Total Synthesis of Brevetoxin A: Part 4: Final Stages and Completion

K. C. Nicolaou,* Janet L. Gunzner, Guo-qiang Shi, Konstantinos A. Agrios, Peter Gärtner, and Zhen Yang[a]

Abstract: The total synthesis of brevetoxin A is described. Our methodology of palladium-catalyzed couplings with cyclic ketene acetal phosphates was utilized to functionalize nine-membered ring lactone **4** followed by a [4+2] singlet oxygen addition to the resulting 1,3-diene (**6**). The product endoperoxide (**7**) was transformed into coupling partners **3a** and **3b** to be reacted with aldehyde **2**. Our first attempted union of **3a** and aldehyde **2** failed, most probably due to steric hindrance, which led us to explore other olefination coupling reactions. Horner–Wittig type coupling was found to be successful on advanced model systems: diphenylphosphine oxides **21** and **28** were each coupled with aldehyde **2**. Key intermediates **3b** and **2** were successfully coupled and ring F oxocene (**44**) was cyclized through the hydroxy dithioketal cyclization methodology. The final manipulations were then executed to complete the first total synthesis of brevetoxin A.

Keywords: brevetoxin A · synthetic methods · total synthesis

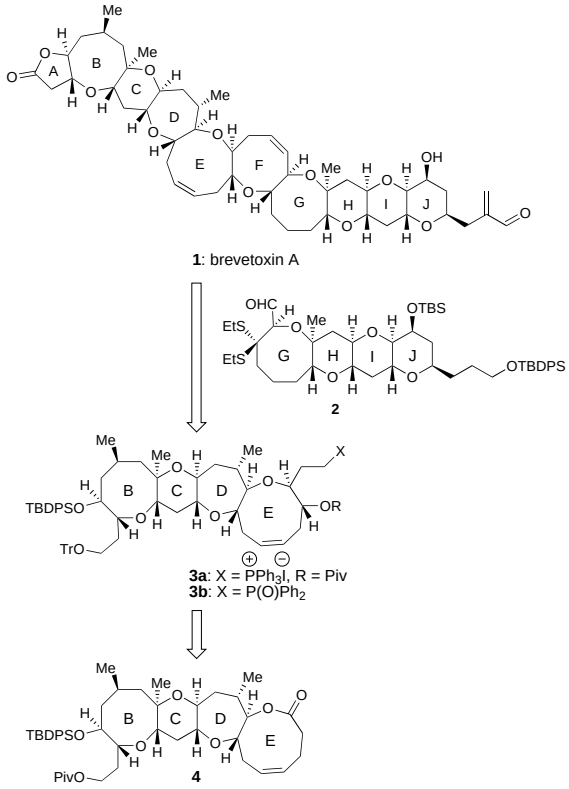
Introduction

In the preceding three papers,[1–3] we described strategies and explorations that projected well for a final approach to the total synthesis of brevetoxin A (**1**, Scheme 1). Besides providing support for our convergent strategy shown in Scheme 1, these studies rendered readily available key intermediates **2** and **4** required for the adopted plan. In this article, we describe the conversion of key intermediate **4** to **3a** and **3b**, and the final maneuvers that led to the total synthesis of brevetoxin A (**1**).

Results and Discussion

The plan

Having assessed all the information gathered during the brevetoxin A project,[1–3] we were confident that the plan shown in Scheme 1 would allow us to complete the total synthesis of brevetoxin A (**1**). The ylide, derived from the phosphonium iodide **3a**, was the first targeted intermediate. As we will see below, this ylide did not perform as well as



Scheme 1. Final strategy for the total synthesis of brevetoxin A (**1**).

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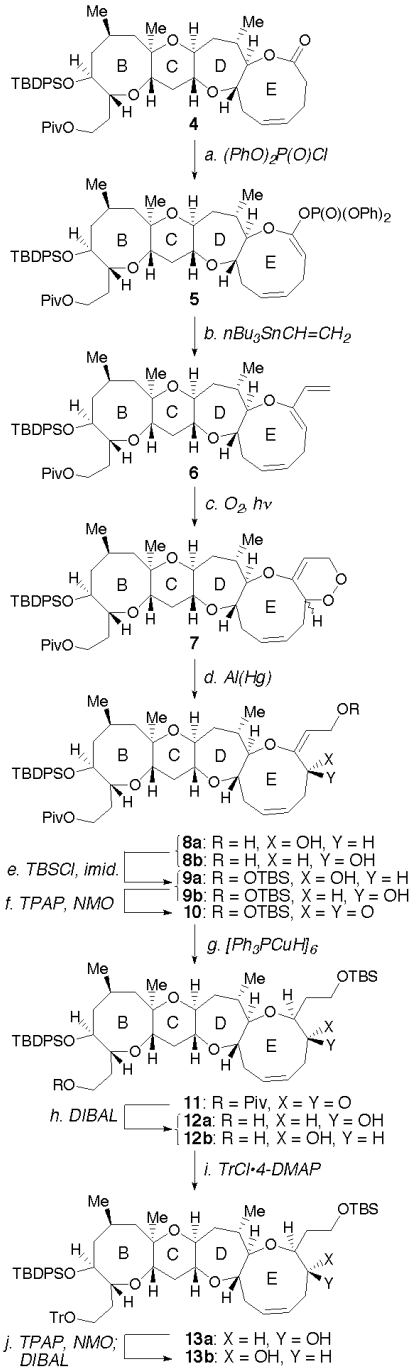
expected, and was later substituted for the less bulky, more reactive anion derived from diphenylphosphine oxide **3b**,[4] which allowed facile coupling of the two fragments of the target molecule. The first task at hand, therefore, was the functionalization of lactone **4** to an ether carrying the appropriate appendages on ring E.

The first attempt: phosphonium salt 3a

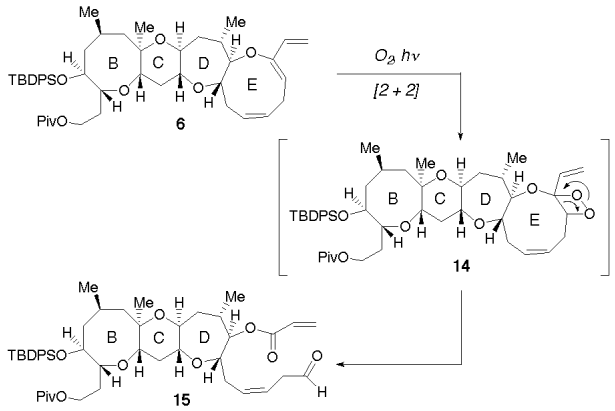
Schemes 2 and 4 present the constructions of BCDE intermediates **12** and **3a** respectively. Thus, lactone **4** was converted[5] to enol phosphate **5**, by treatment with KHMDS then $(PhO)_2P(O)Cl$, and subsequently[5] to diene **6** by coupling of the latter intermediate (**5**) with nBu$_3$SnCH=CH$_2$ in the presence of [Pd(PPh$_3$)$_4$] catalyst and LiCl (81% yield for two steps). Reaction of singlet oxygen (generated from oxygen, halogen lamp and TPP) resulted in selective functionalization of the diene system in **6** and formation of endoperoxide **7** (mixture of diastereoisomers) as the major product.[6] In addition to **7**, the ester aldehyde **15** (Scheme 3) was isolated from this reaction (30% yield). This product was presumably formed by a rupture of ring E via the intermediacy of [2 + 2] cycloaddition product **14**, as shown in Scheme 3. The O–O bond in endoperoxide **7** was easily cleaved by treatment with aluminum amalgam,[7] leading to diol **8a, b** (mixture of diastereoisomers, ca. 1:1, 58% yield for two steps). The bulky TBS group was then selectively attached onto the primary hydroxyl (TBSCl/imidazole, 91%), and the resulting mixture of secondary alcohols (**9a, b**) was oxidized to enone **10** by exposure to TPAP/NMO[8] (82% yield). The enone double bond in **10** was then selectively reduced[9] by the action of Stryker's reagent [Ph$_3$PCuH]$_6$ in benzene at 25 °C (72 h), affording ketone **11** with the desired stereochemistry of the ring E two-carbon appendage. Reduction of the carbonyl group on ring E was carried out with DIBAL (CH_2Cl_2,



Scheme 2. Synthesis of key intermediate **13b**. Reagents and conditions: a) 5.0 equiv of $(PhO)_2P(O)Cl$, 3.0 equiv of KHMDS (0.5 M in toluene), THF, −78 °C, 3 h; b) 3.0 equiv of CH_2=CHSnnBu$_3$, 0.15 equiv of [Pd(Ph$_3$P)$_4$], 5.0 equiv of LiCl, THF, reflux, 2 h, 81% for two steps; c) O_2, $h\nu$, 0.01 equiv of TPP, CCl_4, 25 °C, 15 min; d) Al(Hg) (excess), THF:H_2O (15:1), 25 °C, 2 h, 58% for two steps; e) 1.5 equiv of TBSCl, 10.0 equiv of imidazole, CH_2Cl_2, 25 °C, 1 h, 91%; f) 0.1 equiv of TPAP, 2.0 equiv of NMO, CH_2Cl_2, 25 °C, 3 h, 82%; g) 2.0 equiv of [Ph$_3$PCuH]$_6$, PhH, 25 °C, 72 h, 70%; h) 2.5 equiv of DIBAL, CH_2Cl_2, −78 °C, 1 h, 90%, ca. **12b**:**12a** (4:1); i) **12a, b**, 15 equiv of TrCl·4-DMAP, CH_2Cl_2, reflux, 24 h, 95% (**13a** + **13b**); j) **13a**, 0.05 equiv of TPAP, 1.5 equiv of NMO, CH_2Cl_2, 25 °C, 1 h; then DIBAL, CH_2Cl_2, −78 °C, 30 min, 82%. DIBAL = diisobutylaluminum hydride; 4-DMAP = 4-*N*,*N*-dimethylaminopyridine; KHMDS = potassium bis(trimethylsilyl) amide; NMO = 4-methylmorpholine-*N*-oxide; Piv = trimethylacetyl (pivaloyl); TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl; THF = tetrahydrofuran; TPP = *meso*-tetraphenylporphyrin; TPAP = tetra-*n*-propylammonium perruthenate; Tr = triphenylmethyl.

Abstract in Greek:

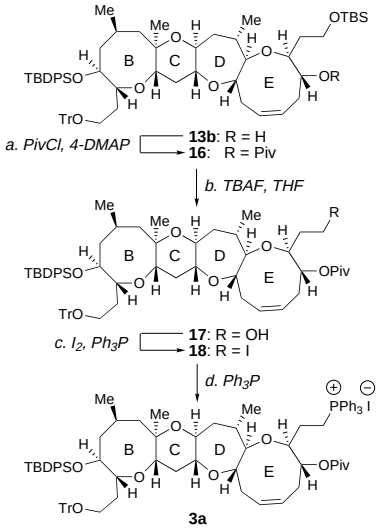
Στο αρθρο αυτο παραθετουμε την ολικη συνθεση της μπρεβετοξινης Α. Η μεθοδολογια μας για τις καταλυομενες απο παλαδιο συζευξεις των κυκλικων φωσφωρικων κετενο–ακεταλων, χρησιμοποιηθηκε για την εισαγωγη των χαρακτηριστικων ομαδων της εννεαμελους λακτονης **4**, που, ακολουθουμενη απο μια [4+2] κυκλοπροσθηκη οξυγονου απλης καταστασης, κατεληξε στην συνθεση του 1,3–διενιου **6**. Το ενδουπεροξειδιακο προιον **7** μετατραπηκε στη συνεχεια στα φωσφωνιακο αλας **3a** και φωσφινικο οξειδιο **3b** με σκοπο την αντιδραση συζευξης τους με την αλδευδη **2**. Οι αρχικες μας προσπαθειες για τη συννενωση του ενδιαμεσου **3a** με την αλδευδη **2** απετυχαν, πιθανα λογω στερεοχημικης παρεμποδισης, αποτελεσμα που οδηγησε στη συνεχεια στην ερευνα αλλων αντιδρασεων ολεφινικης συννενωσης. Αντιδρασεις του τυπου Horner– Wittig αποδειχθηκαν επιτυχεις στα μοντελα. Πιο συγκεκριμενα, τα διφαινυλοφωσφινικα οξειδια **21** και **28** αντεδρασαν επιτυχως με την αλευδη **2**. Παρομοια αντεδρασαν και τα ενδιαμεσα **3b** και **2** οποτε και ο ακορεστος οκταμελης κυκλικος αιθερας F (**44**) σχηματιστηκε μεσω της υδροξυ–θειοκεταλικης μεθοδολογιας κυκλοποιησης. Τα τελικα συνθετικα βηματα που ακολουθησαν ολοκληρωσαν την πρωτη ολικη συνθεση της μπρεβετοξινης Α.



Scheme 3. A side-reaction in the photooxygenation of diene **6**.

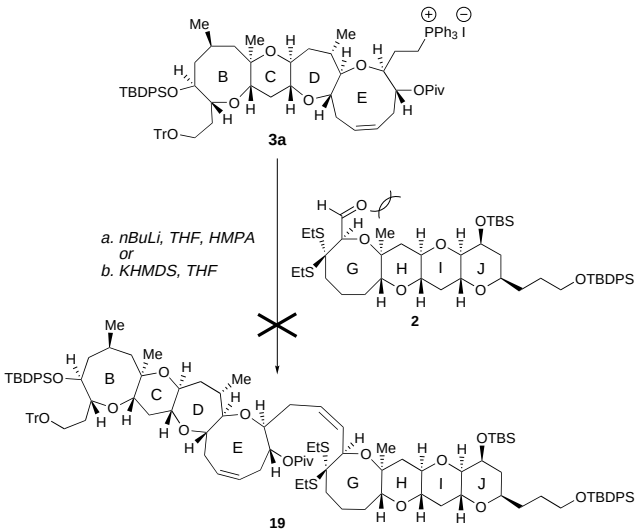
$-78\,^{\circ}C$) resulting in the formation of the desired α-hydroxyl epimer **12b** as the major product (ca. 4:1 ratio with the β-hydroxyl epimer **12a**, 90% combined yield). Concomitantly, the pivaloate ester group was cleaved from the ring B side-chain, resulting in a free hydroxyl group at that position. Thus, mixture **12ab** (**12a**:**12b** ca. 1:4) was converted to the mixture of primary trityl ethers **13a, b** by treatment with TrCl and 4-DMAP (95% yield, **13a**:**13b** ca. 1:4). The desired epimer **13b** was separated by flash column chromatography (silica gel) and the undesired isomer **13a** was recycled by oxidation (TPAP, NMO)[5] and DIBAL reduction (82% overall yield).

The conversion of alcohol **13b** to phosphonium iodide **3a** is depicted in Scheme 4. A pivaloate ester (PivCl, 4-DMAP, 92% yield) was placed on the free secondary alcohol and the TBS



Scheme 4. Synthesis of phosphonium salt **3a**. Reagents and conditions: a) 1.6 equiv of PivCl, 1.8 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 2 h, 94%; b) neutral alumina- 1% H_2O, hexanes, 25 °C, 20 h, 89% c) 1.1 equiv of I_2, 1.7 equiv of Ph_3P, 1.7 equiv of imidazole, CH_2Cl_2, 25 °C, 2 h; d) 10.0 equiv of Ph_3P, fusion (90 °C), 3 h, 83% for two steps. 4-DMAP = 4-*N*,*N*-dimethylaminopyridine; TBAF = tetra-*n*-butylammonium fluoride.

group was removed (TBAF, THF, 25 °C, 82% yield), furnishing primary alcohol **17** via intermediate **16**. Finally, phosphonium salt **3a** was prepared by fusion of the corresponding iodide (**18**, prepared by the action of I_2 and Ph_3P) with Ph_3P at 90 °C (83% for two steps). With phosphonium salt **3a** and aldehyde **2** [3] now available, the stage was set for an attempt to couple them. To this end, the ylide from **3a** was generated by addition of *n*BuLi in THF and in the presence of HMPA, or by the action of KHMDS in THF, and aldehyde **2** was added. However, no olefinic products (e.g. **19**, see Scheme 5), were obtained under these (or a number of other) conditions. Steric congestion around the aldehyde group in **2** and the relatively bulky ylide generated from **3a** were held responsible for the inability of the two components to react. Clearly new exploratory work was needed in order to overcome this latest and unforeseen obstacle.



Scheme 5. Unsuccessful attempts to couple phosphonium salt **3a** with GHIJ aldehyde **2**. Reagents and conditions: a) 1.1 equiv of *n*BuLi, 10 equiv of HMPA, THF, $-78\,^{\circ}C$, 30 min; then add **2**; b) 1.2 equiv of KHMDS, THF, $-78\,^{\circ}C$, 30 min; then add **2**. HMPA = hexamethylphosphoramide.

Further model studies

Having concluded that the phosphorane derived from **3a** was too bulky to break the steric barrier surrounding the aldehyde functionality of **2**, we decided to try a less hindered equivalent. Using diphenylphosphine oxides as alternatives, the study shown in Scheme 6 was thus undertaken. The simple model diphenylphosphine oxide[10] **21**, obtained in one step from phosphonium iodide **20**[11] by reaction with NaOH, was converted to its lithioderivative (*n*BuLi, THF, $-78\,^{\circ}C$), and reacted with aldehyde **2**,[3] affording a mixture of four diastereomeric hydroxyphosphine oxides **22** (83% combined yield). This mixture was then treated with NaH in DMF at 25 °C to afford olefin **23** in 78% yield and as an approximate 2:3 mixture of *Z*:*E* isomers. The overall yield of the coupling was encouraging, but the lack of *Z*:*E* stereoselectivity[4] was of some concern. A more realistic model representing the BCDE fragment was, therefore, chosen to further explore the coupling reaction and subsequent steps in preparation for the final drive towards brevetoxin A.

Scheme 7 outlines these model studies which began with compound **24**.[6] Based on molecular modeling, backed by experimental results with simple model systems, it was hoped that a chelating protecting group would complex with the lithium cation associated with the anion adjacent to the

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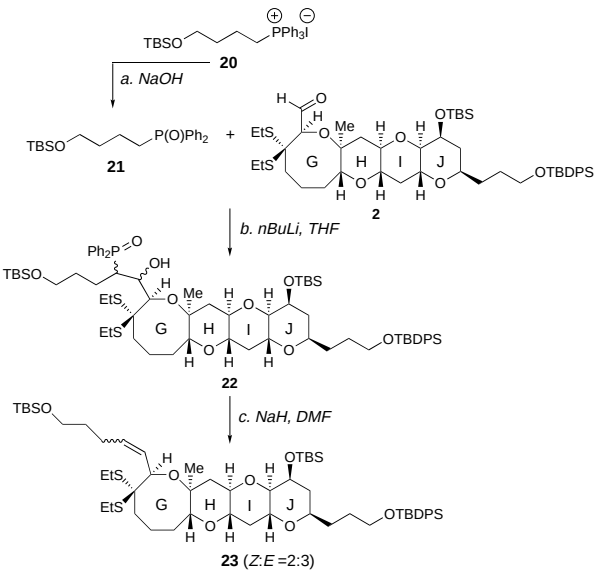
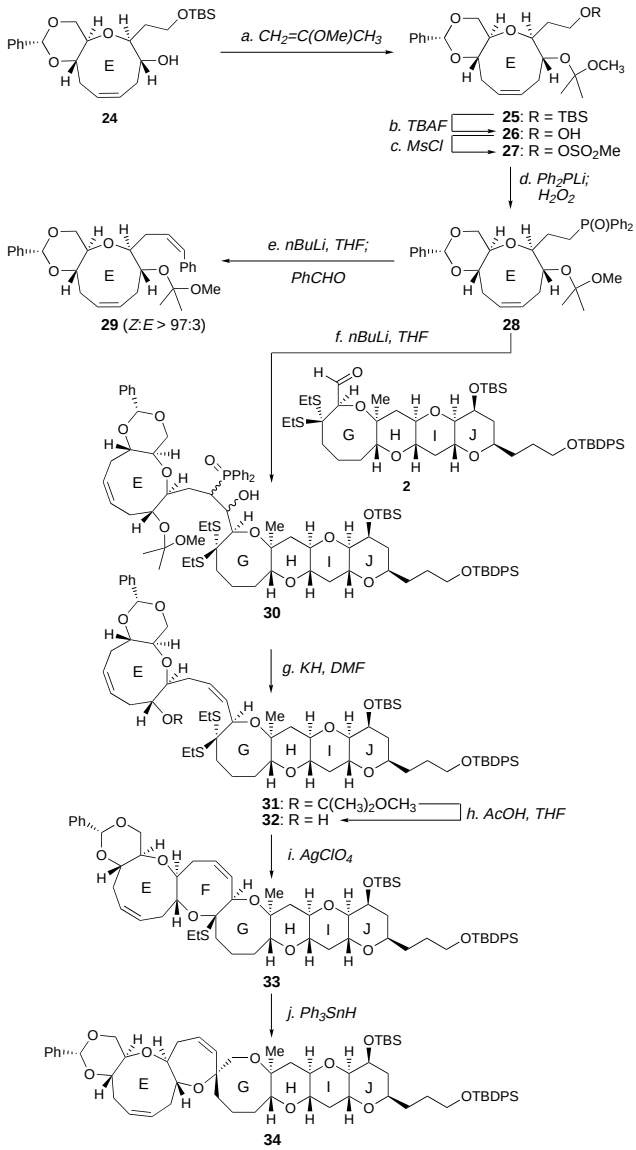


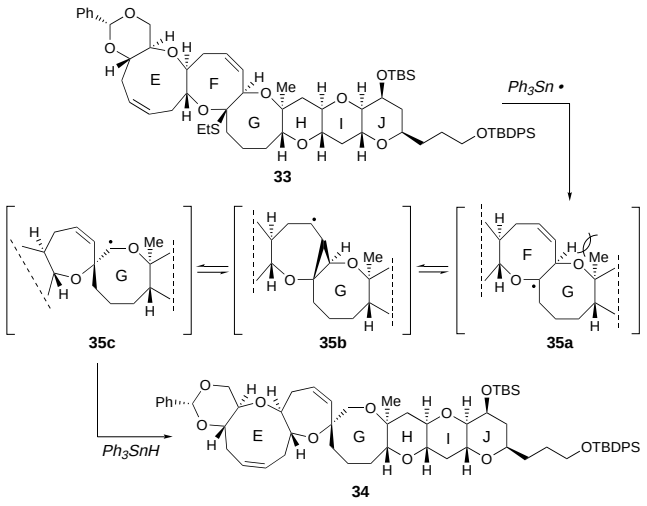
Scheme 6. Reaction of Horner–Wittig reagent **21** with GHIJ aldehyde **2**. Reagents and conditions: a) aq. NaOH, EtOH, 45 °C, 1 h, 80 %; b) 2.0 equiv of **21**, 2.4 equiv of *n*BuLi, THF, −78 °C, 10 min; then add 1.0 equiv of **2**, −78 °C, 10 min, 83 %; c) 2.0 equiv of NaH, DMF, 25 °C, 1 h, 78 %. DMF = *N*,*N*-dimethylformamide.



Scheme 7. Construction of model Horner–Wittig reagent **28** and its coupling with benzaldehyde and GHIJ aldehyde **2**. Reagents and conditions: a) CH_2=C(OMe)Me (excess), $POCl_3$ (trace), 25 °C, 1 h; b) 2.0 equiv of TBAF, THF, 25 °C, 1 h; c) 1.5 equiv of MsCl, 3.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 30 min, 85 % for three steps; d) Ph_2PLi (excess), 3.0 equiv of HMPA, THF, 0 °C, 10 min; then 5 % aq. H_2O_2, 85 %; e) 1.0 equiv of **28**, 1.5 equiv of *n*BuLi, THF, −78 °C, 10 min; then add 2.0 equiv of PhCHO, −78 °C, 10 min; 2.0 equiv of KH, DMF, 25 °C, 30 min, 85 % for two steps; f) 1.0 equiv of **28**, 1.2 equiv of *n*BuLi, THF, −78 °C, 10 min; then add 1.5 equiv of **2**, −78 °C, 10 min, 88 %; g) 2.0 equiv of KH, DMF, 25 °C, 30 min, 88 %; h) 20 % aq. AcOH:THF (1:2), 25 °C, 3 h, 100 %; i) 3.0 equiv of $AgClO_4$, $NaHCO_3$ (excess), SiO_2, 4 Å MS, $MeNO_2$, 25 °C, 3 h, 77 %; j) 10 equiv of Ph_3SnH, $PhCH_3$, 110 °C, 3 h, 48 %. Ms = methanesulfonate; MS = molecular sieves.

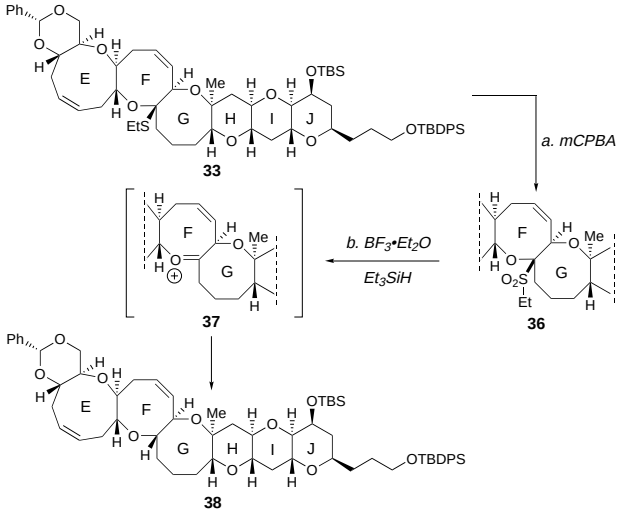
phosphine oxide, and thus provide a rigid and well-defined intermediate for a stereoselective attack on the GHIJ aldehyde. To this end the mixed methoxy dimethylketal group was installed on **24** (Scheme 7) by exposure to 2-methoxy propene and $POCl_3$ catalyst in CH_2Cl_2 to afford compound **25**. The primary hydroxyl group was then formed by desilylation (TBAF) to give **26** and mesylated (MsCl, Et_3N) to afford **27** (85 % overall yield from **24**). Displacement of the leaving group from **27** with $LiPPh_2$, followed by H_2O_2 oxidation of the resulting diphenylphosphine derivative[10] led to phosphine oxide **28** in 85 % overall yield. The reaction of **28** with 1.5 equivalents of *n*BuLi in THF at −78 °C, followed by addition of PhCHO and exposure of the resulting mixture of hydroxy diphenylphosphine oxides to KH was very revealing. Olefin **29** was produced from this reaction in a highly stereoselective manner (Z:E > 97:3) and in 85 % yield. This result encouraged us to attempt the coupling of the lithioderivative of more advanced model system **28** (1.2 equiv *n*BuLi) with GHIJ aldehyde **2**[3] (Scheme 7) which resulted in the formation of hydroxy phosphine oxides **30** (mixture of two diastereoisomers). Treatment of **30** with KH in DMF at 25 °C furnished *Z*-olefin **31** in 77 % yield from **28**.

With the coupling reaction apparently secured with regards to both efficiency and stereoselectivity, and with compound **31** at hand, we decided to proceed further ahead in order to explore the anticipated pathway in the real brevetoxin A system. In particular, we needed information regarding the crucial hydroxydithioketal cyclization and desulfurization steps. Thus, the protecting group was removed from the C-21 hydroxyl group of compound **31** under mild acid conditions (AcOH, THF) to afford **32** (100 % yield), which cyclized[11] smoothly under the influence of $AgClO_4$, $NaHCO_3$, SiO_2, and 4 Å MS in $MeNO_2$, leading to EFGHIJ system **33**. Treatment of **33** with Ph_3SnH and AIBN in refluxing toluene resulted in reductive removal of the EtS group, but careful spectroscopic analysis of the product revealed that rather serious changes had accompanied this radical-based reduction. Based on NMR experiments, the spiro structure **34** was tentatively assigned to the product from this reaction. Apparently, the double bond of ring F, positioned as it was, interfered with the radical generated at C-27 initiating a cascade that eventually leads to **34** via intermediates **35a**, **35b** and **35c** (see Scheme 8 for a presumed mechanism).



Scheme 8. Proposed mechanism for the formation of spiro compound **34**.

In order to circumvent this adverse participation of the ring F double bond, a reductive desulfurization method based on an ionic,[11] rather than a radical mechanism, was adopted next, as shown in Scheme 9. Thus, oxidation of **33** to the corresponding sulfone (**36**) was cleanly effected by the action of *m*CPBA (CH_2Cl_2, 0 °C, 92 % yield), and the latter compound was exposed to $BF_3 \cdot Et_2O$ and Et_3SiH, leading smoothly to the desired compound **38**, presumably via oxonium species **37**. The formation of the assigned skeletal framework was supported by NMR spectroscopy.

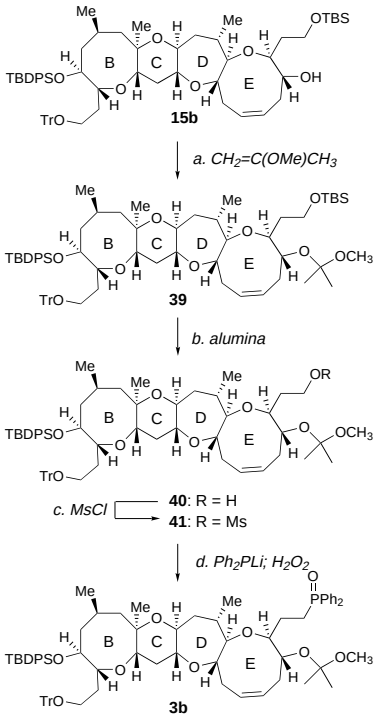


Scheme 9. Successful reduction of mixed ketal **33** by a cationic pathway. Reagents and conditions: a) 2.4 equiv of *m*CPBA, CH_2Cl_2, 0 °C, 1 h, 92 %; b) 5.0 equiv of $BF_3 \cdot Et_2O$, Et_3SiH:CH_2Cl_2 (1:6), −78 °C, 1 h, 90 %. *m*CPBA = 3-chloroperbenzoic acid.

These successful model studies pointed decisively to a rather clear path towards brevetoxin A (**1**), and the final drive was, therefore, undertaken with considerable confidence.

The final stages

Once the final strategy was adopted, our first task was the preparation of BCDE diphenylphosphine oxide system **3b** (Scheme 10). Installation of the mixed methoxydimethyl ketal



Scheme 10. Synthesis of diphenylphosphine oxide **3b**. Reagents and conditions: a) CH_2=C(OMe)Me (excess), $POCl_3$ (trace), 25 °C, 15 h, 96 %; b) neutral alumina-1 % H_2O, hexanes, 25 °C, 20 h, 86 %; c) 2.0 equiv of MsCl, 4.0 equiv of Et_3N, CH_2Cl_2, 0 °C, 15 min; d) Ph_2PLi (0.38 M solution in THF), HMPA (excess), THF, 0 °C, 10 min; then H_2O:30 % H_2O_2 (2.5:1), 95 % for two steps.

group (CH_2=C(OMe)Me, $POCl_3$ catalyst, 96 % yield) gave **39**, which was selectively desilylated at the primary position (cleavage of TBS) by the action of activated alumina,[12] leading to alcohol **40** (86 % yield). Mesylation of **40** (MsCl, Et_3N), followed by displacement with $LiPPh_2$ and oxidation with H_2O_2 afforded the desired diphenylphosphine oxide **3b** (95 % yield, for two steps).

As expected, reaction of the anion generated from BCDE diphenylphosphine oxide **3b** and *n*BuLi in THF with GHIJ aldehyde **2** proceeded smoothly to afford two diastereomeric hydroxy phosphine oxides, **42a** and **42b** [presumed to be of the *anti* arrangement on the basis of their conversion to a *Z*-olefin (vide infra)] (Scheme 11). The mixture of **42a** and **42b** was converted to a single olefin (**43**, 56 % yield for two steps) by the action of KH in DMF, from which the acetonide group at C-21 was cleaved with AcOH/THF, furnishing hydroxydithioketal **44** (88 % yield). The cyclization of **44** was carried out in the presence of $AgClO_4$, $NaHCO_3$, SiO_2, and 4 Å MS in $MeNO_2$, and led to mixed thioketal **45** in 80 % yield. Following the protocol developed in previous model studies, compound **45** was exposed to 2.2 equivalents of *m*CPBA in CH_2Cl_2 at 0 °C, resulting in oxidation at the sulfur atom to furnish sulfone **46**. Treatment of **46** with $BF_3 \cdot Et_2O$ in the presence of excess Et_3SiH in CH_2Cl_2 resulted in the reductive expulsion of both the ethylsulfonyl group and the trityl protecting group. NMR spectroscopy confirmed the formation of compound **47** (68 % yield, for two steps) in which the newly introduced hydrogen atom resided with the appropriate configuration. The primary hydroxyl group in compound **47**

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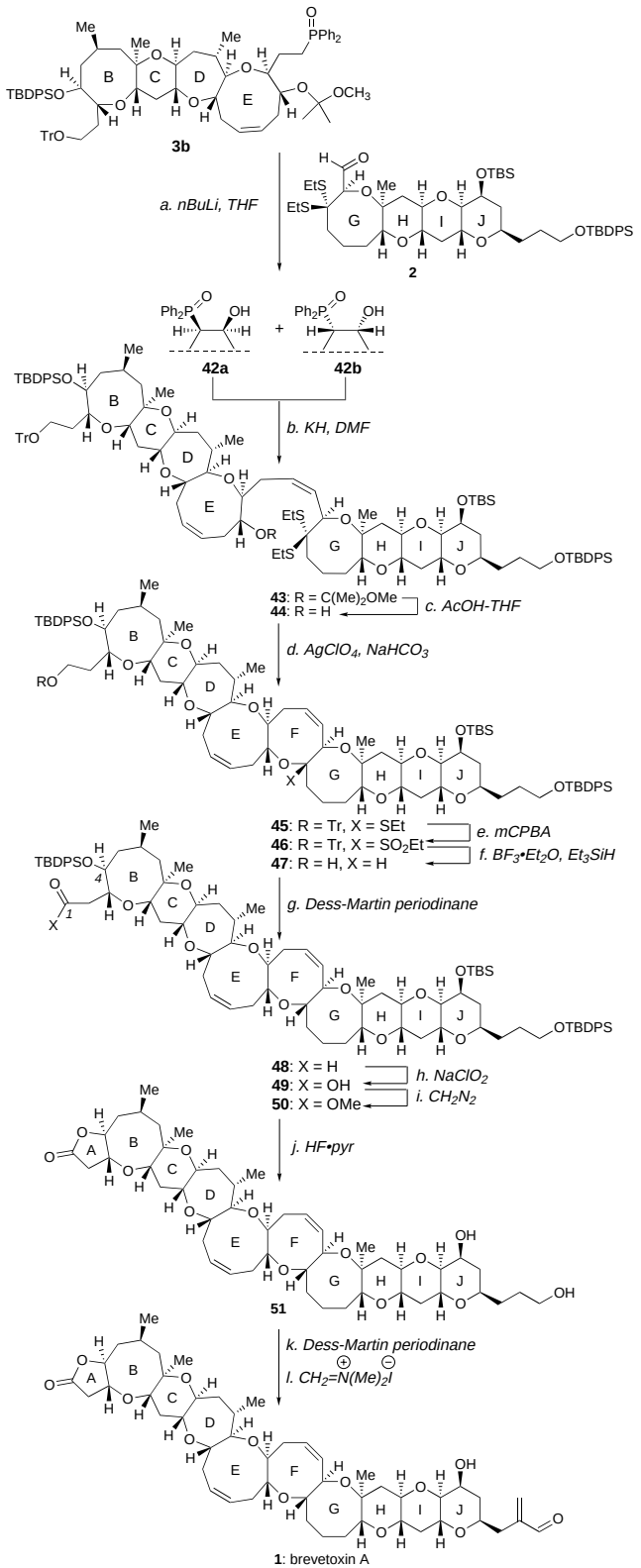

Scheme 11. Final stages of the total synthesis of brevetoxin A (**1**). Reagents and conditions: a) 1.0 equiv of **3b**, 1.0 equiv of *n*BuLi (1.55 M in hexane), THF, −78 °C, 10 min; then add 1.5 equiv of **2**, −78 °C, 45 min; b) 1.4 equiv of KH, DMF, 25 °C, 30 min, 56% for two steps; c) 20% AcOH:THF (1:3), 25 °C, 36 h, 88%; d) 3.0 equiv of $AgClO_4$, 3.0 equiv of $NaHCO_3$, SiO_2, 4 Å MS, $MeNO_2$, 25 °C, 3 h, 67%; e) 2.0 equiv of *m*CPBA, CH_2Cl_2, 0 °C, 2 h; f) 11.4 equiv of $BF_3 \cdot Et_2O$, Et_3SiH:CH_2Cl_2 (1:2), −78 °C, 1 h, 68% for two steps; g) 0.1 equiv of TPAP, 2.0 equiv of NMO, CH_2Cl_2, 25 °C, 30 min; h) 1.5 equiv of $NaClO_2$, 2.3 equiv of NaH_2PO_4, THF:*t*BuOH:H_2O:2-methyl-2-butene (10:5:5:1), 25 °C, 1 h; i) CH_2N_2 (excess), Et_2O, 0 °C, 45 min, 71% for three steps; j) HF · pyr, CH_2Cl_2, 0 °C, 1 h, 92%; k) 1.0 equiv of Dess–Martin periodinane, CH_2Cl_2, 0 °C, 1 h; 3 equiv of $CH_2{=}N^+(Me)_2I^-$ (Eschenmoser's salt), Et_3N:CH_2Cl_2 (1:25), 25 °C, 12 h, 57% for two steps. pyr. = pyridine.

was then sequentially oxidized first to an aldehyde group (Dess–Martin periodinane)[8] and then to a carboxylic acid group ($NaClO_2$, NaH_2PO_2, 2-methyl-2-butene)[13] prior to esterification (CH_2N_2), furnishing compound **50** in 71% overall yield from **47**. It was anticipated that deprotection of the hydroxyl groups would lead to a γ-lactone moiety. This expectation was fulfilled on exposure of **50** to excess HF in pyridine which, indeed, led to the formation of dihydroxy lactone **51** in 92% yield. Of the two hydroxyl groups in intermediate **51**, the primary one was selectively converted to the corresponding aldehyde by treatment with 1.0 equivalents of Dess–Martin periodinane[14] (CH_2Cl_2, 0 °C). Finally, reaction of the aldehyde so obtained with Eschenmoser's salt,[15] $CH_2{=}N^+(Me)_2I^-$, furnished brevetoxin A (**1**) in 57% yield (for two steps). Synthetic brevetoxin A (**1**) crystallized from warm (45 °C) acetonitrile as colorless crystals, m.p. 197–199 °C/218–220 °C (ref. m.p. 197–199 °C/218–220 °C, double melting point from acetonitrile)[16] and exhibited identical chromatographic and spectral data [TLC, HPLC, $[\alpha]_D^{22}$, ^1H and ^{13}C NMR and IR spectroscopy, and mass spectrometry] with those of authentic natural samples very kindly provided by Professors K. Nakanishi and I. Shimizu.

Conclusion

In this and the preceding three articles[1-3] we described the campaign of our total synthesis of brevetoxin A (**1**) which stretched over the decade from 1987 and 1997.[17, 18] This architecturally beautiful molecule, with its 10 fused rings, ranging in size from 5 to 9, and 22 stereogenic centers, presented many challenges to synthetic chemistry and, thus, stimulated new explorations in the fields of synthetic technology and strategy. Numerous new methods were discovered and developed during this program as important and useful spin-offs. In addition to the regio- and stereoselective hydroxyepoxide openings[19] and hydroxydithioketal cyclizations[11] used in this construction and amply discussed previously in conjunction with the total synthesis of brevetoxin B,[20–25] the generation and palladium-catalyzed coupling reactions of cyclic ketene acetal phosphates[5] was, perhaps, the most important and valuable process developed in this endeavor. A more remote spin-off of this reaction (which allows a facile conversion of a lactone to a cyclic ether) is the related reactions of lactams[26] that led to various N-containing heterocycles and unnatural amino acids via the corresponding phosphate intermediates (a similar method for the synthesis of dienes involving coupling of enol phosphates with Grignard reagents in the presence of a nickel catalyst was also developed by Claesson in the early 1980s).[27] The final strategy utilized for this total synthesis emerged as the project evolved and as information regarding resistance points and opportunities accumulated. The devised strategy is quite convergent and efficient considering the complexity and size of the target mole-

cule. Its longest linear sequence from commercially available D-mannose consisted of 66 steps. Despite its rewards and excitements, this campaign reveals both the present power of organic synthesis and at the same time its limitations in terms of efficiency and speed of delivery, as compared to nature's version of the science. Indeed, the biosynthesis of the brevetoxins must be highly admirable and remains, for the most part, unknown.

Experimental Section

General techniques: See paper 1 in this series.[1]

Phosphate 5: A solution of lactone **4** (1 g, 1.29 mmol) in THF (35 mL) was added to a solution of KHMDS (7.74 mL, 0.5 M solution in toluene, 3.87 mmol) and diphenylphosphoryl chloride (1.34 mL, 6.45 mmol) in THF (30 mL) at $-78\,^{\circ}C$, and the reaction mixture was stirred at $-78\,^{\circ}C$ for 2 h. The reaction mixture was quenched by pouring into a 10% aqueous solution of ammonium hydroxide (300 mL) and stirring at $25\,^{\circ}C$ for 30 min. The solution was saturated with NaCl (solid), and the product was extracted into ether (3×200 mL). The combined organic extracts were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford phosphate **5** (1.2 g, 90%). **5** $R_f=0.40$ (silica gel, 2:8, EtOAc:hexanes); $[\alpha]_D^{25}=+17.1$ ($c=1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}=2963, 2933, 2865, 1728, 1682, 1593, 1488, 1382, 1289, 1189, 1160, 1072, 961, 902, 821, 758, 704\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta=7.82-7.74$ (m, 3H, ArH), 7.35-7.18 (m, 8H), 7.13–7.08 (m, 1H, ArH), 6.99-6.74 (m, 8H, ArH), 5.70 (ddd, $J=10.0, 10.0, 6.5$ Hz, 1H, =CH), 5.60 (ddd, $J=10.0, 10.0, 6.5$ Hz, 1H, =CH), 5.16 (ddd, $J=7.5, 7.5, 3.0$ Hz, 1H, =CH), 4.31 (ddd, $J=11.0, 7.0, 4.0$ Hz, 1H), 4.22 (ddd, $J=10.0, 10.0, 5.5$ Hz, 1H), 3.90 (dd, $J=9.5, 3.0$ Hz, 1H), 3.71 (ddd, $J=9.5, 4.0, 4.0$ Hz, 1H), 3.56 (ddd, $J=11.0, 9.0, 2.5$ Hz, 1H), 3.52–3.44 (m, 2H), 3.32 (br t, $J=10.0, 10.0$ Hz, 1H), 3.12–2.96 (m, 2H), 2.76 (ddd, $J=12.0, 9.0, 4.0$ Hz, 1H), 2.56–2.45 (m, 1H), 2.44–2.26 (m, 4H), 2.20 (ddd, $J=12.0, 4.5, 4.5$ Hz, 1H), 2.02–1.90 (m, 2H), 1.87–1.78 (m, 1H), 1.70 (d, $J=14.5$ Hz, 1H), 1.64–1.53 (m, 3H), 1.47–1.38 (m, 1H), 1.26 (s, 9H, *t*Bu), 1.16 (d, $J=7.0$ Hz, 3H, CH_3), 1.15 (s, 9H, *t*Bu), 1.02 (s, 3H, CH_3), 0.51 (d, $J=6.0$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta=177.6, 157.4, 154.5, 151.1, 136.2, 134.7, 134.0, 131.1, 130.1, 130.0, 129.8, 128.1, 127.9, 126.0, 125.6, 120.6, 120.5, 120.0, 115.9, 97.1, 92.0, 83.8, 82.5, 82.4, 78.3, 75.7, 69.4, 69.4, 61.3, 54.6, 47.3, 38.8, 36.4, 35.9, 35.0, 33.9, 32.4, 27.5, 27.4, 27.2, 26.8, 22.1, 21.2, 19.6, 16.6$; HRMS (FAB) calcd for $C_{58}H_{75}O_{11}PSi$ ($[M+Cs^+]$) 1139.3871, found 1139.3809.

Diene 6: A solution of flame-dried lithium chloride (273 mg, 6.45 mmol) in THF (15 mL) was treated with vinyl tributyltin hydride (1.04 mL, 3.87 mmol), a solution of phosphate **5** (1.2 g, 1.16 mmol) in THF (30 mL) and palladium tetrakistriphenylphosphane (234 mg, 0.194 mmol) at $70\,^{\circ}C$ for 2 h. The reaction mixture was cooled, diluted with ether (30 mL), and filtered through a plug of silica gel washing with ether. The filtrate was concentrated and purified by flash column chromatography (silica gel, 1:9, EtOAc:hexanes) to afford diene **6** (823 mg, 90%). **6:** $R_f=0.36$ (silica gel, 1:1, ether:hexanes); $[\alpha]_D^{25}=+66.4$ ($c=1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}=2931, 2862, 1728, 1595, 1458, 1283, 1157, 1108, 1078, 1046, 740, 704, 510\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.68-7.62$ (m, 4H, ArH), 7.46–7.35 (m, 6H, ArH), 6.13 (dd, $J=17.0, 10.5$ Hz, 1H, =CH), 5.69 (ddd, $J=11.0, 10.5, 7.5$ Hz, 1H, =CH), 5.48 (ddd, $J=10.5, 10.5, 7.5$ Hz, 1H, =CH), 5.39 (d, $J=17.0$ Hz, 1H, =C*H*H), 5.08 (dd, $J=9.0, 5.0$ Hz, 1H, =CH), 4.92 (d, $J=10.5$ Hz, 1H, =C*H*H), 4.27 (ddd, $J=10.5, 6.5, 3.5$ Hz, 1H), 4.04 (ddd, $J=10.0, 10.0, 5.0$ Hz, 1H), 3.91 (dd, $J=7.0, 1.5$ Hz, 1H), 3.71 (ddd, $J=10.0, 7.0, 3.0$ Hz, 1H), 3.52 (dd, $J=11.5, 5.0$ Hz, 1H), 3.50–3.35 (m, 3H), 3.05 (ddd, $J=13.5, 9.5, 4.0$ Hz, 1H), 2.95 (ddd, $J=14.5, 9.5, 5.5$ Hz, 1H), 2.69 (dddd, $J=8.0, 8.0, 8.0, 8.0$ Hz, 1H), 2.60 (ddd, $J=13.5, 9.0, 9.0$ Hz, 1H), 2.51 (ddd, $J=13.5, 7.0, 3.5$ Hz, 1H), 2.35–2.21 (m, 2H), 2.14 (ddd, $J=12.0, 4.5, 4.5$ Hz, 1H), 2.05 (ddd, $J=12.5, 2.0$ Hz, 1H), 1.77–1.62 (m, 2H), 1.60–1.34 (m, 6H), 1.26 (s, 9H, *t*Bu), 1.07 (s, 3H, CH_3), 1.06 (d, $J=7.0$ Hz, 3H, CH_3), 1.01 (s, 9H, *t*BuSi), 0.49 (d, $J=7.0$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta=178.2, 157.5, 135.8, 135.7, 134.3, 133.6, 129.7, 129.5, 127.6, 127.4, 127.2, 125.3, 113.0, 112.6, 90.0, 83.7, 83.4, 82.2, 77.7, 75.7, 69.1, 61.0, 54.1, 46.8, 36.0, 35.0, 35.0, 33.2, 27.3, 27.2, 26.9, 26.5, 25.1, 19.4, 18.8, 16.6$; HRMS (FAB) calcd for $C_{48}H_{68}O_7Si$ ($[M+Cs^+]$) 917.3789, found 917.3756.

Diols 8a and 8b: A solution of diene **6** (100 mg, 0.127 mmol) in carbon tetrachloride (40 mL) was treated with tetraphenylporphyrin (≈1 mg, enough to turn the solution a light shade of pink), and was irradiated with a halogen light source, while oxygen was bubbled through the solution at $25\,^{\circ}C$ for 15 min. The reaction mixture containing crude endoperoxide **7** was concentrated, redissolved in THF (30 mL), H_2O (2 mL), and Et_3N (1 mL), and treated with aluminum amalgam. The aluminum amalgam was prepared by successively dipping pieces (5, 7×3 cm) of loosely rolled aluminum foil into aqueous sodium hydroxide (3 M, for 10 s), water, aqueous mercury(II) chloride (3%, for 30 s), and water. The sequence was repeated once followed by a final rinse with ethanol and ether. The heterogeneous reaction mixture was stirred vigorously at $25\,^{\circ}C$ for 2 h, during which time the foil broke into a fine suspension which was removed by filtering through a plug of silica gel eluting with EtOAc. The concentrated filtrate was purified by column chromatography (silica gel, 2:1, EtOAc:hexanes) to afford a mixture of diastereomeric diols **8a** and **8b** (70 mg, 58%). **8** (less polar): $R_f=0.59$ (silica gel, 7:3, EtOAc:hexanes); $[\alpha]_D^{25}=-1.14$ ($c=1.0$, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6): $\delta=7.80-7.74$ (m, 4H, ArH), 7.27–7.19 (m, 6H, ArH), 5.70–5.60 (m, 2H, =CH), 5.08 (dd, $J=7.5, 7.5$ Hz, 1H, =CH), 4.43 (dd, $J=12.0, 8.0$ Hz, 1H), 4.32 (ddd, $J=10.0, 6.0, 3.5$ Hz, 1H), 4.26 (ddd, $J=10.5, 10.5, 5.0$ Hz, 1H), 4.19–4.13 (m, 2H), 3.99 (dd, $J=8.0, 8.0$ Hz, 1H), 3.60–3.45 (m, 4H), 3.42 (ddd, $J=9.0, 9.0, 3.0$ Hz, 1H), 2.91 (ddd, $J=12.0, 9.0, 4.0$ Hz, 1H), 2.86–2.72 (m, 2H), 2.56–2.47 (m, 1H), 2.44–2.37 (m, 1H), 2.33–2.25 (m, 2H), 2.14–2.05 (m, 1H), 1.95 (ddd, $J=16.5, 9.5, 6.5$ Hz, 1H), 1.87–1.77 (m, 1H), 1.76–1.63 (m, 3H), 1.61–1.53 (m, 3H), 1.49–1.40 (m, 1H), 1.25 (s, 9H, *t*Bu), 1.15 (s, 9H, *t*BuSi), 1.12 (d, $J=7.0$ Hz, 3H, CH_3), 1.09 (s, 3H, CH_3), 0.52 (d, $J=6.0$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta=177.7\ 165.4, 136.2, 136.2, 134.7, 134.0, 130.5, 130.1, 130.0, 128.3, 128.1, 127.9, 126.1, 102.0, 88.7, 84.1, 82.3, 81.3, 80.9, 78.2, 75.6, 71.7, 69.6, 61.3, 56.8, 47.4, 38.8, 38.5, 36.3, 35.2, 35.0, 34.4, 33.9, 27.6, 27.4, 27.2, 26.8, 20.8, 19.6, 16.5$; HRMS (FAB) calcd for $C_{48}H_{70}O_9Si$ ($[M+Cs^+]$) 951.3843, found 951.3883.

8 (more polar): $R_f=0.34$ (silica gel, 7:3, EtOAc:hexanes); $[\alpha]_D^{25}=+9.3$ ($c=1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}=3369, 2930, 2872, 1727, 1657, 1457, 1375, 1285, 1156, 1092, 1036, 743, 705\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta=7.80-7.72$ (m, 4H, ArH), 7.27–7.18 (m, 6H, ArH), 5.80 (ddd, $J=10.5, 10.5, 9.0$ Hz, 1H, =CH), 5.47 (ddd, $J=10.5, 10.5, 9.0$ Hz, 1H, =CH), 5.13 (dd, $J=8.0, 8.0$ Hz, 1H, =CH), 4.78–4.71 (m, 1H), 4.31 (ddd, $J=6.5, 3.5$ Hz, 1H), 4.23 (ddd, $J=10.0, 10.0, 5.5$ Hz, 1H), 4.16 (dd, $J=12.0, 8.5$ Hz, 1H), 4.03 (dd, $J=12.0, 7.0$ Hz, 1H), 3.92–3.70 (br m, 1H, OH), 3.81 (dd, $J=8.5, 8.5$ Hz, 1H), 3.65–3.59 (m, 1H), 3.59–3.37 (m, 5H), 3.41 (br t, $J=10.0$ Hz, 1H), 2.90 (ddd, $J=12.5, 9.5, 4.5$ Hz, 1H), 2.84–2.73 (m, 1H), 2.73–2.63 (m, 1H), 2.55–2.45 (m, 1H), 2.44–2.34 (m, 2H), 2.26 (ddd, $J=12.0, 4.5, 4.5$ Hz, 1H), 2.15–2.04 (m, 1H), 2.04–1.94 (m, 1H), 1.85–1.60 (m, 6H), 1.49–1.40 (m, 1H), 1.24 (s, 9H, *t*Bu), 1.20 (d, $J=7.0$ Hz, 3H, CH_3), 1.13 (s, 9H, *t*BuSi), 1.08 (s, 3H, CH_3), 0.52 (br d, $J=5.5$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta=177.7\ 162.9, 136.2, 134.7, 130.1, 130.0, 128.3, 128.1, 127.9, 103.0, 88.3, 84.1, 82.2, 82.0, 81.1, 78.3, 75.6, 69.5, 65.7, 61.4, 57.5, 54.5, 47.4, 38.8, 38.7, 35.7, 34.8, 33.9, 32.9, 30.3, 27.6, 27.4, 27.2, 26.8, 21.3, 19.6, 16.5$; HRMS (FAB) calcd for $C_{48}H_{70}O_9Si$ ($[M+Cs^+]$) 951.3843, found 951.3883.

Alcohols 9a and 9b: A solution of diols **8a** and **8b** (500 mg, 0.610 mmol) in CH_2Cl_2 (20 mL) was treated with imidazole (414 mg, 6.10 mmol), and TBSCl (138 mg, 0.92 mmol) at $25\,^{\circ}C$ for 1 h. The reaction mixture was diluted with ether (50 mL), washed with aqueous saturated sodium bicarbonate solution (50 mL), brine (50 mL), and dried ($MgSO_4$). The organic solution was concentrated, and the residue was purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford a mixture of diastereomeric alcohols **9a** and **9b** (520 mg, 91%). **9** (less polar): $R_f=0.42$ (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25}=-22.5$ ($c=1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}=3439, 2932, 2855, 1728, 1654, 1460, 1429, 1383, 1363, 1281, 1250, 1158, 1083, 836, 703\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta=7.78-7.72$ (m, 4H, ArH), 7.26–7.18 (m, 6H, ArH), 5.72–5.60 (m, 2H, =CH), 5.05 (dd, $J=7.0, 7.0$ Hz, 1H, =CH), 4.53 (dd, $J=12.0, 7.5$ Hz, 1H), 4.34–4.17 (m, 4H), 4.00 (dd, $J=8.0, 8.0$ Hz, 1H), 3.58–3.44 (m, 4H), 3.39 (ddd, $J=9.0, 9.0, 2.0$ Hz, 1H), 2.93–2.85 (m, 1H), 2.84–2.73 (m, 2H), 2.56–2.44 (m, 2H), 2.39–2.30 (m, 2H), 2.25 (ddd, $J=12.0, 4.5, 4.5$ Hz, 1H), 2.14–2.05 (m, 1H), 1.94 (ddd, $J=15.0, 9.5, 6.0$ Hz, 1H), 1.84–1.74 (m, 1H), 1.74–158 (m, 3H), 1.57–1.50 (m, 3H), 1.47–1.38 (m, 1H), 1.24 (s, 9H, *t*Bu),

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1.13 (s, 9H, *t*BuSi), 1.12 (d, $J = 7.0$ Hz, 3H, CH_3), 1.05 (s, 3H, CH_3), 0.93 (s, 9H, *t*BuSi), 0.50 (br d, $J = 5.5$ Hz, 3H, CH_3), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta = 177.6$ 165.3, 136.2, 134.7, 134.0, 130.3, 130.1, 130.0, 128.3, 128.1, 127.9, 126.4, 100.9, 88.8, 84.0, 82.3, 81.3, 81.0, 78.2, 75.6, 71.8, 69.6, 61.3, 58.1, 54.5, 47.3, 38.8, 38.5, 36.0, 35.1, 35.0, 34.4, 33.9, 27.6, 27.4, 26.8, 26.0, 25.9, 20.8, 19.6, 18.4, 16.4, −4.9, −5.0.

9 (more polar): $R_f = 0.28$ (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25} = +1.8$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3468$, 2955, 2860, 1729, 1657, 1460, 1428, 1389, 1283, 1255, 1156, 1082, 835, 776, 741, 704, 600 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.77 - 7.70$ (m, 4H, ArH), 7.26 – 7.18 (m, 6H, ArH), 5.72 (ddd, $J = 9.5$, 9.0, 9.0 Hz, 1H, =CH), 5.51 (ddd, $J = 9.5$, 9.5, 8.0 Hz, 1H, =CH), 5.00 (dd, $J = 7.0$, 7.0 Hz, 1H, =CH), 4.66 (d, $J = 5.0$ Hz, 1H) 4.35 – 4.25 (m, 1H), 4.20 (ddd, $J = 10.0$, 10.0, 5.5 Hz, 1H), 4.12 (d, $J = 7.0$ Hz, 2H), 3.84 (dd, $J = 8.0$, 8.0 Hz, 1H), 3.57 – 3.42 (m, 4H), 3.34 (dd, $J = 8.5$, 8.5 Hz, 1H), 2.92 – 2.84 (m, 1H), 2.67 – 2.34 (m, 6H), 2.28 – 2.20 (m, 1H), 2.02 – 1.87 (m, 2H), 1.82 – 1.73 (m, 1H), 1.72 – 1.48 (m, 5H), 1.46 – 1.36 (m, 1H), 1.23 (s, 9H, *t*Bu), 1.12 (br s, 12H, *t*BuSi and CH_3), 1.02 (s, 3H, CH_3), 0.92 (s, 9H, *t*BuSi), 0.49 (br d, $J = 4.5$ Hz, CH_3), 0.04 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta = 177.5$ 161.7, 136.2, 136.2, 134.7, 134.0, 131.2, 130.1, 130.0, 128.3, 128.1, 127.9, 125.5, 102.0, 88.2, 84.1, 82.2, 81.6, 81.1, 78.2, 75.5, 69.4, 65.8, 61.3, 58.6, 54.5, 47.4, 38.8, 38.6, 35.4, 34.8, 33.9, 33.7, 27.6, 27.5, 27.2, 26.8, 26.1, 21.0, 19.6, 18.4, 16.4, −4.8, −4.9; HRMS (FAB) calcd for $C_{54}H_{84}O_9Si_2$ ($[M + Cs^+]$) 1065.4708, found 1065.4753.

Enone 10: A solution of alcohols **9a** and **9b** (520 mg, 0.557 mmol) in CH_2Cl_2 (35 mL) in the presence of 4 Å MS (5 g), was treated with *N*-methylmorpholine oxide (131 mg, 1.1 mmol) and TPAP (20 mg, 0.056 mmol) at 25 °C for 3 h. The reaction mixture was diluted with ether (50 mL), and filtered through a plug of silica gel, while washing with ether (50 mL). The filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, 1:9, EtOAc:hexanes) to afford enone **10** (425 mg, 82 %). **10**: $R_f = 0.57$ (silica gel, 1:9, EtOAc:hexanes); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.81 - 7.74$ (m, 4H, ArH), 7.28 – 7.17 (m, 6H, ArH), 5.88 (dd, $J =$ 6.5, 5.0 Hz, 1H, =CH), 5.79 (ddd, $J = 10.0$, 10.0, 6.0 Hz, 1H, =CH), 5.54 (ddd, $J = 10.0$, 10.0, 8.0 Hz, 1H, =CH), 4.79 (dd, $J = 16.0$, 7.0 Hz, 1H), 4.67 (dd, $J = 16.0$, 5.0 Hz, 1H), 4.36 – 4.19 (m, 2H), 3.68 (dd, $J = 11.0$, 11.0 Hz, 1H), 3.65 – 3.44 (m, 5H), 3.33 (dd, $J = 9.5$, 9.5 Hz, 1H), 2.90 – 2.74 (m, 2H), 2.64 (dd, $J = 11.0$, 7.0 Hz, 1H), 2.57 – 2.46 (m, 1H), 2.30 – 2.18 (m, 3H), 2.06 – 1.96 (m, 1H), 1.84 (br t, $J = 12.0$ Hz, 1H), 1.74 – 1.65 (m, 2H), 1.60 – 1.52 (m, 4H), 1.47 – 1.38 (m, 1H), 1.27 (s, 9H, *t*Bu), 1.16 (s, 9H, *t*BuSi), 1.04 (s, 3H, CH_3), 1.02 (d, $J = 7.0$ Hz, 3H, CH_3), 0.94 (s, 9H, *t*BuSi), 0.52 (br d, $J = 4.5$ Hz, 3H, CH_3), 0.03 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si); HRMS (FAB) calcd for $C_{54}H_{82}O_9Si_2$ ($[M + Cs^+]$) 1063.4552, found 1063.4593.

Ketone 11: A solution of enone **10** (425 mg, 0.456 mmol) in benzene (75 mL) was degassed by a freeze-thaw method (2 ×) and treated with $[Ph_3PCuH]_6$ (1.8 g, 0.91 mmol) at 25 °C for three days. The reaction mixture was diluted with dichloromethane (100 mL) and washed with a saturated aqueous ammonium chloride solution (50 mL), brine (50 mL), and dried ($MgSO_4$). The organic solution was concentrated, and the residue was purified by column chromatography (silica gel, 1:9, EtOAc:hexanes) to afford ketone **11** (300 mg, 70 %). **11**: $R_f = 0.57$ (silica gel, 1:9, EtOAc:hexanes); $[\alpha]_D^{25} = -46.5$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} = 2931$, 2856, 1727, 1467, 1388, 1284, 1256, 1155, 1088, 833, 777, 742, 704, 610, 513 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.79 - 7.72$ (m, 4H, ArH), 7.27 – 7.18 (m, 6H, ArH), 5.82 (ddd, $J = 10.0$, 10.0, 6.5 Hz, 1H, =CH), 5.60 (ddd, $J = 10.0$, 10.0, 8.0 Hz, 1H, =CH), 4.35 – 4.17 (m, 2H), 4.09 (dd, $J = 6.5$, 6.5 Hz, 1H), 3.84 (dd, $J = 10.0$, 10.0 Hz, 1H), 3.72 – 3.63 (m, 1H), 3.61 – 3.41 (m, 5H), 3.36 (dd, $J = 9.5$, 9.5 Hz, 1H), 3.19 (d, $J = 10.0$ Hz, 1H), 2.95 (ddd, $J = 12.0$, 12.0, 3.0 Hz, 1H), 2.81 (ddd, $J = 10.0$, 10.0, 3.5 Hz, 1H), 2.59 (dd, $J = 8.5$, 8.5 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.31 – 2.14 (m, 3H), 2.04 (ddd, $J = 12.5$, 12.5, 2.5 Hz, 1H), 1.87 – 1.49 (m, 9H), 1.47 – 1.35 (m, 1H), 1.26 (s, 9H, *t*Bu), 1.13 (s, 9H, *t*BuSi), 1.07 (d, $J = 7.0$ Hz, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.92 (s, 9H, *t*BuSi), 0.50 (d, $J = 5.0$ Hz, 3H, CH_3), 0.01 (s, 3H, CH_3Si), −0.01 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta = 209.8$, 177.5, 136.2, 136.2, 134.7, 134.0, 130.1, 130.0, 128.8, 128.1, 127.9, 124.6, 84.1, 83.8, 82.9, 82.5, 82.0, 80.8, 78.3, 75.8, 69.4, 61.2, 58.3, 54.6, 47.3, 38.0, 36.5, 36.1, 35.2, 35.1, 33.8, 32.2, 27.6, 27.5, 27.2, 26.8, 26.0, 23.2, 22.2, 19.6, 18.4, 16.7, −5.3, −5.5; HRMS (FAB) calcd for $C_{54}H_{84}O_9Si_2$ ($[M + Cs^+]$) 1065.4708, found 1065.4750.

Alcohol 13: A solution of ketone **11** (300 mg, 0.321 mmol) in CH_2Cl_2 (20 mL) at −78 °C was treated with DIBAL (800 µL, 1M in CH_2Cl_2, 0.80 mmol) for 1 h. The reaction mixture was quenched by addition of EtOAc (0.5 mL) followed by pouring into aqueous sodium potassium tartrate solution (100 mL), and the biphasic solution was stirred vigorously for 2 h. The organic layer was separated, dried ($MgSO_4$), and concentrated to give an inseparable mixture of epimers 8:2 (α:β) **12a**, **12b**. A solution of crude alcohols **12a** and **12b** (255 mg, 0.294 mmol) in CH_2Cl_2 (30 mL) was treated with trityl chloride. 4-DMAP (91.8 g, 4.4 mmol) at 40 °C for 15 h. The reaction mixture was concentrated and purified by flash column chromatography (silica gel, 2:8, EtOAc:hexanes) to afford the desired α-epimer **13b** (235 mg, 85 % for two steps) and undesired β-epimer **13a** (65 mg, 18 % for two steps). α-epimer **13b**: $R_f = 0.65$ (silica gel, 3:7, EtOAc:hexanes); $[\alpha]_D^{25} = +10.9$ ($c = 1.0$, $CHCl_3$); IR (thin film): $\tilde{\nu}_{max} =$ 3432, 2930, 2863, 1594, 1450, 1384, 1256, 1074, 998, 902, 837, 741, 705, 630, 611, 509 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.76 - 7.71$ (m, 4H, ArH), 7.53 – 7.48 (m, 6H, ArH), 7.47 – 7.36 (m, 6H, ArH), 7.34 – 7.22 (m, 9H, ArH), 5.83 (ddd, $J = 10.5$, 8.5, 8.5 Hz, 1H, =CH), 5.75 (ddd, $J = 10.5$, 8.5, 8.5 Hz, 1H, =CH), 4.09 (d, $J = 2.5$ Hz, 1H), 3.92 – 3.84 (m, 1H), 3.73 (dd, $J = 8.0$, 8.0 Hz, 1H), 3.65 (br m, 1H), 3.55 (dd, $J = 9.0$, 9.0 Hz, 1H), 3.52 – 3.19 (m, 4H), 3.25 – 3.14 (m, 3H), 2.97 (ddd, $J = 9.0$, 9.0, 5.0 Hz, 1H), 2.81 (ddd, $J =$ 12.0, 9.5, 4.0 Hz, 1H), 2.64 – 2.39 (m, 5H), 2.09 – 1.96 (m, 2H), 1.96 – 1.82 (m, 3H), 1.76 – 1.64 (m, 1H), 1.59 – 1.44 (m, 3H), 1.43 – 1.32 (m, 3H), 1.11 (br s, 12H, CH_3 and *t*BuSi), 0.96 (s, 3H, CH_3), 0.92 (s, 9H, *t*BuSi), 0.47 (d, $J = 7.0$ Hz, 3H, CH_3), 0.10 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 144.5$, 135.9, 134.5, 133.8, 129.6, 129.5, 128.7, 128.1, 127.9, 127.9, 127.7, 127.6, 127.4, 126.8, 91.8, 86.9, 86.5, 84.6, 82.1, 82.0, 81.2, 77.8, 75.7, 68.8, 61.0, 59.8, 47.0, 37.4, 36.4, 36.2, 34.6, 34.4, 33.9, 33.0, 27.3, 27.0, 26.5, 25.8, 21.5, 19.5, 18.1, 16.4, 14.2, −5.5, −5.6; HRMS (FAB) calcd for $C_{68}H_{92}O_8Si_2$ ($[M + Cs^+]$) 1225.5385, found 1225.5353.

Pivaloate ester 16: A solution of alcohol **13b** (10 mg, 0.009 mmol) in CH_2Cl_2 (2 mL) at 25 °C was treated with 4-DMAP (2 mg, 0.016 mmol) and PivCl (2.0 µL, 0.014 mmol) for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with a aqueous ammonium chloride solution (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 2:8, EtOAc:hexanes) to afford **16** (10 mg, 94 %). **16**: $R_f = 0.65$ (silica gel, 2:8, EtOAc:hexanes); $[\alpha]_D^{25} = -5.7$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2956$, 2929, 2858, 1727, 1451, 1383, 1282, 1157, 1088, 1008, 836, 775, 741, 705, 508 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.73 - 7.70$ (m, 4H, ArH), 7.51 – 7.47 (m, 6H, ArH), 7.45 – 7.35 (m, 6H, ArH), 7.32 – 7.27 (m, 6H, ArH), 7.25 – 7.21 (m, 3H, ArH), 5.72 (ddd, $J = 10.5$, 8.0, 8.0 Hz, 1H, =CH), 5.53 (ddd, $J = 10.5$, 8.0, 8.0 Hz, 1H, =CH), 4.79 – 4.74 (m, 1H), 3.73 (ddd, $J = 8.5$, 4.5, 4.5 Hz, 1H), 3.68 – 3.57 (m, 2H), 3.54 (dd, $J = 9.0$, 9.0 Hz, 2H), 3.47 – 3.40 (m, 4H), 3.22 (ddd, $J = 9.0$, 9.0, 2.0 Hz, 1H), 3.17 (ddd, $J = 9.0$, 6.5, 3.5 Hz, 1H), 2.94 (ddd, $J = 9.0$, 9.0, 5.5 Hz, 1H), 2.80 (ddd, $J = 12.5$, 8.5, 4.0 Hz, 1H), 2.62 (br t, $J = 10.0$ Hz, 1H), 2.54 – 2.44 (m, 3H), 2.24 – 2.13 (m, 2H), 1.94 (ddd, $J = 12.0$, 4.5, 4.5 Hz, 1H), 1.87 (ddd, $J = 13.5$, 11.0, 2.5 Hz, 1H), 1.75 – 1.43 (m, 6H), 1.40 – 1.30 (m, 4H), 1.22 (s, 9H, *t*Bu), 1.15 (d, $J =$ 7.5 Hz, 3H, CH_3), 1.09 (s, 9H, *t*BuSi), 0.94 (s, 3H, CH_3), 0.86 (s, 9H, *t*BuSi), 0.47 (d, $J = 7.0$ Hz, 3H, CH_3), 0.01 (s, 3H, CH_3Si), 0.00 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.7$, 144.6, 135.9, 134.5, 133.8, 129.6, 129.5, 128.7, 127.7, 127.6, 127.5, 127.5, 126.8, 86.5, 84.4, 82.9, 82.1, 82.0, 77.9, 77.1, 77.0, 75.7, 69.1, 61.0, 58.5, 54.1, 47.0, 38.7, 37.4, 35.3, 34.8, 34.7, 34.5, 33.4, 29.7, 27.3, 27.2, 27.1, 27.0, 26.6, 25.8, 21.9, 19.5, 18.1, 16.5, −5.4; HRMS (FAB) calcd for $C_{73}H_{100}O_9Si_2$ ($[M + Cs^+]$) 1309.5960, found 1309.5879.

Alcohol 17: A solution of pivaloate ester **16** (10 mg, 0.008 mmol) in hexanes (5 mL) at 25 °C was treated with neutral alumina (300 mg, activated by heating at 80 °C for 20 h under high vacuum followed by addition of 1 % H_2O) for 10 h. The reaction mixture was filtered through a pad of celite eluting with EtOAc (50 mL), and the filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford **16** (8 mg, 89 %). **16**: $R_f = 0.62$ (silica gel, 4:6, EtOAc:hexanes); $[\alpha]_D^{25} = +2.5$ ($c = 0.8$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3432$, 2958, 2930, 1726, 1451, 1382, 1283, 1216, 1157, 1074, 1002, 824, 741, 705, 632, 612, 508 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.73 - 7.69$ (m, 4H, ArH), 7.51 – 7.47 (m, 6H, ArH), 7.45 – 7.35 (m, 6H, ArH), 7.32 – 7.26 (m, 6H, ArH), 7.25 – 7.21 (m, 3H, ArH), 5.75 (ddd, $J = 10.5$, 10.5, 8.0 Hz, 1H, =CH), 5.57 (ddd, $J = 10.5$, 10.5, 9.0 Hz, 1H, =CH), 4.90 (dd, $J = 5.5$, 5.5 Hz, 1H), 3.82 – 3.70 (m, 3H), 3.54 (ddd, $J = 10.0$, 10.0, 8.5 Hz, 1H), 3.48 – 3.35 (m, 4H), 3.21 – 3.14 (m, 2H), 2.94 (ddd, $J = 9.0$, 9.0, 5.5 Hz, 1H), 2.79 (ddd, $J = 12.5$, 8.5, 3.5 Hz, 1H), 2.70 (dd, $J = 11.5$, 11.5 Hz, 1H), 2.60 (dd, $J = 11.5$, 11.5 Hz, 1H), 2.52 – 2.46 (m, 1H), 2.43 (ddd, $J = 13.5$, 13.5, 7.0 Hz, 1H), 2.31 – 2.26 (m, 1H), 2.19 – 2.04 (m, 2H), 1.97 – 1.90 (m, 1H), 1.87 (ddd, $J = 14.5$, 11.0, 3.5 Hz, 1H), 1.84 – 1.78 (m, 1H), 1.75 – 1.65 (m, 2H), 1.56 – 1.42 (m, 3H),

1.39 – 1.30 (m, 3H), 1.23 (s, 9H, *t*Bu), 1.19 (d, $J = 7.5$ Hz, 3H), 1.09 (s, 9H, *t*BuSi), 0.93 (s, 3H, CH_3), 0.46 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.8$, 144.6, 135.9, 134.5, 133.8, 129.6, 129.5, 128.7, 128.0, 127.7, 127.6, 127.5, 127.4, 126.8, 86.5, 84.5, 82.4, 82.1, 81.5, 80.7, 77.9, 77.2, 76.3, 75.7, 61.0, 60.0, 54.1, 47.0, 36.0, 35.6, 35.4, 34.7, 32.6, 27.3, 27.2, 27.1, 26.5, 23.3, 23.1, 22.4, 19.6, 19.5, 16.5, 16.5; HRMS (FAB) calcd for $C_{67}H_{86}O_9Si$ ($[M + Cs^+]$) 1195.5095, found 1195.5157.

Phosphonium salt 3a: A solution of alcohol **17** (8 mg, 0.0075 mmol) in CH_2Cl_2 (1 mL) at 25 °C was treated with imidazole (0.9 mg, 0.0128 mmol), iodine (2 mg, 8.25 mmol) and triphenylphosphane (3.3 mg, 0.013 mmol) for 2 h. The reaction mixture was filtered through a pad of silica gel and concentrated to afford crude iodide **18**. Triphenylphosphane (20 mg, 0.075 mmol) and iodide **18** were fused at 90 °C for 3 h. The powder was cooled to 25 °C and purified by flash column chromatography (silica gel, 1:9, acetone:CH_2Cl_2) to afford phosphonium salt **3a**. **3a**: $R_f = 0.40$ (silica gel, 2:8, acetone:CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3055$, 2957, 2930, 1722, 1439, 1282, 1158, 1111, 1078, 702, 541 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.83 – 7.63$ (m, 17H, ArH), 7.55 – 7.34 (m, 14H, ArH), 7.30 – 7.20 (m, 9H, ArH), 5.74 (ddd, $J = 10.0$, 8.5, 8.5 Hz, 1H, =CH), 5.58 (ddd, $J = 10.0$, 10.0, 7.0 Hz, 1H, =CH), 4.84 (br m, 1H), 4.04 – 3.92 (m, 1H), 3.85 (br m, 1H), 3.55 – 3.35 (m, 5H), 3.34 – 3.24 (m, 1H), 3.20 – 3.11 (m, 2H), 2.91 (ddd, $J = 9.0$, 9.0, 5.0 Hz, 1H), 2.57 – 2.42 (m, 3H), 2.39 – 2.30 (m, 1H), 2.20 – 2.10 (m, 1H), 1.95 – 1.80 (m, 3H), 1.79 – 1.64 (m, 2H), 1.60 – 1.27 (m, 8H), 1.12 (s, 9H, *t*Bu), 1.08 (s, 9H, *t*Bu), 1.01 (d, $J = 7.5$ Hz, 3H, CH_3), 0.91 (s, 3H, CH_3), 0.45 (d, $J = 7.0$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 178.2$, 144.6, 135.9, 135.3, 134.5, 133.8, 133.7, 133.6, 132.1, 132.0, 131.9, 130.8, 130.7, 129.7, 129.5, 128.7, 128.5, 128.4, 127.7, 127.7, 127.5, 127.0, 126.8, 118.0, 117.3, 86.5, 84.4, 82.8, 82.3, 82.0, 80.2, 77.9, 75.8, 74.4, 68.9, 61.0, 54.2, 47.0, 38.7, 35.8, 35.0, 34.7, 33.9, 29.3, 27.3, 27.2, 27.1, 26.5, 26.1, 21.2, 19.5, 18.7, 18.2, 16.5.

Olefin 23: A solution of phosphine oxide **21** (39 mg, 0.10 mmol) in THF (1 mL) was treated dropwise with *n*-butyllithium (77 μL, 1.55 M solution in hexanes, 0.12 mmol) at −78 °C. After 10 min, aldehyde **2b** (44 mg, 0.050 mmol) was added as a solid, and the solution was stirred at −78 °C for 10 min and then quenched with water (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography (silica gel, 1:1, EtOAc:hexanes) to afford adduct **22** (52 mg, 83 %) as a mixture of diastereoisomers. Adduct **22** (40 mg, 0.032 mmol) was dissolved in DMF (2 mL) and treated with sodium hydride (2.6 mg, 60 % dispersion in mineral oil, 0.064 mmol) at 25 °C for 1 h. The mixture was diluted with ether (10 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography to yield olefin **23** (26 mg, 78 %) as a 2:3 mixture of *Z*:*E* isomers. **23** (*Z* isomer): $R_f = 0.45$ (silica gel, 1:9, EtOAc:hexanes); **23** (*E* isomer): $R_f = 0.43$ (silica gel, 1:9, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2928$, 2855, 1467, 1384, 1252, 1102, 1056, 835, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.66 – 7.62$ (m, 4H, ArH), 7.46 – 7.30 (m, 6H, ArH), 5.95 – 5.62 (m, 2H, CH=CH), 4.37 (br s, 1H), 4.12 – 4.10 (m, 1H), 3.80 – 3.71 (m, 2H), 3.65 (t, 2H, $J = 6.0$ Hz), 3.61 (t, 2H, $J = 7.0$ Hz), 3.30 (t, $J = 9.5$ Hz, 1H), 3.20 – 3.12 (m, 1H), 3.01 – 2.94 (m, 2H), 2.74 – 2.55 (m, 4H), 2.42 – 2.34 (m, 1H), 2.30 – 1.89 (m, 10H), 1.81 (br d, $J = 15.0$ Hz, 1H), 1.72 – 1.57 (m, 8H), 1.24 (s, 3H, CH_3), 1.21 (t, $J = 7.5$ Hz, 3H, CH_3), 1.16 (t, $J = 7.5$ Hz, 3H, CH_3), 1.03 (s, 9H, *t*Bu), 0.88 (s, 9H, *t*Bu), 0.86 (s, 9H, *t*Bu), 0.04 (s, 6H, $SiCH_3$), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); HRMS calcd for $C_{57}H_{96}O_7S_2Si_3$ ($[M + Cs^+]$) 1173.4960, found 1173.4904.

Mesylate 27: To a solution of alcohol **24** (130 mg, 0.30 mmol) in 2-methoxypropene (2.0 mL) was introduced a trace amount of $POCl_3$ (2.0 μL) by capillary. The resulting solution was kept at 25 °C for 1 h. After addition of Et_3N (0.1 mL), the reaction mixture was concentrated. The residue was dissolved in THF (5.0 mL) and treated with TBAF (0.6 mL of 1 M solution in THF, 0.60 mmol) for 1 h. The solution was diluted with ether (20 mL), washed with brine (50 mL), and dried ($MgSO_4$). Filtration through silica gel and concentration gave essentially pure alcohol **26**, which was dissolved in CH_2Cl_2 (5.0 mL) and treated with Et_3N (0.13 mL, 0.90 mmol) and methanesulfonyl chloride (0.52 μL, 0.45 mmol) at 0 °C for 30 min. The reaction mixture was diluted, washed with brine (50 mL), and dried ($MgSO_4$). Filtration, concentration, and flash column chromatography (silica gel, 3:7, EtOAc:hexanes) gave the mesylate **27** (121 mg, 85 % for three steps). **27**: colorless oil; $R_f = 0.60$ (silica gel, 1:1, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2989$, 2842, 1454, 1381, 1206, 1140, 1088, 1050, 844, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.49 – 7.45$ (m, 2H, ArH), 7.38 – 7.32 (m, 3H, ArH), 5.81 – 5.71 (m, 2H, CH=CH), 5.43 (s, 1H, PhCH), 4.36 – 4.25 (m, 3H), 3.82 – 3.80 (m, 1H), 3.75 (ddd, $J = 9.5$, 9.5, 4.5 Hz, 1H), 3.67 (ddd, $J = 9.0$, 4.0, 4.0 Hz, 1H), 3.59 (d, $J = 10.0$ Hz, 1H), 3.56 (ddd, $J = 7.0$, 7.0, 4.5 Hz, 1H), 3.25 (s, 3H, OCH_3), 3.02 (s, 3H, SO_2CH_3), 2.75 (br m, 1H), 2.61 – 2.57 (m, 1H), 2.52 – 2.41 (m, 2H), 2.06 – 2.01 (m, 1H), 1.92 – 1.87 (m, 1H), 1.38 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.5$, 130.2, 128.9, 128.2, 126.1, 125.9, 101.2, 101.0, 82.9, 78.7, 76.0, 74.0, 69.6, 66.5, 49.3, 37.5, 34.2, 31.5, 30.6, 25.2, 25.1; HRMS calcd for $C_{23}H_{34}O_8S$ ($[M + Na^+]$) 493.1872, found 493.1887.

Phosphine oxide 28: A solution of mesylate **27** (120 mg, 0.25 mmol) and HMPA (0.13 mL, 0.75 mmol) in THF (5.0 mL) was treated dropwise with lithium diphenylphosphide (ca. 0.38 M solution in THF, prepared from diphenylphosphane and *n*-butyllithium) until the color of the reaction mixture became persistently orange. After 10 min at 0 °C, the reaction mixture was treated with water (5.0 mL) and 5 % hydrogen peroxide (2.0 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed successively with sodium sulfite (10 mL) and saturated aqueous sodium bicarbonate solution (20 mL), and dried ($MgSO_4$). Filtration, concentration and chromatography (silica gel, 1 % Et_3N in EtOAc) gave the phosphine oxide **28** (122 mg, 85 %). **28**: colorless oil; $R_f = 0.50$ (silica gel, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 2928$, 1438, 1377, 1183, 1099, 1030, 698 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): $\delta = 7.89 – 7.86$ (m, 4H, ArH), 7.73 – 7.70 (m, 2H, ArH), 7.28 – 7.18 (m, 3H, ArH), 7.11 – 7.09 (m, 6H, ArH), 5.91 – 5.82 (m, 2H, CH=CH), 5.39 (s, 1H, PhCH), 4.21 (dd, $J = 10.0$, 3.5 Hz, 1H), 3.83 (dd, $J = 6.5$, 6.5 Hz, 1H), 3.67 – 3.59 (m, 2H), 3.43 – 3.38 (m, 2H), 3.11 (s, 3H, OCH_3), 2.85 (br m, 1H), 2.61 (dd, $J = 10.5$, 8.5 Hz, 1H), 2.54 – 2.49 (br m, 1H), 2.41 – 2.29 (m, 3H), 2.12 – 2.06 (m, 1H), 1.92 – 1.81 (m, 1H), 1.25 (s, 3H, CH_3), 1.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 137.6$, 133.4, 133.1, 132.9, 132.5, 132.1, 131.7, 130.8, 130.6, 130.1, 128.9, 128.5, 126.0, 101.2, 101.0, 85.4, 79.0, 72.6, 70.0, 49.2, 29.6, 25.7, 25.2, 25.1, 25.0, 24.5; HRMS calcd for $C_{34}H_{41}O_6P$ ($[M + Na^+]$) 599.2538, found 599.2556.

Olefin 29: A solution of phosphine oxide **28** (29 mg, 0.050 mmol) in THF (2 mL) was treated dropwise with *n*-butyllithium (48 μL, 1.55 M solution in hexanes, 0.075 mmol) at −78 °C. The resulting orange-colored solution was stirred at −78 °C for 10 min and then freshly distilled benzaldehyde (10 μL, 0.10 mmol) was added. After 10 min at −78 °C, the reaction mixture was quenched with water (5 mL) and extracted with EtOAc. The organic phase was dried ($MgSO_4$), filtered through a short plug of silica gel, and concentrated to give an oily residue composed of a mixture of Horner–Wittig adducts. The adducts were dissolved in dry DMF (1.0 mL) and treated with potassium hydride (4.0 mg, 0.10 mmol) at 25 °C for 30 min. The mixture was diluted with ether (10 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:9, EtOAc:hexanes) to afford olefin **29** as a single isomer (29 mg, 85 % for two steps). **29**: colorless oil; $R_f = 0.30$ (silica gel, 1:9, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2929$, 1452, 1379, 1204, 1100, 1027, 772, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.48 – 7.46$ (m, 2H, ArH), 7.38 – 7.29 (m, 7H, ArH), 7.24 – 7.21 (m, 1H, ArH), 6.56 (d, $J = 11.5$ Hz, 1H, =CH), 5.86 – 5.73 (m, 2H, =CH), 5.76 (ddd, $J = 11.5$, 8.5, 6.5 Hz, 1H, =CH), 5.41 (s, 1H, PhCH), 4.35 (dd, $J = 10.5$, 4.5 Hz, 1H), 3.81 – 3.79 (m, 1H), 3.70 (ddd, $J = 9.0$, 5.0, 5.0 Hz, 1H), 3.63 (ddd, $J = 12.0$, 10.0, 4.5 Hz, 1H), 3.54 – 3.43 (m, 2H) 3.21 (s, 3H, OCH_3), 2.77 (br m, 1H), 2.65 – 2.49 (m, 5H) 1.27 (s, 6H, CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz): $\delta = 137.8$, 137.2, 131.1, 130.4, 128.9, 128.7, 128.3, 128.2, 126.7, 126.2, 126.1, 101.2, 101.1, 86.6, 79.3, 74.0, 70.4, 65.8, 49.2, 33.4, 30.6, 25.3, 25.0, 15.2; HRMS calcd for $C_{29}H_{36}O_5$ ($[M + Na^+]$) 487.2460, found 487.2445.

***cis*-Olefin 31**: A solution of phosphine oxide **28** (110 mg, 0.191 mmol) in THF (5 mL) was treated dropwise with *n*-butyllithium (148 μL, 1.55 M solution in hexanes, 0.229 mmol) at −78 °C. The resulting orange-colored solution was stirred at −78 °C for 10 min before adding aldehyde **2b** (249 mg, 0.286 mmol) as a solid in one portion. After 10 min at −78 °C, the reaction mixture was quenched with water (20 mL) and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated to give an oily residue which was purified by flash column chromatography (silica gel, 6:4, EtOAc:hexanes) to yield adduct **30** as a mixture of diastereoisomers (145 mg, 0.168 mmol, 88 %). The adduct **30** (145 mg, 0.168 mmol) was dissolved in dry DMF (4.0 mL) and treated with potassium hydride (27 mg, 0.336 mmol) for 30 min, followed by addition of *tert*-butyldiphenylsilyl chloride (87.4 mL, 0.336 mmol) and imidazole (34.3 mg, 0.504 mmol) and stirred for an additional 30 min. The reaction mixture was diluted with

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ether (20 mL) and washed with water (2 × 10 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 2:8, EtOAc:hexanes) to yield *cis*-olefin **31** (180 mg, 77% for two steps) as a single isomer. **31**: amorphous solid; R_f = 0.40 (silica gel, 2:8, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2939, 2858, 1453, 1378, 1206, 1125, 1089, 1049, 846, 755 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ = 7.88–7.68 (m, 6H, ArH), 7.33–7.20 (m, 9H, ArH), 6.09 (dd, J = 9.5, 9.5 Hz, 1H, =CH), 5.98–5.83 (m, 2H, =CH), 5.70–5.68 (m, 1H, =CH), 5.42 (s, 1H, PhCH), 4.85 (d, J = 8.0 Hz, 1H), 4.52 (dd, J = 10.5, 5.0 Hz, 1H), 4.04 (m, 1H), 4.00–3.91 (m, 2H), 3.89–3.75 (m, 5H), 3.66 (ddd, J = 9.0, 5.0, 5.0 Hz, 1H), 3.59 (dd, J = 10.0, 10.0 Hz, 1H), 3.52 (m, 1H), 3.43 (d, J = 9.0 Hz, 1H), 3.21–3.15 (m, 1H), 3.16 (s, 3H, OCH_3), 3.05 (m, 1H), 2.96–2.83 (m, 2H), 2.81–2.72 (m, 2H), 2.67 (dq, J = 11.5, 7.5 Hz, 1H, SC*H*H), 2.62–2.43 (m, 6H), 2.38–2.31 (m, 1H), 2.33 (q, J = 7.5 Hz, 2H, SC*H*H), 2.23–2.03 (br m, 2H), 2.03–1.59 (m, 10H), 1.41 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.25 (s, 9H, *t*Bu), 1.16 (t, J = 7.5 Hz, 3H, CH_3), 1.04 (s, 9H, *t*Bu), 0.90 (t, J = 7.5 Hz, 3H, CH_3), 0.21 (s, 3H, CH_3Si), 0.15 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, C_6D_6): δ = 138.9, 136.1, 136.0, 135.3, 134.4, 133.6, 130.8, 129.9, 129.8, 129.7, 128.8, 127.9, 126.8, 126.6, 101.5, 101.3, 85.5, 83.2, 80.7, 79.2, 79.2, 77.2, 76.2, 75.0, 74.1, 72.5, 70.4, 68.6, 67.5, 65.9, 64.3, 62.5, 49.2, 46.0, 36.4, 36.1, 34.3, 31.1, 30.7, 29.5, 27.1, 26.7, 26.2, 25.6, 25.4, 23.0, 21.2, 19.4, 19.2, 18.5, 16.8, 15.4, 14.5, 13.9, 11.2, −4.0, −5.0; HRMS calcd for $C_{69}H_{104}O_{11}S_2Si_2$ ([M + Cs^+]) 1361.5613, found 1361.5675.

Mixed thioketal 33: A solution of the protected hydroxy dithioketal **31** (70 mg, 0.057 mmol) in a mixture of THF (8.0 mL) and 30% aqueous acetic acid (4.0 mL) was stirred at 25 °C for 3 h. The reaction mixture was diluted with ether (30 mL) and washed with saturated aqueous sodium bicarbonate solution (2 × 20 mL). The organic layer was dried ($MgSO_4$), concentrated to a small volume, and filtered through a short path of silica gel to yield essentially pure hydroxy dithioketal **32** (66 mg, 100%). Hydroxy dithioketal **32** (66 mg, 0.057 mmol) was mixed with powdered 4 Å molecular sieves (300 mg), sodium bicarbonate (200 mg), and silver perchlorate (35 mg, 0.17 mmol) in nitromethane (3.0 mL). The mixture was vigorously stirred at 25 °C for 3 h and then diluted with ether (20 mL), and filtered through silica gel. The filtrate was washed with saturated aqueous sodium bicarbonate solution (2 × 10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 2:8, EtOAc:hexanes) to yield the mixed thioketal **33** (48 mg, 77%). **33**: amorphous solid; R_f = 0.45 (silica gel, 2:8, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2939, 2858, 1377, 1208, 1124, 1049, 847, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.69–7.64 (m, 4H, ArH), 7.50–7.46 (m, 2H, ArH), 7.43–7.33 (m, 9H, ArH), 5.93–5.60 (br m, 4H, =CH), 5.45 (s, 1H, PhCH), 4.60 (br s, 1H), 4.40–4.25 (m, 2H), 4.16–4.09 (m, 1H), 3.92 (br s, 1H), 3.81–3.71 (m, 2H), 3.70–3.62 (m, 4H), 3.48 (br m, 1H), 3.38–3.30 (m, 1H), 3.13 (br m, 1H), 3.04–2.93 (m, 2H), 2.84 (br m, 1H), 2.68 (br m, 1H), 2.54–2.47 (m, 1H), 2.31–2.19 (m, 2H), 2.80–1.50 (m, 15H), 1.59 (s, 3H, CH_3), 1.46–1.12 (m, 4H, CH_2), 1.26 (t, J = 7.5 Hz, 3H, CH_3), 1.05 (s, 9H, *t*Bu), 0.87 (s, 9H, *t*Bu), 0.03 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$); HRMS calcd for $C_{63}H_{90}O_{10}SSi_2$ ([M + Cs^+]) 1227.4848, found 1227.4932.

Spiro ether 34: A mixture of the mixed thioketal **33** (15 mg, 0.013 mmol), 2,2′-azobis(isobutyronitrile) (0.5 mg) and triphenyltin hydride (49 mg, 0.13 mmol) in toluene (0.5 mL) was heated at 110 °C for 3 h. The mixture was concentrated and subjected to preparative TLC (silica gel, 2:8 EtOAc:benzene) to give the spiro ether **34** (6.5 mg, 48%). **34**: amorphous solid; R_f = 0.48 (silica gel, 2:8, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2926, 2855, 1462, 1254, 1104, 836, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.65 (m, 4H, ArH), 7.48–7.45 (m, 2H, ArH), 7.43–7.32 (m, 9H, ArH), 5.77–5.59 (br m, 3H, =CH), 5.42 (s, 1H, PhCH), 5.17 (dd, J = 11.5, 1.5 Hz, 1H, =CH), 4.22–4.15 (m, 1H), 4.14–4.12 (m, 1H), 4.00–3.89 (br m, 1H), 3.81–3.73 (m, 2H), 3.69–3.56 (m, 5H), 3.54–3.42 (m, 2H), 3.13 (ddd, J = 11.0, 9.1, 4.5 Hz, 1H), 2.98 (dd, J = 9.5, 2.5 Hz, 1H), 2.97–2.92 (m, 1H), 2.93–2.78 (br m, 2H), 2.40–2.20 (m, 4H), 2.19–2.08 (br m, 1H), 2.08–1.98 (br m, 1H), 1.95 (ddd, J = 14.0, 7.0, 2.5 Hz, 1H), 1.90–1.83 (m, 1H), 1.79–1.49 (m, 14H), 1.56 (s, 3H, CH_3), 1.05 (s, 9H, *t*Bu), 0.87 (s, 9H, *t*Bu), 0.05 (s, 3H, CH_3), 0.04 (s, 3H, CH_3); HRMS calcd for $C_{61}H_{86}O_{10}Si_2$ ([M + Cs^+]) 1167.4814, found 1167.4871.

Sulfone 36: A solution of the mixed thioketal **33** (4.2 mg, 0.0038 mmol) in CH_2Cl_2 (0.5 mL) was treated with *m*-CPBA (1.6 mg, 0.0091 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, diluted with ether (5 mL) and washed with a 1M aqueous sodium sulfite solution (2 mL) followed by a saturated aqueous sodium bicarbonate solution (2 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by preparative TLC to yield sulfone **36** (3.9 mg, 92%). **36**: amorphous solid; R_f = 0.60 (silica gel, 3:7, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2939, 2858, 1453, 1377, 1260, 1207 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 4H, ArH), 7.49–7.32 (m, 11H, ArH), 5.97 (dd, J = 10.5, 6.0 Hz, 1H, =CH), 5.80–5.69 (m, 2H, =CH), 5.57 (br m, 1H, =CH), 5.43 (s, 1H, PhH), 4.78 (d, J = 6.0 Hz, 1H), 4.72 (br m, 1H), 4.27 (br m, 1H), 4.14–4.12 (m, 1H), 3.81–3.72 (m, 3H), 3.70–3.61 (m, 4H), 3.51–3.42 (br m, 1H), 3.70–3.30 (m, 2H), 3.21 (ddd, J = 13.5, 7.5, 7.5 Hz, 1H), 3.19–3.12 (m, 1H), 3.02–2.92 (m, 2H), 2.79 (br m, 1H), 2.72 (br m, 1H), 2.63 (br m, 1H), 2.38–2.13 (m, 6H), 2.07–1.85 (m, 5H), 1.69 (dd, J = 14.0, 3.0 Hz, 1H), 1.67–1.61 (m, 2H), 1.61–1.52 (m, 1H), 1.46–1.42 (m, 1H), 1.50–1.40 (m, 3H), 1.43 (t, J = 7.5 Hz, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.04 (s, 9H, *t*Bu), 0.87 (s, 9H, *t*Bu), 0.03 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 137.6, 136.0, 135.5, 134.0, 130.7, 129.5, 129.0, 128.3, 127.6, 127.5, 126.1, 125.3, 125.0, 101.1, 92.01, 83.6, 81.8, 80.1, 78.9, 77.5, 76.9, 76.8, 76.1, 73.3, 72.7, 71.0, 70.5, 67.0, 63.8, 62.0, 44.7, 44.0, 35.7, 35.5, 34.7, 33.4, 31.6, 30.1, 29.7, 29.1, 26.9, 25.8, 19.2, 18.3, 17.1, 16.5, 15.3, 5.2, −4.5, −5.0; HRMS calcd for $C_{63}H_{90}O_{12}SSi_2$ ([M + Cs^+]) 1259.4746, found 1259.4817.

Oxocene 38: A solution of sulfone **36** (3.6 mg, 0.0032 mmol) in triethylsilane (0.2 mL) and CH_2Cl_2 (1.2 mL) was treated with $BF_3 \cdot OEt_2$ (2.5 μL, 0.016 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h before being diluted with ether (10 mL) and washed with saturated aqueous sodium bicarbonate solution (2 × 5 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by preparative TLC (silica gel, 2:8, EtOAc:hexanes) to afford oxocene **38** (3.0 mg, 90%); **38**: amorphous solid; R_f = 0.30 (silica gel, 2:8, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2927, 2856, 1465, 1253, 1103, 637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.64 (m, 4H, ArH), 7.49–7.33 (m, 11H, ArH), 5.71 (dd, J = 11.0, 5.5 Hz, 1H, =CH), 5.95–5.61 (br m, 2H, =CH), 5.57 (dt, J = 11.0, 7.8 Hz, 1H, =CH), 5.43 (s, 1H, PhH), 4.42 (m, 1H), 4.31–4.31 (m, 1H), 4.14–4.11 (m, 1H), 3.81–3.72 (m, 3H), 3.69–3.58 (m, 3H), 3.51–3.41 (br m, 1H), 3.27 (d, J = 9.0 Hz, 1H), 3.18–3.16 (m, 1H), 3.01–2.94 (m, 2H), 2.89–2.76 (m, 3H), 2.31–2.16 (m, 4H), 2.15–2.05 (m, 3H), 1.98–1.82 (m, 4H), 1.79–1.50 (m, 10H), 1.57 (s, 3H, CH_3), 1.38–1.44 (m, 1H), 1.04 (s, 9H, *t*BuSi), 0.86 (s, 9H, *t*BuSi), 0.03 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 138.5, 137.5, 135.5, 134.0, 129.4, 128.9, 128.1, 127.5, 127.0, 126.0, 124.0, 101.4, 92.9, 84.6, 83.6, 83.2, 80.2, 78.7, 78.5, 76.1, 72.7, 70.8, 67.0, 65.9, 63.8, 62.0, 44.9, 36.0, 35.7, 35.7, 34.1, 33.0, 30.1, 29.7, 29.1, 26.9, 25.9, 19.2, 18.2, 16.5, 15.3, −4.3, −5.2; HRMS calcd for $C_{61}H_{86}O_{10}SSi_2$ ([M + Cs^+]) 1167.4814, found 1167.4870.

Mixed ketal 39: A solution of alcohol **13b** (235 mg, 0.212 mmol) in 2-methoxypropene (10 mL) was treated with phosphoryl trichloride (5 μL) at 25 °C for 15 h. The reaction mixture was quenched by addition of E_3N (0.5 mL) and concentrated. The residue was purified by flash column chromatography (silica gel, 2:8, ether:hexanes) to afford the desired mixed ketal **39** (235 mg, 96%). **39**: R_f = 0.42 (silica gel, 2:8, ether:hexanes); $[\alpha]_D^{25}$ = −0.6 (c = 1.0, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max}$ = 2929, 2861, 1449, 1428, 1380, 1256, 1206, 1074, 1032, 836, 774, 742, 705, 632, 610, 510 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ = 7.90–7.86 (m, 4H, ArH), 7.73–7.69 (m, 6H, ArH), 7.28–7.18 (m, 12H, ArH), 7.12–7.07 (m, 3H, ArH), 6.16 (ddd, J = 10.5, 10.5, 6.5 Hz, 1H, =CH), 5.99 (ddd, J = 10.5, 10.5, 7.0 Hz, 1H, =CH), 4.06–3.92 (m, 3H), 3.78 (ddd, J = 10.0, 10.0, 4.0 Hz, 1H), 3.70 (dd, J = 9.5, 9.5 Hz, 1H), 3.67–3.59 (m, 2H), 3.56 (ddd, J = 10.0, 5.0, 5.0 Hz, 1H), 3.47–3.36 (m, 3H), 3.29–3.22 (m, 1H), 3.17 (s, 3H, OCH_3), 3.16–3.09 (m, 1H), 2.83–2.74 (m, 2H), 2.70 (dd, J = 11.5, 11.5 Hz, 1H), 2.43–2.26 (m, 3H), 2.17 (ddd, J = 11.5, 11.5, 2.0 Hz, 1H), 2.06 (ddd, J = 11.5, 4.5, 4.5 Hz, 1H), 1.94–1.81 (m, 2H), 1.74 (d, J = 13.5 Hz, 1H), 1.66–1.47 (m, 7H), 1.31 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.31 (d, J = 7.0 Hz, 3H, CH_3), 1.26 (s, 9H, *t*BuSi), 1.02 (s, 3H, CH_3), 0.93 (s, 9H, *t*BuSi), 0.52 (d, J = 6.0 Hz, 3H, CH_3), 0.02 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, C_6D_6): δ = 145.1, 136.3, 134.9, 134.3, 130.3, 130.1, 130.0, 129.2, 128.1, 127.9, 127.2, 126.5, 100.7, 87.2, 84.5, 83.3, 82.5, 82.0, 78.5, 77.5, 75.8, 75.6, 69.6, 61.7, 59.2, 54.8, 48.8, 47.5, 37.9, 36.6, 35.4, 35.3, 34.6, 32.6, 27.6, 27.3, 26.8, 26.0, 25.5, 25.4, 24.6, 23.0, 19.8, 18.2, 16.7, −5.3, −5.4; HRMS (FAB) calcd for $C_{72}H_{100}O_9Si_2$ ([M + Cs^+]) 1297.5960, found 1297.5902.

Alcohol 40: A solution of mixed ketal **39** (220 mg, 0.189 mmol) in hexanes (20 mL) was treated with neutral alumina (5 g, activated by heating at 80 °C for 20 h under high vacuum followed by addition of 1% H_2O) at 25 °C for 20 h. The alumina was filtered off and washed with EtOAc (100 mL). The filtrate was concentrated, and the residue was purified by flash column

chromatography (silica gel, 4:6, EtOAc:hexanes) to afford alcohol **40** (198 mg, 86%). **40**: $R_f = 0.33$ (silica gel, 4:6, EtOAc:hexanes); $[\alpha]_D^{25} = +9.0$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3477, 2930, 1450, 1380, 1206, 1074, 1030, 864, 823, 743, 704, 632\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.90-7.85$ (m, 4H, ArH), 7.74–7.68 (m, 6H, ArH), 7.28–7.19 (m, 12H, ArH), 7.12–7.07 (m, 3H, ArH), 6.12 (ddd, $J = 10.5, 10.5, 6.5$ Hz, 1H, =CH), 5.94 (ddd, $J = 10.5, 10.5, 7.5$ Hz, 1H, =CH), 3.98 (d, $J = 8.0$ Hz, 1H), 3.81 (dd, $J = 9.5, 1.5$ Hz, 2H), 3.75–3.63 (m, 3H), 3.59 (ddd, $J = 11.0, 6.5, 1.5$ Hz, 1H), 3.53–3.47 (m, 1H), 3.45 (dd, $J = 11.5, 5.0$ Hz, 1H), 3.41–3.33 (m, 2H), 3.28–3.21 (m, 1H), 3.07 (s, 3H, OCH_3), 3.07–2.98 (m, 1H), 2.83–2.74 (m, 1H), 2.73–2.63 (m, 2H), 2.34–2.21 (m, 3H), 2.14–2.01 (m, 2H), 1.95–1.87 (m, 1H), 1.83–1.72 (m, 2H), 1.68–1.47 (m, 7H), 1.26 (s, 9H, *t*BuSi), 1.25 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.22 (d, $J = 6.0$ Hz, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.52 (d, $J = 5.5$ Hz, CH_3); ^{13}C NMR (125.7 MHz, C_6D_6): $\delta = 145.2, 136.3, 134.9, 134.3, 130.1, 130.0, 129.2, 128.3, 128.1, 127.9, 127.2, 126.8, 100.9, 87.2, 84.5, 83.5, 83.1, 82.4, 81.9, 81.2, 78.5, 75.7, 75.0, 69.5, 61.7, 60.2, 54.8, 48.9, 47.6, 36.8, 36.6, 35.4, 35.2, 35.2, 32.6, 27.6, 27.4, 27.3, 26.8, 25.3, 25.3, 22.7, 19.8, 16.7$; HRMS (FAB) calcd for $C_{66}H_{86}O_9Si$ ($[M + Cs^+]$) 1183.5095, found 1183.5149.

Phosphine oxide 3b: A solution of alcohol **40** (170 mg, 0.16 mmol) in CH_2Cl_2 (8 mL) was treated with Et_3N (90 μL, 0.65 mmol) and mesyl chloride (25 μL, 0.32 mmol) at 0 °C for 15 min. The reaction mixture was quenched by pouring into saturated aqueous bicarbonate solution (25 mL), and the product was extracted into CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford mesylate **41**. A solution of crude mesylate **41** and HMPA (400 μL) in THF (20 mL) was treated dropwise with lithium diphenylphosphide (ca. 0.38 M solution in THF, prepared from diphenylphosphane and *n*-butyllithium) until the color of the reaction mixture became persistently orange. After 10 min at 0 °C, the reaction mixture was treated with water (5.0 mL) and 1% aqueous hydrogen peroxide (2.0 mL) and extracted with EtOAc (3 × 10 mL). The organic layers were dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 2:8, acetone:hexanes) to afford phosphine oxide **3b** (190 mg, 95%). **3b**: $R_f = 0.15$ (silica gel, EtOAc); $[\alpha]_D^{25} = +15.4$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3056, 2930, 1593, 1449, 1379, 1310, 1262, 1202, 1074, 1038, 901, 823, 741, 704, 632\ cm^{-1}$; ^1H NMR (500 MHz, C_6D_6): $\delta = 7.89-7.85$ (m, 4H), 7.85–7.75 (m, 4H), 7.72–7.68 (m, 6H), 7.28–7.20 (m, 12H), 7.13–7.08 (m, 3H), 7.05–6.93 (m, 6H), 6.11 (ddd, $J = 10.0, 10.0, 6.5$ Hz, 1H), 5.98 (ddd, $J = 10.0, 10.0, 6.5$ Hz, 1H, =CH), 3.99 (br s, 1H), 3.71 (dd, $J = 9.0, 9.0$ Hz, 1H), 3.68–3.57 (m, 3H), 3.50 (dd, $J = 9.0, 2.5$ Hz, 1H), 3.44 (dd, $J = 11.5, 5.0$ Hz, 1H), 3.42–3.35 (m, 1H), 3.29 (dd, $J = 10.0, 10.0$ Hz, 1H), 323 (ddd, $J = 9.0, 9.0, 5.5$ Hz, 1H), 3.14 (s, 3H), 3.04–2.95 (m, 1H), 2.78 (ddd, $J = 15.0, 7.5, 7.5$ Hz, 1H), 2.73–2.62 (m, 2H), 2.47–2.28 (m, 5H), 2.19–2.08 (m, 1H), 2.08–1.85 (m, 5H), 1.74 (d, $J = 14.0$ Hz, 1H), 1.67–1.52 (m, 5H), 1.27 (s, 3H, CH_3), 1.25 (s, 9H, *t*BuSi), 1.23 (s, 3H, CH_3), 0.99 (d, $J = 7.0$ Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 0.51 (d, $J = 6.0$ Hz, 3H, CH_3); ^{13}C NMR (C_6D_6, 125.7 MHz): $\delta = 145.2, 136.3, 135.5, 135.2, 134.9, 134.7, 134.4, 134.3, 131.3, 131.1, 131.1, 131.0, 130.1, 130.0, 129.9, 129.2, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.2, 127.1, 101.2, 87.2, 84.4, 83.4, 83.3, 83.0, 82.3, 82.0, 78.5, 75.7, 73.5, 69.4, 61.6, 54.8, 49.2, 47.5, 36.7, 36.0, 35.4, 35.2, 33.2, 29.3, 27.6, 27.3, 26.7, 25.6, 25.5, 25.3, 25.1, 22.3, 19.7, 16.6$; MS (FAB) calcd for $C_{78}H_{95}O_9PSi$ ($[M + Cs^+]$) 1367.5537, found 1367.5712.

Dithioketal 43: A solution of phosphine oxide **3b** (125 mg, 0.10 mmol) in THF (5 mL) was treated dropwise with *n*-butyllithium (65 μL of 1.55 M solution in hexanes, 0.10 mmol) at −78 °C for 10 min before adding aldehyde **2b** (131 mg, 0.15 mmol) as a solid in one portion. After 45 min at −78 °C, the reaction mixture was quenched by addition of water (20 mL), and extracted with EtOAc (3 × 20 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 5:5, EtOAc:hexanes) to afford Horner–Wittig adduct **42a, b** (300 mg, 0.142 mmol). A solution of Horner–Wittig adduct **42a, b** (300 mg, 0.142 mmol) in DMF (10 mL) was treated with potassium hydride (5.7 mg, 0.142 mmol) at 25 °C for 30 min. The reaction was quenched by addition of water (50 mL) and extracted into EtOAc (3 × 25 mL). The organic layer was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:4, EtOAc:hexanes) to afford dithioketal **43** (200 mg, 56%). **43**: $R_f = 0.54$ (silica gel, 1:3, EtOAc:hexanes); $[\alpha]_D^{25} = +35.6$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2931, 2858, 1458, 1451, 1381, 1329, 1254, 1205, 1146, 1106, 1031, 937, 828, 776, 742, 705\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 7.89-7.85$ (m, 4H, ArH), 7.82–7.78 (m, 4H, ArH), 7.73–7.68 (m, 6H, ArH), 7.28–7.20 (m, 18H, ArH), 7.13–7.08 (m, 3H, ArH), 6.17 (ddd, $J = 10.7, 10.7, 6.4$ Hz, 1H, =CH), 6.10–5.95 (m, 2H, =CH), 5.72 (br m, 1H, =CH), 4.81 (d, $J = 8.7$ Hz, 1H), 4.52 (d, $J = 2.9$ Hz, 1H), 4.21 (d, $J = 7.6$ Hz, 1H), 3.99 (br s, 1H), 3.91–3.84 (m, 2H), 3.82 (br m, 1H), 3.77 (t, $J = 6.4$ Hz, 2H), 3.75–3.65 (m, 4H), 3.64 (ddd, $J = 10.5, 10.5, 2.3$ Hz, 1H), 3.43 (dd, $J = 11.4, 4.8$ Hz, 1H), 3.41–3.35 (m, 3H), 3.28–3.21 (m, 1H), 3.15 (s, 3H, OCH_3), 3.15–3.10 (m, 2H), 3.01–2.97 (m, 1H), 2.86–2.71 (m, 5H), 2.71–2.60 (m, 4H), 2.50–2.25 (m, 9H), 2.16–2.10 (m, 1H), 2.08–1.96 (m, 2H), 1.91–1.52 (m, 15H), 1.49 (dd, $J = 14.1, 3.1$ Hz, 1H), 1.37 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.26 (s, 9H, *t*Bu), 1.25 (s, 3H, CH_3), 1.19 (s, 9H, *t*Bu), 1.11 (t, $J = 7.5$ Hz, 3H, CH_3), 1.07 (t, $J = 7.5$ Hz, 3H, CH_3), 1.01 (d, $J = 7.0$ Hz, 3H, CH_3), 0.99 (s, 9H, *t*Bu), 0.52 (d, $J = 6.5$ Hz, 3H, CH_3), 0.15 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); ^{13}C NMR (150.9 MHz, C_6D_6): $\delta = 145.2, 136.3, 136.3, 136.0, 135.9, 134.9, 134.4, 134.3, 130.1, 130.0, 129.9, 129.2, 128.5, 128.2, 127.7, 127.3, 101.1, 87.2, 84.5, 83.2, 82.9, 82.4, 82.1, 81.7, 80.8, 79.1, 78.5, 77.3, 76.2, 75.6, 74.3, 73.9, 72.4, 69.5, 68.9, 67.5, 64.3, 62.4, 61.7, 54.8, 49.0, 47.5, 45.1, 36.7, 36.5, 36.2, 35.4, 35.3, 35.2, 34.3, 30.7, 30.4, 30.2, 29.6, 27.7, 27.6, 27.3, 27.1, 26.7, 26.2, 26.2, 25.5, 25.4, 25.4, 23.1, 22.8, 21.1, 19.8, 19.5, 18.6, 16.8, 16.7, 14.6, 13.9, −3.9, −4.9$; MS (FAB) calcd for $C_{113}H_{158}O_{14}S_2Si_3$ ($[M + Cs^+]$) 2019.9455, found 2019.9607.

Hydroxy dithioketal 44: A solution of dithioketal **43** (200 mg, 0.106 mmol) in THF (10 mL) was treated with acetic acid (10 mL of 30% aqueous) at 25 °C for 36 h. The reaction mixture was diluted with ether (50 mL) and washed with saturated aqueous sodium bicarbonate solution (2 × 50 mL). The organic layer was dried ($MgSO_4$), concentrated and purified by flash column chromatography (silica gel, 1:4, EtOAc:hexanes) to afford hydroxy dithioketal **44** (10 mg, 88%). **44**: $R_f = 0.30$ (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25} = +56.2$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2932, 2867, 1455, 1376, 1255, 1254, 1098, 826, 773, 741, 703, 600\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 7.84-7.81$ (m, 4H), 7.77–7.73 (m, 4H), 7.67–7.62 (m, 6H), 7.24–7.13 (m, 18H), 7.08–7.04 (m, 3H), 6.13–5.87 (m, 3H, =CH), 5.79 (br m, 1H, =CH), 4.71 (d, $J = 8.4$ Hz, 1H), 3.92 (d, $J = 2.1$ Hz, 1H), 3.86–3.78 (m, 2H), 3.72 (dd, $J = 6.2, 6.2$ Hz, 2H), 3.65–3.63 (m, 2H), 3.63–3.52 (m, 4H), 3.38 (dd, $J = 11.2, 4.6$ Hz, 1H), 3.36–3.23 (m, 5H), 3.22–3.18 (m, 1H), 3.10–3.02 (m, 1H), 2.98–2.92 (m, 1H), 2.85–2.68 (m, 6H), 2.65–2.57 (m, 2H), 2.57–2.52 (m, 2H), 2.50–2.30 (m, 7H), 2.05–1.73 (m, 8H), 1.73–1.40 (m, 11H), 1.22–1.18 (m, 2H), 1.24 (s, 3H, CH_3), 1.20 (s, 9H, *t*BuSi), 1.13 (s, 9H, *t*BuSi), 1.12 (d, $J = 7.3$ Hz, 3H, CH_3), 1.04 (t, $J = 7.3$ Hz, 3H, CH_3), 1.03 (t, $J = 6.8$ Hz, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.94 (s, 9H, *t*BuSi), 0.47 (d, $J = 6.5$ Hz, 3H, CH_3), 0.09 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (150.9 MHz, C_6D_6): $\delta = 145.2, 136.4, 136.4, 136.0, 136.0, 135.1, 134.4, 134.3, 132.9, 130.1, 130.0, 129.9, 129.2, 128.6, 128.3, 127.6, 127.0, 125.8, 91.6, 87.2, 85.7, 84.4, 82.6, 82.3, 82.3, 80.8, 79.1, 78.5, 77.3, 75.6, 73.7, 72.7, 72.4, 69.4, 68.2, 67.5, 64.3, 62.4, 61.6, 54.7, 47.5, 45.1, 37.0, 36.8, 36.5, 36.2, 35.4, 35.1, 34.1, 33.2, 32.5, 32.3, 30.7, 30.4, 29.6, 27.6, 27.3, 27.1, 26.7, 26.2, 25.3, 22.9, 21.7, 21.1, 19.8, 19.5, 18.5, 16.6, 14.4, 13.9, −4.0, −4.9$; MS (FAB) calcd for $C_{109}H_{150}O_{13}S_2Si_3$ ($[M + Cs^+]$) 1947.8880, found 1947.9008.

Mixed thioketal 45: A solution of hydroxy dithioketal **44** (55 mg, 0.030 mmol) in nitromethane (10 mL) and THF (0.5 mL) was treated with 4 Å molecular sieves (110 mg), silica gel (110 mg), sodium bicarbonate (8 mg, 0.09 mmol), and silver perchlorate (19 mg, 0.091 mmol) at 25 °C for 3 h. The mixture was diluted with ether (25 mL) and Et_3N (1 mL) and filtered through a plug of celite. The filtrate was washed with saturated aqueous sodium bicarbonate solution (2 × 25 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:5, EtOAc:hexanes) to afford mixed thioketal **45** (36 mg, 67%). **45**: $R_f = 0.41$ (silica gel, 1:4, EtOAc:hexanes); $[\alpha]_D^{25} = +70.7$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3055, 2930, 2849, 1592, 1452, 1429, 1382, 1257, 1105, 1071, 942, 827, 777, 739, 704, 612\ cm^{-1}$; ^1H NMR (600 MHz, CD_2Cl_2): $\delta = 7.75-7.72$ (m, 4H, ArH), 7.68–7.65 (m, 4H, ArH), 7.50–7.36 (m, 18H), 7.33–7.29 (m, 6H, ArH), 7.27–7.23 (m, 3H, ArH), 5.75–5.45 (br m, 2H, =CH), 5.63 (dd, $J = 10.6, 5.9$ Hz, 1H, =CH), 5.58 (dd, $J = 10.6, 6.0$ Hz, 1H, =CH), 4.59 (br s, 1H), 4.13 (br s, 1H), 3.78–3.71 (m, 2H), 3.68 (dd, $J = 6.1, 6.1$ Hz, 2H), 3.52 (dd, $J = 9.5, 9.5$ Hz, 1H), 3.46 (ddd, $J = 11.0, 11.0, 2.4$ Hz, 1H), 3.42 (dd, $J = 11.4, 4.8$ Hz, 1H), 3.32 (br m, 1H), 3.21–3.09 (m, 4H), 3.03–2.92 (m, 4H), 2.79 (ddd, $J = 10.4, 10.4, 3.9$ Hz, 1H), 2.63 (br m, 1H), 2.55–2.44 (m, 3H), 2.39–2.25 (m, 2H), 2.12 (ddd, $J = 10.7, 4.0, 4.0$ Hz, 1H), 2.06–1.82 (m, 7H), 1.80–1.40 (m, 16H), 1.38–1.25 (m, 8H), 1.26 (s, 3H, CH_3), 1.22 (t, $J = 7.5$ Hz, 3H, CH_3), 1.17 (d, $J = 7.3$ Hz, 3H, CH_3), 1.09 (s, 9H, *t*BuSi), 1.04 (s, 9H, *t*BuSi), 0.92 (s, 3H, CH_3), 0.88 (s, 9H,

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*t*BuSi), 0.46 (d, $J = 7.1$ Hz, 3H, CH_3), 0.06 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (150.9 MHz, C_6D_6): $\delta = 145.2$, 136.3, 136.0, 134.9, 134.4, 134.4, 134.3, 130.1, 130.0, 129.9, 129.9, 129.2, 128.5, 127.2, 87.2, 84.5, 82.4, 82.2, 80.9, 80.0, 78.5, 77.3, 76.8, 75.6, 73.6, 72.4, 69.4, 67.6, 64.3, 62.3, 61.5, 54.7, 47.6, 46.6, 45.5, 37.4, 37.2, 36.6, 36.3, 35.4, 35.1, 32.0, 30.7, 30.5, 30.2, 29.6, 27.6, 27.3, 27.1, 26.8, 26.1, 21.6, 19.8, 19.4, 18.5, 17.0, 16.6, 14.4, 12.2, −3.9, −5.0; MS (FAB) calcd for $C_{107}H_{144}O_{13}SSi_3$ ($[M + Cs^+]$) 1885.8690, found 1885.8514.

Alcohol 47: A solution of mixed thioketal **45** (50 mg, 0.028 mmol) in CH_2Cl_2 (5 mL) was treated portionwise with *m*-chloroperbenzoic acid (9.7 mg, 0.056 mmol) at 0 °C for 2 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous sodium bicarbonate solution (20 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:3, EtOAc:hexanes) to afford sulfone **46**. The sulfone was dissolved in CH_2Cl_2 (4 mL) and triethylsilane (2 mL) and was treated with $BF_3 \cdot OEt_2$ (40 μL, 0.32 mmol) at −78 °C for 1 h. The reaction mixture was quenched by pouring into saturated aqueous sodium bicarbonate solution (25 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The organic layer was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 3:7, EtOAc:hexanes) to afford alcohol **47** (28 mg, 68 % for two steps). **47**: $R_f = 0.40$ (silica gel, 2:8, EtOAc:hexanes); $[\alpha]_D^{25} = +107.0$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3474$, 2929, 2863, 1458, 1424, 1386, 1252, 1083, 824, 704, 607, 506 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.68$–7.64 (m, 8H), 7.45–7.34 (m, 12H), 5.78–5.48 (m, 3H), 5.70 (dd, $J = 11.0$, 5.0 Hz, 1H), 4.48–4.39 (m, 1H), 4.16–4.08 (m, 1H), 3.96–3.62 (m, 8H), 3.59 (dd, $J = 11.5$, 4.9 Hz, 1H), 3.56–3.50 (m, 2H), 3.44–3.36 (m, 1H), 3.33–3.08 (m, 5H), 3.03–2.91 (m, 3H), 2.63 (dd, $J = 11.0$, 11.0 Hz, 1H), 2.38–2.18 (m, 4H), 2.18–2.05 (m, 4H), 2.02–1.82 (m, 6H), 1.98–1.45 (m, 17H), 1.44–1.35 (m, 3H), 1.23 (br s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.04 (s, 9H, *t*BuSi), 1.01 (s, 9H, *t*BuSi), 0.86 (s, 9H, *t*BuSi), 0.48 (d, $J = 7.1$ Hz, 3H, CH_3), 0.03 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 138.4$, 135.8, 135.5, 134.2, 134.1, 134.1, 133.5, 129.8, 129.6, 129.5, 127.7, 127.6, 127.5, 124.4, 85.8, 83.2, 81.9, 81.2, 80.2, 79.2, 78.5, 77.1, 76.7, 76.0, 75.5, 72.7, 71.3, 68.8, 67.0, 63.8, 62.0, 60.2, 53.7, 46.5, 44.9, 37.5, 36.4, 36.2, 35.7, 35.7, 34.7, 34.5, 30.9, 30.1, 29.1, 28.4, 27.2, 27.0, 26.9, 26.5, 25.9, 21.2, 19.4, 19.2, 18.2, 16.6, 16.3, 14.1, −4.3, −5.2; MS (FAB) calcd for $C_{86}H_{126}O_{13}Si_3$ ($[M + Cs^+]$) 1583.7561, found 1583.7396.

Methyl ester 50: A solution of alcohol **47** (37 mg, 0.025 mmol) in CH_2Cl_2 (10 mL) was treated with Dess–Martin periodinane (21.6 mg, 0.051 mmol) at 0 °C for 1 h. The reaction mixture was washed with a saturated aqueous sodium carbonate solution (20 mL), saturated aqueous sodium sulfite solution (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford the crude aldehyde **48**. The aldehyde was dissolved in THF (2 mL), *tert*-butyl alcohol (1 mL), and water (1 mL), and the solution was treated with 2-methyl-2-butene (200 μL), sodium hydrogenphosphate (monobasic) (6.5 mg, 0.056 mmol), and sodium chlorite (3.4 mg, 0.037 mmol) at 25 °C for 1 h. The reaction mixture was then diluted with ether (25 mL) and washed with a saturated aqueous ammonium chloride solution (20 mL). The organic layer was dried ($MgSO_4$), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:1, EtOAc:hexanes) to afford carboxylic acid **49**. A solution of carboxylic acid **49** in ether (5 mL) was treated dropwise with a freshly distilled diazomethane/ether solution at 0 °C until the starting material was consumed (ca. 45 min). The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 2:8, EtOAc:hexanes) to afford methyl ester **50** (21 mg, 71 % for three steps). **50**: $R_f = 0.33$ (silica gel, 1:4, EtOAc:hexanes); $[\alpha]_D^{25} = +94.7$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2929$, 2863, 1740, 1462, 1428, 1389, 1311, 1264, 1105, 939, 888, 824, 805, 778, 739, 704 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2): $\delta =$ 7.69–7.63 (m, 8H, ArH), 7.46–7.35 (m, 12H, ArH), 5.70–5.44 (m, 3H, =CH), 5.64 (dd, $J = 11.1$, 5.0 Hz, 1H, =CH), 4.40 (br m, 1H), 4.12 (br m, 1H), 3.90–3.70 (m, 2H), 3.80 (dd, $J = 8.6$, 8.6 Hz, 1H), 3.74 (br m, 2H), 3.67 (s, 3H, CH_3), 3.52–3.42 (m, 3H), 3.36 (br m, 1H), 3.24 (d, $J = 9.2$ Hz, 1H), 3.21 (dd, $J = 10.2$, 10.2 Hz, 1H), 3.18–3.05 (m, 2H), 3.01–2.88 (m, 4H), 2.61 (dd, $J = 11.6$, 11.6 Hz, 1H), 2.34–2.19 (m, 3H), 2.17–1.98 (m, 5H), 1.96–1.79 (m, 5H), 1.74–1.49 (m, 10H), 1.48–1.40 (m, 3H), 1.39–1.12 (m, 8H), 1.26 (br s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.03 (s, 9H, *t*BuSi), 1.01 (s, 3H, CH_3), 0.99 (s, 9H, *t*BuSi), 0.87 (s, 9H, *t*BuSi), 0.44 (d, $J = 7.0$ Hz, 3H, CH_3), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 173.0$, 138.8, 136.2, 136.2, 135.9, 134.5, 134.5, 133.7, 130.2, 130.0, 129.8, 128.1, 127.9, 127.9, 125.8, 124.7, 92.4, 85.5, 85.0, 83.5, 82.9, 81.6, 80.7, 79.6, 78.8, 77.6, 77.1, 76.3, 75.8, 72.9, 71.6, 69.2, 67.5, 64.3, 64.1, 62.4, 54.4, 51.8, 47.1, 45.3, 40.6, 37.9, 36.8, 36.2, 36.1, 34.7, 31.1, 30.6, 30.4, 30.1, 29.5, 27.5, 27.1, 27.0, 26.9, 26.0, 21.3, 19.6, 19.4, 18.7, 18.5, 18.3, 18.1, 16.7, 16.3, 15.5, −4.2, −5.1; HRMS (FAB) calcd for $C_{87}H_{126}O_{14}Si_3$ ($[M + Cs^+]$) 1611.7510, found 1611.7642.

Lactone 51: A solution of methyl ester **50** (30 mg, 0.020 mmol) was dissolved in CH_2Cl_2 (15 mL) and treated with HF · pyr (300 μL) at 0 °C for 1 h. The reaction mixture was quenched by pouring into a saturated aqueous sodium bicarbonate solution (50 mL), and the lactone was extracted into CH_2Cl_2 (2 × 20 mL). The organic phase was dried ($MgSO_4$), concentrated, and the residue was purified by column chromatography (silica gel, EtOAc) to afford lactone **51** (16 mg, 92 %). **51**: $R_f = 0.32$ (silica gel, 1:4, EtOAc); $[\alpha]_D^{25} = +116.9$ ($c = 1.0$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} =$ 3494, 2931, 1790, 1738, 1462, 1372, 1316, 1289, 1208, 1059, 972, 732 cm^{-1}; ^1H NMR (600 MHz, CD_2Cl_2): $\delta = 5.72$–5.44 (m, 3H, =CH), 5.66 (dd, $J =$ 11.0, 5.1 Hz, 1H, =CH), 4.40 (br t, $J = 6.4$ Hz, 1H), 4.15–4.05 (m, 2H), 3.95 (ddd, $J = 10.1$, 8.1, 8.1 Hz, 1H), 3.90–3.78 (m, 1H), 3.80 (ddd, $J = 10.5$, 6.7, 4.3 Hz, 1H), 3.76 (ddd, $J = 11.2$, 10.2, 4.4 Hz, 1H), 3.60 (dd, $J = 6.0$, 6.0 Hz, 2H), 3.49–3.38 (m, 1H), 3.36 (br m, 1H), 3.30 (br t, $J = 9.8$ Hz, 1H), 3.28–3.22 (m, 3H), 3.14 (br m, 1H), 3.06 (dd, $J = 9.7$, 2.9 Hz, 1H), 3.04–2.96 (m, 2H), 2.79 (dd, $J = 17.3$, 8.1 Hz, 1H), 2.64–2.56 (m, 1H), 2.61 (dd, $J = 17.3$, 10.2 Hz, 1H), 2.32 (br m, 1H), 2.26–2.20 (m, 1H), 2.20 (ddd, $J = 11.0$, 4.2, 4.2 Hz, 1H), 2.13 (d, $J = 13.6$ Hz, 1H), 2.08–1.79 (m, 14H), 1.75 (d, $J =$ 15.0 Hz, 1H), 1.71–1.47 (m, 11H), 1.46–1.37 (m, 2H), 1.20 (d, $J = 7.2$ Hz, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.07 (d, $J = 6.9$ Hz, 3H, CH_3); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 172.8$, 138.8, 129.7, 126.3, 124.6, 91.9, 87.1, 85.2, 85.1, 83.5, 81.8, 80.2, 79.5, 78.7, 77.6, 77.0, 76.2, 72.7, 71.8, 69.3, 66.4, 63.0, 62.2, 52.8, 45.3, 43.4, 38.0, 37.9, 36.7, 35.9, 35.5, 34.2, 30.9, 30.7, 29.8, 27.8, 27.5, 21.3, 19.6, 16.7, 15.3; HRMS (FAB) calcd for $C_{48}H_{72}O_{13}$ ($[M + Cs^+]$) 989.4027, found 989.4065.

Brevetoxin A: A solution of lactone **51** (12 mg, 0.014 mmol) in CH_2Cl_2 (7 mL) was treated with Dess–Martin periodinane (6 mg, 0.014 mmol) at 0 °C for 1 h. The reaction mixture was washed with a saturated aqueous sodium carbonate solution (20 mL), a saturated aqueous sodium sulfite solution (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford the crude aldehyde. The aldehyde was dissolved in CH_2Cl_2 (5 mL) and treated with Et_3N (200 μL, 1.4 mmol) and Eschenmosher's salt (8 mg, 0.042 mmol) at 25 °C for 12 h. The reaction mixture was concentrated and purified by column chromatography (silica gel, 1:1, EtOAc:hexanes) to afford brevetoxin A (**1**) (7 mg, 57 % for two steps). **1**: $R_f = 0.45$ (silica gel, 1:1, EtOAc:hexanes); $[\alpha]_D^{25} = +75.5$ ($c = 0.2$, CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 3425$, 2921, 2849, 1788, 1690, 1455, 1379, 1314, 1266, 1208, 1080, 897, 737 cm^{-1}; ^1H NMR (600 MHz, C_6D_6, 45 °C): $\delta = 9.29$ (s, 1H), 5.90 (s, 1H), 5.87 (dd, $J = 10.8$, 5.2 Hz, 1H), 5.78–5.67 (br m, 2H), 5.71–5.64 (m, 1H), 5.43 (s, 1H), 4.55 (dd, $J = 8.0$, 5.4 Hz, 1H), 3.98–3.91 (m, 3H), 3.74 (br m, 1H), 3.59–3.54 (m, 1H), 3.52 (ddd, $J = 10.6$, 7.9, 2.3 Hz, 1H), 3.46–3.34 (m, 4H), 3.29 (br d, $J = 8.5$ Hz, 1H), 3.19–3.10 (m, 3H), 2.94 (ddd, $J = 12.0$, 8.0, 4.1 Hz, 1H), 2.89 (ddd, $J = 11.9$, 9.2, 4.5 Hz, 1H), 2.80 (dd, $J = 11.9$, 4.6 Hz, 1H), 2.78 (dd, $J = 9.6$, 2.7 Hz, 1H), 2.72–2.40 (br m, 4H), 2.65 (dd, $J = 10.7$, 10.7 Hz, 1H), 2.40 (ddd, $J = 15.2$, 10.8, 4.0 Hz, 1H), 2.36 (dd, $J = 16.9$, 8.2 Hz, 1H), 2.31 (dd, $J = 11.6$, 4.2 Hz, 1H), 2.25–2.21 (m, 1H), 2.24–2.20 (m, 1H), 2.21 (dd, $J = 16.9$, 10.3 Hz, 1H), 2.18–2.10 (m, 1H), 2.05–1.92 (m, 6H), 1.92–1.86 (m, 1H), 1.86–1.74 (m, 3H), 1.72–1.52 (m, 7H), 1.44–1.38 (m, 1H), 1.37–1.24 (m, 1H), 1.24 (s, 3H), 1.20 (d, $J = 7.1$ Hz, 3H), 0.98–0.95 (m, 1H), 0.96 (s, 3H), 0.77 (d, $J =$ 6.8 Hz, 3H); ^{13}C NMR (150.9 MHz, C_6D_6, 45 °C): $\delta = 193.5$, 171.0, 148.9, 139.0, 134.4, 128.5, 127.4, 124.8, 92.0, 88.5, 86.7, 85.1, 84.7, 84.1, 83.8, 82.2, 82.0, 80.4, 79.9, 78.9, 77.8, 76.7, 76.2, 71.9, 71.1, 69.6, 66.3, 62.4, 52.9, 45.6, 43.3, 38.2, 37.5, 36.9, 36.2, 35.9, 33.8, 32.3, 31.4, 29.0, 27.6, 27.2, 21.4, 19.7, 16.8, 15.0 (carbons 17, 20 and 28 were observed at best as weak broad signals at 34.5, 34.5 and 30.9, respectively, as previously reported;[28, 29] HRMS calcd for $C_{49}H_{70}O_{13}$ ($[M + Na^+]$) 889.4714, found 889.4747.

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