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20-Hydroxyeicosatetraenoic Acid (20-HETE): Structural Determinants for Renal Vasoconstriction

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Abstract—The effects of natural and synthetic eicosanoids on the diameter of rat interlobular arteries studied in vitro were compared to that of the potent, endogenous vasoconstrictor 20-HETE. Vasoconstrictor activity was optimum for chain lengths of 20-22 carbons with at least one olefin or epoxide between located between C(13)-C(15) and an oxygen substituent at C(20)-C(22). The presence of Δ (Zou et al. *Am. J. Physiol.* **1996**, *270*, R228; Gebremedhin, D. et al. *Am. J. Physiol.* **1998**, *507*, 771)-, Δ (Carroll et al. *Am. J. Physiol.* **1996**, *271*, R863; Vazquez et al. *Life Sci.* **1995**, *56*, 1455)-, or Δ (Imig et al. *Hypertension* **2000**, *35*, 307; Lopez et al. *Amer. J. Physiol.* **2001**, *281*, F420)-olefins had no influence on the vasoconstrictor response whereas the introduction of a C(7)-thiomethylene enhanced potency. A sulfonamide or alcohol, but not a lactone, could replace the C(1)-carboxylate. These data were used to construct a putative binding domain map of the 20-HETE receptor consisting of: (i) a comparatively open, hydrophilic binding site accommodating the C(1)-functionality; (ii) a hydrophobic trough spanning the olefins; (iii) a shallow pocket containing a critical π–π binding site in the vicinity of the π (Ito et al. *Am. J. Physiol.* **1998**, *274*, F395; Quigley, R.; Baum, M.; Reddy, K. M.; Griener, J. C.; Falck, J. R. *Am. J. Physiol.* **2000**, *278*, F949)-olefin; and (iv) an oxyphilic binding site proximate to the ω-terminus.

Introduction

20-Hydroxyeicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acid (20-HETE, **1**) is a potent vasoconstrictor produced by cytochrome P450 enzymes of the 4A and 4F families.[1] In the last few years, several studies have demonstrated that **1** plays a key role in the control of systemic arterial pressure by regulating both peripheral vascular tone[2] and renal function.[3] **1** depolarizes and constricts vascular smooth muscle cells by blocking K_{Ca}-channels[4,5] and by increasing the conductance of L-type Ca^{2+}-channels.[6] Recent studies have also shown that angiotensin II,[7] vasopressin,[8,9] and endothelin,[10,11] all stimulate the formation of **1** and that the latter contributes to the acute and chronic pressor effects of these vasoconstrictor peptides. Nitric oxide (NO), on the other hand, inhibits[12] the synthesis of **1**; this may be responsible, in part, for the vasodilatory activity of NO.[13]

Additionally, **1** is produced by renal tubular cells[14] where it serves as an endogenous inhibitor of sodium transport in the proximal tubule[15] and thick ascending limb of the loop of Henle[16] as well as a modulator of tubuloglomerular feedback.[17]

Despite the importance of **1**, little is known about the structural features of this molecule that determine its vasoconstrictor properties. To address the urgent need for pharmacological agents to intervene selectively in the ω-hydroxylase pathway[18] and its sequelae,[19] the present study describes the synthesis of a series of structural analogues[20] of **1** and their effects on the diameter of renal interlobular arteries studied in vitro. These data help elucidate the spatial and functional determinants of **1** that contribute to renal vasoconstriction and

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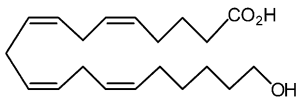
provide the first insights into putative macromolecular recognition[21] and/or binding sites.[22]



1 (20-HETE)

Results and Discussion

Hydroxyl regiochemistry

The effects of various concentrations (10^{-8}, 10^{-7}, and 10^{-6} M) of a representative selection of natural hydroxyeicosanoids and synthetic analogues of **1** on the inner diameter of rat renal interlobular arterioles were compared. The responses are presented in Table 1 and are expressed as a percentage of the contraction induced by 10^{-6} M of **1** applied to the same vessel. Arachidonic acid (**2**), the biogenetic precursor of **1**, as well as the lipoxygenase metabolites 5(*S*)-hydroxyeicosatetraenoic acid [5(*S*)-HETE, **3**], 8(*S*)-HETE (**4**), 12(*S*)-HETE (**5**), and 15(*S*)-HETE (**6**) produced less than 20% of the vasoconstrictor response to **1**. Even 16(*R*)-HETE (**7**) and 19(*S*)-HETE (**8**), despite their close structural similarities to **1**, exhibited very little vasoconstrictor activity. All of these alcohol isomers have the same chain length, degree of unsaturation, and molecular weight as **1**. The diminution of activity appears to have less to do with the nature of the alcohol, that is primary versus secondary (also cf., tertiary alcohol **28**), than the position of the hydroxyl relative to the presumed C(1)-anchor point (vide infra). The positional dependency of the biological response is illustrated by the lack of agonist activity in the C_{19}-congener **9** whereas the response to C_{21}-homologue **10** is identical to that of **1**. Interestingly, we have previously reported that the inactive analogues **3**, **6**, and **8** actually function as competitive antagonists of the vasoconstrictor response to **1**.[19]

Table 1. Percent vasoconstriction versus 20-HETE (**1**) at 10^{-6} M[a]

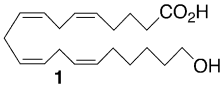
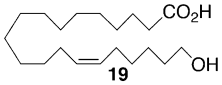
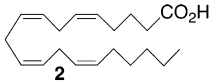
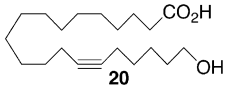
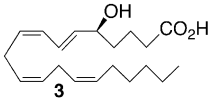
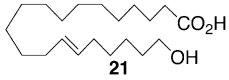
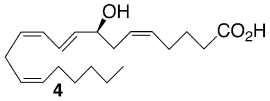
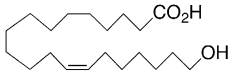
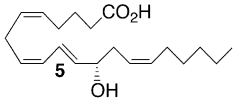
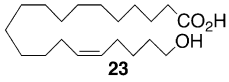
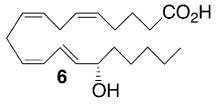
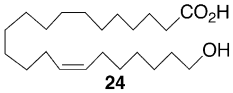
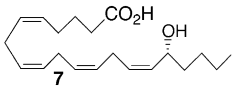
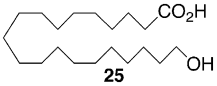
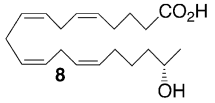
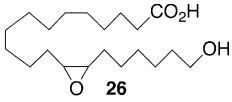
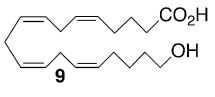
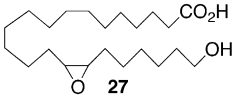
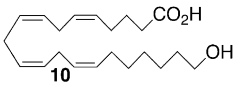
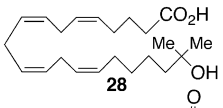
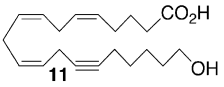
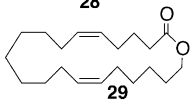
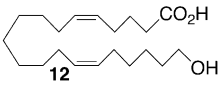
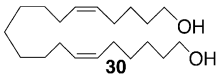
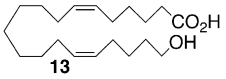
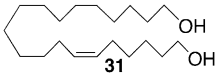
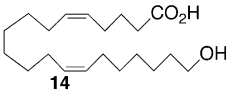
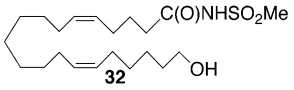
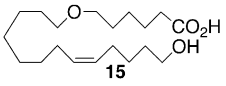
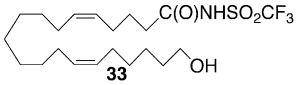
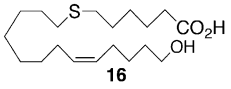
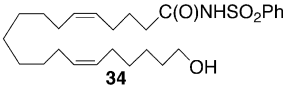
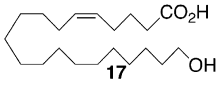
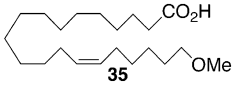
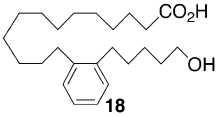
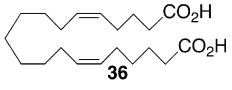
Eicosanoid	Log [M]			Eicosanoid	Log [M]		
	8	7	6		8	7	6
 **1**	25	68	100	 **19**	26	83	105
 **2**	10	5	0	 **20**	22	50	86
 **3**	5	18	17	 **21**	50	65	139
 **4**	5	−8	10	 **22**	20	52	70
 **5**	5	20	15	 **23**	14	61	96
 **6**	5	2	0	 **24**	26	62	132
 **7**	5	5	20	 **25**	2	10	20
 **8**	8	15	20	 **26**	17	48	72
 **9**	0	5	8	 **27**	2	50	165

Table 1 (*continued*)

Eicosanoid	Log [M]			Eicosanoid	Log [M]		
	8	7	6		8	7	6
 **10**	20	50	98	 **28**	22	50	85
 **11**	28	42	65	 **29**	0	10	17
 **12**	25	75	106	 **30**	67	125	170
 **13**	3	10	6	 **31**	36	82	112
 **14**	12	38	165	 **32**	20	65	83
 **15**	22	30	40	 **33**	46	66	88
 **16**	30	98	161	 **34**	20	38	60
 **17**	0	8	14	 **35**	20	49	75
 **18**	15	28	33	 **36**	28	80	130

[a]Mean percent vasoconstriction derived from 3–7 vessels for each test compound compared to response produced by 20-HETE (1) at 10^{-6} M.

Degree of saturation

As evident from the loss of agonist activity in the fully saturated analogue **25**, the olefinic functionality in aggregate influences the vasoconstrictor response to **1**. Consequently, a series of partially saturated analogues was prepared to dissect the contributions of the individual double bonds. As an additional benefit, these simplified structures were easier to prepare and chemically more stable since the 1,4-dienes subunits that make **1** susceptible to autooxidation are partially or completely eliminated. Amongst this group, tetrahydro-analogue **12**[19] is equally potent as **1**, indicating the $\Delta^{8,9}$- and $\Delta^{11,12}$-olefins are not critical determinants of the vsaoconstrictor response to **1**. The location of the remaining two olefins turned out to be an important variable as well. The seemingly innocuous shift of both olefins by just one carbon towards the ω-end virtually abolished the agonist activity of **13**; in fact, the latter regioisomer is an effective competitive antagonist of the vasoconstrictor response to **1** in a variety of vascular beds.[19] Contrast this with **14**, in which relocation of only the $\Delta^{14,15}$-olefin by one carbon in the opposite direction, resulted in a significant increase in vasoconstrictor activity relative to the response seen with an equivalent concentration of **1**. The introduction of oxygen into the carbon chain partially ameliorates the negative effect of shifting the $\Delta^{14,15}$-olefin to $\Delta,^{15,16}$ as revealed by comparing the responses to **15** versus **13**. The heteroatom effect was even more pronounced in analogue **16** wherein introduction of the softer[23] sulfur atom increased the magnitude of the vasoconstrictor response. Replacement of the *cis*-olefin motif at C(14)–(15) with a linear acetylene, as in **11** and **20**, or an ortho-disubstituted phenyl, as in **18** (cf., **19**), diminished the vsaoconstrictor response, suggesting this portion of the molecule has restrictive geometric and/or steric constraints.

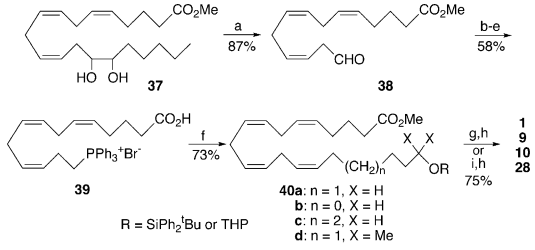
A single olefin, exemplified by *cis*-analogue **19** or *trans*-analogue **21**, was sufficient to elicit as robust a vasoconstrictor response as **1**, provided the unsaturation was between C(14) and (15). Placement of the olefin further away from the carboxylate was acceptable, for example, **23**, even if the chain length was extended by two carbons as in **24**. Examination of the responses to analogues **17** and **22** indicated that reverse deployment of the olefin is not well tolerated and presumably decreases progressively as the olefin approaches C(1). Epoxidation of analogues **22** and **24** furnishing **26** and **27**, respectively, had little impact on their inherent activity.

Modifications at C(1). The loss of vasoconstrictor activity in lactone **29** led us to speculate the carboxylic acid and/or terminal alcohol provide electrostatic and hydrogen bonding essential to the vasoconstrictor response to **1**. This hypothesis, however, was dispelled by finding that the vasoconstrictor response to the diols **30** and **31** was enhanced relative to **12** and **19**, respectively. Bioisosteric replacement of the carboxylic acid with an *N*-methanesulfonamide as embodied in **32** or the slightly more acidic *N*-trifluoromethanesulfonamide **33** had very little effect on vasoconstrictor efficacy relative to **1**. Notably, *N*-benzenesulfonamide **34** also retained substantial activity despite the comparatively large alteration in mass and lipophilicity in this portion of the molecule. From these observations, we infer the binding region around the C(1)-carboxylate has an open architecture and is relatively hydrophilic.

Ether **35**, obtained by alkylation of the C(20)-hydroxyl of **19**, had blunted vasoconstriction activity compared to **1**. In this state, the C(20)-oxygen can no longer act as a hydrogen bond donor, but can still serve as an acceptor or coordinate through its lone pairs. Since longer chain lengths are well accepted, we attribute the loss of activity displayed by **35** to a decrease in hydrophilicity rather than to the increase in steric bulk from replacing hydrogen with methyl. Consistent with this model, oxidation of **12** to the more hydrophilic dicarboxylate **36** increased vasoconstrictor activity with respect to **1**.

Recognition-binding site map of the putative 20-HETE receptor. The foregoing structure–activity relationships can be used to construct a recognition-binding site map for the putative receptor determining the vasoconstrictor response to **1** and its analogues. The representation presented in Figure 1 consists of four general regions and incorporates different binding motifs: (i) the carboxylate region is hydrophilic and can accommodate comparatively large groups attached to C(1). While an ionizable hydrogen at this terminus is essential for full agonist activity, binding is not necessarily ionic since alcohols are comparable to a carboxylic acid or sulfonamide. Rather, this hydrogen most likely participates as the donor partner in a hydrogen bond; (ii) the $\Delta^{5,6}$-, $\Delta^{8,9}$-, $\Delta^{11,12}$-olefins span a mostly lipophilic region with little or no stereochemical constraints. This section makes only a minor contribution to recognition-binding and may only involve van der Waals interactions; (iii) the $\Delta^{14,15}$-olefin, on the other hand, seems to occupy a shallow pocket that conforms to the bent configuration of this *cis*-olefin, but poorly to a linear acetylene or aryl moiety. The presence of an electron lone pair or π–π bond in the C(14)–C(16) vicinity is vital for vasoconstriction; and finally, (iv) an oxygen positioned at C(20)–C(22), irrespective of its nature (ether or primary, secondary, or tertiary alcohol) is essential for vasoconstrictor activity.

Analogue preparation. 20-HETE (**1**) was prepared by our published route[24] utilizing a significant modification that resulted in easier handling and improved yields overall (Scheme 1). Specifically, this meant labile aldehyde **38**, obtained by mild lead tetraacetate cleavage of methyl 14,15-dihydroxyeicosa-5(*Z*),8(*Z*),11(*Z*)-trienoate[24] (**37**), was reduced without delay and the resultant alcohol was converted to phosphonium salt **39** using standard procedures. Wittig *cis*-olefination between the ylide of **39** and aldehyde **42a**[25] (vide infra) in THF/HMPA led to **40a**. Fluoride mediated desilylation and ester hydrolysis completed the preparation of **1**. Simi-



Scheme 1. Reagents and conditions: (a) $Pb(OAc)_4$; (b) $NaBH_4$; (c) CBr_4/Ph_3P; (d) LiOH; (e) Ph_3P; (f) $LiN(SiMe_3)_2$, **42a–c** or **45**; CH_2N_2; (g) *n*-Bu_4NF; (h) NaOH; (i) PPTS/MeOH.

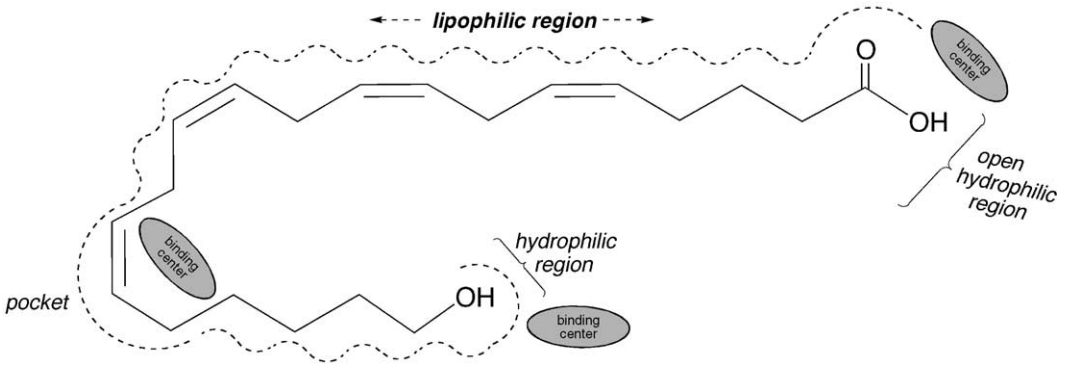


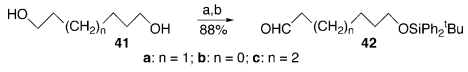
Figure 1. Recognition-binding site map.

larly, aldehydes **42b**,**c**[26,27] and **45** gave rise to homologues **9**, **10**, and **28**, respectively, in comparable yields.

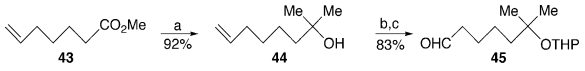
Aldehydes **42a–c** were conveniently made by monosilylation of commercial diols **41a–c** followed by Swern oxidation (Scheme 2).

Dimethyl analogue **45** was prepared by tetrahydropyranylation and ozonolysis of the tertiary alcohol 44[28] resulting from exhaustive methyl lithium addition to methyl 6-heptenoate (**43**) (Scheme 3).

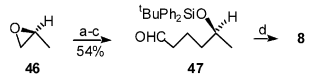
The synthesis of 19(*S*)-HETE (**8**) followed a route analogous to Scheme 1. Addition of but-3-en-1-yl cyanocuprate to commercial *S*-(−)-propylene oxide (**46**), silyl protection of the newly created alcohol, and ozonolysis of the terminal olefin supplied aldehyde **47** (Scheme 4). Wittig condensation with the ylide of **39** and deprotection as described above concluded the preparation of **8**.



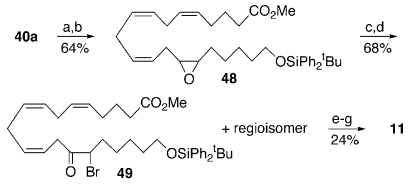
Scheme 2. Reagents and conditions: (a) $^{t}BuPh_2SiCl/AgNO_3$; (b) $DMSO/(COCl)_2/Et_3N$.



Scheme 3. Reagents and conditions: (a) MeLi; (b) DHP/PPTS; (c) O_3.



Scheme 4. Reagents and conditions: (a) $H_2C{=}CH(CH_2)_2{-}MgBr$, CuCN; (b) $^{t}BuPh_2SiCl$; (c) O_3; (d) see Scheme 1.

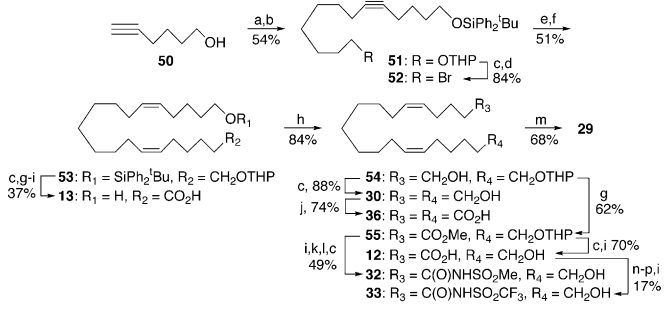


Scheme 5. Reagents and conditions: (a) LiOH; (b) H_2O_2, Im_2CO; CH_2N_2; (c) KBr, HOAc; (d) CrO_3, H_2SO_4; (e) $TsNHNH_2$; (f) *n*-Bu_4NF; (g) LiOH.

For the regioselective epoxidation of **40a**, the ester was converted to the corresponding peracid which was then allowed to react intramolecularly overnight.[29] Re-esterification with diazomethane was rewarded with epoxide **48** (Scheme 5). A mixture of α-bromo-ketone **49** and its regioisomer was prepared from **48** by epoxide opening with KBr/HOAc and chromic acid oxidation of the resultant bromohydrins. Conversion to the *p*-tosylhydrazone, spontaneous elimination, and deprotection secured 14,15-dehydro-20-HETE (**11**) from **49**, albeit in modest overall yield.[30]

5-Hexyn-1-ol (**50**) was elaborated to differentially protected acetylene **51** via silylation and acetylene alkylation with 1-bromo-7-(tetrahydropyran-2-yloxy)-heptane[31] (Scheme 6). Bromide **52**, prepared from **51** by selective removal of the THP ether and CBr_4/Ph_3P treatment, was united with lithium 1-(tetrahydropyran-2-yloxy)hept-6-ynide[32] and then partially hydrogenated over P-2 Ni to give diene **53**. Sequential THP solvolysis, PDC oxidation, desilylation, and saponification gave rise to hydroxy-acid 13.[19] Alternatively, desilyation of **53** yielded **54** which ultimately led to hydroxy-acid **12**[19] passing en route through ester **55**. Lactonization of **12** to **29** proceeded smoothly by way of the 2,4,6-trichlorobenzoyl mixed anhydride. The *N*-methanesulfonamide **32** was also derived from **55** via activation as the *N*-hydroxysuccinimde (NHS) ester, condensation with methanesulfonamide in HMPA at 90 °C, and deprotection. Its *N*-trifluoromethanesulfonamide analogue **33** was derived analogously from **12**. Diol **30** and dicarboxylic acid **36** were obtained sequentially from **54** by THP solvolysis and, then, Jones oxidation.

Intermediate **52** was also utilized to make **56** by catalytic hydrogenation over Pd/C and subsequent coupling with lithium 1-(tetrahydropyran-2-yloxy)-hept-6-ynide[32] (Scheme 7). Selective desilylation translated **56** into **57** from which **20** was obtained after PDC oxidation and removal of the remaining protecting groups. Ester **58** was also available from **56** by semi-hydrogenation over P-2 Ni, desilylation, PDC oxidation, and esterification with diazomethane. The latter segued into **19** in the manner described above or into diol **31** by THP solvolysis and $LiAlH_4$ reduction. Alternatively, **58** gave rise to **35** by sequential THP solvolysis, etherification, and saponification.



Scheme 6. Reagents and conditions: (a) $^{t}BuPh_2SiCl$; (b) *n*-BuLi; $Br{-}(CH_2)_7{-}OTHP$; (c) PPTS; (d) CBr_4, Ph_3P; (e) *n*-BuLi, 1-(tetrahydropyran-2-yloxy)-hept-6-yne; (f) P-2 Ni, H_2; (g) PDC; CH_2N_2; (h) *n*-Bu_4NF; (i) NaOH; (j) CrO_3/H^+; (k) NHS, DCC; (l) H_2NSO_2Me; (m) 2,4,6-$Cl_3C_6H_2C(O)Cl$, DMAP; (n) Ac_2O; (o) $(COCl)_2$; (p) $H_2NSO_2CF_3$.

The trans-analogue of **19**, i.e., **21**, was fashioned out of **57** via dissolving metal reduction to **59** and subsequent oxidation and deprotection (Scheme 8).

A comparable strategy of orthogonal deprotection and elaboration as outlined in Scheme 7 delivered **17** and **23** (Scheme 9). The key precursor 61 was readily accessible from 1-bromo-14-(tetrahydrofuran-2-yloxy)tetradecane[33] (**60**) by alkynylation with 6-(*tert*-butyldiphenylsilyloxy)-hex-1-yne[34] and semi-hydrogenation over P-2 Ni.

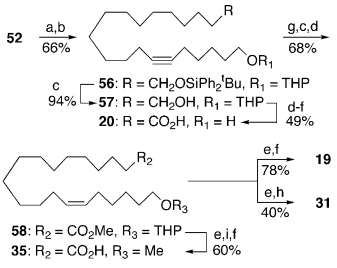
Cross-coupling 1-bromo-6-(*tert*-butyldiphenylsilyloxy)-hexane[35] (**62**) with lithium 6-(tetrahydropyran-2-yloxy)-hex-1-ynide,[34] desilylation, and bromination gave bromide **63** (Scheme 10). Construction of the carbon backbone was consummated by homologation of 63 with 8-(*tert*-butyldiphenylsilyloxy)oct-1-yne.[36] This adduct was advanced to alcohol **64** by THP solvolysis and semi-hydrogenation over P-2 Ni. Final transformation to **14** via PDC oxidation and desilylation was routine.

Analogous alkynylations of homologsue **60** and **65**[37] (Scheme 11) provided ready access to differentially protected diols **66** and **67**, respectively. Elaboration to **22** and **24** paralleled the procedures outlined in Scheme 10. On the other hand, exposure of **66** and **67** to peracid epoxidation during the final functionalization sequence culminated in epoxides **26** and **27**, respectively.

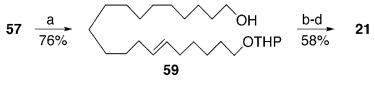
Mild solvolytic cleavage of the THP protecting group in 51 set the stage for a Williamson etherification using 1-iodo-6-(tetrahydrofuran-2-yloxy)hexane[38] (Scheme 12). Transformation of the product, ether **68**, to **15** required another THP cleavage, oxidation of the released alcohol to carboxylate, esterification, desilylation, Lindlar reduction, and finally saponification.

Alternatively, **51** was transformed into **69** via PPTS deprotection, semi-hydrogenation over P-2 Ni, alcohol to bromide interchange, and facile alkylation with methyl 6-mercaptohexanoate (Scheme 13). Liberation of **16** from **69** by the usual means went uneventfully.

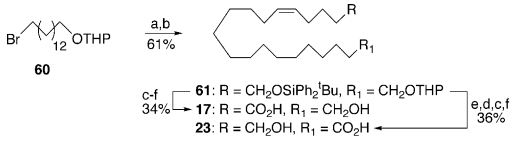
The route to aryl analogue **18** commenced with the Pd-mediated attachment of 1-(tetrahydropyran-2-yloxy)-pent-4-yne[39] to 2-bromobenzyl alcohol (**70**) (Scheme 14). Mild MnO_2 oxidation of the adduct furnished aldehyde **71** which was subjected to Wittig homologation using 11-carboxyundeca(triphenylphosphorane)[40] to give **72** as a mixture of *cis*/*trans*-isomers. Removal of the THP from **72** using acidic methanol was accompanied



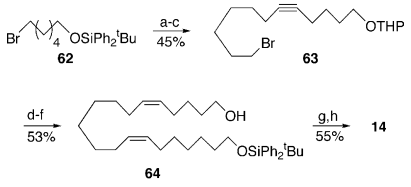
Scheme 7. Reagents and conditions: (a) Pd–C/H_2; (b) *n*-BuLi, 1-(tetrahydropyran-2-yloxy)hept-6-yne; (c) *n*-Bu_4NF; (d) PDC; CH_2N_2; (e) PPTS; (f) NaOH; (g) P-2 Ni/H_2; (h) $LiAlH_4$; (i) $TMSCHN_2$, HBF_4.



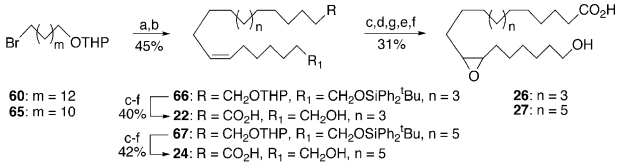
Scheme 8. Reagents and conditions: (a) Na/NH_3, *t*-BuOH; (b) PDC; CH_2N_2; (c) PPTS; (d) NaOH.



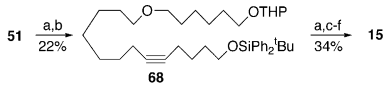
Scheme 9. Reagents and conditions: (a) *n*-BuLi, 6-(*tert*-butyldiphenylsilyloxy)hex-1-yne; (b) P-2 Ni, H_2; (c) *n*-Bu_4NF; (d) PDC; CH_2N_2; (e) PPTS; (f) NaOH.



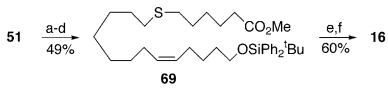
Scheme 10. Reagents and conditions: (a) *n*-BuLi, 6-(tetrahydropyran-2-yloxy)-hex-1-yne; (b) *n*-Bu_4NF; (c) CBr_4, Ph_3P; (d) *n*-BuLi, 8-(*tert*-butyldiphenylsilyloxy)-oct-1-yne; (e) PPTS; (f) P-2 Ni, H_2; (g) PDC; (h) *n*-Bu_4NF.



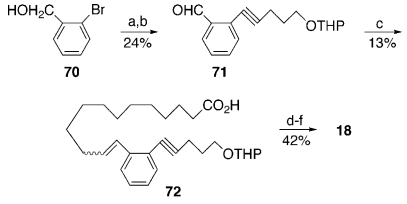
Scheme 11. Reagents and conditions: (a) *n*-BuLi, 8-(*tert*-butyldiphenylsilyloxy)-oct-1-yne; (b) P-2 Ni, H_2; (c) PPTS; (d) PDC; CH_2N_2; (e) *n*-Bu_4NF; (f) NaOH; (g) *m*-CPBA.



Scheme 12. Reagents and conditions: (a) PPTS; (b) NaH; I-$(CH_2)_6$-OTHP; (c) NMO, TPAP; $NaClO_2$; $TMSCHN_2$; (d) *n*-Bu_4NF; (e) Lindlar, H_2; (f) NaOH.



Scheme 13. Reagents and conditions: (a) PPTS; (b) P-2 Ni, H_2; (c) CBr_4, Ph_3P; (d) $HS(CH_2)_5CO_2Me$; (e) *n*-Bu_4NF; (f) NaOH.



Scheme 14. Reagents and conditions: (a) 1-(tetrahydropyran-2-yloxy)-pent-4-yne, $Pd(Ph_3P)_4$, $(i\text{-}Pr)_2NH$; (b) MnO_2; (c) NaH, DMSO, $HO_2C(CH_2)_{11}Ph_3P^+Br^-$; (d) H_2SO_4, MeOH; (e) Pd/C, H_2; (f) LiOH.

by Fischer esterification of the carboxylate. The synthesis was completed by hydrogenation of the *ortho*-substituents over Pd/C and saponification of the methyl ester.

Experimental

Reagents and methods

Eicosanoids **2**–**6**, indomethacin, baicalein, and 17-ODYA were obtained from commercial sources. The CYP 450 metabolite 16(*R*)-HETE[41] (**7**) was made according to literature procedure. All reactions were maintained under an argon atmosphere. Anhydrous solvents were freshly distilled from sodium benzophenone ketyl, except for CH_2Cl_2, toulene and HMPA, which were distilled from CaH_2 under an argon atmosphere. Extracts were dried over anhydrous Na_2SO_4 and filtered prior to evaporation on a rotary evaporator under reduced pressure. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless otherwise stated, and are reported on the δ scale using tetramethylsilane as internal reference. Elemental analyses were performed at Southern Methodist University, Dallas, TX, USA.

Bioassay

Interlobular arterioles (70–120 μm) were microdissected from the kidneys of 10–12-week-old male Sprague–Dawley rats. The vessels were mounted on glass micropipettes in a perfusion chamber at 37 °C containing physiological saline solution equilibrated with 95% O_2/5% CO_2. The vessels were secured to the pipettes and side branches were tied off with 10-0 silk suture. The inflow pipette was connected to a pressurized reservoir to control intraluminal pressure that was monitored using a transducer. Each vessel was stretched to its in vivo length measured before microdissection. The outflow cannula was clamped off and the intraluminal pressure was maintained at 90 mm Hg during the experiment. Vascular diameters were measured with a video system composed of a stereomicroscope (Carl Zeiss, Inc., Germany), a CCTV television camera (KP-130AU, Hitachi, Japan), a videocassette recorder (AG-7300, Panasonic, Japan), a television monitor (CVM-1271, Sony, Japan), and a video measuring system (VIA-100, Boeckeler instrument Co., Tucson, AZ, USA). The composition of the perfusate and bath was (in mM): 119 NaCl, 4.7 KCl, 1.17 $MgSO_4$, 1.6 $CaCl_2$, 12 $NaHCO_3$, 1.18 NaH_2PO_4, 0.03 EDTA, and 10 glucose (pH 7.4). Metabolism of the test samples and the endogenous formation of eicosanoids were blocked by the addition of indomethacin (5 μM), baicalein (0.5 μM), and 17-ODYA (1 μM) to the bath. After an equilibration period of 20–30 min, cumulative dose–response curves were generated in each vessel first for 20-HETE at 10^{-8}, 10^{-7}, and 10^{-6} M. The bath was exchanged and, after a 10 min equilibration period, the vasoconstrictor response to equivalent concentrations of the test substance was determined. The response to each test substance was evaluated in a minimum of 3–7 vessels isolated from different animals.

Methyl 14-oxotetradeca-5(*Z*),8(*Z*),11(*Z*)-trienoate (38). To a vigorously stirring, −40 °C solution of methyl 14,15-dihydroxyeicosa-5(*Z*),8(*Z*),11(*Z*)-trienoate[24] (**37**) (700 mg, 1.98 mmol) in anhydrous CH_2Cl_2 (30 mL) was added $Pb(OAc)_4$ (890 mg, 2.00 mmol) portionwise over 2 min (Scheme 1). After 30 min, the reaction mixture was passed through a pad of silica gel to remove inorganic salts. The filter cake was washed with EtOAc/hexane (1/1, 30 mL) and the combined filtrates were evaporated in vacuo to give aldehyde **38** (435 mg, 87%) as a labile, colorless oil that was used immediately in the next step. ^1H NMR (250 MHz) δ 1.60–1.78 (m, 2H), 2.00–2.15 (m, 2H) 2.30 (t, $J=7.4$ Hz, 2H), 2.70–2.85 (m, 4H), 3.18–3.28 (m, 2H), 3.65 (s, 3H), 5.28–5.75 (m, 6H), 9.65 (t, $J=1.8$ Hz, 1H); TLC: EtOAc/hexane (1:1), $R_f=0.5$.

(12-Carboxy-3(*Z*),6(*Z*),9(*Z*)-dodectrienyl)triphenylphosphonium bromide (39). Sodium borohydride (139 mg, 3.65 mmol) was added portionwise to a stirring solution of crude 38 (435 mg, 1.76 mmol) in MeOH/CH_2Cl_2 (1/2, 10 mL). After 45 min, the mixture was concentrated under reduced pressure and the residue was purified by SiO_2 column chromatography using EtOAc/hexanes (2/3) as eluent furnishing methyl 14-hydroxy-tetradeca-5(*Z*),8(*Z*),11(*Z*)-trienoate (350 mg, 80%) as a colorless oil. ^1H NMR (250 MHz) δ 1.60–1.75 (m, 2H), 2.04–2.15 (m, 2H), 2.25–2.38 (m, 4H), 2.72–2.85 (m, 4H), 3.65 (t, $J=7.2$ Hz, 2H), 3.68 (s, 3H), 5.28–5.60 (m, 6H); TLC: EtOAc/hexanes (1/1), $R_f=0.39$. Anal. calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.29; H, 9.67.

Triphenylphosphine (495 mg, 1.89 mmol) was added portionwise to a stirring, 0 °C solution of the above alcohol (340 mg, 1.35 mmol) and carbon tetrabromide (585 mg, 1.75 mmol) in dry CH_2Cl_2 (15 mL). After 40 min, the solvent was removed in vacuo and the residue was purified by SiO_2 column chromatography using EtOAc/hexanes (1/20) as eluent yielding methyl 14-bromo-tetradeca-5(*Z*),8(*Z*),11(*Z*)-trienoate (375 mg, 88%) as a mobile, colorless oil. ^1H NMR (250 MHz) δ 1.64–1.75 (m, 2H), 2.04–2.15 (m, 2H), 2.25–2.36 (m, 2H), 2.60–2.70 (m, 2H), 2.75–2.84 (m, 4H), 3.38 (t, $J=7.2$ Hz, 2H), 3.65 (s, 3H), 5.30–5.60 (m, 6H); TLC: EtOAc/hexane (1/1) $R_f=0.61$. Anal. calcd for $C_{15}H_{23}BrO_2$: C, 57.15; H, 7.35. Found: C, 57.26; H, 7.24.

Aqueous LiOH (2 mL of 1 M soln) was added dropwise to a 0 °C solution of the above bromo-ester (375 mg, 1.19 mmol) in tetrahydrofuran (THF)/H_2O (5/1, 20 mL). After stirring at ambient temperature for 12 h, the pH was adjusted to 4.5 using 1 M aqueous oxalic acid and the THF was evaporated under reduced pressure. The residue was diluted with H_2O (15 mL) and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with H_2O (15 mL), dried, and evaporated to give 14-bromo-tetradeca-5(*Z*),8(*Z*),11(*Z*)-trienoic acid (318 mg, 89%) as a colorless oil. ^1H NMR (250 MHz) δ 1.63–1.76 (m, 2H), 2.08–2.16 (m, 2H), 2.40 (t, $J=7.1$ Hz, 2H), 2.60–2.70 (m, 2H), 2.75–2.86 (m, 4H), 3.40 (t, $J=7.2$ Hz, 2H), 5.30–5.55 (m, 6H); TLC:

EtOAc/hexanes (3/1), $R_f = 0.34$. Anal. calcd for $C_{14}H_{21}BrO_2$: C, 55.82; H, 7.03. Found: C, 55.70; H, 6.97.

A mixture of triphenylphosphine (524 mg, 2 mmol, 3.5 equiv) and the above bromo-acid (305 mg, 1 mmol) in dry CH_3CN (6 mL) was heated at 85 °C in a sealed tube for 60 h. Solvent evaporation and SiO_2 chromatographic purification using $MeOH/CH_2Cl_2$ (5/95) as eluent afforded phosphonium salt **39** (530 mg, 92%) as a hygroscopic semi-solid. ^1H NMR (250 MHz) δ 1.55–1.70 (m, 2H), 1.96–2.10 (m, 2H), 2.40 (t, $J = 7.1$ Hz, 2H), 2.42–2.60 (m, 2H), 2.62–2.70 (m, 4H), 3.75–3.88 (m, 2H), 5.20–5.50 (m, 6H), 7.65–7.80 (m, 15H); TLC: $MeOH/CH_2Cl_2$ (1/7), $R_f = 0.21$. Anal. calcd for $C_{32}H_{36}BrO_2P$: C, 68.21; H, 6.44. Found: C, 68.44; H, 6.61.

Methyl 20-(*tert*-butyldiphenylsilyloxy)-eicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate (40a). Lithium bis(trimethylsilyl)amide (0.32 mL of a 1 M solution in THF) was added dropwise to a −78 °C solution of phosphonium salt **39** (90 mg, 0.16 mmol) in THF/hexamethylphosphoramide (HMPA) (4/1, 2.5 mL). The reaction mixture was kept at −40 °C for 1 h during which time it developed a dark yellow coloration. It was then recooled to −78 °C and a solution of aldehyde **42a**[25] (30 mg, 0.133 mmol) in anhydrous THF (1 mL) was added dropwise. Following an additional 1.5 h, the reaction was quenched with 50% aqueous NH_4OAc and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with H_2O (2×5 mL), brine (5 mL), dried over Na_2SO_4, and the solvent was evaporated in vacuo. The residue was redissolved in $MeOH/Et_2O$ (1/5, 4 mL) and treated with excess ethereal diazomethane at 0 °C for 0.5 h. Removal of all volatiles and SiO_2 chromatographic purification of the residue using EtOAc/hexanes (1/10) furnished a mixture of silyl-ester **40a** and $\Delta^{14,15}$-*trans*-**40a** (9/1, 73%) that was more conveniently resolved after the next step. ^1H NMR of **40a**/$\Delta^{14,15}$-*trans*-**40a** mixture (250 MHz) δ 0.84 (s, 9H), 1.20–1.75 (m, 8H), 2.00–2.18 (m, 4H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.72–2.85 (m, 6H), 3.60 (t, $J = 7.3$ Hz, 2H), 3.65 (s, 3H), 5.30–5.40 (m, 8H), 7.38–7.45 (m, 6H), 7.59–7.68 (m, 4H); TLC: EtOAc/hexanes (1/2), $R_f = 0.62$.

A solution of **40a**/$\Delta^{14,15}$-*trans*-**40a** (63 mg, 0.11 mmol) and *n*-tetrabutylammonium fluoride (0.22 mmol, 5 equiv) in THF (8 mL) was maintained at room temperature for 3 h. The solvent was evaporated and the residue was dissolved in EtOAc (10 mL), then washed with H_2O (2×5 mL), brine (8 mL), dried, and concentrated in vacuo. Column chromatography (SiO_2) of the residue using Et_2O/hexanes (7/3) gave a 6/1 mixture of methyl 20-HETE (methyl 1) and its $\Delta^{14,15}$-*trans*-isomer (83%) as a colorless oil which was resolved by HPLC on a Varian Microsorb Si 5 μ (10×250 mm) column eluted isocratically with hexane/EtOH (99.4/0.6) at 6 mL/min and monitored at 205 nm (methyl **1**: $R_t = 32.4$ min; methyl $\Delta^{14,15}$-*trans*-**1**: $R_t = 34.8$ min). ^1H NMR (250 MHz) δ 1.25–1.75 (m, 8H), 2.00–2.20 (m, 5H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.72–2.85 (m, 6H), 3.65 (t, $J = 7.3$ Hz, 2H), 3.70 (s, 3H), 5.30–5.50 (m, 8H).[24] For preparative purposes, the isomers were resolved on $AgNO_3$-impregnated TLC plates using 10% $MeOH/CH_2Cl_2$ as eluent.

Aqueous NaOH (0.149 mL of a 1 M soln, 0.149 mmol) was added to a 0 °C solution of the above ester (12.4 mg, 0.037 mmol) in THF/H_2O (3/1, 2 mL). After stirring at ambient temperature overnight, the reaction mixture was diluted with H_2O (3 mL), adjusted to pH 5 by dropwise addition of 1 M aqueous oxalic acid, then extracted with EtOAc (3×3 mL). The combined organic extracts were washed with H_2O (10 mL), dried, and evaporated to give 20-HETE (**1**) (10.5 mg, 90%) as a colorless oil identical in all respects with an authentic sample.[24] HPLC: Phenomenex Nucleosil 5 μ C_{18} (4.6×250 mm) column eluted linearly from CH_3CN/H_2O/HOAc (49.95/49.95/0.1) to CH_3CN/HOAc (99.9/0.1) over 40 min at 1 mL/min and monitored at 205 nm ($R_t = 18$ min). TLC: $MeOH/CH_2Cl_2$ (1/10), $R_f = 0.45$.

6-(*tert*-Butyldiphenylsilyloxy)hexanal (42a). *tert*-Butylchlorodiphenylsilane (400 mg, 1.45 mmol) and $AgNO_3$ (250 mg, 1.47 mmol) were added to a solution of 1,6-hexanediol (**41a**) (343 mg, 2.90 mmol) in THF/pyridine (15/1, 32 mL). After stirring in the dark for 12 h, the reaction mixture was filtered through a bed of Celite® and the filter cake was washed with THF (10 mL). The combined filtrates were evaporated and the residue was purified by SiO_2 column chromatography using $MeOH/CH_2Cl_2$ (1/49) to give 6-(*tert*-butyldiphenylsilyloxy)-hexan-1-ol[42] (495 mg, 96% based on silylating agent). ^1H NMR (250 MHz) δ 1.04 (s, 9H), 1.16–1.70 (m, 8H), 3.48–3.76 (m, 4H), 7.38–7.44 (m, 6H), 7.61–7.66 (m, 4H); TLC: $MeOH/CH_2Cl_2$ (5/95), $R_f = 0.49$.

Freshly distilled oxalyl chloride (353 mg, 2.78 mmol) was added to a −78 °C solution of methyl sulfoxide (DMSO) (543 mg, 6.95 mmol) in anhydrous CH_2Cl_2 (5 mL). After 10 min, the above silyl ether (495 mg, 1.39 mmol) in CH_2Cl_2 (3 mL) was added dropwise and the mixture was stirred for an additional 1.5 h. Triethylamine (702 mg, 6.95 mmol) was added and the mixture was warmed to −20 °C over 30 min, then poured into saturated aqueous $NaHCO_3$ and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (2×10 mL). The combined organic extracts were washed with brine (15 mL), dried, evaporated, and the residue was purified by SiO_2 column chromatography using CH_2Cl_2 to give aldehyde **42a**[25] (450 mg, 92%). ^1H NMR (250 MHz) δ 1.04 (s, 9H), 1.36–1.80 (m, 8H), 2.24–2.52 (m, 2H), 3.64 (t, $J = 6$ Hz, 2H), 7.32–7.44 (m, 6H), 7.63–7.70 (m, 4H), 9.72 (t, $J = 1.8$ Hz, 1H); TLC: $MeOH/CH_2Cl_2$ (1/49), $R_f = 0.71$.

19-Hydroxynonadeca-5(*Z*),8(*Z*),11(*Z*),14(*Z*) - tetraenoic acid (9). Condensation of Wittig salt **39** with aldehyde 42b,[26]rotection, HPLC purification, and saponification as described for **1** (Scheme 1) afforded **9** in comparable yields. ^1H NMR (250 MHz) of methyl **9**: δ 1.25–1.74 (m, 6H), 2.00–2.20 (m, 5H), 2.30 (t, $J = 7.5$ Hz, 2H), 2.71–2.83 (m, 6H), 3.64 (t, $J = 7.3$ Hz, 2H), 3.70 (s, 3H), 5.30–5.50 (m, 8H); HRMS (CI, CH_4) of methyl **9** calcd for $C_{20}H_{33}O_3$ (M + 1) *m*/*z* 321.2430, found *m*/*z* 321.2418.

21-Hydroxyheneicosa - 5(*Z*),8(*Z*),11(*Z*),14(*Z*) - tetraenoic acid (10). Condensation of Wittig salt **39** with aldehyde **42c**,[27] deprotection, HPLC purification, and saponification as described for **1** (Scheme 1) afforded **10** in comparable yields. ^{1}H NMR (250 MHz) of methyl **10**: δ 1.25–1.74 (m, 10H), 2.00–2.23 (m, 5H), 2.32 (t, $J=7.5$ Hz, 2H), 2.70–2.85 (m, 6H), 3.66 (t, $J=7.3$ Hz, 2H), 3.70 (s, 3H), 5.30–5.50 (m, 8H); HRMS (CI, CH_4) of methyl **10** calcd for $C_{22}H_{37}O_3$ (M + 1) m/z 349.2743, found m/z 349.2752.

2-Methyl-7-octen-2-ol (44). MeLi (1.4 M solution in Et_2O, 10.4 mL, 14.6 mmol) was added dropwise to a stirring, room temperature solution of methyl 6-heptenoate (**43**) (946 mg, 6.65 mmol) in anhydrous Et_2O (30 mL) under argon (Scheme 3). After 12 h, the reaction mixture was adjusted to pH 4 using 5% aq hydrochloric acid and extracted with EtOAc (3×10 mL). The combined organic extracts were dried and all volatiles were removed in vacuo to afford 2-methyl-7-octen-2-ol[28] (44) (950 mg, 100%) sufficiently pure to be used directly in the next step. ^{1}H NMR (250 MHz) δ 1.22 (s, 6H), 1.26–1.46 (m, 6H), 2.03–2.18 (m, 2H), 4.92–5.08 (m, 2H), 5.72–5.90 (m, 1H); TLC: EtOAc/hexanes (1/4), $R_f=0.38$.

6-Methyl - 6 - [(tetrahydro - 2H - pyran-2-yl)oxy]-heptanal (45). A mixture of 44 (870 mg, 6.1 mmol), 3,4-dihydro-2*H*-pyran (DHP)(1.12 mL, 12.2 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (153 mg, 0.61 mmol) in CH_2Cl_2 (43 mL) was stirred at ambient temperature for 12 h, then diluted with Et_2O (50 mL) and filtered. The filtrate was evaporated in vacuo and the residue was chromatographed on SiO_2 using EtOAc/hexanes (5/95) to afford 2-[(1,1-dimethyl-6-heptenyl)oxy]tetrahydro-2H-pyran (1.13 g, 82%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.19 (s, 3H), 1.21 (s, 3H), 1.30–1.42 (m, 4H), 1.42–1.58 (m, 6H), 1.60–1.68 (m, 1H), 1.75–1.90 (m, 1H), 2.01–2.12 (m, 2H), 3.38–3.44 (m, 1H), 3.90–3.99 (m, 1H), 4.67–4.70 (m, 1H), 4.92–5.08 (m, 2H), 5.72–5.90 (m, 1H); TLC: EtOAc/hexanes (15/85), $R_f=0.64$. Anal. calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.01; H, 11.49.

A 0 °C solution of the above THP ether (565 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was saturated with a continuous stream of O_3 for 10 min. After purging with argon to remove excess O_3, neat Me_2S (1 mL) was added and the mixture was stirred at room temperature for 2 h. Evaporation of all volatiles in vacuo and chromatographic purification of the residue on SiO_2 using EtOAc/hexane (15/85) as eluent yielded aldehyde **45** (476 mg, 83%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.18 (s, 3H), 1.21 (s, 3H), 1.40–1.80 (m, 12H), 2.43 (dt, $J=1.5$, 6.4 Hz, 2H), 3.40–3.52 (m, 1H), 3.90–4.00 (m, 1H), 4.68–4.74 (m, 1H), 9.78 (t, $J=1.5$ Hz, 1H); TLC: EtOAc/hexanes (1/9), $R_f=0.19$. Anal. calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.59; H, 10.64.

Methyl 20-methyl-20-(tetrahydropyran-2-yloxy)-heneicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoate (40d). Phosphonium salt **39** was condensed with aldehyde **45** as reported for the preparation of **40a**. The crude product was dissolved in Et_2O and treated with excess ethereal CH_2N_2 for 15 min. Evaporation of all volatiles in vacuo and purification of the residue via PTLC [SiO_2: Et_2O/hexanes (7/3), $R_f=0.56$] gave THP-methyl ester **40d** as a colorless oil. Removal of a small amount of *trans*-14,15-isomer was postponed until the next step. ^{1}H NMR (250 MHz) δ 1.20 (s, 3H), 1.23 (s, 3H), 1.23–1.85 (m, 12H), 1.95–2.20 (m, 4H), 2.34 (t, $J=7.6$ Hz, 2H), 2.70–2.90 (m, 6H), 3.35–3.50 (m, 1H), 3.68 (s, 3H), 3.85–4.00 (m, 1H) 4.68–4.74 (m, 1H), 5.20–5.45 (m, 8H).

20,20-Dimethyl-20-HETE (28). A mixture of **40d** (35 mg, 0.08 mmol) and PPTS (2 mg) in MeOH (1 mL) was stirred at room temperature for 1 h. Evaporation of the solvent in vacuo and purification of the residue via PTLC [SiO_2: Et_2O/hexane (7/3), $R_f=0.38$] and HPLC as described above afforded methyl **28** (23 mg, 70%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.23 (s, 6H), 1.31–1.52 (m, 6H), 1.71 (quintet, $J=7.2$ Hz, 2H), 2.02–2.20 (m, 4H), 2.35 (t, $J=7.4$ Hz, 2H), 2.74–2.90 (m, 6H), 3.67 (s, 3H), 5.25–5.46 (m, 8H). HRMS (CI, CH_4) of methyl **28** calcd for $C_{23}H_{39}O_3$ (M + 1) m/z 363.2899, found m/z 363.2911.

A mixture of the above ester (11 mg, 0.03 mmol) and aqueous NaOH (0.17 mL of a 1 M soln, 0.17 mmol) in THF/H_2O (4/1, 2.5 mL) was stirred at room temperature for 12 h. The pH of the reaction was adjusted to 4 by addition of 1 M aqueous oxalic acid and the acidified solution was extracted with EtOAc (3×5 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), and evaporated in vacuo to furnish 20,20-dimethyl-20-HETE (**28**) (9.8 mg, 93%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.21 (s, 6H), 1.30–1.52 (m, 6H), 1.71 (quintet, $J=7.3$ Hz, 2H), 2.03–2.20 (m, 4H), 2.33 (t, $J=7.6$ Hz, 2H), 2.72–2.87 (m, 6H), 5.25–5.45 (m, 8H).

5(*S*)-*tert*-Butyldiphenylsilyloxyhexanal (47). An ethereal solution (2 mL) of 4-bromobut-1-ene (1.31 g, 9.76 mmol) was added dropwise to a suspension of freshly activated magnesium turnings (238 mg, 9.79 mmol) in Et_2O (7 mL) at 0 °C (Scheme 4). The reaction was warmed to room temperature and maintained for 3 h. The resultant homogenous, pale yellow Grignard solution was transferred via cannula under positive nitrogen pressure to a stirring suspension of CuCN (88 mg, 0.98 mmol) in dry THF (10 mL) at −20 °C. After 20 min, (*S*)-(−)-propylene oxide (**46**) (94.6 mg, 1.62 mmol) was added neat to the homogenous cuprate solution which was then allowed to stir at 0 °C for 12 h. The reaction was quenched using saturated aq NH_4Cl solution and extracted with EtOAc (3×10 mL). The combined organic extracts were washed with H_2O (2×10 mL), brine (50 mL), dried over Na_2SO_4, and evaporated in vacuo. Purification of the residue via SiO_2 column chromatography afforded 2(*S*)-hydroxyhept-6-ene[43] (623 mg, 81%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.20 (d, $J=6.7$ Hz, 3H), 1.32–1.37 (m, 4H), 1.91–2.12 (m, 2H), 3.80–3.82 (m, 1H), 4.93–5.05 (m, 2H), 5.79–5.88 (m, 1H), TLC/SiO_2, Et_2O/hexane (1/1), $R_f=0.52$.

$AgNO_3$ (543 mg, 3.21 mmol) and *tert*-butylchlorodiphenylsilane (840 mg, 3.05 mmol) were added sequentially to a room temperature solution of the above alcohol (317 mg, 2.78 mmol) in THF/pyridine (14/1, 10 mL). After 12 h, the reaction mixture was filtered through a pad of Celite® and the filter cake was washed with Et_2O (10 mL). The aqueous filtrate layer was separated, extracted with Et_2O (2×10 mL), and the combined ethereal extracts were washed with saturated aqueous $CuSO_4$ solution, H_2O (2×50 mL), brine (50 mL), dried, and all volatiles were removed under reduced pressure. Purification of the residue via SiO_2 column chromatography (5% Et_2O/hexane) furnished 2(*S*)-*tert*-butyldiphenylsilyloxyhept-6-ene (820 mg, 84%) as a mobile, colorless oil. ^{1}H NMR (250 MHz) δ 1.05 (s, 9H), 1.08 (d, J = 6.4 Hz, 3H), 1.32–1.60 (m, 4H), 1.92–2.01 (m, 2H), 3.80–3.92 (m, 1H), 4.91–5.00 (m, 2H), 5.70–5.81 (m, 1H), 7.33–7.48 (m, 6H), 7.64–7.75 (m, 4H); TLC: SiO_2, EtOAc/hexane (1/9), R_f = 0.9.

Ozone was bubbled through a 0 °C solution of the above olefin (500 mg, 1.42 mmol) in dry CH_2Cl_2 (5 mL) for 15 min, at which time TLC analysis revealed no remaining starting material. The reaction mixture was briefly flushed with argon, then excess Me_2S (2 mL) was added with stirring as the mixture was warmed to room temperature. After 12 h, all volatiles were removed in vacuo and the residue was purified via SiO_2 column chromatography to give aldehyde **47**[44] (387 mg, 77%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.05 (s, 9H), 1.08 (d, J = 6.2 Hz, 3H), 1.39–1.50 (m, 2H), 1.51–1.70 (m, 2H), 2.29 (dt, J = 1.8, 7.1 Hz, 2H), 3.78–3.95 (m, 1H), 7.32–7.49 (m, 6H), 7.62–7.73 (m, 4H), 9.67 (t, J = 1.8 Hz, 1H); TLC: SiO_2, EtOAc/hexane (1/9), R_f = 0.39.

19(*S*)-HETE (8). Wittig condensation of aldehyde **47** (1.81 mg, 0.507 mmol) with the ylide of **39** (220 mg) and esterification of the adduct using diazomethane as described in Scheme 1 provided the methyl ester *tert*-butyldiphenylsilyl ether of **8** (144 mg, 66%) as a colorless oil following PTLC purification [SiO_2: EtOAc/hexane (1/4), R_f = 0.64]. ^{1}H NMR (250 MHz) δ 1.05 (s, 9H), 1.07 (d, J = 6.3 Hz, 3H), 1.30–1.49 (m, 4H), 1.72 (quintet, J = 7.3 Hz, 2H), 1.90–2.03 (m, 2H), 2.05–2.15 (m, 2H), 2.33 (t, J = 7.4 Hz, 2H), 2.64–2.89 (m, 6H), 3.67 (s, 3H), 3.75–3.90 (m, 1H), 5.20–5.47 (m, 8H), 7.28–7.49 (m, 6H), 7.62–7.71 (m, 4H).

Desilylation of the above adduct (450 mg) gave the methyl ester of **8** (210 mg, 78%). ^{1}H NMR (250 MHz) δ 1.20 (d, J = 6.3 Hz, 3H), 1.40–1.53 (m, 4H), 1.71 (quintet, J = 7.4 Hz, 2H), 2.06–2.17 (m, 4H), 2.33 (t, J = 7.4, 2H), 2.74–2.88 (m, 6H), 3.68 (s, 3H), 3.75–3.86 (m, 1H), 5.32–5.49 (m, 8H); TLC: SiO_2, EtOAc/hexane (1/3), R_f = 0.23. Hydrolysis as described above provided 19(*S*)-HETE (**8**) identical in all respects with an authentic sample.[42]

Methyl 20-(*tert*-butyldiphenylsilyloxy)-14,15-oxido-eicosa-5(*Z*),8(*Z*),11(*Z*)-trienoate (48). A mixture of ester **40a** (1.0 g, 1.74 mmol) and LiOH (9 mL of a 1 M soln, 9 mmol) in THF/H_2O (4/1, 20 mL) was stirred at room temperature for 12 h, then the organic solvent was evaporated in vacuo (Scheme 5). The residue was diluted with H_2O (10 mL), acidified to pH 5.5 with 1 M oxalic acid, and extracted with EtOAc (3×50 mL). The combined organic extracts were washed with H_2O (50 mL), brine (50 mL), dried, and evaporated in vacuo to give 20-(*tert*-butyldiphenylsilyloxy)-eicosa-5(*Z*),8(*Z*),11(*Z*),14(*Z*)-tetraenoic acid (960 mg, 98%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.03 (s, 9H), 1.20–1.42 (m, 4H), 1.44–1.60 (m, 2H), 1.67 (quintet, J = 7.1 Hz, 2H), 1.92–2.18 (m, 4H), 2.34 (t, J = 7.2 Hz, 2H), 2.68–2.88 (m, 6H), 3.63 (t, J = 7.4 Hz, 2H), 5.25–5.46 (m, 8H), 7.28–7.47 (m, 6H), 7.55–7.70 (m, 4H); TLC: SiO_2, EtOAc/hexanes (1/4), R_f = 0.15. HRMS (CI, CH_4) calcd for $C_{36}H_{51}O_3Si$ (M + 1) m/z 559.3607, found m/z 559.3594.

A mixture of the above acid (960 mg, 1.72 mmol) and 1,1′-carbonyldiimidazole (Im_2CO) (418 mg, 2.58 mmol) in dry CH_2Cl_2 (35 mL) was stirred for 40 min at room temperature, then transferred via cannula to a stirring, 0 °C ethereal 3.5 M H_2O_2 solution (20 mL, 69 mmol) containing a catalytic amount of lithium imidazole.[29] After 5 min, the reaction mixture was diluted with CH_2Cl_2 (25 mL), powdered KH_2PO_4 (1.4 g, 10.32 mmol) was added, and the stirring was continued at 0 °C for an additional 5 min. The resultant suspension was filtered through a cotton plug into an argon flushed flask containing a suspension of anhydrous Na_2SO_4 (3 g) in CH_2Cl_2 (30 mL). The reaction mixture was stored at room temperature under an argon atmosphere for 12 h, then filtered and washed with brine (40 mL) until the aqueous layer tested negative for hydrogen peroxide with starch-I_2 paper. The organic layer was evaporated in vacuo and the residue was dissolved in Et_2O/MeOH (3/1, 15 mL) to which excess ethereal CH_2N_2 was added slowly at 0 °C until the yellow coloration persisted for 15 min. Removal of the solvent in vacuo and chromatographic purification of the residue on a SiO_2 column afforded epoxide **48** (650 mg, 65%) as a colorless oil accompanied by recovered **40a** (200 mg). ^{1}H NMR (250 MHz) δ 1.05 (s, 9H), 1.29–1.65 (m, 8H), 1.73 (quintet, J = 7.2 Hz, 2H), 2.12 (dt, J = 6.3, 12.5 Hz, 2H), 2.18–2.47 (m, 2H), 2.34 (t, J = 7.4 Hz, 2H), 2.67–3.00 (m, 6H), 3.64 (s, 3H), 3.66 (t, J = 7.1 Hz, 2H), 5.28–5.58 (m, 6H), 7.30–7.50 (m, 6H), 7.60–7.74 (m, 4H); TLC: SiO_2, EtOAc/hexane (1/4), R_f = 0.39. HRMS (CI, CH_4) calcd for $C_{37}H_{53}O_4Si$ (M + 1) m/z 589.3713, found m/z 589.3718.

Methyl 15-bromo-20-(*tert*-butyldiphenylsilyloxy)-14-oxo-eicosa-5(*Z*),8(*Z*),11(*Z*)-trienoate (49) and 14-bromo-15-oxo regioisomer. A solution of epoxide 48 (650 mg, 1.1 mmol) in peroxide-free THF (5 mL) was added dropwise to a stirring, 0 °C mixture of AcOH/THF/saturated aq KBr (20/4/3, 27 mL) under argon. After 10 h, the reaction mixture was reduced in vacuo to one-quarter volume, diluted with H_2O (10 mL) and extracted thrice with Et_2O. The combined ethereal extracts were washed with 10% aqueous $NaHCO_3$ solution, H_2O, brine, dried over Na_2SO_4, and evaporated to dryness in vacuo. Passage of the residue through a short SiO_2 column furnished an inseparable ~1/1 mixture of methyl 15-bromo-20-(*tert*-butyldiphenylsilyloxy)-14-hydroxy-eicosa-5(*Z*),8(*Z*),11(*Z*)-trienoate and its 14-bromo-15-hydroxy regioisomer (700 mg, 94%). ^{1}H

NMR (250 MHz) δ 1.05 (s, 9H), 1.16–1.48 (m, 4H), 1.49–1.64 (m, 2H), 1.71 (quintet, $J=7.3$ Hz, 2H), 1.80–2.07 (m, 2H), 2.13 (dt, $J=6.5$, 13.3 Hz, 2H), 2.35 (t, $J=7.3$ Hz, 2H), 2.42 (t, $J=6.5$ Hz, 1H, D_2O exchangeable), 2.66–2.95 (m, 4H), 3.41–3.57 (m, 1H), 3.64 (t, $J=7.2$ Hz, 2H), 3.65 (s, 3H), 4.00–4.15 (m, 1H), 5.27–5.61 (m, 6H), 7.27 (m, 6H), 7.59–7.70 (m, 4H); TLC: SiO_2, EtOAc/hexanes (1/4), $R_f=0.39$. HRMS (CI, CH_4) calcd for $C_{37}H_{54}BrO_4Si$ (M + 1) m/z 669.2975, found m/z 669.2985.

The above mixture of bromohydrins (700 mg, 1.05 mmol) in acetone (4 mL) was added dropwise to a −20 °C solution of Jones reagent (0.7 mL of a 2 M soln, 1.57 mmol) in acetone (15 mL). The reaction was quenched after 30 min by the slow addition of excess *i*-PrOH, filtered to remove chromium salts, and the filtrate was evaporated in vacuo. The residue was partitioned between H_2O (10 mL) and Et_2O (8 mL). The layers were separated and the aqueous fraction was extracted twice more with Et_2O. The combined ethereal extracts were washed with brine (10 mL), dried over Na_2SO_4, and evaporated in vacuo. Purification of the residue on a SiO_2 column produced bromo-ketone **49** and its regioisomer (500 mg, 72%) as a colorless oil that was immediately used in the next step. ^{1}H NMR (250 MHz) δ 1.07 (s, 9H), 1.20–1.80 (m, 8H), 2.02–2.17 (m, 2H), 2.34 (t, $J=7.4$ Hz, 2H), 2.64–2.91 (m, 4H), 3.40–3.54 (m, 2H), 3.64 (s, 3H), 3.66 (t, $J=6.1$ Hz, 2H), 4.17–4.85 (m, 1H), 5.25–5.70 (m, 6H), 7.30–7.48 (m, 6H), 7.60–7.78 (m, 4H); TLC: SiO_2, EtOAc/hexane (1/4), $R_f=0.46$.

14,15-Dehydro-20-HETE (11). The above mixture of bromo-ketone **49** and its regioisomer (400 mg, 0.599 mmol), tosylhydrazine (224 mg, 1.199 mmol), and hydroquinone (7 mg, 0.06 mmol) was stirred in CH_2Cl_2/HOAc (2/1, 9 mL) at room temperature under an argon atmosphere for 32 h, then diluted with H_2O (20 mL), and extracted with Et_2O (3×50 mL).[30] The combined ethereal extracts were washed with H_2O, brine, dried, and evaporated in vacuo. Purification via SiO_2 column chromatography afforded methyl 20-(*tert*-butyldiphenylsilyloxy)eicosa-5(*Z*),8(*Z*),11(*Z*)-trien-14-ynoate (140 mg, 41%) as a colorless oil. ^{1}H NMR (250 MHz) δ 1.05 (s, 9H), 1.41–1.60 (m, 6H), 1.72 (quintet, $J=7.2$ Hz, 2H), 1.97–2.19 (m, 4H), 2.31 (t, $J=7.3$ Hz, 2H), 2.68–2.84 (m, 4H), 2.85–2.98 (m, 2H), 3.63 (t, $J=7.1$ Hz, 2H), 3.65 (s, 3H), 5.29–5.50 (m, 6H), 7.33–7.48 (m, 6H), 7.63–7.72 (m, 4H); TLC: SiO_2, Et_2O/hexane (1/1), $R_f=0.53$.

A mixture of the above silyl-methyl ester (140 mg, 0.245 mmol) and *n*-tetrabutylammonium fluoride (1.2 mL of 1 M soln, 1.2 mmol) in anhydrous THF (5 mL) was stirred at 0 °C under an argon atmosphere for 12 h, then evaporated to dryness in vacuo. The residue was dissolved in EtOAc (50 mL) and washed with H_2O (30 mL), brine (30 mL), dried, and evaporated in vacuo. Purification of the residue via SiO_2 column chromatography gave methyl 14,15-dehydro-20-HETE (50 mg, 62%) as a labile, colorless oil. ^{1}H NMR (250 MHz) δ 1.36–1.67 (m, 6H), 1.72 (quintet, $J=7.3$ Hz, 2H), 2.02–2.24 (m, 4H), 2.33 (t, $J=7.5$ Hz, 2H), 2.75–2.88 (m, 4H), 2.89–3.00 (m, 2H), 3.65 (t, $J=6.8$ Hz, 2H), 3.67 (s, 3H), 5.30–5.53 (m, 6H); TLC: SiO_2, EtOAc/hexane (1/3), $R_f=0.14$. HRMS (CI, CH_4) calcd for $C_{21}H_{33}O_3$ (M + 1) m/z 333.2430, found m/z 333.2425.

The above ester (4.8 mg, 0.014 mmol) and LiOH (72 μL of a 1 M soln, 0.072 mmol) were stirred at room temperature in THF/H_2O (5/2, 1.5 mL) under an argon atmosphere for 12 h. The reaction mixture was adjusted to pH 5.5 with 1 M oxalic acid and extracted thrice with EtOAc. The combined organic extracts were washed with H_2O, brine, dried, and evaporated in vacuo to afford **11** (4.7 mg, >95%) as a labile, colorless oil. ^{1}H NMR (250 MHz) δ 1.35–1.65 (m, 6H), 1.71 (quintet, $J=7.3$ Hz, 2H), 2.02–2.24 (m, 4H), 2.37 (t, $J=7.3$ Hz, 2H), 2.70–2.88 (m, 4H), 2.89–2.99 (m, 2H), 3.67 (t, $J=6.4$ Hz, 2H), 5.28–5.54 (m, 6H); TLC: SiO_2, EtOAc/hexane (3/7), $R_f=0.15$.

1-(*tert* - Butyldiphenylsilyloxy) - 13 - (tetrahydropyran-2-yloxy)-tridec-5-yne (51). Silylation of 5-hexyn-1-ol[45] as described in Scheme 4 gave 1-(*tert*-butyldiphenylsilyloxy)-5-hexyne[34] (86%) as a pale yellow oil. ^{1}H NMR (400 MHz) δ 7.65 (dd, $J=1.6$, 7.6 Hz, 4H), 7.35–7.42 (m, 6H), 3.65 (t, $J=6.8$ Hz, 2H), 2.19–2.22 (m, 2H), 1.92–1.94 (m, 1H), 1.55–1.71 (m, 4H), 1.10 (s, 9H); TLC: SiO_2, EtOAc/hexane (15/85), $R_f=0.56$.

n-BuLi (0.66 mL of a 1.6 M soln in hexane, 1.05 mmol) was added dropwise to a −40 °C solution of the above silyl ether (320 mg, 0.96 mmol) in THF (6 mL) followed by the addition of anhydrous HMPA (1.5 mL). After 1 h, a solution of 1-bromo-7-(tetrahydropyranyloxy)heptane[31] (291 mg, 1.05 mmol) in THF (2 mL) was slowly added. The reaction mixture was brought to room temperature over 2 h and maintained at that temperature for 12 h, then quenched at 0 °C using saturated aqueous NH_4Cl solution. The mixture was extracted thrice with Et_2O and the combined ethereal extracts were washed with H_2O, brine, dried, and evaporated in vacuo. Purification of the residue via SiO_2 column chromatography (5% EtOAc/hexane) gave **51** (310 mg, 63%) as a colorless, mobile oil. ^{1}H NMR (400 MHz) δ 7.66 (dd, $J=1.6$, 7.6 Hz, 4H), 7.35–7.42 (m, 6H), 4.56–4.58 (m, 1H), 3.83–3.88 (m, 1H), 3.71–3.75 (m, 1H), 3.67 (t, $J=6$ Hz, 2H), 3.46–3.50 (m, 1H), 3.34–3.39 (m, 1H), 2.11–2.16 (m, 4H), 1.78–1.88 (m, 2H), 1.42–1.77 (m, 12H), 1.29–1.41 (m, 6H), 1.08 (s, 9H); TLC: SiO_2, EtOAc/hexane (15/85), $R_f=0.70$. Anal. calcd for $C_{34}H_{50}O_3Si$: C, 76.35; H, 9.42. Found: C, 76.55; H, 9.37.

1-(*tert*-Butyldiphenylsilyloxy) - 13 - (bromo) - tridec-5-yne (52). Solvolysis of the THP ether in acetylene **51** as described in Scheme 1 gave 1-(*tert*-butyldiphenylsilyloxy)-tridec-5-yn-13-ol (92%) as a colorless oil. ^{1}H NMR (400 MHz) δ 7.66 (dd, $J=1.6$, 7.6 Hz, 4H), 7.35–7.41 (m, 6H), 3.67 (t, $J=6.4$ Hz, 2H), 3.59–3.65 (m, 2H), 2.11–2.17 (m, 4H), 1.62–1.68 (m, 2H), 1.52–1.60 (m, 4H), 1.41–1.49 (m, 2H), 1.32–1.39 (m, 6H), 1.04 (s, 9H); TLC: SiO_2, EtOAc/hexane (2/3), $R_f=0.33$. HRMS (CI, CH_4) calcd for $C_{29}H_{43}O_2Si$ (M + 1) m/z 451.3032, found m/z 451.3021.

Conversion of the above alcohol to bromide as described in Scheme 1 provided 52 (91%) as a colorless oil. ^{1}H NMR (400 MHz) δ 7.66 (dd, J = 1.6 and 8 Hz, 4H), 7.35–7.41 (m, 6H), 3.67 (t, J = 6.2 Hz, 2H), 3.38 (t, J = 6.4 Hz, 2H), 2.11–2.16 (m, 4H), 1.84 (quintet, J = 7.4 Hz, 2H), 1.62–1.67 (m, 2H), 1.55–1.61 (m, 2H), 1.31–1.48 (m, 8H), 1.04 (s, 9H); TLC: SiO_2, EtOAc/hexane (1/9), R_f = 0.58. HRMS (CI, CH_4) calcd for $C_{29}H_{42}BrOSi$ (M + 1) m/z 513.2188, found m/z 513.2186.

1-(*tert*-Butyldiphenylsilyloxy) - 20 - (tetrahydropyran - 2 - yloxy)-eicosa-5,14-diene (53). Alkynylation of bromide **52** with 7-(tetrahydropyran-2-yloxy)-1-heptyne[32] as described for the preparation of **51** gave 1-(*tert*-butyldiphenylsilyloxy) - 20 - (tetrahydropyran-2-yloxy)-eicosa-5,14-diyne (61%) as a pale yellow oil. ^{1}H NMR (400 MHz) δ 7.66 (dd, J = 1.6, 8 Hz, 4H), 7.35–7.41 (m, 6H), 4.55–4.57 (m, 1H) 3.84–3.89 (m, 1H), 3.70–3.76 (m, 1H), 3.67 (t, J = 6.2 Hz, 2H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 2.10–2.17 (m, 8H), 1.88–1.92 (m, 1H), 1.41–1.65 (m, 19H), 1.28–1.40 (m, 6H), 1.04 (s, 9H); TLC: SiO_2, EtOAc/hexane (1/9), R_f = 0.7. Anal. calcd for $C_{41}H_{60}O_3Si$: C, 78.29; H, 9.61. Found: C, 78.04; H, 9.56.

$NaBH_4$ (32 mg, 0.8 mmol) was added portionwise to a stirring solution of nickel(II) acetate tetrahydrate (200 mg, 0.8 mmol) in EtOH (600 mL) under a hydrogen blanket (1 atm). After 30 min, freshly distilled ethylenediamine (4.8 g) was added followed by the above diyne (5.80 g, 16 mmol) in EtOH (50 mL). The heterogeneous mixture was maintained at room temperature under hydrogen (1 atm) for 3 h, then diluted with Et_2O (600 mL) and filtered through a pad of SiO_2. Concentration of the filtrate in vacuo yielded 53 (84%) as a colorless oil that required no further purification. ^{1}H NMR (400 MHz) δ 7.66 (dd, J = 1.6, 8 Hz, 4H), 7.35–7.41 (m, 6H), 5.30–5.35 (m, 4H), 4.55–4.57 (m, 1H), 3.70–3.76 (m, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.47–3.50 (m, 1H), 3.35–3.40 (m, 1H), 1.96–2.09 (m, 8H), 1.80–1.91 (m, 1H), 1.65–1.79 (m, 1H), 1.51–1.62 (m, 8H), 1.21–1.42 (m, 16H), 1.04 (s, 9H); TLC: SiO_2, EtOAc/hexane (1/9), R_f = 0.75. HRMS (CI, CH_4) calcd for $C_{41}H_{65}O_3Si$ (M + 1) m/z 633.4703, found m/z 633.4709.

20-(Tetrahydropyran-2-yloxy)-eicosa-5(*Z*),14(*Z*)-dien-1-ol (54). Desilylation of diene **53** as described in Scheme 1 afforded **54** (84%) as a colorless oil. ^{1}H NMR (400 MHz) δ 5.34–5.40 (m, 4H), 4.56–4.58 (m, 1H), 3.84–3.89 (m, 1H), 3.70–3.76 (m, 1H), 3.62–3.65 (m, 2H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 1.96–2.09 (m, 8H), 1.79–1.90 (m, 1H), 1.62–1.78 (m, 1H), 1.51–1.61 (m, 8H), 1.22–1.43 (m, 16H); TLC: EtOAc/hexane (3/7), R_f = 0.52. HRMS (CI, CH_4) calcd for $C_{25}H_{47}O_3$ (M + 1) m/z 395.3525, found m/z 395.3530.

1,20-Dihydroxyeicosa-5(*Z*),14(*Z*)-diene (30). Solvolysis of the THP ether in **54** as described in Scheme 1 generated diol **30** (88%) as a colorless oil. ^{1}H NMR (400 MHz) δ 1.25–1.46 (m, 18H), 1.54–1.62 (m, 4H), 1.98–2.10 (m, 8H), 3.64 (t, J = 6.4 Hz, 2H) 3.65 (6, J = 6.4 Hz, 2H), 5.31–5.41 (m, 4H); ^{13}C NMR (100 MHz) δ 25.6, 26.0, 27.1, 27.3, 27.4, 29.4, 29.7, 29.9, 32.5, 32.8, 63.0, 129.5, 129.7, 130.3, 130.5. HRMS (CI, CH_4) calcd for $C_{20}H_{39}O_2$ (M + 1) m/z 311.2950, found m/z 311.2957.

Methyl 20-(tetrahydropyran-2-yloxy)-eicosa-5(*Z*),14(*Z*)-dienoate (55). A solution of alcohol 54 (11.4 mg, 0.036 mmol) and pyridinium dichromate (PDC) (81 mg, 0.216 mmol) in dry DMF (1.5 mL) was stirred at room temperature for 20 h, then diluted with H_2O (2 mL) and extracted with EtOAc (3×5 mL). The combined organic extracts were washed with H_2O, brine, dried, and evaporated. The residue was dissolved in Et_2O/MeOH (4/1, 3 mL) and exposed to excess CH_2N_2 at 0 °C for 30 min. All volatiles were removed in vacuo and the residue was purified by PTLC [SiO_2, EtOAc/hexane (2/3), R_f = 0.65] to give **55** (7 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz) δ 5.35–5.41 (m, 4H), 4.56–4.58 (m, 1H), 3.84–3.89 (m, 1H), 3.70–3.76 (m, 1H), 3.66 (s, 3H), 3.47–3.52 (m, 1H), 3.35–3.41 (m, 1H), 2.31 (t, J = 7.6 Hz, 2H), 1.94–2.09 (m, 8H), 1.78–1.90 (m, 1H), 1.64–1.78 (m, 1H), 1.45–1.62 (m, 6H), 1.21–1.42 (m, 16H).

20-Hydroxyeicosa-5(*Z*),14(*Z*)-dienoic acid (12). Solvolysis of **55** as described in the preparation of **52** gave methyl 20-hydroxyeicosa-5(*Z*),14(*Z*)-dienoic acid (80%) as a colorless oil after purification via PTLC (SiO_2: EtOAc/hexane (2/3), R_f = 0.42). ^{1}H NMR (400 MHz) δ 5.36–5.42 (m, 4H), 3.67 (s, 3H), 3.66 (t, J = 6.8 Hz, 2H), 2.31 (t, J = 7.2 Hz, 2H), 1.99–2.08 (m, 8H), 1.68 (quintet, J = 7.2 Hz, 2H), 1.55–1.61 (m, 2H), 1.28–1.39 (m, 15H). HRMS (CI, CH_4) calcd for $C_{21}H_{39}O_3$ (M + 1) m/z 339.2899, found m/z 339.2898.

Saponification of the above ester as described in Scheme 1 gave **12** (88%) as a pale yellow oil. ^{1}H NMR (300 MHz) δ 5.36–5.42 (m, 4H), 3.66 (t, J = 6.8 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.98–2.11 (m, 8H), 1.69 (quintet, J = 7.5 Hz, 2H), 1.56–1.60 (m, 2H), 1.28–1.39 (m, 15H); TLC: SiO_2, EtOAc/hexane (1/1), R_f = 0.3.

***N*-(20-Hydroxy - eicosa - 5(*Z*),14(*Z*) - dienoyl)-methanesulfonamide (32).** Methyl ester **55** was saponified (90%) as described for the preparation of **12**. The resultant carboxylic acid (118 mg, 0.29 mmol) and *N*-hydroxysuccinimide (NHS) were dried azeotropically with anhydrous benzene (3×20 mL). The mixture was dissolved in THF (5 mL), cooled to 0 °C, and DCC (70 mg, 0.33 mmol) was added all at once. After 12 h at room temperature, the solvent was removed in vacuo and the residue was purified by SiO_2 chromatography using 10% EtOAc/hexane as eluent to give the NHS ester of 20-(tetrahydropyran-2-yloxy)-eicosa-5(*Z*),14(*Z*)-dienoic acid (140 mg, 96%) that was used immediately in the next step.

The above NHS-ester (140 mg, 0.28 mmol), methanesulfonamide (264 mg, 2.8 mmol), and DMAP (37 mg, 0.31 mmol) were dried in vacuo for 24 h, then suspended in dry HMPA (250 μL) and heated at 90 °C. After 1.5 h, the reaction mixture was cooled, diluted with H_2O (2 mL), and extracted with EtOAc (3×15 mL). The combined organic extracts were dried, concentrated in vacuo, and the residue was purified by SiO_2

chromatography using 10% EtOAc/hexane to give *N*-[20-(tetrahydropyran-2-yloxy)-eicosa-5(*Z*),14(*Z*)-dienoyl]-methanesulfonamide (89 mg, 65%) as a colorless oil. ^{1}H NMR (400 MHz) δ 1.26–1.41 (m, 17H), 1.51–1.62 (m, 6H), 1.69–1.76 (m, 3H), 1.79–1.87 (m, 1H), 1.98–2.13 (m, 8H), 2.33 (t, J = 7.6 Hz, 2H), 3.30 (s, 3H), 3.36–3.42 (m, 1H), 3.49–3.54 (m, 1H), 3.70–3.76 (m, 1H), 3.85–3.91 (m, 1H), 4.58–4.60 (m, 1H), 5.23–5.47 (m, 4H); ^{13}C NMR (100 MHz) δ 19.8, 24.4, 25.7, 26.1, 26.4, 27.3, 27.5, 29.4, 29.5, 29.6, 29.8, 29.9, 30.9, 35.9, 41.7, 41.9, 62.6, 67.6, 99.1, 99.3, 128.0, 129.9, 130.2, 131.8, 172.2.

Solvolysis of the THP ether as described for the synthesis of **12** evolved **32** (90%) as a colorless oil. ^{1}H NMR (400 MHz) δ 1.28–1.41 (m, 15H), 1.50–1.57 (m, 2H), 1.68 (quintet, J = 7.2 Hz, 2H), 2.02–2.12 (m, 8H), 2.31 (t, J = 7.4 Hz, 2H), 3.22 (s, 3H), 3.54 (t, J = 6.6 Hz, 2H), 5.31–5.46 (m, 4H); ^{13}C NMR (100 MHz) δ 25.7, 26.7, 27.5, 28.3, 28.5, 30.5, 30.6, 30.7, 30.9, 31.0, 33.7, 36.5, 41.5, 41.5, 63.1, 129.6, 130.1, 131.1, 132.3, 174.9. HRMS (CI, CH_4) calcd for $C_{21}H_{40}NO_4S$ (M + 1) m/z 402.2678, found m/z 402.2667.

***N*-(20-Hydroxyeicosa-5(*Z*),14(*Z*)-dienoyl)-benzenesulfonamide (34).** Methyl ester **55** was transformed into **34** using benzenesulfonamide as described for the preparation of **32**. ^{1}H NMR (400 MHz) δ 1.21–1.48 (m, 12H), 1.55–1.66 (m, 6H), 1.90–2.05 (m, 8H), 2.23 (t, J = 7.3 Hz, 2H), 3.66 (t, J = 6.7 Hz, 2H), 5.18–5.40 (m, 4H), 7.52–7.56 (m, 2H), 7.62–7.66 (m, 1H), 8.05–8.07 (m, 2H); IR (neat) 2925, 2853, 1714, 1346 cm^{-1}. HRMS (CI, CH_4) calcd for $C_{26}H_{42}NO_4S$ (M + 1) m/z 464.2835, found m/z 464.2842.

***N*-(20-Hydroxyeicosa-5(*Z*),14(*Z*)-dienoyl)-trifluoromethanesulfonamide (33).** Hydroxy-acid **12** (200 mg, 0.617 mmol) and Ac_2O (189 mg, 1.85 mmol) were stirred at room temperature in pyridine (1.5 mL) (Scheme 6). After 1 day, the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL×2). The combined organic extracts were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via SiO_2 column chromatography to give 20-acetyloxyeicosa-5(*Z*),14(*Z*)-dienoic acid (190 mg, 84%) as a colorless oil. ^{1}H NMR (200 MHz) δ 1.21–1.80 (m, 18H), 1.94–2.18 (m, 11H), 2.37 (t, J = 7.6 Hz, 2H), 4.06 (t, J = 6.7 Hz, 2H), 5.24–5.51 (m, 4H); IR (neat) 3005, 2929, 2854, 1740, 1708, 1456, 1365, 1236, 1048, 952, 724, 606 cm^{-1}; MS (ES+) m/z 389 (M + Na)$^+$, (ES-) m/z 365 (M−H)$^-$.

The preceding acetyloxy-acid (223 mg, 0.609 mmol) was stirred with oxalyl chloride (410 mg, 3.23 mmol) and NaCl (10 mg) in dry DMF (0.06 mL) at room temperature. After 15 min, all volatiles were remove in vacuo and the residue was dissolved in toluene (1.5 mL). To this was added $CF_3SO_2NH_2$ (289 mg, 1.94 mmol) and DBU (1.082 g, 7.1 mmol) and the whole was then heated under reflux for 3 h, cooled to room temperature, diluted with EtOAc (50 mL), washed with aqueous HCl (20 mL, 1.0 M), H_2O (30 mL), brine (30 mL), dried, and concentrated in vacuo. The residue was purified via SiO_2 column chromatography to give *N*-(20-acetyloxy-eicosa-5(*Z*),14(*Z*)-dienoyl)-trifluoromethanesulfonamide (100 mg, 33% for both steps). ^{1}H NMR (200 MHz) δ 1.18–1.86 (m, 18H), 1.90–2.18 (m, 11H), 2.49 (t, J = 7.4 Hz, 2H), 4.07 (t, J = 6.8 Hz, 2H), 5.02–5.55 (m, 4H); IR (neat) 3006, 2930, 2855, 1740, 1708, 1456, 1392, 1239, 1202, 1138, 1050, 947, 882, 724, 612, 502 cm^{-1}; MS (ES+) m/z 520 (M + Na)$^+$, (ES-) m/z 496 (M−H)$^-$.

Saponification of the preceding acetate as described above gave **33** as a colorless oil. ^{1}H NMR (300 MHz) δ 1.20–1.46 (m, 14H), 1.52–1.79 (m, 4H), 1.92–2.54 (m, 10H), 3.59–3.75 (m, 2H), 5.24–5.49 (m, 4H); IR (neat) 3400, 3006, 2930, 2854, 1740, 1646, 1510, 1494, 1462, 1456, 1392, 1316, 1208, 1138, 1052, 882, 853, 724, 612, 504 cm^{-1}; MS (ES-) m/z 454 (M−H)$^-$.

20-Hydroxyeicosa-6(*Z*),15(*Z*)-dienoic acid (13). Diene **53** was transformed to **13** as described for **12** (Scheme 6). ^{1}H NMR (300 MHz) δ 5.30–5.42 (m, 4H), 3.66 (dt, J = 0.9, 6.3 Hz, 2H), 2.35 (t, J = 7.2 Hz, 2H), 1.98–2.09 (m, 8H), 1.54–1.67 (m, 4H), 1.24–1.50 (m, 15H); TLC: EtOAc/hexane (1/1), R_f = 0.3. HRMS (CI, CH_4) of methyl ester calcd for $C_{21}H_{39}O_3$ (M + 1) m/z 339.2899, found m/z 339.2905.

Eicosa-5(*Z*),14(*Z*)-dien-1,20-dioic acid (36). Diol **30** (31 mg, 0.1 mmol) in acetone (2 mL) was added dropwise to a stirring, 0 °C mixture of Jones reagent (1.0 mL of 2.6 M solution in H_2O) and acetone (3 mL). After 15 min, the reaction was quenched by the slow addition of excess *iso*-propanol, filtered to remove Cr salts, and the solvent was evaporated in vacuo. The residue was dissolved in EtOAc (5 mL), washed with H_2O, brine, dried, and all volatiles were removed. PTLC purification (SiO_2, EtOAc/hexane, 1/1, R_f = 0.1) of the residue gave **36** (25 mg, 74%) as a colorless, viscous oil. ^{1}H NMR (400 MHz) δ 1.28–1.43 (m, 14H), 1.58–1.68 (m, 4H), 2.01–2.11 (m, 8H), 2.24–2.34 (m, 4H), 5.31–5.43 (m, 4H); ^{13}C NMR (100 MHz) δ 27.8, 28.0, 28.3, 30.5, 30.55, 30.6, 30.65, 31.0, 130.0, 130.5, 131.4, 132.0, 174.1. HRMS (CI, CH_4) of dimethyl ester calcd for $C_{22}H_{39}O_4$ (M + 1) m/z 367.2848, found m/z 367.2855.

20-Hydroxyeicosa-5(*Z*),14(*Z*)-dienoic acid lactone (29). A mixture of hydroxy-acid **12** (32 mg, 0.1 mmol), Et_3N (82 μL, 0.6 mmol), and 2,4,6-trichlorobenzoyl chloride (79 mL, 0.5 mmol) in THF (1.4 mL) was stirred at 0 °C for 30 min, then added to a room temperature solution of DMAP (122 mg, 0.1 mmol) in toluene (50 mL). After 1 h, the reaction was reduced to one-half volume, passed through a 2-cm pad of SiO_2, and the silica gel was washed with Et_2O/hexane (2:3, 5 mL). The combined organic filtrates were concentrated in vacuo and the residue was purified on SiO_2 using 2% EtOAc/hexane as eluent furnishing lactone **29** (21 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz) δ 1.25–1.42 (m, 16H), 1.58–1.73 (m, 4H), 1.99–2.12 (m, 8H), 2.31 (t, J = 7.0 Hz, 2H), 4.80 (t, J = 6.4 Hz, 2H), 5.27–5.43 (m, 4H); ^{13}C NMR (100 MHz) δ 24.9, 25.4, 26.5, 26.9, 26.95, 27.1, 28.7, 28.75, 29.0, 29.1, 29.2, 29.3, 29.7, 33.6, 64.6, 128.9, 130.0, 130.6, 131.6, 174.1. HRMS (CI, CH_4) calcd for $C_{20}H_{35}O_2$ (M + 1) m/z 307.2637, found m/z 307.2640.

1-(Tetrahydropyran-2-yloxy)-20-(*tert*-butyldiphenylsilyloxy)-eicosa-6-yne (56). A mixture of bromo-acetylene **52** (35 mg, 0.068 mmol) and 10% Pd/C (7 mg) in MeOH (10 mL) was stirred under hydrogen (1 atm) for 2.5 h, then filtered over Celite®, and the filter cake was washed with more MeOH (4 mL) (Scheme 7). Evaporation of the combined filtrates afforded 1-(*tert*-butyldiphenylsilyloxy)-13-(bromo)-tridecane (35 mg, 99%) as a colorless oil suitable for use in the next reaction without further purification. ^{1}H NMR (400 MHz) δ 1.05 (s, 9H), 1.23–1.35 (m, 16H), 1.39–1.46 (m, 2H), 1.52–1.59 (m, 2H), 1.85 (quintet, J = 7.2 Hz, 2H), 3.40 (t, J = 7.0 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 7.35–7.42 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR (100 MHz) δ 19.4, 26.0, 27.0, 27.1, 28.4, 29.0, 29.6, 29.7, 29.8, 29.82, 29.86, 32.8, 33.1, 34.3, 64.2, 127.8, 127.9, 129.7, 134.4, 135.8. Anal. calcd for $C_{29}H_{45}BrOSi$: C, 67.29; H, 8.76. Found: C, 67.32; H, 8.84. Alkynylation of the above bromide using lithium 1-(tetrahydropyran-2-yloxy)-hept-6-ynide[32] according to the precedent in Scheme 6 gave **56** (67%). ^{1}H NMR (400 MHz) δ 1.04 (s, 9H), 1.20–1.40 (m, 22H), 1.42–1.64 (m, 16H), 1.67–1.75 (m, 1H), 1.78–1.86 (m, 1H), 2.11–2.19 (m, 4H), 3.36–3.42 (m, 1H), 3.47–3.53 (m, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.71–3.77 (m, 1H), 3.84–3.90 (m, 1H), 4.56–4.60 (m, 1H), 7.35–7.42 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR (100 MHz) δ 18.9, 19.0, 19.4, 19.9, 25.7, 26.0, 27.0, 27.1, 29.1, 29.2, 29.4, 29.5, 29.6, 29.8, 29.9, 29.92, 31.0, 32.8, 62.5, 64.2, 67.7, 80.2, 80.6, 99.0, 127.8, 129.7, 134.4, 135.8. HRMS (CI, CH_4) calcd for $C_{41}H_{65}O_3Si$ (M + 1) m/z 633.4703, found m/z 633.4710.

1-(Tetrahydropyran-2-yloxy)-20-(hydroxy)-eicosa-6-yne (57). Desilylation as described above delivered alcohol **57**. ^{1}H NMR (400 MHz) δ 1.20–1.40 (m, 27H), 1.47–1.64 (m, 9H), 1.64–1.78 (m, 1H), 1.80–1.90 (m, 1H), 1.98–2.07 (m, 4H), 3.35–3.41 (m, 1H), 3.47–3.53 (m, 1H), 3.68 (dd, J = 6.3, 10.6 Hz, 2H), 3.70–3.76 (m, 1H), 3.84–3.90 (m, 1H), 4.56–4.59 (m, 1H), 5.37–5.33 (m, 2H); ^{13}C NMR (100 MHz) δ 19.8, 25.7, 26.0, 27.3, 27.4, 29.5, 29.6, 29.7, 29.8, 29.85, 29.9, 30.9, 33.0, 62.5, 63.2, 67.8, 129.8, 130.2. HRMS (CI, CH_4) calcd for $C_{25}H_{47}O_3$ (M + 1) m/z 395.3525, found m/z 395.3521.

Methyl 20-(tetrahydropyran-2-yloxy)eicosa-14(*Z*)-enoate (58). Partial hydrogenation over P-2 Ni converted **56** to 1-(tetrahydropyran-2-yloxy)-20-(*tert*-butyldiphenylsilyloxy)-eicosa-6(*Z*)-ene. ^{1}H NMR (400 MHz) δ 1.04 (s, 9H), 1.20–1.41 (m, 25H), 1.48–1.64 (m, 9H), 1.67–1.75 (m, 1H), 1.78–1.86 (m, 1H), 1.98–2.06 (m, 4H), 3.35–3.41 (m, 1H), 3.47–3.52 (m, 1H), 3.65 (t, J = 6.6 Hz, 2H), 3.70–3.76 (m, 1H), 3.84–3.90 (m, 1H), 4.56–4.60 (m, 1H), 5.32–5.38 (m, 2H), 7.35–7.42 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR (100 MHz) δ 19.4, 19.9, 26.0, 26.1, 27.1, 27.4, 27.42, 29.6, 29.65, 29.8, 29.82, 29.86, 29.88, 29.9, 29.95, 30.0, 31.0, 32.8, 62.5, 64.2, 67.8, 99.0, 127.7, 129.8, 130.0, 130.3, 134.4, 135.8.

Desilylation of the above compound generated 1-(tetrahydropyran-2-yloxy)-20-(hydroxy)-eicosa-6(*Z*)-ene. ^{1}H NMR (400 MHz) δ 1.24–1.40 (m, 24H), 1.54–1.64 (m, 6H), 1.98–2.07 (m, 4H), 2.30 (t, J = 7.6 Hz, 2H), 3.65 (t, J = 6.4 Hz, 2H), 3.67 (s, 3H), 5.33–5.37 (m, 2H); ^{13}C NMR (100 MHz) δ 25.3, 25.7, 27.5, 27.55, 29.5, 29.6, 29.65, 29.7, 29.8, 29.9, 30.0, 30.1, 33.0, 34.4, 51.7, 63.3, 129.6, 130.3, 174.4.

PDC oxidation of the above alcohol and CH_2N_2 esterification gave 58. ^{1}H NMR (400 MHz) δ 1.20–1.40 (m, 23H), 1.50–1.64 (m, 9H), 1.68–1.75 (m, 1H), 1.79–1.87 (m, 1H), 1.98–2.06 (m, 4H), 2.30 (t, J = 7.6 Hz, 2H), 3.35–3.41 (m, 1H), 3.47–3.53 (m, 1H), 3.67 (s, 3H), 3.70–3.76 (m, 1H), 3.84–3.90 (m, 1H), 5.33–5.37 (m, 2H); ^{13}C NMR (100 MHz) δ 19.9, 25.2, 25.7, 26.1, 27.4, 27.45, 29.4, 29.5, 29.55, 29.6, 29.8, 29.82, 29.86, 29.88, 29.9, 30.0, 31.0, 34.3, 51.6, 51.65, 62.5, 67.8, 99.0, 129.8, 130.2, 174.5. HRMS (CI, CH_4) calcd for $C_{26}H_{49}O_4$ (M + 1) m/z 425.3631, found m/z 425.3635.

20-Hydroxyeicosa-14(*Z*)-enoic acid (19). Solvolysis of the THP in **58** and saponification gave **19.** ^{1}H NMR (400 MHz) δ 1.25–1.39 (m, 24H), 1.54–1.66 (m, 4H), 1.98–2.04 (m, 4H), 2.34 (t, J = 7.4 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 5.33–5.37 (m, 2H); ^{13}C NMR (100 MHz) δ 24.9, 25.6, 27.3, 27.4, 29.2, 29.4, 29.5, 29.6, 29.7, 29.75, 29.8, 29.9, 32.8, 34.2, 63.2, 129.7, 130.4, 179.6. HRMS (CI, CH_4) of methyl ester calcd for $C_{21}H_{41}O_3$ (M + 1) m/z 341.3056, found m/z 341.3051.

20-Methoxyeicosa-14(*Z*)-enoic acid (35). The THP ether in **58** was removed as described for the preparation of **19**. Four portions of $TMSCHN_2$ (0.142 mg, 0.284 mmol, 2.0 N in hexane) were added dropwise at intervals of 20 min to a stirred, 0 °C mixture of the resultant alcohol (44 mg, 0.129 mmol) and aqueous 48% HBF_4 (25 mg, 0.142 mmol) in CH_2Cl_2 (2.6 mL). After 4 h at 0 °C, the reaction was quenched with AcOH (0.2 mL), poured into water, and extracted with EtOAc (30 mL×2). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), dried, and concentrated in vacuo. The residue was purified via SiO_2 column chromatography to give methyl 20-methoxyeicos-14(*Z*)-enoate (42 mg, 92%) as a colorless oil. ^{1}H NMR (200 MHz) δ 1.10–1.66 (m, 26H), 1.89–2.09 (m, 4H), 2.30 (t, J = 7.6 Hz, 2H), 3.33 (s, 3H), 3.37 (t, J = 6.8 Hz, 2H), 3.67 (s, 3H), 5.26–5.45 (m, 2H); IR (neat) 2924, 2854, 1740, 1462, 1436, 1364, 1246, 1197, 1170, 1121, 1018, 856, 722 cm^{-1}; MS (ES+) m/z 377 $(M + Na)^+$.

Saponification of the preceding ester as described above afforded 35 as a white solid. ^{1}H NMR (200 MHz) δ 1.08–1.73 (m, 26H), 1.88–2.13 (m, 4H), 2.35 (t, J = 7.5 Hz, 2H), 3.34 (s, 3H), 3.38 (t, J = 6.4 Hz, 2H), 5.26–5.45 (m, 2H); IR (neat) 3004, 2918, 2850, 1702, 1686, 1682, 1464, 1412, 1300, 1228, 1204, 1188, 1121, 940, 721, 688, 547 cm^{-1}; MS (ES+) m/z 363 $(M + Na)^+$, (ES-) m/z 339 $(M-H)^-$.

Eicosa-6(*Z*)-en-1,20-diol (31). The THP ether in **58** was removed as described for the preparation of **19**. An ethereal solution (0.5 mL) of the resultant hydroxy-ester (25 mg, 0.0734 mmol) was added to a 0 °C suspension of $LiAlH_4$ (3.1 mg, 0.081 mmol) in Et_2O (1 mL). After 1 h at room temperature, the reaction mixture was slowly poured into aqueous HCl (5 mL, 1.0 M) and extracted

with Et_2O (30 mL×2). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified via SiO_2 column chromatography to give 31 (14 mg, 61%) as a white solid. ^{1}H NMR (200 MHz) δ 1.13–1.70 (m, 28H), 1.90–2.12 (m, 4H), 3.65 (t, J = 6.6 Hz, 4H), 5.27–5.43 (m, 2H); IR (KBr) 3419, 3358, 3016, 2924, 2850, 1726, 1641, 1469, 1356, 1262, 1059, 1031, 998, 973, 802, 722, 629, 508, 426 cm^{-1}; MS (ES+) m/z 335 $(M+Na)^+$, (ES-) m/z 311 $(M-H)^-$.

20-Hydroxyeicosa-14-ynoic acid (20). PDC oxidation and CH_2N_2 esterification of **57** gave methyl 20-(tetrahydropyran-2-yloxy)eicosa-14-ynoate. ^{1}H NMR (400 MHz) δ 1.25–1.40 (m, 16H), 1.42–1.53 (m, 6H), 1.55–1.66 (m, 4H), 2.10–2.19 (m, 4H), 2.30 (t, J = 7.5 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (75 MHz) δ 19.0, 25.2, 25.3, 29.1, 29.2, 29.5, 29.7, 29.8, 29.9, 32.6, 34.4, 51.7, 63.1, 80.0, 80.7, 174.4.

The THP ether was solvolyzed as described for 52 to give methyl 20-hydroxyeicosa-14-ynoate. ^{1}H NMR (300 MHz) δ 1.24–1.40 (m, 16H), 1.42–1.52 (m, 6H), 1.54–1.66 (m, 4H), 2.10–2.19 (m, 4H), 2.34 (t, J = 7.5 Hz, 2H), 3.66 (t, J = 6.6 Hz, 2H); ^{13}C NMR (75 MHz) δ 19.0, 25.0, 25.2, 29.1, 29.2, 29.3, 29.4, 29.5, 29.7, 29.8, 29.85, 32.5, 63.1, 80.1, 80.7, 179.4. HRMS (CI, CH_4) calcd for $C_{21}H_{39}O_3$ (M + 1) m/z 399.2899, found m/z 399.2895. Hydrolysis of the above ester according to precedent above produced **20** as a colorless oil.

^{1}H NMR (300 MHz) δ 1.24–1.40 (m, 16H), 1.42–1.52 (m, 6H), 1.54–1.66 (m, 4H), 2.10–2.19 (m, 4H), 2.34 (t, J = 7.5 Hz, 2H), 3.66 (t, J = 6.66 Hz, 2H); ^{13}C NMR (75 MHz) δ 19.0, 25.0, 25.2, 29.1, 29.2, 29.3, 29.4, 29.5, 29.7, 29.8, 29.85, 32.5, 63.1, 80.1, 80.7, 179.4.

1-(Tetrahydropyran-2-yloxy)-20-hydroxyeicosa-6(*Z*)-ene (59). A solution of **57** (200 mg, 0.51 mmol) in dry THF (3 mL) was added dropwise to a stirring mixture of Na (115 mg, 5 mmol) and *t*-BuOH (37 mg, 0.5 mmol) in liquid NH_3 (5 mL) at −33 °C (Scheme 8). After 1.5 h, the reaction was quenched with solid NH_4OAc (100 mg) and the NH_3 was allowed to evaporate at rt overnight. The residue was suspended in H_2O (10 mL) and extracted with Et_2O (5 mL×3). The combined ethereal extracts were washed with brine, dried, and evaporated in vacuo. Purification of the residue by SiO_2 chromatography using 30% EtOAc/hexanes gave **59** (155 mg, 76%) as a colorless oil. ^{1}H NMR (400 MHz) δ 1.24–1.39 (m, 24H), 1.49–1.63 (m, 8H), 3.35–3.41 (m, 1H), 3.47–3.53 (m, 1H), 3.64 (t, J = 6.6 Hz, 2H), 3.70–3.76 (m, 1H), 3.84–3.90 (m, 1H), 4.56–4.59 (m, 1H), 5.34–5.44 (m, 2H); ^{13}C NMR (100 MHz) δ 19.9, 25.8, 26.0, 29.4, 29.7, 29.72, 29.76, 29.8, 29.85, 29.9, 31.0, 32.7, 32.8, 33.0, 62.6, 63.3, 67.8, 99.0, 130.3, 130.8.

20-Hydroxyeicosa-14(*E*)-enoic acid (21). PDC oxidation/esterification, THP solvolysis, and saponification of **59** as described above yielded **21**. ^{1}H NMR (400 MHz) δ 1.27–1.40 (m, 22H), 1.53–1.64 (m, 4H), 1.94–2.02 (m, 4H), 2.28 (t, J = 7.6 Hz, 2H), 3.54 (t, J = 6.8 Hz, 2H), 5.35–5.42 (m, 2H); ^{13}C NMR (75 MHz) δ 25.7, 26.3, 30.1, 30.3, 30.35, 30.4, 33.1, 33.4, 33.6, 34.3, 62.4, 130.9, 131.0, 174.6. HRMS (CI, CH_4) of methyl ester calcd for $C_{21}H_{41}O_3$ (M + 1) m/z 341.3056, found m/z 341.3062.

1-(*tert*-Butyldiphenylsilyloxy)-20-(tetrahydropyran-2-yloxy)-eicosa-5-yne (61). Alkynylation of 1-(bromo)-14-(tetrahydropyran-2-yloxy)tetradecane[33] (**60**) as described above with 6-(*tert*-butyldiphenylsilyloxy)hex-1-yne[34] and catalytic reduction over P-2 Ni produced **61** (Scheme 9). ^{1}H NMR (300 MHz) δ 1.04 (s, 9H), 1.22–1.40 (m, 26H), 1.42–1.61 (m, 10H), 1.63–1.82 (m, 2H), 1.96–2.05 (m, 4H), 3.34–3.42 (m, 1H), 3.46–3.53 (m, 1H), 3.66 (t, J = 8.6 Hz, 2H), 3.69–3.77 (m, 1H), 3.83–3.91 (m, 1H), 4.56–4.59 (m, 1H), 5.28–5.40 (m, 2H), 7.35–7.42 (m, 6H), 7.64–7.69 (m, 4H); ^{13}C NMR (75 MHz): δ 19.6, 25.8, 26.3, 26.6, 27.0, 27.1, 27.2, 27.3, 27.6, 29.8, 30.0, 30.1, 31.1, 32.5, 62.6, 64.0, 67.9, 98.9, 99.1, 127.7, 129.6, 134.2, 135.7. HRMS (CI, CH_4) calcd for $C_{41}H_{67}O_3Si$ (M + 1) m/z 635.4860, found m/z 635.4853.

20-Hydroxyeicosa-5(*Z*)-enoic acid (17). **61** was transformed into **17** as described for the conversion of **56** to **20**. ^{1}H NMR (400 MHz) δ 1.22–1.38 (m, 24H), 1.57 (quintet, J = 6.8 Hz, 2H), 1.70 (quintet, J = 7.6 Hz, 2H), 2.01 (q, J = 6.8 Hz, 1H), 2.10 (q, J = 7.6 Hz, 1H), 2.36 (t, J = 7.8 Hz, 2H), 3.65 (t, J = 6.8 Hz, 2H), 5.29–5.45 (m, 2H); ^{13}C NMR (100 MHz) δ 24.9, 25.9, 26.7, 27.4, 29.4, 29.6, 29.7, 29.72, 29.8, 29.9, 32.9, 33.1, 63.3, 128.4, 131.6, 179.2. HRMS (CI, CH_4) of methyl ester calcd for $C_{21}H_{41}O_3$ (M + 1) m/z 341.3056, found m/z 341.3057.

20-Hydroxyeicosa-15(*Z*)-enoic acid (23). The title compound was obtained from **61** following the procedures described above. ^{1}H NMR (400 MHz) δ 5.41–5.30 (m, 2H), 3.66 (t, J = 6.4 Hz, 2H), 2.38–2.28 (m, 2H), 2.10–2.00 (m, 4H), 1.68–1.56 (m, 4H), 1.46–1.38 (m, 2H), 1.36–1.21 (m, 20H); ^{13}C NMR (100 MHz) δ 179.3, 130.6, 129.5, 63.1, 34.4, 32.5, 29.9, 29.8, 29.75, 29.7, 29.6, 29.5, 29.4, 29.3, 27.4, 27.1, 26.1, 25.0. HRMS (CI, CH_4) of methyl ester calcd for $C_{21}H_{41}O_3$ (M + 1) m/z 341.3056, found m/z 341.3063.

20-Hydroxyeicosanoic acid (25). Saturation of **1** over 10% Pd/C as described for the synthesis of **56** afforded 20-hydroxyeicosanoate[46] (**25**) (98%), mp 86 °C. ^{1}H NMR (250 MHz, CD_3OD) δ 1.20–1.45 (m, 30H), 1.45–1.63 (m, 4H), 2.28 (t, J = 7.4 Hz, 2H), 3.55 (t, J = 6.5 Hz, 2H). ^{1}H NMR (250 MHz) of methyl ester: δ 1.20–1.42 (m, 30H), 1.51–1.68 (m, 4H), 2.32 (t, J = 7.3 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 3.68 (s, 3H).

1-(Tetrahydropyran-2-yloxy)-12-bromo-dodec-5-yne (63). Alkynylation of 1-bromo-6-(*tert*-butyldiphenylsilyloxy)hexane[35] (**62**) with the lithium anion derived from 6-(tetrahydropyran-2-yloxy)hex-1-yne as described above gave 12-(*tert*-butyldiphenylsilyloxy)-1-(tetrahydropyran-2-yloxy)-dodec-5-yne (Scheme 10). ^{1}H NMR (400 MHz) δ 1.05 (s, 9H), 1.32–1.40 (m, 3H), 1.42–1.64 (m, 10H), 1.64–1.77 (m, 3H), 1.78–1.88 (m, 1H), 2.09–2.21 (m, 4H), 3.37–3.44 (m, 1H), 3.46–3.54 (m, 2H), 3.65 (t, J = 6.4 Hz, 2H), 3.71–3.80 (m, 1H),

3.82–3.90 (m, 1H), 4.58 (t, $J=2.4$ Hz, 1H), 7.53–7.44 (m, 6H), 7.64–7.69 (m, 4H). HRMS (CI, CH_4) calcd for $C_{33}H_{49}O_3Si$ (M + 1) m/z 521.3451, found m/z 521.3454.

Desilylation of the above compound yielded 1-(tetrahydropyran-2-yloxy)-dodec-5-yn-12-ol. ^{1}H NMR (400 MHz) δ 1.32–1.62 (m, 14H), 1.65–1.76 (m, 3H), 1.77–1.80 (m, 1H), 2.11–2.22 (m, 4H), 3.37–3.44 (m, 1H), 3.46–3.53 (m, 1H), 3.64 (t, $J=6.7$ Hz, 2H), 3.71–3.79 (m, 1H), 3.82–3.90 (m, 1H), 4.58 (t, $J=2.4$ Hz, 1H). HRMS (CI, CH_4) calcd for $C_{17}H_{31}O_3$ (M + 1) m/z 283.2273, found m/z 283.2291.

Bromination of the above alcohol as described above gave 63. ^{1}H NMR (400 MHz) δ 1.37–1.64 (m, 12H), 1.65–1.76 (m, 3H), 1.78–1.82 (m, 3H), 2.11–2.23 (m, 4H), 3.37–3.45 (m, 3H), 3.46–3.54 (m, 1H), 3.70–3.72 (m, 1H), 3.83–3.91 (m, 1H), 4.58 (t, $J=2.7$ Hz, 1H). HRMS (CI, CH_4) calcd for $C_{17}H_{30}BrO_2$ (M + 1) m/z 345.1429, found m/z 345.1439.

20-(*tert*-Butyldiphenylsilyloxy)-eicosa-5(*Z*),13(*Z*)-dien-1-ol (64). Homologation of **63** using 8-(*tert*-butyldiphenylsilyloxy)oct-1-yne,[36] THP removal, and hydrogenation over P-2 Ni according to Scheme 9 led to **64**. ^{1}H NMR (400 MHz) δ 1.04 (s, 9H), 1.22–1.45 (m, 16H), 1.50–1.62 (m, 4H), 1.95–2.10 (m, 8H), 3.60–3.69 (m, 4H), 5.31–5.40 (m, 4H), 7.34–7.44 (m, 6H), 7.64–7.69 (m, 4H). HRMS (CI, CH_4) calcd for $C_{42}H_{68}O_3Si$ (M + 1) m/z 649.5016, found m/z 649.5014.

20-Hydroxyeicosa-5(*Z*),13(*Z*)-dienoic acid (14). PDC oxidation of **64** and desilylation according to Scheme 9 furnished **14**. ^{1}H NMR (400 MHz) δ 1.23–1.40 (m, 14H), 1.57 (quintet, $J=6.7$ Hz, 2H), 1.69 (quintet, $J=7.3$ Hz, 2H), 1.95–2.13 (m, 8H), 2.34 (t, $J=7.3$ Hz, 2H), 3.65 (t, $J=6.4$ Hz, 2H), 5.27–5.45 (m, 4H). Anal. calcd for $C_{20}H_{36}O_3$: C, 74.03; H, 11.18. Found: C, 73.95; H, 11.24.

20-Hydroxydocosa-15(*Z*)-enoic acid (24). Alkynylation of 1-bromo-12-(tetrahydropyran-2-yloxy)tetradecane[33] (**60**) with the lithium anion derived from 8-(*tert*-butyldiphenylsilyloxy)oct-1-yne[36] yielded **67** (Scheme 11) which was further elaborated to **24** as described for the preparation of **14**. ^{1}H NMR (400 MHz) δ 1.22–1.40 (m, 26H), 1.53–1.68 (m, 4H), 1.97–2.07 (m, 4H), 2.34 (t, $J=7.3$ Hz, 2H), 3.65 (t, $J=6.4$ Hz, 2H), 5.30–5.40 (m, 2H). HRMS (CI, CH_4) calcd for $C_{22}H_{43}O_3$ (M + 1) m/z 355.3212, found m/z 355.3215.

20-Hydroxyeicosa-13(*Z*)-enoic acid (22). Alkynylation of 1-bromo-12-(tetrahydropyran-2-yloxy)dodecane[37] (**65**) with the lithium anion derived from 8-(*tert*-butyldiphenylsilyloxy)oct-1-yne[36] yielded **66** (Scheme 11) which was further elaborated to **22** as described for the preparation of **14**. ^{1}H NMR (400 MHz) δ 1.22–1.40 (m, 22H), 1.52–1.68 (m, 4H), 1.96–2.07 (m, 4H), 2.33 (t, $J=7.6$ Hz, 2H), 3.64 (t, $J=6.7$ Hz, 2H), 5.30–5.40 (m, 2H); ^{13}C NMR (100 MHz) δ 24.9, 25.8, 27.3, 27.4, 29.3, 29.4, 29.5, 29.6, 29.7, 29.74, 29.8, 29.9, 32.8, 34.3, 63.1, 129.9, 130.2, 177.0. HRMS (CI, CH_4) calcd for $C_{20}H_{39}O_3$ (M + 1) m/z 327.2899, found m/z 327.2890.

(*Z*)-20-Hydroxy-15,16-epoxyeicosanoic acid (26). Solvolysis of the THP in **66** as described in Scheme 10 led to 1-(*tert*-butyldiphenylsilyloxy)-eicosa-7(*Z*)-en-20-ol. ^{1}H NMR (400 MHz) δ 1.06 (s, 9H), 1.24–1.40 (m, 24H), 1.48–1.62 (m, 4H), 1.95–2.07 (m, 4H), 2.42 (s, 1H, D_2O exchangeable), 3.63 (t, $J=6.7$ Hz, 2H), 3.66 (t, $J=6.4$ Hz, 2H), 5.29–5.39 (m, 2H), 7.30–7.39 (m, 6H), 7.65–7.70 (m, 4H). HRMS (CI, CH_4) calcd for $C_{36}H_{59}O_2Si$ (M + 1) m/z 551.4284, found m/z 551.4290. Following PDC oxidation of the above alcohol and diazomethane esterification as described in Scheme 9, the olefin was epoxidized by addition to a stirring solution of *m*-chloroperbenzoic acid (57%, 1.5 equiv) in CH_2Cl_2 (10 mL/mmol of olefin). After 6 h, the reaction was quenched using a saturated aq solution of $Na_2S_2O_3$. The organic layer was separated, washed with half-saturated aq $NaHCO_3$ solution, H_2O, brine, and dried. Evaporation in vacuo and SiO_2 purification of the residue afforded methyl (*Z*)-20-hydroxy-15,16-epoxy-eicosanoate (82%). ^{1}H NMR (400 MHz) δ 1.23–1.34 (m, 14H), 1.35–1.54 (m, 10H), 1.55–1.66 (m, 4H), 2.30 (t, $J=7.3$ Hz, 2H), 2.87–2.95 (m, 2H), 3.62 (s, 3H), 3.65 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz) δ 25.1, 25.8, 26.7, 26.8, 27.8, 28.0, 29.3, 29.4, 29.5, 29.6, 29.69, 29.7, 32.8, 34.3, 51.7, 57.4, 57.5, 63.1, 174.6. Saponification yielded **26**: ^{1}H NMR (400 MHz) δ 1.24–1.54 (m, 24H), 1.55–1.67 (m, 4H), 2.34 (t, $J=7.6$ Hz, 2H), 2.88–2.95 (m, 2H), 3.65 (t, $J=6.7$ Hz, 2H); ^{13}C NMR (100 MHz) δ 24.9, 25.8, 26.7, 26.8, 27.9, 28.0, 29.2, 29.5, 29.55, 29.6, 29.7, 32.8, 34.2, 57.5, 57.53, 63.1, 179.1. HRMS (CI, CH_4) calcd for $C_{20}H_{39}O_4$ (M + 1) m/z 343.2848, found m/z 343.2855.

(*Z*)-22-Hydroxy-17,18-epoxy-docosanoic acid (27). Elaboration of **67** as described above led to **27**. ^{1}H NMR (400 MHz) δ 1.26–1.54 (m, 30H), 1.55–1.67 (m, 4H), 2.34 (t, $J=7.3$ Hz, 2H), 2.88–2.95 (m, 2H), 3.65 (t, $J=6.4$ Hz, 2H). HRMS (CI, CH_4) calcd for $C_{22}H_{43}O_4$ (M + 1) m/z 371.3161, found m/z 371.3155.

6-(Tetrahydropyran-2-yloxy)hexyl 13-(*tert*-butyldiphenylsilyloxy)tridec-8-ynyl ether (68). The THP ether in **51** was solvolyzed in methanol (Scheme 12) as described in Scheme 11. The resultant alcohol (9.24 g, 20.5 mmol) was added to a 0 °C suspension of NaH (1.48 g, 61.5 mmol) in THF (205 mL). After stirring for 30 min at room temperature, 1-iodo-6-(tetrahydropyran-2-yloxy)-hexane[47] (7.68 g, 24.6 mmol), 15-crown-5 (452 mg, 2.05 mmol) and *n*-Bu_4NCl (570 mg, 2.05 mmol) were added and the mixture was refluxed for 4 h, then poured into H_2O (500 mL) and extracted with Et_2O (400 mL×2). The combined ethereal extracts were washed with saturated aqueous NH_4Cl (500 mL), dried, concentrated in vacuo and purified via SiO_2 column chromatography to afford **68** (4.04 g, 31%) as a colorless oil. ^{1}H NMR (200 MHz) δ 1.05 (s, 9H), 1.10–1.94 (m, 28H), 2.02–2.22 (m, 4H), 3.27–3.95 (m, 10H), 4.54–4.62 (m, 1H), 7.32–7.48 (m, 6H), 7.61–7.72 (m, 4H); IR (neat) 2934, 2857, 1428, 1361, 1112, 1033, 823, 702, 614, 505 cm^{-1}; MS (ES+) m/z 657 $(M+Na)^+$.

6-(13-Hydroxytridec-8(*Z*)-enyloxy)-hexanoic acid (15). After stirring a methanolic solution (15 mL) of **68** (1.93 g, 3.04 mmol) and PPTS (38 mg) at room temperature

for 2 days, the solvent was remove in vacuo, and the residue was dissolved in EtOAc (50 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo (Scheme 12). Purification of the residue via SiO_2 column chromatography gave 6-[13-(*tert*-butyldiphenylsilyloxy)-tridec-8-ynyloxy]-hexan-1-ol (1.04 g, 62%) as a colorless oil. ^{1}H NMR (200 MHz) δ 1.05 (s, 9H), 1.16–1.88 (m, 23H), 2.05–2.24 (m, 4H), 3.38 (t, J = 6.7 Hz, 2H), 3.39 (t, J = 6.5 Hz, 2H), 3.57–3.76 (m, 4H), 7.31–7.49 (m, 6H), 7.62–7.74 (m, 4H); IR (neat) 3368, 2930, 2857, 1472, 1428, 1111, 823, 741, 702, 614, 505 cm^{-1}; MS (ES+) m/z 573 $(M+Na)^+$. A mixture of the above alcohol (1.03 g, 1.87 mmol), 4-methylmorpholine *N*-oxide (329 mg, 2.80 mmol), tetrapropylammonium perruthenate (32.9 mg, 0.09 mmol), and 4 Å molecular sieves (935 mg) in CH_2Cl_2 (18 mL) was stirred for 2 h, then passed through a pad of SiO_2. The filtrate was concentrated in vacuo and the residue was dissolved in *t*-BuOH (15 mL) and H_2O (3.7 mL) at room temperature. To this was added $NaClO_2$ (574 mg, 6.36 mmol), $NaH_2PO_4{\cdot}2H_2O$ (292 mg, 1.87 mmol) and 2-methyl-2-butene (577 mg, 8.23 mmol). After 1 h, the reaction was diluted with brine (100 mL) and extracted with Et_2O (100 mL×2), dried over $MgSO_4$, and concentrated in vacuo. The residue was dissolved in absolute EtOH (18.7 mL) to which was added Me_3SiCHN_2 (1.87 mL of a 2.0 M solution in hexane, 3.74 mmol) at 0 °C. After 1 h at 0 °C, AcOH (0.2 mL) was added and the mixture was stirred at room temperature overnight. The residue obtained after removal of all volatiles in vacuo was dissolved in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and the residue was purified via SiO_2 column chromatography to give methyl 6-[13-(*tert*-butyldiphenylsilyloxy)-tridec-8-ynyloxy]-hexanoate (719 mg, 66%) as a colorless oil. ^{1}H NMR (200 MHz) δ 1.05 (s, 9H), 1.16–1.74 (m, 20H), 1.98–2.21 (m, 4H), 2.32 (t, J = 7.5 Hz, 2H), 3.37 (t, J = 6.6 Hz, 2H), 3.39 (t, J = 6.5 Hz, 2H), 3.67 (s, 3H), 3.68 (t, J = 6.0 Hz, 2H), 7.31–7.48 (m, 6H), 7.60–7.72 (m, 4H); IR (neat) 2931, 2858, 2359, 1740, 1714, 1462, 1429, 1362, 1169, 1112, 1008, 824, 741, 702, 614, 506, 418, 408 cm^{-1}; MS (ES+) m/z 601$(M+Na)^+$.

n-Bu_4NF (480 mg, 1.84 mmol) was added to a 0 °C solution of the above ester (710 mg, 1.23 mmol) in THF (24.5 mL). After 4 h at room temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (50 mL×2). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo, and the residue was purified via SiO_2 column chromatography to give methyl 6-(13-hydroxytridec-8-ynyloxy)hexanoate (368 mg, 88%) as a colorless oil. ^{1}H NMR (300 MHz) δ 1.22–1.74 (m, 21H), 2.10–2.24 (m, 4H), 2.32 (t, J = 7.5 Hz, 2H), 3.39 (t, J = 6.8 Hz, 2H), 3.40 (t, J = 6.6 Hz, 2H), 3.60–3.71 (m, 2H), 3.67 (s, 3H); IR (neat) 3437, 2935, 2859, 1740, 1730, 1720, 1714, 1698, 1682, 1638, 1628, 1456, 1436, 1364, 1332, 1202, 1169, 1116, 1063, 730 cm^{-1}; MS (ES+) m/z 363 $(M+Na)^+$.

A mixture of the above acetylenic ester (205 mg, 0.60 mmol), Lindlar catalyst (41 mg), and quinoline (20 μg) in absolute EtOH (12 mL) was stirred under H_2 (1 atm). After 2.5 h, the reaction mixture was filtered through a pad of Celite® and concentrated in vacuo. The residue was purified via SiO_2 column chromatography to give methyl 6-(13-hydroxytridec-8(*Z*)-enyloxy)hexanoate (199 mg, 97%) as a colorless oil. ^{1}H NMR (300 MHz) δ 1.24–1.71 (m, 21H), 1.96–2.11 (m, 4H), 2.32 (t, J = 7.5 Hz, 2H), 3.38 (t, J = 6.7 Hz, 2H), 3.40 (t, J = 6.5 Hz, 2H), 3.60–3.69 (m, 2H), 3.67 (s, 3H), 5.29–5.43 (m, 2H); IR (neat) 3436, 3004, 2930, 2857, 1740, 1730, 1714, 1698, 1682, 1456, 1436, 1364, 1202, 1169, 725, 418, 408 cm^{-1}; MS (ES+) m/z 365 $(M+Na)^+$.

A mixture of the above ester (181 mg, 0.528 mmol) and aqueous NaOH (2.1 mL, 1.0 M, 2.1 mmol) in THF/H_2O (5/1, 24.3 mL) was stirred for 3 days at room temperature. The reaction mixture was acidified to pH 4 with aqueous oxalic acid (1.0 M), extracted with EtOAc (50 mL×2), and washed with brine (20 mL). The combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification of the residue via SiO_2 column chromatography gave **15** (170 mg, 98%) as colorless oil. ^{1}H NMR (300 MHz) δ 1.18–1.73 (m, 22H), 1.95–2.11(m, 4H), 2.36 (t, J = 7.5 Hz, 2H), 3.39 (t, J = 6.6 Hz, 2H), 3.40 (t, J = 6.5 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 5.29–5.43 (m, 2H); IR (neat) 3368, 3004, 2930, 2858, 1734, 1718, 1712, 1708, 1702, 1698, 1686, 1682, 1654, 1632, 1456, 1412, 1370, 1234, 1116, 726 cm^{-1}; MS (ES+) m/z 351 $(M+Na)^+$, (ES-) m/z 327 $(M-H)^-$.

Methyl 6-[13-(*tert*-butyldiphenylsilyloxy)-tridec-8(*Z*)-enylsulfanyl]-hexanoate (69). To a vigorously stirred solution of $Ni(OAc)_2{\cdot}4H_2O$ (80 mg, 0.28 mmol) in absolute EtOH (10 mL) under H_2 (1 atm) was added a solution of $NaBH_4$ (21 mg, 0.56 mmol) in absolute EtOH (2 mL) (Scheme 13). After 1 h, a solution of freshly distilled ethylenediamine (0.12 mL, 1.77 mmol) was added followed by 13-(*tert*-butyldiphenylsilyloxy)tridec-8-yn-1-ol (420 mg, 0.93 mmol) (see synthesis of **15** for preparation) in absolute EtOH (6.6 mL). After another 3.5 h, the reaction mixture was diluted with Et_2O (50 mL), filtered through a pad of SiO_2 and concentrated in vacuo. The colorless residue (410 mg, 81%) was sufficiently pure to be used in the next reaction without further purification. ^{1}H NMR (200 MHz) δ 1.05 (s, 9H), 1.10–1.66 (m, 14H), 1.90–2.09 (m, 4H), 3.56–3.72 (m, 4H), 5.25–5.44 (m, 2H), 7.32–7.48 (m, 6H), 7.61–7.74 (m, 4H).

CBr_4 (330 mg, 0.996 mmol), PPh_3 (261 mg, 0.996 mmol), and pyridine (0.081 mL, 0.996 mmol) were added to a 0 °C solution of the above alcohol (410 mg, 0.906 mmol) in CH_2Cl_2 (10 mL). After 4.5 h at room temperature, the reaction mixture was concentrated in vacuo and the residue was purified via SiO_2 column chromatography to give 1-(*tert*-butyldiphenylsilyloxy)-13-bromo-tridec-5(*Z*)-ene (384 mg, 82%) as colorless oil. ^{1}H NMR (200 MHz) δ 1.05 (s, 9H), 1.10–1.68 (m, 12H), 1.72–2.14 (m, 6H), 3.40 (t, J = 6.8 Hz, 2H), 3.66 (t, J = 6.3 Hz, 2H), 5.24–5.44 (m, 2H), 7.32–7.48 (m, 6H), 7.61–7.72 (m, 4H); IR (neat) 3070, 3000, 2930, 2856, 1472, 1462, 1428, 1389, 1362, 1257, 1188, 1112, 998, 939, 824, 741 cm^{-1}; MS (FAB+): m/z 515 $(M + H)^+$.

To a stirred, 0 °C suspension of NaH (18 mg, 0.449 mmol, 60% in oil, washed with hexane) in THF (0.5 mL) was added a solution of methyl 6-mercaptohexanoate (66 mg, 0.407 mmol). After 45 min at room temperature, the above bromide (70 mg, 0.136 mmol) was added at 0 °C. The stirring was continued at room temperature while four further portions of methyl 6-mercaptohexanoate (15 mg, 0.0924 mmol; 18 mg, 0.111 mmol; 25 mg, 0.154 mmol; and 30 mg, 0.185 mmol) were added at 10-min intervals. After stirring for a day at room temperature, the reaction mixture was diluted with Et_2O (50 mL), washed with saturated aqueous NH_4Cl (30 mL) and brine (30 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and the residue was purified via SiO_2 column chromatography to afford **69** (80 mg, 99%) as a colorless oil. ^{1}H NMR (300 MHz) δ 1.04 (s, 9H), 1.21–1.70 (m, 20H), 1.92–2.08 (m, 4H), 2.32 (t, J = 7.5 Hz, 2H), 2.44–2.56 (m, 4H), 3.66 (t, J = 6.4 Hz, 2H), 3.67 (s, 3H), 5.28–5.42 (m, 2H), 7.33–7.46 (m, 6H), 7.61–7.73 (m, 4H); IR (neat) 3070, 2999, 2930, 2855, 1740, 1714, 1590, 1462, 1428, 1389, 1362, 1257, 1198, 1171, 1112, 1008, 940, 824, 741, 702, 688, 614, 506 cm^{-1}; MS (ES+) m/z 619 $(M+Na)^+$.

6-[13-Hydroxytridec - 8(*Z*) - enylsulfanyl]-hexanoic acid (16). Desilyation and saponification of **69** as described in Scheme 12 afforded **16** (60% overall) as a white solid (Scheme 13). ^{1}H NMR (200 MHz) δ 1.21–1.76 (m, 20H), 1.93–2.13 (m, 4H), 2.37 (t, J = 7.4 Hz, 2H), 2.39–2.64 (m, 4H), 3.67 (t, J = 6.4 Hz, 2H), 5.34–5.44 (m, 2H); IR (KBr) 3334, 3002, 2923, 2854, 1690, 1561, 1546, 1509, 1468, 1439, 1410, 1358, 1331, 1286, 1269, 1238, 1198, 1056, 990, 918, 727, 521, 474, 435, 421, 412 cm^{-1}; MS (ES+) m/z 367 $(M+Na)^+$, (ES-) m/z 343 $(M-H)^-$.

2-[5-(Tetrahydropyran - 2 - yloxy) - pent-1-ynyl]benzaldehyde (71). A mixture of 2-bromobenzyl alcohol (**70**) (2.332 g, 12.5 mmol) and $Pd(PPh_3)_4$ (288 mg, 0.25 mmol) in i-Pr_2NH (42 mL) was stirred at 40 °C. After 30 min, 1-(tetrahydropyran-2-yloxy)-pent-4-yne[39] (2.52 g, 150 mmol) was added and the reaction mixture was heated at 85 °C. After 16 h, all volatiles were removed in vacuo and the residue was dissolved with hexane/EtOAc (1/1, 200 mL), washed with saturated aqueous NH_4Cl (100 mL), aqueous HCl (100 mL, 1.0 M), and saturated $NaHCO_3$ (100 mL). The organic layer was dried over $MgSO_4$, concentrated in vacuo, and the residue was purified via SiO_2 column chromatography to afford 2-[5-(tetrahydropyran-2-yloxy)pent-1-ynyl]benzyl alcohol (1.13 g, 33%). ^{1}H NMR (200 MHz) δ 1.42–2.06 (m, 9H), 2.59 (t, J = 7.0 Hz, 2H), 3.44–3.64 (m, 2H), 3.80–3.99 (m, 2H), 4.57–4.68 (m, 1H), 4.80 (s, 2H), 7.17–7.45 (m, 4H); IR (neat) 3437, 3066, 2946, 2870, 2227, 1483, 1452, 1386, 1354, 1323, 1284, 1262, 1201, 1158, 1138, 1120, 1062, 1035, 995, 900, 868, 811, 760, 606 cm^{-1}; MS (ES+) m/z 297 $(M + Na)^+$.

A mixture of the above benzyl alcohol (340 mg, 1.24 mmol) and MnO_2 (3.40 g) in CH_2Cl_2 (25 mL) was vigorously stirred for a day, then filtered through a pad of Celite®, and concentrated in vacuo. The residue was purified via SiO_2 column chromatography to afford **71** (243 mg, 72%). ^{1}H NMR (200 MHz) δ 1.45–2.08 (m, 8H), 2.63 (t, J = 7.1 Hz, 2H), 3.46–3.62 (m, 2H), 3.82–4.00 (m, 2H), 4.59–4.69 (m, 2H), 7.34–7.58 (m, 3H), 7.85–7.94 (m, 1H), 10.55 (d, J = 0.7 Hz, 1H); IR (neat) 2942, 2870, 2228, 1698, 1654, 1595, 1477, 1451, 1387, 1354, 1323, 1274, 1193, 1158, 1137, 1121, 1075, 1034, 993, 900, 869, 825, 764, 638 cm^{-1}; MS (ES+) m/z 295 $(M+Na)^+$.

13-{2 - [5 - (Tetrahydro - pyran - 2 - yloxy) - pent-1-ynyl]-phenyl}-tridec-12-enoic acid (72). A solution of methylsulfinyl carbanion (2.0 mL, 2.0 M, prepared from dimethyl sulfoxide-sodium hydride at 60 °C, 1.5 h) was added to a room temperature solution of 11-carboxyundecyltriphenylphosphonium bromide[40] (497 mg, 0.918 mmol) in dry DMSO (4.0 mL). After 30 min, a solution of **71** (200 mg, 0.734 mmol) in DMSO (1 mL) was added and then warmed to 55 °C. After 24 h, the mixture was acidified to pH 3 with aqueous HCl (1.0 M), extracted with EtOAc (50 mL×2), and washed with brine (30 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo, and purified via SiO_2 column chromatography to give **72** (55 mg, 13%, ca. 1:1 E/Z mixture) as a colorless oil. ^{1}H NMR (200 MHz) δ 1.12–2.11 (m, 24H), 2.16–2.42 (m, 4H), 2.50–2.65 (m, 2H) 3.44–3.64 (m, 2H), 3.82–3.98 (m, 2H), 4.61–4.68 (m, 1H), 5.73 (dt, J = 11.7, 7.1 Hz, 3/5H), 6.27 (dt, J = 15.6, 7.5 Hz, 2/5H), 6.60–6.71 (m, 3/5H), 6.78–6.92 (m, 2/5H), 7.01–7.53 (m, 4H); IR (neat) 2924, 2854, 1734, 1708, 1702, 1478, 1466, 1446, 1354, 1284, 1202, 1138, 1121, 1062, 1035, 1020, 995, 900, 869, 816, 756 cm^{-1}; MS (ES-) m/z 477 $(M+Na)^+$, (ES-) m/z 453 $(M-H)^-$.

3-[2-(5-Hydroxy-pentyl)-phenyl]-tridecanoic acid (18). The THP ether of **72** was removed as described above in 69% yield. ^{1}H NMR (200 MHz) δ 1.02–1.70 (m, 16H), 1.78–1.98 (m, 2H), 2.15–2.36 (m, 4H) 2.52–2.65 (m, 2H), 3.67 (s, 3H), 3.78–3.90 (m, 2H), 5.74 (dt, J = 11.8, 7.4 Hz, 3/5H), 6.27 (dt, J = 15.8, 6.9 Hz, 2/5H), 6.58–6.70 (m, 3/5H), 6.77–6.90 (m, 2/5H), 7.06–7.57 (m, 4H); IR (neat) 3436, 2925, 2854, 2226, 1730, 1714, 1740, 1698, 1682, 1478, 1436, 1352, 1197, 1173, 1098, 1060, 967, 756, 724, 502, 416 cm^{-1}; MS (ES+) m/z 407 $(M+Na)^+$.

Catalytic reduction of the preceding alcohol using hydrogen and Pd/C followed by saponification as described above gave **18** as a colorless oil. ^{1}H NMR (200 MHz) δ 1.16–1.76 (m, 26H), 2.35 (t, J = 7.4 Hz, 2H), 2.52–2.70 (m, 4H), 3.58–3.78 (m, 2H), 7.06–7.24 (m, 4H); IR (neat) 3368, 3016, 2925, 2854, 1712, 1702, 1708, 1686, 1681, 1654, 1648, 1490, 1466, 1412, 1243, 1047, 751, 504 cm^{-1}; MS (ES+) m/z 399 $(M+Na)^+$, (ES-) m/z 375 $(M-H)^-$.

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