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Semisynthesis of fuscoside B analogues and eunicosides, and analysis of anti-inflammatory activity

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ABSTRACT

A small library of semisynthetic analogues of fuscol and eunicol have been prepared and evaluated for in vivo topical anti-inflammatory activity using the mouse-ear edema assay. The first glycosylation of fuscol and eunicol has been achieved using a modified Koenigs–Knorr glycosylation to synthesize new fuscosides and eunicosides, a novel structural class of diterpene glycosides. The availability of adequate glycosylation methods for this synthesis was limited owing to the instability of the glycosyl acceptors. Glycosyl donor protecting group type had a pronounced effect on overall glycosylation yields of a model glycosyl acceptor. This synthesis provided access to the unnatural β-glycosides allowing for an evaluation of the effect of differing anomeric stereochemistry on anti-inflammatory activity. The PEGylated derivatives of fuscol and eunicol were also synthesized by a convenient acid-promoted solvolysis of the natural product aglycones. This work highlights the importance of the glycan portion of fuscoside B, notably the stereochemical configuration of the glycosidic linkage, in the observed anti-inflammatory activity.

1. Introduction

The fuscosides are a family of diterpene arabinose glycosides first isolated from the Caribbean gorgonian *Eunicea fusca* by Shin and Fenical.[1] Fuscosides A (**1**) and B (**2**) are topical anti-inflammatory agents reducing phorbol myristate acetate (PMA)-induced edema in a mouse-ear model with potencies comparable to the industry standard indomethacin.[2,3] Fuscoside B (**2**) is noted for being a selective inhibitor of 5-lipoxygenase having no effect on cyclooxygenases and prostaglandin biosynthesis.[4] This family of glycosides has drawn interest from the synthetic community as the enantioselective synthesis of fuscol was accomplished by Yamada et al. establishing its absolute stereochemistry.[5] Although an alternative and more efficient synthesis was later reported by Kosugi et al.,[6] neither group had accomplished the glycosylation to synthesize **2**.

E. fusca is also a source of fuscol (**3**),[7] the aglycone precursor of **2**, and the biosynthetically related dilophol diterpene eunicol (**4**).[8] While **2** is a trace metabolite, **3** and **4** are major constituents of the gorgonian and readily available in hundreds of milligrams. Access to **3** and **4** represents an opportunity to synthesize a library of fuscosides as well as a new class of glycosides of eunicol. Although fuscol also inhibits arachidonic acid metabolism in leukocytes,[4] its anti-inflammatory potential has not yet been fully explored; therefore the importance of the carbohydrate moiety for the anti-inflammatory activity of **2** is not well understood. As a preliminary effort to assess structure–activity relationships, this study focused on the synthesis of the unnatural β-glycosides to investigate the importance of anomeric stereochemistry of **2**. PEGylated derivatives of **3** and **4** were also prepared and all compounds were assessed in a murine model of inflammation.

The synthesis of the glycosides was restricted by the poor availability of compatible glycosylation methods as the glycosyl acceptors were unstable across a range of glycosylation conditions. Furthermore, introducing carbohydrate functionalities to hindered glycosyl acceptors remains a challenging task even with current glycosylation methodology.[9,10] Glycosylations of more sterically hindered tertiary alcohols often occur with lower yields when compared to their corresponding primary and secondary glycosyl accepting alcohols.[11] We describe herein the first glycosylation of **3** to generate fuscosides, and of **4** to afford the new class, eunicosides, using a modified Koenigs–Knorr method (Fig. 1).

2. Results and discussion

A review of the glycosylation literature indicates the scope and versatility of the method reported by Schmidt,[12–14] which involves mild activation of glycosyl trichloroacetimidate donors by catalytic amounts of $BF_3 \cdot Et_2O$. 2-Methyl-3-buten-2-ol (**5**) was used as a model glycosyl acceptor in preliminary studies due to its

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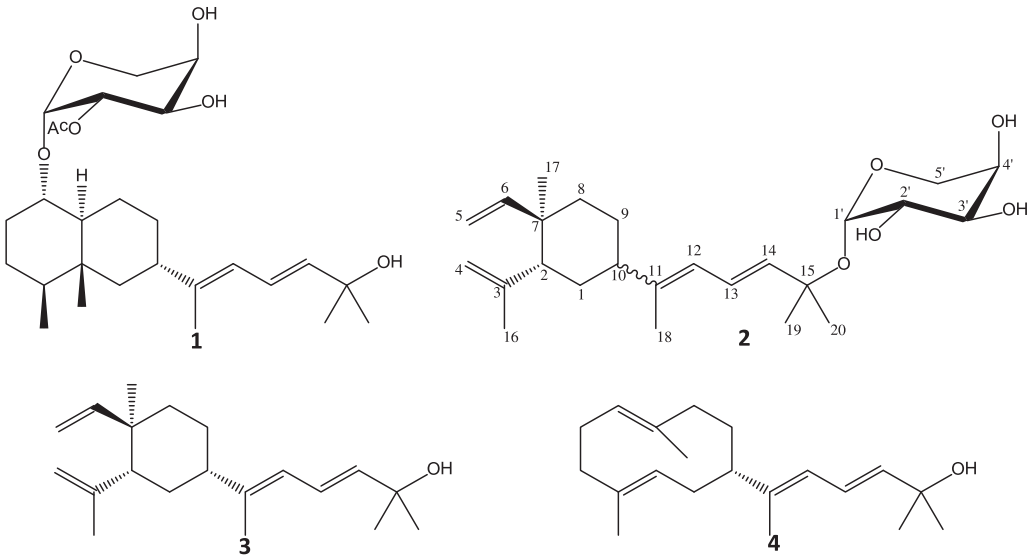


Fig. 1. Diterpenes from the Caribbean gorgonian *E. fusca*.

commercial availability. Attempts to glycosylate **5** with freshly synthesized 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl trichloroacetimidate[15] led to the unexpected degradation of **5**. As suspected, **3** and **4** also readily decomposed under these conditions to a mixture of nonpolar hydrocarbons, as indicated by TLC analysis. Oxophilic $BF_3 \cdot Et_2O$ presumably facilitates the departure of the tertiary hydroxyl group to form the tertiary π-allylic carbocation intermediate, which may undergo rearrangement and elimination. Unfortunately, further attempts to glycosylate **5** using Nicoloau's[16] and Kahne's[17] methodologies were also unsuccessful.

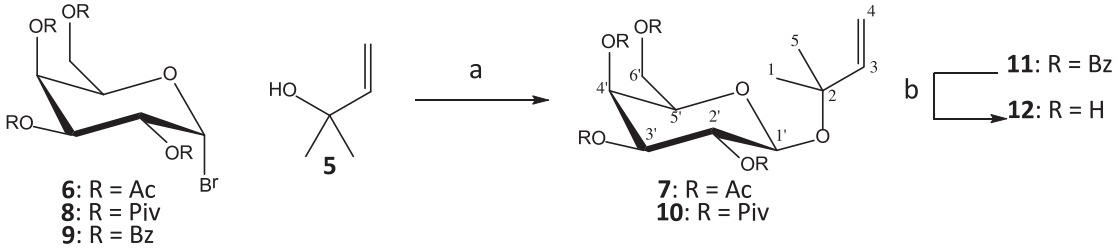
Introducing carbohydrate functionalities to hindered substrates still remains a formidable challenge despite recent progress being made in this area.[18] However, the successful glycosylation of a variety of tertiary alcohols using glycosyl bromides drew our attention to the Koenigs–Knorr method.[11,19–21] This glycosylation may take place under neutral or basic reaction conditions[22] circumventing the need for acidic activating reagents. Traditionally, activation of glycosyl bromides is achieved by Ag_2CO_3,[23,24] although more efficient methodologies have been developed that combine Ag_2CO_3 with AgOTf or $AgClO_4$.[25,26] The glycosyl bromides were fashioned with ester protecting groups, which provided β-glycosides by means of neighbouring group participation.[27]

2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**6**) was freshly prepared according to known methods.[28] The glycosylation of **5** with AgOTf, Ag_2CO_3 and donor **6** proceeded to afford glycoside **7**, which was isolated by normal phase flash chromatography (Scheme 1). Increasing the reaction time led to an increase in glycosylation yield (Table 1). To further improve glycosylation yields, the glycosyl donor was modified to one with pivaloate (**8**) and benzoate esters (**9**). A slight improvement in yields was observed with the pivaloylated donor **8**, however, the benzoylated donor **9** was far superior providing glycosylation yields that are comparable to the literature for tertiary alcohols.[11,19] Deprotection of **11** was achieved by treatment with K_2CO_3/CH_3OH and afforded glycoside **12** in good yields.

Table 1
Effect of protecting group manipulations on the glycosylation of **5**

Entry	**5** (equiv)	Glycosyl bromide (equiv)	Reaction time (Days)	Product yield (%)
1	1.0	(**6**) 4.0	0.6	(**7**) 15
2	1.0	(**6**) 4.1	3.5	(**7**) 26
3	1.0	(**8**) 4.0	0.6	(**10**) 36
4	1.0	(**8**) 4.0	3.5	(**10**) 46
5	1.0	(**9**) 2.8	1.6	(**11**) 57
6	1.0	(**9**) 4.2	3.1	(**11**) 63
7	1.0	(**9**) 3.9	3.5	(**11**) 67

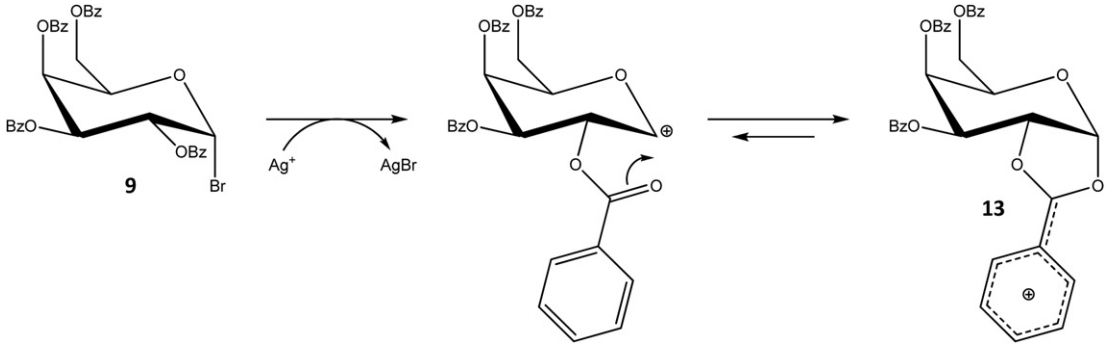
Varying the glycosyl donor protecting groups is well known to influence donor reactivity[29,30] and glycosylation yields.[31] With regards to the glycosylation of tertiary alcohol **5**, the steric bulkiness of the protecting groups was initially expected to be the most significant factor as glycosyl donors bearing pivaloate esters typically reduce overall glycosylation yields relative to that of acetates.[32] Contrary to our expectations, **8** provided higher glycosylation yields than **6**. Self-stabilization of the glycosyl cation by neighbouring group participation[33] may instead be the dominant factor in controlling yields (Scheme 2). Therefore, **8** could have resulted in higher yields due to greater stabilization of the acyloxonium intermediate via induction. Consistent with this explanation, the highest glycosylation yields were achieved with the



Scheme 1. Glycosylation of tertiary alcohol **5** with different glycosyl donors. Reagents and conditions: (a) **5** (1.0 equiv), AgOTf (0.4 equiv), Ag_2CO_3 (4.0 equiv), 3 Å MS, CH_2Cl_2; (b) K_2CO_3, CH_3OH.

benzoylated donor, presumably due to carbocation delocalization across the phenyl group (**13**). Although further study is required to confirm the correlation with higher glycosylation yields, Garegg et al. have also observed the same trend with these protecting groups using thioglycosides.[34]

purification by HPLC less attractive. Instead, a more rational approach was to utilize the mixture of **3** and **4** as they are virtually identical with regards to the environment of the tertiary alcohol. The products of glycosylation could be separated after successful transformations, thereby providing two new glycosides for each



Scheme 2. Acyloxonium formation and proposed stabilization for benzoylated glycosyl donor **9**.

Glycosylation yields were adversely affected by rearrangement of glycosyl acceptor **5**. Isolation of prenyl 2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranoside **14** and prenyl-β-D-galactopyranoside **15** from the glycosylation and deprotection crudes, respectively, was indicative of acceptor **5** rearrangement to prenyl alcohol, which underwent subsequent glycosylation (Fig. 2). This finding was consistent with our earlier explanations regarding the tertiary hydroxyl group's instability under acidic conditions.

reaction and minimizing the overall HPLC work load. The products would also be acquired with sufficient purity for anti-inflammatory evaluation.

Initial attempts to glycosylate **3** and **4** with the Koenigs–Knorr method established for model **5** resulted in complete and rapid degradation of the glycosyl acceptors. This was not entirely unexpected as the presence of **14** and **15** in earlier glycosylation and deprotection crudes suggested that heterogeneous Ag_2CO_3 did not

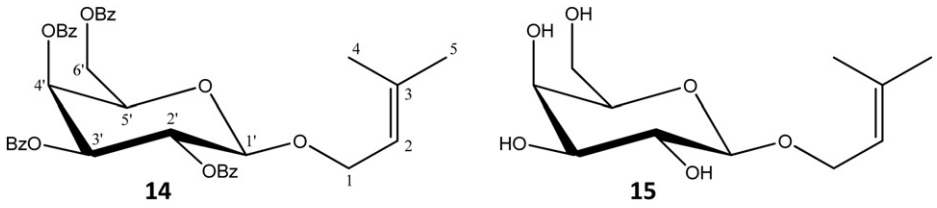
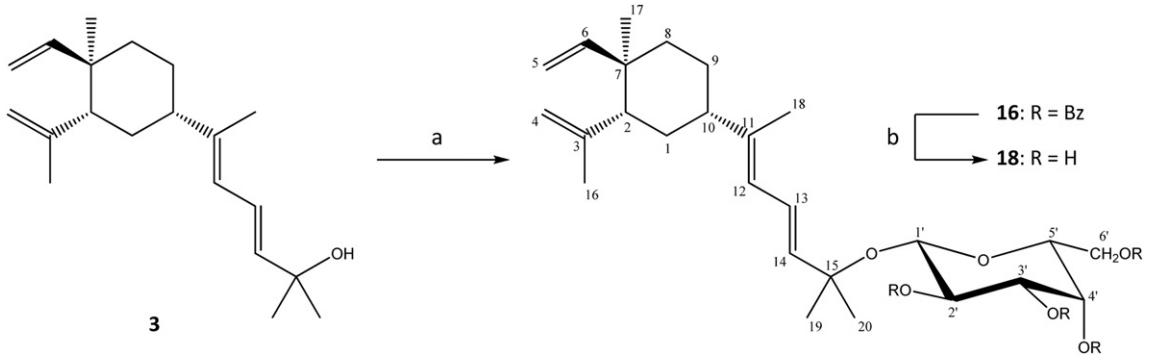


Fig. 2. Glycosylation products of rearranged glycosyl acceptor **5**.

From the *E. fusca* crude extract, **3** was isolated as a mixture with biosynthetically related dilophol **4**. Although the two diterpenes are separable by RP-HPLC over a semi-preparative phenyl-hexyl column, it was impractical to purify each metabolite in sufficient quantities for glycosylation chemistry. The reaction was found to be inconsistent at times with model acceptor **5**, and would therefore quickly consume any pure samples. Also from our experience, the ratio of **3** and **4** changes throughout the duration of the glycosylation indicating possible degradation, thus rendering an upfront

adequately quench HOTf formation. Surprisingly, **3** and **4** continued to degrade even in the presence of excess TMU. Use of the stronger base DIEA proved successful as glycosylation was observed. The glycosylation product mixture containing **16** and **17** was immediately treated with K_2CO_3/CH_3OH providing access to glycosides **18** and **19**. Similarly, the fuscoside B anomer (**20**) and eunico-β-D-arabinopyranoside (**21**) were synthesized via glycosylation with the appropriate arabinopyranosyl donor followed immediately by deprotection of the glycosylation reaction mixture (Scheme 3, Fig. 3).



Scheme 3. Glycosylation of fuscol followed by removal of benzoate esters. Reagents and conditions: (a) **3** (1.0 equiv), AgOTf (0.4 equiv), Ag_2CO_3 (4.0 equiv), **9** (4.0 equiv), DIEA (4.0 equiv), 3 Å MS, CH_2Cl_2 (15%); (b) K_2CO_3, CH_3OH (9%, two steps).

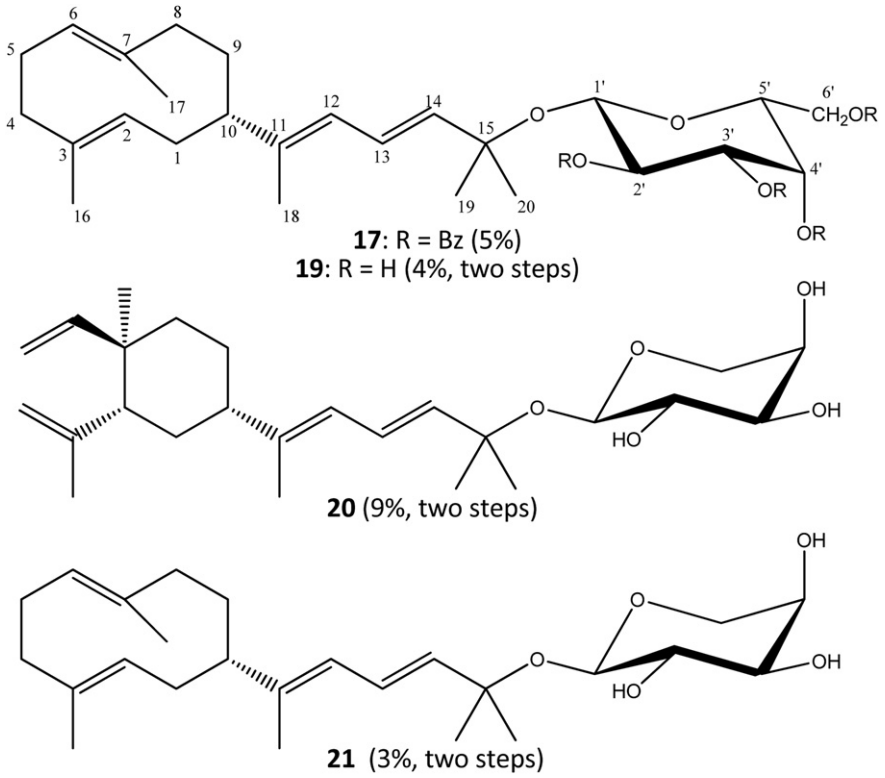


Fig. 3. Novel fuscosides and eunicosides.

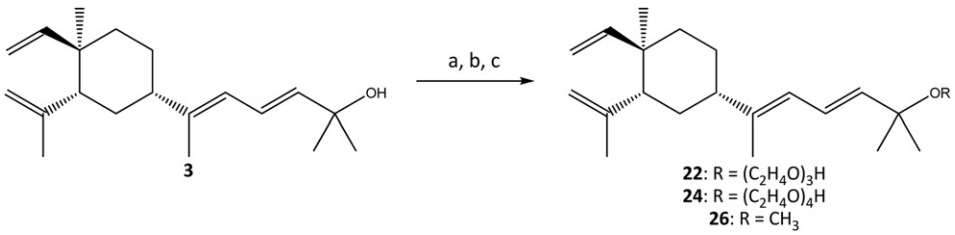
All glycosides (**16**–**21**) were purified by RP-HPLC. NMR spectroscopic analysis of all glycosides demonstrated the presence of the glycosidic linkage via $^{3}J_{CH}$ correlation between H-1′ and C-15. The expected 1′,2′-trans configurations were verified by coupling constant measurements and NOESY spectra, which exhibited strong correlations between the anomeric H-1′ and axially oriented H-3′/5′ of all glycosides.

Since **3** is roughly comparable to **2** with respect to inhibition of arachidonic acid metabolism,[4] we also synthesized PEGylated derivatives of **3** and **4** rationalizing that such derivatives should be straightforward to be prepared and may offer similar anti-inflammatory activity to the glycoside **2**. Considering the ease of tertiary carbocation formation under acidic conditions, we developed fuscoside and eunicoside mimics (PEGylated derivatives) via displacement of the tertiary alcohol by solvolysis. Treatment of **3** and **4** with tri- and tetra-ethylene glycol under acidic conditions allowed the smooth transformation to their derivatives **22**–**25**, respectively. It was postulated that the glycol functionalities may behave like carbohydrate mimics in the sense that they would increase the polarity of the compound. This convenient reaction was readily accomplished by either $BF_3{\cdot}Et_2O$ or AcOH with the former providing higher yields. Methyl ethers **26** and **27** were similarly prepared using CH_3OH (Scheme 4, Fig. 4).

The new fuscosides (**18** and **20**), PEGylated derivatives (**22**–**25**) and methyl ethers (**26** and **27**) of **3** and **4** were assayed for in vivo topical anti-inflammatory activity in the mouse-ear edema assay.[35] The known topical anti-inflammatory agent indomethacin was administered as a positive control. We did not have access to fuscoside B (**2**) for comparison in our bioassays, however, fuscol (**3**) is known to exhibit similar anti-inflammatory activity in this assay. Our data indicate that all unnatural glycosides and PEGylated derivatives are either inactive or pro-inflammatory. The unnatural anomer of **2** (**20**) had no effect while the galactoside (**18**) was pro-inflammatory. All PEGylated derivatives of **3** (**22** and **24**) and of **4** (**23** and **25**) were either inactive or pro-inflammatory. The tertiary hydroxyl group of **3** may be required for anti-inflammatory activity as its methyl ether **26** was pro-inflammatory. We recognize that this library of fuscosides and related compounds is limited in size, however this preliminary study suggests that the stereochemistry of the glycosidic linkage and the identity of the carbohydrate moiety are important for topical anti-inflammatory activity (Fig. 5).

3. Conclusion

A modification of the Koenigs–Knorr glycosylation method has been used to synthesize novel fuscoside B analogues and two glycosides of eunicol, the eunicosides, with β-glycosidic linkages.



Scheme 4. Synthesis of PEGylated and methyl ether derivatives of fuscol. Reagents and conditions: **22**: (a) $BF_3{\cdot}Et_2O$, THF/HO$(C_2H_4O)_3H$ (1:1) (60%); **24**: (b) $BF_3{\cdot}Et_2O$, THF/HO$(C_2H_4O)_4H$ (1:1) (36%); **26**: (c) $BF_3{\cdot}Et_2O$, CH_3OH (54%).

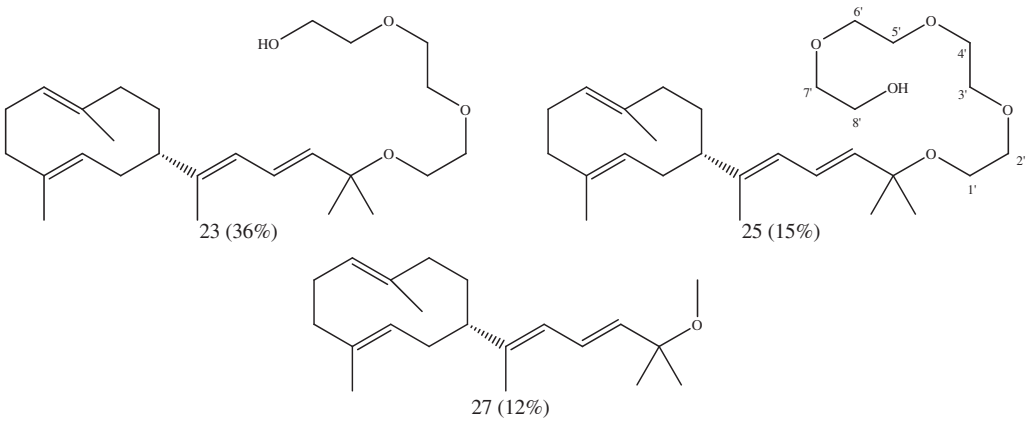


Fig. 4. PEGylated and methyl ether derivatives of eunicol.

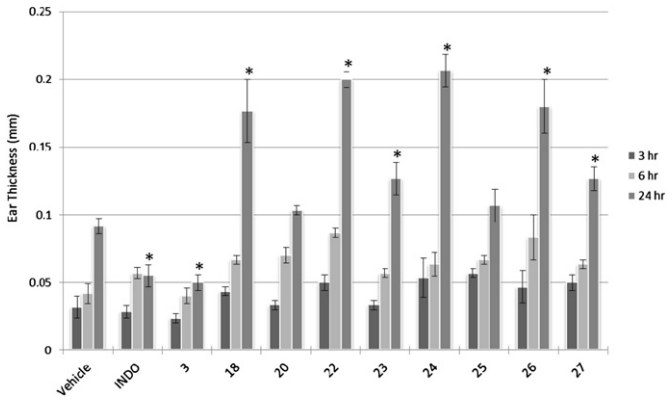


Fig. 5. PMA-induced mouse-ear edema assay results (INDO=Indomethacin, *Indicates statistically significant difference ($p<0.05$) between PMA-control and test groups at 24 h post-PMA treatment).

The latter group represents a new structural class of diterpene glycosides that may exist as trace metabolites in *E. fusca*. For the glycosylation of model glycosyl acceptor 2-methyl-3-buten-2-ol, the benzoylated glycosyl donor provided the highest yields. A trend was observed in which the predicted acyloxonium stability correlated with overall glycosylation yields. This may be of future interest when dealing with unreactive nucleophiles. Since the activity of fuscoside B, the α-arabinoside, is known, this preliminary study focused on exploring β-glycoside analogues to determine the importance of anomeric stereochemistry. The bioassay data illustrates the importance of the natural α-anomeric stereochemistry of the glycosidic linkage of fuscoside B and suggests that the identity of the carbohydrate moiety may be important for in vivo anti-inflammatory activity in the mouse-ear edema assay. Although both the natural glycoside and aglycone are active in this assay, 'unnatural' substitution at the glycan position had a marked impact on activity as the methyl ether and PEGylated derivatives were pro-inflammatory.

4. Experimental section

4.1. General

All commercially available anhydrous solvents and reagents were generally obtained from VWR, Sigma–Aldrich, or Fisher Scientific and utilized without further purification. All reactions were performed at room temperature unless otherwise specified. Evaporation of all solutions was performed in vacuo at 30 °C. All freshly prepared glycosyl donors were utilized within one week and stored under high vacuum over anhydrous $CaSO_4$. Molecular sieves (MS) (3 Å) were activated by microwave heating, and all anhydrous reactions were performed with oven-dried glassware. Glycosyl acceptor **5** was dried in the presence of anhydrous 3 Å MS prior to utilization. All flash chromatography was performed over RediSep Columns using a Teledyne Combiflash R_f unless otherwise specified. Separation of products was carried out using Phenomenex 'Luna 5 μ phenyl-hexyl' (250×10 mm, 5 μm) or Phenomenex 'Gemini 5 μ C18 110A' (250×10.00 mm, 5 μm) reversed-phase semi-preparative columns.

All ^1H and ^{13}C NMR spectra were acquired on a Bruker 600 MHz NMR spectrometer operating at 600 and 150 MHz, respectively. All chemical shifts are reported in parts per million and were relative to residual solvent signals: CD_3OD (^1H: 3.31 ppm, ^{13}C: 49.05 ppm), C_6D_6 (^1H: 7.15 ppm, ^{13}C: 128.02 ppm). Assignments were made on the basis of the COSY and HSQC spectra, and ascertained by HMBC experiments, while NOESY spectra confirmed stereochemistry. High resolution mass spectra were measured by Xiao Feng at Dalhousie University on a Bruker microTOF Focus orthogonal ESI-TOF mass spectrometer. Analysis of samples by LC with hyphenated MS-ELSD-UV was performed using a Finnigan LXQ ion trap mass spectrometer and an analytical C_{18} RP-HPLC column. Optical rotations were measured on a Rudolph Autopol III Polarimeter. Infrared spectra were acquired using attenuated total reflectance on a Thermo Nicolet 6700 FT-IR spectrometer.

4.2. Collection and isolation of 3 and 4

E. fusca was collected from Hillsboro Ledge, Florida by SCUBA, air dried at the surface, and kept frozen during transportation. The taxonomy was ascertained by TLC analysis comparison with a pure sample of fuscol. After lyophilization, the gorgonians (124.6 g) were exhaustively extracted with CH_2Cl_2. The crude extracts were combined and concentrated to provide a viscous oil (11.47 g), which was partitioned between hexane and CH_3OH/H_2O (9:1). The hexane layer was evaporated (6.319 g) and separated by silica gel vacuum flash chromatography by a stepwise gradient elution by hexane/EtOAc mixtures. The hexane/EtOAc 4:1 fraction (592.0 mg) contained **3**/**4** according to LC–MS analysis. Reversed phase flash chromatography (CH_3OH/H_2O gradient) of this fraction provided **3**/**4** (289.9 mg, 2.3% of dry coral wt.) as an approximate 1:2.3 (**3**:**4**) mixture whose ^1H NMR spectrum was in accord with the literature.[7,8]

4.3. In vivo mouse-ear edema assay

The assay was completed by Amplia PharmaTek Inc. as previously described by Martinez et al.[36,37] The 7–8 week-old female CD-1 mice (Charles River Canada Inc.) were provided with food and water *ad libitum*. PMA (100 μg mL^{-1}, n=6), indomethacin (150 mg mL^{-1}, n=6), and the test compounds (5 mg mL^{-1}, n=3) were formulated in acetone, DMSO, and ethanol, respectively. At time 0, the right ears of each mouse were treated with vehicle (ethanol, 20 μL), test compounds (100 μg, 20 μL), or indomethacin (3 mg, 20 μL). All of the left ears were treated with ethanol (20 μL). One hour later, PMA (2 μg, 20 μL) was applied to the right ears of all animals. Edema was measured at 3, 6, and 24 h post-PMA treatment using a digital calliper and calculated by subtracting the thickness of the left ear from the right. To determine statistical significance, the student's *t*-test was used to compare between test articles and vehicle controls. The data is shown with standard error of mean (SEM) to represent the variation.

4.4. Preparation of galactosyl (6,8,9) and arabinopyranosyl bromides

The glycosyl bromides were synthesized by known methods,[38] using CH_3OH/AcBr to generate HBr in situ,[31] and purified according to the following procedure. The brominated reaction mixture was diluted with cold EtOAc and washed successively with cold satd $NaHCO_{3(aq)}$, until gas evolution ceased, followed by cold satd $NaCl_{(aq)}$. The organic extract was dried ($MgSO_4$), filtered, and evaporated to provide a crude oil. Silica gel flash chromatography (TBME/hexane gradient) yielded the galactosyl bromide as a white powder (**6**: 38%, **8**: 26%, **9**: 36%, arabinopyranosyl bromide: 50%). All spectroscopic data for **6**, **8**, and **9** was in accord with the literature.[38–41]

4.5. General procedure A: modified Koenigs–Knorr glycosylation of 2-methyl-3-buten-2-ol (5)

To a stirred mixture of AgOTf (49 mg, 0.19 mmol), Ag_2CO_3 (530 mg, 1.92 mmol), and 3 Å MS (0.5 g) in anhydrous CH_2Cl_2 (5 mL) under N_2 atmosphere was added glycosyl acceptor **5** (50 μL, 0.48 mmol). After stirring for 15 min, the mixture was cooled to −78 °C followed by the dropwise addition of glycosyl bromide (1.922 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 3.5 days and afterward diluted with EtOAc and filtered through Celite®. Washing with satd $Na_2S_2O_{3(aq)}$ and satd $NaCl_{(aq)}$ and evaporation of the organic extract yielded the glycosylation crude as an oil.

4.6. General procedure B: deprotection of benzoylated glycosides

To a stirred solution of the glycosylation crude in CH_3OH was added K_2CO_3 (53 mg, 0.38 mmol). The reaction was stirred until TLC analysis indicated the disappearance of benzoylated starting materials. The reaction was neutralized by addition of NH_4OAc and concentrated to 0.5 mL. This mixture was chromatographed over a C_{18} plug eluting with H_2O/CH_3OH 19:1 into fractions. Fractions containing the deprotected glycosides were evaporated and lyophilized to provide a white amorphous solid that was separated by RP-HPLC (CH_3OH/H_2O).

4.7. General procedure C: modified Koenigs–Knorr glycosylation of fuscol/eunicol (3/4)

A mixture of aglycones **3** and **4** (30 mg, 0.10 mmol) were glycosylated using a variation of general procedure A (3 Å MS: 0.1 g; CH_2Cl_2: 5 mL) in which DIEA (75 μL, 0.42 mmol) was added prior to **3** and **4**.

4.8. General procedure D: deprotection of benzoylated fuscosides/eunicosides (18/19)

Deprotection was carried out according to general procedure B. Upon completion, the mixture was diluted with EtOAc and washed successively with 0.1 M $NH_4OAc_{(aq)}$ and satd $NaCl_{(aq)}$. The organic extract was dried ($MgSO_4$), filtered, and evaporated yielding a crude oil that was separated by RP-HPLC (CH_3OH/H_2O).

4.9. General procedure E: solvolysis of fuscol/eunicol (3/4)

To a stirred solution of **3** and **4** (10 mg, 35 μmol) in THF (2 mL) was added an excess of primary alcohol ($HO(C_2H_4O)_3H$, $HO(C_2H_4O)_4H$, CH_3OH) (2 mL). After cooling in an ice bath, $BF_3 \cdot Et_2O$ (5 μL) was added. After approximately 30 min, TLC analysis indicated the disappearance of **3**/**4**, and the reaction was diluted with EtOAc. Once this mixture was washed with satd $NaHCO_{3(aq)}$ and satd $NaCl_{(aq)}$, the organic extract was dried ($MgSO_4$), filtered, and concentrated to provide a crude oil that was separated by RP-HPLC (CH_3OH/H_2O).

*4.9.1. 2-Methyl-3-buten-2-yl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (**7**).* Aglycone **5** was glycosylated using **6** (790 mg, 1.92 mmol) according to general procedure A. The glycosylation crude was separated by silica gel flash chromatography (hexane/TBME gradient) to yield the desired glycoside **7** (26%): $[\alpha]_D^{27}$+8.98 (c 3.67×10^{-3} in CH_2Cl_2); IR: 3088, 2982, 1744, 1216, 1643, 1072, 1040. ^{1}H NMR (600 MHz, C_6D_6): δ H-3: 5.86 (dd, J=17.7, 10.5, 1H), H-2′: 5.57 (dd, J=10.5, 8.3, 1H), H-4′: 5.41 (dd, J=3.4, 0.8, 1H), H-3′: 5.12 (dd, J=10.5, 3.4, 1H), H-4: 5.07 (dd, J=17.7, 1.1, 1H), H-4: 4.99 (dd, J=10.5, 1.1, 1H), H-1′: 4.39 (d, J=8.3, 1H), H-6′: 4.11 (dd, J=10.9, 6.8, 1H), H-6′: 4.05 (dd, J=10.9, 6.4, 1H), H-5′: 3.24 (ddd, J=6.4, 1.1, 1H), 1.75 (s, 3H), 1.73 (s, 3H), 1.65 (s, 3H), 1.53 (s, 3H), H-1: 1.24 (s, 3H), H-5: 1.18 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6): 170.2 (C), 169.8 (C), 169.5 (C), 168.6 (C), C-3: 143.7 (CH), C-4: 113.9 (CH_2), C-1′: 96.9 (CH), C-2: 78.0 (C), C-3′: 71.6 (CH), C-5′: 70.6 (CH), C-2′: 69.6 (CH), C-4′: 67.5 (CH), C-6′: 61.6 (CH_2), C-5: 27.4 (CH_3), C-1: 26.2 (CH_3), 20.5 (CH_3), 20.3 (CH_3), 20.2 (CH_3), 19.9 (CH_3). HRMS (ESI-TOF): ($C_{19}H_{28}O_{10}Na$) calcd 439.1575, found 439.1564.

*4.9.2. 2-Methyl-3-buten-2-yl 2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranoside (**10**).* Aglycone **5** was glycosylated using **8** (1.11 g, 1.92 mmol) according to general procedure A. The glycosylation crude was separated by silica gel flash chromatography (hexane/TBME gradient) to yield the desired glycoside **10** (46%): $[\alpha]_D^{27}$+8.56 (c 1.37×10^{-3} in CH_2Cl_2); IR: 2975, 2936, 2909, 2874, 1737, 1139, 1073, 1037. ^{1}H NMR (600 MHz, C_6D_6): δ H-3: 5.93 (dd, J=17.7, 10.9, 1H), H-2′: 5.56 (dd, J=10.2, 7.9, 1H), H-4′: 5.41 (dd, J=3.0, 1.1, 1H), H-3′: 5.12 (dd, J=10.5, 3.4, 1H), H-4: 5.06 (dd, J=17.7, 1.1, 1H), H-4: 5.00 (dd, J=10.9, 1.1, 1H), H-1′: 4.42 (d, J=8.0, 1H), H-6′: 4.12 (dd, J=10.9, 7.2, 1H), H-6′: 4.06 (dd, J=10.9, 6.0, 1H), H-5′: 3.25 (ddd, J=7.2, 6.4, 1.1, 1H), H-1: 1.28 (s, 3H), H-5: 1.22 (s, 3H), 1.21 (s, 9H), 1.17 (s, 9H), 1.17 (s, 9H), 1.10 (s, 9H). ^{13}C NMR (150 MHz, C_6D_6): 177.1 (C), 177.1 (C), 177.0 (C), 176.0 (C), C-3: 143.9 (CH), C-4: 114.1 (CH_2), C-1′: 96.9 (CH), C-2: 78.0 (C), C-3′: 71.8 (CH), C-5′: 70.8 (CH), C-2′: 69.5 (CH), C-4′: 67.4 (CH), C-6′: 62.0 (CH_2), 39.0 (C), 38.9 (C), 38.8 (C), 38.7 (C), C-5: 28.0 (CH_3), 27.5 (CH_3), 27.3 (CH_3), 27.3 (CH_3), 27.1 (CH_3), C-1: 26.2 (CH_3). HRMS (ESI-TOF): ($C_{31}H_{52}O_{10}Na$) calcd 607.3453, found 607.3426.

*4.9.3. 2-Methyl-3-buten-2-yl 2,3,4,6-tetra-O-benzoyl-β-D-galactopyranoside (**11**).* Aglycone **5** was glycosylated using **9** (1.27 g, 1.92 mmol) according to general procedure A. The glycosylation crude was

separated by silica gel flash chromatography (hexane/TBME gradient) to yield the desired glycoside **11** (67%): $[\alpha]_D^{27}$+162.4 (*c* 2.833×10^{-3} in CH_2Cl_2); IR: 3065, 2980, 1728, 1265, 1108, 710. ^{1}H NMR (600 MHz, C_6D_6): δ 8.21 (dd, 2H), 8.12 (dd, 2H), 8.08 (dd, 2H), 7.98 (dd, 2H), 7.11 (tt, 1H), 7.06 (tt, 2H), 7.03 (tt, 1H), 7.00 (tt, 1H), 6.95 (tt, 2H), 6.87 (tt, 2H), 6.83 (tt, 1H), 6.71 (tt, 2H), H-2′: 6.29 (dd, *J*=10.5, 8.3, 1H), H-4′: 6.09 (dd, *J*=3.8, 1.1, 1H), H-3: 5.90 (dd, *J*=17.6, 10.8, 1H), H-3′: 5.70 (dd, *J*=10.2, 3.4, 1H), H-4: 5.01 (dd, *J*=17.6, 1.1, 1H), H-4: 4.89 (dd, *J*=10.8, 1.1, 1H), H-1′: 4.70 (d, *J*=8.0, 1H), H-6′: 4.65 (dd, *J*=11.3, 7.5, 1H), H-6′: 4.29 (dd, *J*=11.3, 5.6, 1H), H-5′: 3.58 (ddd, *J*=5.6, 1.1, 1H), H-1: 1.26 (s, 3H), H-5: 1.14 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6): 165.8 (C), 165.8 (C), 165.7 (C), 165.2 (C), C-3: 143.7 (CH), 133.2 (CH), 133.1 (CH), 133.1 (CH), 133.0 (CH), 130.5 (C), 130.4 (C), 130.3 (CH), 130.0 (CH), 130.0 (CH), 129.9 (CH), 129.6 (C), 129.6 (C), 128.8 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), C-4: 114.1 (CH_2), C-1′: 97.1 (CH), C-2: 78.4 (C), C-3′: 72.5 (CH), C-5′: 71.3 (CH), C-2′: 70.7 (CH), C-4′: 68.8 (CH), C-6′: 62.6 (CH_2), C-5: 27.2 (CH_3), C-1: 26.4 (CH_3). HRMS (ESI-TOF): ($C_{39}H_{36}O_{10}Na$) calcd 687.2201, found 687.2186.

*4.9.4. 2-Methyl-3-buten-2-yl-β-D-galactopyranoside (**12**).* The glycosylation crude from general procedure A using **9** was deprotected according to general procedure B. The desired glycoside was isolated by C_{18} RP-HPLC (30% CH_3OH/H_2O). **12**: $[\alpha]_D^{27}$−9.29 (*c* 1.17×10^{-3} in CH_3OH); IR: 3379, 3090, 2980, 2933, 2881, 1642, 1579, 1059. ^{1}H NMR (600 MHz, CD_3OD): δ H-3: 6.03 (dd, *J*=17.7, 10.9, 1H), H-4: 5.20 (dd, *J*=17.7, 1.1, 1H), H-4: 5.10 (dd, *J*=10.9, 1.1, 1H), H-1′: 4.28 (d, *J*=7.2, 1H), H-4′: 3.83 (dd, *J*=3.0, 0.8, 1H), H-6′: 3.71 (dd, *J*=10.9, 5.7, 1H), H-6′: 3.67 (dd, *J*=10.9, 6.4, 1H), H-2′: 3.47 (dd, *J*=9.8, 7.2, 1H), H-3′: 3.44 (dd, *J*=9.8, 3.4, 1H), H-5′: 3.41 (ddd, *J*=6.4, 0.8, 1H), H-1: 1.37 (s, 3H), H-5: 1.33 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-3: 145.6 (CH), C-4: 114.2 (CH_2), C-1′: 100.2 (CH), C-2: 79.0 (C), C-5′: 76.3 (CH), C-3′: 75.1 (CH), C-2′: 72.6 (CH), C-4′: 70.2 (CH), C-6′: 62.3 (CH_2), C-5: 27.9 (CH_3), C-1: 26.7 (CH_3). HRMS (ESI-TOF): ($C_{11}H_{20}O_6Na$) calcd 271.1152, found 271.1159.

*4.9.5. Prenyl 2,3,4,6-tetra-O-benzoyl-β-D-galactopyranoside (**14**).* Glycoside **14** was isolated as a side product from the glycosylation crude reaction mixture of **11** by phenyl-hexyl RP-HPLC (86% CH_3OH/H_2O). Compound **14**: IR: 3063, 2970, 2931, 1726, 1266, 1108, 1070, 709. ^{1}H NMR (600 MHz, C_6D_6): δ 8.19 (dd, 2H), 8.11 (dd, 2H), 8.09 (dd, 2H), 7.98 (dd, 2H), 7.09 (tt, 2H), 7.03 (m, 2H), 7.03 (m, 1H), 6.97 (tt, 2H), 6.91 (tt, 1H), 6.89 (tt, 1H), 6.83 (tt, 2H), 6.71 (tt, 1H), H-2′: 6.35 (dd, *J*=10.5, 7.9, 1H), H-4′: 6.19 (dd, *J*=3.8, 1.1, 1H), H-3′: 5.76 (dd, *J*=10.5, 3.8, 1H), H-2: 5.29 (m, *J*=7.9, 6.4, 1.5, 1H), H-6′: 4.74 (dd, *J*=11.3, 7.2, 1H), H-1′: 4.70 (d, *J*=8.0, 1H), H-6′: 4.33 (dd, *J*=11.3, 6.4, 1H), H-1: 4.29 (dd, 12.0, 6.4 1H), H-1: 4.22 (dd, *J*=11.8, 7.7, 1H), H-5′: 3.75 (ddd, *J*=6.4, 1.1, 1H), H-5: 1.45 (s, 3H), H-4: 1.39 (s, 3H). ^{13}C NMR (150 MHz, C_6D_6): 165.3 (C), 165.2 (C), 165.2 (C), 165.1 (C), C-3: 137.8 (C), 132.7 (CH), 132.5 (CH), 132.5 (CH), 132.4 (CH), 130.4 (C), 130.2 (C), 129.8 (C), 129.8 (C), 129.6 (CH), 129.6 (CH), 129.5 (CH), 129.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH) C-2: 120.4 (CH), C-1′: 99.7 (CH), C-3′: 72.2 (CH), C-5′: 71.0 (CH), C-2′: 70.2 (CH), C-4′: 68.4 (CH), C-1: 64.9 (CH_2), C-6′: 62.0 (CH_2), C-5: 25.1 (CH_3), C-4: 17.3 (CH_3).

*4.9.6. Prenyl-β-D-galactopyranoside (**15**).* Glycoside **15** was isolated as a side product from the glycosylation reaction mixture crude of **12** by C_{18} RP-HPLC (30% CH_3OH/H_2O). **15**: $[\alpha]_D^{27}$−21.4 (*c* 1.33×10^{-3} in CH_3OH); IR: 3384, 3027, 2970, 2915, 2881, 1671, 1646, 1063. ^{1}H NMR (600 MHz, CD_3OD): δ H-2: 5.38 (m, *J*=7.9, 6.4, 1.5, 1H), H-1: 4.32 (dd, *J*=12.0, 6.4, 1H), H-1′: 4.24 (d, *J*=7.9, 1H), H-1: 4.22 (dd, *J*=12.0, 7.9, 1H), H-4′: 3.83 (dd, *J*=3.2, 1.0, 1H), H-6′: 3.76 (dd, *J*=11.3, 6.8, 1H), H-6′: 3.73 (dd, *J*=11.3, 5.6, 1H), H-2′: 3.51 (dd, *J*=9.8, 7.5, 1H), H-5′: 3.48 (ddd, *J*=6.8, 1.1, 1H), H-3′: 3.45 (dd, *J*=9.8, 3.4, 1H), H-4: 1.69 (s, CH_3), H-5: 1.75 (s, CH_3). ^{13}C NMR (150 MHz, CD_3OD): C-3: 138.4 (C), C-2: 121.9 (CH_2), C-1′: 103.5 (CH), C-5′: 76.7 (CH), C-3′: 75.1 (CH), C-2′: 72.6 (CH), C-4′: 70.4 (CH), C-1: 66.3 (CH_2), C-6′: 62.5 (CH_2), C-5: 25.9 (CH_3), C-4: 18.1 (CH_3). HRMS (ESI-TOF): ($C_{11}H_{20}O_6Na$) calcd 271.1152, found 271.1157.

*4.9.7. Fusco-2,3,4,6-tetra-O-benzoyl-β-D-galactopyranoside and eunico-2,3,4,6-tetra-O-benzoyl-β-D-galactopyranoside (**16**/**17**).* Aglycones **3** and **4** (34.5 mg, 200 μmol) were glycosylated using **9** according to general procedure C. The glycosylation crude was chromatographed over silica gel (MTBE/hexane gradient) and the desired glycosides were separated by C_{18} RP-HPLC (94% CH_3OH/H_2O). **16** (8.6 mg, 15%): $[\alpha]_D^{27}$+135.1 (*c* 1.192×10^{-3} in CH_2Cl_2); IR: 3070, 2975, 2929, 2859, 1729, 1265, 1107, 1069, 709. ^{1}H NMR (600 MHz, CD_3OD): δ 8.11 (dd 2H), 8.02 (dd, 2H), 7.98 (dd, 2H), 7.72 (dd, 2H), 7.67 (t, 1H), 7.60 (t, 1H), 7.57 (t, 1H), 7.54 (t, 2H), 7.46 (t, 2H), 7.45 (t, 1H), 7.43 (t, 2H), 7.25 (t, 2H), H-13: 6.46 (dd, *J*=15.5, 10.7, 1H), H-4′: 5.95 (dd, *J*=3.0, 1H), H-6: 5.84 (dd, *J*=17.5, 10.8, 1H), H-3′: 5.74 (dd, *J*=10.2, 3.4, 1H), H-12: 5.71 (br d, *J*=10.2, 1H), H-2′: 5.69 (dd, *J*=9.8, 7.5, 1H), H-14: 5.50 (d, *J*=15.5, 1H), H-1′: 5.09 (d, *J*=7.2, 1H), H-5: 4.91 (dd, *J*=17.3, 1.4, 1H), H-5: 4.88 (dd, *J*=10.5, 1.5, 1H), H-4: 4.83 (br s, 1H), H-4: 4.61 (br s, 1H), H-6′: 4.54 (dd, *J*=10.5, 7.2, 1H), H-5′: 4.49 (ddd, *J*=7.2, 5.0, 1H), H-6′: 4.44 (dd, *J*=10.5, 4.9, 1H), H-2: 2.03 (ddd, *J*=12.7, 3.0, 1H), H-10: 1.95–1.89 (m, 1H), H-18: 1.74 (s, 3H), H-16: 1.72 (s, 3H), H-1: 1.63 (ddd, *J*=12.8, 12.4, 1H), H-8: 1.56–1.48 (m, *J*=11.3, 3.8, 1H), H-9: 1.52–1.47 (m, 2H), H-1: 1.46–1.40 (m, *J*=12.8, 1H), H-8: 1.46–1.41 (m, 1H), H-19: 1.40 (s, 3H), H-20: 1.26 (s, 3H), H-17: 1.02 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): 166.8 (C), 166.7 (C), 167.4 (C), 167.3 (C), C-6: 151.5 (CH), C-3: 149.0 (C), C-11: 145.3 (C), C-14: 136.8 (CH), 134.9 (CH), 134.7 (CH), 134.6 (CH), 134.5 (CH), 131.0 (CH), 131.0 (C), 130.8 (C), 130.8 (CH), 130.8 (CH), 130.6 (CH), 130.6 (C), 130.3 (C), 129.9 (CH), 129.7 (CH), 129.7 (CH), 129.5 (CH), 127.9 (CH), C-12: 123.8 (CH), C-4: 112.8 (CH_2), C-5: 110.5 (CH_2), C-1′: 97.6 (CH), C-15: 79.9 (C), C-3′: 73.4 (CH), C-5′: 72.2 (CH), C-2′: 71.8 (CH), C-4′: 70.3 (CH), C-6′: 63.8 (CH_2), C-2: 54.0 (CH), C-10: 49.3 (CH), C-8: 41.1 (CH_2), C-7: 40.8 (C), C-1: 33.9 (CH_2), C-20: 28.8 (CH_3), C-9: 27.8 (CH_2), C-19: 26.7 (CH_3), C-16: 25.4 (CH_3), C-17: 17.2 (CH_3), C-18: 15.3 (CH_3). HRMS (ESI-TOF): ($C_{54}H_{58}O_{10}Na$) calcd 889.3922, found 889.3950. **17** (6.9 mg, 5%): $[\alpha]_D^{27}$+56.3 (*c* 1.67×10^{-4} in CH_2Cl_2); IR: 3068, 3034, 2975, 2929, 2860, 1729, 1265, 1107, 1069, 710. ^{1}H NMR (600 MHz, C_6D_6): δ 8.23 (dd 2H), 8.19 (dd, 2H), 8.08 (dd, 2H), 7.97 (dd, 2H), 7.12 (br tt, 1H), 7.08 (br tt, 1H), 7.05 (m, 2H), 7.05 (m, 2H), 7.02 (m, 1H), 6.87 (t, 2H), 6.83 (br tt, 1H), 6.71 (t, 2H), H-13: 6.53 (dd, *J*=15.8, 10.9, 1H), H-2′: 6.33–6.28 (m, 1H), H-4′: 6.07 (dd, *J*=3.0, 1H), H-12: 6.09–5.99 (br m, 0.5H), H-12: 5.94 (br d, *J*=10.5, 0.5H), H-3′: 5.66–5.59 (m, 1H), H-14: 5.76 (d, *J*=15.8, 1H), H-2/6: 5.20–5.03 (br m, 1H), H-1′: 4.82 (d, *J*=7.5, 1H), H-6: 4.83–4.80 (br m, 0.5H), H-6′: 4.72–4.67 (m, 1H), H-2′: 4.55 (br d, 10.2, 0.5H), H-6′: 4.32–4.26 (m, 1H), H-8: 2.39–2.33 (m, *J*=12.8, 7.5, 1H), H-1: 2.28–2.23 (m, 1H), H-5: 2.23–2.17 (m, *J*=12.8, 4.5, 1H), H-1: 2.18–2.13 (m, 1H), H-4: 2.14–2.09 (m, 1H), H-8: 2.10–2.04 (m, 1H), H-5: 2.07–2.02 (m, 1H), H-10: 1.96 (ddd, 9.8, 1H), H-4: 1.92–1.87 (m, 1H), H-18: 1.69 (s, 3H), H-9: 1.71–1.64 (m, 1H), H-9: 1.55–1.49 (m, 1H), H-16: 1.47 (s, 1.5H), H-17: 1.44 (s, 3H), H-19: 1.44 (s, 3H), H-16: 1.36–1.32 (br s, 1.5H), H-20: 1.28 (br s, 3H). ^{13}C NMR (150 MHz, C_6D_6): 165.3 (C), 165.3 (C), 165.2 (C), 165.1 (C), C-11: 146.9 (C), C-7: 137.8 (C), C-14: 137.0 (CH), 133.3 (CH), 133.2 (CH), 133.1 (CH), 133.1 (CH), 132.9 (C), 132.8 (C), 132.7 (C), 132.7 (C), C-2: 131.7 (CH), 130.4 (CH), 130.1 (CH), 130.1 (CH), 130.0 (CH), C-3: 129.6 (C), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), C-6: 127.0 (CH), C-13: 126.6 (CH), C-12: 122.4 (CH), C-1′: 97.3 (CH), C-15: 78.8 (C) C-3′: 72.6 (CH), C-2′: 71.0 (CH), C-5′: 71.0 (CH), C-4′: 68.7 (CH), C-6′: 62.3 (CH_2) C-10: 53.7 (CH), C-8: 42.0 (CH_2), C-4: 39.5 (CH_2), C-1: 35.2 (CH_2), C-9: 33.9 (CH_2), C-20: 28.9 (CH_3), C-5: 27.1 (CH_2), C-19: 26.3 (CH_3), C-16: 16.8 (CH_3), C-17: 16.5 (CH_3), C-18: 14.4 (CH_3). HRMS (ESI-TOF): ($C_{54}H_{58}O_{10}Na$) calcd 889.3922, found 889.3974.

*4.9.8. Fusco-β-D-galactopyranoside/eunico-β-D-galactopyranoside (**18**/**19**).* Aglycones **3** and **4** (31.0 mg, 108 μmol) were glycosylated using **9** according to general procedure C and the glycosylation

crude was deprotected according to general procedure D. The desired glycosides were separated by phenyl-hexyl RP-HPLC (81% CH_3OH/H_2O). **18** (1.4 mg, 9%): $[\alpha]_D^{27}$ −8.06 (*c* 5.00×10^{-4} in CH_3OH); IR: 3381, 3081, 3046, 2973, 2928, 2860, 1635, 1056. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.48 (dd, *J*=15.4, 10.5, 1H), H-12: 5.90 (d, *J*=10.5, 1H), H-6: 5.84 (dd, *J*=17.3, 10.8, 1H), H-14: 5.76 (d, *J*=15.4, 1H), H-5: 4.90 (dd, *J*=17.3, 1.1, 1H), H-5: 4.87 (dd, *J*=10.9, 1.1, 1H), H-4: 4.81 (br s, 1H), H-4: 4.60 (br s, 1H), H-1′: 4.29 (d, *J*=7.5, 1H), H-4′: 3.81 (dd, *J*=3.4, 1.1, 1H), H-6′: 3.70 (dd, 11.3, *J*=6.0, 1H), H-6′: 3.68 (dd, *J*=11.3, 6.0, 1H), H-2′: 3.48 (dd, *J*=9.8, 7.5, 1H), H-3′: 3.44 (dd, *J*=9.8, 3.4, 1H), H-5′: 3.40 (ddd, *J*=6.0, 1.1, 1H), H-2: 2.04 (ddd, *J*=12.8, 3.0, 1H), H-10: 2.03–1.97 (m, 1H), H-18: 1.78 (s, 3H), H-16: 1.71 (s, 3H), H-1: 1.66 (ddd, *J*=12.8, 12.4, 1H), H-9: 1.57–1.52 (m, 2H), H-8: 1.55–1.51 (m, 1H), H-1: 1.49–1.45 (m, *J*=12.8, 1H), H-8: 1.46–1.42 (m, 1H), H-19: 1.41 (s, 3H), H-20: 1.36 (s, 3H), H-17: 1.03 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-6: 151.6 (CH), C-3: 149.0 (C), C-11: 144.3 (C), C-14: 138.4 (CH), C-13: 127.1 (CH), C-12: 124.2 (CH), C-4: 112.7 (CH_2), C-5: 110.4 (CH_2), C-1′: 100.3 (CH), C-15: 79.1 (C), C-5′: 76.3 (CH), C-3′: 75.1 (CH), C-2′: 72.7 (CH), C-4′: 70.2 (CH), C-6′: 62.4 (CH_2), C-2: 54.1 (CH), C-10: 49.2 (CH), C-8: 41.1 (CH_2), C-7: 40.8 (C), C-1: 34.1 (CH_2), C-20: 28.7 (CH_3), C-9: 27.8 (CH_2), C-19: 27.4 (CH_3), C-16: 25.3 (CH_3), C-17: 17.2 (CH_3), C-18: 15.4 (CH_3). HRMS (ESI-TOF): ($C_{26}H_{42}O_6Na$) calcd 473.2874, found 473.2861. Compound **19** (1.6 mg, 4%): IR: 3373, 3047, 2971, 2923, 2856, 1648, 1591, 1054. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.43 (dd, *J*=15.1, 10.5, 1H), H-12: 5.85 (d, *J*=10.2, 1H), H-14: 5.74 (d, *J*=15.4, 1H), H-2/6: 5.25–4.95 (br m, 1.2H), H-6: 4.79 (br d, *J*=11.3, 0.4H), H-2: 4.55 (br d, *J*=10.2, 0.4H), H-1′: 4.32–4.28 (m, 1H), H-4′: 3.82 (br dd, *J*=3.0, 1H), H-6′: 3.71 (dd, *J*=11.3, 6.0, 1H), H-6′: 3.68 (dd, *J*=11.3, 6.4, 1H), H-2′: 3.50–3.45 (m, 1H), H-3′: 3.47–3.43 (m, 1H), H-5′: 3.43–3.39 (m, 1H), H-8: 2.40–2.33 (m, 1H), H-5: 2.33–2.25 (m, *J*=12.4, 4.5, 1H), H-1: 2.22–2.17 (m, 1H), H-4: 2.20–2.15 (m, 1H), H-1: 2.10–2.05 (m, 1H), H-5: 2.08–2.04 (m, 1H), H-8: 2.07–2.05 (m, 1H), H-10: 2.01–1.95 (m, 1H), H-4: 1.94–1.88 (m, 1H), H-18: 1.77 (s, 1.2H), H-18: 1.75 (s, 1.8H), H-9: 1.72–1.63 (m, 2H), H-16: 1.59–1.53 (br s, 1.2H), H-16: 1.54 (s, 1.8H), H-17: 1.53–1.47 (br s, 1.8H), H-17: 1.41 (s, 1.2H), H-19: 1.41 (s, 3H), H-20: 1.36 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-11: 147.8 (C), C-7: 138.9 (C), C-14: 138.3 (CH), C-2: 132.6 (CH), C-3: 130.2 (C), C-6: 127.6 (CH), C-13: 127.0 (CH), C-12: 123.2 (CH), C-1′: 100.2 (CH), C-15: 79.1 (C), C-5′: 76.3 (CH), C-3′: 75.1 (CH), C-2′: 72.7 (CH), C-4′: 70.2 (CH), C-6′: 62.4 (CH_2) C-10: 54.8 (CH), C-8: 42.8 (CH_2), C-4: 40.6 (CH_2), C-1: 35.8 (CH_2), C-9: 34.8 (CH_2), C-20: 28.8 (CH_3), C-5: 27.6 (CH_2), C-19: 27.4 (CH_3), C-16: 17.0 (CH_3), C-17: 16.6 (CH_3), C-18: 14.8 (CH_3). HRMS (ESI-TOF): ($C_{26}H_{42}O_6Na$) calcd 473.2874, found 473.2868.

*4.9.9. Fusco-β-D-arabinopyranoside/eunico-β-D-arabinopyranoside (**20**/**21**).* Aglycones **3** and **4** (33.8 mg, 117 μmol) were glycosylated using **9** according to general procedure C and the glycosylation crude was deprotected according to general procedure D. The desired glycosides were separated by phenyl-hexyl RP-HPLC (81% CH_3OH/H_2O). **20** (1.3 mg, 9%): $[\alpha]_D^{27}$ −6.13 (*c* 6.67×10^{-4} in CH_3OH); IR: 3382, 3081, 2972, 2926, 2856, 1636, 1085. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.48 (dd, *J*=15.8, 10.9, 1H), H-12: 5.89 (d, *J*=10.5, 1H), H-6: 5.84 (dd, *J*=17.3, 10.9, 1H), H-14: 5.72 (d, *J*=15.4, 1H), H-5: 4.90 (dd, *J*=17.3, 1.5, 1H), H-5: 4.88 (dd, *J*=10.9, 1.5, 1H), H-4: 4.81 (br s, 1H), H-4: 4.61 (br s, 1H), H-1′: 4.27 (d, *J*=6.8, 1H), H-5′: 3.79 (dd, *J*=12.4, 2.6, 1H), H-4′: 3.78–3.76 (m, 1H), H-2′: 3.51–3.49 (m, 1H), H-3′: 3.51–3.49 (m, 1H), H-5′: 3.47 (dd, *J*=12.4, 1.1, 1H), H-2: 2.05 (ddd, *J*=12.8, 3.4, 1H), H-10: 2.04–1.98 (m, 1H), H-18: 1.79 (s, 3H), H-16: 1.71 (s, 3H), H-1: 1.67 (ddd, *J*=12.8, 1H), H-9: 1.57–1.53 (m, 2H), H-8: 1.56–1.52 (m, 1H), H-1: 1.49–1.45 (m, 1H), H-8: 1.44 (dd, *J*=9.0, 2.6, 1H), H-19: 1.39 (s, 3H), H-20: 1.35 (s, 3H), H-17: 1.03 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-6: 151.6 (CH), C-3: 149.0 (C), C-11: 144.4 (C), C-14: 138.1 (CH), C-13: 127.1 (CH), C-12: 124.1 (CH), C-4: 112.7 (CH_2), C-5: 110.4 (CH_2), C-1′: 100.2 (CH), C-15: 79.1 (C), C-3′: 74.4 (CH), C-2′: 72.7 (CH), C-4′: 69.8 (CH), C-5′: 66.8 (CH), C-2: 54.0 (CH), C-10: 49.2 (CH), C-8: 41.1 (CH_2), C-7: 40.8 (C), C-1: 34.0 (CH_2), C-20: 28.7 (CH_3), C-9: 27.9 (CH_2), C-19: 27.3 (CH_3), C-16: 25.3 (CH_3), C-17: 17.2 (CH_3), C-18: 15.3 (CH_3). HRMS (ESI-TOF): ($C_{25}H_{40}O_5Na$) calcd 443.2768, found 443.2768. **21** (1.0 mg, 3%): $[\alpha]_D^{27}$ −34.4 (*c* 5.00×10^{-5} in CH_3OH); IR: 3379, 3081, 3041, 2970, 2924, 2854, 1634, 1083, 1002. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.47–6.40 (m, 1H), H-12: 5.85 (d, *J*=10.5, 1H), H-14: 5.71 (d, *J*=15.8, 1H), H-2/6: 4.95–5.25 (br m, 1.2H), H-6: 4.80 (br d, *J*=13.2, 0.4H), H-2: 4.55 (br d, *J*=9.8, 0.4H), H-1′: 4.30–4.24 (m, 1H), H-5′: 3.80 (dd, *J*=12.4, 2.6, 1H), H-4′: 3.78–3.76 (m, 1H), H-2′: 3.52–3.49 (m, 1H), H-3′: 3.51–3.49 (m, 1H), H-5′: 3.47 (dd, *J*=11.7, 3.8, 1H), H-8: 2.40–2.34 (m, 1H), H-5: 2.33–2.25 (m, *J*=12.8, 4.9, 1H), H-1: 2.22–2.17 (m, 1H), H-4: 2.19–2.15 (m, 1H), H-1: 2.10–2.04 (m, 1H), H-8: 2.10–2.04 (m, 1H), H-5: 2.07–2.03 (m, 1H), H-10: 2.01–1.96 (m, 1H), H-4: 1.94–1.87 (m, *J*=12.0, 4.9, 1H), H-18: 1.77 (s, 1.2H), H-18: 1.75 (s, 1.8H), H-9: 1.71–1.63 (m, 2H), H-16: 1.60–1.52 (br s, 1.2H), H-16: 1.54 (s, 1.8H), H-17: 1.53–1.47 (br s, 1.8H), H-17: 1.41 (s, 1.2H), H-19: 1.40 (s, 3H), H-20: 1.35 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-11: 147.9 (C), C-7: 138.9 (C), C-14: 138.0 (CH), C-2: 132.6 (CH), C-3: 130.2 (C), C-6: 127.7 (CH), C-13: 127.1 (CH), C-12: 123.1 (CH), C-1′: 100.2 (CH), C-15: 79.1 (C), C-3′: 74.4 (CH), C-2′: 72.7 (CH), C-4′: 69.8 (CH), C-5′: 66.7 (CH_2), C-10: 54.8 (CH), C-8: 42.8 (CH_2), C-4: 40.6 (CH_2), C-1: 35.8 (CH_2), C-9: 34.8 (CH_2), C-20: 28.9 (CH_3), C-5: 27.6 (CH_2), C-19: 27.3 (CH_3), C-16: 17.0 (CH_3), C-17: 16.6 (CH_3), C-18: 14.7 (CH_3). HRMS (ESI-TOF): ($C_{25}H_{40}O_5Na$) calcd 443.2768, found 443.2747.

*4.9.10. Fuscol-PEG-3/eunicol-PEG-3 (**22**/**23**).* Solvolysis of **3** and **4** (3.8 mg, 13 μmol) was performed according to general procedure E using triethylene glycol and the desired products were separated by phenyl-hexyl RP-HPLC (87% CH_3OH/H_2O). Compound **22** (1.1 mg, 60%): $[\alpha]_D^{27}$ +5.31 (*c* 5.83×10^{-4} in CH_3OH); IR: 3435, 3080, 2972, 2927, 2864, 1637, 1122, 1082. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.45 (dd, *J*=15.4, 10.5, 1H), H-12: 5.90 (d, *J*=10.5, 1H), H-6: 5.84 (dd, *J*=17.7, 10.9, 1H), H-14: 5.58 (d, *J*=15.4, 1H), H-5: 4.90 (dd, *J*=17.7, 1.1, 1H), H-5: 4.88 (dd, *J*=10.9, 1.1, 1H), H-4: 4.81 (br s, 1H), H-4: 4.61 (br s, 1H), H-6′: 3.66 (dd, *J*=5.3, 4.2, 2H), H-3′: 3.67–3.63 (m, 2H), H-4′: 3.67–3.63 (m, 2H), H-2′: 3.59 (dd, *J*=5.8, 4.4, 2H), H-5′: 3.56 (dd, *J*=5.5, 4.5, 2H), C-1′: 3.47 (dd, *J*=5.8, 4.4, 2H), H-2: 2.05 (ddd, *J*=12.8, 3.0, 1H), H-10: 2.03–1.98 (m, 1H), H-18: 1.79 (s, 3H), H-16: 1.71 (s, 3H), H-1: 1.67 (ddd, *J*=12.8, 12.4, 1H), H-9: 1.57–1.53 (m, 2H), H-8: 1.56–1.53 (m, 1H), H-1: 1.49–1.45 (m, 1H), H-8: 1.46–1.43 (m, 1H), H-19/20: 1.30 (s, 6H), H-17: 1.03 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-6: 151.6 (CH), C-3: 149.0 (C), C-11: 144.3 (C), C-14: 137.8 (CH), C-13: 127.4 (CH), C-12: 124.0 (CH), C-4: 112.7 (CH_2), C-5: 110.4 (CH_2), C-15: 76.7 (C), C-5′: 73.7 (CH_2), C-2′: 72.2 (CH_2), C-3′: 71.7 (CH_2), C-4′: 71.5 (CH_2), C-1′: 63.2 (CH_2), C-6′: 62.3 (CH_2), C-2: 54.0 (CH), C-10: 49.2 (CH), C-8: 41.1 (CH_2), C-7: 40.8 (C), C-1: 34.1 (CH_2), C-9: 27.9 (CH_2), C-19: 26.9 (CH_3), C-20: 26.9 (CH_3), C-16: 25.3 (CH_3), C-17: 17.2 (CH_3), C-18: 15.3 (CH_3). HRMS (ESI-TOF): ($C_{26}H_{44}O_4Na$) calcd 443.3132, found 443.3124. **23** (1.5 mg, 36%): $[\alpha]_D^{27}$ −14.3 (*c* 5.83×10^{-4} in CH_3OH); IR: 3449, 3040, 2971, 2923, 2860, 1650, 1122, 1081. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.40 (dd, *J*=15.4, 10.9, 1H), H-12: 5.85 (d, *J*=10.5, 1H), H-14: 5.57 (d, *J*=15.4, 1H), H-2/6: 5.25–4.94 (br m, 1.2H), H-6: 4.80 (br d, *J*=13.2, 0.4H), H-2: 4.56 (br d, *J*=10.2, 0.4H), H-6′: 3.66 (dd, *J*=5.3, 4.5, 2H), H-3′: 3.66–3.62 (m, 2H), H-4′: 3.66–3.62 (m, 2H), H-2′: 3.61–3.58 (m, 2H), H-5′: 3.57 (dd, *J*=5.3, 4.5, 2H), H-1′: 3.49–3.46 (m, 2H), H-8: 2.40–2.34 (m, 1H), H-5: 2.33–2.25 (m, *J*=12.0, 4.5, 1H), H-1: 2.21–2.16 (m, 1H), H-4: 2.19–2.15 (m, 1H), H-1: 2.10–2.04 (m, 1H), H-8: 2.08–2.03 (m, 1H), H-5: 2.07–2.02 (m, 1H), H-10: 2.02–1.96 (m, 1H), H-4: 1.93–1.87 (m, *J*=11.7, 4.9, 1H), H-18: 1.78 (s, 1.2H), H-18: 1.75 (s, 1.8H), H-9: 1.69–1.64 (m, 2H), H-16: 1.60–1.54 (br s, 1.2H), H-16: 1.54 (s, 1.8H), H-17: 1.54–1.46 (br s, 1.8H), H-17: 1.41 (s, 1.2H), H-19/20: 1.31 (s, 6H). ^{13}C NMR (150 MHz, CD_3OD): C-11: 147.8 (C), C-7:

138.9 (C), C-14: 137.6 (CH), C-2: 132.6 (CH), C-3: 130.2 (C), C-6: 127.6 (CH), C-13: 127.3 (CH), C-12: 123.0 (CH), C-15: 76.8 (C), C-5′: 73.7 (CH_2), C-2′: 72.1 (CH_2), C-3′: 71.6 (CH_2), C-4′: 71.4 (CH_2), C-1′: 63.1 (CH_2), C-6′: 62.2 (CH_2), C-10: 54.8 (CH), C-8: 42.8 (CH_2), C-4: 40.6 (CH_2), C-1: 35.8 (CH_2), C-9: 34.7 (CH_2), C-5: 27.6 (CH_2), C-19: 26.9 (CH_3), C-20: 26.9 (CH_3), C-16: 17.0 (CH_3), C-17: 16.6 (CH_3), C-18: 14.8 (CH_3). HRMS (ESI-TOF): ($C_{26}H_{44}O_4Na$) calcd 443.3132, found 443.3111.

*4.9.11. Fuscol-PEG-4/eunicol-PEG-4 (**24**/**25**).* Solvolysis of **3** and **4** (11.4 mg, 39.5 mmol) was performed according to general procedure E using tetraethyleneglycol and the desired products were separated by phenyl-hexyl RP-HPLC (86% CH_3OH/H_2O). Compound **24** (2.2 mg, 36%): $[\alpha]_D^{27}$ +2.38 (*c* 1.75×10^{-3} in CH_3OH); IR: 3419, 3080, 2971, 2925, 2864, 1638, 1124, 1081. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.44 (dd, *J*=15.4, 10.5, 1H), H-12: 5.89 (d, *J*=10.2, 1H), H-6: 5.84 (dd, *J*=17.7, 11.3, 1H), H-14: 5.58 (d, *J*=15.4, 1H), H-5: 4.90 (dd, *J*=17.3, 1.1, 1H), H-5: 4.88 (dd, *J*=10.5, 1.5, 1H), H-4: 4.81 (br s, 1H), H-4: 4.61 (br s, 1H), H-8′: 3.66 (dd, *J*=5.5, 4.3, 2H), H-3′: 3.67–3.62 (m, 2H), H-3′: 3.67–3.62 (m, 2H), H-3′: 3.67–3.62 (m, 2H), H-3′: 3.67–3.62 (m, 2H), H-2′: 3.58 (dd, *J*=5.8, 4.2, 2H), H-7′: 3.56 (dd, *J*=5.6, 4.2, 2H), H-1′: 3.47 (dd, *J*=5.7, 4.1, 2H), H-2: 2.05 (ddd, *J*=12.8, 3.4, 1H), H-10: 2.04–1.98 (m, 1H), H-18: 1.79 (s, 3H), H-16: 1.71 (s, 3H), H-1: 1.67 (ddd, *J*=12.8, 12.4, 1H), H-9: 1.58–1.54 (m, 2H), H-8: 1.56–1.52 (m, 1H), H-1: 1.49–1.45 (m, 1H), H-8: 1.46–1.41 (m, 1H), H-19/20: 1.31 (s, 6H), H-17: 1.03 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD): C-6: 151.6 (CH), C-3: 148.9 (C), C-11: 144.3 (C), C-14: 137.8 (CH), C-13: 127.3 (CH), C-12: 124.0 (CH), C-4: 112.8 (CH_2), C-5: 110.5 (CH_2), C-15: 76.8 (C), C-7′: 73.7 (CH_2), C-2′: 72.1 (CH_2), C-3′: 71.6 (CH_2), C-4′: 71.5 (CH_2), C-5′: 71.5 (CH_2), C-6′: 71.3 (CH_2), C-1′: 63.2 (CH_2), C-8′: 62.3 (CH_2), C-2: 54.0 (CH), C-10: 49.2 (CH), C-8: 41.1 (CH_2), C-7: 40.8 (C), C-1: 34.1 (CH_2), C-9: 27.9 (CH_2), C-19: 26.9 (CH_3), C-20: 26.9 (CH_3), C-16: 25.4 (CH_3), C-17: 17.2 (CH_3), C-18: 15.4 (CH_3). HRMS (ESI-TOF): ($C_{28}H_{48}O_5Na$) calcd 487.3394, found 448.3394. **25** (2.0 mg, 15%): $[\alpha]_D^{27}$ −12.0 (*c* 1.58×10^{-3} in CH_3OH); IR: 3436, 3040, 2970, 2922, 2860, 1650, 1121, 1079. ^{1}H NMR (600 MHz, CD_3OD): δ H-13: 6.40 (dd, *J*=15.5, 10.9, 1H), H-12: 5.85 (d, *J*=9.5, 1H), H-14: 5.57 (d, *J*=15.6, 1H), H-2/6: 5.26–4.94 (br m, 1.2H), H-6: 4.80 (br d, *J*=12.1, 0.4H), H-2: 4.55 (br d, *J*=10.4, 0.4H), H-8′: 3.67 (dd, *J*=5.3, 4.5, 2H), H-3′: 3.67–3.63 (m, 2H), H-4′: 3.67–3.63 (m, 2H), H-5′: 3.67–3.63 (m, 2H), H-6′: 3.67–3.63 (m, 2H), H-2′: 3.60–3.56 (m, 2H), H-7′: 3.56 (dd, *J*=5.3, 4.1, 2H), H-1′: 3.49–3.46 (m, 2H), H-8: 2.40–2.34 (m, 1H), H-5: 2.33–2.25 (m, 1H), H-1: 2.22–2.18 (m, 1H), H-4: 2.20–2.15 (m, 1H), H-1: 2.10–2.07 (m, 1H), H-8: 2.09–2.04 (m, 1H), H-5: 2.08–2.03 (m, 1H), H-10: 2.02–1.96 (m, 1H), H-4: 1.94–1.87 (m, *J*=12.4, 5.3, 1H), H-18: 1.78 (s, 1.2H), H-18: 1.75 (s, 1.8H), H-9: 1.70–1.64 (m, 2H), H-16: 1.60–1.54 (br s, 1.2H), H-16: 1.54 (s, 1.8H), H-17: 1.54–1.46 (br s, 1.8H), H-17: 1.41 (s, 1.2H), H-19/20: 1.31 (s, 6H). ^{13}C NMR (150 MHz, CD_3OD): C-11: 147.8 (C), C-7: 138.9 (C), C-14: 137.7 (CH), C-2: 132.6 (CH), C-3: 130.2 (C), C-6: 127.7 (CH), C-13: 127.3 (CH), C-12: 123.0 (CH), C-15: 76.8 (C), C-7′: 73.7 (CH_2), C-2′: 72.2 (CH_2), C-3′: 71.6 (CH_2), C-4′: 71.5 (CH_2), C-5′: 71.5 (CH_2), C-6′: 71.4 (CH_2), C-1′: 63.2 (CH_2), C-8′: 62.2 (CH_2), C-10: 54.8 (CH), C-8: 42.8 (CH_2), C-4: 40.6 (CH_2), C-1: 35.8 (CH_2), C-9: 34.8 (CH_2), C-5: 27.6 (CH_2), C-19: 26.9 (CH_3), C-20: 26.9 (CH_3), C-16: 17.0 (CH_3), C-17: 16.6 (CH_3), C-18: 14.8 (CH_3). HRMS (ESI-TOF): ($C_{28}H_{48}O_5Na$) calcd 487.3394, found 487.3389.

*4.9.12. Fuscol and eunicol methyl ethers (**26**/**27**).* Solvolysis of **3** and **4** (9.4 mg, 33 μmol) was performed according to general procedure E (THF not required) using methanol and separation by phenyl-hexyl RP-HPLC (94% CH_3OH/H_2O) yielded **26** (1.8 mg, 54%) and **27** (0.9 mg, 12%). All spectroscopic data were in accord with the literature.[8]

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of novel fuscol and eunicol derivatives are available. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.006.

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