Supporting Information
(Part I, experimentals for biochemistry/crystallography)

Selective Oxidation of C-H Bonds by an Engineered Macrolide P450 Monooxygenase

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Methods

Antibacterial assay

Two-fold serial dilutions of 40 mM (10 mM for positive control erythromycin) DMSO solutions of test compounds with DMSO generated a series of stock solutions with concentrations ranging from 0.31 ~ 40 mM. Then, a ten-time dilution of each was performed by using dd H_2O to make a 31 ~ 4000 μM series. Cultures of target strains were grown in appropriate media at 37 °C (30 °C for *Deinococcus radiodurans*) with shaking (180 rpm). An overnight seed culture was diluted to an OD_{600} of 0.05, grown to an OD_{600} of 0.4 ~ 0.6, back diluted to an OD_{600} of 0.004, and 45 μL of this diluted culture was added to each well of a 384-well microtiter plate that contained 5 μL of a given dilution of compound in dd H_2O. Plate cultures were grown for 16 h (60 h for *D. radiodurans*) and OD_{600} measurements were taken. All measurements were performed in duplicate.

Steady-state kinetics of $PikC_{D50N}$-RhFRED

The reaction contains 40 nM of PikC-RhFRED-D50N with 3.5 μM spinach ferredoxin and 0.1 U/ml spinach ferredoxin-$NADP^+$ reductase, 10~160 μM substrate in 400 μl of desalting buffer (50 mM NaH_2PO_4, pH 7.3, 1 mM EDTA, 0.2 mM DTE, 10% glycerol). After pre-incubation at 30 ^oC for 5 min, the reaction was initiated by adding 4 μl of 50 mM NADPH and 100 μl aliquots were taken at 0s, 20s, and 40s (or 0s, 30s, and 60s when substrate concentrations are greater than 100 μM) to thoroughly mix with 100 μl of methanol for reaction termination. After centrifugation at 13,000 g for 15 min to pellet protein, the supernatants were analyzed by HPLC. The HPLC conditions were: Xbridge C18 5 μm 250 mm reverse-phase column, 20-80% solvent B (A: deionized water + 0.1% trifluoroacetic acid, B: acetonitrile + 0.1% trifluoroacetic acid) at 1.0 ml/min over 18 min, UV wavelength 226 nm. The initial velocity of substrate consumption was deduced from decreased area under the curve (AUC) of specific substrate peaks. Finally, the data from duplicated experiments were fit to Michaelis-Menten equation.

Preparation of the oxidized product of desosaminyl pyrene 19

An enzymatic reaction containing 0.8 μM $PikC_{D50N}$-RhFRED, 750 μM glucose-6-phosphate, 0.15 Unit/ml glucose-6-phosphate dehydrogenase, 500 μM NADPH, and 15 mg **19** in 200 ml reaction buffer (50 mM NaH_2PO_4, pH7.3, 1 mM EDTA, 0.2 mM dithioerythritol, and 10% glycerol) was carried out at 30 ^oC for 20 h. The hydroxylated product **20** (yield ~8% based on HPLC analysis) was purified by reverse phase C18 preparative HPLC. Upon chloroform extraction from the aqueous solution of **20**, 0.2 mg of **20** was recovered. The oxidation site was determined based on the 600M ^1H NMR and COSY performed by using this small amount of **20** in $CDCl_3$.

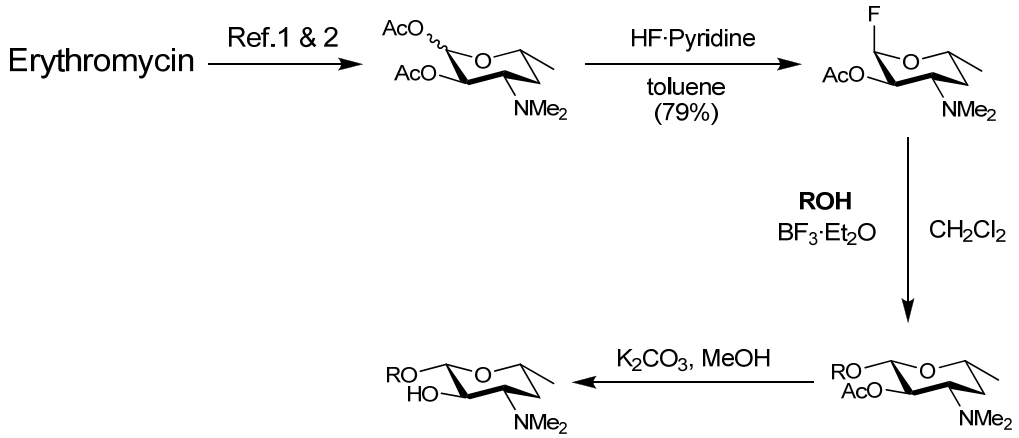


Figure S1 General synthetic strategy for glycosylation of diverse alcohols with desosamine. (Ref.: 1. Chen, H., Yamase, H., Murakami, K., Chang, C.-w., Zhao, L., Zhao, Z. and Liu, H.-w. 2002, *Biochemistry* **41**, 9165–9183. 2. Anzai, Y., Li, S., Chaulagain, M. R., Kinoshita, K., Kato, F., Montgomery, J. and Sherman, D. H. 2008, *Chem. Biol.* **15,** 950-959)

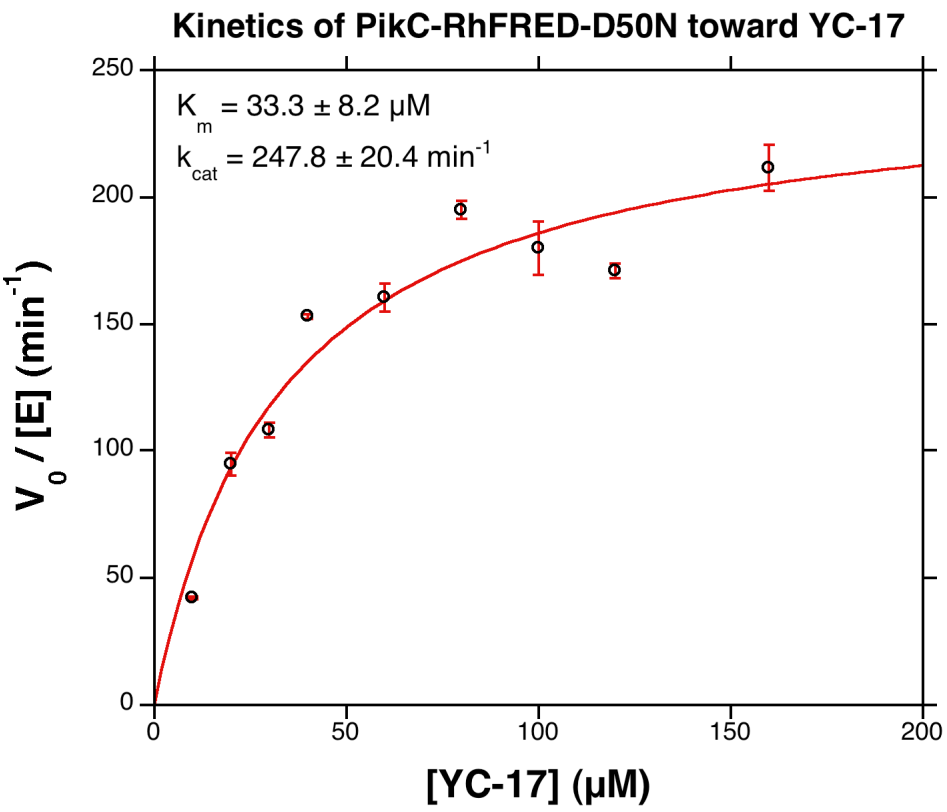


Figure S2 Michaelis-Menten curve of PikC-RhFRED-D50N using YC-17 **1** as substrate.

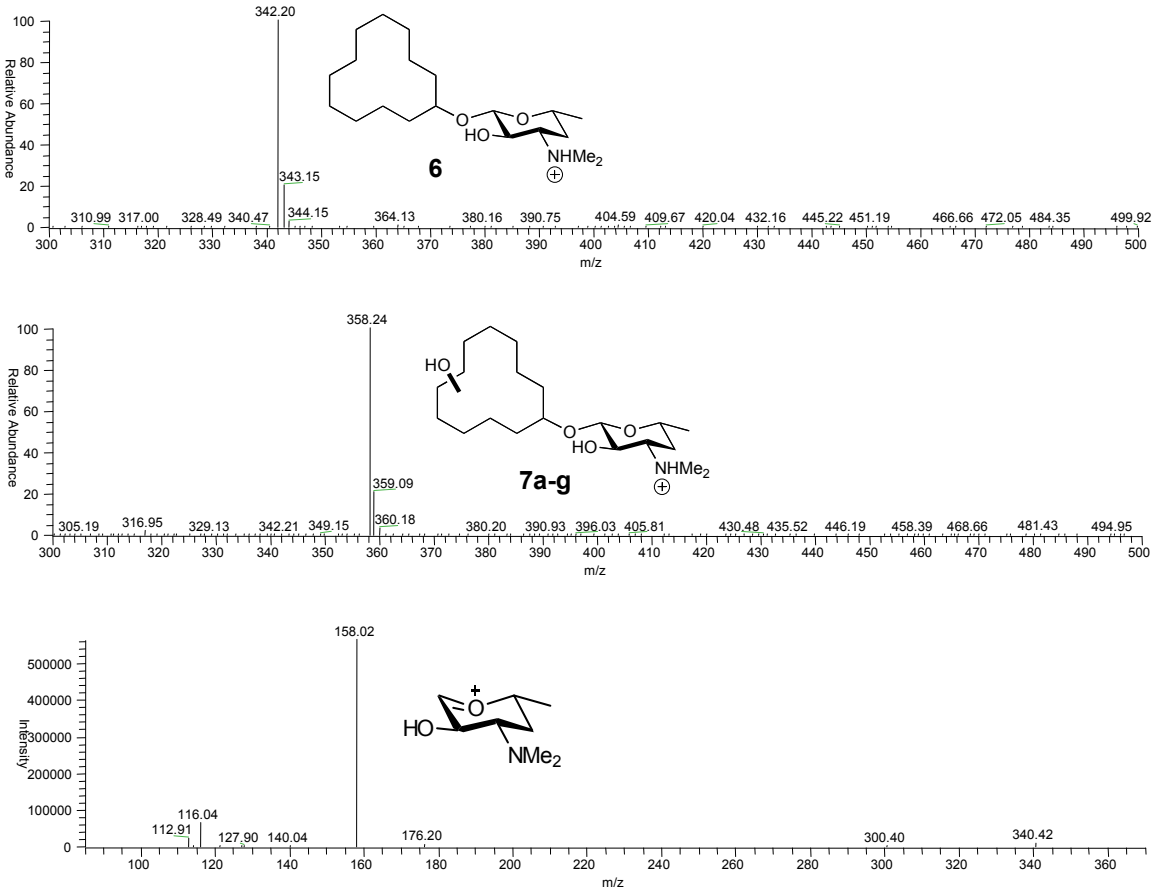


Figure S3 Mass spectra of **6** (top panel) and its hydroxylated products **7a-g** (middle panel). The bottom panel shows the MS-MS pattern of one of products. Notably, all desosaminyl derivatives in this study show the same MS-MS pattern.

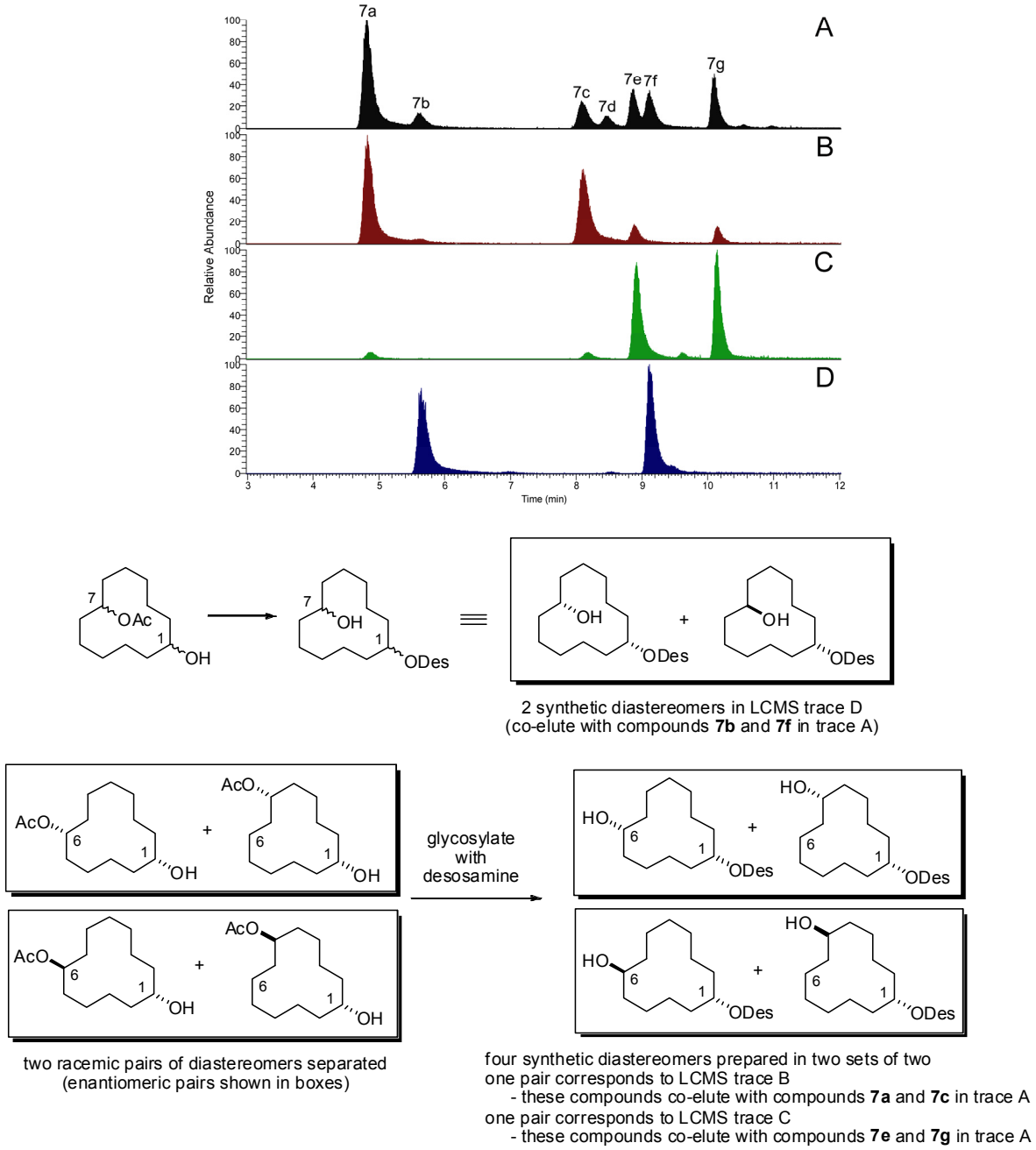


Figure S4 Structural determination of mono-hydroxylated products of **6** through LC-MS comparison of synthetic authentic standards to **7a-g** regarding retention times. (A) Product profile of $PikC_{D50N}$-RhFRED reaction using **6** as substrate; (B) Authentic standard containing a pair of C6/C8 hydroxylated diastereomers; (C) Authentic standard containing the other pair of C6/C8 hydroxylated diastereomers; (D) Authentic standard containing the pair of C7 hydroxylated diastereomers. The products assignment was further confirmed by co-injections.

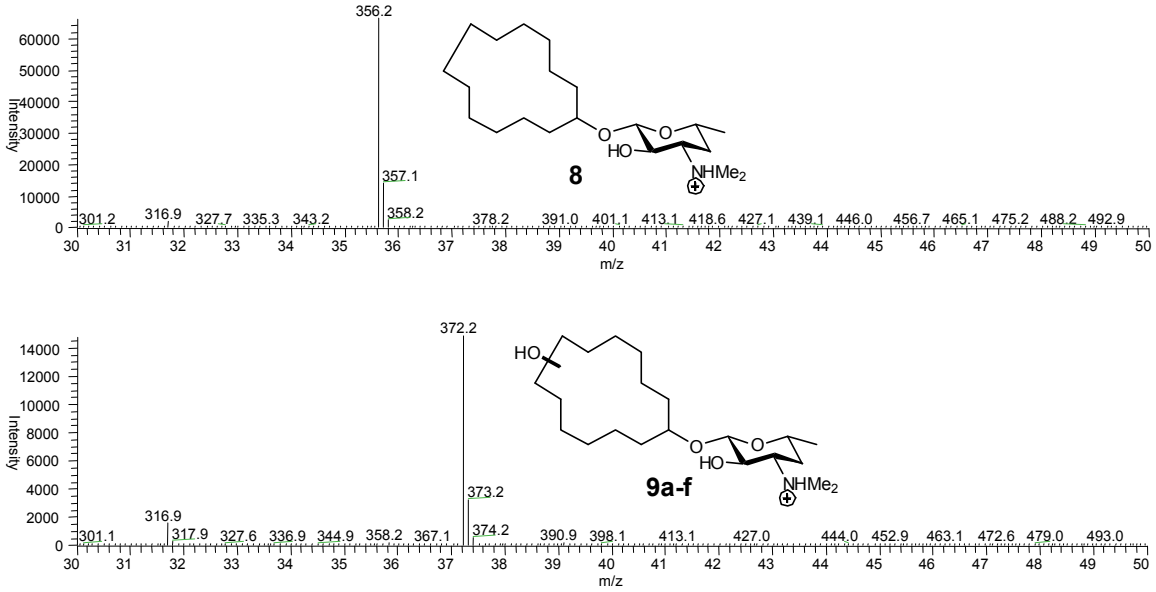
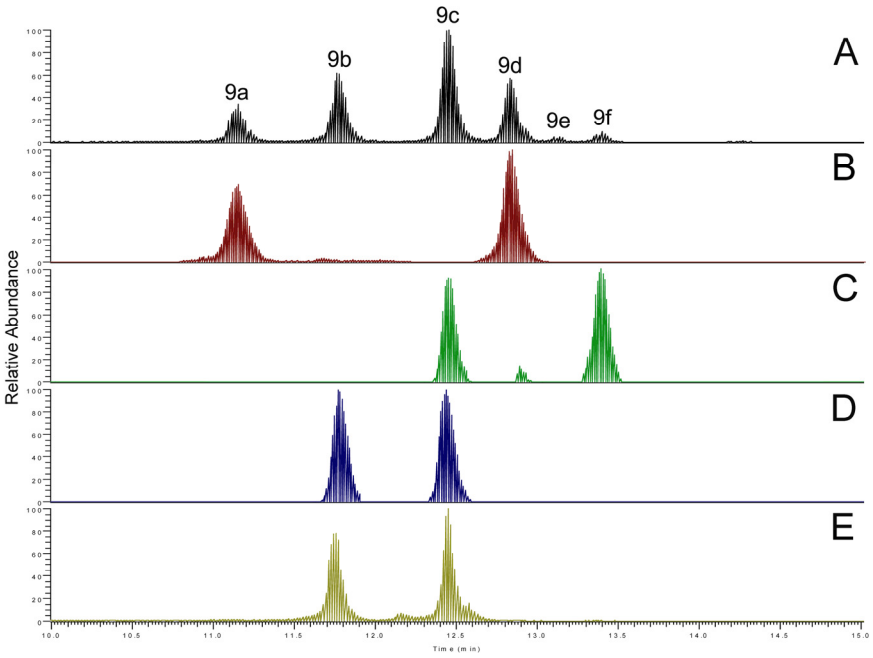
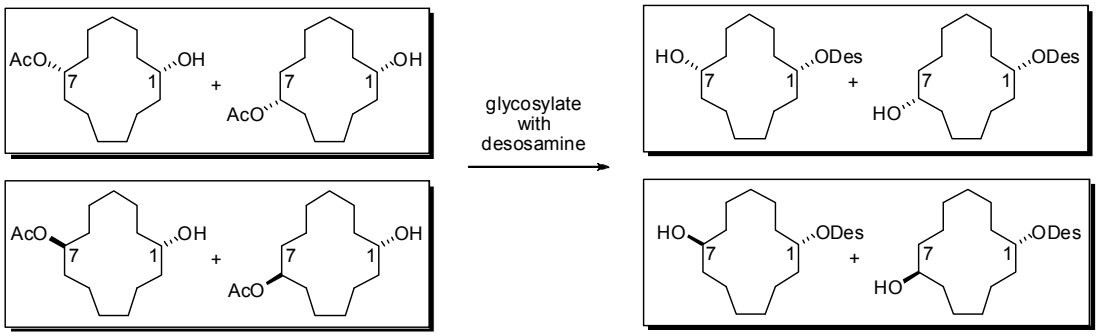


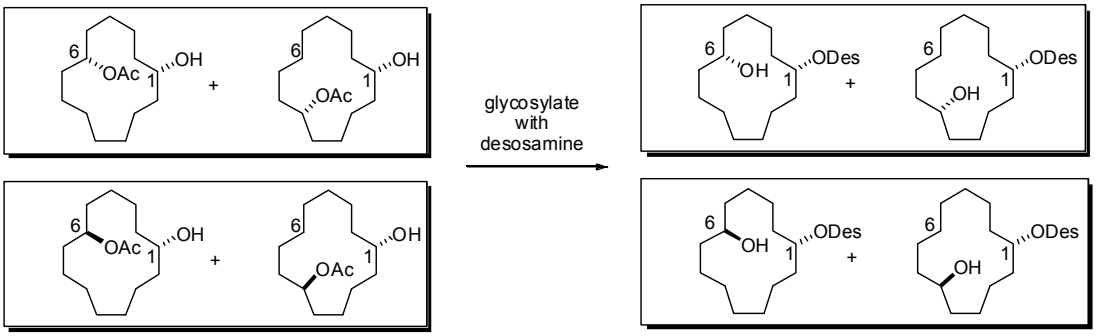
Figure S5 Mass spectra of **8** (upper panel) and its hydroxylated products **9a-f** (lower panel).





two racemic pairs of diastereomers separated
(enantiomeric pairs shown in boxes)

four synthetic diastereomers prepared in two sets of two
one pair corresponds to LCMS trace D
- these compounds co-elute with compounds **9b** and **9c** in trace A
one pair corresponds to LCMS trace E
- these compounds co-elute with compounds **9b** and **9c** in trace A



two racemic pairs of diastereomers separated
(enantiomeric pairs shown in boxes)

four synthetic diastereomers prepared in two sets of two
one pair corresponds to LCMS trace B
- these compounds co-elute with compounds **9a** and **9d** in trace A
one pair corresponds to LCMS trace C
- these compounds co-elute with compounds **9c** and **9f** in trace A

Figure S6 Structural determination of mono-hydroxylated products of **8** through LC-MS comparison of synthetic authentic standards to **9a-f** regarding retention times. (A) Product profile of $PikC_{D50N}$-RhFRED reaction using **8** as substrate; (B) Authentic standard containing a pair of C6/C9 hydroxylated diastereomers; (C) Authentic standard containing the other pair of C6/C9 hydroxylated diastereomers; (D) Authentic standard containing a pair of C7/C8 hydroxylated diastereomers; (E) Authentic standard containing the other pair of C7/C8 hydroxylated diastereomers. The products assignment was further confirmed by co-injections. Some diastereomers are not distinguishable due to identical retention times (e.g. traces D and E) Notably, to get a better separation of similar diastereomers, an optimized LC condition other than the one described in the main text was employed: mobile phase, 10% B for 3 min, 10-80% B over 25 min, 80-100% B over 1 min, 100% B for 5 min, 100-10% solvent B over 2 min, 10% solvent B for 15 min. All other conditions remained the same.

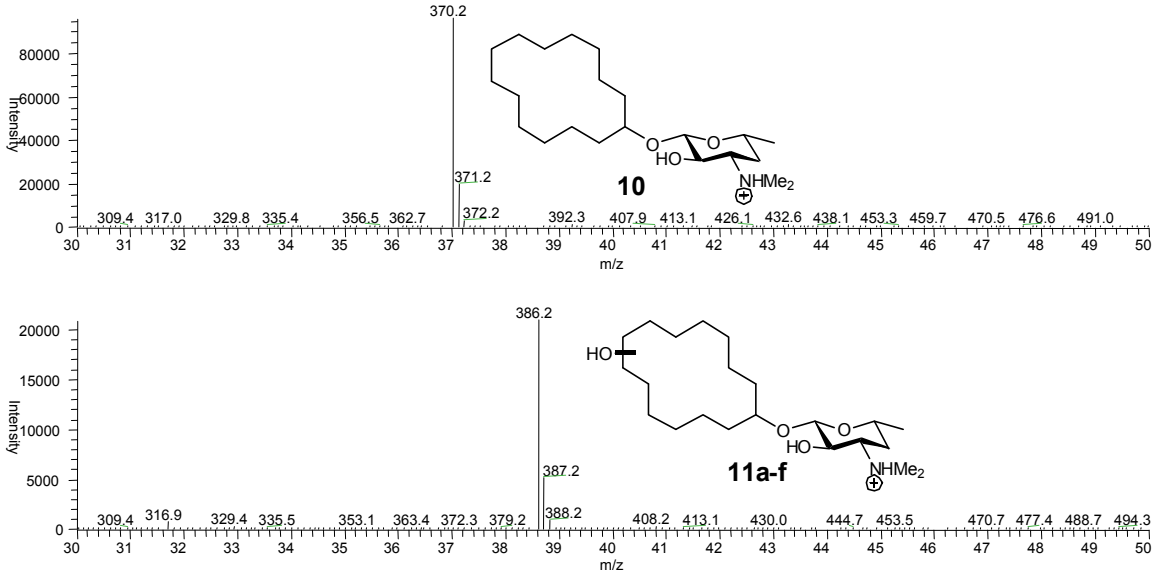


Figure S7 Mass spectra of **10** (upper panel) and its hydroxylated products **11a-f** (lower panel).

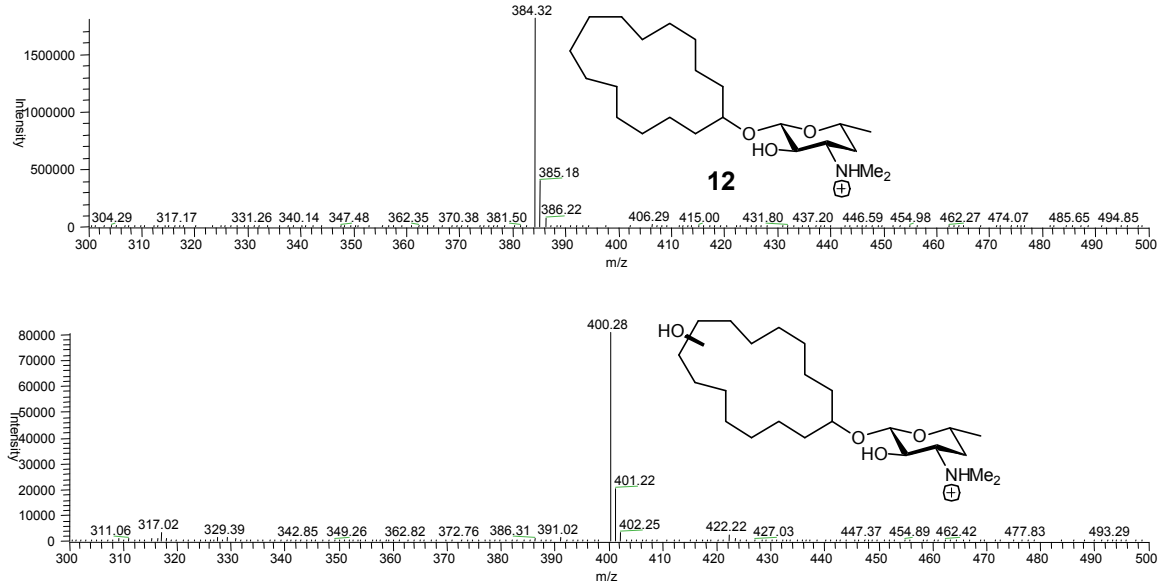


Figure S8 Mass spectra of **12** (upper panel) and its hydroxylated products (lower panel).

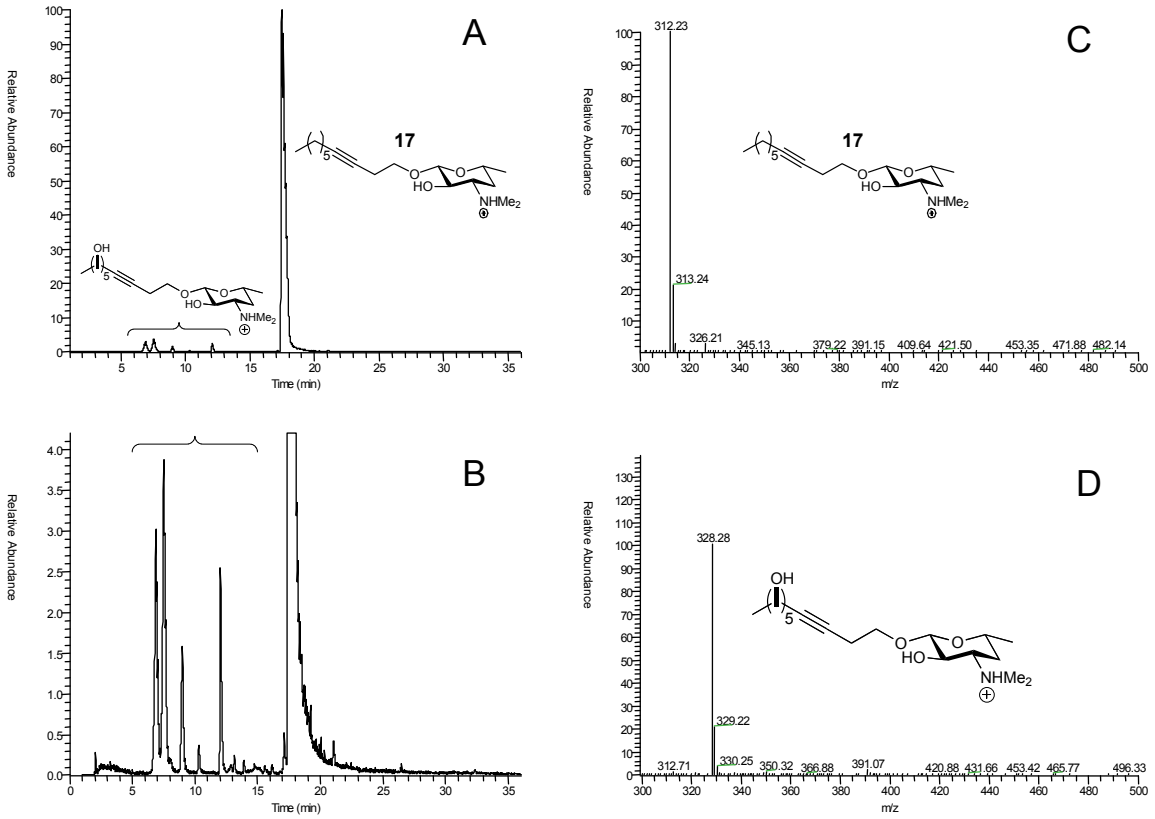


Figure S9 (A) Product profile of $PikC_{D50N}$-RhFRED reaction using linear desosaminyl derivative **17** as substrate. (B) Amplified product profile to visualize the hydroxylated products in small amounts. Mass spectra of **17** (C) and its hydroxylated products (D).

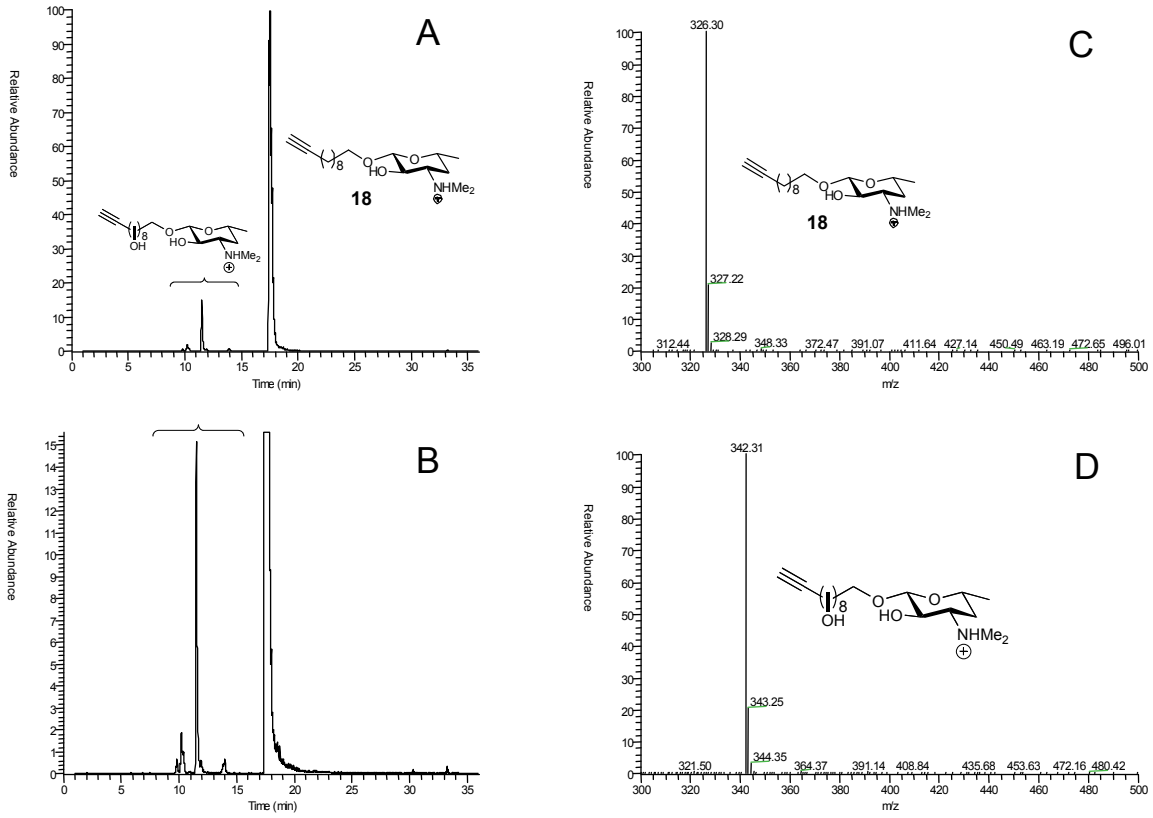


Figure S10 (A) Product profile of $PikC_{D50N}$-RhFRED reaction using linear desosaminyl derivative **18** as substrate. (B) Amplified product profile to visualize the hydroxylated products in small amounts. Mass spectra of **18** (C) and its hydroxylated products (D).

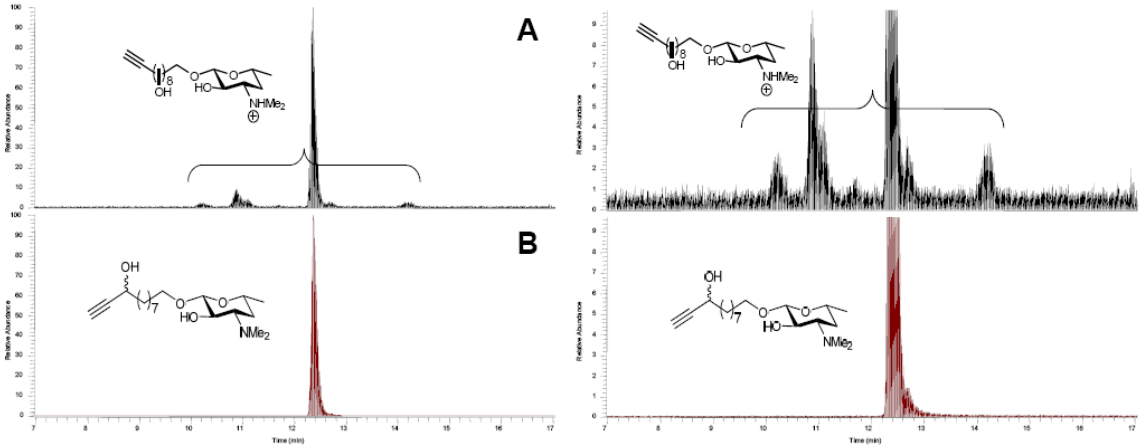


Figure S11 (A) Product profile of PikC$_{D50N}$-RhFRED reaction using linear desosaminyl derivative **18** as substrate. (B) Authentic standard containing a pair of C9 hydroxylated diastereomers. The products assignment was further confirmed by co-injection. The right panel shows the amplified chromatograms to visualize the hydroxylated products in small amounts.

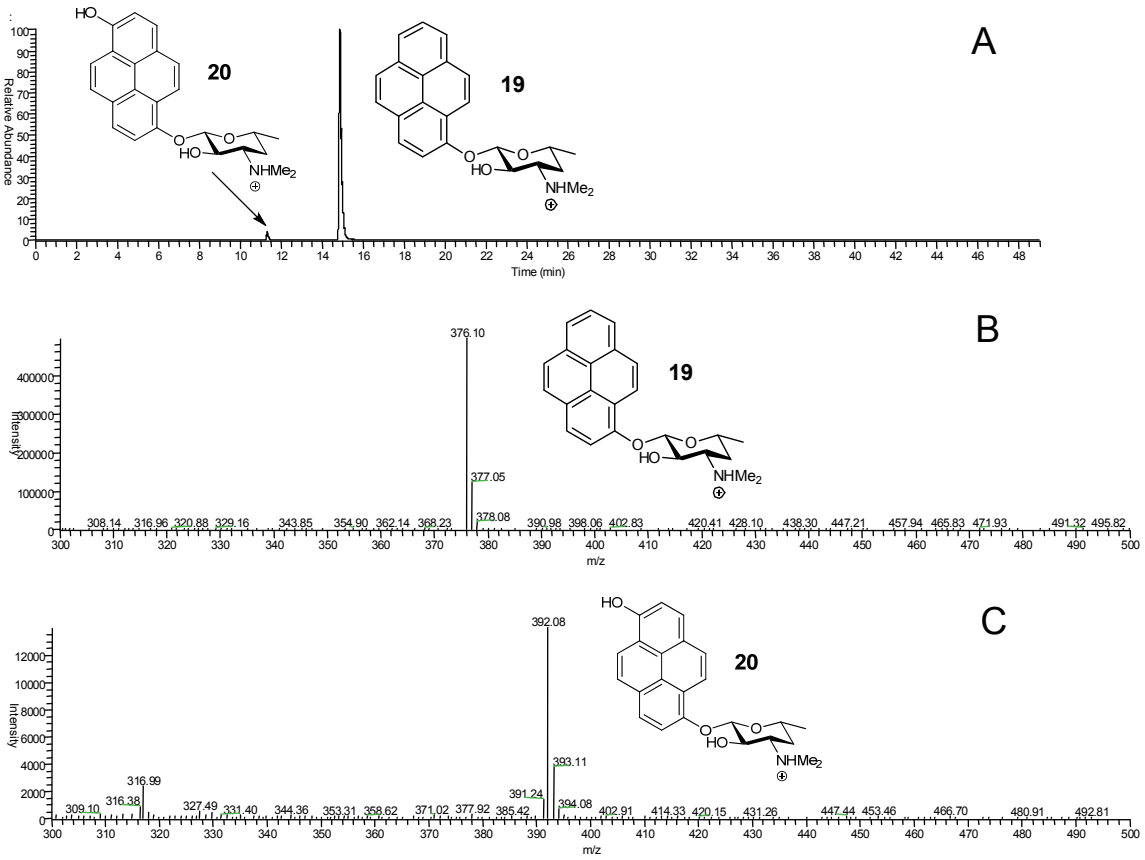
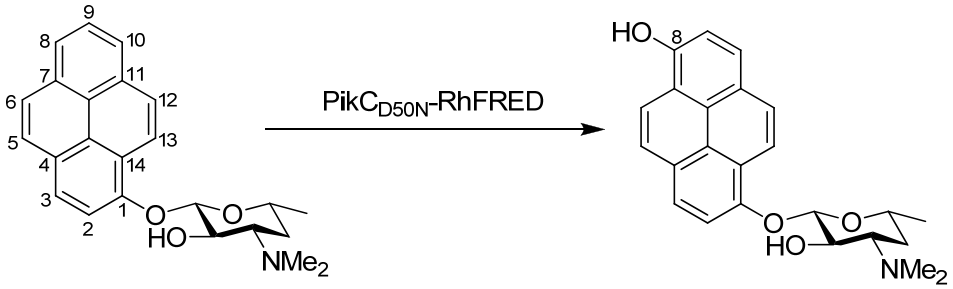


Figure S12 (A) Product profile of $PikC_{D50N}$-RhFRED reaction using aromatic desosaminyl pyrene **19** as substrate. Mass spectra of **19** (B) and its C8 hydroxylated product **20** (C).

Structural determination of 20



19 **20**

Table S1 ^{1}H NMR data of 19 and 20

Proton Position	Proton assignment (ppm) in $CDCl_3$	
	19	**20**
H-2	7.81 (d, J = 8.3 Hz, 1H)	7.78 (d, J = 8.3 Hz, 1H)
H-3	8.12 (d, J = 8.3 Hz, 1H)	8.02 (d, J = 8.3 Hz, 1H)
H-5	7.94 (d, J = 9.1 Hz, 1H)	7.95 (d, J = 9.3 Hz, 1H)
H-6	8.00 (d, J = 9.1 Hz, 1H)	8.17 (d, J = 9.1 Hz, 1H)
H-8	8.13 (d, J = 7.7 Hz, 1H)	-
H-9	7.96 (t, J = 7.7, 7.7 Hz, 1H)	7.44 (d, J = 8.1 Hz, 1H)
H-10	8.14 (d, J = 7.7 Hz, 1H)	7.96 (d, J = 8.2 Hz, 1H)
H-12	8.06 (d, J = 9.1 Hz, 1H)	7.92 (d, J = 9.2 Hz, 1H)
H-13	8.63 (d, J = 9.1 Hz, 1H)	8.41 (d, J = 9.1 Hz, 1H)

The assignment of the aromatic protons of desosaminyl pyrene **19** was conducted based on a full set of 1D and 2D NMR spectra and consistency with the published ^{1}H NMR data for 1-hydroxypyrene (Applied and Environmental Microbiology, 1994, 60, 3597-3601). The structure of **20** was determined based on the 600M ^{1}H NMR and COSY spectra, using **19** as reference.

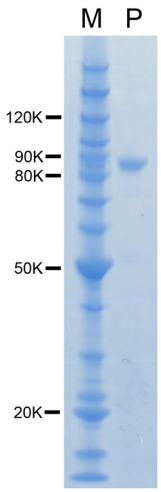


Figure S13 SDS-PAGE analysis of purified $PikC_{D50N}$-RhFRED (M, Marker; P, Purified $PikC_{D50N}$-RhFRED)

Table S2. Crystallographic data and statistics.

Protein complex **PDB ID**	**PikC-cyclododecane** **PDB ID 2WI9**	**PikC-cyclotridecane** **PDB ID 2WHW**
Data collection		
Wavelength, Å	1.11587	1.11587
Resolution, Å	2.0	2.2
Unique reflections	68456	52386
Redundancy	3.9 (3.4)[a]	4.2 (4.3)
Completeness, %	98.2 (87.7)	100.0 (99.8)
Space group	$P2_12_12_1$	$P2_12_12_1$
Cell dimensions (a,b,c), Å (α, β, γ), °	65.3, 109.1, 153.2 90.0, 90.0, 90.0	60.2, 109.5, 153.1 90.0, 90.0, 90.0
Molecules in asymmetric unit	2	2
Solvent content, %	55.1	55.2
R_{sym}[b], %	7.2 (39.0)	9.8 (49.7)
I/σ	21.2 (2.7)	20.9 (3.6)
Refinement		
Reflections used in refinement		49541
$R_{cryst}(R_{free})$[c], %	18.9/23.9	17.6/25.6
No. of atoms	6978	7098
Protein	6229	
Heme	86	86
Ligand	72	
Water/ions	576/15	/10
Wilson plot B-values, Å^2	30.0	29.8
Mean B-factor, Å^2	31.2	29.46
Protein	30.8	27.0
Heme	16.4	12.6
Ligand	**A:** 62.9, **B:** 35.3	**A:** 65.9, **B:** 57.0
Water/ions	34.8/85.3	35.3/84.8
r.m.s. deviations		
Bond length, Å	0.022	0.024
Bond angles, °	1.9	1.9
Ramachandran[d] (%)	**A:** 89.9/9.2/0.6/0.3 **B:** 92.3/7.7/0.0/0.0	**A:** 92.0/7.4/0.3/0.3 **B:** 92.3/7.7/0.0/0.0

[a]Numbers in parentheses correspond to the highest resolution shell.

[b]$R_{sym}=\Sigma|I_i - \langle I\rangle|/\Sigma I_i$, where I_i is the intensity of the i^{th} observation, and $\langle I\rangle$ is the mean intensity of reflection.

[c]$R_{cryst}=\Sigma\ ||Fo|-|Fc||/\Sigma|Fo|$, calculated with the working reflection set. R_{free} is the same as R_{cryst} but calculated with the reserved reflection set.

[d]Program PROCHECK (Laskowski, R. A., MacArthur, M. W., Moss, D. S. and Thornton J. M. 1993, PROCHECK: a program to check the stereochemical quality of protein structures. *J. Appl. Crystallogr.* **26**, 283-291), portions of the protein residues in most favored/additional allowed/generously allowed/disallowed regions.

Table S3 Antibacterial activities of desosaminyl derivatives against selected strains

	Minimal inhibitory concentration (μM)							
	Kocuria rhizophila ATCC9341[a]	*Staphylococcus aureus* ATCC6538P	*Bacillus subtillis* DHS5333	*Deinococcus radiodurans*[b]	*Escherichia. coli* TolC[c]	*S. aureus* NorA[d]	*Acinetobacter baumannii*	Multidrug resistant *S. aureus* (MRSA)
Media	Nutrient broth	LB	LB	Special media[f]	Mueller Hinten	Mueller Hinten	Mueller Hinten	Mueller Hinten
Compound								
Erythromycin	< 0.8	< 0.8	< 0.8	6.2	< 0.8	< 0.8	25	> 100
DMSO	-	-	-	-	-	-	-	-
1	100	100	100	400	100	100	> 400	> 400
2	50	100	100	200	50	100	> 400	> 400
4	< 3.1	6.2	< 3.1	100	25	3.1	> 400	> 400
5	6.2	25	12.5	100	100	12.5	> 400	> 400
6	50	> 400	200	100	50	200	> 400	400
8	50	400	200	100	50	200	> 400	200
10	50	> 400	200	50	50	400	> 400	400
12	50	200	100	50	50	100	> 400	100
13	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
14	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
15	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
8-C6OH-a[e]	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
8-C6OH-b[e]	> 400	> 400	> 400	400	> 400	> 400	> 400	> 400
8-C7OH-a[e]	> 400	> 400	> 400	400	> 400	> 400	> 400	> 400
8-C7OH-b[e]	> 400	> 400	> 400	100	400	> 400	> 400	> 400
17	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
18	> 400	> 400	> 400	> 400	400	> 400	> 400	> 400
19	25	25	6.2	25	25	25	100	25
Cyclododecanol	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
Cyclotridecanol	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400
Cyclopentadecanol	> 400	> 400	> 400	> 400	> 400	> 400	> 400	> 400

[a] Previously known as *Micrococcus luteus* ATCC 9341, which is sensitive to macrolide antibiotics.

[b] A gift from Prof. Ada E. Yonath (Structural Biology Department, Weizmann Institute of Science, Rehovot, Israel)

[c] *E. coli* W3110 TolC disruption mutant that is more sensitive to antibiotics

[d] *S. aureus* 8325 NorA disruption mutant that is more sensitive to antibiotics

[e] **8**-C6OH-a, b and **8**-C7OH-a, b correspond to synthetic C6/C9 and C7/C8 hydroxylated standards of 13-membered carbolide, each of which contains a pair of diastereomers as shown in trace B, C and D, E, respectively in Fig. S6

[f] Media recipe: 10 g caseine peptone (tryptic digest), 5 g yeast extract, 5 g NaCl and 5 g glucose (add after sterilization) in 1 liter water, pH 7.2.

Supporting Information
(Part II, experimentals for synthetic chemistry)

Selective Oxidation of C-H Bonds by an Engineered Macrolide P450 Monooxygenase

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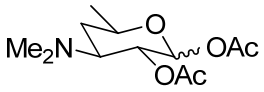
General Protocols.

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-400-3. $Ni(COD)_2$ (Strem Chemicals, Inc., used as received), 1,3-Bis(2,4,6-trimethyl-phenyl)imidazolium chloride (IMes·HCl), 1,3-Bis(2,6-di-*iso*-propylphenyl)imidazolium chloride (IPr·HCl), and potassium *tert*-butoxide were stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under nitrogen atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt (25 ^oC), unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. Low resolution electrospray mass spectra were obtained on a Micromass LCT spectrometer, low resolution chemical ionization mass spectra were obtained on a Micromass VG-70-250-S spectrometer, and high resolution electrospray mass spectra were obtained on a Micromass AutoSpec Ultima spectrometer at the University of Michigan Mass Spectrometry Laboratory.

Isolation of desosamine diacetate from (-)-erythromycin hydrate as the bis(acetate) protected desosamine

(3*R*,4*S*)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2,3-diyl diacetate

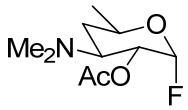


A modification of a literature procedure was followed.[i] To a solution of 7.0 g erythromycin hydrate (7.043 g, 9.54 mmol) (Aldrich) in 50 mL ethanol in a 250 mL round bottomed flask, 130 mL 6N HCl was added slowly at rt. The mixture was heated at reflux for 3 h and was allowed to cool to rt. The reaction mixture was then washed with 50 mL of chloroform three times and the orange-colored aqueous layer was concentrated under vacuum to obtain crude 4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diol as an orange solid, which was subjected to the next step without further purification. To

the suspension of crude desosamine in acetic anhydride (10 mL), 2 mL of conc. H_2SO_4 was added at 0 ºC and stirred at rt for 12 h. The reaction mixture was poured into ice water and neutralized slowly with solid sodium bicarbonate and extracted with dichloromethane. The combined organic layer was concentrated and purified by column chromatography (SiO_2, 95:5 CH_2Cl_2:MeOH) to afford 4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diyl diacetate (2.189 g, 8.45 mmol, 88 % over 2 steps) as a light orange liquid. (Spectral data of the compound was identical with that previously reported).[ii]

Conversion of bis-acetate into the glycosyl fluoride[iii]

(2*R*,3*R*,4*S*,6*R*)-4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2*H*-pyran-3-yl acetate



To a stirring solution of HF/pyridine (1.50 mL) in a clean and dry polyethylene vial, the solution of 4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2,3-diyl diacetate (240 mg, 0.92 mmol) in toluene (1 mL) was added and stirred for 30 min at 0 °C. The reaction mixture was diluted with 10 mL brine solution, neutralized with $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography (SiO_2, ethyl acetate) to afford the α-anomer of 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (160 mg, 0.73 mmol, 79%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dd, *J* = 54.4, 2.8 Hz, 1H) 4.82 (ddd, *J* = 24, 11.2, 2.8 Hz, 1H) 4.06 (dqd, *J* = 12.4, 6.4, 2.0 Hz, 1H) 3.10 (td, *J* = 12.0, 4.0 Hz, 1H) 2.23 (s, 6H), 2.06 (s, 3H) 1.81 (ddd, *J* = 13.2, 4.0, 2.4 Hz, 1H) 1.36 (q, *J* = 12.0 Hz, 1H) 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 106.5 (d, *J* = 22.7 Hz), 69.6 (d, *J* = 24.9 Hz), 67.4 (d, *J* = 3.6 Hz), 57.3, 40.4, 31.4, 21.1, 20.8; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 220.1349, found 220.1351

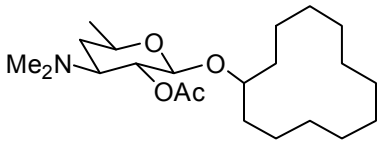
General procedure for glycosylation with desosamine[iv]

A suspension of alcohol (1.0 equiv), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2*H*-pyran-3-yl acetate (2.0 equiv) and molecular sieves (4A) in dichloromethane was stirred for 30 min. $BF_3.OEt_2$ (4.0 equiv, freshly distilled from CaH_2) was added to the ice

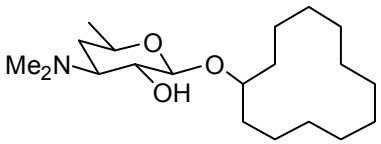
cooled reaction mixture and stirred for 1 h at 0 °C. The reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography (SiO_2, 1:19 MeOH: CH_2Cl_2).

General procedure for acetate deprotection

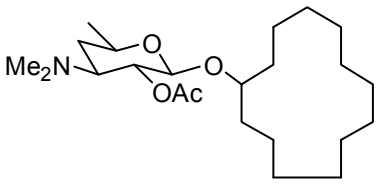
To the solution of the acetate obtained above (1 equiv) in methanol (20 mL/mmol), K_2CO_3 (4 equiv) was added as a solid and stirred at rt until the starting material was consumed as judged by TLC analysis. The reaction mixture was diluted with brine and extracted with ethyl acetate. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to afford the deprotected desosamine conjugate.



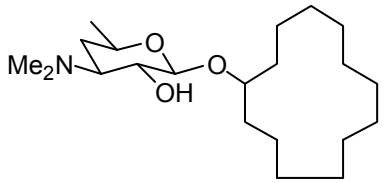
2-(Cyclododecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, cyclododecanol (19 mg, 0.11 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.2 mmol) were employed to obtain 2-(cyclododecyloxy-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate (20 mg, 0.052 mmol, 52 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (dd, *J* = 10.5, 7.5 Hz, 1H) 4.34 (d, *J* = 7.5 Hz, 1H) 3.72 (m, 1H) 3.54 (dqd, *J* = 12.5, 6.0, 2.0 Hz, 1H) 2.76 (ddd, *J* = 12.5, 11.0, 4.5 Hz, 1H) 2.28 (s, 6H) 2.07 (s, 3H) 1.74 (ddd, *J* = 13.0, 4.5, 2.0 Hz, 1H) 1.70-1.28 (m, 23H) 1.27 (d, *J* = 6.0Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 101.3, 77.3, 71.1, 69.0, 63.2, 40.6, 30.9, 30.2, 29.0, 24.5, 24.4, 24.0, 23.3, 23.2, 23.1, 21.3, 21.2, 20.9, 20.4; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 384.3114, found 384.3115.



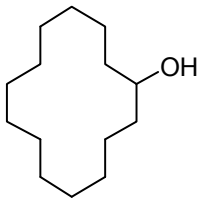
2-(Cyclododecyloxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (6). Following the general procedure, 2-(cyclododecyloxy-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate (20 mg, 0.052 mmol) , K_2CO_3 (27 mg, 0.2 mmol), and methanol were employed to afford 2-(cyclododecyloxy-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-ol (15 mg, 0.045 mmol, 86 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.31 (d, *J* = 7.0 Hz, 1H) 3.88-3.82 (m, 1H) 3.56 (dqd, *J* = 11.0, 6.0, 2.0 Hz, 1H) 3.28 (dd, *J* = 10.5, 7.5 Hz, 1H) 2.60 (ddd, *J* = 12.5, 10.0, 4.0 Hz, 1H) 1.78-1.29 (m, 25H) 1.27 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 102.5, 76.6, 70.0, 69.3, 65.3, 40.3, 30.1, 29.1, 24.5, 24.4, 24.1, 23.5, 23.4, 23.0, 22.0, 21.3, 21.0, 20.5; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 342.3008, found 342.3000.



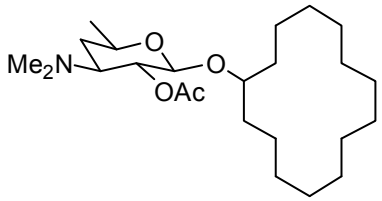
2-(Cyclotridecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, cyclotridecanol (21 mg, 0.11 mmol, prepared by $NaBH_4$ reduction of cyclotridecanone), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (30 mg, 0.14 mmol), molecular sieves (150 mg) and BF_3•OEt_2 (28 μL, 2.8 mmol) were employed to obtain 2-(cyclotridecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (28 mg, 0.07 mmol, 64 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 10.4, 7.6 Hz, 1H) 4.33 (d, *J* = 7.6 Hz, 1H) 3.62 (quint, *J* = 6.0 Hz, 1H) 3.52 (dqd, *J* = 10.8, 6.0, 2.0 Hz, 1H) 2.74 (ddd, *J* = 12.8, 10.4, 4.4 Hz, 1H) 2.27 (s, 6H) 2.05 (s, 3H) 1.72 (ddd, *J* = 13.2, 4.4, 2.0 Hz, 1H) 1.66-1.32 (m, 25H), 1.25 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 101.5, 79.0, 71.1, 69.0, 63.2, 40.6, 32.7, 31.5, 30.9, 26.6, 26.5, 26.1, 26.0, 25.80, 25.78, 25.6, 22.7, 22.4, 21.3, 21.2; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 398.3270 found 398.3260.



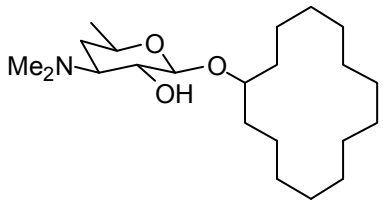
2-(Cyclotridecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (8). Following the general procedure, 2-(cyclotridecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (16 mg, 0.04 mmol), K_2CO_3 (50 mg, 0.36 mmol), and methanol (2 ml) were employed to afford 2-(cyclotridecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (13 mg, 0.037 mmol, 91 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (d, *J* = 6.8 Hz, 1H) 3.73 (quint, *J* = 5.8 Hz, 1H) 3.53 (dqd, *J* = 10.4, 6.4, 2.0 Hz, 1H) 3.26 (dd, *J* = 10.0, 6.8 Hz, 1H) 3.09 (br s, 1H) 2.53 (ddd, *J* = 12.0, 10.0, 3.8 Hz, 1H) 2.28 (s, 6H) 1.61-1.52 (m, 5H) 1.36-1.17 (m, 21H) 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR 102.8, 78.3, 70.0, 69.4, 65.4, 40.4, 32.8, 31.7, 28.9, 26.59, 26.57, 26.1, 26.0, 25.9, 25.7, 25.6, 22.7, 22.6, 21.4; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 356.3165 found 356.3164.



Cyclotetradecanol. To the solution of (*E*)-cyclotetradec-2-enol[v,vi] (9 mg, 0.043 mmol) in 2 mL dry ethyl acetate under nitrogen, PtO_2 (2 mg, 0.007 mmol) was added and purged with hydrogen gas in a balloon with a needle and stirred for 2 h. The reaction mixture was filtered through a small silica plug and concentrated to afford cyclotetradecanol (8 mg, 0.038 mmol, 89 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.78-3.86 (m, 1H) 1.23-1.64 (m, 27 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.6, 33.6, 25.4, 25.3, 24.8, 24.7, 21.9.

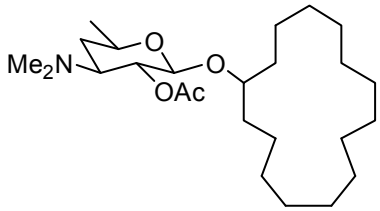


2-(Cyclotetradecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, cyclotetradecanol (8 mg, 0.038 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (10 mg, 0.045 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (10 μL, 0.1 mmol) were employed to obtain 2-(cyclotetradecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (10 mg, 0.024 mmol, 64 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (dd, *J* = 10.6, 7.4 Hz, 1H) 4.33 (d, *J* = 7.2 Hz, 1H) 3.69 (quint, *J* = 5.8 Hz, 1H) 3.52 (dqd, *J* = 10.8, 6.0, 1.8 Hz, 1H) 2.73 (ddd, *J* = 12.0, 10.4, 4.4 Hz, 1H) 2.27 (s, 6H) 2.05 (s, 3H) 1.72 (ddd, *J* = 13.2, 4.6, 2.0 Hz, 1H) 1.59-1.51 (m, 4H) 1.46-1.25 (m, 23 H) 1.25 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 101.5, 78.1, 71.2, 69.0, 63.2, 40.6, 31.8, 31.0, 30.4, 26.0, 25.8, 25.61, 25.57, 24.61, 24.59, 24.5, 24.4, 21.7, 21.3, 21.2, 21.1; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 412.3427, found 412.3436.

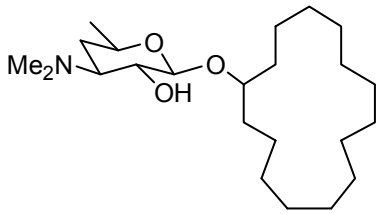


2-(Cyclotetradecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (10). Following the general procedure, 2-(cyclotetradecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (8 mg, 0.019 mmol), K_2CO_3 (15 mg, 0.11 mmol), and methanol (2 ml) were employed to afford 2-(cyclotetradecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (6 mg, 0.016 mmol, 86 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (d, *J* = 7.2 Hz, 1H) 3.81 (quint, *J* = 5.7 Hz, 1H) 3.54 (dqd, *J* = 10.4, 6.4, 2.0 Hz, 1H) 3.28 (dd, *J* = 10.0, 7.6 Hz) 3.00 (br s, 1H) 2.58 (ddd, *J* = 12.4, 10.0, 4.0 Hz, 1H) 2.32 (s, 6H) 1.72-1.25 (m, 28H) 1.25 (d, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.7, 77.6, 70.1, 69.4, 65.4, 40.4, 31.8, 30.4,

29.2, 25.9, 25.8, 25.67, 25.65, 25.5, 24.64, 24.59, 24.4, 24.3, 21.6, 21.4, 21.3; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 370.3321 found 370.3307.

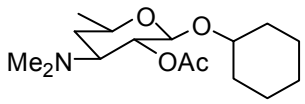


2-(Cyclopentadecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, cyclopentadecanol (35 mg, 0.15 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (200 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 2-(cyclopentadecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (19 mg, 0.045 mmol, 45 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.76 (dd, *J* = 10.8, 7.6 Hz, 1H) 4.29 (d, *J* = 7.6 Hz, 1H) 3.53-3.60 (m, 1H) 3.48 (dqd, *J* = 12.4, 6.4, 2.0 Hz, 1H) 2.70 (ddd, *J* = 12.4, 10.8, 4.4 Hz, 1H) 2.23 (s, 6H) 2.01 (s, 3H) 1.69 (ddd, *J* = 13.2, 4.4, 2.0 Hz, 1H) 1.23-1.60 (m, 29 H) 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 101.3, 78.8, 71.0, 68.9, 63.1, 40.5, 33.1, 31.7, 30.9, 27.3, 27.2, 26.8, 26.7, 26.6, 26.5, 23.1, 22.5, 21.2, 21.1; LRMS (ESI) *m/z* calculated for $[M+H]^+$ 426.3 found 426.3.

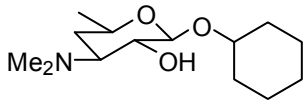


2-(Cyclopentadecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (12). Following the general procedure, 2-(cyclopentadecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (10 mg, 0.023 mmol), K_2CO_3 (15 mg, 0.10 mmol), and methanol (2ml) were employed to afford 2-(cyclopentadecyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (8 mg, 0.021 mmol, 91 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, *J* = 7.0 Hz, 1H) 3.72 (quint, *J* = 6.0 Hz, 1H) 3.55 (dqd, *J* = 12.5, 6.0, 2.0 Hz, 1H) 3.32 (dd, *J* = 10.0, 7.5 Hz, 1H) 2.70 (ddd, *J*

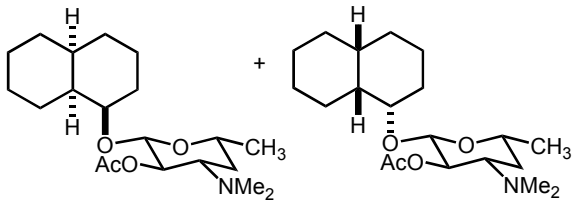
= 12.5, 10.5, 4.0 Hz, 1H) 1.75 (ddd, *J* = 12.5, 4.5, 2.0 Hz, 1H) 1.54-1.68 (m, 4H) 1.28-1.45 (m, 25H) 1.27 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 102,6, 78.5, 70.0, 69.1, 65.0, 45.0, 40.1, 33.2, 32.0, 29.6, 27.3, 27.2, 26.9, 26.8, 26.7, 26.6, 26.5, 23.1, 22.9, 21.2; LRMS (ESI) *m/z* calculated for $[M+H]^+$ 384.3 found 384.3.



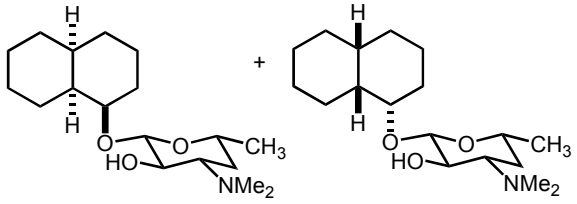
2-(Cyclohexyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, cyclohexanol (6 mg, 0.057 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 2-(cyclohexyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (10 mg, 0.033 mmol, 59 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. Spectral data matches that previously reported.[vii]



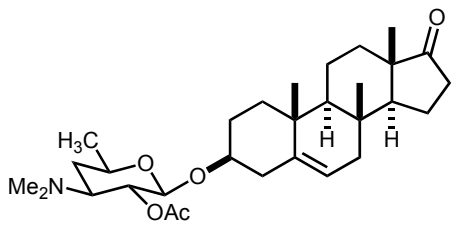
2-(Cyclohexyloxy)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-ol (13). Following the general procedure, 2-(cyclohexyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (9 mg, 0.03 mmol), K_2CO_3 (16 mg, 0.12 mmol), and methanol were employed to afford 2-(cyclohexyloxy)-4-(dimethylamino)- 6-methyltetrahydro-2H-pyran-3-ol (7 mg, 0.027 mmol, 90 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (br s, 1H), 4.37 (d, *J* = 7.0 Hz, 1H), 3.67 (tt, *J* = 10.0, 4.0 Hz, 1H), 3.57 (dqd, *J* = 11.0, 6.0, 2.0 Hz, 1H), 3.34 (dd, *J* = 10.5, 7.5 Hz, 1H), 2.74 (ddd, *J* = 12.5, 10.0, 4.0 Hz, 1H), 2.40 (s, 6H), 1.97 (m, 2H), 1.71 (m, 3H), 1.2-1.55 (m, 7H), 1.28 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.9, 69.9, 69.2, 65.0, 40.1, 33.7, 32.0, 29.7, 25.6, 24.1, 21.3; LRMS (ESI) *m/z* calculated for $[M+H]^+$ 258.1, found 258.1.



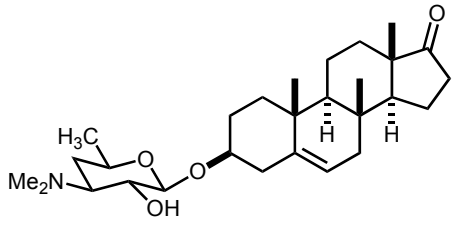
2-(Decahydronaphthalen-1-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, (±)-decahydronaphthalen-1-ol (16 mg, 0.10 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 2-(decahydronaphthalen-1-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (20 mg, 0.58 mmol, 58 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (dd, *J* = 10.8, 7.6 Hz, 0.5H) 4.77 (dd, 10.8, 7.6 Hz, 0.5H) 4.36 (d, J = 7.6 Hz, 0.5H) 4.33 (d, *J* = 7.6 Hz, 0.5H) 3.44-3.60 (m, 2H) 2.66-2.76 (m, 1H) 2.24 (s, 3H) 2.23 (s, 3H) 2.01 (s, 1.5H) 2.00 (s, 1.5H) 1.80-1.95 (m, 1H) 1.06-1.76 (m, 17H) 1.22 (d, J = 6.0 Hz, 3H).



2-(Decahydronaphthalen-1-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (14). Following the general procedure, 2-(decahydronaphthalen-1-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (15 mg, 0.042 mmol), K_2CO_3 (30 mg, 0.22 mmol), and methanol (2 ml) were employed to afford 1:1 mixture of diastereomers 2-(decahydronaphthalen-1-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (12 mg, 0.038 mmol, 92 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (br s, 1H), 4.33 (d, *J* = 7.2 Hz, 0.5H), 4.29 (d, *J* = 7.2 Hz, 0.5H), 3.68 (dt, *J* = 15.0, 4.4 Hz, 0.5H), 3.62 (dt, *J* = 15.0, 4.4 Hz, 0.5H), 3.47-3.58 (m, 1H), 3.31 (dd, *J* = 10.0, 7.2 Hz, 1H), 2.73-2.83 (m, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 1.10-1.78 (m, 21H); LRMS (ESI) *m/z* calculated for $[M+H]^+$ 312.2 found 312.2.

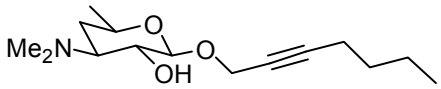


(2S,3R,4S,6R)-2-((3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[α]phenanthren-3-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate. Following the general procedure, *trans*-dehydroandrosterone (57 mg, 0.26 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2*H*-pyran-3-yl acetate (57 mg, 0.26 mmol), molecular sieves (100 mg), and $BF_3{\cdot}OEt_2$ (110 μL, 0.87 mmol) were employed to obtain (2S,3R,4S,6R)-2-((3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[α]phenanthren-3-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate (19 mg, 38 %) as a white solid after column chromatography (1:19 methanol: ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (d, *J* = 5.2 Hz, 1H) 4.79 (dd, *J* = 10.6, 7.8 Hz, 1H) 4.38 (d, *J* = 7.2 Hz, 1H) 3.51 (dqd, *J* = 10.8, 6.0, 1.6 Hz, 1H) 3.45 (tt, *J* = 11.2, 4.8 Hz, 1H) 2.74 (ddd, *J* = 12.8, 10.8, 4.0 Hz, 1H) 2.45 (dd, *J* = 19.0, 8.6 Hz, 1H) 2.31-2.27 (m, 1H) 2.27 (s, 6H) 2.20-2.02 (m, 3H) 2.07 (s, 3H) 1.95-1.90 (m, 2H) 1.84 (dq, *J* = 12.8, 3.6 Hz, 2H) 1.72 (ddd, *J* = 12.8, 4.4, 2.0 Hz, 1H) 1.69-1.27 (m, 10H) 1.05 (dt, *J* = 3.6, 14.0 Hz, 1H) 1.24 (d, *J* = 6.4 Hz, 3H) 1.00 (s, 3H) 0.97 (m, 1H) 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.0, 169.9, 141.1, 120.9, 101.0, 78.8, 77.3, 71.0, 69.2, 63.1, 51.8, 50.3, 47.5, 40.6, 39.1, 37.2, 36.9, 35.8, 31.5, 31.4, 30.9, 30.8, 29.5, 21.9, 21.4, 21.2, 20.3, 19.4, 13.5; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 488.3376, found 488.3380.

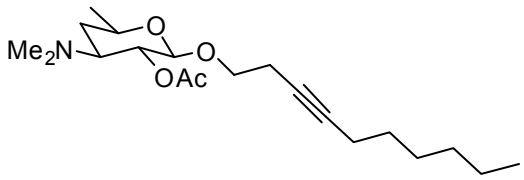


(3S,8R,9S,10R,13S,14S)-3-((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yloxy)-10,13-dimethyl-3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-1H-cyclopenta[α]phenanthren-17(2H)-one (15). Following the general

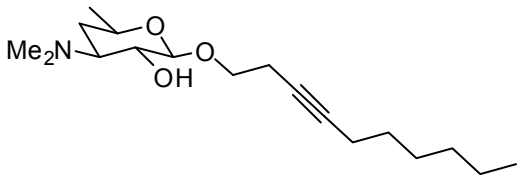
procedure, (2S,3R,4S,6R)-2-((3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[α]phenanthren-3-yloxy)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate (11 mg, 0.022 mmol), K_2CO_3 (9 mg, 0.066 mmol), and methanol (3 mL) were employed to obtain (3S,8R,9S,10R,13S,14S)-3-((2S,3R,4S,6R)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yloxy)-10,13-dimethyl-3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-1H-cyclopenta[α]phenanthren-17(2H)-one (14 mg, quantitative) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (d, *J* = 5.2 Hz, 1H) 4.36 (d, *J* = 7.2 Hz, 1H) 3.59 (tt, *J* = 11.2, 4.4 Hz, 1H) 3.54 (dqd, *J* = 16.8, 6.4, 2.0 Hz, 1H) 3.26 (dd, *J* = 10.2, 7.0 Hz, 1H) 2.54 (ddd, *J* = 12.0, 10.2, 4.0 Hz, 1H) 2.48-2.42 (m, 2H) 2.36-2.29 (m, 1H) 2.29 (s, 6H) 2.14-1.81 (m, 6H) 1.72-1.42 (m, 7H) 1.32-1.23 (m, 3H) 1.25 (d, *J* = 5.6 Hz, 3H) 1.08 (dt, *J* = 4.0, 13.6 Hz, 1H) 1.03 (s, 3H) 1.01-0.96 (m, 1H) 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.1, 141.1, 120.9, 102.3, 78.2, 69.8, 69.5, 65.4, 51.8, 50.3, 47.5, 40.3, 38.9, 37.3, 36.9, 35.8, 31.5, 31.4, 30.8, 29.6, 28.7, 21.9, 21.3, 20.3, 19.4, 13.5; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 446.3270, found 446.3276.



4-(Dimethylamino)-2-(hept-2-ynyloxy)-6-methyltetrahydro-2*H*-pyran-3-ol (16). Following the general procedure, 2-heptynol (6 mg, 0.057 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 4-(dimethylamino)-2-(hept-2-ynyloxy)-6-methyltetrahydro-2*H*-pyran-3-ol (9 mg, 0.033 mmol, 58 %) after column chromatography (SiO_2, 1:19 methanol:CH_2Cl_2) as a white solid (acetate hydrolysis occurred during workup and purification). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.47 (d, *J* = 7.5 Hz, 1H) 4.44 (dt, *J* = 15.5, 2.5 Hz, 1H) 4.37 (dt, *J* = 15.0, 2.5 Hz, 1H) 3.58 (dqd, *J* = 12.5, 6.5, 2.0 Hz, 1H) 3.32 (dd, *J* = 10.5, 7.5 Hz, 1H) 2.59 (ddd, *J* = 12.5, 10.5, 4.0 Hz, 1H) 2.32 (s, 6H) 2.22 (tt, *J* = 6.5, 2.5 Hz, 2H) 1.73 (ddd, *J* = 13.0, 4.0, 2.0 Hz, 1H) 1.37-1.53 (m, 4H) 1.24-1.33 (m, 1H) 1.28 (d, *J* = 6.5 H, 3H) 0.91 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 101.5, 87.3, 75.2, 69.7, 69.6, 65.2, 56.2, 40.3, 30.6, 28.8, 21.9, 21.2, 18.5, 13.5; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 292.1889, found 292.1880.

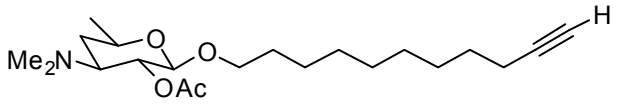


2-(Dec-3-ynyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, 3-decynol (9 mg, 0.057 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 2-(dec-3-ynyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (13 mg, 0.037 mmol, 65 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (dd, *J* = 10.5, 7.5 Hz, 1H) 4.36 (d, *J* = 7.5 Hz, 1H) 3.83-3.91 (m, 1H) 3.52-3.65 (m, 2H) 2.71-2.81 (m, 1H) 2.40 (m, 2H) 2.28 (s, 6H) 2.10-2.16 (m, 2H) 2.08 (s, 3H) 1.73-1.80 (m, 1H) 1.28-1.52 (m, 9H) 1.27 (d, *J* = 6.0 Hz, 3H) 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 102.2, 81.4, 76.1, 70.7, 69.3, 68.0, 63.0, 40.6, 31.3, 30.9, 28.9, 28.5, 22.5, 21.2, 21.1, 20.2, 18.7, 14.0; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 376.2464, found 376.2446.

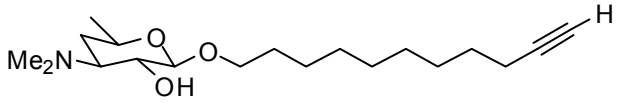


2-(Dec-3-ynyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (17). Following the general procedure, 2-(dec-3-ynyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (11 mg, 0.031 mmol), K_2CO_3 (20 mg, 0.14 mmol), and methanol were employed to afford 2-(dec-3-ynyloxy)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-ol (9 mg, 0.029 mmol, 94 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, *J* = 7.0 Hz, 1H) 3.95 (ddd, *J* = 9.5, 8.0, 6.5 Hz, 1H) 3.69 (ddd, *J* = 9.5, 8.5, 7.0 Hz, 1H) 3.57 (dqd, *J* = 12.5, 6.5, 2.0 Hz, 1H) 3.30 (dd, *J* = 10.0, 7.5 Hz, 1H) 2.51-2.62 (m, 3H) 2.34 (s, 6H) 2.13 (tt, *J* = 7.0, 2.5 Hz, 2H) 1.73 (ddd, *J* = 13.0, 3.5, 2.0 Hz, 1H) 1.43-1.51 (m, 2H) 1.23-1.40 (m, 7H) 1.28 (d, *J* = 6.0 Hz, 3H) 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.0, 81.7, 76.1, 69.9, 69.6,

68.2, 65.1, 40.3, 31.3, 28.9, 28.5, 22.5, 21.2, 20.2, 18.7, 14.0; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 312.2539 found 312.2534.

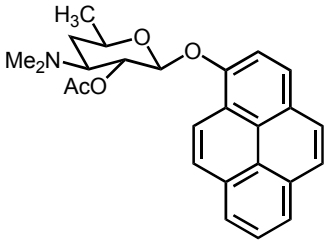


4-(Dimethylamino)-6-methyl-2-(undec-10-ynyloxy)tetrahydro-2*H*-pyran-3-yl acetate. Following the general procedure, 10-undecynol (10 mg, 0.057 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 4-(dimethylamino)-6-methyl-2-(undec-10-ynyloxy)tetrahydro-2*H*-pyran-3-yl acetate (11 mg, 0.03 mmol, 52 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (dd, *J* = 10.5, 7.5 Hz, 1H) 4.30 (d, *J* = 7.5 Hz, 1H) 3.84 (dt, *J* = 9.5, 6.5 Hz, 1H) 3.56 (dqd, *J* = 12.5, 6.0, 2.0 Hz, 1H) 3.43 (dt, *J* = 9.5, 7.0 Hz, 1H)2.73-2.81 (m, 1H) 2.29 (s, 6H) 2.19 (dt, *J* = 7.5, 2.5 Hz, 2H) 2.08 (s, 3H) 1.94 (t, *J* = 2.5 Hz, 1H) 1.73-1.80 (m, 1H) 1.49-1.62 (m, 4H) 1.26-1.42 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 102.2, 70.9, 69.4, 69.2, 68.0, 66.8, 63.0, 40.6, 30.9, 29.5, 29.4, 29.3, 29.0, 28.7, 28.4, 25.8, 21.3, 21.1, 18.3; HRMS (ESI MS) *m/z* calculated for $[M+H]^+$ 368.2801 found 368.2784.

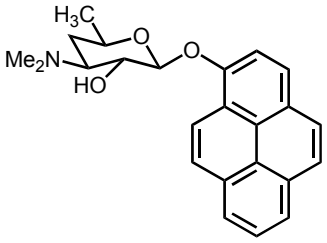


4-(Dimethylamino)-6-methyl-2-(undec-10-ynyloxy)-tetrahydro-2*H*-pyran-3-ol (18). Following the general procedure, 4-(dimethylamino)-6-methyl-2-(undec-10-ynyloxy)tetrahydro-2*H*-pyran-3-yl acetate (7 mg, 0.019mmol), K_2CO_3 (12 mg, 0.09 mmol), and methanol were employed to afford 4-(dimethylamino)-6-methyl-2-(undec-10-ynyloxy)-tetrahydro-2*H*-pyran-3-ol (6 mg, 0.018 mmol, 95 % yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.26, (d, *J* = 7.5 Hz, 1H) 3.89 (dt, *J* = 9.0, 7.0 Hz, 1H) 3.51-3.61 (m, 2H) 3.31 (dd, *J* = 10.5, 7.5 Hz, 1H) 2.61 (ddd, *J* = 12.0, 10.0, 4.0 Hz, 1H) 2.34 (s, 6H) 2.19 (dt, *J* = 7.0, 2.5 Hz, 2H) 1.95 (t, *J* = 2.5 Hz, 1H) 1.76 (ddd, *J* = 13.0, 4.0, 2.0 Hz, 1H) 1.66 (quint, *J* = 7.0 Hz, 2H) 1.52 (quint, *J* = 7.0 Hz, 2H) 1.26-1.42 (m, 12H) 1.28

(d, J = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 103.9, 69.9, 69.7, 69.4, 68.0, 65.2, 40.3, 29.7, 29.3, 29.0, 28.7, 28.4, 25.9, 21.2, 19.1, 18.3; HRMS (ESI MS) *m/z* calculated for $[M+H]^+$ 326.2695 found 326.2687.



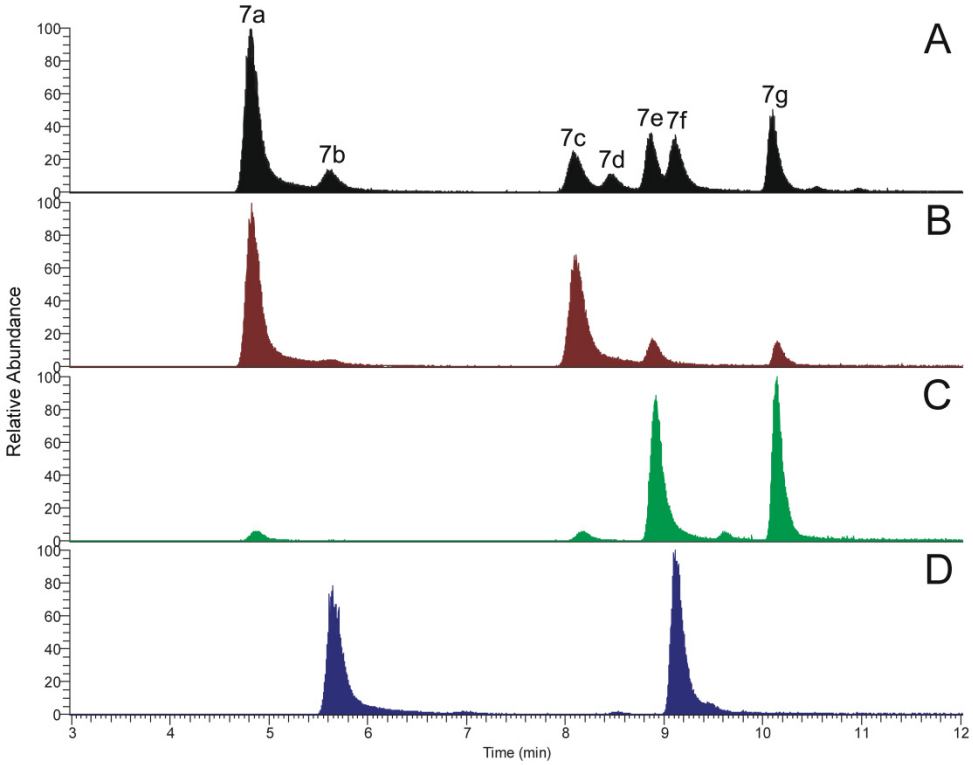
4-(Dimethylamino)-6-methyl-2-(pyren-1-yloxy)tetrahydro-2H-pyran-3-yl acetate. Following the general procedure, 1-hydroxypyrene (20 mg, 0.091 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (25 mg, 0.114 mmol), molecular sieves (200 mg) and BF_3•OEt_2 (25 μL, 0.25 mmol) were employed to obtain 4-(dimethylamino)-6-methyl-2-(pyren-1-yloxy)tetrahydro-2H-pyran-3-yl acetate (23 mg, 0.055 mmol, 61 %) after column chromatography (SiO_2, ethyl acetate) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 9.2 H, 1H) 7.99-8.11 (m, 4H) 7.88-7.96 (m, 3H) 7.69 (d, J = 8.4 Hz, 1H) 5.39 (dd, J = 10.4, 8.0 Hz, 1H) 5.19 (d, J = 7.6 Hz, 1H) 3.82 (dqd, J = 12.0, 6.0, 1.6 Hz, 1H) 2.91 (ddd, J = 12.0, 10.8, 4.4 Hz, 1H) 2.35 (s, 6H) 2.03 (s, 3H) 1.86 (ddd, J = 13.2, 4.4, 1.6 Hz, 1H) 1.55 (q, J = 12.4 H, 1H) 1.37 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 151.4, 131.4, 127.0, 126.9, 126.5, 126.1, 125.6, 125.5, 125.2, 124.6, 124.5, 124.4, 121.0, 112.2, 101.7, 70.6, 69.8, 62.9, 40.7, 30.8, 21.3, 21.2; HRMS (ESI MS) *m/z* calculated for $[M+H]^+$ 418.2018 found 418.2008.



4-(Dimethyl amino)-6-methyl-2-(pyren-1-yloxy)tetrahydro-2*H*-pyran-3-ol (19). Following the general procedure, 4-(dimethyl amino)-6-methyl-2-(pyren-1-yloxy)tetrahydro-2H-pyran-3-yl acetate (23 mg, 0.055 mmol), K_2CO_3 (30 mg, 0.22 mmol), and methanol were employed to afford 4-(dimethyl amino)-6-methyl-2-(pyren-1-

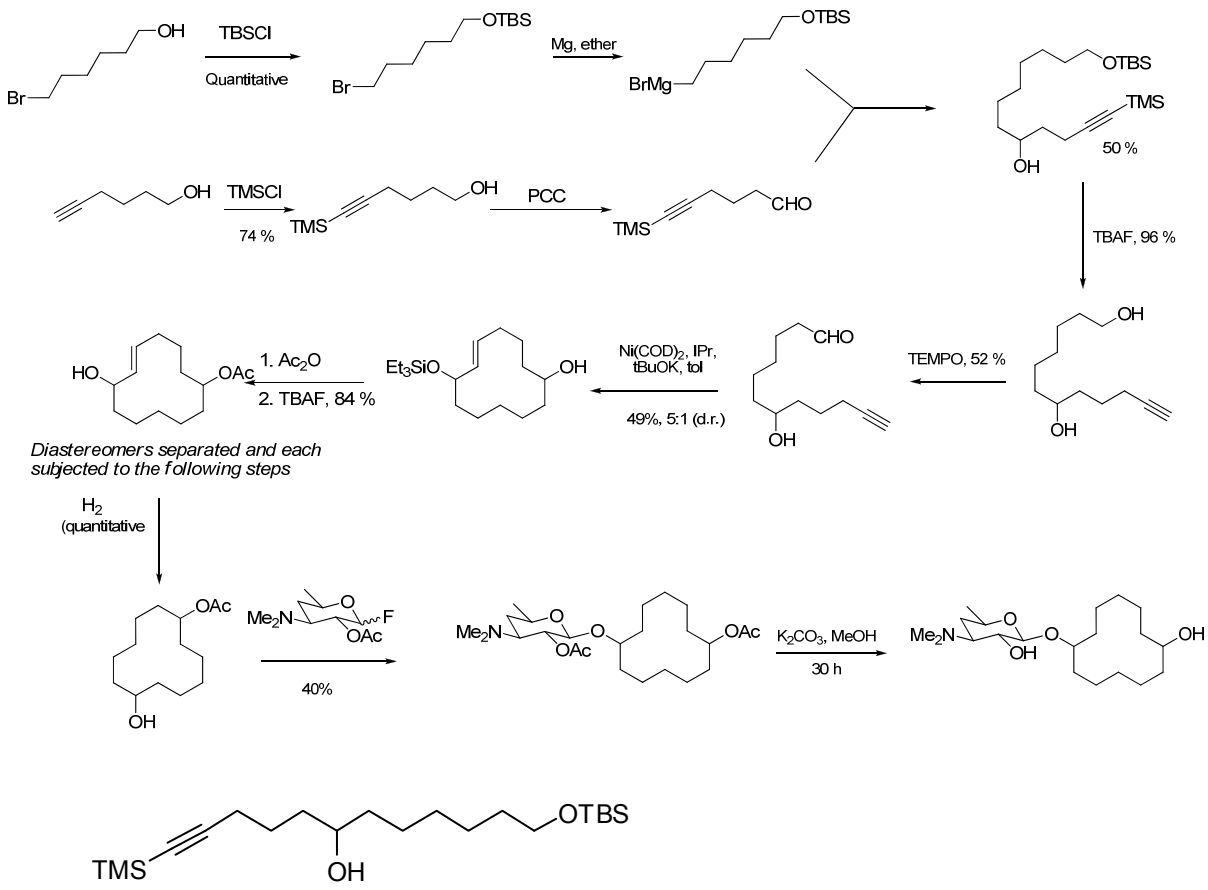
yloxy)tetrahydro-2*H*-pyran-3-ol (14 mg, 0.037 mmol, 68 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 9.2 Hz, 1H) 8.00-8.14 (m, 4H) 7.88- 7.99 (m, 3H) 7.76 (d, *J* = 8.4 Hz, 1H) 5.14 (d, *J* = 7.2 Hz, 1H) 3.80 (dd, *J* = 10.4, 7.6 Hz, 1H) 3.72 (dqd, *J* = 12.4, 10.0, 1.6 Hz, 1H) 3.59 (br s, 1H) 2.71 (ddd, *J* = 12.4, 10.4, 4.0 Hz, 1H) 2.38 (s, 6H) 1.78 (ddd, *J* = 12.8, 4.0, 2.0 Hz, 1H) 1.42 (q, *J* = 12.4 Hz, 1H) 1.31 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 151.3, 131.5, 131.4, 127.0, 126.7, 126.0, 125.6, 125.2, 124.7, 124.5, 124.4, 121.7, 121.6, 113.8, 103.7, 70.1, 69.8, 65.5, 40.3, 28.6, 21.3; HRMS (ESI MS) *m/z* calculated for $[M+H]^+$ 376.1913 found 376.1907.

Characterization of the products of oxidations of compound 6.

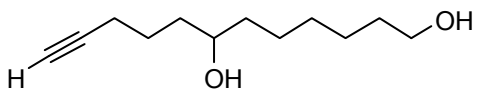


LCMS trace A refers to pikC oxidation reactions, traces B-D refer to synthetic samples described below. See other supporting information document for LCMS details.

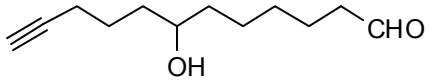
Synthesis of C-7 authentic hydroxylated products in 12-membered ring series:



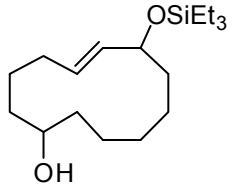
12-(*tert*-Butyldimethylsilyloxy)-1-trimethylsilyl)dodec-1-yn-6-ol. Magnesium turnings (25 mg, 1.04 mmol) were added to an ether solution of (6-bromohexyloxy)(*t*-butyl)dimethylsilane (200 mg, 1.02 mmol, Aldrich) in an oven dried flask and stirred for 2 h. An ether solution (5 mL) of 6-(trimethylsilyl)hex-5-ynal[viii] (160 mg, 0.952 mmol), was added to the reaction mixture at 0 °C and stirred for 2 h. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The combined organic layers were concentrated to afford the alcohol 12-(*tert*-butyldimethylsilyloxy)-1-trimethylsilyl)dodec-1-yn-6-ol (216 mg, 0.562 mmol, 59 %) as a white solid after column chromatography (SiO_2, 1:5 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66-3.60 (m, 1H) 3.60 (t, *J* = 6.5Hz, 2H) 2.25 (t, *J* = 7.0 Hz, 2H) 1.25-1.65 (m, 14H), 0.90 (s, 9H), 0.15 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.3, 84.7, 71.3, 63.2, 37.4, 36.4, 32.8, 29.4, 25.9, 25.8, 25.7, 25.6, 24.6, 19.8, 18.3, 0.1, -5.2.



Dodec-11-yne-1,7-diol. A 1.0 M *n*-Bu_4NF solution (0.70 ml, 0.70 mmol) in THF was added to a solution of (*E*)-cyclotetradec-2-enol-12-(*tert*-butyldimethylsilyloxy)-1-trimethylsilyl)dodec-1-yn-6-ol (66 mg, 0.17 mmol) in 4 mL THF and stirred for 1.5 h at rt. The reaction mixture was concentrated and purified by column chromatography (SiO2, 1:5 EtOAc, hexanes) to afford dodec-11-yne-1,7-diol (29 mg, 0.146 mmol, 86 %) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.59-3.65 (m, 3H) 2.22 (dt, *J* = 6.5, 2.5 Hz, 2H) 1.96 (t, *J* = 2.5 Hz, 1H) 1.30-1.74 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.4, 71.3, 68.5, 62.8, 37.4, 36.3, 32.6, 29.3, 25.6, 25.5, 24.5, 18.4.

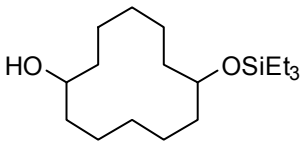


7-Hydroxydodec-11-ynal. To the stirring solution of dodec-11-yne-1,7-diol (40 mg, 0.20 mmol), a solution of TEMPO (3 mg, 0.02 mmol) and tetrabutylammonium chloride (5 mg, 0.02 mmol) in 2 mL CH_2Cl_2 was added. An aqueous solution (2 mL) of K_2CO_3 (0.05 M) and Na_2CO_3 (0.5 M) was added to the solution followed by the addition of *N*-chlorosuccinamide (40 mg, 0.3 mmol) and stirred for 3 h. The organic layer was separated and the aqueous layer was extracted twice with 10 mL CH_2Cl_2. The combined organic layers were dried with magnesium sulfate, filtered, concentrated, and purified by column chromatography (SiO_2, 1:3 ethyl acetate/hexanes) to afford 7-hydroxydodec-11-ynal (30 mg, 0.12 mmol, 76% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H) 3.53-3.61 (m, 1H) 2.39 (dt, *J* = 7.2, 1.6 Hz, 2H) 2.18 (dt, *J* = 6.4, 2.8 Hz, 2H) 1.91 (t, *J* = 2.8 Hz, 1H) 1.27-1.70 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 84.2, 71.2, 68.4, 43.7, 37.2, 36.3, 29.0, 25.3, 24.5, 21.9, 18.3.

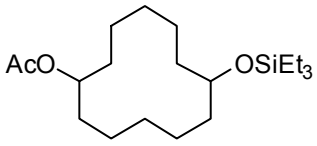


(*E*)-7-Triethylsilyloxy)cyclododec-5-enol. Toluene (10 mL) was injected to a mixture of $Ni(cod)_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and potassium

tert-butoxide (4 mg, 0.03 mmol) at rt and was stirred for 10 min. An additional 20 mL toluene and triethylsilane (0.10 ml, 0.30 mmol) were added, followed by syringe drive addition of a 10 mL toluene solution of 7-hydroxydodec-11-ynal (30 mg, 0.15 mmol) over 2 h. The reaction mixture was then stirred in air for 1 h, concentrated, and purified by column chromatography (SiO_2, 1:20 EtOAc : hexanes) to afford (*E*)-7-triethysiloxy)cyclododec-5-enol (10 mg, 0.032 mol, 21 %) as a white solid (1:1 mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (ddd, *J* = 14.8, 8.4, 6.4 Hz, 0.5H) 5.28-5.42 (m, 1.5H) 4.05 (dt, *J* = 8.8, 4.4 Hz, 0.5H) 3.95 (ddd, *J* = 10.4, 6.8, 3.6 Hz, 0.5H) 3.76- 3.85 (m, 0.5H) 3.67- 3.76 (m, 0.5H) 1.90- 2.27 (m, 2H) 1.02-1.74 (m, 14H) 0.85-0.93 (m, 9H) 0.48-0.58 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 134.6, 131.0, 130.5, 74.7, 73.2, 69.4, 67.9, 35.9, 34.9, 33.5, 33.4, 33.1, 31.9, 30.3, 26.1, 24.6, 24.4, 23.0, 22.2, 22.1, 22.0, 6.7, 4.8.



7-(Triethylsilyloxy)cyclododecanol. Following the procedure used to synthesize cyclotetradecanol, (*E*)-7-triethysiloxy)cyclododec-5-enol (10 mg, 0.032 mmol) PtO_2 (3 mg, 0.013 mol) and hydrogen gas were employed to afford 7-(triethylsilyloxy)cyclododecanol (9 mg, 0.028 mmol, 90 %) as a white solid (1:1 mixture of diastereomers). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51-3.75 (m, 2H) 1.20-1.54 (m, 21 H) 0.95 (t, *J* = 8.1 Hz, 9H) 0.58 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.9, 69.2, 69.0, 32.6, 32.3, 31.3, 30.7, 26.0, 24.4, 20.9, 20.8, 19.1, 18.9, 6.9, 4.9, 4.8.



7-(Triethylsilyloxy)cyclododecyl acetate. To the solution of 7-(triethylsilyloxy)cyclododecanol (30 mg, 0.095 mmol) in 5 mL CH_2Cl_2, K_2CO_3 (20 mg) and 4-dimethylamino pyridine (2 mg) were added and stirred for 10 min. The reaction mixture was cooled to 0 ^{o}C and Ac_2O (100 μL, 1.05 mmol) was added and stirred for 2 h.

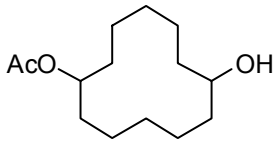
The reaction mixture was passed through a small plug of silica gel and washed with dichloromethane to afford 7-(triethylsilyloxy)cyclododecyl acetate as a 1:1 mixture of diastereomers. The diastereomers were then separated by column chromatography (SiO_2, 1:15 ethyl acetate/hexanes). Relative stereochemistry of the two diastereomers was not determined.

Diastereomer A:

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94-5.00 (m, 1H) 3.80-3.86 (m, 1H) 2.02 (s, 3H) 1.30-1.75 (m, 20H) 0.97 (t, *J* = 8.0 Hz, 9H) 0.61 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 72.1, 69.4, 32.5, 28.8, 24.4, 20.7, 6.9, 4.9; LRMS (ESI) *m/z* calculated for $[M+Na]^+$ 379.3 found 379.3.

Diastereomer B:

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (tt, *J* = 8.0, 3.0 Hz, 1H) 3.80 (m, 1H) 2.02 (s, 3H) 1.65-1.74 (m, 2H) 1.30-1.63 (m, 18H) 0.96 (t, *J* = 8.0 Hz, 9H) 0.59 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 73.7, 70.9, 31.2, 27.3, 25.9, 21.3, 19.1, 19.0, 6.9, 4.8; LRMS (ESI) *m/z* calculated for $[M+Na]^+$ 379.3 found 379.3.



7-Hydroxycyclododecyl acetate.

Diastereomer A:

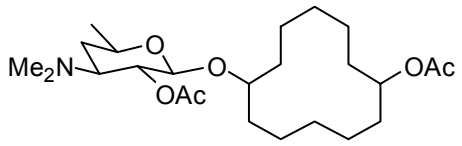
Following the procedure used to prepare dodec-11-yn-1,7-diol, 7-(triethylsilyloxy)cyclododecyl acetate (10 mg, 0.028 mmol) and 1 M *n*-Bu_4NF (0.12 ml, 0.12 mmol) were employed to afford 7-hydroxycyclododecyl acetate (6 mg, 0.025 mmol, 89%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95-5.01 (m, 1H) 3.90 (br s, 1H) 2.02 (s, 3H) 1.65-1.75 (m, 4H) 1.20-1.54 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 71.6, 68.7, 32.4, 29.1, 24.0, 21.3, 21.0, 20.9, 18.6 (carbonyl signal not detected).

Diastereomer B :

Following the procedure used to prepare (*E*)-cyclotetradec-2-enol, 7-(triethylsilyloxy)cyclododecyl acetate (10 mg, 0.028 mmol) and 1 M *n*-Bu_4NF (0.12 ml, 0.12 mmol) were employed to afford 7-hydroxycyclododecyl acetate (6 mg, 0.025 mmol, 89%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90 (tt, *J* = 8.0, 3.0 Hz, 1H) 3.83-

3.89 (m, 1H) 2.02 (s, 3H) 1.20-1.78 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 73.5, 70.8, 30.8, 27.4, 25.8, 21.3, 19.1, 18.9; LRMS (CI, NH_3) calc'd for $[M+NH_4]^+$ 260.2, found 260.3.

7-((2S,3R,4S,6R)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yloxy)cyclododecyl acetate.

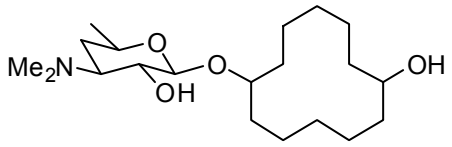


Diastereomer A:

Following the general procedure, 7-hydroxycyclododecyl acetate (6 mg, 0.025 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (11 mg, 0.05 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (10 μL, 0.10 mmol) were employed to obtain the glycoside 7-((2S,3R,4S,6R)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-2-yloxy)cyclododecyl acetate (8 mg, 0.018 mmol, 72 %) after column chromatography (SiO_2, ethyl acetate) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96-5.02 (m, 1H) 4.81 (dd, *J* = 10.5, 7.5 Hz, 1H) 4.35 (d, *J* = 8.0, 1H) 3.68-3.75 (m, 1H) 3.57 (dqd, *J* = 12.5, 6.0, 1.5 Hz, 1H) 2.76 (ddd, *J* = 12.0, 11.0, 4.0 Hz, 1H) 2.28 (s, 6H) 2.07 (s, 3H) 2.03 (s, 3H) 1.3-1.8 (m, 22H) 1.27 (d, *J* = 6.0 Hz, 3H).

Diastereomer B:

Following the general procedure, 7-hydroxycyclododecyl acetate (6 mg, 0.025 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (11 mg, 0.05 mmol), molecular sieves (100 mg) and $BF_3.OEt_2$ (10 μL, 0.10 mmol) were employed to obtain the glycoside (7 mg, 0.016 mmol, 64%) after column chromatography (SiO_2, ethyl acetate) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (tt, *J* = 8.0, 3.0 Hz, 1H) 4.81 (dd, *J* = 10.5, 8.0 Hz, 1H) 4.37 (d, *J* = 7.5 Hz, 1H) 3.73-3.79 (m, 1H) 3.54 (dqd, *J* = 12.5, 6.0, 2.0 Hz, 1H) 2.76 (ddd, *J* =12.5, 11.0, 4.5 Hz, 1H) 2.28 (s, 6H) 2.06 (s, 3H) 2.02 (s, 3H) 1.30-1.77 (m, 22H) 1.27 (d, *J* = 6.0, 3H); LRMS (ESI) *m/z* calculated for $[M+H]^+$ 442.2 found 442.3.



4-(Dimethylamino)-2-(7-hydroxycyclododecyloxy)-6-methyltetrahydro-2H-pyran-3-ol (diastereomers 7b and 7f in LCMS trace A, synthetic sample shown as trace D, see p. 16).

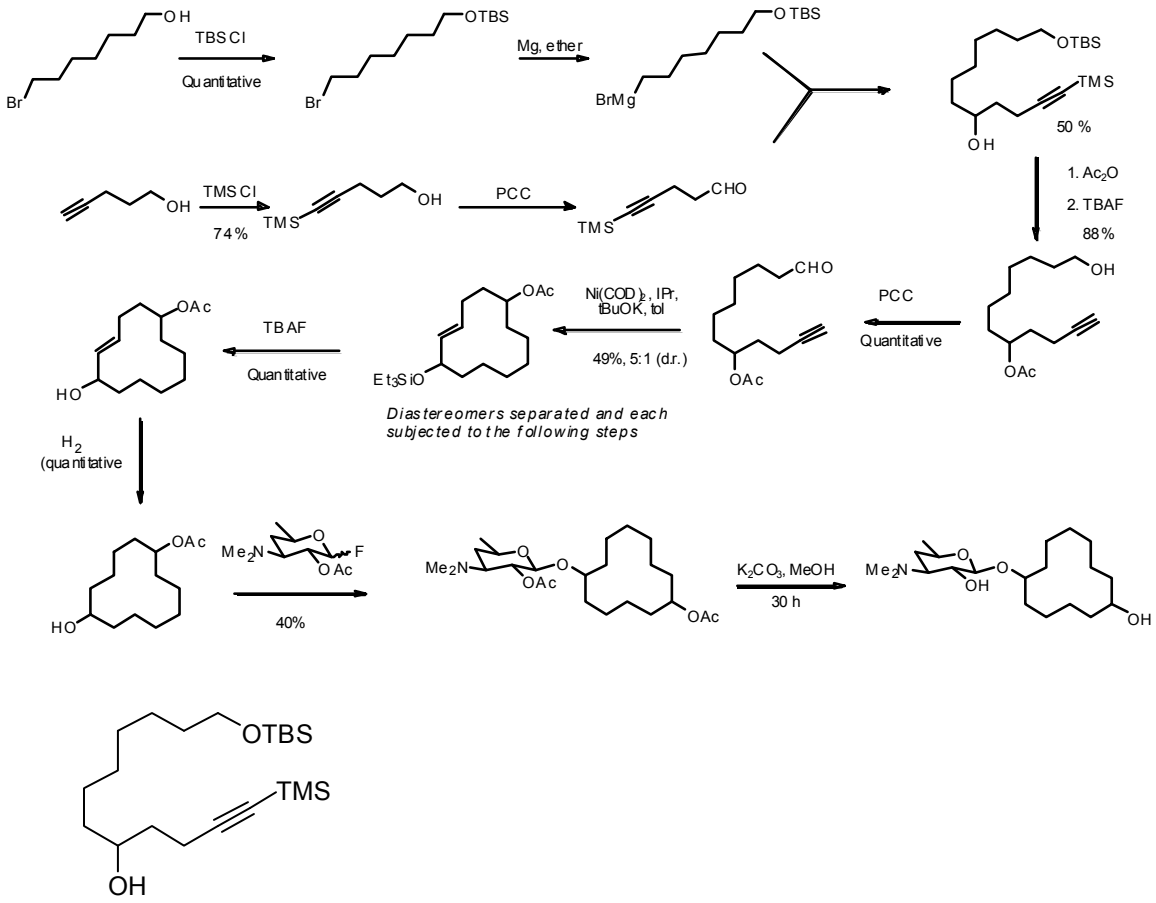
Diastereomer A:

Following the general procedure, diastereomer A of 7-((2*S*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclododecyl acetate (3 mg, 0.007 mmol), K_2CO_3 (10 mg, 0.072 mmol), and methanol were employed to afford diastereomer A of the product (2 mg, 0.056 mmol, 93% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (d, *J* = 7.5 Hz, 1H) 3.78-3.86 (m, 2H) 3.57 (dqd, *J* = 12.5, 6.5, 2.0 Hz, 1H) 3.31 (dd, *J* = 10.0, 7.0 Hz, 1H) 2.62-2.72 (m, 1H) 2.38 (s, 6H) 1.20-1.82 (m, 25H); LRMS (ESI) *m/z* calculated for $[M+H]^+$ 358.3 found 358.3.

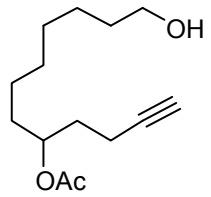
Diastereomer B:

Following the general procedure, diastereomer B of 7-((2*S*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclododecyl acetate (3 mg, 0.007 mmol), K_2CO_3 (10 mg, 0.072 mmol), and methanol were employed to afford diastereomer B of the product (2 mg, 0.056 mmol, 93% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (d, *J* = 7.5 Hz, 1H) 3.83-3.91 (m, 2H) 3.56 (dqd, *J* = 12.5, 6.0, 2.0 Hz, 1H) 3.30 (dd, *J* = 10.0, 7.5 Hz, 1H) 2.60-2.66 (m, 1H) 2.34 (s, 6H) 1.30-1.78 (m, 22H) 1.28(d, *J* = 6.0 H, 3H); LRMS (ESI) *m/z* calculated for $[M+H]^+$ 358.3 found 358.3.

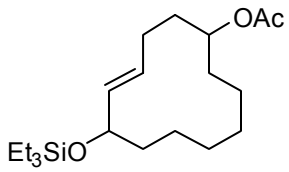
Synthesis of C-6/C-8 hydroxylated authentic compounds in 12-membered ring series.



12-(*tert*-Butyldimethylsiloxy)-1-(trimethylsilyl)dodec-1-yn-5-ol. Following the procedure used to synthesize 12-(*tert*-butyldimethylsilyloxy)-1-trimethylsilyl)dodec-1-yn-6-ol, (7-bromoheptyloxy)(*tert*-butyl)dimethylsilane[ix] (600 mg, 1.94 mmol), 5-(trimethylsilyl)pent-4-ynal[x] (369 mg, 2.39 mmol) and magnesium (48 mg, 2.00 mmol) were employed to afford 12-(tert-butyldimethylsiloxy)-1-(trimethylsilyl)dodec-1-yn-5-ol (200 mg. 0.78 mmol, 40 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (br s, 1H) 3.54 (t, J = 6.4 Hz, 1H) 2.31 (t, J = 7.2 Hz, 2H) 1.77 (br s, 1H) 1.36-1.68 (m, 14H) 0.84 (s, 9H) 0.09 (m, 9H) 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.0, 58.2, 71.1, 63.2, 37.2, 35.6, 32.8, 29.5, 29.3, 25.9, 25.7, 25.4, 18.3, 16.5, 0.0, -5.3.



12-Hydroxydodec-1-yn-5-yl acetate. Following the procedure used to prepare dodec-11-yn-1,7-diol, 12-(*tert*-butyldimethylsiloxy)-1-(trimethylsilyl)dodec-1-yn-5-yl acetate (180 mg, 0.42 mol) and 1 M *n*-Bu_4NF (2 mL, 2.00 mmol) were employed to afford 12-hydroxydodec-1-yn-5-yl acetate (70 mg, 0.29 mmol, 69%) as white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.90-4.97 (m, 1H) 3.60 (t, *J* = 6.5 Hz, 2H) 2.16-2.23 (m, 2H) 2.03 (s, 3H) 1.94 (t, *J* = 2.5 Hz, 1.22-1.80 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 83.4, 73.1, 68.6, 62.8, 33.8, 32.8, 32.6, 29.3, 29.2, 25.6, 25.0, 21.1, 14.7.



(E)-6-(Triethylsiloxy)cyclododec-4-enyl acetate. The above alcohol was oxidized by the same procedure described for 7-hydroxydodec-11-ynal and was directly used in the next transformation. Following the procedure used to synthesize (*E*)-(cyclotetradec-2-enyloxy)triethylsilane, $Ni(COD)_2$ (14 mg, 0.05 mmol), IPr·HCl (22 mg, 0.05 mmol), potassium tert-butoxide (6 mg, 0.05 mmol), triethylsilane (0.1 ml, 0.5 mmol) and 12-oxododec-1-yn-5-yl acetate (60 mg, 0.25 mmol) were employed to afford (*E*)-6-(triethylsiloxy)cyclododec-4-enyl acetate as 5:1 a mixture of diastereomers which were separated as diastereomer A (36 mg, 0.102 mol, 41%) and diastereomer B (7 mg, 0.020, 8%) as a colorless oil with column chromatography (SiO_2, 1:15 ethyl acetate/hexanes). The 1,6-stereochemical relationship of the diastereomers was not established.

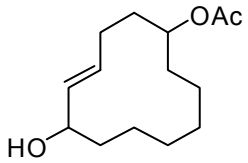
Diastereomer A (Major isomer)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (dt, *J* = 15.5, 7.0 Hz, 1H) 5.44 (dd, *J* = 15.5, 7.5 Hz, 1H) 4.86- 4.92 (m, 1H) 4.10 (dt, *J* = 8.0, 4.0 Hz, 1H) 2.20 (q, *J* = 7.0 Hz, 2H) 2.03 (s, 3H) 1.62-1.82 (m, 4H) 1.02-1.58 (m, 10H) 0.93 (t, *J* = 8.0 Hz, 9H) 0.57 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 134.6, 130.1, 74.4, 73.0, 35.6, 30.8, 28.6,

27.6, 25.5, 25.4, 22.0, 21.4, 21.0, 6.8, 4.8; LRMS (ESI) *m/z* calculated for $[M+Na]^+$ 377.2 found 377.3.

Diastereomer B (Minor isomer)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (ddd, *J* = 15.0, 9.5, 5.5 Hz, 1H) 5.42 (dd, *J* = 15.0, 8.0 Hz, 1H) 4.76-4.82 (m, 1H) 3.99-4.06 (m, 1H) 2.24-2.32 (m, 1H) 2.05 (s, 3H) 1.20-80 (m, 15H) 0.94 (t, *J* = 8.0, 9H) 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.69, 134.4, 131.0, 74.4, 74.1, 35.8, 31.6, 30.5, 28.5, 25.1, 24.9, 21.4. 21.3, 21.0, 6.7, 4.8; LRMS (ESI) *m/z* calculated for $[M+Na]^+$ 377.2 found 377.2.



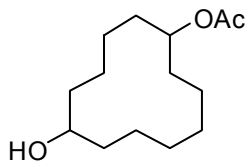
(*E*)-6-Hydroxycyclododec-4-enyl acetate.

Diastereomer A (Major isomer)

Following the procedure used to prepare (*E*)-cyclotetradec-2-enol, (*E*)-6-(triethylsiloxy)cyclododec-4-enyl acetate (36 mg, 0.102 mol) and *n*-Bu_4NF (0.30 ml, 0.30 mmol) were employed to afford (*E*)-6-hydroxycyclododec-4-enyl acetate (24 mg, 0.10 mmol, 98%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59 (dt, *J* = 15.2, 7.6 Hz, 1H) 5.42 (dd, *J* = 15.2, 8.0 Hz, 1H) 4.80-4.88 (m, 1H) 4.09 (dt, *J* = 8.4, 4.4 Hz, 1H) 2.13-2.20 (m, 2H) 1.97 (s, 3H) 1.0- 1.80 (m, 14H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 133.7, 131.9, 74.3, 72.9, 34.4, 30.5, 28.5, 27.5, 25.6, 25.4, 22.0, 21.3, 20.8; LRMS (CI, NH_3) M^+ calc'd for 240.2, found 240.2.

Diastereomer B (Minor isomer)

The identical procedure as described for diastereomer A was followed. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 15.5, 9.5, 5.5 Hz, 1H) 5.48 (dd, *J* = 15.0, 8.0 Hz, 1H) 4.76-4.81 (m, 1H) 4.07-4.13 (m, 1H) 2.27-2.34 (1H) 2.05-2.14 (m, 1H) 2.04 (s, 3H) 1.75-1.84 (m, 2H) 1.20-1.65 (m, 12H).



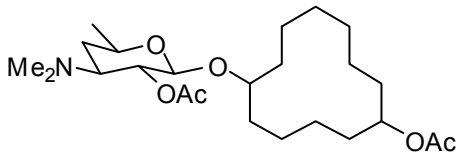
6-Hydroxycyclododecyl acetate.

Diastereomer A:

Following the procedure used to synthesize cyclotetradecanol, (*E*)-6-hydroxycyclododec-4-enyl acetate (24 mg, 0.10 mmol) PtO_2 (5 mg, 0.02 mol) and hydrogen gas were employed to afford 6-hydroxycyclododecyl acetate (20 mg, 0.083 mmol, 83%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94-5.04 (m, 1H) 3.81 (br s, 1H) 2.03 (s, 3H) 1.24-1.82 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 72.2, 69.4, 32.8, 31.0, 29.5, 27.8, 24.4, 24.3, 22.2, 22.0, 21.3, 19.6, 19.2; LRMS (ESI) *m/z* calculated for $[M+Na]^+$ 265.2 found 265.2.

Diastereomer B:

The identical procedure as described for diastereomer A was followed. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96-5.06 (m, 1H) 3.82- 3.90 (m, 1H) 2.03 (s, 3H) 1.20-1.76 (m, 20H).

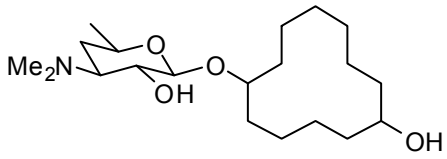


6-((2*S*,3*R*,4*S*,6*R*)-3-Acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclododecyl acetate.

Diastereomer A

Following the general procedure, 6-hydroxycyclododecyl acetate (7 mg, 0.029 mmol), 4-(dimethylamino)-2-fluoro-6-methyltetrahydro-2H-pyran-3-yl acetate (22 mg, 0.10 mmol), molecular sieves (100 mg) and BF_3•OEt_2 (20 μL, 0.20 mmol) were employed to obtain 6-((2*S*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclododecyl acetate (8 mg, 0.018 mmol, 62%) after column chromatography (SiO_2, ethyl acetate) as a white solid. Major isomer (obtained as a 1:1 mixture of two diastereomers): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95-5.01 (m, 1H) 4.78-

4.84 (m, 1H) 4.35 (d, *J* = 6.5 Hz, 0.5 H) 4.33 (d, *J* = 7.0 Hz, 0.5H) 3.65-3.75 (m, 1H) 3.50-3.59 (m, 1H) 2.72-2.80 (m, 1H) 2.28 (s, 6H) 2.07 (s, 2H) 2.06 (s, 2H) 1.24-1.89 (m, 22H) 1.22 (d, *J* = 6.0 Hz, 3H); HRMS (ESI) *m/z* calculated for $[M+H]^+$ 442.3169 found 442.3164. The same procedure was repeated for diastereomer B on 1-2 mg of material. The diastereomer B product (1:1 mixture of diastereomers) was not characterized and was carried through to the next step.



4-(Dimethylamino)-2-(6-hydroxycyclododecyloxy)-6-methyltetrahydro-2H-pyran-3-ol. The four diastereomers **7a**, **7c**, **7e**, and **7g** were obtained as one pair with the 1,6-trans relationship and one pair with the 1,6-cis relationship. The trans pair and cis pair were not stereochemically characterized, but all four compounds were distinguished by LCMS analysis.

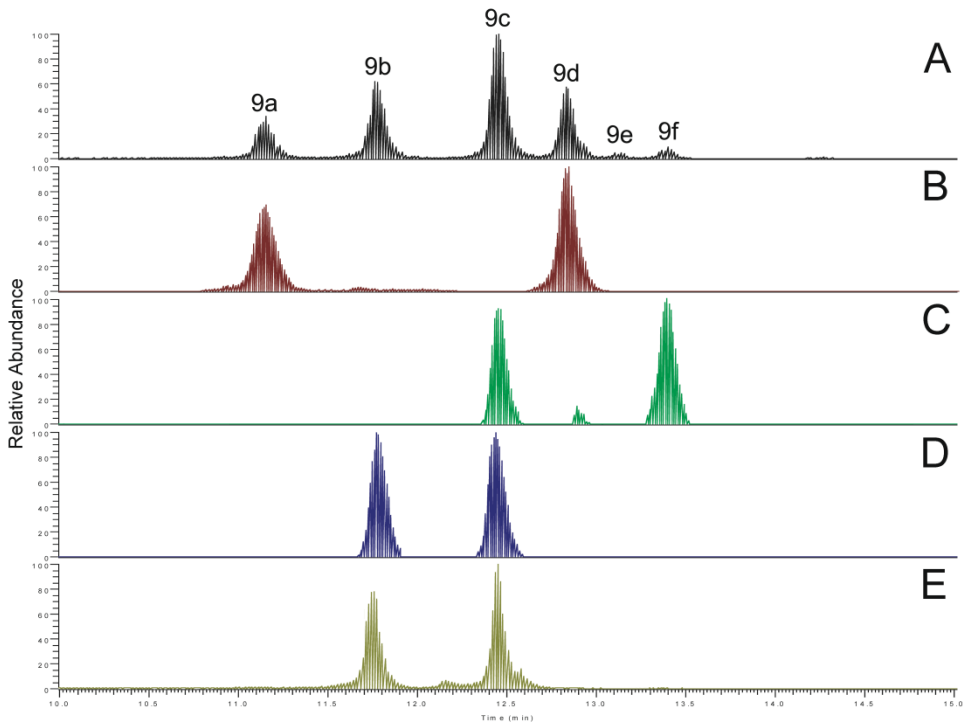
Diastereomers A (7a and 7c in LCMS trace A, synthetic sample shown as trace B, see p 16)

Following the general procedure, acetate 6-((2*S*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclododecyl acetate (3 mg, 0.007 mmol), K_2CO_3 (10 mg, 0.072 mmol), and methanol were employed to afford 4-(dimethylamino)-2-(6-hydroxycyclododecyloxy)-6-methyltetrahydro-2H-pyran-3-ol (2 mg, 0.0056 mmol, 80% yield) as a white solid. Major isomer (obtained as a 1:1 mixture of two diastereomers): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (d, *J* = 7.5 Hz, 0.5 H) 4.31 (d, *J* = 7.5 Hz, 0.5 H) 3.79-3.89 (m, 2H) 3.60-3.69 (m, 2H) 3.48-3.54 (m, 1H) 3.21 (br s, 1H) 2.81 (s, 6H) 2.46 (br s, 1H) 1.22-1.82 (m, 25H); HRMS (ESI MS) *m/z* calculated for $[M+H]^+$ 358.2957 found 358.2967.

Diastereomers B (7e and 7g in LCMS trace A, synthetic sample shown as trace C, see p 16)

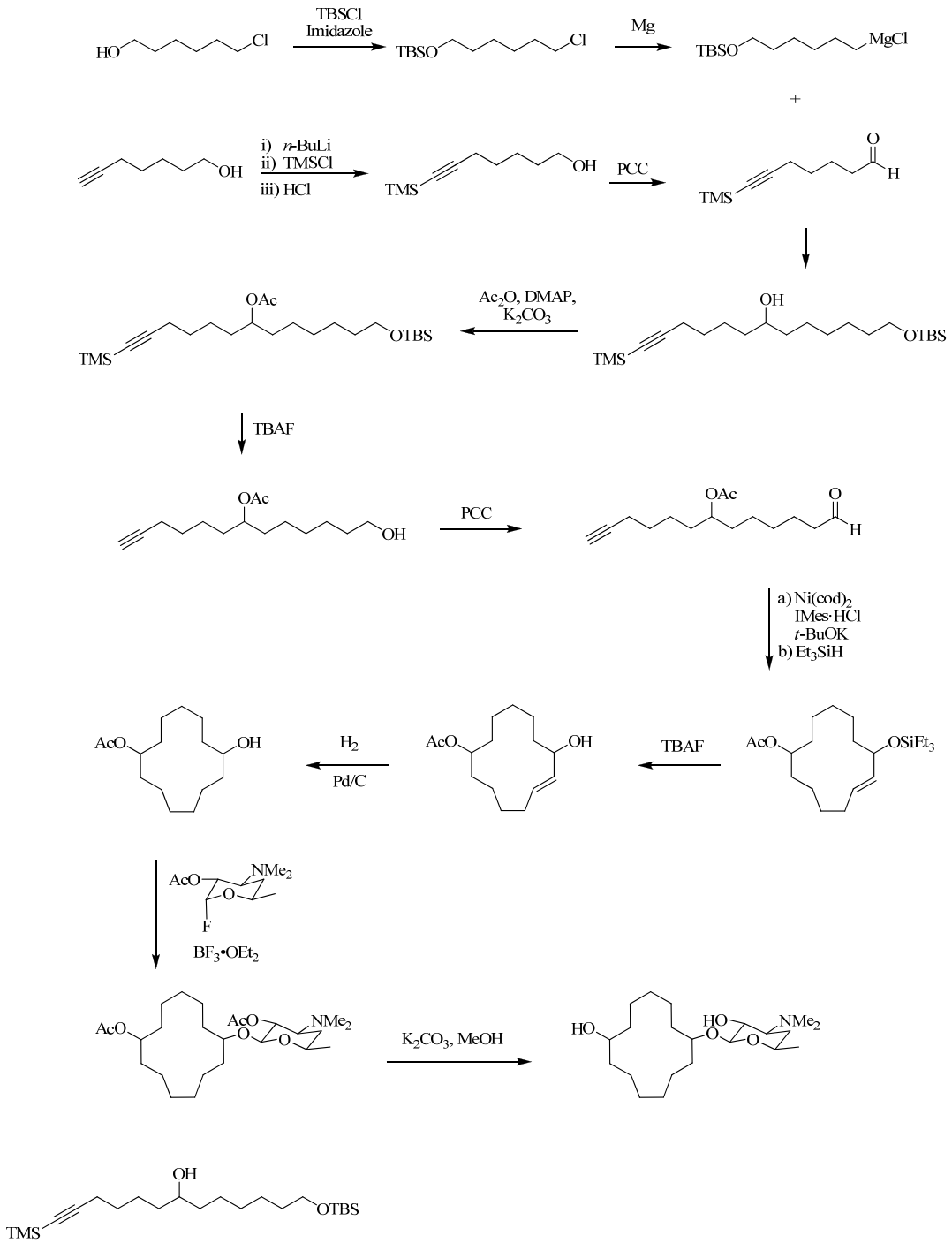
The same procedure was repeated for diastereomer B on 1-2 mg of material. The diastereomer B product (1:1 mixture of diastereomers) obtained in trace amount was only characterized by LCMS analysis.

Characterization of the products of oxidations of compound 8.



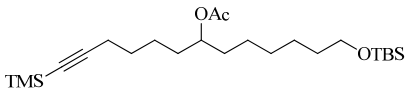
LCMS trace A refers to pikC oxidation reactions, traces B-E refer to synthetic samples described below. See other supporting information document for LCMS details.

Synthesis of C7/C8 authentic hydroxylated products in 13-membered ring series:

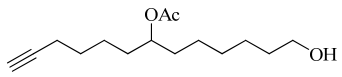


13-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-7-ol. Razor scraped Mg turnings (161 mg, 6.6 mmol) were added and a reflux condenser was attached. *tert*-

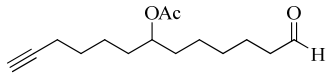
Butyl(6-chlorohexyloxy)dimethylsilane[xi] (553 mg, 2.2 mmol) was added as a solution in THF (2 mL). Several drops of 1,2-dibromoethane were added and the reaction mixture was heated to reflux for 1 h. Several more drops of 1,2-dibromoethane were added. 7-(Trimethylsilyl)-hept-6-ynal[xii,xiii,xiv] (268 mg, 1.5 mmol) was then added dropwise over 20 min to the refluxing mixture as a solution in THF (2 mL). This was allowed to reflux overnight and was then removed from heat. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. Flash column chromatography (5 % ethyl acetate/ hexanes) afforded 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-7-ol (245 mg, 42 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (t, J = 6.8 Hz, 3H), 2.20 (t, J = 6.8 Hz, 2H), 1.55-1.29 (m, 16H), 0.86 (s, 9H), 0.11 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.4, 84.5, 71.8, 63.2, 37.4, 36.9, 32.8, 29.5, 28.6, 26.0, 25.8, 25.6, 24.8, 19.8, 18.4, 0.2, -5.3 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 421.2934, found 421.2917.



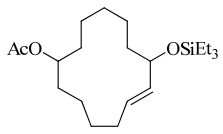
Following the procedure used to synthesize 7-(triethylsilyloxy)cyclododecyl acetate, 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-7-ol (200 mg, 0.50 mmol), K_2CO_3 (97 mg, 0.70 mmol), 4-dimethylamino pyridine (6 mg, 0.050 mmol), and acetic anhydride (0.5 mL, 5.0 mmol) were employed to obtain 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-7-yl acetate (203 mg, 92 %) as a clear oil after flash column chromatography (SiO_2, 5 % ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (quint, J = 6.1 Hz, 1H), 3.58 (t, J = 6.8 Hz, 2H), 2.21 (t, J = 7.2 Hz, 2H), 2.03 (s, 3H), 1.53-1.29 (m, 16H), 0.88 (s, 9H), 0.14 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 107.2, 84.6, 74.1, 63.2, 34.0, 33.5, 32.8, 29.3, 28.4, 25.8, 25.7, 25.3, 24.4, 21.3, 19.7, 18.4, 0.2, -5.3 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 463.3040, found 463.3042.



13-Hydroxytridec-1-yn-7-yl acetate. Following the procedure used to prepare dodecy-11-yne-1,7-diol, 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-7-yl acetate (190 mg, 0.43 mmol) and *n*-Bu_4NF (1 M in THF, 0.86 mL, 0.86 mmol) were employed to obtain 13-hydroxytridec-1-yn-7-yl acetate (109 mg, 99 %) after flash column chromatography (SiO_2, 30 % ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (quint, *J* = 6.1 Hz, 1H), 3.56 (t, *J* = 6.4 Hz, 2H), 2.13 (dt, *J* = 6.8, 3.5 Hz, 2H), 1.99 (s, 3H), 1.90 (t, *J* = 3.5, 1H), 1.53-1.20 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 84.2, 74.0, 68.3, 62.7, 33.9, 33.5, 32.6, 29.2, 28.2, 25.6, 25.2, 24.3, 21.2, 18.2 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 277.1780, found 277.1776.



13-Oxotridec-1-yn-7-yl acetate. To a stirring solution of 13-hydroxytridec-1-yn-7-yl acetate (100 mg, 0.39 mmol) in CH_2Cl_2 (3 mL) was added PCC (170 mg, 0.78 mmol). The reaction was allowed to stir for 4 h and was then filtered through a plug of silica gel to afford 13-oxotridec-1-yn-7-yl acetate (81 mg, 82 %) after flash column chromatography (SiO_2, 25 % ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.6 Hz, 1H), 4.84 (quint, *J* = 5.6 Hz, 1H), 2.40 (d.t., *J* = 7.3, 1.7 Hz, 2H), 2.156 (d.t., *J* = 7.0, 2.5 Hz, 2H), 2.02 (s, 3H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.63-1.24 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 170.8, 84.1, 73.7, 68.3, 42.7, 33.7, 33.4, 28.9, 28.1, 25.0, 24.2, 21.8, 21.1, 18.2 ppm.



8-(Triethylsilyloxy)cyclotridec-6-enyl acetate. A flame dried round bottom flask was charged with $Ni(cod)_2$ (5 mg, 0.018 mmol), IMes·HCl (6 mg, 0.018 mmol), and *t*-BuOK

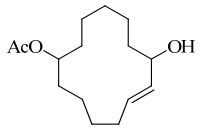
(2 mg, 0.018 mmol) in the glove box. To this was added THF (5 mL) and the catalyst was allowed to form for 10 min. The catalyst system was then diluted with THF (10 mL) and a solution of 13-oxotridec-1-yn-7-yl acetate (46 mg, 0.18 mmol) and Et_3SiH (58 μL, 0.36 mmol) in THF (15 mL) was added over 2 h via syringe pump. Another flask was charged with $Ni(cod)_2$ (5 mg, 0.018 mmol), IMes·HCl (6 mg, 0.018 mmol), and *t*-BuOK (2 mg, 0.018 mmol), THF (3 mL) was added, and the catalyst was allowed to form over 10 min. This second batch of catalyst was added dropwise to the first flask after addition of the ynal had completed. The reaction was stirred for 1 h, then opened to air and stirred for 30 min. The reaction mixture was poured through a plug column and then purified via flash column chromatography (SiO_2, 1.5 % ethyl acetate/ hexanes) to afford 8-(triethylsilyloxy)cyclotridec-6-enyl acetate as a 1:1 mixture of diastereomer A (16 mg, 24 %) and diastereomer B (15 mg, 22 %), both as colorless oils.

Diastereomer A

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.44 (ddd, *J* = 15.2, 9.2, 4.0 Hz, 1H), 5.35 (dd, *J* = 15.2, 7.6 Hz, 1H), 4.70 (dq, *J* = 5.2, 8.0 Hz, 1H), 4.06 (dt, *J* = 3.6, 8.4 Hz, 1H), 2.22 (m, 1H), 2.01 (s, 3H), 1.89 (m, 1H), 1.66-1.07 (m, 16H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 7.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.7, 131.6, 73.4, 73.0, 37.1, 31.7, 31.0, 30.0, 26.5, 25.6, 22.2, 22.2, 21.9, 21.4, 6.8, 4.9 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 391.2644, found 391.2635.

Diastereomer B

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (td, *J* = 15.6, 6.8 Hz, 1H), 5.39 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.79 (dq *J* = 6.4, 4.8 Hz, 1H), 4.00 (ddd, *J* = 9.4, 7.0, 2.8 Hz, 1H), 2.08 (q, *J* = 6.1 Hz, 2H), 2.00 (s, 3H), 1.70-1.07 (m, 16H), 0.93 (t, *J* = 11.8 Hz, 9H), 0.57 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 135.5, 130.3, 73.6, 73.5, 37.6, 30.8, 30.4, 29.9, 27.4, 27.0, 22.0, 21.5, 21.4, 21.1, 6.8, 4.9 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 391.2644, found 391.2644.



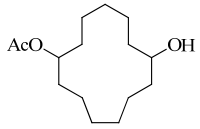
8-Hydroxycyclohex-6-enyl acetate.

Diastereomer A

Following the procedure to make dodec-11-yne-1,7-diol, 8-(triethylsilyloxy)cyclotridec-6-enyl acetate (24 mg, 0.065 mmol) and *n*-Bu_4NF (1 M, 0.1 mL, 0.098 mmol) afforded 8-hydroxycyclohex-6-enyl acetate (15 mg, 91 %) as a colorless oil after purification by flash column chromatography (SiO_2, 15 % ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.57 (ddd; *J* = 15.6, 9.6, 4.4 Hz, 1H), 5.40 (ddd, *J* = 13.6, 10.0, 1.2 Hz, 1H), 4.70 (sextet, *J* = 4.4 Hz, 1H), 4.11 (d.t., *J* = 3.6, 9.2 Hz, 1H), 2.25 (m, 1H), 2.01 (s, 3H), 1.92 (m, 1H), 1.77-0.69 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.1, 133.5, 73.2, 72.9, 35.6, 31.7, 31.1, 30.0, 26.3, 25.4, 22.5, 22.2, 22.0, 21.4.

Diastereomer B

Following the procedure to make dodec-11-yne-1,7-diol, 8-(triethylsilyloxy)cyclotridec-6-enyl acetate (23 mg, 0.061 mmol) and *n*-Bu_4NF (1 M, 0.1 mL, 0.092 mmol) afforded 8-hydroxycyclohex-6-enyl acetate (8 mg, 51 %) as a colorless oil after purification by flash column chromatography (SiO_2, 15% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (d.t., *J* = 15.6, 7.6 Hz, 1H), 5.44 (d.d., *J* = 15.2, 7.6 Hz, 1H), 4.79 (quint, *J* = 5.6 Hz, 1H), 4.04 (d.t., *J* = 10.0, 3.2 Hz, 1H), 2.12 (q, *J* = 6.4 Hz, 2H), 2.01 (s, 3H), 1.77 (m, 1H), 1.63-0.69 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 134.8, 132.3, 73.5, 73.3, 36.2, 30.8, 30.4, 30.0, 27.2, 27.1, 22.3, 21.8, 21.4, 21.0.



7-Hydroxycyclotridecyl acetate.

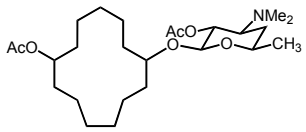
Diastereomer A

To a solution of 8-hydroxycyclohex-6-enyl acetate (15 mg, 0.059 mmol) in methanol (10 mL) was added 10 % Pd/C (5 mg). The system was purged with a H_2 balloon for 20 min.

The balloon was then refilled and the reaction was allowed to react at rt under a H_2 atmosphere overnight. The reaction mixture was run through a plug of silica gel and flushed with 1:1 ethyl acetate: hexanes to afford 7-hydroxycyclotridecyl acetate (6 mg, 40 %) after flash column chromatography (15% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (quint, J = 5.9 Hz, 1H), 3.79 (quint, J = 6.0 Hz, 1H), 1.95 (s, 3H), 1.60-1.25 (m, 21H) 1.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 73.3, 70.5, 34.9, 34.2, 31.4, 30.9, 25.5, 26.4, 25.9, 22.7, 22.7, 22.40, 22.36, 21.4 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 279.1936, found 279.1928.

Diastereomer B

Following the procedure used for diastereomer A, 8-hydroxycyclohex-6-enyl acetate (8 mg, 0.031 mmol) and 10 % Pd/C (5 mg) in methanol (10 mL) afforded 7-hydroxycyclotridecyl acetate (7 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (quint, J = 6.0 Hz, 1H), 3.72 (quint, J = 5.6 Hz, 1H), 2.02 (s, 3H), 1.62-1.37 (m, 21H) 1.25 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 73.5, 70.9, 34.8, 34.7, 31.4, 31.1, 27.1, 25.4, 25.4, 22.64, 22.61, 22.5, 22.3, 21.4 ppm; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 279.1936, found 279.1941.



(2S,3R,4S,6R)-4-(dimethylamino)-6-methyl-2-(7-(triethylsilyloxy)cyclotridecyloxy)tetrahydro-2H-pyran-3-yl acetate.

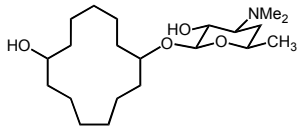
Diastereomer A

Following the general procedure, 7-hydroxycyclotridecyl acetate (6 mg, 0.023 mmol), (2S,3R,4S,6R)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (8 mg, 0.035 mmol), 4Å molecular sieves (~100 mg), and $BF_3{\cdot}OEt_2$ (14 μL, 0.12 mmol) were employed to afford the product after column chromatography (SiO_2, 1 % Et_3N / ethyl acetate). A trace amount of product (1-2 mg) was obtained and was carried on to the next step without characterization.

Diastereomer B

Following the general procedure, 7-hydroxycyclotridecyl acetate (1 mg, 0.0039 mmol), (2S,3R,4S,6R)-4-(dimethylamino)-6-methyltetrahydro-2H-pyran-3-yl acetate (1 mg,

0.0046 mmol), 4Å molecular sieves (~20 mg), and $BF_3{\cdot}OEt_2$ (3 μL, 0.024 mmol) were used to obtain the product, which was carried on to the next step without further purification.



(2S,3R,4S,6R)-4-(dimethylamino)-2-(7-hydroxycyclotridecyloxy)-6-methyltetrahydro-2H-pyran-3-ol. The four diastereomers were obtained as one pair with the 1,7-*trans* relationship and one pair with the 1,7-*cis* relationship. The pairs were not stereochemically characterized.

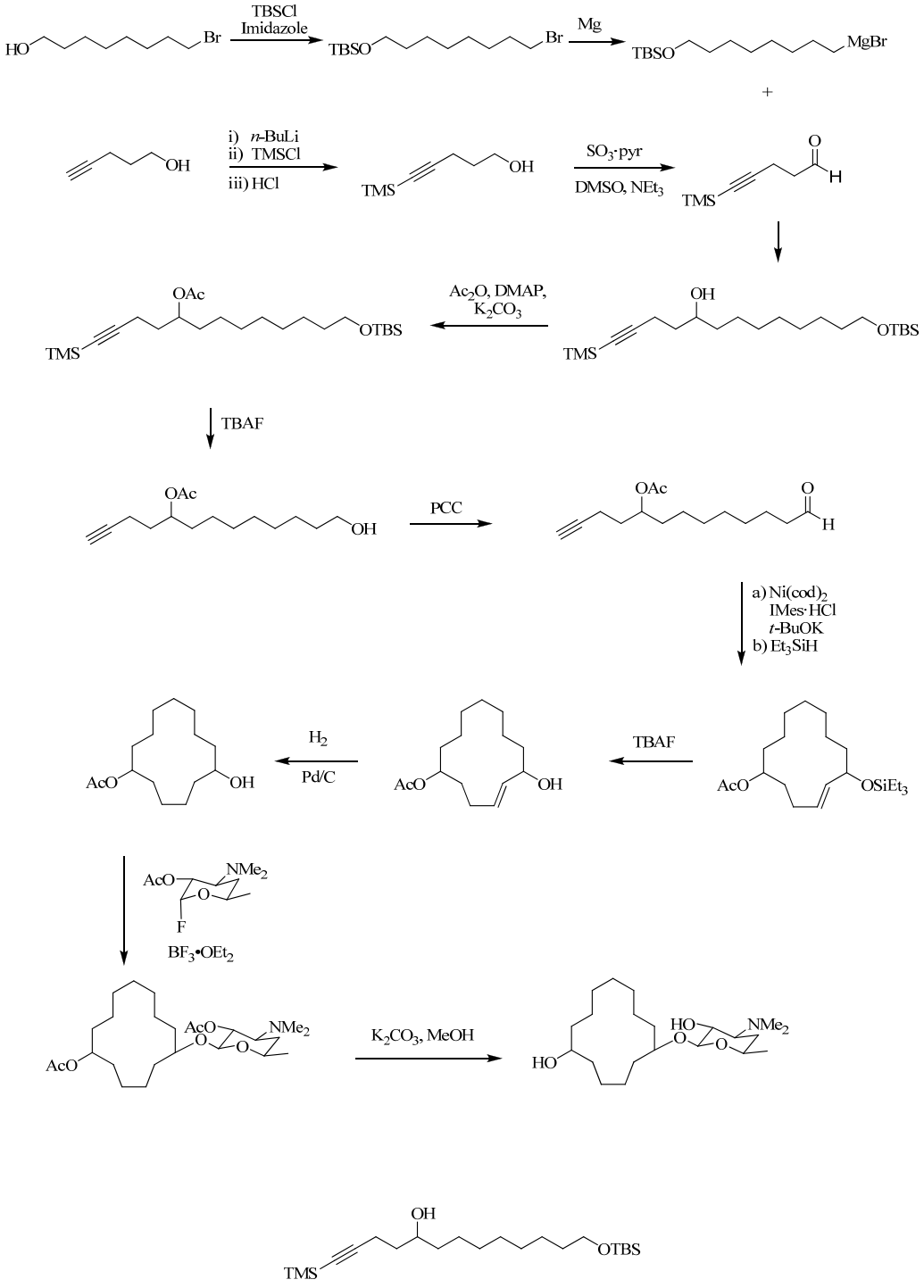
Diastereomers A (9b and 9c in LCMS trace A, synthetic sample shown as trace D, see p. 28)

Following the general procedure, (2S,3R,4S,6R)-4-(dimethylamino)-6-methyl-2-(7-(triethylsilyloxy)cyclotridecyloxy)tetrahydro-2H-pyran-3-yl acetate and K_2CO_3 were used to afford the crude product, which was analyzed without purification. LRMS (ESI) *m/z* calculated for $[M+H]^+$ 372.3, found 372.3.

Diastereomers B (9b and 9c in LCMS trace A, synthetic sample shown as trace E, see p. 28)

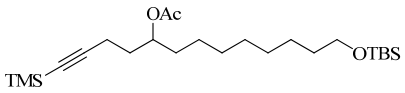
Following the general procedure, (2S,3R,4S,6R)-4-(dimethylamino)-6-methyl-2-(7-(triethylsilyloxy)cyclotridecyloxy)tetrahydro-2H-pyran-3-yl acetate and K_2CO_3 were used to afford the crude product, which was analyzed without purification. LRMS (ESI) *m/z* calculated for $[M+H]^+$ 372.3, found 372.3.

Synthesis of C6/C9 authentic hydroxylated products in 13-membered ring series:

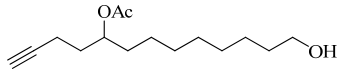


13-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-5-ol. Following the procedure used to synthesize 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-7-ol, (8-bromooctyloxy)(*tert*-butyl)dimethylsilane[xv] (1.0 g, 3.1 mmol), Mg turnings (376 mg, 15.5 mmol), and 5-(trimethylsilyl)-pent-4-ynal[x] (370 mg, 2.5 mmol) were

employed to yield the product (577 mg, 60 %) as a colorless oil after flash column chromatography (SiO_2, 5 % ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (m, 1H) 3.59 (t, *J* = 6.8 Hz, 2H) 2.36 (t, *J* = 7.0 Hz, 2H) 1.78 (d, *J* = 4.8 Hz, 1H) 1.70 (quint of d, *J* = 7.1, 3.4 Hz, 1H) 1.60 (quint of d, *J* = 7.5, 6.9 Hz, 1H) 1.52-1.41 (m, 4H) 1.29 (s, 10H) 0.90 (s, 9H) 0.14 (s, 9H) 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.1, 85.3, 71.2, 63.3, 37.3, 35.7, 32.9, 29.58, 29.56, 29.4, 26.0, 25.8, 25.6, 18.4, 16.6, 0.0, -5.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 421.2934, found 421.2933.

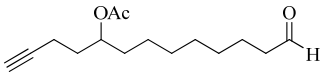


13-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-5-yl acetate. Following the procedure used to synthesize 7-(triethylsilyloxy)cyclododecyl acetate, 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-5-ol (219 mg, 0.55 mmol), acetic anhydride (0.5 mL, 5.5 mmol), K_2CO_3 (106 mg, 0.77 mmol), and 4-dimethylamino pyridine (7 mg, 0.06 mmol) were employed to obtain the product (227 mg, 94%) as a colorless oil after flash column chromatography (SiO_2, 5% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (quint, *J* = 6.4 Hz, 1H) 3.58 (t, *J* = 6.4 Hz, 2H) 2.23 (dt, *J* = 3.6, 7.6 Hz, 2H) 2.02 (s, 3H) 1.77 (t, *J* = 7.6 Hz, 1H) 1.76 (td, *J* = 7.6, 2.8 Hz, 1H) 1.54-1.45 (m, 4H) 1.27 (m, 10H) 0.88 (s, 9H) 0.13 (s, 9H) 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 106.4, 84.8, 73.3, 63.3, 33.8, 33.0, 32.8, 29.5, 29.4, 29.3, 26.0, 25.8, 25.2, 21.2, 18.3, 16.1, 0.1, -5.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 463.3040, found 463.3044.

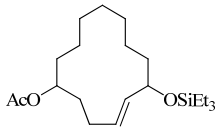


13-hydroxytridec-1-yn-5-yl acetate. Following the procedure used to prepare dodec-11-yne-1,7-diol, 13-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)tridec-1-yn-5-yl acetate (227 mg, 0.51 mmol) and 1 M *n*-Bu_4NF (1.03 mL, 1.03 mmol) were employed to obtain 13-hydroxytridec-1-yn-5-yl acetate (128 mg, 98%) as a light yellow oil after column chromatography (SiO_2, 40% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (quint, *J* = 6.2 Hz, 1H) 3.58 (t, *J* = 7.0 Hz, 2H) 2.17 (tt, *J* = 7.4, 2.8 Hz, 2H) 2.01 (s, 3H) 1.92 (t, *J* = 2.6 Hz, 1H) 1.75 (t, *J* = 7.4 Hz, 1H) 1.74 (td, *J* = 7.2, 2.0 Hz, 1H) 1.51 (m, 4H) 1.25 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 83.5, 73.1, 68.6, 63.0, 33.9,

32.9, 32.7, 29.4, 29.31, 29.25, 25.7, 25.1, 21.2, 14.8; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 277.1780, found 277.1775.



13-oxotridec-1-yn-5-yl acetate. Following the procedure used to synthesize 13-oxotridec-1-yl-7-yl acetate, 13-hydroxytridec-1-yn-5-yl acetate (102 mg, 0.4 mmol) and PCC (173 mg, 0.8 mmol) were employed to yield the product (84 mg, 83 %) as a colorless oil after flash column chromatography (SiO_2, 40% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (t, *J* = 1.8 Hz, 1H) 4.89 (qd, *J* = 5.6, 3.2 Hz, 1H) 2.36 (td, *J* = 7.4, 2.0 Hz, 2H) 2.15 (tt, *J* = 7.4, 2.8 Hz, 2H) 1.99 (s, 3H) 1.90 (t, *J* = 2.6 Hz, 1H) 1.73 (t, *J* = 7.4 Hz, 1H) 1.71 (td, *J* = 7.2, 1.6 Hz, 1H) 1.58-1.45 (m, 4H) 1.24 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 170.6, 83.4, 73.0, 68.6, 43.8, 33.8, 32.8, 29.1, 29.0, 25.0, 21.9, 21.1, 14.7.



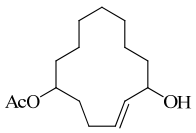
(*E*)-6-(triethylsilyloxy)cyclotridec-4-enyl acetate. Using the procedure to synthesize 8-(triethylsilyloxy)cyclotridec-6-enyl acetate, 13-oxotridec-1-yn-5-yl acetate (150 mg, 0.59 mmol), $Ni(cod)_2$ (16 mg, 0.06 mmol), IMes·HCl (20 mg, 0.06 mmol), *t*-BuOK (7 mg, 0.06 mmol), and triethylsilane (190 μL, 1.2 mmol) were employed to yield a 2.7:1 mixture of diastereomers, which were separated by column chromatography (1.5 % ethyl acetate/hexanes) to obtain diastereomer A (27 mg, 17 %) and diastereomer B (10 mg, 7 %), both as colorless oils. The 1,6-stereochemical relationship of the diastereomers was not established.

Diastereomer A (major)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (dt, *J* = 15.2, 7.2 Hz, 1H) 5.42 (dd, *J* = 15.6, 8.0 Hz, 1H) 4.93 (quint, *J* = 6.4 Hz, 1H) 3.93 (td, *J* = 8.8, 3.0 Hz, 1H) 2.11 (q, *J* = 6.4 Hz, 2H) 2.03 (s, 3H) 1.79 (quint, *J* = 6.4 Hz, 1H) 1.75 (m, 1H) 1.66-1.53 (m, 2H) 1.43-1.08 (m, 12H) 0.93 (t, *J* = 8.0 Hz, 9H) 0.56 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 135.8, 130.3, 74.0, 71.8, 37.5, 33.4, 31.0, 27.5, 26.8, 25.4, 24.8, 22.5, 22.3, 21.3, 6.8, 4.9; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 391.2644, found 391.2646.

Diastereomer B (minor)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (m, 2H) 4.71 (tt, *J* = 7.4, 3.9 Hz, 1H) 4.12 (ddd, *J* = 8.4, 6.8, 4.8 Hz, 1H) 2.21 (ddt, *J* = 14.4, 7.2, 2.4 Hz, 1H) 2.03 (s, 3H) 1.98 (m, 1H) 1.80 (dtd, *J* = 14.8, 7.2, 2.0 Hz, 1H) 1.63-1.16 (m, 15H) 0.93 (t, *J* = 8.0 Hz, 9H) 0.56 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 134.8, 131.4, 73.5, 73.1, 36.6, 33.2, 33.1, 28.9, 26.6, 24.82, 24.80, 22.8, 22.0, 21.4, 6.8, 5.0; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 391.2644, found 391.2635.



(*E*)-6-hydroxycyclotridec-4-enyl acetate.

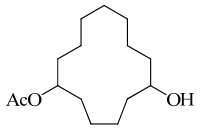
Diastereomer A (major diastereomer)

Following the procedure used to synthesize dodec-11-yne-1,7-diol, (*E*)-6-(triethylsilyloxy)cyclotridec-4-enyl acetate (27 mg, 0.07 mmol) and 1 M *n*-Bu_4NF (80 μL, 0.08 mmol) were employed to afford (*E*)-6-hydroxycyclotridec-4-enyl acetate (16 mg, 84 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dt, *J* = 15.2, 7.2 Hz, 1H) 5.47 (dd, *J* = 15.2, 8.4 Hz, 1H) 4.91 (quint, *J* = 6.4 Hz), 4.00 (td, *J* = 7.4, 3.2 Hz, 1H) 2.15 (q, *J* = 6.5 Hz, 2H), 2.03 (s, 3H) 1.81 (m, 2H) 1.61 (m, 2H) 1.50 (s, 1H) 1.43-1.16 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 135.1, 132.1, 73.7, 71.8, 36.2, 32.9, 30.8, 27.5, 26.8, 25.3, 24.8, 22.7, 22.3, 21.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 277.1789, found 277.1794.

Diastereomer B (minor diastereomer)

Following the procedure used to synthesize (*E*)-cyclotetradec-2-enol, (*E*)-6-(triethylsilyloxy)cyclotridec-4-enyl acetate (23 mg, 0.06 mmol) and 1 M *n*-Bu_4NF (90 μL, 0.09 mmol) were employed to afford (*E*)-6-hydroxycyclotridec-4-enyl acetate (16 mg, 99 %) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (ddd, *J* = 15.2, 9.2, 4.4 Hz, 1H) 5.46 (ddd, *J* = 15.2, 7.6, 1.2 Hz, 1H) 4.71 (tt, *J* = 7.6, 4.0 Hz, 1H) 4.17 (br s, 1H)

2.23 (m, 1H) 2.03 (s, 3H) 1.98 (m, 1H) 1.80 (dtd, J = 10.4, 7.2, 2.0 Hz, 1H) 1.75-1.15 (m, 15 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.1, 133.2, 73.4, 72.8, 35.3, 33.2, 33.1, 28.9, 26.7, 24.7, 24.5, 22.9, 21.8, 21.4; HRMS (ESI) calculated for $[M+Na]^+$ 277.1780, found 277.1782.



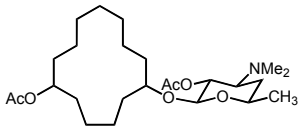
6-hydroxycyclotridecyl acetate.

Diastereomer A (major diastereomer)

Following the procedure used to synthesize 7-hydroxycyclotridecyl acetate, *(E)*-6-hydroxycyclotridec-4-enyl acetate (16 mg, 0.06 mmol), Pd/C (10 % Pd) and hydrogen gas were employed to afford 6-hydroxycyclotridecyl acetate (10 mg, 63 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (quint, J = 6.0 Hz, 1H) 3.70 (quint, J = 5.6 Hz, 1H) 2.02 (s, 3H) 1.64-1.36 (m, 22H) 1.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 73.3, 70.6, 35.1, 34.6, 31.7, 31.4, 26.0, 25.7, 25.4, 23.5, 23.3, 22.78, 22.76, 21.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 279.1936, found 279.1924.

Diastereomer B (minor diastereomer)

Following the procedure used to synthesize 7-hydroxycyclotridecyl acetate, *(E)*-6-hydroxycyclotridec-4-enyl acetate (15 mg, 0.06 mmol), Pd/C (10 % Pd) and hydrogen gas were employed to afford 6-hydroxycyclotridecyl acetate (8 mg, 53 %) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (quint, J = 6.4 Hz, 1H) 3.79 (m, 1H) 2.02 (s, 3H) 1.63-1.30 (m, 22H) 1.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 73.1, 70.1, 34.8, 34.7, 31.4, 31.2, 26.3, 26.2, 25.9, 23.1, 22.9, 22.8, 22.7, 21.4; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 279.1936, found 279.1941.



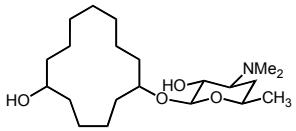
6-((2S,3R,4S,6R)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclotridecyl acetate.

Diastereomer A (major diastereomer)

Following the general procedure, 7-hydroxycyclotridecyl acetate (10 mg, 0.04 mmol), (2S,3R,4S,6R)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (19 mg, 0.09 mmol), 4Å MS (100 mg), and $BF_3{\cdot}OEt_2$ (24 μL, 0.20 mmol) were employed to obtain the product (11 mg, 61 %, as a mixture of two diastereomers) after flash column chromatography (SiO_2, 1 % NEt_3, 5 % MeOH/ ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.84 (q, *J* = 6.0 Hz, 1H) 4.79 (dd, *J* = 10.0, 8.0 Hz, 1H) 4.31 (dd, *J* = 7.5, 2.0 Hz, 1H) 3.54 (m, 2H) 2.74 (m, 1H) 2.27 (s, 6H) 2.05 (s, 3H) 2.02 (s, 3H) 1.75-1.25 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 169.9, 101.8, 101.6, 79.3, 78.9, 73.3, 73.2, 71.1, 69.0, 63.2, 40.7, 40.6, 32.8, 32.4, 31.80, 31.77, 31.7, 31.6, 31.5, 31.2, 30.9, 29.7, 29.3, 26.3, 26.0, 25.6, 25.5, 25.4, 25.2, 23.9, 23.6, 23.12, 23.08, 23.0, 22.9, 22.7, 22.4, 21.4, 21.3, 21.2, 14.1; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 478.3145, found 478.3144.

Diastereomer B (minor diastereomer)

Following the general procedure, 7-hydroxycyclotridecyl acetate (5 mg, 0.02 mmol), (2S,3R,4S,6R)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (8 mg, 0.04 mmol), 4Å MS (100 mg), and $BF_3{\cdot}OEt_2$ (12 μL, 0.09 mmol) were employed to obtain the product (2.5 mg, 29 %, as a mixture of two diastereomers) after flash column chromatography (SiO_2, 1 % NEt_3, 5 % MeOH/ ethyl acetate). ^{1}H NMR δ 4.31 (d, *J* = 7.5 Hz, 1H) 3.64 (quint, *J* = 5.0 Hz, 1H) 3.51 (ddt, *J* = 11.0, 6.0, 5.0 Hz, 1H) 2.74 (m, 1H) 2.27 (s, 6H) 2.06 (s, 3H) 2.02 (s, 3H) 1.72 (m, 1H) 1.66-1.17 (m, 26H).



(2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-2-(6-hydroxycyclotridecyloxy)-6-methyltetrahydro-2*H*-pyran-3-ol.

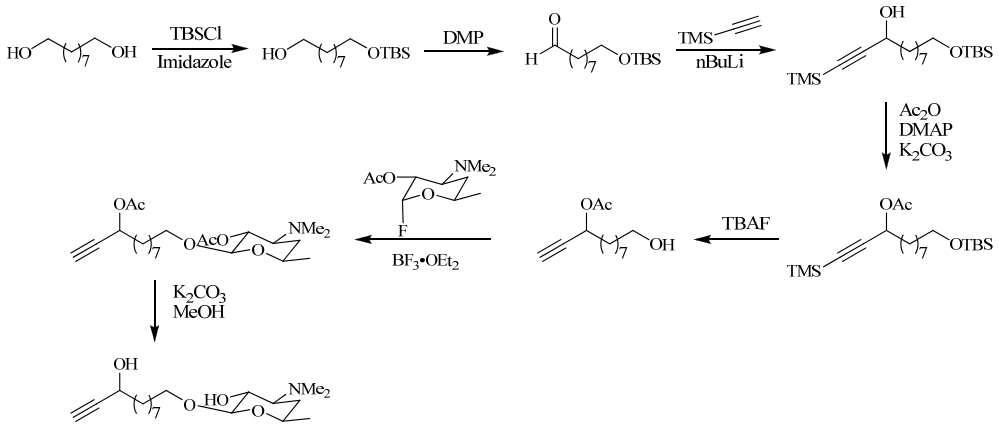
Diastereomers A (major) (9a and 9d in LCMS trace A, synthetic sample shown as trace B, see p. 28)

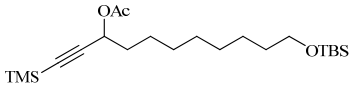
Following the general procedure, the diastereomeric mixture of 6-((2*S*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclotridecyl acetate (10 mg, 0.02 mmol) and K_2CO_3 (13 mg, 0.09 mmol) were used to afford the product (6 mg, 71 %, as a mixture of two diastereomers) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (d, *J* = 7.6 Hz, 1H) 3.72-3.63 (m, 2H) 3.53 (dq, *J* = 9.6, 7.0 Hz, 1H) 3.26 (dd, *J* = 10.0, 7.6 Hz, 1H) 2.55 (m, 1H) 2.29 (s, 6H) 1.69-1.17 (m, 26 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.1, 102.7, 78.5, 77.9, 70.6, 70.4, 70.00, 69.99, 69.4, 65.4, 40.3, 35.3, 35.1, 34.8, 34.5, 33.0, 32.5, 32.0, 31.9, 29.7, 28.9, 26.2, 26.1, 25.9, 25.8, 25.7, 25.3, 23.8, 23.7, 23.3, 23.0, 22.9, 22.72, 22.68, 21.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 394.2933, found 394.2917.

Diastereomers B (minor) (9c and 9f in LCMS trace A, synthetic sample shown as trace C, see p. 28)

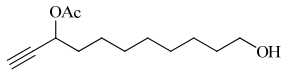
Following the general procedure, the diastereomeric mixture of 6-((2*S*,3*R*,4*S*,6R)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)cyclotridecyl acetate (2.5 mg, 0.005 mmol) and K_2CO_3 (4 mg, 0.03 mmol) were used to afford the product (2 mg, 99 %, as a mixture of two diastereomers). HRMS (ESI) *m/z* calculated for $[M+H]^+$ 372.3114, found 372.3107.

Synthesis of authentic propargyl alcohol:



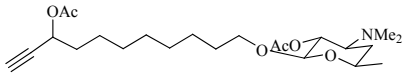


11-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)undec-1-yn-3-yl acetate. Following the procedure used to synthesize 7-(triethylsilyloxy)cyclododecyl acetate, 5-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)pent-1-yn-3-ol[xvi] (77 mg, 0.21 mmol), acetic anhydride (0.2 mL, 2.1 mmol), K_2CO_3 (40 mg, 0.29 mmol), and DMAP (3 mg, 0.02 mmol) were employed to obtain the product (80 mg, 93%) as a pale yellow oil after flash column chromatography (SiO_2, 5% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (t, *J* = 6.8 Hz, 1H) 3.60 (t, *J* = 6.8 Hz, 2H) 2.09 (s, 3H) 1.74 (dtd, *J* = 8.4, 6.6, 2.4 Hz, 2H) 1.51 (quint, *J* = 6.4 Hz, 2H) 1.42 (quint, *J* = 7.2 Hz, 2H) 1.30 (m, 8H) 0.90 (s, 9H) 0.18 (s, 9H) 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 102.8, 90.2, 64.4, 63.3, 34.8, 32.8, 29.4, 29.3, 29.0, 26.0, 25.8, 24.3, 21.1, 18.4, -0.2, -5.3; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 435.2727, found 435.2724.

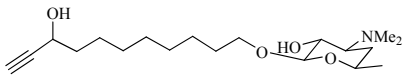


5-hydroxypent-1-yn-3-yl acetate. Following the procedure used to prepare dodec-11-yne-1,7-diol, 11-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)undec-1-yn-3-yl acetate

(72 mg, 0.17 mmol) and 1 M TBAF (0.35 mL, 0.35 mmol) were employed to obtain 5-hydroxypent-1-yn-3-yl acetate (37 mg, 95%) as a light yellow oil after column chromatography (SiO_2, 20% ethyl acetate/ hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (td, *J* = 6.8, 2.1 Hz, 1H) 3.64 (t, *J* = 6.6 Hz, 2H) 2.45 (d, *J* = 2.0 Hz, 1H) 2.09 (s, 3H) 1.80-1.74 (m, 2H) 1.57 (quint, *J* = 7.0 Hz, 2H) 1.46-1.40 (m, 2H) 1.37-1.32 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 81.3, 73.4, 63.8, 63.0, 34.5, 29.3, 29.2, 29.0, 25.7, 24.8, 21.0; HRMS (ESI) *m/z* calculated for $[M+Na]^+$ 249.1467, found 249.1463.



5-((2*R*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)pent-1-yn-3-yl acetate. Following the general procedure, 5-hydroxypent-1-yn-3-yl acetate (31 mg, 0.14 mmol), (2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-3-yl acetate (45 mg, 0.21 mmol), 4Å molecular sieves (~150 mg), and $BF_3{\cdot}OEt_2$ (85 μL, 0.68 mmol) were employed to afford the product (13 mg, 22 %) after column chromatography (SiO_2, ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (td, *J* = 6.6, 1.9 Hz, 1H) 4.82 (dd, *J* = 10.4, 7.6 Hz, 1H) 4.29 (d, *J* = 7.6 Hz, 1H) 3.84 (dt, *J* = 9.6, 6.2 Hz, 1H) 3.55 (dqd, *J* = 11.2, 6.3, 1.8 Hz, 1H) 3.42 (dt, *J* = 9.6, 6.8 Hz, 1H) 2.75 (ddd, *J* = 12.4, 10.6, 4.2 Hz, 1H) 2.45 (d, *J* = 2.0 Hz, 1H) 2.28 (s, 6H) 2.09 (s, 3H) 2.07 (s, 3H) 1.79-1.72 (m, 3H) 1.59-1.49 (m, 2H) 1.45-1.27 (m, 10H) 1.27 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 169.9, 102.2, 81.3, 73.4, 70.9, 69.4, 69.2, 63.8, 63.1, 40.6, 34.5, 30.9, 29.6, 29.3, 29.2, 29.0, 25.9, 24.8, 22.0, 21.1, 21.0; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 426.2856, found 426.2853.



(2*R*,3*R*,4*S*,6*R*)-4-(dimethylamino)-2-(3-hydroxypent-4-ynyloxy)-6-methyltetrahydro-2*H*-pyran-3-ol. Following the general procedure, 5-((2*R*,3*R*,4*S*,6*R*)-3-acetoxy-4-(dimethylamino)-6-methyltetrahydro-2*H*-pyran-2-yloxy)pent-1-yn-3-yl acetate (6 mg, 0.014 mmol) and K_2CO_3 (10 mg, 0.070 mmol) were employed to afford the product (5

mg, quantitative). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.37 (td, *J* = 6.4, 1.2 Hz, 1H) 4.26 (d, *J* = 7.2 Hz, 1H) 3.89 (dt, *J* = 9.2, 6.8 Hz, 1H) 3.60-3.51 (m, 2H) 3.32 (dd, *J* = 10.2, 7.4 Hz, 1H) 2.65 (m, 1H) 2.47 (d, *J* = 1.6 Hz, 1H) 2.37 (s, 6H) 1.81-1.63 (m, 3H) 1.59-1.49 (m, 2H) 1.46-1.26 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.8, 85.0, 72.8, 69.9, 69.7, 69.4, 65.3, 62.3, 40.3, 37.6, 29.7, 29.6, 29.3, 29.2, 29.0, 25.9, 24.9, 21.2; HRMS (ESI) *m/z* calculated for $[M+H]^+$ 342.2644, found 342.2636.

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