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SYNTHETIC STUDY ON CURACIN A: A NOVEL ANTIMITOTIC AGENT FROM THE CYANOBACTERIUM *Lyngbya majuscula*

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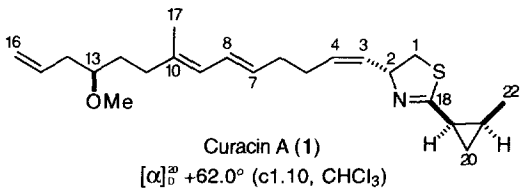
Abstract: Curacin A (**1**), a novel antimitotic agent, was synthesized in a highly stereo-controlled manner. The four stereoisomers of a partial structure at the thiazoline moiety, **2** were also synthesized to aid in elucidation of the absolute configurations of three chiral centers in curacin A. The effects on porcine brain tubulin assembly of several synthetic compounds related to curacin A were examined.

Microtubules are the main component of spindles in the mitotic apparatus of eucaryotic cells, and are also involved in other cell functions, such as axonal transport, motility, and determination of cell shape. The major constituent of the microtubule system is the protein tubulin.[1] There are a number of natural and synthetic compounds that interfere with tubulin function to inhibit the formation of microtubules and to cause the mitotic arrest of eucaryotic cells. Such antimitotic agents show a broad spectrum of biological activities, and have potential applications in the fields of medicine and agriculture. They can also be used as molecular probes for investigating the dynamics of microtubule networks. Studies on the mechanism of molecular recognition between inhibitors and tubulin are important, because the inhibitor-binding domain is expected to have a close relationship to the domain that functions in tubulin assembly.[2]



Curacin A (**1**)
$[\alpha]_D^{20}$ +62.0° (c1.10, $CHCl_3$)

Curacin A (**1**) is a novel antimitotic agent isolated from a Caribbean cyanobacterium, *Lyngbya majuscula*,[3] and consists of a disubstituted thiazoline bearing a chiral cyclopropane ring and an aliphatic side chain. It was reported that curacin A inhibits tubulin assembly by binding to the colchicine-binding site[3], which is one of the two distinct drug-binding sites on tubulin. This result is intriguing because curacin A has little structural similarity to known natural and synthetic colchicine-site ligands. Thus, elucidation of the nature of curacin A-binding to tubulin should afford further insight into the molecular mechanism of tubulin-ligand interaction at this site, and could lead to the development of new bioactive agents.

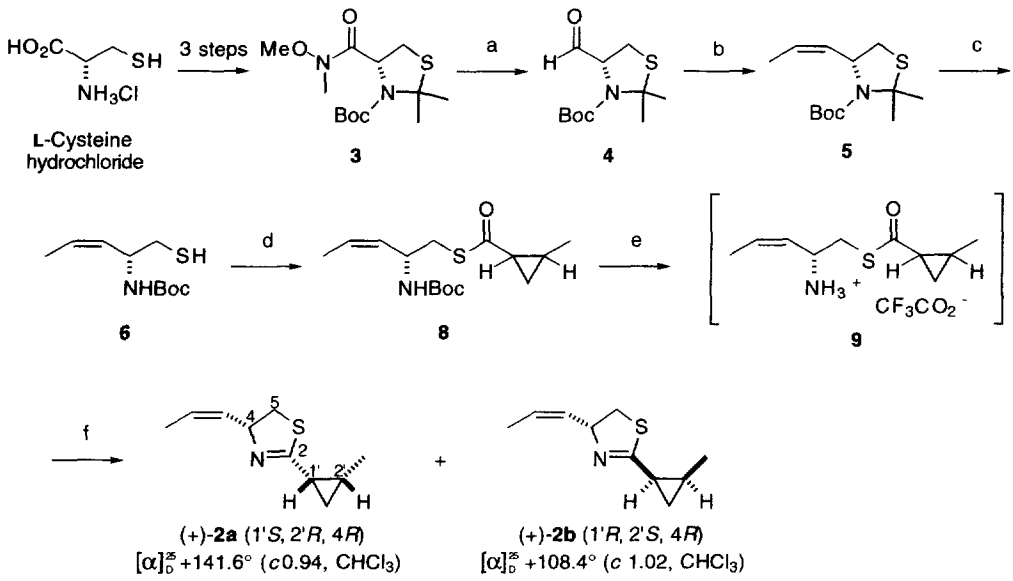
Several groups have reported synthetic approaches to curacin A.[4-6] Here we describe a highly stereocontrolled total synthesis of curacin A and synthesis of the four stereoisomers of a partial structure of curacin A, 2-(2-methyl)cyclopropyl-4-(1-propenyl)thiazoline, (+)-**2a**, (+)-**2b**, (-)-**2a** and (-)-**2b**, aiming at the elucidation of the absolute configuration at positions 2, 19 and 21 of curacin A.[5, 6d] We also discuss the structure-activity relationships of curacin A, and related molecules.

In the first paper on the structure of curacin A[3], the *E*, *E* geometry of the conjugated diene (C(7-10)) and *cis* relative configuration at the cyclopropyl moiety (C(19) and (21)) were established. Subsequently, the absolute structure of curacin A was determined to be 2*R*, 13*R*, 19*R* and 21*S* by chemical degradation and total synthesis by White *et al.*[4, 6a] In the course of our study on curacin A, we first planned to synthesize the four stereoisomers of 2-(2-methyl)cyclopropyl-4-(1-propenyl)thiazoline, (+)-**2a**, (+)-**2b**, (-)-**2a** and (-)-**2b**, since one of them should compose the partial structure of curacin A and was expected to be a significant structural element in the interaction with tubulin. We intended to define the absolute configuration at the three chiral centers of the thiazoline-methylcyclopropane moiety in curacin A by comparison of the physicochemical data of **2a** and **2b** with those of curacin A, as well as from their biological activities. In our synthesis of the thiazolines **2**, we used a selective deprotection of the *N*, *S*-acetal **5** to give the *N*-Boc amino thiol **6**, which was readily converted to the thiol ester **8**. The thiazoline ring was constructed by a facile conversion of **8** *via* the thiol ester ammonium salt **9**.[7]

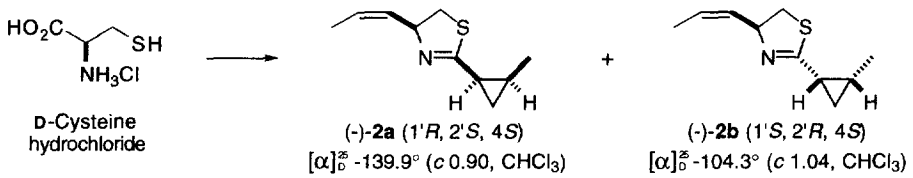
The starting material, **3**, was easily prepared from L-cysteine hydrochloride in three steps.[8, 9] Reduction of the amide **3** with $LiAlH_4$ gave the corresponding aldehyde **4** in 92% yield. Wittig reaction of **4** with ethyltriphenylphosphonium bromide gave a mixture of olefins (*Z*/*E*=11/1). The *Z*/*E* ratio of **5** was determined from the ^{1}H-NMR integration of the H-5 methylene proton peak of the thiazoline moiety at δ 3.26 ppm. The major *Z*-isomer **5** could be purified by recrystallization from aqueous MeOH in 56% yield (*Z*/*E*=56/1).[9] In deprotection of the *N*, *S*-acetal group of **5**, it was found that **5** was unstable on exposure to TFA in CH_2Cl_2 at high concentrations or for long times, and the addition of thiophenol or ethanethiol was ineffective. However, selective deprotection of the *N*, *S*-acetal group proceeded in diluted TFA in water-saturated CH_2Cl_2 to give the *N*-Boc amino thiol **6** in 64% yield. The thiol **6** was converted to the thiol ester **8** using (±)-*cis*-2-methylcyclopropanecarboxylic acid **7**[10] and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl)[11]. Deprotection of the *tert*-Boc group of **8** with TFA gave the thiol ester ammonium salt **9**, which was heated to reflux in benzene to yield the thiazolines **2a** and **2b** as a mixture of diastereomers (42% yield from **6**) containing traces of the *E*-isomer. The double bond geometry of each olefin isomer was assigned based on the ^{1}H-NMR coupling constants of 10.7 Hz (desired *Z*-isomer) and 15.1 Hz (*E*-isomer) for the olefinic protons. The mixture of diastereomers was found to be easily separable by HPLC using a TSK-gel, ODS-120T column to give (+)-**2a** ($[\alpha]_D^{25}$ +141.6° (*c* 0.94, $CHCl_3$)) and (+)-**2b** ($[\alpha]_D^{25}$ +108.4° (*c* 1.02, $CHCl_3$)). The corresponding (4*S*)-isomers were synthesized by the same procedure from D-cysteine hydrochloride to give

(-)-**2a** ($[\alpha]_D^{25}$ -139.9° (*c* 0.90, $CHCl_3$)) and (-)-**2b** ($[\alpha]_D^{25}$ -104.3° (*c* 1.04, $CHCl_3$)), respectively (**Scheme 1**).

Scheme 1

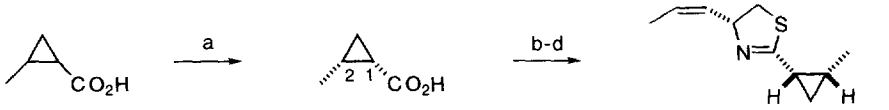


Reagents and conditions: (a) $LiAlH_4$, ether, 0°C, 0.5 h (92%); (b) $Ph_3PC_2H_5Br$, *n*-BuLi, THF, 0°C, 0.5 h, then **4**, THF, 5°C, 2.5 h, and recrystallization (56%, *Z*/*E*=56/1); (c) TFA, CH_2Cl_2, 20°C, 2 h (64%); (d) (±)-*cis*-2-methylcyclopropanecarboxylic acid (±)-**7**, BOPCl, Et_3N, CH_2Cl_2, 20°C, 5 h; (e) TFA, CH_2Cl_2, 0°C, 1.5 h; (f) benzene, reflux, 1 h (42% from **6**)



In order to identify the stereochemistry of the four isomers thus prepared, an authentic sample of (+)-**2a** ($[\alpha]_D^{25}$ +145.6° (*c* 1.025, $CHCl_3$)) was synthesized from the *N*-Boc amino thiol **6** and (+)-(1*S*, 2*R*)-2-methylcyclopropanecarboxylic acid ((+)-**7**) (**Scheme 2**). The acid (+)-**7** was prepared by optical resolution of the (±)-**7** quinine salt.[10] Recrystallization of (±)-**7** quinine salt from acetone four times gave pure colorless crystals (mp 138-140.5 °C, $[\alpha]_D^{25}$ -125.0° (*c* 0.515, $CHCl_3$)) and treatment of the crystals in aqueous HCl regenerated the desired carboxylic acid ((+)-**7**) ($[\alpha]_D^{25}$ +24.9° (*c* 0.495, 95% EtOH)). The configurations of the other three isomers, (+)-**2b**, (-)-**2a** and (-)-**2b**, could accordingly be assigned from their ^{1}H-NMR spectra and optical rotations.

Scheme 2



(±)-**7** (+)-(1*S*, 2*R*)-**7** (+)-**2a** (1'*S*, 2'*R*, 4*R*)

$[\alpha]_D^{25}$ +24.9° (*c* 0.495, 95%EtOH)

$[\alpha]_D^{25}$ +145.6° (*c* 1.025, $CHCl_3$)

Reagents: (a) quinine, acetone, crystallization, 4 times, then HCl, aq. EtOH; (b) **6**, BOPCl, Et_3N, CH_2Cl_2; (c) TFA, CH_2Cl_2; (d) benzene, reflux (34%)

^{1}H-NMR data of curacin A compared with those of the isomers of **2** showed that the chemical shifts of curacin A were not greatly different from those of (+)-**2a** and (+)-**2b**, but that the values of the coupling constants were closer to those of (+)-**2b** (**Figure 1** and **Table 1**), suggesting that the relative stereochemistry of curacin A at positions 2, 19 and 21 is the same as that of **2b**. The relatively large optical dextrorotation of (+)-**2b** ($[\alpha]_D^{25}$ +108.4° (*c* 1.02, $CHCl_3$)) was compatible with that of curacin A ($[\alpha]_D^{20}$ +62.0° (*c* 1.10, $CHCl_3$))[6b]. Based on these physicochemical data, the absolute configuration of the partial structure of curacin A was concluded to be 2*R*, 19*R* and 21*S*. Our result is in agreement with that reported independently by White *et al.*[4, 6a]

Figure 1. ^{1}H-NMR chemical shifts of (+)-**2a**, (+)-**2b** and curacin A

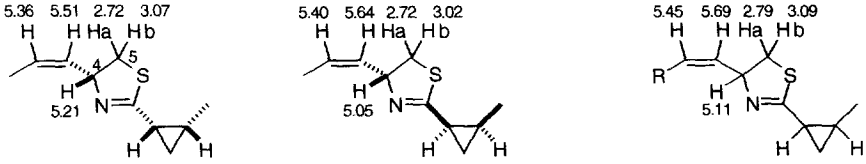


Table 1. ^{1}H-NMR coupling constants of (+)-**2a**, (+)-**2b** and curacin A

Compound	$J_{5a, 5b}$ (Hz)	$J_{5a, 4}$ (Hz)	$J_{5b, 4}$ (Hz)
(+)-**2a**	10.8	6.7	8.4
(+)-**2b**	10.8	9.8	8.3
Curacin A[a)]	10.7	10.0	-[b)]

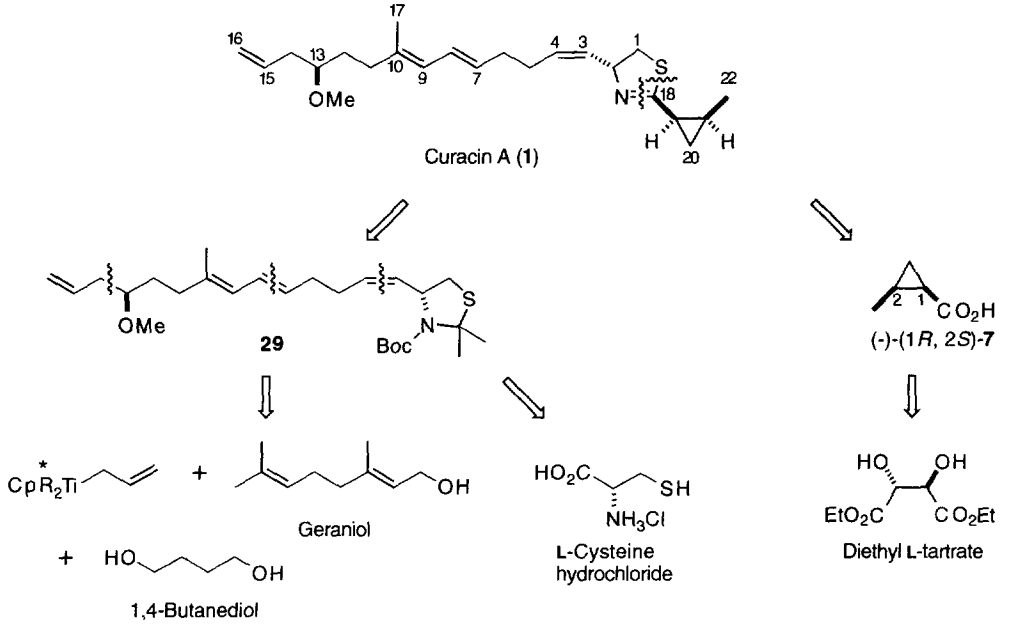
a) Reported by Gerwick *et al.*[3] b) Not available

Contrary to our expectation, none of the four isomers of **2** showed inhibitory activity either on microtubule assembly, even at 100 μM concentration under the conditions used[12], or on some cancer-derived cell lines, even at 100 μg/mL concentration. Therefore, the approach to confirm the stereochemistry of curacin A by evalution of the biological activities of **2** was not feasible.

Next, we planned an asymmetric total synthesis of curacin A (**1**). The retrosynthetic analysis and disconnections are shown in **Scheme 3**. We expected that the necessary three double bond-geometries could be prepared from geraniol (C(9-10)) by

semistabilized Wittig or Wittig-Horner reaction (C(7-8)) and Wittig reaction (C(3-4)). The chiral centers at C(2) and C(13) should be derived from a chiral synthon (L-cysteine) and an asymmetric allylation using a chiral allyltitanium reagent[13], respectively. The chiral methylcyclopropane moiety could be efficiently prepared from diethyl L-tartrate, using a double-asymmetric Simmons-Smith cyclopropanation as a key step.[14] We intended to construct the thiazoline moiety by coupling of the carboxylic acid (-)-**7** with the *N*-Boc thiazolidine **29** through selective deprotection of the *N*, *S*-acetal group, using a similar procedure to that employed for **2**. Since the chiral center attached to the nitrogen atom readily epimerizes and the thiazoline ring is unstable under basic conditions[15], this ring system should be constructed at the final stage of the total synthesis.

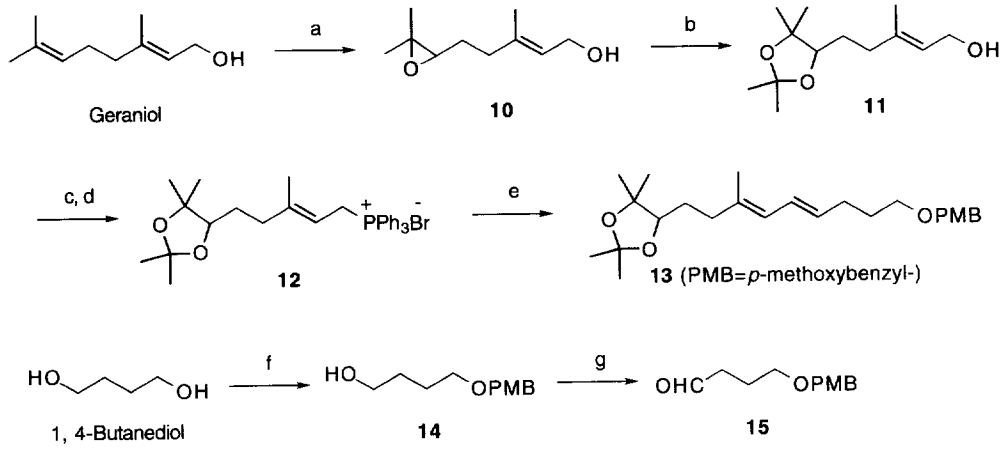
Scheme 3



In regioselective epoxidation of geraniol using the OXONE®-acetone system[16], the 2, 3:6, 7-diepoxide was obtained in 70% yield at high conversions. At moderate conversions of geraniol, however, production of the 2, 3:6, 7-diepoxide was considerably reduced and the desired 6, 7-epoxide **10** was obtained in 39% total yield (two cycle, plus 37% recovery of geraniol). Simultaneous acid-catalyzed hydrolysis and acetalization gave the 1, 3-dioxolane **11**, a synthetic equivalent of aldehyde. First, we intended to form the conjugated *E*, *E*-diene unit by Wittig reaction of **12** with **15**. Compound **11** was converted, *via* the bromide[17], to the corresponding phosphonium salt **12** in 69% yield. Monoprotection[18] of 1, 4-butanediol with *p*-methoxybenzyl chloride gave the PMB-protected alcohol **14** in 84% yield, and this was oxidized to the PMB-protected aldehyde **15** in 89% yield by Swern's method. Wittig reaction of **12** with **15** (*n*-BuLi, THF) afforded the desired diene **13** in 73% yield with low *E* selectivity (*E*/*Z*=1.9/1). The *E*/*Z* ratio of **13** was determined from the ^{1}H-NMR integration of the olefinic protons at H-6 (the *E*-isomer, δ 5.83 ppm; the *Z*-isomer, δ 6.12 ppm). The mixture of olefins was found to be separable by HPLC using a packed silica gel column to give the desired *E*-isomer (**Scheme 4**). In this Wittig reaction, the influence of a number of factors, such as solvent

(ether, CH_2Cl_2, toluene and DME), base (KHMDS, NaHMDS and *t*-BuOK), inorganic halides[19] (LiI), excess reactant, reaction time and temperature, on the reaction stereochemistry was investigated. However, all attempts to improve the stereoselectivity were unsuccessful.

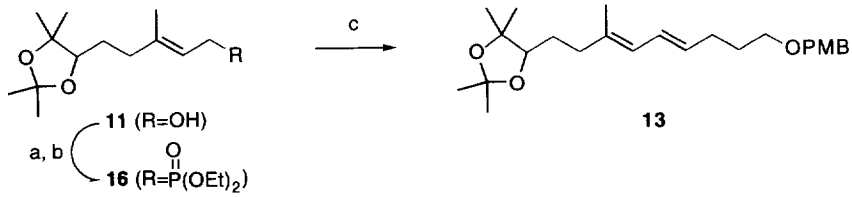
Scheme 4



Reagents and conditions: (a) OXONE®, acetone-CH_2Cl_2/phosphate buffer, pH 7.5~8.0, 0°C, 2 h (39% and recovery of geraniol, 37%); (b) PTSA, aq. acetone, 20°C, 2 h (67%); (c) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1 h; (d) PPh_3, benzene, 20°C, 16 h (69% from **11**); (e) **12**, *n*-BuLi, THF, -78°C, 0.5 h, then **15**, THF, -78-20°C, 16 h (73%, *E*/*Z*=1.9/1), and HPLC separation; (f) PMBCl, NaH, DMF, -15-20°C, 1.5 h (84%); (g) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -50-20°C, 1.5 h (89%)

In order to obtain the diene **13** with higher *E* selectivity, Wittig-Horner reaction[20] of the corresponding phosphonate **16** with **15** was employed. Compound **11** was converted, *via* the bromide, to the phosphonate **16** in 75% yield. Wittig-Horner reaction of **16** with the aldehyde **15** afforded the diene **13** (51%, *E*/*Z*=8.5/1) (**Scheme 5**). In this reaction, the desired diene could be obtained only when *t*-BuOK was added to a mixture of **16** and **15** in THF. Since the aldehyde **15** was unstable under this reaction condition, the use of excess amounts of **15** improved the yield.

Scheme 5

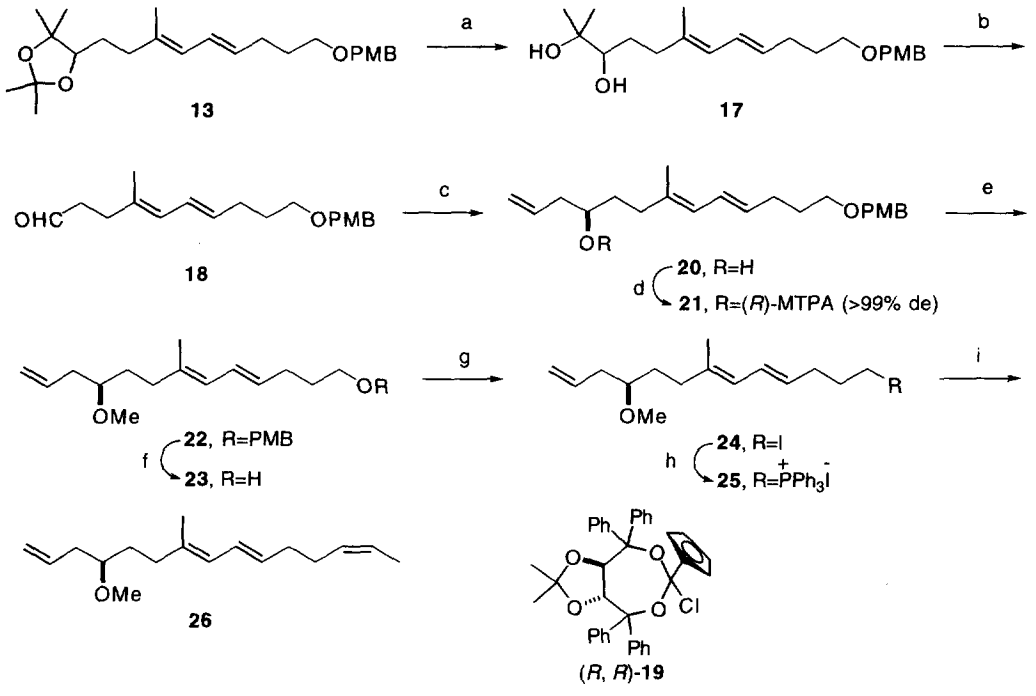


Reagents and conditions: (a) CBr_4, Ph_3P, CH_2Cl_2, 0°C, 1 h; (b) $(EtO)_3P$, benzene, reflux, 2.5 h (75% from **11**); (c) **15**, *t*-BuOK, THF, 20°C, 1.5 h (51%, *E*/*Z*=8.5/1 and recovery of **16**, 13%)

The side chain of **1** was finally synthesized as shown in **Scheme 6**. Deacetalization of **13** with PTSA (two cycle) followed by oxidative cleavage of the diol **17** (three cycle) gave the aldehyde **18** in 93% total yield. The asymmetric allylation of **18** with a chiral allyltitanium reagent[13], prepared from [(4*R*, 5*R*)-2,

2-dimethyl-1, 3-dioxolane-4, 5-bis(diphenylmethoxy)]cyclopentadienyl-chlorotitanium ((*R*, *R*)-**19**) and allylmagnesium chloride, proceeded cleanly at -78°C to give the homoallylic alcohol **20** in 95% yield and with excellent enantioselectivity (>99% ee), as determined from the ^{1}H- and ^{13}C-NMR spectra of its Mosher ester **21** (**Figure 2**).

Scheme 6

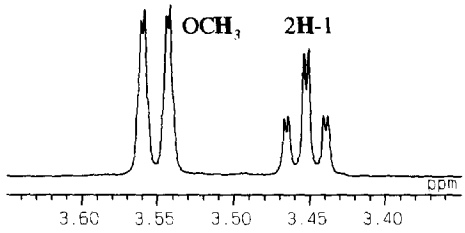


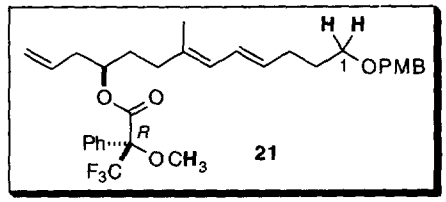
Reagents and conditions: (a) PTSA, aq. MeOH, 20°C, 5 h (99%); (b) $NaIO_4$, aq. acetone, 20°C, 2 h (94%); (c) allylMgCl, (*R*, *R*)-**19**, THF, 0°C, 1 h, then **18**, THF, -78°C, 1.5 h (95%); (d) (*S*)-(+)-MTPACl, pyridine, CH_2Cl_2, 20°C, 0.5 h (66%); (e) MeI, NaH, DMF, 20°C, 2.5 h (89%); (f) $MgBr_2{\cdot}OEt_2$, Me_2S, CH_2Cl_2, 20°C, 2 h (76% and recovery of **22**, 6%); (g) MsCl, pyridine, 0°C, 1 h, then NaI, acetone, reflux, 2 h (87%); (h)Ph_3P, MeCN, reflux, 7 h (quant.); (i) **25**, LiHMDS, THF, -78°C, 0.5 h, then MeCHO, THF, -78-0°C, 1.5 h (41%)

The alcohol **20** was converted to its methyl ether **22** in 89% yield. In deprotection of the PMB group in **22**, treatment with DDQ or CAN resulted a complex mixture, but treatment with TFA in CH_2Cl_2[21] gave a mixture of the desired alcohol **23** and decomposition products. We next sought a suitable condition to cleave the PMB ether in **22** by using a variety of combinations of hard Lewis acids and soft nucleophiles[22], and found that $MgBr_2{\cdot}OEt_2$-Me_2S treatment in CH_2Cl_2 was optimal to give the known and desired alcohol (-)-**23** in 76% total yield (five cycle).[6a, 23] In ether, this system resulted in complete recovery of the starting material, and the use of ethanethiol instead of Me_2S gave a mixture containing **23** and ethanethiol-adducts. The alcohol **23** was converted, *via* the iodide **24**, to the phosphonium salt **25** according to the reported procedure[6a]. In order to obtain information on the structure-activity relationships of curacin A, the tetraene **26**, a lipid side chain moiety of curacin A, was also prepared through Wittig reaction of **25** with acetaldehyde in 41% yield (**Scheme 6**).

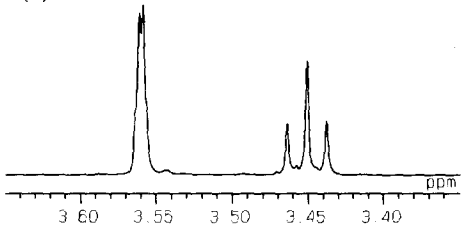
Figure 2. ^{1}H-NMR spectra of the Mosher ester **21** (500 MHz, $CDCl_3$)

(a) from racemic **20**



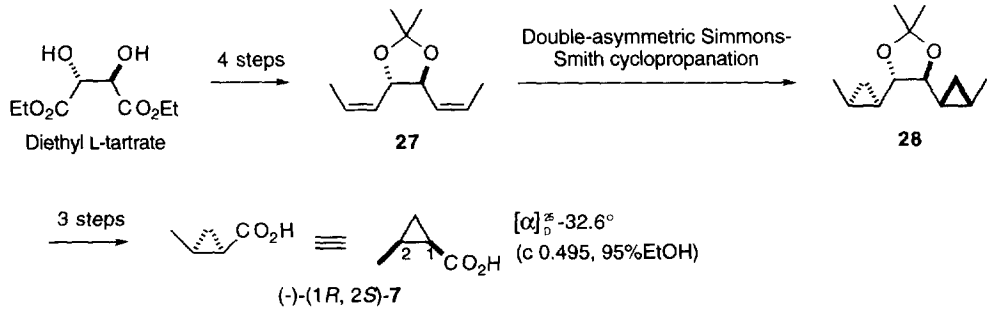


(b) from (+)-**20**



Asymmetric synthesis of the cyclopropane moiety of **1** is shown in **Scheme 7**. We have developed a versatile method for the synthesis of enantiomerically pure *cis*-2-methylcyclopropanecarboxylic acid **7**.[14] Double-asymmetric Simmons-Smith cyclopropanation of the diene **27** derived from diethyl L-tartrate in 4 steps proceeded with excellent diasterofacial selectivity (>99% de) to give the dicyclopropane **28**, which was converted to the desired carboxylic acid (-)-**7** in 3 steps.

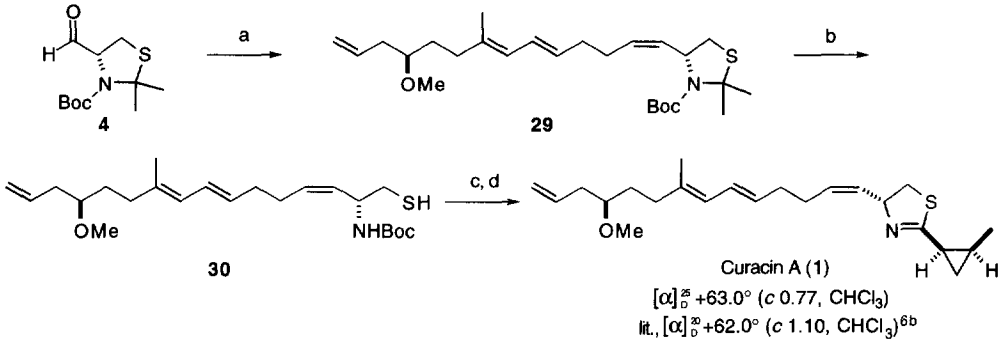
Scheme 7



The total synthesis of curacin A was completed as shown in **Scheme 8**. Wittig reaction of the phosphonium salt **25** with the aldehyde **4** afforded the thiazolidine **29** in 60% yield. None of the *E*-isomer was detected by ^{1}H-NMR analysis. The ylide generated from **25** with LiHMDS was very sensitive to reaction temperature and moisture. Therefore the phosphonium salt **25** was azeotropically dehydrated by refluxing in dry benzene for 1 h just before use, and a liquid N_2-ethanol cooling bath was used to keep the temperature of the reaction mixture at < -78 °C during additions of LiHMDS and the aldehyde **4**. The thiazoline moiety of **1** was synthesized from the *N*-Boc thiazolidine **29** in a stepwise manner.[5,7] Selective deprotection of the *N*, *S*-acetal group of **29** was carried out in diluted TFA in water-saturated CH_2Cl_2 to give the *N*-Boc amino thiol

30 (three cycle, 54% total yield), which was converted to the corresponding thiol ester using the carboxylic acid (-)-**7** and bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl). Deprotection of the *tert*-Boc group of the thiol ester, followed by refluxing in benzene, gave curacin A in 10% yield from **29**. The physicochemical properties (^{1}H- and ^{13}C-NMR spectra, optical rotation) of the synthesized curacin A are identical to those reported.[3, 6b]

Scheme 8



Reagents and conditions: (a) **25**, LiHMDS, THF, -78°C, 0.5 h, then **4**, THF, -78-0°C, 2 h (60% and recovery of **4**, 25%); (b) TFA, CH_2Cl_2, 20°C, 6 h; (c) (-)-**7**, BOPCl, Et_3N, CH_2Cl_2, 20°C, 3 h; (d) TFA, CH_2Cl_2, 20°C, 2 h, then benzene, reflux, 2.5 h (10% from **29**)

The effects of the synthesized curacin A and the related compounds, **2**, **22**, **23**, **26** and **29**, on microtubule assembly were examined. Curacin A showed high anti-tubulin activity (IC_{50}=2.5 μM) under the conditions used[12], whereas the PMB ether **22**, the alcohol **23**, the tetraene **26**, the *N*-Boc thiazolidine **29** and all the diastereomers of the thiazoline **2** did not inhibit tubulin polymerization. These results demonstrate that the combination of heterocyclic and lipid side chain moieties in curacin A is important for its anti-tubulin activity.

In conclusion, we propose the absolute configurations of three chiral centers in curacin A to be 2*R*, 19*R* and 21*S*, based on the spectral and physical data of four stereoisomers, (+)-**2a**, (+)-**2b**, (-)-**2a** and (-)-**2b**, synthesized as a partial structure of curacin A. We also achieved the total synthesis of curacin A in a highly stereo-controlled manner. Further studies on the structure-activity relationship of curacin A are in progress.

Acknowledgement

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Experimental Section

All ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ with TMS and the solvent peak as internal standards, and recorded on a JEOL JMN-A500 spectrometer. IR spectra were recorded on a JASCO A-102

infrared spectrophotometer. Mass spectra (MS) were obtained on a JEOL JMS-HX110 spectrometer. Optical rotations were measured on a JASCO DIP-100 digital polarimeter. All reactions were carried out in an atmosphere of dry argon at room temperature unless otherwise stated. Column chromatography was carried out on Wakogel C-200. Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates, and compounds were visualized by UV illumination (254 nm) or by heating to 150 °C after spraying phosphomolybdic acid in ethanol. Dry diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium-benzophenone ketyl and dry benzene (PhH) and dichloromethane (CH_2Cl_2) were distilled from phosphorus pentoxide and calcium hydride, respectively under an inert atmosphere. Anhydrous *N*, *N*-dimethylformamide (DMF) and OXONE® (containing potassium peroxomonosulfate, $KHSO_5$) were purchased from Aldrich. [(4*R*, 5*R*)-2, 2-Dimethyl-1, 3-dioxolane-4, 5-bis(diphenylmethoxy)]cyclopentadienyl-chlorotitanium, (*R*, *R*)-**19** was purchased from Fluka AG. All other organic solvents and reagents were obtained from commercial sources and used without further purification. Organic extracts were dried over magnesium sulfate ($MgSO_4$), filtered, and concentrated using a rotary evaporator at < 40 °C bath temperature. Involatile oils and solids were vacuum dried at < 2 mmHg.

(4*R*)-*N*-(*tert*-Butyloxy)carbonyl-2, 2-dimethyl-4-(*N*-methoxy-*N*-methylcarbamoyl)thiazolidine (3).

The title compound was prepared according to the method of Duthaler[9]: mp 97.0-97.5 °C, lit. mp 99.0-99.5 °C[9]; $[\alpha]_D^{25}$ -65.3° (*c* 1.02, $CHCl_3$), lit. $[\alpha]_D^{20}$ -64.1° (*c* 1.25, $CHCl_3$)[9]; IR ($CHCl_3$) 3000, 2950, 1700, 1680, 1460, 1390, 1370, 1320, 1170, 1130, 1090, 1070, 1010, 860 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$, 2 rotamer) δ 1.41 and 1.49 (s, 9H, $(CH_3)_3C$), 1.78, 1.83, 1.89 and 1.91 (s, 6H, $(CH_3)_2$-2), 2.99 (dd, 1H, J=12.0, 3.6 Hz, H-5), 3.22 (s, 3H, NCH_3), 3.34 (dd, 1H, J=12.0, 7.3 Hz, H-5), 3.73 and 3.78 (s, 3H, $NOCH_3$), 5.04 and 5.17 (m, 1H, H-4); FABMS *m/z*: 305 $(M+H)^+$; HRFABMS calcd. for $C_{13}H_{25}O_4N_2S$ $(M+H)^+$ 305.1535, found 305.1546.

(4*S*)-enantiomer was prepared according to the method above: mp 98.0-98.5 °C; $[\alpha]_D^{25}$ +62.4° (*c* 1.02, $CHCl_3$)

(4*R*)-*N*-(*tert*-Butyloxy)carbonyl-2, 2-dimethyl-4-formylthiazolidine (4).

$LiAlH_4$ (2.18 g, 57.4 mmol) was added portionwise to a solution of **3** (25.0 g, 82.1 mmol) in dry Et_2O (300 mL) at 0 °C. The reaction mixture was stirred vigorously for 0.5 h at 0 °C and diluted with Et_2O (300 mL). After the slow addition of aqueous $KHSO_4$ (5.0 g, 36.7 mmol/H_2O 15 mL), the resulting slurry was filtered through Celite and the precipitate was washed well with Et_2O. The combined filtrates were washed with aqueous HCl (0.1 N, 200 mL), saturated aqueous $NaHCO_3$ and NaCl (200 mL), dried and concentrated. Kugelrohr distillation of the residue (150-180 °C, 1.5 mmHg) gave **4** (18.54 g, 92% yield) as a colorless oil: $[\alpha]_D^{25}$ -97.1° (*c* 1.01, $CHCl_3$), lit. $[\alpha]_D^{20}$ -99.1° (*c* 0.94, $CHCl_3$)[9]; IR ($CHCl_3$) 3000, 2950, 1750, 1710, 1680, 1460, 1400, 1370, 1290, 1170, 1130, 1100, 1080, 860 cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6, 70 °C) δ 1.34 (s, 9H, $(CH_3)_3C$), 1.70 and 1.79 (s, 6H, $(CH_3)_2$-2), 2.57 (dd, 1H, J=12.0, 6.6 Hz, H-5), 2.61 (dd, 1H, J=12.0, 3.0 Hz, H-5), 4.30 (br, 1H, H-4), 9.38 (s, 1H, CHO); FABMS *m/z*: 246 $(M+H)^+$; HRFABMS calcd. for $C_{11}H_{20}O_3NS$ $(M+H)^+$ 246.1164, found 246.1170.

(4*S*)-enantiomer was prepared according to the method above: $[\alpha]_D^{25}$ +98.3° (*c* 1.03, $CHCl_3$)

(4*R*)-*N*-(*tert*-Butyloxy)carbonyl-2, 2-dimethyl-4-[(1*Z*)-1-propen-1-yl]thiazolidine (5).

A suspension of ethyltriphenylphosphonium bromide (37.6 g, 0.101 mol) in dry THF (370 mL) was cooled to 0 °C and *n*-BuLi (58.6 mL, 1.6 M in hexane, 93.8 mmol) was added dropwise to the suspension. The reaction mixture was stirred for 0.5 h at 0 °C. A solution of **4** (18.41 g, 75.0 mmol) in dry THF (74 mL) was added dropwise to the resulting dark red solution at 0 °C over 20 min. The reaction mixture was stirred for 2.5 h at 5 °C and quenched slowly by the addition of a mixed solution of aqueous NaOH (1 M, 110 mL) and NaH_2PO_4 (1 M, 190 mL). The resulting mixture was filtered and the filtrate was extracted with EtOAc (2x220 mL). The combined organic phases were dried and concentrated to afford a white insoluble solid, which was washed with hexane/EtOAc (10/1, 350 mL). The washing solution was concentrated and

chromatography of the residue on silica gel (645 g, 30/1 hexane/EtOAc) gave **5** (16.74 g, 87% yield, *E*/*Z*=10.7/1) as a colorless solid. Recrystallization of the solid from aqueous MeOH (2.7/1 MeOH/H_2O, 110 mL) at 0 °C gave **5** (10.77 g, 56% yield, *E*/*Z*=55.9/1) as pure clear, colorless crystals: mp 33.0-33.5 °C, lit. mp 34.0 °C[9]; $[\alpha]_D^{25}$ +46.7° (*c* 0.985, $CHCl_3$), lit. $[\alpha]_D^{20}$ +48.9° (*c* 0.45, $CHCl_3$)[9]; IR ($CHCl_3$) 3000, 2950, 1690, 1480, 1380, 1340, 1300, 1190, 1120, 1090, 1000, 940, 860 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.45 (s 9H, $(CH_3)_3C$), 1.71 (dd, 3H, J=6.9, 1.5 Hz, CH_3-2'), 1.78 and 1.80 (s, 6H, $(CH_3)_2$-2), 2.58(dd, 1H, J=11.6, 2.1 Hz, H-5), 3.26 (dd, 1H, J=11.6, 6.2 Hz, H-5), 5.11 (br, 1H, H-4), 5.50 (dq, 1H, J=10.8, 6.9 Hz, H-2'), 5.68 (ddq, 1H, J=10.8, 8.9, 1.5 Hz, H-1'); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.12, 28.50 (x3), 29.65, 30.13, 34.06, 60.79, 70.25, 79.91, 124.44, 132.11, 152.46; FABMS *m/z*: 258 $(M+H)^+$; HRFABMS calcd. for $C_{13}H_{24}O_2NS$ $(M+H)^+$ 258.1528, found 258.1524; Anal. Calcd for $C_{13}H_{23}O_2NS$: C, 60.66; H, 9.01; N, 5.44; S, 12.46. Found: C, 60.84; H, 9.05; N, 5.39; S, 12.28.

(4*S*)-enantiomer was prepared according to the method above: mp 31.5-32.0 °C; $[\alpha]_D^{25}$ -45.6° (*c* 0.99, $CHCl_3$)

(3*Z*, 2*R*)-*N*-(*tert*-Butyloxy)carbonyl-2-amino-3-pentenethiol (6).

TFA (4.49 mL, 58.3 mmol) was added to a solution of **5** (1.00 g, 3.89 mmol) in water-saturated CH_2Cl_2 (250 mL). The reaction mixture was stirred for 2 h and quenched by the addition of H_2O (50 mL). The organic phase was washed repeatedly with H_2O (50 mL), dried and concentrated. Chromatography of the residue on silica gel (70 g, 15/1 hexane/EtOAc) gave **6** (543.0 mg, 64% yield) as a colorless oil: $[\alpha]_D^{25}$ +16.8° (*c* 0.485, $CHCl_3$); IR ($CHCl_3$) 3450, 2970, 2930, 1710, 1490, 1390, 1370, 1330, 1310, 1230, 1160, 1050, 1020, 860 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.45 (s 9H, $(CH_3)_3C$), 1.73 (dd, 3H, J=7.0, 1.8 Hz, CH_3-4), 2.65(ddd, 1H, J=13.4, 8.5, 6.5 Hz, H-1), 2.73 (ddd, 1H, J=13.4, 8.5, 4.6 Hz, H-1), 4.55 (m, 1H, H-2), 5.30 (ddq, 1H, J=10.8, 8.9, 1.8 Hz, H-3), 5.68 (dqd, 1H, J=10.8, 7.0, 1.1 Hz, H-4); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.60, 28.34 (x3), 29.98, 49.16, 79.54, 128.44, 128.71, 155.05; FABMS *m/z*: 218 $(M+H)^+$; HRFABMS calcd. for $C_{10}H_{20}O_2NS$ $(M+H)^+$ 218.1215, found 218.1238; Anal. Calcd for $C_{10}H_{19}O_2NS$: C, 55.27; H, 8.81; N, 6.44; S, 14.75. Found: C, 55.42; H, 8.92; N, 6.33; S, 14.50.

(4*S*)-enantiomer was prepared according to the method above: $[\alpha]_D^{25}$ -16.0° (*c* 0.825, $CHCl_3$)

(4*R*)-2-[(1*S*, 2*R*)-2-methylcyclopropyl]-4-[(1*Z*)-1-propen-1-yl]thiazoline (+)-2a and **(4*R*)-2-[(1*R*, 2*S*)-2-methylcyclopropyl]-4-[(1*Z*)-1-propen-1-yl]thiazoline (+)-2b.**

Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 2.32 g, 9.11 mmol) was added to a solution of **6** (1.59 g, 7.32 mmol), (±)-*cis*-2-methylcyclopropanecarboxylic acid **7** (795.4 mg, 7.94 mmol) and Et_3N (2.53 mL, 18.2 mmol) in dry CH_2Cl_2 (32 mL). The reaction mixture was stirred for 5 h and quenched by the addition of aqueous HCl (5%, 50 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and NaCl (50 mL), dried and concentrated. Chromatography of the residue on silica gel (165 g, 15/1 hexane/EtOAc) gave **8** (1.57 g, 72% yield) as a white gummy solid. A solution of the foregoing thiol ester **8** (1.54 g, 5.14 mmol) in CH_2Cl_2 (39 mL) was cooled to 0 °C and TFA (7.95 mL, 0.103 mol) was added to the solution. The reaction mixture was stirred for 1.5 h at 0 °C and concentrated under reduced pressure. Dry benzene (77 mL) was added to the resulting residue and concentrated twice for replacing the reaction solvent with benzene. A solution of the residue containing the corresponding thiol ester ammonium salt **9** in dry benzene (77 mL) was heated to reflux for 1 h and quenched by the addition of saturated aqueous $NaHCO_3$ (39 mL). The organic phase was washed with saturated aqueous NaCl (39 mL), dried and concentrated. Chromatography of the residue on silica gel (86 g, 20/1 to 5/1 hexane/EtOAc) gave a mixture of (+)-**2a** and (+)-**2b** (546.3 mg, 42% yield from **6**). HPLC purification of the mixture (444.0 mg) using a TSK-gel, ODS-120T column (21.5 ϕ x 600 mm, eluent: 35/65 MeCN/H_2O, detector: UV 235 nm, flow rate: 20 mL/min) gave (+)-**2a** (32.0 mg) and (+)-**2b** (45.2 mg) as a colorless oil, respectively: (+)-**2a**: $[\alpha]_D^{25}$ +141.6° (*c* 0.94, $CHCl_3$); IR ($CHCl_3$) 2970, 2900, 1620, 1440, 1390, 1290, 1180, 1140, 1120, 1080, 1010, 970, 920 cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 0.72 (td, 1H, J=8.4, 4.3 Hz, H-3'), 0.96 (tq, 1H, J=8.4, 6.3 Hz, H-2'), 1.19 (d, 3H, J=6.3 Hz, CH_3-2'), 1.15-1.19 (m, 1H, H-3'), 1.45 (dd, 3H, J=6.9, 1.7 Hz, CH_3-2"), 1.64 (tdd, 1H, J=8.4, 5.5, 1.2 Hz, H-1'), 2.72 (dd, 1H,

J=10.8, 6.7 Hz, H-5), 3.07 (dd, 1H, J=10.8, 8.4 Hz, H-5), 5.21 (dddt, 1H, J=8.8, 8.4, 6.7, 1.2 Hz, H-4, observed as brq signal), 5.36 (dqd, 1H, J=10.7, 6.9, 1.2 Hz, H-2"), 5.51 (ddq, 1H, J=10.7, 8.8, 1.8 Hz, H-1"); ^{13}C-NMR (125 MHz, C_6D_6) δ 12.35 (CH_3-2'), 13.27 (CH_3-2"), 14.19 (C-3'), 16.02 (C-2'), 19.96 (C-1'), 39.90 (C-5), 73.88 (C-4), 125.53 (C-2"), 131.58 (C- 1"), 168.06 (C-2); FABMS *m/z*: 182 $(M+H)^+$; HRFABMS calcd. for $C_{10}H_{16}NS$ $(M+H)^+$ 182.1003, found 182.0992. (+)-**2b**: $[\alpha]_D^{25}$ +108.4° (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 2970, 2900, 1620, 1440, 1390, 1290, 1180, 1150, 1130, 1080, 1020, 970, 920 cm^{-1}; ^{1}H-NMR (500 MHz, C_6D_6) δ 0.71 (td, 1H, J=8.4, 4.3 Hz, H-3'), 0.95 (tq, 1H, J=8.4, 6.3 Hz, H-2'), 1.17 (d, 3H, J=6.3 Hz, CH_3-2'), 1.14-1.18 (m, 1H, H-3'), 1.42 (dd, 3H, J=6.9, 1.8 Hz, CH_3-2"), 1.67 (td, 1H, J=8.4, 5.3 Hz, H-1'), 2.72 (dd, 1H, J=10.8, 9.8 Hz, H-5), 3.02 (dd, 1H, J=10.8, 8.3 Hz, H-5), 5.05 (dddd, 1H, J=9.8, 8.8, 8.3, 1.2 Hz, H-4, observed as brq signal), 5.40 (dqd, 1H, J=10.7, 6.9, 1.2 Hz, H-2"), 5.64 (ddq, 1H, J=10.7, 8.8, 1.8 Hz, H-1"); ^{13}C-NMR (125 MHz, C_6D_6) δ 12.34 (CH_3-2'), 13.24 (CH_3-2"), 14.22 (C-3'), 15.97 (C-2'), 20.15 (C-1'), 39.77 (C-5), 74.00 (C-4), 125.61 (C-2"), 131.92 (C-1"), 168.34 (C-2); FABMS *m/z*: 182 $(M+H)^+$; HRFABMS calcd. for $C_{10}H_{16}NS$ $(M+H)^+$ 182.1003, found 182.0995.

(4*S*)-2-[(1*R*, 2*S*)-2-methylcyclopropyl]-4-[(1*Z*)-1-propen-1-yl]thiazoline (-)-2a and **(4*S*)-2-[(1*S*, 2*R*)-2-methylcyclopropyl]-4-[(1*Z*)-1-propen-1-yl]thiazoline (-)-2b.**

By the procedure described for the preparation of (+)-**2a** and (+)-**2b**, (-)-**6** was converted to a mixture of diastereomers of (-)-**2** and HPLC purification of the mixture (98.3 mg) under the same condition shown above gave (-)-**2a** (25.2 mg) and (-)-**2b** (24.6 mg) as a colorless oil, respectively: (-)-**2a**: $[\alpha]_D^{25}$ -139.9° (*c* 0.90, $CHCl_3$) (-)-**2b**: $[\alpha]_D^{25}$ -104.3° (*c* 1.04, $CHCl_3$)

(4*R*)-2-[(1*S*, 2*R*)-2-methylcyclopropyl]-4-[(1*Z*)-1-propen-1-yl]thiazoline (+)-2a.

By the procedure described for the preparation of **2**, (+)-**6** (244.6 mg, 1.13 mmol) was converted to (+)-**2a** (70.3 mg, 34% yield) as a major product, using (+)-(1*S*, 2*R*)-2-methylcyclopropanecarboxylic acid (+)-**7** ($[\alpha]_D^{25}$ +24.9° (*c* 0.495, 95% EtOH)) prepared according to the method of Bergman[10]. HPLC purification of the resulting residue (70.3 mg) under the same condition shown above gave (+)-**2a** (34.0 mg) as a colorless oil: $[\alpha]_D^{25}$ +145.6° (*c* 1.025, $CHCl_3$)

(2*E*)-3, 7-dimethyl-6, 7-epoxy-2-octen-1-ol (10).

The title compound was prepared according to the following procedure from geraniol.[16] Geraniol (25.00 g, 0.162 mol) was dissolved in CH_2Cl_2 (375 mL), acetone (375 mL) and buffered water (pH 7.5 adjusted by 0.2 M KH_2PO_4 and 0.2M Na_2HPO_4, 500 mL) and the reaction mixture was cooled to 0 °C. A freshly prepared solution of OXONE® (containng potassium peroxomonosulfate, $KHSO_5$, 29.89 g, 48.6 mmol) in H_2O (150 mL) was added dropwise to the biphasic mixture during 1 h at 0 °C. The reaction mixture was stirred for 2 h at 0 °C. The apparent pH of the mixture was monitored and kept constant at pH 7.5-8.0 by the addition of aqueous KOH (3 N) by use of a pH stat during the entire reaction time. Then the mixture was quenched by the addition of aqueous $Na_2S_2O_3 \cdot 5H_2O$ (4.02 g/H_2O 50 mL). The aqueous phase was extracted with CH_2Cl_2 (2x100mL), and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (625 g, 3/1 to 2/1 hexane/EtOAc), followed by Kugelrohr distillation (160-180 °C, 1-2 mmHg) gave **10** (4.28 g, 16% yield) as a pale yellow oil, with recovery of geraniol (17.03 g, 68%) and a mixture of **10** and the 2, 3-epoxide (2.71 g). The same procedure with the recovered geraniol was carried out again and chromatography of the residue containing **10** on silica gel (2 times, 595 g and 164 g) gave **10** (10.66 g, 39% total yield), with recovery of geraniol (9.20 g, 37%): IR ($CHCl_3$) 3630, 3470 (broad), 2980, 2950, 2900, 1670, 1450, 1390, 1330, 1230, 1120, 1050, 1000, 870 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H, CH_3-7), 1.31 (s, 3H, H-8), 1.66 (m, 2H, H-5), 1.70 (d, 3H, J=1.4 Hz, CH_3-3), 2.18 (m, 2H, H-4), 2.71 (t, 1H, J=6.2 Hz, H-6), 4.17 (d, 2H, J=6.9 Hz, H-1), 5.46 (tq, 1H, J=6.9, 1.4 Hz, H-2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.19, 18.68, 24.78, 27.09, 36.19, 58.35, 59.16, 64.00, 124.02, 138.41; FABMS *m/z*: 153 $(M-OH)^+$; HRFABMS calcd. for $C_{10}H_{17}O$ $(M-OH)^+$ 153.1279, found 153.1276; Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.68; H, 10.76.

(2*E*)-3-Methyl-5-(2, 2, 5, 5-tetramethyl-1, 3-dioxolan-4-yl)-2-penten-1-ol (11).

A solution of **10** (10.43 g, 61.3 mmol) and TsOH·H_2O (11.65 g, 61.2 mmol) in aqueous acetone (9/1 acetone/H_2O, 260 mL) was stirred for 2 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ (5.15 g, 61.3 mmol/H_2O 100mL) and concentrated. After the addition of NaCl (10 g), the resulting mixture was extracted with EtOAc (3x100 mL) and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (2 times, 521 g and 319 g, 3/1 hexane/EtOAc), followed by Kugelrohr distillation (160-180 °C, 1-2 mmHg) gave **11** (9.43 g, 67% yield) as a colorless oil: IR ($CHCl_3$) 3630, 3000, 2950, 2900, 1450, 1380, 1370, 1220, 1200, 1120, 1060, 1000, 910, 850 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.08, 1.23, 1.31 and 1.40 (s, 12H, $(CH_3)_2$-2' and $(CH_3)_2$-5'), 1.48 (dddd, 1H, J=13.6, 10.8, 6.0, 3.4 Hz, H-5), 1.58-1.68 (m, 1H, H-5), 1.68 (d, 3H, J=1.2 Hz, CH_3-3), 2.05 (ddd, 1H, J=14.2, 10.4, 6.0 Hz, H-4), 2.25 (ddd, 1H, J=14.2, 10.8, 4.9 Hz, H-4), 3.64 (dd, 1H, J=9.5, 3.4 Hz, H-4'), 4.14 (d, 2H, J=6.9 Hz, H-1), 5.44 (tq, 1H, J=6.9, 1.2 Hz, H-2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.32, 22.90, 26.01, 26.85, 27.53, 28.53, 36.62, 59.28, 80.10, 82.88, 106.55, 123.66, 139.00; FABMS *m/z*: 229 $(M+H)^+$; HRFABMS calcd. for $C_{13}H_{25}O_3$ $(M+H)^+$ 229.1804, found 229.1786; Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60. Found: C, 68.24; H, 10.63.

(2*E*)-3-Methyl-5-(2, 2, 5, 5-tetramethyl-1, 3-dioxolan-4-yl)-2-penten-1-yl Triphenylphosphonium Bromide (12).

CBr_4 (13.34 g, 40.2 mmol) and PPh_3 (10.55 g, 40.2 mmol) were added to a solution of **11** (7.99 g, 35.0 mmol) in dry CH_2Cl_2 (80 mL) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. After evaporation of the solvent, the residue was triturated repeatedly with Et_2O (4x80 mL) and filtered. The combined filtrates were concentrated and another PPh_3 (13.76 g, 52.5 mmol) was added to a solution of the residue containing the corresponding bromide in dry benzene (80 mL). The reaction mixture was stirred for 16 h and filtered. The obtained precipitate was washed with Et_2O (2x250 mL) and dried under vacuum at 50 °C to give **12** (13.33 g, 69% yield from **11**) as a white solid: mp 154.0-155.5 °C; IR ($CHCl_3$) 3670, 3400 (broad), 3050, 2960, 2870, 1620, 1590, 1440, 1370, 1220, 1200, 1120, 1000, 910, 850 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.04, 1.19, 1.26 (s, each 3H) and 1.38 (s, 6H, $(CH_3)_2$-2', $(CH_3)_2$-5' and CH_3-3), 1.34-1.50 (m, 2H, H-5), 1.99 (ddd, 1H, J=19.5, 10.5, 4.5 Hz, H-4), 2.20 (ddd, 1H, J=19.5, 10.5, 4.5 Hz, H-4), 3.54 (dd, 1H, J=9.5, 3.0 Hz, H-4'), 4.69 (td, 1H, J=15.5, 7.5 Hz, H-1), 4.79 (td, 1H, J=15.5, 7.5 Hz, H-1), 5.19 (m, 1H, H-2), 7.68 (td, 6H, J=8.0, 3.5 Hz), 7.79 (tq, 3H, J=8.0, 1.5 Hz) and 7.89 (ddd, 6H, J=12.5, 8.0, 1.5 Hz, C_6H_5x3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 17.00, 22.82, 24.40 (d, J=48.1 Hz), 25.95, 26.81, 27.41, 28.44, 37.13, 80.00, 82.81, 106.53, 108.65 (d, J=7.4 Hz), 118.25 (d, J=85.1 Hz, x3), 130.25 (d, J=11.1 Hz, x6), 133.82 (d, J=9.3 Hz, x6), 134.93 (x3), 146.63 (d, J=12.6 Hz); FABMS *m/z*: 473 $(M-Br)^+$; HRFABMS calcd. for $C_{31}H_{38}O_2P$ $(M-Br)^+$ 473.2609, found 473.2628; Anal. Calcd for $C_{31}H_{38}O_2BrP·1/2H_2O$: C, 66.19; H, 6.99. Found: C, 66.26; H, 6.81.

4-(4-Methoxybenzyl)oxy-1-butanol (14).

A solution of 1, 4-butanediol (7.00 g, 77.7 mmol) in anhydrous DMF (35 mL) was cooled to -15 °C and a solution of NaH (60% oil suspension, 3.42 g, 85.5 mmol) in anhydrous DMF (35 mL) was added. The reaction mixture was stirred for 0.5 h at -15 °C, and then a solution of 4-methoxybenzyl chloride (13.38 g, 85.4 mmol) in anhydrous DMF (21 mL) was added to the reaction mixture at the same temperature. After an additional 0.5 h, the reaction mixture was allowed to warm to 20 °C and stirred for another 1 h. It was quenched by slowly pouring it into ice-H_2O (195 mL) and extracted with Et_2O (3x130 mL). The combined organic phases were washed with saturated aqueous NaCl (3x130 mL), dried and concentrated. Chromatography of the residue on silica gel (350 g, 2/1 to 1/1 hexane/EtOAc), followed by Kugelrohr distillation (250 °C, 1-2 mmHg) gave **14** (13.66 g, 84% yield) as a colorless oil: IR ($CHCl_3$) 3620, 3440, 2950, 2870, 1610, 1590, 1510, 1460, 1360, 1300, 1230, 1170, 1090, 1030, 960, 820 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.64-1.74 (m, 4H, H-2 and H-3), 2.21 (t, 1H, J=6.0 Hz, OH), 3.50 (t, 2H, J=6.0 Hz, H-4), 3.64 (q, 2H, J=6.0 Hz, H-1), 3.80 (s, 3H, OCH_3), 4.45 (s, 2H, -CH_2O-), 6.88 and 7.26 (m, 4H, -C_6H_4-); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 26.69, 30.15, 55.21, 62.62, 70.00, 72.66, 113.78 (x2), 129.30 (x2), 130.18, 159.18; FABMS *m/z*: 210 $(M)^+$; HRFABMS calcd. for $C_{12}H_{18}O_3$ $(M)^+$ 210.1256, found 210.1288; Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C,

68.43; H, 8.59.

4-(4-Methoxybenzyl)oxy-1-butanal (15).

A mixture of dry CH_2Cl_2 (8 mL) and DMSO (890.6 mg, 11.4 mmol) was cooled below -50 °C and a solution of oxalyl chloride (964.6 mg, 7.60 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise to the stirred cold solution. After 0.5 h at -50 °C, a solution of **14** (799.0 mg, 3.80 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise to the reaction mixture at the same temperature. The mixture was stirred for 0.5 h at -50 °C, followed by the addition of Et_3N (2.12 mL, 15.2 mmol) dropwise. The reaction mixture was kept at or below -50 °C until the addition of Et_3N was complete, and it was allowed to warm slowly to 20 °C for 1.5 h and quenched by the addition of aqueous HCl (5%, 16 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and NaCl (16 mL), dried and concentrated. Kugelrohr distillation of the residue (200-210 °C, 1-2 mmHg) gave **15** (704.5 mg, 89% yield) as a pale yellow oil: IR ($CHCl_3$) 2950, 2850, 2750, 1720, 1610, 1590, 1510, 1460, 1360, 1300, 1230, 1170, 1090, 1030, 820 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.93 (tt, 2H, J=7.0, 6.0 Hz, H-3), 2.53 (td, 2H, J=7.0, 1.8 Hz, H-2), 3.48 (t, 2H, J=6.0 Hz, H-4), 3.80 (s, 3H, OCH_3), 4.42 (s, 2H, -CH_2O-), 6.88 and 7.24 (m, 4H, -C_6H_4-), 9.77 (t, 1H, J=1.8 Hz, CHO); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 22.54, 40.93, 55.24, 68.81, 72.57, 113.77 (x2), 129.19 (x2), 130.33, 159.18, 202.24; FABMS *m/z*: 208 $(M)^+$; HRFABMS calcd. for $C_{12}H_{16}O_3$ $(M)^+$ 208.1099, found 208.1139; Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.08; H, 7.63.

(4*E*, 6*E*)-1-(4-Methoxybenzyl)oxy-7-methyl-9-(2, 2, 5, 5-tetramethyl-1, 3-dioxolan-4-yl)nona-4, 6-diene (13).

(a) Wittig reaction of **12** with **15**: A suspension of **12** (12.93 g, 23.4 mmol) in dry THF (390 mL) was cooled to -78 °C and *n*-BuLi (14.60 mL, 1.6 M in hexane, 23.4 mmol) was added dropwise to the suspension. The reaction mixture was stirred for 0.5 h at -78 °C. A solution of **15** (6.32 g, 30.3 mmol) in dry THF (64 mL) was added dropwise to the resulting dark red solution at -78 °C over 20 min. The reaction mixture was allowed to warm slowly to 20 °C for 16 h and quenched slowly by the addition of saturated aqueous NH_4Cl (650 mL). The resulting mixture was extracted with EtOAc (800 and 2x600 mL) and the combined organic phases were washed with saturated aqueous NaCl (650 mL), dried and concentrated to afford a white insoluble solid. The solid was washed with hexane/EtOAc (20/1, 100 mL) and the washing solution was concentrated. Chromatography of the residue on silica gel (650 g, 15/1 to 10/1 hexane/EtOAc) gave **13** (6.87 g, 73% yield, *E*/*Z*=1.9/1) as a pale yellow oil. HPLC purification of the mixture (6.87 g) using Senshu Pak. SSC-Silica-5251-N and Shiseido Silica SG120Å column (each 20 ϕ x 250 mm, eluent: CH_2Cl_2, detector: UV 254 nm, flow rate: 30-35 mL/min) gave **13** (3.46 g, *E*/*Z*=99.8/0.2) and the corresponding (4*Z*)-isomer (2.16 g, *E*/*Z*=6/94) as a pale yellow oil, respectively: **13**: IR ($CHCl_3$) 2950, 2860, 1610, 1590, 1520, 1450, 1370, 1220, 1170, 1110, 1040, 1000, 960, 910, 820 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.09, 1.24, 1.33, 1.42 and 1.75 (s, 15H, $(CH_3)_2$-2', $(CH_3)_2$-5' and CH_3-7), 1.50 (dddd, 1H, J=13.8, 10.5, 6.5, 3.5 Hz, H-9), 1.60-1.68 (m, 1H, H-9), 1.70 (tt, 2H, J=7.0, 6.5 Hz, H-2, observed as quint signal), 2.07 (ddd, 1H, J=14.0, 10.5, 6.5 Hz, H-8), 2.18 (qd, 2H, J=7.0, 1.5 Hz, H-3, observed as brq signal), 2.27 (ddd, 1H, J=14.0, 10.5, 5.0 Hz, H-8), 3.46 (t, 2H, J=6.5 Hz, H-1), 3.66 (dd, 1H, J=9.5, 3.5 Hz, H-4'), 3.80 (s, 3H, OCH_3), 4.43 (s, 2H, -CH_2O-), 5.58 (dt, 1H, J=15.0, 7.0 Hz, H-4), 5.83 (d, 1H, J=11.0 Hz, H-6), 6.25 (ddt, 1H, J=15.0, 11.0, 1.5 Hz, H-5), 6.88 and 7.26 (m, 4H, -C_6H_4-); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.56, 22.91, 26.03, 26.82, 27.72, 28.54, 29.48, 29.57, 36.84, 55.22, 69.47, 72.52, 80.07, 82.87, 106.47, 113.72 (x2), 124.94, 126.93, 129.18 (x2), 130.69, 131.88, 135.66, 159.09; FABMS *m/z*: 402 $(M)^+$; HRFABMS calcd. for $C_{25}H_{38}O_4$ $(M)^+$ 402.2770, found 402.2758; Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.53; H, 9.51.

(4*Z*)-isomer: IR ($CHCl_3$) 2950, 2860, 1610, 1580, 1520, 1450, 1370, 1220, 1170, 1110, 1030, 1000, 910, 820 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.08, 1.22, 1.31, 1.41 and 1.75 (s, 15H, $(CH_3)_2$-2', $(CH_3)_2$-5' and CH_3-7), 1.49 (dddd, 1H, J=13.8, 10.5, 6.5, 3.5 Hz, H-9), 1.60-1.68 (m, 1H, H-9), 1.68 (tt, 2H, J=7.5, 7.0 Hz, H-2, observed as quint signal), 2.11 (ddd, 1H, J=14.0, 10.0, 6.5 Hz, H-8), 2.24 (q, 2H, J=7.5 Hz, H-3), 2.29 (ddd, 1H, J=14.0, 10.5, 4.5 Hz, H-8), 3.44 (t, 2H, J=7.0 Hz, H-1), 3.64 (dd, 1H, J=9.5, 3.5 Hz, H-4'), 3.78 (s,

3H, OCH_3), 4.41 (s, 2H, -CH_2O-), 5.34 (dt, 1H, J=10.5, 7.5 Hz, H-4), 6.12 (d, 1H, J=11.5 Hz, H-6), 6.18 (dd, 1H, J=11.5, 10.5, H-5, observed as t signal), 6.85 and 7.24 (m, 4H, -C_6H_4-); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.35, 22.91, 24.19, 26.01, 26.84, 27.78, 28.54, 29.72, 37.35, 55.24, 69.47, 72.54, 80.06, 82.79, 106.49. 113.74 (x2), 120.37, 125.00, 129.16 (x2), 129.47, 130.71, 137.83, 159.09; FABMS *m/z*: 402 $(M)^+$; HRFABMS calcd. for $C_{25}H_{38}O_4$ $(M)^+$ 402.2770, found 402.2728; Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.90; H, 9.52.

(b) Wittig-Horner reaction of **16** with **15**: A solution of *t*-BuOK (161.0 mg, 1.43 mmol) in dry THF (2 mL) was added to a mixed solution of **15** (300.0 mg, 1.44 mmol) and **16** (200.0 mg, 0.574 mmol) in dry THF (2 mL). The reaction mixture was stirred vigorously for 1.5 h and quenched by the addition of saturated aqueous NaCl (8 mL). The aqueous phase was extracted with EtOAc (3x8 mL), and the combined organic phases were washed with saturated aqueous NaCl (8 mL), dried and concentrated. Chromatography of the residue on silica gel (10 g, 20/1 to 1/2 hexane/EtOAc) gave **13** (117.9 mg, 51% yield, *E*/*Z*=8.5/1) as a pale yellow oil, with recovery of **16** (26.0 mg, 13%).

Diethyl (2*E*)-[3-methyl-5-(2, 2, 5, 5-tetramethyl-1, 3-dioxolan-4-yl)-2-penten-1-yl] phosphonate (16).

CBr_4 (4.40 g, 13.3 mmol) and PPh_3 (3.48 g, 13.3 mmol) were added to a solution of **11** (2.52 g, 11.0 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C, and the reaction mixture was stirred for 1 h at 0 °C. After evaporation of the solvent, the residue was triturated repeatedly with Et_2O (4x25 mL) and filtered. The combined filtrates were concentrated and triethyl phosphite ($(EtO)_3P$, 5.68 mL, 33.1 mmol) was added to a solution of the residue containing the corresponding bromide in dry benzene (10 mL). The reaction mixture was heated to reflux for 2.5 h and distilled at 160-180 °C (20 mmHg) to remove low-boiling substances. Chromatography of the residue on silica gel (125 g, 1/2 hexane/EtOAc), followed by Kugelrohr distillation (250 °C, 1-2 mmHg) twice gave **16** (2.88 g, 75% yield from **11**) as a colorless oil: IR ($CHCl_3$) 3400 (broad), 3000, 2950, 2870, 1450, 1370, 1240, 1110, 1030, 1000, 970, 850 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.07, 1.22, 1.30 and 1.39 (s, 12H, $(CH_3)_2$-2' and $(CH_3)_2$-5'), 1.29 (t, 6H, J=7.5 Hz, $(OCH_2\underline{CH_3})_2$), 1.47 (dddd, 1H, J=13.5, 10.5, 6.5, 3.5 Hz, H-5), 1.57-1.66 (m, 1H, H-5), 1.65 (d, 3H, J=3.5 Hz, CH_3-3), 2.07 (m, 1H, H-4), 2.25 (ddd, 1H, J=19.3, 10.5, 5.0 Hz, H-4), 2.55 (dd, 2H, J=21.5, 7.5 Hz, H-1), 3.64 (dd, 1H, J=9.5, 3.5 Hz, H-4'), 4.03-4.11 (m, 4H, $(O\underline{CH_2}CH_3)_2$), 5.22 (qq, 1H, J=7.5, 1.5 Hz, H-2); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.31, 16.41, 16.45, 22.87, 26.00, 26.35 (d, J=140.5 Hz), 26.81, 27.53, 28.51, 36.66, 61.68 (x2), 80.02, 82.65, 106.47, 112.98 (d, J=9.3 Hz), 139.47 (d, J=14.7 Hz); FABMS *m/z*: 349 $(M+H)^+$; HRFABMS calcd. for $C_{17}H_{34}O_5P$ $(M+H)^+$ 349.2144, found 349.2136; Anal. Calcd for $C_{17}H_{33}O_5P$: C, 58.60; H, 9.54; P, 8.89. Found: C, 58.35; H, 9.45; P, 8.86.

(4*E*, 6*E*)-10, 11-Dihydroxy-7, 11-dimethyl-1-(4-methoxybenzyl)oxydodeca-4, 6-diene (17).

A solution of **13** (3.31 g, 8.22 mmol) and $TsOH{\cdot}H_2O$ (938.4 mg, 4.93 mmol) in aqueous MeOH (9/1 MeOH/H_2O, 83 mL) was stirred for 5 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ (415.0 mg, 4.94 mmol/H_2O 20 mL) and concentrated. After the addition of saturated aqueous NaCl (30 mL), the resulting mixture was extracted with EtOAc (3x50 mL), and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (165 g, 2/1 hexane/EtOAc) gave **17** (2.75 g, 92% yield) as a pale yellow oil, with recovery of **13** (318.7 mg, 10%). The same procedure with the recovered **13** was carried out again to afford **17** (2.95 g) in 99% total yield from **13**: IR ($CHCl_3$) 3580, 2950, 2870, 1620, 1590, 1510, 1440, 1360, 1300, 1240, 1170, 1090, 1040, 970, 820 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.16, 1.21 and 1.74 (s, 9H, CH_3-7, CH_3-11 and H-12), 1.44 (dddd, 1H, J=14.0, 10.5, 9.0, 5.5 Hz, H-9), 1.62 (dddd, 1H, J=14.0, 9.5, 7.0, 1.5 Hz, H-9), 1.70 (tt, 2H, J=7.0, 6.5 Hz, H-2, observed as quint signal), 2.08-2.17 (m, 1H, H-8), 2.18 (qd, 2H, J=7.0, 1.5 Hz, H-3, observed as brq signal), 2.31 (ddd, 1H, J=14.0, 9.5, 5.5 Hz, H-8), 3.35 (dd, 1H, J=10.5, 1.5 Hz, H-10, observed as brd signal), 3.46 (t, 2H, J=6.5 Hz, H-1), 3.80 (s, 3H, OCH_3), 4.43 (s, 2H, -CH_2O-), 5.58 (dt, 1H, J=15.0, 7.0 Hz, H-4), 5.85 (d, 1H, J=11.0 Hz, H-6), 6.24 (ddt, 1H, J=15.0, 11.0, 1.5 Hz, H-5), 6.88 and 7.26 (m, 4H, -C_6H_4-); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.44, 23.24, 26.45, 29.49, 29.56, 29.69, 36.86, 55.25, 69.47, 72.51, 73.04, 78.17, 113.74 (x2), 125.19, 126.86, 129.20 (x2), 130.71,

132.03, 136.06, 159.09; FABMS *m/z*: 362 $(M)^+$; HRFABMS calcd. for $C_{22}H_{34}O_4$ $(M)^+$ 362.2457, found 362.2410; Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.67; H, 9.62.

(4*E*, 6*E*)-9-Formyl-1-(4-methoxybenzyl)oxy-7-methylnona-4, 6-diene (18).

$NaIO_4$ (3.27 g, 15.3 mmol) was added to a solution of **17** (2.22 g, 6.12 mmol) in a mixture of acetone (111 mL) and H_2O (22 mL). The reaction mixture was stirred vigorously for 2 h and quenched by the addition of saturated aqueous NaCl (220 mL). The resulting mixture was extracted with EtOAc (3x220 mL) and the combined organic phases were washed with saturated aqueous NaCl (110 mL), dried and concentrated. Chromatography of the residue on silica gel (220 g, 4/1 to 1/1hexane/EtOAc) gave **18** (1.43 g, 77% yield) as a pale yellow oil, with recovery of **17** (598.5 mg, 27%). The same procedure with the recovered **17** was repeated two more times to afford **18** (1.74 g) in 94% total yield from **17**: IR ($CHCl_3$) 2950, 2850, 2730, 1720, 1610, 1590, 1510, 1440, 1360, 1240, 1170, 1100, 1040, 970, 900, 820 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.70 (tt, 2H, J=7.0, 6.5 Hz, H-2, observed as quint signal), 1.74 (s, 3H, CH_3-7), 2.18 (dtd, 2H, J=7.5, 7.0, 1.5 Hz, H-3, observed as brq signal), 2.37 (t, 2H, J=7.5 Hz, H-8), 2.55 (td, 2H, J=7.5, 1.5 Hz, H-9), 3.45 (t, 2H, J=6.5 Hz, H-1), 3.80 (s, 3H, OCH_3), 4.43 (s, 2H, -CH_2O-), 5.59 (dt, 1H, J=15.0, 7.5 Hz, H-4), 5.80 (d, 1H, J=10.5 Hz, H-6), 6.22 (ddt, 1H, J=15.0, 10.5, 1.5 Hz, H-5), 6.88 and 7.26 (m, 4H, -C_6H_4-), 9.77 (t, 1H, J=1.5 Hz, CHO); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.53, 29.47 (x2), 31.79, 41.98, 55.19, 69.40, 72.49, 113.69 (x2), 125.44, 126.58, 129.15 (x2), 130.66, 132.68, 133.87, 159.06, 202.15; FABMS *m/z*: 302 $(M)^+$; HRFABMS calcd. for $C_{19}H_{26}O_3$ $(M)^+$ 302.1882, found 302.1860; Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.50; H, 8.66.

(4*E*, 6*E*, 10*R*)-10-hydroxy-1-(4-methoxybenzyl)oxy-7-methyltrideca-4, 6, 12-triene (20).

The following procedure is a modification of that reported by Hafner *et al.*[13] Allylmagnesium chloride (8.02 mL, 2.0 M in THF, 16.0 mmol) was added dropwise over 20 min at 0 °C to a 82 mM solution of [(4*R*, 5*R*)-2, 2-dimethyl-1, 3-dioxolane-4, 5-bis(diphenylmethoxy)]cyclopentadienyl-chlorotitanium, (*R*, *R*)-**19** (10.92 g, 17.8 mmol) in dry THF (217 mL). The reaction mixture was stirred for 1 h at 0 °C and the slightly orange suspension was formed. A solution of **18** (1.80 g, 5.95 mmol) in dry THF (15 mL) was added to the suspension at -78 °C over 20 min. The reaction mixture was stirred for 1.5 h at -78 °C and quenched by the addition of aqueous NH_4F (45%, 36 mL). After hydrolysis with aqueous NH_4F for 12 h at 20 °C, the resulting mixture was filtered through Celite and extracted with EtOAc (2x200 mL). The combined organic phases were washed with saturated aqueous NaCl (2x100 mL), dried and concentrated. Chromatography of the residue on silica gel (2 times, 2x360 g, 8/1 to 5/1 hexane/EtOAc and CH_2Cl_2 to 20/1 CH_2Cl_2/EtOAc) gave **20** (1.95 g, 95% yield) as a colorless oil: $[\alpha]_D^{25}$ +3.6° (*c* 0.985, $CHCl_3$); IR ($CHCl_3$) 3580, 2950, 2850, 1610, 1510, 1440, 1360, 1300, 1240, 1170, 1090, 1030, 960, 910 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.53-1.65 (m, 2H, H-9), 1.70 (tt, 2H, J=7.5, 6.5 Hz, H-2, observed as quint signal), 1.73 (d, 3H, J=0.5 Hz, CH_3-7), 2.06-2.24 (m, 3H, H-8 and H-11), 2.17 (qd, 2H, J=7.5, 1.5 Hz, H-3, observed as brq signal), 2.30 (dddt, 1H, J=13.8, 6.5, 4.5, 1.5 Hz, H-11), 3.45 (t, 2H, J=6.5 Hz, H-1), 3.63 (ddd, 1H, J=12.0, 8.0, 4.5 Hz, H-10), 3.80 (s, 3H, OCH_3), 4.43 (s, 2H, -CH_2O-), 5.12 and 5.14 (m, 2H, H-13), 5.57 (dt, 1H, J=15.0, 7.5 Hz, H-4), 5.78-5.87 (m, 1H, H-12), 5.83 (d, 1H, J=10.5 Hz, H-6), 6.24 (ddt, 1H, J=15.0, 10.5, 1.5 Hz, H-5), 6.87 and 7.26 (m, 4H, -C_6H_4-); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.47, 29.47, 29.56, 34.79, 35.93, 41.93, 55.22, 69.46, 70.37, 72.49, 113.71 (x2), 118.08, 124.91, 126.90, 129.18 (x2), 130.68, 131.84, 134.71, 136.12, 159.06; FABMS *m/z*: 344 $(M)^+$, 343 $(M-H)^+$; HRFABMS calcd. for $C_{22}H_{31}O_3$ $(M-H)^+$ 343.2273, found 343.2264; Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.20; H, 9.22.

[(4*E*, 6*E*, 10*R*)-1-(4-methoxybenzyl)oxy-7-methyltrideca-4, 6, 12-trien-10-yl] (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetate (21), the Mosher ester of 20.

Pyridine (120 μL, 1.48 mmol) and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (29 μL, 0.155 mmol) were added to a solution of **20** (10.5 mg, 0.030 mmol) in dry CH_2Cl_2 (0.2 mL). The reaction mixture was stirred for 0.5 h, quenched by the addition of aqueous HCl (5%, 1 mL) and extracted with EtOAc

(2x3 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and NaCl (2 mL), dried and concentrated. Preparative TLC purification of the residue (3/1 hexane/EtOAc) gave **21** (11.3 mg, 66% yield) as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.64 (d, 3H, J=1.0 Hz, CH_3-7), 1.65-1.74 (m, 4H, H-2 and H-9), 1.92 (m, 2H, H-8), 2.17 (qd, 2H, J=7.0, 1.5 Hz, H-3, observed as brq signal), 2.43 (t, 2H, J=7.0 Hz, H-11), 3.45 (t, 2H, J=6.5 Hz, H-1), 3.56 (m, 3H, OCH_3 of MTPA), 3.80 (s, 3H, OCH_3 of PMB), 4.43 (s, 2H, -CH_2O-), 5.08-5.16 (m, 3H, H-10 and H-13), 5.55 (dt, 1H, J=15.0, 7.0 Hz, H-4), 5.67 (dq, 1H, J=11.0, 1.0 Hz, H-6), 5.75 (ddt, 1H, J=16.5, 10.5, 7.0 Hz, H-12), 6.20 (ddt, 1H, J=15.0, 11.0, 1.5 Hz, H-5), 6.87 and 7.26 (m, 4H, -C_6H_4- of PMB), 7.39 and 7.55 (m, 5H, C_6H_5 of MTPA); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.35, 29.50, 29.56, 31.48, 34.88, 38.19, 55.25, 55.53, 69.49, 72.53, 76.18, 84.45 (q), 113.74 (x2), 118.53, 123.37 (q, J=288.2 Hz), 125.16, 126.78, 127.34 (x2), 128.31 (x2), 129.21 (x2), 129.53, 130.71, 132.16, 132.37, 132.96, 134.90, 159.09, 166.17; FABMS *m/z*: 560 $(M)^+$.

(4*E*, 6*E*, 10*R*)-10-Methoxy-1-(4-methoxybenzyl)oxy-7-methyltrideca-4, 6, 12-triene (22).

A solution of **20** (1.90 g, 5.52 mmol) in anhydrous DMF (19 mL) was cooled to 0 °C and NaH (60% oil suspension, 441.4 mg, 11.0 mmol) was added to the solution. The reaction mixture was stirred for 0.5 h at 0 °C, and then a solution of MeI (1.03 mL, 16.5 mmol) in anhydrous DMF (1.9 mL) was added to the mixture at the same temperature. The reaction mixture was allowed to warm to 20 °C and stirred for 2.5 h. It was quenched by slowly pouring it into cold saturated aqueous NaCl (380 mL) and extracted with EtOAc (3x190 mL). The combined organic phases were washed with saturated aqueous NaCl (190 mL), dried and concentrated. Chromatography of the residue on silica gel (190 g, 20/1 hexane/EtOAc) gave **22** (1.76 g, 89% yield) as a colorless oil: $[\alpha]_D^{25}$ -2.1° (*c* 1.015, $CHCl_3$); IR ($CHCl_3$) 2950, 2850, 1640, 1610, 1510, 1450, 1360, 1300, 1240, 1170, 1090, 1030, 960, 890 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.59 (td, 2H, J=8.0, 6.0 Hz, H-9), 1.70 (tt, 2H, J=7.0, 6.5 Hz, H-2, observed as quint signal), 1.72 (s, 3H, CH_3-7), 2.01-2.16 (m, 2H, H-8), 2.17 (qd, 2H, J=7.0, 1.5 Hz, H-3, observed as brq signal), 2.27 (m, 2H, H-11), 3.19 (quint, 1H, J=6.0 Hz, H-10), 3.34 (s, 3H, OCH_3-10), 3.45 (t, 2H, J=6.5 Hz, H-1), 3.80 (s, 3H, OCH_3 of PMB), 4.43 (s, 2H, -CH_2O-), 5.04-5.11 (m, 2H, H-13), 5.56 (dt, 1H, J=15.0, 7.0 Hz, H-4), 5.78-5.82 (m, 1H, H-6), 5.81 (ddt, 1H, J=17.0, 10.0, 7.0 Hz, H-12), 6.24 (ddt, 1H, J=15.0, 10.5, 1.5 Hz, H-5), 6.87 and 7.26 (m, 4H, -C_6H_4-); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.53, 29.50, 29.60, 31.59, 35.34, 37.65, 55.25, 56.53, 69.52, 72.53, 79.90, 113.74 (x2), 116.93, 124.72, 127.03, 129.19 (x2), 130.72, 131.61, 134.75, 136.34, 159.09; FABMS *m/z*: 358 $(M)^+$, 357 $(M-H)^+$; HRFABMS calcd. for $C_{23}H_{33}O_3$ $(M-H)^+$ 357.2430, found 357.2382; Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.21; H, 9.55.

(4*E*, 6*E*, 10*R*)-10-Methoxy-7-methyltrideca-4, 6, 12-trien-1-ol (23).

Me_2S (3.24 mL, 44.1 mmol) and $MgBr_2 \cdot OEt_2$ (3.41 g, 13.2 mmol) were added to a solution of **22** (1.52 g, 4.41 mmol) in dry CH_2Cl_2 (152 mL). The reaction mixture was stirred vigorously for 2 h, quenched by the addition of saturated aqueous NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3x50 mL). The combined organic phases were washed with saturated aqueous NaCl (100 mL), dried and concentrated. Chromatography of the residue on silica gel (150 g, 8/1 to 5/1 hexane/EtOAc) gave **23** (0.24 g, 23% yield) as a pale yellow oil, with recovery of **22** (1.09 g, 72%). The same procedure with the recovered **22** was repeated four more times to afford **23** (802.6 mg) in 76% total yield from **22**, with recovery of **22** (89.0 mg. 6%): $[\alpha]_D^{25}$ -2.8° (*c* 2.53, $CHCl_3$), lit. $[\alpha]_D^{23}$ -1.4° (*c* 2.90, $CDCl_3$)[68a]; IR ($CHCl_3$) 3450 (broad), 2940, 1640, 1610, 1510, 1440, 1350, 1090, 960, 910 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.60 (td, 2H, J=8.0, 6.0 Hz, H-9), 1.68 (tt, 2H, J=7.0, 6.5 Hz, H-2, observed as quint signal), 1.73 (s, 3H, CH_3-7), 2.01-2.16 (m, 2H, H-8), 2.19 (qd, 2H, J=7.0, 1.5 Hz, H-3, observed as brq signal), 2.27 (m, 2H, H-11), 3.20 (quint, 1H, J=6.0 Hz, H-10), 3.34 (s, 3H, OCH_3-10), 3.67 (t, 2H, J=6.5 Hz, H-1), 5.04-5.11 (m, 2H, H-13), 5.58 (dt, 1H, J=15.0, 7.0 Hz, H-4), 5.80 (ddt, 1H, J=17.3, 10.0, 7.0 Hz, H-12), 5.81 (d, 1H, J=10.5 Hz, H-6), 6.28 (ddt, 1H, J=15.0, 10.5, 1.5 Hz, H-5); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.56, 29.22, 31.59, 32.47, 35.35, 37.66, 56.54, 62.54, 79.90, 116.96, 124.59, 127.25, 131.36, 134.75, 136.66; FABMS *m/z*: 238 $(M)^+$; HRFABMS calcd. for $C_{15}H_{26}O_2$ $(M)^+$ 238.1933, found 238.1918.

(4*E*, 6*E*, 10*R*)-1-Iodo-10-methoxy-7-methyltrideca-4, 6, 12-triene (24).

Methanesulfonyl chloride (414 μL, 5.35 mmol) was added to a solution of **23** (637.4 mg, 2.67 mmol) in pyridine (6.4 mL) at 0 °C and the reaction mixture was stirred for 1 h at 0 °C. The resulting mixture was quenched by the addition of H_2O (30 mL) and extracted with EtOAc (30 mL). The organic phase was washed with aqueous HCl (5%, 2x30 mL), saturated aqueous $NaHCO_3$ and NaCl (30 mL), dried and concentrated. Chromatography of the residue on silica gel (64 g, 5/1 hexane/EtOAc) gave the corresponding mesylate (767.8 mg, quant.) as a colorless oil. NaI (1.62 g, 10.8 mmol) was added to a solution of the foregoing mesylate (767.8 mg, 2.70 mmol) in acetone (23 mL). The reaction mixture was heated to reflux for 2 h and concentrated. After the addition of saturated aqueous NaCl (40 mL), the resulting mixture was extracted with EtOAc (2x40 mL), dried and concentrated. Chromatography of the residue on silica gel (77 g, 40/1 hexane/EtOAc) gave **24** (809.5 mg, 87% yield from **23**) as a pale brown oil: $[\alpha]_D^{25}$ -2.5° (*c* 4.05, $CHCl_3$), lit. $[\alpha]_D^{23}$ -0.9° (*c* 4.35, $CHCl_3$)[6a]; IR ($CHCl_3$) 2930, 1640, 1430, 1360, 1160, 1090, 990, 960, 910 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.60 (td, 2H, J=8.0, 6.0 Hz, H-9), 1.74 (s, 3H, CH_3-7), 1.91 (tt, 2H, J=7.0, 6.5 Hz, H-2, observed as quint signal), 2.02-2.16 (m, 2H, H-8), 2.21 (qd, 2H, J=7.0, 1.5 Hz, H-3, observed as brq signal), 2.27 (m, 2H, H-11), 3.17-3.23 (m, 1H, H-10), 3.19 (t, 2H, J=6.5 Hz, H-1), 3.34 (s, 3H, OCH_3-10), 5.04-5.12 (m, 2H, H-13), 5.49 (dt, 1H, J=15.0, 7.0 Hz, H-4), 5.80 (d, 1H, J=10.5 Hz, H-6), 5.81 (ddt, 1H, J=17.3, 10.0, 7.0 Hz, H-12), 6.30 (ddt, 1H, J=15.0, 10.5, 1.5 Hz, H-5); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 6.56, 16.59, 31.59, 33.07, 33.44, 35.37, 37.66, 56.59, 79.90, 116.96, 124.47, 128.13, 129.52, 134.74, 137.15; FABMS *m/z*: 348 $(M)^+$; HRFABMS calcd. for $C_{15}H_{25}OI$ $(M)^+$ 348.0950, found 348.0953.

(4*E*, 6*E*, 10*R*)-10-Methoxy-7-methyltrideca-4, 6, 12-trien-1-yl Triphenylphosphonium Iodide (25).

PPh_3 (2.42 g, 9.22 mmol) was added to a solution of **24** (803.4 mg, 2.31 mmol) in acetonitrile (24 mL). The reaction mixture was heated to reflux for 7 h and concentrated. The residue was triturated repeatedly with Et_2O (3x50 mL) and filtered. The precipitate was dried under vacuum to afford **25** (1.41 g, quant.) as a gummy white solid: $[\alpha]_D^{25}$ -0.5° (*c* 7.20, $CHCl_3$), lit. $[\alpha]_D^{23}$ -0.0° (*c* 7.0, $CHCl_3$)[6a]; IR ($CHCl_3$) 2930, 1640, 1590, 1440, 1110, 995, 965, 915 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.57 (m, 2H, H-9), 1.71 (s, 3H, CH_3-7), 1.75 (m, 2H, H-2), 1.99-2.15 (m, 2H, H-8), 2.26 (m, 2H, H-11), 2.49 (m, 2H, H-3), 3.18 (quint, 1H, J=6.0 Hz, H-10), 3.33 (s, 3H, OCH_3-10), 3.74 (m, 2H, H-1), 5.03-5.10 (m, 2H, H-13), 5.42 (dt, 1H, J=15.0, 7.5 Hz, H-4), 5.75 (d, 1H, J=11.0 Hz, H-6), 5.79 (ddt, 1H, J=17.3, 10.0, 7.0 Hz, H-12), 6.31 (dd, 1H, J=15.0, 11.0 Hz, H-5), 7.71 and 7.82 (m, 15 H, C_6H_5x3); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.71, 22.18, 22.67, 31.55, 33.09 (d, J=16.6 Hz), 35.34, 37.59, 56.51, 79.84, 116.94, 117.81, 118.49, 124.23, 129.08 (d, J=16.7 Hz, x3), 130.50 (d, J=12.1 Hz, x6), 133.71 (d, J=9.2 Hz, x6), 134.67, 135.05 (x3), 137.93; FABMS *m/z*: 483 $(M\text{-}I)^+$; HRFABMS calcd. for $C_{33}H_{40}OP$ $(M\text{-}I)^+$ 483.2817, found 483.2791.

(2*Z*, 6*E*, 8*E*, 12*R*)-12-Methoxy-9-methylpentadeca-2, 6, 8, 14-tetraene (26).

A solution of **25** (81.9 mg, 0.134 mmol) in dry THF (1.64 mL) was cooled to -78 °C and LiHMDS (240 μL, 0.5 M in THF, 0.120 mmol) was added dropwise to the solution. The reaction mixture was stirred for 0.5 h at -78 °C. A solution of acetaldehyde (29.5 mg, 0.670 mmol) in dry THF (0.2 mL) was added dropwise to the resulting red solution at -78 °C over 20 min. The reaction mixture was allowed to warm slowly to 0 °C for 1.5 h and quenched by the addition of saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (2x10 mL) and the combined organic phases were dried and concentrated. Chromatography of the residue on silica gel (17 g, 3/1 to 2/1 hexane/CH_2Cl_2), followed by preparative TLC purification (benzene) gave **26** (13.6 mg, 41% yield) as a colorless oil: $[\alpha]_D^{25}$ -2.9° (*c* 0.31, $CHCl_3$); IR ($CHCl_3$) 2940, 2860, 1640, 1430, 1360, 1260, 1090, 970, 910 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.60 (td, 2H, J=8.0, 6.0 Hz, H-11), 1.61 (dd, 3H, J=6.0, 1.5 Hz, H-1), 1.73 (s, 3H, CH_3-9), 2.02-2.17 (m, 6H, H-4, H-5 and H-10), 2.27 (m, 2H, H-13), 3.20 (q, 1H, J=6.0 Hz, H-12), 3.34 (s, 3H, OCH_3-12), 5.04-5.12 (m, 2H, H-15), 5.40 (m, 1H, H-2), 5.46 (dtq, 1H, J=11.0, 7.0, 1.5 Hz, H-3), 5.59 (dt, 1H, J=15.0, 6.5 Hz, H-6), 5.81 (ddt, 1H, J=17.3, 10.5, 7.0 Hz, H-14), 5.81 (d, 1H, J=10.5 Hz, H-8), 6.26 (dd, 1H, J=15.0, 10.5 Hz, H-7); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 12.81, 16.53, 26.90, 31.57, 32.82, 35.35, 37.65, 56.54, 79.90, 116.94, 124.16, 124.78, 126.84,

129.91, 131.84, 134.75, 136.33; FABMS *m/z*: 248 $(M)^+$; HRFABMS calcd. for $C_{17}H_{28}O$ $(M)^+$ 248.2140, found 248.2137.

(4*R*)-*N*-(*tert*-Butyloxy)carbonyl-2, 2-dimethyl-4-[(1*Z*, 5*E*, 7*E*, 11*R*)-11-methoxy-8-methyltetradeca-1, 5, 7, 13-tetraen-1-yl]thiazolidine (29).

A solution of **25** (602.1 mg, 0.986 mmol) in dry THF (12 mL) was cooled to -78 °C and LiHMDS (887 μL, 1.0 M in THF, 0.887 mmol) was added dropwise to the solution. The reaction mixture was stirred for 0.5 h at -78 °C. A solution of **4** (241.9 mg, 0.986 mmol) in dry THF (1 mL) was added dropwise to the resulting red solution at -78 °C over 20 min. The reaction mixture was allowed to warm slowly to 0 °C for 2 h and quenched by the addition of saturated aqueous NH_4Cl (15 mL). The resulting mixture was extracted with EtOAc (3x24 mL), and the combined organic phases were washed with saturated aqueous NaCl (15 mL), dried and concentrated. Chromatography of the residue on silica gel (2 times, 120 g and 14 g, CH_2Cl_2/hexane 10/1 to CH_2Cl_2) gave **29** (264.2 mg, 60% yield) as a colorless oil, with recovery of **4** (60.9 mg, 25%): $[\alpha]_D^{25}$ +55.2° (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 2980, 2930, 1680, 1450, 1360, 1280, 1165, 1080, 970, 920, 850 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H, $(CH_3)_3C$), 1.59 (td, 2H, J=8.0, 6.0 Hz, H-10'), 1.73 (s, 3H, CH_3-8'), 1.77 and 1.79 (s, 6H, $(CH_3)_2$-2), 2.01-2.33 (m, 8H, H-3', H-4', H-9' and H-12'), 2.57 (dd, 1H, J=12.0, 2.5 Hz, H-5), 3.19 (q, 1H, J=6.0 Hz, H-11'), 3.24 (dd, 1H, J=12.0, 6.5 Hz, H-5), 3.34 (s, 3H, OCH_3-11'), 5.04-5.12 (m, 3H, H-4 and H-14'), 5.43 (dt, 1H, J=10.5, 7.0 Hz, H-2'), 5.56 (dt, 1H, J=15.0, 7.0 Hz, H-5'), 5.69 (dd, 1H, J=10.5, 9.0 Hz, H-1'), 5.79 (d, 1H, J=10.5 Hz, H-7'), 5.81 (ddt, 1H, J=17.0, 10.0, 7.0 Hz, H-13'), 6.25 (dd, 1H, J=15.0, 10.5 Hz, H-6'); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 16.51, 27.59, 28.48 (x3), 29.63, 30.12, 31.55, 32.80, 34.25, 35.32, 37.59, 56.50, 61.01, 70.21, 79.81, 79.88, 116.91, 124.61, 127.24, 129.49, 131.23, 131.51, 134.68, 136.58, 152.35; FABMS *m/z*: 450 $(M)^+$; HRFABMS calcd. for $C_{26}H_{44}O_3NS$ $(M+H)^+$ 450.3042, found 450.2975.; Anal. Calcd for $C_{26}H_{43}O_3NS$: C, 69.44; H, 9.64; N, 3.11; S, 7.13. Found: C, 69.36; H, 9.71; N, 3.10; S, 6.99.

Curacin A (1).

TFA (970 μL, 12.6 mmol) was added to a solution of **29** (377.3 mg, 0.839 mmol) in water-saturated CH_2Cl_2 (94 mL). The reaction mixture was stirred for 6 h and quenched by the addition of H_2O (20 mL). The organic phase was washed repeatedly with H_2O (20 mL), dried and concentrated. Chromatography of the residue on silica gel (38 g, 10/1 hexane/EtOAc) gave **30** (121.3 mg, 35% yield) as a pale yellow oil, with recovery of **29** (131.4 mg, 35%). The same procedure with the recovered **29** was repeated two more times to afford **30** (184.9 mg) in 54% total yield from **29**. Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl, 90.5 mg, 0.356 mmol) was added to a solution of **30** (121.3 mg, 0.296 mmol), (-)-(1*R*, 2*S*)-2-methylcyclopropanecarboxylic acid (-)-**7** (32.6 mg, 0.326 mmol) and Et_3N (103 μL, 0.739 mmol) in dry CH_2Cl_2 (2.5 mL). The reaction mixture was stirred for 3 h, quenched by the addition of aqueous HCl (5%, 10 mL) and diluted with CH_2Cl_2 (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and NaCl (10 mL), dried and concentrated. Chromatography of the residue on silica gel (12 g, 15/1 hexane/EtOAc) gave the corresponding thiol ester (120.0 mg, 82% yield) as a pale yellow oil. TFA (376 μL, 4.88 mmol) was added to a solution of the foregoing thiol ester (120.0 mg, 0.244 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was allowed to warm to 20 °C for 2 h and concentrated under reduced pressure. Dry benzene (6 mL) was added to the resulting mixture and concentrated twice for replacing the reaction solvent with benzene. A solution of the residue containing the corresponding thiol ester ammonium salt in dry benzene (6 mL) was heated to reflux for 2.5 h and quenched by the addition of saturated aqueous $NaHCO_3$ (12 mL). The organic phase was washed with saturated aqueous NaCl (12 mL), dried and concentrated. Chromatography of the residue on silica gel (2 times, 12 g and 8 g, 15/1 hexane/EtOAc and 30/1 benzene/EtOAc) gave curacin A (**1**) (19.6 mg, 10% yield from **29**) as a colorless oil: $[\alpha]_D^{25}$ +63.0° (*c* 0.77 $CHCl_3$), lit. $[\alpha]_D^{20}$ +62.0° (*c* 1.10, $CHCl_3$)[6b]; IR ($CHCl_3$) 2930, 2860, 1720, 1640, 1610, 1430, 1360, 1280, 1170, 1140, 1070, 1000, 960, 910 cm^{-1}; The numbering of curacin A follows that reported by Gerwick *et al.*[3] ^{1}H-NMR (500 MHz, C_6D_6) δ 0.72 (td, 1H, J=8.5, 4.5 Hz, H-20), 0.94 (ddq, 1H, J=14.8, 8.5, 6.0 Hz, H-21), 1.18 (d, 3H,

J=6.0 Hz, CH_3-21), 1.18 (m, 1H, H-20), 1.60 (m, 1H, H-19), 1.66 (m, 2H, H-12), 1.67 (s, 3H, CH_3-10), 2.00-2.27 (m, 8H, H-5, H-6, H-11 and H-14), 2.75 (dd, 1H, J=11.0, 10.0 Hz, H-1), 3.05 (dd, 1H, J=11.0, 8.5 Hz, H-1), 3.05 (m, 1H, H-13), 3.14 (s, 3H, OCH_3-13), 5.02-5.08 (m, 3H, H-2 and H-16), 5.41 (m, 1H, H-4), 5.54 (dt, 1H, J=15.0, 6.5 Hz, H-7), 5.65 (dd, 1H, J=10.5, 9.0 Hz, H-3), 5.83 (ddt, 1H, J=17.0, 10.0, 7.0 Hz, H-15), 5.97 (d, 1H, J=10.5 Hz, H-9), 6.34 (dd, 1H, J=15.0, 10.5 Hz, H-8); ^{13}C-NMR (125 MHz, C_6D_6) δ 12.33, 14.23, 16.00, 16.59, 20.11, 28.14, 32.17, 33.13, 35.79, 38.04, 39.95, 56.31, 74.34, 79.93, 116.79, 125.53, 127.88, 130.85, 131.31, 131.35, 135.32, 136.44, 168.40; FABMS *m/z*: 374 $(M+H)^+$; HRFABMS calcd. for $C_{23}H_{36}ONS$ $(M+H)^+$ 374.2518, found 374.2524.

Preparation of the compound **27**, **28** and (-)-**7** was reported in detail in our previous paper.[14]

References and notes

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