Elucidation of the stereostructure of the annonaceous acetogenin (+)-montecristin through total synthesis

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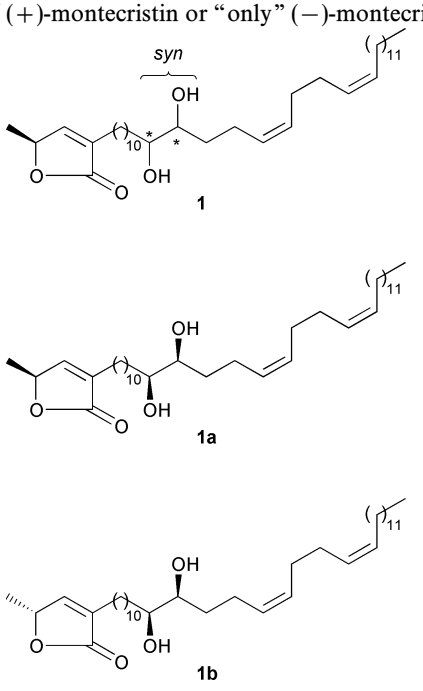
Total syntheses of *ent*-5-*epi*-montecristin (**1a**) and of (−)-montecristin (**1b**) were accomplished. The stereocenters of compounds **1a** and **1b** were established by asymmetric dihydroxylations of the *trans*-configurated β,γ-unsaturated esters **6** (→**4**, up to 80% ee; Scheme 3; improved procedure with up to 94% ee: Scheme 7) and **56** (→**55**, 97% ee: Scheme 9) while the stereogenic C=C bonds stem from the carbocuprations **48** → **49** and **50** → **51** (Scheme 9). Treating hydroxylactones **27** (Scheme 7), **3a** (Scheme 12) and **3b** (Scheme 13) with PPh_3 and DEAD, we found a racemization-free dehydration giving butenolide **26** and epimerization-free dehydrations giving butenolides **2a** and **2b**. Relating the $[\alpha]_D$ values of synthetic **1a** and **1b** to the $[\alpha]_D$ value of natural (+)-montecristin, the absolute configuration of its side-chain stereocenters was determined to be *R*.

Annonaceous acetogenins are an ever more numerous class of natural products isolated from *Annonaceae*.[1] They are γ-methylbutenolides or γ-methylbutyrolactones with an unbranched C_{30} or C_{32} side-chain at C-α. This side-chain is usually oxidized, exhibiting one, two or three THF rings and/or hydroxy, acetoxy, epoxy or carbonyl groups. The synthesis of such compounds has attracted much attention recently,[2] in part because of their strong anti-tumor, anti-parasitic and insecticide activities. A few annonaceous acetogenins contain *cis*-configurated C=C bonds in the place of of oxygenated side-chain functions, such as muridienin[3,4] or chatenaytrienin.[4] These compounds are probably biogenetic precursors of the more heavily oxygenated annonaceous acetogenins.

Given this background, the annonaceous acetogenin (+)-montecristin (**1**; Scheme 1) isolated in 1997 from the roots of *Annona muricata* L.[5] might be an intermediate *en route* between the less and the more oxygenated acetogenins. Montecristin is an α,γ-disubstituted butenolide with a C_{32} side-chain at C-α. The constitution of montecristin was established by NMR spectroscopy, chemical derivatization and mass spectrometric analysis.[5] It has a side-chain which contains a glycol moiety and two *cis*-configurated C=C bonds. The relative configuration of the glycol moiety was shown to be *syn*, while the absolute configuration remained unknown. Montecristin also consists of a butenolide moiety which possesses the *S*-configuration that is common to all butenoide-containing annonaceous acetogenins.

In recent years, we have prepared many kinds of γ-chiral butanolides and butenolides by means of Sharpless' asymmetric dihydroxylation[6] of *trans*-configurated β,γ-unsaturated carboxylic esters.[7] However, we had not yet synthesized a γ-chiral butenolide having the substitution pattern displayed by **1**. Therefore, we chose this compound (or its enantiomer) as a synthetic target. Since, however, the stereostructure of natural montecristin, *i.e.* (+)-montecristin, was not known beyond formula **1** (Scheme 1, *absolute* configuration shown), and since we also wished to determine the absolute configuration of its side-chain, we had to synthesize two compounds rather than one; as such, we chose structures **1a** and **1b** (Scheme 1, *absolute* configurations shown), which are the two possible diastereomers of structure **1** considering its *relative* configuration. Considering *absolute* configurations, synthetic **1a** *might turn out to be identical with* (+)-*montecristin* because the former and the latter possess identically configurated butenolide moieties. Conversely, synthetic **1b** *might turn out to be the enantiomer of* (+)-*montecristin* (i.e. levorotatory *montecristin*) because the former and the latter possess oppositely configurated butenolide moieties. Accordingly, as soon as we would have synthesized both **1a** and **1b** we would know the complete stereostructure of (+)-montecristin. However, we could not know beforehand whether at that point we would have also *synthesized* (+)-montecristin or "only" (−)-montecristin.



Scheme 1

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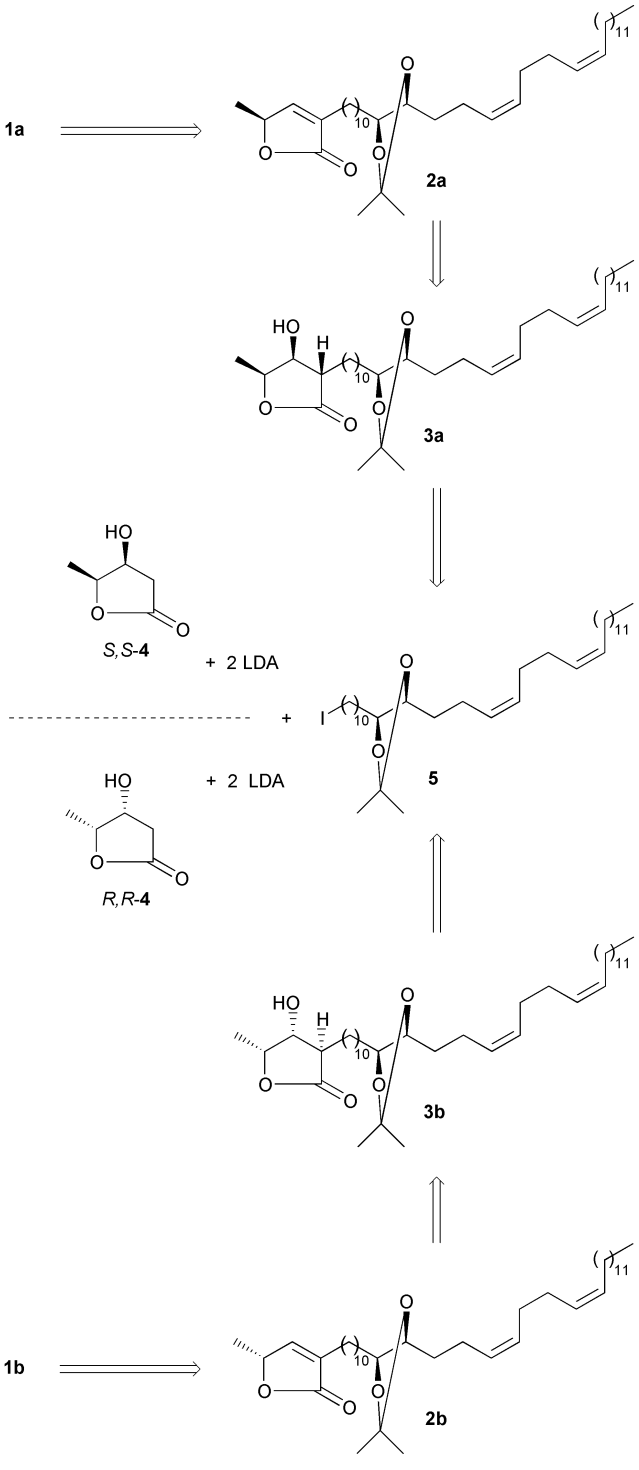
It was evident that **1a** and **1b** would not be distinguishable from one another spectroscopically since their stereocenters are 13 carbon atoms apart. However, the specific rotations of **1a** and **1b** would be distinct and therefore suitable for comparison with the specific rotation reported for **1**.

Results and discussion

Retrosynthesis

Our retrosynthetic analysis started by tracing back butenolides **1a** and **1b** *via* the acetonides **2a** and **2b** to the acetonide-containing hydroxylactones **3a** and **3b**, respectively (Scheme 2). The latter were thought to arise from the alkylation of the dilithio derivatives of hydroxylactones *S*,*S*-**4** and *R*,*R*-**4**, respectively, with the acetonide-containing iodide **5**. Hydroxylactones *S*,*S*-**4** and *R*,*R*-**4** were alkylated in a similar manner by simpler iodides than compound **5** in earlier work of ours.[7c–e,g]



Scheme 2

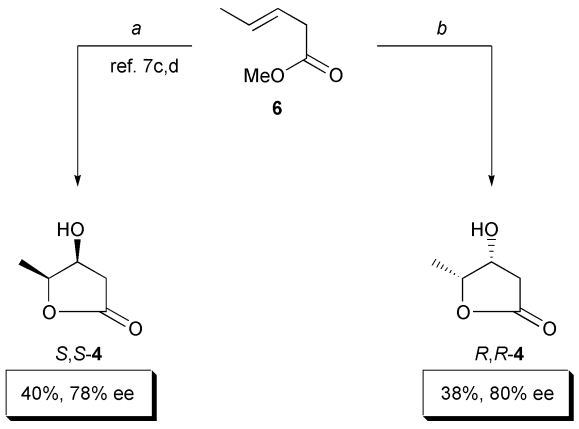
Our original preparation of hydroxylactone *S*,*S*-**4**[7c,8] was by the asymmetric dihydroxylation of the commercially available pentenoic ester **6** (Scheme 3). The enantiomeric hydroxylactone *R*,*R*-**4** could be accessed analogously. Unfortunately, these preparations suffered from low yields ($\leqslant$40%) and selectivities ($\leqslant$80% ee). Since continuous extraction did not increase these yields, we could exclude the possibility that some **4**, because of its miscibility with water, escaped our isolation procedure. The low ee values were probably due to the smallness of the methyl substituent at the C=C bond of our dihydroxylation substrate **6**. The adverse effect of too small substituents was precedented.[9]

The retrosynthetic simplification of iodide **5** (Scheme 2) followed two strategies (Scheme 4). By "strategy A", we wanted to dihydroxylate enantioselectively the C=C bond of the enediynol precursor **9** and then hydrogenate its C=C bonds *cis*-selectively. Precursor **9** would originate from an alkylation of a *trans*-configurated alkenyl metal **7** with the alkyl halide (or sulfonate) **8** or from a coupling between a *trans*-configurated alkenyl iodide **7** and an organometallic **8**. By "strategy B", iodide **5** would stem from a saturated precursor **10** and from an unsaturated precursor **11** with two *cis*-C=C bonds. We left open the question whether **10** should be the nucleophile and **11** the electrophile or *vice versa*. The glycol underlying compound **10** would be synthesized by the asymmetric dihydroxylation of an appropriate *trans*-olefin.

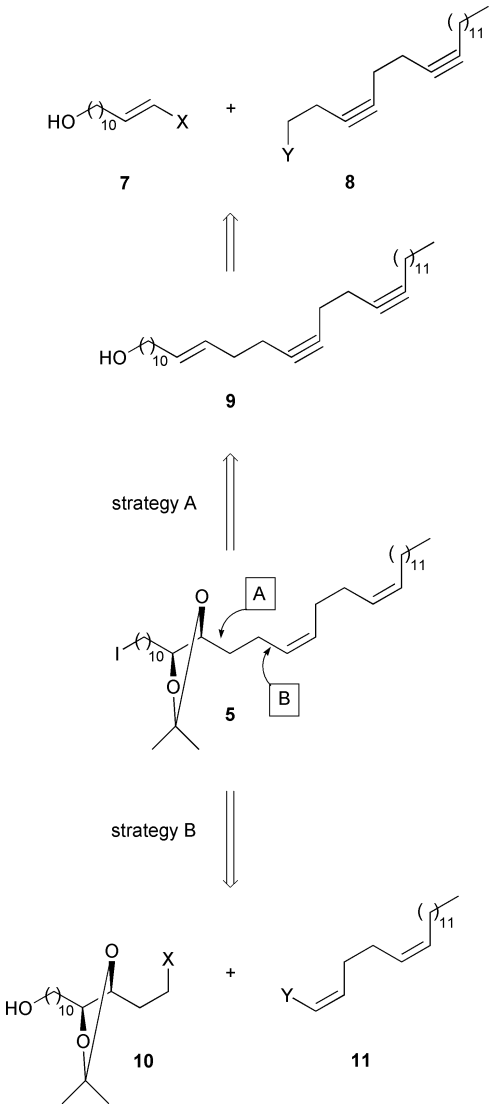
Synthesis of the lactone moiety

The discussion of Scheme 3 implied that the desired hydroxylactones *S*,*S*-**4** and *R*,*R*-**4** might be reached with >95% ee[7] by modifying the β,γ-unsaturated ester substrate of the dihydroxylation such that the small CH_3 group at C-γ would be made more voluminous by introducing one or several bulky substituents. Scheme 5 shows our vain efforts to prepare, in this sense, the tribromo analog **12** of the previous dihydroxylation substrate **6**. Tribromoacetaldehyde (**18**) did not react with the ylide derived from zwitterion **17** by various deprotonating agents[10] to give the underlying tribromoacid **13**; this was unexpected since tribromoacetaldehyde forms an olefin with $Ph_3P{=}CH{-}CH{=}O$.[11] Also, we could not add vinylmagnesium bromide to tribromoacetaldehyde in order to attain alcohol **16**. But 5% of this compound could at least be obtained following a protocol for saturated aldehydes.[12] This was insufficient for advancing to the next step, which would have been the Buechi rearrangement[13] **16** → **14**.

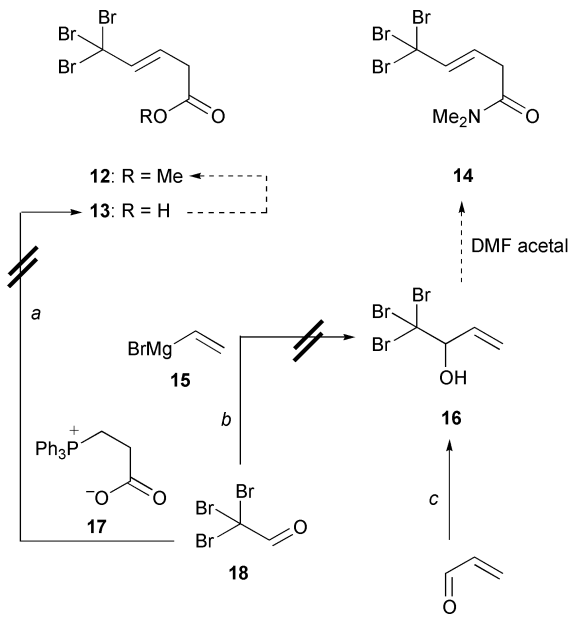
More modest size increases of the "too small methyl group" of dihydroxylation substrate **6** were possible—now introducing a single dummy substituent instead of three of them (Scheme 6). We started from the known[14] hydroxyester **20**. It



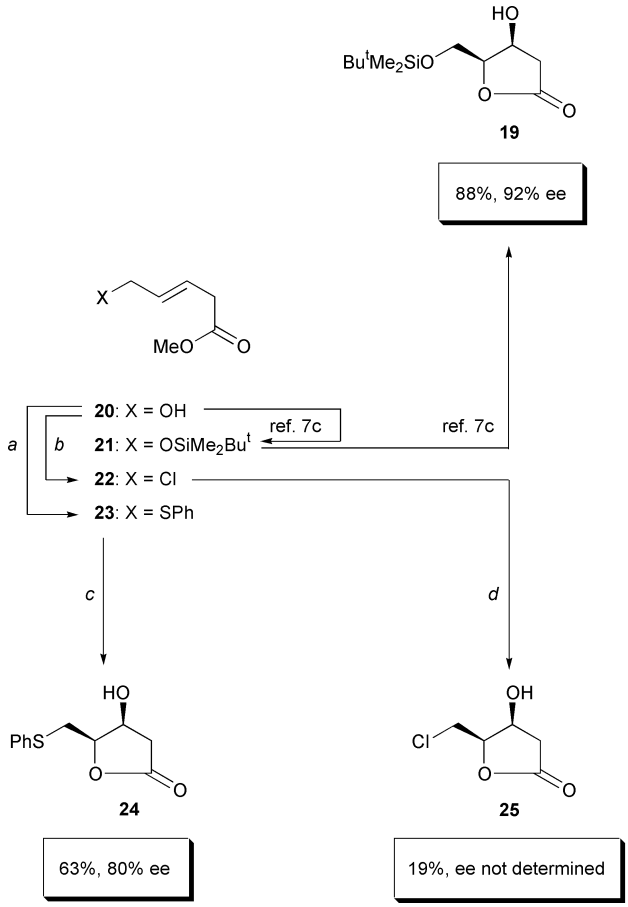
Scheme 3 *a*: AD-mix α (1.4 g $mmol^{-1}$), $Bu^tOH{-}H_2O$ (1 : 1), 0 °C, 4 days; 40%. *b*: AD-mix β (1.4 g $mmol^{-1}$), $Bu^tOH{-}H_2O$ (1 : 1), 0 °C, 4 days; 38%.



Scheme 4



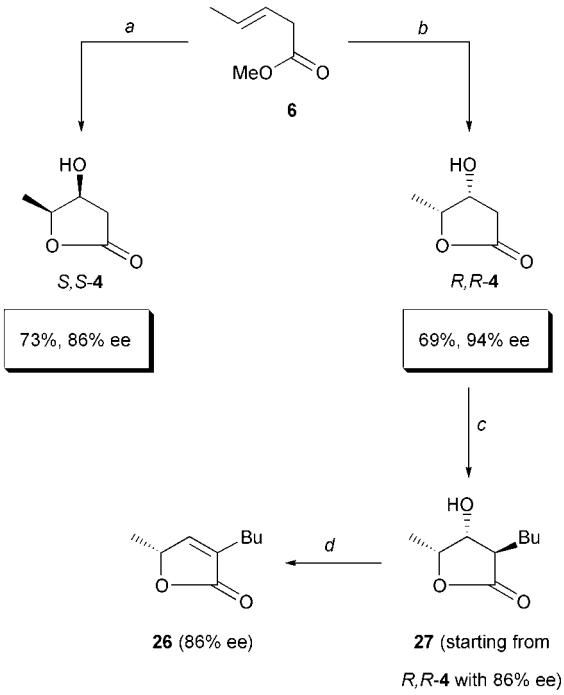
Scheme 5 *a*: (2-Carboxyethyl)triphenylphosphonium bromide (1.0 equiv.), NaH (2.0 equiv.) or KOBu^t (2.0 equiv.), THF–DMSO 1 : 1, room temperature, 20 h. *b*: $CeCl_3$ (5 mol %), THF, room temperature, 1 h; **15** (1.1 equiv.), room temperature, 2 h; 0%. *c*: Acrolein, CBr_4 (3 equiv.), SnF_2 (1 equiv.), DMSO, room temperature, 5 min; SnF_2 (1 equiv.), 5 min; 5%.



Scheme 6 *a*: Ph_2S_2 (3.0 equiv.), Bu_3P (4.0 equiv.), toluene, room temperature, 2 h; 81%. *b*: NCS (1.2 equiv.), Me_2S (1.2 equiv.), CH_2Cl_2, 0 °C → room temperature, 16 h; 83%. *c*: AD-mix α (1.4 g $mmol^{-1}$), $MeSO_2NH_2$ (1.0 equiv.), Bu^{t}OH–H_2O (1 : 1), 0 °C, 36 h; 63%. *d*: AD-mix α (1.4 g $mmol^{-1}$), $NaHCO_3$ (3.0 equiv.), $MeSO_2NH_2$ (1.0 equiv.), Bu^{t}OH–H_2O (1 : 1), 0 °C, 24 h; 19%.

was converted into the phenylthio-containing ester **23** by a Mukaiyama redox condensation.[15] Its asymmetric dihydroxylation gave the desired lactone **24** but the ee was 80% and thereby no better than the ee of the dihydroxylations of Scheme 3. As an alternative, hydroxyester **20** was transformed into the chlorinated ester **22**[16] under Corey's conditions.[17] The dihydroxylation of chloroester **22** gave only 19% of the corresponding lactone **25**, even when working in bicarbonate-buffered solution as recommended for the asymmetric dihydroxylation of allyl halides.[18] This 19% yield was too little to pursue this approach. The only substituent tested that improved the yield of the ester → lactone conversion *and* the enantioselectivity (92% ee instead of 78% in the case of *S*,*S*-**4**) was the Bu^{t}Me$_2$SiO group of ester **21**.[7c] While **21** could be carried on towards the silylated aglycone **19** of ranunculin as reported,[7c] there was no straightforward way for converting it into the desired *S*,*S*-**4**.

Fortunately, we then found a chemically and stereochemically improved synthesis of hydroxylactones *S*,*S*- and *R*,*R*-**4** (Scheme 7). An "improved asymmetric dihydroxylation" had been reported for a 1,1-disubstituted olefin using 10 times more ligand and osmate;[19] thereby, this olefin could be dihydroxylated with 97% ee rather than with 85% ee under the standard conditions. Following the same procedure, we dihydroxylated ester **6** with ees up to 86% (AD α, →*S*,*S*-**4**) and 94% (AD β, →*R*,*R*-**4**). However, these values were not exactly reproducible. Rather, they oscillated between 80 and 86% in the case of *S*,*S*-**4** and between 86 and 94% in the case of *R*,*R*-**4**. (This random variation explains why starting material **4** of *different* ee was used in the reactions of Schemes 7, 12 and 13). The improved dihydroxylation procedure also conveniently



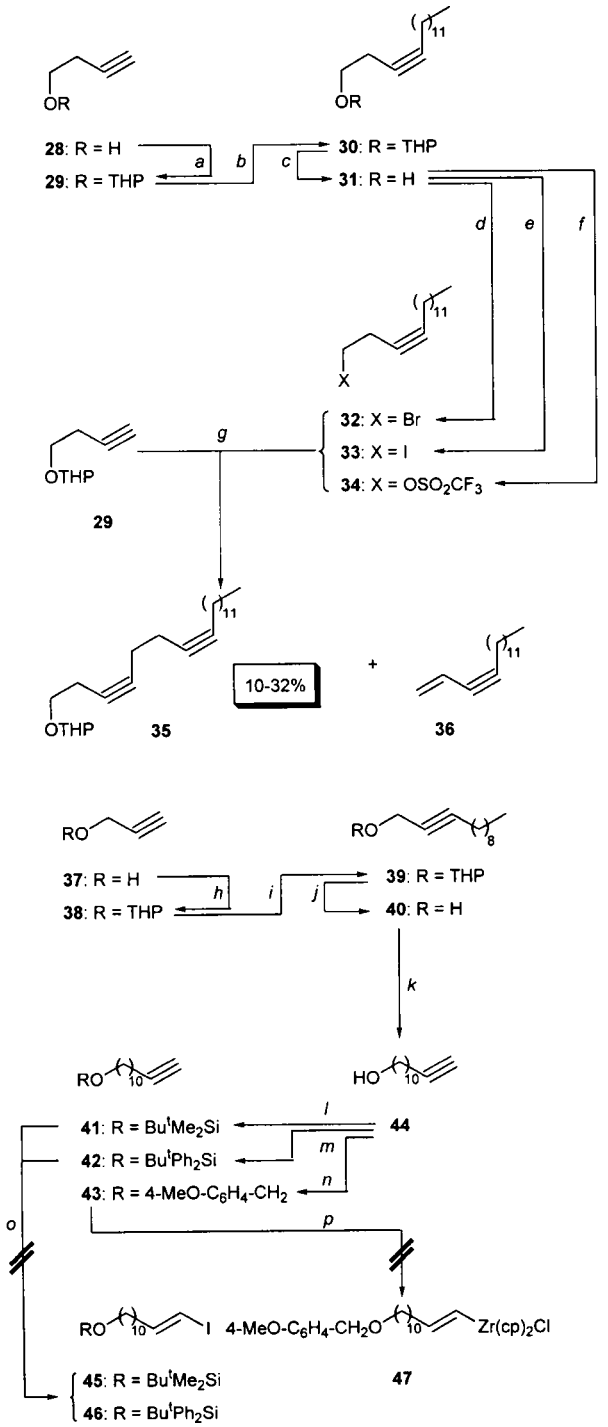
Scheme 7 *a*: $K_3Fe(CN)_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $(DHQ)_2PHAL$ (10 mol %), K_2OsO_4 (2.0 mol %), $Bu^tOH–H_2O$ (1 : 1), 0 °C, 16 h; 73%. *b*: $K_3Fe(CN)_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $(DHQD)_2PHAL$ (10 mol %), K_2OsO_4 (2.0 mol %), $Bu^tOH–H_2O$ (1 : 1), 0 °C, 16 h; 69%. *c*: Pr^i_2NH (2.5 equiv.), BuLi (2.5 equiv.), THF, −78 °C, 30 min; addition of *R*,*R*-**4**, THF, −78 °C, 2 h; BuI (1.2 equiv.), THF–DMPU (1 : 1), −45 °C, 20 h; 84%. *d*: PPh_3 (2.0 equiv.), DEAD (2.0 equiv.), THF, −20 °C → room temperature, 3 h; 89%.

reduced the reaction time to one-tenth (from 5 days to 16 h) and almost doubled the yields [from 40% *S*,*S*-**4** (Scheme 3) to 73% (Scheme 7) and from 38% *R*,*R*-**4** (Scheme 3) to 69% (Scheme 7)]. In addition, we recovered the chiral ligand almost quantitatively (up to 94% yield) by extraction into aqueous hydrochloric acid, addition of NaOH and back-extraction into dichloromethane.

Repeating the completely *trans*-selective butylation previously performed[7c,d] with *S*,*S*-**4** (78% ee) with the newly accessible *R*,*R*-**4** (here: of 86% ee) we obtained compound **27**[20] (*ent*-5-*epi*-blastmycinolactole; 86% ee). Compound **27** served to probe whether dehydration giving butenolide **26**[21] would be possible without partial racemization. This was of great interest since the penultimate step of our synthesis of montecristin would be an exactly analogous dehydration **3** → **2** (*cf.* Scheme 2). The problem is that butenolides such as compounds **26** or **2** can give up their stereochemical integrity even at room temperature when a base as weak as diethylamine is present.[22] Thus, we were afraid that the dehydration procedure appropriate for *S*,*S*-**4**—treatment with MsCl and NEt_3 in dichloromethane at 0 °C, 30 min[7d]—would put product stereochemistry at stake when applied to compound **27** (or later to **3**) because starting from **27** it lasted several hours at room temperature without even then having gone to completion. Therefore, we were glad to find that the dehydration **27** → **26** could be brought about by treatment with 2 equivalents of both triphenylphosphine and diethylazodicarboxylate.[23] The reaction proceeded in 89% yield and conserved the optical purity (86% ee) completely. This was reassuring as concerned the envisaged approach to the butenolide moiety of montecristin (Scheme 2).

Synthesis of the side-chain

Scheme 8 summarizes our efforts to access iodide **5** by means of strategy A of Scheme 4. The upper part of this scheme concerns the synthesis of the diyne equivalent **35** of the diyne

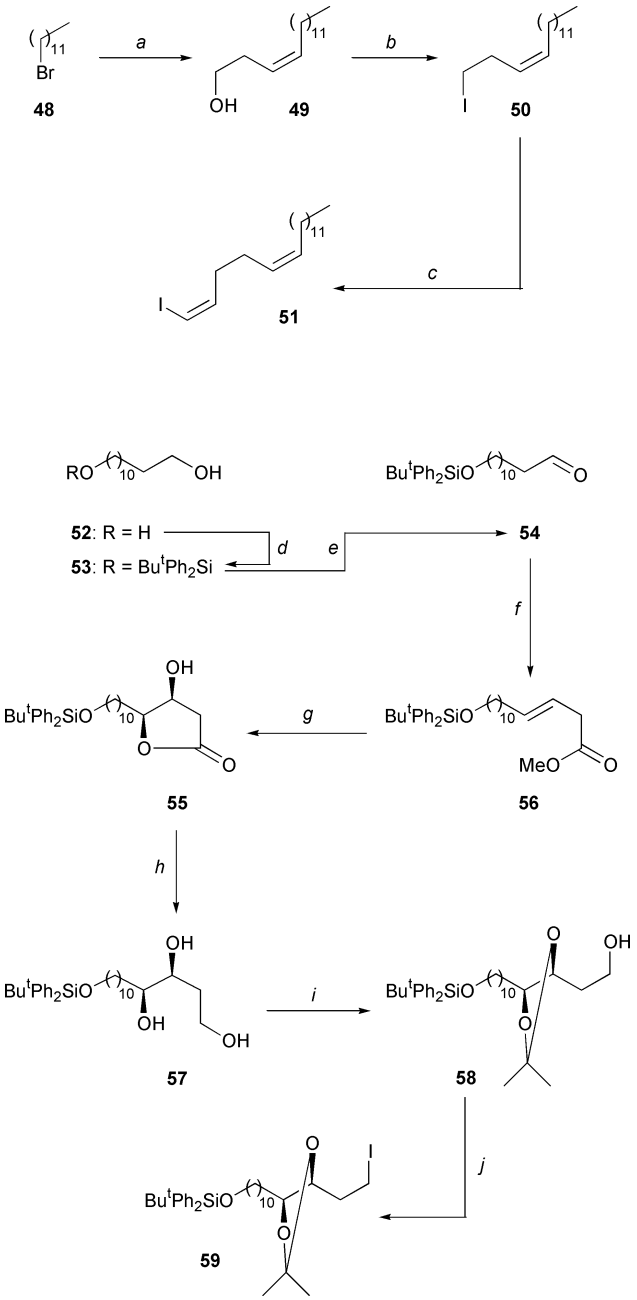


Scheme 8 *a*: Dihydro-2*H*-pyran (3.0 equiv.), camphor sulfonic acid (calatytic amount), CH_2Cl_2, 0 °C → room temperature, 3 h; 96%. *b*: $NaNH_2$ (1.1 equiv.), THF, 0 °C, 1 h; 1-bromododecane (1.1 equiv.), DMSO, room temperature, 2.5 h; 53%. *c*: *p*-TsOH (0.4 equiv.), MeOH, room temperature, 30 min; 99%. *d*: PPh_3 (1.2 equiv.), NBS (1.1 equiv.), THF, −20 °C → 0 °C, 4 h; 88%. *e*: PPh_3 (1.1 equiv.), imidazole (2.2 equiv.), I_2 (1.1 equiv.), THF, 0 °C, 1 h; 88%. *f*: NEt_3 (1.2 equiv.), Tf_2O (1.2 equiv.), CH_2Cl_2, 0 °C, 2 h; quantitative. *g*: BuLi (1.1 equiv.), THF, 0 °C, 30 min; addition of alkylating agent (1.0 equiv.), THF, room temperature, 16 h; 10–32%. Dihydro-2*H*-pyran (3.0 equiv.), PPTS (cat.), CH_2Cl_2, 0 °C → room temperature, 16 h; 84%. *i*: Bu^nLi (1.2 equiv.), THF, 0 °C, 30 min; Non-Br (1.1 equiv.), DMSO, room temperature, 24 h; 68%. *j*: TsOH (cat.), MeOH, room temperature, 2 h; 84%. *k*: Li (6.0 equiv.), 1,2-diaminopropane, reflux, 30 min; $KOBu^t$ (4.0 equiv.), room temperature, 30 min; addition of **40**, room temperature, 1 h; 74%. *l*: Bu^tMe_2SiCl (1.1 equiv.), imidazole (2.1 equiv.), CH_2Cl_2, room temperature, 1 h; 97%. *m*: Bu^tPh_2SiCl (1.0 equiv.), imidazole (2.1 equiv.), CH_2Cl_2, 0 °C → room temperature, 1 h; 99%. *n*: NaH (1.2 equiv.), *para*-methoxybenzyl chloride (1.2 equiv.), DMF–THF 1 : 1, room temperature, 3 h; 96%. *o*: DIBAL (1.05 equiv.), hexane, room temperature, 1 h; I_2 (1.0 equiv.). *p*: $Zr(cp)_2ClH$ (0.95 equiv.), THF, room temperature, 1 h.

synthon **8** of Scheme 4. First, we protected[24] 3-butynol (**28**) as the THP ether **29**.[25] This compound was less easy to alkylate than the homologous THP ether **38** of propargyl alcohol. Deprotonating compound **29** with *n*-BuLi in a mixture of THF and DMSO[26] and adding dodecyl bromide thereafter led mainly to the formation of 1-dodecene and only 7% of the alkylation product **30**.[27] Changing the solvent to DMPU increased the yield of **30** to 17%. Replacing dodecyl bromide by dodecyl triflate gave 48% **30**. A 53% yield was finally obtained in THF–DMSO, using the cheaper dodecyl bromide as the alkylating agent but deprotonating the substrate with sodium amide. The resulting THP ether **30** was cleaved in methanol through the action of TsOH (99% yield).[28] The alkynol **31**[29] thus obtained was converted into a series of alkylating agents by treatment with NBS–PPh_3[30] (→bromide **32**, 88%) or PPh_3–imidazole–I_2[31] (→iodide **33**, 88%) or Tf_2O–NEt_3[32] (→triflate **35**, quantitative yield). However, none of them could be introduced into THP ether **29** in satisfactory yield: the sodium acetylide of compound **29** and bromide **32** gave the desired diyne **35** in only 4% yield[33] besides *ca.* 50% of the elimination product **36**. Similarly, the lithium acetylide of compound **29** and iodide **33** furnished only trace amounts of diyne **35** besides 55% of enyne **36**. The same lithium acetylide and triflate **34** were a better combination (as expected[34]), delivering diyne **35** as the major product and only traces of **36**. However, the yield of **35** was 10–32% and never became higher or reliable.

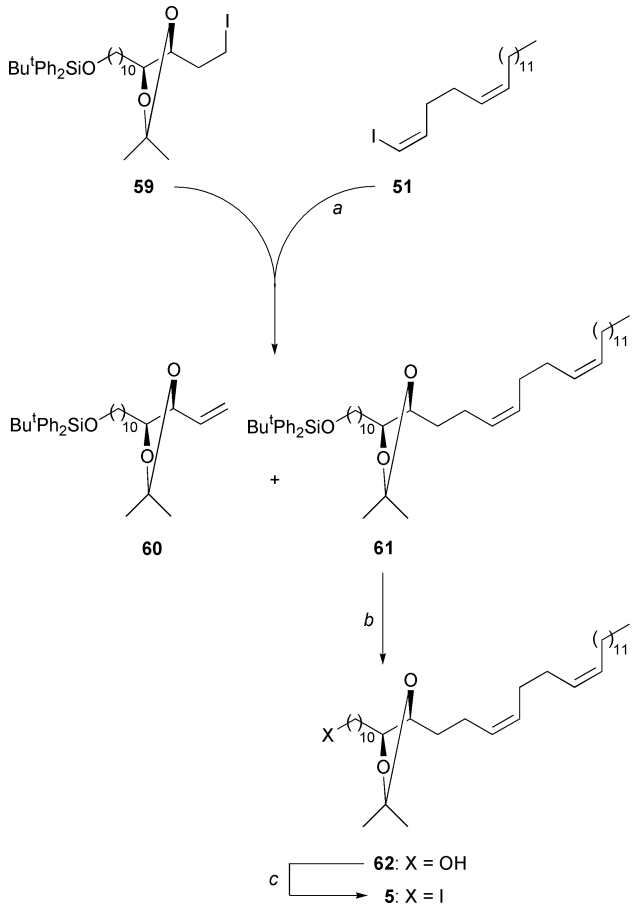
The lower part of Scheme 8 shows our approach to the *trans*-olefin equivalents **45**–**47** of synthon **7** of Scheme 4. Protecting[24] propargyl alcohol (**37**) as the THP ether **38**,[35] alkylating the latter *via* its anion[26] with nonyl bromide, deprotecting[28] the resulting chain-elongated THP ether **39** (→**40**), shifting its C≡C bond to the end of the molecule[36] (→**44**[37]), and protecting the OH group led to the terminal alkynes **41**–**43**. DIBAL reduction/iodination of compounds **41** and **42** seemed to suffer from the sensitivity of the silyl ethers towards the reductant. When the hydrozirconation of **41**–**43** started with unpromising yields of the respective addition product **47**, we stopped pursuing strategy A of Scheme 4 towards iodide **5** and began to test strategy B. As shown in the upper part of Scheme 9, we synthesized the *cis,cis*-dienyliodide **51** as a realization of synthon **11** of Scheme 4. To this end, dodecyl bromide (**48**) was converted *via* the corresponding Gilman cuprate into a mixed cuprate (with a hexynyl group). It was added to acetylene whereupon the resulting *cis*-vinylcuprate was transmetalated with hexynyllithium, giving a mixed cuprate that was hydroxyalkylated with ethylene oxide, all as described in the pionieering study of Alexakis *et al.*[38] Thus we advanced in a single step and 81% yield to homoallyl alcohol **49**.[39] It was converted into iodide **50** by treatment with PPh_3–imidazole–I_2.[31] Compound **50** was subjected to a Li/I exchange reaction with Bu^tLi.[40] Conversion into a Gilman cuprate followed by addition to acetylene and iodiation of the resulting alkenylcopper intermediate[41] rendered the dienyliodide **51** with the desired *cis,cis*-configuration in 66% yield. We found that the cuprate precursor of compound **51** did not react well with iodide **5**. Quenching this cuprate as shown here and regenerating the organolithium derivative later (first reaction of Scheme 10) worked much better.

Next, we synthesized acetonide **59** (Scheme 9, bottom half) as an equivalent of synthon **10** of Scheme 4. We started by monosilylating 1,12-dodecanediol (**52**) with Bu^tPh_2SiCl. Silylether **53** was formed in 59% yield. It was oxidized by the method of Omura and Swern[42] but at slightly higher temperature (−40 °C → 0 °C) and longer than usual times in order to make up for the poor solubility of the substrate in cold dichloromethane. Aldehyde **54**, obtained in 83% yield, was subjected to a deconjugating decarboxylating Knoevenagel condensation with monomethyl malonate.[43] It provided 66%



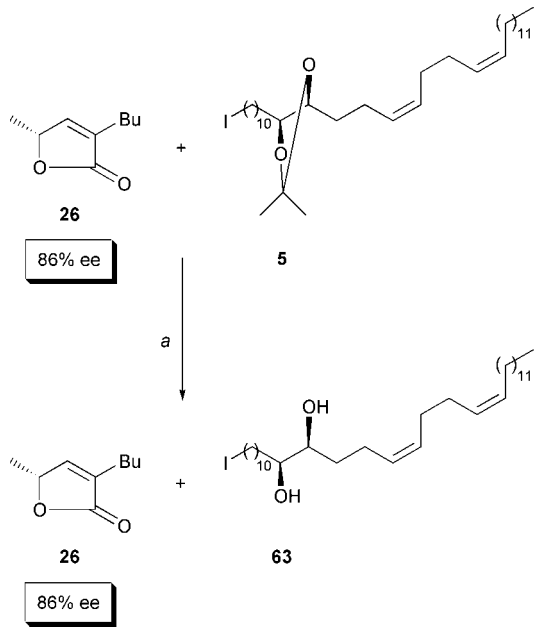
Scheme 9 *a*: Li (3.0 equiv.), Et_2O, 0 °C, 3 h; CuI (0.5 equiv.), Et_2O, −35 °C, 30 min; acetylene (1.0 equiv.), −50 °C → −25 °C, 30 min; → −30 °C; ethylene oxide (1.0 equiv.); hexynyl lithium (0.5 equiv.), Et_2O, −15 °C, 3 h; 81%. *b*: PPh_3 (1.1 equiv.), imidazole (2.2 equiv.), I_2 (1.1 equiv.), THF, 0 °C → room temperature, 30 min; 99%. *c*: Bu^tLi (2.0 equiv.), Et_2O–hexane (1 : 1), −20 °C, 30 min; CuI (0.5 equiv.), Et_2O, −35 °C, 30 min; acetylene (1.0 equiv.), −50 °C → −25 °C, 1 h; I_2 (1.0 equiv.), −60 °C → −10 °C, 2 h; 66%. *d*: Bu^tPh_2SiCl (1.0 equiv.), imidazole (2.0 equiv.), DMF, room temperature, 15 h; 59%. *e*: $(ClCO)_2$ (1.1 equiv.), DMSO (2.2 equiv.), CH_2Cl_2, −78 °C, 3 min; addition of **53**, −40 °C, 1 h; NEt_3 (5.0 equiv.), −40 °C → 0 °C, 1 h; 83%. *f*: $HO_2CCH_2CO_2Me$ (1.1 equiv.), NEt_3 (1.1 equiv.), 90 °C, 12 h, 66%. *g*: $K_3Fe(CN)_6$ (3.0 equiv.), K_2CO_3 (3.0 equiv.), $(DHQ)_2PHAL$ (1.0 mol %), K_2OsO_4 (0.2 mol %), $MeSO_2NH_2$ (1.0 equiv.), Bu^tOH–H_2O (1 : 1), 0 °C, 4 days; 68%. *h*: $LiAlH_4$ (1.0 equiv.), THF, −78 °C → room temperature, 30 min; 98%. *i*: 2,2-Dimethoxypropane (8.0 equiv.), Amberlyst 15, acetone, room temperature, 2 h. *j*: PPh_3 (1.0 equiv.), imidazole (2.0 equiv.), I_2 (1.0 equiv.), THF, 0 °C → room temperature, 15 min; 94% for two steps.

of the *trans*-configurated β,γ-unsaturated ester **56**. The asymmetric dihydroxylation of this compound[7] using AD-mix α furnished the hydroxylactone **55** in 68% yield. The enantiomeric purity of this material was determined to be 97% ee by ^{1}H-NMR analysis of the methoxy singlets of its *R*-Mosher ester.

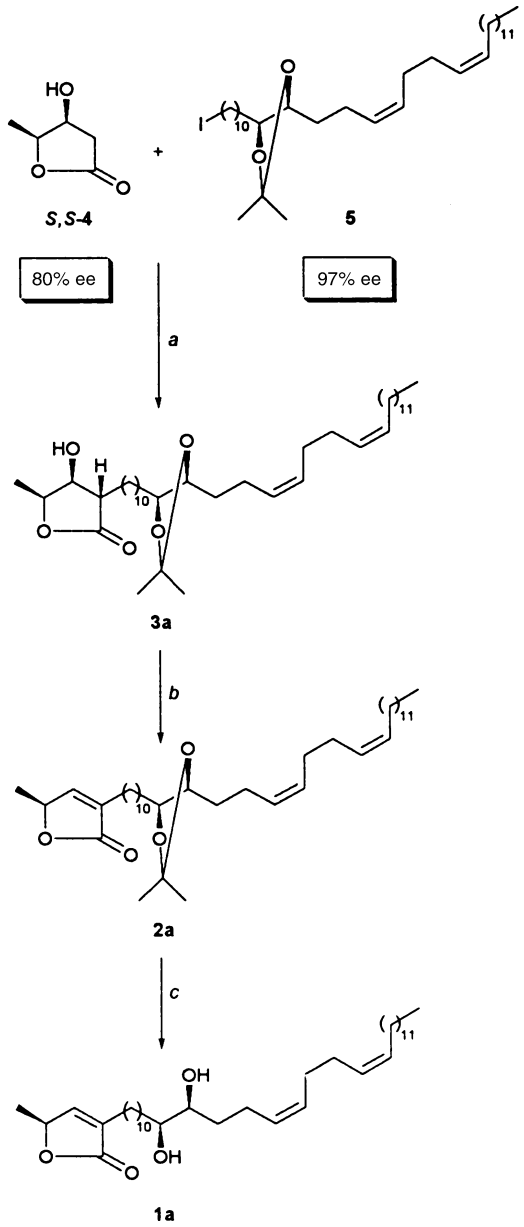


Scheme 10 *a*: **51**, Bu^{t}Li (2.2 equiv.), Et_2O, −50 °C, 30 min; **59** (1.0 equiv.), THF, →room temperature, 4 h; 64%. *b*: TBAF (1.2 equiv.), THF, room temperature, 20 h; 99%. *c*: PPh_3 (1.2 equiv.), imidazole (2.4 equiv.), I_2 (1.2 equiv.), THF, 0 °C → room temperature, 30 min; 96%.

Hydroxylactone **55** was reduced with $LiAlH_4$, giving the 1,3,4-triol **57**. After hydrolytic work-up, extraction by dichloromethane, and evaporation of the solvent 98% of a white solid remained, which was used without purification. Meyer's selective acetalizations of the butanetriol obtained from optically active malic acid revealed that under thermodynamic control acetone is preferentially taken up by the



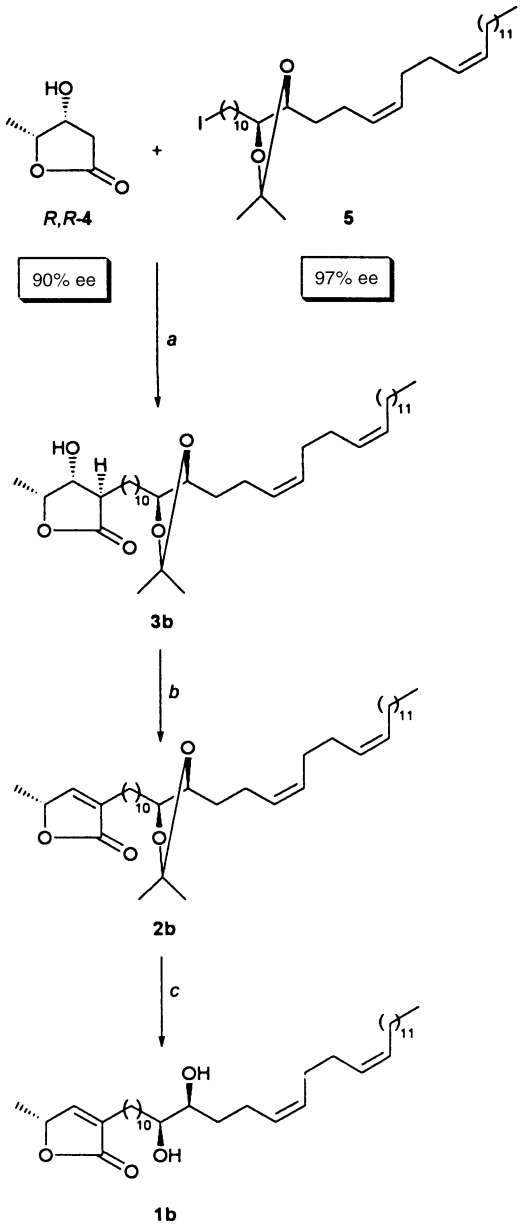
Scheme 11 *a*: HCl (4.0 equiv.), MeOH–CH_2Cl_2 (5 : 1), room temperature, 24 h; 50%; 76% of reisolated **26**.



Scheme 12 *a*: Pr^i_2NH (2.5 equiv.), BuLi (2.5 equiv.), THF, −78 °C, 30 min; addition of *S*,*S*-**4**, THF, −78 °C, 2 h; **5** (1.0 equiv.), THF–DMPU (1 : 1), −45 °C, 20 h; 56%; 38% of reisolated **5**. *b*: PPh_3 (2.0 equiv.), DEAD (2.0 equiv.), THF, −20 °C → room temperature, 4 h; 94%. *c*: HCl (4.0 equiv.), MeOH–CH_2Cl_2 (5 : 1), room temperature, 24 h; 88%.

1,2-diol moiety, giving a dioxolane, rather than by the 1,3-diol moiety, which would give a 1,3-dioxane.[44] Exploiting this effect, triol **57**, excess dimethoxypropane in acetone and Amberlyst as a catalyst provided, after 2 h at room temperature, essentially 1,3-dioxane **58**. This compound was so sensitive towards hydrolysis that we could not purify it even by flash chromatography on deactivated (NEt_3) silica gel. However, we could use it *crude* and transform it by treatment with PPh_3–imidazole–I_2[31] into iodide **59** (94% yield from lactone **56**). Thereby, the latter became accessible from 1,12-dodecanediol (**52**) in seven steps (20% overall yield).

The ultimate steps to the key precursor **5** of montecristin are shown in Scheme 10. To combine the alkyl iodide **59** with the alkenyl iodide **51** we had the options of performing a transition metal catalyzed coupling between an *alkyl* metal and an *alkenyl* halide or of performing a nucleophilic substitution of an *alkenyl* metal at an *alkyl* halide. Lithiation of alkyl iodide **59** with *tert*-BuLi, followed by transmetalation with $MgBr_2$ and the addition of alkenyl iodide **51** and a catalytic amount of $NiCl_2(PPh_3)_4$[45] gave a ≈1 : 1 mixture of the desired coup-



Scheme 13 *a*: Pr^i_2NH (2.5 equiv.), BuLi (2.5 equiv.), THF, −78 °C, 30 min; addition of *R,R*-**4**, THF, −78 °C, 2 h; **5** (1.0 equiv.), THF–DMPU (1 : 1), −45 °C, 20 h; 62%; 34% reisolated **5**. *b*: PPh_3 (2.0 equiv.), DEAD (2.0 equiv.), THF, −20 °C → room temperature, 4 h; 97%. *c*: HCl (4.0 equiv.), MeOH–CH_2Cl_2 (5 : 1), room temperature, 24 h; 83%.

ling product **61** and the β-hydride elimination product—which is a vinyl-substituted dioxolane—of the alkyl nickel derivative of **59**. Conversely, clean C–C bond formation occurred when we switched polarities: lithiated the alkenyl iodide **51**, added the alkyl iodide **59**, and isolated the alkylation[46] product **61** in 64% yield. Desilylation liberated the underlying alcohol **62**. It reacted with PPh_3–imidazole–I_2 [31] to give the key iodide **5**.

One issue needed to be clarified before iodide **5** was fully qualified for introducing the side-chain of montecristin (**1**) because the *vic*-glycol moiety of **1** was protected as an acetonide in **5**. We wondered whether we would be able to release this acetonide at the butenolide stage **2a**/**2b** (*cf.* Scheme 2) without destroying the stereocenter C-γ. We modelled the answer to this question by effecting the related acetonide cleavage **5** → **63** with concentrated HCl–MeOH–CH_2Cl_2 [47] (Scheme 11). What mattered in this context was hardly the 50% yield of diol **63** but rather that the model butenolide **26**, *which was present while the acetonide was cleaved, could be re-isolated with undiminished enantiomeric purity* (86% ee; 77% yield). This meant that these conditions were suitable for deprotecting butenolides **2a** (Scheme 12) and **2b** (Scheme 13) without affecting their stereostructures.

Combining the building blocks

Reassured by the result from Scheme 11, we performed the final steps of our syntheses in parallel experiments. We headed for the stereoisomer **1a** of montecristin as shown Scheme 12 and for its diastereomer **1b** as shown in Scheme 13.

Each sequence lasted three steps. The start was deprotonating the enantiomeric β-hydroxylactones *S,S*-**4** (here 80% ee; Scheme 12) and *R,R*-**4** (here 90% ee; Scheme 13) twice using 2.5 equiv. of LDA. In HMPA-containing THF the α-alkylation of dilithiated β-hydroxy-γ-lactones occurs such that the α-substituent is oriented exclusively *trans* with respect to the β-OH group.[48] Conveniently, alkylating the dilithiated hydroxylactones *S,S*- and *R,R*-**4** with iodide **5** (97% ee) in 6 : 1 THF–DMPU[49] delivered also nothing but *trans*-alkylated hydroxylactones, namely compounds **3a** (56% yield; 90% considering that 38% **5** was recovered) and **3b** (62% yield; 94% considering that 34% **5** was recovered), respectively.

The ensuing β-eliminations followed the protocol developed for the dehydration **27** → **26** of Scheme 7, that is under Mitsunobu conditions: 2 equiv. each of PPh_3 and DEAD were added to THF solutions of hydroxylactones **3a** (Scheme 12) and **3b** (Scheme 13). The resulting mixtures were gradually warmed from −20 °C to room temperature. Thereupon we isolated 94% of butenolide **2a** and 97% of butenolide **2b**, respectively. The terminating steps were the acetonide cleavages. They were effected under the "stereochemically benign" conditions of Scheme 11. This led to diastereomers **1a** and **1b** in yields of 88 and 83%, respectively.

As expected, the ^{1}H-NMR, ^{13}C-NMR and IR data of compounds **1a** and **1b** were identical with one another and identical to those of montecristin. However, their specific rotations were distinct. They demonstrated unequivocally[50] that **1a** is *ent*-5-*epi*-montecristin while **1b** is the enantiomer of (+)-montecristin. This statement is justified even if our specimen of **1a** must have been a *ca.* 90 : 10 mixture with **1b** and our specimen of **1b** a *ca.* 95 : 5 mixture with **1a**; the occurrence of these mixtures is an inevitable consequence of the incomplete optical purity of the building blocks *S,S*-**4** (80% ee), *R,R*-**4** (90% ee) and **5**: (97% ee) incorporated into **1a** and **1b**.

In summary, we have accomplished the first total syntheses of *ent*-5-*epi*-montecristin (**1a**) and (−)-montecristin (**1b**). In the longest linear sequence 13 steps were needed, which gave an overall yield of 6% (=81% per step). The side-chain configuration of (+)-montecristin was established to be 11′*R*,12′*R*.

Experimental

General

All reactions were performed in oven-dried (80 °C) glassware under N_2. THF was freshly distilled from K, Et_2O from Na, CH_2Cl_2, DMSO, DMPU and 1,2-diaminopropane from CaH_2. Products were purified by flash chromatography[51] on Macherey–Nagel silica gel 40–63 μm (eluents given in brackets). Yields refer to analytically pure samples. Isomer ratios were derived from suitable ^{1}H NMR integrals. ^{1}H NMR [$CHCl_3$ (7.26 ppm) as internal standard in $CDCl_3$ or C_6HD_5 (7.16 ppm) as internal standard in C_6D_6] and ^{13}C NMR [$CDCl_3$ (77.00 ppm) as internal standard in $CDCl_3$] were recorded on Varian VXR 200, Bruker AMX 300, and Varian VXR 500S spectrometers. For ^{1}H NMR spectra the integrals were in accord with assignments; coupling constants are in Hz. In APT ^{13}C NMR spectra the peak orientations were in accord with asssignments. The assignments of ^{1}H and

^{13}C NMR resonances refer to the IUPAC nomenclature with primed numbers belonging to the side-chains in the order of their appearance in the IUPAC name. Combustion analyses were obtained by F. Hambloch, (Institute of Organic Chemistry, University of Göttingen) and MS by Dr. G. Remberg (Institute of Organic Chemistry, University of Göttingen). IR spectra were recorded on a Perkin–Elmer 1600 Series FTIR spectrometer neat or in KBr. Specific rotations were measured on a Perkin–Elmer polarimeter 241 at 589 nm; the underlying rotational values were averaged over 5 measurements (undertaken with a given solution of the respective sample). Melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected.

Syntheses

(5*S*,11′*S*,12′*S*)-*Z*,*Z*-3-(10,11-Dihydroxy-15,19-dotriacontadienyl)-5-methyl-2(5*H*)-furanone (*ent*-5-*epi*-montecristin) (1a). HCl (12 M, 15 μl, 0.18 mmol, 4.0 equiv.) was added to a solution of the acetonide **2a** (27.0 mg, 0.0441 mmol) in MeOH–CH_2Cl_2 (5 : 1, 0.6 ml) and the mixture was stirred for 24 h at room temperature. Water (2 ml) was added and the organic phase extracted with Bu^{t}OMe (3 × 10 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was removed. The residue was purified by flash chromatography (2.5 cm, petroleum ether–Bu^{t}OMe 2 : 1 → fraction 13, 1 : 1 → fraction 20, fractions 8–18) to give the title compound (22.3 mg, 88%) as a white solid (mp 52 °C). $[\alpha]_D^{25} = +1.9$ ($c = 0.4$). Calculating the specific rotation for the 100% enantiopure product, taking into account the ees of the different building blocks (lactone *S*,*S*-**4** 80% ee; iodide **5** 97% ee) as well as the specific rotation measured for compound **1b** (*vide infra*) leads to $[\alpha]_D^{25} = +4.7$ ($c = 0.4$)[52] {lit.[5]: $[\alpha]_D^{25} = +25$ for montecristin ($c = 0.1$, MeOH)}. ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{32',31'} = 6.8$, 32′-H_3), 1.24–1.38 (m, 2′-H_2 to 9′-H_2, 22′-H_2 to 31′-H_2), 1.41 (d, $J_{5,5\text{-Me}} = 6.7$, 5-Me), 1.44–1.60 (m, 10′-H_2, 13′-H_2), *ca.* 1.94 (very br s, 2 OH), in part superimposed by 2.02 (td, $J_{21',22'} \approx J_{21',20'} \approx 6.5$, 21′-$H_2$), 2.11 ($m_c$, 17′-$H_2$, 18′-$H_2$), in part superimposed by 2.13–*ca.* 2.23 (m, 14′-H_2), in part superimposed by 2.26 (tdd, $J_{1',2'} = 7.8$, $^4J_{1',4} = {}^5J_{1',5} = 1.7$, 1′-$H_2$), 3.38–3.48 (m, 11′-H, 12′-H), 5.00 (qdt, $J_{5,5\text{-Me}} = 6.6$, $J_{5,4} = {}^5J_{5,1'} = 1.8$, 5-H), 5.30–5.47 (m, 15′-H, 16′-H, 19′-H, 20′-H), 6.99 (td, $^4J_{4,1'} = J_{4,5} = 1.5$, 4-H). ^{13}C NMR (125.7 MHz, APT; slightly contaminated at $\delta = 29.1$): $\delta = 14.05$ (C-32′), 19.10 (5-Me), 22.61, 23.45, 25.06, 25.58, 27.19 (2-fold intensity), 27.29 (2-fold intensity), 29.07, 29.18, 29.25, 29.28, 29.37, 29.43, 29.46, 29.49, 29.58 (2-fold intensity), 29.60, 29.61, 29.65, 31.84, 33.39 and 33.51 (C-1′ to C-10′, C-13′, C-14′, C-17′, C-18′, C-21′ to C-31′; 21 resonances of 24-fold total intensity for 25 C atoms), 73.94 and 74.39 (C-11′, C-12′), 77.42 (C-5), 128.88, 129.35, 129.99 and 130.45 (C-15′, C-16′, C-19′, C-20′), 134.16 (C-3), 148.93 (C-4), 173.93 (C-2). IR (KBr): $\nu = 3415$, 3355, 3000, 2920, 2850, 1740, 1655, 1465, 1365, 1320, 1205, 1085, 1065, 1025, 930, 895, 720 cm^{-1}. $C_{37}H_{66}O_4$ (574.9) calcd. C 77.30, H 11.57; found C 77.27, H 11.33.

(5*R*,11′*S*,12′*S*)-*Z*,*Z*-3-(11,12-Dihydroxy-15,19-dotriacontadienyl)-5-methyl-2(5*H*)-furanone (*ent*-montecristin) (1b). 1b was prepared as for **1a** using HCl (12 M, 20 μl, 0.22 mmol, 4.0 equiv.) and acetonide **2b** (33.0 mg, 0.0544 mmol). The residue obtained after work-up was purified by flash chromatography (2.5 cm, petroleum ether–Bu^{t}OMe 2 : 1 → fraction 12, 1 : 1 → fraction 20, fractions 8–19) to give the title compound (25.8 mg, 83%) as a white solid (mp 58 °C, lit.[5]: for the enantiomer 62 °C). $[\alpha]_D^{25} = -24.2$ ($c = 2.48$). Calculating the specific rotation for the 100% enantiopure product, taking into account the ees of the different building blocks (lactone *R*,*R*-**4** 90% ee; iodide **5** 97% ee) as well as the specific rotation measured for compound **1a** (*vide supra*) leads to $[\alpha]_D^{25} = -25.9$ ($c = 0.4$)[52] {lit.[5]: $[\alpha]_D^{25} = +25$ for montecristin ($c = 0.1$, MeOH)}. ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{32',31'} = 6.8$, 32′-H_3), 1.25–1.38 (m, 2′-H_2 to 9′-H_2, 22′-H_2 to 31′-H_2), 1.41 (d, $J_{5,5\text{-Me}} = 6.7$, 5-Me), 1.43–1.60 (m, 10′-H_2, 13′-H_2), *ca.* 1.82 (very br s, 2 OH), 2.02 (td, $J_{21',22'} \approx J_{21',20'} \approx 6.5$, 21′-$H_2$), in part superimposed by 2.11 (m_c, 17′-H_2, 18′-H_2), in part superimposed by 2.13–*ca.* 2.23 (m, 14′-H_2), in part superimposed by 2.26 (tdd, $J_{1',2'} = 7.8$, $^4J_{1',4} = {}^5J_{1',5} = 1.7$, 1′-$H_2$), 3.38–3.47 (m, 11′-H, 12′-H), 5.00 (qdt, $J_{5,5\text{-Me}} = 6.8$, $J_{5,4} = {}^5J_{5,1'} = 1.8$, 5-H), 5.30–5.47 (m, 15′-H, 16′-H, 19′-H, 20′-H), 6.98 (td, $^4J_{4,1'} = J_{4,5} = 1.5$, 4-H). ^{13}C NMR (125.7 MHz, APT): $\delta = 14.00$ (C-32′), 19.05 (5-Me), 22.56, 23.40, 25.02, 25.56, 27.15 (2-fold intensity), 27.24 (2-fold intensity), 29.03, 29.15, 29.20, 29.23, 29.34, 29.40, 29.45, 29.53 (2-fold intensity), 29.56 (2-fold intensity), 29.61, 31.79, 33.36 and 33.47 (C-1′ to C-10′, C-13′, C-14′, C-17′, C-18′, C-21′ to C-31′, 19 resonances of 23-fold total intensity for 25 C atoms), 73.86 and 74.31 (C-11′, C-12′), 77.40 (C-5), 128.85, 129.34, 129.86 and 130.36 (C-15′, C-16′, C-19′, C-20′), 134.08 (C-3), 148.93 (C-4), 173.90 (C-2). $C_{37}H_{66}O_4$ (574.9) calcd. C 77.30, H 11.57; found C 77.41, H 11.50.

(5*S*,4″*S*,5″*S*)-*Z*,*Z*-3-{10-[5-(3,7-Eicosadienyl)-2,2-dimethyl-1,3-dioxolan-4-yl]decyl}-5-methyl-2(5*H*)-furanone (2a). A solution of the β-hydroxylactone **3a** (42 mg, 0.066 mmol) in THF (2 ml) was treated with PPh_3 (40.8 mg, 0.132 mmol, 2.0 equiv.) and DEAD (40% in toluene, 68 μl, 26 mg, 0.13 mmol, 2.0 equiv.) at −20 °C. The reaction mixture was warmed to room temperature within 4 h. Water (2 ml) was added and the resulting mixture was extracted with Bu^{t}OMe (3 × 10 ml). The organic phase was dried over $MgSO_4$ and the solvent was removed. From the residue the title compound (38.2 mg, 94%) was isolated as a colorless oil by flash chromatography (2 cm, petroleum ether–Bu^{t}OMe 10 : 1, fractions 4–9). $[\alpha]_D^{25} = -1.5$ ($c = 1.4$). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{20''',19'''} = 6.8$, 20‴-H_3), 1.24–*ca.* 1.38 (m, 2′-H_2 to 9′-H_2, 10‴-H_2 to 19‴-H_2), superimposed by 1.379 and 1.382 [2 s, 2″-$(CH_3)_2$], 1.41 (d, $J_{5,5\text{-Me}} = 6.7$, 5-Me), 1.47–1.60 (m, 10′-H_2, 1‴-H_2), 2.02 (td, $J_{9''',10'''} \approx J_{9''',8'''} \approx 6.6$, 9‴-$H_2$), in part superimposed by 2.10 (m_c, 5‴-H_2, 6‴-H_2), in part superimposed by 2.13–*ca.* 2.23 (m, 2‴-H_2), in part superimposed by 2.26 (tdd, $J_{1',2'} = 7.1$, $^4J_{1',4} = {}^5J_{1',5} = 1.7$, 1′-$H_2$), 3.60 ($m_c$, 4″-H, 5″-H), 4.99 (qdt, $J_{5,5\text{-Me}} = 6.8$, $J_{5,4} = {}^5J_{5,1'} = 1.7$, 5-H), 5.30–5.46 (m, 3‴-H, 4‴-H, 7‴-H, 8‴-H), 6.98 (td, $^4J_{4,1'} = J_{4,5} = 1.5$, 4-H). IR (neat): $\nu = 2985$, 2925, 2855, 1760, 1460, 1370, 1320, 1240, 1080, 1025, 950, 870, 725 cm^{-1}. $C_{40}H_{70}O_4$ (615.0) calcd. C 78.12, H 11.47; found C 78.01, H 11.39.

(5*R*,4″*S*,5″*S*)-*Z*,*Z*-3-{10-[5-(3,7-Eicosadienyl)-2,2-dimethyl-1,3-dioxolan-4-yl]decyl}-5-methyl-2(5*H*)-furanone (2b). 2b was prepared as for **2a** using β-hydroxylactone **3b** (64 mg, 0.101 mmol) in THF (2 ml), PPh_3 (52.9 mg, 0.202 mmol, 2.0 equiv.) and DEAD (40% in toluene, 102 μl, 38.6 mg, 0.202 mmol, 2.0 equiv.). From the residue of the work-up the title compound (60.1 mg, 97%) was isolated as a colorless oil by flash chromatography (2.5 cm, petroleum ether–Bu^{t}OMe 10 : 1, fractions 4–10). $[\alpha]_D^{25} = -20.0$ ($c = 2.25$). ^{1}H NMR (300 MHz; contains 1.2 wt.% dihydro-DEAD; quartet at $\delta = 4.99$): $\delta = 0.88$ (t, $J_{20''',19'''} = 6.8$, 20‴-H_3), 1.24–*ca.* 1.38 (m, 2′-H_2 to 9′-H_2, 10″-H_2 to 19‴-H_2), superimposed by 1.38 [br s, $(CH_3)_2$], 1.41 (d, $J_{5,5\text{-Me}} = 6.8$, 5-Me), 1.45–1.60 (m, 10′-H_2, 1‴-H_2), 2.02 (td, $J_{9''',10'''} \approx J_{9''',8'''} \approx 6.4$, 9‴-$H_2$), in part superimposed by 2.10 (m_c, 5‴-H_2, 6‴-H_2), in part superimposed by 2.13–*ca.* 2.23 (m, 2‴-H_2), 2.26 (incompl. res. tdd, $J_{1',2'} = 7.5$, $^4J_{1',4} = {}^5J_{1',5} = 1.7$, 1′-$H_2$), 3.60 ($m_c$, 4″-H, 5″-H), 4.99 (qdt, $J_{5,5\text{-Me}} = 6.7$, $J_{5,4} = {}^5J_{5,1'} = 1.7$, 5-H), 5.30–5.45 (m, 3‴-H, 4‴-H, 7‴-H, 8‴-H), 6.98 (td, $^4J_{4,1'} = J_{4,5} = 1.5$, 4-H). IR (neat): $\nu = 2980$, 2925, 2855, 1760, 1460, 1370, 1320, 1240, 1080, 1025, 870, 725 cm^{-1}. $C_{40}H_{70}O_4$ (615.0) calcd. C 78.12, H 11.47; found C 78.00, H 11.29.

(3*S*,4*S*,5*S*,4″*S*,5″*S*)-*Z*,*Z*-3-{10-[5-(3,7-Eicosadienyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-decyl}-4,5-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (3a). n-BuLi (1.90 M in hexane, 0.66 ml, 1.3 mmol, 2.5 equiv.) was added to a solution of i-Pr_2NH (0.16 ml, 0.13 g, 1.3 mmol, 2.5 equiv.) in THF (2.5 ml) at −78 °C. After 30 min a solution of the β-hydroxylactone *S*,*S*-**4** (58 mg, 0.50 mmol) in THF (2.5 ml) was added. After 2 h at −78 °C a solution of iodide **5** (322 mg, 0.500 mmol, 1.0 equiv.) in THF–DMPU (1 : 1, 2 ml) was added dropwise. The mixture was stirred for 20 h at −45 °C and worked up by the addition of HCl (2 M, 2.5 ml). After extraction with Bu^tOMe (3 × 20 ml), drying over $MgSO_4$ and removal of the solvents the residue was separated by flash chromatography (3 cm, petroleum ether–Bu^tOMe 1 : 1) to give unreacted **5** (fractions 2–3, 121 mg, 38%) and the title compound (fractions 5–11, 175 mg, 56%; 90% based on recovered starting material) as colorless oils. $[\alpha]_D^{25} = -21.8$ ($c = 0.78$). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{20''',19'''} = 6.8$, 20‴-H_3), *ca.* 1.24–*ca.* 1.40 (m, 2′-H_2 to 9′-H_2, 10‴-H_2 to 19‴-H_2), superimposed by 1.379 and 1.383 [2 s, 2″-$(CH_3)_2$], 1.41 (d, $J_{5,\,5\text{-Me}} = 6.7$, 5-Me), 1.43–1.63 (m, 1′-H^1, 10′-H_2, 1‴-H_2), 1.69–1.79 (m, 1′-H^2), 2.02 (td, $J_{9''',10'''} \approx J_{9''',8'''} \approx 6.5$, 9‴-$H_2$), in part superimposed by 2.10 (m_c, 5‴-H_2, 6‴-H_2), in part superimposed by *ca.* 2.13–2.26 (m, 2‴-H_2), 2.54 (ddd, $J_{3,\,1'\text{-H}(1)} \approx J_{3,\,1'\text{-H}(2)} \approx 7.1$, $J_{3,4} = 3.6$, 3-H), 3.60 (m_c, 4″-H, 5″-H), 4.20 (dd, $J_{4,5} = 4.7$, $J_{4,3} = 3.6$, 4-H), 4.63 (qd, $J_{5,\,5\text{-Me}} = 6.4$, $J_{5,4} = 4.9$, 5-H), 5.30–5.46 (m, 3‴-H, 4‴-H, 7‴-H, 8‴-H). IR (neat): $\nu = 3445$, 2985, 2925, 2855, 1760, 1460, 1375, 1240, 1185, 1100, 1055, 995, 725 cm^{-1}. $C_{40}H_{72}O_5$ (633.0) calcd. C 75.90, H 11.47; found C 75.69, H 11.15.

(3*R*,4*R*,5*R*,4″*S*,5″*S*)-*Z*,*Z*-3-{10-[5-(3,7-Eicosadienyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-decyl}-4,5-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (3b). 3b was prepared as for **3a** using β-hydroxylactone *R*,*R*-**4** (58 mg, 0.50 mmol). The residue after extraction and solvent removal was separated by flash chromatography (3 cm, petroleum ether–Bu^tOMe 1 : 1) to give unreacted **5** (fractions 2–3, 111 mg, 34%) and the title compound (fractions 6–12, 195 mg, 62%; 94% based on recovered starting material) as colorless oils. $[\alpha]_D^{25} = +6.02$ ($c = 0.93$). ^{1}H NMR (300 MHz, slightly contaminated around $\delta = 0.9$): $\delta = 0.88$ (t, $J_{20''',19'''} = 7.2$, 20‴-H_3), 1.24–*ca.* 1.40 (m, 2′-H_2 to 9′-H_2, 10‴-H_2 to 19‴-H_2), superimposed by 1.38 [br s, 2″-$(CH_3)_2$], 1.41 (d, $J_{5,\,5\text{-Me}} = 6.4$, 5-Me), 1.43–1.63 (m, 1′-H^1, 10′-H_2, 1‴-H_2), 1.69–1.79 (m, 1′-H^2), 2.02 (td, $J_{9''',10'''} \approx J_{9''',8'''} \approx 6.5$, 9‴-$H_2$), in part superimposed by 2.10 (m_c, 5‴-H_2, 6‴-H_2), in part superimposed by 2.13–2.26 (m, 2‴-H_2), 2.54 (ddd, $J_{3,\,1'\text{-H}(1)} \approx J_{3,\,1'\text{-H}(2)} \approx 7.0$, $J_{3,4} = 3.7$, 3-H), 3.60 (m_c, 4″-H, 5″-H), 4.20 (poorly res. dd, $J_{4,5} = 4.6$, $J_{4,3} = 3.6$, 4-H), 4.63 (qd, $J_{5,\,5\text{-Me}} = 6.4$, $J_{5,4} = 4.9$, 5-H), 5.30-5.45 (m, 3‴-H, 4‴-H, 7‴-H, 8‴-H). IR (neat): $\nu = 3445$, 2985, 2925, 2855, 1755, 1460, 1375, 1240, 1185, 1100, 1055, 995, 725 cm^{-1}. $C_{40}H_{72}O_5$ (633.0) calcd. C 75.90, H 11.47; found C 75.80, H 11.31.

(4*S*,5*S*)-4,5-Dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (*S*,*S*-4). Method A: Ref. 7d. **Method B**: At 0 °C $K_3Fe(CN)_6$ (987 mg, 3.00 mmol, 3.0 equiv.), K_2CO_3 (414 mg, 3.00 mmol, 3.0 equiv.), $(DHQ)_2PHAL$ [= 1,4-bis(dihydroquininyl)phthalazine; 78.0 mg, 0.100 mmol, 10.0 mol.%], K_2OsO_4 (6.6 mg, 0.020 mmol, 2.0 mol.%) and methyl *trans*-3-pentenoate (123 µl, 114 mg, 1.00 mmol) were added to a 1 : 1 mixture of Bu^tOH and H_2O (5 ml each). After this mixture had been stirred for 16 h the reaction was terminated by the addition of aqueous Na_2SO_3 solution (10 ml). After extraction with CH_2Cl_2 (10 × 50 ml) the organic extracts were washed with diluted HCl. $(DHQ)_2PHAL$ (74 mg, 95%) could be reisolated from this extract after neutralization and extraction. The organic phase was dried over Na_2SO_4. After removal of the solvent *S*,*S*-**4** (85 mg, 73%) was obtained from the residue by flash chromatography (2.5 cm, Bu^tOMe, fractions 6–12). Chiral capillary gas chromatography revealed ee = 86% [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 *R*,*R* enantiomer 44.3 min]. $[\alpha]_D^{25} = -62.2$ ($c = 0.73$) {lit.: $[\alpha]_D^{25} = -73.7$ ($c = 0.93$, EtOH)}. ^{1}H 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 $J_{A,4} = 1.0$, $J_{B,4} = 5.7$, 3-H_2), 4.45 (br dd, $J_{4,\,3\text{-H(B)}} \approx J_{4,5} \approx 4$, 4-H), 4.58 (qd, $J_{5,1'} = 6.5$, $J_{5,4} = 3.8$, 5-H).

(4*R*,5*R*)-4,5-Dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (*R*,*R*-4). Method A: AD-mix β [14.0 g; containing 1,4-bis-(dihydroquinidinyl)phthalazine (1 mol.%), $K_3Fe(CN)_6$ (3 equiv.), K_2CO_3 (3 equiv.), K_2OsO_4 (0.2 mol.%)] and methyl *trans*-3-pentenoate (1.23 ml, 1.14 g, 10.0 mmol) were added to a 1 : 1 mixture of Bu^tOH and H_2O (50 ml each) at 0 °C. After stirring for 4 days the reaction was terminated by the addition of aqueous Na_2SO_3 solution (30 ml). After extraction with CH_2Cl_2 (10 × 50 ml) the organic extracts were dried over Na_2SO_4. Removal of the solvent yielded a residue that was purified by flash chromatography (3 cm, Bu^tOMe, fractions 12–24) to give *R*,*R*-**4** (441 mg, 38%). Chiral capillary gas chromatography revealed ee = 80% [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 44.3 min, R_T of *S*,*S* enantiomer 45.4 min].

Method B: Same as for *S*,*S*-4 using $(DHQD)_2PHAL$ [= 1,4-bis(dihydroquinidinyl)phthalazine; 78.0 mg, 0.100 mmol, 10.0 mol.%]. After extraction with CH_2Cl_2 (10 × 50 ml) the organic phase was dried over Na_2SO_4. After removal of the solvent *R*,*R*-**4** (80 mg, 69%) was obtained from the residue by flash chromatography (2.5 cm, Bu^tOMe, fractions 6–12). Chiral capillary gas chromatography revealed ee = 94% [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 44.3 min, R_T of *S*,*S* enantiomer 45.4 min].

(4*S*,5*S*)-*Z*,*Z*-4-(3,7-Eicosadienyl)-5-(10-iododecyl)-2,2-dimethyl-1,3-dioxolane (5). At 0 °C, PPh_3 (605 mg, 2.31 mmol, 1.2 equiv.), imidazole (315 mg, 4.63 mmol, 2.4 equiv.) and I_2 (587 mg, 2.31 mmol, 1.2 equiv.) were added to a solution of alcohol **62** (1.03 g, 1.93 mmol) in THF (20 ml). The reaction mixture was warmed to room temperature within 30 min, followed by the addition of water (20 ml). The organic phase was separated and the aqueous phase extracted with Bu^tOMe (50 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (3 cm, deactivated silica, petroleum ether–Bu^tOMe 100 : 1, fractions 3–9). The title compound (1.19 g, 96%) was obtained as a colorless liquid. $[\alpha]_D^{25} = -8.29$ ($c = 0.76$). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{20',19'} = 7.2$, 20′-H_3), 1.24–*ca.* 1.43 (m, 10′-H_2 to 19′-H_2, 2″-H_2 to 8″-H_2), superimposed by 1.38 [s, 2-$(CH_3)_2$], 1.45–1.60 (m, 1′-H_2, 1″-H_2), 1.82 (tt, $J_{9'',10''} = J_{9'',8''} = 7.2$, 9″-$H_2$), 2.02 (br td, $J_{9',10'} \approx J_{9',8'} \approx 6.4$, 9′-$H_2$), in part superimposed by 2.10 (m_c, 5′-H_2, 6′-H_2), in part superimposed by *ca.* 2.14–2.26 (m, 2′-H_2), 3.19 (t, $J_{10'',9''} = 6.9$, 10″-H_2), 3.60 (m_c, 4-H, 5-H), 5.30–5.46 (m, 3′-H, 4′-H, 7′-H, 8′-H). ^{13}C NMR (50.3 MHz, APT): $\delta = 7.05$ (C-10″), 14.04 (C-20′), 22.61, 23.83, 26.06, 27.19, 27.27, 28.44, 29.25, 29.29,* 29.30,* 29.38,# 29.49, 29.58,# 29.62,# 29.65,* 30.41, 31.85, 32.89, 32.92 and 33.47 (19 resonances for 24 C atoms: C-1′, C-2′, C-5′, C-6′, C-9′ to C-19′, C-1″ to C-9″), 27.24 [$C(CH_3)_3$], 80.30 and 80.86 (C-4, C-5), 107.75 [$C(CH_3)_3$], 129.00, 129.19, 130.06 and 130.45 (C-3′, C-4′, C-7′, C-8′); * increased but not 2-fold intensity; #2-fold intensity. IR (neat): $\nu = 2985$, 2925, 2855, 1460, 1370, 1240, 1175, 1100, 1000, 875, 720 cm^{-1}. $C_{35}H_{65}O_2$ (644.8) calcd. C 65.20, H 10.16, found C 64.94, H 10.13.

1,1,1-Tribromo-2-hydroxy-3-butene (16). SnF_2 (0.237 g, 3 mmol, 1 equiv.) was added to a mixture of CBr_4 (2.98 g, 9

mmol, 3 equiv.) and acrolein (0.2 ml, 3 mmol) in DMSO (12 ml) and the solution was stirred for 5 min. Another portion of SnF_2 (0.237 g, 3 mmol, 1 equiv.) was added and stirring was continued for a further 5 min. The mixture was diluted with CH_2Cl_2 (5 ml) and HCl (2 M, 5 ml). After 30 min the organic materials were extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated with a rotary evaporator. The resultant crude product was purified by flash chromatography (pentane–ether 8 : 2) to give the desired product (40 mg, 5%) as a pale yellow oil. ^{1}H NMR (300 MHz): $\delta = 2.98$ (br s, OH), 4.54 (d, $J_{2,3} = 3.8$, 2-H), 5.58 (dt, $J_{cis} = 10.5$, $^4J_{Z\text{-}4,2} = 1.3$, 4-H^Z), 5.58 (dt, $J_{trans} = 17.3$, $^4J_{E\text{-}4,2} = 1.3$, 4-H^E), 6.14 (ddd, $J_{trans} = 17.0$, $J_{cis} = 10.5$, $J_{3,2} = 5.2$, 3-H). ^{13}C (50.3 MHz, APT, $CDCl_3$ as internal standard): $\delta = ″ - ″$ 52.96 (C-1), $″ + ″$ 84.50 (C-2), $″ - ″$ 121.84 (C-4), $″ + ″$ 132.80 (C-3).

Methyl *E*-5-chloro-3-pentenoate (22^{16}). Hydroxyester **20**[14] (290 mg, 2.23 mmol) was added to a solution of NCS (356 mg, 2.68 mmol, 1.2 equiv.) and Me_2S (0.20 ml, 0.17 g, 2.7 mmol, 1.2 equiv.) in CH_2Cl_2 (10 ml) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. After addition of water (10 ml) and extraction with CH_2Cl_2 (3 × 20 ml) the organic phases were dried over $MgSO_4$. After removal of the solvent the title compound (273 mg, 83%) was obtained by flash chromatography (3 cm, petroleum ether–Bu^{t}OMe 50 : 1 → fraction 12, 20 : 1 → fraction 22, fractions 13–22) as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 3.13$ (br d, $J_{2,3} = 6.7$, 2-H$_2$), 3.70 (s, OCH_3), 4.06 (poorly res. dd, $J_{5,4} = 6.6$, $^4J_{5,3} = 1.0$, 5-H$_2$), 5.75 (dtt, $J_{trans} = 15.0$, $J_{3,2} = 6.8$, $^4J_{3,5} = 1.4$, 3-H*), 5.90 (dt with shoulders, $J_{trans} = 15.4$, $J_{4,5} = 6.8$, 4-H*); * assignments interchangeable.

Methyl *E*-5-(phenylthio)-3-pentenoate (23). Ph_2S_2 (4.53 g, 20.8 mmol, 3.0 equiv.) and Bu_3P (6.89 ml, 5.60 g, 27.7 mmol, 4.0 equiv.) were dissolved in toluene (40 ml). Hydroxyester **20**[14] (900 mg, 6.92 mmol) in THF (5 ml) was added after 2 h at room temperature. After stirring overnight the solvent was removed. The residue was purified by flash chromatography (6 cm, petroleum ether → fraction 10, petroleum ether–Bu^{t}OMe 10 : 1 → fraction 35, fractions 23–35). The title compound (1.24 g, 81%) was isolated as a colorless liquid. ^{1}H NMR (300 MHz; with MeO-containing impurity at $\delta = 3.63$): $\delta = 3.03$ (d, $J_{2,3} = 3.8$, 2-H$_2$), 3.54 (dm$_c$, $J_{5,4} \approx 4$, 5-H$_2$), 3.65 (s, OMe), 5.57–5.71 (m, 3-H, 4-H), 7.15–7.22 (m, 1 Ar-H), 7.24–7.36 (m, 4 Ar-H). IR (neat): $\nu = 3055$, 3000, 2950, 1735, 1585, 1480, 1435, 1355, 1290, 1255, 1195, 1170, 1025, 970, 740, 690 cm^{-1}. No combustion analysis was performed.

(4*S*,5*R*)-4,5-Dihydro-4-hydroxy-5-[(phenylthio)methyl]-2(3*H*)-furanone (24). At 0 °C AD-mix α [2.80 g containing 1,4-bis(dihydroquininyl)phthalazine (1 mol%), $K_3Fe(CN)_6$ (3 equiv.), K_2OsO_4 (0.2 mol%)], methanesulfoneamide (190 mg, 2.00 mmol, 1.0 equiv.) and the β,γ-unsaturated ester **23** (444 mg, 2.00 mmol) in Bu^{t}OH (1 ml) were added to a 1 : 1 mixture of Bu^{t}OH and H_2O (6 ml each). After stirring for 36 h, the mixture was hydrolyzed by the addition of aqueous Na_2SO_3 solution (2 ml) and water (10 ml). After extraction with Bu^{t}OMe (3 × 50 ml) the organic extracts were dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (3 cm, petroleum ether–Bu^{t}OMe 2 : 1 → fraction 12, 1 : 1 → fraction 20, Bu^{t}OMe → fraction 32, fractions 14–30). **24** (283 mg, 63%) was isolated as a colorless oil. Chiral capillary gas chromatography of traces of the subsequently obtained (Raney Ni treatment in acetone–EtOH, 5 bar H_2, room temperature, 5 days), desulfurized material revealed ee = 80% [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 44.3 min, R_T of *R*,*R* enantiomer 43.2 min]. ^{1}H NMR (300 MHz; contains 1.4 wt% Bu^{t}OMe): $\delta = 2.42$ (br s, OH), AB signal ($\delta_A = 2.58$, $\delta_B = 2.76$, $J_{AB} = 17.9$, split by $J_{B,4} = 5.6$, 3-H$_2$), AB signal ($\delta_A = 3.29$, $\delta_B = 3.44$, $J_{AB} = 13.6$, split by $J_{A,5} = 9.5$, $J_{B,5} = 5.3$, 1′-H$_2$), 4.45 (ddd, $J_{5,1'\text{-H(A)}} = 9.8$, $J_{5,1'\text{-H(B)}} = 4.9$, $J_{5,4} = 3.4$, 5-H), 4.64 (br dd, $J_{4,5} \approx J_{4,3\text{-H(B)}} \approx 4.5$, 4-H), 7.23–7.36 (m, 3 Ar-H), 7.41–7.46 (m, 2 Ar-H). No combustion analysis was performed.

(4*S*,5*R*)-5-Chloro-4,5-dihydro-4-hydroxy-2(3*H*)-furanone (25). AD-mix α (1.72 g, 3.69 mmol, 3.0, equiv.), $NaHCO_3$ (309 mg, 3.69 mmol, 3.0 equiv.), methanesulfoneamide (117 mg, 1.23 mmol, 1.0 equiv.) and the β,γ-unsaturated ester **22** (182 mg, 1.23 mmol) in Bu^{t}OH (1 ml) were added to a 1 : 1 mixture of Bu^{t}OH and H_2O (6 ml each) at 0 °C. After this mixture had been stirred for 24 h the reaction was terminated by the addition of aqueous Na_2SO_3 solution (2 ml) and water (10 ml). After extraction with Bu^{t}OMe (3 × 50 ml) the organic extracts were dried over Na_2SO_4. Removal of the solvent yielded a residue that was purified by flash chromatography (3 cm, petroleum ether–Bu^{t}OMe 2 : 1 → fraction 12, 1 : 1 → fraction 26, fractions 13–24) to give **25** (53 mg, 19%). ^{1}H NMR (300 MHz): $\delta =$ AB signal ($\delta_A = 2.64$, $\delta_B = 2.85$, $J_{AB} = 17.8$, split by $J_{A,4} = 1.2$, $J_{B,4} = 5.8$, 3-H$_2$), superimposed by 2.64 (br d, $J_{OH,4} = 4.1$, OH), 3.86 (d, $J_{1',5} = 7.2$, 1′-H$_2$), 4.59 (td, $J_{5,1'} = 7.2$, $J_{5,4} = 3.7$, 5-H), 4.72 (br ddd, $J_{4,5} \approx J_{4,3\text{-H(B)}} \approx J_{4,OH} \approx 4.5$, 4-H). No combustion analysis was performed.

(5*R*)-3-Butyl-5-methyl-2(5*H*)-furanone (26). PPh_3 (334 mg, 1.28 mmol, 2.0 equiv.) and DEAD (40% in toluene, 0.58 ml, 0.22 g, 1.3 mmol, 2.0 equiv.) were added to a solution of the β-hydroxylactone **27** (110 mg, 0.640 mmol; 86% ee) in THF (10 ml) at −20 °C. The reaction mixture was allowed to warm to room temperature within 3 h. Water (10 ml) was added, followed by extraction with Bu^{t}OMe (3 × 20 ml). The organic phase was dried over $MgSO_4$ and the solvent was removed. The residue yielded the title compound (88.0 mg, 89%) as a colorless liquid after flash chromatography (2.5 cm, petroleum ether–Bu^{t}OMe 4 : 1, fractions 3–6). $[\alpha]_D^{25} = -48.3$ ($c = 1.09$); since the starting material **27** had 86% ee, this measured specific rotation corresponds to $-48.3/0.86 = -56.1$ for enantiopure **26** {lit.: $[\alpha]_D^{25} = -53.7$ (c not given, $CHCl_3$)}. ^{1}H NMR (300 MHz): $\delta = 0.93$ (t, $J_{4',3'} = 7.4$, 4′-H$_3$), 1.29–1.44 (m, 3′-H$_2$), superimposed by 1.41 (d, $J_{5,5\text{-Me}} = 6.8$, 5-Me), 1.49–1.60 (m, 2′-H$_2$), 2.28 (tdd, $J_{1',2'} = 7.5$, $^4J_{1',4} = {}^5J_{1',5} = 1.6$, 1′-H$_2$), 4.99 (qdt, $J_{5,5\text{-Me}} = 6.8$, $J_{5,4} = {}^5J_{5,1'} = 1.8$, 5-H), 6.99 (td, $^4J_{4,1'} = J_{4,5} = 1.6$, 4-H).

(3*R*,4*R*,5*R*)-3-Butyl-4,5-dihydro-4-hydroxy-5-methyl-2(3*H*)-furanone (27). Bu^{n}Li (1.90 M in hexane, 2.63 ml, 5.00 mmol, 2.5 equiv.) was added to a solution of Pr^i_2NH (0.66 ml, 0.51 g, 5.0 mmol, 2.5 equiv.) in THF (20 ml) at −78 °C. After 30 min a solution of the β-hydroxylactone *R*,*R*-**4** (232 mg, 2.00 mmol, 86% ee) in THF (5 ml) was added. After stirring the mixture for 2 h at this temperature 1-iodobutane (0.27 ml, 0.44 g, 2.4 mmol, 1.2 equiv.) in THF–DMPU (1 : 1, 8 ml) was added. After stirring at −45 °C for 20 h the mixture was hydrolyzed with HCl (1 M, 10 ml). After extracting the aqueous phase with Bu^{t}OMe (3 × 30 ml) the combined organic phases were dried over $MgSO_4$ and the solvent was removed. Flash chromatography (3 cm, petroleum ether–Bu^{t}OMe 4 : 1 → fraction 10, 2.5 : 1 → fraction 26, fractions 15–23) of the residue yielded the title compound (298 mg, 84%) as a colorless oil. $[\alpha]_D^{20} = +58.4$ ($c = 1.18$) {lit.: $[\alpha]_D^{20} = +71$ ($c = 0.5$, MeOH)}; since the starting material *R*,*R*-**4** had 86% ee this measured specific rotation corresponds to $[\alpha]_D^{20} = +58.4/0.86 = +67.9$ for enantiopure **27**. ^{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$_2$), in part superimposed by 1.41 (d, $J_{5\text{-Me},5} = 6.8$, 5-Me), 2.21 (m$_c$, OH), 2.55 (poorly res. 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, $J_{4,5} \approx$

$J_{4,3} \approx J_{4,OH} \approx 4.5$, 4-H), 4.64 (qd, $J_{5,5\text{-Me}} = 6.4$, $J_{5,4} = 4.9$, 5-H).

1-[(2-Tetrahydropyranyl)oxy]-3-butyne (29). A mixture of 3,4-dihydro-(2*H*)-pyran (27.4 ml, 25.2 g, 300 mmol, 3.0 equiv.) and 3-butyn-1-ol (9.30 ml, 8.41 g, 100 mmol) in CH_2Cl_2 (100 ml) and a catalytic amount of camphor sulfonic acid was stirred for 3 h at room temperature. Water (50 ml) was added and the phases were separated. The aqueous phase was extracted with Bu^{t}OMe (100 ml) and the combined organic phases were dried over $MgSO_4$. After removal of the solvent the title compound (14.81 g, 96%) was isolated from the residue by distillation under reduced pressure (bp 74 °C at 20 mbar). ^{1}H NMR (300 MHz): $\delta = 1.46$–1.90 (m, 3′-H_2, 4′-H_2, 5′-H_2), 1.98 (t, $^4J_{4,2} = 2.7$, 4-H), 2.50 (td, $J_{2,1} = 7.2$, $^4J_{2,4} = 2.7$, 2-H_2), *ca.* 3.52 (m_c, 6′-H^1), heavily superimposed by A branch of AB signal ($\delta_A = 3.57$, $\delta_B = 3.83$, $J_{AB} = 9.8$, split by $J_{A,2} = 7.0$, $J_{B,2} = 7.2$, 1-H_2), B branch severely superimposed by *ca.* 3.88 (m_c, 6′-H^2), 4.65 (dd, $J_{2',3'\text{-H}(1)} \approx J_{2',3'\text{-H}(2)} = 3.4$, 2′-H).

1-[(2-Tetrahydropyranyl)oxy]-3-hexadecyne (30). Alkyne **29** (15.7 ml, 15.4 g, 100 mmol) was added dropwise to a suspension of $NaNH_2$ (4.29 g, 111 mmol, 1.1 equiv.) in THF (50 ml) at 0 °C. 1-Bromododecane (26.4 ml, 27.4 g, 110 mmol, 1.1 equiv.) and DMSO (50 ml) were added to the yellowish solution after 1 h. The reaction mixture was stirred for 2.5 h at room temperature and hydrolyzed with water (50 ml). After extraction of the aqueous phase with Bu^{t}OMe (3 × 200 ml) the combined organic phases were dried over $MgSO_4$. After removal of the solvent flash chromatography (8 cm, petroleum ether → fraction 8, petroleum ether–Bu^{t}OMe 50 : 1 → fraction 12, 20 : 1 → fraction 20, fractions 8–18) yielded the title compound (16.73 g, 53%) as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{16,15} = 6.8$, 16-H_3), 1.22–1.90 (m, 6-H_2 to 15-H_2, 3′-H_2, 4′-H_2, 5′-H_2), 2.13 (tt, $J_{5,6} = 7.0$, $^5J_{5,2} = 2.3$, 5-H_2), 2.46 (tt, $J_{2,1} = 7.4$, $^5J_{2,5} = 2.5$, 2-H_2), AB signal ($\delta_A = 3.52$, $\delta_B = 3.79$, $J_{AB} = 9.6$, split by $J_{A,2} = J_{B,2} = 7.2$, 1-H_2), A branch superimposed by *ca.* 3.50 (m_c, 6′-H^A), B branch of AB signal (broadened, $\delta_B = 3.89$, $J_{AB} = 11.3$, split by $J_{6'\text{-H(B)},5'\text{-H}(1)} = 7.9$, $J_{6'\text{-H(B)},5'\text{-H}(2)} = 3.4$, 6′-$H^B$), 4.65 (dd, $J_{2',3'\text{-H}(1)} \approx J_{2',3'\text{-H}(2)} \approx 3.4$, 2′-H).

3-Hexadecyn-1-ol (31). While stirring, *p*-TsOH (1.56 g, 8.22 mmol, 0.4 equiv.) was added to a solution of the THP ether **30** (6.62 g, 20.6 mmol) in MeOH (60 ml) at room temperature. After 30 min water (50 ml) and Bu^{t}OMe (50 ml) were added and the phases separated. After extraction of the aqueous phase with Bu^{t}OMe (2 × 50 ml) the combined organic phases were dried over $MgSO_4$. After removal of the solvent the alkynol **31** (4.90 g, 99%) was isolated as a white solid (mp 41 °C). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{16,15} = 6.8$, 16-H_3), 1.23–1.54 (m, 6-H_2 to 15-H_2), 1.81 (br s, OH), 2.16 (tt, $J_{5,6} = 7.0$, $^5J_{5,2} = 2.3$, 5-H_2), 2.43 (tt, $J_{2,1} = 6.1$, $^5J_{2,5} = 2.3$, 2-H_2), 3.68 (br t, $J_{1,2} = 6.2$, 1-H_2). IR (neat): $\nu = 3320$, 2925, 2850, 1465, 1435, 1380, 1335, 1185, 1045, 720 cm^{-1}. $C_{16}H_{30}O$ (238.4) calcd. C 80.61, H 12.68; found C 80.88, H 12.45.

1-Bromo-3-hexadecyne (32). A solution of alkynol **31** (715 mg, 3.00 mmol) in THF (6 ml) at −20 °C was successively treated with PPh_3 (943 mg, 3.60 mmol, 1.2 equiv.) and NBS (587 mg, 3.30 mmol, 1.1 equiv.). The reaction mixture was warmed to 0 °C. After 4 h NH_4Cl solution (10 ml) was added and the organic phase was separated. After extraction with petroleum ether (2 × 50 ml) the combined organic phases were dried and the solvent removed. The residue was purified *via* flash chromatography (3 cm, petroleum ether, fractions 4–6) to yield the title compound (794 mg, 88%) as a colorless liquid. ^{1}H NMR (300 MHz, contains traces of Ph_3P): $\delta = 0.88$ (t, $J_{16,15} = 6.6$, 16-H_3), 1.22–1.54 (m, 6-H_2 to 15-H_2), 2.14 (tt, $J_{5,6} = 7.0$, $^5J_{5,2} = 2.3$, 5-H_2), 2.71 (tt, $J_{2,1} = 7.3$, $^5J_{2,5} = 2.3$, 2-H_2), 3.41 (t, $J_{1,2} = 7.4$, 1-H_2). No combustion analysis was performed.

1-Iodo-3-hexadecyne (33). A solution of alkynol **31** (1.90 g, 7.89 mmol) in THF (30 ml) at 0 °C was successively treated with PPh_3 (2.30 g, 8.78 mmol, 1.1 equiv.), imidazole (1.19 g, 17.6 mmol, 2.2 equiv.) and I_2 (2.23 g, 8.78 mmol, 1.1 equiv.). After 1 h NH_4Cl solution (10 ml) was added and the organic phase was separated. After extraction with petroleum ether (2 × 100 ml) the combined organic phases were dried and the solvent removed. The residue was purified *via* flash chromatography (4 cm, petroleum ether, fractions 3–9) to provide the title compound (2.433 g, 88%) as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{16,15} = 6.8$, 16-H_3), 1.24–1.54 (m, 6-H_2 to 15-H_2), 2.13 (tt, $J_{5,6} = 6.8$, $^5J_{5,2} = 2.3$, 5-H_2), 2.73 (tt, $J_{2,1} = 7.4$, $^5J_{2,5} = 2.3$, 2-H_2), 3.21 (t, $J_{1,2} = 7.4$, 1-H_2). IR (neat): $\nu = 2925$, 2850, 1465, 1435, 1250, 1170, 720 cm^1. No combustion analysis was performed.

3-Hexynyl trifluoromethanesulfonate (34) and 1-[(2-tetrahydropyranyl)oxy]-3,7-eicosadiyne (35). The alkynol **31** (770 mg, 3.24 mmol) was dissolved in CH_2Cl_2 (10 ml); NEt_3 (0.54 ml, 0.39 g, 3.9 mmol, 1.2 equiv.) and Tf_2O (0.65 ml, 1.1 g, 3.9 mmol, 1.2 equiv.) were added at 0 °C. After 2 h the solvent was removed and the residue filtered over a short silica column (3 cm, petroleum ether–Bu^{t}OMe–CH_2Cl_2 5 : 1 : 1). The resulting crude triflate **34** was dissolved in THF (2 ml). This solution was added at 0 °C to a solution prepared from alkyne **29** (505 mg, 3.24 mmol, 1.0 equiv.) and Bu^{n}Li (1.50 M in hexane, 2.37 ml, 3.56 mmol, 1.1 equiv.) in THF (8 ml; deprotonation time 30 min). After stirring at room temperature for 16 h an aqueous NH_4Cl solution (10 ml) was added. After extracting the aqueous phase with Bu^{t}OMe (3 × 20 ml) the combined organic phases were dried over $MgSO_4$. After removal of the solvent flash chromatography (3 cm, petroleum ether–Bu^{t}OMe 50 : 1 → fraction 10, 20 : 1 → fraction 20, fractions 9–18) provided **35** (383 mg, 32%) as a colorless liquid. ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{20,19} = 6.8$, 20-H_3), 1.22–1.88 (m, 10-H_2 to 19-H_2, 3′-H_2, 4′-H_2, 5′-H_2), 2.13 (br t, $J_{9,10} = 7.0$, 9-H_2), 2.33 (br s, 5-H_2, 6-H_2), 2.46 (t, $J_{2,1} = 7.2$, 2-H_2), AB signal ($\delta_A = 3.52$, $\delta_B = 3.79$, $J_{AB} = 9.8$, split by $J_{A,2} = J_{B,2} = 7.2$, 1-H_2), A branch superimposed by *ca.* 3.50 (m_c, 6′-H^1), B branch of AB signals ($\delta_B = 3.88$, $J_{AB} = 11.2$, split by $J_{B,5'\text{-H}(1)} = 7.5$, $J_{B,5'\text{-H}(2)} = 3.7$, 6′-$H^2$), 4.64 (dd, $J_{2',3'\text{-H}(1)} \approx J_{2',3'\text{-H}(2)} \approx 3.4$, 2′-H). This compound was not characterized by combustion analysis.

1-Hexadecen-3-yne (36). The title compound was obtained instead of the desired diyne **35** in the following experiment. At 0 °C, BuLi (1.43 M in hexane, 5.61 ml, 8.03 mmol, 1.2 equiv.) was added to the THP ether **29** (1.03 g, 6.69 mmol) in THF (20 ml). After 30 min iodide **33** (2.33 g, 6.69 mmol, 1.0 equiv.) in DMSO (50 ml) was added and the mixture was allowed to warm to room temperature. After stirring for 12 h water (50 ml) and Bu^{t}OMe (50 ml) were added. The aqueous phase was extracted with Bu^{t}OMe (2 × 50 ml). The combined organic phases were washed with brine and dried over $MgSO_4$. After removal of the solvent the residue was purified *via* flash chromatography (4 cm, petroleum ether, fractions 2–5) to yield enyne **36** (1.377 g, 93%). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{16,15} = 6.8$, 16-H_3), 1.24–1.57 (m, 6-H_2 to 15-H_2), 2.29 (td, $J_{5,6} = 7.2$, $^5J_{5,2} = 1.9$, 5-H_2), 5.37 (dd, $J_{cis} = 11.0$, $J_{gem} = 2.3$, 1-H^E), 5.54 (dd, $J_{trans} = 17.3$, $J_{gem} = 2.3$, 1-H^Z), 5.78 (ddt, $J_{trans} = 17.3$, $J_{cis} = 10.9$, $^5J_{2,5} = 2.1$, 2-H). IR (neat): $\nu = 2920$, 2855, 1610, 1455, 1380, 1330, 970, 910, 720 cm^{-1}. $C_{16}H_{28}$ (220.4) calcd. C 87.19, H 12.81; found C 87.22, H 12.57.

1-(2-Tetrahydropyranyloxy)-2-dodecyne (39). Bu^nLi (1.90 M, 11.7 ml, 22.2 mmol, 1.2 equiv.) was added to a solution of the alkyne **38**[35] (2.60 g, 18.5 mmol) in THF at 0 °C. After 30 min 1-bromononane (3.90 ml, 4.22 g, 20.4 mmol, 1.1. equiv.) and DMSO (50 ml) were added. After stirring at room temperature for 24 h the reaction was terminated by the addition of water (50 ml). After extraction with Bu^tOMe (2 × 50 ml) the organic phase was dried over $MgSO_4$. After removal of the solvent flash chromatography (5 cm, petroleum ether–Bu^tOMe 50 : 1, fractions 12–17) of the residue yielded the title compound (3.36 g, 68%) as a colorless liquid. ^1H NMR (300 MHz): $\delta = 0.88$ (t, $J_{12,11} = 6.8$, 12-H_3), 1.27 and 1.33–1.73 (m_c and m, respectively, 5-H_2–11-H_2, 4′-H_2, 5′-H_2), 2.21 (tt, $J_{4,5} = 7.2$, $^5J_{4,1} = 2.2$, 4-H_2), 3.49–3.56 and 3.81–3.89 (2m, 6′-H_2), AB signal ($\delta_A = 4.22$, $\delta_B = 4.27$, $J_{AB} = 15.5$, split by $^5J_{A,4} = 2.2$, $^5J_B = 2.3$, 1-H_2), 4.81 (t, $J_{2',3'} = 3.4$, 2′-H). No IR spectrum was recorded. $C_{17}H_{30}O_2$ (266.4) calcd. C 76.64, H 11.35; found C 76.43, H 11.15.

2-Dodecyn-1-ol (40). A solution of THP ether **39** (3.18 g, 10.8 mmol) and TsOH monohydrate (0.830 g, 4.36 mmol, 0.4 equiv.) in methanol (80 ml) was stirred at room temperature for 2 h. Distribution between water and ether, drying of the etheral phase over $MgSO_4$, concentration *in vacuo* and flash chromatography (pentane–ether 8 : 1) yielded the title compound (1.92 g, 84%). ^1H NMR (300 MHz): $\delta = 0.88$ (t, $J_{12,11} = 6.7$, 12-H_3), 1.27–1.45 (m, 6-H_2–11-H_2), 1.68 (br s, OH), 2.21 (tt, $J_{4,5} = 7.2$, $^5J_{4,1} = 2.3$, 4-H_2), 4.25 (t, $^5J_{1,4} = 2.3$, 1-H_2). ^{13}C NMR (50.3 MHz, APT): $\delta = 14.09$ (C-12), 18.72, 22.66, 28.59, 28.86, 29.13, 29.27, 29.46 and 31.85 (C-4–C-11), 51.38 (C-1), 78.23 and 86.61 (C-2, C-3). IR (KBr): $\nu = 3175$, 2955, 2945, 2850, 1470, 1400, 1135, 1025, 780, 715 cm^{-1}. $C_{12}H_{22}O$ (182.3) calcd. C 79.06, H 12.16; found C 78.81, H 12.11.

12-(*tert*-Butyldiphenylsiloxy)-1-dodecyne (42). At 0 °C Bu^tPh_2SiCl (3.47 ml, 3.67 g, 13.7 mmol, 1.0 equiv.) and imidazole (1.92 g, 28.1 mmol, 2.1 equiv.) were added to a solution of alcohol **44** (2.43 g, 13.4 mmol) in CH_2Cl_2 (50 ml). After stirring for 1 h at room temperature the mixture was hydrolyzed with diluted HCl (1 M, 20 ml). The aqueous phase was extracted with Bu^tOMe (3 × 50 ml) and the combined organic phases were dried. After removal of the solvent the title compound (5.58 g, 99%) was obtained without the need for further purification. ^1H NMR (300 MHz): $\delta = 1.05$ (s, $SiBu^t$), 1.22–1.44 (m, 5-H_2 to 10-H_2), 1.46–1.60 (m, 4-H_2, 11-H_2), 1.94 (t, $^4J_{1,3} = 2.6$, 1-H), 2.18 (td, $J_{3,4} = 7.0$, $^4J_{3,1} = 2.7$, 3-H_2), 3.65 (t, $J_{12,11} = 6.4$, 12-H_2), 7.34–7.45 (m, 6 Ar-H), 7.64–7.70 (m, 4 Ar-H). $C_{28}H_{40}SiO$ (420.7) calcd. C 79.94, H 9.58; found C 79.85, H 9.45.

11-Dodecyn-1-ol (44[37]). Li (391 mg, 56.3 mmol, 6.0 equiv.) was added in small pieces to 1,2-diaminopropane (40 ml). After 10 min the deep-blue solution was heated under reflux until the blue color disappeared. After cooling the mixture to room temperature $KOBu^t$ (4.21 g, 37.6 mmol, 4.0 equiv.) was added. The olive-brown suspension was stirred for 30 min and the alkyne **40** (1.71 g, 9.39 mmol) was added. After 1 h ice water was added and the mixture was extracted with Bu^tOMe (3 × 100 ml). The combined organic phases were dried and the solvent was removed. The isolated residue was purified by flash chromatography (4 cm, petroleum ether–Bu^tOMe 3 : 1 → fraction 8, 2 : 1 → fraction 12, fractions 5–11). Alkynol **44** (1.266 g, 74%) was isolated as a white solid (mp 25 °C). ^1H NMR (300 MHz): $\delta = 1.24$–1.45 (m, 3-H_2 to 8-H_2), 1.46–1.62 (m, 2-H_2, 9-H_2), 1.94 (t, $^4J_{12,10} = 2.7$, 12-H), 2.18 (td, $J_{10,9} = 7.0$, $^4J_{10,12} = 2.6$, 10-H_2), 3.64 (t, $J_{1,2} = 6.8$, 1-H_2); the resonance of the OH was not detected. ^{13}C NMR (50.3 MHz, APT): $\delta = 18.36$, 25.69, 28.44, 28.70, 29.05, 29.37, 29.49 and 32.74 (C-2-C-9), 62.97 (C-1), 68.02 (C-12), 84.73 (C-11). IR (KBr): $\nu = 3285$, 2920, 2850, 1470, 1060, 1030, 725 cm^{-1}.

***Z*-3-Hexadecen-1-ol (49[38]).** Li (2.07 g, 300 mmol, 3.0 equiv.) was cut into small pieces and suspended in Et_2O (50 ml). Within 1 h 1-bromododecane (14.0 ml, 24.9 g, 100 mmol) in Et_2O (50 ml) was added dropwise at 0 °C to this mixture. After stirring for an additional 2 h at 0 °C the concentration of the resulting 1-lithiododecane was determined by titration of a hydrolyzed sample of known volume (1.0 ml) with HCl (0.1 M) using phenolphthalein as an indicator. Subsequently, the solution of this organolithium compound (103 ml, 0.95 M, 98.0 mmol) was transferred to a suspension of CuI (9.31 g, 49.0 mmol, 0.50 equiv.) in Et_2O (100 ml) at −35 °C. After 30 min acetylene (2.4 l, 98 mmol, 1.0 equiv.) was introduced at −50 °C into the dark-grey suspension. After another 30 min of stirring at −25 °C a green suspension was obtained. At −30 °C it was treated with previously condensed ethylene oxide (4.9 ml, 4.3 g, 98 mmol, 1.0 equiv.) and a previously prepared solution of hexynyllithium [from BuLi (2.05 M in hexane, 23.9 ml, 49.0 mmol, 0.50 equiv.) and 1-hexyne (5.62 ml, 4.02 g, 49.0 mmol, 0.50 equiv.)] in Et_2O (100 ml). The black reaction mixture was stirred for 3 h at −15 °C and then hydrolyzed with HCl (6 M, 40 ml) and sat. NH_4Cl solution (40 ml). After removing insoluble material by filtration Bu^tOMe (200 ml) was added, the organic phase separated and the aqueous phase extracted with Bu^tOMe (2 × 100 ml). The organic phases were dried over $MgSO_4$ and the solvent was removed. Flash chromatography (8 cm, petroleum ether–Bu^tOMe 10 : 1 → fraction 10, 5 : 1 → fraction 25, fractions 7–22) of the residue provided the title compound (19.07 g, 81%) as a colorless liquid. ^1H NMR (300 MHz): $\delta = 0.88$ (t, $J_{16,15} = 6.6$, 16-H_3), 1.24–1.41 (m, 6-H_2 to 15-H_2), 1.49 (br s, OH), 2.06 (td, $J_{5,4} = J_{5,6} = 6.7$, 5-H_2), 2.33 (td, $J_{2,1} \approx J_{2,3} \approx 6.6$, 2-$H_2$), 3.65 (t, $J_{1,2} = 6.6$, 1-H_2), 5.36 (br dtt,* $J_{cis} = 10.8$, $J_{3,2} = 7.4$, $^4J_{3,5} = 1.5$, 4-H), 4.57 (br dtt,* $J_{cis} = 10.8$, $J_{4,5} = 7.5$, $^4J_{4,2} = 1.5$, 3-H); *with additional peaks of the beginning of a transition to a higher order signal.

***Z*-1-Iodo-3-hexadecene (50).** At 0 °C PPh_3 (2.88 g, 11.0 mmol, 1.1 equiv.), imidazole (1.50 g, 22.0 mmol, 2.2 equiv.) and I_2 (2.79 g, 11.0 mmol, 1.1 equiv.) were added to a solution of the alcohol **49** (2.40 g, 10.0 mmol) in THF (100 ml). The reaction mixture was warmed to room temperature within 30 min. Subsequently water (100 ml) was added. The organic phase was separated and the aqueous phase extracted with Bu^tOMe (100 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (4 cm, petroleum ether, fractions 4–6). The title compound (3.48 g, 99%) was obtained as a colorless liquid. ^1H NMR (300 MHz): $\delta = 0.88$ (t, $J_{16,15} = 6.8$, 16-H_3), 1.24–1.38 (m, 6-H_2 to 15-H_2), 2.02 (br td, $J_{5,6} = J_{5,4} = 6.9$, 5-H_2), 2.63 (br td, $J_{2,1} = J_{2,3} = 7.0$, 2-H_2), 3.13 (t, $J_{1,2} = 7.2$, 1-H_2), 5.31 (dtt, $J_{cis} = 10.9$, $J_{vic} = 7.2$, $J_{allyl} = 1.5$, 4-H*), 5.53 (dtt, $J_{cis} = 10.6$, $J_{vic} = 7.5$, $J_{allyl} = 1.5$, 3-H*); *assignments interchangeable. IR (neat): $\nu = 3010$, 2925, 2850, 1695, 1460, 1375, 1300, 1240, 1170, 970, 720 cm^{-1}. $C_{16}H_{31}I$ (350.3) calcd. C 54.86, H 8.92; found C 54.97, H 8.99.

***Z*,*Z*-1-Iodo-1,5-octadecadiene (51).** Iodide **50** (6.20 g, 17.7 mmol) was dissolved in Et_2O–hexane (1 : 1, 40 ml), and at −20 °C Bu^tLi (1.52 M in Et_2O, 23.3 ml, 35.4 mmol, 2.0 equiv.) was added. After 30 min the resulting solution was transferred to a −35 °C suspension of CuI (1.68 g, 8.85 mmol, 0.5 equiv.) in Et_2O (20 ml). The dark-grey suspension was stirred for another 30 min at −35 °C. At −50 °C acetylene (425 ml, 17.7 mmol, 1.0 equiv.) was introduced. The mixture was allowed to warm to −25 °C and stirred again for 1 h. At −60 °C powdered I_2 (4.49 g, 17.7 mmol, 1.0 equiv.) was added to the greenish-black suspension. The reaction mixture was warmed to −10 °C within 2 h and hydrolyzed thereafter at the same

temperature with water (10 ml) and sat. NH_4Cl solution (10 ml). After separation from insoluble material by filtration the filtrate was extracted with petroleum ether (100 ml). The organic phase was washed with diluted NH_3 solution (10 ml) and $Na_2S_2O_3$ solution (0.5 M, 10 ml). The now colorless solution was dried and the solvent removed. Flash chromatography (6 cm, petroleum ether, fractions 4–6) yielded the title iodide (4.41 g, 66%) as a colorless liquid. ^{1}H NMR (300 MHz, C_6D_6; in $CDCl_3$ the olefinic signals superimpose each other): $\delta = 0.92$ (t, $J_{18,17} = 6.4$, 18-H_3), 1.29–1.38 (m, 8-H_2 to 17-H_2), 1.96–2.16 (m, 3-H_2, 4-H_2, 7-H_2), AB signal ($\delta_A = 5.35$, $\delta_B = 5.45$, $J_{AB} = 10.9$, A branch split by $J_{vic} = 7.0$, B branch split by $J_{vic} = 7.2$, 5-H, 6-H), 5.80 (td, $J_{2,3} \approx J_{cis} \approx 6.8$, 2-H), 5.92 (br d, $J_{cis} = 7.5$, 1-H). ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): $\delta = 14.15$ (C-18), 22.72, 25.65, 27.29, 29.34, 29.39, 29.60, 29.70 (3-fold intensity), 31.96 and 34.83 (C-3, C-4, C-7 to C-17), 82.56 (C-1), 127.99, 131.20 and 140.70 (C-2, C-5, C-6). IR (neat): $\nu = 3005$, 2925, 2850, 1610, 1460, 1285, 1240, 720 cm^{-1}. $C_{18}H_{33}I$ (376.4) calcd. C 57.44, H 8.84; found C 57.27, H 8.69.

12-(*tert*-Butyldiphenylsiloxy)-1-dodecanol (53). At room temperature imidazole (10.2 g, 150 mmol, 2.0 equiv.) and Bu^tPh_2SiCl (19.3 ml, 20.6 g, 75.0 mmol, 1.0 equiv.) were added to a solution of 1,12-dodecanediol (15.2 g, 75.0 mmol) in DMF (150 ml). After 15 h the reaction was terminated by the addition of water (100 ml) and EtOAc (100 ml). After extraction of the aqueous phase with EtOAc (3 × 200 ml) the combined organic phases were washed with water (50 ml) and dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (8 cm, petroleum ether–Bu^{t}OMe 20 : 1 → fraction 15, 10 : 1 → fraction 25, 5 : 1 → fraction 40, 2 : 1 → fraction 52, fractions 22–46) to yield the title compound (19.60 g, 59%). ^{1}H NMR (300 MHz): $\delta = 1.05$ (s, Bu^{t}Si), 1.22–1.40 (m, 3-H_2 to 10-H_2), 1.50–1.61 (m, 2-H_2, 11-H_2), 3.63 (t, $J_{1,2} = 6.6$, 1-H_2),* in part superimposed by 3.65 (t, $J_{12,11} = 6.4$, 12-H_2),* 7.34–7.44 (m, 6 Ar-H), 7.64–7.70 (m, 4 Ar-H); *assignments interchangeable. IR (neat): $\nu = 3340$, 3070, 2930, 2855, 1465, 1430, 1390, 1360, 1190, 1110, 825, 740, 705 cm^{-1}. $C_{28}H_{40}O_2Si$ (440.7) calcd. C 76.30, H 10.06; found C 76.39, H 9.91.

12-(*tert*-Butyldiphenylsiloxy)dodecanal (54). At −78 °C DMSO (6.72 ml, 7.39 g, 94.8 mmol, 2.2 equiv.) was added dropwise to a solution of oxalylic chloride (4.15 ml, 6.02 g, 47.4 mmol, 1.1 equiv.) in CH_2Cl_2 (120 ml). After 3 min alcohol **53** (19.0 g, 43.1 mmol) in CH_2Cl_2 (10 ml) was added. After stirring for 1 h at −40 °C NEt_3 (29.9 ml, 21.8 g, 216 mmol, 5.0 equiv.) was added. Within 1 h the mixture was allowed to warm to 0 °C and water (150 ml) was added. The organic phase was separated, washed with HCl (2 M, 100 ml) and $NaHCO_3$ solution (10 ml) and dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (8 cm, petroleum ether–Bu^{t}OMe 15 : 1, fractions 7–12) to yield the title compound (15.43 g, 83%). ^{1}H NMR (300 MHz, contains traces of petroleum ether): $\delta = 1.05$ (s, Bu^{t}Si), 1.23–1.38 (m, 4-H_2 to 10-H_2), 1.55 (m_c, 3-H_2),* in part superimposed by 1.63 (m_c, 11-H_2),* 2.41 (td, $J_{2,3} = 7.4$, $J_{2,1} = 1.9$, 2-H_2), 3.65 (t, $J_{12,11} = 6.6$, 12-H_2), 7.34–7.44 (m, 6 Ar-H), 7.64–7.70 (m, 4 Ar-H), 9.76 (t, $J_{1,2} = 1.9$, 1-H); *assignments interchangeable. IR (neat): $\nu = 3070$, 2930, 2855, 1710, 1465, 1430, 1390, 1360, 1185, 1110, 825, 740, 705, 615 cm^{-1}. $C_{28}H_{42}O_2Si$ (438.7) calcd. C 76.65, H 9.65; found C 76.51, H 9.69.

(4*S*,5*S*)-5-[10-(*tert*-Butyldiphenylsiloxy)decyl]-4,5-dihydro-4-hydroxy-2(3*H*)-furanone (55). At 0 °C $K_3Fe(CN)_6$ (22.1 g, 67.3 mmol, 3.0 equiv.), K_2CO_3 (9.29 g, 67.3 mmol, 3.0 equiv.), $(DHQ)_2PHAL$ (174 mg, 0.224 mmol, 1.0 mol.%), K_2OsO_4 (17 mg, 0.045 mmol, 0.2 mol.%), methanesulfoneamide (2.13 g, 22.4 mmol, 1.0 equiv.) and the unsaturated ester **56** (11.1 g, 22.4 mmol) were added to a 1 : 1 mixture of Bu^{t}OH and H_2O (110 ml each). This mixture was stirred for 4 days. The reaction was worked up by the addition of aqueous Na_2SO_3 solution (100 ml). After extraction with EtOAc (3 × 200 ml) the organic extracts were dried over Na_2SO_4. Removal of the solvent yielded a residue that was purified by flash chromatography (6 cm, petroleum ether–Bu^{t}OMe 3 : 1 → fraction 8, 1 : 1 → fraction 18, 1 : 2 → fraction 50, fractions 5–24) to yield **55** (7.56 g, 68%) as a colorless liquid. $[\alpha]_D^{25} = -17.9$ ($c = 0.84$). The *R*-Mosher ester of **55** revealed ee = 97% by $\delta_{MeO} = 3.48$ *vs.* δ_{MeO} in the diastereomer = 3.54. ^{1}H NMR (300 MHz, contains 11 wt.% Bu^{t}OMe): $\delta = 1.05$ (s, Bu^{t}Si), 1.22–1.60 (m, 2′-H_2 to 9′-H_2), 1.65–1.92 (m, 1′-H_2), 2.11 (d, $J_{OH,4} = 4.5$, OH), AB signal ($\delta_A = 2.54$, $\delta_B = 2.78$, $J_{AB} = 17.7$, split by $J_{B,4} = 5.3$, 3-H_2), 3.65 (t, $J_{10',9'} = 6.6$, 10′-H_2), 4.35 (ddd, $J_{5,1'\text{-H(1)}} = 8.8$, $J_{5,1'\text{-H(2)}} = 5.7$, $J_{5,4} = 3.6$, 5-H), 4.46 (ddd, $J_{4,3\text{-H(B)}} \approx J_{4,5} \approx J_{4,OH} \approx 4.5$, 4-H), 7.34–7.45 (m, 6 Ar-H), 7.64–7.70 (m, 4 Ar-H). IR (neat): $\nu = 3435$, 3070, 2930, 2855, 1765, 1465, 1430, 1390, 1360, 1200, 1170, 1110, 1015, 825, 740, 705, 610 cm^{-1}. $C_{30}H_{44}SiO_4$ (496.8) calcd. C 72.53, H 8.96; found C 72.30, H 9.33.

Methyl *E*-14-(*tert*-butyldiphenylsiloxyl)-3-tetradecenoate (56). A mixture of aldehyde **54** (15.0 g, 34.2 mmol), monomethylmalonate (4.44 g, 37.6 mmol, 1.1 equiv.) and NEt_3 (5.20 ml, 3.80 g, 37.6 mmol, 1.1 equiv.) was heated at 90 °C overnight. After the addition of ice (100 ml), diluted HCl (2 M, 40 ml) and Bu^{t}OMe (100 ml) the organic phase was separated and dried over $MgSO_4$. After removal of the solvent the residue was purified by flash chromatography (6 cm, petroleum ether–Bu^{t}OMe 50 : 1 → fraction 7, 20 : 1 → fraction 15, fractions 7–13) to give the title compound (11.15 g, 66%). ^{1}H NMR [300 MHz; contains 6 mol.% methyl *trans*-14-(*tert*-butyldiphenylsiloxy)-2-dodecenoate as determined from the integral intensity of its CO_2Me group at $\delta = 3.72$]: $\delta = 1.05$ (s, Bu^{t}Si), 1.20–1.40 (m, 6-H_2 to 12-H_2), 1.55 (tt, $J_{13,14} \approx J_{13,12} \approx 6.9$, 13-$H_2$), 2.02 (dt, $J_{5,4} \approx J_{5,6} \approx 6.4$, 5-$H_2$), 3.03 (d, $J_{2,3} = 5.3$, 2-H_2), 3.65 (t, $J_{14,13} = 6.4$, 14-H_2), in part superimposed by 3.68 (s, OMe), extreme AB signal with additional peaks indicating transition to higher order signal ($\delta_A = 5.50$, $\delta_B = 5.57$, $J_{AB} = 15.5$, split by $J_{A,2} = 5.6$,* $J_{B,5} = 5.6$,* 3-H, 4-H; *assignments of coupling partners interchangeable), 7.34–7.44 (m, 6 Ar-H), 7.64–7.70 (m, 4 Ar-H). IR (neat): $\nu = 3050$, 2930, 2855, 1740, 1465, 1430, 1390, 1360, 1255, 1165, 1110, 970, 825, 740, 705, 610 cm^{-1}.($C_{31}H_{46}SiO_3$ (494.8) calcd. C 75.25, H 9.37; found C 75.41, H 9.51.

(3*S*,4*S*)-14-(*tert*-Butyldiphenylsiloxy)-1,3,4-tetradecanetriol (57). At −78 °C a solution of hydroxylactone **55** (5.67 g, 11.4 mmol) in THF (25 ml) was slowly added to a suspension of $LiAlH_4$ (433 mg, 11.4 mmol, 1.0 equiv.) in THF (25 ml). The reaction mixture was warmed to room temperature and after 30 min hydrolyzed with diluted H_2SO_4 (3 wt.%, 40 ml). The mixture was extracted with EtOAc (4 × 100 ml). The combined organic extracts were thoroughly dried over Na_2SO_4. After removal of the solvent the title compound (5.59 g, 98%) was obtained as a colorless liquid. $[\alpha]_D^{25} = -4.4$ ($c = 0.45$). ^{1}H NMR (300 MHz): $\delta = 1.05$ (s, Bu^t), 1.20–1.38 (m, 6-H_2 to 12-H_2), 1.39–1.58 (m, 5-H_2, 13-H_2), 1.68–1.83 (m, 2-H_2), *ca.* 2.80 (very br s, 2 × OH), *ca.* 3.30 (very br s, 1 × OH), 3.45 (m_c, 4-H), 3.65 (t, $J_{14,13} = 6.6$, 14-H_2), superimposed by *ca.* 3.68 (m_c, 3-H), 3.86 (m_c, 1-H_2), 7.33–7.44 (m, 6 Ar-H), 7.64–7.70 (m, 4 Ar-H). The *H*–C–O signals in the ^{1}H NMR spectrum were assigned as in the related compound (3*S*,4*S*)-14-(*tert*-butyldi*methyl*siloxy)-1,3,4-tetradecanetriol in which the corresponding signals are less superimposed. IR (neat): $\nu = 3380$, 3070, 2930, 2855, 1465, 1430, 1390, 1110, 825, 740, 705 cm^{-1}. $C_{30}H_{48}SiO_4$ (500.8) calcd. C 71.95, H 9.66; found C 71.72, H 9.86.

(4′*S*,5′*S*)-2-{5-[10-(*tert*-Butyldiphenylsiloxy)decyl]- 2,2-dimethyl-1,3-dioxolan-4-yl}ethanol (58). Triol **57** (3.10 g, 6.20 mmol) was dissolved in acetone (25 ml); 2,2-dimethoxypropane (6.12 ml, 5.20 g, 50.0 mmol, 8.0 equiv.) and Amberlyst 15 ion exchange resin (120 mg) were added. After stirring the mixture for 2 h at room temperature the resin was removed by filtration and the solvent evaporated. The residue obtained was used in the next reaction without further purification. $[\alpha]_D^{25} = -12$ ($c = 0.81$). ^{1}H NMR (500 MHz): $\delta = 1.05$ (s, Bu^t), 1.24–1.38 (m, 2″-H_2 to 8″-H_2), 1.40 [s, C(Me)$_2$], 1.45–1.59 (m, 1′-H_2, 9″-H_2), AB signal ($\delta_A = 1.74$, $\delta_B = 1.84$, $J_{AB} = 14.4$, split by $J_{A,4'} = 9.0$, $J_{A,1\text{-}H(1)} = 6.6$, $J_{A,1\text{-}H(2)} = 5.2$, $J_{B,1\text{-}H(1)} = 5.6$,* $J_{B,1\text{-}H(2)} = 5.2$,* $J_{B,4'} = 3.2$, 2-H_2), 2.41 (br t, $J_{OH,1} = 4.7$, OH), 3.65 (t, $J_{10'',9''} = 6.5$, 10″-H_2), superimposed by 3.68 (probably interpretable as ddd, $J_{5',4'} = 8.3$, $J_{5',1''\text{-}H(1)} = 7.1$, $J_{5',1''\text{-}H(2)} = 4.2$, 5′-H**), 3.77 (ddd, $J_{4',5'} = J_{4',2\text{-}H(A)} = 8.6$, $J_{4',2\text{-}H(B)} = 3.0$, 4′-H), 3.83 (br td, $J_{1,2} \approx J_{1,OH} \approx 5.2$, 1-$H_2$), 7.36–7.45 (m, 6 Ar-H), 7.66–7.70 (m, 4 Ar-H); *assignments interchangeable; **analysis of the coupling constants performed as in (4′*S*,5′*S*)-2-{5-[10-(*tert*-butyldi*methyl*siloxy)decyl]-2,2-dimethyl-1,3-dioxolan-4-yl}ethanol where the 5-H signal and the 10″-H_2 signal do not coincide. IR (neat): $\nu = 3425$, 3070, 2930, 2855, 1465, 1430, 1375, 1240, 1110, 875, 825, 740, 705 cm^{-1}. $C_{33}H_{52}SiO_4$ (540.9) calcd. C 73.28, H 9.69; found C 73.34, H 9.98.

(4*S*,5*S*)-4-[10-(*tert*-Butyldiphenylsiloxy)decyl]-2,2-dimethyl-5-(2-iodoethyl)-1,3-dioxolane (59). At 0 °C PPh_3 (1.62 g, 6.20 mmol, 1.0 equiv.), imidazole (843 mg, 12.4 mmol, 2.0 equiv.) and I_2 (1.58 g, 6.20 mmol, 1.0 equiv.) were added to a solution of alcohol **58** (crude product from 3.10 g of triol **57**, 6.20 mmol) in THF (50 ml). The reaction mixture was allowed to warm to room temperature within 15 min. Water (100 ml) was added, the organic phase separated and the aqueous phase extracted with Bu^{t}OMe (100 ml). The combined organic phases were dried over $MgSO_4$ and the solvent was removed. The residue was purified by flash chromatography (4 cm, deactivated silica, petroleum ether–Bu^{t}OMe 50 : 1, fractions 3–10). The title compound (3.814 g, 94% over the two steps from triol **57**) was obtained as a colorless liquid. $[\alpha]_D^{25} = -20.0$ ($c = 1.09$). ^{1}H NMR (500 MHz): $\delta = 1.05$ (s, Bu^t), 1.23–1.38 (m, 2′-H_2 to 8′-H_2), 1.37 and 1.39 [2 s, C(Me)$_2$], 1.42–1.58 (m, 1′-H_2, 9′-H_2), AB signal ($\delta_A = 2.03$, $\delta_B = 2.08$, $J_{AB} = 14.3$, split by $J_{A,4} = J_{A,2''\text{-}H(A)} = 8.3$, $J_{A,2''\text{-}H(B)} = 5.3$, $J_{B,2''\text{-}H(B)} = J_{B,2''\text{-}H(A)} = 8.3$, $J_{B,4} = 3.0$, 1″-H_2), AB signal ($\delta_A = 3.24$, $\delta_B = 3.34$, $J_{AB} = 9.6$, split by $J_{A,1''\text{-}H(A)} = J_{A,1''\text{-}H(B)} = 8.0$, $J_{B,1''\text{-}H(B)} = 7.3$, $J_{B,1''\text{-}H(A)} = 5.1$, 2″-$H_2$), 3.66 (t, $J_{10',9'} = 6.7$, 10′-H_2), completely superimposed by (m_c, 4-H, 5-H), 7.36–7.45 (m, 6 Ar-H), 7.66–7.70 (m, 4 Ar-H); *assignments and analysis of coupling constants as in the ^{1}H NMR spectrum of the alcohol precursor **58**. ^{13}C NMR (50.3 MHz, APT): 1.87 (C-2″), 19.22 [*C*(CH$_3$)$_3$], 25.76, 26.03, 29.35, 29.50 (2-fold intensity), 29.57, 29.73, 32.58, 32.78 and 37.45 (C1′ to C-9′ C-1″), 26.87 [C(*C*H$_3$)$_3$], 27.23 and 27.30 (2 × Me), 63.98 (C-10′), 80.32 and 80.57 (C-4, C-5), 108.31 (C-2), 127.52, 129.42 and 135.52 (4 *ortho*, 4 *meta* and 2 *para* C), 134.12 (2 *ipso* C). IR (neat): $\nu = 3070$, 2930, 2855, 1465, 1430, 1375, 1235, 1175, 1110, 825, 740, 705 cm^{-1}. $C_{33}H_{51}SiO_3I$ (650.8) calcd. C 60.91, H 7.90; found C 61.09, H 7.79.

(4*S*,5*S*)-*Z*,*Z*-4-[10-(*tert*-Butyldiphenylsiloxy)decyl]-5-(3,7-eicosadienyl)-2,2-dimethyl-1,3-dioxolane (61). Vinyl iodide **51** (94.0 mg, 0.250 mmol) was dissolved in Et$_2$O (1 ml) and Bu^{t}Li (1.52 M in Et$_2$O, 0.36 ml, 0.55 mmol, 2.2 equiv.) was added at −50 °C. After 30 min alkyl iodide **59** (163 mg, 0.250 mmol, 1.0 equiv.) in THF (1 ml) was added. The mixture was warmed to room temperature and stirred for another 4 h. The reaction was terminated by the addition of HCl (1 M, 2 ml). After extraction with Bu^{t}OMe (2 × 20 ml) the combined organic phases were dried over $MgSO_4$. After removal of the solvent flash chromatography (2.5 cm, petroleum ether–Bu^{t}OMe 100 : 1, fractions 6–14) yielded the title compound (123 mg, 64%). $[\alpha]_D^{25} = -7.4$ ($c = 0.64$). ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{20',19'} = 6.6$, 20′-H_3), 1.05 (s, Bu^t), 1.24–1.38 (m, 10′-H_2 to 19′-H_2, 2′-H_2 to 8″-H_2), 1.39 [br s, 2-(CH$_3$)$_2$], 1.47–1.60 (m, 1′-H_2, 1″-H_2, 9″-H_2), 2.02 (td, $J_{9',10'} \approx J_{9',8'} \approx 6.3$, 9′-$H_2$), in part superimposed by 2.10 (m_c, 5′-H_2, 6′-H_2), in part superimposed by 2.14–2.26 (m, 2′-H_2), 3.61 (m_c, 4-H, 5-H), in part superimposed by 3.65 (t, $J_{10'',9''} = 6.4$, 10″-H_2), 5.30–5.46 (m, 3′-H, 4′-H, 7′-H, 8′-H), 7.34–7.46 (m, 6 Ar-H), 7.65–7.70 (m, 4 Ar-H). IR (neat): $\nu = 3050$, 2925, 2855, 1465, 1430, 1370, 1240, 1110, 825, 740, 705 cm^{-1}. $C_{51}H_{84}SiO_3$ (773.3) calcd. C 79.21, H 11.95; found C 79.73, H 11.94.

(4′*S*,5′*S*)-*Z*,*Z*-10-[5-(3,7-Eicosadienyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-decanol (62). At room temperature silylether **61** (1.64 g, 2.12 mmol) in THF (20 ml) was treated with Bu_4NF (1.0 M in THF, 2.55 ml, 2.55 mmol, 1.2 equiv.). Stirring was continued for 20 h. After hydrolysis with water (20 ml) the aqueous phase was extracted with Bu^{t}OMe (3 × 50 ml). The organic phases were dried over $MgSO_4$ and the solvent was evaporated. Flash chromatography (3 cm, petroleum ether–Bu^{t}OMe 10 : 1 → fraction 12, 2 : 1 → fraction 30, fractions 17–26) yielded **62** (1.133 g, 99%). $[\alpha]_D^{25} = -9.33$ ($c = 1.20$). ^{1}H NMR (300 MHz, slightly contaminated around $\delta = 0.9$): $\delta = 0.88$ (t, $J_{20'',19''} = 6.5$, 20″-H_3), 1.24–*ca.* 1.38 (m, 10″-H_2 to 19″-H_2, 3-H_2 to 9-H_2), 1.38 [s, 2′-(CH$_3$)$_2$], 1.45–1.62 (m, 2-H_2, 10-H_2, 1″-H_2), 2.02 (td, $J_{9'',10''} \approx J_{9'',8''} \approx 6.4$, 9″-$H_2$), in part superimposed by 2.10 (m_c, 5″-H_2, 6″-H_2), in part superimposed by 2.13–2.26 (m, 2″-H_2), 3.60 (m_c, 4′-H, 5′-H), in part superimposed by 3.64 (t, $J_{1,2} = 6.6$, 1-H_2), 5.30–5.46 (m, 3″-H, 4″-H, 7″-H, 8″-H). IR (neat): $\nu = 3360$, 2925, 2855, 1460, 1375, 1240, 1170, 1090, 1060, 875, 725 cm^{-1}. $C_{35}H_{66}O_3$ (534.9) calcd. C 78.59, H 12.44; found C 78.71, H 12.52.

(11*S*,12*S*)-*Z*,*Z*-1-Iodo-15,19-dotriacontadien-11,12-diol (63). HCl (12 M, 10 μl, 0.10 mmol, 4.0 equiv.) was added to a solution of the acetonide **5** (30.0 mg, 0.0466 mmol) and the butenolide **26** (40.0 mg, 0.260 mmol) in MeOH–CH_2Cl_2 (5 : 1, 0.6 ml) and the mixture was stirred for 24 h at room temperature. Water (2 ml) was added and the organic phase extracted with Bu^{t}OMe (3 × 10 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was removed. The residue was purified by flash chromatography (2.5 cm, petroleum ether–Bu^{t}OMe 10 : 1 → fraction 12, 5 : 1 → fraction 18, 2.5 : 1 → fraction 34). The unconsumed butenolide **26** {fractions 10–15, 30.6 mg, 76%; $[\alpha]_D^{25} = -48.4$ ($CHCl_3$, $c = 0.8$)} and the title compound (fractions 28–34, 14.1 mg, 50%) were obtained as colorless liquids. ^{1}H NMR (300 MHz): $\delta = 0.88$ (t, $J_{32,31} = 6.8$, 32-H_3), 1.24–*ca.* 1.43 (m, 3-H_2 to 9-H_2, 22-H_2 to 31-H_2), *ca.* 1.45–1.60 (m, 10-H_2, 13-H_2), 1.82 (tt, $J_{2,1} = J_{2,3} = 7.1$, 2-H_2), 2.02 (br td, $J_{21,22} \approx J_{21,20} \approx 6.5$, 21-$H_2$), in part superimposed by 2.11 (m_c, 17-H_2, 18-H_2), in part superimposed by *ca.* 2.14–2.25 (m, 14-H_2), 3.19 (t, $J_{1,2} = 7.0$, 1-H_2), 3.36–3.47 (m, 11-H, 12-H), 5.30–5.47 (m, 15-H, 16-H, 19-H, 20-H). No combustion analysis was performed.

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