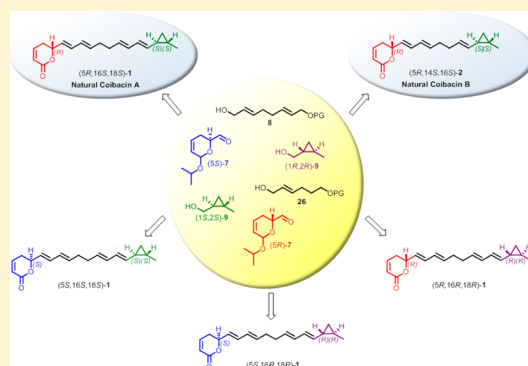


## Coibacins A and B: Total Synthesis and Stereochemical Revision

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## S Supporting Information

**ABSTRACT:** The interface between synthetic organic chemistry and natural products was explored in order to unravel the structure of coibacin A, a metabolite isolated from the marine cyanobacterium cf. *Oscillatoria* sp. that exhibits selective antileishmanial activity and potent anti-inflammatory properties. Our synthetic plan focused on a convergent strategy that allows rapid access to the desired target by coupling of three key fragments involving *E*-selective Wittig and modified Julia olefinations. CD measurements and comparative HPLC analyses of the natural product and four synthetic stereoisomers led to determination of its absolute configuration, thus correcting the original assignment at C-5 and unambiguously establishing those at C-16 and C-18. Additionally, we synthesized coibacin B on the basis of the assignment of configuration for coibacin A.



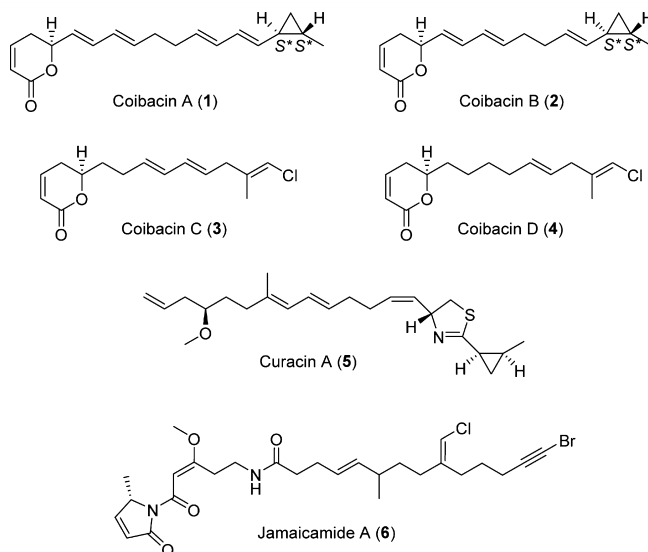
## 1. INTRODUCTION

Marine organisms are a rich source of diverse and biologically active natural products that have inspired the development of novel pharmacologically relevant compounds.<sup>1</sup> The  $\alpha,\beta$ -unsaturated  $\delta$ -lactone moiety is a privileged scaffold widely distributed among natural products that display a broad range of biological activities, such as fostriecin,<sup>2–4</sup> leptomycins,<sup>5</sup> and callistatin A.<sup>6,7</sup>

The unequivocal assignment of the absolute configuration of the structure of a novel compound is one of the key issues in natural products chemistry. In this regard, and despite the fact that spectroscopic and crystallographic techniques are highly advanced, chemical synthesis still makes important contributions in natural product elucidation.<sup>8,9</sup>

Recently, we described the isolation and structure elucidation of four unsaturated polyketide lactone derivatives named coibacins A–D (compounds 1–4, Figure 1) from the marine cyanobacterium cf. *Oscillatoria* sp. that display the dihydropyran-2-one moiety as well as either a cyclopropyl ring (coibacins A and B) or a methyl vinyl chloride (coibacins C and D).<sup>10</sup> The methylcyclopropyl ring and methyl vinyl chloride are similar to those observed in other marine cyanobacterial metabolites such as curacin A (5)<sup>11</sup> and jamaicamide A (6),<sup>12</sup> respectively. These co-occurring metabolites in a single organism suggest an intriguing flexibility in the biosynthetic pathway.<sup>10</sup>

Among these cyanobacterial metabolites, coibacin A (1) displayed potent and selective activity against axenic amastigotes of *Leishmania donovani* ( $IC_{50}$  = 2.4  $\mu$ M). Coibacin

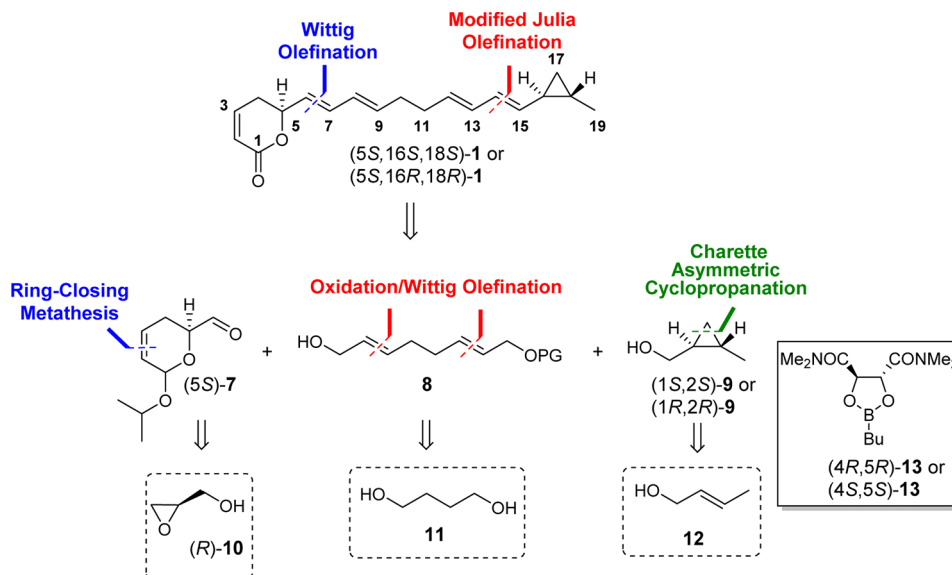


**Figure 1.** Structures of marine cyanobacterial metabolites: coibacins A–D (1–4), curacin A (5), and jamaicamide A (6).

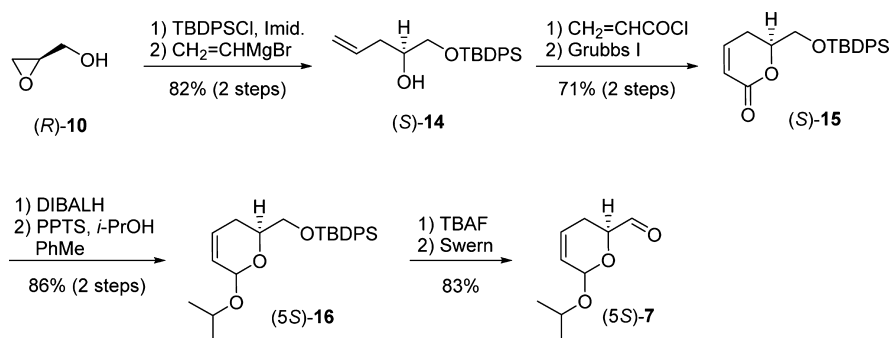
B (2) was less active as a leishmanicidal drug ( $IC_{50}$  = 7.2  $\mu$ M); however, it exhibited higher cytotoxicity against human cancer lung cell lines (NCI-H460), with an  $IC_{50}$  value of 17.0  $\mu$ M

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Scheme 1. Retrosynthetic Plan for Coibacin A (1) Isomers



Scheme 2. Preparation of Aldehyde (5S)-7



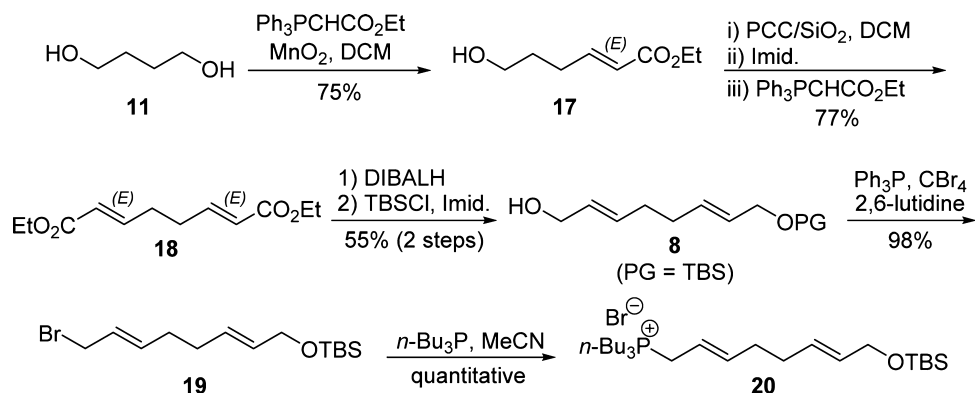
compared with 31.5  $\mu\text{M}$  for coibacin A (1). Evaluation of anti-inflammatory activity by cell-based nitric oxide (NO) inhibition assay<sup>13</sup> revealed that coibacin B (2) was the most active coibacin representative ( $\text{IC}_{50} = 5 \mu\text{M}$ ). Because coibacin A (1) was isolated in the largest amount, it was further evaluated and shown to reduce gene transcription of several inflammatory cytokines, including TNF- $\alpha$ , IL1- $\beta$ , IL-6, and iNOS (1 at 10  $\mu\text{g}/\text{mL}$ ).<sup>10</sup>

The absolute configuration of the dihydropyran-2-one moiety was determined to be *S* on the basis of a positive Cotton effect at  $\lambda = 259 \text{ nm}$  observed in circular dichroism (CD) measurements, while the *trans* relationship of the substituents in the methylcyclopropyl ring was established using NOESY correlations and *J* coupling constant analysis. However, because of the scarcity of the natural products, the absolute configuration of the cyclopropyl portion could not be assigned.<sup>10</sup>

Because of our interest in the synthesis and biological properties of  $\alpha,\beta$ -unsaturated  $\delta$ -lactones,<sup>14–18</sup> we embarked on the total synthesis of stereoisomers of coibacin A (1) with the aim of establishing its absolute configuration and providing enough material for further exploration of its biological properties. Additionally, coibacin B (2) was synthesized on the basis of the assignment of configuration for coibacin A (1) by a similar synthetic route.

## 2. RESULTS AND DISCUSSION

Assuming the *S* absolute configuration of the  $\delta$ -lactone moiety and the *trans* relationship between the substituents in the cyclopropyl ring, we envisioned a convergent strategy based on the coupling of three key fragments to quickly provide the two possible isomers (5S,16S,18S)- and (5S,16R,18R)-1 (Scheme 1). This synthetic route would be carried out by *E*-selective Wittig olefination of dihydropyran aldehyde (5S)-7 with a tri-*n*-butylphosphorane derived from alcohol 8. The resulting tetrahydropyran would be converted to the corresponding aldehyde for the final modified Julia olefination with a sulfone derived from (1S,2S)- or (1R,2R)-9. The enantiomerically pure fragment (5S)-7 would be synthesized from commercially available (*R*)-glycidol [(*R*)-10] by methodology similar to that previously reported for its enantiomer (*SR*)-7, involving as key steps the ring opening of a chiral epoxide and the ring-closing metathesis reaction of the corresponding diene.<sup>19,20</sup> The preparation of fragment 8 could be performed in a few steps from 1,4-butanediol (11) using tandem oxidation/Wittig olefination.<sup>21</sup> The synthesis of *trans*-cyclopropyl fragment (1S,2S)-9 using Charette asymmetric cyclopropanation of *trans*-crotyl alcohol (12) mediated by dioxaborolane-derived chiral ligand (4R,5R)-13 has been described.<sup>22</sup> Similarly, the enantiomer (1R,2R)-9 could be obtained by employing (4S,5S)-13.

Scheme 3. Synthesis of Tri-*n*-butylphosphonium Salt 20

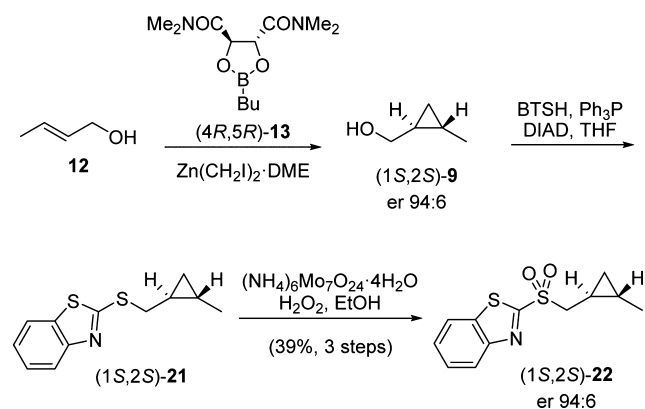
Our synthesis began with the preparation of aldehyde (5*S*)-7 from (*R*)-10 according to a modification of the procedures described by Crimmins and King<sup>20</sup> and Boger et al.<sup>19</sup> for (5*R*)-7. Protection of (*R*)-10 with *tert*-butyldiphenylsilyl chloride (TBDPSCl) and Cu(I)-mediated epoxide opening with vinylmagnesium bromide were carried out to provide allylic alcohol (5*S*)-14 in 82% overall yield.<sup>20</sup> The dihydropyran-2-one (5*S*)-15 was obtained in good yield after conversion of secondary alcohol (5*S*)-14 to the corresponding ester followed by ring-closing metathesis using Grubbs I catalyst (71% yield, two steps). Reduction of (5*S*)-15 with diisobutylaluminum hydride (DIBALH) and protection of the resulting lactol as the corresponding isopropyl ketal afforded (5*S*)-16 in 86% yield as a single isomer.<sup>19,23</sup> Deprotection of the silyl ether group of (5*S*)-16 (83% yield) and Swern oxidation furnished the desired aldehyde (5*S*)-7,<sup>20</sup> which was synthesized from (*R*)-10 in eight steps and 42% overall yield (Scheme 2).

The synthesis of fragment **8** started with the conversion of 1,4-butanediol (**11**) to the diester **18**. Two reaction steps were necessary to perform this transformation because treatment of **11** with 20 equiv of magnesium dioxide ( $\text{MnO}_2$ ) and 2.5 equiv of [(ethoxycarbonyl)methylene]triphenylphosphorane in dichloromethane or chloroform furnished the desired bisolefinated compound **18** in very poor yield (15–18%) even after reflux for 3 days. Thus, mild conditions were employed to conduct a desymmetrization reaction via tandem oxidation of unactivated **11** with  $\text{MnO}_2$  and in situ Wittig olefination to provide olefin (E)-17 in 75% yield.<sup>21</sup> The scale-up of this reaction (from 2 to 30 mmol of substrate) required increased reaction time from 2 to 7 days, and optimization studies indicated that a 50% reduction in the amount of  $\text{MnO}_2$  did not affect the yield. The byproducts diester **18** (about 4% yield) and (Z)-17 (10% yield) were obtained from this reaction. Intermediate **17** was homologated to afford **18** in good yield (77%) after one-pot oxidation with pyridinium chlorochromate (PCC) and Wittig olefination. In this reaction, the (2*E*,6*Z*) isomer of **18** was isolated as a byproduct in 7% yield (Scheme 3).

Reduction of **18** to the corresponding diol with DIBALH and monoprotection with *tert*-butyldimethylsilyl chloride (TBSCl) afforded fragment **8** (PG = TBS) in 55% yield for two steps. Conversion to the allylic bromide **19** upon treatment with triphenylphosphine ( $\text{Ph}_3\text{P}$ ) and carbon tetrabromide ( $\text{CBr}_4$ ) in the presence of 2,6-lutidine was accomplished in high yield (98%);<sup>24</sup> however, in the absence of base the yield decreased to 45% and the dibromide byproduct was obtained in 28% yield. Subsequently, substitution with tri-*n*-butylphosphine ( $n\text{-Bu}_3\text{P}$ )

afforded phosphonium salt **20** in quantitative yield. Therefore, **20** was prepared in six steps and 31% overall yield from readily available diol **11** (Scheme 3).

*trans*-Cyclopropyl fragment (1*S*,2*S*)-9 was obtained from Charette asymmetric cyclopropanation of *trans*-crotyl alcohol (**12**) mediated by dioxaborolane-derived chiral ligand (4*R*,5*R*)-13.<sup>22,25</sup> Treatment of (1*S*,2*S*)-9 with 2-mercaptobenzothiazole (BTSH),  $\text{Ph}_3\text{P}$  and diisopropyl azodicarboxylate (DIAD) afforded (1*S*,2*S*)-21 after Mitsunobu reaction.<sup>25</sup> Oxidation with ammonium molybdate/ $\text{H}_2\text{O}_2$  provided sulfone (1*S*,2*S*)-22 in 39% yield for three steps with an enantiomeric ratio (er) of 94:6 (Scheme 4). The preparation of (1*R*,2*R*)-22 was

Scheme 4. Synthesis of Sulfone (1*S*,2*S*)-22

accomplished from the same starting material **12** using dioxaborolane (4*S*,5*S*)-13, and the overall yield was 31%. The enantiomeric ratio of (1*S*,2*S*)-22 and (1*R*,2*R*)-22 was determined by chiral HPLC analysis.<sup>26</sup>

The synthesis of the C-1/C-14 fragment of isomers (5*S*,16*R*,18*R*)- and (5*S*,16*S*,18*S*)-1 (Scheme 1) involved the coupling of aldehyde (5*S*)-7 with tri-*n*-butylphosphonium salt **20** by *E*-selective Wittig olefination (Scheme 5). When this reaction was performed with potassium *tert*-butoxide (*t*-BuOK) in a 5:1 toluene/THF mixture, the desired product (5*S*)-23 was obtained as a 5:1 mixture of *E* and *Z* isomers. With the DMSO-derived lithium base  $\text{LiCH}_2\text{S}(\text{O})\text{CH}_3$  in toluene, a *E*:*Z* isomeric ratio of 7:1 was formed. However, in both cases the yields were low (46% or less) regardless of the reaction scale and modifications in the amount of base or Wittig salt **20** employed. Therefore, we used sodium hexamethyldisilazide (NHMSD) as a more hindered base to prevent deprotonation  $\alpha$  to the carbonyl group of (5*S*)-7. Fortunately, the yield was

## Scheme 5. Synthesis of Aldehyde (5S)-24

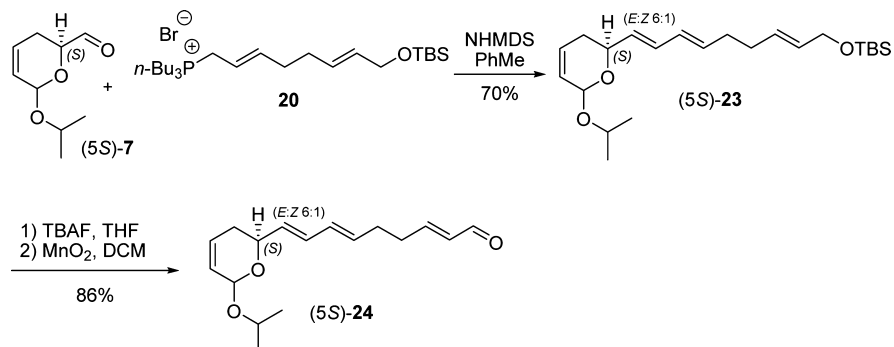


Table 1. Modified Julia Olefination Involving Aldehyde (5S)-24 and Racemic Sulfone 22

entry <sup>a</sup>	solvent	MHMDS	time	E:Z ratio at C-14 <sup>b</sup>	yield (%)
1	DMF	NHMDS	1.5 h (−78 °C), 1.5 h (rt)	1.7:1	4 <sup>c</sup>
2	THF	NHMDS	1.5 h (−78 °C), 1.5 h (rt)	1.7:1	28 <sup>c</sup>
3	THF	NHMDS	10 min	1.7:1	65 <sup>d,e</sup>
4	DME	NHMDS	20 min	2.7:1	95 <sup>d</sup>
5	4:1 THF/HMPA	NHMDS	1.5 h	1.7:1	66 <sup>d</sup>
6	4:1 DME/HMPA	NHMDS	1.5 h	2:1	53 <sup>d</sup>
7	DME	LHMDS	10 min	1:10	54 <sup>d</sup>
8	DME	KHMDS	10 min	2.4:1	95 <sup>d</sup>

<sup>a</sup>Scale: 0.06 mmol of (5S)-24. Volume of solvent: 2.5 mL. <sup>b</sup>E:Z ratio of the double bond at C-14 for the isomers with *E* geometry of the C-6 double bond. <sup>c</sup>Addition order: sulfone, NHMDS, and aldehyde. <sup>d</sup>Addition order: sulfone, aldehyde, and NHMDS. <sup>e</sup>When the scale was duplicated, the yield was 70%.

increased to about 70% (*E*:*Z* ratio = 6:1) by using 2 equiv of NHMDS and 1.5 equiv of **20** in toluene. The moderate *E* selectivity of this reaction may be attributed to the low steric hindrance of the ylide.<sup>27</sup> The triene (5S)-23 was converted uneventfully to aldehyde (5S)-24 upon deprotection of the TBS ether followed by MnO<sub>2</sub>-mediated allylic alcohol oxidation in 86% yield for two steps (Scheme 5).

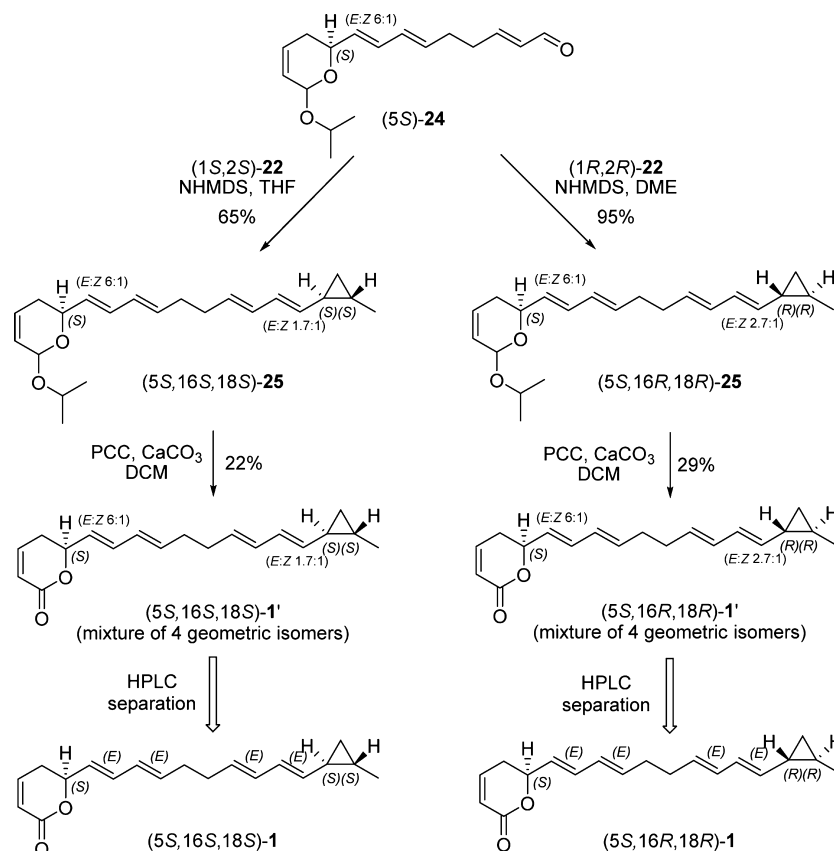
The final coupling between aldehyde (5S)-24 and sulfonylbenzothiazole **22** required extensive optimization in order to improve the *E*:*Z* ratio of the newly formed double bond.<sup>28</sup> To avoid the use of expensive enantiomerically enriched substrate, racemic **22** was employed in the modified Julia olefination reaction (Table 1). When NHMDS was used, either DMF or THF afforded (5S)-25 as a 1.7:1 mixture of *E* and *Z* isomers at C-14 in moderate to low yields (entries 1–3). Under the same conditions, a reduction in the reaction time led to an increase in the yield from 28% to 65%, probably as a result of reduced decomposition of the product in the reaction medium (entries 2 and 3). Using DME as the solvent increased the *E*:*Z* ratio at C-14 to 2.7:1 and the yield to 95% (entry 4). Addition of hexamethylphosphoramide (HMPA) did not affect the selectivity (entries 5 and 6), although studies in the literature have shown improvement of the *E* selectivity in the presence of this additive.<sup>29,30</sup> While LHMDS, as expected, favored the *Z* configuration of the newly formed double bond

(entry 7), KHMDS displayed results similar to those reported for NHMDS (entry 8).

The isomers (5S,16S,18S)- and (5S,16R,18R)-**1** were prepared as described in Scheme 6. Coupling of aldehyde (5S)-24 with sulfones (1S,2S)- and (1R,2R)-**22** provided the tetraenes (5S,16S,18S)- and (5S,16R,18R)-**25**, respectively, as mixtures of four geometric isomers, with the major isomer displaying the all-*E* configuration.<sup>31</sup> The mixtures of isomers (5S,16S,18S)- and (5S,16R,18R)-**1'** were obtained after oxidation of (5S,16S,18S)- and (5S,16R,18R)-**25** with PCC and CaCO<sub>3</sub><sup>32</sup> in 22% and 29% yield, respectively. Separation of the major isomers by semipreparative reversed-phase HPLC<sup>33</sup> afforded dihydropyran-2-ones (5S,16S,18S)- and (5S,16R,18R)-**1**, with <sup>1</sup>H- and <sup>13</sup>C-NMR data identical to each other as well as to those reported for natural coibacin A (**1**) in spite of their diastereoisomeric relationship.

Comparison of the specific optical rotations of the synthetic samples of (5S,16S,18S)-**1** ([α]<sub>D</sub><sup>20</sup> −10, *c* 0.1, CHCl<sub>3</sub>) and (5S,16R,18R)-**1** ([α]<sub>D</sub><sup>20</sup> −100, *c* 0.1, CHCl<sub>3</sub>) with that reported for natural coibacin A (**1**) ([α]<sub>D</sub><sup>20</sup> +46, *c* 0.1, CHCl<sub>3</sub>) indicated the nonidentity of the compounds. On the basis of the opposed signal of the specific optical rotation of the synthetic and natural compounds, we suspected that the original assignment of the absolute configuration of the lactone moiety was in error. Therefore, we conducted the total synthesis of the isomers (5R,16S,18S)- and (5R,16R,18R)-**1** by a route similar to that



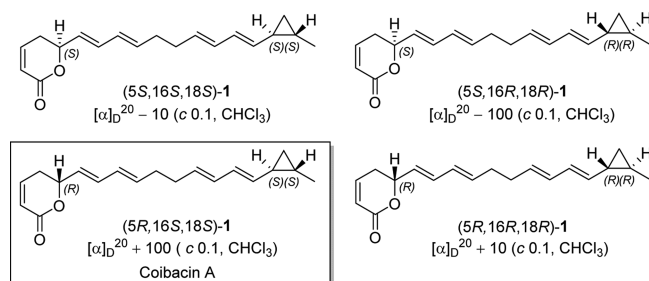
Scheme 6. Synthesis of Enantiomerically Pure Isomers (5*S*,16*S*,18*S*)- and (5*S*,16*R*,18*R*)-1

described above for their enantiomers (see the Experimental Section for further details). As expected, these compounds also displayed <sup>1</sup>H and <sup>13</sup>C NMR data identical to those reported for natural coibacin A (**1**). Despite their dextrorotatory values, the specific optical rotations of (5*R*,16*S*,18*S*)-1 ( $[\alpha]_D^{20} +100$ ,  $c$  0.1, CHCl<sub>3</sub>) and (5*R*,16*R*,18*R*)-1 ( $[\alpha]_D^{20} +10$ ,  $c$  0.1, CHCl<sub>3</sub>) proved to be significantly different from that reported for the natural coibacin A (**1**).

Because of the difficulty of unequivocal assignment of the absolute configuration of coibacin A (**1**) based only on NMR and specific optical rotation data, we carried out HPLC comparisons<sup>34</sup> of natural coibacin A (**1**) with all four synthetic stereoisomers displaying a *trans* configuration of the cyclopropane ring (Figure 2). When a mixture of these four compounds was coinjected with natural coibacin A (**1**), an enhancement in the intensity of the peak corresponding to (5*R*,16*S*,18*S*)-1 was observed, unequivocally establishing the

absolute configuration of the natural product. Additionally, the CD curve of (5*R*,16*S*,18*S*)-1 was identical to the one described for coibacin A (**1**), with both displaying a positive Cotton effect (see the CD curves in the Supporting Information). Therefore, these results led to the revision of the configuration at C-5 in our original publication, which was previously assigned to be *S*,<sup>10</sup> possibly as a result of a misapplication of the rules described by Beecham.<sup>35</sup>

It is interesting to compare the chirality established here for coibacin A (**1**) with that of curacin A (**5**) (Figure 1), a methylcyclopropane-containing metabolite isolated from another marine cyanobacterium, *Moorea producens* (formerly *Lyngbya majuscula*). There, detailed biosynthetic mechanism studies have shown that the *S* configuration of the secondary methyl group appended to the cyclopropyl ring is established by the trajectory of hydride delivery to the  $\beta$ -position of an achiral enone.<sup>36</sup> However, the adjacent cyclopropylmethine center is rendered chiral (and in the case of curacin A, *cis*-configured relative to the methyl substituent) after collapse of the enolate to displace chloride and form the three-membered ring. Thus, because curacin A (**5**) and coibacin A (**1**) possess secondary methyl groups of identical chirality, the divergence in their biosynthetic pathways must lie within this second step. A range of possibilities exist, including the geometry of the intermediate enone formed by the enoyl CoA hydratase 1, the relative positions of the oxyanion and primary chloride substituents to the methyl group prior to cyclopropyl ring formation, and the overall orientation of the substrate in the enoyl reductase. Thus, similar to the subtle alternate functioning of  $\beta$ -branch-forming enzymes that lead to the diverse functional groups observed in curacin A (**5**) and

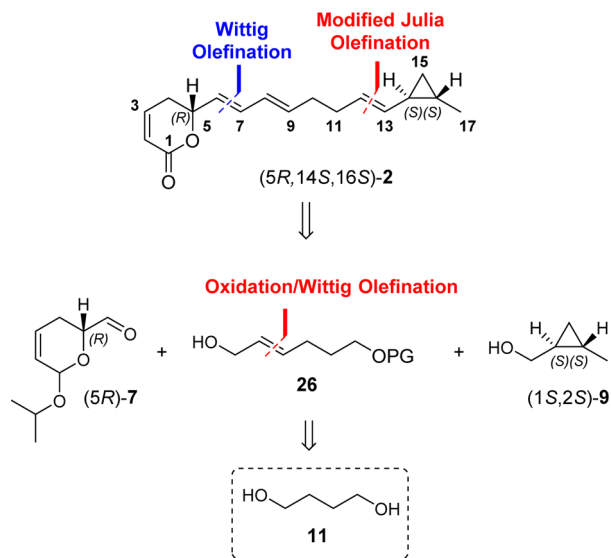


**Figure 2.** Specific optical rotations of the four isomers of coibacin A (**1**).

jamaicamide A (**6**) (cyclopropyl ring vs vinyl chloride; Figure 1),<sup>37</sup> the stereostructures of the coibacins implicate additional dimensions of flexibility in this biosynthetic manifold.

A similar synthetic approach was applied to the synthesis of coibacin B (**2**) displaying the 5*R*,14*S*,16*S* configuration, the same one found for coibacin A (**1**) (Scheme 7). Fragment **26** was planned to be obtained after two steps from alcohol **17**, which was already prepared from diol **11** for the synthesis of coibacin A (**1**).

**Scheme 7. Retrosynthetic Plan for the Correct Isomer of Coibacin B (2)**



Protection of alcohol **17** with TBSCl followed by reduction of ester group with excess DIBALH furnished fragment **26** (PG = TBS) in high yield (94%, two steps). Appel reaction converted alcohol **26** to the corresponding bromide **27** in 91% yield, and **27** was treated with *n*-Bu<sub>3</sub>P to give tri-*n*-butylphosphonium salt **28** in quantitative yield (Scheme 8).

The *E*-selective Wittig reaction between (5*R*)-**7** and **28** mediated by NHMDS in toluene furnished (5*R*)-**29** as a 6:1 mixture of *E* and *Z* isomers at C-6 in 69% yield. Alcohol (5*R*)-**30**, obtained in 94% yield from deprotection of TBS ether (5*R*)-**29**, was oxidized under Swern conditions, and the unstable crude product was immediately used in the modified Julia olefination with sulfone (1*S*,2*S*)-**22** to afford (5*R*,14*S*,16*S*)-**31** as a mixture of geometric isomers. While the use of NHMDS in DME provided a 1:1 mixture of geometric isomers at the C-12 double bond, better *E* selectivity (*E*:*Z* ratio = 2.2:1) was obtained by using KHMDS. The moderate yield for the Swern oxidation and Julia olefination (41%) can be

explained by the instability of the aldehyde derived from alcohol (5*R*)-**30**. The mixture containing (5*R*,14*S*,16*S*)-**31** was treated with PCC in the presence of CaCO<sub>3</sub> to give a mixture of four geometric isomers (5*R*,14*S*,16*S*)-**2'** in 46% yield. The major isomer (5*R*,14*S*,16*S*)-**2**, with all of the double bonds displaying the *E* configuration, was isolated by semipreparative reversed-phase HPLC (Scheme 9).<sup>38</sup>

Synthetic (5*R*,14*S*,16*S*)-**2** and natural coibacin B displayed identical spectra within the limits of NMR data (see the Supporting Information). As for coibacin A (**1**), the specific optical rotation for the synthetic sample of coibacin B (**2**) ( $[\alpha]_D^{20} +95$ , *c* 0.1, CHCl<sub>3</sub>) was higher than that reported for the natural compound ( $[\alpha]_D +59$ , *c* 0.1, CHCl<sub>3</sub>). Fortunately, the CD curve of synthetic (5*R*,14*S*,16*S*)-**2** closely resembles that of natural coibacin A (**1**), providing strong evidence that this represents the correct isomer of coibacin B (**2**).

### 3. CONCLUSION

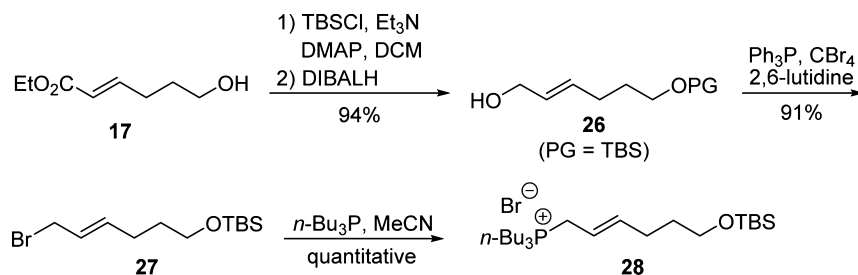
In summary, total syntheses of four coibacin A (**1**) stereoisomers displaying a *trans*-configured cyclopropane ring revealed the natural substance to possess the 5*R*,16*S*,18*S* absolute configuration. The total synthesis of coibacin A (**1**) was carried out in 12 steps (longest linear route) and 3.4% overall yield. Additionally, we synthesized the correct isomer of coibacin B (**2**) on the basis of the assignment of configuration for coibacin A (**1**). Studies aimed at assessing the cytotoxic and anti-inflammatory properties of these compounds are underway.

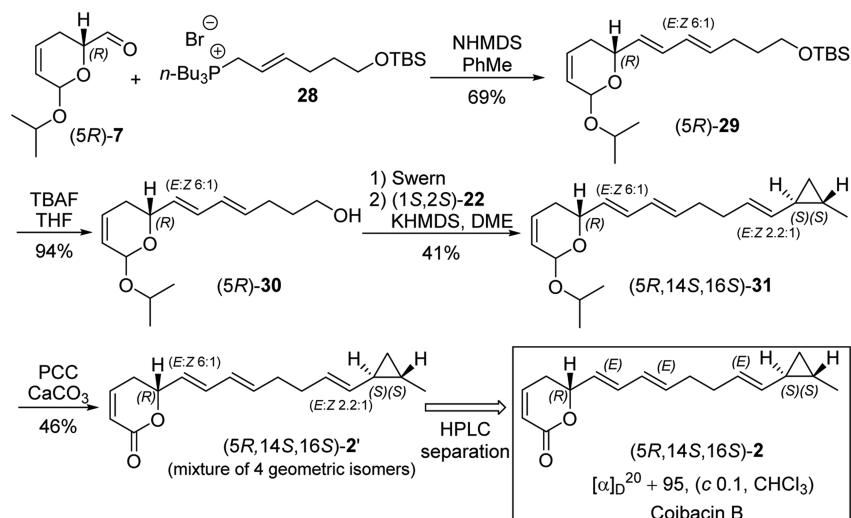
### 4. EXPERIMENTAL SECTION

**General Information.** THF and DME were freshly distilled from sodium/benzophenone. DCM, DMF, HMPA, and Et<sub>3</sub>N were freshly distilled over CaH<sub>2</sub>. PhMe and MeCN were dried over 4 Å molecular sieves for 48 h prior to use. TLC analyses were performed on silica gel plates, and the spots were revealed using UV and/or the following solutions: phosphomolybdic acid in EtOH, vanillin in EtOH/H<sub>2</sub>SO<sub>4</sub>, and *p*-anisaldehyde in EtOH/AcOH/H<sub>2</sub>SO<sub>4</sub>. Flash column chromatography was carried out using silica gel 60 (35–60 μm). <sup>1</sup>H–<sup>1</sup>H COSY (90°) and <sup>1</sup>H–<sup>13</sup>C HSQC NMR experiments were used for confirmation of NMR peak assignments. The HPLC analyses were performed at room temperature with a photodiode array detector. All melting points were measured in open capillaries and are uncorrected. HRMS analyses were performed using an ESI-TOF mass spectrometer. IUPAC names of the compounds were generated using ChemBioDraw Ultra 13.0; however, the usual numbering of the carbon atoms as shown in Scheme 1 was adopted to refer to the compounds and NMR peak assignments.

(*S*)-1-((*tert*-Butyldiphenylsilyloxy)pent-4-en-2-ol [(*S*)-**14**]. To a solution of (*R*)-**10** (3.35 g, 45.2 mmol) and imidazole (4.00 g, 58.8 mmol) in anhydrous DCM (100 mL) was added TBDPSCI (15.4 mL, 54.3 mmol) at 0 °C under N<sub>2</sub>. The solution was allowed to warm to rt and stirred for 2 h. The reaction was quenched by the addition of

**Scheme 8. Synthesis of Tri-*n*-butylphosphonium Salt **28****



Scheme 9. Synthesis of (5*R*,14*S*,16*S*)-2 (Coibacin B)

water (100 mL). The layers were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The crude product was purified by flash column chromatography (hexanes/Et<sub>2</sub>O 9:1) to provide (*S*)-*tert*-butyl(oxiran-2-ylmethoxy)diphenylsilane (13.5 g, 43.3 mmol, 87%) as a colorless oil.  $[\alpha]_D^{20}$  −2.6 (c 9.4, CHCl<sub>3</sub>) {lit.<sup>39</sup>  $[\alpha]_D^{23}$  −2.46 (c 9.07, CHCl<sub>3</sub>)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>39</sup>

To a solution of (*S*)-*tert*-butyl(oxiran-2-ylmethoxy)diphenylsilane (13 g, 42 mmol) in anhydrous THF (19 mL) under N<sub>2</sub> was added CuI (0.634 g, 3.32 mmol, 8 mol %) at rt. This suspension was stirred for 15 min. After that, the temperature was reduced to −30 °C, and vinylmagnesium bromide (100 mL, 100 mmol, 1 M in THF) was added by syringe pump (over 1 h). The mixture was then stirred for an additional 1 h at this temperature, and the reaction was carefully quenched with saturated NH<sub>4</sub>Cl solution (100 mL) at −30 °C. The cooling bath was removed, and the reaction mixture was stirred for more 20 min. The layers were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/Et<sub>2</sub>O 7:3) to afford alcohol (*S*)-14 (13.4 g, 39.4 mmol, 94%) as a colorless oil.  $[\alpha]_D^{20}$  −2.4 (c 9.6, CHCl<sub>3</sub>) {lit.<sup>40</sup>  $[\alpha]_D^{20}$  −2.6 (c 9.17, CHCl<sub>3</sub>)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>40</sup>

**(*S*)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2*H*-pyran-2-one [(*S*)-15].** To a solution of alcohol (*S*)-14 (12.97 g, 38.08 mmol) and Et<sub>3</sub>N (10.6 mL, 76.2 mmol) in anhydrous DCM (131 mL) was added freshly prepared acryloyl chloride<sup>41</sup> (4.62 mL, 57.1 mmol) dropwise at 0 °C under N<sub>2</sub>. At this time a color change from light yellow to dark yellow was observed. The mixture was stirred for 1 h at the same temperature, and then the reaction was quenched by the addition of brine (50 mL) and saturated Rochelle's salt solution (50 mL). The emulsion was stirred until complete layer separation (~3 h). The layers were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (2 × 100 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/Et<sub>2</sub>O 7:3) to give (*S*)-1-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-2-yl acrylate (12.92 g, 32.74 mmol, 86%) as a yellow oil.  $[\alpha]_D^{20}$  −9 (c 1.05, CHCl<sub>3</sub>) {lit.<sup>42</sup> (antipode)  $[\alpha]_D^{26}$  +8.3 (c 1, CHCl<sub>3</sub>)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature for its enantiomer.<sup>42</sup>

To a solution of (*S*)-1-((*tert*-butyldiphenylsilyl)oxy)pent-4-en-2-yl acrylate (4.00 g, 10.1 mmol) in anhydrous DCM (1 L) at reflux was

added first-generation Grubbs catalyst (0.823 g, 1.03 mmol, 10 mol %) in three portions (275 mg each hour) dissolved in anhydrous DCM (10 mL). The reaction mixture was refluxed for 20 h and then cooled to rt, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/AcOEt 6:4) to provide lactone (*S*)-15 (3.08 g, 8.40 mmol, 83%) as a brown oil.  $[\alpha]_D^{20}$  −48 (c 1.03, CHCl<sub>3</sub>) {lit.<sup>42</sup> (antipode)  $[\alpha]_D^{26}$  +47.8 (c 1, CHCl<sub>3</sub>)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature for its enantiomer.<sup>42</sup>

***tert*-Butyl(((2*S*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)-methoxy)diphenylsilane [(*SS*)-16].** To a solution of lactone (*S*)-15 (1.2 g, 3.27 mmol) in anhydrous DCM (40 mL) under N<sub>2</sub> was added a solution of DIBALH (4 mL, 1.2 M in toluene) at −78 °C. The reaction mixture was stirred for 1 h at the same temperature, and then the reaction was quenched by the addition of saturated NaHCO<sub>3</sub> solution (40 mL) and Rochelle's salt solution (60 mL). The emulsion formed was stirred until complete phase separation was achieved (~3 h). The layers were separated, and the aqueous phase was extracted with DCM (3 × 100 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The product was used in the next step without purification.

The crude product was taken up in toluene (16 mL), and then isopropyl alcohol (8.00 mL, 105 mmol) and PPTS (0.025 g, 0.098 mmol, 3 mol %) were added at rt. The reaction mixture was stirred for 12 h at the same temperature, and the reaction was quenched by the addition of saturated NaHCO<sub>3</sub> solution (20 mL). The mixture was stirred for 30 min. The layers were separated, and the aqueous phase was extracted with DCM (3 × 40 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The product was purified by flash column chromatography (hexanes/AcOEt 6:4) to give (*SS*)-16 (1.16 g, 2.82 mmol, 86%, two steps) as a yellow oil and as a single isomer.  $[\alpha]_D^{20}$  −28 (c 0.66, DCM) {lit.<sup>20</sup> (antipode)  $[\alpha]_D^{24}$  +28.2 (c 0.68, DCM)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature for its enantiomer.<sup>20,23</sup>

**(*R*)-1-((*tert*-Butyldiphenylsilyl)oxy)pent-4-en-2-ol [(*R*)-14].** (*R*)-*tert*-Butyl(oxiran-2-ylmethoxy)diphenylsilane was prepared from (*S*)-10 (3.66 g, 49.5 mmol) by a procedure similar to that described above for its enantiomer. The crude product was purified by flash column chromatography (gradient elution, 2 to 4% AcOEt in hexanes) to provide the expected product (13.6 g, 43.5 mmol, 88%) as a colorless oil.  $[\alpha]_D^{20}$  +2.5 (c 2, CHCl<sub>3</sub>) {lit.<sup>43</sup>  $[\alpha]_D^{20}$  +2.3 (c 2, CHCl<sub>3</sub>)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>43</sup>

Alcohol (*R*)-14 was obtained from (*R*)-*tert*-butyl(oxiran-2-ylmethoxy)diphenylsilane (13.4 g, 42.9 mmol) as described above for (*S*)-14. The crude product was purified by flash column



chromatography (hexanes/AcOEt 75:25) to give (R)-**14** (12.8 g, 37.6 mmol, 87%) as a colorless oil. [ $\alpha_D^{20}$  +3 (c 1, CHCl<sub>3</sub>)] {lit.<sup>43</sup> [ $\alpha_D^{20}$  +2.9 (c 1, CHCl<sub>3</sub>)]}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>43</sup>

(R)-6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5,6-dihydro-2H-pyran-2-one [(R)-**15**]. (R)-1-(((*tert*-Butyldiphenylsilyl)oxy)pent-4-en-2-yl acrylate was prepared from (R)-**14** (12.7 g, 37.3 mmol) using a procedure similar to that reported above for its enantiomer. The crude product was purified by flash column chromatography (hexanes/Et<sub>2</sub>O 8:2) to furnish the desired product (13.9 g, 35.2 mmol, 94%) as a yellow oil. [ $\alpha_D^{20}$  +11 (c 1, CHCl<sub>3</sub>)] {lit.<sup>42</sup> [ $\alpha_D^{26}$  +8.3 (c 1, CHCl<sub>3</sub>)]}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>42</sup>

Lactone (R)-**15** was obtained from (R)-1-(((*tert*-butyldiphenylsilyl)oxy)pent-4-en-2-yl acrylate (5.0 g, 13 mmol) by procedure similar to that described for (S)-**15**. The crude product was purified by flash column chromatography (hexanes/AcOEt 7:3) to provide (R)-**15** (3.81 g, 10.4 mmol, 82%) as a brown oil. [ $\alpha_D^{20}$  +41 (c 1, CHCl<sub>3</sub>)] {lit.<sup>42</sup> [ $\alpha_D^{26}$  +47.8 (c 1, CHCl<sub>3</sub>)]}; lit.<sup>43</sup> [ $\alpha_D^{23}$  +34.2 (c 1.5, CHCl<sub>3</sub>)]}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>42,43</sup>

*tert*-Butyl(((2R)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-methoxy)diphenylsilane [(S)-**16**]. Compound (S)-**16** was prepared from (R)-**15** (3.0 g, 8.4 mmol) in the same manner as described for (S)-**16**. The product was purified by flash column chromatography (hexanes/AcOEt 6:4) to give (S)-**16** (3.05 g, 7.42 mmol, 88%, two steps) as a yellow oil and as a single isomer. [ $\alpha_D^{20}$  +30 (c 0.65, DCM)] {lit.<sup>20</sup> [ $\alpha_D^{24}$  +28.2 (c 0.68, DCM)]}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>20,23</sup>

**Ethyl (E)-6-Hydroxyhex-2-enoate (17).** To a solution of 1,4-butanediol (**11**) (3.10 g, 34.3 mmol) in DCM (1.2 L) were successively added (ethoxycarbonylmethylene)triphenylphosphorane (14.3 g, 41.2 mmol) and MnO<sub>2</sub> (10.0 g, 115 mmol), and the mixture was stirred at rt. After 24 and 48 h, two additional portions of MnO<sub>2</sub> (2 × 10.0 g) were added. The mixture was stirred for a further 5 days and filtered through Celite using DCM for washing. The solvent was evaporated under reduced pressure, and the residue was treated with Et<sub>2</sub>O to allow precipitation of Ph<sub>3</sub>PO. After filtration and solvent evaporation, the crude product was purified by flash chromatography (hexanes/AcOEt 1:1) to afford the *E* isomer **17** (4.595 g, 25.92 mmol, 75%) as the major product together with its *Z* isomer ethyl (Z)-6-hydroxyhex-2-enoate (622 mg, 3.93 mmol, 11%) and diester **18** (316 mg, 1.40 mmol, 4%) as byproducts. All three compounds were obtained as colorless oils, and their spectral data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>21</sup>

**Diethyl (2E,6E)-Octa-2,6-dienedioate (18).** A mixture of **17** (2.35 g, 14.9 mmol) and PCC (6.5 g, 30.1 mmol, ground with 12.9 g of silica) in DCM (0.6 L) was stirred at rt for 5 h. Imidazole was added (2.02 g, 29.7 mmol), and the reaction mixture was stirred for an additional 1 h. After addition of (ethoxycarbonylmethylene)triphenylphosphorane (12.4 g, 35.6 mmol), stirring was continued for 24 h. The mixture was filtered through Celite using DCM for washing. The solvent was removed under reduced pressure, and the crude material was treated with Et<sub>2</sub>O to promote precipitation of Ph<sub>3</sub>PO. After filtration, the solvent was evaporated, and the residue was purified by flash chromatography (hexanes/AcOEt 8:2) to give (E,E)-diester **18** (2.598 g, 11.48 mmol, 77%) and its *Z,E* isomer diethyl (2Z,6E)-octa-2,6-dienedioate (228 mg, 1.00 mmol, 7%) as colorless oils. The spectral data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) of **18** and its geometric isomer are in accordance with those reported in the literature.<sup>21</sup>

**(2E,6E)-8-(((*tert*-Butyldimethylsilyl)oxy)octa-2,6-dien-1-ol (8).** To a solution of **18** (2.598 g, 11.48 mmol) in anhydrous DCM (50 mL) was slowly added via cannula a solution of DIBALH (9 mL, 50.5 mmol) in DCM (15 mL) at −78 °C under N<sub>2</sub>. The reaction mixture was stirred under reduced temperature for 2 h. After that, Et<sub>2</sub>O (150 mL) and a saturated solution of Rochelle's salt (50 mL) were added, while vigorous stirring was maintained for 1 h. After phase separation, the aqueous layer was extracted with Et<sub>2</sub>O (2 × 50 mL). The

combined organic phases were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (AcOEt) to afford the corresponding diol (2E,6E)-octa-2,6-diene-1,8-diol (1.539 g, 10.82 mmol, 94%) as a light-yellow oil. The spectral data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>44</sup>

To a solution of (2E,6E)-octa-2,6-diene-1,8-diol (1.27 mg, 8.93 mmol) in anhydrous DMF (18 mL) were added TBSCl (897 mg, 5.95 mmol) and imidazole (608 mg, 8.93 mmol). The resulting mixture was stirred at rt for 24 h, and the reaction was quenched by addition of H<sub>2</sub>O (50 mL). After extraction with AcOEt (3 × 100 mL), the combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution, 10 to 100% AcOEt in hexanes) affording the monoprotected compound **8** (894 mg, 3.49 mmol, 59%), the bis(silyl ether) (6E,10E)-2,2,3,3,14,14,15,15-octamethyl-4,13-dioxo-3,14-disilahexadeca-6,10-diene (251 mg, 0.677 mmol, 11%) as a byproduct, and recovered starting material (532 mg, 3.74 mmol, 42%). The spectral data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) of the isolated compounds are in agreement with the literature data.<sup>44</sup>

**((2E,6E)-8-Bromoocta-2,6-dien-1-yl)oxy(tert-butyl)-dimethylsilane (19).** To a solution of **8** (611 mg, 2.38 mmol) in anhydrous MeCN (14 mL) were added Ph<sub>3</sub>P (1.25 mg, 4.77 mmol), 2,6-lutidine (0.55 mL, 4.75 mmol), and CBr<sub>4</sub> (1.58 g, 4.76 mmol) at 0 °C. The resulting solution was stirred at rt for 10 min. The reaction was quenched with H<sub>2</sub>O (50 mL), and the mixture was extracted with Et<sub>2</sub>O (2 × 100 and 1 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to give **19** (744 mg, 2.3 mmol, 98%) as a colorless oil. *R*<sub>f</sub>: 0.64 (hexanes/AcOEt 95:5). IR (ATR)  $\nu_{\text{max}}$ /cm<sup>−1</sup>: 2928, 2856, 1472, 1254, 966, 835, 775. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.06 (s, 6H), 0.90 (s, 9H), 2.14 (br s, 4H), 3.93 (d, *J* = 5.0 Hz, 2H), 4.11 (d, *J* = 2.5 Hz, 2H), 5.49–5.73 (m, 4H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : −5.1 (2C), 18.4, 26.0 (3C), 31.4, 31.6, 33.3, 63.8, 126.8, 129.7, 130.3, 135.6. HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>14</sub>H<sub>27</sub>BrOSiNa 341.09067; found 341.09049.

**2-(((1S,2S)-2-Methylcyclopropyl)methyl)sulfonyl)benzo[d]thiazole [(1S,2S)-**22**].** To a mixture of DME (2 mL, 19 mmol) and anhydrous DCM (18 mL) was added a solution of diethylzinc (1 M in hexanes, 19 mL) at −10 °C under N<sub>2</sub>. Diiodomethane (3 mL, 37 mmol) was added dropwise, and the solution was stirred at −10 °C for 20 min. This fresh Zn(CH<sub>2</sub>I)<sub>2</sub>-DME solution was added by cannula over a solution of *trans*-crotyl alcohol (**12**) (540 mg, 7.50 mmol) and butylboronic acid *N,N,N',N'*-tetramethyl-*L*-tartaric acid diamide ester [(4R,5R)-**13**] (2.2 g, 8.1 mmol) in DCM (37 mL) at −10 °C, and the mixture was stirred at 0 °C for 4 h. Saturated aqueous NH<sub>4</sub>Cl (50 mL) was added, and the mixture was extracted with Et<sub>2</sub>O (4 × 50 mL). The combined organic phases were stirred with 2 M NaOH (100 mL) overnight. After phase separation, the organic layer was washed with an aqueous solution of 1 M HCl (50 mL), a saturated solution of NaHCO<sub>3</sub> (50 mL), and brine (50 mL). The organic phase was dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure (450 mbar). The crude product ((1S,2S)-2-methylcyclopropyl)methanol [(1S,2S)-**9**] was obtained as a light-yellow oil and used in the next step without purification to avoid losses due to its volatility. The enantiomeric ratio was determined to be 94:6 after analysis of the corresponding Mosher's ester by <sup>1</sup>H NMR (500 MHz).

To a solution of the (1S,2S)-**9** obtained above in THF (15 mL) were successively added 2-mercaptobenzothiazole (1.0 g, 6.0 mmol), Ph<sub>3</sub>P (1.57 g, 5.97 mmol), and DIAD (1.3 mL, 6.6 mmol). The mixture was stirred at rt for 24 h, and the excess solvent was removed under reduced pressure. Et<sub>2</sub>O was added to the residue, and the precipitate was removed by filtration. After solvent evaporation, the crude material was partially purified by flash chromatography (hexanes/AcOEt 95:5) to give 2-(((1S,2S)-2-methylcyclopropyl)methyl)thio)benzo[d]thiazole [(1S,2S)-**21**] (1.033 g), as a light-yellow oil. This intermediate was not characterized because it was still impure.

To a solution of (1S,2S)-**21** (1.033 g) in EtOH (40 mL) was added a solution of ammonium molybdate tetrahydrate (540 mg, 0.437



mmol) in H<sub>2</sub>O<sub>2</sub> (30% v/v, 2 mL) at 0 °C under N<sub>2</sub>. The resulting mixture was stirred at rt for 18 h, and the solvent was removed under reduced pressure. The residue was diluted with H<sub>2</sub>O (50 mL) and extracted with DCM (5 × 50 mL). The combined organic phases were washed with brine (50 mL), dried with MgSO<sub>4</sub>, and evaporated, and the residue was purified by flash chromatography (hexanes/AcOEt 8:2) to afford (1*S*,2*S*)-**22** (890 mg, 3.33 mmol, 39% for three steps, er 94:6) as a white solid. Mp: 77–80 °C (lit.<sup>25</sup> 94–96 °C). [ $\alpha$ ]<sub>D</sub><sup>20</sup> +8 (c 1.13, CHCl<sub>3</sub>) {lit.<sup>25</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> +7 (c 1.14, CHCl<sub>3</sub>)}. The enantiomeric ratio of (1*S*,2*S*)-**22** was determined by chiral HPLC analysis,<sup>26</sup> and its spectral data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) are in agreement with the literature data.<sup>25</sup>

**2-(((1*R*,2*R*)-2-Methylcyclopropyl)methyl)sulfonyl)benzo[d]-thiazole [(1*R*,2*R*)-**22**].** Sulfone (1*R*,2*R*)-**22** was prepared from **12** in 31% overall yield and er 94:6 employing a procedure similar to that described above for (1*S*,2*S*)-**22** but using butylboronic acid *N,N,N'*,*N'*-tetramethyl-*D*-tartaric acid diamide ester [(4*S*,5*S*)-**13**]. Mp: 79–82 °C. [ $\alpha$ ]<sub>D</sub><sup>20</sup> –8 (c 1.11, CHCl<sub>3</sub>) {lit.<sup>25</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> (antipode) +7 (c 1.14, CHCl<sub>3</sub>)}. The enantiomeric ratio of (1*R*,2*R*)-**22** was determined by chiral HPLC analysis,<sup>26</sup> and its spectroscopic data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) are in accordance with those for its enantiomer reported by Charette.<sup>25</sup>

**2-(((trans)-2-Methylcyclopropyl)methyl)sulfonyl)benzo[d]-thiazole (**22**).** Racemic sulfone **22** was produced from **12** in 83% overall yield using a procedure similar to that described for (1*S*,2*S*)-**22** but employing Simmons–Smith cyclopropanation in place of asymmetric Charette's reaction. Mp: 84–86 °C. The spectral data for racemic **22** (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR) are in accordance with those for (1*S*,2*S*)-**22** reported by Charette.<sup>25</sup>

**tert-Butyl(((2*E*,6*E*,8*E*)-9-((2*S*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)nona-2,6,8-trien-1-yl)oxy)dimethylsilane [(5*S*)-**23**].** To a solution of **19** (664 mg, 2.08 mmol) in anhydrous MeCN (9.5 mL) was added *n*-Bu<sub>3</sub>P (0.77 mL, 3.1 mmol), and the mixture was stirred at rt for 12 h. After that, the excess solvent was removed under reduced pressure, and the crude product was maintained under high vacuum (0.2 mmHg) for 8 h. The tri-*n*-butylphosphonium salt **20** was used in the Wittig olefination without purification.

To a solution of dihydropyran (5*S*)-**16** (1.41 g, 3.43 mmol) in anhydrous THF (35 mL) at 0 °C under N<sub>2</sub> was added a solution of TBAF (3.6 mL, 1 M in THF). The solution was allowed to warm to rt and stirred for 3 h. The reaction was quenched by the addition of H<sub>2</sub>O (35 mL). The layers were separated, and the aqueous layer was extracted with AcOEt (5 × 40 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexanes/AcOEt 6:4) to give the corresponding alcohol ((2*S*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)methanol (0.492 g, 2.85 mmol, 83%) as a white solid. Mp: 43–45 °C. [ $\alpha$ ]<sub>D</sub><sup>20</sup> –47 (c 1, DCM) {lit.<sup>20</sup> (antipode) [ $\alpha$ ]<sub>D</sub><sup>24</sup> +40.4 (c 0.47, DCM)}. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature for its enantiomer.<sup>20</sup>

To a solution of oxalyl chloride (0.192 mL, 2.23 mmol) in anhydrous DCM (10 mL) at –78 °C under N<sub>2</sub> was added dropwise DMSO (0.227 mL, 3.12 mmol). After 15 min of stirring, a solution of the alcohol obtained above (0.240 g, 1.39 mmol) in anhydrous DCM (4 mL) was added dropwise by cannula. The resultant white emulsion was stirred for an additional 15 min, and then Et<sub>3</sub>N (1.0 mL, 6.9 mmol) was added. After 5 min, the mixture was allowed to warm to rt. The reaction was quenched by the addition of saturated NH<sub>4</sub>Cl solution (15 mL). The layers were separated, and the aqueous phase was extracted with Et<sub>2</sub>O (3 × 25 mL). The organic layers were combined, washed with brine (20 mL), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and carefully concentrated (bath temperature 30 °C, pressure 400–420 mbar) to prevent loss of the volatile aldehyde. The crude product, (2*S*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-carbaldehyde [(5*S*)-**7**], was obtained as a colorless oil and was used in the next step without purification because of its instability. *R*<sub>f</sub>: 0.57 (hexanes/AcOEt 7:3).

**Wittig Olefination.** To a solution of freshly prepared aldehyde (5*S*)-**7** (236 mg, 1.39 mmol) and tri-*n*-butylphosphonium salt **20** (2.08 mmol) in anhydrous PhMe (25 mL) was added dropwise a solution of NHMDS (2.8 mL, 2.8 mmol, 1 M in THF) at –78 °C under N<sub>2</sub>. The

mixture was warmed slowly and stirred over 6 h. The reaction was quenched with H<sub>2</sub>O (50 mL), and the mixture was extracted with AcOEt (3 × 100 mL). The combined organic phases were washed with brine (50 mL) and dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to furnish (5*S*)-**23** (383 mg, 0.975 mmol, 70%) as a light-yellow oil and as a 6:1 mixture of the two isomers at the C-6/C-7 double bond. *R*<sub>f</sub>: 0.50 (hexanes/AcOEt 95:5). IR (ATR)  $\nu_{\text{max}}$ /cm<sup>–1</sup>: 2958, 2926, 2895, 2851, 1254, 1125, 1099, 1028, 988, 836, 776. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : (major isomer) 0.06 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.90 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.16 (d, *J* = 5.0 Hz, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.22 (d, *J* = 5.0 Hz, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.97–2.26 (m, 6H, H-4, H-10, and H-11), 4.00 (sept, *J* = 5.0 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.11 (d, *J* = 4.7 Hz, 2H, H-14), 4.42–4.46 (m, 1H, H-5), 5.10 (br s, 1H, H-1), 5.52–5.72 (m, 5H, H-13, H-6, H-12, H-9, and H-2), 5.97–6.08 (m, 2H, H-3 and H-8), 6.22 (dd, *J* = 15.3 and 10.5 Hz, 1H, H-7). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : (major isomer) –5.1 (2 CH<sub>3</sub>, Si(CH<sub>3</sub>)<sub>2</sub>), 18.4 (C, Si–C), 22.0 (CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>), 23.8 (CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>), 26.0 (3CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>3</sub>), 30.7 (CH<sub>3</sub>, C-4), 31.8 (CH<sub>2</sub>, C-11), 32.2 (CH<sub>2</sub>, C-10), 63.9 (CH<sub>2</sub>, C-14), 66.4 (CH, C-5), 69.4 (CH, C(CH<sub>3</sub>)<sub>2</sub>), 93.1 (CH, C-1), 126.1 (CH, C-2), 128.4 (CH, C-3), 129.7 (CH, C-13), 130.0 (CH, C-8), 130.2 (CH, C-12\*), 130.8 (CH, C-6\*), 131.1 (CH, C-7), 134.5 (CH, C-9) (asterisks indicate that the assignments may be interchanged). HRMS (ESI-TOF) *m/z*: [M – OCH(CH<sub>3</sub>)<sub>2</sub>]<sup>+</sup> calcd for C<sub>20</sub>H<sub>33</sub>O<sub>2</sub>Si 333.22443; found 333.22458.

**(2*E*,6*E*,8*E*)-9-((2*S*)-6-isopropoxy-3,6-dihydro-2*H*-pyran-2-yl)nona-2,6,8-trienal [(5*S*)-**24**].** To a solution of (5*S*)-**23** (0.375 g, 0.955 mmol) in anhydrous THF (48 mL) was added a solution of TBAF (1 mL, 1 mmol, 1 M in THF) at 0 °C under N<sub>2</sub>. The yellow solution was allowed to warm to rt and stirred for 2 h. The reaction was quenched by the addition of H<sub>2</sub>O (30 mL) and AcOEt (60 mL). The layers were separated, and the aqueous phase was extracted with AcOEt (4 × 50 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The product was used in the next step without purification.

To a solution of the alcohol obtained above in anhydrous DCM (95 mL) was added MnO<sub>2</sub> (5 g, 57.3 mmol, ≥ 85% activated, Sigma-Aldrich) in three portions (one every 24 h). The reaction mixture was allowed to stir for an additional 24 h. The crude reaction mixture was directly filtered through a plug of silica gel, eluted with a mixture of hexanes/AcOEt 1:1, and concentrated under reduced pressure. The product was purified by flash chromatography (hexanes/AcOEt 6:4) to give (5*S*)-**24** (227 mg, 0.821 mmol, 86%, two steps) as a light-yellow oil and as a 6:1 mixture of the two isomers at the C-6/C-7 double bond. *R*<sub>f</sub>: 0.54 (hexanes/AcOEt 1:1). IR (ATR)  $\nu_{\text{max}}$ /cm<sup>–1</sup>: 2959, 2922, 2850, 1691, 1124, 1099, 1026, 993, 668, 651. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : (major isomer) 1.19 (d, *J* = 6.1 Hz, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.25 (d, *J* = 6.1 Hz, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 2.01–2.14 (m, 2H, H-4), 2.32–2.36 (m, 2H, H-10), 2.45–2.49 (m, 2H, H-11), 4.02 (sept, *J* = 6.1 Hz, 1H, CH(CH<sub>3</sub>)<sub>2</sub>), 4.46–4.49 (m, 1H, H-5), 5.13 (br s, 1H, H-1), 5.66–5.79 (m, 3H, H-6, H-9, and H-2), 6.00–6.03 (m, 1H, H-3), 6.09–6.17 (m, 2H, H-8 and H-13), 6.25 (dd, *J* = 15.4 and 10.5 Hz, 1H, H-7), 6.85 (dd, *J* = 15.6 and 6.7 Hz, 1H, H-12), 9.52 (d, *J* = 7.9 Hz, 1H, H-14). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : (major isomer) 22.0 (CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>), 23.8 (CH<sub>3</sub>, C(CH<sub>3</sub>)<sub>2</sub>), 30.6 (CH<sub>2</sub>, C-4), 30.7 (CH<sub>2</sub>, C-10), 32.2 (CH<sub>2</sub>, C-11), 66.2 (CH<sub>2</sub>, C-5), 69.5 (CH, C(CH<sub>3</sub>)<sub>2</sub>), 93.1 (CH, C-1), 126.1 (CH, C-2), 128.3 (CH, C-3), 130.5 (CH, C-7), 131.1 (CH, C-8), 131.9 (CH, C-9\*), 132.5 (CH, C-6\*), 133.3 (CH, C-13), 157.4 (CH, C-12), 193.9 (CHO, C-14) (asterisks indicate that the assignments may be interchanged). HRMS (ESI-TOF) *m/z*: [M + Na]<sup>+</sup> calcd for C<sub>17</sub>H<sub>24</sub>O<sub>3</sub>Na 299.1623; found 299.1637.

**(2*S*)-6-isopropoxy-2-((1*E*,3*E*,7*E*,9*E*)-10-((1*S*,2*S*)-2-methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-3,6-dihydro-2*H*-pyran [(5*S*,16*S*,18*S*)-**25**]** (Julia Olefination with THF). To a solution of aldehyde (5*S*)-**24** (16 mg, 0.058 mmol) and sulfone (1*S*,2*S*)-**22** (23 mg, 0.086 mmol) in anhydrous THF (2.5 mL) was added dropwise a solution of NHMDS (120  $\mu$ L, 0.12 mmol, 1 M in THF) at –78 °C under N<sub>2</sub>. The resulting light-yellow mixture was stirred for 10 min, and the reaction was quenched with H<sub>2</sub>O (6 mL). The mixture was extracted with AcOEt (30 + 10 mL), and the organic

layer was washed with brine (10 mL), dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to afford (5S,16S,18S)-**25** as 1.7:1 *E*:*Z* mixture at the C-14 double bond (12.4 mg, 0.0377 mmol, 65%) contaminated with minor amounts of the 6Z double-bond isomers as a light-yellow oil.  $R_f$ : 0.67 (hexanes/AcOEt 9:1). IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 2969, 2925, 1654, 1447, 1380, 1316, 1181, 1099, 1027, 985, 718.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : (major isomer) 0.47–0.50 (m, 1H), 0.53–0.57 (m, 1H), 0.72–0.79 (m, 1H), 1.04–1.10 (m, 1H), 1.06 (d,  $J = 6.0$  Hz, 3H), 1.17 (d,  $J = 6.2$  Hz, 3H), 1.24 (d,  $J = 6.2$  Hz, 3H), 2.03–2.25 (m, 6H), 4.01 (sept,  $J = 6.2$  Hz, 1H), 4.42–4.47 (m, 1H), 5.10 (br s, 1H), 5.15 (dd,  $J = 14.8$  and 8.9 Hz, 1H), 5.48–5.56 (m, 1H), 5.62 (d,  $J = 15.3$  and 6.1 Hz, 1H), 5.68–5.76 (m, 2H), 5.94–6.09 (m, 4H), 6.22 (dd,  $J = 15.3$  and 10.2 Hz, 1H); (second-largest isomer) 0.53–0.57 (m, 2H), 0.72–0.79 (m, 1H), 1.04–1.10 (m, 1H), 1.09 (d,  $J = 5.8$  Hz, 3H), 1.17 (d,  $J = 6.1$  Hz, 3H), 1.24 (d,  $J = 6.2$  Hz, 3H), 2.03–2.25 (m, 6H), 4.01 (sept,  $J = 6.2$  Hz, 1H), 4.42–4.47 (m, 1H), 4.72 (t,  $J = 10.4$  Hz, 1H), 5.10 (br s, 1H), 5.48–5.56 (m, 1H), 5.68–5.76 (m, 2H), 5.87 (t,  $J = 10.9$  Hz, 1H), 5.94–6.09 (m, 4H), 6.47 (dd,  $J = 14.8$  and 11.2 Hz, 1H).  $^{13}\text{C}$  NMR (63 MHz,  $\text{CDCl}_3$ )  $\delta$ : (major isomer) 15.6 (2C), 18.5, 22.0, 22.9, 23.9, 30.7, 32.3, 32.6, 66.4, 69.4, 93.1, 126.1, 127.5, 128.5, 130.0, 130.1, 130.7, 130.9, 131.2, 134.6, 136.1; (second-largest isomer) 15.8, 16.0, 18.5, 19.3, 21.9, 23.9, 30.8, 32.2, 32.7, 62.7, 69.3, 92.8, 126.3, 126.5, 128.6, 130.0, 130.9, 131.2, 132.8, 134.2, 134.6, 136.2. HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{22}\text{H}_{32}\text{O}_2\text{Na}$  351.2300; found 351.2288.

(S)-6-((1E,3E,7E,9E)-10-((1S,2S)-2-Methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-5,6-dihydro-2H-pyran-2-one [(5S,16S,18S)-**1**]. A mixture of PCC (323 mg, 1.50 mmol) and  $\text{CaCO}_3$  (600 mg, 6 mmol) in anhydrous DCM (6 mL) was stirred at rt for 30 min. Then a solution of (5S,16S,18S)-**25** (100 mg, 0.304 mmol) in DCM (13 mL) was added by cannula, and the reaction mixture was stirred at rt for 1 h. After filtration over silica gel and solvent evaporation under reduced pressure, the crude product was purified by flash chromatography (gradient elution, 20 to 30% AcOEt in hexanes) to give (5S,16S,18S)-**1'** (19 mg, 0.067 mmol, 22%) as a mixture of *E* and *Z* isomers at the C-14/C-15 double bond contaminated with minor amounts of the 6Z isomers. This mixture was separated using preparative HPLC with a SunFire Prep  $\text{C}_{18}$  OBD column (particle size 5  $\mu\text{m}$ , dimensions 19 mm  $\times$  100 mm, 60% MeCN/40%  $\text{H}_2\text{O}$ , 17 mL/min) to yield the major isomer with *E*-configured double bonds, (5S,16S,18S)-**1** (6.7 mg,  $t_R = 18.4$  min), as a colorless oil.  $R_f$ : 0.41 (hexanes/AcOEt 7:3).  $[\alpha]_D^{20} -10$  ( $c$  0.1,  $\text{CHCl}_3$ ). IR (ATR)  $\nu_{\text{max}}/\text{cm}^{-1}$ : 2995, 2918, 1720, 1658, 1381, 1244, 986, 816.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$ : 0.47–0.51 (m, 1H, H-17), 0.54–0.58 (m, 1H, H-17), 0.73–0.80 (m, 1H, H-18), 1.05 (d,  $J = 6.0$  Hz, 3H, H-19), 1.05–1.10 (m, 1H, H-16), 2.14–2.18 (m, 4H, H-10 and H-11), 2.43–2.45 (m, 2H, H-4), 4.92–4.96 (m, 1H, H-5), 5.15 (dd,  $J = 14.7$  and 9.0 Hz, 1H, H-15), 5.50 (dt,  $J = 14.1$  and 6.6 Hz, 1H, H-12), 5.64 (dd,  $J = 15.3$  and 6.6 Hz, 1H, H-6), 5.77 (dt,  $J = 15.2$  and 6.6 Hz, 1H, H-9), 5.94–6.06 (m, 4H, H-2, H-8, H-13, and H-14), 6.30 (dd,  $J = 15.3$  and 10.4 Hz, 1H, H-7), 6.85–6.89 (m, 1H, H-3).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ : 15.7 ( $\text{CH}_2$ , C-17; CH, C-18), 18.5 ( $\text{CH}_3$ , C-19), 22.8 (CH, C-16), 29.8 ( $\text{CH}_2$ , C-4), 32.1 ( $\text{CH}_2$ , C-11), 32.6 ( $\text{CH}_2$ , C-10), 77.9 (CH, C-5), 121.6 (CH, C-2), 126.7 (CH, C-6), 127.4 (CH, C-14), 129.1 (CH, C-8), 129.9 (CH, C-12), 130.8 (CH, C-13), 133.7 (CH, C-7), 136.3 (CH, C-15), 136.8 (CH, C-9), 144.6 (CH, C-3), 164.0 (CO, C-1). HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{19}\text{H}_{24}\text{O}_2\text{Na}$  307.1674; found 307.1663.

(2S)-6-Isopropoxy-2-((1E,3E,7E,9E)-10-((1R,2R)-2-methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-3,6-dihydro-2H-pyran [(5S,16R,18R)-**25**] (Julia Olefination with DME). To a solution of aldehyde (5S)-**24** (103 mg, 0.373 mmol) and sulfone (1R,2R)-**22** (150 mg, 0.561 mmol) in anhydrous DME (17 mL) was added dropwise a solution of NHMDS (0.78 mL, 0.78 mmol, 1 M in THF) at  $-78^\circ\text{C}$  under  $\text{N}_2$ . The light-yellow mixture was stirred for 10 min, and the reaction was quenched with brine (50 mL). The mixture was extracted with AcOEt (3  $\times$  50 mL), and the organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The

crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to afford (5S,16R,18R)-**25** as a 2.7:1 *E*:*Z* mixture at the C-14 double bond (116 mg, 0.353 mmol, 95%) contaminated with minor amounts of the 6Z double-bond isomers as a light-yellow oil.  $R_f$ : 0.67 (hexanes/AcOEt 9:1). The IR and NMR data for (5S,16R,18R)-**25** are identical to those described for (5S,16S,18S)-**25** despite their diastereoisomeric relationship. HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{K}]^+$  calcd for  $\text{C}_{22}\text{H}_{32}\text{O}_2\text{K}$  367.2039; found 367.2030.

(S)-6-((1E,3E,7E,9E)-10-((1R,2R)-2-Methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-5,6-dihydro-2H-pyran-2-one [(5S,16R,18R)-**1**]. A mixture of PCC (361 mg, 1.67 mmol) and  $\text{CaCO}_3$  (670 mg, 6.70 mmol) in anhydrous DCM (7 mL) was stirred at rt for 2 h. Then a solution of (5S,16R,18R)-**25** (111 mg, 0.338 mmol) in DCM (12 mL) was added by cannula, and the reaction mixture was stirred at rt for 2 h. After filtration over silica gel and solvent evaporation under reduced pressure, the crude product was purified by flash chromatography (gradient elution, 20 to 30% AcOEt in hexanes) to afford (5S,16R,18R)-**1'** (28 mg, 0.098 mmol, 29%) as a mixture of *E* and *Z* isomers at the C-14/C-15 double bond contaminated with minor amounts of the 6Z isomers. This mixture was separated using preparative HPLC with a SunFire Prep  $\text{C}_{18}$  OBD column (particle size 5  $\mu\text{m}$ , dimensions 19 mm  $\times$  100 mm, 60% MeCN/40%  $\text{H}_2\text{O}$ , 17 mL/min) to give the major isomer with *E*-configured double bonds, (5S,16R,18R)-**1** (12.9 mg,  $t_R = 18.4$  min), as a colorless oil.  $R_f$ : 0.41 (hexanes/AcOEt 7:3).  $[\alpha]_D^{20} -100$  ( $c$  0.1,  $\text{CHCl}_3$ ). The IR and NMR data for (5S,16R,18R)-**1** are identical to those described for (5S,16S,18S)-**1** despite their diastereoisomeric relationship. HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{25}\text{O}_2$  285.1855; found 285.1866.

tert-Butyl(((2E,6E,8E)-9-((2R)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)nona-2,6,8-trien-1-yl)oxy)dimethylsilane [(5R)-**23**]. To a solution of **19** (568 mg, 1.78 mmol) in anhydrous MeCN (8 mL) was added *n*- $\text{Bu}_3\text{P}$  (0.70 mL, 2.8 mmol), and the mixture was stirred at rt for 12 h. After that, the excess solvent was removed under reduced pressure, and the crude product was maintained under high vacuum (0.2 mmHg) for 8 h. The tri-*n*-butylphosphonium salt **20** was used without purification.

Deprotection of (5R)-**16** (3.05 g, 7.31 mmol) employing a procedure similar to that described above for its enantiomer provided the corresponding alcohol. The crude product was purified by column chromatography (hexanes/AcOEt 6:4) to give the desired product ((2R)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)methanol (1.14 g, 6.62 mmol, 90%) as a white solid. Mp: 42–44  $^\circ\text{C}$ .  $[\alpha]_D^{20} +46$  ( $c$  1, DCM) {lit.<sup>20</sup>  $[\alpha]_D^{24} +40.4$  ( $c$  0.47, DCM)}. The spectral data ( $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR) are in accordance with those reported in the literature.<sup>20</sup>

The aldehyde (2R)-6-isopropoxy-3,6-dihydro-2H-pyran-2-carbaldehyde [(5R)-**7**] was prepared from the alcohol prepared above (0.205 g, 1.19 mmol) as described for (5S)-**7**. The crude product was obtained as a colorless oil that was used in the next step without purification because its instability.  $R_f$ : 0.57 (hexanes/AcOEt 7:3).

**Wittig Olefination.** Compound (5R)-**23** was obtained from freshly prepared aldehyde (5R)-**7** (202 mg, 1.19 mmol) and tri-*n*-butylphosphonium salt **20** (1.78 mmol) following the procedure described above for (5S)-**23**. The crude product was purified by flash chromatography (gradient elution, 0 to 10% AcOEt in hexanes) to furnish (5R)-**23** (368 mg, 0.937 mmol, 79%) as a light-yellow oil and as a 5:1 mixture of the two isomers at the C-6/C-7 double bond.  $R_f$ : 0.50 (hexanes/AcOEt 95:5). The IR and NMR data for (5R)-**23** are identical to those described for its enantiomer (5S)-**23**. HRMS (ESI-TOF)  $m/z$ :  $[\text{M} + \text{Na}]^+$  calcd for  $\text{C}_{23}\text{H}_{40}\text{O}_3\text{SiNa}$  415.2644; found 415.2633.

(2E,6E,8E)-9-((2R)-6-Isopropoxy-3,6-dihydro-2H-pyran-2-yl)-nona-2,6,8-trienal [(5R)-**24**]. Aldehyde (5R)-**24** was obtained from (5R)-**23** (0.699 g, 1.78 mmol) using a procedure similar to that described for (5S)-**24** except for the reaction time of the  $\text{MnO}_2$  oxidation, which was reduced from 96 to 72 h by using another batch of  $\text{MnO}_2$  (6.19 g, 71.2 mmol,  $\geq 90\%$  activated, Fluka Analytical). The product was purified by flash chromatography (hexanes/AcOEt 6:4) to give (5R)-**24** (371 mg, 1.34 mmol, 75%, two steps) as a light-yellow oil and as a 5:1 mixture of the two isomers at the C-6/C-7 double



bond.  $R_f$ : 0.54 (hexanes/AcOEt 1:1). The IR and NMR data for (SR)-24 are identical to those described for its enantiomer (SS)-24. HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{17}H_{24}O_3Na$  299.1623; found 299.1618.

**(2R)-6-Isopropoxy-2-((1E,3E,7E,9E)-10-((1S,2S)-2-methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-3,6-dihydro-2H-pyran [(SR,16S,18S)-25].** Intermediate (SR,16S,18S)-25 was prepared from aldehyde (SR)-24 (105 mg, 0.380 mmol) and sulfone (1S,2S)-22 (150 mg, 0.561 mmol) as described for (SS,16R,18R)-25. The crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to afford (SR,16S,18S)-25 as a 2.7:1 *E:Z* mixture at the C-14 double bond (117 mg, 0.356 mmol, 94%) contaminated with minor amounts of the 6Z double-bond isomers as a light-yellow oil.  $R_f$ : 0.67 (hexanes/AcOEt 9:1). The IR and NMR data for (SR,16S,18S)-25 are identical to those described for (SS,16S,18S)-25 despite their diastereoisomeric relationship. HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{22}H_{32}O_2Na$  351.2300; found 351.2306.

**(R)-6-((1E,3E,7E,9E)-10-((1S,2S)-2-Methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-5,6-dihydro-2H-pyran-2-one [(SR,16S,18S)-1].** Compound (SR,16S,18S)-1 was synthesized from (SR,16S,18S)-25 (111 mg, 0.338 mmol) using a procedure similar to that described for (SS,16R,18R)-1. The crude product was purified by flash chromatography (gradient elution, 20 to 30% AcOEt in hexanes) to give (SR,16S,18S)-1' (31 mg, 0.11 mmol, 33%) as a mixture of *E* and *Z* isomers at the C-14/C-15 double bond contaminated with minor amounts of the 6Z isomers. After separation by preparative HPLC with a SunFire Prep C<sub>18</sub> OBD column (particle size 5  $\mu$ m, dimensions 19 mm  $\times$  100 mm, 60% MeCN/40% H<sub>2</sub>O, 17 mL/min), the major isomer with *E*-configured double bonds, (SR,16S,18S)-1 (11.9 mg,  $t_R$  = 18.4 min), was obtained as a colorless oil.  $R_f$ : 0.41 (hexanes/AcOEt 7:3).  $[\alpha]_D^{20} +10$  (*c* 0.1, CHCl<sub>3</sub>). IR (ATR)  $\nu_{max}/cm^{-1}$ : 2995, 2918, 1720, 1658, 1381, 1244, 986, 816. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.47–0.51 (m, 1H, H-17), 0.54–0.58 (m, 1H, H-17), 0.73–0.80 (m, 1H, H-18), 1.05 (d, *J* = 6.0 Hz, 3H, H-19), 1.05–1.10 (m, 1H, H-16), 2.14–2.18 (m, 4H, H-10 and H-11), 2.43–2.45 (m, 2H, H-4), 4.92–4.96 (m, 1H, H-5), 5.15 (dd, *J* = 14.7 and 9.0 Hz, 1H, H-15), 5.50 (dt, *J* = 14.1 and 6.6 Hz, 1H, H-12), 5.64 (dd, *J* = 15.3 and 6.6 Hz, 1H, H-6), 5.77 (dt, *J* = 15.2 and 6.6 Hz, 1H, H-9), 5.94–6.06 (m, 4H, H-2, H-8, H-13, and H-14), 6.30 (dd, *J* = 15.3 and 10.4 Hz, 1H, H-7), 6.85–6.89 (m, 1H, H-3). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$ : 15.7 (CH<sub>2</sub>, C-17; CH, C-18), 18.5 (CH<sub>3</sub>, C-19), 22.8 (CH, C-16), 29.8 (CH<sub>2</sub>, C-4), 32.1 (CH<sub>2</sub>, C-11), 32.6 (CH<sub>2</sub>, C-10), 77.9 (CH, C-5), 121.6 (CH, C-2), 126.7 (CH, C-6), 127.4 (CH, C-14), 129.1 (CH, C-8), 129.9 (CH, C-12), 130.8 (CH, C-13), 133.7 (CH, C-7), 136.3 (CH, C-15), 136.8 (CH, C-9), 144.6 (CH, C-3), 164.0 (CO, C-1). HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{19}H_{24}O_2Na$  307.1674; found 307.1678.

**(2R)-6-Isopropoxy-2-((1E,3E,7E,9E)-10-((1R,2R)-2-methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-3,6-dihydro-2H-pyran [(SR,16R,18R)-25].** Intermediate (SR,16R,18R)-25 was synthesized from aldehyde (SR)-24 (105 mg, 0.380 mmol) and sulfone (1R,2R)-22 (145 mg, 0.543 mmol) as described for (SS,16R,18R)-25. The crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to furnish (SR,16R,18R)-25 as a 2.7:1 *E:Z* mixture at the C-14 double bond (118 mg, 0.359 mmol, 95%) contaminated with minor amounts of the 6Z double-bond isomers as a light-yellow oil.  $R_f$ : 0.67 (hexanes/AcOEt 9:1). The IR and NMR data for (SR,16R,18R)-25 are identical to those described for (SS,16S,18S)-25. HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{22}H_{32}O_2Na$  351.2300; found 351.2294.

**(R)-6-((1E,3E,7E,9E)-10-((1R,2R)-2-Methylcyclopropyl)deca-1,3,7,9-tetraen-1-yl)-5,6-dihydro-2H-pyran-2-one [(SR,16R,18R)-1].** Compound (SR,16R,18R)-1 was synthesized from (SR,16R,18R)-25 (110 mg, 0.335 mmol) using a procedure similar to that described above for (SS,16R,18R)-1. The crude product was purified by flash chromatography (gradient elution, 20 to 30% AcOEt in hexanes) to furnish (SR,16R,18R)-1' (23 mg, 0.081 mmol, 24%) as a mixture of *E* and *Z* isomers at the C-14/C-15 double bond contaminated with minor amounts of the 6Z isomers. After separation by preparative HPLC with a SunFire Prep C<sub>18</sub> OBD column (particle size 5  $\mu$ m, dimensions 19 mm  $\times$  100 mm, 60% MeCN/40% H<sub>2</sub>O, 17

mL/min), the major isomer with *E*-configured double bonds, (SR,16R,18R)-1 (6.2 mg,  $t_R$  = 18.4 min), was obtained as a colorless oil.  $R_f$ : 0.41 (hexanes/AcOEt 7:3).  $[\alpha]_D^{20} +10$  (*c* 0.1, CHCl<sub>3</sub>). The IR and NMR data for (SR,16R,18R)-1 are identical to those described for (SS,16S,18S)-1. HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{19}H_{24}O_2Na$  307.1674; found 307.1663.

**Ethyl (E)-6-Hydroxyhex-2-enoate (26).** To a solution of 17 (1.54 g, 9.74 mmol) in anhydrous DCM (40 mL) were added Et<sub>3</sub>N (3.3 mL, 23.4 mmol), DMAP (120 mg, 1.15 mmol), and TBSCl (1.76 g, 11.7 mmol) under N<sub>2</sub>. The resulting mixture was stirred at rt for 4.5 h, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/AcOEt 95:5) to afford ethyl (E)-6-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (2.54 g, 9.32 mmol, 96%) as a colorless oil. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>45</sup>

To a solution of ethyl (E)-6-((*tert*-butyldimethylsilyl)oxy)hex-2-enoate (2.35 g, 8.63 mmol) in anhydrous DCM (40 mL) was slowly added via cannula a solution of DIBALH (3.9 mL, 21.6 mmol) in DCM (10 mL) at –78 °C under N<sub>2</sub>. The reaction mixture was stirred under reduced temperature for 2 h. After that, Et<sub>2</sub>O (100 mL) and saturated solution of Rochelle's salt (50 mL) were added while maintaining vigorous stirring for 30 min at 0 °C and 1 h at rt. After phase separation, the aqueous layer was extracted with Et<sub>2</sub>O (2  $\times$  100 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 7:3) to afford 26 (1.95 g, 8.46 mmol, 98%) as a colorless oil. The spectral data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) are in accordance with those reported in the literature.<sup>46</sup>

***tert*-Butyl(((4E,6E)-7-((2R)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)hepta-4,6-dien-1-yl)oxy)dimethylsilane [(SR)-29].** To a solution of 26 (1.00 g, 4.34 mmol) in anhydrous MeCN (14 mL) were added 2,6-lutidine (1.0 mL, 8.9 mmol), Ph<sub>3</sub>P (2.28 mg, 8.69 mmol), and CBr<sub>4</sub> (2.88 g, 8.68 mmol) at 0 °C, and the resulting solution was stirred for 10 min. The reaction was quenched with H<sub>2</sub>O (50 mL), and the mixture was extracted with Et<sub>2</sub>O (3  $\times$  100 mL). The combined organic phases were washed with brine (50 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (gradient elution, 0 to 5% AcOEt in hexanes) to give (E)-((6-bromohex-4-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (27) (1.16 g, 3.97 mmol, 91%) as a colorless oil.  $R_f$ : 0.64 (hexanes/AcOEt 95:5). IR (ATR)  $\nu_{max}/cm^{-1}$ : 2929, 2857, 1472, 1255, 1104, 835, 775. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$ : 0.04 (s, 6H), 0.89 (s, 9H), 1.54–1.65 (m, 2H), 2.04–2.17 (m, 2H), 3.60 (t, *J* = 6.3 Hz, 2H), 3.94 (d, *J* = 6.6 Hz, 2H), 5.63–5.85 (m, 2H). <sup>13</sup>C NMR (63 MHz, CDCl<sub>3</sub>)  $\delta$ : –5.3 (2C), 18.3, 25.9 (3C), 28.4, 31.9, 33.5, 62.3, 126.6, 136.1. We were unable to obtain HRMS data for 27 using ESI-TOF and APCI mass spectrometry techniques.

To a solution of 27 (912 mg, 3.12 mmol) in anhydrous MeCN (17.2 mL) was added *n*-Bu<sub>3</sub>P (1.15 mL, 4.66 mmol), and the mixture was stirred at rt for 12 h. After that, the excess solvent was removed under reduced pressure, and the crude product was maintained under high vacuum (0.2 mmHg) for 8 h. The tri-*n*-butylphosphonium salt 28 was employed in the Wittig reaction without purification.

**Wittig Olefination.** To a solution of freshly prepared aldehyde (SR)-7 (354 mg, 2.08 mmol) and tri-*n*-butylphosphonium salt 28 (3.12 mmol) in anhydrous PhMe (38 mL) was added dropwise a solution of NHMDS (4.2 mL, 4.2 mmol, 1 M in THF) at –78 °C under N<sub>2</sub>. The mixture was stirred for 13 h at –78 °C and for 1 h at rt. The reaction was quenched with H<sub>2</sub>O (50 mL), and the mixture was extracted with AcOEt (100 mL and 2  $\times$  50 mL). The combined organic phases were washed with brine (50 mL) and dried over MgSO<sub>4</sub>, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 95:5) to furnish (SR)-29 (526 mg, 1.43 mmol, 69%) as a colorless oil and as a 6:1 mixture of the two isomers at the C-6/C-7 double bond.  $R_f$ : 0.50 (hexanes/AcOEt 95:5). IR (ATR)  $\nu_{max}/cm^{-1}$ : 2955, 2929, 2893, 2857, 1255, 1181, 1100, 1028, 988, 835, 775. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : (major isomer) 0.04 (s, 6H, Si(CH<sub>3</sub>)<sub>2</sub>), 0.89 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 1.17 (d, *J* = 6.2 Hz, 3H, C(CH<sub>3</sub>)<sub>2</sub>), 1.23 (d, *J* = 6.2 Hz, 3H,

$C(CH_3)_2$ , 1.57–1.63 (m, 2H, H-11), 1.99–2.04 (m, 1H, H-4), 2.07–2.10 (m, 1H, H-4), 2.12–2.16 (m, 2H, H-10), 3.61 (t,  $J = 6.4$  Hz, 1H, H-12), 4.01 (sept,  $J = 6.2$  Hz, 1H,  $CH(CH_3)_2$ ), 4.43–4.47 (m, 1H, H-5), 5.11 (br s, 1H, H-1), 5.62 (dd,  $J = 15.4$  and 6.3 Hz, 1H, H-6), 5.70–5.75 (m, 2H, H-9 and H-2), 5.99–6.01 (m, 1H, H-3), 6.05 (dd,  $J = 15.4$  and 10.6 Hz, 1H, H-8), 6.23 (dd,  $J = 15.4$  and 10.6 Hz, 1H, H-7).  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$ : (major isomer) –5.3 ( $2CH_3$ ,  $Si(CH_3)_2$ ), 18.3 (C, Si–C), 22.0 ( $CH_3$ ,  $C(CH_3)_2$ ), 23.9 ( $CH_3$ ,  $C(CH_3)_2$ ), 26.0 ( $3CH_3$ ,  $C(CH_3)_3$ ), 28.9 ( $CH_2$ , C-10), 30.7 ( $CH_2$ , C-4), 32.3 ( $CH_2$ , C-11), 62.5 ( $CH_2$ , C-12), 66.4 (CH, C-5), 69.5 (CH,  $C(CH_3)_2$ ), 93.1 (CH, C-1), 126.1 (CH, C-2), 128.5 (CH, C-3), 129.9 (CH, C-8), 130.7 (CH, C-6), 131.3 (CH, C-7), 135.0 (CH, C-9). HRMS (ESI-TOF)  $m/z$ :  $[M - C(CH_3)_2 + Na]^+$  calcd for  $C_{18}H_{32}O_3SiNa$  347.20129; found 347.20134.

**(4E,6E)-7-((2R)-6-isopropoxy-3,6-dihydro-2H-pyran-2-yl)-hepta-4,6-dien-1-ol [(5R)-30]**. To a solution of (5R)-29 (520 mg, 1.42 mmol) in anhydrous THF (71 mL) was added a solution of TBAF (1.5 mL, 1.5 mmol, 1 M in THF) at 0 °C under  $N_2$ . The yellow solution was allowed to warm to rt and stirred for 5.5 h. The reaction was quenched by the addition of  $H_2O$  (50 mL) and AcOEt ( $3 \times 100$  mL). The combined organic layers were washed with brine (50 mL), dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 7:3) to give (5R)-30 (334.5 mg, 1.326 mmol, 94%) as a colorless oil and as a 6:1 mixture of the two isomers at the C-6/C-7 double bond.  $R_f$ : 0.30 (hexanes/AcOEt 7:3). IR (ATR)  $\nu_{max}/cm^{-1}$ : 3409, 2971, 2930, 2887, 1657, 1181, 1099, 1027, 989.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : (major isomer) 1.17 (d,  $J = 6.2$  Hz, 3H,  $C(CH_3)_2$ ), 1.23 (d,  $J = 6.2$  Hz, 3H,  $C(CH_3)_2$ ), 1.64–1.70 (m, 2H, H-11), 1.98–2.04 (m, 1H, H-4), 2.06–2.13 (m, 1H, H-4), 2.16–2.20 (m, 2H, H-10), 3.66 (t,  $J = 6.4$  Hz, 1H, H-12), 4.00 (sept,  $J = 6.2$  Hz, 1H,  $CH(CH_3)_2$ ), 4.43–4.47 (m, 1H, H-5), 5.10 (br s, 1H, H-1), 5.63 (dd,  $J = 15.4$  and 6.3 Hz, 1H, H-6), 5.69–5.75 (m, 2H, H-9 and H-2), 5.99–6.01 (m, 1H, H-3), 6.07 (dd,  $J = 14.8$  and 10.5 Hz, 1H, H-8), 6.23 (dd,  $J = 15.4$  and 10.5 Hz, 1H, H-7).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$ : (major isomer) 22.0 ( $CH_3$ ,  $C(CH_3)_2$ ), 23.8 ( $CH_3$ ,  $C(CH_3)_2$ ), 28.9 ( $CH_2$ , C-10), 30.7 ( $CH_2$ , C-4), 32.1 ( $CH_2$ , C-11), 62.4 ( $CH_2$ , C-12), 66.4 (CH, C-5), 69.5 (CH,  $C(CH_3)_2$ ), 93.1 (CH, C-1), 126.1 (CH, C-2), 128.4 (CH, C-3), 130.2 (CH, C-8), 131.0 (CH, C-6\*), 131.1 (CH, C-7\*), 134.4 (CH, C-9) (asterisks indicate that the assignments may be interchanged). HRMS (ESI-TOF)  $m/z$ :  $[M - CH_2(CH_3)_2 + H]^+$  calcd for  $C_{12}H_{17}O_3$  209.11722; found 209.11709.

**(2R)-6-Isopropoxy-2-((1E,3E,7E)-8-((1S,2S)-2-methylcyclopropyl)octa-1,3,7-trien-1-yl)-3,6-dihydro-2H-pyran [(5R,14S,16S)-31]**. To a solution of oxalyl chloride (133  $\mu$ L, 1.54 mmol) in DCM (16 mL) was added DMSO (160  $\mu$ L, 2.19 mmol) at –78 °C under  $N_2$ . After 15 min, (5R)-30 (240 mg, 0.951 mmol) in DCM (7 mL) was added dropwise, and the mixture was stirred for a further 15 min.  $Et_3N$  (0.7 mL, 4.8 mmol) was added, and after 5 min the mixture was allowed to warm to rt. The reaction was quenched by the addition of saturated  $NH_4Cl$  solution (20 mL). The layers were separated, and the aqueous phase was extracted with  $Et_2O$  ( $3 \times 50$  mL). The organic layers were combined, washed with brine (20 mL), dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The crude product was obtained as a yellow oil, which was used in the next step without purification.  $R_f$ : 0.67 (hexanes/AcOEt 7:3).

To a solution of the crude aldehyde obtained in the previous step and sulfone (1S,2S)-22 (390 mg, 1.46 mmol) in anhydrous DME (40 mL) was added dropwise a solution of potassium hexamethyldisilazide (1.9 mL, 1.9 mmol, 1 M in THF) at –78 °C under  $N_2$ . The resulting dark-brown mixture was stirred for 30 min, and the reaction was quenched with brine (100 mL). The mixture was extracted with AcOEt ( $3 \times 100$  mL), and the organic layer was washed with brine (50 mL), dried over  $MgSO_4$ , and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexanes/AcOEt 9:1) to afford (5R,14S,16S)-31 as 2.2:1 *E*:*Z* mixture at the C-12 double bond (119.3 mg, 0.394 mmol, 41%) contaminated with minor amounts of the 6Z double-bond isomers as a light-yellow oil.  $R_f$ : 0.58 (hexanes/AcOEt 9:1). IR (ATR)  $\nu_{max}/cm^{-1}$ : 2969, 2924, 1659, 1400,

1380, 1316, 1181, 1099, 1027, 988.  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$ : (major isomer) 0.39–0.41 (m, 1H), 0.46–0.49 (m, 1H), 0.66–0.72 (m, 1H), 1.00–1.10 (m, 1H), 1.05 (d,  $J = 6.0$  Hz, 3H), 1.17 (d,  $J = 6.2$  Hz, 3H), 1.23 (d,  $J = 6.2$  Hz, 3H), 1.99–2.28 (m, 6H), 4.01 (sept,  $J = 6.2$  Hz, 1H), 4.43–4.47 (m, 1H), 5.01 (dd,  $J = 15.3$  and 8.6 Hz, 1H), 5.11 (br s, 1H), 5.44 (dt,  $J = 15.3$  and 6.7 Hz, 1H), 5.62 (d,  $J = 15.3$  and 6.2 Hz, 1H), 5.68–5.76 (m, 2H), 5.99–6.11 (m, 2H), 6.23 (dd,  $J = 15.3$  and 10.2 Hz, 1H); (second-largest isomer) 0.46–0.49 (m, 2H), 0.76–0.72 (m, 1H), 1.00–1.10 (m, 1H), 1.07 (d,  $J = 5.9$  Hz, 3H), 1.17 (d,  $J = 6.1$  Hz, 3H), 1.23 (d,  $J = 6.2$  Hz, 3H), 1.99–2.28 (m, 6H), 4.01 (sept,  $J = 6.2$  Hz, 1H), 4.43–4.47 (m, 1H), 4.79 (t,  $J = 10.3$  Hz, 1H), 5.11 (br s, 1H), 5.26 (dt,  $J = 10.3$  and 7.4 Hz, 1H), 5.60–5.65 (m, 1H), 5.68–5.76 (m, 2H), 5.99–6.11 (m, 2H), 6.21–6.27 (m, 1H).  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$ : (major isomer) 15.1, 15.5, 18.5, 22.0, 22.4, 23.9, 30.7, 32.2, 32.8, 66.4, 69.5, 93.1, 126.1, 126.6, 128.5, 129.8, 130.8, 131.3, 134.1, 134.9; (second-largest isomer) 15.1, 15.5, 18.6, 18.7, 22.0, 23.9, 27.3, 30.7, 32.8, 66.5, 69.5, 93.1, 126.1, 126.5, 128.5, 129.9, 130.8, 131.3, 134.2, 135.0. HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{20}H_{30}O_2Na$  325.21380; found 325.21354.

**(R)-6-((1E,3E,7E)-8-((1S,2S)-2-Methylcyclopropyl)octa-1,3,7-trien-1-yl)-5,6-dihydro-2H-pyran-2-one [(5R,14S,16S)-2]**. A mixture of PCC (395 mg, 1.82 mmol) and  $CaCO_3$  (730 mg, 7.28 mmol) in anhydrous DCM (10 mL) was stirred at rt for 2 h. Then a solution of (5R,14S,16S)-31 (110 mg, 0.364 mmol) in DCM (10 mL) was added by cannula, and the reaction mixture was stirred at rt for 2 h. After filtration over silica gel and solvent evaporation under reduced pressure, the crude product was purified by flash chromatography (hexanes/AcOEt 7:3) to afford (5R,14S,16S)-2' (43 mg, 0.166 mmol, 46%) as a mixture of *E* and *Z* isomers at the C-12/C-13 double bond contaminated with minor amounts of the 6Z isomers. This mixture was separated using preparative HPLC with a SunFire Prep  $C_{18}$  OBD column (particle size 5  $\mu$ m, dimensions 19 mm  $\times$  100 mm, 55% MeCN/45%  $H_2O$ , 17 mL/min) to yield the major isomer with *E*-configured double bonds, (5R,14S,16S)-2 (14.5 mg,  $t_R = 18.6$  min), as a colorless oil.  $R_f$ : 0.64 (hexanes/AcOEt 7:3).  $[\alpha]_D^{20} +95$  (c 0.1,  $CHCl_3$ ). IR (ATR)  $\nu_{max}/cm^{-1}$ : 2996, 2925, 1720, 1382, 1244, 991, 961, 816.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$ : 0.38–0.42 (m, 1H, H-15), 0.46–0.49 (m, 1H, H-15), 0.66–0.71 (m, 1H, H-16), 0.99–1.05 (m, 1H, H-14), 1.04 (d,  $J = 6.2$  Hz, 3H, H-17), 2.04–2.08 (m, 2H, H-11), 2.10–2.16 (m, 2H, H-10), 2.43–2.45 (m, 2H, H-4), 4.92–4.96 (m, 1H, H-5), 5.00 (dd,  $J = 15.2$  and 8.6 Hz, 1H, H-13), 5.43 (dt,  $J = 15.3$  and 6.9 Hz, 1H, H-12), 5.64 (dd,  $J = 15.3$  and 6.6 Hz, 1H, H-6), 5.77 (dt,  $J = 15.2$  and 6.6 Hz, 1H, H-9), 6.01–6.05 (m, 2H, H-2, H-8), 6.31 (dd,  $J = 15.4$  and 10.5 Hz, 1H, H-7), 6.85–6.89 (m, 1H, H-3).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ )  $\delta$ : 14.7 (CH, C-16), 14.8 ( $CH_2$ , C-15), 18.5 ( $CH_3$ , C-17), 22.4 (CH, C-14), 29.8 ( $CH_2$ , C-4), 32.0 ( $CH_2$ , C-11), 32.8 ( $CH_2$ , C-10), 77.9 (CH, C-5), 121.7 (CH, C-2), 126.3 (CH, C-12), 126.5 (CH, C-6), 128.9 (CH, C-8), 133.7 (CH, C-7), 134.3 (CH, C-13), 137.1 (CH, C-9), 144.6 (CH, C-3), 164.0 (CO, C-1). HRMS (ESI-TOF)  $m/z$ :  $[M + Na]^+$  calcd for  $C_{17}H_{22}O_2Na$  281.15120; found 281.15065.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, full spectroscopic data for new compounds, HPLC chromatograms, and CD curves. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.



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