Total Synthesis of Patulolide C and Its Homo, Nor, and Iso Analogs

Frank M. C. Leemhuis, Lambertus Thijs, and Binne Zwanenburg*

Department of Organic Chemistry, NSR Center for Molecular Structure, Design and Synthesis, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

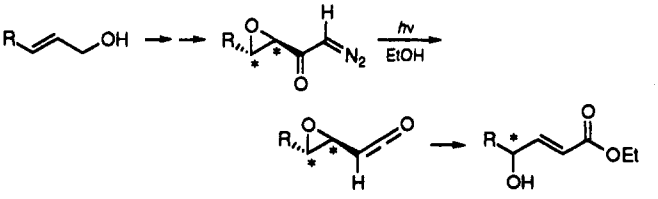
Received March 2, 1993 (Revised Manuscript Received September 8, 1993•)

The stereospecific total synthesis of the naturally occurring macrolide patulolide C **19*E*b** as well as its iso, nor, and homo analogs is described by applying the photoinduced rearrangement of enantiomerically pure epoxy diazomethyl ketones **14** to γ-hydroxy α,β-unsaturated esters **15** as the key step. The required epoxy diazomethyl ketones **14** are obtained by a Sharpless epoxidation of an appropriate allylic alcohol, followed by ruthenium tetraoxide oxidation to an oxiranecarboxylic acid, conversion into a mixed anhydride, and treatment with diazomethane. Macrolide **19*Z*b**, which is a geometrical isomer of **19*E*b**, turned out to be a diastereomer of natural macrolide isopatulolide C, which implies the 4*R*,11*R* configuration for this natural material. X-ray diffraction analyses of **19*E*a** and **19*E*b** show that there is a considerable difference in spatial arrangement; particularly, the different torsion angles between the carbonyl and olefinic bonds are noteworthy. The conformational behavior of these macrolides is also deduced from the NMR and UV spectra.

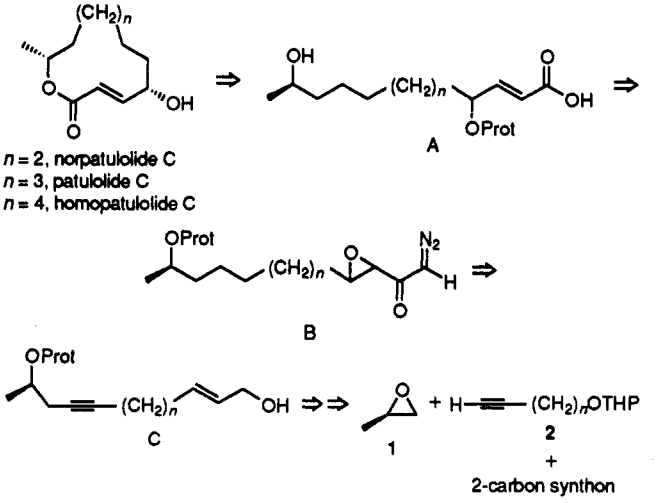
In our study of the chemistry of functionalized epoxides, we showed that epoxy diazomethyl ketones undergo an interesting photoinduced rearrangement leading to γ-hydroxy α,β-unsaturated esters.[1,2] Initially, an epoxy ketene is being formed,[1] which subsequently reacts with an alcoholic solvent to give a hydroxy alkene ester (Scheme I). With optically active substrates, which are readily accessible from allylic alcohols using the Sharpless epoxidation and subsequent oxidation to the corresponding oxiranecarboxylic acids, the γ-hydroxy function in these alkene esters can be introduced in an enantiocontrolled fashion.[2] The conversion of allylic alcohols into γ-hydroxy alkene esters is of synthetic value as was demonstrated by the total synthesis of various naturally occurring macrocyclic lactones such as aspicilin,[3] colletallol,[4] and pyrenophorol[5] and the macrocyclic subunit of cytochalasan B.[6]

In this paper, we describe the total synthesis[7] of patulolide C, a macrolide that has been isolated from the culture broth of *Penicillium urticae*.[8,9] In addition, the synthesis of the 11-membered ring (norpatulolide C) and 13-membered ring (homopatulolide C) analogs as well as the corresponding *Z* isomers of these three patulolides will be reported. The retrosynthesis of patulolide C and its nor and homo analogs is outlined in Scheme II. Delactonization leads to diol alkene acid **A** which in principle is accessible via epoxy diazomethyl ketone **B** by applying the chemistry shown in Scheme I. The required allylic alcohol **C** can be built up from methyloxirane, an acetylenic alcohol, and a suitable two-carbon synthon. The involvement of enantiomerically pure methyloxirane ensures the introduction of the chiral center adjacent to the lactone oxygen.

Scheme I



Scheme II



Results and Discussion

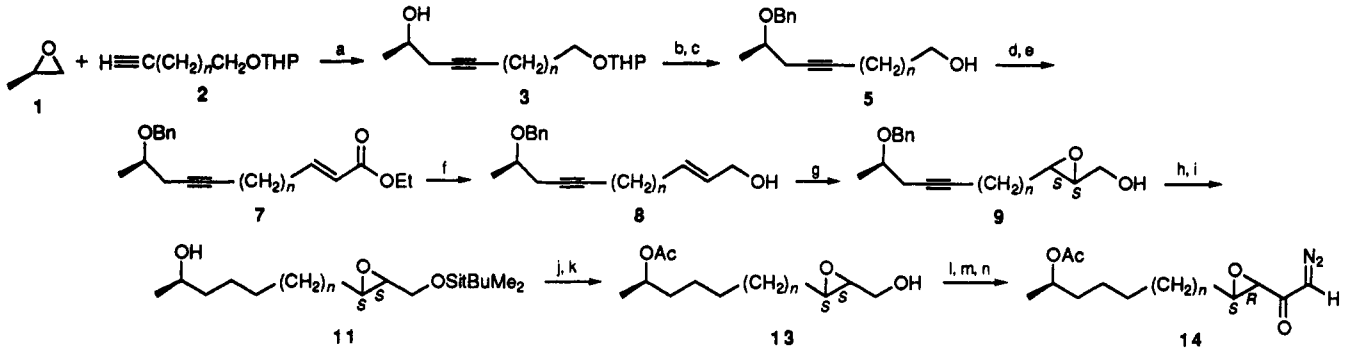
The actual synthesis of the epoxy diazomethyl ketones **B** is shown in Scheme III. The alkynols, viz 4-pentyn-1-ol,[10] 5-hexyn-1-ol,[11] and 6-heptyn-1-ol,[12] required for the opening of (*R*)-(+)-methyloxirane[13] (**1**) were prepared by known procedures. The secondary alcohol function obtained in this ring-opening reaction was protected as a benzyl ether.[14] Chain elongation of compounds **5** was achieved by oxidizing the primary alcohol of **5** to an

• Abstract published in *Advance ACS Abstracts*, October 15, 1993.

(1) van Haard, P. M. M.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1975**, 803.
(2) Thijs, L.; Dommerholt, F. J.; Leemhuis, F. M. C.; Zwanenburg, B. *Tetrahedron Lett.* **1990**, *31*, 6589.
(3) Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 2409.
(4) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1495.
(5) Dommerholt, F. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1499.
(6) Thijs, L.; Stokkingreef, E. H. M.; Lemmens, J. M.; Zwanenburg, B. *Tetrahedron*, **1985**, *41*, 2949.
(7) Thijs, L.; Egenberger, D. M.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 2153.
(8) Sekiguchi, J.; Kuroda, H.; Yamada, Y.; Okada, H. *Tetrahedron Lett.* **1985**, *26*, 2341.
(9) Rodphaya, D.; Sekiguchi, J.; Yamada, Y. *J. Antibiot.* **1986**, *39*, 629.
(10) Eglinton, G.; Jones, E. R. H.; Whiting, M. C. *J. Chem. Soc.* **1952**, 2873.
(11) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Amsterdam: Elsevier, 1988; p 61.

0022-3263/93/1958-7170$04.00/0

Scheme III



	reaction conditions	chemical yields (%)		
		$n=2$	$n=3$	$n=4$
a	BuLi, HMPA, THF	46	65	86
b	BnBr, n-Bu_4NI, THF	75	68	90
c	p-TosOH, MeOH	93	99	94
d	Et_3N, $(COCl)_2$, DMSO, CH_2Cl_2	94	99	95
e	$(EtO)_2P(O)CH_2COOEt$, LiCl, i-Pr_2NEt, CH_3CN	74	75	87
f	DIBALH, Et_2O	78	80	97
g	$Ti(O\text{-}i\text{-}Pr)_4$, L(+)-DET, t-BuOOH, CH_2Cl_2	94	92	78
h	t-$BuMe_2SiCl$, imidazole, DMF	94	99	99
i	H_2/Pd/C, EtOH	72	65	70
j	Ac_2O, pyridine, DMAP	100	92	96
k	n-Bu_4NF, THF	90	92	99
l	$RuCl_3 \cdot H_2O$, $NaIO_4$, CH_3CN, CCl_4, H_2O			
m	ClCOO-i-Bu, Et_3N, THF			
n	CH_2N_2, Et_2O	63[a]	63[a]	69[a]

[a] Yields after step l, m, and n.

aldehyde group using the Swern oxidation and a subsequent Wittig–Horner coupling with triethyl phosphonoacetate using lithium chloride and diisopropylethylamine as condensing agents.[15] The thus-obtained (*E*)-alkene esters **7** were reduced with DIBALH to allylic alcohols **8**, which were subjected to a Sharpless epoxidation[16] using L-(+)-diethyl tartrate as chiral inductor to give *S,S* epoxy alcohols **9** in excellent chemical and optical yields as was evident from extensive GC analysis of **9** and product **10** derived thereof (the *R,R,R* diastereomers were only present in minor amounts, less than 5%).

After proper protection[17] of the primary alcohol function, the triple bond was removed by hydrogenation together with the benzyl protecting group. In fact, this benzyl ether function was chosen as the protecting group in **3** for this purpose, allowing the introduction of an acetate at this position which is appropriate for the rest of the sequence. After liberation of the primary alcohol with fluoride, alcohols **13** were converted into diazo ketones **14** successively by oxidation with ruthenium oxide[18] to the corresponding oxiranecarboxylic acids, treatment with isobutyl chloroformate to give mixed anhydrides, and addition of excess of diazomethane. It should be noted that an alternative to the ruthenium oxide method is a two-step procedure involving first a Swern oxidation to the aldehyde and then conversion to the epoxy acid using sodium chlorite.[19] This last-mentioned methodology is more generally applicable. The yields of epoxy diazomethyl ketones based on epoxy alcohols **13** are in the range of 50–70% for both oxidation routes.

Irradiation of key intermediates **14** at 300 nm in ethanol resulted in γ-hydroxy α,β-unsaturated esters **15**, which were immediately protected as silyl ethers (Scheme IV). It should be noted that for this protection a 2-fold excess of silylating agent was required to achieve complete conversion. Chromatography of thus-obtained compounds **16** gave predominantly the *E* isomers, along with a small amount of the *Z* isomers. In all three cases the *E*:*Z* ratio amounted to 10:1. The formation of *E* as well as *Z* alkene esters has been explained previously.[2] In the present case, advantage was taken of this production of both geometrical isomers of alkene esters **16** as it enabled us to prepare the corresponding *Z* isomers of the target macrolides. Accordingly, both isomers of **16** were deprotected to hydroxy acids **17*E*** and **17*Z***, respectively. This deprotection was performed with either lithium hydroxide in THF or sodium hydroxide in ethanol. The acetate function is readily saponified; however, the unsaturated ester was removed very slowly. The use of pig liver esterase was explored for the hydrolysis of the alkene ester; however, the results were disappointing.

For the macrolactonization of **17*E*b**, several methods were investigated, namely, the Masamune reaction using diethyl phosphochloridate,[20] closure with (trimethylsilyl)-ethoxyethyne,[21] and reaction with cyanuric chloride[22] and

(12) 6-Heptyn-1-ol was prepared in the followimg manner: tetrahydropyran and acetyl bromide were heated in the presence of $ZnBr_2$ (Ames, D. E.; Islip, P. J. *J. Chem. Soc.* **1963**, 4363). Removal of the acetyl function with K_2CO_3 in MeOH gave 5-bromopentanol. Protection of the alcohol function with dihydropyran and coupling with lithium acetylide gave the corresponding 6-heptyn-1-ol.

(13) (a) Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316. (b) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1985**, *50*, 470.

(14) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

(15) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(16) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

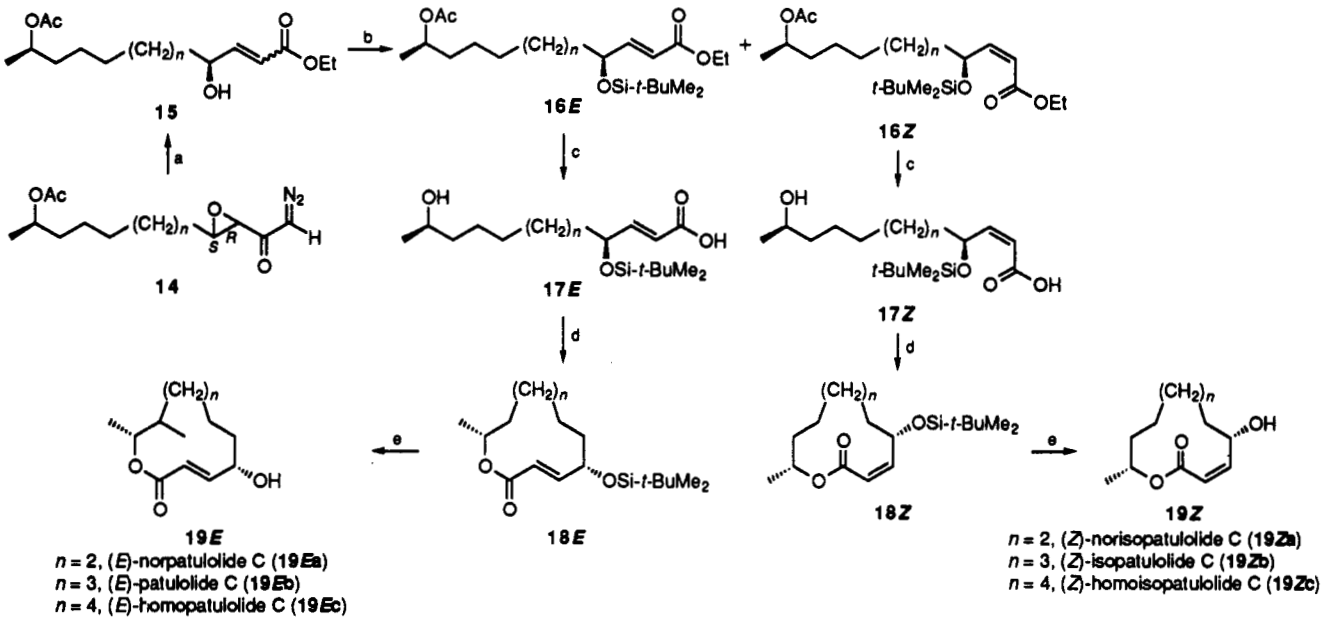
(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(19) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(20) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

Scheme IV



	reaction conditions	chemical yield (%)					
		n = 2		*n* = 3		*n* = 4	
		E	***Z***	***E***	***Z***	***E***	***Z***
a	*hν* (300 nm), EtOH	89		98		99	
b	*t*-$BuMe_2SiCl$, imidazole, DMAP, DMF	46	3	48	6	42	4
c	LiOH, THF–H_2O 1:1, or	97			71		
	NaOH, EtOH		99	99		97	99
d	2,6-$Cl_2C_6H_3C(O)Cl$, Et_3N, THF; DMAP, toluene	58	30	67	32	28	21
e	TBAF, THF, or	56	71	69	64	66	
	CH_3COOH/THF/H_2O 3:1:1						49

DMF/$SOCl_2$.[23] None of these conditions resulted in the desired lactonization. Better results were obtained by applying the Yamaguchi procedure,[24] as previously used by us in a slightly modified form.[3,4,5,7] In all six cases, acceptable yields of silyl-protected macrolides **18** were obtained. However, during ring closure of **17Zb** to **18Zb**, considerable *Z* to *E* isomerization was observed, producing a mixture of **18Eb** and **18Zb** in a ratio of approximately 1:1. A similar isomerization has been noticed by Mori *et al.*[25] Apparently the ring strain in the macrolide causes isomerization probably induced by the (dimethylamino)-pyridine (DMAP) via an addition/elimination reaction, although *Z* to *E* isomerization prior to the ring-closure reaction is a possibility that must be considered. Keck *et al.*[26] used a DMAP-catalyzed *Z* to *E* isomerization to obtain pure *trans* unsaturated thiol esters.

The final step involves the removal of the silyl protecting function, which was performed with TBAF in THF at 0 °C in the usual manner.[17] However, these conditions failed for **19Zc**, which had to be deprotected with 3:1:1 acetic acid/THF/H_2O. All six products were purified by flash chromatography and characterized by spectral measurements [^{1}H NMR (400 MHz), ^{13}C NMR, IR, MS, and peak match].

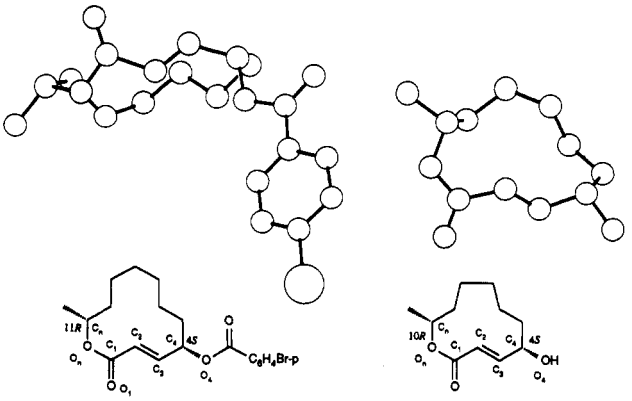
The spectral features of **19Eb** were identical with those obtained[27] from authentic natural patulolide C. This was not the case, however, for the optical rotation. For natural patulolide C, an $[\alpha]^{25}_D$ value of −1.89° [*c* 2, EtOH] has been reported,[9] while for **19Eb**, an $[\alpha]^{20}_D$ value of +6.6° [*c* 0.4, EtOH] was determined. X-ray diffraction analysis[28] of the *p*-bromobenzoate of **19Eb** (mp 136–138 °C, lit.[9] mp 134–135 °C) confirmed our conviction that the reported rotation for the natural product is not correct.

The detailed pattern of the ^{1}H NMR spectrum of (*E*)-norpatulolide C (**19Ea**) was rather different from that of (*E*)-patulolide C (**19Eb**) (*vide infra*). Therefore, the structure of (*E*)-norpatulolide C (**19Ea**) was ascertained by X-ray diffraction analysis.[29] The absolute configuration was established for both compounds and is 4*S*,10*R* for (*E*)-norpatulolide C (**19Ea**) and 4*S*,11*R* for (*E*)-patulolide C (**19Eb**).

It is of interest to note that (*Z*)-isopatulolide C has recently been isolated from the culture broth of *P. urticae*

(21) Kita, Y.; Akai, S.; Yamamoto, M.; Taniguchi, M.; Tamura, Y. *Synthesis* **1989**, 334.
(22) (a) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893. (b) Ayyangar, N. R.; Chanda, B.; Wakharkar, R. D.; Kasar, R. A. *Synth. Commun.* **1988**, *18*, 2103.
(23) Arrieta, A.; Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1984**, *25*, 3365.
(24) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(25) Mori, K.; Sakai, T. *Liebigs Ann. Chem.* **1988**, 13. See also: Yvergnaux, F.; Le Floc'h, Y.; Gree, R. *Tetrahedron Lett.* **1989**, *30*, 7393.
(26) (a) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896. (b) Keck, G. E.; Murry, J. A. *J. Org. Chem.* **1991**, *56*, 6606. (c) Keck, G. E.; Boden, E. P.; Mayburry, S. J. *J. Org. Chem.* **1985**, *50*, 709.
(27) We thank Professor Y. Yamada of the Osaka University in Japan for supplying us the physicochemical data of the natural compounds patulolide C and isopatulolide C.
(28) Beurskens, G.; Smits, J. M. M.; Beurskens, P. T.; Thijs, L., Egenberger, D. M.; Zwanenburg, B. *J. Crystallogr. Spectrosc. Res.* **1989**, *19*, 919.
(29) Details will be published elsewhere. Admiraal, G.; Beurskens, P. T.; Leemhuis, F. M. C.; Thijs, L.; Zwanenburg, B. *J. Crystallogr. Spectrosc. Res.*

Table I



(*E*)-patulolide C (**19Eb**) (*E*)-norpatulolide C (**19Ea**)

entry	patulolide C	norpatulolide C
C_1–C_2	1.517 Å	1.484 Å
C_2–C_3	1.200 Å	1.318 Å
C_1–O_1	1.197 Å	1.210 Å
O_1–C_1–C_2–C_3	26.7°	48.1°
C_2–C_3–C_4–O_4	17.2°	129.0°
O_1–C_1–O_n–C_n	−26.9°	−166.3°

mutant S11R59.[30] The configuration at C_{11} was assumed to be *R* as in all related patulolides; the *R* configuration was suggested for C_4 although no unambiguous evidence was provided. This natural compound has an $[\alpha]^{20}_D$ of −70.5° (*c* 2.4, EtOH),[27] which is almost the same value but opposite in sign of that observed for the synthetic material **19Zb** ($[\alpha]^{20}_D$ +71°) described above. These data would suggest that the natural and synthetic compound are enantiomers, but their ^{1}H NMR spectra are distinctly different although both have the same absorption characteristics and are in full accord with the (*Z*)-isopatulolide structure. Our synthetic compound has the 4*S*,11*R* configuration as is evident from its synthesis; therefore we suggest that the natural product mentioned above is diastereomeric with **19Zb** and has the 4*R*,11*R* configuration.

The conformations of the respective macrolides deserve some further comments. It is already apparent from the X-ray structures of (*E*)-norpatulolide C (**19Ea**) and (*E*)-patulolide C (**19Eb**) that there is a considerable difference in spatial arrangement. In Table I the most important structural parameters taken from the X-ray structures are listed. The different torsion angles between the carbonyl and olefinic bonds are particularly noteworthy. These angles indicate that in both compounds ring strain enforces an out of plane twist of the enone moiety, most strikingly in the 11-membered ring lactone. As a consequence, there will be loss of conjugation in this enone unit. Nonplanarity of the enone moiety has also been observed for other macrocyclic α,β-unsaturated lactones.[31]

The conformational differences of these macrolides are also reflected in their spectral features. The essential spectral data of the six macrolides **19** are collected in Table II. Loss of conjugation in the alkene ester unit will result in a more isolated double bond character, hence, a less polarized double bond. Both in the ^{1}H NMR and ^{13}C NMR such a diminished conjugation will lead to a smaller difference in chemical shift of the olefinic protons and carbon atoms, respectively, compared to the more conjugated case. In the UV spectrum, loss of conjugation results in a hypsochromic effect when compared with an unstrained "open" compound, for which ethyl (*E*)-4-hydroxynon-2-enoate (**20**)[2] was taken as reference in the present case. The data in Table II reveal that in the *E* series (*E*)-norpatulolide C (**19Ea**) is the most strained molecule. The 12- and 13-membered ring lactones are much less deformed and show rather normal data compared with the open chain compound **20**. The iso series (**19Z**) also exhibits considerable ring strain as is indicated by the difference in chemical shift of the olefinic protons and carbon atoms, respectively. The same is reflected in the UV spectra. Apparently both (*Z*)-norisopatulolide C and (*Z*)-homoisopatulolide C almost completely loose the alkene ester conjugation.

^{1}H NMR spectra of **19Ea** have been recorded in solvents other than $CDCl_3$ and show a high solvent dependency. In particular, the positions of the olefinic protons in the spectrum change considerably. Figure 1 shows the chemical shifts of the olefinic protons when recorded in $CDCl_3$ and in CD_3CN. The spectra of **19Ea** in acetone-d_6 and methanol-d_4 were very similar to that recorded in CD_3CN (Table III). In these polar solvents proton H_2 is observed at lower field than H_3. This can be interpreted in terms of a twist of the C=CC=O moiety, which causes deconjugation and a more localized charge on the carbonyl function. This twisted conformation is apparently stabilized by polar solvents. Another phenomenom could be the compressing effect of polar solvents on the apolar paraffinic methylene groups, causing a further increase of the torsion angle (Table I). The UV spectra of **19Ea** are consistent with these NMR results. A maximum absorption at 205 nm was found when the spectrum was recorded in isooctane; in acetonitrile this absorption appeared at 194 nm. In general, for α,β-unsaturated carbonyl compounds[32] the increase of solvent polarity will cause a red shift of the maximum absorption. In our case the opposite, a blue shift, was found. This solvent dependence is an interesting aspect in view of conformationally controlled reactions with macrolides, which appear frequently in the literature.[33]

In conclusion, the strategy for the total synthesis of patulolides as outlined in Scheme II successfully leads to the desired 11-, 12-, and 13-membered macrolides. In addition, the corresponding macrolides with a *cis* double bond could also be prepared. The six macrolides show remarkable differences in their conformational behavior.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded on a Varian EM 390 (90 MHz, CW), a Bruker WH 90 (90 MHz, FT), a Bruker AM 100 (100 M Hz, FT), or a Bruker AM 400 (400 MHz, FT) spectrometer with TMS, $CHCl_3$, or CH_2Cl_2 as internal standard. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer and UV spectra on a Perkin-Elmer Lambda 5 UV/vis spectrophotometer. For mass spectroscopy a double focusing VG 7070 E was used. For the chemical ionization (CI) technique, methane was used as reacting gas. GC was performed

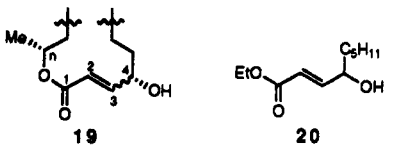
(30) Rodphaya, D.; Nihira, T.; Yamada, Y. *J. Antibiot.* **1989**, 752.

(31) (a) Amstutz, R.; Hungerbühler, E.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 1796. (b) Quinkert, G.; Heim, N.; Bats, J. W.; Oschkinat, H.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 987. (c) Weber, H. P.; Hauser, D.; Sigg, H. P. *Helv. Chim. Acta* **1971**, *54*, 2763.

(32) Hesse, M.; Meier, H.; Zeeh, B. *Spektroskopische Methoden in der organischen Chemie*; Georg Thieme Verlag: Stuttgart, 1987.

(33) (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (b) Vedejs, E.; Dent, W. H., III; Gapinski, D. M.; McClure, C. K. *J. Am. Chem. Soc.* **1987**, *109*, 5437. (c) Keller, T. H.; Weiler, L. *Tetrahedron Lett.* **1990**, *31*, 6307. (d) Takahashi, T.; Yokoyama, H.; Haino, T.; Yamada, H. *J. Org. Chem.* **1992**, *57*, 3521. (e) Fouque, E.; Rousseau, G.; Seyden-Penne, J. *J. Org. Chem.* **1990**, *55*, 4807.

Table II



	^{1}H NMR ($CDCl_3$, ppm)								^{13}C NMR ($CDCl_3$, ppm)			UV (CH_3CN, nm)	
compd	δH_2	δH_3	$\delta H_3-\delta H_2$	δH_4	δH_n	J_{23}	J_{34}	J_{24}	C_1	C_2	C_3	λ_{max}	ϵ_{max}
19*E*a[a]	6.34	6.46	0.12	4.40	4.65	16.1	8.9		168.87	122.61	145.70	194	8058[b]
19*E*b	6.07	6.82	0.75	4.45	5.04	16.5	6.0	1.2	168.09	121.49	149.69	208	7380
19*E*c	6.02	6.89	0.87	4.50	5.11	15.8	6.9	1.0	166.93	121.46	149.38	206	10440
19*Z*a	5.87	5.91	0.05	4.82	5.02	12.0	7.1		166.82	122.05	143.75	191	1529
19*Z*b	5.79	6.02	0.23	5.12–5.02		11.9	8.5		166.38	121.08	146.80	201	8967
19*Z*c	5.88	5.90	0.04	5.26–5.13		11.4	8.4		166.78	121.93	146.21	<190	
20	6.02	6.93	0.91	4.28		16.0	5.0	1.5	167.2	119.30	151.30	208	8756

[a] For ^{1}H-NMR spectrum in CD_3CN, see Experimental Section. [b] In isooctane, λ_{max} = 205 nm, ϵ_{max} = 7180.

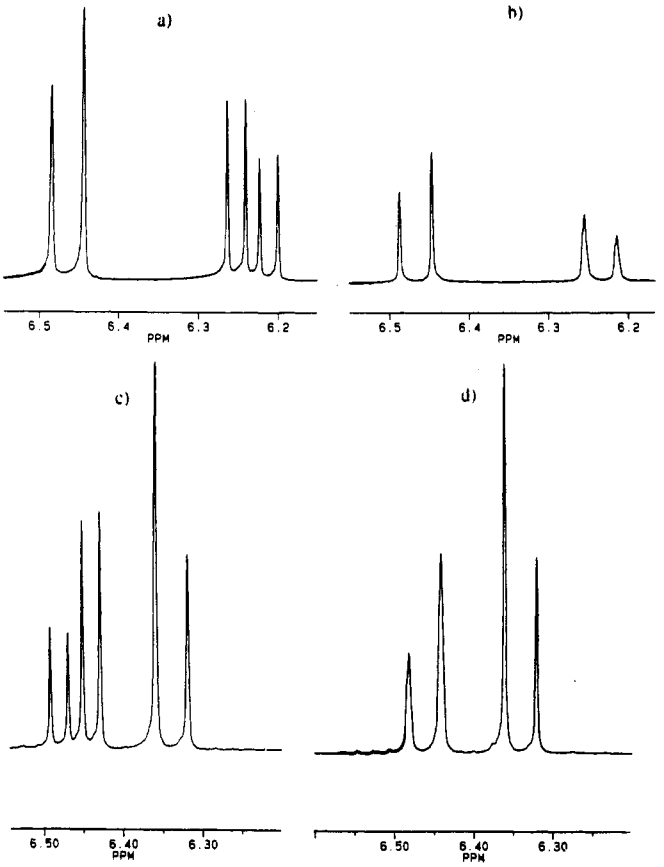


Figure 1. (a) ^{1}H-NMR spectrum of 19*E*a in CD_3CN. (b) ^{1}H-NMR spectrum of 19*E*a in CD_3CN, irradiated at H_4. (c) ^{1}H-NMR spectrum of 19*E*a in $CDCl_3$. (d) ^{1}H-NMR spectrum of 19*E*a in $CDCl_3$, irradiated at H_4.

Table III

solvent	H_2 (ppm)	H_3 (ppm)	J_{23} (Hz)	J_{34} (Hz)
$CDCl_3$[a]	6.34	6.46	16.1	8.9
CD_3CN[a]	6.46	6.23	16.2	9.2
acetone-d_6[b]	6.45	6.20	16.0	8.1
CD_3OD[b]	6.59	6.29	16.0	8.4

[a] 400-MHz ^{1}H NMR. [b] 90-MHz ^{1}H NMR.

on a Hewlett-Packard 5790A or 5890 instrument equipped with a capillary HP cross-linked silicone (25 m × 0.31 mm) column, connected to a HP 3390 or HP 5890 calculating integrator. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Melting points were determined on a Reichert Thermopan microscope and are uncorrected. Column chromatography was performed with silica gel 60H (Merck). A pressure of 1.5–2.0 bar was used to obtain the necessary flow rate.

Dry solvents were obtained as follows. Petroleum ether (60–80 °C) was distilled from NaH. CH_2Cl_2 was distilled from P_2O_5. Et_2O was predried on $CaCl_2$ and then distilled from CaH_2. THF was distilled from $LiAlH_4$. Pyridine, Et_3N, diisopropylethylamine were distilled from KOH. DMSO was distilled from CaH_2. Toluene was distilled from sodium. All other solvents were of either p.a. or "reinst" quality. *n*-BuLi and DIBALH were used as stock solutions of 1.6 and 1.0 M in hexane, respectively.

(*R*)-8-(Tetrahydropyranyl-2-oxy)-4-octyn-2-ol (3a). *n*-BuLi (1.6 M in hexane, 56 mL, 90.3 mmol) was added to a solution of **2a** (15.17 g, 90.3 mmol) in THF (200 mL) at −78 °C under an argon atmosphere. After 45 min at 0 °C, the reaction mixture was cooled to −50 °C and HMPA (25 mL) and (*R*)-methyloxirane (1) (5 g, 86 mmol) were rapidly added, and the reaction mixture was allowed to reach rt. After being stirred overnight, the dark brown reaction mixture was quenched with 50 mL of 5 N NH_4Cl and the layers were separated. The aqueous layer was extracted three times with hexane. The combined organic layers were washed with water, dried with $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc 5:1) gave 9.46 g of **3a** (41.9 mmol, 46%) and 3.38 g of recovered **2a**. **3a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.55 (s, 1H), 4.07–3.30 (m, 5H), 2.43–3.13 (m, 4H), 2.57 (s, 1H), 1.95–1.33 (m, 8H), 1.26 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3640–3100, 3580; MS (CI$^+$) *m/e* (rel intensity) 227 (M^+ + 1, 8), 209 (4), 143 (23), 125 (13), 85 (100).

(*R*)-9-(Tetrahydropyranyl-2-oxy)-4-nonyn-2-ol (3b). The procedure described for **3a** was followed. From 12.7 g of **2b** (70 mmol) and 4.4 g of (*R*)-methyloxirane (76 mmol), 11 g of **3b** (45.8 mmol, 65%) was obtained after chromatography (hexane/EtOAc 3:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.57 (s, 1H), 4.20–3.25 (m, 5H), 2.43–2.05 (m, 4H), 2.00 (s, 1H), 1.92–1.37 (m, 10H), 1.23 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3640–3200; MS (CI$^+$) *m/e* (rel intensity) 241 (M^+ + 1, 3), 223 (7), 205 (1), 157 (62), 139 (53), 85 (100).

(*R*)-10-(Tetrahydropyranyl-2-oxy)-4-decyn-2-ol (3c). The procedure described for **3a** was followed. From 13.5 g of **2c** (69 mmol) and 4.0 g of (*R*)-methyloxirane (69 mmol), 15.0 g of **3c** (59 mmol, 86%) was obtained after chromatography (hexane/EtOAc 3:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.59 (bs, 1H), 4.13–4.20 (m, 5H), 2.43–2.00 (m, 4H), 1.93–1.33 (m, 12H), 1.23 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3620–3120, 3580; MS (CI$^+$) *m/e* (rel intensity) 255 (M^+ + 1, 15), 237 (2), 171 (85), 153 (9), 85 (100).

(*R*)-7-(Benzyloxy)-1-(tetrahydropyranyl-2-oxy)-4-octyne (4a). A solution of **3a** (9.3 g, 41 mmol) in 70 mL of THF under an argon atmosphere was treated with NaH (1.34 g, 44.5 mmol), followed by addition of *n*-Bu_4NI (151 mg, 0.41 mmol) and benzyl bromide (7 g, 41 mmol). After being stirred overnight, the reaction mixture was quenched with 70 mL of water and THF was evaporated. The resulting mixture was extracted three times with ether. The organic layers were combined, washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. Chromatography (hexane/EtOAc 10:1) gave **4a** (9.69 g, 30.7 mmol) in a yield of 75%: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.40–7.12 (m, 5H), 4.57 (s, 3H), 4.04–3.31 (m, 5H), 2.53–2.09 (m, 4H), 2.00–1.40 (m, 8H), 1.29 (d, 3H, J = 6 Hz); MS (CI$^+$) *m/e* (rel intensity) 317 (M^+ + 1, 2), 233 (32), 215 (15), 91 (67), 85 (100).

(*R*)-8-(Benzyloxy)-1-(tetrahydropyranyl-2-oxy)-5-nonyne (4b). The procedure described for **4a** was followed. From 11.36 g of **3b** (47.3 mmol), 10.6 g of **4b** (32.1 mmol) was obtained after chromatography (hexane/EtOAc 7:1) in a yield of 68%: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.20 (m, 5H), 4.50 (s, 3H), 4.10–3.22 (m, 5H), 2.50–2.05 (m, 4H), 1.90–1.40 (m, 10H), 1.27 (d, 3H, J = 6 Hz); MS (CI$^+$) m/e (rel intensity) 331 (M^+ + 1, 19), 247 (100), 229 (22).

(*R*)-9-(Benzyloxy)-1-(tetrahydropyranyl-2-oxy)-6-decyne (4c). The procedure described for **4a** was followed. From 14.55 g of **3c** (57.3 mmol), 19 g of crude **4c** was obtained as a slightly yellowish oil which was sufficiently pure for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.57–7.12 (m, 5H), 4.77–4.55 (m, 3H), 4.07–3.20 (m, 5H), 2.67–2.00 (m, 4H), 2.00–1.20 (m, 12H), 1.27 (d, 3H, J = 6 Hz).

(*R*)-7-(Benzyloxy)-4-octyn-1-ol (5a). *p*-TsOH (160 mg, 0.93 mmol) was added to a solution of **4a** (9.90 g, 31 mmol) in 70 mL of MeOH. After the solution was stirred for 2 h, 4 mL of saturated $NaHCO_3$ was added and the MeOH was evaporated. Water was added and the solution was extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. **5a** (6.67 g) was obtained as a colorless oil, after chromatography (hexane/EtOAc 3:1), in a yield of 93%: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.10 (m, 5H), 4.53 (s, 2H), 3.83–3.48 (m, 3H), 2.48–2.10 (m, 5H), 1.70 (sext., 2H), 1.23 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3630, 3700–3200; MS (CI$^+$) m/e (rel intensity) 233 (M^+ + 1, 49), 215 (100), 187 (14), 125 (22), 91 (90).

(*R*)-8-(Benzyloxy)-5-nonyn-1-ol (5b). The procedure described for **5a** was followed. From 10.3 g of **4b** (31.2 mmol), 7.6 g of **5b** was obtained which was sufficiently pure (98% on GC) for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.47–7.10 (m, 5H), 4.55 (s, 2H), 3.80–3.43 (m, 3H), 2.50–2.07 (m, 4H), 1.98 (bs, 1H), 1.83–1.43 (m, 4H), 1.28 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3640, 3600–3100; MS (CI$^+$) m/e (rel intensity) 247 (M^+ + 1, 3), 229 (7), 211 (4), 173 (25), 135 (32), 105 (71), 91 (90).

(*R*)-9-(Benzyloxy)-6-decyn-1-ol (5c). The procedure described for **5a** was used. From 19 g of crude **4c** (55 mmol), 13.44 g of pure **5c** (51.7 mmol, 94%) was obtained, after chromatography (hexane/EtOAc 2:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.43–7.13 (m, 5H), 4.53 (s, 2H), 3.83–3.43 (m, 3H), 2.70–1.90 (m, 4H), 1.80 (bs, 1H), 1.70–1.37 (m, 6H), 1.23 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3630, 3600–3100; MS (CI$^+$) m/e (rel intensity) 261 (M^+ + 1, 2), 243 (21), 225 (1), 91 (100).

(*R*)-7-(Benzyloxy)-4-octynal (6a). Oxalyl chloride (2.49 mL, 28.7 mmol) was dissolved in 60 mL of CH_2Cl_2 at −78 °C under an argon atmosphere and DMSO (4.29 mL, 60.6 mmol) in 8 mL of CH_2Cl_2 and **5a** (6.66 g, 28.7 mmol) in CH_2Cl_2 (20 mL) was added. After 20 min of stirring at −78 °C, Et_3N (20 mL) was added and the reaction mixture was allowed to warm up to rt. Water was added and then the solution was extracted three times with CH_2Cl_2. The combined organic layers were washed with saturated NaCl, 1% HCl (twice), and 5% Na_2CO_3 (twice). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*, giving aldehyde **6a** (6.18 g, 26.9 mmol) almost quantitatively. Because of the low stability of aldehydes in general, products **6** were not purified but directly used in the next step. IR showed that no starting material was present. ^{1}H NMR (90 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.40–7.10 (m, 5H), 4.52 (s, 2H), 3.62 (sext., 1H), 2.70–2.13 (m, 6H), 1.25 (d, 3H, J = 6 Hz). IR (CCl_4, cm^{-1}): 1725.

(*R*)-8-(Benzyloxy)-5-nonynal (6b). The procedure described for **6a** was used. From 11.0 g of **5b** (44.7 mmol), 10.9 g of crude **6b** was obtained, which was sufficiently pure for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.50–7.13 (m, 5H), 4.53 (s, 2H), 3.63 (sext., 1H), 2.67–2.07 (m, 6H), 1.97–1.58 (m, 2H), 1.27 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 1725.

(*R*)-9-(Benzyloxy)-6-decynal (6c). The procedure described for **6a** was used. From **5c** (12.44 g), **6c** was obtained in an almost quantitative yield: IR (CCl_4, cm^{-1}) 1725.

Ethyl (2*E*,9*R*)-9-(Benzyloxy)dec-2-en-6-ynoate (7a). LiCl (1.36 g) was suspended in CH_3CN under argon. To this suspension were added triethyl phosphonoacetate (7.6 g, 32 mmol) and diisopropylethylamine (3.6 g, 28 mmol). After 15 min of stirring at rt, **6a** (6.18 g, 26.9 mmol) in CH_3CN (20 mL) was added. The reaction was monitored by GC. After the solution was stirred overnight, the solvent was concentrated under reduced pressure and water was added. This mixture was extracted three times with ether. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. After chromatography (hexane/EtOAc 10:1), 6.00 g of **7a** (20 mmol) was obtained in 74% yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.58–7.18 (m, 5H), 7.18–6.77 (m, 1H), 5.88 (d, 1H, J = 16.0 Hz), 4.56 (s, 2H), 4.20 (q, 2H, J = 7.3 Hz), 3.66 (sext., 1H), 2.70–2.11 (m, 6H), 1.29 (d, 3H, J = 6.0 Hz), 1.27 (t, 3H, J = 7.0 Hz); IR (CCl_4, cm^{-1}) 1715, 1650; MS (CI$^+$) m/e (rel intensity) 301 (M^+ + 1, 3), 283 (1), 269 (10), 255 (3), 209 (11), 193 (11), 91 (100).

Ethyl (2*E*,10*R*)-10-(Benzyloxy)undec-2-en-7-ynoate (7b). The procedure described for **7a** was followed. From crude **6b** (10.9 g) and triethyl phosphonoacetate (10.5 mL, 52.8 mmol), **7b** (10.39 g, 33.0 mmol, 75%) was obtained after chromatography (hexane/EtOAc 10:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.25 (m, 5H), 6.97 (dt, 1H, J = 15.0, 6.8 Hz), 5.85 (d, 1H, J = 15.0 Hz), 4.58 (s, 2H), 4.17 (q, 2H, J = 7.5 Hz), 3.67 (sext., 1H), 2.60–2.05 (m, 6H), 1.90–1.47 (m, 2H), 1.43–1.13 (m, 6H); IR (CCl_4, cm^{-1}) 1720, 1655; MS (CI$^+$) m/e (rel intensity) 315 (M^+ + 1, 100), 297 (11), 269 (13), 223 (22), 207 (13), 91 (82).

Ethyl (2*E*,11*R*)-11-(Benzyloxy)dodec-2-en-8-ynoate (7c). The procedure described for **7a** was followed. From **6c** (12.3 g) and triethyl phosphonoacetate (12.86 g, 57.4 mmol) was obtained, after chromatography (hexane/EtOAc 10:1), **7c** (13.66 g, 41.6 mmol, 87%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.47–7.18 (m, 5H), 6.93 (dt, 1H, J = 15.0, 6.8 Hz), 5.83 (d, 1H, J = 15.0 Hz), 4.58 (s, 2H), 4.17 (q, 2H, J = 7.0 Hz), 3.65 (sext., 1H), 2.70–1.97 (m, 6H), 1.77–1.42 (m, 4H), 1.42–1.20 (m, 6H); IR (CCl_4, cm^{-1}) 1720, 1655; MS (CI$^+$) m/e (rel intensity) 329 (M^+ + 1, 25), 311 (3), 283 (4), 265 (4), 237 (9), 91 (100).

(2*E*,9*R*)-9-(Benzyloxy)dec-2-en-6-yn-1-ol (8a). DIBALH (41 mL) was added to a solution of **7a** (6.0 g, 20 mmol) in ether (120 mL) at 0 °C under argon. After 2.5 h the reaction was complete. The reaction mixture was quenched with $Na_2SO_4 \cdot 10H_2O$ (7 g). This mixture was stirred for 1 h. After filtration of the insoluble salts, the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*, giving 6.1 g of crude product. GC analysis showed that still 35% of starting material was present; separation by chromatography (hexane/EtOAc 3:1) gave pure **8a** (3.34 g, 12.9 mmol) and starting material **7a** (1.06 g, 3.5 mmol) which was again treated with DIBALH to give, after work up and chromatography, 0.65 g of **8a** (total yield 78%): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.20 (m, 5H), 5.77–5.60 (m, 2H), 4.53 (m, 2H), 4.00 (d, 2H, J = 3 Hz), 3.62 (sext., 1H), 2.47–2.13 (m, 6H), 2.00 (bs, 1H), 1.25 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3610, 3700–3200; MS (CI$^+$) m/e (rel intensity) 259 (M^+ + 1, 5), 241 (14), 223 (11), 197 (25), 183 (40), 135 (58), 91 (100).

(2*E*,10*R*)-10-(Benzyloxy)undec-2-en-7-yn-1-ol (8b). The procedure described for **8a** was followed. From **7b** (10.0 g, 32 mmol), 5.00 g of **8b** (18.4 mmol, 57%) was obtained, after chromatography (hexane/EtOAc 3:1). Repetition of the procedure with fresh DIBALH gave **8b** in 80% yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.10 (m, 5H), 5.77–5.60 (m, 2H), 4.57 (m, 2H), 4.00 (d, 2H, J = 3 Hz), 3.63 (sext., 1H), 2.60–2.00 (m, 7H), 1.83–1.40 (m, 2H), 1.27 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3620, 3600–3250, 1670.

(2*E*,11*R*)-11-(Benzyloxy)undec-2-en-8-yn-1-ol (8c). The procedure described for **8a** was followed. From **7c** (12.66 g, 38.6 mmol) and fresh DIBALH (85 mL), 10.73 g of **8c** (37.5 mmol, 97%) was obtained, which was sufficiently pure (98% on GC) for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.53–7.13 (m, 5H, 5.76–5.55 (m, 2H), 4.57 (m, 2H), 4.03 (d, 2H, J = 3 Hz), 3.83–3.40 (m, 1H), 2.67–1.80 (m, 7H), 1.73–1.17 (m, 4H), 1.28 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3620, 3700–3100; MS (CI$^+$) m/e (rel intensity) 287 (M^+ + 1, 1), 269 (5), 199 (8), 173 (25), 135 (45), 91 (100).

(2*S*,3*S*,9*R*)-9-(Benzyloxy)-2,3-epoxy-6-decyn-1-ol (9a). (+)-Diethyl L-tartrate [(+)-L-DET] (113 μL, 0.66 mmol) and Ti(O-*i*-Pr)$_4$ (164 μL, 0.55 mmol) were added to a suspension of 1 g of powdered molecular sieves (4 Å) in 100 mL of CH_2Cl_2 at −20 °C under argon. Then *t*-BuOOH (5.4 mL, 22 mmol, M = 4.08 in dichloroethane) was slowly introduced. After being stirred between −20 and −15 °C for 0.5 h, a solution of **8a** (2.83 g, 11 mmol) in CH_2Cl_2 (5 mL) was added in 20 min. The reaction was monitored by TLC. After 3.5 h of stirring at −20 °C to −15 °C, the reaction mixture was quenched with a precooled solution of

$FeSO_4$ (3.7 g) and DL-tartaric acid (1.1 g) in water (11 mL). After the solution was stirred for 5 min, the layers were separated, the aqueous layer was extracted twice with ether, and the combined organic layers were cooled to 0 °C and then treated with a precooled 30% NaOH (3 mL) in saturated NaCl solution. This mixture was stirred for another 1 h. Water was added and the solution was extracted three times with ether. The combined organic layers were dried and concentrated *in vacuo*. After chromatography (hexane/EtOAc 1:1), 2.83 g of pure **9a** (10.3 mmol, 94%) was obtained as a colorless oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.53–7.17 (m, 5H), 4.53 (s, 2H), 3.93–3.33 (m, 3H), 3.12–2.83 (m, 2H), 2.62–2.07 (m, 5H), 1.93–1.53 (m, 2H), 1.23 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3600, 3650–3200; MS (CI$^+$) m/e (rel intensity) 275 (M^+ + 1, 21), 257 (40), 239 (8), 231 (51), 167 (34), 91 (100); $[\alpha]^{20}_D$ −17.7° (*c* 0.94, $CHCl_3$).

(2*S*,3*S*,10*R*)-10-(Benzyloxy)-2,3-epoxy-7-undecyn-1-ol (9b). The procedure described for **9a** was followed. From **8b** (5.00 g, 18.4 mmol), 4.86 g of **9b** was obtained, after chromatography (hexane/EtOAc 2:1), in a yield of 92%: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.20 (m, 5H), 4.56 (s, 2H), 4.00–3.33 (m, 3H), 3.07–2.80 (m, 2H), 2.67–2.00 (m, 5H), 1.90–1.43 (m, 4H), 1.27 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3650–3200; MS (CI$^+$) m/e (rel intensity) 287 (M^+ − 1, 0.4), 271 (0.14), 181 (4), 91 (52).

(2*S*,3*S*,11*R*)-11-(Benzyloxy)-2,3-epoxy-8-dodecyn-1-ol (9c). The procedure described for **9a** was followed. From **8c** (10.73 g, 38.6 mmol), 9.13 g of **9c** (30.2 mmol, 78%) was obtained, after chromatography (petroleum ether (60–80 °C)/EtOAc 2:1); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.50–7.13 (m, 5H), 4.53 (s, 2H), 3.97–3.30 (m, 3H), 3.00–2.73 (m, 2H), 2.67–1.93 (m, 5H), 1.83–1.20 (m, 6H), 1.27 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3650–3200; MS (CI$^+$) m/e (rel intensity) 301 (M^+ − 1, 0.4), 285 (5), 173 (7), 105 (68), 91 (100); $[\alpha]^{20}_D$ −11.9° (*c* 0.96, $CHCl_3$).

(2*R*,8*S*,9*S*)-2-(Benzyloxy)-8,9-epoxy-10-(*tert*-butyldimethylsiloxy)-4-decyne (10a). Imidazole (1.85 g, 27.2 mmol) and TBDMSCl (1.75 g, 11.6 mmol), dissolved in DMF (36 mL), were added to a solution of **9a** (3 g, 10.9 mmol) in DMF (36 mL) under argon. The reaction was monitored by TLC. After 2 h of stirring, water was added and the mixture was extracted three times with hexane. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*, giving 3.97 g of crude **10a** (10.2 mmol, 94%), which was sufficiently pure for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.45–7.18 (m, 5H, Ph), 4.60 (s, 2H), 4.02–3.57 (m, 3H), 3.13–2.88 (m, 2H), 2.60–2.10 (m, 4H), 2.00–1.67 (m, 2H), 1.37 (d, 3H, J = 6 Hz), 1.03 (s, 9H), 0.18 (s, 6H); IR (CCl_4, cm^{-1}) 1250; MS (CI$^+$) m/e (rel intensity) 389 (M^+ + 1, 2), 371 (12), 281 (17), 257 (8), 195 (28), 149 (17), 91 (100).

(2*R*,9*S*,10*S*)-2-(Benzyloxy)-9,10-epoxy-11-(*tert*-butyldimethylsiloxy)-4-undecyne (10b). The procedure described for **10a** was followed. From **9b** (4.86 g, 16.9 mmol), 6.74 g of **10b** (16.8 mmol, 99%) was obtained after chromatography (hexane/EtOAc 10:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.56–7.20 (m, 5H), 4.60 (s, 2H), 3.97–3.37 (m, 3H), 3.10–2.77 (m, 2H), 2.57–2.10 (m, 4H), 1.97–1.53 (m, 2H), 1.37 (d, 3H, J = 6 Hz), 0.98 (s, 9H), 0.18 (s, 6H); IR (CCl_4, cm^{-1}) 1250.

(2*R*,10*S*,11*S*)-2-(Benzyloxy)-10,11-epoxy-12-(*tert*-butyldimethylsiloxy)-4-dodecyne (10c). The procedure described for **10a** was followed. From **9c** (7.62 g, 25.2 mmol), 10.55 g of crude **10c** (25 mmol, 99%) was obtained which was sufficiently pure (99% on GC) for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.60–7.25 (m, 5H), 4.67 (s, 2H), 4.00–3.53 (m, 3H), 3.00–2.80 (m, 2H), 2.60–2.10 (m, 4H), 1.97–1.50 (m, 2H), 1.40 (d, 3H, J = 6 Hz), 1.03 (s, 9H), 0.23 (s, 6H); IR (CCl_4, cm^{-1}) 1250; MS (CI$^+$) m/e (rel intensity) 417 (M^+ + 1, 0.5), 399 (1.4), 309 (4), 267 (4), 117 (36), 91 (100).

(2*R*,8*S*,9*S*)-8,9-Epoxy-10-(*tert*-butyldimethylsiloxy)decan-2-ol (11a). **10a** (3.83 g, 9.86 mmol) was dissolved in absolute EtOH (200 mL). This solution was hydrogenated for 2.5 h with ≈100 mg of Pd/C (10%) as a catalyst. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. After chromatography (hexane/EtOAc 3:1), pure **11a** (2.14 g, 7.1 mmol) was obtained in 72% yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.93–3.50 (m, 3H), 2.92–2.70 (m, 2H), 1.93–1.30 (m, 11H), 1.30 (d, 3H, J = 6 Hz), 0.93 (s, 9H), 0.12 (s, 6H); IR (CCl_4, cm^{-1}) 3620, 3700–3140, 1250; MS (CI$^+$) m/e (rel intensity) 303 (M^+ + 1, 10), 285 (44), 267 (13), 227 (18), 171 (17), 153 (67), 135 (100), 109 (68).

(2*R*,9*S*,10*S*)-9,10-Epoxy-11-(*tert*-butyldimethylsiloxy)undecan-2-ol (11b). The procedure described for **11a** was followed. Conversion of **10b** (5.27 g, 13.1 mmol) gave 2.70 g of **11b** after chromatography (hexane/EtOAc 4:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.95–3.50 (m, 3H), 2.93–2.67 (m, 2H), 1.80–1.25 (m, 13H), 1.30 (d, 3H, J = 6.3 Hz), 0.92 s, 9H), 0.10 (s, 6H); IR (CCl_4, cm^{-1}) 3620, 3600–3200, 1250; MS (CI$^+$) m/e (rel intensity) 317 (M^+ + 1, 8), 299 (57), 281 (10), 241 (26), 149 (100), 117 (98).

(2*R*,10*S*,11*S*)-10,11-Epoxy-12-(*tert*-butyldimethylsiloxy)-dodecan-2-ol (11c). The procedure described for **11a** was followed. **10c** (4.85 g) gave **11c** (2.70 g, 8.2 mmol) in a yield of 70% after chromatography (petroleum ether (60–80 °C)/EtOAc 4:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.00–3.53 (m, 3H), 3.00–2.73 (m, 2H), 1.80–1.20 (m, 15H), 1.27 (d, 3H, J = 7.0 Hz), 0.97 (s, 9H), 0.20 (s, 6H); IR (CCl_4, cm^{-1}) 3620, 3650–3140; MS (CI$^+$) m/e (rel intensity 331 (M^+ + 1, 49), 313 (100), 295 (21), 163 (100).

(2*R*,8*S*,9*S*)-2-Acetoxy-8,9-epoxy-10-(*tert*-butyldimethylsiloxy)decane (12a). Ac_2O (2.5 g, 24.5 mmol) and DMAP (10 mg) were added to a solution of **11a** (2.04 g, 6.74 mmol) in pyridine (17 mL). After the solution was stirred for 1.5 h, the reaction was complete and ice was added. This mixture was extracted three times with ether. The organic layers were washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated *in vacuo*. After stripping with toluene, 2.32 g of **12a** (6.74 mmol, 100%) was obtained: ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.07–4.60 (m, 1H), 3.90–3.47 (m, 2H), 2.95–2.63 (m, 2H), 2.00 (s, 3H), 1.77–1.27 (m, 10H), 1.17 (d, 3H, J = 6 Hz), 0.90 (s, 9H), 0.10 (s, 6H); IR (CCl_4, cm^{-1}) 1730, 1250.

(2*R*,9*S*,10*S*)-2-Acetoxy-9,10-epoxy-11-(*tert*-butyldimethylsiloxy)undecane (12b). The procedure described for **12a** was followed. From **11b** (2.71 g, 8.6 mmol), 2.84 g of **12b** (7.93 mmol, 92%) was obtained after the usual workup. This compound was sufficiently pure (90% on GC) for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.93 (sext., 1H), 3.95–3.55 (m, 2H), 2.98–2.75 (m, 2H), 2.07 (s, 3H), 1.83–1.20 (m, 12H), 1.17 (d, 3H, J = 6 Hz), 1.00 (s, 9H), 0.17 (s, 6H); IR (CCl_4, cm^{-1}) 1730, 1240.

(2*R*,10*S*,11*S*)-2-Acetoxy-10,11-epoxy-12-(*tert*-butyldimethylsiloxy)dodecane (12c). The procedure described for **12a** was followed. From **11c** (5.6 g, 17 mmol), 6.09 g of **12c** (16.4 mmol, 96%) was obtained after workup, which was sufficiently pure (99% on GC) for further use: ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.90 (sext., 1H), 3.93–3.53 (m, 2H), 2.97–2.67 (m, 2H), 2.00 (s, 3H), 2.73–2.17 (m, 12H), 2.22 (d, 3H, J = 6 Hz), 0.93 (s, 9H), 0.10 (s, 6H); IR (CCl_4, cm^{-1}) 1740, 1240; MS (CI$^+$) m/e (rel intensity) 373 (M^+ + 1, 26), 355 (48), 313 (21), 295 (15), 255 (36), 163 (100).

(2*S*,3*S*,9*R*)-9-Acetoxy-2,3-epoxydecan-1-ol (13a). *n*-Bu_4NF (6.8 mL, 1 M in THF) was added to a solution of **12a** (3.34 g, 6.8 mmol) in 40 mL of THF at 0 °C via syringe. The reaction was monitored by GC. After 15 min, the reaction was complete and saturated NH_4Cl was added. This mixture was extracted three times with ether. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Chromatography (hexane/EtOAc 1:1) gave **13a** (1.41 g, 6.12 mmol) in 90% yield: ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.90 (sext., 1H), 4.00–3.40 (m, 2H), 3.03–2.73 (m, 3H), 2.00 (s, 3H), 1.77–1.27 (m, 10H), 1.20 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3650–3200, 1725; MS (CI$^+$) m/e (rel intensity) 231 (M^+ + 1, 1), 213 (1), 171 (13), 153 (21), 135 (90), 109 (100).

(2*S*,3*S*,10*R*)-10-Acetoxy-2,3-epoxyundecan-1-ol (13b). The procedure described for **13a** was followed. From **12b** (2.84 g, 7.93 mmol), **13b** (1.77 g, 7.25 mmol) was obtained in 92% yield after chromatography (hexane/EtOAc 1:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.66 (sext., 1H), 3.85 and 3.61 (dq, 2H, J = 12, 2 Hz, respectively, J = 12, 4 Hz), 3.05–2.80 (m, 2H), 2.40 (bs, 1H), 2.03 (s, 3H), 1.75–1.10 (m, 12H), 1.17 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3600–3200, 1730.

(2*S*,3*S*,11*R*)-11-Acetoxy-2,3-epoxydodecan-1-ol (13c). The procedure described for **13a** was followed. From **12c** (6.0 g, 16.1 mmol), 4.15 g of crude **13c** (16 mmol, 99%) was formed: ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.10–4.67 (m, 1H), 4.05–3.40 (m, 2H), 3.07–2.73 (m, 2H), 2.50 (bs, 1H), 2.00 (s, 3H), 1.73–1.10 (m, 14H), 1.20 (d, 3H, J = 6 Hz); IR (CCl_4, cm^{-1}) 3650–3200, 1730; MS (CI$^+$) m/e (rel intensity) 259 (M^+ + 1, 42), 241 (10), 199 (70), 181 (32), 163 (100).

(3*R*,4*S*,10*R*)-10-Acetoxy-1-diazo-3,4-epoxyundecan-2-one (14a). $NaIO_4$ (4.2 g, 19.6 mmol, 3.1 molar equiv) and $RuCl_3 \cdot H_2O$ (31 mg, 2.2 mol %) were added to a solution of **13a**

(1.45 g, 6.32 mmol) in CCl_4 (13 mL), CH_3CN (13 mL), and H_2O (20 mL). The reaction was monitored by TLC. After the solution was stirred for 2 h, CH_2Cl_2 (30 mL) and water (30 mL) were added and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The black residue was dissolved in dry ether (40 mL) and cooled to 0 °C under argon atmosphere. Isobutyl chloroformate (860 mg, 6.32 mmol) and Et_3N (960 mg, 9.48 mmol) were added to this solution. This mixture was stirred for 1 h at 0 °C. The precipitate was filtered off under argon flow and the filtrate was added to an excess of a diazomethane solution (100 mL, ≈0.3 M) in ether. This mixture was left overnight. Excess diazomethane was removed by flushing with nitrogen. After evaporation, the residue was purified by chromatography (hexane/EtOAc 3:1), giving **14a** (1.07 g, 4.0 mmol) in 63% yield (yellow oil): ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.48 (s, 1H), 4.87 (sext., 1H), 3.20 (d, 1H, J = 2 Hz), 3.07–2.87 (m, 1H), 2.00 (m, 3H), 1.73–1.25 (m, 10H), 1.17 (d, 3H, J = 7.0 Hz); IR (CCl_4, cm^{-1}) 3120, 2120, 1725, 1640; MS (CI$^+$) m/e (rel intensity) 269 (M^+ + 1, 100), 241 (9), 181 (17), 163 (7), 135 (20), 121 (30), 109 (30), 95 (49), 81 (48).

(3*R*,4*S*,11*R*)-11-Acetoxy-1-diazo-3,4-epoxydodecan-2-one (14b). The procedure described for **14a** was followed. From **13b** (1.77 g, 7.25 mmol), 1.29 g of **14b** (4.57 mmol, 63%) was obtained as a yellow oil after chromatography (hexane/EtOAc 3:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.47 (s, 1H), 4.88 (sext., 1H), 3.20 (d, 1H, J = 1.5 Hz), 3.07–2.83 (m, 1H), 2.02 (m, 3H), 1.77–1.20 (m, 12H), 1.10 (d, 3H, J = 6.0 Hz); IR (CCl_4, cm^{-1}) 3120, 2120, 1725, 1640; MS (CI$^+$) m/e (rel intensity) 283 (M^+ + 1, 31), 255 (4), 223 (17), 195 (9), 177 (6), 135 (22), 109 (26), 95 (40), 81 (57), 69 (43), 55 (68), 43 (100).

(3*R*,4*S*,12*R*)-12-Acetoxy-1-diazo-3,4-epoxytridecan-2-one (14c). The procedure described for **14a** was followed. From **13c** (3.66 g, 14.2 mmol), 2.90 g of **14c** (9.80 mmol, 69%) was obtained as a yellow oil after chromatography (petroleum ether/EtOAc 3:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 5.47 (s, 1H), 4.90 (sext., 1H), 3.17 (d, 1H, J = 2.0 Hz), 3.07–2.83 (m, 1H), 2.00 (m, 3H), 1.87–1.33 (m, 14H), 1.20 (d, 3H, J = 6.0 Hz); IR (CCl_4, cm^{-1}) 3120, 2120, 1730, 1640; MS (CI$^+$) m/e (rel intensity) 297 (M^+ + 1, 18), 269 (5), 237 (12), 209 (7), 191 (4), 149 (16), 111 (18), 95 (35), 81 (41), 69 (33), 55 (39).

Ethyl (2*E*/*Z*,4*S*,10*R*)-10-Acetoxy-4-hydroxy-2-undecenoate (15a). A nitrogen-flushed solution of **14a** (1.07 g, 3.98 mmol) in EtOH (500 mL) was irradiated with UV light (300 nm). The rearrangement was monitored by IR spectroscopy (disappearance of the diazo absorption at 2120 cm^{-1}) and was complete after 2 h. Evaporation of the EtOH gave product **15a** as a light brown oil (1.01 g, 89%) which was immediately used in the next step.

Ethyl (2*E*/*Z*,4*S*,11*R*)-11-Acetoxy-4-hydroxy-2-dodecenoate (15b). The procedure described for **15a** was followed. Conversion of 1.25 g of **14b** (4.43 mmol) gave 1.30 g of crude **15b** (98%) as a brown/yellow oil which was immediately used in the next step.

Ethyl (2*E*/*Z*,4*S*,12*R*)-12-Acetoxy-4-hydroxy-2-tridecenoate (15c). The procedure described for **15a** was followed. From **14c** (2.58 g, 8.72 mmol), crude **15c** (2.7 g, 99%) was obtained, which was immediately used in the next step.

Ethyl (2*E*/*Z*,4*S*,10*R*)-10-Acetoxy-4-(*tert*-butyldimethylsiloxy)-2-undecenoate (16*E*a and 16*Z*a). Imidazole (600 mg, 8.85 mmol) and TBDMSCl (1.07 g, 7.08 mmol) in DMF (10 mL) were added to a stirred solution of crude **15a** (1.01 g, 3.54 mmol) in DMF (15 mL) under argon. Finally a catalytic amount of DMAP was added. After stirring for 2.5 h, the reaction was quenched with 10 mL of water. This mixture was extracted three times with hexane. The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography (hexane/EtOAc 15:1 later 5:1), giving pure **16Ea** (656 mg, 1.64 mmol, 46%) and **16Za** (48 mg, 0.12 mmol, 3.4%). **16Ea**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.70 (dd, 1H, J = 16.0, 7.0 Hz), 5.73 (dd, 1H, J = 16.0, 3 Hz), 5.05–4.63 (m, 1H), 4.37–3.98 (m, 3H), 2.00 (s, 3H), 1.68–1.10 (m, 16H), 0.75 (s, 9H), 0.05 (s, 6H); IR (CCl_4, cm^{-1}) 1715, 1655, 1250; MS (CI$^+$) m/e (rel intensity) 401 (M^+ + 1, 13), 355 (5), 341 (13), 327 (6), 295 (10), 283 (16), 269 (42), 223 (100), 209 (100), 163 (38), 75 (55). **16Za**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.15 (dd, 1H, J = 12.0, 7.5 Hz), 5.70 (dd, 1H, J = 12.0, 1.0 Hz), 5.48–5.20 (m, 1H), 5.12–4.73 (m, 1H), 4.18 (q, 2H, J = 7.0 Hz), 2.05 (s, 3H), 1.70–1.13 (m, 16H), 0.93 (s, 9H), 0.10 (s, 6H); IR (CCl_4, cm^{-1}) 1715, 1645, 1240; MS (CI$^+$) m/e (rel intensity) 401 (M^+ + 1, 7), 385 (17), 355 (3), 343 (25), 325 (8), 283 (53), 269 (75), 223 (42), 209 (100), 181 (52), 163 (77), 75 (63).

Ethyl (2*E*/*Z*,4*S*,11*R*)-11-Acetoxy-4-(*tert*-butyldimethylsiloxy)-2-dodecenoate (16*E*b and 16*Z*b). The procedure described for **16a** was followed. Conversion of **15b** (1.30 g, 4.33 mmol) gave pure **16Eb** (868 mg, 2.1 mmol, 48%) and pure **16Zb** (110 mg, 0.27 mmol, 6%), after chromatography (hexane/EtOAc 15:1). **16Eb**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.90 (dd, 1H, J = 16.0, 4.5 Hz), 5.73 (dd, 1H, J = 16.0, 2.0 Hz), 5.15–4.65 (m, 1H), 4.47–4.07 (m, 3H), 2.07 (s, 3H), 1.80–1.20 (m, 18H), 0.98 (s, 9H), 0.13 (s, 6H); IR (CCl_4, cm^{-1}) 1720, 1655, 1245; MS (CI$^+$) m/e (rel intensity) 415 (M^+ + 1, 27), 369 (4), 355 (11), 309 (13), 283 (49), 237 (60), 223 (100), 177 (30), 75 (59). **16Zb**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.15 (dd, 1H, J = 12.0, 7.5 Hz), 5.68 (d, 1H, J = 12.0 Hz), 5.50–5.20 (m, 1H), 5.08–4.70 (m, 1H), 4.20 (q, 2H, J = 7.5 Hz), 2.07 (s, 3H), 1.80–1.20 (m, 18H), 0.99 (s, 9H), 0.11 (s, 6H); IR (CCl_4, cm^{-1}) 1720, 1645, 1240; MS (CI$^+$) m/e (rel intensity) 415 (M^+ + 1, 3), 399 (3), 357 (20), 297 (100), 283 (18), 237 (11), 223 (34), 177 (20), 75 (49).

Ethyl (2*E*/*Z*,4*S*,12*R*)-12-Acetoxy-4-(*tert*-butyldimethylsiloxy)-2-tridecenoate (16*E*c and 16*Z*c). The procedure described for **16a** was followed. Conversion of **15c** (2.7 g) gave 3.5 g of crude product. This product was purified by chromatography (petroleum ether/hexane 15:1), giving a fraction of pure **16Ec** and a fraction which contained both **16Ec** and **16Zc**. The latter fraction was again purified by chromatography (petroleum ether (60–80 °C)/EtOAc 20:1), giving the pure isomers. The fractions with **16Ec** were merged, giving 1.55 g (3.6 mmol, 42%) of pure product. Compound **16Zc** (152 mg, 0.36 mmol) was obtained in 4% yield. **16Ec**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.87 (dd, 1H, J = 15.0, 5.0 Hz), 5.90 (dd, 1H, J = 15.0, 1.5 Hz), 4.83 (sext., 1H), 4.36–4.13 (m, 1H), 4.13 (q, 2H, J = 6.7 Hz), 1.95 (s, 3H), 1.80–1.20 (m, 17H), 1.15 (d, 3H, J = 6.0 Hz), 0.86 (s, 9H), 0.02 and 0.00 (s, 6H); IR (CCl_4, cm^{-1}) 1715, 1640, 1245; MS (CI$^+$) m/e (rel intensity) 429 (M^+ + 1, 17), 383 (9), 369 (34), 323 (27), 311 (42), 297 (56), 251 (74), 237 (100), 191 (21), 75 (48). **16Zc**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.17 (dd, 1H, J = 11.0, 7.5 Hz), 5.70 (d, 1H, J = 11.0 Hz), 5.47–5.18 (m, 1H), 4.93 (sext., 1H), 4.23 (q, 2H, J = 7.0 Hz), 2.07 (s, 3H), 1.83–1.13 (m, 20H), 0.93 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); IR (CCl_4, cm^{-1}) 1720, 1655, 1240; MS (CI$^+$) m/e (rel intensity) 429 (M^+ + 1, 4), 413 (8), 383 (5), 371 (76), 311 (100), 297 (39), 251 (5), 237 (45), 191 (8), 75 (19).

Saponification of Compound 16*E*a with LiOH (General Procedure). LiOH (1.5 mmol, 36 mg) was added to a stirred solution of **16Ea** (100 mg, 0.25 mmol) in THF (5 mL) and H_2O (5 mL). This solution was heated at 50 °C for 6 h. (The reaction was monitored by TLC.) The reaction mixture was acidified with tartaric acid to pH 4 and extracted three times with ether. The combined etheral layers were dried ($MgSO_4$) and concentrated *in vacuo*, giving (2*E*,4*S*,10*R*)-10-hydroxy-4-(*tert*-butyldimethylsiloxy)-2-undecenecarboxylic acid (**17Ea**) (80 mg, 0.242 mmol) in 97% yield. This product was used without purification in the next step: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.00 (dd, 1H, J = 15.0, 5.2 Hz), 6.55 (bs, 2H), 6.00 (dd, 1H, J = 15.0, 1.5 Hz), 4.47–4.10 (m, 1H), 4.00–3.57 (m, 1H), 1.77–1.10 (m, 10H), 1.20 (d, 3H, J = 6.0 Hz), 0.90 (s, 9H), 0.10 (s, 6H).

(2*Z*,4*S*,10*R*)-10-Hydroxy-4-(*tert*-butyldimethylsiloxy)-2-undecenecarboxylic Acid (17*Z*b). The procedure for **17Ea** was followed. From **16Zb** (110 mg, 0.266 mmol), 65 mg of crude **17Zb** (0.19 mmol, 71%) was obtained after 4 days at 60 °C. This product was immedately used in the text step: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.27 (dd, 1H, J = 11.3, 8.3 Hz), 6.07 (bs, 2H), 5.73 (d, 1H, J = 11.3 Hz), 5.43–5.10 (m, 1H), 4.07–3.63 (m, 1H), 1.77–1.17 (m, 12H), 1.20 (d, 3H, J = 6.0 Hz), 0.93 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H).

Saponification of 16*E*b with NaOH (General Procedure). A solution of NaOH (20 mg, 0.5 mmol) in absolute EtOH (2 mL) was added to a solution of **16Eb** (100 mg, 0.241 mmol) in absolute EtOH (5 mL). After 5 h of stirring at 50 °C, the reaction mixture was concentrated, followed by addition of water. This solution was extracted once with ether to remove minor impurities. Then the aqueous layer was acidified with citric acid to pH 4 and extracted three times with ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*, giving (2*E*,4*S*,-

11*R*)-11-hydroxy-4-(*tert*-butyldimethylsiloxy)-2-dodecenecarboxylic acid (17*E*b) (82 mg, 0.238 mmol, 99%). This product was without purification used in the next step: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.03 (dd, 1H, J = 15.0, 4.50 Hz), 6.03 (dd, 1H, J = 15.0, 2.0 Hz), 5.20 (bs, 2H), 4.53–4.20 (m, 1H), 4.00–3.57 (m, 1H), 1.80–1.20 (m, 12H), 1.27 (d, 3H, J = 6.0 Hz), 0.97 (s, 9H), 0.17 (s, 6H).

(2*E*,4*S*,10*R*)-10-Hydroxy-4-(*tert*-butyldimethylsiloxy)-2-undecenecarboxylic Acid (17*Z*a). The synthesis of 17*Z*a was carried out using the procedure described for product 17*E*b, giving crude 17*Z*a (0.115 mmol, 99%) after 9.5 h at 78 °C. This product was used in the next step without purification: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.6 (bs, 2H), 6.27 (dd, 1H, J = 12.0, 7.5 Hz), 5.70 (dd, 1H, J = 12.0, 1.0 Hz), 5.40–5.11 (m, 1H), 4.00–3.60 (m, 1H), 1.70–1.11 (m, 10H), 1.20 (d, 3H, J = 7.0 Hz), 0.90 (s, 9H), 0.07 (s, 6H).

(2*E*,4*S*,12*R*)-12-Hydroxy-4-(*tert*-butyldimethylsiloxy)-2-tridecenecarboxylic Acid (17*E*c). The procedure for the synthesis of 17*E*b was followed. From 16*E*c (100 mg, 0.23 mmol), 80 mg of crude 17*E*c (0.223 mmol, 97%) was obtained after 30 h at 60 °C. The product was immediately used in the next step: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.04 (dd, 1H, J = 15.0, 5.00 Hz), 6.30 (bs, 2H), 6.00 (dd, 1H, J = 15.0, 1.5 Hz), 4.50–4.10 (m, 1H), 4.00–3.57 (m, 1H), 1.73–1.07 (m, 14H), 1.20 (d, 3H, J = 6.0 Hz), 0.93 (s, 9H), 0.10 (s, 6H).

(2*Z*,4*S*,12*R*)-12-Hydroxy-4-(*tert*-butyldimethylsiloxy)-2-tridecenecarboxylic Acid (17*Z*c). The procedure for the synthesis of 17*E*b was followed. From 16*Z*c (96 mg, 0.224 mmol), 80 mg of 17*Z*c (0.223 mmol, 99%) was obtained after 24 h at 78 °C. This product was used in the next step without purification: ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.37 (bs, 2H), 6.27 (dd, 1H, J = 12.0, 8.0 Hz), 5.73 (d, 1H, J = 12.0 Hz), 5.47–5.10 (m, 1H), 4.05–3.60 (m, 1H), 1.77–1.20 (m, 14H), 1.25 (d, 3H, J = 6.0 Hz), 0.97 (s, 9H), 0.10 (s, 6H).

(2*E*,4*S*,10*R*)-4-(*tert*-Butyldimethylsiloxy)-2-undecen-10-olide (18*E*a). To a solution of 17*E*a (81 mg, 0.25 mmol) in THF (5 mL) under argon was added Et_3N (0.275 mmol, 28 mg) followed by 2,6-dichlorobenzoyl chloride (0.25 mmol, 52 mg). After the solution was stirred for 2 h, the precipitate was removed by filtration under argon flow. The filtrate was diluted with 130 mL of dry toluene and slowly added (in 2 h) to a refluxing solution of DMAP (181 mg, 1.5 mmol) in toluene. After continued heating for 1 h, the reaction mixture was allowed to cool down to rt and stirring was continued for 16 h. The reaction mixture was diluted with ≈100 mL of ether and washed with saturated tartaric acid and saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (hexane/ether 20:1), giving 45 mg of 18*E*a (0.144 mmol, 58%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.50 (dd, 1H, J = 16.1, 8.5 Hz), 6.22 (d, 1H, J = 16.1 Hz), 4.69–4.59 (m, 1H), 4.36–4.28 (m, 1H), 1.76–1.25 (m, 10H), 1.33 (d, 3H, J = 6.2 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); IR (CCl_4, cm^{-1}) 1715, 1640, 1250; MS (CI$^+$) m/e (rel intensity) 313 (M$^+$ + 1, 36), 297 (40), 279 (7), 255 (71), 237 (22), 215 (22), 181 (82), 163 (54), 135 (100), 75 (98).

(2*Z*,4*S*,10*R*)-4-(*tert*-Butyldimethylsiloxy)-2-undecen-10-olide (18*Z*a). The procedure for the synthesis of 18*E*a was carried out with 17*Z*a (38 mg, 0.115 mmol), giving 11 mg of 18*Z*a (30%), after chromatography (hexane/EtOAc 30:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, 1H, J = 11.9, 7.55 Hz), 5.78 (d, 1H, J = 11.9 Hz), 5.55–4.96 (m, 1H), 4.81–4.73 (m, 1H), 1.87–1.13 (m, 10H), 1.28 (d, 3H, J = 6.4 Hz), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); IR (CCl_4, cm^{-1}) 1720, 1640, 1255; MS (CI$^+$) m/e (rel intensity) 313 (M$^+$ + 1, 44), 297 (89), 255 (100), 237 (17), 215 (21), 181 (100), 163 (84), 135 (57), 75 (38).

(2*E*,4*S*,11*R*)-4-(*tert*-Butyldimethylsiloxy)-2-dodecen-11-olide (18*E*b). The procedure for the synthesis of 18*E*a was followed. From 17*E*b (82 mg, 0.238 mmol) 53 mg of 18*E*b (0.163 mmol, 67%) was obtained after chromatography (hexane/ether 20:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.63 (dd, 1H, J = 16.0, 5.6 Hz), 6.10 (dd, 1H, J = 16.0, 1.5 Hz), 5.33–4.97 (m, 1H), 4.67–4.40 (m, 1H), 1.93–1.10 (m, 12H), 1.27 (d, 3H, J = 6.0 Hz), 1.00 (s, 9H), 0.13 (s, 6H); IR (CCl_4, cm^{-1}) 1715, 1645, 1250; MS (CI$^+$) m/e (rel intensity) 327 (M$^+$ + 1, 26), 309 (26), 269 (100), 251 (26), 195 (30), 149 (53), 75 (89).

(2*Z*,4*S*,11*R*)-4-(*tert*-Butyldimethylsiloxy)-2-dodecen-11-olide (18*Z*b). The procedure for 18*E*a was followed. From 17*Z*b (65 mg, 0.19 mmol), 20 mg of 18*Z*b (0.061 mmol, 32%) and 17 mg of 18*E*b (0.052 mmol, 27%) were obtained after chromatography (hexane/ether 20:1): ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.05 (dd, 1H, J = 12.0, 7.80 Hz), 5.73 (d, 1H, J = 12.0 Hz), 5.33–4.93 (m, 2H), 2.17–1.15 (m, 12H), 1.38 (d, 3H, J = 6.0 Hz), 0.99 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); IR (CCl_4, cm^{-1}) 1715, 1650, 1255; MS (CI$^+$) m/e (rel intensity) 327 (M$^+$ + 1, 33), 269 (100), 251 (23), 195 (30), 177 (22), 149 (53), 75 (89).

(2*E*,4*S*,12*R*)-4-(*tert*-Butyldimethylsiloxy)-2-tridecen-12-olide (18*E*c). The procedure for the synthesis of 18*E*a was followed. From 17*E*c (80 mg, 0.223 mmol), 18*E*c (21 mg, 0.062 mmol) was obtained in 28% yield after chromatography (hexane/ether 30:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (dd, 1H, J = 15.6, 5.7 Hz), 6.02 (dd, 1H, J = 15.6, 1.3 Hz), 5.18–5.13 (m, 1H), 4.50–4.42 (m, 1H), 1.80–1.10 (m, 14H), 1.27 (d, 3H, J = 6.4 Hz), 0.89 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); IR (CCl_4, cm^{-1}) 1715, 1655; MS (CI$^+$) m/e (rel intensity) 341 (M$^+$ + 1, 11), 323 (13), 283 (100), 265 (25), 209 (13), 191 (13), 163 (26), 75 (71).

(2*Z*,4*S*,12*R*)-4-(*tert*-Butyldimethylsiloxy)-2-tridecen-12-olide (18*Z*c). The procedure for the synthesis of 18*E*a was followed. From 17*Z*c (82 mg, 0.23 mmol), 18*Z*c (16.4 mg, 0.048 mmol) was obtained in 21% yield after chromatography (petroleum ether (60–80 °C)/ether 30:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (dd, 1H, J = 12.0, 8.50 Hz), 5.79 (dd, 1H, J = 12.0, 1.0 Hz), 5.28–5.16 (m, 2H), 1.72–1.10 (m, 14H), 1.23 (d, 3H, J = 6.3 Hz), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); IR (CCl_4, cm^{-1}) 1715, 1640, 1250; MS (CI$^+$) m/e (rel intensity) 341 (M$^+$ + 1, 51), 325 (16), 283 (100), 265 (23), 209 (47), 191 (18), 163 (22), 75 (45).

(2*E*,4*S*,10*R*)-4-Hydroxy-2-undecen-10-olide (19*E*a). *n*-Bu_4NF (0.18 mL, 1 M, in THF) was added via a syringe to a solution of 18*E*a (55 mg, 0.18 mmol) in THF at −10 °C under argon. After 3 h of stirring at −10 °C, the reaction mixture was quenched with saturated NH_4Cl solution. The mixture was extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by chromatography (ether), giving 20 mg of pure 19*E*a (0.10 mmol, 56%) as a white solid which was recrystallized from hexane: mp 126–128 °C; $[\alpha]^{20}_D$ −3.25° (*c* 0.40, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (dd, 1H, J = 16.1, 8.9 Hz), 6.34 (d, 1H, J = 16.1 Hz), 4.65–4.54 (m, 1H), 4.45–4.35 (m, 1H), 2.50 (bs, 1H), 2.00–1.35 (m, 10H), 1.34 (d, 3H, J = 6.4 Hz); ^{1}H NMR (400 MHz, CD_3CN) δ 6.46 (d, 1H, J = 16.2 Hz), 6.23 (dd, 1H, J = 16.2, 9.2 Hz), 4.59–4.53 (m, 1H), 4.30–4.24 (m, 1H), 3.17 (bs, 1H), 1.87–1.13 (m, 10H), 1.26 (d, 3H, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.87, 145.70, 122.61, 74.86, 72.39, 35.10, 33.70, 23.48, 23.13, 22.14, 21.24; IR (CCl_4, cm^{-1}) 3590, 3700–3100, 1710, 1655; MS (CI$^+$) m/e (rel intensity) 199 (M$^+$ + 1, 19), 181 (93), 163 (60), 153 (51), 135 (100), 121 (78), 111 (47), 99 (41), 95 (74), 83 (67), 55 (37); HRMS calcd for $C_{11}H_{16}O_2$ (M − H_2O) 180.1150, found 180.1151; UV (CH_3CN) λ_{max} 193.9 nm (ϵ = 8058 mol^{-1} cm^{-1}).

(2*Z*,4*S*,10*R*)-4-Hydroxy-2-undecen-10-olide (19*Z*a). The procedure for the synthesis of 19*E*a was followed. From 11 mg of 18*Z*a (0.035 mmol), 5 mg of 19*Z*a (0.025, mmol, 71%) was obtained as a white solid after chromatography (ether): mp 93–95 °C; $[\alpha]^{20}_D$ +23.6° (*c* 0.11, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (dd, 1H, J = 12.0, 6.1 Hz), 6.87 (d, 1H, J = 12.0 Hz), 5.05–4.98 (m, 1H), 4.84–4.79 (m, 1H), 2.17 (bs, 1H), 1.78–1.42 (m, 10H), 1.26 (d, 3H, J = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.82, 143.75, 122.05, 72.15, 67.90, 35.77, 33.84, 26.08, 23.24, 22.44, 20.63; IR (CCl_4, cm^{-1}) 3610, 3600–3150, 1720; MS (CI$^+$) m/e (rel intensity) 199 (M$^+$ + 1, 6), 181 (22), 163 (26), 135 (23), 101 (100), 83 (48), 55 (35); HRMS calcd for $C_{11}H_{16}O_2$ (M − H_2O) 180.1150, found 180.1149; UV (CH_3CN) λ_{max} 191.0 nm (ϵ = 1529 mol^{-1} cm^{-1}), λ 216 nm (ϵ = 716 mol^{-1} cm^{-1}).

(2*E*,4*S*,11*R*)-4-Hydroxy-2-dodecen-11-olide (19*E*b). The procedure for the preparation of 19*E*a was used. From 48 mg of 18*E*b (0.150 mmol), 22 mg of 19*E*b (0.104 mmol, 69%) was obtained as a colorless oil after chromatography (hexane/ether 2:1): $[\alpha]^{20}_D$ + 6.6° (*c* 0.42, EtOH); ^{1}H NMR (90 MHz, $CDCl_3$) δ 6.82 (dd, 1H, J = 16.5, 6.3 Hz), 6.07 (d, 1H, J = 16.5 Hz), 5.23–4.85 (m, 1H), 4.58–4.33 (m, 1H), 2.03–0.93 (m, 12H), 1.32 (d, 3H, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.10, 149.69, 121.49, 73.18, 70.89, 35.89, 32.84, 28.26, 27.83, 22.16, 20.74, 19.34; IR (CCl_4, cm^{-1}) 3610, 3650–3150, 1715, 1645; MS (CI$^+$) m/e (rel intensity) 213 (M$^+$ + 1, 65), 195 (64), 177 (23), 149 (100); HRMS

calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1413; UV (CH_3CN) λ_{max} 207.8 nm (ϵ 7380 mol^{-1} cm^{-1}).

(2*Z*,4*S*,11*R*)-4-Hydroxy-2-dodecen-11-olide (19*Z*b). The procedure for the preparation of 19*E*a was followed. The deprotection was carried out starting from 20 mg of 18*Z*b (0.095 mmol). This gave 13 mg of 19*Z*b (0.061 mmol, 64%) as a white solid after chromatography (hexane/ether 2:1). The product was chromatographed again (petroleum ether (60–80 °C)/ether 2:1) and recrystallized from hexane, giving 5 mg of colorless crystals: mp 75 °C; $[\alpha]^{20}_D$ +71.7° (*c* 0.42, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (dd, 1H, *J* = 11.9, 8.5 Hz), 5.79 (dd, 1H, *J* = 11.9, 1.2 Hz), 5.12–5.00 (m, 2H), 1.83 (bs, 1H), 1.68–1.25 (m, 12H), 1.28 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.38, 146.80, 121.08, 72.18, 66.54, 34.02, 29.64, 24.66, 22.58, 22.37, 20.11, 17.36; IR (CCl_4, cm^{-1}) 3615, 3600–3300, 1710; MS (CI^+) *m/e* (rel intensity) 213 (M^+ + 1, 7), 195 (36), 177 (23), 149 (35); HRMS calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1413; UV (CH_3CN) λ_{max} 201.0 nm (ϵ = 8967 mol^{-1} cm^{-1}).

(2*E*,4*S*,12*R*)-4-Hydroxy-2-tridecen-12-olide (19*E*c). The procedure described for 19*E*a was followed. From 21 mg of 18*E*c (0.062 mmol), 9.3 mg of 19*E*c (0.041 mmol, 66%) was obtained as a white solid after chromatography (petroleum ether (60–80 °C)/ether 2:1): mp 49–51 °C; $[\alpha]^{20}_D$ +1.33° (*c* 0.40, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (dd, 1H, *J* = 15.8, 6.9 Hz), 6.02 (dd, 1H, *J* = 15.8, 1.0 Hz), 5.17–5.05 (m, 1H), 4.53–4.44 (m, 1H), 1.90–1.07 (m, 15H), 1.27 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.93, 149.38, 121.46, 72.26, 70.81, 34.77, 34.50, 28.44, 28.20, 26.43, 23.25, 20.40, 20.22; IR (CCl_4, cm^{-1}) 3610, 3650–3100, 1715, 1650; MS (CI^+) *m/e* (rel intensity) 227 (M^+ + 1, 66), 209 (55), 191 (19), 163 (100), 149 (23), 111 (35), 84 (46), 69 (44), 55 (52); HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1570; UV (CH_3CN) λ_{max} <190 nm, λ 205.7 nm (ϵ = 10440 mol^{-1} cm^{-1}), λ 270 nm (ϵ = 595 mol^{-1} cm^{-1}).

(2*Z*,4*S*,12*R*)-4-Hydroxy-2-tridecen-12-olide (19*Z*c). Since the conditions used for 19*E*a failed to convert 18*Z*c, the following procedure was used. 18*Z*c (16 mg, 0.047 mmol) was dissolved in 3:1:1 HOAc/THF/H_2O (1 mL). After overnight stirring, the reaction mixture was extracted three times with ether. The combined organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by chromatography (petroleum ether (60–80 °C)/ether 1:1), giving 19*Z*c (5.3 mg, 0.023 mmol, 49%) as a white solid: mp 44–47 °C; $[\alpha]^{20}_D$ +45.7° (*c* 0.27, EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (dd, 1H, *J* = 11.4, 8.4 Hz), 5.88 (d, 1H, *J* = 11.4 Hz), 5.26–5.13 (m, 2H), 1.96 (bs, 1H), 1.77–1.12 (m, 14H), 1.24 (d, 3H, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 146.21, 121.93, 71.80, 66.85, 35.18, 34.86, 27.08, 26.67, 25.86, 24.22, 23.63, 20.90; IR (CCl_4, cm^{-1}) 3610, 3650–3100, 1715, 1640; MS (CI^+) *m/e* (rel intensity) 227 (M^+ + 1, 5), 209 (25), 191 (22), 163 (31), 149 (40), 101 (100); HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1574; UV (CH_3CN) λ_{max} <190 nm, λ 216.0 nm (ϵ = 4318 mol^{-1} cm^{-1}), λ 280 nm (ϵ = 284 mol^{-1} cm^{-1}).

Ethyl (2*E*,4*S*)-4-hydroxy-2-nonenoate (20):[2] ^1H NMR (90 MHz, $CDCl_3$) δ 6.93 (dd, 1H, *J* = 16.0, 5.0 Hz), 6.02 (dd, *J* = 16.0, 1.5 Hz), 4.43–4.13 (m, 3H), 2.00–0.73 (m, 15H); UV (CH_3CN) λ_{max} 207.6 nm (ϵ = 8756 mol^{-1} cm^{-1}).

Supplementary Material Available: Copies of ^1H NMR spectra for most compounds (60 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.