*-acetyl-L-fucopyranose-1-trichloroacetimidate **16** (128 mg, 0.295 mmol, 1.2 equiv); dichloromethane (7 mL) and activated, powdered 4 Å molecular sieves (0.482 g); $BF_3{\cdot}OEt_2$ (three drops); saturated aqueous $NaHCO_3$ (5 mL), and the mixture was warmed to room temperature. The mixture was diluted with dichloromethane (10 mL), the organic phase was separated and filtered through a pad of anhydrous sodium sulfate and Celite®. The filter cake was rinsed with dichloromethane (15 mL), and the combined filtrates were concentrated in vacuo to afford the crude material as a clear viscous yellow oil. TLC (pentane/Et_2O 60:40, UV, PMA): R_f=0.32.

The crude product was purified by chromatography using the flash technique (30 mm OD; 40 g 230–400 mesh silica gel, packed pentane/Et_2O 75:25; compound was applied on silica gel (5 g); run pentane/Et_2O 70:30 (0.15 L), 60:40 (0.4 L), 10 mL fractions) 140 mg (0.216 mmol, 88%) of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-fucopyranoside as a clear, colorless glass. IR (neat): 2933, 2560, 1749, 1487, 1369, 1257, 1224, 908, 837, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 3H, Si–CH_3), 0.21 (s, 3H, Si–CH_3), 1.00 (s, 9H, Si–*t*-Bu), 1.14 (m, 3H, C21–H), 1.30–1.80 (8H, C2/3/9/10–H), 1.58 (s, 3H, C15–H), 1.67 (s, 3H, C14–H), 1.94–2.05 (4H, C11/14–H), 1.97 (s, 3H, –OAc), 1.98 (s, 3H, –OAc), 2.19 (s, 3H, –OAc), 2.50–2.95 (3H, C1/4–H), 3.75 (m, 1H, C20H), 5.00 (dd, *J*=10.3 Hz, 3.5, C18–H), 5.12 (m, 1H, C12–H), 5.17–5.45 (3H, C16/17/19–H), 6.61 (m, 1H, C7–H), 6.79 (m, 1H, C8–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.5, 169.8, 169.7, 145.4, 145.2, 143.3, 143.2, 135.6, 135.5, 132.9, 132.6, 131.5, 124.9, 124.8, 124.7, 124.6, 124.5, 117.8, 117.7, 99.4, 99.3, 71.8, 70.6, 70.5, 70.3, 70.2, 69.5, 69.4, 37.3, 37.2, 36.9, 36.6, 28.4, 27.8, 27.7, 27.2, 27.1, 26.1, 25.9, 24.6, 24.5, 21.1, 21.0, 20.9, 20.8, 19.3, 19.2, 18.5, 17.9, 16.1, 16.0, −3.9, −4.0. ESI-MS (TOF, +): 669 (M^++Na, base), 647 (M^++H, 5), 273 (9), 153 (7). HRMS (ESI/TOF, +): calcd for $C_{35}H_{54}O_9Si$+Na 669.3435, found 669.3387.

3.36. Preparation of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hyrdoxy-1-yloxy)-β-L-fucopyranoside (4c)

To a solution of (5,6,7,8-tetrahydronaphthalen-2-*tert*-butyldimethylsilyloxy-1-yloxy)-2,3,4-tri-*O*-acetyl-β-L-fucoyranoside (236 mg, 0.365 mmol) in methanol (35 mL) was added 0.5 M NaOMe in MeOH (7.30 mL, 3.65 mmol, 10 equiv). The mixture was placed in a 40 °C oil bath and was allowed to stir, under argon, for 2 h. The mixture was allowed to cool to room temperature, and then the methanol was removed in vacuo and the residue was dissolved in water (95 mL). The pH was adjusted to ca. pH=6 with 0.1 N aqueous HCl to produce a cloudy aqueous phase. The mixture was transferred to a separatory funnel with $CHCl_3$ (100 mL), the aqueous phase was saturated with salt, and the organic phase was separated. The aqueous layer was extracted with $CHCl_3$ (2×100 mL) and the combined organic phases were dried (Na_2SO_4). Filtration and concentration in vacuo gave the crude product as a yellow, glassy, semi-solid. TLC (hexanes/EtOAc 50:50, UV, PMA): R_f=0.05.

The crude product was purified using the flash technique (15 mm OD; 10 g 230–400 mesh silica gel, packed CH_2Cl_2; run CH_2Cl_2 50 mL; CH_2Cl_2/MeOH, 98:2, 75 mL; CH_2Cl_2/MeOH, 97:3, 500 mL) to afford 124 mg (0.305 mmol, 84%) of 2-methyl-6-(5-(5-methylhex-4-enyl)-5,6,7,8-tetrahydronaphthalen-2-hydroxy-1-yloxy)-β-L-fucopyranoside (**4c**) as a white solid. Mp 54.3–60.7 °C. IR (neat): 3392 (br), 2931, 2859, 1579, 1439, 1243, 1168, 1080, 908, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.25 (d, *J*=6.4 Hz, 3H, C21–H), 1.20–1.75 (8H, C2/3/9/10–H), 1.61 (s, 3H, C15–H), 1.70 (s, 3H, C14–H), 2.00 (m, 2H, C11–H), 2.40–2.95 (3H, C1/4–H), 3.49 (br q, *J*=6.4 Hz, 1H, C20–H), 3.75 (br d, *J*=13.2 Hz, 1H, C18–H), 3.82 (br s, 1H, C19–H), 3.95 (br s, 1H, –OH), 4.12 (m, 1H, C17–H), 4.47 (m, 1H, C18–H), 4.61 (m, 1H, C16–H), 5.13 (m, 1H, C12–H), 5.34 (br, 1H, –OH), 5.65 (br, 1H, –OH), 6.70 (d, *J*=8.0 Hz, 1H, C7–H), 6.82 (m, 1H, C8–H), 8.14 (br, 1H, –OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 146.7, 142.5, 142.4, 134.3, 131.7, 131.6, 131.5, 126.3, 124.9, 124.8, 114.4, 106.0, 105.8, 77.4, 74.2, 71.8, 71.6, 37.2, 37.1, 36.8, 28.6, 28.4, 28.2, 27.9, 27.8, 27.0, 25.9, 19.1, 17.9, 16.3. ESI-MS (TOF, +): 429 (M^++Na, base), 407 (M^+, 6), 401 (10). HRMS (ESI/TOF, +): calcd for $C_{23}H_{34}O6$+Na 429.2248, found 429.2259.

3.37. Biological assessment: cell culture

Stock cultures of wild type *T. thermophila* cells (strain sb210) were grown in axenic 2% proteose peptone media supplemented with 0.003% FeEDTA and kept at room temperature in the dark. Stock cultures were transferred to fresh media every two weeks.

In order to prevent chromosome losses and mutations it is very important to discard old stock cultures (8–12 months old) and replace them with fresh cells from the same strain (previously frozen in liquid nitrogen). *T. thermophila* cells were harvested by transferring a small aliquot of stock culture into a flat bottom flask containing 2% proteose peptone and incubating them at 30 °C for 24–48 h.

3.38. Measurement of phagocytotic activity in *T. thermophila* cells

The effect of drugs on phagosome formation in *T. thermophila* cells was measured by visualizing the newly formed phagosomes containing India ink by light microscopy. For these experiments, the cells were washed twice with 10 mM HEPES buffer by centrifuging at 450 g for 5 min. The pellet was then resuspended in calcium free HEPES buffer. The final cell concentration for each experimental treatment was 250,000 cells/mL in a total volume of 4 mL. Cell suspensions were placed in 13×100 mm test tubes in a 25 °C water bath and allowed to acclimate for 1 h. Drugs were prepared at desired concentrations in 0.4 mL volumes. For control samples, 0.4 mL buffer and vehicle were added to the incubation mixture. Diluted India ink (0.45 mL, 1.25, v\v) was added to each of the test drug volumes in order to visualize newly formed phagosomes. The experiment was started when the drug/ink mixture was added to the *T. thermophila* cells and was terminated after 10 min when 500 μL of cell suspension (approximately 125,000 cells/mL) were removed and fixed in 500 μL of formalin solution. A minimum of 100 cells from each treatment was examined for the incidence of phagosome formation under light microscopy (40× magnifications). Phagocytic activity was assessed by calculating the ratio of cells with food vacuoles compared to the cells with no food vacuoles.

3.39. Materials

Phagocytic activity measurement experiments were carried out in calcium free HEPES buffer containing 10 mM HEPES, 0.1 mM EGTA at pH 7.4. On the day of the experiment, a stock aliquot was dissolved in loading buffer (10 mM HEPES, 2.5 mM probenecid, pH 7.4). Proteose peptone was obtained from DIFCO. PsA (**1**) was repurified by normal phase HPLC and was diluted in ethanol. Prior to each experiment, stock solutions of drugs were diluted in 10 mM HEPES buffer, pH 7.4. Compounds or drugs that were insoluble in aqueous solution were first dissolved in a small quantity of ethanol and then diluted into the buffer solution at a dilution of 1:10,000 or higher.

3.40. Data analysis

Results were based on pooled values from a minimum of six experiments. Potency estimates (ED_{50} values) were interpolated from dose responses by least squares regression analysis. Student's *t*-tests were performed in order to determine if the changes in activity due to drug exposure were significantly different from paired controls. Data are expressed as mean±SE mean unless otherwise stated. KD values were interpolated from a double reciprocal plot.

3.41. In vitro binding studies to adenosine receptors

These studies were performed by Cerep, Inc.[24] Binding affinity to the A_{2A} receptor was measured in human recombinant (HEK-293 cells). The A_{2A} specific radio labeled agonist, [^3H]CGS 21680, and the specific A_{2A} agonist, NECA, were used to estimate the binding affinity to the receptor.

Acknowledgements

We gratefully acknowledge the U.S. Army Medical Research Program (Grant number W81XWH-06-1-0089) for its support of this research.

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