Total Syntheses of (−)-Grandinolide and (−)-Sapranthin by the Sharpless Asymmetric Dihydroxylation of Methyl *trans*-3-Pentenoate: Elucidation of the Stereostructure of (−)-Sapranthin

Christian Harcken, Reinhard Brückner, and Elisabeth Rank*

Dedicated to Professor Reinhard W. Hoffmann on the occasion of his 65th birthday

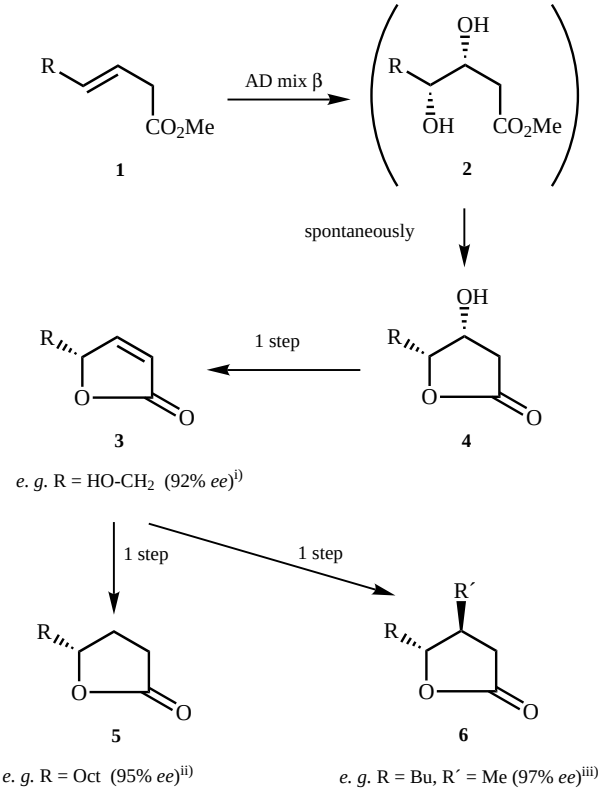
Abstract: Methyl *trans*-3-pentenoate (**7**) was converted into the *cis*-substituted γ-lactone **8** in a single step with 78% *ee*. The derived enolate dilithio-**8** was alkylated *trans*-selectively with primary iodoalkanes. with 1-iodobutane dilithio-**8** afforded, after esterification with isovaleroyl chloride, the *epi*-blastmycinone **9**. Dilithio-**8** gave (−)-grandinolide (**11**) with 1-iodo-19-phenylnonadecane (**20**). A third *trans*-selective alkylation of dilithio-**8** was undertaken with 16-iodo-1,5-hexadecadiene-7,9-diyne (**21**). This gave the γ-lactone **12**, which had the published relative configuration of (−)-sapranthin but different spectroscopic data. When the OH group of lactone **8** was inverted (to hydroxylactone **40**) and the derived enolate dilithio-**40** alkylated with iodide **21**, lactone **41** resulted. Its ^{1}H and ^{13}C NMR spectra and the sign and value of optical rotation coincide with the data of natural sapranthin. These findings establish that (−)-sapranthin possesses the relative and absolute configuration of stereoformula **41**. The synthesis of iodide **21** was performed via the dienoic carboxylic ester *trans*-**23** which stemmed from the Claisen–Ireland rearrangement (**27** → **28**/**29**)/esterification (**28**/**29** → **26**)/Cope rearrangement (**26** → **23**) sequence shown in Scheme 5.

Keywords: asymmetric synthesis · dihydroxylations · γ-lactones · rearrangements · structure elucidation

Introduction

Enantiomerically pure or enantiomerically enriched γ-chiral γ-lactones[1] and γ-chiral butenolides[2] demand syntheses which are broadly applicable and highly efficient. Recently, we presented a straightforward and, as we have since experienced in several projects, versatile novel access to such compounds.[3] It is based upon the Sharpless asymmetric dihydroxylation (AD)[4] of β,γ-unsaturated esters. This reaction had been almost overlooked previously.[5]

The principle and first applications of our route in target-oriented work are summarized in Scheme 1.[3] ADs of a number of β,γ-unsaturated esters **1** initially provided the enantiopure or enantio-enriched dihydroxylation products **2**. These compounds lactonized spontaneously under the alkaline reaction conditions. The isolable reaction products were γ-chiral γ-lactones **4** of 92–97% *ee*. The absolute configuration of these lactones only depends on whether the AD is performed with AD mix β[6] (as in the cases of Scheme 1) or with AD mix α[6] (where the major isomers would represent the mirror images of the structures of Scheme 1). In fact, the lactones **4** were not yet the target molecules of our previous



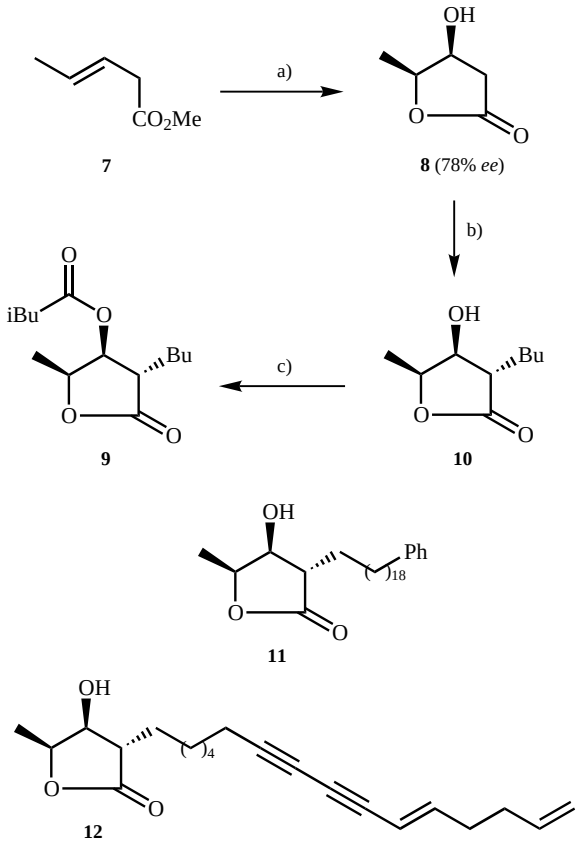
Scheme 1. i) Equivalent to levorotatory aglycon of ranunculin;[7] ii) equivalent to (+)-dodecanolide;[8] iii) equivalent to (−)-*trans* quercus lactone.[9]

[*] Prof. Dr. R. Brückner, Dipl.-Chem. C. Harcken, Dipl.-Chem. E. Rank
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-392944
E-mail: rbrueck@gwdg.de

0947-6539/98/0411-2342 $ 17.50+.50/0

study.[3] Rather, each of them was carried on to a γ-chiral butenolide **3** by a β-elimination induced by mesyl chloride/triethylamine. For $R = HO-CH_2$ butenolide **3** constitutes the aglycon of ranunculin,[7] for $R = Oct$ a precursor of the pheromone (+)-dodecanolide (**5**;[8] available from **3** by catalytic hydrogenation), and for $R = Bu$ a precursor of the flavorant (−)-*trans* quercus lactone (**6**;[9] available from **3** through the 1,4-addition of Me_2CuLi).

Another target reached in our previous study[3] was the *epi*-blastmycinone **9** (Scheme 2). To achieve this, the commercially available methyl pentenoate **7** was asymmetrically dihydroxylated with AD mix α. The resulting lactone **8**[10] exhibited only 78% *ee*, which is not surprising in view of the substitution pattern[11] of the substrate. In addition, this lactone formed in a considerably slower reaction (0 °C, 5 d instead of 1–2 d) with distinctly lower yield (40% instead of 81–92%) than the closely related lactones **4** in Scheme 1. This was because lactone **8** unlike its congeners **4** had to be prepared in the absence of methanesulfonamide which accelerates ADs,[4] a modus procedendi required since methanesulfonamide was inseparable from lactone **8** by flash chromatography on silica gel.[12] The α-alkylation of dilithiated β-hydroxy-γ-lactones occurs in HMPA-containing THF such that the α-substituent is oriented exclusively *trans* with respect to the β-OH group.[13] Conveniently, butylation of the dilithiated hydroxylactone **8** in 4:1 THF/DMPU[14] also resulted in an exclusively *trans*-alkylated hydroxylactone **10** (*epi*-blastmycinolactol; 53% yield). Treatment of **10** with isovaleroyl chloride gave the isovalerate **9** in 85% yield. Compound **9** is an *epi*-blastmycinone, that is, an epimer of the antimycin A_3 degradation product blastmycinone. Several other syntheses for **9** are known; however, they are less stereoselective.[15].



Scheme 2. a) AD mix α (1.4 g mmol^{-1} **7**), *t*BuOH/H_2O (1:1), addition of **7**, 0 °C, 5 d; 40%; b) LDA (3.0 equiv), addition of **8**, THF, −78 °C, 2 h; 1-iodobutane (1.5 equiv) in THF/DMPU (1:1), −35 °C, 20 h; 53%; c) isovaleroyl chloride (3.0 equiv), CH_2Cl_2/pyridine (5:1), 0 °C to room temperature, 6 h; 83%.

Our synthesis of the *epi*-blastmycinolactol **10** was also a training reaction for synthesizing the natural products (−)-grandinolide (**11**)[16] and (−)-sapranthin (**12**)[17] analogously; these are constituents of bark from *Iryanthera grandis* and *Sapranthus palanga*, respectively (Scheme 2). The relative configurations of these compounds had been deduced from their ^{1}H NMR spectra. The absolute configuration of grandinolide (**11**) was established in its first and hitherto only synthesis,[18] whereas the absolute configuration of sapranthin (**12**) was unknown.

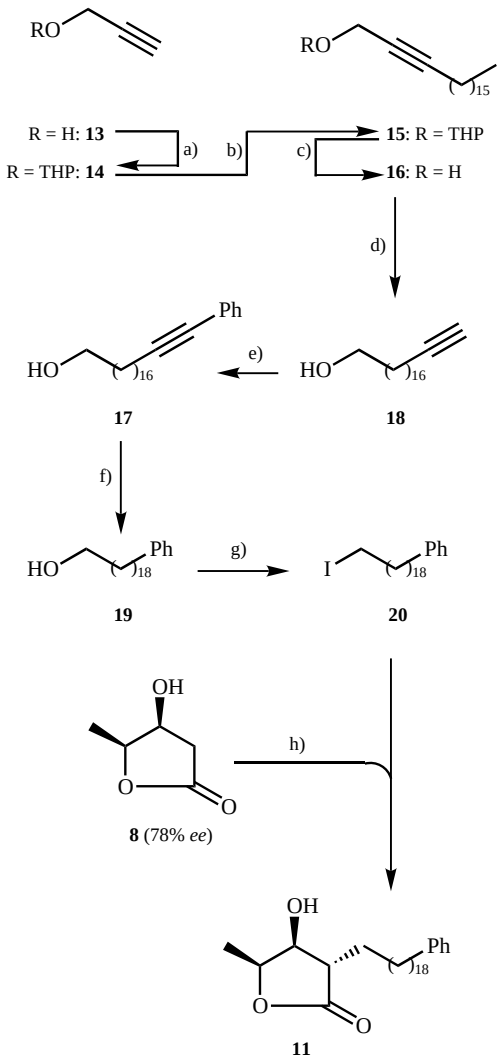
Results and Discussion

The major effort in synthesizing grandinolide (**11**; Scheme 3) was achieving the iodoalkane **20**. The THP ether **14** of propargyl alcohol was alkylated[19] with 1-bromohexadecane giving the chain-elongated THP ether **15** in 76% yield. Methanolysis[20] provided 92% of the underlying C_{19} alcohol **16**. The internal C≡C bond of this compound was shifted in a modified[21] alkyne zipper reaction[22] until it became terminal. The resulting alkynol **18** (84% yield) was coupled with iodobenzene under standard conditions[23] (5 mol% [$PdCl_2(PPh_3)_2$], 15 mol% CuI, THF/*i*Pr_2NH, room temperature) to give 84% of the unsaturated alcohol **17**. Its C≡C bond was hydrogenated to saturation (H_2, Pd/C; to 82% **19**). Subse-

Abstract in German: *Methyl-trans-3-pentenoat (**7**) wurde durch asymmetrische Sharpless-Dihydroxylierung und eine sich anschließende spontane Lactonisierung in das cis-substituierte γ-Lacton **8** (78% ee) umgewandelt. Dessen Enolat Dilithio-**8** wurde mit primären Iodalkanen trans-selektiv alkyliert. Mit Iodbutan und nach Veresterung mit Isovaleroylchlorid ergab es das epi-Blastmycinon **9**. Mit 1-Iod-19-phenylnonadecan (**20**) lieferte Dilithio-**8** (−)-Grandinolid (**11**). Eine analoge trans-Alkylierung mit 16-Iod-1,5-hexadecadien-7,9-diin (**21**) führte zu dem Lacton **12**. Dieses besaß zwar die für (−)-Sapranthin publizierte Relativkonfiguration, aber abweichende ^{1}H- und ^{13}C-NMR-Daten. Nachdem die OH-Gruppe des Ausgangslactons **8** invertiert worden war, wurde das Enolat des erhaltenen Hydroxylactons **40** mit dem Iodid **21** zum Lacton **41** trans-alkyliert. Die NMR-Spektren und das Vorzeichen der spezifischen Drehung dieser Verbindung **41** stimmten mit den Werten von (−)-Sapranthin überein. Dessen relative und absolute Konfiguration wird folglich durch Stereoformel **41** angegeben. Das Iodid **21** wurde aus dem Diencarbonsäureester trans-**23** gewonnnen. Letzterer entstammte der Reaktionssequenz Claisen/Ireland-Umlagerung **27**→**28/29**, Veresterung **28/29**→**26** und Cope-Umlagerung **26**→**23** von Schema 5.*

Table 1. ^{1}H NMR comparison in $CDCl_3$ between synthetic and natural grandinolide (**11**) and between synthetic and natural sapranthin (**41**); chemical shifts in ppm, coupling constants in Hz (for the numbering see Table 2 and Scheme 7, respectively).

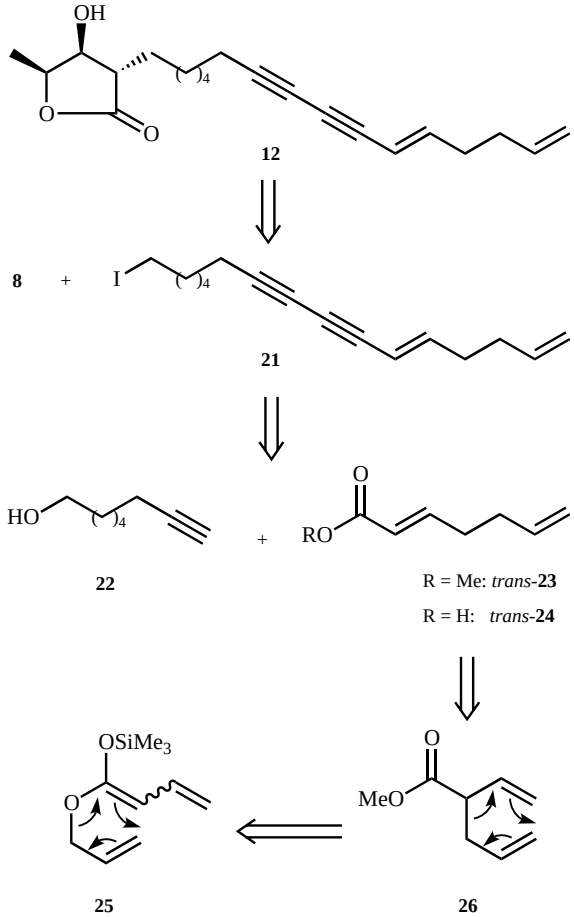
	5-H	4-H	3-H	1′-H_A	1′-H_B	$J_{5,4}$	$J_{4,3}$	$J_{3,1H(A)}$	$J_{3,1H(B)}$	Field strength [MHz]
natural **11**[16]	4.54	4.14	2.45	–	–	5	3	–	–	60
synthetic **11**	4.63	4.20	2.53	–	–	5.0	3.6	–	–	300
natural **41**[17]	4.20	3.86	2.54	1.81 – 1.87	1.81 – 1.87	7.1	1.5[47]	7.3	7.3	360
synthetic **41**	4.20	3.84	2.55	ca. 1.62	1.86	7.2	8.7	7.4	5.7	500



Scheme 3. a) Dihydro-2*H*-pyran (3.0 equiv), pyridinium *p*-toluenesulfonate (1.0 mol%), CH_2Cl_2, 16 h; 84%; b) *n*BuLi (1.2 equiv), 0 °C, 15 min; 1-bromohexadecane (1.1 equiv), DMSO, room temperature, 14 h; 76%; c) *p*-toluenesulfonic acid (0.4 equiv), MeOH, room temperature, 2 h; 92%; d) Li (6.0 equiv), 1,2-diaminopropane, room temperature to reflux, 30 min; KO*t*Bu (4.0 equiv), room temperature, 30 min; addition of **16**, room temperature, 1 h; 84%; e) $PdCl_2(PPh_3)_2$ (5.0 mol%), CuI (15.0 mol%), PhI (1.2 equiv), $(i\text{Pr})_2\text{NH}$ (10.0 equiv), THF, 0 °C, 15 min; room temperature, 12 h; 84%; f) Pd (10% on charcoal, 5.0 mol%), H_2 (5 bar), EtOAc, room temperature, 16 h; 82%; g) $P(OPh)_3$ (1.0 equiv), CH_2Cl_2, room temperature, 10 min; I_2 (1.0 equiv), 0 °C, 1 h; 82%; h) LDA (3.0 equiv), addition of **8**, THF, −78 °C, 2.5 h; addition of **20** (1.0 equiv) in THF/DMPU (1:1), −78 °C, 1 h; −40 °C, 20 h; 53%.

quent exchange of the OH group for iodine by successive treatments with $P(OPh)_3$ and I_2[24] gave the needed alkylating agent **20**. It was added to the dilithio derivative of hydroxylactone **8** in 1:1 THF/DMPU. After warming the resulting mixture gradually from −78 °C (1 h) to −40 °C and maintaining it at that temperature for 20 h, the diastereopure lactone **11** was isolated in 53% yield. It was identical to (−)-grandinolide, as shown by NMR spectroscopy (selected data: Table 1), polarimetry (**11**: $[\alpha]_D^{20} = -23$ corrected for an *ee* of only 78% $\Rightarrow [\alpha]_D^{20}$ of optically pure **11** $= -23/0.78 = -30$ ($c =$ 0.5 in MeOH); (−)-grandinolide: $[\alpha]_D^{20} = -34$ (MeOH)[16]), and melting point determination (**11**: 76 °C; (−)-grandinolide: 76 – 78 °C[16]).

The envisaged synthesis (Scheme 4) of the literature structure **12** of sapranthin required constructing the side chain **21**. We traced it back retrosynthetically to the terminal alkynol **22**

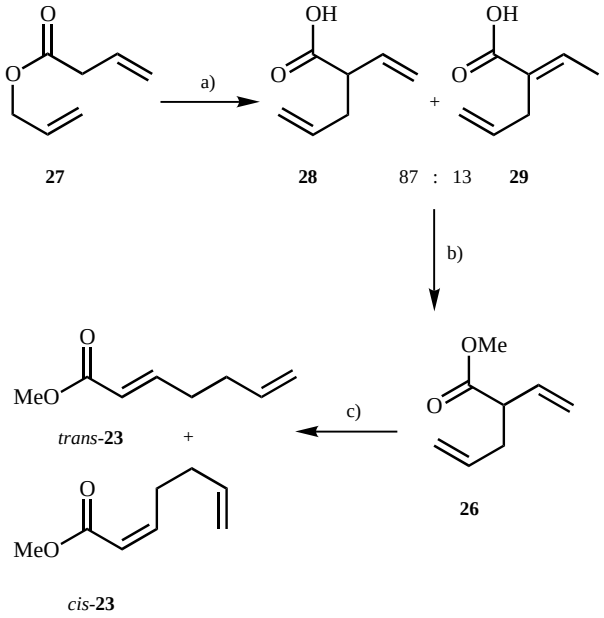


Scheme 4. Retrosynthetic analysis of target structure **12**.

(accessible through an alkyne zipper reaction from the pentylation product **32** of propargyl alcohol; see Scheme 6) and the heptadienoic carboxylic ester *trans*-**23**.[25] The latter was thought to arise from a Cope rearrangement[26] of the isomeric ester **26**. This, in turn should be the product of a Claisen – Ireland rearrangement [27] of the silylketeneacetal **25**.[28]

0947-6539/98/0411-2344 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 11

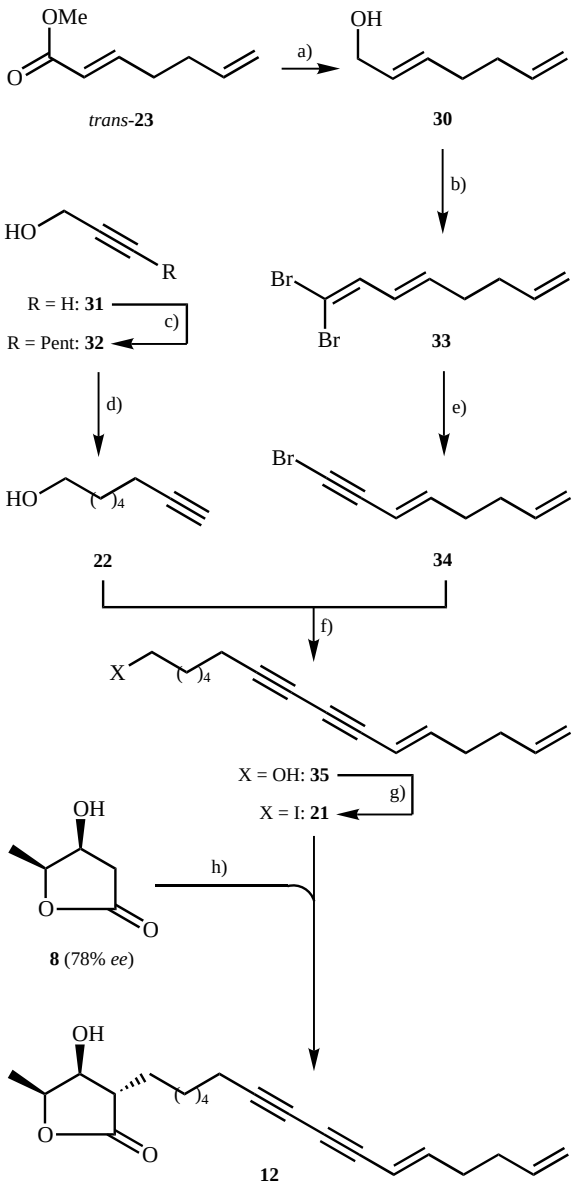
Unlike most Claisen–Ireland rearrangements, the conceived rearrangement **25**→**26** had to start from a conjugated silylketeneacetal. Such rearrangements are scarce but were described starting from α,β-unsaturated[29] or β,γ-unsaturated allylesters.[30] Another concern was whether the envisaged Cope rearrangement **26**→**23** (Scheme 5) would have a sufficient driving force in the desired direction. However, precedence[28, 31] indicated that if a Cope rearrangement product is an α,β-unsaturated ester, like ester **23**, the conjugation energy of this substructure makes Cope rearrangements proceed at least to some extent if not to completion.



Scheme 5. a) LiHMDS (1.0 equiv), THF, −78 °C, 30 min; Me_3SiCl (1.1 equiv), 10 min, −78 °C; to room temperature to reflux; quantitative; b) MeOH (2.0 equiv), *p*-TsOH (2 mol %), $CHCl_3$, azeotropic removal of water, 16 h; 63 %; c) 240 °C, 16 h; 75 % *trans*-**23**, 8 % *cis*-**23**.

The β,γ-unsaturated allylester **27**[32] was deprotonated at −78 °C in THF with LiHMDS (Scheme 5). Addition of Me_3SiCl, warming to reflux temperature, and an aqueous work-up[33] followed, giving a quantitative yield of crude carboxylic acids. It comprised a 87:13 mixture of the deconjugated acid **28** (desired) and the conjugated acid **29** (undesired). Esterification with methanol in $CHCl_3$, with azeotropic removal of water, turned this mixture into 63 % of a single ester **26**[34] as required. Evidently, the *conjugated* acid **29** was not esterified under these conditions because it is more stable than the *deconjugated* acid **28**. The ensuing Cope rearrangement **26**→**23** proceeded to completion according to TLC during 16 h at 240 °C. We isolated 75 % of the needed ester *trans*-**23** and 8 % of its undesired isomer *cis*-**23** after an easy-to-perform separation by flash chromatography on silica gel.[12, 35]

The remaining steps of our route to compound **12** are shown in Scheme 6. The unsaturated ester *trans*-**23** was reduced with DIBAL in 92 % yield giving the allyl alcohol **30**.[36] Swern oxidation[37] gave a crude aldehyde which was combined with the Corey/Fuchs reagent[38] to provide the dibromotriene **33** in 53 % yield over the two steps. A β-elimination of HBr effected by Bu_4NF[39] ensued and gave 78 % of the bromodienyne **34**. This compound was C–C coupled with the alkynol **22** under the Cadiot–Chodkievicz conditions developed by Vasella and Cai,[40] that is, in DMSO solution in the presence of CuI, $Pd(dba)_2$, LiI, and pentamethylpiperidine; after 2 h at room temperature the dienediynol **35** had formed in 60 % yield. The



Scheme 6. a) DIBAL (1.0 M in toluene, 2.2 equiv), THF, −78 °C to room temperature, 30 min; 92 %; b) $(ClCO)_2$ (1.1 equiv), DMSO (2.2 equiv), CH_2Cl_2, −78 °C, 3 min; addition of **30**, 15 min; NEt_3 (5.0 equiv), 30 min; aqueous work-up; PPh_3 (4.0 equiv), CBr_4 (2.0 equiv), CH_2Cl_2, 0 °C, 10 min; addition of aldehyde, room temperature, 1 h; 53 % for the two steps; c) Li (3.0 equiv), $Fe(NO_3)_2$ (0.2 mol %), liquid NH_3, −78 °C, 30 min; addition of **31**, 5 min; 1-bromopentane (0.8 equiv), 1.5 h; to room temperature; 75 %; d) Li (6.0 equiv), 1,2-diaminopropane, room temperature to reflux, 30 min; KO*t*Bu (4.0 equiv), room temperature, 30 min; addition of **32**, room temperature, 1 h; 82 %; e) Bu_4NF (1.0 M in THF, 3.0 equiv), THF, 40 °C, 24 h; 78 %; f) $Pd(dba)_2$ (5.0 mol %), CuI (2.5 mol %), LiI (20 mol %), addition of **34** (1.1 equiv) and **22**, degassed DMSO, room temperature, 10 min; pentamethylpiperidine (2.8 equiv), 2 h; 60 %; g) PPh_3 (1.1 equiv), imidazole (2.2 equiv), I_2 (1.1 equiv), THF, 0 °C, 1 h; 88 %; h) LDA (2.2 equiv), THF, addition of **8**, −78 °C, 2 h; addition of **21** (1.0 equiv) in THF/DMPU (1:1), −45 °C, 20 h; 69 %.

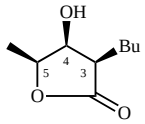
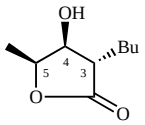
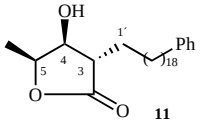
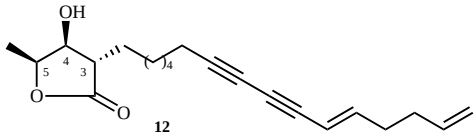
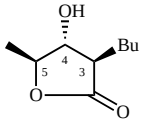
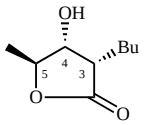
alkynol **22** used in this coupling was derived from its isomer **32** by the modified[20] alkyne zipper reaction[22] already mentioned in connection with the analogous isomerization **16** →**18** of Scheme 3. Compound **32**, in turn, was obtained by pentylating the dianion of propargyl alcohol by using Brandsma's protocol.[19]

The Cadiot–Chodkievicz product **35**, an alcohol, was converted into the analogous iodide **21** through a reaction with $Ph_3P-I^+\ I^-$ (Scheme 6).[41] This was the iodide with which, according to our retrosynthetic analysis in Scheme 4, we required to alkylate the enolate of the enantio-enriched lactone **8**. Indeed, in THF/DMPU this alkylation was realized as smoothly and *trans*-selectively as the related alkylations **8** + BuI →**10** (Scheme 2) or **8** + **20** →**11** (Scheme 3). Compound **12** formed as the only stereoisomer in 69% yield.

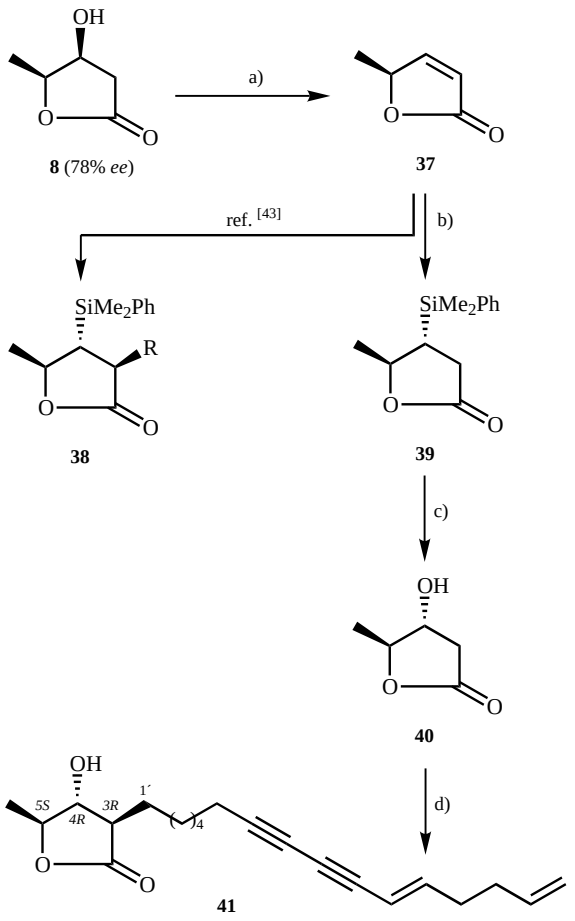
Astonishingly, the ^1H and ^{13}C NMR shifts of the ring protons and ring ^{13}C nuclei as well as the associated H,H coupling constants in compound **12** differed from the respective values of (−)-sapranthin[17] (Table 2, cf. entries 4 and 5). Of course, the alkylation affording **12** was strictly analogous to the alkylation which had furnished compound **11** (grandinolide), and the latter's NMR data (select δ_H and $J_{H,H}$ values: Table 1, top half) match exactly the values of the natural product. In addition, the selected NMR data in Table 2 are almost identical for compound **12**, for grandinolide (**11**), and for the *epi*-blastmycinolactol **10** (equivalent to *cis*,*trans*-**36**). Consequently, there was no doubt as to the correctness of the stereostructure of compound **12**. This meant, however, that the published structure of sapranthin was incorrect. If one excluded that sapranthin was structurally fundamentally different from **12**, it had to be a diastereomer. A good approximation of the nature of this diastereomer emerged from comparisons of the NMR spectra of sapranthin[17] and representatives of all four kinds of diastereomeric α,γ-dialkyl-β-hydroxy-γ-lactones (see Table 2). The groupwise similarities/discrepancies of the δ values compiled in Table 2 (cf. entries 5 and 6) suggested that sapranthin was a *trans*,*trans*-disubstituted γ-lactone (**41**; Scheme 7) rather than the *cis*,*trans*-disubstituted γ-lactone **12**. This analysis was confirmed through synthesis (Scheme 7).

En route to compound **41**, the OH group of the starting lactone **8** had to be inverted. Under Mitsunobu conditions,[42] a β-elimination occurred instead of the desired *direct* inversion. Therefore, recourse was made to the three-step alternative of Scheme 7. Treatment of hydroxylactone **8** with mesyl chloride and triethylamine effected the same β-elimination more readily and provided butenolide **37**[10] in 81% yield. From other work in our laboratory[43] we knew that Fleming's higher order cuprate $Li_2(Me_2PhSi)_2Cu(CN)$[44] adds to butenolide **37** *trans*-selectively giving a lactone enolate which was alkylated to form trisubstituted lactones **38.**[43, 45] Perform-

Table 2. ^1H and ^{13}C NMR shifts (*cis*,*cis*-**36**, *trans*,*trans*-**36**, and *trans*,*cis*-**36** at 270 MHz/67.9 MHz,[15b] *cis*,*trans*-**36** at 500 MHz/125.7 MHz,[15d] **11** at 60 MHz/15 MHz,[16] and (−)-sapranthin at 360 MHz/90.5 MHz,[17] respectively, in $CDCl_3$) of differently substituted α,γ-dialkyl-β-hydroxy-γ-lactones.

Entry			$\delta_{5\text{-H}}$	$\delta_{4\text{-H}}$	$\delta_{3\text{-H}}$	$\delta_{C\text{-}5}/\delta_{C\text{-}4}$	$\delta_{C\text{-}3}$
1		*cis*,*cis*-**36**	4.56	4.33	2.58	71.26/78.63	47.60
2		*cis*,*trans*-**36**	4.64	4.18	2.55	73.85/78.69	49.23
3	 **11**		4.63	4.20	2.54	74.0/78.5	49.2
4	 **12**		4.64	4.21	2.54	73.91/78.41	49.05
5	(-)-sapranthin		4.20	3.86	2.54	78.7/80.1	48.4
6		*trans*,*trans*-**36**	4.21	3.81	2.57	79.00/79.91	48.65
7		*trans*,*cis*-**36**	4.52	4.19	2.59	73.63/82.78	43.74

0947-6539/98/0411-2346 $ 17.50+.50/0 *Chem. Eur. J.* **1998**, *4*, No. 11



Scheme 7. a) NEt_3 (2.1 equiv), methanesulfonyl chloride (1.1 equiv), CH_2Cl_2, 0 °C, 30 min; 81%; b) Li (10.0 equiv), $PhMe_2SiCl$ (4.0 equiv), THF, 0 °C, 16 h; transferred to CuCN (2.0 equiv), THF, −10 °C, 30 min; addition of **37**, −78 °C, 15 min; 80%;c) AcOOH (32% in AcOH, 10.0 equiv), KBr (2.0 equiv), NaOAc (12.0 equiv), AcOH, 0 °C to room temperature, 16 h; 32%; d) LDA (2.5 equiv), addition of **40**, THF, −78 °C, 2 h; addition of **21** (1.0 equiv) in THF/DMPU (1:1), −40 °C, 20 h; 45%.

ing the same 1,4-addition of $Li_2(Me_2PhSi)_2Cu(CN)$ to butenolide **37** but quenching the resulting enolate with water rather than with an alkylating agent, we obtained the silyllactone **39** in 80% yield. Therein, the $C_{methine}$–Si bond was oxidized to a $C_{methine}$–O bond under the conditions developed by Fleming et al.[46] Hydroxylactone **40** with the inverted OH group resulted. It was isolated in only 32% yield—a drawback of its high polarity and the associated difficulty in extracting it from an aqueous solution without losses. Nonetheless, we obtained enough lactone **40** for realizing another completely *trans*-selective alkylation with iodide **21**. It delivered lactone **41** in 45% yield. Juxtaposing selected NMR data of this compound with the corresponding data of sapranthin (Table 1, bottom half) proves that the latter possesses the former's *relative* configuration. The specific rotation of (−)-sapranthin ($[\alpha]_D^{20} = -30$ ($c = 0.01$, $CHCl_3$)) and the specific rotation of **41** ($[\alpha]_D^{20} = -22$ ($c = 0.28$, $CHCl_3$)), after correcting for the latter's *ee* of only 78% (equivalent to $[\alpha]_D^{20}$ of optically pure **41** $= -22/-0.78 = -28$) coincide within a reasonable error span. This proves that (−)-sapranthin possesses also the *absolute* configuration of compound **41**.

The stereochemical key reaction **7** →**8** of the present study is just one example of our very general **1** →**4** approach to γ-chiral γ-lactones.[3] We deem it likely that many more applications will be found. In the above context this access to lactones underlines the virtue of synthetic work in verifying or reassigning the structure of poorly accessible natural products.

Experimental Section

General methods: All reactions were performed in oven-dried glassware under N_2. THF was freshly distilled from K; toluene from Na; CH_2Cl_2, DMPU, DMSO, 1,2-diaminopropane, and pyridine from CaH_2. Products were purified by flash chromatography[12] on Macherey-Nagel silica gel [230–400 mesh; eluents given in brackets; volume of each collected fraction (mL)/column diameter (cm): 1.3/1.0, 4/1.5, 8/2.0, 14/2.5, 20/3.0, 30/4, 50/5, 80/6, 125/75; which fractions contained the isolated product is indicated in each description by product in fractions xx–yy]. Yields refer to analytically pure samples. Isomer ratios were derived from suitable ^1H NMR integrals. ^1H NMR [$CHCl_3$ ($\delta = 7.26$) as internal standard in $CDCl_3$], ^{13}C NMR [$CDCl_3$ ($\delta = 77.00$) as internal standard in $CDCl_3$]: Bruker AMX 300, and Varian VXR 500S; integrals in accord with assignments; coupling constants in Hz. APT ^{13}C NMR spectra: + sign before δ value gives peak orientation of CH or CH_3 resonances, − sign before δ value gives peak orientation of CH_2 or C_{quat} resonances. The assignments of ^1H and ^{13}C NMR resonances refer to the IUPAC nomenclature; primed numbers belong to the side chain. MS: Dr. G. Remberg, Institut für Organische Chemie der Universität Göttingen; combustion analyses: F. Hambloch, Institut für Organische Chemie der Universität Göttingen; IR spectra: Perkin-Elmer 1600 Series FTIR; optical rotations: Perkin–Elmer polarimeter 241 at 589 nm; rotational values are the average of five measurements of α in a given solution of the respective sample. Melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected.

(4*S*,5*S*)-4,5-Dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (**8**): AD mix α (14.0 g) and ester **7** (1.23 mL, 1.14 g, 10.0 mmol) were added to a 1:1 mixture of *t*BuOH and H_2O (30 mL each) at 0 °C. After the mixture had been stirred for four days, the reaction was terminated by adding aqueous Na_2SO_3. After extraction with CH_2Cl_2 (10 × 50 mL), the organic extracts were dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified by flash chromatography (3 cm, *t*BuOMe, fractions 8–20) to obtain **8** (462 mg, 40%). $[\alpha]_D^{25} = -62.2$ ($c = 0.73$ in MeOH); chiral capillary gas chromatography revealed *ee* = 78% [20% heptakis-(2,6-di-O-methyl-3-O-pentyl-β-cyclodextrin) in 80% OV1701 (25 m), 70 kPa H_2, 110 °C isothermal; R_T 45.4 min, R_T of enantiomer 44.3 min]. ^1H NMR (300 MHz): $\delta = 1.45$ (d, $J_{1',5} = 6.8$, $1'H_3$), 2.49 (br s, OH), AB signal ($\delta_A = 2.58$, $\delta_B = 2.82$, $J_{AB} = 17.8$, in addition split by $J_{A,4} = 1.0$, $J_{B,4} = 5.7$, $3H_2$), 4.45 (br dd, $J_{4,3\text{-}H(B)} \approx J_{4,5} \approx 4$, 4-H), 4.58 (qd, $J_{5,1'} = 6.4$, $J_{5,4} = 3.8$, 5-H). IR (neat): $\tilde{\nu} = 3420$, 2985, 2935, 1775, 1345, 1235, 1205, 1170, 1135, 1060, 995, 945 cm^{-1}. $C_5H_8O_3$ (116.1): calcd C 51.72, H 6.94; found C 51.64, H 7.24.

[(3*S*,4*S*,5*S*)-3-Butyl-4,5-dihydro-5-methyl-2-oxo-(3*H*)-4-furyl] 3-methylbutanoate (**9**): Isovaleroyl chloride (96 μL, 94 mg, 0.78 mmol, 3.0 equiv) was added to a solution of hydroxylactone **10** (45 mg, 0.26 mmol) in CH_2Cl_2/pyridine (5:1, 6 mL) at 0 °C. After the mixture had been stirred for 6 h at room temperature, aqueous HCl (2 M, 1 mL) was added. After extraction with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried over $MgSO_4$. After removing the solvents flash chromatography (2 cm, petroleum ether/*t*BuOMe 10:1 → fraction 14, fractions 5–11) yielded the title compound (55 mg, 83%). $[\alpha]_D^{20} = -35.1$ ($c = 0.9$ in CH_2Cl_2); the *ee* of the starting material **10** was 78%, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -35.1/0.78 = -45.0$ for optically pure **9** {ref. [15a] $[\alpha]_D^{20} = 51$ for the enantiomer ($c = 0.53$, MeOH)}. ^1H NMR (300 MHz, slightly impure): $\delta = 0.92$ (t, $J_{4'',3''} = 7.2$, $4''H_3$), 0.97 (d, $J_{3Me,3} = 6.8$, 3-Me_2), 1.29–1.53 (m, $2''H_2$, $3''H_2$), partially superimposed by 1.34 (d, $J_{5'\text{-}Me,5'} = 6.4$, 5′-Me), 1.54–1.83 (m, $1''H_2$), 2.11 (tqq, central seven peaks of theoretical nine visible, $J_{3,2} = J_{3,4} = J_{3,3\text{-}Me} = 6.5$, 3-H), 2.25 ($m_c$, which probably can be interpreted as d, $J_{2,3} = 6.4$, $2H_2$), 2.59 (ddd, $J_{3',1''\text{-}H(1)} = 8.9$, $J_{3',1''\text{-}H(2)} = 6.4$, $J_{3',4'} = 3.0$, 3′-H), 4.78 (qd, $J_{5',5'\text{-}Me} = 6.6$, $J_{5',4'} = 4.9$, 5′-H), 5.18 (dd, $J_{4',5'} = 4.9$, $J_{4',3'} = 2.6$, 4′-H). ^{13}C NMR (75 MHz):

$\delta = +13.68$ and $+14.24$ (5′-Me, C-4″), $+22.28$ and $+22.31$ (C-4, 3-Me), $+25.55$ (C-3), -28.14 and -29.05 (C-1″, C-2″, C-3″), -43.04 (C-2), $+47.10$ (C-3′), $+75.23$ and $+76.66$ (C-4′, C-5′), -172.18 and -176.57 (C-2′, C-1). IR (neat): $\tilde{\nu} = 2960, 2935, 2870, 1780, 1740, 1465, 1390, 1370, 1340, 1295, 1250, 1185, 1120, 1040, 995, 945\ cm^{-1}$.

(3*S*,4*S*,5*S*)-3-Butyl-4,5-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (**10**): BuLi (1.44 M in hexane, 4.44 mL, 6.40 mmol, 3.2 equiv) was added to a solution of diisopropylamine (0.79 mL, 0.61 g, 6.0 mmol, 3.0 equiv) in THF (20 mL) at $-78\,^{\circ}C$. After 30 min, a solution of the β-hydroxylactone **8** (232 mg, 2.00 mmol) in THF (5 mL) was added. After continuous stirring for 2 h at this temperature, 1-iodobutane (0.34 mL, 0.55 g, 3.0 mmol, 1.5 equiv) in THF/DMPU (1:1, 8 mL) was slowly added. The reaction mixture was stirred for 20 h at $-35\,^{\circ}C$, and then terminated by adding aqueous HCl (1 M, 10 mL). After extracting the aqueous phase with *t*BuOMe (3×30 mL), the combined organic extracts were dried over $MgSO_4$ and the solvent was evaporated. Flash chromatography (3 cm, petroleum ether/*t*BuOMe 4:1 → fraction 10, 2.5:1 → fraction 26, fractions 15–23) of the residue yielded the title compound (179 mg, 53%) as a colorless liquid. $[\alpha]_D^{20} = -57.0$ ($c = 1.46$ in MeOH); the *ee* of the starting material **8** was 78%, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -57.0/0.78 = -73.1$ for optically pure **10** (ref. [15a] $[\alpha]_D^{20} = +71$ for the enantiomer ($c = 0.5$, MeOH)). ^{1}H NMR (300 MHz): $\delta = 0.92$ (t, $J_{4',3'} = 7.2$, 4′-H$_3$), 1.30–1.80 (m, 1′-H$_2$, 2′-H$_2$, 3′-H$_2$), partially superimposed by 1.41 (d, $J_{5\text{-Me},5} = 6.8$, 5-Me), 2.21 (m$_c$, OH), 2.55 (ddd, $J_{3,1'\text{-H}(1)} = 7.8$, $J_{3,1'\text{-H}(2)} = 6.4$, $J_{3,4} = 3.4$, 3-H), 4.21 (br ddd, $J_{4,5} \approx J_{4,3} \approx J_{4,\text{OH}} \approx 4.5$, 4-H), 4.64 (qd, $J_{5,5\text{-Me}} = 6.4$, $J_{5,4} = 4.9$, 5-H).

(3*S*,4*S*,5*S*)-4,5-Dihydro-4-hydroxy-5-methyl-3-(19-phenylnonadecyl)-2(3*H*)-furanone (**11**): BuLi (1.44 M in hexane, 1.11 mL, 1.60 mmol, 3.2 equiv) was added to a solution of diisopropylamine (0.20 mL, 0.15 g, 1.5 mmol, 3.0 equiv) in THF (5 mL) at $-78\,^{\circ}C$. After 30 min, a solution of lactone **8** (58 mg, 0.50 mmol) in THF (5 mL) was added. After continuous stirring at this temperature for 2.5 h the iodide **20** (235 mg, 0.500 mmol, 1.0 equiv) in THF/DMPU (1:1, 4 mL) was slowly added. The mixture was stirred for 20 h at $-40\,^{\circ}C$. The reaction was terminated by adding aqueous HCl (1 M, 5 mL). After extraction of the aqueous phase with *t*BuOMe (3×20 mL), the combined organic extracts were dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (2 cm, petroleum ether/*t*BuOMe 2:1 → fraction 6, 1:1 → fraction 20, fractions 10–18) to obtain the title compound (121 mg, 53%) as a white solid of m.p. 76 °C (ref. [16] 76–78°C). From fractions 1–4 unconverted iodide **20** (102 mg, 43%) was reisolated. $[\alpha]_D^{20} = -23$ ($c = 0.5$ in MeOH); the *ee* of the starting material **8** was 78%, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -23/0.78 = -30$ for optically pure **11** (ref. [16] $[\alpha]_D^{20} = -34$ (MeOH)). ^{1}H NMR (300 MHz): $\delta = 1.22-1.88$ (m, 1′-H$_2$ to 18′-H$_2$, OH), partially superimposed by 1.41 (d, $J_{5\text{-Me},5} = 6.6$, 5-Me), 2.53 (ddd, $J_{3,1'\text{-H}(1)} = 8.2$, $J_{3,1'\text{-H}(2)} = 6.0$, $J_{3,4} = 3.6$, 3-H), partially superimposed by 2.60 (dd, $J_{19',18'\text{-H}(1)} \approx J_{19',18'\text{-H}(2)} \approx 7.8$, 19′-H$_2$), 4.20 (dd, $J_{4,5} \approx J_{4,3} \approx 4.2$, 4-H), 4.63 (qd, $J_{5,5\text{-Me}} = 6.8$, $J_{5,4} = 5.0$, 5-H), 7.13–7.20 (m, 3 Ar-H), 7.24–7.31 (m, 2 Ar H). ^{13}C NMR (50 MHz): $\delta = 13.84$ (5-CH$_3$), 27.21, 28.40, 29.30 (relative intensity = 2), 29.37 (relative intensity = 2), 29.47 (relative intensity = 2), 29.55 (relative intensity = 3), 29.65 (relative intensity = 7), 31.49 and 35.93 (C-1′ to C-19′, that is, 9 resonance frequencies for 19 C atoms), 49.26 (C-3), 73.82 and 78.62 (C-4 and C-5), 125.44 (*p*-C), 128.11 and 128.29 (2 *o*-C and 2 *m*-C), 142.84 (*ipso*-C), 178.28 (C-2). IR (KBr): $\tilde{\nu} = 3130, 2920, 2850, 1745, 1660, 1495, 1470, 1400, 1340, 1235, 1195, 1050, 995, 720, 695\ cm^{-1}$. $C_{30}H_{50}O_3$ (458.7): calcd C 78.55, H 10.99; found C 78.54, H 10.69.

(3*S*,4*S*,5*S*)-3-(11,15-Hexadecadiene-7,9-diynyl)-4,5-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (**12**): *n*BuLi (2.5 M in hexane, 0.44 mL, 1.1 mmol, 2.2 equiv) was added to a solution of diisopropylamine (0.14 mL, 0.11 g, 1.1 mmol, 2.2 equiv) in THF (5 mL) at $-78\,^{\circ}C$. After 30 min a solution of lactone **8** (58.1 mg, 0.500 mmol) in THF (5 mL) was added. After a further 2 h, the iodide **21** (170 mg, 0.500 mmol, 1.0 equiv) in THF/DMPU (1:1, 4 mL) was added within 15 min. Stirring was continued for 20 h at $-45\,^{\circ}C$. The reaction was terminated by adding aqueous HCl (1M, 10 mL). After extraction of the aqueous phase with *t*BuOMe (3×30 mL) the combined organic phases were dried over $MgSO_4$ and the solvent was removed. Flash chromatography (3 cm, petroleum ether/Et_2O 2:1 → fraction 16, 1.5:1 → fraction 33, 1:1 → fraction 60, fractions 42–54) of the residue yielded the title compound (113 mg, 69%; 79% based on recovered iodide) as a colorless oil. Unconverted iodide **21** (22.5 mg, 13%) was reisolated from fractions 3–5. $[\alpha]_D^{20} = -25$ ($c = 0.37$ in $CHCl_3$); the *ee* of the starting material **8** was 78%, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -25/0.78 = -32$ for optically pure **12**. ^{1}H NMR (500 MHz): $\delta = 1.32-1.62$ (m, 1′-H^1, 2′-H$_2$, 3′-H$_2$, 4′-H$_2$, 5′-H$_2$), superimposed by 1.41 (d, $J_{5\text{-Me},5} = 6.6$, 5-Me), 1.74 (m$_c$, 1′-H$_2$), 1.83 (br s, OH), 2.12–2.25 (m, 13′-H$_2$, 14′-H$_2$), 2.31 (t, $J_{6',5'} = 7.0$, 6′-H$_2$), 2.53 (ddd, $J_{3,1'\text{-H}(1)} = 7.9$*, $J_{3,1'\text{-H}(2)} = 6.6$*, $J_{3,4} = 3.7$, 3-H), 4.21 (br dd, $J_{4,5} \approx J_{4,3} \approx 4.1$, 4-H), 4.63 (qd, $J_{5,5\text{-Me}} = 6.5$, $J_{5,4} = 5.1$, 5-H), 4.99 (dm$_c$, $J_{cis} = 10.2$, 16′-H^E), partially superimposed by 5.02 (dtd, $J_{trans} = 17.2$, $^4J_{16',14'} = J_{gem} = 1.6$, 16′-H^Z), 5.51 (dm$_c$, $J_{trans} = 15.9$, 11′-H), 5.77 (ddt, $J_{trans} = 17.1$, $J_{cis} = 10.3$, $J_{15',14'} = 6.4$, 15′-H), 6.27 (dt, $J_{trans} = 15.9$, $J_{12',13'} = 7.0$, 12′-H); *assignments interchangeable. ^{13}C NMR (75 MHz): $\delta = +13.85$ (5-Me), -19.41 (C-6′)*, -26.98, -28.00, -28.27, -28.40 and -28.72 (C-1′, C-2′, C-3′, C-4′, C-5′), -32.45 and -32.58 (C-13′, C-14′)*, $+49.05$ (C-3), -65.28, -73.00, -73.88 and -83.55 (C-7′, C-8′, C-9′, C-10′), $+73.91$ (C-4)*, $+78.41$ (C-5)*, $+109.06$ (C-11′)*, -115.34 (C-16′), $+137.23$ (C-15′)*, $+147.13$ (C-12′)*, -177.89 (C-2) (*assignments verified by a C,H-COSY spectrum (75 MHz/ 300 MHz)). IR (neat): $\tilde{\nu} = 3440, 3075, 2935, 2860, 2235, 2140, 1770, 1640, 1445, 1340, 1190, 1135, 1055, 995, 955, 915\ cm^{-1}$. $C_{21}H_{28}O_3$ (328.5): calcd C 76.79, H 8.59; found C 74.90, H 8.55. Due to the instability of **12**, no better combustion analysis could be obtained. MS (DCI with NH_3): 348.3 (4%), 347.3 (20%), 346.3 (100%), 330.3 (4%), 329.3 (12%), 328.3 (46%).

Tetrahydro-2-(2-propinyloxy)pyran (**14**): 3,4-Dihydro-2*H*-pyran (23.5 mL, 21.7 g, 258 mmol, 3.0 equiv) and a catalytic amount of pyridinium *p*-toluenesulfonate were added to a stirred solution of propargyl alcohol (5.00 mL, 4.82 g, 85.9 mmol) in CH_2Cl_2 (100 mL). After 16 h the reaction mixture was hydrolyzed with aqueous NaCl (50 mL). After extraction with *t*BuOMe (2×50 mL) and drying over Na_2SO_4, the solvent was removed. The residue was distilled (b.p. 100 °C/20 mbar) and the title compound was obtained as a colorless liquid (10.12 g, 84%). ^{1}H NMR (300 MHz): $\delta = 1.48-1.91$ (m, 3-H$_2$, 4-H$_2$, 5-H$_2$), 2.42 (t, $^4J_{3',1'} = 2.5$, 3′-H), 3.49–3.59 and 3.79–3.89 (2 m each 1 H, 6-H$_2$), AB signal ($\delta_A = 4.24$, $\delta_B = 4.29$, $J_{AB} = 15.8$, in addition split by $^4J_{A,3'} = 2.3$, $^4J_{B,3'} = 2.6$, 1′-H$_2$), 4.83 (t, $J_{2,3} = 3.2$, 2-H). IR (neat): $\tilde{\nu} = 3290, 2940, 2870, 2120, 1445, 1390, 1350, 1265, 1205, 1180, 1120, 1025, 975, 950, 900, 870, 815, 665\ cm^{-1}$. $C_8H_{12}O_2$ (140.2): calcd C 68.55, H 8.63; found C 68.69, H 8.61.

1-(Tetrahydropyran-2-yloxy)-2-nonadecyne (**15**): *n*BuLi (1.40 M, 6.29 mL, 8.81 mmol, 1.2 equiv) was added to a solution of **14** (1.00 g, 7.35 mmol) in THF (10 mL) at 0 °C. After 15 min stirring 1-bromohexadecane (2.47 mL, 2.47 g, 8.08 mmol, 1.1 equiv) and DMSO (25 mL) were added. After stirring at room temperature for 14 h, the reaction was terminated by adding H_2O (30 mL). After extraction with *t*BuOMe (2×20 mL) and aqueous NaCl (2×30 mL), then drying over Na_2SO_4, the solvent was removed. Flash chromatography (petroleum ether/*t*BuOMe 30:1, fractions 4–11) of the residue yielded the title compound (2.05 g, 76%). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{19,18} = 6.8$, 19-H$_3$), 1.26 and approximately 1.30–1.90 (m$_c$ and m, relative intensity difficult to estimate, 5-H$_2$ to 18-H$_2$, 3′-H$_2$, 4′-H$_2$, 5′-H$_2$), 2.21 (tt, $J_{4,5} = 7.1$, $^5J_{4,1} = 2.1$, 4-H$_2$), 3.48–3.58 and 3.80–3.89 (2 m each 1-H, 6′-H$_2$), AB signal ($\delta_A = 4.21$, $\delta_B = 4.29$, $J_{AB} = 15.4$, in addition split by $^5J_{A,4} = 2.1$, $^5J_{B,4} = 2.2$, 1-H$_2$), 4.82 (t, $J_{2',3'} = 3.4$, 2′-H). ^{13}C NMR (50 MHz): $\delta = +14.12$ (C-19), -18.84, -19.14, -22.70, -25.40, -28.62, -28.89, -29.14, -29.37, -29.55, -29.68 (fourfold intensity), -30.30 and -31.92 (15 resonances for 18 C atoms: C-4 to C-18, C-3′, C-4′, C-5′), -54.63 and -61.96 (C-1, C-6′), -75.67 (C-3), -86.76 (C-2), $+96.60$ (C-2′). IR (neat): $\tilde{\nu} = 2925, 2850, 2225, 1460, 1345, 1265, 1200, 1180, 1120, 1075, 1025, 970, 950, 905, 870, 815, 720\ cm^{-1}$. $C_{24}H_{44}O_2$ (364.6): calcd C 79.06, H 12.16; found C 79.25, H 12.04.

2-Nonadecyn-1-ol (**16**): *p*-Toluenesulfonic acid monohydrate (390 mg, 2.05 mmol, 0.4 equiv) was added to the THP ether **15** (1.87 g, 5.13 mmol) in MeOH (40 mL) and the reaction mixture was stirred for 2 h. The solvent was removed after hydrolysis with H_2O (30 mL), extraction with *t*BuOMe (2×30 mL), and drying over Na_2SO_4, and the title compound (1.32 g, 92%) was obtained as a white solid (m.p. 62 °C). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{19,18} = 6.6$, 19-H$_3$), 1.26 and approximately 1.30–1.55 (m$_c$ and m, relative intensity difficult to estimate, 5-H$_2$ to 18-H$_2$, OH), 2.21 (tt, $J_{4,5} = 7.0$, $^5J_{4,1} = 2.2$, 4-H$_2$), 4.25 (m$_c$, 1-H$_2$). ^{13}C NMR (50 MHz): $+14.15$ (C-19), -18.75, -22.71, -28.62, -28.88, -29.15, -29.37, -29.53, -29.70 (fourfold intensity) and -31.93 (12 resonances for 15 C atoms: C-4 to C-18). -51.47 (C-1), -78.22 (C-3), -86.72 (C-2). IR ($CDCl_3$): $\tilde{\nu} = 3155, 2985, 2925, 2855, 2255, 1795, 1640, 1560, 1470, 1380, 1295, 1215, 1165, 1095, 915, 740, 650\ cm^{-1}$. $C_{19}H_{36}O$ (280.5): calcd C 81.36, H 12.94; found C 81.41, H 12.98.

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19-Phenyl-18-nonadecyn-1-ol (**17**): The following reagents were added to a solution of the alkynol **18** (1.24 g, 4.42 mmol) in THF (30 mL) at 0 °C: $PdCl_2(PPh_3)_2$ (155 mg, 0.221 mmol, 5.0 mol %), copper iodide (126 mg, 0.663 mmol, 15 mol %), iodobenzene (593 μL, 1.08 g, 5.30 mmol, 1.2 equiv), and diisopropylamine (5.80 mL, 4.47 g, 44.2 mmol, 10.0 equiv). The reaction mixture was stirred at room temperature for 12 h. Water (10 mL) was added, the phases were separated, and the aqueous phase was extracted with *t*BuOMe (3 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed. Flash chromatography (5 cm, petroleum ether/*t*BuOMe 4:1 → fraction 12, 1:1 → fraction 16, fractions 5–12) yielded **17** (1.33 g, 84 %) as a slightly brownish solid (m.p. 55 °C). ^{1}H NMR (300 MHz): $\delta = 1.24-1.65$ (m, 2-H_2 to 16-H_2), 2.40 (t, $J_{17,16} = 7.0$, 17-H_2), 3.64 (t, $J_{1,2} = 6.6$, 1-H_2), 7.24–7.31 (m, 3 Ar-H), 7.36–7.42 (m, 2 Ar-H); the resonance of the OH group was not detected. IR (KBr): $\tilde{\nu} = 3420$, 3180, 2915, 2850, 1640, 1615, 1470, 1400, 1075, 755, 690 cm^{-1}. $C_{25}H_{40}O$ (356.6): calcd C 84.21, H 11.31; found C 84.51, H 11.35.

18-Nonadecyn-1-ol (**18**): Li (0.371 g, 53.5 mmol, 6.0 equiv) was added to dry 1,2-diaminopropane (50 mL) and stirred for 15 min. The resulting blue solution was refluxed for 15 min, until the blue color disappeared. Subsequently, KO*t*Bu (4.00 g, 35.7 mmol, 4.0 equiv) was added at room temperature. After stirring for 30 min, the alkyne **16** (2.00 g, 7.13 mmol) was added slowly. The reaction mixture was hydrolyzed with ice water (40 mL) after 1 h. The solvent was removed after extraction with *t*BuOMe (3 × 50 mL), H_2O, aqueous HCl (2 M), and aqueous NaCl (50 mL each), and drying over Na_2SO_4. Flash chromatography (6 cm, petroleum ether/*t*BuOMe 7:1 → *t*BuOMe, fractions 23–40) yielded the title compound (1.67 g, 84 %) as a white solid (m.p. 59 °C). ^{1}H NMR (300 MHz): $\delta = 1.26$ and approximately 1.27–1.63 (m_c and m, relative intensity difficult to estimate, 2-H_2 to 16-H_2, OH), 1.94 (t, $^4J_{19,17} = 2.9$, 19-H), 2.18 (td $J_{17,16} = 7.0$, $^4J_{17,19} = 6.8$, 5-H_2), 3.64 (dt, $J_{1,2} = J_{1,OH} = 5.9$, 1-H_2). ^{13}C NMR (50 MHz): −18.42, −25.76, −28.51, −28.79, −29.14, −29.45, −29.53, −29.62 (threefold intensity), −29.69 (fourfold intensity), −29.84 and −32.83 (11 resonances for 15 C atoms: C-2 to C-16), −63.11 (C-1), +68.02 (C-19), −84.83 (C-18). IR ($CDCl_3$): $\tilde{\nu} = 3305$, 3155, 2925, 1855, 1155, 1795, 1645, 1560, 1465, 1380, 1295, 1165, 1095, 915, 740, 650 cm^{-1}. $C_7H_{12}O$ (112.1): calcd C 81.36, H 12.94; found C 81.30, H 12.93.

19-Phenyl-1-nonadecanol (**19**): The alkynol **17** (210 mg, 0.590 mmol) was dissolved in EtOAc (10 mL). Pd (10 % on charcoal, 31 mg, 0.029 mmol, 5.0 mol %) was added and the mixture stirred in an H_2 atmosphere (5 bar) in the autoclave for 16 h. After diluting the mixture, filtration through Celite, and evaporation of the solvent the title compound (173 mg, 82 %) was isolated as a white solid (m.p. 64 °C). ^{1}H NMR (300 MHz): $\delta = 1.24-1.38$ (m, 3-H_2 to 17-H_2), 1.51–1.66 (m, 2-H_2, 18-H_2), 2.60 (br t, $J_{19,18} = 7.9$, 19-H_2), 3.64 (t, $J_{1,2} = 6.6$, 1-H_2), 7.13–7.20 (m, 3 Ar-H), 7.24–7.30 (m, 2 Ar-H); the resonance of the OH group was not detected. IR (KBr): $\tilde{\nu} = 3180$, 2915, 2850, 1635, 1460, 1400, 1075, 745, 700 cm^{-1}. $C_{25}H_{44}O$ (360.6): calcd C 83.26, H 12.30; found C 83.05, H 12.41.

1-Iodo-19-phenylnonadecane (**20**): The alcohol **19** (90 mg, 0.25 mmol) and triphenylphosphite (66 μL, 78 mg, 0.25 mmol, 1.0 equiv) were dissolved in CH_2Cl_2 (3 mL). After the mixture had been stirred for 10 min at room temperature, I_2 (64 mg, 0.25 mmol, 1.0 equiv) was added at 0 °C. Water (5 mL) was added to the brown solution after 1 h and the colorless organic phase was removed. After extraction of the aqueous phase with petroleum ether (2 × 20 mL), the combined organic extracts were dried over $MgSO_4$. After the solvent had been removed, flash chromatography (2 cm, petroleum ether → fraction 10, fractions 2–4) of the residue yielded the iodide **20** (91 mg, 82 %) as a white solid (m.p. 50 °C). ^{1}H NMR (300 MHz): $\delta = 1.23-1.41$ (m, 3-H_2 to 17-H_2), 1.61 (br tt, $J_{18,17} = J_{18,19} = 7.4$, 18-$H_2$), 1.82 (tt, $J_{2,1} = J_{2,3} = 7.2$, 2-H_2), 2.60 (br t, $J_{19,18} = 7.7$, 19-H_2), 3.18 (t, $J_{1,2} = 7.2$, 1-H_2), 7.13–7.20 (m, 3 Ar-H), 7.24–7.32 (m, 2 Ar-H). ^{13}C NMR (50 MHz): $\delta = 7.34$ (C-1), 28.56, 29.36, 29.44, 29.53, 29.57, 29.61, 29.63, 29.69, 30.52, 31.55, 33.58 and 35.99 (i.e. 12 resonances for 18 C atoms, C-2 to C-19), 125.49 (*p*-C), 128.16 and 128.34 (2 × *o*-C, 2 × *m*-C), 142.89 (*ipso*-C). IR (KBr): $\tilde{\nu} = 2915$, 2850, 1615, 1470, 1400, 1165, 745, 715, 695, 600 cm^{-1}. $C_{25}H_{43}I$ (470.5): calcd C 63.82, H 9.21; found C 63.96, H 8.93.

***E*-16-Iodo-1,5-hexadecadiene-7,9-diyne** (**21**): A solution of the alcohol **35** (345 mg, 1.50 mmol) in THF (10 mL) was successively treated with PPh_3 (432 mg, 1.65 mmol, 1.1 equiv), imidazole (224 mg, 3.30 mmol, 2.2 equiv), and I_2 (419 mg, 1.65 mmol, 1.1 equiv) at 0 °C. After 1 h a saturated NH_4Cl solution (5 mL) was added to the reaction mixture, followed by extraction with *t*BuOMe (2 × 50 mL). After the organic phase had been dried over $MgSO_4$, the solvent was removed. Flash chromatography (3 cm, petroleum ether/*t*BuOMe 20:1, fractions 8–15) yielded the iodo compound (449 mg, 88 %). ^{1}H NMR (300 MHz): $\delta = 1.37-1.49$ (m, 13-H_2, 14-H_2), 1.49–1.60 (m, 11-H_2), 1.83 (tt, $J_{15,14} = J_{15,16} = 6.9$, 15-$H_2$), 2.10–2.27 (m, 3-$H_2$, 4-$H_2$), 2.32 (t, $J_{11,12} = 6.8$, 11-H_2), 3.19 (t, $J_{16,15} = 7.0$, 16-H_2), 4.99 (dm_c, $J_{cis} \approx 10.2$, 1-H^E), partially superimposed by 5.02 (dm_c, $J_{trans} \approx 17.4$, 1-H^Z), 5.51 (poorly resolved dd, $J_{trans} = 16.0$, $^7J_{6,11} = 0.9$, 6-H), 5.77 (ddt, $J_{trans} = 17.2$, $J_{cis} = 10.3$, $J_{2,3} = 6.4$, 2-H), 6.27 (dt, $J_{trans} = 15.9$, $J_{5,4} = 6.7$, 5-H). ^{13}C NMR (50 MHz): $\delta = -6.95$ (C-16), −19.42, −27.65, −27.97, −29.92, −32.45, −32.59 and −33.27 (C-3, C-4, C-11, C-12, C-13, C-14, C-15), −65.35, −72.97, −73.89 and −83.33 (C-7, C-8, C-9, C-10), +109.08 (C-6), −115.32 (C-1), +137.19 and +147.03 (C-2, C-5). IR (neat): $\tilde{\nu} = 3075$, 2930, 2855, 2235, 2140, 1640, 1450, 1425, 1360, 1300, 1245, 1200, 1165, 1080, 990, 955, 915 cm^{-1}. $C_{16}H_{21}I$ (340.2): calcd C 56.48, H 6.22; found C 56.48, H 6.24.

7-Octyn-1-ol (**22**) was prepared in the same way as **18** using 1,2-diaminopropane (60 mL), Li (1.00 g, 144 mmol, 6.0 equiv), KO*t*Bu (10.8 g, 96.2 mmol, 4.0 equiv) and alcohol **32** (3.00 g, 23.8 mmol). Flash chromatography (3 cm, pentane/Et_2O 2:1 → 1:2, fractions 5–17) yielded the title compound (2.46 g, 82 %). ^{1}H NMR (300 MHz): $\delta = 1.28-1.45$ and 1.46–1.60 (2 m each 4-H, 2-H_2, 3-H_2, 4-H_2 and 5-H_2), 1.92 (t, $^4J_{8,6} = 2.6$, 8-H), superimposed by (br s, detectable by the integral only, OH), 2.16 (tt, $J_{6,5} = 6.9$, $^4J_{6,8} = 2.5$, 6-H_2), 3.60 (t, $J_{1,2} = 6.6$, 1-H_2). IR (neat): $\tilde{\nu} = 3295$, 2935, 2860, 2115, 1460, 1435, 1330, 1055, 1035, 630 cm^{-1}. $C_8H_{14}O$ (126.2) calcd C 76.14, H 11.18; found 76.04, H 11.08.

Methyl *E*-2,6-heptadienoate (*trans*-23) and methyl *Z*-2,6-heptadienoate (*cis*-23): The unsaturated ester **26** (4.06 g, 29.0 mmol) was heated for 16 h to 240 °C in a pressure-resistant flask in a sand bath. Flash chromatography (6 cm, pentane/Et_2O 30:1 → fraction 10, 20:1 → fraction 20) of the colorless residue yielded *cis*-**23** (fraction 7–10, 325 mg, 8 %) and *trans*-**23** (fraction 11–18, 3.055 g, 75 %). *trans*-**23**: ^{1}H NMR (300 MHz): $\delta = 2.18-2.36$ (m, 4-H_2, 5-H_2), 3.73 (s, OMe), 5.01 (dtd, $J_{cis} \approx 10.6$, $^4J_{7,5} \approx J_{gem} \approx 1.4$, 7-$H^E$), partially superimposed by 5.05 (dtd, $J_{trans} \approx 16.9$, $^4J_{7,5} \approx J_{gem} \approx 1.7$, 7-$H^Z$), 5.80 (ddt, $J_{trans} = 17.0$, $J_{cis} = 10.2$, $J_{6,5} = 6.2$, 6-H), severely superimposed by 5.84 (dt, $J_{trans} = 15.8$, $^4J_{2,4} = 1.5$, 2-H), 6.97 (dt, $J_{trans} = 15.8$, $J_{3,4} = 6.6$, 3-H). IR (neat): $\tilde{\nu} = 3080$, 2980, 2950, 2845, 1725, 1660, 1645, 1435, 1320, 1270, 1210, 1175, 1040, 990, 915 cm^{-1}. $C_8H_{12}O_2$ (140.2): calcd C 68.54, H 8.63; found C 68.71, H 8.83. *cis*-**23:** ^{1}H NMR (300 MHz): $\delta = 2.15$ (tdt, $J_{5,4} = J_{5,6} = 7.2$, $^4J_{5,7} = 1.3$, 5-H_2), 2.71 (tdd, $J_{4,5} = J_{4,3} = 7.5$, $^4J_{4,2} = 1.7$, 4-H_2), 3.65 (s, OMe), 4.94 (dm_c, $J_{cis} \approx 10$, 7-H^E), partially superimposed by 4.99 (dtd, $J_{trans} \approx 17$, $^4J_{7,5} \approx J_{gem} \approx 1.8$, 7-$H^Z$), 5.74 (dt, $J_{cis} = 11.7$, $^4J_{2,4} = 1.5$, 2-H), completely superimposed by 5.76 (ddt, $J_{trans} = 17.0$, $J_{cis} = 10.2$, $J_{6,5} = 6.6$, 6-H), 6.17 (dt, $J_{cis} = 11.6$, $J_{3,4} = 7.6$, 3-H). IR (neat): $\tilde{\nu} = 3080$, 2950, 1720, 1645, 1440, 1405, 1210, 1175, 995, 910, 820, 735, 650 cm^{-1}. $C_8H_{12}O_2$ (140.2): calcd C 68.54, H 8.63; found C 68.42, H 8.49.

Methyl (2-ethenyl-4-pentenoate) (**26**): BuLi (2.5 M in hexane, 20.0 mL, 50.0 mmol, 1.0 equiv) was added to a solution of HMDS (10.5 mL, 8.05 g, 50.0 mmol, 1.0 equiv) in THF (200 mL) at −78 °C. After 30 min, ester **27** (6.31 g, 50.0 mmol) was added and after another 30 min, Me_3SiCl (6.94 mL, 5.94 g, 55.0 mmol, 1.1 equiv) was added. The reaction mixture was gradually warmed to room temperature after continuous stirring for 10 min at −78 °C and finally refluxed for 30 min. After the mixture had cooled down, aqueous HCl (1 M, 300 mL) was added in one go with vigorous stirring. After extraction of the aqueous phase with *t*BuOMe (3 × 200 mL), the combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The ^{1}H NMR spectrum revealed the residue (6.30 g) to be a 87:13 mixture of 2-vinyl-4-pentenoic acid (**28**) and a sterically homogenous 2-ethyliden-4-pentenoic acid (**29**) of unknown configuration [$\delta_{=CHMe} = 7.10$ (q, $J \approx 7$)]. The residue was dissolved in $CHCl_3$ (60 mL), and MeOH (4.05 mL, 3.20 g, 100 mmol, 2.0 equiv) and *p*-TsOH (190 mg, 1.00 mmol, 2.0 mol %) were added. This mixture was connected to an inverse water trap and refluxed for 16 h. After removal of most of the solvent at room temperature, the deconjugated ester **26** (4.380 g, 63 %) was isolated by flash chromatography (8 cm, pentane/Et_2O 40:1 → fraction 6, 20:1 → fraction 12, 10:1 → fraction 16, fractions 8–15). ^{1}H NMR (300 MHz): δ = AB signal ($\delta_A = 2.33$, $\delta_B = 2.51$, $J_{AB} = 14.2$, in addition split by $J_{A,2} \approx J_{A,4} \approx 6.8$, $J_{B,2} \approx J_{B,4} \approx 7.2$, signals broadened by nonresolved J_{allyl}, 3-H_2), 3.12 (ddd, $J_{2,1'} = J_{2,3\text{-}H(A)} = J_{2,3\text{-}H(B)} = 7.7$, 2-H), 3.69 (s, OMe), 5.01–5.18 (m, 5-H_2, 2′-H_2), 5.74 (dddd, $J_{trans} = 17.4$, $J_{cis} = 10.2$, $J_{4,3\text{-}H(A)} = J_{4,3\text{-}H(B)} = 7.0$, 4-H), superimposed by 5.83 (ddd with small extra peaks indicating transition to higher order splitting, $J_{trans} = 17.3$, $J_{cis} = 9.8$, $J_{1',2} = 8.3$, 1′-H). IR (neat): $\tilde{\nu} = 3080$, 2980, 2950, 1740, 1640, 1435, 1345,

1270, 1240, 1195, 1170, 995, 920 cm^{-1}. $C_8H_{12}O_2$ (140.2): calcd C 68.54, H 8.63; found C 68.75, H 8.48.

Allyl 3-butenoate (**27**): A solution of 3-butenoic acid (8.50 mL, 8.61 g, 0.100 mol), allyl alcohol (6.79 mL, 5.80 g, 0.100 mol, 1.0 equiv) and *p*-TsOH (0.19 g, 1.0 mmol, 1 mol %) in $CHCl_3$ (50 mL) was connected to an inverse water trap and refluxed for 16 h. Distillation (b.p. 73 °C/15 mbar) yielded the title ester (12.2 g, 97 %). ^{1}H NMR (300 MHz): $\delta = 3.13$ (dt, $J_{2,3} = 6.9$, $^4J_{2,4} = 1.3$, 2-H$_2$), 4.60 (dt, $J_{1',2'} = 5.6$, $^4J_{1',3'} = 1.3$, 1′-H$_2$), 5.14 to approximately 5.22 (m, 4-H$_2$), partially superimposed by 5.24 (ddt, $J_{cis} = 10.3$, $J_{gem} = {}^4J_{3',1'} = 1.3$, 3′-H^E), 5.32 (ddt, $J_{trans} = 17.2$, $J_{gem} = {}^4J_{3',1'} = 1.5$, 3′-H^Z), 5.86 – 6.01 (m, 3-H, 2′-H).

***E*-2,6 Heptadien-1-ol** (**30**): DIBAL (1.0 M in toluene, 66 mL, 66 mmol, 2.2 equiv) was added to a solution of the ester *trans*-**23** (4.20 g, 30.0 mmol) in THF (100 mL) at −78 °C. The reaction mixture was slowly warmed to room temperature. After 30 min, the reaction was terminated by careful addition of aqueous HCl (2 M, 35 mL). The organic phase was separated and the aqueous phase extracted with *t*BuOMe (3 × 50 mL). After the combined organic phases had been dried over $MgSO_4$, the solvent was removed. The residue was purified by flash chromatography (7 cm, petroleum ether → fraction 10, petroleum ether/*t*BuOMe 2:1 → fraction 24, fractions 14 – 20) to yield the title compound (3.08 g, 92 %) as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 1.41$ (m$_c$, OH), 2.13 – 2.17 (m, 4-H$_2$, 5-H$_2$), 4.09 (d, $J_{1,2} = 4.5$, 1-H$_2$), 4.97 (dm$_c$, $J_{cis} \approx 11$, 7-H^E), partially superimposed by 5.02 (dm$_c$, $J_{trans} \approx 17$, 7-H^Z), 5.61 – 5.88 (m, 2-H, 3-H, 6-H). IR (neat): $\tilde{\nu}$ = 3330, 3075, 2980, 2920, 2845, 1670, 1640, 1440, 1415, 1090, 1000, 970, 910 cm^{-1}. $C_7H_{12}O$ (112.2): calcd C 74.95, H 10.78; found C 75.11, H 11.02.

2-Octyn-1-ol (**32**): A catalytic amount of $Fe(NO_3)_3$ (approximately 100 mg) and Li (4.16 g, 600 mmol, 3.0 equiv) were added to liquid ammonia (350 mL). After 30 min, 2-propyn-1-ol (14.8 mL, 14.0 g, 250 mmol, 1.25 equiv) was added dropwise. 1-Bromopentane (24.8 mL, 30.2 g, 200 mmol) was slowly added after 5 min. The ammonia was evaporated after 1.5 h and the residue hydrolyzed with ice water (100 mL). After extraction with Et_2O (6 × 100 mL) and drying over Na_2SO_4, the solvent was removed. Distillation of the residue (b.p. 105 °C/30 mbar) yielded the title compound (19.0 g, 75 %). ^{1}H NMR (300 MHz; slightly impure): $\delta = 0.90$ (t, $J_{8,7} = 7.2$, CH$_3$), 1.25 – 1.43 (m, 6-H$_2$, 7-H$_2$), 1.47 – 1.57 (m, 5-H$_2$), 1.60 (br s, OH), 2.21 (tt, $J_{4,5} = 7.0$, $^5J_{4,1} = 2.1$, 4-H$_2$), 4.25 (poorly resolved t, $^5J_{1,4} = 2.1$, 1-H$_2$). IR (neat): $\tilde{\nu}$ = 3325, 2955, 2930, 2860, 2360, 2290, 2225, 1460, 1430, 1380, 1330, 1135, 1010, 725 cm^{-1}. $C_8H_{14}O$ (126.2): calcd C 76.14, H 11.18; found C 76.27, H 11.05.

***E*-1,1-Dibromo-1,3,7-octatriene** (**33**): DMSO (4.17 mL, 4.63 g, 59.4 mmol, 2.2 equiv) was slowly added to a solution of oxalyl chloride (2.60 mL, 3.77 g, 29.7 mmol, 1.1 equiv) in CH_2Cl_2 (60 mL) at −78 °C. After 3 min, the allyl alcohol **30** (3.00 g, 27.0 mmol) was added. NEt_3 (18.7 mL, 13.6 g, 135 mmol, 5.0 equiv) was added after 15 min followed by water (50 mL) after another 30 min. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were extracted with HCl (2 M, 65 mL), dried over $MgSO_4$, and the solvent was removed at room temperature. The isolated residue was used without purification to prepare **33**: CBr_4 (17.9 g, 54.0 mmol, 2.0 equiv) was added to a solution of PPh_3 (28.3 g, 108 mmol, 4.0 equiv) in CH_2Cl_2 (250 mL) at 0 °C. After 10 min, the isolated aldehyde (2.97 g, 27.0 mmol) was added to the orange solution. Most of the solvent was removed after 1 h at room temperature. Petroleum ether (500 mL) was added to the residue and the precipitated solid was filtered off. After thoroughly washing the solid residue with petroleum ether, the solvent was removed from the filtrate. Flash chromatography (5 cm, petroleum ether → fraction 10, fractions 3 – 5) of the dark brown residue yielded the dibromotriene **33** (3.82 g, 53 % overall yield) as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 2.19$ (m$_c$, 5-H$_2$, 6-H$_2$), 5.00 (dtd, $J_{cis} = 10.6$, $^4J_{8,6} = J_{gem} = 1.0$, 8-H^E), partially superimposed by 5.04 (dtd, $J_{trans} = 16.9$, $^4J_{8,6} = J_{gem} = 1.5$, 8-H^Z), 5.73 – 5.96 (m, 4-H, 7-H), 6.11 (incompletely resolved ddt, $J_{trans} = 15.3$, $J_{3,2} = 10.0$, $^4J_{3,5} = 1.4$, 3-H), 6.90 (d, $J_{2,3} = 9.8$, 2-H). IR (neat): $\tilde{\nu}$ = 3075, 2975, 2925, 2850, 2340, 1765, 1725, 1640, 1620, 1445, 1270, 1170, 1075, 995, 970, 915, 810 cm^{-1}. $C_8H_{10}Br_2$ (266.0): calcd C 36.13, H 3.79; found C 34.36, H 3.57. Because of the instability of this compound no better combustion analysis could be obtained.

***E*-8-Bromo-1,5-octadiene-7-yne** (**34**): Bu_4NF (1.0 M in THF, 27.0 mL, 27.0 mmol, 3.0 equiv) was added to a solution of the dibromotriene **33** (2.39 g, 9.00 mmol) in THF (40 mL) and the mixture was stirred for 24 h at 40 °C. After dilution of the dark brown solution with Et_2O (50 mL), water (100 mL) was added and the organic phase was separated. After extraction of the aqueous phase with Et_2O (2 × 50 mL) the organic phases were combined and dried. The solvent was removed at 0 °C, and the residue was purified by flash chromatography (5 cm, petroleum ether → fraction 12, fractions 5 – 11) to give the title compound (1.29 g, 78 %). ^{1}H NMR (300 MHz): $\delta = 2.10 - 2.25$ (m, 3-H$_2$, 4-H$_2$), 4.99 (dm$_c$, $J_{cis} \approx 10.2$, 1-H^E), partially superimposed by 5.03 (dm$_c$, $J_{trans} \approx 17.0$, 1-H^Z), 5.46 (dt, J_{trans} = 16.2, $^4J_{6,4} = 1.5$, 6-H), 5.78 (ddt, $J_{trans} = 16.9$, $J_{cis} = 10.4$, $J_{2,3} = 6.4$, 2-H), 6.21 (dt, $J_{trans} = 15.8$, $J_{5,4} = 6.8$, 5-H). ^{13}C NMR (50 MHz): $\delta = 32.21$ and 32.60 (C-3, C-4), 47.60 (C-8), 78.76 (C-7), 109.52 and 115.31 (C-1, C-6), 137.29 and 145.62 (C-2, C-5). IR (neat): $\tilde{\nu}$ = 3075, 3025, 3000, 2975, 2925, 2845, 2210, 2165, 1760, 1730, 1640, 1435, 1415, 1300, 990, 960, 915 cm^{-1}. C_8H_9Br (185.1): calcd C 51.92, H 4.90; found C 52.03, H 4.77.

***E*-11,15 Hexadecadiene-7,9-diyn-1-ol** (**35**): A mixture of $Pd(dba)_2$ (169 mg, 0.294 mmol, 5 mol %), CuI (28.0 mg, 0.147 mmol, 2.5 mol %), and LiI (157 mg, 1.18 mmol, 20 mol %) was treated with a solution of bromoalkyne **34** (1.20 g, 6.46 mmol, 1.1 equiv) and alkyne **22** (742 mg, 5.88 mmol) in degassed DMSO (40 mL). After 10 min 1,2,2,6,6-pentamethylpiperidine (2.97 mL, 2.55 g, 16.5 mmol, 2.8 equiv) was added. After continued stirring for 2 h the mixture was diluted with Et_2O (50 mL), water (50 mL), and aqueous HCl (2 M, 8 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (2 × 50 mL). The combined organic phases were extracted with water (50 mL) and dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (4 cm, petroleum ether/*t*BuOMe 3:1 → fraction 30, 2:1 → fraction 45, 1:1 → fraction 60, fractions 36 – 58) to yield the title compound (808 mg, 60 %). The homocoupling product of the bromoalkyne **34** (176 mg, 11 %) was obtained from fractions 5 – 6. ^{1}H NMR (300 MHz): $\delta = 1.30 - 1.49$ (m, 3-H$_2$, 4-H$_2$, OH), 1.50 – 1.63 (m, 2-H$_2$, 5-H$_2$), 2.10 – 2.27 (m, 13-H$_2$, 14-H$_2$), 2.32 (br t, $J_{6,5} = 6.8$, 6-H$_2$), 3.65 (t, $J_{1,2} = 6.4$, 1-H$_2$), 4.99 (dm$_c$, $J_{cis} \approx 10.2$, 16-H^E), partially superimposed by 5.02 (dtd, $J_{trans} \approx 17.4$, $^4J_{16,14} = J_{gem} = 1.5$, 16-H^Z), 5.51 (br d, $J_{trans} = 15.8$, 11-H), 5.77 (ddt, $J_{trans} = 17.0$, $J_{cis} = 10.5$, $J_{15,14} = 6.3$, 15-H), 6.27 (dt, $J_{trans} = 15.8$, $J_{12,13} = 6.7$, 12-H). IR (neat): $\tilde{\nu}$ = 3330, 3075, 2935, 2860, 2235, 2140, 1640, 1435, 1350, 1300, 1075, 1055, 1030, 995, 955, 915 cm^{-1}. $C_{16}H_{22}O$ (230.4): calcd C 83.43, H 9.63; found C 83.18, H 9.93.

(5*S*)-5-Methyl-2(5*H*)-furanone (**37**): Lactone **8** (546 mg, 4.70 mmol) was dissolved in CH_2Cl_2 (30 mL). At 0 °C NEt_3 (1.37 mL, 1.00 g, 9.87 mmol, 2.1 equiv) and methanesulfonyl chloride (0.40 mL, 0.59 g, 5.2 mmol, 1.1 equiv) were added. After 1 h the reaction was terminated by adding saturated NH_4Cl solution (10 mL) and water (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). After drying the combined organic phases over $MgSO_4$ the solvent was removed at 0 °C. Flash chromatography (4 cm, pentane/Et_2O 1:2, fractions 10-18) of the residue yielded the butenolide **37** (370 mg, 81 %) as a colorless liquid. $[\alpha]_D^{20} = 80.7$ ($c = 0.65$ in $CHCl_3$); the *ee* of the starting material **8** was 78 %, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = 80.7/0.78 = 104$ for optically pure **37** {ref. [10] $[\alpha]_D^{20} = -107$ for the enantiomer ($c = 1.61$, $CHCl_3$)}. ^{1}H NMR (300 MHz): $\delta = 1.46$ (d, $J_{5\text{-Me},5} = 6.8$, 5-Me), 5.15 (qdd, $J_{5,5\text{-Me}} = 6.9$, $J_{5,4} \approx {}^4J_{5,3} = 1.7$, 5-H), 6.11 (dd, $J_{3,4} = 5.6$, $^4J_{3,5} = 1.9$, 3-H), 7.46 (dd, $J_{4,3} = 5.7$, $J_{4,5} = 1.5$, 4-H).

(4*R*,5*S*)-4-[(Dimethylphenyl)silyl]-4,5-dihydro-5-methyl-2(3*H*)-furanone (**39**): A solution of $Me_2PhSiCl$ (2.53 mL, 2.58 g, 15.1 mmol, 4.0 equiv) in THF (30 mL) was stirred for 24 h at 0 °C with Li (260 mg, 37.8 mmol, 10.0 equiv). The dark red solution was slowly added to a suspension of CuCN (696 mg, 7.56 mmol, 2.0 equiv) in THF (50 mL) at −10 °C. After an additional 30 min the mixture was cooled to −78 °C and treated dropwise with a solution of butenolide **37** (370 mg, 3.78 mmol) in THF (10 mL). Aqueous HCl (1 M, 20 mL) was added after 15 min at the same temperature. After extraction of the aqueous phase with *t*BuOMe (3 × 30 mL), the organic phase was dried over $MgSO_4$. After removal of the solvent, the silane **39** (708 mg, 80 %) was obtained by flash chromatography (3 cm, petroleum ether/*t*BuOMe 3:1 → fraction 18, 2:1 → fraction 24, fractions 10 – 22) as a colorless oil. $[\alpha]_D^{20} = -22$ ($c = 0.44$ in $CHCl_3$); the *ee* of the starting material **8** was 78 %, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -22/0.78 = -28$ for optically pure **39**. ^{1}H NMR (300 MHz): $\delta = 0.38$ and 0.39 (2 s, $SiMe_2$), 1.29 (d, $J_{5\text{-Me},5} = 6.0$, 5-Me), 1.61 (ddd, $J_{4,3\text{-H(A)}} = 12.0$, $J_{4,5} = 10.4$, $J_{4,3\text{-H(B)}} = 9.2$, 4-H), AB signal ($\delta_A = 2.39$, $\delta_B = 2.55$, $J_{AB} = 17.5$, in addition split by $J_{A,4} = 12.8$, $J_{B,4} = 9.2$, 3-H$_2$), 4.45 (dq, $J_{5,4} = 10.4$, $J_{5,5\text{-Me}} = 6.2$, 5-H), 7.36 – 7.50 (m, 5 Ar-H). IR (neat): $\tilde{\nu}$ = 3070, 3050, 2975, 2935, 2900, 1770, 1430, 1385, 1360, 1345, 1255, 1225, 1190, 1155,

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1115, 1085, 1050, 945, 930, 895, 835, 785, 735, 700, 650 cm^{-1}. $C_{13}H_{18}SiO_2$ (234.4): calcd C 68.62, H 7.74; found C 68.87, H 7.58.

(4*R*,5*S*)-4,5-Dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (**40**): A solution of the silane **39** (234 mg, 1.00 mmol) in diluted HOAc (3 mL) was mixed with KBr (238 mg, 2.00 mmol, 2.0 equiv), NaOAc (980 mg, 12.0 mmol, 12.0 equiv), and peroxyacetic acid (32% in diluted HOAc, 2.10 mL, 10.0 mmol, 10.0 equiv) at 0 °C. After stirring the mixture at room temperature for 16 h, aqueous $Na_2S_2O_3$ solution (10 mL) was added to the brown solution. K_2CO_3 solution was added to adjust the pH to 7, followed by extraction with CH_2Cl_2 (5 × 30 mL). After the mixture had been dried over $MgSO_4$, and the solvent was removed, and the residue was purified by flash chromatography (3 cm, *t*BuOMe, fractions 8–16) to yield **40** (37.0 mg, 32%). $[\alpha]_D^{20} = -8.40$ ($c = 1.20$ in $CHCl_3$); the *ee* of the starting material **8** was 78%, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -8.40/0.78 = -10.8$ for optically pure **40** {ref. [10] $[\alpha]_D^{20} = +10.87$ for the enantiomer ($c = 2.42$, $CHCl_3$)}. ^{1}H NMR (300 MHz): $\delta = 1.38$ (d, $J_{5\text{-Me},5} = 6.7$, 5-Me), AB signal ($\delta_A = 2.53$, $\delta_B = 2.85$, $J_{AB} = 17.9$, in addition split by $J_{A,4} = 3.6$, $J_{B,4} = 6.4$, 3-H_2), superimposed by approximately 2.84 (br s, OH), 4.25 (m_c, 4-H), 4.58 (qd, $J_{5,5\text{-Me}} = 6.6$, $J_{5,4} = 2.8$, 5-H).

(3*R*,4*R*,5*S*)-3-(11,15Hexadecadiene-7,9-diinyl)-4,5-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (**41**) was prepared in the same way as **12** using diisopropylamine (88 μL, 68 mg, 0.67 mmol, 2.5 equiv), *n*BuLi (2.5 M in hexane, 0.27 mL, 0.67 mmol, 2.5 equiv), β-hydroxylactone **40** (31.4 mg, 0.270 mmol), and iodo compound **21** (92.0 mg, 0.270 mmol, 1.0 equiv). The alkylation step was carried out at −40 °C for 20 h. Flash chromatography (2 cm, petroleum ether/*t*BuOMe 2:1 → fraction 24, 1:1 → fraction 38, fractions 27–36) of the residue yielded the title compound (39.8 mg, 45%; 62% based on recovered iodide) as white, light-sensitive crystals melting at 77 °C (decomp; ref. [17] 88 °C). From fractions 2–5 unconverted iodide **21** (24.5 mg, 27%) was reisolated. $[\alpha]_D^{20} = -22$ ($c = 0.28$); the *ee* of the starting material **8** was 78%, therefore, the measured specific rotation corresponds to $[\alpha]_D^{20} = -22/0.78 = -28$ for optically pure **41** {ref. [17] $[\alpha]_D^{20} = -30$ ($c = 0.01$, $CHCl_3$)}. ^{1}H NMR (500 MHz): $\delta = 1.32-1.64$ (m, 1′-H^1, 2′-H_2, 3′-H_2, 4′-H_2, 5′-H_2), superimposed by 1.46 (d, $J_{5\text{-Me},5} = 6.3$, 5-Me), 1.86 (dddd, $J_{gem} = 13.4$, $J_{1'\text{-H}(2),2'\text{-H}(1)} = 10.8$, $J_{1'\text{-H}(2),2'\text{-H}(2)} = J_{1'\text{-H}(2),3} = 5.4$, 1′-$H_2$), 2.06 (br d, $J_{OH,4} = 5.1$, OH), 2.12–2.17 and 2.20–2.25 (2 m each 2-H, 13′-H_2, 14′-H_2), 2.32 (poorly resolved td, $J_{6',5'} = 6.9$, $^7J_{6',11'} = 0.6$, 6′-H_2), 2.55 (ddd, $J_{3,4} = 8.7$*, $J_{3,1'\text{-H}(1)} = 7.4$*, $J_{3,1'\text{-H}(2)} = 5.7$, 3-H), 3.84 (br ddd, $J_{4,5} \approx J_{4,3} \approx 8.0$, $J_{4,OH} \approx 4.6$, 4-H), 4.20 (dq, $J_{5,4} = 7.2$, $J_{5,5\text{-Me}} = 6.4$, 5-H), 4.99 (dm_c, $J_{cis} \approx 10$, 16′-H^E), partially superimposed by 5.02 (dtd, $J_{trans} = 17.0$, $^4J_{16',14'} = J_{gem} = 1.7$, 16′-$H^Z$), 5.51 ($dm_c$, $J_{trans} = 16.0$, 11′-H), 5.77 (ddt, $J_{trans} = 17.0$, $J_{cis} = 10.3$, $J_{15',14'} = 6.4$, 15′-H), 6.27 (dt, $J_{trans} = 16.0$, $J_{12',13'} = 6.9$, 12′-H); *assignments interchangeable. ^{13}C NMR (75 MHz): $\delta = +18.19$ (5-Me), −19.43 (C-6′)*, −26.49, −28.03, −28.32, −28.45 and −28.90 (C-1′, C-2′, C-3′, C-4′, C-5′), −32.46 and −32.59 (C-13′, C-14′)*, +48.51 (C-3), −65.27, −73.04, −73.89 and −83.62 (C-7′, C-8′, C-9′, C-10′), +78.95 (C-4)*, +79.98 (C-5)*, +109.09 (C-11′)*, −115.35 (C-16′), +137.24 (C-15′)*, +147.13 (C-12′)*, −176.13 (C-2); *assignments verified by a C,H-COSY (300 MHz/75 MHz). IR (KBr): $\tilde{\nu} =$ 3425, 3075, 2935, 2860, 2235, 2140, 1765, 1640, 1460, 1445, 1385, 1335, 1230, 1195, 1135, 1055, 995, 955, 915 cm^{-1}. MS (DCI with NH_3): 347.2 (6%), 346.2 (38%), 329.3 (18%), 328.3 (100%).

Acknowledgments: This work was supported by the Fonds der Chemischen Industrie, for which we are very grateful. In addition, we thank BASF AG for donating chemicals.

Received: January 14, 1998
Revised version: May 28, 1998 [F 962]

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[47] This value was published (ref. [17]) erroneously and interpreted accidentally (ref. [48]). The 360 MHz ^{1}H NMR spectrum of (−)-sapranthin shows a 4-H signal which is identical to the 4-H signal of synthetic **41** (ref. [48]).
[48] P. G. Waterman, personal communication.

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