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Note

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Stereoselective Synthesis of Conjugated Polyenes Based on Tethered Olefin Metathesis and Carbonyl Olefination: Application to the Total Synthesis of (+)-Bretonin B

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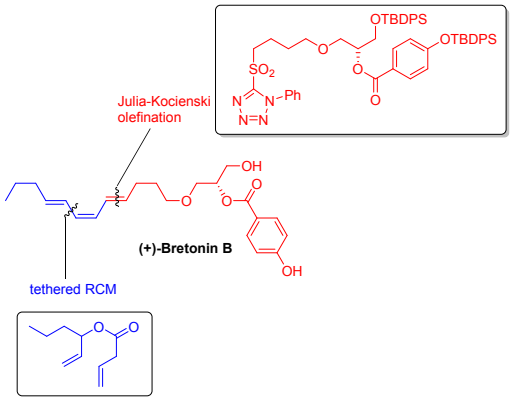
Supporting Information



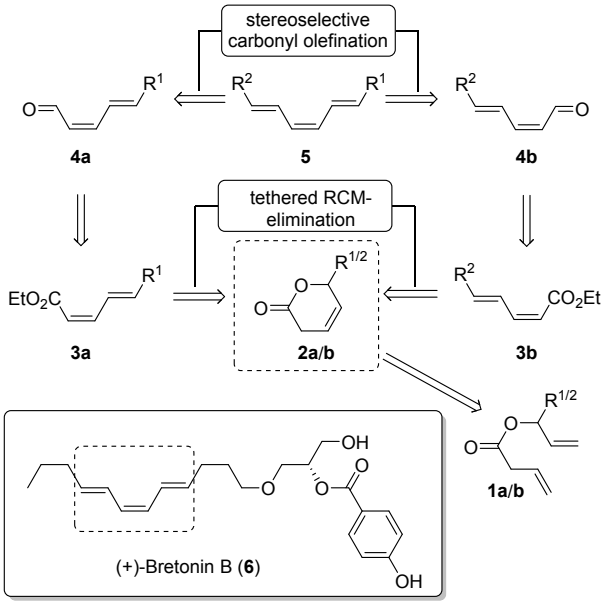
ABSTRACT: The combination of a highly stereoselective tethered olefin metathesis reaction and a Julia-Kocienski olefination is presented as a strategy for the synthesis of conjugated polyenes with at least one *Z*-configured C-C-double bond. The strategy is exemplified for the synthesis of the marine natural product (+)-bretonin B.

The stereoselective construction of polyenes is a challenging task in natural product synthesis[1,2] as products and intermediates are often prone to decomposition through photochemical[3,4] or oxidative pathways.[5-7] In those cases where one or more double bonds are *Z*-configured, isomerization to the all-*E*-isomers, which are in general more stable, arises as an additional problem.[8] The most commonly used methods for the total synthesis of polyene natural products are Pd-catalyzed coupling and cross coupling reactions.[2] These methods have been successfully applied in several cases, e. g. very recently for the synthesis of xanthomonadin analogues,[7] in the construction of the *Z*,*Z*,*E*-configured triene moiety in fostriecin[9] and in an iterative approach to a truncated amphotericin B fragment.[10] The stereoselective synthesis of the required coupling partners, ω-iodo- or bromodienes and vinyl metal compounds, can be a drawback because these often start from unstable haloenals,[11] which are subjected to carbonyl olefination reactions to furnish iodo- or bromodienes. One possibility to circumvent these difficulties has been devised by Maulide and coworkers, who developed the stereospecific electrocyclic ring opening of cyclobutenes into a method for the diastereoselective synthesis of functionalized conjugated dienes,[12] including ω-halodienes.[13] Olefin cross metathesis (CM) has also been investigated as a method for the synthesis of conjugated polyenes, e. g. in the total synthesis of violaxanthin,[14] η-carotene[6] or dermostatin A.[15,16] For the latter example, a moderate *E*/*Z*-selectivity of 4 : 1 was reported for the cross metathesis step, which might explain why this otherwise attractive and straightforward method has so far found only limited application in polyene synthesis.

Herein, we report an alternative approach to the stereoselective synthesis of conjugated polyenes for the example of *E*,*Z*,*E*-configured triene pattern **5**. As outlined above, polyenes with at least one *Z*-configured double bond have a strong tendency to isomerize to the all-*E*-configured isomers for thermodynamic reasons, which makes the methodology development more challenging. Over the past few years we investigated a novel type of tethered olefin metathesis reaction that makes *Z*,*E*-configured dienoates **3** accessible in high yields and diastereoselectivities from allylic butenoates **1**.[17,18] In the olefin metathesis field, the tether approach[19,20] is mainly used to address stereoselectivity and reactivity issues often associated with CM reactions by

temporarily connecting the reactants through a labile bond. The metathesis step then becomes a ring closing metathesis (RCM) reaction. Traceless removal of the tether after the RCM reaction, e. g. by hydrolysis, furnishes acyclic *Z*-alkenes that can not be obtained by standard CM reactions.[21,22] In our tethered RCM variant cleavage of the tether is accomplished by a base-induced elimination of RCM products **2** that generates an additional *E*-configured double bond conjugated to a *Z*-double bond. A further difference to other tethered RCM reactions is that the tether is retained in the product as a valuable carboxylate group. In our approach to *E*,*Z*,*E*-configured trienes **5** we envisaged a conversion of this functional group to aldehydes **4**, which could subsequently undergo an *E*-selective olefination. Advantageously, this strategy allows the construction of *E*,*Z*,*E*-trienes from both directions which increases the number of available synthetic routes (**Scheme 1**).

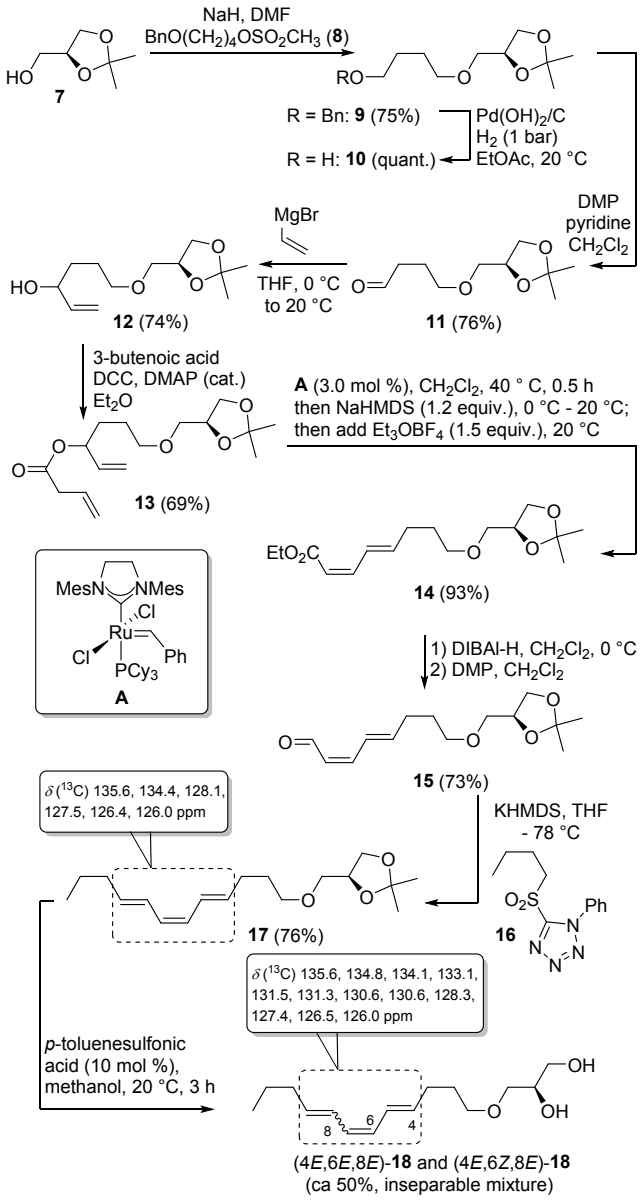
Scheme 1. *E*,*Z*,*E*-Configured trienes by tethered RCM.



As a showcase example for the application of this strategy we chose the marine natural product (+)-bretonin B (**6**) as a target molecule. Bretonins and isobretonins[23] are glyceryl mono ethers with a dodecatrienyl substituent at one primary position and a *para*-hydroxybenzoate at the secondary position (bretonins) or at the other primary position (isobretonins). They were isolated from a demosponge found at the coast of Brittany and structurally characterized.[24] Bretonin A and isobretonin A are more abundant and possess a (4*E*,6*E*,8*E*)-dodecatrienyl substituent, whereas bretonin B is 6*Z*-configured. Two syntheses of bretonin B have been published previously. Both rely on the construction of the C6-C7-double bond by olefination methods: in the first synthesis an unselective Wittig-olefination was used that furnished the (4*E*,6*E*,8*E*)- and (4*E*,6*Z*,8*E*)-isomers in a ca. 1 : 1 ratio.[25] More recently, Bach and coworkers used a Peterson elimination of a stereodefined β-silyl alcohol for the stereoselective construction of the (4*E*,6*Z*,8*E*)-moiety of bretonin B.[26]

Our first approach to bretonin B along the lines of the concept shown in scheme 1 required diol **18** as an advanced intermediate (**Scheme 2**). The synthesis started from commercially available enantiopure acetonide **7**, which was reacted with mesylate **8**[27] to furnish benzyl ether **9**.

Scheme 2. Acetonide protected bretonin B precursor.

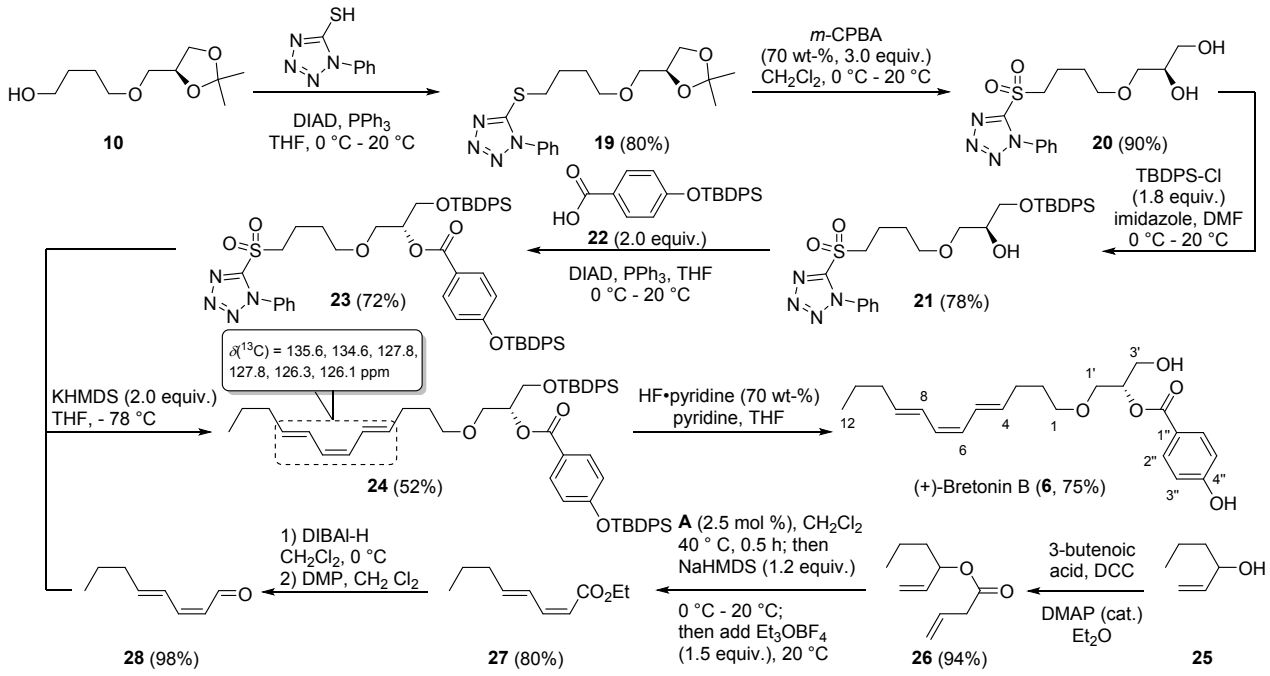


Hydrogenolytic cleavage of the benzyl ether in compound **9** with Pd/C had previously been reported to furnish alcohol **10** selectively,[28] but in our hands this reaction was accompanied by a cleavage of the acetal. The problem was circumvented by using $Pd(OH)_2/C$ as catalyst in the solvent ethyl acetate. Oxidation of **10** with Dess-Martin periodinane[29] furnished aldehyde **11**,[28] which was reacted with vinylmagnesium bromide to allylic alcohol **12**. Compound **12** was converted to butenoate **13** by Steglich esterification.[30] This butenoate was subjected to the tethered RCM-ring opening conditions in a one-flask reaction by subsequently treating it with second generation Grubbs' catalyst **A**[31] and the base NaHMDS to induce deprotonation and eliminative ring opening of the intermediate RCM product. The resulting Na-2,4-dienoate was trapped by addition of Meerwein's salt[32] (Et_3OBF_4) to give ester **14** in

very high diastereoselectivity (no other diastereomer was detected by ^{1}H-NMR spectroscopy) and high yield. To prepare for the envisaged carbonyl olefination step ester **14** was reduced to the alcohol, which is known to be very sensitive to decomposition and isomerization,[18] and was therefore not purified but immediately oxidized to aldehyde **15**. As the stereoselectivity of the following step is crucial, we chose a highly *E*-selective Julia-Kocienski-olefination.[33,34] It should be noted that the number of examples where this reaction has been used to construct fully conjugated trienes through olefination of dienals is rather limited, and we are only aware of reactions involving *E*,*E*-configured dienals.[35-37] Known sulfone **16**[38] was metallated with KHMDS and then treated with aldehyde **15** (which should best be freshly synthesized to avoid any decomposition) to give acetonide protected triene **17** in good yield as a single diastereoisomer. Assignment of the (4*E*,6*Z*,8*E*)-configuration is not straightforward based on routine ^{1}H-NMR-measurements due to overlapping signals in the olefinic region. However, a reliable configurational assignment is possible by comparison of the ^{13}C-NMR data for **17** listed in scheme 2 with those previously reported for all-*E* configured 4,6,8-dodecatriene-1-ol (δ(^{13}C) = 134.6, 133.3, 131.3, 131.1, 130.6, 130.6)[23,25] and (4*E*,6*Z*,8*E*)-dodecatriene-1-ol (δ(^{13}C) = 135.8, 134.3, 128.3, 127.4, 126.6, 126.0).[25,39] With compound **17** in hand, completion of the synthesis of (+)-bretonin B (**6**) required deprotection of the acetonide and selective introduction of the *para*-hydroxybenzoate at the secondary position via Mitsunobu inversion. Unfortunately, we were unable to find conditions for the acetal cleavage that proceed without substantial isomerization to the all-*E*-configured triene. For instance, treatment with a catalytic amount of *p*-TSA in methanol at ambient temperature furnished an inseparable mixture of (4*E*,6*E*,8*E*)-**18** and (4*E*,6*Z*,8*E*)-**18** in ca. 50% yield. Reducing the reaction time, lowering the amount of catalyst or replacing *p*-TSA by the milder acid pyridinium *p*-tosylate (PPTS) still resulted in considerable amounts of isomerized products and incomplete conversion.

This prompted us to investigate the construction of the (4*E*,6*Z*,8*E*)-triene from the opposite terminus via formation of the C4-C5-double bond rather than the C8-C9-double bond by a Julia-Kocienski-olefination. This route should allow us to avoid the deprotection of the acetonide at a late stage, when the acid-sensitive (4*E*,6*Z*,8*E*)-triene is already in place, and still use the acetonide **7** as a conveniently available enantiopure building block (**Scheme 3**). Sulfone **23** required for this approach had previously been synthesized by Bach and co-workers.[26] We chose a modified and somewhat shorter route to **23** that starts from compound **10**, an intermediate in our first approach to the bretonin skeleton (see scheme 2). Coupling with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions[40] furnished **19**, which was oxidized to sulfone **20** with *m*-CPBA. This oxidant had previously been used for tetrazole sulfides[41] and was, in a comparative investigation, found to give the cleanest and most selective conversion to the desired sulfones.[42] Although unplanned, the concomitant acetal cleavage led to a significant shortening of the synthesis, because with diol **20** in hand the synthesis of Julia-Kocienski-reagent **23** was completed in just two steps by selective protection of the primary alcohol with a sterically demanding TBDPS group and introduction of a TBDPS-protected *para*-hydroxy benzoate via Mitsunobu inversion of the secondary alcohol **21** with acid **22**[26] as a nucleophile. As coupling partner for the envisaged Julia-Kocienski-olefination (2*Z*,4*E*)-octa-2,4-dienal (**28**) was required. This compound was synthesized from allylic alcohol **25**[43] in analogy to the synthesis of dienal **15** (see scheme 2) via Steglich esterification, tethered RCM-electrophilic trapping sequence and reduction with DIBAl-H/oxidation with Dess-Martin periodinane. Deprotonation of sulfone **23** with KHMDS and coupling with aldehyde **28** furnished protected bretonin B **24** as the single (4*E*,6*Z*,8*E*)-diastereomer. Full NMR-spectroscopic structure elucidation and signal assignment at 500 MHz revealed the ^{13}C-NMR chemical shift pattern for *E*,*Z*,*E*-configured conjugated trienes.

Scheme 3. Successful route to (+)-bretonin B based on tethered RCM and Julia-Kocienski-olefination.



The synthesis of (+)-bretonin B was completed by deprotection of both TBDPS-ethers in **24** with HF•pyridine. All analytical data obtained by us for (+)-bretonin B, including the specific rotation, match those previously reported by Bach and coworkers.[26] We found, in agreement with the report from the Bach group, that (+)-bretonin B (**6**) undergoes isomerization to the all-*E*-configured diastereomer (i. e. bretonin A) to a significant extent within a few hours. Interestingly, the TBDPS-protected bretonin B (**24**), which was not an intermediate in Bach's total synthesis, was found to be configurationally stable at ambient temperature over a period of at least several days.

In summary, we have demonstrated that the combination of a tethered RCM reaction (with cleavage of the tether by base-induced eliminative ring opening) and a Julia-Kocienski olefination provides an efficient and versatile synthesis of *E*,*Z*,*E*-trienes, as exemplified in two approaches to the natural product (+)-bretonin B. This triene pattern is synthetically particularly challenging due to a strong tendency towards isomerization. Our synthesis provides a short and highly diastereoselective access to partially *Z*-configured tri- and perspectively polyenes that relies on mild conditions. Thus, it can be expected that this strategy will become a valuable method in target molecule synthesis in the future.

EXPERIMENTAL SECTION

All experiments involving air- and moisture sensitive chemicals were conducted using standard Schlenk technique under an atmosphere of dry nitrogen. Dichloromethane (DCM), diethyl ether, methanol and toluene were purified with a solvent purification system. All other chemicals were either purchased or prepared according to cited literature. Dry column vacuum chromatography[44] or standard flash column chromatography were performed on silica gel 60. ^{1}H NMR spectra were obtained in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$) as an internal standard. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext. (sextet) and m (multiplet). Coupling constants are given in Hz. ^{13}C NMR spectra were recorded with proton decoupling in $CDCl_3$ with $CDCl_3$ ($\delta = 77.16$) as an internal standard. The following instruments were used for NMR-measurements: Bruker ARX-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), Bruker DRX-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz), Bruker DRX-600 (^{1}H: 600 MHz; ^{13}C: 151 MHz). Whenever signal assignments are given they are based on a combination of 2D-NMR experiments (H,H-COSY, HMBC, HSQC). IR measurements were carried out as ATR-FTIR spectra using a Perkin-Elmer UART TWO instrument. Wavenumbers (ν) are given in cm^{-1} and the peak intensities are denoted as: strong (s), medium (m), weak (w). High-resolution mass spectra were obtained by ESI-TOF or EI-TOF on Micromass Manchester Waters Inc. instruments. Specific rotations were measured using Jasco DIP-1000 and P-2000 polarimeters in a 10 cm cuvette at 589 nm. Concentrations are given in g•100mL^{-1}. Compound **7** was purchased and used without further purification. 4-(Benzyloxy)butan-1-ol,[45] 4-((*tert*-butyldiphenylsilyl)oxy)benzoic acid (**22**)[26] and hex-1-en-3-ol (**25**)[43] were synthesized following the cited literature procedures.

4-(Benzyloxy)butyl methanesulfonate (8).[46] To a solution of 4-(benzyloxy)butan-1-ol (6.11 g, 34.7 mmol) in THF (150 mL) at 0 °C were added Et_3N (5.27 g, 6.99 mL, 52.1 mmol) and methanesulfonyl chloride (MsCl) (4.38 g, 2.95 mL, 38.2 mmol). The reaction mixture was stirred at 0 °C for 5 h. A satd. aq. solution of NH_4Cl (40 mL) was added. The aqueous layer was extracted with Et_2O (3 times 40 mL) and the combined organic layers were washed with brine (30 mL), dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product **8** (8.90 g, 34.7 mmol, quant.) was used in the next step without further purification: colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.24 (m, 5H), 4.50 (s, 2H), 4.26 (t, $J = 6.3$ Hz, 2H), 3.51 (t, $J = 6.0$ Hz, 2H), 2.97 (s, 3H), 1.94 – 1.80 (m, 2H), 1.78 – 1.67 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.4, 128.5, 127.8, 127.8, 73.1, 70.1, 69.5. Analytical data match those previously reported in the literature.[46]

(*S*)-4-((4-(Benzyloxy)butoxy)methyl)-2,2-dimethyl-1,3-dioxolane (9).[28] To a solution of **7** (3.78 g, 3.53 mL, 28.6

mmol) in DMF (325 mL) at 0 °C was added NaH (1.26 g, 60 wt-% dispersion in mineral oil, 31.3 mmol) in small portions. After stirring at this temperature for 1.5 h a solution of mesylate **8** (8.52 g, 29.5 mmol) in DMF (55 mL) was added dropwise and the reaction mixture was warmed to ambient temperature and stirred for 16 h. The reaction was quenched by addition of a satd. aq. solution of NH_4Cl (250 mL) and the mixture was extracted with Et_2O (5 times 30 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / ethyl acetate mixtures of increasing polarity) to give compound **9** (6.29 g, 21.4 mmol, 75%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.50 (s, 2H), 4.25 (p, J = 6.0 Hz, 1H), 4.04 (dd, J = 8.2, 6.4 Hz, 1H), 3.72 (dd, J = 8.2, 6.4 Hz, 1H), 3.57 – 3.42 (m, 5H), 3.41 (dd, J = 9.9, 5.6 Hz, 1H), 1.74 – 1.60 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.8, 128.5, 127.7, 127.6, 109.5, 74.9, 73.0, 72.0, 71.6, 70.3, 67.1, 26.9, 26.6, 26.5, 25.6; IR (ATR) ν 2961 (m), 1736 (s), 1249 (m), 1170 (s), 918 (s); HRMS (EI) *m/z*: [M$^+$] calcd for $C_{17}H_{26}O_4$ 294.1831; found 294.1839; $[\alpha]_D^{23}$ +9.4 (*c* 1.0, $CHCl_3$). Analytical data match those previously reported in the literature.[28]

(*S*)-4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)butan-1-ol (10).[28] Benzyl ether **9** (5.00 g, 17.0 mmol) was dissolved in EtOAc (85 mL) and $Pd(OH)_2$/C (20 wt-%, 2.04 g) was added. The system was flushed with H_2 and the reaction mixture was then exposed to H_2 (1 bar) at ambient temperature for 2 h. The heterogeneous mixture was filtered through celite and washed with EtOAc. The product **10** (3.48 g, 17.0 mmol, quant.) was used in the next step without further purification: colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (p, J = 5.9 Hz, 1H), 4.03 (dd, J = 8.2, 6.5 Hz, 1H), 3.70 (dd, J = 8.2, 6.4 Hz, 1H), 3.67 – 3.57 (m, 2H), 3.57 – 3.38 (m, 4H), 2.37 (s, 1H), 1.72 – 1.58 (m, 4H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 109.6, 74.8, 72.0, 71.8, 66.9, 62.7, 30.0, 26.9, 26.5, 25.5; IR (ATR) ν 3420 (s, broad), 2936 (m), 2868 (m), 1455 (w), 1371 (m), 1052 (s); HRMS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{10}H_{21}O_4$ 205.1440; found 205.1430; $[\alpha]_D^{22}$ +8.6 (*c* 1.0, $CHCl_3$). Analytical data match those previously reported in the literature.[28]

(*S*)-4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)butanal (11).[28] To a solution of **10** (1.33 g, 6.53 mmol) and pyridine (3.99 mL, 49.0 mmol) in CH_2Cl_2 (65 mL) at 0 °C was added Dess-Martin periodinane (4.16 g, 9.80 mmol) in portions. The reaction mixture was stirred at 20 °C for 2 h. The reaction was quenched by addition of satd. aq. solutions of $NaHCO_3$/$Na_2S_2O_3$ (1 : 1). The aqueous layer was extracted with CH_2Cl_2 (3 times 30 mL), dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give aldehyde **11** (1.01 g, 4.99 mmol, 76%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (t, J = 1.6 Hz, 1H), 4.17 (p, J = 5.9 Hz, 1H), 3.99 (dd, J = 8.3, 6,4 Hz, 1H), 3.65 (dd, J = 8.3, 6.4 Hz, 1H), 3.53 – 3.41 (m, 3H), 3.37 (dd, J = 10.0, 5.4 Hz, 1H), 2.47 (td, J = 7.1, 1.6 Hz, 2H), 1.87 (p, J = 6.7 Hz, 2H), 1.36 (s, 3H), 1.30 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 202.1, 109.4, 74.7, 71.9, 70.5, 66.8, 40.8, 26.8, 25.4, 22.5; IR (ATR) ν 2934 (m), 2869 (m), 1723 (s), 1370 (m), 1118 (s), 1078 (s), 843 (m); HRMS (ESI) *m/z*: [M+Na]$^+$ calcd for $C_{10}H_{18}O_4Na$ 225.1103; found 225.1098; $[\alpha]_D^{22}$ +3.3 (*c* 1.0, $CHCl_3$). Analytical data match those previously reported in the literature.[28]

3-(*R*,*S*)-6-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)hex-1-en-3-ol (12). A solution of **11** (959 mg, 4.74 mmol) in THF (25 mL) was cooled to 0 °C. Vinylmagnesium bromide (5.69 mL, 1 M in THF, 5.69 mmol) was added dropwise and the reaction was stirred at ambient temperature for 18 h. The reaction was quenched with satd. aq. solution of NH_4Cl (25 mL) and the aqueous layer was separated and extracted with Et_2O (3 times 25 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / ethyl acetate mixtures of increasing polarity) to give allylic alcohol **12** (807 mg, 3.50 mmol, 74%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddd, J = 17.3, 10.4, 6.0 Hz, 1H), 5.20 (dt, J = 17.2, 1.5 Hz, 1H), 5.07 (dt, J = 10.4, 1.4 Hz, 1H), 4.24 (p, J = 6.0 Hz, 1H), 4.16 – 4.06 (m, 1H), 4.03 (dd, J = 8.3, 6.4 Hz, 1H), 3.70 (dd, J = 8.3, 6.3 Hz, 1H), 3.56 – 3.38 (m, 4H), 2.30 (s (br.), 1H), 1.76 – 1.50 (m, 4H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 141.2, 114.6, 109.5, 74.8, 72.8, 72.0, 71.8, 66.9, 34.1, 26.9, 25.7, 25.5; IR (ATR) ν 3448 (s, br.), 2935 (w), 2866 (w), 1371 (m), 1212 (s), 1052 (s); HRMS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{12}H_{23}O_4$ 231.1596; found 231.1605; $[\alpha]_D^{22}$ +7.8 (*c* 1.0, $CHCl_3$).

6-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)hex-1-en-3-yl but-3-enoate (13). Allyl alcohol **12** (639 mg, 2.77 mmol), DMAP (51.3 mg, 0.42 mmol) and 3-butenoic acid (286 mg, 0.28 mL, 3.32 mmol) were dissolved in Et_2O (28 mL). The solution was cooled to 0 °C and DCC (684 mg, 3.32 mmol) was added. The reaction mixture was warmed to 20 °C and stirred at this temperature for 36 h. It was then cooled to 0 °C again, filtered and washed with Et_2O. The filtrate was washed with aq. HCl (1 M) and satd. aq. solution of $NaHCO_3$. The organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give ester **13** (570 mg, 1.91 mmol, 69%): colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (ddt, J = 16.8, 10.0, 7.0 Hz, 1H), 5.76 (ddd, J = 17.0, 10.5, 6.3 Hz, 1H), 5.30 – 5.10 (m, 5H), 4.24 (p, J = 6.0 Hz, 1H), 4.04 (dd, J = 8.2, 6.4 Hz, 1H), 3.71 (dd, J = 8.2, 6.4 Hz, 1H), 3.54 – 3.35 (m, 4H), 3.09 (dt, J = 7.0, 1.5 Hz, 2H), 1.73 – 1.52 (m, 4H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 170.8, 136.4, 130.4, 118.6, 117.0, 109.5, 74.9, 74.8, 72.0, 71.3, 67.0, 39.5, 30.9, 26.9, 25.6, 25.3; IR (ATR) ν 2986 (w), 1735 (s), 1370 (w), 1170 (s); HRMS (ESI) *m/z*: [M+H]$^+$ calcd for $C_{16}H_{27}O_5$ 299.1858; found 299.1869; $[\alpha]_D^{22}$ +6.5 (*c* 1.0, $CHCl_3$).

Ethyl (2*Z*,4*E*)-8-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)octa-2,4-dienoate (14). To a solution of **13** (287 mg, 0.96 mmol) in degassed dry CH_2Cl_2 (10 mL) at 40 °C was added second generation Grubbs' catalyst **A** (24.4 mg, 3.0 mol%). The reaction mixture was stirred at 40 °C until the starting material was fully consumed, as indicated by TLC (2 h). The solution was cooled to 0 °C and NaHMDS (1 M solution in THF, 1.15 mL, 1.15 mmol) was added. The reaction was warmed to 20 °C and stirred for 3 h. After this time, Meerwein's salt $[Et_3O]BF_4$ (273 mg, 1.44 mmol) was added and the reaction mixture was stirred for 3 h. The solution was then filtered through celite and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure and the crude product was purified by dry column vacuum

chromatography (SiO_2; eluent: hexanes / ethyl acetate mixtures of increasing polarity) to give the ethyl dienoate **14** (267 mg, 0.89 mmol, 93%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (ddm, J = 15.2, 11.3 Hz, 1H), 6.52 (t, J = 11.3 Hz, 1H), 6.04 (dt, J = 15.3, 7.0 Hz, 1H), 5.56 (d, J = 11.3 Hz, 1H), 4.25 (p, J = 6.1 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 4.04 (dd, J = 8.2, 6.4 Hz, 1H), 3.71 (dd, J = 8.2, 6.4 Hz, 1H), 3.56 – 3.35 (m, 4H), 2.26 (q, J = 7.3 Hz, 2H), 1.72 (p, J = 6.7 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.6, 145.2, 144.6, 127.4, 116.0, 109.5, 74.9, 72.0, 71.1, 67.0, 60.0, 29.7, 28.8, 26.9, 25.6, 14.4; IR (ATR) ν 2935 (w), 1712 (s), 1637 (m), 1601 (m), 1370 (m), 1175 (s), 1031 (m); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{16}H_{27}O_5$ 299.1858; found 299.1869; $[\alpha]_D^{24}$ +10.3 (*c* 1.0, $CHCl_3$).

(2*Z*,4*E*)-8-(((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)octa-2,4-dienal (15). A solution of ester **14** (188 mg, 0.62 mmol) in CH_2Cl_2 (6 mL) was cooled to 0 °C. DIBAl-H (0.92 mL, 1 M solution in hexane, 0.92 mmol) was added slowly, the reaction was warmed to 20 °C and stirred for 10 min.. Brine (5 mL) was added, followed by HCl (aq., 1 M, minimum amount required to dissolve the precipitate). The aqueous layer was separated and extracted with CH_2Cl_2 (3 times 10 mL). The combined organic layers were washed with satd. aq. solution of $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was immediately redissolved in CH_2Cl_2 (6 mL) and the solution was cooled to 0 °C. Dess-Martin-periodinane[29] (533 mg, 1.24 mmol) was added and the reaction was stirred at 20°C for 2 h. It was quenched with satd. aq. aolutions of $NaHCO_3$ and $Na_2S_2O_3$ (1 : 1 (v/v)). The aqueous layer was separated and extracted with CH_2Cl_2 (3 times 10 mL), dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / ethyl acetate mixtures of increasing polarity) to give dieneal **15** (114 mg, 0.45 mmol, 73%): yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.14 (d, J = 7.9 Hz, 1H), 7.04 (ddm, J = 14.6, 11.8 Hz, 1H), 6.89 (dd, J = 11.3, 11.3 Hz, 1H), 6.16 (dt, J = 14.6, 7.1 Hz, 1H), 5.78 (ddm, J = 10.8, 7.9 Hz, 1H), 4.25 (p, J = 6.0 Hz, 1H), 4.04 (dd, J = 8.2, 6.4 Hz, 1H), 3.71 (dd, J = 8.3, 6.4 Hz, 1H), 3.55 – 3.35 (m, 4H), 2.31 (q, J = 7.5 Hz, 2H), 1.74 (p, J = 6.8 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 190.5, 147.9, 146.2, 126.1, 124.8, 109.6, 74.9, 72.1, 70.9, 66.9, 29.8, 28.7, 26.9, 25.5; IR (ATR) ν 2932 (w), 1666 (s), 1635 (s), 1370 (m), 1115 (s); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{23}O_4$ 255.1596; found 255.1586; $[\alpha]_D^{24}$ +8.5 (*c* 1.0, $CHCl_3$).

5-(Butylsulfonyl)-1-phenyl-1*H*-tetrazole (16). *5-(Butylthio)-1-phenyl-1H-tetrazole*:[38] 1-Butanol (222 mg, 0.27 mL, 3.00 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (1.07 g, 6.00 mmol) and PPh_3 (1.18 g, 4.50 mmol) were dissolved in THF (120 mL). DIAD (639 mg, 3.15 mmol) was added dropwise at 0 °C. After 30 min the reaction mixture was allowed to warm to ambient temperature and stirred for 16 h. It was quenched with satd. aq. NH_4Cl (90 mL) and the aqueous layer was extracted with Et_2O (3 times 60 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give *pre*-**16** (549 mg, 2.34 mmol, 78%): colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 5H), 3.39 (t, J = 7.4 Hz, 2H), 1.80 (p, J = 7.4 Hz, 2H), 1.47 (sext., J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.6, 133.9, 130.2, 129.9, 124.0, 33.2, 31.2, 21.9, 13.6; IR (ATR) ν 2959 (m), 1597 (m), 1499 (s), 1385 (s), 759 (s); HRMS (EI) *m/z*: $[M]^+$ calcd for $C_{11}H_{14}N_4S$ 234.0939; found 234.0930. Analytical data match those previously reported in the literature.[38] *5-(Butylsulfonyl)-1-phenyl-1H-tetrazole (16)*:[38] 5-(Butylthio)-1-phenyl-1H-tetrazole (500 mg, 2.14 mmol) was dissolved in CH_2Cl_2 and the solution was cooled to 0 °C. *m*-CPBA (70 wt-% aq. dispersion, 1.48 g, 6.42 mmol) was added and the reaction mixture was stirred at ambient temperature for 12 h. The reaction was quenched by addition of satd. aq. solution of $Na_2S_2O_3$ (80 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 times 60 mL). The combined organic layers were washed with satd. aq. solution of $NaHCO_3$, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give sulfone **16** (476 mg, 1.79 mmol, 84%): colourless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.54 (m, 5H), 3.77 – 3.68 (m, 2H), 1.93 (p, J = 7.7 Hz, 2H), 1.53 (sext., J = 7.8 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.7, 133.2, 131.6, 129.8, 125.2, 55.9, 24.0, 21.6, 13.5; IR (ATR) ν 2963 (w), 1595 (w), 1497 (m), 1335 (s), 1149 (s), 762 (s); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{11}H_{15}N_4O_2S$ 267.0916; found 267.0903. Analytical data match those previously reported in the literature.[38]

(*S*)-4-((((4*E*,6*Z*,8*E*)-Dodeca-4,6,8-trien-1-yl)oxy)methyl)-2,2-dimethyl-1,3-dioxolane (17). To a solution of sulfone **16** (240 mg, 0.90 mmol) in THF (21 mL) at −78 °C was added KHMDS (1.28 mL, 0.7 M solution in toluene, 0.90 mmol) dropwise. The resulting yellow solution was stirred for 3 min., followed by dropwise addition of a solution of dienal **15** (114 mg, 0.45 mmol) in THF (14 mL). The reaction mixture was stirred at −78 °C for 1 h and then quenched at this temperature by slowly adding a satd. aq. solution of NH_4Cl (45 mL). The mixture was allowed to warm to ambient temperature, the aqueous phase was separated and extracted with Et_2O (3 times 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give triene **17** (99.4 mg, 0.34 mmol, 76%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 – 6.41 (m, 2H), 5.94 – 5.78 (m, 2H), 5.75 – 5.60 (m, 2H), 4.26 (p, J = 6.1 Hz, 1H), 4.06 (dd, J = 8.2, 6.4 Hz, 1H), 3.73 (dd, J = 8.2, 6.4 Hz, 1H), 3.59 – 3.37 (m, 4H), 2.19 (q, J = 7.4 Hz, 2H), 2.10 (q, J = 7.2 Hz, 2H), 1.69 (p, J = 7.0 Hz, 2H), 1.46 – 1.39 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 135.6, 134.4, 128.1, 127.5, 126.4, 126.0, 109.5, 74.9, 72.0, 71.2, 67.0, 35.2, 29.5, 29.3, 26.9, 25.6, 22.7, 13.9; IR (ATR) ν 2929 (m), 1455 (w), 1117 (m), 962 (s); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{18}H_{30}O_3Na$ 317.2093; found 317.2087; $[\alpha]_D^{25}$ +6.6 (*c* 1.0, $CHCl_3$).

(*R*)-3-(((4*E*,6*E*,*Z*,8*E*)-Dodeca-4,6,8-trien-1-yl)oxy)propane-1,2-diol ((4*E*,6*E*,8*E*)-18 and (4*E*,6*Z*,8*E*)-18). Acetonide **17** (42.5 mg, 0.14 mmol) was dissolved in MeOH (0.5 mL) and CH_2Cl_2 (0.5 mL). p-TSA•3H_2O (2.52 mg, 10 mol%) was added and the reaction mixture was stirred at ambient temperature for 4 h. $NaHCO_3$ (100 mg) and water (2 mL) were added. The aqueous phase was separated and extracted with EtOAc (5 mL). The combined organic extracts were dried with $MgSO_4$, filtered and evaporated under reduced pressure to furnish crude diol **18** (ca. 20 mg, 0.07

mmol, ca. 50%) as a ca. 2 : 3 mixture of (4*E*,6*E*,8*E*)- and (4*E*,6*Z*,8*E*)-isomers. Selected characteristic NMR-data were obtained from the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 – 6.40 (m, 2H, (*E*,*Z*,*E*)-isomer), 6.21 – 5.98 (m, 4H, (*E*,*E*,*E*)-isomer), 5.91 – 5.77 (m, 2H, (*E*,*Z*,*E*)-isomer), 5.77 – 5.66 (m, 2H, (*E*,*Z*,*E*)- and (*E*,*E*,*E*)-isomer)); ^{13}C NMR data of (4*E*,6*Z*,8*E*)-**18**: ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 135.8, 134.1, 128.3, 127.4, 126.5, 126.0; ^{13}C{^{1}H} NMR data of (4*E*,6*E*,8*E*)-**18**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 133.1, 131.5, 131.3, 130.6, 130.6; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{15}H_{27}O_3$ 255.1960; found 255.1973.

(*S*)-5-((4-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)butyl)thio)-1-phenyl-1*H*-tetrazole (19). Alcohol **10** (1.20 g, 5.87 mmol), 1-phenyl-1*H*-tetrazole-5-thiol (2.09 g, 11.7 mmol) and PPh_3 (2.30 g, 8.81 mmol) were dissolved in THF (225 mL) and cooled to 0 °C. DIAD (1.26 g, 1.23 mL, 6.22 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. It was quenched with satd. aq. solution of NH_4Cl (100 mL) and the aqueous layer was extracted with Et_2O (3 times 60 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give **19** (1.70 g, 4.67 mmol, 80%): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.48 (m, 5H), 4.23 (p, *J* = 6.0 Hz, 1H), 4.03 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.69 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.58 – 3.45 (m, 3H), 3.45 – 3.36 (m, 3H), 1.90 (p, *J* = 6.8 Hz, 2H), 1.72 (p, *J* = 6.5 Hz, 2H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 154.4, 133.8, 130.2, 129.9, 123.9, 109.5, 74.8, 72.1, 70.9, 66.9, 33.2, 28.6, 26.9, 26.1, 25.5; IR (ATR) *v* 2985 (w), 2867 (w), 1597 (w), 1499 (s), 1241 (m); HRMS (EI) *m/z*: $[M^+]$ calcd for $C_{17}H_{24}N_4O_3S$ 364.1569; found 364.1564; $[\alpha]_D^{23}$ +8.9 (*c* 1.0, $CHCl_3$).

(*R*)-3-(4-((1-Phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)propane-1,2-diol (20). To a solution of **19** (1.91 g, 5.24 mmol) in CH_2Cl_2 (120 mL) at 0 °C was added *m*-CPBA (2.69 g, 15.7 mmol, 70 wt-% suspension in water) in portions. The reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of satd. aq. solution of $Na_2S_2O_3$ (80 mL), the aqueous layer was separated and extracted with CH_2C_{l2} (3 times 60 mL). The combined organic layers were washed with satd. aq. solution of $NaHCO_3$, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by filtration through a pad of silica gel to give sulfone **20** (1.68 g, 4.71 mmol, 90%): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.52 (m, 5H), 3.90 – 3.75 (m, 3H), 3.70 (dd, *J* = 11.3, 3.9 Hz, 1H), 3.60 (dd, *J* = 11.4, 5.7 Hz, 1H), 3.56 – 3.43 (m, 4H), 2.70 (s (br.), 2H), 2.06 (p, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 6.8, 6.4 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.5, 133.1, 131.6, 129.9, 125.2, 72.5, 70.8, 70.4, 64.0, 55.8, 27.9, 19.6; IR (ATR) *v* 3401 (s, broad), 2873 (w), 1598 (w), 1497 (m), 1338 (s), 1149 (s); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{14}H_{21}N_4O_5S$ 357.1233; found 357.1215; $[\alpha]_D^{24}$ –1.5 (*c* 1.0, $CHCl_3$).

(*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)-propan-2-ol (21). Diol **20** (1.64 g, 4.60 mmol) was dissolved in DMF (60 mL). A solution of imidazole (611 mg, 8.97 mmol) and TBDPSCl (1.35 g, 1.27 mL, 4.92 mmol) in DMF (25 mL) was added dropwise at 0 °C. The reaction was stirred at ambient temperature for 16 h. The reaction was quenched with satd. aq. solution of NH_4Cl (40 mL) and the aqueous layer was extracted with Et_2O (4 times 30 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / ethyl acetate mixtures of increasing polarity) to give **21** (2.14 g, 3.60 mmol, 78%): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, 6H), 7.63 – 7.55 (m, 3H), 7.47 – 7.35 (m, 6H), 3.94 – 3.85 (m, 1H), 3.84 – 3.74 (m, 2H), 3.71 (d, *J* = 5.5 Hz, 2H), 3.58 – 3.44 (m, 4H), 2.58 (d (br.), *J* = 4.5 Hz, 1H), 2.04 (p, *J* = 7.5 Hz, 2H), 1.76 (p, *J* = 6.4 Hz, 2H), 1.08 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 153.6, 135.7, 133.3, 133.2, 131.6, 130.0, 129.9, 127.9, 125.3, 72.0, 70.9, 70.4, 65.0, 55.9, 28.1, 27.0, 19.6, 19.4; IR (ATR) *v* 3562 (s, broad), 2930 (w), 2858(w), 1340 (m), 1111 (s); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{30}H_{39}N_4O_5SSi$ 595.2410; found 595.2398; $[\alpha]_D^{24}$ –3.2 (*c* 1.0, $CHCl_3$).

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(4-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)butoxy)-propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (23).[26] Alcohol **21** (1.28 g, 2.15 mmol), acid **22** (1.62 g, 4.30 mmol) and PPh_3 (1.13 g, 4.30 mmol) were dissolved in THF (60 mL) and cooled to 0 °C. DIAD (870 mg, 0.85 mL, 4.30 mmol) was added dropwise and the reaction mixture was stirred at ambient temperature for 16 h. The reaction was quenched by addition of satd. aq. solution of NH_4Cl (50 mL) and the aqueous layer was extracted with Et_2O (3 time 40 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give sulfone **23** (1.47 g, 1.54 mmol, 72%): pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.74 – 7.66 (m, 6H), 7.64 – 7.57 (m, 7H), 7.49 – 7.30 (m, 9H), 7.29 – 7.22 (m, 3H), 6.78 (d, *J* = 8.7 Hz, 2H), 5.27 (p, *J* = 4.9 Hz, 1H), 3.86 (d, *J* = 4.7 Hz, 2H), 3.78 – 3.62 (m, 4H), 3.57 – 3.44 (m, 2H), 2.01 (p, *J* = 7.4 Hz, 2H), 1.73 (p, *J* = 6.2 Hz, 2H), 1.12 (s, 5H), 1.02 (s, 5H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 165.8, 160.0, 153.6, 135.7, 135.6, 133.4, 133.3, 133.2, 132.4, 132.4, 131.7, 131.5, 130.3, 129.8, 129.8, 128.0, 127.8, 127.8, 125.2, 123.1, 119.7, 73.1, 70.5, 69.5, 62.8, 55.9, 28.2, 26.9, 26.6, 19.6, 19.6, 19.4; IR (ATR) *v* 2931 (w), 1714 (m), 1603 (m), 1259 (s), 1112 (s), 700 (s); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{53}H_{60}N_4NaO_7SSi_2$ 975.3613; found 975.3626; $[\alpha]_D^{25}$ –7.8 (*c* 1.0, $CHCl_3$). Analytical data match those previously reported in the literature,[26] except for the specific rotation (reported value:[26] $[\alpha]_D^{20}$ +7.8 (*c* 1.0, $CHCl_3$)).

Hex-1-en-3-yl but-3-enoate (26).[47] Alcohol **25** (1.56 g, 15.6 mmol), DMAP (281 mg, 2.30 mmol) and 3-butenoic acid (1.61 g, 1.60 mL, 18.7 mmol) were dissolved in Et_2O (160 mL). The solution was cooled to 0 °C and DCC (3.85 g, 18.7 mmol) was added. The reaction was stirred at 20 °C for 36 h. The reaction mixture was cooled to 0 °C, filtered and washed with Et_2O. The filtrate was washed with aq. HCl (1 M) and a satd. aq. solution of $NaHCO_3$. The organic phase was dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give **26** (2.46 g, 14.7 mmol, 94%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.0, 9.7, 6.9 Hz, 1H), 5.77 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 5.32 – 5.09 (m, 5H), 3.09 (d, *J* = 7.0 Hz, 2H), 1.73 – 1.46 (m, 2H), 1.40 – 1.25 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H}

NMR (75 MHz, $CDCl_3$) δ 170.9, 136.6, 130.5, 118.6, 116.7, 75.0, 39.6, 36.4, 18.4, 13.9; IR (ATR) ν 2961 (m), 1736 (s), 1249 (m), 1170 (s), 918 (s); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{10}H_{16}NaO_2$ 191.1048; found 191.1044. Analytical data match those previously reported in the literature.[47]

Ethyl (2*Z*,4*E*)-octa-2,4-dienoate (27).[17] To a solution of **26** (500 mg, 2.97 mmol) in degassed dry CH_2Cl_2 (30 mL) was added second generation Grubbs' catalyst **A** (75.6 mg, 3.0 mol%) at 40 °C. The reaction mixture was stirred at this temperature until the starting material was fully consumed, as indicated by TLC (ca. 2 h). The solution was cooled to 0 °C and NaHMDS (1 M solution in THF, 3.56 mL, 3.56 mmol) was added. The reaction was warmed to ambient temperature and stirred for 3 h. Meerwein's salt $[Et_3O]BF_4$ (845 mg, 4.46 mmol) was added and the reaction mixture was stirred for another 3 h. The solution was filtered through celite and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give **27** (400 mg, 2.38 mmol, 80%): pale yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (ddm, J = 15.2, 11.3 Hz, 1H), 6.54 (t, J = 11.3 Hz, 1H), 6.06 (dt, J = 14.9, 7.0 Hz, 1H), 5.56 (dd, J = 11.4, 0.9 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.18 (q, J = 7.0 Hz, 2H), 1.47 (sext., J = 7.3 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.7, 145.6, 145.5, 127.2, 115.7, 60.0, 35.2, 22.1, 14.5, 13.9; IR (ATR) ν 2961 (m), 1713 (m), 1422 (w), 1178 (s); HRMS (EI) *m/z*: $[M^+]$ calcd for $C_{10}H_{16}O_2$ 168.1150; found 168.1156. Analytical data match those previously described in the literature.[17]

(2*Z*,4*E*)-Octa-2,4-dienal (28). A solution of ester **27** (421 mg, 2.50 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C. DIBAl-H (5.0 mL, 1 M solution in hexane, 5.00 mmol) was added slowly, the reaction was allowed to warm to ambient temperature and stirred for 10 min.. Brine (15 mL) and a minimum amount of aq. HCl (1 M) were then added and the aqueous layer was extracted with CH_2Cl_2 (3 times 30 mL). The combined organic layers were washed with satd. aq. solution of $NaHCO_3$ and brine, dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was immediately redissolved in CH_2Cl_2 (25 mL) and the solution was cooled to 0 °C. Dess- Martin-periodinane (DMP)[29] (2.13 g, 5.00 mmol) was added and the reaction was stirred at 20 °C for 2 h. It was quenched by addition of satd. aq. solutions of $NaHCO_3$ and $Na_2S_2O_3$ (1 : 1 (v/v)). The aqueous layer was extracted with CH_2Cl_2 (3 times 30 mL), dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give aldehyde **28** (305.2 mg, 2.46 mmol, 98%): yellowish liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.17 (d, J = 7.9 Hz, 1H), 7.04 (ddm, J = 14.4, 12.0 Hz, 1H), 6.92 (dd, J = 12.0, 10.7 Hz, 1H), 6.17 (dt, J = 14.4, 7.1 Hz, 1H), 5.78 (dd, J = 10.5, 8.0 Hz, 1H), 2.21 (q, J = 7.2 Hz, 2H), 1.50 (sext., J = 7.3 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 190.5, 148.1, 147.1, 125.9, 124.6, 35.2, 22.0, 13.8; IR (ATR) ν 2960 (m), 1664 (s), 1634 (s), 1229 (m), 953 (m); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_8H_{13}O$ 125.0966; found 125.0962. (2*Z*,4*E*)-Octa-2,4-dienal (**28**) was reported to be a volatile oxidation product of sunflower oils and detected by GC-MS, but no other analytical data of this compound have previously been reported.[48]

(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)-3-(((4*E*,6*Z*,8*E*)-dodeca-4,6,8-trien-1-yl)oxy)propan-2-yl 4-((*tert*-butyldiphenylsilyl)oxy)benzoate (24). To a solution of **23** (618 mg, 0.648 mmol) in THF (15 mL) at −78 °C was KHMDS (0.93 mL, 0.7 M solution in toluene, 0.648 mmol) added dropwise. The resulting yellow solution was stirred for 3 min.. A solution of aldehyde **28** (40.2 mg, 0.324 mmol) in THF (12 mL) was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. Satd. aq. solution of NH_4Cl (30 mL) was added dropwise at −78 °C and the mixture was allowed to warm to ambient temperature. The aqueous phase was extracted with Et_2O (3 times 30 mL) and the combined organic layers were dried with $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give TBDPS-protected bretonin B **24** (143 mg, 0.168 mmol, 52%): colourless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.8 Hz, 2H, H2''), 7.74 – 7.70 (m, 4H, Ph), 7.65 – 7.61 (m, 4H, Ph), 7.47 – 7.42 (m, 2H, Ph), 7.41 – 7.23 (m, 10H, Ph), 6.78 (d, J = 8.8 Hz, 2H, H3''), 6.47 (dd, J_{trans} = 14.8, 10.4 Hz, 2H, H5, H8), 5.86 (dd, J = 10.8, 10.8 Hz, 1H, H6/7), 5.82 (dd, J = 10.8, 10.8 Hz, 1H, H6/7), 5.70 (dt, J = 15.1, 7.3 Hz, 1H, H9), 5.65 (dt, J = 15.1, 7.3 Hz, 1H, H4), 5.28 (p, J = 5.0 Hz, 1H, H2'), 3.89 (d, J = 4.6 Hz, 2H, H3'), 3.72 (dd, J = 5.3, 1.6 Hz, 2H, H1'), 3.52 – 3.41 (m, 2H, H1), 2.15 (q, J = 7.2 Hz, 2H, H3), 2.10 (q, J = 7.2 Hz, 2H, H10), 1.70 – 1.60 (m, 2H, H2), 1.49 – 1.38 (m, 2H, H11), 1.12 (s, 9H, OSiC(CH_3)$_3$), 1.02 (s, 9H, C_{ar}OSiC(CH_3)$_3$), 0.92 (t, J = 7.4 Hz, 3H, H12); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 165.8 (C=O), 160.0 (C4''), 135.7 (Ph), 135.6, 134.6 (C4, C9), 133.5 (Ph), 132.4 (Ph), 131.7 (C2''), 130.3 (Ph), 129.8 (Ph), 129.8 (Ph), 128.1 (Ph), 127.8, 127.8 (C6, C7), 127.6 (Ph), 126.3, 126.1 (C5, C8), 123.3 (C1''), 119.7 (C3''), 73.3 (C2'), 71.1 (C1), 69.1 (C1'), 62.8 (C3'), 35.2 (C10), 29.6 (C3), 29.5 (C2), 26.9 (SiC(CH_3)$_3$), 26.6 (SiC(CH_3)$_3$), 22.7 (C11), 19.6 (SiC(CH_3)$_3$), 19.4 (SiC(CH_3)$_3$), 13.9 (C12); IR (ATR) ν 3072 (w), 2957 (m), 2931 (m), 1716 (m), 1603 (m), 1508 (m), 1428 (m), 125 9 (s), 1164 (m), 1112 (s), 911 (m), 735 (m) 700 (s); HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{54}H_{66}NaO_5Si_2$ 873.4341; found 873.4348; $[\alpha]_D^{24}$ −8.1 (*c* 1.0, $CHCl_3$).

(+)-Bretonin B (6). HF•pyridine complex (0.62 mL, ~70% HF and 30% pyridine) was added dropwise to a solution of **24** (138 mg, 0.163 mmol) and dry pyridine (1.27 mL) in THF (8 mL) at 20 °C. After 2 h the reaction mixture was filtered through a pad of silica gel, eluted with Et_2O. The crude product was purified by dry column vacuum chromatography (SiO_2; eluent: hexanes / MTBE mixtures of increasing polarity) to give (+)-bretonin B (**6**) (45.7 mg, 0.122 mmol, 75%): colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.7 Hz, 2H, H2''), 6.79 (d, J = 8.8 Hz, 2H, H3''), 6.48 (ddt, J = 15.1, 10.4, 1.4 Hz, H5/8), 6.45 (ddt, J = 15.1, 10.4, 1.4 Hz, H5/8), 5.86 (dd, J = 10.8, 10.8 Hz, H6/7), 5.81 (dd, J = 10.8, 10.8 Hz, H6/7), 5.69 (dt, J = 15.1, 7.3 Hz, 1H, H4/9), 5.65 (dt, J = 15.1, 7.3 Hz, 1H, H4/9), 5.22 (p, J = 4.6 Hz, 1H, H2'), 4.00 – 3.95 (m, 2H, H3'), 3.80 (dd, J = 10.7, 5.0 Hz, 1H, H1'), 3.75 (dd, J = 10.7, 4.8 Hz, 1H, H1'), 3.58 – 3.45 (m, 2H, H1), 2.21 – 2.11 (m, 2H, H3), 2.10 – 2.02 (m, 2H, H10), 1.72 – 1.64 (m, 2H, H2), 1.45 – 1.36 (m, 2H, H11), 0.90 (t, J = 7.1 Hz, 3H, H12); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 166.6 (C=O), 161.1 (C4''), 135.8, 134.0 (C4, C9), 132.2 (C2''), 128.3, 127.4 (C6, C7), 126.6, 126.0 (C5, C8), 121.7 (C1''), 115.5 (C3''), 73.2 (C2'), 71.4 (C1), 70.5 (C1'), 63.3 (C3'), 35.1 (C10), 29.5 (C3), 29.3 (C2), 22.6

(C11), 13.9 (C12); IR (ATR) *v* 3329 (s, broad), 2929 (m), 2871 (m), 1711 (m), 1687 (m), 1608 (m), 1593 (m), 1272 (s), 1165 (m), 1114 (m), 851 (w), 700 (w); HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{31}O_5$ 375.2171; found 375.2158; $[\alpha]_D^{22}$ +4.5 (*c* 1.0, $CHCl_3$). All analytical data match those previously reported by Bach and coworkers.[26] Isomerization to all-E-configured bretonin A was observed upon standing at ambient temperature (signals emerging in the region of 6.07 – 5.98 ppm in the 1H-NMR-spectrum).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at...
Copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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