JOC Article

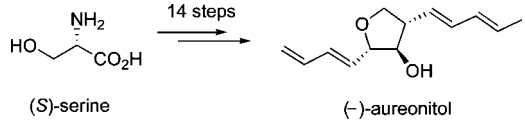
Total Synthesis and Proof of Relative Stereochemistry of (−)-Aureonitol

Peter J. Jervis and Liam R. Cox*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom

l.r.cox@bham.ac.uk

Received June 20, 2008



Two trisubstituted epimeric tetrahydrofurans, **1** and **2**, have been synthesized in order to confirm the relative stereochemistry in the natural product aureonitol. The key step in the synthesis of **1** and **2** involved a stereoselective intramolecular allylation of an allylsilane with an aldehyde, which introduced the stereotriad in the five-membered ring. The major tetrahydrofuran diastereoisomer **18** from this cyclization reaction was subsequently elaborated to tetrahydrofuran **1**. Its 3-epimer (**2**) was then prepared from **1** via an oxidation−reduction sequence. Compound **1** exhibits identical ^{1}H NMR data to those reported for aureonitol, which was isolated from *Helichrysum aureonitons* by Bohlmann in 1979, whereas the ^{1}H NMR data for **2** are markedly different. The ^{1}H NMR data (in $CDCl_3$, CD_3OD, and C_6D_6) and ^{13}C NMR data (in $CDCl_3$) for **1** are also identical with those reported for a natural product isolated from various *Chaetomium* sp. by Abraham, Seto, and Teuscher. These findings support Abraham's conclusion that the structure of aureonitol should be revised from **2** to **1**. The enantioselective synthesis of **1** has also confirmed that (−)-aureonitol isolated by Abraham contains the (2*S*,3*R*,4*S*) absolute configuration of stereocenters on the tetrahydrofuran ring.

Introduction

In 1979, Bohlmann isolated a tetrahydrofuran metabolite from the plant *Helichrysum aureonitens*.[1,2] He named the compound aureonitol, and used a combination of ^{1}H NMR, IR, mass, and UV data to elucidate its basic structure. Although he did not comment on the absolute stereochemistry, from analysis of the ^{1}H NMR coupling constants, he proposed an *all-syn* arrangement of the substituents on the tetrahydrofuran ring (Figure 1). This compound was structurally similar to one isolated by Burrows in 1967 from the fungus *Chaetomium coarctatum*.[3,4] At the same time as Burrows, who reported just the basic structure of the metabolite, Mason and Vane also published on the same sample.[5] They compared the CD spectrum of their compound with those of the corresponding cyclopentane derivatives and concluded that there was an *anti* relationship between the two dienyl arms (Figure 1). Seto and co-workers later investigated the biosynthesis of this compound (isolated again from *C. coarctatum*) using labeling studies and showed it to be a polyketide metabolite. While the group again confirmed the basic structure, they too did not comment on the relative

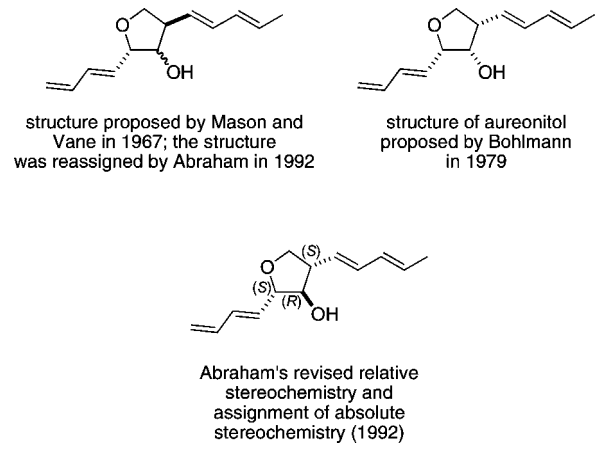


FIGURE 1. Proposed structures of aureonitol.

* Corresponding author. Phone: +44 (0)121 414 3524. Fax: +44 (0)121 414 4403.

(1) Bohlmann, F.; Ziesche, J. *Phytochemistry* **1979**, *18*, 664–665.

(2) *Helichrysum aureonitens* is a hairy perennial herb that grows in the Kwazulu-Natal province of South Africa. It belongs to a large genus of about 500 species. According to folklore, it has been used for centuries by the people of this province against infection. In 1995, Meyer (Meyer, J. J. M.; Afolayan, A. J. *J. Ethnopharmacol.* **1995**, *47*, 109–111.) found that the dichloromethane extract of *H. aureonitens* was active against a wide range of gram-positive bacteria, yet inactive against all gram-negative bacteria tested (including *Escherichia coli*).

10.1021/jo801338t CCC: $40.75
Published on Web 09/06/2008

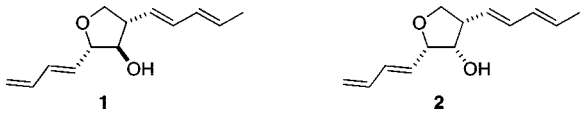


FIGURE 2. Targets for total synthesis.

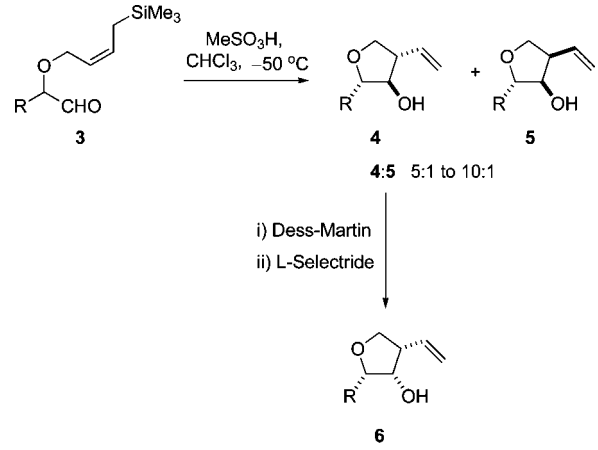
stereochemistry in the tetrahydrofuran core.[6] Since Bohlmann did not refer to these reports in his paper, it was unknown at that time whether or not Bohlmann had isolated the same diastereoisomeric product from his plant source as Burrows, Mason and Vane, and Seto had from their fungal source.

In 1992, Abraham reported the isolation of a tetrahydrofuran derivative from the fungus *C. cochlioides*.[7] Since the ^{1}H NMR data were identical with those reported by Bohlmann for aureonitol, Abraham concluded that he had isolated the same molecule. Abraham used a Mosher ester analysis to elucidate the absolute stereochemistry at the 3-position of the tetrahydrofuran ring. From NOE experiments he also showed that the molecule contained the "down−up−down" relative stereochemistry. He reasoned that as the data for this compound were identical with those of Bohlmann's aureonitol, the structure of aureonitol should be revised (Figure 1). Abraham also fermented *C. coarctatum* to isolate the tetrahydrofuran reported earlier by Burrows,[3] Mason and Vane,[5] and Seto.[6] The ^{1}H NMR and ^{13}C NMR spectra of the tetrahydrofuran isolated from *C. coarctatum* were identical with those for the "aureonitol" obtained from *C. cochlioides*, suggesting that the structure proposed by Mason and Vane in 1967 should also be revised, and that Burrows had indeed isolated aureonitol. In 2005, Teuscher isolated the same molecule as Abraham from *C. globosum*.[8]

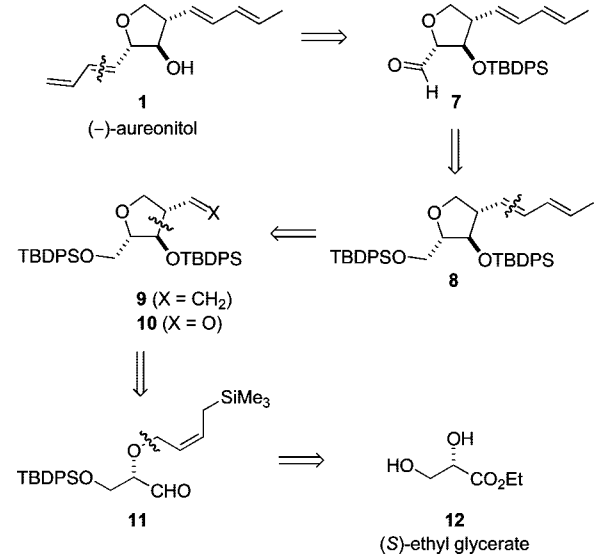
Despite Abraham's findings and report,[7] aureonitol is still described on the Chemical Database as having the *all-syn* relative stereochemistry suggested originally by Bohlmann.[1] Independent total syntheses of (2*S*,3*R*,4*S*)-2-(buta-1′,3′-dienyl)-3-hydroxy-4-(penta-1″,3″-dienyl)tetrahydrofuran, **1**, and (2*S*,3*S*,4*S*)-2-(buta-1′,3′-dienyl)-3-hydroxy-4-(penta-1″,3″-dienyl)tetrahydrofuran, **2**, (Figure 2) would, once and for all, prove the relative stereochemistry of this interesting natural product.

As part of a research program investigating the use of silyl nucleophiles in cyclization strategies,[9] we have used an intramolecular allylation of an allylsilane with an aldehyde to synthesize a number of oxygen-containing heterocycles. We recently reported that the intramolecular allylation of aldehyde **3** generates two (out of a possible four) 2,3,4-trisubstituted tetrahydrofuran products **4** and **5** (Scheme 1).[9c] Significantly, the major diastereoisomer **4** contains the same

SCHEME 1. Stereoselective Synthesis of 2,3,4-Trisubstituted Tetrahydrofurans



SCHEME 2. Retrosynthesis of (−)-Aureonitol



relative stereochemistry as that proposed by Abraham for aureonitol.[7] We therefore identified this tetrahydrofuran as a possible precursor to the structure of aureonitol as proposed by Abraham. Furthermore, having also shown previously that the major diastereoisomer **4** from our intramolecular allylation can be converted to its 3-epimer **6** via an oxidation−reduction sequence,[9c] we argued that a similar approach could be employed to obtain the *all-syn* diastereoisomer **2** (the structure proposed by Bohlmann[1]) from **1**.

Results and Discussion

The retrosynthesis of our first tetrahydrofuran target **1** is shown in Scheme 2. This compound should also provide a route to its 3-epimer **2** via an oxidation−reduction sequence. Although we did not expect particularly serious stability problems, the C-2 dienyl unit in tetrahydrofuran **1** was deemed to be the most labile portion of the molecule[10] and therefore was disconnected first to provide aldehyde **7**; various olefination strategies exist for elaborating an aldehyde into a diene. From aldehyde **7**, a change of oxidation state and protection of the resulting alcohol

(3) Burrows, B. F. *J. Chem. Soc., Chem. Commun.* **1967**, 597.

(4) *Chaetomium* spp. are filamentous fungi found in soil, air, and plant debris. As well as being a contaminant, *Chaetomium* spp. are also causative agents of infections in humans. The *Chaetomium* genus contains over 100 species, with the most common being *C. atrobrunneum*, *C. funicola*, *C. globosum*, and *C. strumarium*.

(5) Mason, S. F.; Vane, G. W. *J. Chem. Soc., Chem. Commun.* **1967**, 598.

(6) (a) Seto, H.; Saito, M.; Uzawa, J.; Yonehara, H. *Heterocycles* **1979**, *13*, 247–253. (b) Saito, M.; Seto, H.; Yonehara, H. *Agric. Biol. Chem.* **1983**, *47*, 2935–2937.

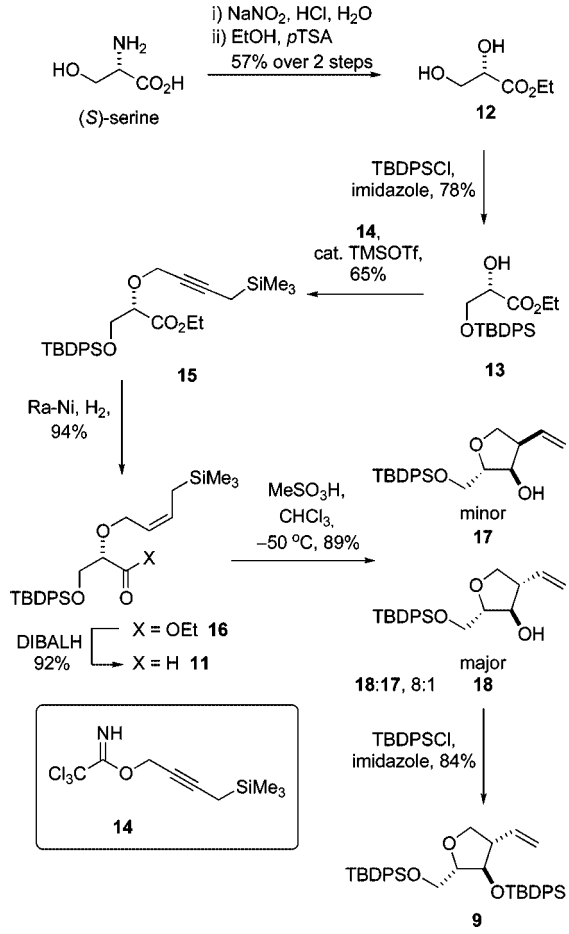
(7) Abraham, W. R.; Arfmann, H. A. *Phytochemistry* **1992**, *31*, 2405–2408.

(8) Teuscher, F. Ph.D. thesis, Heinrich-Heine-Universität, Germany, 2005.

(9) (a) Beignet, J.; Jervis, P. J.; Cox, L. R. *J. Org. Chem.* **2008**, *73*, 5462–5475. (b) Ramalho, R.; Jervis, P. J.; Kariuki, B. M.; Humphries, A. C.; Cox, L. R. *J. Org. Chem.* **2008**, *73*, 1631–1634. (c) Jervis, P. J.; Kariuki, B. M.; Cox, L. R. *Tetrahedron Lett.* **2008**, *49*, 2514–2518. (d) Jervis, P. J.; Cox, L. R. *Beilstein J. Org. Chem.* **2007**, *3*, 6. (e) Jervis, P. J.; Kariuki, B. M.; Cox, L. R. *Org. Lett.* **2006**, *8*, 4649–4652. (f) Ramalho, R.; Beignet, J.; Humphries, A. C.; Cox, L. R. *Synthesis* **2005**, 3389–3397. (g) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971–3974. (h) Beignet, J.; Cox, L. R. *Org. Lett.* **2003**, *5*, 4231–4234.

(10) Activation of the ring oxygen could potentially result in the opening of the tetrahydrofuran ring at C-2 to generate a stabilized pentadienyl cation.

SCHEME 3. Diastereo- and Enantioselective Synthesis of Tetrahydrofuran 9 from (*S*)-Serine



affords tetrahydrofuran **8**. We envisaged that the right-hand dienyl arm could be installed either by a cross-metathesis of vinyl tetrahydrofuran **9** or by an olefination procedure from aldehyde **10**, which could be accessed from vinyl tetrahydrofuran **9** by oxidative cleavage of the double bond. Tetrahydrofuran **9** would be accessed from aldehyde **11**, which in turn could be prepared from (*S*)-ethyl glycerate **12**. In this way, we would also have an enantioselective synthesis of aureonitol, which would allow us to confirm the absolute stereochemistry of the natural product isolated by Abraham.[7]

(*S*)-Ethyl glycerate **12** was prepared in a two-step procedure,[11] involving a stereospecific substitution of the amine group in (*S*)-serine with a hydroxyl group to afford (*S*)-glyceric acid, followed by Fischer esterification of the carboxylic acid with *p*-toluenesulfonic acid (*p*TSA) as the catalyst (Scheme 3).[12] Selective protection of the less hindered primary hydroxyl group with *tert*-butyldiphenylsilyl chloride (TBDPSCl) afforded silyl ether **13** in good yield, which was primed for attaching the allylsilane nucleophile. A nonbasic etherification procedure was used to avoid potential epimerization of the stereogenic center. Thus trichloroacetimidate **14** was prepared as described previously,[9e] and then reacted with α-hydroxy ester **13** in the presence of TMSOTf to provide ether **15**. Partial hydrogenation of the triple bond in the resulting alkyne was achieved with excellent selectivity, using Raney-nickel (Ra-Ni) under a hydrogen atmosphere, to provide alkene **16** (along with traces of the corresponding over-reduction product). Diisobutylaluminum hydride (DIBALH) reduction of the ester in **16** proceeded uneventfully to provide the desired cyclization precursor **11** in excellent yield. Compound **11** reacted with $MeSO_3H$ under our optimized conditions[9c] to provide an 8:1 mixture of diastereoisomers **18** and **17** in high yield.[13] The relative stereochemistry in cyclization product **18** was assigned by analogy with other similarly substituted tetrahydrofurans prepared previously by us using this methodology.[9c] The multiplicity and chemical shifts of the proton resonances attached directly to the ring are particularly characteristic of a tetrahydrofuran containing a "down−up−down" relationship of substituents around the ring.[9c] While separation of the two diastereoisomers at this stage proved impossible, TBDPS protection of the remaining secondary alcohol afforded the corresponding silyl ethers, which were now separable by HPLC.

Having successfully assembled the trisubstituted tetrahydrofuran, all that remained was to install the two dienyl side chains. This proved to be more challenging than we had expected. In a first approach to introducing the right-hand pentadienyl side chain, we sought to employ the vinyl substituent in **9** in a cross-metathesis reaction. To this end, commercially available (*E*)-1,3-pentadiene **19** was identified as a potential cross-metathesis partner, as this would potentially deliver the required diene **8** in a single step. There is precedent for this type of diene cross-metathesis,[14] although previous examples all involve a monosubstituted olefin partner that is considerably less sterically hindered than that in tetrahydrofuran **9**. In these cases, the reaction of a sterically unhindered monosubstituted olefin partner (a type I olefin in Grubbs' classification[15]) with a relatively unreactive diene partner (a type III olefin in Grubbs' classification[15]) gives rise to the cross-metathesis product efficiently. This would not necessarily be the case with the two reacting olefins which we wanted to employ since both are relatively unreactive cross-metathesis partners (two type III olefins according to Grubbs' classification), and as such, we expected this to be a more difficult metathesis reaction. Unfortunately these predictions were borne out: heating a solution of tetrahydrofuran **9** in toluene at reflux for 48 h with 4 equiv of diene **19** in the presence of 10 mol % Grubbs II catalyst in a sealed tube[16] led to no consumption of the starting material, although a number of volatile nonpolar homodimers from the starting diene were tentatively identified (Scheme 4). The use of catalysts **20** and **21** led to no improvement.[17]

To circumvent this problem, we next employed a masked diene metathesis partner, which we expected would be more reactive toward cross-metathesis and bring us back to a system where a reactive alkene is reacting with a less-reactive alkene, and therefore a much better substrate set for obtaining a high-yielding cross-metathesis product. To this end, we envisaged cross-metathesis of alkenes **22**−**24** with vinyl tetrahydrofuran

(11) (a) Goubert, M.; Toupet, L.; Sinibaldi, M. E.; Canet, I. *Tetrahedron* **2007**, *63*, 8255–8266. (b) Yokokawa, F.; Inaizumi, A.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 5903–5908.

(12) Fischer, E.; Speier, A. *Chem. Ber.* **1895**, *28*, 3252–3258.

(13) Confirmation that no loss of stereochemical integrity had occurred along the synthetic sequence was confirmed by chiral HPLC analysis of **18** and comparison with a racemic sample (see the Supporting Information).

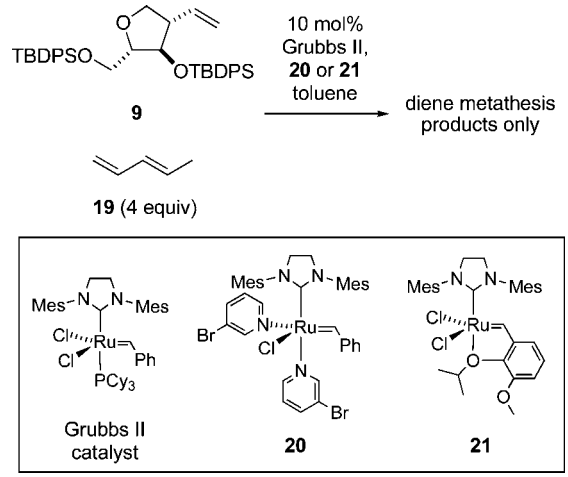
(14) (a) Dewi, P.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 577–580. (b) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187–190. (c) Moura-Letts, G.; Curran, D. P. *Org. Lett.* **2007**, *9*, 5–8.

(15) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

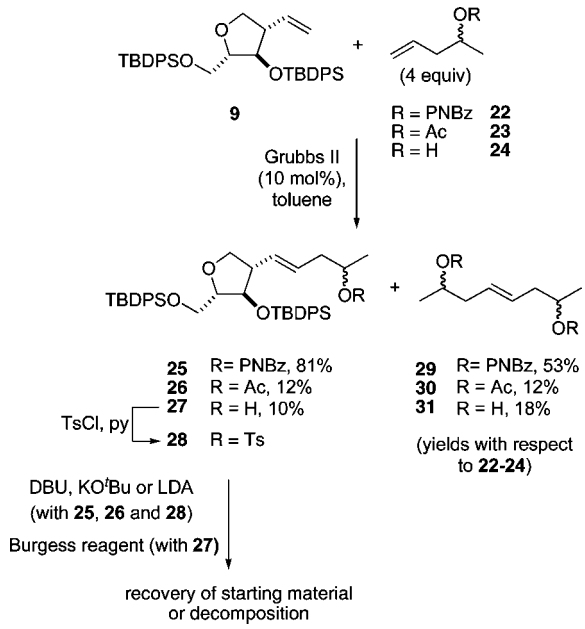
(16) A sealed tube was employed owing to the volatility of diene **19** (bp 42 °C).

(17) Metathesis catalyst **20** and **21** were provided by Dr. David Lindsay, University of Reading, UK.

SCHEME 4. Attempted Cross-Metathesis Route to Diene 8

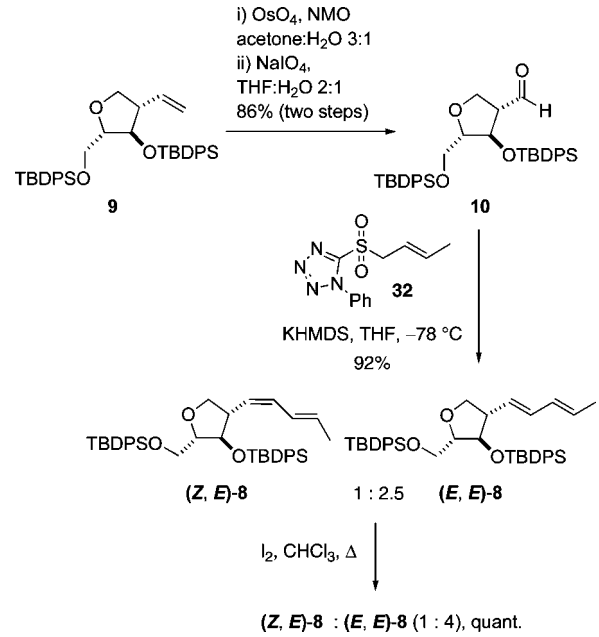


SCHEME 5. Attempted Cross-Metathesis Routes to Diene 8 Using a Masked Diene Metathesis Partner



9 would provide an alkene product and the required diene **8** after elimination (Scheme 5). Heating a solution of tetrahydrofuran **9** and 4 equiv of alkene **22** in the presence of Grubbs' II catalyst provided alkene **25** in high yield and with complete (*E*)-stereoselectivity, along with a large amount of alkene **29** arising from the background homodimerization process (Scheme 5). Homodimer **29** was not a substrate for secondary metathesis; thus an excess of alkene **22** was crucial to ensure a high conversion of tetrahydrofuran **9** to product. The reaction where the 4-nitrobenzoyl (PNBz) group in **22** was replaced by an acetyl group (**23**), or where the free homoallylic alcohol (**24**) was employed, provided much poorer yields of the corresponding cross-metathesis products **26** and **27**, respectively. Frustratingly, all attempts to eliminate ester **25** to diene **8** by using various bases (DBU, KO^{t}Bu, LDA)[18] were unsuccessful: either no reaction was observed and the starting material was recovered intact, or the starting material decomposed under the reaction conditions. This was also the case with acetate **26** and tosylate **28** (prepared from alcohol **27**). Attempted dehydration of alcohol **27** by using the Burgess reagent[19] also led to decomposition of the starting material.

SCHEME 6. Installation of the Right-Hand Pentadienyl Unit



At this juncture, we reluctantly abandoned our cross-metathesis approach and switched our attention to olefination strategies involving aldehyde **10**, which was readily prepared from **9** in a two-step dihydroxylation−periodate cleavage operation (Scheme 6).[20] Attempts to carry out this reaction sequence in a one-pot operation following a procedure reported by Jin et al.[21] resulted in a much lower yield of the desired aldehyde (15%). Horner−Wadsworth−Emmons olefination of aldehyde **10** with (*E*)-diethyl crotylphosphonate gave only trace amounts of any diene product, and instead led to preferential elimination of the β-siloxy group in the starting aldehyde to provide an enal product (see the Supporting Information).[22] The corresponding Wittig reaction was more successful;[23] however, the desired (*E*,*E*)-diene product was formed as the minor stereoisomer (2:1 ratio of (*Z*,*E*)-**8** to (*E*,*E*)-**8**). In light of these disappointing results, we turned our attention to the Julia-Kocienski olefination, which often proceeds with high levels of (*E*)-stereoselectivity,[24] although the stereochemical outcome

(18) (a) Yamamoto, K.; Ohta, O.; Tsuji, J. *Chem. Lett.* **1979**, 713–716. (b) Tucker, J. R.; Riley, D. P. *J. Organomet. Chem.* **1985**, *279*, 49–62. (c) Crousse, B.; Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1997**, *38*, 5297–5300. (d) Tuckett, M. W.; Watkins, W. J.; Whitby, R. J. *Tetrahedron Lett.* **1998**, *39*, 123–126.

(19) (a) Hoffmann, R. W.; Schäfer, F.; Haeberlin, E.; Rohde, T.; Körber, K. *Synthesis* **2000**, 2060–2068. (b) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31. (c) Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Am. Chem. Soc.* **1970**, *92*, 5224–5226. (d) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744–4745.

(20) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973–1976. (b) Betancort, J. M.; Martín, T.; Palazón, J. M.; Martín, V. S. *J. Org. Chem.* **2003**, *68*, 3216–3224.

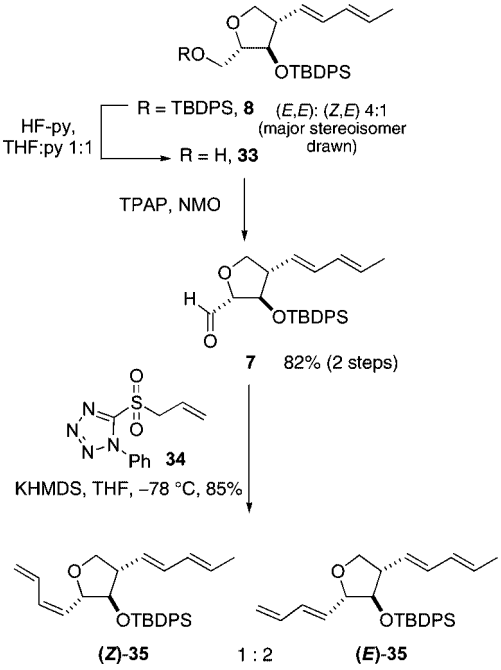
(21) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.

(22) Wang, Y.; West, F. G. *Synthesis* **2002**, 99–103.

(23) (a) Sodeoka, M.; Yamada, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4906–4911. (b) Bestmann, H. J.; Süss, J.; Vostrowsky, O. *Liebigs Ann. Chem.* **1981**, 2117–2138.

(24) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. (c) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366.

SCHEME 7. Installation of the Left-Hand Dienyl Unit

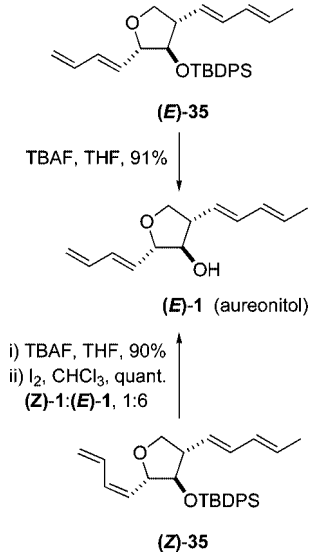


is admittedly less-predictable when the procedure is used to install a diene.[24] However, encouraged by the work of Ōmura et al.,[25] who used a highly (*E*)-selective Julia-Kocienski olefination to install the central diene unit of the natural product nafuredin, aldehyde **10** was reacted with the anion of sulfone **32** (Scheme 6). This reaction again provided the product as a mixture of geometric isomers, although now the ratio was 2.5:1 in favor of the required diene, (*E*,*E*)-**8**. Heating a solution of the two diene stereoisomers in chloroform in the presence of 5 mol % of iodine for 30 min isomerized this diene mixture from 2.5:1 to 4:1 in favor of the required (*E*,*E*)-**8**, which at this stage was inseparable from (*Z*,*E*)-**8** (Scheme 6).[26]

Selective deprotection of the primary TBDPS ether in **8** with HF-pyridine provided alcohol **33**,[27,28] which was oxidized to the corresponding aldehyde **7** by using tetra-*n*-propylammonium perruthenate (TPAP) (Scheme 7). Aldehyde **7** proved to be labile and was therefore used immediately, without further purification, in a second Julia-Kocienski olefination.[24] Thus, deprotonation of sulfone **34** with potassium hexamethyldisilazane (KHMDS), followed by treatment with aldehyde **7** provided a mixture of dienes, (*E*)-**35** and (*Z*)-**35**, in a good yield and a 2:1 ratio (Scheme 7). Attempts to improve this ratio by isomerization in the presence of iodine were unsuccessful and only led to decomposition. Fortunately, both (*E*)-**35** and (*Z*)-**35** were separable by flash column chromatography from one another, and from residual traces of minor stereoisomers that had been carried through from earlier steps.

In a final step, (*E*)-**35** was treated with TBAF to provide our target molecule (*E*)-**1** [(−)-aureonitol] in 91% yield (Scheme 8). Although isomerization of (*Z*)-**35** to (*E*)-**35** was unsuccessful,

SCHEME 8. Completing the Total Synthesis of Aureonitol



we reasoned that (*Z*)-**1** might still be channeled to our target (−)-aureonitol if isomerization could be carried out after this final deprotection step. To this end, silyl ether (*Z*)-**35** was deprotected in the same way as for its (*E*)-stereoisomer, to form (*Z*)-**1** in 90% yield. Pleasingly, heating a solution of this material in chloroform in the presence of 5 mol % of iodine at reflux for 30 min provided a 6:1 ratio of (*E*)-**1** [(−)-aureonitol] to (*Z*)-**1**,[26] which could be separated by flash column chromatography to afford pure (−)-aureonitol (Scheme 8).

The ^{1}H NMR and ^{13}C NMR spectra of (*E*)-**1** were consistent with the basic structure of the target molecule. Further evidence came from COSY and HSQC experiments (which allowed a full assignment of the resonances) as well as electrospray, HRMS, and IR data. We next compared the ^{1}H NMR data for our synthesized (*E*)-**1** with those reported by Bohlmann for the aureonitol isolated from *H. aureonitens*.[1] The chemical shifts and coupling constants are identical in the solvent $CDCl_3$ (see the Supporting Information). Since our synthesized (*E*)-**1** is known to contain the (2*S*,3*R*,4*S*) relative stereochemistry, independent synthesis supports Abraham's conclusion that the structure of aureonitol should be revised (Abraham also had matching ^{1}H NMR data with Bohlmann).[7] Although at this point we had shown that the ^{1}H NMR data for the (2*S*,3*R*,4*S*) diastereoisomer matches those reported for Bohlmann's aureonitol, we had still not disproved the (2*S*,3*S*,4*S*) relative stereochemistry that was originally proposed for the structure of aureonitol. To this end, (*E*)-**1** was oxidized to ketone **36** in good yield with Dess−Martin periodinane (Scheme 9). Subsequent reduction with the bulky reducing agent, L-selectride, provided the epimerized tetrahydrofuran **2**, with high diastereoselectivity (>10:1).[29] Comparing the ^{1}H NMR data of this synthesized *all-syn* diastereoisomer with the ^{1}H NMR data for Bohlmann's *Helichrysum* aureonitol in $CDCl_3$ revealed marked differences, with the resonances for the protons situated on the tetrahydrofuran ring exhibiting particularly large differences in chemical shift values (see the Supporting Information).[1] It was clear from this comparison that **2** and Bohlmann's aureonitol are not the same compound; thus we have proven by independent synthesis that aureonitol does not contain the *all-syn* relative stereochemistry as is currently listed in the Chemical Database.

(25) Takano, D.; Nagamitsu, T.; Ui, H.; Shiomi, K.; Yamaguchi, Y.; Masuma, R.; Kuwajima, I.; Ōmura, S. *Org. Lett.* **2001**, *3*, 2289–2291.

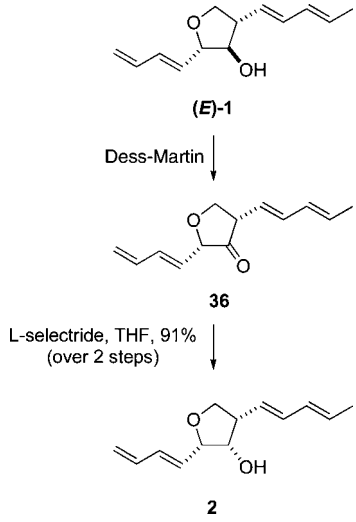
(26) (a) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026–3038. (b) Adger, B. J.; Barrett, C.; Brennan, J.; McGuigan, P.; McKervey, M. A.; Tarbit, B. *J. Chem. Soc., Chem. Commun.* **1993**, 1220–1222.

(27) (a) Chattopadhyay, S. K.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2429–2454. (b) Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833–5871.

(28) The ratio of (*E*,*E*)-**33**:(*E*,*Z*)-**33** improved from 4:1 to 5:1 after purification by column chromatography.

(29) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580–3581.

SCHEME 9. Epimerization of (*E*)-1



Having confirmed that we had prepared the same diastereoisomer as Bohlmann, we now wished to confirm that (*E*)-**1** was the same diastereoisomer as the tetrahydrofuran isolated by Abraham from *C. cochlioides*.[7] Our ^{1}H NMR data are identical with those reported by Abraham in $CDCl_3$ and C_6D_6[7] and Seto in $CDCl_3$ (see the Supporting Information).[6] The ^{13}C NMR data in $CDCl_3$ were also identical. We observed the same NOE data reported by Abraham (performed in C_6D_6 as the resonances are more separated in this solvent).[7] We also confirmed that the metabolite isolated by Teuscher in 2005 has the same relative stereochemistry as our synthesized (*E*)-**1** by comparing our crude ^{1}H NMR spectrum with the ^{1}H NMR spectrum of aureonitol isolated from *C. globosum* in the solvent CD_3OD (see the Supporting Information).[8,30]

The specific rotation for our synthesized aureonitol was −6.9 (*c* 1, 23 °C, $CHCl_3$), which is in the region of the specific rotations reported by Abraham (−7.8, *c* 1, $CHCl_3$) and later by Teuscher (−8, *c* 1, $CHCl_3$).[7,8] The absolute configuration of our synthesized aureonitol is known to be (2*S*,3*R*,4*S*) around the tetrahydrofuran ring as the configuration at the 2-position is derived from (*S*)-serine. This supports Abraham's assignment of absolute configuration, and that Abraham and Teuscher had both also isolated the (2*S*,3*R*,4*S*)-enantiomer. More importantly, we had confirmed that our synthesized molecule was the same natural product isolated by Abraham and later Teuscher. It should be noted, however, that the absolute stereochemistry of the molecule isolated by Abraham and the molecule synthesized by us is not necessarily the same absolute configuration as that of the *Helichrysum* aureonitol, as Bohlmann never reported any optical rotation data for his isolate.[1]

Our synthesized (−)-aureonitol also has identical ^{1}H NMR and ^{13}C NMR data to those shown by a molecule recently isolated from *Chaetonium sp*. by Fatope.[31] From the information available, it would appear that Fatope isolated (+)-aureonitol, the enantiomer of **1**, owing to the specific rotation being of the opposite sign to that recorded by ourselves, Abraham,[7] and Teuscher.[8] In addition, Fatope determined the configuration at C-3 to be (*S*) by Mosher ester analysis (cf. Abraham determined the configuration at C-3 to be (*R*) by Mosher ester analysis).[31]

(30) Interestingly, purified aureonitol was insoluble in CD_3OD.

(31) Marwah, R. G.; Fatope, M. O.; Deadman, M. L.; Al-Maqbali, Y. M.; Husband, J. *Tetrahedron* **2007**, *63*, 8174–8180.

Conclusions

(−)-Aureonitol ((*E*)-**1**) has been synthesized for the first time as a single enantiomer in 14 steps from (*S*)-serine. The key step involved a Brønsted acid-promoted intramolecular allylation of aldehyde **11**. This reaction provided the required tetrahydrofuran framework with good diastereoselectivity, with the major diastereoisomer **18** containing the desired relative stereochemistry around the ring. Subsequent elaboration of the tetrahydrofuran **18** allowed the dienyl arms to be installed with moderate (*E*)-stereoselectivity. Julia-Kocienski olefination was found to offer the best stereoselectivity, and this could be further increased through heating the diene mixture in chloroform in the presence of iodine at reflux. Our synthesized (−)-aureonitol displays identical spectral data with those reported for aureonitol in the literature,[1,6−8] whereas **2**, prepared via an oxidation−reduction sequence of **1**, was shown to have markedly different NMR data to those reported in the literature. This comparison of data conclusively demonstrates that the structure of (−)-aureonitol is **1** and not its 3-epimer as it is currently described on the Chemical Database.

Experimental Section

(*S*)-Ethyl 3-*tert*-Butyldiphenylsilanyloxy-2-hydroxypropanoate (13). TBDPSCl (8.73 mL, 33.58 mmol) was added dropwise over 15 min to a stirred solution of (*S*)-ethyl glycerate **12** (4.50 g, 33.58 mmol) and imidazole (6.86 g, 100.75 mmol) in CH_2Cl_2 (70 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for a further 2 h, and then quenched by the addition of $NaHCO_3$ solution (70 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 70 mL). The combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by flash column chromatography (15% EtOAc in hexane) to afford silyl ether **13** as a viscous, colorless oil (9.74 g, 78%): R_f 0.21 (15% EtOAc in hexane); $[\alpha]^{23}_D$ +12.4 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 3425 s br (OH), 1738 s (C═O); δ_H (300 MHz) 1.03 (s, 9H), 1.30 (t, *J* 6.7, 3H), 3.15 (br s, 1H), 3.91 (A of ABX, $J_{A\text{-}B}$ = 10.4 Hz, $J_{A\text{-}X}$ = 2.9 Hz, 1H), 3.97 (B of ABX, $J_{B\text{-}A}$ = 10.4 Hz, $J_{B\text{-}X}$ = 2.7 Hz, 1H), 4.19−4.33 (stack, 3H), 7.33−7.57 (stack, 6H), 7.60−7.71 (stack, 4H); δ_C (75 MHz) 14.2 (CH_3), 19.2 (C), 26.6 (CH_3), 61.6 (CH_2), 65.8 (CH_2), 127.6 (CH), 127.7 (CH), 129.7 (CH), 132.8 (C), 133.0 (C), 135.4 (CH), 135.5 (CH), 172.8 (C); *m*/*z* (TOF ES+) 395.1 ([M + Na]$^+$, 100%); HRMS calcd for $C_{21}H_{28}NaO_4Si$ [M + Na]$^+$ 395.1655, found 395.1664. Anal. Calcd for $C_{21}H_{28}O_4Si$: C, 67.71; H, 7.58. Found: C, 67.87; H, 7.61.

(*S*)-Ethyl 3-*tert*-Butyldiphenylsilanyloxy-2-(4′-trimethylsilanyl-but-2′-ynyloxy)propanoate (15). TMSOTf (270 μL, 1.5 mmol) was added to a solution of trichloroacetimidate **14**[9e] (4.30 g, 15.0 mmol) and α-hydroxy ester **13** (8.37 g, 22.5 mmol) in cyclohexane (150 mL) at 0 °C. After warming to rt, the reaction mixture was stirred for 5 h and then quenched by the addition of $NaHCO_3$ solution (150 mL). The two phases were separated and the aqueous phase was extracted with Et_2O (2 × 150 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (6% EtOAc in hexane) afforded ether **15** as a colorless oil (4.84 g, 65%): R_f 0.34 (6% EtOAc in hexane); $[\alpha]^{23}_D$ −4.5 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 2212 w (C≡C), 1752 s (C═O); δ_H (300 MHz) 0.07 (s, 9H), 1.03 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.47 (t, *J* = 2.4 Hz, 2H), 3.87−4.00 (m, 2H), 4.16−4.38 (stack, 5H), 7.32−7.44 (stack, 6H), 7.58−7.68 (stack, 4H); δ_C (75 MHz) −2.1 (CH_3), 7.1 (CH_2), 14.2 (CH_3), 19.2 (C), 26.6 (CH_3), 58.2 (CH_2), 60.8 (CH_2), 64.6 (CH_2), 73.8 (C), 77.5 (CH), 85.8 (C), 127.6 (CH), 129.6 (CH), 133.1 (C), 133.2 (C), 135.50 (CH), 135.55 (CH), 170.6 (C); *m*/*z* (TOF

ES+) 519.2 ([M + Na]$^+$, 100%); HRMS calcd for $C_{28}H_{40}NaO_4Si_2$ [M + Na]$^+$ 519.2363, found 519.2367. Anal. Calcd for $C_{28}H_{40}O_4Si_2$: C, 67.70; H, 8.12. Found: 67.75; H, 7.77.

(*Z*,*S*)-Ethyl 3-*tert*-Butyldiphenylsilanyloxy-2-(4′-trimethylsilanylbut-2′-enyloxy)propanoate (16). Ra-Ni (a spatula tip) was added to a solution of alkyne **15** (4.50 g, 9.1 mmol) in EtOH (270 mL) at rt. The reaction flask was charged with H_2 gas (3 × vacuum−H_2 flushes) and the resulting suspension stirred for 5 min under an atmosphere of H_2. Filtration through Celite and removal of the solvent under reduced pressure left a residue, which was purified by flash column chromatography (6% EtOAc in hexane) to afford alkene **16** as a colorless oil (4.26 g, 94%): R_f 0.35 (10% EtOAc in hexane); $[\alpha]^{23}_D$ −7.8 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 1748 s (C═O), 1648 w (C═C); δ_H (300 MHz) −0.02 (s, 9H), 1.02 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.49 (d, *J* = 8.8 Hz, 2H), 3.90 (d, *J* = 5.5 Hz, 2H), 3.98−4.26 (stack, 5H), 5.43 (dt, *J* = 10.7, 7.0 Hz, 1H), 5.57−5.69 (m, 1H), 7.33−7.43 (stack, 4H), 7.62−7.70 (stack, 6H); δ_C (75 MHz) −1.9 (CH_3), 14.3 (CH_3), 19.2 [(CH_2), (C), coincident peaks)], 26.7 (CH_3), 60.8 (CH_2), 64.7 (CH_2), 65.9 (CH_2), 79.1 (CH), 123.0 (CH), 127.59 (CH), 127.60 (CH), 129.6 (CH), 130.5 (CH), 133.16 (C), 133.24 (C), 135.6 (CH), 135.7 (CH), 171.1 (C); *m*/*z* (TOF ES+) 521.3 ([M + Na]$^+$, 100%); HRMS calcd for $C_{28}H_{42}NaO_4Si_2$ [M + Na]$^+$ 521.2519, found 521.2503.

(*Z*,*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-(4′-trimethylsilanylbut-2′-enyloxy)propanal (11). DIBALH (5.1 mL of a 1.5 M solution in toluene, 7.7 mmol) was added dropwise over 30 min to a solution of ester **16** (3.50 g, 7.0 mmol) in CH_2Cl_2 (115 mL) at −78 °C. After 1 h, the reaction was quenched with MeOH (280 μL, 7.0 mmol) and H_2O (760 μL, 42 mmol) at −78 °C. The resulting slurry was warmed to rt and then filtered through $MgSO_4$ and Celite. Removal of the solvent under reduced pressure provided a yellow liquid, which was purified by flash column chromatography (8% EtOAc in hexane) to afford aldehyde **11** as a colorless oil (2.92 g, 92%): R_f 0.24 (8% EtOAc in hexane); $[\alpha]^{23}_D$ −6.4 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 1736 s (C═O), 1648 w (C═C); δ_H (300 MHz) −0.02 (s, 9H), 1.03 (s, 9H), 1.48 (d, *J* = 9.6 Hz, 2H), 3.79−3.86 (m, 1H), 3.88−3.94 (m, 2H), 4.12 (d, *J* = 6.6 Hz, 2H), 5.43 (dt, *J* = 11.0, 6.6 Hz, 1H), 5.59−5.72 (m, 1H), 7.33−7.45 (stack, 6H), 7.61−7.70 (stack, 4H), 9.74 (d, *J* = 1.5 Hz, 1H); δ_C (75 MHz) −1.9 (CH_3), 19.2 (C), 19.3 (CH_2), 26.7 (CH_3), 63.4 (CH_2), 66.1 (CH_2), 83.8 (CH), 122.7 (CH), 127.6 (CH), 127.7 (CH), 129.8 (CH), 131.0 (CH), 132.9 (C), 133.0 (C), 135.57 (CH), 135.61 (CH), 202.9 (CH); *m*/*z* (TOF ES+) 509.3 ([M + Na + MeOH]$^+$, 30%), 477.2 (100, [M + Na]$^+$); HRMS calcd for $C_{26}H_{38}NaO_3Si_2$ [M + Na]$^+$ 477.2257, found 477.2253.

(2*S*,3*R*,4*S*)-2-*tert*-Butyldiphenylsilanyloxymethyl-3-hydroxy-4-vinyltetrahydrofuran (18) and (2*S*,3*R*,4*R*)-2-*tert*-Butyldiphenylsilanyloxymethyl-3-hydroxy-4-vinyltetrahydrofuran (17). $MeSO_3H$ (0.4 mL, 6.1 mmol) was added to a solution of aldehyde **11** (2.50 g, 5.5 mmol) in $CHCl_3$ (55 mL) at −60 °C. After 5 min, the reaction was quenched by the addition of $NaHCO_3$ solution (55 mL) at −78 °C. The reaction mixture was warmed to rt over 30 min. The two phases were then separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 55 mL). The combined organic extracts were washed with H_2O (55 mL) and brine (55 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded a residue, which was purified by flash column chromatography to provide a mixture of alcohol diastereoisomers **18** and **17** (8:1, **18**:**17**) as a colorless oil, which was inseparable by flash column chromatography (1.81 g, 86%); data on the mixture of diastereoisomers unless specified otherwise: R_f 0.29 (25% EtOAc in hexane); $[\alpha]^{23}_D$ −5.0 (*c* 1.00, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3481 s br (OH), 1642 w (C═C); major diastereoisomer **18**: δ_H (300 MHz) 1.06 (s, 9H), 1.25 (s, 1H), 2.85 (app. quintet, *J* = 8.1 Hz, 1H), 3.69 (app. t, *J* = 9.2 Hz, 1H), 3.73 (stack, 3H), 4.03−4.11 (stack, 2H), 5.13 (d, *J* = 10.3 Hz, 1H), 5.20 (d, *J* = 16.9 Hz, 1H), 5.66−5.80 (m, 1H), 7.31−7.48 (stack, 6H), 7.61−7.71 (stack, 4H); selected data for minor diastereoisomer **17**: δ_H (300 MHz) 5.81−5.92 (m, 1H); major diastereoisomer **18**: δ_C (75 MHz) 19.1 (C), 26.8 (CH_3), 52.2 (CH), 64.4 (CH_2), 71.1 (CH_2), 77.8 (CH), 84.3 (CH), 117.1 (CH_2), 127.62 (CH), 127.64 (CH), 129.6 (CH), 129.7 (CH), 133.0 (C), 133.1 (C), 135.4 (CH), 135.5 (CH), 136.1 (CH); selected data for the minor diastereoisomer **17**: δ_C (75 MHz) 19.1 (C), 26.7 (CH_3), 48.3 (CH), 64.5 (CH_2), 70.6 (CH_2), 75.2 (CH), 86.6 (CH), 118.8 (CH_2); *m*/*z* (TOF ES+) 405.2 ([M + Na]$^+$, 100%); HRMS calcd for $C_{23}H_{30}NaO_3Si$ [M + Na]$^+$ 405.1862, found 405.1842.

(2*S*,3*R*,4*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-*tert*-butyldiphenylsilanyloxymethyl-4-vinyltetrahydrofuran (9). TBDPSCl (1.02 mL, 3.93 mmol) was added dropwise over 15 min to a stirred solution of alcohol **18** (and **17**) (1.50 g, 3.93 mmol, **18**:**17**, 8:1) and imidazole (813 mg, 11.94 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The reaction mixture was warmed to rt, stirred for a further 3 h, and then quenched by the addition of $NaHCO_3$ solution (9 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 9 mL). The combined organic extracts were washed with brine (9 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (6% Et_2O in hexane) and then by HPLC to afford silyl ether **9** as a viscous, colorless oil (2.05 g, 84%): R_f 0.30 (6% Et_2O in hexane); $[\alpha]^{23}_D$ −43.2 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 1642 w (C═C); δ_H (400 MHz) 1.14 (s, 9H), 1.23 (s, 9H), 2.99−3.09 (m, 1H), 3.58 (A of ABX, $J_{A\text{-}B}$ = 11.1 Hz, $J_{A\text{-}X}$ = 4.9 Hz, 1H), 3.74 (B of ABX, $J_{B\text{-}A}$ = 11.1 Hz, $J_{B\text{-}X}$ unresolved, 1H), 3.88 (app. t, *J* = 7.1 Hz, 1H), 4.20−4.29 (stack, 2H, 2-*H*), 4.39 (s with unresolved fine coupling, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.97 (d, *J* = 15.5 Hz, 1H), 5.54−5.61 (m, 1H), 7.39−7.55 (stack, 12H), 7.71−7.85 (stack, 8H); δ_C (75 MHz) 19.10 (C), 19.11 (C), 26.8 (CH_3), 27.0 (CH_3), 53.3 (CH), 64.2 (CH_2), 71.6 (CH_2), 79.4 (CH), 87.2 (CH), 116.2 (CH_2), 127.52 (CH), 127.55 (CH), 127.6 (CH), 129.4 (CH), 129.7 (CH), 133.33 (C), 133.37 (C), 133.42 (C), 133.6 (C), 135.6 (CH), 135.8 (CH), 135.9 (CH), 136.8 (CH); *m*/*z* (TOF ES+) 643.3 ([M + Na]$^+$, 100%); HRMS calcd for $C_{39}H_{48}NaO_3Si_2$ [M + Na]$^+$ 643.3040, found 643.3030.

(2*S*,3*R*,4*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-*tert*-butyldiphenylsilanyloxymethyl-4-formyltetrahydrofuran (10). OsO_4 (121 μL of a 4% w/w solution in H_2O, 0.019 mmol) was added to a stirred solution of alkene **9** (600 mg, 0.96 mmol) and NMO (225 mg, 1.92 mmol) in acetone:H_2O (5:1, 10 mL) at rt. After 2 h, the reaction mixture was quenched by the addition of $NaHSO_3$ solution (10 mL) and then diluted with EtOAc (50 mL) and H_2O (35 mL). The phases were separated and the organic phase was washed with H_2O (2 × 10 mL) and brine (10 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded a viscous, colorless oil, which was dissolved in THF:H_2O (7:3, 10 mL). $NaIO_4$ (411 mg, 1.92 mmol) was added. After being stirred for 15 min at rt, the reaction mixture was diluted with EtOAc (25 mL) and H_2O (25 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic extracts were washed with brine (25 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded aldehyde **10** as a viscous, colorless oil (514 mg, 86% over two steps), which was used in the next step without further purification: R_f 0.65 (15% EtOAc in hexane); $[\alpha]^{23}_D$ +4.5 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 1727s (C═O); δ_H (300 MHz) 0.92 (s, 9H), 1.05 (s, 9H), 2.85−2.92 (m, 1H), 3.42 (A of ABX, $J_{A\text{-}B}$ = 11.2 Hz, $J_{A\text{-}X}$ = 4.8 Hz, 1H), 3.55 (B of ABX, $J_{B\text{-}A}$ = 11.2 Hz, $J_{B\text{-}X}$ = 3.0 Hz, 1H), 3.98 (app. q, *J* = 4.1 Hz, 1H), 4.05 (A of ABX, $J_{A\text{-}B}$ = 9.2 Hz, $J_{A\text{-}X}$ = 7.0 Hz, 1H), 4.22 (B of ABX, $J_{B\text{-}A}$ = 9.2 Hz, $J_{B\text{-}X}$ = 3.7 Hz, 1H), 4.68 (t, *J* = 3.7 Hz, 1H), 7.20−7.48 (stack, 12H), 7.50−7.64 (stack, 8H), 9.04 (d, *J* = 1.5 Hz, 1H); δ_C (75 MHz) 19.08 (C), 19.10 (C), 26.7 (CH_3), 26.9 (CH_3), 61.4 (CH), 63.4 (CH_2), 66.8 (CH_2), 74.8 (CH), 87.7 (CH), 127.59 (CH), 127.61 (CH), 127.86 (CH), 127.92 (CH), 129.6 (CH), 130.0 (CH), 130.1 (CH), 132.9 (C), 133.0 (C), 133.1 (C), 133.2 (C), 135.55 (CH), 135.59 (CH), 135.7 (CH), 135.8 (CH), 199.7 (CH); *m*/*z* (TOF ES+) 677.3 ([M + MeOH + Na]$^+$, 100%), 645.3 (35, [M + Na]$^+$); HRMS calcd for $C_{38}H_{46}NaO_4Si_2$ [M + Na]$^+$ 645.2832, found 645.2844.

(1′*E*,3′*E*,2*S*,3*R*,4*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-*tert*-butyldiphenylsilanyloxymethyl-4-penta-1′,3′-dienyltetrahydrofuran ((*E*,*E*)-8) and (1′*Z*,3′*E*,2*S*,3*R*,4*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-*tert*-butyldiphenylsilanyloxymethyl-4-penta-1′,3′-dienyltetrahydrofuran ((*Z*,*E*)-8). KHMDS (140 μL of a 0.5 M solution in toluene, 0.70 mmol) was added dropwise to a cooled (−78 °C) solution of (*E*)-crotyl sulfone **32** (203 mg, 0.77 mmol) in THF (5 mL). After 30 min, a cooled (−78 °C) solution of aldehyde **10** (400 mg, 0.64 mmol) in THF (5 mL) was added dropwise over 1 min. The reaction mixture was stirred at −78 °C for 1 h and then quenched by the addition of H_2O (10 mL). After warming to rt over 30 min, the phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded dienes (*E*,*E*)-**8** and (*Z*,*E*)-**8** as a ∼2.5:1 mixture of geometric isomers, which were inseparable by flash column chromatography. This mixture was dissolved in $CHCl_3$ (2 mL) before I_2 (16 mg, 0.064 mmol) was added. The reaction mixture was stirred at reflux for 1 h. After cooling to rt, the reaction mixture was washed with $Na_2S_2O_3$ solution (2 × 2 mL) and brine (2 mL) and then dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded (*E*,*E*)-**8** and (*Z*,*E*)-**8** as a ∼4:1 mixture of geometric isomers as a colorless oil (342 mg, 81%); data for the mixture unless specified otherwise: R_f 0.27 (6% EtOAc in hexane); ν_{max} (film)/cm^{-1} 1603 w (C═C), 1589 w (C═C); major stereoisomer (*E*,*E*)-**8**: δ_H (300 MHz) 0.94 (s, 9H), 1.02 (s, 9H), 1.69 (d, J = 6.6 Hz, 3H), 2.74−2.86 (m, 1H), 3.40 (A of ABX, $J_{A\text{-}B}$ = 11.0 Hz, $J_{A\text{-}X}$ = 4.8 Hz, 1H), 3.54 (B of ABX, $J_{B\text{-}A}$ = 11.0 Hz, $J_{B\text{-}X}$ = 3.3 Hz, 1H), 3.63 (A of ABX, $J_{A\text{-}B}$ = 8.5 Hz, $J_{A\text{-}X}$ = 6.3 Hz, 1H), 3.97−4.07 (stack, 2H), 4.14 (app. t, J 4.4, 1H), 5.01 (dd, J = 14.3, 8.8 Hz, 1H), 5.43 (dq, J = 13.6, 6.6 Hz, 1H), 5.55−5.75 (stack, 2H), 7.25−7.42 (stack, 12H), 7.49−7.69 (stack, 8H); selected data for minor stereoisomer (*Z*,*E*)-**8**: δ_H (300 MHz) 1.60 (d, J = 6.6 Hz, 3H); major stereoisomer (*E*,*E*)-**8**: δ_C (75 MHz) 18.0 (CH_3), 19.1 (C), 19.2 (C), 26.8 (CH_3), 26.9 (CH_3), 52.4 (CH), 64.2 (CH_2), 72.0 (CH_2), 79.6 (CH), 87.0 (CH), 127.5 (CH), 127.9 (CH), 129.1 (CH), 129.5 (CH), 129.7 (CH), 131.3 (CH), 132.2 (CH), 133.4 (C), 133.5 (C), 135.6 (CH), 135.9 (CH), 136.1 (CH); *m*/*z* (TOF ES+) 683.3 ([M]$^+$, 100%); HRMS calcd for $C_{42}H_{52}NaO_3Si_2$ [M + Na]$^+$ 683.3353, found 683.3381.

(1′*E*,3′*E*,2*S*,3*R*,4*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-hydroxymethyl-4-penta-1′,3′-dienyltetrahydrofuran ((*E*,*E*)-33) and (1′*Z*,3′*E*,2*S*,3*R*,4*S*)-3-*tert*-Butyldiphenylsilanyloxy-2-hydroxymethyl-4-penta-1′,3′-dienyltetrahydrofuran ((*Z*,*E*)-33). HF−pyridine (0.1 mL of a 70% solution in pyridine) was added dropwise over 1 min to a cooled (0 °C) solution of a 4:1 mixture of bis-silyl ethers (*E*,*E*)-**8** and (*Z*,*E*)-**8** (120 mg, 0.18 mmol) in THF/pyridine (1:1, 2 mL). The reaction mixture was stirred at this temperature for 30 min, then diluted with EtOAc (10 mL) and washed with $CuSO_4$ solution (3 × 5 mL), H_2O (2 × 5 mL), and brine (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford alcohols (*E*,*E*)-**33** and (*Z*,*E*)-**33** as a 4:1 mixture. Purification by flash column chromatography (20% EtOAc in hexane) increased the ratio of (*E*,*E*)-**33** to (*Z*,*E*)-**33** to 5:1, a mixture that was obtained as a colorless oil (65 mg, 82%); data for the mixture unless specified otherwise: R_f 0.28 (20% EtOAc in hexane); ν_{max}(film)/cm^{-1} 3344 s br (OH), 1662 m (C═C); data for major stereoisomer (*E*,*E*)-**33**: δ_H (300 MHz) 1.04 (s, 9H), 1.71 (d, J = 7.0 Hz, 3H), 3.85−3.94 (m, 1H), 3.18 (A of ABX, $J_{A\text{-}B}$ = 12.2 Hz, $J_{A\text{-}X}$ = 5.1 Hz, 1H), 3.36 (B of ABX, $J_{B\text{-}A}$ = 12.2 Hz, $J_{B\text{-}X}$ unresolved, 1H), 3.61 (A of ABX, $J_{A\text{-}B}$ = 8.5 Hz, $J_{A\text{-}X}$ = 5.9 Hz, 1H), 3.86−3.94 (stack, 2H), 4.05 (B of ABX, $J_{B\text{-}A}$ = 8.5 Hz, $J_{B\text{-}X}$ = 7.0 Hz, 1H), 5.07 (dd, J = 14.3, 8.8 Hz, 1H), 5.50 (dq, J = 13.6, 6.6 Hz, 1H), 5.70−5.85 (stack, 2H), 7.29−7.48 (stack, 6H), 7.57−7.69 (stack, 4H); selected data for minor stereoisomer (*Z*,*E*)-**33**: δ_H (300 MHz) 1.62 (d, J = 6.6 Hz, 3H); data for major stereoisomer (*E*,*E*)-**33**: δ_C (75 MHz) 18.0 (CH_3), 19.1 (C), 26.9 (CH_3), 52.1 (CH), 62.3 (CH_2), 71.5 (CH_2), 79.3 (CH), 86.6 (CH), 127.6 (CH), 127.7 (CH), 128.5 (CH), 128.7 (CH), 129.8 (CH), 129.9 (CH), 131.0 (CH), 132.4 (CH), 133.3 (C), 133.49 (C), 135.9 (CH), 136.0 (CH); *m*/*z* (TOF ES+) 445 ([M + Na]$^+$, 100%); HRMS calcd for $C_{26}H_{34}NaO_3Si$ [M + Na]$^+$ 445.2175, found 445.2182.

(1′*E*,1″*E*,3″*E*,3*S*,3*R*,4*S*)-2-Buta-1′,3′-dienyl-3-*tert*-butyldiphenylsilanyloxy-4-penta-1″,3″-dienyltetrahydrofuran ((*E*)-35) and (1′*Z*,1″*E*,3″*E*,3*S*,3*R*,4*S*)-2-buta-1′,3′-dienyl-3-*tert*-butyldiphenylsilanyloxy-4-penta-1″,3″-dienyltetrahydrofuran ((*Z*)-35). TPAP (2.9 mg, 0.011 mmol) was added to a cooled (0 °C) solution of alcohol **33** (46 mg, 0.11 mmol), NMO (26 mg, 0.22 mmol), and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at this temperature for 30 min and then filtered through a short silica plug (washing with CH_2Cl_2). Concentration of the filtrate under reduced pressure afforded aldehyde **7** (42 mg, quant) as a colorless oil, which was immediately dissolved in THF (1 mL) and cooled to −78 °C. KHMDS (220 μL of a 0.5 M solution in toluene, 0.109 mmol) was added dropwise to a cooled (−78 °C) solution of allyl sulfone **34** (30 mg, 0.119 mmol) in THF (1 mL). After 30 min, the cooled (−78 °C) solution of aldehyde **7** (42 mg, 0.100 mmol) in THF (5 mL) was added dropwise over 1 min. The reaction mixture was stirred at −78 °C for 1 h and then diluted with EtOAc (9 mL) and quenched by the addition of H_2O (10 mL). After warming to rt over 30 min, the phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded dienes (*E*)-**35** and (*Z*)-**35** as a 2:1 mixture, which were separated by flash column chromatography to afford, in order of elution, major diene (*E*)-**35** as a colorless oil (28 mg, 57%): R_f 0.27 (70% CH_2Cl_2 in hexane); $[\alpha]^{23}_D$ −14.8 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 1605 w (C═C); δ_H (300 MHz) 1.04 (s, 9H), 1.70 (d, J = 6.6 Hz, 3H), 2.75−2.87 (m, 1H), 3.65 (A of ABX, $J_{A\text{-}B}$ = 8.5 Hz, $J_{A\text{-}X}$ = 5.5 Hz, 1H), 3.84 (app. t, J = 4.4 Hz, 1H), 4.08 (B of ABX, $J_{B\text{-}A}$ = 8.5 Hz, $J_{B\text{-}X}$ = 7.0 Hz, 1H), 4.26 (dd, J = 6.6, 4.4 Hz, 1H), 4.99−5.15 (stack, 3H), 5.25 (dd, J = 14.3, 7.0 Hz, 1H), 5.49 (dq, J = 14.3, 6.6 Hz, 1H), 5.65−5.88 (stack, 2H), 5.98−6.22 (stack, 2H), 7.29−7.45 (stack, 6H), 7.53−7.70 (stack, 4H); δ_C (75 MHz) 18.0 (CH_3), 26.9 (CH_3), 29.7 (C), 52.3 (CH), 71.6 (CH_2), 83.8 (CH), 86.6 (CH), 117.4 (CH_2), 127.566 (CH), 127.574 (CH), 127.6 (CH), 129.2 (CH), 129.72 (CH), 129.75 (CH), 131.2 (CH), 131.7 (CH), 132.3 (CH), 132.6 (CH), 133.5 (C), 133.6 (C), 136.08 (CH), 136.11 (CH), 136.3 (CH); *m*/*z* (TOF ES+) 467.2 ([M + Na]$^+$, 100%); HRMS calcd for $C_{29}H_{36}NaO_2Si$ [M + Na]$^+$ 467.2382, found 467.2388; and then minor diene (*Z*)-**35** as a colorless oil (14 mg, 28%): R_f 0.25 (70% CH_2Cl_2 in hexane); $[\alpha]^{23}_D$ −27.6 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 1654 w (C═C), 1590 w (C═C); δ_H (300 MHz) 1.04 (s, 9H), 1.69 (d, J = 5.5 Hz, 3H), 2.68−2.82 (m, 1H), 3.67 (A of ABX, $J_{A\text{-}B}$ = 8.5 Hz, $J_{A\text{-}X}$ = 4.8 Hz, 1H), 3.81−3.90 (m, 1H), 4.06 (B of ABX, $J_{B\text{-}A}$ = 8.5 Hz, $J_{B\text{-}X}$ = 6.6 Hz, 1H), 4.75 (dd, J = 8.8, 4.4 Hz, 1H), 4.98−5.31 (stack, 4H), 5.44 (dd, J = 15.1, 7.0 Hz, 1H), 5.57 (d, J = 15.5, 10.7 Hz, 1H), 5.66−5.86 (m, 1H), 6.04 (app. t, J = 11.4 Hz, 1H), 6.73 (dt, J = 16.9, 11.0 Hz, 1H), 7.28−7.45 (stack, 6H), 7.52−7.71 (stack, 4H); δ_C (75 MHz) 18.0 (CH_3), 19.1 (C), 26.9 (CH_3), 52.1 (CH), 71.5 (CH_2), 82.1 (CH), 84.4 (CH), 119.3 (CH_2), 127.44 (CH), 127.47 (CH), 127.54 (CH), 128.3 (CH), 129.1 (CH), 129.5 (CH), 129.67 (CH), 129.69 (CH), 129.73 (CH), 131.1 (CH), 132.0 (CH), 132.1 (CH), 132.7 (CH), 133.2 (C), 133.7 (C), 136.0 (CH), 136.1 (CH); *m*/*z* (TOF ES+) 467.3 ([M + Na]$^+$, 100%); HRMS calcd for $C_{29}H_{36}NaO_2Si$ [M + Na]$^+$ 467.2382, found 467.2378.

(1′*E*,1″*E*,3″*E*,2*S*,3*R*,4*S*)-2-Buta-1′,3′-dienyl-3-hydroxy-4-penta-1″,3″-dienyl-tetrahydrofuran ((−)-Aureonitol; (*E*)-1). TBAF (140 μL of a 1.0 M solution in THF, 0.14 mmol) was added dropwise over 1 min to a cooled (0 °C) solution of silyl ether (*E*)-**35** (30 mg, 0.067 mmol) in THF (1 mL). The reaction mixture was warmed to rt, stirred for 1 h, and then diluted with EtOAc (9 mL). H_2O (10 mL) was added and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 10 mL) and the combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a residue that

was purified by flash column chromatography (25% EtOAc in hexane) to afford alcohol (*E*)-**1** as a white solid (13 mg, 91%): mp 64−65 °C (lit.[7] mp 65 °C); R_f 0.22 (25% EtOAc in hexane); $[\alpha]^{23}_D$ −6.9 (*c* 1.00, $CHCl_3$) (lit.[7] −7.8 (*c* 1.00, $CHCl_3$)); ν_{max} (film)/cm^{-1} 3405 s br (OH), 1605 w (C=C); δ_H (500 MHz) 1.75 (d with unresolved fine coupling, *J* = 6.6 Hz, 3H, 5″-*H*), 1.84 (s (br), 1H, O*H*), 2.85 (app. pentet, *J* = 8.1 Hz, 1H, 4-*H*), 3.72 (app. t, *J* = 8.4 Hz, 1H, 5-H_a), 3.76 (app. t, *J* = 7.2 Hz, 1H, 3-*H*), 4.11 (app. t, *J* = 8.4 Hz, 1H, 5-H_b), 4.13 (app. t, *J* = 7.2 Hz, 1H, 2-*H*), 5.12 (d with unresolved fine coupling, *J* = 9.2 Hz, 1H, 4′-H_{cis}), 5.24 (d with unresolved fine coupling, *J* = 16.0 Hz, 1H, 4′-H_{trans}), 5.43 (dd, *J* = 15.1, 8.8 Hz, 1H, 1″-*H*), 5.63−5.76 (stack, 2H, 1′-*H*, 4″-*H*), 6.03 (dd with unresolved fine coupling, *J* = 15.1, 10.4 Hz, 1H, 3″-*H*), 6.15 (dd, *J* = 15.1, 10.4 Hz, 1H, 2″-*H*), 6.28−6.41 (stack, 2H, 2′-*H*, 3′-*H*); δ_H (500 MHz, C_6D_6) 1.61 (d, *J* = 7.0 Hz, 3H, 5″-*H*), 2.60 (app. pentet, *J* = 8.1 Hz, 1H, 4-*H*), 3.46 (app. t, *J* = 6.4 Hz, 1H, 3-*H*), 3.62 (app. t, *J* = 8.3 Hz, 1H, 5-H_a), 3.97 (app. t, *J* = 8.4 Hz, 1H, 5-H_b), 4.15 (app. t, *J* = 6.4 Hz, 1H, 2-*H*), 4.99 (d, *J* = 9.7 Hz, 1H, 4′-H_{cis}), 5.12 (d, *J* = 17.1 Hz, 1H, 4′-H_{trans}), 5.26 (dd, *J* = 14.5, 8.8 Hz, 1H, 1″-*H*), 5.51 (dq, *J* = 14.2, 6.8 Hz, 1H, 4″-*H*), 5.73 (dd, *J* = 15.2, 6.4 Hz, 1H, 1′-*H*), 5.94−6.06 (stack, 2H, 3″-*H*, 2″-*H*), 6.31 (dt, *J* = 16.9, 10.3 Hz, 1H, 3′-*H*), 6.41 (dd, *J* = 14.9, 10.6 Hz, 1H, 2′-*H*); δ_H (500 MHz, CD_3OD) 1.73 (d, *J* = 6.2 Hz, 3H, 5″-*H*), 2.80 (app. pentet, *J* = 7.7 Hz, 1H, 4-*H*), 3.65−3.74 (stack, 2H, 3-*H*, 5-H_a), 4.02−4.10 (stack, 2H, 2-*H*, 5-H_b), 5.10 (d, *J* = 9.6 Hz, 1H, 4′-H_{cis}), 5.23 (d, *J* 16.0, 1H, 4′-H_{trans}), 5.46 (dd, *J* = 14.9, 8.4 Hz, 1H, 1″-*H*), 5.66 (dq, *J* = 14.9, 6.8 Hz, 1H, 4″-*H*), 5.73 (dd, *J* = 14.9, 6.9 Hz, 1H, 1′-*H*), 5.98−6.18 (stack, 2H, 3″-*H*, 2″-*H*), 6.29−6.42 (stack, 2H, 2′-*H*, 3′-*H*); δ_C (125 MHz) 18.0 (CH_3, *C*-5″), 51.5 (CH, *C*-4), 71.0 (CH_2, *C*-5), 81.5 (CH, *C*-3), 84.7 (CH, *C*-2), 118.2 (CH_2, *C*-4′), 128.2 (CH, *C*-1″), 129.3 (CH, *C*-4″), 130.8 (CH, *C*-3″), 131.5 (CH, *C*-1′), 133.2 (CH, *C*-2″), 133.3 (CH, *C*-2′), 136.1 (CH, *C*-3′); *m*/*z* (TOF ES−) 205.1 ([M − H]$^-$, 100%); HRMS calcd for $C_{13}H_{17}O_2$ [M − H]$^-$ 205.1229, found 205.1236.

(1′*Z*,1″*E*,3″*E*,2*S*,3*R*,4*S*)-2-Buta-1′,3′-dienyl-3-hydroxy-4-penta-1″,3″-dienyltetrahydrofuran ((*Z*)-1). TBAF (70 μL of a 1.0 M solution in THF, 0.70 mmol) was added dropwise over 1 min to a cooled (0 °C) solution of silyl ether (*Z*)-**35** (14 mg, 0.032 mmol) in THF (1 mL). The reaction mixture was warmed to rt. After 1 h, EtOAc (9 mL) and H_2O (10 mL) were added. The phases were separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a residue, which was filtered through a short plug of silica (washing with 25% EtOAc in hexane). Concentration under reduced pressure afforded alcohol (*Z*)-**1** as a colorless oil, which was immediately dissolved in $CHCl_3$ (1 mL). I_2 (0.76 mg, 0.003 mmol) was added and the reaction mixture was stirred at reflux for 1 h. After cooling to rt, the reaction mixture was washed with $Na_2S_2O_3$ solution (2 × 2 mL) and brine (2 mL) and then dried ($MgSO_4$). Filtration and concentration under reduced pressure afforded a 6:1 mixture of (*E*)-**1** (aureonitol) and (*Z*)-**1**. Purification by flash column chromatography (25% EtOAc in hexane) afforded (*E*)-**1** as a white solid (5 mg, 75%).

(1′*E*,1″*E*,3″*E*,2*S*,3*S*,4*S*)-2-Buta-1′,3′-dienyl-3-hydroxy-4-penta-1″,3″-dienyltetrahydrofuran (2). Dess−Martin periodinane (10 mg, 0.024 mmol) was added to a solution of alcohol (*E*)-**1** (2.5 mg, 0.012 mmol) in CH_2Cl_2 (1 mL) at rt. The reaction mixture was stirred for 30 min and then diluted with CH_2Cl_2 (5 mL) and quenched with $NaHCO_3$ solution (3 mL) and $Na_2S_2O_3$ solution (3 mL) and stirred for a further 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 6 mL). The combined organic extracts were washed with H_2O (3 mL) and brine (6 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure produced a residue, which was dissolved in THF (1 mL). After cooling to −78 °C, L-Selectride (12 μL of a 1.0 M solution in THF, 0.012 mmol) was added dropwise over 5 min. The reaction mixture was stirred at −78 °C for 1 h and then diluted with Et_2O (5 mL) before being quenched with hydrochloric acid (2 M, 6 mL). After stirring for 30 min, the phases were separated and the aqueous phase was extracted with Et_2O (2 × 6 mL). The combined organic extracts were washed with H_2O (6 mL) and brine (6 mL) and dried over $MgSO_4$. Concentration under reduced pressure produced a mixture of alcohols (>10:1 **2**:(*E*)-**1**), which was purified by flash column chromatography (25% EtOAc in hexane) to afford major alcohol **2** as a colorless semisolid (2.4 mg, 91%): R_f 0.24 (25% EtOAc in hexane); $[\alpha]^{23}_D$ −11.2 (*c* 1.00, $CHCl_3$); ν_{max} (film)/cm^{-1} 3408 s br (OH), 1605 w (C=C); δ_H (300 MHz) 1.72 (d, *J* = 6.6 Hz, 3H), 2.95−3.14 (m, 1H), 3.85 (app. q, *J* = 8.7 Hz, 1H), 3.99 (app. q, *J* = 8.3 Hz, 1H), 4.04−4.17 (m, 1H), 4.44−4.54 (m, 1H), 5.11 (d, *J* = 7.7 Hz, 1H), 5.23 (d, *J* = 15.8 Hz, 1H), 5.55−5.83 (stack, 3H), 5.98−6.20 (stack, 2H), 6.30−6.60 (stack, 2H); δ_C (75 MHz) 18.0 (CH_3), 48.9 (CH), 70.5 (CH_2), 75.7 (CH), 83.7 (CH), 118.2 (CH_2), 125.1 (CH), 128.6 (CH), 129.3 (CH), 131.1 (CH), 134.0 (CH), 134.2 (CH), 136.1 (CH); *m*/*z* (TOF ES−) 205.2 ([M − H]$^-$, 100%); HRMS calcd for $C_{13}H_{17}O_2$ [M − H]$^-$ 205.1229, found 205.1223.

Acknowledgment. We thank the Engineering and Physical Sciences Research Council and the University of Birmingham for a studentship (to P.J.J.), Astra Zeneca for an unrestricted award (to L.R.C), Dr. David Lindsay (University of Reading, United Kingdom) for the generous gift of metathesis catalysts **20** and **21**, and Professor Majekodunmi Fatope (Sultan Qaboos University, Oman) for providing NMR spectra of the tetrahydrofuran metabolite isolated from *Chaetomium* sp.

Supporting Information Available: Chiral HPLC analysis of tetrahydrofuran **18**, attempted dienylation of aldehyde **10** with phosphorus olefination methods, general experimental details, experimental procedures and compound characterization data for **12**, **27**, **31**, **32**, and **34**, scanned ^{1}H NMR spectra and ^{13}C NMR spectra for all new compounds, and tables and scanned spectra comparing the NMR data of synthetic aureonitol with those reported by Bohlmann, Abraham, Teuscher, Fatope, and Seto. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801338T