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Asymmetric Synthesis of Stigmatellin and Crocacin C

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The crystalline sulfone **18** (X-ray analysis), prepared from the monoacetate product [i.e., (+)-**12**; 98.2% ee] of the lipase PS-catalyzed acetylation of *anti*,*anti*-2,4-dimethyl-1,3,5-pentantriol (**19a**), has been elaborated either to crocacin C (**10**) or stigmatellin (**1**), thereby providing a convenient divergent access to these two natural antibiotics.

Stigmatellin (**1**), a potent inhibitor of electron flow within the mitochondrial cytochrome bc_1 and the thylakoid b_6f complex,[1] was isolated from a strain of the myxobacterium *Stigmatella aurentiaca* by Reichenbach and Höfle.[2] Owing both to poor stability in acidic conditions—slow decomposition was noticed in aqueous solution at below pH 5—and toxicity, using this product as a phytosanitory agent is precluded. However, the ability of the stigmatellin molecule to form stable adducts with the aforementioned complexes makes this compound an invaluable tool for studying the respiration system.[3] The absolute configuration of stigmatellin (**1**) was established by Enders, at first by identifying the diacid (i.e., **3**) formed along the diphenol **2a** by degradation of natural stigmatellin with a sample,[4a] and next by synthesizing stigmatellin (**1**) from the monoacid **4a** (Scheme 1).[4b] As shown, alkylation of 3-pentanone with the O-PMB derivative of 3-iodopropanol by means of the SAMP [i.e., (*S*)-1-amino-2-methoxymethylpyrrolidine]hydrazone methodology was followed by titanium(IV)-mediated aldol condensation of the resulting ketone and benzyloxyacetaldehyde. *Anti* reduction of the main aldol product then afforded the indicated *anti*,*anti*,*syn*-stereotetrad diol, which was converted into the acid **4a** in a few steps. Condensing **4a** and the MOM derivative **2b** then gave the ester **5a**, which was cyclized to the chromone **6a** under basic conditions. Hydrogenation of the benzyl group of **6a** was followed by oxidation of the formed alcohol **6b** to the aldehyde **7** to furnish, after hydrolysis of the MOM group, the sensitive aldehyde **8**, which was elaborated to stigmatellin (**1**) by Horner–Wittig olefination with the phosphonate **9a**.

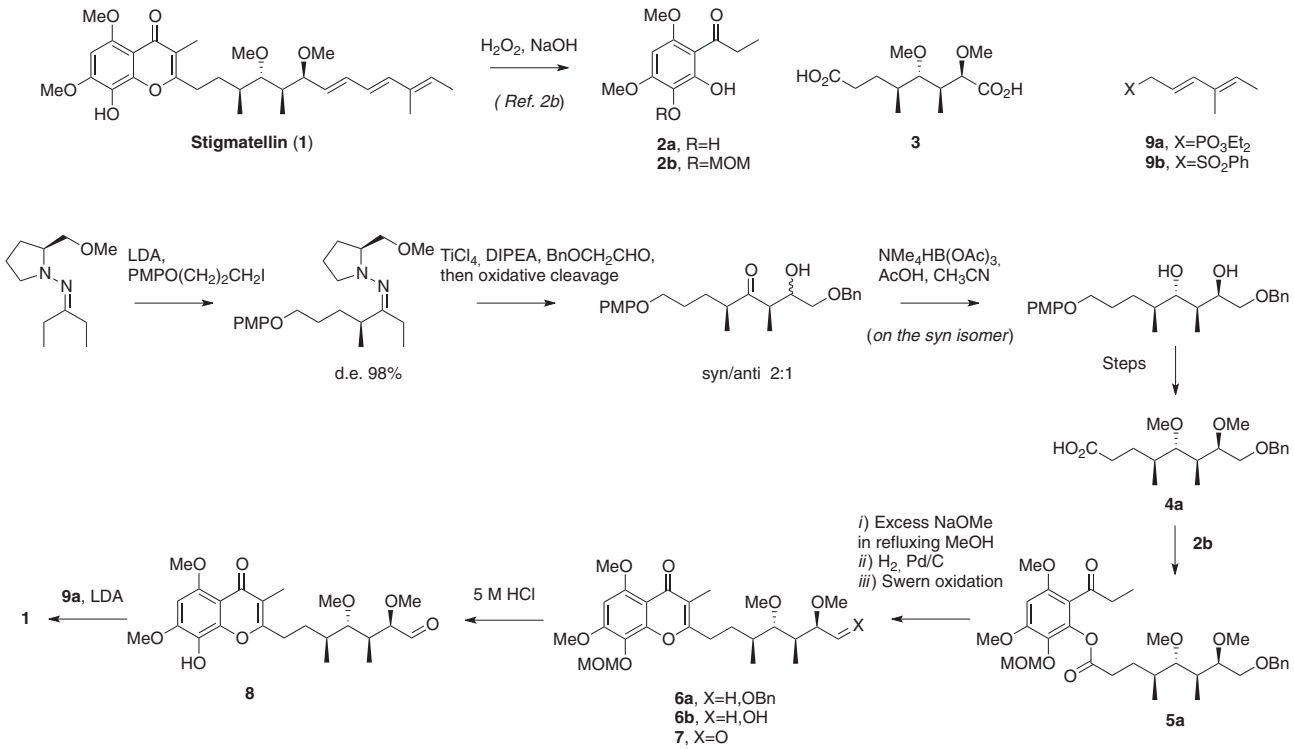
Further examination of myxobacteria has resulted in the isolation of crocacin C (**10**), alongside a mixture of the crocacins A, B, and D from strains of *Chondromyces crocatus* and *Chondromyces pediculatus* (Scheme 2).[5] Not too surprisingly, given the similarities of the crocacin and the stigmatellin molecule, these cytotoxic compounds also inhibit the flow of electrons in the bc_1 and the b_6f complexe.[5,6] Various approaches to the crocacins have been reported,[7,8] and discussed in reviews.[9] The absolute configuration of crocacin C (**10**) has been established by Rizzacasa.[7] As shown, condensation of the depicted ketone and cinnamaldehyde was followed by *anti* reduction of the main aldol product to obtain, after O-methylation of the resulting diol and desilylation, the indicated *anti*-*anti*-*syn*-stereotetrad alcohol, which was elaborated to (+)-crocacin C (**10**) via the methyl ester **11**.

Previously, we had attempted to synthesize stigmatellin (**1**) by using a sulfone-mediated alkylation procedure [*a*] strategy in Scheme 3].[10a] To this end, the monoacetate (+)-**12**, the 2*R*,3*S*,4*S* configuration of which had previously been established,[10b] had been converted to the aldehyde **13** by way of the diolsulfide **14a**. Coupling **13** and the dienyl sulfone **9b** under the conditions of the Julia olefination reaction had indeed afforded the unsaturated sulfide **15a**. However, owing to the sensitivity of the hexatrienyl residue, oxidizing this sulfide into the corresponding sulfone **15b** had proved unfeasible. Using the *b*) strategy was no more rewarding.[10c] Thus, reacting the chromone aldehyde **16**, prepared in a few steps from **14a**, with the organolithium generated by treating the stannane **17** with butyllithium, and then quenching the reaction mixture with MeI had afforded a trienyl chromone that could not be *strictly* identified with a sample of the O-benzyl derivative of stigmatellin.

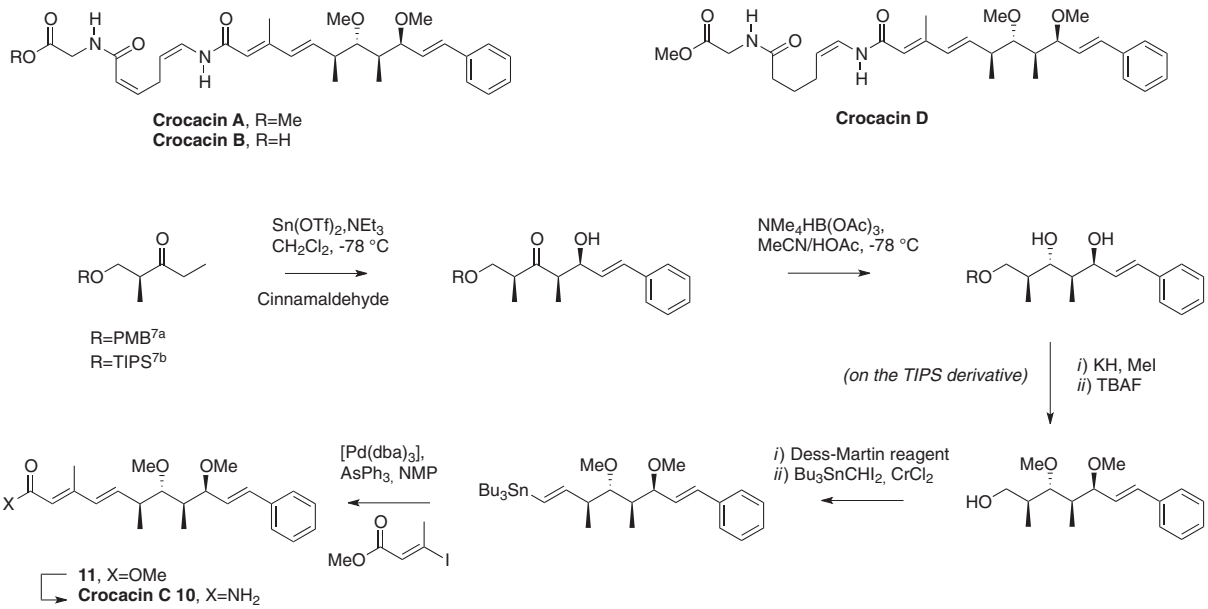
Bearing all preceding observations in mind with a view to designing a divergent approach to stigmatellin (**1**) and to crocacin C (**10**), the alternate plan depicted in Scheme 3 [i.e., *c*) strategy] has been examined, and we describe in this publication the results of this study.

Results and Discussion

Central in this plan was the stereocontrolled elaboration of the aldehyde **13** to the key sulfone intermediate **18** (Scheme 4). Keeping with the strategy previously used to prepare the sulfide **15a**, the *anti*,*anti*-stereotriad triol **19a**, which was obtained in pure state by methanolysis of the known[11] silyl ether **19b** (see Experimental), was reacted with vinyl acetate in THF and added *Pseudomonas fluorescens* lipase (PFL) at rt for ca. 5–6 d to obtain, as reported,[10b] the monoacetate (+)-**12** [70%; 97.0% ee (by GC on Cyclodextrin B®)]. Brief screening of available lipases showed the rate of this esterification to be significantly increased by using Amano lipase PS (PSL) as a catalyst, the reaction then going to completion in ca. 1 h at rt, at the expense



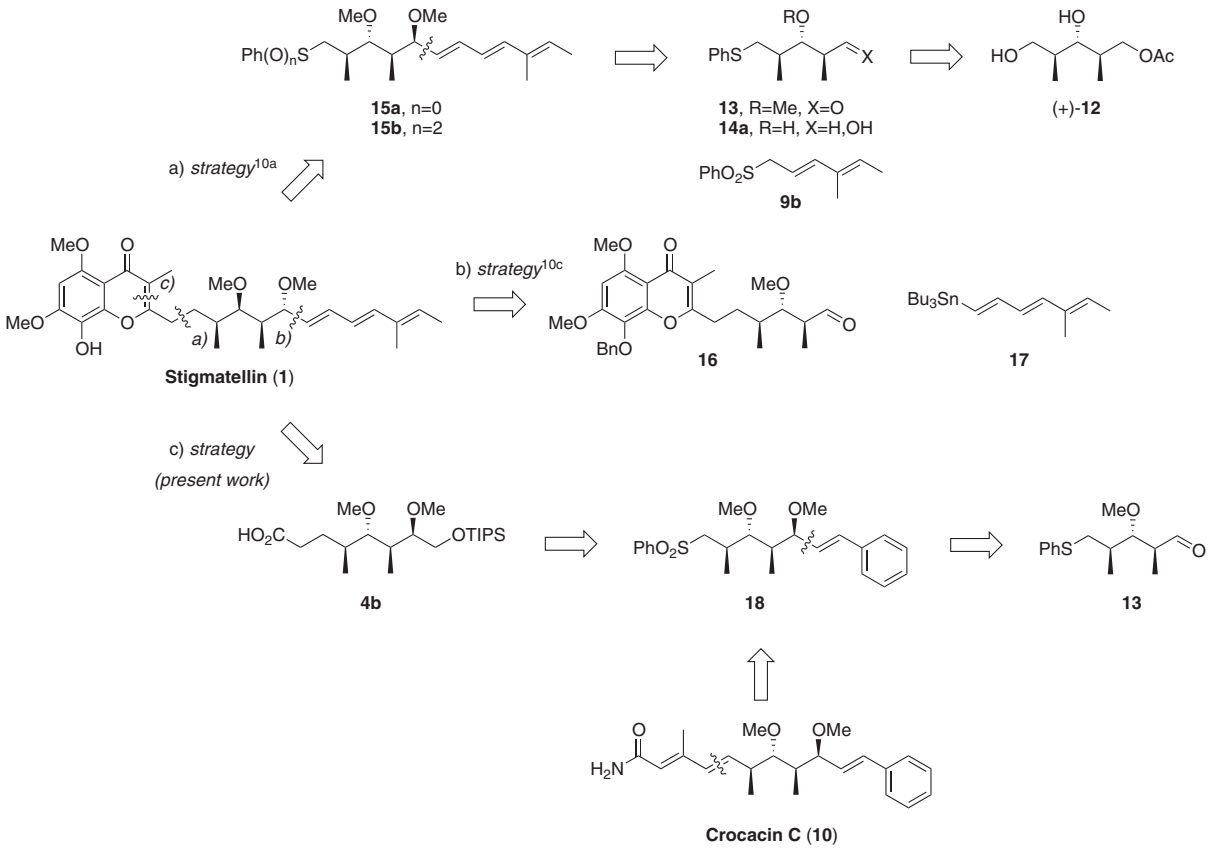
Scheme 1. Enders synthesis of stigmatellin (**1**).[4b]



Scheme 2. Rizzacasa synthesis of crocacin C (**11**).[7]

of the selectivity however (91% ee), a problem that was solved by lowering temperature. Thus, reacting **19a** with vinyl acetate in THF with added PSL 6 h at ca. −15 °C, and then at 0 °C for a further 6 h, when the variation of the enantiomeric ratio was insignificant in GC, afforded, after separation of the bis-acetylation product **20** (31%) by column chromatography, the monoacetate (+)-**12** (69%) with acceptable selectivity (98.2% ee). Interestingly, treating **20** with K_2CO_3 in methanol gave the triol **19a** in good yield (92%).

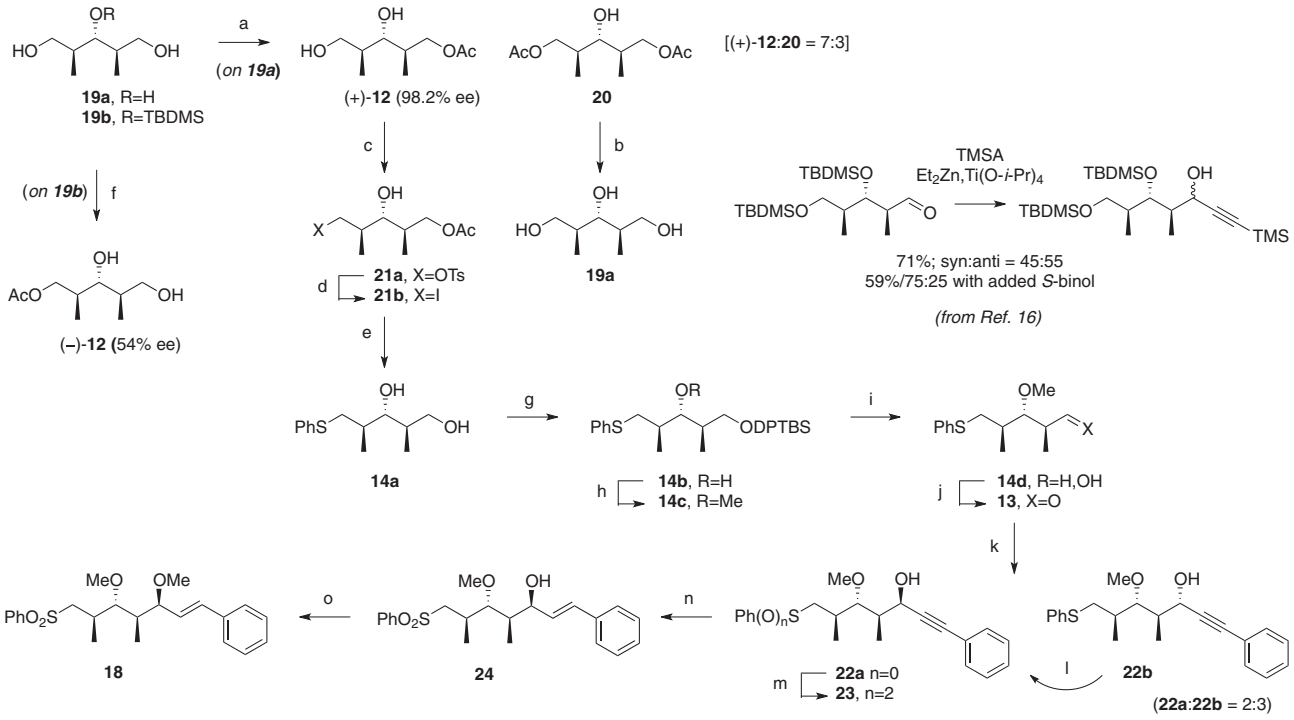
Another possibility was to submit the O-TBDMS derivative **19b** to the preceding acetylation conditions. *Pseudomonas* lipase was verified not to be selective: the corresponding bis-acetate was the main product. By contrast, a good selectivity (97% ee) has been observed with *Candida rugosa* lipase (CRL) as a catalyst, the pro-*S* branch being affected in this case.[12] However, possibly due to discrepancy in the grade of the enzyme used, this result could not be perfectly reproduced. Treating, as described, the monoacetate product thus obtained



Scheme 3.

with buffered TBAF indeed afforded the monoacetate (−)-**12** but the optical purity of this product was only moderate (54% ee; by GC) and no more effort was expended in this direction. Although effective on milligram scale, changing the primary hydroxy group of (+)-**12** to a phenylthio substituent by using the $PhSSPh \cdot PPh_3$ reagent proved problematic on scale-up: after two days, the reaction was incomplete and a little racemization of the used acetate was observed by GC. Accordingly, the conversion of this monoacetate to the diolsulfide **14a** was realized by means of the indicated tosylation/nucleophilic displacement reaction sequence [conditions c) and d) in Scheme 4] to obtain successively the tosylate **21a** and the light-sensitive iodide **21b**, which was immediately reacted with sodium thiophenoxide in EtOH. In situ addition of K_2CO_3 to hydrolyse the acetate then afforded **14a** in good yield [overall 92%, from (+)-**12**]. Importantly, the optical purity of the used acetate was not altered during the tosylation process, as evidenced by ^{1}H NMR analysis of **14a** with added [Eu(hfc)$_3$].[13] Next, diolsulfide **14a** was reacted with DPTBSCl to give **14b**, which was methylated to **14c** by treatment with methyl iodide and freshly sublimed potassium *t*-butoxide; this was easier to manipulate, and gave a better result in this case, than potassium hydride. Treating **14c** with TBAF then afforded the hydroxysulfide **14d** (95% overall, from **14a**), which was quantitatively oxidized to **13** under Swern conditions, with DIPEA used as a base to avoid epimerization.[14]

Of the various options available to install the styryl residue, condensing the aldehyde **13** and phenylacetylene, then reducing the carbon–carbon triple bond of the resulting acetylenic alcohol appeared as the most convenient. Various conditions have been designed to control the stereochemical course of the addition of terminal acetylenes onto the aldehyde carbonyl group.[15] Of great concern to us was the reagent matching–mismatching effect observed by Marshall in a strongly related case.[16] As shown, whereas the condensation of the depicted *anti*,*anti* aldehyde and a zinc derivative of trimethylsilylacetylene (TMSA) proceeded with poor selectivity, a variation of the isomeric ratio was observed by using the Ti(O-*i*-Pr)$_4$/BINOL complex as a catalyst,[17] with the *syn* condensation product favoured when the *S*-BINOL ligand was used; both the effect and the yield were only moderate, however. Deceptively, reacting **13** with phenylacetylene under these conditions resulted in extensive decomposition with loss of the methoxy group (by NMR) and a similar observation was made by using Carreira conditions [viz. Zn(OTf)$_2$-*N*-methylephedrine complex in CH_2Cl_2].[18] It is likely that, due to bidentate coordination of the sulfur and the methoxy oxygen atom to a zinc ion,[19] Lewis acid-assisted elimination of the methoxy group occurred and a possibility would have been to convert acetate (+)-**12** to the Marshall substrate. A more practical solution was found by reacting **13** with the lithio derivative of phenylacetylene in ether at low temperature to obtain an approximately 2:3 mixture (by ^{1}H NMR) of the diastereomeric alcohols **22a** and **22b** in good yield (94% from **14c**). Owing to a large difference in the polarity of the two components on TLC, separation of this mixture was efficiently realized on a multi-gram scale by column chromatography to afford successively **22a** (39.5%) and its epimer **22b** (54.5%); these structures were attributed



Scheme 4. Reagents and conditions: a) Vinyl acetate (2 equiv), PSL (143 mg mmol^{-1}), THF; −15 °C, 6 h, then 0 °C, 6 h (69%). b) 0.7 M (in MeOH) K_2CO_3 (1 equiv); rt, 16 h (92%). c) Tosyl chloride (1.1 equiv), pyridin (6.2 equiv); 0 °C, 1 h, then 18 h in a refrigerator (100%). d) NaI (3.1 equiv), acetone; rt, 4 h, then 50 °C, 2 h (100%). e) NaSPh (2 equiv), EtOH; rt, 5 h, then K_2CO_3, rt, 1 h (92%). f) Vinyl acetate, CRL, then TBAF·3H_2O/HOAc as described in Ref. 12 (47%). g) DPTBSCl (1 equiv), imidazole (2.5 equiv), DMF; rt, 14 h (100%). h) KO-*t*-Bu (2 equiv), MeI (1.8 equiv), THF; −78 °C, 15 min, then rt, 2 h (95%). i) TBAF·3H_2O (2 equiv), THF, rt, 16 h (100%). j) Oxalyl chloride (1.5 equiv), DMSO (2.4 equiv), DIPEA (5.1 equiv), CH_2Cl_2; −78 °C, 30 min, then 0 °C, 30 min. k) Lithium phenylacetylide (1.5 equiv), 1:6 hexane/ether; −78 °C, 2 h (94%, from **14c**); l) Benzoic acid (2.5 equiv), DEAD (2.1 equiv), PPh_3 (2.7 equiv), benzene; rt, 22 h, then 1 M (in MeOH) KOH (9 equiv), rt, 1.5 h (70%). m) 30% H_2O_2 (5 equiv), $MnSO_4$·H_2O (0.05 equiv), 1:1 0.2 M aqueous $NaHCO_3$/acetonitrile; rt, 16 h (98%). n) 70% (in toluene) Red-Al (1.6 equiv), ether; −20 °C, 5 h (100%). o) KO-*t*-Bu/MeI in conditions h) (90%).

later. Reacting the more polar component **22b** with benzoic acid under the conditions of the Mitsunobu reaction,[20] and then hydrolyzing the resulting benzoate product afforded additional sulfide **22a** (70%; total 77.6%). Oxidation of this sulfide using the mild conditions designed by Nàjera[21] then provided the acetylenic sulfone **23** in good yield (98%). Mono-hydrogenation of the carbon–carbon triple bond of **23** was conveniently realized by using Red-Al in a toluene/ether mixture at −20 °C[22] to give almost quantitatively the pure E (NMR) sulfone **24**. Reacting this product in preceding methylation conditions (MeI/KO-*t*-Bu) then afforded, after a brief purification by column chromatography, and recrystallization from ether of the solid product thus obtained, the sulfone **18** (90%) as white crystals that could be analyzed by X-ray crystallography. The Mercury structure generated from the collected data showed this compound to have the desired *anti*,*anti*,*syn* configuration (Figure 1). Since the monoacetate (+)-**12** used as a precursor was 2*R*,3*S*,4*S*, it follows that the structure of this sulfone was indeed **18**, that the less polar product of the **13**/phenylacetylene condensation was **22a**, and that the more polar product was **22b**. This was further confirmed by converting **18** into crocacin C (**10**) (Scheme 5).

Synthesis of Crocacin C. Not too surprisingly, given the low acidity of this sulfone, almost no conversion was observed by reacting **18** with the bromoester **25** under the conditions originally designed by Julia for preparing retinoic acid (*viz.* excess KO-*t*-Bu/THF at rt);[23] a poor result was also obtained by first deprotonating **18** with BuLi, and reacting the resulting sulfone anion with **25**: the product mainly consisted of **18**, together with a complex mixture of unidentified polar products (TLC). A better result was acquired by using the O-TBDMS derivative **26a** of γ-bromoprenol **26b** as an isoprenylation reagent.[24]

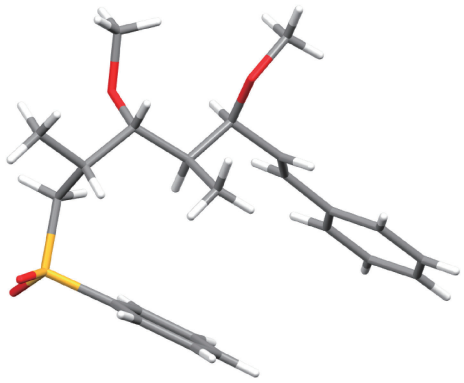
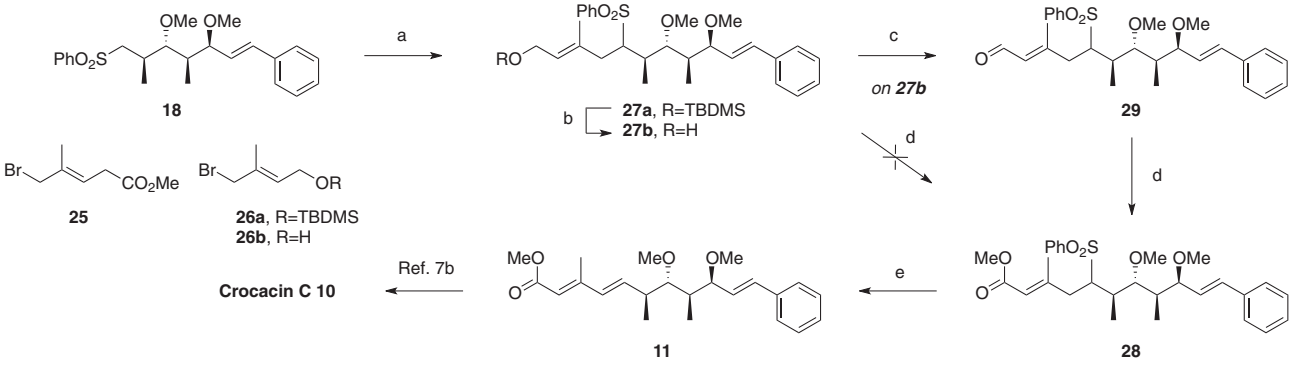
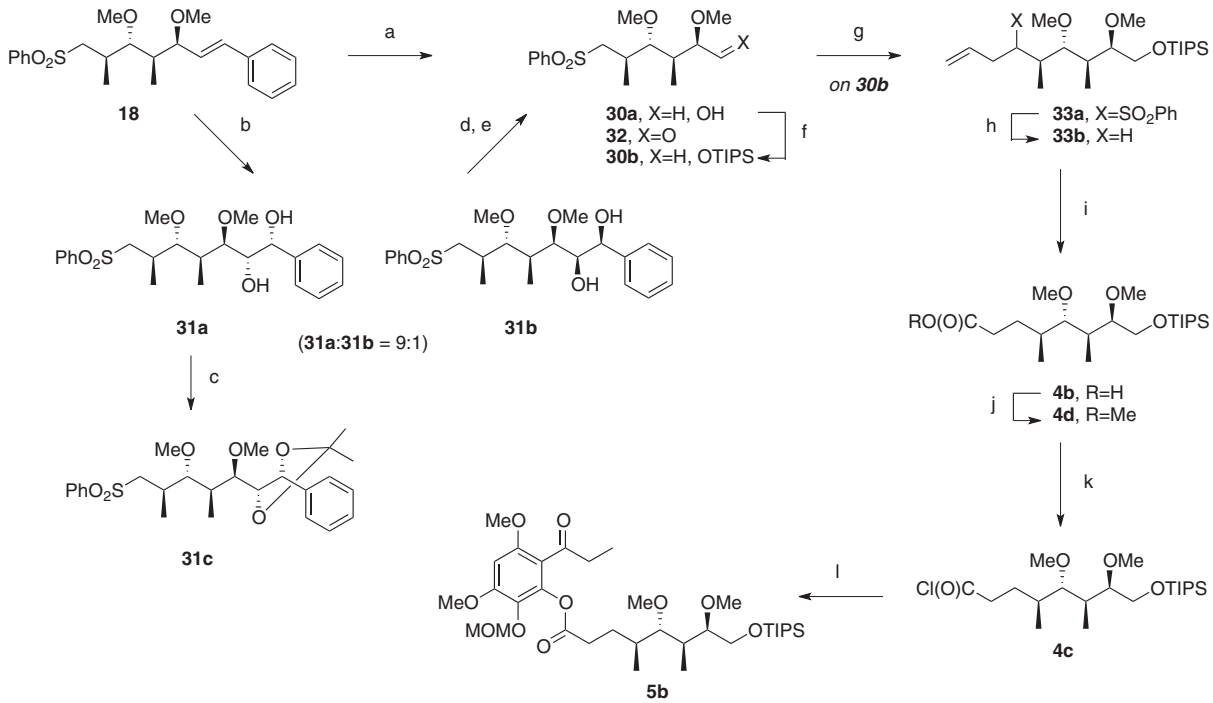


Figure 1. X-ray structure of sulfone **18**.

Thus, reacting the lithium anion of **18** with **26a** at ca. −78 °C in a THF/HMPT mixture afforded the sulfone **27a** (65%) as a



Scheme 5. a) 1.6 M (in hexane) BuLi (1.3 equiv), **26a** (1.5 equiv), HMPT (1.3 equiv), THF; −78 °C, then rt, 2 h (65%). b) TBAF·$3H_2O$ (1.1 equiv), THF; 0 °C, 2 h (95%). c) MnO_2 (20 equiv), 5:1 hexane/CH_2Cl_2; 0 °C, 2 h (82%). d) MnO_2 (20 equiv), NaCN (5.3 equiv), MeOH; rt, 1 h (69%). e) KO-*t*-Bu (1.8 equiv), THF; −5 °C, 1.5 h (67%).



Scheme 6. a) O_3/O_2, 4:1 CH_2Cl_2/MeOH; −78 °C, then $NaBH_4$ (2 equiv), rt, 5 h (89%). b) 0.15 M aqueous OsO_4 (0.2 equiv), NMO (1.1 equiv), 10:3:1 *t*-BuOH/THF/H_2O (33 mL mmol^{-1}); rt, 15 h (100%). c) 2-methoxypropene (2 equiv), PPTS (0.1 equiv), CH_2Cl_2; rt, 48 h (67%). d) $NaIO_4$ (2 equiv), 10:3:1 *t*-BuOH/THF/H_2O; 35–40 °C, 15 h. e) $NaBH_4$ (2 equiv), MeOH; rt, 3 h (92%, from **18**). f) TIPSOTf (1.1 equiv), 2,6-lutidine (2.2 equiv), CH_2Cl_2; rt, 30 min (98%). g) *n*-BuLi (1.3 equiv), HMPA (1.3 equiv), allyl bromide (1.5 equiv); −78 °C, 1 h (93%). h) Mg (20 equiv), MeOH; reflux, 3 h (88%). i) $RuCl_3 \cdot xH_2O$ (0.2 equiv), $NaIO_4$ (4.1 equiv), 3:3:2 $CCl_4/CH_3CN/H_2O$; rt, 15 h (60%). j) TMSDM (1.5 equiv), 2:3 toluene/MeOH, rt, 1 h (98%). k) 3 M aqueous KOH, MeOH (1.5 M); 35–40 °C, 15 h, then $(COCl)_2$ (2 equiv), DMF (3 drops), ether; rt, 3 h (99%). l) **2b** (1 equiv), NBu_4HSO_4 (0.06 equiv), 1:1 20% aqueous K_2CO_3/benzene; rt, 20 h (84%).

mixture of diastereomers (ratio 9:1 by ^{1}H NMR); **18** (9%) was also isolated. Treating **27a** with TBAF then afforded the hydroxy sulfone **27b** (95%; same isomeric ratio). Owing to the sensitivity of the styryl residue to strong oxidants, oxidation of **27b** to the methyl ester **28** was attempted using the mild conditions designed by Corey to convert allylic alcohols into corresponding methyl acrylates.[25a] Reacting, as described, **27b** with activated MnO_2 in methanol with added sodium cyanide afforded a complex mixture (by TLC) and no more success was encountered by using a thiazolium salt in place of the cyanide.[25b] However, oxidizing **27b** with MnO_2, and then reacting the isolated aldehyde **29** (83%) under the aforementioned oxidation conditions afforded the sulfone **28** in acceptable yield (69%). Finally, treating **28** with potassium *t*-butoxide in THF furnished the methyl ester **11** (67%; same NMR features and optical properties as reported), which has been converted to crocacin C **10**.[7b] Attempt to convert directly the aldehyde **29** to **10** by using a Gilman modification[25c] of the Corey procedure resulted only in decomposition.

Synthesis of Stigmatellin. The elaboration of the sulfone **18** to stigmatellin (**1**) by way of the acid **4b** was next examined (Scheme 6). In a first mmol-scale experiment, **18** was treated

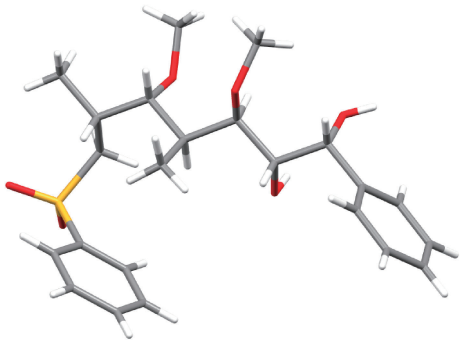


Figure 2. X-ray structure of diol **31a**.

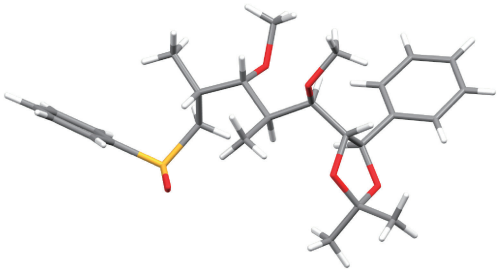


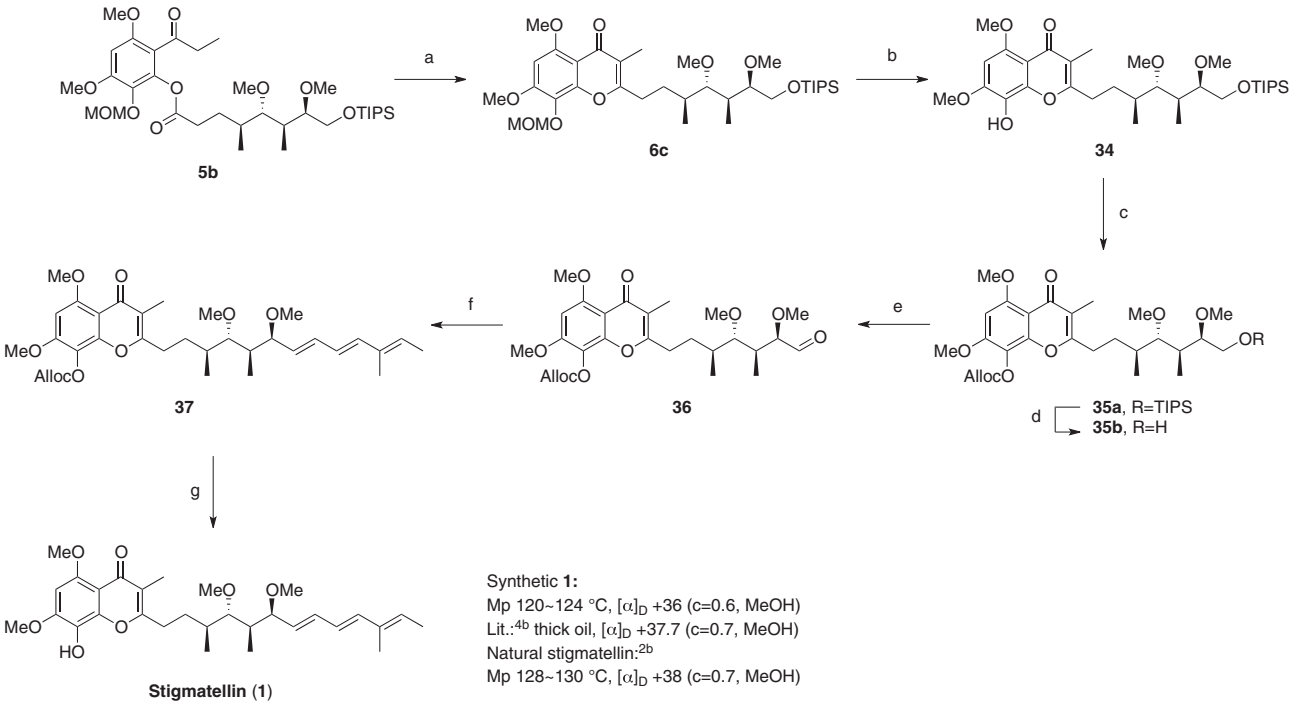
Figure 3. X-ray structure of acetonide **31c**.

with ozonised oxygen under standard conditions (MeOH/CH_2Cl_2, −78 °C) to give, after treatment with sodium borohydride, the hydroxy sulfone **30a** in good yield (89%). Surprisingly, extensive decomposition occurred on scale-up, as evidenced by TLC analysis. Having failed to identify the origin of this discrepancy, we experimented with various oxidative cleavage methodologies[26] but none of them proved satisfactory, giving either over-oxidized products ($KMnO_4$/$NaIO_4$) or, after treatment with $NaBH_4$, partially epimerised **30a** (OsO_4/$NaIO_4$). A better result was observed by proceeding in two steps.

Reacting **18** with OsO_4 in a *t*-BuOH/THF/H_2O mixture with added *N*-methylmorpholine *N*-oxide (NMO) resulted in the progressive precipitation of the dihydroxy sulfone **31a** (73%), as established by X-ray analysis (Figure 2). Treating the filtrate with sodium sulfite and then processing the resulting mixture gave additional **31a**, admixed with an isomeric diol whose structure is, by deduction, **31b** (100% total; ratio 9:1); an X-ray structure was also obtained for the acetonide (i.e., **31c**) derived from diol **31a** by treatment with excess 2-methoxypropene and added PPTS (Figure 3).

This oxidation deserves a few comments. Using a low concentration (ca. 0.03 M) proved essential: attempts at lowering the dilution in order to complete the precipitation of the diol **31a** resulted in the formation of a grey gummy product containing osmium and treatment with sodium sulfite afforded the diol product in moderate yield (56%). Lower yields were also observed using NMO monohydrate as a co-reagent, or aqueous acetone as a solvent. Surprisingly, Sharpless reagent conditions [$Fe(CN)_6K_3$/OsO_4] were ineffective. Finally, reacting the **31a/31b** mixture with $NaIO_4$ at ca. 30–35 °C in the preceding ternary solvent system afforded the sensitive aldehyde **32**, which was immediately reduced into the alcohol **30a** with sodium borohydride (overall 92% from **18**) to obtain, after treatment with TIPSOTf under standard conditions, the O-TIPS derivative **30b** in good yield (98%). Treating **30b** with butyllithium at low temperature, and then reacting the resulting lithium derivative with allyl bromide afforded the sulfone **33a** (93%), which was heated with magnesium in methanol to give **33b** (88%). Cleavage of the C=C bond of **33b** was then realized using the $RuCl_3$/$NaIO_4$ reagent to give the acid **4b** in satisfactory yield (60%). An attempt at converting **4b** into the acid chloride **4c** by treatment with oxalyl chloride resulted in partial decomposition into aldehydic compounds (NMR). A better result was acquired by first reacting **4b** with trimethylsilyldiazomethane (TMSDM) to obtain the methyl ester **4d** (98%). Next, treating **4d** with methanolic KOH afforded, after removal of the solvents in vacuo, a salt mixture that was thoroughly dried (see Experimental) before being reacted with oxalyl chloride to give pure **4c** in excellent yield (99%). Condensing **2b** and **4c** in a two-phase solvent system (aqueous K_2CO_3/benzene) with added NBu_4HSO_4[27] then afforded the keto-ester **5b** in good yield (84%). Although the final steps to stigmatellin (**1**) were realized in line with Enders' indications, a few modifications proved useful (Scheme 7).

Notwithstanding the sensitivity of the MOM group to acids, Hirao chromonisation conditions,[28] which had proved efficient in a related case,[10a] were attempted but, as anticipated, a complex mixture of polar products was shown by TLC. Accordingly, **5b** was heated with excess sodium methoxide in methanol for two hours, the reaction mixture then being processed as described for keto-ester **5a**. Deceptively, the chromone **6c** was obtained in low yield (35%), which can be compared with the 75% yield achieved with **5a**. However, acidifying the aqueous phase afforded, after extraction and separation by chromatography, the phenol **2b** and the acid **4b** (63% each) and by recycling these compounds three times the yield could be increased to 90%. The Baker–Vankataraman rearrangement, which is basically a Claisen condensation reaction,[29] was attempted with **5b** by targeting the corresponding titanium enolate.[30] The only result was the selective cleavage of the MOM group, an observation that offered the possibility to circumvent the difficulties experienced by Enders to hydrolyse the MOM group by installing a more suitable protection. This was efficiently realized by reacting the chromone **6c** with $TiCl_4$ in CH_2Cl_2 at low temperature in dilute conditions (−5 °C, 0.05 M). Neutralizing the medium with aqueous sodium bicarbonate as soon as the reaction was complete by TLC—prolonged contact with $TiCl_4$ resulted in cleavage of the silyl ether—afforded quantitatively the hydroxychromone **34**. Prevailing conditions for cleaving sensitive allylic carbonates[31] having been estimated to be compatible with the hexatrienyl residue, **34** was converted into the mixed carbonate **35a** (85%) by using allyl l-benzotriazoyl carbonate (AllocOBT) as a reagent.[32] Treating **35a** with buffered TBAF then afforded the primary alcohol **35b**, which was oxidized to aldehyde **36** under Swern conditions (100%). Adding **36** to the lithium derivative of the phosphonate **9a** as described with **8** was not so effective. The best result was obtained by slowly adding the phosphonate anion to the aldehyde to furnish the O-Alloc derivative of stigmatellin **37** in moderate yield (34%); aldehyde **36** was also isolated (25%). Finally, the Alloc protecting group was smoothly removed by treating **37** with 2-ethylhexanoic acid in CH_2Cl_2 with added [$Pd(PPh_3)_4$] to give, after chromatography



Scheme 7. a) MeONa (20 equiv), MeOH; reflux, 2 h (35%). b) $TiCl_4$ (3 equiv), CH_2Cl_2; 0 °C, 10 min, then saturated $NaHCO_3$ (100%). c) Alloc-OBT (3 equiv), DMAP (1 equiv), CH_2Cl_2; rt, 15 h (85%). d) TBAF·$3H_2O$ (4.8 equiv), HOAc (6 equiv), THF; rt, 5 d (100%). e) DMSO (2.4 equiv), $(COCl)_2$ (1.5 equiv), DIPEA (5.1 equiv), CH_2Cl_2; −78 °C, 30 min, then 0 °C, 30 min (100%). f) **9a** (1.1 equiv), LDA (1.2 equiv), THF; −78 °C, 12 h (34%). g) 2-Ethylhexanoic acid (1.5 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), CH_2Cl_2; rt, 2 h (85%).

on buffered silica gel, a colorless thick oil mainly constituted of **1**, along traces of triphenylphosphine oxide, as revealed by TLC and ^{1}H NMR analyses (85%). Further purification of this product by chromatography on silica gel, followed by slow diffusion of hexane into a concentrated toluene solution of the glassy product thus obtained then afforded a white powder showing data in good agreement with those reported for stigmatellin (**1**).

Conclusion

Persevering in the use of sulfone chemistry proved to be a good option, resulting in a convenient divergent access to stigmatellin (**1**) and crocacin C (**10**). Interestingly, the key stereotetrad sulfone **18** was obtained in crystalline form, thus allowing for structure assignment by X-ray analysis. Also worthy of interest is the use of a sulfone isoprenylation/elimination sequence to elaborate this sulfone to crocacin C (**10**). Although the cyanide-catalyzed oxidation of the allylic alcohol **27b** into the ester **28** would merit further investigation, this procedure compares quite favourably with the previously used C_2/C_3 homologation process.

Moreover, in comparison with the aldol condensation methodologies that have been used in early syntheses of these two antibiotic compounds to introduce asymmetry, the lipase-catalyzed acetylation of the readily available *meso* triol **19a** offers a few advantages. Good levels of diastereo- and enantioselectivity were achieved simply by optimizing the homogeneity of this triol by recrystallization and by prolonging the acetylation process—i.e. "The meso trick"—respectively. In addition, the coproduced bis-acetate **20**, easily separated from the mono-acetate product by column chromatography, could be recycled. Altogether, the results presented herein further illustrate the potential of the meso strategy,[33] and of sulfone chemistry, in organic synthesis.

Experimental

General. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-300 instrument at 300 and 75 MHz, respectively; Bruker AC-200 and Bruker DPX-400 for 200/50 and 400/100 MHz for ^{1}H and ^{13}C NMR experiments. Chemical shifts (δ) are reported in parts per million relative to the solvent resonance as the internal standard [$CD(H)Cl_3$, 7.26 and 77 ppm respectively]. Signal multiplicity is described as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. X-ray and elemental analyses were realized at the laboratory of crystallography and the laboratory of analyses of the Faculty of Chemistry of the University of Strasbourg, respectively. Optical rotations were measured at 20 °C using a Perkin-Elmer 341 polarimeter equipped with a sodium lamp (589.3 nM). GC analyses were performed on a HP 6890 apparatus equipped with a J&W Cyclodextrin B column (30 m × 0.32 m × 0.25 mm). Melting points were measured on an Electrothermal apparatus. TLC analyses were performed on silica gel (60 GF254 Merck), with spot visualisation by exposure to UV light (254 nm) or treatment with the H_2SO_4/vanillin reagent. Column chromatography refers to the Stille method using Merck 60H silica gel; unless otherwise stated, a slow gradient elution was utilised. All experiments were performed in dried glassware, under an argon atmosphere (three freeze/pump/thaw cycles for all anionic condensation and alkylation

experiments) with magnetic stirring. All solvents used were freshly distilled from an appropriate reagent [Na benzophenone (ether, THF, DME, benzene, toluene); Mg (MeOH, EtOH), K (*t*-BuOH), CaH_2 (DMSO, DMF, pyridine, diisopropylamine, triethylamine, tributylamine, 2,6-lutidine); K_2CO_3 (EtOAc); CaH_2, then P_4O_{10} (CH_2Cl_2, acetonitrile); P_4O_{10} (hexane, $CHCl_3$, CCl_4); $KMnO_4$ (acetone, HOAc, H_2O)]. Tosyl chloride, benzoic acid and PPh_3 were recrystallized from hexane. KO-*t*-Bu was sublimed just before use. Allyl bromide, allyl chloroformate, oxalyl chloride, TMSCl, thiophenol, and $TiCl_4$ were freshly distilled from CaH_2. Methyl iodide was distilled from CaH_2 and kept over K_2CO_3 with added copper bronze under argon in a sealed flask protected from light. Vinyl acetate was freshly distilled over $CaCl_2$ in a flask equipped with a 25-cm Vigreux column; only middle cuts with constant boiling point (bp 71 °C) were used. *t*-Butyldimethylsilyl chloride, triisopropylsilyl triflate, imidazole, Redal (70% in toluene), $[Pd(PPh_3)_4]$, trimethylsilyldiazomethane (2 M in ether), diethyl azodicarboxylate, OsO_4, hydroxybenzotriazole, and Amano lipase PS were used as received (all reagents from Fluka-Sigma-Aldrich). All other reagents were available. *n*-BuLi solutions (in hexane; only freshly-opened bottles were used) were titrated with *N*-pivaloyl-*o*-toluidine.[34] Diethyl phosphonate **9a** (bp 86 °C at 0.05 Torr) was prepared from tiglinaldehyde as described.[4b] Alloc-OBT was prepared according to Ref. 32 and stored under argon in the dark. Active manganese dioxide was prepared from $KMnO_4$ and $MnSO_4$ as described.[35] 0.15 M OsO_4 solution was prepared just before use by diluting OsO_4 (1 g, 3.93 mmol) with H_2O (26.5 mL). pH 2 and pH 5 tartaric buffers were prepared by adding NaOH pellets to 0.7 M tartaric acid (Universal paper as an indicator), and pH 7 phosphate buffer by mixing 0.06 M Na_2HPO_4 (500 mL) and 0.06 M KH_2PO_4 (500 mL). Buffered silica gel was prepared by suspending 60-H Merck silica gel in 10% $NaHCO_3$ and siphoning off the supernatant. The resulting slurry was thoroughly rinsed with water, until almost neutral (pH 8), and dried in air. The crusty solid thus obtained was heated at ca. 110–120 °C in an oven for 4 d before being finely ground with a mortar.

(2*R*,3*s*,4*S*)-3-[(*t*-Butyldimethylsilyl)oxy]-2,4-dimethylpentane-1,5-diol (19b). This compound was prepared, as described in Ref. 11c, by reacting the O-TBDMS derivative of 2,4-dimethyl-1,5-hexadien-3-ol (10 g, 44 mmol) with excess 9-BBN and then treating the resulting hydroboration product with alkaline H_2O_2 to obtain, after chromatography on silica gel (hexane/EtOAc), followed by recrystallization from hot hexane, the diol **19b** as a white solid (8.32 g; 73%). Although practically pure in NMR, this product was dissolved in warm EtOAc (ca. 4–5 mL) and hexane (ca. 40 mL) was cautiously added so as two layers were formed, and then allowed to slowly diffuse at rt for 2 d to obtain **19b** as white crystals (5.7 g; 49.4%). Mp 87–90 °C (Lit.:[11c] mp 45–45.5 °C); TLC (hexane:EtOAc = 1:1) $R_f = 0.45$; ^{1}H NMR ($CDCl_3$): δ 0.14 (s, 6H), 0.93 (s, 9H), 1.00 (d, $J = 7.5$ Hz, 6H), 1.89–2.02 (m, 2H), 2.28 (br s, 2H, O*H*), 3.64 (d, $J = 5.6$ Hz, 4H), 3.72 (t, $J = 4.8$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ −4.2, 15.0, 18.4, 26.0, 38.9, 65.4, 79.6.

(2*R*,3*s*,4*S*)-2,4-Dimethylpentane-1,3,5-triol (19a). Owing to difficulties experienced to fully eliminate residual H_2O, the procedure described in Ref. 11b was modified as follows.

In a flame-dried flask connected to a column of $CaCl_2$, dry HCl (generated by adding 96% H_2SO_4 to NaCl, and dried over $CaCl_2$) was passed into anhydrous methanol with cooling (ice/methanol bath) and the concentration of the resulting solution was estimated by titration with 0.1 M aqueous NaOH using phenolphthalein as indicator. In a flask connected to an argon line, with stirring, 0.77 M methanolic HCl (13 mL, 9.5 mmol) was added dropwise to a cooled (ice bath) stirred solution of diol **19b** (4.93 g, 19 mmol) in anhydrous methanol (55 mL). The resulting mixture was stirred at rt for a further 2 h before being evaporated to dryness in vacuo at ca. 10–15 °C (water bath). The colored solid residue thus obtained was purified by column chromatography (CH_2Cl_2/methanol) to give, after removal of the solvents in vacuo, a white powder that was further dried for 5 d at ca. 10^{-1} Torr in a desiccator over P_4O_{10} and KOH, renewing periodically the drying reagents. Recrystallization from hot anhydrous acetone (ca. 8–9 mL) then afforded the triol **19a** as white crystals (2.66 g; 94%). Mp 92–93 °C (Lit.:[10b] mp 87–90 °C); TLC (CH_2Cl_2:MeOH = 9:1) $R_f =$ 0.25; ^{1}H NMR ($CDCl_3$): δ 1.00 (d, $J = 7.2$ Hz, 6H), 1.87–1.99 (m, 2H), 3.09 (m, 2H, O*H*), 3.55 (m, 1H), 3.63–3.69 (m, 2H), 3.89–3.94 (m, 2H), 4.21 (m, 1H, O*H*); ^{13}C NMR (MHz, $CDCl_3$): δ 14.3, 36.8, 66.9, 83.4.

N. B. Drying **19a** as indicated proved essential to avoid the formation of acetonide during the recrystallization process.

By Hydrolysis of the Diacetate 20. K_2CO_3 (dried 24 h at 110 °C in an oven; 1.36 g, 10 mmol) was added to a solution of **20** (1.66 g, 7.16 mmol) in anhydrous MeOH (10 mL) and the resulting mixture was stirred at rt for 16 h before being evaporated to dryness in a vacuum. The residue was diluted with 1:1 CH_2Cl_2/MeOH (ca. 25–30 mL) and the resulting suspension was filtered on a sintered funnel (washings with 1:1 CH_2Cl_2/MeOH). The pooled filtrates were evaporated and the oily residue was chromatographed on silica gel (CH_2Cl_2/MeOH) to give, after recrystallization from hot acetone, the triol **19a** as white crystals (0.97 g; 92%).

(2*R*,3*S*,4*S*)-3,5-Dihydroxy-2,4-dimethylpentyl Acetate [(+)-12]. In a flask connected to an argon line, and equipped with a tube containing Amano lipase PS (1 g), triol **19a** (1.05 g, 7.1 mmol) was diluted with THF (15 mL). Vinyl acetate (1.3 mL, 14.2 mmol) was added with a syringe and the flask was immersed in an ice/methanol bath, and protected from light with a foil of aluminium. The lipase was added and the resulting mixture was stirred 6 h at −15 °C, and then allowed to warm to 0 °C in ca. 2 h. TLC analysis (CH_2Cl_2:MeOH = 9:1) then indicated that **19a** was mostly reacted. Stirring was pursued at 0 °C (ice bath) and, 6 h later, when variation of the enantiomeric ratio was insignificant (GC), the reaction mixture was diluted with ether (50 mL) and filtered on a bed of Celite (previously washed with ether). The solids were washed with ether and the pooled filtrates were evaporated in vacuo at ca. 10–15 °C (water bath). Chromatography of the residue on silica gel (hexane/EtOAc), followed by elimination of the solvents as above, afforded successively the diacetate **20** (493 mg; 31%) and the monacetate (+)-**12** (875 mg; 69%). (+)-**12**: Colorless oil. $[\alpha]_D$ +26.0 (*c* 5.0, CH_2Cl_2); Lit.:[10b] $[\alpha]_D$ +25.6 (*c* 4.3, CH_2Cl_2); TLC (CH_2Cl_2:MeOH = 9:1) $R_f = 0.41$; ^{1}H NMR ($CDCl_3$): δ 0.99 (d, $J = 2.4$ Hz, 3H), 1.02 (d, $J = 2.4$ Hz, 3H), 1.80–2.00 (m, 2H), 2.01 (s, 3H), 2.59 (br s, 1H, O*H*), 3.16–3.66

(m, 3H, in which O*H*), 3.83–3.88 (m, 1H), 4.20 (d, $J = 5.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.5, 14.8, 20.9, 35.9, 36.6, 66.2, 66.9, 79.4, 171.6; GC (130 °C, isotherm) $R_t = 64.5$ and 62.8 min for (+)-**12** (99.1%) and (−)-**12** (0.9%), respectively; Anal. Found: C, 56.80, H, 9.53%. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54%. **20**: colorless oil. TLC (CH_2Cl_2:MeOH = 9:1) $R_f = 0.64$; ^{13}C NMR ($CDCl_3$): δ 14.9, 20.9, 35.5, 66.2, 76.4, 171.3; Anal. Found: C, 56.74, H, 9.04%. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68%.

Conversion of the Monoacetate (+)-12 to the Diolsulfide 14a. Since being only briefly described in the literature,[10b] the procedures used are described thereafter.

(2*R*,3*R*,4*S*)-3-Hydroxy-2,4-dimethyl-5-(tosyloxy)pentyl Acetate (21a). In a flask connected to an argon line, with stirring, tosyl chloride (3.1 g, 16.5 mmol) was added portionwise to a cooled (ice bath) solution (+)-**12** (2.75 g, 14.5 mmol) in pyridine (7.5 mL, 91 mmol). Stirring was continued 1 h at ca. 5 °C and the flask was placed in a refrigerator for 18 h. Sodium tetraborate (1.65 g, 4.35 mmol) was added and the resulting mixture was stirred 2 h at ca. 0 °C before being diluted with CH_2Cl_2 (100 mL) and poured into iced 1 M HCl (100 mL) with stirring. The aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL) and the pooled organic extracts were washed with 1 M HCl (2 × 50 mL), 1% $CuSO_4$ (4 × 50 mL), brine (4 × 50 mL), and dried ($MgSO_4$). The solvents were evaporated and the residue was dried in a vacuum (ca. 10^{-2} Torr) for a few hours to give **21a** as a pale-yellow oil (4.81 g; 100%). $[\alpha]_D$ −13.5 (*c* 0.2, CH_2Cl_2); TLC (ether) $R_f = 0.51$; ^{1}H NMR ($CDCl_3$): δ 0.94 (d, $J = 0.5$ Hz, 3H), 0.97 (d, $J = 0.4$ Hz, 3H), 1.86–2.05 (m, 5H), 2.41 (s, 3H), 2.49 (d, $J = 5.6$ Hz, 1H, O*H*), 3.24–3.33 (m, 1H), 4.06 (d, $J = 5.9$ Hz, 2H), 4.07 (d, $J = 5.5$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 2H), 7.78 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 14.6, 14.9, 20.9, 21.6, 35.2, 35.9, 65.9, 72.5, 74.9, 127.9, 129.9, 132.9, 144.9, 171.4; Anal. Found: C, 55.67, H, 7.35%. Calcd for $C_{16}H_{24}O_6S$: C, 55.80; H, 7.02%.

(2*R*,3*R*,4*R*)-3-Hydroxy-5-iodo-2,4-dimethylpentyl Acetate (21b). NaI (6.41 g, 42.8 mmol) was weighed in a flask and a magnetic stirring bar was added. Air was evacuated to ca. 0.1 Torr and the flask was flamed 15 min before being filled with argon and immersed in an ice bath. In the dark, with stirring, a degassed solution of tosylate **21a** (4.74 g, 13.8 mmol) in anhydrous acetone (27 mL) was added with a syringe and the resulting mixture was stirred 30 min at 0 °C, then 2 h at rt, and finally 4 h at 50 °C (bath). After cooling, the reaction mixture was diluted with hexane (100 mL) and poured into iced water (100 mL). The aqueous phase was extracted with hexane (3 × 50 mL) and the pooled organic extracts were washed with 10% Na_2SO_3 (2 × 50 mL), brine (2 × 50 mL), and dried in a flask wrapped in a foil of aluminium (1:1 K_2CO_3/Na_2SO_3). Still protected from light, the solvents were evaporated and the residue was dried in a desiccator over P_4O_{10} and KOH to give the iodide **21b** as a pale-yellow oil (4.09 g; 100%). $[\alpha]_D$ −14.7 (*c* 8.5, CH_2Cl_2); TLC (hexane:ether = 1:1) $R_f = 0.30$; ^{1}H NMR ($CDCl_3$): δ 1,06 (d, $J = 6.9$ Hz, 6H), 1.58–1.70 (m, 1H), 1.99–2.12 (m, 5H), 3.27–3.31 (m, 1H), 3.39–3.43 (m, 2H), 4.09–4.21 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.3, 15.2, 18.1, 22.6, 34.9, 37.4, 65.9, 77.4, 171.3.

N. B. Owing to sensitivity to light, this product was immediately used for the next step.

(2*R*,3*R*,4*R*)-2,4-Dimethyl-5-(phenylthio)pentane-1,3-diol (14a). Iodide **21b** (4.09 g, 13.6 mmol) was diluted with anhydrous ethanol (16 mL) in a flask connected to an argon line, and equipped with a funnel with a pressure-equalizing system. Anhydrous ethanol was added with a syringe to a flask charged with sodium (0.69 g), and connected to an argon line. When most of the metal was reacted, thiophenol (2.8 mL, 27.3 mmol) was added with a syringe and the resulting solution was siphoned into the funnel with a cannula, and then added dropwise to the cooled (ice bath) iodide solution with stirring. The bath was removed and the stirring was pursued until TLC analysis (ether) showed the reaction was complete (ca. 5 h). K_2CO_3 (1.85 g, 13.65 mmol) was added and the resulting mixture was further stirred at rt for 1 h before being diluted with CH_2Cl_2 and brine (100 mL each). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the pooled organic extracts were washed with 2 M NaOH (1 × 50 mL), brine (2 × 50 mL), and dried (K_2CO_3). The residue left by evaporation of the solvents was purified by column chromatography (hexane/ether) and the oily residue left by elimination of the solvents was dried in a desiccator over P_4O_{10} and K_2CO_3 to give the diolsulfide **14a** as a clear colorless oil (2.99 g; 92%). $[\alpha]_D$ −64.0 (*c* 2.1, CH_2Cl_2); Lit.:[10b] $[\alpha]_D$ −65.0 (*c* 2, CH_2Cl_2); TLC (hexane:ether = 3:7) $R_f = 0.20$; ^{1}H NMR ($CDCl_3$): δ 0.88 (d, $J = 7.0$ Hz, 3H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.82–2.02 (m, 2H), 2.43 (bs, 2H, O*H*), 2.78 (dd, $J = 9.0$, 12.6 Hz, 1H), 3.27 (dd, $J = 3.5$, 12.6 Hz, 1H), 3.43–3.47 (m, 1H), 3.60 (dd, $J = 6.6$, 10.7 Hz, 1H), 3.79 (dd, $J = 3.4$, 10.7 Hz, 1H), 7.13–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 14.2, 16.9, 36.0, 36.1, 36.6, 67.3, 81.1, 125.9, 128.9, 129.2, 137.0; Anal. Found: C, 64.80, H, 8.13%. Calcd for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39%.

(2*R*,3*R*,4*R*)-1-*t*-Butyldiphenylsilyloxy-2,4-dimethyl-5-(phenylthio)pentan-3-ol (14b). In a flask connected to an argon line, DPTBSCl (1.75 mL, 6.73 mmol) and imidazole (1.13 g, 16.6 mmol) were added to DMF (4.6 mL). After 30 min stirring at rt, a solution of the diolsulfide **14a** (1.6 g, 6.66 mmol) in DMF (24 mL) was added with a syringe and the resulting mixture was stirred for 14 h at rt before being diluted with hexane (100 mL) and poured into brine (100 mL). The aqueous phase was extracted with hexane (3 × 30 mL) and the pooled organic extracts were washed with brine (2 × 70 mL), and dried (K_2CO_3). The residue left by evaporation of the solvents was purified by column chromatography (CH_2Cl_2) to afford, after drying in a vacuum, **14b** as a colorless oil (3.2 g; 100%). $[\alpha]_D = -58.2$ (*c* 1.2, CH_2Cl_2); TLC (CH_2Cl_2) $R_f = 0.46$; ^{1}H NMR ($CDCl_3$): δ 0.86 (d, $J = 7.0$ Hz, 3H), 1.06 (s, 9H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.86–1.96 (m, 2H), 2.76 (dd, $J = 9.8$, 12.8 Hz, 1H), 3.37–3.46 (m, 2H), 3.61 (dd, $J = 6.3$, 10.3 Hz, 1H), 3.79 (m, 1H, O*H*)), 3.80 (dd, $J = 3.6$, 10.3 Hz, 1H), 7.12–7.68 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 14.3, 16.9, 19.1, 26.8, 35.9, 36.5, 36.6, 68.4, 80.6, 125.6, 127.8, 128.8, 128.9, 129.9, 132.6, 135.6, 137.4; Anal. Found: C, 72.38; H, 8.31%. Calcd for $C_{29}H_{38}O_2SSi$: C, 72.75; H, 8.00%.

(2*R*,3*R*,4*R*)-1-*t*-Butyldiphenylsilyloxy-2,4-dimethyl-3-methoxy-5-(phenylthio)pentane (14c). Freshly sublimed KO-*t*-Bu (224 mg, 2 mmol) was charged in a flask connected to an argon/vacuum line. THF (5 mL) was added with a syringe and the resulting mixture was thoroughly degassed (three freeze/pump/thaw cycles) before being cooled to −78 °C (dry ice/

acetone bath). With stirring, a degassed solution of the hydroxysulfide **14b** (478 mg, 1 mmol) in THF (5 mL) was added with a syringe, followed 45 min later by methyl iodide (0.09 mL, 1.8 mmol). The reaction mixture was stirred 15 min at −78 °C, then 2 h at rt before being diluted with ether (20 mL) and poured into iced brine (30 mL). The aqueous layer was extracted with ether (3 × 30 mL) and the pooled organic phases were washed with brine (3 × 5 mL), dried (Na_2SO_4/Na_2SO_3), and filtered on a short column of silica gel (washings with ether). The residue left by evaporation of the solvents was dried in a vacuum to give **14c** as a colorless oil (467 mg; 95%). $[\alpha]_D = -11.7$ (*c* 2.8, CH_2Cl_2); TLC (CH_2Cl_2) $R_f = 0.66$; ^{1}H NMR ($CDCl_3$): δ 0.93 (d, $J = 6{,}8$ Hz, 3H), 1.06 (s, 9H), 1.10 (d, $J = 6.9$ Hz, 3H), 1.82–2.03 (m, 2H), 2.71 (dd, $J = 9.5$, 12.5 Hz, 1H), 3.06 (dd, $J = 5.0$, 6.9 Hz, 1H), 3.15 (dd, $J = 3.4$, 12.5 Hz, 1H), 3.38 (s, 3H), 3.68 (d, $J = 7.5$ Hz, 2H), 7.12–7.46 (m, 10H), 7.63–7.68 (m, 5H); NMR ^{13}C ($CDCl_3$): δ 14.8, 17.3, 19.3, 27.0, 35.4, 36.3, 38.5, 61.2, 65.4, 87.0, 125.6, 127.6, 128.8, 129.0, 129.6, 133.9, 135.7, 137.4; Anal. Found: C, 73.11; H, 8.24%. Calcd for $C_{30}H_{40}O_2SSi$: C, 73.12; H, 8.18%.

(2*R*,3*R*,4*R*)-3-Methoxy-2,4-dimethyl-5-(phenylthio)-pentan-1-ol (14d). In a flask connected to an argon line, TBAF·$3H_2O$ (9 g, 28.5 mmol) diluted with THF (28 mL) was added with a syringe to a solution of sulfide **14c** (7.02 g, 14.45 mmol) in THF (18 mL). After 16 h stirring at rt, the reaction mixture was diluted with CH_2Cl_2 (250 mL) and poured into iced brine (350 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the pooled organic extracts were washed with brine (2 × 200 mL), and dried (Na_2SO_4). The residue left by evaporation of the solvents was purified by column chromatography (hexane/ether) to give **14d** as a colorless oil (3.61 g; 100%). $[\alpha]_D = -33.6$ (*c* 3.4, CH_2Cl_2); TLC (ether) $R_f = 0.38$; ^{1}H NMR ($CDCl_3$): δ 0.97 (d, $J = 7.0$ Hz, 3H), 1.12 (d, $J =$ 7.0 Hz, 3H), 1.84–1.96 (m, 1H), 1.98–2.11 (m, 1H), 2.43 (bs, 1H, O*H*), 2.77 (dd, $J = 9.0$, 12.6 Hz, 1H), 3.06–3.10 (m, 1H), 3.22 (dd, $J = 3.8$, 12.6 Hz, 1H), 3.50 (s, 3H), 3.60 (dd, $J = 5.5$, 11.0 Hz, 1H), 3.69 (dd, $J = 3.8$, 11.0 Hz, 1H), 7.14–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 15.4, 17.0, 36.1, 36.6, 37.1, 61.5, 65.9, 90.7, 125.8, 128.9, 129.1, 137.0; Anal. Found: C, 65.87; H, 9.09%. Calcd for $C_{14}H_{22}O_2S$: C, 66.10; H, 8.72%.

(2*S*,3*R*,4*R*)-3-Methoxy-2,4-dimethyl-5-(phenylthio)-pentanal (13). In a flask connected to an argon line, oxalyl chloride (0.57 mL, 6.38 mmol) was diluted with CH_2Cl_2 (9.5 mL). The flask was immersed in a dry ice/acetone bath and DMSO (0.87 mL, 10.2 mmol) was added, followed 30 min later by the hydroxy sulfide **14d** (1.08 g, 3 mmol) diluted with CH_2Cl_2 (4.5 mL). After 30 min stirring, DIPEA (3.58 mL, 21.68 mmol) was added and the stirring was continued 30 min. The reaction mixture was allowed to warm to ca. 0–5 °C, and then further stirred 30 min before being diluted with ether (50 mL) and poured into a mixture of iced brine (100 mL) and ether (50 mL) with vigorous stirring. After 10 min stirring, the aqueous layer was extracted with ether (4 × 50 mL) and the pooled organic phases were washed with water (10 mL), brine (3 × 10 mL), and dried (Na_2SO_4). The solvents were evaporated in vacuo and the residue was dried in a good vacuum (ca. 10^{-2} Torr) for 30 min to give **13** as a strongly-smelling yellow oil (1.09 g). TLC (ether): $R_f = 0.70$; (9:1 hexane/EtOAc) $R_f = 0.23$; ^{1}H NMR ($CDCl_3$): δ 1.05 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 7.1$ Hz, 3H), 1.99–2.12 (m, 1H), 2.62–2.70 (m, 1H), 2.83 (dd, $J = 8.5$, 12.8 Hz, 1H), 3.21 (dd, $J = 4.0$, 12.8 Hz, 1H), 3.36–3.41 (m, 4H), 7.15–7.37 (m, 5H), 9.74 (d, $J = 2.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.0, 16.3, 35.8, 36.9, 48.4, 60.0, 85.9, 126.0, 128.9, 129.1, 136.9, 204.0.

N. B. This sensitive product was immediately used for the next step.

(3*R*,4*R*,5*R*,6*R*)-5-Methoxy-4,6-dimethyl-1-phenyl-7-(phenylthio)hept-1-yn-3-ol (22a); (3*S*,4*R*,5*R*,6*R*)-5-methoxy-4,6-dimethyl-1-phenyl-7-(phenylthio)hept-1-yn-3-ol (22b). In a flask connected to an argon/vacuum line, phenylacetylene (5.5 ml, 49.9 mmol) was diluted with ether (71 mL) and the resulting solution was degassed (three freeze/pump/thaw cycles) before being cooled to −78 °C (dry ice/acetone bath). With stirring, 1.5 M (in hexane) BuLi (27.1 mL, 43.29 mmol) was added with a syringe and the resulting yellow solution was stirred for a further 90 min. A degassed solution of aldehyde **13** (8.4 g, 33.3 mmol) in ether (67 mL) was added progressively with a cannula and the stirring was continued 2 h at −78 °C. Cooled (ice/methanol bath) 2 M aqueous HCl (26 mL) was added dropwise with vigorous stirring and the resulting mixture was allowed to warm to rt. The aqueous layer was extracted with ether (4 × 150 mL) and the pooled organic phases were washed with brine (4 × 50 mL), and dried (K_2CO_3). The residue left by evaporation of the solvents was chromatographed on silica gel (hexane/ether) to give successively the acetylenic alcohol **22a** (4.68 g; 39.5%) and its epimer **22b** (6.45 g; 54.5%). **22a**: Thick colorless oil. $[\alpha]_D = -20.6$ (*c* 1.2, CH_2Cl_2); TLC (hexane:ether = 7:3) $R_f = 0.46$; ^{1}H NMR ($CDCl_3$): δ 1.01 (d, $J = 7.0$ Hz, 3H,), 1.22 (d, $J = 7.0$ Hz, 3H), 1.99–2.09 (m, 1H), 2.11–2.22 (m, 1H), 2.80 (dd, $J = 9.4$, 12.8 Hz, 1H), 3.20 (dd, $J = 4.0$, 12.9 Hz, 1H), 3.45 (dd, $J =$ 3.2, 8.5 Hz, 1H), 3.58 (s, 3H), 4.00 (br s, 1H, O*H*), 4.71 (d, $J =$ 2.3 Hz, 1H, C*H*OH), 7.16–7.48 (m, 10H); ^{13}C RMN ($CDCl_3$): δ 13.8 (C^4CH_3), 17.6 (C^6CH_3), 35.5 (C^6), 36.8 (C^7), 41.0 (C^4), 61.2 (OCH_3), 66.3 (C^3), 85.6 (C^1), 89.1 (C^5), 89.3 (C^2), 122.9 (C_{arom}), 126.0 (C_{arom}), 128.3 (C_{arom}), 128.6 (C_{arom}), 129.1 (C_{arom}), 129.4 (C_{arom}), 131.7 (C_{arom}), 136.8 (C_{arom}); Anal. Found: C, 74.85; H, 7.15%. Calcd for $C_{22}H_{26}O_2S$: C, 74.54; H, 7.39%. **22b**: Thick colorless oil. $[\alpha]_D = -37.1$ (*c* 1.2, CH_2Cl_2); TLC (hexane:ether = 7:3) $R_f = 0.26$; ^{1}H RMN ($CDCl_3$): δ 1.00 (d, $J = 6.8$ Hz, 3H), 1.21 (d, $J = 6.8$ Hz, 3H), 2.04–2.20 (m, 2H), 2.42 (br s, 1H, O*H*), 2.77 (m, 1H), 3.12–3.21 (m, 2H), 3.52 (s, 3H), 4.88 (d, $J = 5.3$ Hz, 1H), 7.14–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 12.8 (C^4CH_3), 17.5 (C^6CH_3), 35.6 (C^6), 35.9 (C^7), 42.1 (C^4), 61.6 (OCH_3), 65.2 (C^3), 86.4 (C^1), 88.3 (C^2), 88.9 (C^5), 122.7 (C_{arom}), 126.0 (C_{arom}), 128.3 (C_{arom}), 128.4 (C_{arom}), 128.9 (C_{arom}), 129.5 (C_{arom}), 131.7 (C_{arom}), 136.9 (C_{arom}).

(3*R*,4*R*,5*R*,6*R*)-5-Methoxy-4,6-dimethyl-1-phenyl-7-(phenylthio)hept-1-yn-3-ol 22a by Epimerization of 22b. Alcohol **22b** (1.04 g, 2.94 mmol) and PPh_3 (2.11 g, 8.05 mmol) were charged in a flask connected to an argon line, and equipped with a funnel with a pressure-equalizing system. Benzene (13 mL) was added with a syringe and the resulting solution was cooled to ca. 10 °C (cold-water bath). A degassed solution of benzoic acid (0.90 g, 7.4 mmol) and DEAD (1.14 mL, 6.23 mmol) in benzene (21 mL) was charged in the funnel with a cannula, and then added portionwise over a period of

ca. 10 h with stirring. The bath was removed and the reaction mixture was further stirred at rt for 16 h. The solvents were removed in vacuo (cold-water bath) and 1 M methanolic KOH (26.2 mL) was added to the crude benzoate product. After 1.5 h stirring at rt, the resulting mixture was diluted with iced brine (100 mL) and extracted with ether (3 × 100 mL). The pooled organic extracts were washed with brine (3 × 20 mL), and dried (Na_2SO_4). The yellow oil left by evaporation of the solvents (5.4 g) was chromatographed on silica gel (ether/hexane) to give pure **22a** (730 mg; 70%).

(3*R*,4*R*,5*R*,6*R*)-5-Methoxy-4,6-dimethyl-1-phenyl-7-(phenylsulfonyl)hept-1-yn-3-ol (23). In a flask connected to an argon line, and equipped with a dropping funnel with a pressure-equalizing system, $MnSO_4 \cdot H_2O$ (0.11 g) was added to a stirred solution of hydroxysulfide **22a** (4.68 g, 13.2 mmol) in acetonitrile (264 mL). With cooling (ice/brine bath), 0.2 M sodium bicarbonate (230 mL) was added to 30% hydrogen peroxide (6.56 mL, 66.0 mmol) and the resulting solution was transferred into the funnel, and then added dropwise over ca. 30 min with vigorous stirring. The resulting mixture was further stirred at rt until TLC analysis (hexane/EtOAc) indicated the reaction was complete (ca. 16 h). NaCl (30 g) was added and, after 30 min stirring, the resulting mixture was extracted with EtOAc (3 × 150 mL). The pooled organic extracts were washed with brine (3 × 50 mL), and dried (Na_2SO_4). The residue left by evaporation of the solvents was chromatographed on silica gel (hexane/EtOAc) to give, after drying in a vacuum, the sulfone **23** as a colorless oil (5 g; 98%). $[\alpha]_D = +9.5$ (*c* 1.1, CH_2Cl_2); TLC (hexane:EtOAc = 7:3) $R_f = 0.27$; ^{1}H NMR ($CDCl_3$): δ 0.92 (d, $J = 7.0$ Hz, 3H), 1.34 (d, $J = 7.0$ Hz, 3H), 1.83–1.95 (m, 1H), 2.37–2.47 (m, 1H), 2.97 (dd, $J = 9.2$, 14.5 Hz, 1H), 3.25 (dd, $J = 2.1$, 14.5 Hz, 1H), 3.37 (dd, $J = 1.7$, 9.6 Hz, 1H), 3.58 (s, 3H), 3.63 (d, $J = 8.6$ Hz, 1H, O*H*), 4.59 (dd, $J = 2.8$, 8.7 Hz, 1H), 7.31–7.96 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 13.7 (C^4CH_3), 19.6 (C^6CH_3), 31.2 (C^4), 41.5 (C^6), 58.1 (C^7), 61.6 (OCH_3), 66.4 (C^3), 85.5 (C^1), 88.8 (C^2), 89.6 (C^5), 122.6 (C_{arom}), 127.9 (C_{arom}), 128.4 (C_{arom}), 128.5 (C_{arom}), 129.4 (C_{arom}), 131.6 (C_{arom}), 133.7 (C_{arom}), 139.9 (C_{arom}); Anal. Found: C, 67.98; H, 7.04%. Calcd for $C_{22}H_{26}O_4S$: C, 68.37; H, 6.78%.

(3*S*,4*R*,5*R*,6*R*,*E*)-5-Methoxy-4,6-dimethyl-1-phenyl-7-(phenylsulfonyl)hept-1-en-3-ol (24). 70% (in toluene) Red-Al (3.39 mL, 12.14 mmol) was diluted with ether (30 mL) in a flask connected to an argon/vacuum line and the resulting solution was thoroughly degassed (three freeze/pump/thaw cycles), then cooled to −30 °C (bath equipped with a refrigeration system). In a flask connected to an argon/vacuum line, a solution of sulfone **23** (2.92 g, 7.59 mmol) in ether (19 mL) was degassed similarly, and then added in ca. 5 min to the stirred Redal solution with a cannula. The reaction mixture was warmed to −20 °C and, after 5 h stirring, cooled to −30 °C before being diluted with ether (200 mL) and poured into iced pH 2 tartaric buffer (200 mL) with vigorous stirring. The aqueous layer was extracted with ether (3 × 150 mL) and the pooled organic extracts were washed with 10% $NaHCO_3$ (75 mL), brine (2 × 75 mL), and dried (Na_2SO_4). The solvents were evaporated in vacuo and the residue was dried in a good vacuum (ca. 10^{-2} Torr) for a few hours to give **24** as a colored oil (2.95 g) that was used for the next step without further purification. TLC (hexane:EtOAc 1:1) $R_f = 0.39$; ^{1}H NMR ($CDCl_3$): δ 0.86 (d, $J = 7.1$ Hz, 3H), 1.29 (d, $J = 6.9$ Hz, 3H), 1.72–1.82 (m, 1H), 2.38–2.48 (m, 1H), 2.79 (d, $J = 5.3$ Hz, 1H, O*H*), 2.98 (dd, $J = 9.4$, 14.3 Hz, 1H), 3.15 (dd, $J = 3.6$, 7.9 Hz, 1H), 3.27 (dd, $J = 2.3$, 14.3 Hz, 1H), 3.49 (s, 3H), 4.50 (m, 1H), 6.21 (dd, $J = 5.2$, 15.9 Hz, 1H), 6.62 (dd, $J = 1.5$, 15.8 Hz, 1H), 7.40–7.96 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 11.6 (C^4CH_3), 18.8 (C^6CH_3), 31.3 (C^6), 40.7 (C^4), 58.2 (C^7), 61.6 (OCH_3), 72.6 (C^3), 89.0 (C^5), 126.4 (C_{arom}), 127.5 (C_{arom}), 127.9 (C_{arom}), 128.6 (C_{arom}), 129.4 (C_{arom}), 130.2 (C^1), 130.7 (C^2), 133.7 (C_{arom}), 136.8 (C_{arom}), 140.0 (C_{arom}).

N. B. Using perfectly deaerated solvents was essential to observe a good yield.[22b]

{[(2*R*,3*R*,4*R*,5*S*,*E*)-3,5-Dimethoxy-2,4-dimethyl-7-phenylhept-6-en-1-yl]sulfonyl}benzene (18). With cooling (dry ice/acetone bath), a degassed solution of crude **24** (2.95 g) in THF (75 mL) was added with stirring to freshly sublimed KO-*t*-Bu (1.70 g; 15.18 mmol) diluted with THF (75 mL), followed 45 min later by methyl iodide (0.85 mL, 13.66 mmol). The resulting mixture was further stirred 15 min at −78 °C, then 10 min at rt before being poured into iced pH 7 phosphate buffer (200 mL). The aqueous phase was extracted with ether (4 × 100 mL) and the pooled organic extracts were washed with an iced mixture of pH 7 buffer and 10% sodium $NaHSO_3$ (2 × 50 mL), brine (3 × 50 mL), and dried (K_2CO_3). The solid residue left by evaporation of the solvents was purified by column chromatography (hexane/ether) to give, after recrystallization from hot ether, the sulfone **18** as white prisms (2.75 g; 90% from **23**). Mp 112 °C; $[\alpha]_D = -1.8$ (*c* 1.1, CH_2Cl_2); TLC (hexane:ether = 1:1) $R_f = 0.31$; ^{1}H NMR ($CDCl_3$): δ 0.76 (d, $J = 7.0$ Hz, 3H), 1.32 (d, $J = 7.0$ Hz, 3H), 1.43–1.54 (m, 1H), 2.35–2.45 (m, 1H), 2.96 (dd, $J = 9.8$, 14.3 Hz, 3.11–3.17 (m, 2H), 3.30 (s, 3H), 3.48 (s, 3H), 3.96–4.00 (m, 1H), 6.10 (dd, $J = 7.5$, 16.0 Hz, 1H), 6.50 (d, $J = 16.0$ Hz, 1H), 7.23–7.93 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 9.7 (C^4CH_3), 19.4 (C^6CH_3), 30.6 (C^6), 42.0 (C^4), 56.4 (C^5OCH_3), 57.7 (C^7), 61.6 (C^3OCH_3), 80.9 (C^3), 86.9 (C^5), 126.4 (C_{arom}), 127.7 (C_{arom}), 127.8 (C_{arom}), 128.6 (C_{arom}), 129.0 (C^2), 129.3 (C_{arom}), 132.3 (C^2), 133.5 (C_{arom}), 136.6 (C_{arom}), 140.2 (C_{arom}).

(*E*)-[(4-Bromo-3-methylbut-2-en-1-yl)oxy](*t*-butyl)dimethylsilane (26a). γ-Bromoprenol **26b** (85:15 mixture of the E and the Z isomer; by ^{1}H NMR) was prepared from isoprene as described in the literature.[36a] The procedure described thereafter is adapted from Ref. 36b.

In a flask connected to an argon line, and equipped with a tube containing 60% (in paraffin) NaH (226.8 mg, 5.66 mmol), the γ-bromophenol **26b** (465 mg, 2.83 mmol) was diluted with THF (40 mL). The flask was immersed in a cold-water bath and NaH was added with stirring. After 45 min stirring at ca. 10–15 °C, when the Z alkoxide was fully reacted, as evidenced by quenching an aliquot with excess TMSCl and examining the resulting product in ^{1}H NMR [diagnostic signal for the Z product: s at δ 1.0 ppm (200 MHz)], TBDMSCl (427.3 mg, 2.83 mmol) was added. After 2 h stirring at rt, the reaction mixture was poured into iced 10% $NaHCO_3$ (50 mL) and extracted with ether (3 × 20 mL). The pooled organic extracts were washed with brine (2 × 10 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was diluted with pentane and filtered on a short column of silica gel (washings with ether) to

give, after removal of the solvents, a colorless oil that was further purified by bulb-to-bulb distillation to give the pure E bromide **26a** (473 mg; 59%). Bp 65–70 °C (bath) at 0.2 Torr; Lit.:[24a] Bp 103 °C at 3 Torr; TLC (CH_2Cl_2) $R_f = 0.66$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.10 (s, 6H), 0.90 (s, 9H), 1.75 (s, 3H), 3.96 (s, 2H), 4.21 (d, $J = 6.0$ Hz, 2H), 5.72 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.2, 15.0, 18.3, 25.9, 40.6, 61.2, 130.7, 132.7.

***t*-Butyl{[(2*E*,5*R*/5*S*,6*R*,7*R*,8*R*,9*S*,10*E*)-7,9-dimethoxy-3,6,8-trimethyl-11-phenyl-5-(phenylsulfonyl)undeca-2,10-dien-1-yl]oxy}dimethylsilane (27a).** In a flask connected to an argon/vacuum line, a solution of sulfone **18** (91 mg, 0.226 mmol) in THF (1 mL) was thoroughly degassed (three freeze/pump/thaw cycles), and then cooled to −78 °C (dry ice/acetone bath). With stirring, 1.6 M (in hexane) BuLi (0.18 mL, 0.288 mmol) was added, followed 1 h later by HMPA (0.05 mL, 0.294 mmol), and the bromide **26a** (94.4 mg, 0.339 mmol) diluted with THF (0.5 mL). The resulting mixture was further stirred 1 h at −78 °C, then 2 h at rt before being diluted with ether (10 mL) and poured into iced 10% $NaHCO_3$ (10 mL). The aqueous phase was extracted with ether (3 × 20 mL) and the pooled organic extracts were washed with brine (3 × 5 mL), and dried (Na_2SO_4). The residue left by evaporation of the solvents was chromatographed on silica gel (hexane/EtOAc) to give successively **27a** (80.7 mg; 65%) as a 9:1 mixture of two diastereomers (^{1}H NMR) and the sulfone **18** (8 mg; 9%). TLC (1:1 hexane:EtOAc) $R_f = 0.64$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.01/0.03 (s, 6H), 0.87/0.88 (s, 9H), 0.95/1.10 (d, $J = 7.0$ Hz, 3H), 1.20–1.29 (m, 6H), 1.68–1.77 (m, 1H), 2.17–2.82 (m, 3H), 3.19 (dd, $J = 4.0$, 8.1 Hz, 1H), 3.28/3.29 (s, 3H), 3.42/3.45 (s, 3H), 3.67–4.05 (m, 4H), 5.23–5.27 (m, 1H), 6.11/6.15 (dd, $J = 7.5$, 15.9 Hz, 1H), 6.53/6.59 (d, $J = 15.9$ Hz, 1H), 7.23–7.89 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ −5.2 (Si*C*H$_3$), 10.3/11.8 (C^8*C*H$_3$), 12.8/14.1 (C^6*C*H$_3$), 15.1 (C^3*C*H$_3$), 18.3 [Si*C*(CH$_3$)$_3$], 25.9 [SiC(*C*H$_3$)$_3$], 32.6/37.2 (C^6), 35.1/37.9 (C^4), 41.2/42.0 (C^8), 56.2/56.3 (C^{9}O*C*H$_3$), 59.4 (C^5), 59.8/59.9 (C^1), 60.9 (C^{7}O*C*H$_3$), 81.5/83.3 (C^9), 84.3/87.0 (C^7), 126.4/126.5 (C$_{arom}$), 127.5/127.7 (C^{11}), 127.9/128.2 (C$_{arom}$), 128.5/128.6 (C$_{arom}$), 128.7/128/8 (C^2), 128.9/129.0 (C^{10}), 129.2/129.6 (C$_{arom}$), 131.6/132.6 (C^3), 132.3/132.4 (C$_{arom}$), 133.1/133.2 (C$_{arom}$), 136.6/136.8 (C$_{arom}$), 140.3/140.5 (C$_{arom}$).

(2*E*,5*R*/*5S*,6*R*,7*R*,8*R*,9*S*,10*E*)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenyl-5-(phenylsulfonyl)undeca-2,10-dien-1-ol (27b). The sulfone **27a** (80.7 mg, 0.135 mmol) was reacted with TBAF·3H$_2$O (0.148 mmol) in THF (0.4 mL) 1 h at 0 °C, then 2 h at rt. The reaction mixture was processed as described above for the **14c**/**14d** conversion to give, after purification by column chromatography (hexane/ether), the hydroxy sulfone **27b** (62.4 mg; 95%) as a mixture of two diastereomers (same ratio; by ^{1}H NMR). TLC (hexane:EtOAc = 1:1) $R_f = 0.22$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88/1.19 (d, $J = 7.0$ Hz, 3H), 1.27–1.41 (m, 6H), 1.55–1.78 (m, 1H), 2.03–2.83 (m, 3H), 3.16 (dd, $J = 3.5$, 7.5 Hz, 1H), 3.25/3.26 (s, 3H), 3.39/3.55 (s, 3H), 3.65–3.90 (m, 4H), 5.30–5.39 (m, 1H), 6.11 (dd, $J = 7.8$, 15.9 Hz, 1H), 6.50/6.53 (d, $J = 15.9$ Hz, 1H), 7.21–7.87 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.1/11.8 (C^8*C*H$_3$), 13.3/14.0 (C^6*C*H$_3$), 15.1/15.2 (C^3*C*H$_3$), 32.6/37.2 (C^6), 34.8/37.9 (C^4), 40.8/40.9 (C^8), 56.2/56.4 (C^{9}O*C*H$_3$), 58.8/58.9 (C^1), 59.7/60.4 (C^5), 60.8/60.9 (C^{7}O*C*H$_3$), 81.5/83.6 (C^9), 84.8/86.8 (C^7), 126.3/126.4 (C$_{arom}$), 126.5/127.5 (C^{11}), 127.7/127.9 (C$_{arom}$), 128.1/128.5 (C$_{arom}$), 128.6/128.7 (C^2), 128.9/129.0 (C^{10}), 129.1/129.4 (C$_{arom}$), 132.2/132.5 (C$_{arom}$), 133.2 (C$_{arom}$), 134.0//135.3 (C^3), 136.5/136.8 (C$_{arom}$), 140.0/140.4 (C$_{arom}$); Anal. Found: C, 68.78; H, 8.29%. Calcd for $C_{28}H_{38}O_5S$: C, 69.10; H, 7.87%.

(2*E*,5*R*/5*S*,6*R*,7*R*,8*R*,9*S*,10*E*)-7,9-Dimethoxy-3,6,8-trimethyl-11-phenyl-5-(phenylsulfonyl)undeca-2,10-dienal (29). In a flask connected to an argon line, freshly prepared MnO_2 (223.4 mg, 2.57 mmol) was added progressively to a cooled (ice bath) solution of alcohol **27b** (62.4 mg, 0.128 mmol) in a mixture of hexane (2.5 mL) and CH_2Cl_2 (0.5 mL) with stirring. The resulting mixture was further stirred at 0 °C for 2 h before being diluted with ether (5 mL) and filtered on a short column of Celite (washings with ether). Evaporation of the solvents in vacuo afforded the aldehyde **29** (51.5 mg; 83%) as an 88:12 mixture of diastereomers (^{1}H NMR). TLC (hexane:EtOAc = 1:1) $R_f = 0.52$, 0.47; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.77/1.12 (d, $J = 7.0$ Hz, 3H), 1.14–1.33 (m, 3H), 1.47–1.67 (m, 1H), 1.74/1.96 (s, 3H), 1.99–2.73 (m, 3H), 3.02–3.31 (m, 4H), 3.41–4.03 (m, 5H), 5.77 (d, $J = 7.5$ Hz, 1H), 6.07/6.10 (d, $J = 8.2$, 15.8 Hz, 1H), 6.50/6.53 (d, $J = 15.8$ Hz, 1H), 7.21–7.87 (m, 10H), 9.65/9.72 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.7/11.7 (C^8*C*H$_3$), 14.0/14.3 (C^6*C*H$_3$), 16.5/17.0 (C^3*C*H$_3$), 32.4/38.3 (C^6), 35.8/38.8 (C^4), 40.7/42.1 (C^8), 56.1/56.2 (C^{9}O*C*H3), 59.9 (C^5), 61.3/61.4 (C^{7}O*C*H$_3$), 81.0/83.5 (C^9), 85.0/87.5 (C^7), 126.4 (C^2), 127.7/127.6 (C^{11}), 128.1 (C$_{arom}$), 128.5/128.6 (C$_{arom}$), 128.9 (C$_{arom}$),129.1/129.2 (C^{10}), 129.7 (C$_{arom}$), 132.5/132.6 (C$_{arom}$), 133.6/133.8 (C$_{arom}$), 136.4/136.6 (C$_{arom}$), 138.7/140.0 (C$_{arom}$), 157.5/160.2 (C^3), 190.4/190.5 (C^1).

(2*E*,5*R*/5*S*,6*R*,7*R*,8*R*,9*S*,10*E*)-Methyl 7,9-Dimethoxy-3,6,8-trimethyl-11-phenyl-5-(phenylsulfonyl)undeca-2,10-dienoate (28). In a flask connected to an argon line, NaCN (27.5 mg, 0.106 mmol) and freshly prepared MnO_2 (193.3 mg, 2.22 mmol) were added sequentially with stirring to a cooled (ice bath) solution of aldehyde **29** (51.4 mg, 0.106 mmol) in MeOH (1.3 mL). After 5 min stirring at 0 °C, the bath was removed and the reaction mixture was stirred for a further 1 h at rt before being diluted with ether (10 mL) and poured into iced brine (10 mL). Celite (spatula) was added and the resulting mixture was vigorously stirred before being filtered on a short column of Celite (washings with ether). The aqueous layer was extracted with ether (3 × 10 mL) and the pooled organic extracts were washed with brine (3 × 5 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was chromatographed on silica gel (hexane/EtOAc) to afford **28** (same diastereomeric ratio as above) as a colorless paste (37.6 mg; 69%). TLC (hexane:EtOAc = 1:1) $R_f = 0.56$; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87/1.11 (d, $J = 7.0$ Hz, 3H), 1.24/1.30 (d, $J = 7.0$ Hz, 3H), 1.47–1.67 (m, 1H), 1.82/1.85 (d, $J = 1.1$ Hz, 3H), 2.03–3.03 (m, 3H), 3.19 (dd, $J = 3.2$, 8.6 Hz, 1H), 3.24/3.29 (s, 3H), 3.41–4.05 (m, 8H), 5.62 (d, $J = 8.9$ Hz, 1H), 6.12/6.15 (dd, $J = 7.5$, 15.9 Hz, 1H), 6.50/6.56 (d, $J = 15.9$ Hz, 1H), 7.20–7.90 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 9.9/11.9 (C^8*C*H$_3$), 13.2/14.3 (C^6*C*H$_3$), 17.0 (C^3*C*H$_3$), 32.4/37.9 (C^6), 36.3/39.1 (C^4), 41.0/42.1 (C^8), 50.7/50.9 (C^{1}O*C*H$_3$), 56.2/56.3 (C^{9}O*C*H$_3$), 59.7/60.0 (C^5), 61.1/61.2 (C^{7}O*C*H$_3$), 81.2/83.4 (C^9), 84.8/87.2 (C^7), 117.7/118.5 (C^2),

126.4/126.5 (C^{11}), 127.5/127.7 (C_{arom}), 128.2/128.6 (C_{arom}), 128.5/128.7 (C_{arom}), 129.0/129.1 (C^{10}), 129.2/129.5 (C_{arom}), 132.2/132.5 (C_{arom}), 133.4/133.5 (C_{arom}), 136.5/136.7 (C_{arom}), 139.3/140.1 (C_{arom}), 154.2/155.9 (C^3), 161.4/166.4 (C^1); Anal. Found: C, 67.81; H, 7.31%. Calcd for $C_{29}H_{38}O_6S$: C, 67.68; H, 7.44%.

(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*,10*E*)-Methyl 7,9-Dimethoxy-3,6,8-trimethyl-11-phenylundeca-2,4,10-trienoate (11). In a flask connected to an argon/vacuum line, and equipped with a tube charged with freshly sublimed KO-*t*-Bu (14.6 mg, 0.13 mmol), a solution of sulfone **28** (37.3 mg, 0.72 mmol) in THF (1.3 mL) was thoroughly degassed (three freeze/pump/thaw cycles) before being cooled to −15 °C (ice/methanol bath). With stirring, KO-*t*-Bu was added and the resulting mixture was allowed to warm to −5 °C over 1.5 h before being diluted with ether (10 mL) and poured into iced brine (10 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the pooled organic extracts were washed with brine (3 × 5 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was purified by column chromatography (hexane/EtOAc) to give the ester **11** as a colorless oil (18.1 mg; 67%). $[\alpha]_D = +57.2$ (*c* 0.3, CH_2Cl_2); Lit.:[7b] $[\alpha]_D = +58.0$ (*c* 1.1, CH_2Cl_2); TLC (hexane:EtOAc = 1:1) $R_f = 0.65$; (hexane:ether = 7:3) $R_f = 0.38$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, $J = 7.0$ Hz, 3H), 1.19 (d, $J = 7.0$ Hz, 3H), 1.49–1.59 (m, 1H), 2.26 (d, $J = 1.0$ Hz, 3H), 2.52–2.66 (m, 1H), 3.19 (dd, $J = 2.0$, 7.0 Hz, 1H), 3.31 (s, 3H), 3.54 (s, 3H), 3.67 (s, 3H), 4.07 (dd, $J = 1.0$, 6.0 Hz, 1H), 5.68 (br s, 1H), 6.07 (d, $J = 16.1$ Hz, 1H), 6.15 (dd, $J = 7.5$, 16.1 Hz, 1H), 6.16 (dd, $J = 8.5$, 15.6 Hz, 1H), 6.56 (d, $J = 16.1$ Hz, 1H), 7.18–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.7 (C^3CH_3), 14.0 (C^8CH_3), 18.7 (C^6CH_3), 40.1 (C^6), 42.7 (C^8), 50.9 (C^1OCH_3), 56.3 (C^9OCH_3), 61.5 (C^7OCH_3); 81.1 (C^9), 86.4 (C^7), 117.6 (C^2), 126.4 (C_{arom}), 127.4 (C_{arom}), 128.6 (C_{arom}), 129.1 (C^{10}), 132.0 (C^{11}), 133.9 (C^4), 136.8 (C^5), 138.3 (C_{arom}), 153.9 (C^3), 167.6 (C^1).

(1*R*,2*S*,3*R*,4*S*,5*R*,6*R*)-3,5-Dimethoxy-4,6-dimethyl-1-phenyl-7-(phenylsulfonyl)heptane-1,2-diol (31a); (1*S*,2*R*,3*R*,4*S*,5*R*,6*R*)-3,5-dimethoxy-4,6-dimethyl-1-phenyl-7-(phenylsulfonyl)heptane-1,2-diol (31b). In a flask connected to an argon line, with stirring, anhydrous NMO (1.03 g, 8.75 mmol) and 0.15 M aqueous OsO_4 (10.6 mL, 1.59 mmol) were added sequentially to the sulfone **18** (3.22 g, 8.0 mmol) diluted with 10:3:1 *t*-BuOH/THF/H_2O (265 mL). A white precipitate was formed progressively. After 15 h stirring at rt, the solids were filtered on a sintered funnel, and then thoroughly washed with water before being dried in a desiccator over P_4O_{10} and KOH. Although practically pure in NMR, this product was re-crystallized from hot ether to give the diol **31a** as white crystals (2.55 g; 73%). All of the aqueous and the ethereal filtrates were pooled and 10% aqueous Na_2SO_3 (350 mL) was added. After 30 min vigorous stirring at rt, the resulting mixture was extracted with EtOAc (3 × 350 mL) and the pooled organic extracts were washed with 10% $NaHCO_3$ (200 mL), brine (2 × 200 mL), and dried (K_2CO_3). The solvents were evaporated to give, after drying of the residue in a vacuum, a 68:32 mixture (by ^{1}H NMR) of the diols **31a** and **31b** respectively (0.95 g; 27%, 100% total). **31a**: Mp 179 °C; $[\alpha]_D = -26.4$ (*c* 0.2, CH_2Cl_2); TLC (hexane:ether = 1:2) $R_f = 0.18$; ^{1}H NMR ($CDCl_3$): δ 0.83 (d, $J = 7.0$ Hz, 3H), 1.31 (d, $J = 7.0$ Hz, 3H), 1.86–1.96 (m, 1H), 2.23 (d, $J = 5.1$ Hz, 1H, O*H*), 2.41–2.51 (m, 1H), 2.74 (d, $J = 4.7$ Hz, 1H, O*H*), 2.94–3.04 (m, 2H), 3.24 (dd, $J = 2.2$, 14.4 Hz, 1H), 3.46–3.49 (m, 7H), 3.69 (dd, $J = 2.5$, 7.5 Hz, 1H), 4.88 (d, $J = 2.3$ Hz, 1H), 7.27–7.96 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 10.9 (C^4CH_3), 19.2 (C^6CH_3), 31.0 (C^6), 37.2 (C^4), 58.0 (C^7), 60.0 (C^5OCH_3), 61.2 (C^3OCH_3), 72.6 (C^1), 75.2 (C^2), 80.3 (C^3), 88.2 (C^5), 126.1 (C_{arom}), 127.7 (C_{arom}), 127.9 (C_{arom}), 128.5 (C_{arom}), 129.3 (C_{arom}), 133.5 (C_{arom}), 140.2 (C_{arom}), 141.8 (C_{arom}). **31b**: TLC (hexane:ether = 1:2) $R_f = 0.11$; ^{1}H NMR ($CDCl_3$): δ 0.74 (d, $J = 7.1$ Hz, 3H), 1.17 (d, $J = 7.0$ Hz, 3H), 1.49–1.60 (m, 2H), 2.23–2.34 (m, 1H), 2.81–2.93 (m, 3H), 3.09 (dd, $J = 2.1$, 14.5 Hz, 1H), 3.15 (br s, 1H, O*H*), 3.25 (t, $J = 3.6$ Hz, 1H), 3.29 (s, 3H), 3.47 (s, 3H), 3.57 (dd, $J = 5.9$, 9.5 Hz, 1H), 4.57 (d, $J = 6.4$ Hz, 1H), 7.24–7.89 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 11.3 (C^4CH_3), 19.2 (C^6CH_3), 30.9 (C^6), 39.1 (C^4), 57.9 (C^7), 60.5 (C^5OCH_3), 60.8 (C^3OCH_3), 75.7 (C^1), 77.0 (C^2), 79.6 (C^3), 87.9 (C^5), 127.2 (C_{arom}), 127.9 (C_{arom}), 128.1 (C_{arom}), 128.5 (C_{arom}), 129.3 (C_{arom}), 133.6 (C_{arom}), 140.1 (C_{arom}), 141.8 (C_{arom}).

(4*R*,5*R*)-4-[(1*R*,2*S*,3*R*,4*R*)-1,3-Dimethoxy-2,4-dimethyl-5-(phenylsulfonyl)pentyl]-2,2-dimethyl-5-phenyl-1,3-dioxolane (31c). In a flask connected to an argon line, 2-methoxypropene (0.04 mL, 0.42 mmol) and PPTS (5.28 mg, 0.021 mmol) were added sequentially to a cooled (ice bath) solution of diol **31a** (90 mg, 0.21 mmol) in CH_2Cl_2 (0.42 mL). After 30 min stirring at 0 °C, the bath was removed and the reaction mixture was stirred at rt overnight. TLC analysis (CH_2Cl_2) then indicated the reaction was not complete. Methoxypropene (0.02 mL) and PPTS (5.28 mg) were added and the stirring was pursued at rt for 2 d. Although residual diol was shown by TLC, the reaction mixture was diluted with EtOAc (2 mL) and washed with 10% $NaHCO_3$ (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL) and the pooled organic extracts were washed with water (1 mL), brine (3 × 5 mL), and dried (Na_2SO_4). The solvents were removed in a vacuum and the residue was dissolved in ether. Hexane was added cautiously so as two layers were formed, and then allowed to slowly diffuse to give the acetonide **31c** as white crystals (66 mg; 67%). Mp 135 °C; $[\alpha]_D = +4.2$ (*c* 1.1, CH_2Cl_2); TLC (hexane:ether = 1:1) $R_f = 0.55$; ^{1}H NMR ($CDCl_3$): δ 0.74 (d, $J = 7.2$ Hz, 3H), 1.26 (d, $J = 6.8$ Hz, 3H), 1.48 (s, 3H), 1.51 (s, 3H), 1.73–1.83 (m, 1H), 2.31–2.42 (m, 1H), 2.88–3.00 (m, 2H), 3.20 (dd, $J = 1.6$, 14.4 Hz, 1H), 3.29 (s, 3H), 3.35 (s, 3H), 3.47 (dd, $J = 2.3$, 5.1 Hz, 1H), 4.04 (dd, $J = 5.2$, 7.8 Hz, 1H), 4.83 (d, $J = 7.9$ Hz, 1H), 7.27–7.93 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 10.8, 19.1, 27.2, 30.6, 37.4, 58.0, 59.7, 60.8, 80.3, 80.8, 83.1, 87.5, 109.2, 127.1, 127.9, 128.2, 128.5, 129.3, 133.6, 138.7, 140.1.

(2*R*,3*S*,4*R*,5*R*)-2,4-Dimethoxy-3,5-trimethyl-6-(phenylsulfonyl)hexanal (32). In a flask connected to an argon line, a mixture of diols **31a** and **31b** (3.5 g, 8.02 mmol) was diluted with 10:3:1 *t*-BuOH/THF/H_2O (160 mL) and the resulting mixture was warmed to ca. 35–40 °C (hot water bath). With stirring, $NaIO_4$ (3.43 g, 8.02 mmol) was added and, after 15 h stirring, the solids were eliminated by filtration on a sintered funnel (washings with ether). The pooled filtrates were evaporated to dryness in vacuo at ca. 10–15 °C (cold water bath) and the oily residue was further dried in a good vacuum

(ca. 10^{-2} Torr) for 30 min to give crude **32** (2.75 g) as a pale-yellow oil. TLC (hexane:ether = 1:1) $R_f = 0.45$; ^{1}H NMR ($CDCl_3$): δ 0.70 (d, $J = 7.2$ Hz, 3H), 1.28 (d, $J = 7.0$ Hz, 3H), 1.83–1.94 (m, 1H), 2.33–2.43 (m, 1H), 2.94 (dd, $J = 9.5$, 14.5 Hz, 1H), 3.02 (dd, $J = 1.8$, 9.8 Hz, 1H), 3.16 (dd, $J = 2.1$, 14.5 Hz, 1H), 3.41 (s, 3H), 3.70 (s, 3H), 3.71 (d, $J = 3.2$ Hz, 1H), 7.53–7.93 (m, 5H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 11.3, 19.4, 30.5, 37.8, 57.7, 58.3, 61.3, 85.9, 86.6, 127.8, 129.3, 133.6, 137.0, 203.1.

N. B. This sensitive product was immediately reduced into **30a** (see below) without further purification.

(2*R*,3*S*,4*R*,5*R*)-2,4-Dimethoxy-3,5-dimethyl-6-(phenylsulfonyl)hexan-1-ol (30a). By Ozonolysis of the Sulfone 18: Ozonised oxygen was passed into a stirred solution of sulfone **18** (250 mg, 0.627 mmol) in 1:4 MeOH/CH_2Cl_2 (10 mL) at −78 °C (dry ice/bath) until the characteristic blue color persisted for 5 min. The reaction mixture was then flushed with nitrogen and $NaBH_4$ (47.4 mg, 1.254 mmol) was added with stirring. The cooling bath was removed and the reaction mixture was further stirred for 5 h at rt before being poured in iced 10% NH_4Cl (20 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL) and the pooled organic extracts were washed with brine (4 × 5 mL), and dried (K_2CO_3). The solvents were eliminated in a vacuum and the residue was chromatographed on silica gel (hexane/ether) to give the hydroxy sulfone **30a** as a colorless oil (182 mg; 89%). $[\alpha]_D = +5.3$ (*c* 1.3, CH_2Cl_2); TLC (ether) $R_f = 0.15$; ^{1}H NMR ($CDCl_3$): δ 0.70 (d, $J = 7.1$ Hz, 3H), 1.25 (d, $J = 6.8$ Hz, 3H), 1.53–1.65 (m, 1H), 2.04 (br s, 1H, O*H*), 2.30–2.40 (m, 1H), 2.92 (dd, $J = 9.6$, 14.5 Hz, 1H), 3.00 (dd, $J = 2.4$, 8.9 Hz, 1H), 3.18 (dd, $J = 1.8$, 14.4 Hz, 1H), 3.40 (s, 3H), 3.42 (s, 3H), 3.43–3.49 (m, 1H), 3.53–3.68 (m, 2H), 7.51–7.91 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 10.5 (C^3CH_3), 15.3 (C^5CH_3), 30.8 (C^5), 37.9 (C^3), 57.8 (C^6), 58.4 (C^2OCH_3), 61.3 (C^4OCH_3), 62.8 (C1), 80.6 (C2), 87.3 (C4), 127.8 (C_{arom}), 129.3 (C_{arom}), 133.6 (C_{arom}), 140.1 (C_{arom}); Anal. Found: C, 57.83; H, 8.31%. Calcd for $C_{16}H_{26}O_5S$: C, 58.16; H, 7.93%.

By Reduction of the Aldehyde 32: In a flask connected to an argon line, $NaBH_4$ (0.6 g, 16.04 mmol) was added with stirring to a cooled (ice bath) solution of crude **32** (2.75 g) in methanol (160 mL). The stirring was pursued for 30 min at 0 °C, then 30 min at rt and the reaction mixture was poured into iced 10% NH_4Cl, and extracted with CH_2Cl_2 (3 × 200 mL). The pooled organic phases were washed with brine (2 × 200 mL), and dried (K_2CO_3). Evaporation of the solvents in vacuo was followed by a chromatography on silica gel (hexane/ether) to afford, after drying in a vacuum, the hydroxysulfone **30a** as a colorless oil (2.41 g; 92% from **31a**/**31b**).

{[(2*R*,3*S*,4*R*,5*R*)-2,4-Dimethoxy-3,5-dimethyl-6-(phenylsulfonyl)hexyl]oxy}triisopropylsilane (30b). In a flask connected to an argon line, 2,6-lutidine (1.87 mL, 16.04 mmol) and TIPSOTf (2.42 mL, 8.69 mmol) were added sequentially with a syringe to a cooled (ice bath) solution of **30a** (2.41 g, 7.29 mmol) in CH_2Cl_2 (14.6 mL). Stirring was continued for 30 min and the reaction mixture was poured into iced 10% NH_4Cl (125 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The pooled organic phases were washed with iced 0.1 M HCl (75 mL), 10% NH_4Cl (125 mL), brine (3 × 125 mL), and dried (Na_2SO_4). The residue left by elimination of the solvents was purified by column chromatography (hexane/ether) to give, after drying in a good vacuum (ca. 10^{-2} Torr), the silyl ether **30b** as a colorless oil (3.5 g; 98%). $[\alpha]_D = +12.0$ (*c* 1.1, CH_2Cl_2); TLC (hexane:ether = 1:1) $R_f = 0.40$; ^{1}H NMR ($CDCl_3$): δ 0.64 (d, $J = 7.0$ Hz, 3H), 1.04–1.06 (m, 21H), 1.30 (d, $J = 7.0$ Hz, 3H), 1.59–1.70 (m, 1H), 2.32–2.43 (m, 1H), 2.95 (dd, $J = 9.8$, 14.5 Hz, 1H), 3.03 (dd, $J = 1.9$, 9.6 Hz, 1H), 3.15 (dd, $J = 1.6$, 14.4 Hz, 1H), 3.43–3.50 (m, 8H), 3.85 (dd, $J = 5.7$, 9.9 Hz, 1H), 7.52–7.89 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 9.5, 11.9, 18, 19.4, 30.7, 37.1, 57.9, 58.3, 61.4, 63.7, 80.2, 87.2, 127.8, 129.2, 133.4, 140.3; Anal. Found: C, 62.02; H, 9.61%. Calcd for $C_{25}H_{46}O_5SSi$: C, 61.68; H, 9.52%.

{[(2*R*,3*S*,4*R*,5*R*,6*R*/6*S*)-2,4-Dimethoxy-3,5-dimethyl-6-(phenylsulfonyl)non-8-en-1-yl]oxy}triisopropylsilane (33a). In a flask connected to an argon/vacuum line, a solution of sulfone **30b** (1.92 g, 3.9 mmol) in THF (13 mL) was thoroughly degassed before being cooled to −78 °C (dry ice/acetone bath). With stirring, 1.5 M (in hexane) BuLi (3.2 mL, 5.1 mmol) was added dropwise. After 1 h stirring, HMPA (0.89 mL) was added, followed 10 min later by allyl bromide (0.5 mL, 5.9 mmol). The reaction mixture was further stirred at −78 °C for 1 h before being diluted with ether (150 mL) and poured into iced 10% NH_4Cl (200 mL). The aqueous phase was extracted with ether (4 × 75 mL) and the pooled organic extracts were washed with brine (3 × 50 mL), and dried (Na_2SO_4). The residue left by evaporation of the solvents was purified by column chromatography (hexane/ether) to give, after drying in a desiccator, the sulfone **33a** (9:1 mixture of two diastereomers; by ^{1}H NMR) as a thick colorless oil (1.93 g; 93%). TLC (hexane:ether = 1:1) $R_f = 0.59$. ^{1}H NMR ($CDCl_3$): δ 0.73 (d, $J = 7.2$ Hz, 3H), 1.06–1.07 (m, 21H), 1.18 (d, $J = 7.1$ Hz, 3H), 1.78–1.87 (m, 1H), 2.42–2.81 (m, 3H), 3.02 (dd, $J = 4.7$, 7.4 Hz, 1H), 3.34–3.44 (m, 8H), 3.52–3.82 (m, 2H), 4.79–4.95 (m, 2H), 5.55–5.68 (m, 1H), 7.50–7.92 (m, 5H); ^{13}C NMR ($CDCl_3$), *major isomer*: δ 10.2, 11.9, 17.6, 18.0, 28.9, 33.3, 36.6, 58.1, 61.3, 63.0, 64.1, 80.2, 87.6, 116.3, 128.8, 129.0, 133.4, 136.0, 139.2; Anal. Found: C, 64.04; H, 9.68%. Calcd for $C_{28}H_{50}O_5SSi$: C, 63.83; H, 9.57%.

{[(2*R*,3*S*,4*S*,5*S*)-2,4-Dimethoxy-3,5-dimethylnon-8-en-1-yl]oxy}triisopropylsilane (33b). In a flask equipped with a condenser connected to an argon line, the sulfone **33a** (3.2 g, 6.1 mmol) was refluxed with stirring in MeOH (200 mL) with magnesium turnings (3.4 g). After 2 h, TLC analysis (CH_2Cl_2) showed the reaction was incomplete. Magnesium (3.4 g) was added and reflux was pursued for ca. 2–3 h. After cooling, the reaction mixture was diluted with ether (150 mL) and poured into iced pH 2 tartaric buffer (600 mL). The aqueous layer was extracted with ether (4 × 300 mL) and the pooled organic extracts were washed with 10% $NaHCO_3$ (2 × 100 mL), brine (3 × 100 mL), and dried (Na_2SO_4). The solvents were removed in a vacuum and the residue (2.17 g) was chromatographed on silica gel (hexane/ether) to give **33b** as a colorless oil (2.07 g; 88%). $[\alpha]_D = +7.9$ (*c* 1, CH_2Cl_2); TLC (hexane:ether = 1:1) $R_f = 0.62$; ^{1}H NMR ($CDCl_3$): δ 0.77 (d, $J = 7.1$ Hz, 3H), 1.03 (d, $J = 7.0$ Hz, 3H), 1.06–1.07 (m, 21H), 1.19–1.32 (m, 1H), 1.44–1.55 (m, 1H), 1.63–1.76 (m, 1H), 1.79–1.89 (m, 1H), 1.91–2.01 (m, 1H), 2.12–2.24 (m, 1H), 3.01 (dd, $J = 2.4$, 9.2 Hz, 1H), 3.48 (s, 3H), 3.49 (s, 3H), 3.57–3.67 (m, 2H), 3.89

(dd, $J = 5.8$, 9.5 Hz, 1H), 4.91–5.04 (m, 2H), 5.73–5.86 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 10.4, 11.9, 17.6, 18.0, 29.0, 31.8, 34.4, 37.1, 58.7, 61.1, 64.8, 80.9, 87.7, 114.2, 139.2; Anal. Found: C, 68.53; H, 12.13%. Calcd for $C_{22}H_{46}O_3Si$: C, 68.33; H, 11.99%.

(4*S*,5*S*,6*S*,7*R*)-5,7-Dimethoxy-4,6-dimethyl-8-[(triisopropylsilyl)oxy]octanoic acid (4b). In a flask connected to an argon line, a solution of **33b** (603 mg, 1.56 mmol) in 1:1 CCl_4/CH_3CN (6.6 mL) was cooled to ca. 0 °C (ice bath). With vigorous stirring, $NaIO_4$ (1.37 g, 6.4 mmol) diluted with H_2O (4.4 mL) was added, followed by $RuCl_3 \cdot xH_2O$ (62 mg, 0.3 mmol). The resulting mixture was vigorously stirred 15 h at rt before being diluted with CH_2Cl_2 (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL) and the pooled organic extracts were washed with brine (35 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was chromatographed on silica gel (2:1 hexane/ether) to give **4b** as a colorless oil (380 mg; 60%). $[\alpha]_D = +4.1$ (*c* 1, CH_2Cl_2); TLC (hexane:CH_2Cl_2:ether = 7:7:1) $R_f = 0.69$; ^{1}H NMR ($CDCl_3$): δ 0.78 (d, $J = 7.0$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 1.06–1.07 (m, 21H), 1.43–1.56 (m, 1H), 1.68–1.90 (m, 3H), 2.25–2.35 (m, 1H), 2.41–2.51 (m, 1H), 3.02 (dd, $J = 2.4$, 9.2 Hz, 1H), 3.48 (s, 3H), 3.49 (s, 3H), 3.56–3.67 (m, 2H), 3.7 (dd, $J = 6.0$, 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 10.3, 11.9, 17.4, 18.0, 24.9, 31.9, 34.3, 37.3, 58.7, 61.2, 64.8, 80.9, 87.5, 179.5.

(4*S*,5*S*,6*S*,7*R*)-Methyl 5,7-Dimethoxy-4,6-dimethyl-8-[(triisopropylsilyl)oxy]octanoate (4d). Under argon, 2 M (in ether) TMSDM (1.31 mL, 2.62 mmol) was added dropwise to a cooled (ice bath) stirred solution of acid **4b** (706 mg, 1.74 mmol) in 2:3 toluene/MeOH (1.8 mL). After 1 h stirring at rt, the solvents were evaporated and the residue was purified by column chromatography (7:7:1 hexane/CH_2Cl_2/ether) to give the methyl ester **4d** as a colorless oil (712 mg; 98%). $[\alpha]_D = +4.2$ (*c* 1.1, CH_2Cl_2); TLC (hexane:CH_2Cl_2:ether = 7:7:1) $R_f = 0.70$; ^{1}H NMR ($CDCl_3$): δ 0.78 (d, $J = 7.2$ Hz, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 1.06–1.09 (m, 21H), 1.41–1.54 (m, 1H), 1.65–1.89 (m, 3H), 2.21–2.31 (m, 1H), 2.37–2.47 (m, 1H), 3.01 (dd, $J = 2.5$, 9.3 Hz, 1H), 3.48 (s, 3H), 3.49 (s, 3H), 3.56–3.68 (m, 5H), 3.88 (dd, $J = 6.1$, 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 10.2, 11.9, 17.4, 18.0, 25.2, 32.1, 34.3, 37.3, 51.4, 58.7, 61.3, 64.9, 80.9, 87.4, 174.4; Anal. Found: C, 63.20; H, 11.25%. Calcd for $C_{22}H_{46}O_5Si$: C, 63.11; H, 11.07%.

(4*S*,5*S*,6*S*,7*R*)-5,7-Dimethoxy-4,6-dimethyl-8-[(triisopropylsilyl)oxy]octanoyl Chloride (4c). In a flask connected to an argon line, a solution of KOH (1.7 g) in H_2O (10 mL) was added to a solution of ester **4d** (0.9 g, 2.15 mmol) in MeOH (8.6 mL) and the resulting mixture was stirred at ca. 35–40 °C (hot-water bath) for 15 h before being evaporated to dryness in vacuo. The residue was slurried in toluene and the solvents were distilled out in a vacuum at ca. 45–50 °C (bath). These operations were repeated twice and the residue finally obtained was further dried in a good vacuum (ca. 10^{-2} Torr) at 50 °C for a few hours. The flask was filled with argon and ether (26 mL) was added. With cooling (ice bath), freshly distilled oxalyl chloride (0.37 mL, 4.3 mmol) was added with a syringe, followed by DMF (3 drops). The resulting mixture was stirred 3 h at rt before being filtered in a Schlenk tube equipped with a sintered funnel, and connected to an argon/vacuum line. The solids were washed with CCl_4 and the pooled filtrates were evaporated to dryness in vacuo. The residue was further dried in a vacuum (ca. 10^{-2} Torr) to give **4c** as a pale-yellow oil (0.9 g; 99%). ^{1}H NMR ($CDCl_3$): δ 0.79 (d, $J = 7.0$ Hz, 3H), 1.04–1.11 (m, 24H), 1.53–1.63 (m, 1H), 1.71–1.91 (m, 3H), 2.81–2.91 (m, 1H), 2.96–3.07 (m, 2H), 3.48 (s, 6H), 3.54–3.67 (m, 2H), 3.89 (dd, $J = 5.8$, 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 10.2, 11.9, 17.6, 18.0, 25.3, 33.8, 37.2, 45.2, 58.5, 61.5, 64.3, 80.6, 87.2, 174.1.

1-[2-Hydroxy-4,6-dimethoxy-3-(methoxymethoxy)phenyl]propan-1-one (2b). As described,[4b] the bis-phenol **2a** (1.5 g, 6.63 mmol) was reacted with MOMCl (0.65 mL) in CH_2Cl_2 (9 mL) with added DIPEA (7.5 mL, 43.1 mmol) for 15 h at rt to obtain **2b** as a yellow solid (1.7 g; 95%). TLC (hexane:CH_2Cl_2:EtOAc = 10:10:1) $R_f = 0.67$; ^{1}H NMR: δ 1.16 (t, $J = 6.0$ Hz, 3H), 3.03 (q, $J = 6.0$ Hz, 2H), 3.62 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 5.09 (s, 2H), 5.98 (s, 1H), 13.91 (s, 1H, O*H*); ^{13}C NMR ($CDCl_3$): δ 8.5, 37.7, 55.6, 55.8, 57.2, 86.4, 98.0, 106.1, 126.8, 158.3, 158.8, 159.2, 207.0.

4*S*,5*S*,6*S*,7*R*)-3,5-Dimethoxy-2-(methoxymethoxy)-6-propionylphenyl 5,7-Dimethoxy-4,6-dimethyl-8-[(triisopropylsilyl)oxy]octanoate (5b). In a flask connected to an argon line, 20% aqueous K_2CO_3 (4.7 mL) and NBu_4HSO_4 (24 mg, 0.07 mmol) were added to a stirred solution of **2b** (310 mg, 1.16 mmol) in benzene (4.7 mL). Chloride **4c** (490 mg, 1.16 mmol) diluted with benzene (2 mL) was added with a syringe and the resulting mixture was vigorously stirred at rt for 20 h before being diluted with ether (20 mL) and poured into iced 1 M HCl (20 mL). The aqueous phase was extracted with ether (3 × 10 mL) and the pooled organic extracts were washed with brine (2 × 10 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents in vacuo was chromatographed on silica gel (EtOAc) to give the ester **5b** as a pale-yellow oil (630 mg; 84%). $[\alpha]_D = +1.7$ (*c* 1, CH_2Cl_2); TLC (hexane:EtOAc = 3:2) $R_f = 0.89$; ^{1}H NMR ($CDCl_3$): δ 0.71 (d, $J = 7.2$ Hz, 3H), 0.96–1.03 (m, 27H), 1.42–1.49 (m, 1H), 1.69–1.82 (m, 3H), 2.36–2.60 (m, 2H), 2.69 (q, $J = 7.3$ Hz, 2H), 2.95 (dd, $J = 2.4$, 9.1 Hz, 1H), 3.40–3.60 (m, 11H), 3.60–3.81 (m, 7H), 4.91 (s, 2H), 6.30 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 8.1, 10.3, 11.9, 17.3, 18.0, 24.6, 31.6, 34.1, 37.4, 56.1 (2C), 57.2, 58.8, 61.2, 65.4, 81.0, 87.4, 94.4, 98.6, 117.6, 132.1, 142.3, 153.7, 154.7, 171.5, 174.1, 202.5; Anal. Found: C, 61.82; H, 9.53%. Calcd for $C_{34}H_{60}O_{10}Si$: C, 62.16; H, 9.21%.

2-[(3*S*,4*S*,5*S*,6*R*)-4,6-Dimethoxy-3,5-dimethyl-7-{(triisopropylsilyl)oxy}heptyl]-5,7-dimethoxy-8-(methoxymethoxy)-3-methyl-4*H*-chromen-4-one (6c). In a flask equipped with a condenser connected to an argon line, sodium (3.18 g, 0.138 mmol) was added to MeOH (230 mL) with cooling (ice bath). After the metal was reacted, a degassed solution of ester **5b** (1.195 g, 1.82 mmol) in MeOH (90 mL) was added with a syringe and the resulting mixture was refluxed 2 h. TLC analysis (EtOAc) showed the reaction was complete. The solvents were evaporated to dryness in a vacuum and the residue was dissolved in EtOAc (125 mL) and washed with 1 M HCl (2 × 50 mL), brine (75 mL), and dried ($MgSO_4$). The residue left by evaporation of the solvents was chromatographed on silica gel (CH_2Cl_2/EtOAc) to afford successively the chromone **6c** as a colorless oil (403 mg; 35%), the phenol **2b** (310 mg; 63.2%) and the acid **4b** (472 mg; 63.7%). $[\alpha]_D = +4.4$ (*c* 1, CH_2Cl_2); TLC (EtOAc) $R_f = 0.50$; ^{1}H NMR ($CDCl_3$): δ 0.73 (d, $J = 7.1$

Hz, 3H), 1.05–1.06 (m, 21H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.53–1.65 (m, 1H), 1.73–1.89 (m, 3H), 1.99 (s, 3H), 2.52–2.62 (m, 1H), 2.71–2.80 (m, 1H), 3.03 (dd, $J = 2.5$, 9.1 Hz, 1H), 3.48 (s, 6H), 3.53–3.57 (m, 1H), 3.60–3.66 (m, 4H), 3.83–3,96 (m, 7H), 5.09 (s, 2H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.7, 10.3, 11.9, 17.8, 18.0, 27.7, 30.1, 34.8, 37.4, 56.1, 56.4, 57.2, 58.7, 61.3, 65.9, 80.9, 87.4, 92.1, 98.7, 108.1, 117.0, 126.7, 151.8, 155.8, 156.6, 162.6, 177.3; Anal. Found: C, 63.49; H, 9.03%. Calcd for $C_{34}H_{58}O_9Si$: C, 63.92; H, 9.15%.

2-[(3*S*,4*S*,5*S*,6*R*)-4,6-Dimethoxy-3,5-dimethyl-7-{(triisopropylsilyl)oxy}heptyl]-8-hydroxy-5,7-dimethoxy-3-methyl-4*H*-chromen-4-one (34). In a flask connected to an argon/vacuum line, a solution of chromone **6c** (440 mg, 0.69 mmol) in CH_2Cl_2 (15 mL) was thoroughly degassed, and then cooled to ca. −5 °C (ice/brine bath). With stirring, freshly distilled $TiCl_4$ (0.23 mL, 2.07 mmol) was added with a syringe. A red-brown color immediately developed and, 10 min later, when TLC analysis showed the reaction was complete, cold 10% $NaHCO_3$ (35 mL) was rapidly added, the stirring being continued at 0 °C until discoloration (ca. 5–10 min). The aqueous phase was extracted CH_2Cl_2 (3 × 50 mL) and the pooled organic extracts were washed with brine (2 × 50 mL), and dried (Na_2SO_4). Evaporation of the solvents, followed by drying of the residue in a vacuum, afforded the hydroxychromone **34** as a pale-yellow oil (410 mg; 100%). TLC (EtOAc) $R_f = 0.26$; ^{1}H NMR ($CDCl_3$): δ 0.77 (d, $J = 7.0$ Hz, 3H), 1.04–1.05 (m, 21H), 1.11 (d, $J = 6.8$ Hz, 3H), 1.48–1.99 (m, 7H), 2.59–2.70 (m, 1H), 2.76–2.85 (m, 1H), 3.04 (dd, $J = 3.5$, 8.2 Hz, 1H), 3.43–3.54 (m, 7H), 3.62 (dd, $J = 5.9$, 10.3 Hz, 1H), 3.80 (dd, $J = 6.0$, 10.0 Hz, 1H), 3.93 (s, 3H), 4.00 (s, 3H), 5.84 (br s, 1H, O*H*), 6.43 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.7, 10.5, 11.9, 17.6, 17.9, 27.5, 29.7, 34.9, 37.2, 56.4, 56.8, 58.6, 61.2, 64.5, 80.9, 87.7, 92.4, 108.0, 116.9, 127.3, 145.9, 149.2, 153.0, 162.4, 177.4.

N. B. Monitoring the reaction by TLC was essential to avoid the cleavage of the silyl ether. Owing to sensitivity on silica gel, this crude product was used immediately for the next step.

Allyl {2-[(3*S*,4*S*,5*S*,6*R*)-4,6-Dimethoxy-3,5-dimethyl-7-|(triisopropylsilyl)oxy|heptyl]-5,7-dimethoxy-3-methyl-4-oxo-4*H*-chromen-8-yl} Carbonate (35a). Under argon, Alloc-OBT (420 mg, 2.07 mmol) and DMAP (84 mg, 0.69 mmol) were added to a solution of chromone **34** (409 mg, 0.69 mmol) in CH_2Cl_2 (3.5 mL). After 15 h stirring at rt, the reaction mixture was evaporated to dryness in a vacuum and the residue was chromatographed on silica gel (EtOAc) to give the carbonate **35a** as a thick colorless oil (400 mg; 85%). $[\alpha]_D = +3.1$ (*c* 1, CH_2Cl_2); TLC (EtOAc) $R_f = 0.51$; ^{1}H NMR ($CDCl_3$): δ 0.72 (d, $J = 7.2$ Hz, 3H), 1.05–1.06 (m, 21H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.53–1.65 (m, 1H), 1.69–1.83 (m, 3H), 1.97 (s, 3H), 2.50–2.62 (m, 1H), 2.66–2.77 (m, 1H), 3.02 (dd, $J = 2.3$, 9.0 Hz, 1H), 3.47 (s, 3H), 3.48 (s, 3H), 3.53–3.58 (m, 1H), 3.63 (dd, $J = 5.5$, 10.0 Hz, 1H), 3.86 (dd, $J = 6.3$, 10.0 Hz, 1H), 3.96 (s, 3H), 3.97 (s, 3H), 4.76 (d, $J = 5.6$ Hz, 2H), 5.33 (d, $J = 10.5$ Hz, 1H), 5.44 (d, $J = 17.1$ Hz, 1H), 6.01 (ddt, $J = 5.5$, 10.5, 17.1 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.6, 10.3, 11.9, 17.6, 18.0, 27.5, 29.8, 34.7, 37.4, 56.3, 56.5, 58.7, 61.2, 65.0, 69.5, 81.0, 87.4, 91.6, 107.7, 117.3, 119.1, 121.2, 131.2, 150.6, 152.9, 154.7, 158.4, 162.5, 176.8; Anal. Found: C, 63.31; H, 8.81%. Calcd for $C_{36}H_{58}O_{10}Si$: C, 63.69; H, 8.61%.

Allyl {2-[(3*S*,4*S*,5*S*,6*R*)-7-Hydroxy-4,6-dimethoxy-3,5-dimethylheptyl]-5,7-dimethoxy-3-methyl-4-oxo-4*H*-chromen-8-yl} Carbonate (35b). Under argon, with stirring, HOAc (0.2 mL, 3.51 mmol) was added to 1 M (in THF) TBAF·$3H_2O$ (2.81 mL, 2.81 mmol) and the resulting mixture was added with a syringe to a degassed solution of chromone **35a** (397 mg, 0.585 mmol) in THF (1 mL). After 5 d stirring at rt, the solvents were eliminated in a vacuum and the residue was chromatographed on silica gel (50:1 EtOAc/MeOH) to give the chromone **35b** as a thick colorless oil (306 mg; 100%). $[\alpha]_D = -3.4$ (*c* 1, EtOAc); TLC (EtOAc: MeOH = 50:1) $R_f = 0.24$; ^{1}H NMR ($CDCl_3$): δ 0.74 (d, $J = 7.0$ Hz, 3H), 1.09 (d, $J = 6.8$ Hz, 3H), 1.49–1.57 (m, 1H), 1.68–1.90 (m, 3H), 1.98 (s, 3H), 2.07 (br s, 1H, O*H*), 2.53–2.63 (m, 1H), 2.67–2.77 (m, 1H), 2.98 (dd, $J = 3.4$, 8.3 Hz, 1H), 3.44–3.49 (m, 7H), 3.65 (m, 2H), 3.95 (s, 3H), 3.97 (s, 3H), 4.76 (d, $J = 5.7$ Hz, 2H), 5.33 (d, $J = 10.5$ Hz, 1H), 5.44 (d, $J = 17.2$ Hz, 1H), 6.00 (ddt, $J = 5.7$, 10.5, 17.2 Hz, 1H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 9.7, 11.4, 17.7, 27.6, 29.6, 34.6, 37.7, 56.3, 56.5, 58.4, 61.3, 62.9, 69.6, 81.2, 87.9, 91.5, 107.6, 117.5, 119.3, 121.1, 131.1, 150.5, 152.9, 154.7, 158.4, 162.2, 176.7; Anal. Found: C, 61.87; H, 7.67%. Calcd for $C_{27}H_{38}O_{10}$: C, 62.05; H, 7.33%.

Allyl {2-[(3*S*,4*S*,5*S*,6*R*)-4,6-Dimethoxy-3,5-dimethyl-7-oxoheptyl]-5,7-dimethoxy-3-methyl-4-oxo-4*H*-chromen-8-yl} Carbonate (36). Using the conditions described above for the oxidation of **14d** to **13**, DMSO (0.123 mL, 1.61 mmol) in CH_2Cl_2 (3.5 mL) was treated at −78 °C with oxalyl chloride (0.13 mL, 1.43 mmol) before adding chromone **35b** (350 mg, 0.67 mmol) diluted with CH_2Cl_2 (4.5 mL), followed by DIPEA (0.592 mL, 3.42 mmol). After 30 min stirring at −78 °C, the reaction mixture was diluted with ether (15 mL) and poured into iced brine (15 mL) and ether (15 mL) with vigorous stirring. The aqueous phase was extracted with ether (4 × 15 mL). The pooled extracts were washed with 10% NH_4Cl (2 × 15 mL), brine (3 × 15 mL), and dried (Na_2SO_4). Elimination of the solvents in a vacuum then afforded the aldehyde **36** as a smelly yellow oil (346 mg; 100%). TLC (EtOAc) $R_f = 0.34$; ^{1}H NMR ($CDCl_3$): δ 0.74 (d, $J = 7.0$ Hz, 3H), 1.12 (d, $J = 6.8$ Hz, 3H), 1.50–1.88 (m, 3H), 1.98 (s, 3H), 2.07–2.20 (m, 1H), 2.53–2.63 (m, 1H), 2.69–2.79 (m, 1H), 3.01 (dd, $J = 2.4$, 9.5 Hz, 1H), 3.40 (s, 3H), 3.43 (s, 3H), 3.78 (dd, $J = 1.3$, 3.4 Hz, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.76 (d, $J = 5.6$ Hz, 2H), 5.33 (d, $J = 10.5$ Hz, 1H), 5.44 (d, $J = 17.2$ Hz, 1H), 6.00 (ddt, $J = 5.6$, 10.5, 17.2 Hz, 1H), 6.40 (s, 1H), 9.57 (d, $J = 1.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 9.7, 11.6, 17.5, 27.1, 29.5, 34.3, 37.3, 56.3, 56.5, 58.3, 61.0, 69.5, 86.7, 86.9, 91.6, 107.6, 117.5, 119.2, 121.2, 131.1, 150.5, 152.9, 154.8, 158.4, 161.9, 176.7, 202.6.

N. B. Owing to sensitivity on silica gel, this product was used for the next step without purification.

Allyl {2-[(3*S*,4*S*,5*S*,6*S*,7*E*,9*E*,11*E*)-4,6-Dimethoxy-3,5,11-trimethyltrideca-7,9,11-trien-1-yl]-5,7-dimethoxy-3-methyl-4-oxo-4*H*-chromen-8-yl} Carbonate (37). In a flask connected to an argon/vacuum line, 1.56 M (in hexane) BuLi (0.49 mL, 0.76 mmol) was added with a syringe to a cooled (ice bath) degassed solution of di-*i*-propylamine (97 mL, 0.69 mmol) in THF (9.9 mL). After 30 min stirring at 0 °C, the flask was immersed in a dry ice/acetone bath and a degassed solution of phosphonate **9a** (0.160 g, 0.69 mmol) in THF (9.9 mL) was

added with a cannula. The stirring was continued 1 h at −78 °C and a degassed solution of aldehyde **36** (328 mg, 0.63 mmol) in THF (18 mL) was slowly added with a cannula. The reaction mixture was further stirred 12 h at −78 °C, then 24 h at rt before being diluted with ether (25 mL) and poured into iced 10% NH_4Cl (50 mL). The aqueous phase was extracted with ether (50 mL) and EtOAc (4 × 50 mL), and the pooled organic extracts were washed with brine (2 × 30 mL), and dried (Na_2SO_4). The residue left by evaporation of the solvents in vacuo was chromatographed on buffered silica gel (CH_2Cl_2/EtOAc) to give successively the aldehyde **36** (40 mg; 25%) and the chromone **37** (127 mg; 34%). $[\alpha]_D = +20$ (*c* 1, CH_2Cl_2); TLC (CH_2Cl_2: EtOAc = 1:1) $R_f = 0.60$ (2 elutions); ^{1}H NMR ($CDCl_3$): δ 0.74 (d, $J = 7.1$ Hz, 3H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.49–1.85 (m, 10H), 1.97 (s, 3H), 2.47–2.57 (m, 1H), 2.67–2.76 (m, 1H), 3.10 (dd, $J = 1.5$, 9.4 Hz, 1H), 3.25 (s, 3H), 3.46 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.07 (m, 1H), 4.73 (d, $J =$ 5.6 Hz, 2H), 5.31 (d, $J = 10.3$ Hz, 1H), 5.42 (d, $J = 17.1$ Hz, 1H), 5.56–5.69 (m, 2H), 5.98 (ddt, $J = 5.6$, 10.3, 17.1 Hz, 1H), 6.09–6.27 (m, 3H), 6.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 10.1, 10.4, 12.3, 14.4, 18.0, 27.2, 30.1, 34.8, 42.2, 56.6, 56.7, 56.9, 61.8, 69.9, 81.4, 87.3, 91.9, 108.0, 117.7, 119.5, 121.5, 125.6, 128.1, 131.5, 132.1, 133.4, 135.0, 138.0, 151.0, 153.3, 155.1, 158.8, 162.8, 177.2; Anal. Found: C, 68.53; H, 8.12%. Calcd for $C_{34}H_{46}O_9$: C, 68.21; H, 7.74%.

Stigmatellin (1). In a flask connected to an argon line, PPh_3 (4 mg, 0.016 mmol), $[Pd(PPh_3)_4]$ (6.6 mg, 0.006 mmol), and 2-ethylhexanoic acid (13.5 mL) were added sequentially to a solution of **37** (34 mg, 0.057 mmol) in CH_2Cl_2 (0.8 mL). After 2 h stirring at rt, TLC analysis (EtOAc) showed the reaction was complete. The reaction mixture was deposited onto a column of de-activated silica gel (washings with CH_2Cl_2). Eluting with a gradient CH_2Cl_2/EtOAc, and then eliminating the solvents in a good vacuum (ca. 10^{-2} Torr) for a few hours afforded stigmatellin (**1**) as a thick oil polluted with traces of triphenylphosphine oxide, as evidenced by TLC and ^{1}H NMR analyses (25 mg; 85%). This product was further purified by chromatography over a thick layer of silica gel (EtOAc; 2 elutions). The colorless glass thus obtained (10 mg) was diluted in a tube with toluene (0.5 mL) and hexane (1 mL) was cautiously added so as two layers were formed. The tube was placed in a refrigerator to obtain, after 5 d, stigmatellin (**1**) as a white powder (4 mg). Mp 120–124 °C (Lit.:[2] 128–130 °C); $[\alpha]_D = +36.0$ (*c* 0.6, MeOH); Lit.:[2] $[\alpha]_D = +38.0$ (*c* 0.7, MeOH); Lit.:[4b] $[\alpha]_D = +37.7$ (*c* 0.7, MeOH); TLC (EtOAc) $R_f = 0.40$ (Lit.:[2] 0.40); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, $J = 6.8$ Hz, 3H), 1.11 (d, 3H, $J = 6.8$ Hz, 3H), 1.48–1.78 (m, 9H), 1.87–1.98 (m, 4H), 2.57–2.65 (m, 1H), 2.76–2.83 (m, 1H), 3.10 (dd, $J = 3.4$, 8.8 Hz, 1H), 3.24 (s, 3H), 3.49 (s, 3H), 3.92 (s, 3H), 3.99 (s, 3H), 5.28 (dd, $J = 2.7$, 7.8 Hz, 1H), 5.45 (br s, 1H, O*H*), 5.56–5.65 (m, 2H), 6.10–6.31 (m, 3H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.1, 10.7, 12.3, 14.4, 18.0, 27.4, 29.9, 35.1, 42.1, 56.6, 56.8, 57.2, 61.7, 81.7, 87.6, 92.8, 108.4, 117.3, 125.6, 127.7, 128.2, 132.1, 133.6, 135.0, 138.1, 146.3, 149.5, 153.4, 162.7, 177.7.

Crystallographic data have been deposited with Cambridge Crystallographic Data Centre: Deposition numbers CCDC-1021898, CCDC-1021891, and CCDC-1021895 for compounds **18**, **31a**, and **31c** respectively. Copies of the data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information

^{1}H and ^{13}C NMR spectra of synthetic stigmatellin (**1**). This material is available free of charge on J-STAGE.

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