Total Synthesis of Brevetoxin A: Part 2: Second Generation Strategy and Construction of EFGH Model System

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Abstract: Our second generation strategy for the total synthesis of brevetoxin A involved dissection of the molecule at the ring F oxocene. Synthetically, the F ring formation was expected to occur through Wittig coupling of requisite polycyclic fragments **2** and **3**, followed by a hydroxy dithioketal cyclization. In order to test this synthetic plan, model phosphonium salt **9** and aldehyde **10** were successfully synthesized and coupled. The deprotected product (**46**) was shown to undergo an efficient hydroxy dithioketal cyclization and the product (**47**) was selectively reduced to the EFGH ring system of brevetoxin A (**8**). The synthesis of phosphonium salt **9** utilized our cyclic ketene acetal phosphate methodology and a [4+2] addition of singlet oxygen to generate intermediate endoperoxide **11**. The success of this model study facilitated a synthetic plan to form and functionalize ring E nonacene and ring F oxocene for the total synthesis of brevetoxin A.

Keywords: brevetoxin A · synthetic methods · total synthesis

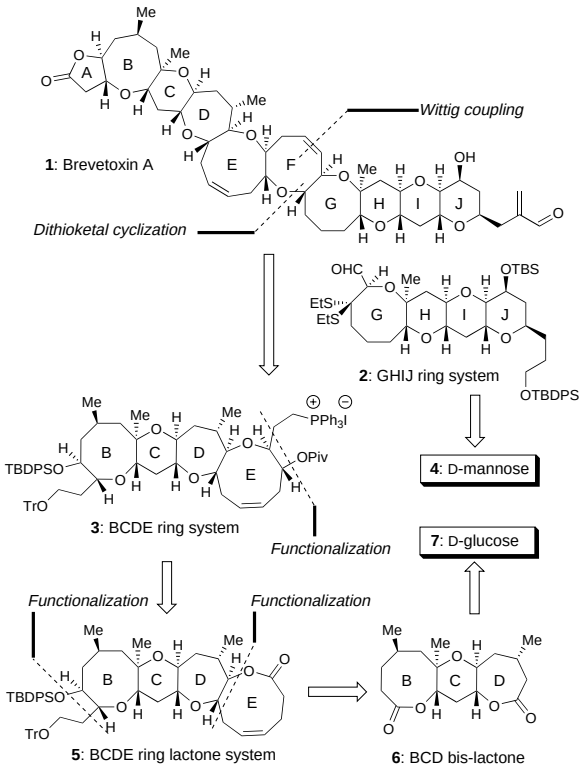
Introduction

In the preceding paper,[1] we presented our first generation strategy towards the total synthesis of brevetoxin A (**1**, Scheme 1) and model studies assessing the validity of that strategy. Failure of the key step for generating the nine-membered ring, by a late-stage hydroxy dithioketal cyclization, led us to abandon that approach. In this article, we describe the emergence of a second generation strategy for the total synthesis of brevetoxin A and its validation by the successful construction of an EFGH model system.[2]

Results and Discussion

Second generation retrosynthetic analysis and strategy

The first generation strategy towards brevetoxin A (**1**) called for a convergent approach in which two fragments representing the ABCD[3] and FGHIJ[4] segments were to be built separately and brought together by a Wittig coupling, setting the stage for the nine-membered ring (E ring) construction.



Scheme 1. Second generation retrosynthetic analysis and strategic bond disconnections of brevetoxin A (**1**).

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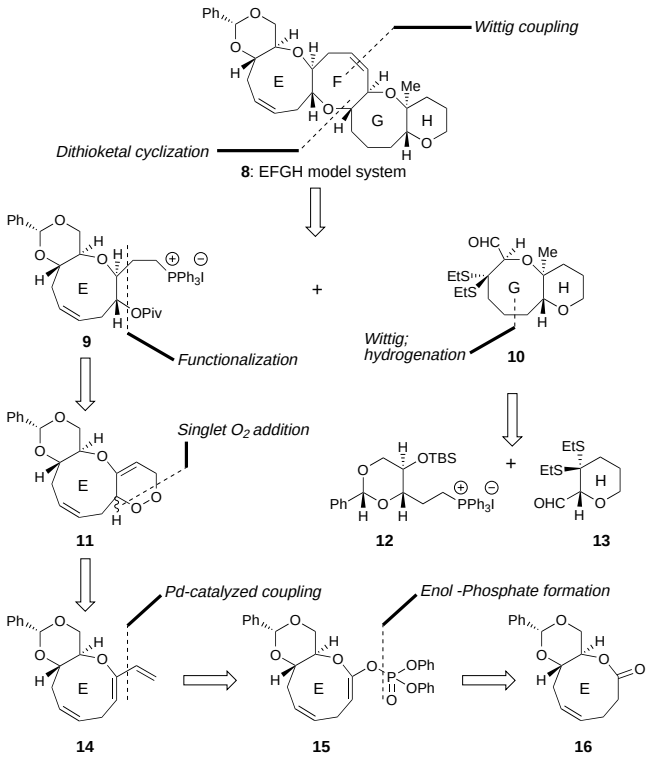
Our model studies cast doubts upon the feasibility of a late stage hydroxy dithioketal ring closure to form ring E. This forced us to redesign the strategy by moving the convergency point to ring F. Thus, the modified strategy (Scheme 1) postulated intermediates **3** (BCDE ring system) and **2** (GHIJ ring system) as requisite precursors by disassembling the structure at ring F through a retro-Wittig type coupling and a retro-hydroxy dithioketal ring closure. Our previous success with the latter cyclization in constructing oxocene systems[5] was encouraging for the new strategy, even though the formation of the nine-membered ring remained a severe challenge.[6] Overcoming this problem at an earlier stage of the synthetic scheme, and the determination to develop a new method to solve it, became prime objectives of the new approach. The synthesis of fragment **2** was traced to D-mannose (**4**) through hydroxy epoxide openings[7] and a hydroxy dithioketal cyclization.[5] The construction of **3** defined BCDE lactone **5** as the required precursor whose origin was further traced back to bis(lactone) **6**[3] and eventually to D-glucose (**7**). This strategy of using lactones as precursors of cyclic ethers meant the requirement for a reliable method to convert medium-sized lactones to cyclic ethers. To this end a number of methods were developed in this and in other laboratories. Among them are the nucleophilic addition to lactone-derived thionolactones followed by desulfurization,[8] the Murai cuprate coupling with lactone-derived cyclic ketene acetal triflates,[9] the Holmes–Tebbe methylenation of lactones followed by hydroboration,[10] the Nozaki–Takai–Hiyama–Kishi Cr/Ni-induced coupling of cyclic ketene acetal triflates with aldehydes[11] and others.[12] None of these methods, however, proved suitable for the task at hand and, therefore, a new method was deemed necessary. As part of the search for such a method, a program was launched to investigate the chemistry of cyclic ketene acetal phosphates. As described elsewhere,[13] these phosphates proved to be quite accessible, stable enough for isolation, and highly reactive towards palladium-catalyzed coupling reactions. They were found to be particularly useful for the construction of medium-sized ring ethers within complex frameworks as will be discussed in this and the following papers.

Abstract in Greek:

Η δευτερη στη συνεχεια συνθετικη μας στρατηγικη για την ολικη συνθεση της μπρεβετοξινης Α επικεντρωνεται στην νοητη διχοτομηση του μοριου στον ακορεστο οκταμελη αιθερικο δακτυλιο F. Συνθετικα, η δημιουργια του δακτυλιου F αναμενοταν να πραγματοποιηθει μεσω μιας αντιδρασης Wittig μεταξυ των πολυκυκλικων ενδιαμεσων **2** και **3**, ακολουθουμενη απο μια ενδομοριακη υδροξυ–θειοκεταλικη κυκλοποιηση. Για τη μελετη της στρατηγικης αυτης συνθετικα μοντελα, το φωσφωνιακο αλας **9** και η αλδευδη **10**, συντεθηκαν και συνδεθηκαν επιτυχως. Το αποπροστατευμενο προιον **46** αντεδρασε επιτυχως στην διεργασια της ενδομοριακης υδροξυ–θειοκεταλικης κυκλοποιησης και το προιον **47** αναχθηκε επιλεκτικα παραγοντας τον EFGH πολυκυκλικο σκελετο, παροντα στην μπρεβετοξινη Α (**8**). Η συνθεση του φωσφωνιακου αλατος **9** επιτευχθηκε χρησιμοποιοντας διαδοχικα την κυκλικη φωσφωρικη κετενο–ακεταλικη μεθοδολογια, που αναπτυχθηκε στα εργαστηρια μας, ακολουθουμενη απο μια [4+2] κυκλοπροσθηκη οξυγονου απλης καταστασης για τη δημιουργια του ενδιαμεσου ενδουπεροξειδιου **11**. Η επιτυχια αυτου του μοντελου καθιερωσε τη συγκεκριμενη συνθετικη οδο για την κατασκευη του εννεαμελους δακτηλιου Ε και του ακορεστου αιθερα F, με αποτερο σκοπο την ολικη συνθεση της μπρεβετοξινης Α.

Construction of EFGH model system 8

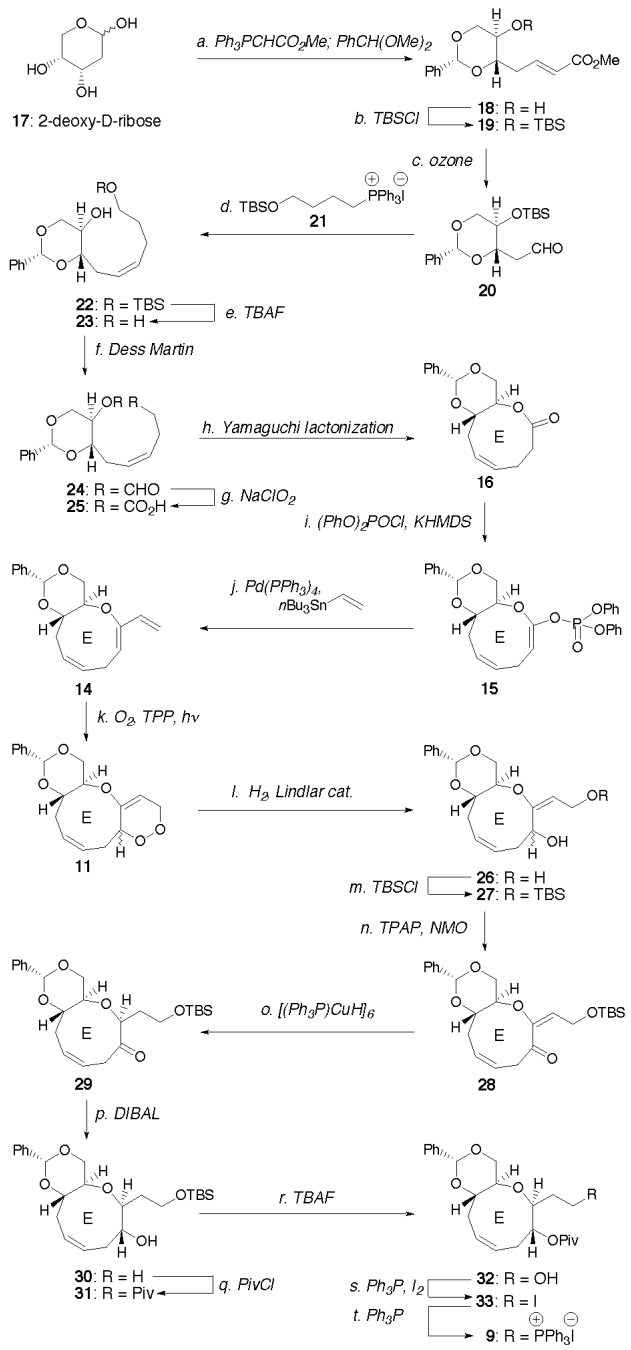
Our experience so far has clearly demonstrated that the most challenging aspect in synthesizing brevetoxin A (**1**) would be the EFG region with its fused medium-sized rings. To explore a path for its construction we targeted model system **8** (Scheme 2), which represents the EFGH ring system of **1**.



Scheme 2. Retrosynthetic analysis of EFGH model system (**8**).

Disassembling ring F at the indicated sites (Scheme 2) allows the generation of key building blocks **9** (phosphonium salt) and **10** (dithioketal aldehyde). While fragment **10** can easily be traced to intermediates **12** and **13**, the E ring **9** was simplified stepwise as outlined in Scheme 2. Thus, the intermediacy of endoperoxide **11** was invoked as a possible precursor to **9** through O–O bond cleavage and appropriate functionalizations. Endoperoxide **11** could, in turn, be traced to conjugated diene **14** (singlet oxygen addition)[14] whose origin could be traced to lactone **16** via phosphate **15** (palladium-catalyzed C–C bond formation).

The novel strategy towards the EFGH framework **8** derived from the above analysis was set in motion as outlined in Schemes 3–6. Phosphonium salt **9** was synthesized from compound **20** (derived from 2-deoxy-D-ribose, **17**) as shown in Scheme 3. Thus, 2-deoxy-D-ribose (**17**) was subjected to a



Scheme 3. Synthesis of phosphonium salt **9**. Reagents and conditions: a) 1.1 equiv of Ph_3PCHCO_2Me, DMF, 25 °C, 15 h; 1.1 equiv of $PhCH(OMe)_2$, 25 °C, 15 h, 78%; b) 1.5 equiv of TBSCl, 2.0 equiv of imidazole, CH_2Cl_2, 25 °C, 12 h, 90%; c) ozone, CH_2Cl_2, −78 °C, 10 min; 2.0 equiv of Ph_3P, 25 °C, 3 h, 85%; d) 1.2 equiv of **21**, 1.2 equiv of LiHMDS in THF, toluene, 0 °C; then 1.0 equiv of **20**, 8 h, 84%; e) 2.4 equiv of TBAF, THF, 25 °C , 7 h, 82%; f) 1.2 equiv of Dess–Martin reagent, CH_2Cl_2, 25 °C, 4.5 h, 87%; g) 3.0 equiv of $NaClO_2$, 1.2 equiv of NaH_2PO_4, 3.3 equiv of 2-methyl-2-butene, *t*BuOH:H_2O (5:1), 25 °C, 3 h, 96%; h) 1.1 equiv of 2,4,6-trichlorobenzoyl chloride, 1.1 equiv of Et_3N, THF, 0 °C, 20 min; then 1.5 equiv of 4-DMAP, benzene, 80 °C, 1 h, 70%; i) 2.7 equiv of KHMDS, 3.2 equiv of $(PhO)_2POCl$, 4.0 equiv of HMPA, THF, −78 °C, 1 h, 90%; j) 2.2 equiv of $nBu_3SnCH{=}CH_2$, 0.05 equiv of $[Pd(PPh_3)_4]$, 3.0 equiv of LiCl, THF, 80 °C, 1.5 h, 95%; k) 0.045 equiv of TPP, CCl_4, O_2, *hν*, 0 °C, 3 h, 85%; l) H_2, Lindlar's catalyst, MeOH, 25 °C, 20 min, 99%; m) 1.05 equiv of TBSCl, 1.2 equiv of imidazole, CH_2Cl_2, 25 °C, 0.5 h, 93%; n) 0.05 equiv of TPAP, 1.5 equiv of NMO, CH_2Cl_2, 25 °C, 1 h, 85%; o) 0.67 equiv of $[(Ph_3P)CuH]_6$, benzene, 25 °C, 3 h, 96%; p) 1.4 equiv of DIBAL, CH_2Cl_2, −78 °C, 20 min, 87%; q) 3.1 equiv of PivCl, 4.1 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 8 h, 91%; r) 1.5 equiv of TBAF, THF, 25 °C, 4 h, 91%; s) 1.7 equiv of imidazole, 1.7 equiv of Ph_3P, 1.1 equiv of I_2, CH_2Cl_2, 25 °C, 10 min; t) 10.0 equiv of Ph_3P, fusion (90 °C), 3 h, 87% for two steps. DIBAL = diisobutylaluminum hydride; 4-DMAP = 4-*N*-dimethylaminopyridine; DMF = *N*,*N*-dimethylformamide; HMPA = hexamethylphosphoramide; KHMDS = potassium bis(trimethylsilyl)amide; LiHMDS = lithium bis(trimethylsilyl)amide; NMO = 4-methylmorpholine-*N*-oxide; PivCl = trimethylacetyl chloride (pivaloyl); TBAF = tetra-*n*-butylammonium fluoride; TBS = *tert*-butyldimethylsilyl; TPAP = tetra-*n*-propylammonium perruthenate; TPP = *meso*-tetraphenylporphyrin.

Wittig homologation followed by benzylidene acetal formation to give **18**. The alcohol was protected as a silyl ether, then ozonolysis yielded aldehyde **20**.[4] The ylide obtained from **21**[2] by basic treatment (LiHMDS) was treated with aldehyde **20** leading to olefinic compound **22** in 84% yield. Compound **22** was desilylated by exposure to excess TBAF (82% yield). The resulting diol (**23**) was selectively oxidized with Dess–Martin periodinane[15] to the corresponding hydroxy aldehyde (**24**, 87% yield) and thence to carboxylic acid **25** (96% yield). Yamaguchi lactonization[16] of hydroxy acid **25** produced lactone **16** in 70% yield. Compound **16** was converted to ketene acetal phosphate **15** by treatment with KHMDS in the presence of $(PhO)_2POCl$ (90% yield). Ketene acetal phosphate **15** entered into a smooth coupling with $nBu_3SnCH{=}CH_2$ in the presence of $[Pd(PPh_3)_4]$ catalyst and LiCl, furnishing triene system **14** in 95% yield. Of the three double bonds in **14**, those in the conjugated 1,3-diene system required selective oxygenation at their termini. An excellent solution to this problem was provided by singlet oxygen,[17] which, upon generation from oxygen with light (halogen) in the presence of *meso*-tetraphenylporphyrin,[18] reacted selectively with the 1,3-diene system of **14** to form endoperoxide **11** (ca. 1:1 inconsequential mixture of diastereoisomers, 85% yield based on recovered starting material). In order to elaborate **11** into intermediates with appropriate appendages on ring E, we needed to effect a number of selective reduction steps. To this end, the O–O endoperoxide bond was cleaved with H_2 in the presence of Lindlar's catalyst[14a] affording diol **26** (ca. 1:1 mixture of isomers) in 99% yield. Selective silylation of the primary hydroxyl group in **26** under standard TBSCl/imidazole conditions gave hydroxy silyl ether **27** (93% yield), which was oxidized to enone **28** (85%) by the action of TPAP/NMO.[19] A highly selective reduction of the enone C=C in **28** was achieved by reaction with $[(Ph_3P)CuH]_6$,[20] which resulted in the formation of ketone **29** in 96% yield as a single stereoisomer. The configuration of the newly generated stereogenic center was confirmed by X-ray crystallographic analysis of compound **30b** (see Scheme 4). DIBAL reduction of the ketone functionality in **29** proceeded selectively from the top face of the molecule as drawn, furnishing hydroxy compound **30** (87% yield) which reacted with trimethylacetyl chloride (PivCl) in the presence of 4-DMAP to afford pivaloate **31** (91% yield). Deprotection at the primary position of **31** was effected by TBAF, leading to alcohol **32** (91%) which was converted smoothly to the desired phosphonium salt **9** via iodide **33** (87% yield for two steps).

Assignments of the relative stereochemistries within **30** and its relatives were challenging due to the slow conformational changes on the NMR time scale of the nine-membered ring (reminis-

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cent to those of brevetoxin A).[21] They were eventually secured by X-ray crystallographic analysis (see Figure 1) of derivative **30b** (formed from **30** as shown in Scheme 4) and 2D NMR studies on dialdehyde **30c**. The latter compound was obtained by ozonolysis of **30b** and, devoid of the nine-membered ring, exhibited normal behavior with regards to NMR spectroscopy. Thus, using ROSEY and COESY experiments, all relevant NMR signals and stereogenic centers were fully assigned. Furthermore, the information gained proved to be extremely useful for subsequent assignments in related compounds (vide infra).

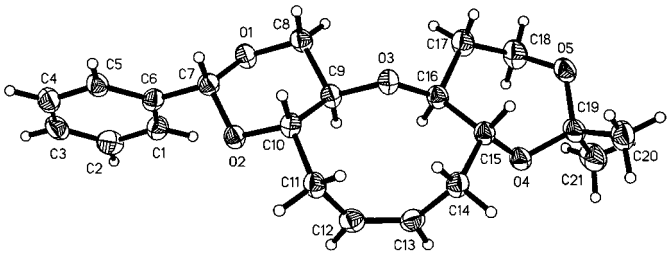
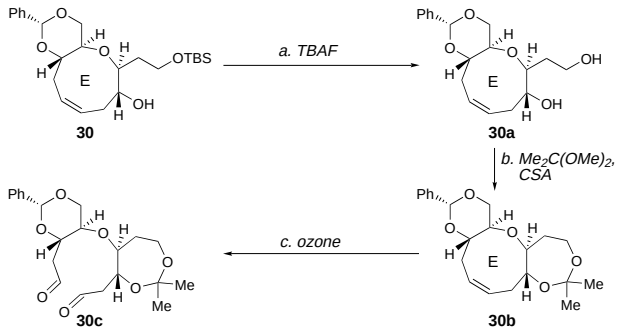
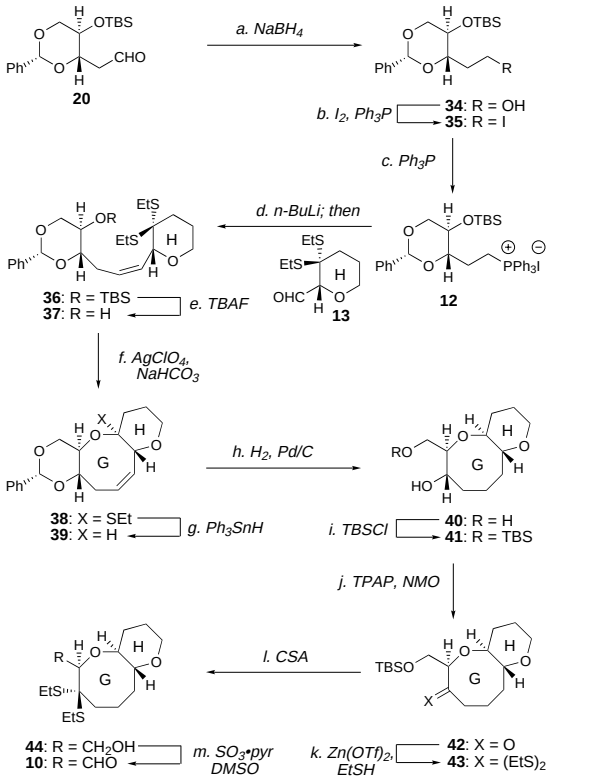


Figure 1. X-Ray structure of compound **30b**.



Scheme 4. Synthesis of crystalline derivative **30b** and dialdehyde **30c**. Reagents and conditions: a) 1.3 equiv of TBAF, THF, 25 °C, 3 h, 92 %; b) 3.8 equiv of $Me_2C(OMe)_2$, 0.1 equiv of CSA, CH_2Cl_2, 25 °C, 20 min, 95 %; c) O_3, CH_2Cl_2, −78 °C; 17 equiv of Ph_3P, 25 °C, 30 min, 89 %. CSA = 10-camphorsulfonic acid.

Phosphonium salt **12** was formed by reduction ($NaBH_4$) of aldehyde **20**, followed by treatment with iodine and Ph_3P to yield the intermediate iodide **35** and subsequent reaction with excess Ph_3P (Scheme 5). Generation of the ylide from phosphonium salt **12** (*n*BuLi) was followed by coupling with aldehyde **13** in the presence of HMPA to afford, the *cis*-olefin **36** in 87 % yield. Desilylation of **36** was effected with TBAF (82 % yield) and the resulting hydroxy dithioketal **37** was subjected to the normal cyclization conditions ($AgClO_4$, $NaHCO_3$, 4 Å MS, silica gel, CH_3NO_2), leading to oxocene **38** (72 % yield). Radical-mediated desulfurization of **38** (Ph_3SnH/AIBN, 110 °C) resulted in the formation of the reduced product **39** (81 %) with the desired stereochemistry, while hydrogenation of **39** (H_2, Pd/C) was accompanied by cleavage of the benzylidene system furnishing diol **40** (94 % yield). The primary hydroxyl group in the latter compound (**40**) was temporarily blocked (TBSCl/imidazole, 90 %), while the secondary hydroxyl group was oxidized to ketone **42** (TPAP/NMO, 89 %)[19] and converted to the dithioketal **43**

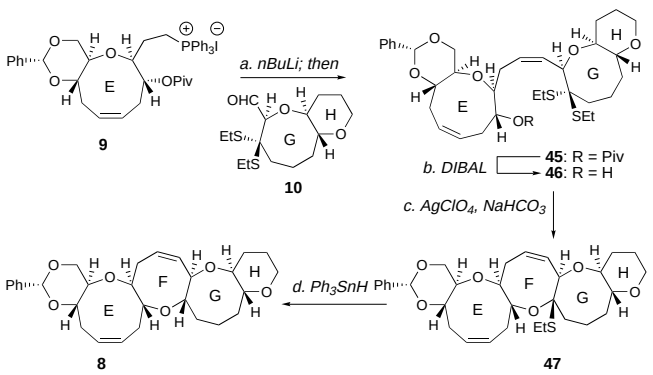


Scheme 5. Synthesis of aldehyde **10**. Reagents and conditions: a) 1.3 equiv of $NaBH_4$, THF, 25 °C, 30 min, 93 %; b) 1.4 equiv of imidazole, 1.4 equiv of I_2, 1.3 equiv of Ph_3P, ether:acetonitrile (1:1.5), 25 °C, 30 min, 84 %; c) 1.1 equiv of Ph_3P, MeCN, 80 °C, 48 h, 89 %; d) 1.0 equiv of **12**, 1.1 equiv of *n*BuLi, −78 °C, then 10.0 equiv of HMPA, 1.2 equiv of **13**, −78 °C (0.5 h) →25 °C (1 h), 87 %; e) 1.4 equiv of TBAF, THF, 25 °C, 0.5 h, 82 %; f) 3.0 equiv of $AgClO_4$, 10.0 equiv of $NaHCO_3$, 4 Å MS, silica gel, CH_3NO_2, 25 °C, 3 h, 72 %; g) 2.0 equiv of Ph_3SnH, 0.1 equiv of AIBN, $PhCH_3$, 110 °C, 2 h, 81 %; h) H_2, 10% Pd/C, CH_3OH, 25 °C, 17 h, 94 %; i) 1.1 equiv of TBSCl, 1.2 equiv of imidazole, CH_2Cl_2, 25 °C, 30 min, 90 %; j) 0.1 equiv of TPAP, 1.5 equiv of NMO, CH_2Cl_2:CH_3CN (1:1), 25 °C, 30 min, 89 %; k) 15 equiv of EtSH, CH_2Cl_2, 0.2 equiv of $Zn(OTf)_2$, 25 °C, 4 h; l) 0.05 equiv of CSA, CH_3OH:CH_2Cl_2 (1:1), 1 h, 87 % for two steps; m) 3.0 equiv of SO_3·pyr, DMSO, Et_3N, CH_2Cl_2, 0 °C, 30 min, 89 %. DMSO = dimethyl sulfoxide; HMPA = hexamethylphosphoramide; NMO = 4-methylmorpholine-*N*-oxide; Ms = methanesulfonate; pyr. = pyridine; Tf = trifluoromethanesulfonate.

(EtSH/$Zn(OTf)_2$). Finally, the primary hydroxyl group was liberated with CSA in CH_2Cl_2:MeOH (1:1) in 87 % yield (from **42**) and oxidized with SO_3·pyridine and DMSO[22] to afford the targeted aldehyde **10** (89 % yield).

Coupling of building blocks **9** and **10** proceeded smoothly through the ylide of **9** (*n*BuLi) affording *cis*-olefin **45** in 77 % yield (Scheme 6). DIBAL-induced removal of the pivaloate group from **45** led to hydroxy dithioketal **46** in 83 % yield, which upon processing through the standard ring-closure conditions, furnished pentacyclic system **47** in 81 % yield. The radical pathway described above for **38** (Ph_3SnH/AIBN) also served well in this instance, leading to the desired system **8** (80 % yield, single stereoisomer).

The relative stereochemistry within **8** was secured by ^{1}H-COSY, ^{1}H ROESY, ^{1}H ^{13}C HMQC, and HMBC NMR experiments. Thus, having established the configurations at C-3, C-23, C-4, C-18 (ring E), C-9, and C-13 (ring G) stereocenters by X-ray crystallography (vide supra, compound **30b**) and by



Scheme 6. Construction of EFGH ring system **8**. Reagents and conditions: a) 1.0 equiv of **9**, 1.1 equiv of *n*BuLi, THF, −78 °C, 20 min; then 6.5 equiv of HMPA, 1.3 equiv of **10**, −78 °C, 30 min; then 25 °C, 20 min, 77 %; b) 1.05 equiv of DIBAL, CH_2Cl_2, −78 °C, 1 h, 83 %; c) 3.0 equiv of $AgClO_4$, 10 equiv of $NaHCO_3$, 4 Å MS, SiO_2, $MeNO_2$, 25 °C, 1 h, 81 %; d) 10 equiv of Ph_3SnH, 0.1 equiv of AIBN, toluene, reflux, 2 h, 80 %. AIBN = 2,2′-azobisisobutyronitrile; MS = molecular sieves.

virtue of the compound's origins (i.e. 2-deoxy-D-ribose and tri-*O*-acetyl-D-glucal), the only remaining centers to be determined were those at C-8 and C-17. The NMR experiments proved revealing, not only for establishing the configurations at these centers, but also for confirming other stereochemical assignments. Thus, the ^{1}H ROESY spectrum[2] revealed a strong NOE between H-8 ($\delta = 4.08$) and H-9 ($\delta = 3.09$) pointing to a *syn* relationship between these protons, while the absence of NOE between H-8 ($\delta = 4.08$) and H-17 ($\delta = 3.33$), H-9 ($\delta = 3.09$) and H-13 ($\delta = 2.99$) gave some evidence towards a *trans* relationship at those fusions (Figure 2). The *trans* arrangement between H-8 and H-17 was also evident from the 10.0 Hz coupling constant between these protons as determined from ^{1}H COSY experiments. A number of additional NOEs were in agreement with structure **2**.[2]

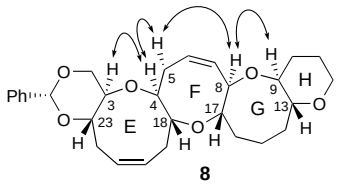


Figure 2. NOE correlations for **8**.

Conclusion

The feasibility of a second generation strategy proposed for the total synthesis of brevetoxin A (**1**) (see Scheme 1) was supported by the important model study described above. Specifically, a powerful sequence of reactions was developed for the construction of the most challenging region of the target molecule containing the medium-sized rings E, F and G. The most important developments employed during the construction of this successful model system were: a) the conversion of a nine-membered ring lactone to its ether counterpart via the corresponding cyclic enol acetal phosphate and a subsequent palladium-catalyzed process;[13] b) a singlet oxygen-mediated functionalization of a conjugated diene system;[2] and c) a hydroxy dithioketal cyclization to form the oxocene ring F.[5]

The chemistry described here sets the stage for the implementation of the final strategy towards brevetoxin A (**1**). In the following article, we present the construction of the required building blocks for brevetoxin A (**1**).

Experimental Section

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

Bis-silyl ether 22: The phosphonium salt **21** (4.32 g, 7.5 mmol) was suspended in toluene (50 mL), and the mixture was cooled to 0 °C. After treatment with LiHMDS (7.5 mL of 1 M in THF, 7.5 mmol), the yellow solution was stirred at 0 °C for 20 min. A solution of aldehyde **20** (2.1 g, 6.25 mmol) in toluene (15 mL) was added at 0 °C, and the reaction mixture was stirred at this temperature for 1 h and at 25 °C for 7 h. It was quenched by addition of saturated aqueous ammonium chloride solution (15 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 3:17, ether:hexanes) to afford olefin **22** (2.65 g, 84 %). **22**: colorless oil; $R_f = 0.75$ (silica gel, 1:6, ether:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 2928, 2856, 1462, 1390, 1256, 1106, 1029, 836 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50-7.48$ (m, 2H, ArH), 7.38–7.32 (m, 3H, ArH), 5.67–5.59 (m, 1H, =CH), 5.56–5.51 (m, 1H, =CH), 5.48 (s, 1H, PhCH), 4.19 (dd, J = 9.5, 3.5 Hz, 1H), 3.65–3.55 (m, 5H), 2.67 (dd, J = 14.5, 7.0 Hz, 1H), 2.27 (ddd, J = 14.5, 7.5, 7.5 Hz, 1H), 2.18–2.07 (m, 2H), 1.66–1.55 (m, 2H), 0.92 (s, 9H, *t*BuSi), 0.91 (s, 9H, *t*BuSi), 0.13 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.04 (2 s, 6H, CH_3Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 138.0, 131.4, 128.7, 128.0, 125.9, 125.4, 100.8, 82.4, 71.7, 66.6, 62.3, 32.7, 29.5, 26.0, 25.7, 24.0, 18.4, 17.9, −4.2, −4.8, −5.3, −5.3; HRMS (FAB) calcd for $C_{28}H_{50}O_4Si_2$ ([M + Na^+]) 529.3145, found 529.3132.

Diol 23: A solution of bis-silyl ether **22** (13.1 g, 26.0 mmol) in THF (150 mL) was treated with TBAF (62.0 mL of 1 M in THF, 62.0 mmol) at 25 °C for 7 h. The mixture was diluted with saturated aqueous ammonium chloride solution (100 mL) and extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 9:1, EtOAc:hexanes) to afford diol **23** (5.92 g, 82 %). **23**: colorless oil; $R_f = 0.5$ (silica gel, 1:9, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 3388, 2931, 1454, 1396, 1072, 1028, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.54-7.44$ (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.73–5.64 (m, 1H, =CH), 5.52–5.44 (m, 1H, =CH), 5.46 (s, 1H, PhCH), 4.21 (dd, J = 10.5, 4.5 Hz, 1H), 4.12 (br m, 1H, OH), 3.65–3.53 (m, 5H), 2.72 (br s, 1H), 2.57 (br m, 2H), 2.38–2.27 (m, 1H), 2.17–2.06 (m, 1H), 1.68–1.50 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.8, 131.2, 128.9, 128.3, 126.0, 125.7, 101.0, 81.7, 71.1, 64.3, 61.3, 31.6, 29.1, 23.0; MS (electrospray) calcd for $C_{16}H_{22}O_4$ ([M + H^+]) 279, found 279.

Hydroxy aldehyde 24: A solution of diol **23** (6.63 g, 24.0 mmol) in CH_2Cl_2 (100 mL) was treated with Dess–Martin reagent (12.2 g, 28.8 mmol) at 25 °C for 4.5 h. The reaction mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (50 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (5 × 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 7:3, EtOAc:hexanes) to afford the hydroxy aldehyde **24** (5.74 g, 87 %). **24**: colorless oil; $R_f = 0.65$ (silica gel, 7:3, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max}$ = 3429, 2924, 2855, 1715, 1458, 1396, 1075, 1028, 753, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (s, 1H, CH(O)), 7.53–7.42 (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.69–5.62 (m, 1H, =CH), 5.48–5.40 (m, 1H, =CH), 5.47 (s, 1H, PhCH), 4.26 (dd, J = 10.5, 4.5 Hz, 1H), 3.70–3.60 (m, 2H), 3.58 (dd, J = 10.0, 10.0 Hz, 1H), 2.70 (d, J = 5.0 Hz, 1H, OH), 2.63–2.54 (m, 4H), 2.53–2.43 (m, 1H), 2.40–2.28 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 202.7, 137.8, 130.0, 128.9, 128.2, 126.1, 101.0, 81.3, 71.1, 64.9, 43.6, 29.6, 20.0; HRMS (FAB) calcd for $C_{16}H_{20}O_4$ ([M + Na^+]) 299.1259, found 299.1265.

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Hydroxy acid 25: A solution of aldehyde **24** (5.74 g, 21.0 mmol), $NaClO_2$ (5.7 g, 62.0 mmol), NaH_2PO_4 (3.02 g, 25.2 mmol), and 2-methyl-2-butene (35 mL of 2 M in THF) in *t*BuOH (40 mL) and water (8 mL) was vigorously stirred at 25 °C for 3 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, EtOAc) to afford hydroxy acid **25** (5.83 g, 96 %). **25**: colorless oil; $R_f = 0.35$ (silica gel, 1:49 acetic acid:EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3409, 1709, 1399, 1073, 1028, 698\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.51-7.41$ (m, 2H, ArH), 7.40–7.28 (m, 3H, ArH), 5.71–5.65 (m, 1H, =CH), 5.49–5.43 (m, 1H, =CH), 5.46 (s, 1H, PhCH), 4.23 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.70–3.60 (m, 2H), 3.55 (dd, $J = 10.0, 10.0$ Hz, 1H), 2.62–2.56 (m, 2H), 2.50–2.41 (m, 3H), 2.39–2.29 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 178.4, 137.7, 129.8, 129.0, 128.3, 126.3, 126.1, 101.0, 81.2, 70.8, 64.7, 33.7, 29.5, 22.5$; HRMS (FAB) calcd for $C_{16}H_{20}O_5$ ($[M + Na^+]$) 315.1208, found 315.1219.

Lactone 16: A solution of hydroxy acid **25** (2.2 g, 7.53 mmol) and Et_3N (1.15 mL, 8.28 mmol) in THF (15 mL) was treated with 2,4,6-trichlorobenzoyl chloride (1.24 mL, 7.91 mmol) at 0 °C for 20 min. The reaction mixture was diluted with benzene (100 mL) and added by cannula to a solution of DMAP (1.39 g, 11.3 mmol) in benzene (300 mL) at 80 °C over 1 h. It was stirred at 80 °C for an additional 1 h, cooled to room temperature, and treated with saturated aqueous ammonium chloride solution (50 mL). The aqueous phase was separated and extracted with ether (3×50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford lactone **16** (1.43 g, 70 %). **16**: colorless oil; $R_f =$ 0.35 (silica gel, 3:7 ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2959, 2868, 1738, 1456, 1383, 1334, 1252, 1206, 1147, 1094, 1000, 699\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.55-7.47$ (m, 2H, ArH), 7.42–7.30 (m, 3H, ArH), 5.81–5.73 (m, 1H, =CH), 5.71–5.64 (m, 1H, =CH), 5.53 (s, 1H, PhCH), 4.87 (br m, 1H), 4.36 (dd, $J = 10.5, 5.0$ Hz, 1H), 3.85 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.78 (ddd, $J = 9.5, 5.0, 5.0$ Hz, 1H), 2.50–2.40 (m, 4H), 2.39–2.30 (m, 1H), 2.26–2.19 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 175.4, 137.3, 129.2, 128.6, 128.4, 126.2, 102.2, 80.4, 73.2, 69.2, 34.2, 31.5, 24.6$; HRMS (FAB) calcd for $C_{16}H_{18}O_4$ ($[M + Na^+]$) 297.1103, found 297.1108.

Ketene acetal phosphate 15: A solution of lactone **16** (2.1 g, 7.66 mmol), HMPA (5.1 mL, 31.0 mmol), and diphenyl chlorophosphate (5.1 mL, 24.5 mmol) in THF (50 mL) was treated with KHMDS (42 mL, 0.5 M in toluene, 21 mmol) at −78 °C for 1 h. The reaction mixture was diluted with ether (50 mL) and quenched by the addition of 5 % aqueous ammonium hydroxide solution (20 mL). The resulting biphasic solution was stirred at 25 °C for 30 min, whereupon the aqueous phase was separated and extracted with ether (2×50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:4, EtOAc:hexanes) to afford ketene acetal phosphate **15** (3.5 g, 90 %). **15**: colorless oil; $R_f = 0.42$ (silica gel, 1:4, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 1682, 1590, 1489, 1299, 1187, 1109, 770, 688\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.51-7.23$ (m, 15H, ArH), 5.83 (ddd, $J = 10.5, 10.5, 7.0$ Hz, 1H, =CH), 5.73 (ddd, $J = 10.5, 10.5, 7.0$ Hz, 1H, =CH), 5.46 (s, 1H, PhCH), 5.11 (ddd, $J = 8.0, 8.0, 2.5$ Hz, 1H, =CH), 4.30 (dd, $J = 10.5, 5.0$ Hz, 1H), 4.11 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 3.99 (ddd, $J = 9.0, 4.0, 4.0$ Hz, 1H), 3.66 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.26–3.17 (m, 2H), 2.45–2.34 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 153.3, 150.2, 137.2, 131.1, 129.7, 128.9, 128.1, 126.0, 125.5, 124.9, 119.9, 101.4, 96.9, 80.0, 77.8, 69.1, 29.1, 21.6$; HRMS (FAB) calcd for $C_{28}H_{27}O_7P$ ($[M + Cs^+]$): 639.0549, found 639.0526.

Diene 14: A solution of ketene acetal phosphate **15** (3.5 g, 6.9 mmol), tri-*n*-butyl(vinyl)tin (4.85 g, 15.4 mmol), LiCl (877 mg, 20.7 mmol), and $[Pd(Ph_3P)_4]$ (440 mg, 0.38 mmol) in THF (35 mL) was heated at 80 °C for 1.5 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 1:4, EtOAc:hexanes) to afford diene **14** (1.88 g, 95 %). **14**: colorless oil; $R_f = 0.78$ (silica gel, 1:4, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2920, 2866, 1597, 1450, 1387, 1094, 1031, 749, 696\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.52-7.48$ (m, 2H, ArH), 7.41–7.35 (m, 3H, ArH), 6.24 (dd, $J = 17.0, 11.0$ Hz, 1H, =CH), 5.81–5.70 (m, 2H, =CH), 5.52 (s, 1H, PhCH), 5.32 (d, $J = 17.0$ Hz, 1H, =CH), 5.29 (dd, $J = 8.0, 8.0$ Hz, 1H, =CH), 5.01 (d, $J = 11.0$ Hz, 1H, =CH), 4.40–4.33 (m, 1H), 4.03–3.98 (m, 1H), 3.85–3.79 (m, 2H), 3.24–3.12 (m, 2H), 2.61 (ddd, $J = 13.0, 7.0, 7.0$ Hz, 1H), 2.51 (ddd, $J = 13.5, 6.5, 5.0$ Hz, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 157.5, 137.7, 135.2, 129.5, 129.0, 128.3, 126.1, 125.0, 116.5, 112.5, 101.2, 79.4, 76.4, 70.4, 30.0, 23.7$; HRMS (FAB) calcd for $C_{18}H_{20}O_3$ ($[M + H^+]$) 285.1491, found 285.1498.

Endoperoxide 11: Oxygen (gas) was bubbled through a solution of diene **14** (512 mg, 1.8 mmol) and *meso*-tetraphenylporphyrin (50 mg, 0.082 mmol) in CCl_4 (50 mL) for 5 min. The reaction mixture was irradiated with a 150 W projection lamp at 25 °C for 3 h. The solvent was removed in vacuo, and the residue was purified by flash column chromatography (silica gel, benzene) to afford endoperoxide **11** (410 mg, 72 %) as a mixture of diastereoisomers (ca. 1:1 ratio) and recovered starting material **14** (82 mg, 16 %). **11a** (polar isomer): colorless oil; $R_f = 0.35$ (silica gel, benzene); IR (thin film): $\tilde{\nu}_{max} =$ 2927, 2857, 1726, 1676, 1677, 1452, 1294, 1209, 1116, 1088, 1028, 753, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.50-7.40$ (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.94 (ddd, $J = 10.5, 10.5, 7.5$ Hz, 1H, =CH), 5.76 (ddd, $J = 10.5, 10.5, 6.5$ Hz, 1H, =CH), 5.48 (s, 1H, PhCH), 5.35 (br m, 1H), 4.82 (br d, $J = 10.5$ Hz, 1H), 4.79 (ddd, $J = 15.5, 2.0, 2.0$ Hz, 1H), 4.46 (ddd, $J =$ 15.5, 3.5, 2.0 Hz, 1H), 4.31 (dd, $J = 10.0, 4.0$ Hz, 1H), 3.88–3.80 (m, 2H), 3.72 (dd, $J = 10.0, 10.0$ Hz, 1H), 2.93 (dd, $J = 11.5, 11.5$ Hz, 1H), 2.75 (ddd, $J = 14.0, 10.0, 8.0$ Hz, 1H), 2.38 (ddd, $J = 14.0, 6.5, 2.5$ Hz, 1H), 2.18–2.10 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 152.3, 137.3, 129.0, 128.9, 128.2, 127.1, 126.0, 104.5, 101.5, 78.0, 77.7, 69.6, 68.6, 68.3, 27.8$.

Diols 26a and 26b: A solution of diastereomeric endoperoxides **11** (340 mg, 1.08 mmol) in methanol (20 mL) was treated with Lindlar catalyst (40 mg) under an atmosphere of hydrogen at 25 °C for 20 min. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, EtOAc) to afford diols **26a** (165 mg, 48 %) and **26b** (173 mg, 51 %). **26a**: colorless oil; $R_f = 0.52$ (silica gel, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3360, 2964, 2928, 1661, 1452, 1397, 1079, 1024, 750, 691\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.52-7.43$ (m, 2H, ArH), 7.41–7.30 (m, 3H, ArH), 5.81 (ddd, $J = 10.5, 10.5, 7.5$ Hz, 1H, =CH), 5.54 (ddd, $J = 10.5, 10.5, 6.0$ Hz, 1H, =CH), 5.50 (s, 1H, PhCH), 5.29 (dd, $J = 8.0, 8.0$ Hz, 1H, =CH), 4.73 (dd, $J = 10.5, 4.5$ Hz, 1H), 4.46 (dd, $J = 10.5, 4.5$ Hz, 1H), 4.21 (dd, $J = 12.5, 8.5$ Hz, 1H), 4.09 (dd, $J = 12.5, 7.5$ Hz, 1H), 3.95 (ddd, $J = 8.5, 5.0, 3.0$ Hz, 1H), 3.87 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.74 (ddd, $J = 10.0, 10.0, 4.5$ Hz, 1H), 3.25 (br m, 1H, OH), 3.05–2.96 (m, 1H), 2.75 (ddd, $J = 12.0, 11.0, 11.0$ Hz, 1H), 2.40–2.31 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 163.4, 137.2, 129.0, 128.4, 128.2, 127.3, 126.0, 109.7, 101.7, 80.1, 79.5, 70.8, 66.4, 57.1, 31.4, 30.2$; HRMS (FAB) calcd for $C_{18}H_{22}O_5$ ($[M + Na^+]$) 341.1365, found 341.1360. **26b**: colorless oil; $R_f =$ 0.62 (silica gel, EtOAc); IR (thin film): $\tilde{\nu}_{max} = 3296, 2928, 2867, 1659, 1452, 1394, 1127, 1085, 1024, 983, 737\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.52–7.45 (m, 2H, ArH), 7.45–7.32 (m, 3H, ArH), 5.83–5.73 (m, 2H, =CH), 5.48 (s, 1H, PhCH), 5.27 (dd, $J = 7.5, 7.5$ Hz, 1H), 4.43–4.39 (m, 1H), 4.39 (dd, $J = 10.5, 5.0$ Hz, 1H), 4.29 (dd, $J = 12.0, 7.5$ Hz, 1H), 4.21 (dd, $J = 12.0, 7.5$ Hz, 1H), 4.09 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 3.79 (br m, 1H, OH), 3.76 (dd, $J = 11.0, 11.0$ Hz, 1H), 3.75–3.72 (m, 1H), 2.80 (br m, 1H, OH), 2.63–2.52 (m, 4H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 164.5, 137.3, 129.0, 128.3, 128.2, 127.9, 126.0, 107.4, 101.5, 79.0, 78.4, 70.9, 69.9, 56.6, 34.2, 31.2$; HRMS (FAB) calcd for $C_{18}H_{22}O_5$ ($[M + Na^+]$) 341.1365, found 341.1358.

Silyl ether 27b: A solution of diol **26b** (500 mg, 0.95 mmol) in CH_2Cl_2 (30 mL) was treated with imidazole (78 mg, 1.14 mmol) and TBSCl (150 mg, 1.0 mmol) at 25 °C for 30 min. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL), and the aqueous phase was separated and extracted with ether (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography to afford alcohol **27b** (566 mg, 93 %). $R_f = 0.47$ (silica gel, 1:4, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 3423, 2928, 1654, 1254, 1083, 1028, 836, 696\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.52-7.46$ (m, 2H, ArH), 7.40–7.31 (m, 3H, 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), 5.47 (s, 1H, PhCH), 5.19 (dd, $J = 7.0, 7.0$ Hz, 1H), 4.44 (d, $J = 5.5$ Hz, 1H), 4.40–4.34 (m, 1H), 4.38 (dd, $J = 10.5, 5.0$ Hz, 1H), 4.30 (d, $J = 7.0$ Hz, 2H), 4.08 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 3.75 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.75–3.70 (m, 1H), 2.66–2.50 (m, 4H), 0.93 (s, 9H, *t*BuSi), 0.13 (s, 3H, CH_3Si), 0.13 (s, 3H, CH_3Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 164.8, 137.5, 129.2, 129.1, 128.3, 127.4, 126.2, 107.1, 101.7, 79.2, 78.4, 70.9, 70.0, 57.7, 34.3, 31.3, 25.9, 18.1, -5.0, -5.1$; HRMS (FAB) calcd for $C_{24}H_{36}O_5Si$ ($[M + Cs^+]$) 565.1386, found 565.1395.

***α,β*-Unsaturated ketone 28**: A solution of hydroxy silyl ether **27** (550 mg, 1.27 mmol) and 4-methylmorpholine *N*-oxide (225 mg, 1.9 mmol) in CH_2Cl_2 (25 mL) was treated with tetrapropylammonium perruthenate (23 mg, 0.064 mmol) at 25 °C for 1 h. The reaction mixture was filtered through a short silica gel pad, eluting with ether. The filtrate was

concentrated, and the residue was purified by flash column chromatography (silica gel, 1:3, ether:hexanes) to afford α,β-unsaturated ketone **28** (462 mg, 85%). **28**: colorless oil; $R_f = 0.47$ (silica gel, 1:3, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2928, 2855, 1694, 1614, 1462, 1325, 1257, 1066, 1028, 837, 777, 697, 604\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.50-7.42$ (m, 2H, ArH), 7.38–7.32 (m, 3H, ArH), 5.89 (ddd, $J = 10.0, 10.0, 6.0$ Hz, 1H, =CH), 5.78 (dd, $J = 5.0, 5.0$ Hz, 1H), 5.70 (ddd, $J = 10.5, 10.5, 6.0$ Hz, 1H, =CH), 5.49 (s, 1H, PhCH), 4.61–4.51 (m, 2H), 4.41 (dd, $J = 10.5, 4.5$ Hz, 1H), 4.00 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.97–3.95 (m, 1H), 3.81 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.69 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 3.11 (ddd, $J = 15.0, 11.0, 4.5$ Hz, 1H), 2.82 (dd, $J = 10.5, 6.0$ Hz, 1H), 2.47 (dd, $J = 14.0, 5.0$ Hz, 1H), 0.92 (s, 9H, *t*BuSi), 0.09 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 197.3, 149.3, 137.3, 133.8, 129.0, 128.8, 128.2, 126.1, 125.0, 101.6, 78.2, 73.8, 68.5, 59.7, 40.4, 29.3, 25.8, 18.1, -5.3, -5.3$; HRMS (FAB) calcd for $C_{24}H_{34}O_5Si$ ($[M + Cs^+]$) 563.1230, found 563.1218.

Ketone 29: A solution of α,β-unsaturated ketone **28** (460 mg, 1.07 mmol) in benzene (10 mL) was treated with hydrido(triphenylphosphane)copper(I) hexamer (1.4 g, 0.72 mmol). After stirring the reaction mixture at 25 °C for 3 h, it was concentrated, and the residue was purified by flash column chromatography (silica gel, 2:5, ether:hexanes) to furnish ketone **29** (443 mg, 96%). **29**: colorless oil; $R_f = 0.86$ (silica gel, 2:5, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2928, 2857, 1715, 1464, 1257, 1103, 837, 776\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.49-4.43$ (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.85 (ddd, $J = 10.5, 10.5, 6.5$ Hz, 1H, =CH), 5.66 (ddd, $J = 10.5, 10.5, 6.5$ Hz, 1H, =CH), 5.45 (s, 1H, PhCH), 4.34 (dd, $J = 10.5, 4.5$ Hz, 1H), 4.07 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.99 (dd, $J = 8.5, 4.5$ Hz, 1H), 3.85 (ddd, $J = 9.0, 4.0, 2.5$ Hz, 1H), 3.71–3.67 (m, 2H), 3.63 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.43 (ddd, $J = 10.0, 10.0, 4.5$ Hz, 1H), 3.06 (ddd, $J = 14.5, 10.5, 4.0$ Hz, 1H), 2.69 (dd, $J = 10.0, 6.5$ Hz, 1H), 2.41 (ddd, $J = 14.0, 6.5, 2.0$ Hz, 1H), 1.80–1.68 (m, 2H), 0.90 (s, 9H, *t*BuSi), 0.06 (s, 3H, CH_3Si), 0.06 (s, 3H, CH_3Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 211.3, 137.5, 129.1, 128.5, 128.3, 126.2, 124.9, 101.8, 82.3, 78.3, 71.2, 68.5, 58.0, 37.9, 35.6, 29.1, 25.8, 18.3, -5.3, -5.4$; HRMS (FAB) calcd for $C_{24}H_{36}O_5Si$ ($[M + H^+]$) 433.2410, found 433.2420.

Secondary alcohol 30: A solution of ketone **29** (120 mg, 0.28 mmol) in CH_2Cl_2 (5 mL) was treated with DIBAL-H (0.4 mL, 1.0 M CH_2Cl_2, 0.4 mmol) at −78 °C for 20 min. The reaction mixture was quenched by the addition of EtOAc (1.5 mL), followed by a saturated aqueous sodium potassium tartrate solution (2 mL). The resulting mixture was stirred for 4 h, whereupon the aqueous layer was separated and extracted with EtOAc (3×5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 2:5, EtOAc:hexanes) to afford alcohol **30** (105 mg, 87%). **30**: colorless oil; $R_f = 0.47$ (silica gel, 2:5, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 3446, 2929, 2859, 1456, 1456, 1392, 1255, 1105, 1028, 836, 778, 698\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.47-7.42$ (m, 2H, ArH), 7.38–7.32 (m, 3H, ArH), 5.85 (ddd, $J = 9.5, 9.0, 9.0$ Hz, 1H, =CH), 5.78 (ddd, $J = 10.0, 9.0, 9.0$ Hz, 1H, =CH), 5.43 (s, 1H, PhCH), 4.23 (br d, $J = 8.5$ Hz, 1H), 3.98 (d, $J = 3.0$ Hz, 1H), 3.83 (ddd, $J = 10.5, 6.0, 3.5$ Hz, 1H), 3.73 (ddd, $J = 11.5, 8.5, 3.0$ Hz, 1H), 3.69–3.55 (m, 4H), 3.47–3.40 (m, 1H), 2.63 (br m, 2H), 2.56 (br m, 2H), 1.92–1.80 (m, 2H), 0.91 (s, 9H, *t*BuSi), 0.10 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 137.7, 130.2, 128.9, 128.3, 126.2, 126.1, 101.3, 88.2, 80.4, 79.9, 73.3, 70.4, 59.9, 39.8, 33.7, 31.8, 25.8, 18.2, -5.4, -5.5$; HRMS (FAB) calcd for $C_{24}H_{38}O_5Si$ ($[M + H^+]$) 435.2567, found 435.2552.

Silyl ether 31: A solution of secondary alcohol **30** (40 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was treated with 4-DMAP (45 mg, 0.37 mmol) and PivCl (34 mL, 0.28 mmol) at 25 °C for 8 h. The reaction mixture was quenched with a saturated aqueous ammonium chloride solution (1 mL) and extracted with EtOAc (3×40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 2:5, ether:hexanes) to afford silyl ether **31** (44 mg, 91%). **31**: colorless oil; $R_f = 0.78$ (silica gel, 3:7, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2929, 2856, 1729, 1458, 1395, 1157, 1028, 836\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.51-7.42$ (m 2H, ArH), 7.40–7.32 (m, 3H, ArH), 5.81 (ddd, $J = 9.0, 9.0, 9.0$ Hz, 1H, =CH), 5.72 (ddd, $J = 10.5, 9.0, 9.0$ Hz, 1H, =CH), 5.43 (s, 1H, PhCH), 4.76 (br m, 1H), 4.43 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.78–3.62 (m, 5H), 3.58 (dd, $J = 10.5, 10.5$ Hz, 1H), 2.72 (br m, 1H), 2.58 (br m, 2H), 2.49 (br m, 1H), 1.72–1.53 (m, 2H), 1.21 (s, 9H, OC(O)*t*Bu), 0.90 (s, 9H, *t*BuSi), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 177.5, 137.8, 129.0, 128.9, 128.3, 126.9, 126.2, 101.2, 80.8, 78.5, 77.7, 75.7, 69.6, 58.2, 37.9, 31.3, 29.5, 27.1, 26.5, 25.8, 18.2, -5.3, -5.4$; HRMS (FAB) calcd for $C_{29}H_{46}O_6Si$ ($[M + H^+]$) 519.3142, found 519.3164.

Primary alcohol 32: A solution of silyl ether **31** (100 mg, 0.2 mmol) in THF (2 mL) was treated with TBAF (300 μL, 1 M in THF, 0.3 mmol) at 25 °C for 4 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 2:5, EtOAc:hexanes) to afford primary alcohol **32** (71 mg, 91%). **32**: colorless oil; $R_f = 0.45$ (silica gel, 2:5, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 3499, 2960, 1727, 1396, 1282, 1159, 1102, 698\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.49-7.42$ (m, 2H, ArH), 7.39–7.32 (m, 3H, ArH), 5.81 (ddd, $J = 9.5, 9.5, 8.5$ Hz, 1H, =CH), 5.73 (ddd, $J = 10.5, 8.5, 8.5$ Hz, 1H, =CH), 5.43 (s, 1H, PhCH), 4.89 (br m, 1H), 4.38 (dd, $J = 10.5, 4.5$ Hz, 1H), 3.79–3.65 (m, 6H), 3.60 (dd, $J = 10.0, 10.0$ Hz, 1H), 2.78 (br m, 1H), 2.53 (br m, 3H), 1.82–1.75 (m, 1H), 1.70–1.62 (m, 1H), 1.22 (s, 9H, OC(O)*t*Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 177.5, 137.8, 128.9, 128.7, 128.2, 127.2, 126.0, 101.3, 82.2, 78.5, 77.1, 74.7, 69.6, 58.7, 38.7, 36.3, 30.9, 28.9, 26.9$; HRMS (FAB) calcd for $C_{23}H_{32}O_6$ ($[M + Cs^+]$) 537.1253, found 537.1273.

Phosphonium salt 9: A solution of primary alcohol **32** (71 mg, 0.18 mmol), imidazole (24 mg, 0.31 mmol), and triphenylphosphane (92 mg, 0.31 mmol) in CH_2Cl_2 (5 mL) was treated with iodine (50 mg, 0.2 mmol) at 25 °C for 10 min. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 2:5, EtOAc:hexanes) to afford iodide **33**. Iodide **33** and triphenylphosphane (470 mg, 1.80 mmol) were fused at 90 °C for 3 h. The mixture was purified by flash column chromatography (silica gel, 2:5, acetone:CH_2Cl_2) to afford phosphonium salt **9** (118 mg, 87% for two steps). Iodide **33**: colorless oil; $R_f = 0.92$ (silica gel, 2:5, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2946, 2858, 1730, 1454, 1396, 1281, 1156, 1103, 1028, 975, 734\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.54-7.45$ (m, 2H, ArH), 7.40–7.30 (m, 3H, ArH), 5.83 (ddd, $J = 9.0, 9.0, 9.0$ Hz, 1H, =CH), 5.72 (ddd, $J = 10.0, 9.0, 9.0$ Hz, 1H, =CH), 5.44 (s, 1H, PhCH), 4.79 (br m, 1H), 4.39 (dd, $J = 10.0, 4.5$ Hz, 1H), 3.78–3.60 (m, 3H), 3.59 (dd, $J = 10.0, 10.0$ Hz, 1H), 3.25 (ddd, $J = 9.5, 6.0, 6.0$ Hz, 1H), 3.10 (ddd, $J = 9.0, 9.0, 9.0$ Hz, 1H), 2.75 (br m, 1H), 2.54 (br m, 3H), 2.00–1.95 (m, 2H), 1.25 (s, 9H, OC(O)*t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.3, 137.6, 128.9, 128.6, 128.2, 127.1, 126.1, 101.1, 83.4, 78.3, 76.2, 74.7, 69.8, 38.7, 38.6, 30.9, 28.9, 27.1, 1.9$; HRMS (FAB) calcd for $C_{23}H_{31}O_5I$ ($[M + Cs^+]$) 647.0271, found 647.0247. Phosphonium salt **9**: white solid; $R_f = 0.32$ (silica gel, 1:4, acetone:CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} = 2930, 2865, 1724, 1439, 1156, 1097, 1028, 917, 723\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.80-7.64$ (m, 15H, ArH), 7.42–7.32 (m, 2H, ArH), 7.28–7.19 (m, 3H, ArH), 5.76 (ddd, $J = 9.0, 9.0, 8.5$ Hz, 1H, =CH), 5.64 (ddd, $J = 9.0, 9.0, 8.5$ Hz, 1H, =CH), 5.42 (s, 1H, PhCH), 4.86 (br m, 1H), 3.95 (br m, 1H), 3.85–3.64 (m, 5H), 3.28–3.17 (m, 1H), 2.70 (br m, 1H), 2.51 (br m, 1H), 2.39 (br m, 2H), 1.80–1.68 (m, 1H), 1.60–1.50 (m, 1H), 1.03 (s, 9H, OC(O)*t*Bu); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.8, 137.5, 135.4, 133.4, 132.2, 130.7, 128.7, 128.0, 126.2, 117.5, 116.8, 101.1, 83.4, 77.9, 72.6, 69.5, 46.5, 38.6, 31.2, 28.7, 26.8, 17.9$.

Dialdehyde 30c: A solution of secondary alcohol **30** (50 mg, 0.115 mmol) in THF (2 mL) was treated with TBAF (150 μL, 1 M in THF, 0.15 mmol) at 25 °C for 3 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, EtOAc) to afford diol **30a** (33 mg, 90%). A solution of diol **30a** (33 mg, 0.104 mmol) in CH_2Cl_2 (2.0 mL) was treated with 2,2-dimethoxypropane (50 μL, 0.4 mmol) and CSA (2 mg) at 25 °C for 20 min. The reaction mixture was quenched by the addition of Et_3N (5 μL) and concentrated. The residue was purified by flash column chromatography (silica gel, 2:5, EtOAc:hexanes) to afford ketal **30b** (35 mg, 95%). Ketal **30b** (35 mg, 0.099 mmol) was dissolved in CH_2Cl_2 (3 mL) and cooled to −78 °C. Ozone was bubbled through the solution until a blue color persisted (ca. 3 min.). The excess ozone was then removed by bubbling oxygen through the solution until the blue color dissipated. After addition of Ph_3P (45 mg, 1.70 mmol), the reaction mixture was stirred at 25 °C for 30 min and then concentrated. The residue was purified by flash column column chromatography (silica gel, 2:5, EtOAc:hexanes) to provide dialdehyde **30c** (34 mg, 89%). **30c**: colorless oil; $R_f = 0.32$ (silica gel, 2:5, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2942, 1725, 1379, 1220, 1102, 1027\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.85$ (s, 1H, CH(O)), 9.75 (s, 1H, CH(O)), 7.48–7.40 (m, 2H, ArH), 7.40–7.32 (m, 3H, ArH), 5.50 (s, 1H, PhCH), 4.29 (dd, $J = 11.0, 5.0$ Hz, 1H), 4.23 (ddd, $J = 8.5, 8.5, 4.5$ Hz, 1H), 4.14 (ddd, $J = 8.5, 8.5, 3.5$ Hz, 1H), 3.71 (dd, $J = 12.0, 12.0$ Hz, 1H), 3.65–3.58 (m, 2H), 3.42 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 3.30 (ddd,

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$J = 9.5, 9.5, 5.0$ Hz, 1H), 2.86 (ddd, $J = 16.0, 4.0, 1.0$ Hz, 1H), 2.77 (ddd, $J = 16.0, 5.0, 2.5$ Hz, 1H), 2.71 (ddd, $J = 16.0, 8.0, 2.5$ Hz, 1H), 2.54 (ddd, $J = 16.0, 8.5, 2.5$ Hz, 1H), 2.03 (ddd, $J = 13.5, 4.0, 4.0$ Hz, 1H), 1.65–1.58 (m, 1H), 1.34 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 200.6, 200.1, 137.0, 129.1, 128.3, 126.0, 102.1, 100.9, 81.0, 76.1, 71.8, 70.4, 69.4, 65.8, 47.2, 45.7, 36.3, 24.9, 24.6$.

Primary alcohol 34: A solution of aldehyde **20** (5.0 g, 14.8 mmol) in methanol (50 mL) was treated with $NaBH_4$ (0.75 g, 19.5 mmol) at 25 °C for 30 min. The reaction mixture was concentrated, and the residue was dissolved in ether (150 mL) and washed with saturated aqueous ammonium chloride solution (2×20 mL). The organic phase was dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 3:2, ether:hexanes) to afford alcohol **34** (4.68 g, 93%). **34**: colorless oil; $R_f = 0.8$ (silica gel, 4:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} =$ 3450, 3040, 2940, 2875, 1470, 1140 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 7.51–7.40 (m, 2H, ArH), 7.39–7.30 (m, 3H, ArH), 5.50 (s, 1H, PhCH), 4.19 (dd, $J = 10.0, 4.5$ Hz, 1H), 3.84 (dd, $J = 6.0, 6.0$ Hz, 2H), 3.79 (ddd, $J = 9.0, 9.0, 3.0$ Hz, 1H), 3.63 (ddd, $J = 10.0, 10.0, 4.5$ Hz, 1H), 3.58 (dd, $J = 10.0, 10.0$ Hz, 1H), 2.26 (br m, 1H, OH), 2.18–2.09 (m, 1H), 1.87–1.76 (m, 1H), 0.89 (s, 9H, *t*BuSi), 0.10 (s, 3H, CH_3Si), 0.09 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.6, 129.0, 128.3, 126.0, 101.0, 81.8, 71.8, 66.4, 60.4, 34.0, 25.7, 17.9, -4.2, -4.8$; HRMS (FAB) calcd for $C_{18}H_{30}O_4Si$ ($[M + H^+]$) 339.1992, found 339.2003.

Phosphonium salt 12: To a solution of primary alcohol **34** (27.6 g, 82 mmol), imidazole (7.8 g, 114 mmol), and triphenylphosphane (27.7 g, 106 mmol) in ether (110 mL) and acetonitrile (160 mL) at 25 °C was added iodine (28.9 g, 114 mmol) in three equal portions over 30 min. The reaction mixture was quenched with a saturated aqueous sodium thiosulfate solution (20 mL) and diluted with ether (700 mL). The organic phase was washed with $NaHCO_3$ (3×100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, 1:19, ether:petroleum ether) furnished pure iodide **35.** A solution of iodide **35** (31 g, 69.2 mmol) and triphenylphosphane (19.9 g, 76.0 mmol) in acetonitrile (140 mL) was heated at 80 °C for 48 h. The reaction mixture was cooled to room temperature, and the solvent was removed under vacuum. Flash chromatography of the resulting oil (silica gel, 1:9, acetone:CH_2Cl_2) afforded pure phosphonium salt **12** (43.6 g, 89%). **12**: white solid; $R_f = 0.5$ (silica gel, 1:19, acetone:CH_2Cl_2); IR (thin film): $\tilde{\nu}_{max} =$ 3050, 3040, 2980, 2860, 1600, 1450, 1114 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.78-7.32$ (m, 20H, ArH), 5.67 (s, 1H, PhCH), 4.20–4.00 (m, 3H), 3.60–3.51 (m, 1H), 3.51–3.32 (m, 2H), 2.22 (br m, 1H), 1.65–1.50 (m, 1H), 0.72 (s, 9H, *t*BuSi), −0.1 (s, 3H, CH_3Si), −0.2 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.6, 135.2, 133.5, 130.7, 128.9, 128.2, 126.4, 118.1, 117.4, 101.0, 80.1, 71.1, 67.2, 25.5, 25.4, 19.0, 17.7, -4.3, -4.9$; elemental analysis calcd for $C_{36}H_{44}O_3SiPI$ (%): C 69.11, H 6.81; found C 68.47, H 6.75.

Olefin 36: Phosphonium salt **12** (8.0 g, 11.3 mmol) was suspended in THF (100 mL) and cooled to −78 °C. After addition of *n*BuLi (7.5 mL, 1.6 M solution in hexanes, 12.0 mmol), the yellow-colored solution was stirred at −78 °C for 20 min. Then, HMPA (20 mL, 0.113 mol), and a solution of aldehyde **13** (3.4 g, 13.6 mmol) in THF (15 mL) were added successively at −78 °C, and the reaction mixture was stirred at this temperature for 30 min and at 25 °C for 1 h. It was quenched with a saturated aqueous ammonium chloride solution (15 mL), and the separated aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash column chromatography (silica gel, 1:9, ether:hexanes) to afford olefin **36** (6.46 g, 87%). **36**: colorless oil, $R_f = 0.65$ (silica gel, 1:6, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} =$ 3002, 2960, 2857, 1460, 1258, 1106, 1035, 840, 778 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.52-7.43$ (m, 2H, ArH), 7.40–7.29 (m, 3H, ArH), 5.94–5.87 (m, 1H, =CH), 5.73–5.67 (m, 1H, =CH), 5.48 (s, 1H, PhCH), 4.29 (d, $J = 8.5$ Hz, 1H), 4.22–4.14 (m, 1H), 4.07–3.98 (m, 1H), 3.66–3.53 (m, 2H), 3.45 (ddd, $J = 11.5, 11.5, 3.0$ Hz, 1H), 3.06–2.94 (m, 1H), 2.68–2.54 (m, 4H), 2.36–2.11 (m, 4H), 1.78–1.70 (m, 1H), 1.57–1.48 (m, 1H), 1.24 (t, $J = 7.5$ Hz, 3H), 1.10 (t, $J = 7.5$ Hz, 3H), 0.93 (s, 9H, *t*BuSi), 0.16 (s, 3H, CH_3Si), 0.11 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.8, 130.8, 128.6, 128.0, 127.8, 126.0, 100.7, 82.2, 81.3, 71.6, 67.6, 66.8, 62.9, 35.1, 30.6, 25.7, 23.6, 22.7, 22.0, 17.8, 14.0, 13.8, -4.3, -4.8$; HRMS (FAB) calcd for $C_{28}H_{46}O_4S_2Si$ ($[M + Na^+]$) 561.2505, found 561.2517.

Hydroxy dithioketal 37: A solution of olefin **36** (4.65 g, 7.1 mmol) in THF (40 mL) was treated with TBAF (10.0 mL, 1 M solution in THF, 10.0 mmol) at 25 °C for 0.5 h. The reaction mixture was diluted with a saturated aqueous ammonium chloride solution (20 mL), and the aqueous phase was extracted with EtOAc (3×20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:1, EtOAc:hexanes) to afford alcohol **37** (3.15 g, 82%). **37**: colorless oil; $R_f = 0.52$ (silica gel, 1:1, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} =$ 3428, 2927, 2855, 1455, 1395, 1085, 1027, 733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.50-7.45$ (m, 2H, ArH), 7.38–7.27 (m, 3H, ArH), 6.00–5.93 (m, 1H, =CH), 5.88–5.83 (m, 1H, =CH), 5.49 (s, 1H, PhCH), 4.38 (d, $J = 8.0$ Hz, 1H), 4.24 (dd, $J = 10.5, 4.0$ Hz, 1H), 4.10–4.04 (m, 1H), 3.67 (br m, 2H), 3.61–3.57 (m, 1H), 3.55 (ddd, $J = 11.5, 11.5, 2.5$ Hz, 1H), 3.45 (br m, 1H, OH), 2.79–2.64 (m, 2H), 2.67 (q, $J = 7.5$ Hz, 2H), 2.59 (q, $J = 7.5$ Hz, 2H), 2.30–2.15 (m, 2H), 1.84–1.76 (m, 1H), 1.60–1.55 (m, 1H), 1.26 (t, $J = 7.5$ Hz, 3H), 1.18 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.7, 131.7, 128.8, 128.1, 127.4, 126.0, 100.9, 81.0, 80.8, 70.6, 67.7, 66.2, 62.1, 34.6, 32.4, 23.9, 22.6, 22.0, 13.9, 13.8$; HRMS (FAB) calcd for $C_{22}H_{32}O_4S_2$ ($[M + Na^+]$) 447.1640, found 447.1652.

Mixed thioketal 38: A heterogeneous mixture of hydroxy dithioketal **37** (3.1 g, 5.7 mmol), powdered 4 Å molecular sieves (freshly activated, 3.0 g), silica gel (dried under vacuum, 3.0 g), sodium bicarbonate (4.8 g, 57.0 mmol), and silver perchlorate (3.5 g, 17.0 mmol) in dry nitromethane (50 mL) was vigorously stirred at 25 °C for 3 h. The reaction mixture was treated with Et_3N (10 mL), diluted with ether (200 mL), and filtered through a pad of celite. The filtrate was washed with a saturated aqueous ammonium chloride solution (3×30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:3, EtOAc:hexanes) to afford mixed thioketal **38** (1.97 g, 72%). **38**: colorless oil; $R_f = 0.35$ (1:3, EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.50-7.45$ (m, 2H, ArH), 7.42–7.34 (m, 3H, ArH), 5.96–5.90 (m, 1H, =CH), 5.73 (dd, $J = 11.0, 7.0$ Hz, 1H, =CH), 5.43 (s, 1H, PhCH), 4.65 (ddd, $J = 10.0, 10.0, 5.0$ Hz, 1H), 4.09 (dd, $J = 10.0, 4.0$ Hz, 1H), 4.05 (dd, $J = 6.5, 1.0$ Hz, 1H), 4.01–3.96 (m, 2H), 3.59 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.42 (ddd, $J = 12.0, 12.0, 2.5$ Hz, 1H), 2.80 (dddd, $J = 15.5, 9.5, 5.5, 1.0$ Hz, 1H), 2.61–2.53 (m, 1H), 2.50–2.41 (m, 2H), 2.23–2.15 (m, 2H), 1.74–1.59 (m, 2H), 1.29 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.5, 132.2, 128.9, 128.6, 128.2, 126.1, 101.4, 91.7, 83.2, 81.8, 69.9, 68.1, 64.4, 34.9, 30.7, 24.1, 20.6, 14.1$; HRMS (FAB) calcd for $C_{20}H_{26}O_4S$ ($[M + H^+]$) 363.1630, found 363.1638.

Oxocene 39: A solution of mixed ketal **38** (1.9 g, 4.0 mmol) and triphenyltin hydride (2.06 mL, 8.0 mmol) in toluene (30 mL) was treated with AIBN (120 mg in 3 mL of toluene) and stirred at 110 °C over a period of 1 h. The resulting black solution was stirred at the same temperature for an additional 1 h. It was concentrated, and the residue was purified by flash column chromatography (silica gel, 1:3, EtOAc:hexanes) to afford oxocene **39** (1.27 g, 81%). **39**: colorless oil; $R_f = 0.35$ (silica gel, 1:3, EtOAc:hexanes); IR (thin film): $\tilde{\nu}_{max} =$ 2940, 2856, 1463, 1390, 1218, 1093, 1028, 969, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.49-7.42$ (m, 2H, ArH), 7.40–7.31 (m, 3H, ArH), 5.83–5.75 (m, 2H, =CH), 5.42 (s, 1H, PhCH), 4.17 (dd, $J = 10.0, 4.5$ Hz, 1H), 3.92–3.87 (m, 1H), 3.85 (dd, $J = 8.5, 4.0$ Hz, 1H), 3.82–3.77 (m, 2H), 3.65–3.58 (m, 1H), 3.30–3.20 (m, 2H), 2.81 (ddd, $J = 13.5, 8.5, 4.0$ Hz, 1H), 2.44 (dd, $J = 14.5, 6.0$ Hz, 1H), 2.12–2.06 (m, 1H), 1.70–1.62 (m, 2H), 1.48–1.40 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.6, 135.5, 128.8, 128.1, 126.1, 125.8, 101.5, 82.0, 79.9, 78.3, 71.2, 69.6, 67.0, 31.2, 30.3, 25.3$; HRMS (FAB) calcd for $C_{18}H_{22}O_4$ ($[M + H^+]$) 303.1596, found 303.1580.

Diol 40: A solution of oxocene **39** (1.25 g, 4.1 mmol) in methanol (20 mL) was treated with 10% Pd/C (250 mg) and stirred under an atmosphere of hydrogen at 25 °C for 17 h. The reaction mixture was filtered through a pad of celite, the filtrate was concentrated, and the residue was purified by flash column chromatography (silica gel, EtOAc) to afford diol **40** (840 mg, 94%). **40**: colorless oil; $R_f = 0.45$ (silica gel, EtOAc); IR (thin film): $\tilde{\nu}_{max} =$ 3417, 2932, 2860, 1636, 1456, 1272, 1118, 1094, 1032 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 3.83$ (br d, $J = 9.0$ Hz, 1H), 3.78–3.70 (m, 1H), 3.68–3.60 (m, 2H), 3.43 (ddd, $J = 9.0, 4.5, 4.5$ Hz, 1H), 3.30–3.23 (m, 1H), 3.17 (ddd, $J = 10.0, 10.0, 4.5$ Hz, 1H), 3.03 (ddd, $J = 9.5, 9.5, 1.0$ Hz, 1H), 2.74 (br m, 1H, OH), 2.63 (br m, 1H, OH), 2.12–1.90 (m, 4H), 1.68–1.55 (m, 5H), 1.48–1.40 (m, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 86.0, 84.0, 81.7, 72.5, 67.4, 65.1, 36.3, 35.8, 32.0, 25.8, 20.1$; HRMS (FAB): calcd for $C_{11}H_{20}O_4$ ($[M + Na^+]$) 239.1259, found 239.1257.

Primary silyl ether 41: A solution of diol **40** (800 mg, 3.7 mmol) and imidazole (300 mg, 4.4 mmol) in CH_2Cl_2 (10 mL) was treated with TBSCl (590 mg, 3.9 mmol) at 25 °C for 30 min. After addition of a saturated

aqueous ammonium chloride solution (3 mL), the aqueous phase was separated, and extracted with CH_2Cl_2 (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford primary silyl ether **41** (1.1 g, 90%). **41**: colorless oil; $R_f = 0.40$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2931, 2858, 1459, 1255, 1134, 1095, 837, 778\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.79$ (br d, $J = 11.5$ Hz, 1H), 3.67 (dd, $J = 10.0$, 6.0 Hz, 1H), 3.64–3.57 (m, 2H), 3.40 (ddd, $J = 9.0$, 6.5, 6.5 Hz, 1H), 3.25–3.18 (m, 1H), 3.16 (br s, 1H, OH), 3.11 (ddd, $J = 11.0$, 9.5, 4.5 Hz, 1H), 2.99 (dd, $J = 9.0$, 9.0 Hz, 1H), 2.06–1.95 (m, 2H), 1.95–1.85 (m, 2H),1.72–1.62 (m, 1H), 1.61–1.50 (m, 4H), 1.40–1.30 (m, 1H), 0.85 (s, 9H, *t*BuSi), 0.04 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 84.4, 83.6, 81.5, 74.1, 67.4, 67.0, 35.4, 33.9, 31.8, 25.8, 25.7, 19.8, 18.0, -5.7, -5.8$; HRMS (FAB) calcd for $C_{17}H_{34}O_4Si$ ($[M + H^+]$) 331.2305, found 331.2302.

Ketone 42: A solution of alcohol **41** (270 mg, 0.82 mmol) and 4-methylmorpholine *N*-oxide (144 mg, 1.23 mmol) in CH_2Cl_2 (5 mL) and acetonitrile (5 mL) was treated with tetrapropylammonium perruthenate (29 mg, 0.08 mmol) and stirred at 25 °C for 30 min. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford ketone **42** (240 mg, 89%). **42**: colorless oil; $R_f = 0.52$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2935, 2857, 1715, 1256, 1125, 835, 778\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.90–3.85$ (m, 1H), 3.80 (d, $J = 4.5$ Hz, 2H), 3.72 (t, $J = 4.5$ Hz, 1H), 3.31 (ddd, $J = 11.0$, 11.0, 3.0 Hz, 1H), 3.28–3.23 (m, 1H), 3.20 (dd, $J = 9.0$, 9.0 Hz, 1H), 2.98 (ddd, $J = 10.5$, 9.0, 4.0 Hz, 1H), 2.16–2.06 (m, 2H), 1.96–1.83 (m, 3H), 1.70–1.54 (m, 4H), 0.87 (s, 9H, *t*BuSi), 0.05 (s, 3H, CH_3Si), 0.04 (s, 3H, CH_3Si); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 218.1, 89.5, 83.5, 81.8, 67.7, 65.4, 37.2, 33.7, 31.4, 25.8, 25.7, 23.5, 18.0, -5.5, -5.5$; HRMS (FAB) calcd for $C_{17}H_{32}O_4Si$ ($[M + Cs^+]$) 461.1124, found 461.1136.

Aldehyde 10: A solution of ketone **42** (282 mg, 0.87 mmol) and EtSH (1.0 mL, 13.5 mmol) in CH_2Cl_2 (1 mL) was treated with $Zn(OTf)_2$ (20 mg, 0.06 mmol) and stirred at 25 °C for 4 h. After evaporation of the solvent, the residue was filtered through a pad of silica gel, and the filtrate was concentrated to afford an oil identified as a mixture of the primary TBS silyl ether and the primary free alcohol. This mixture was dissolved in MeOH (2 mL) and treated with CSA (20 mg, 0.08 mmol) at 25 °C for 20 min. After addition of Et_3N (20 mL, 0.14 mmol), the solvent was removed under vacuum, and the residue was purified by flash column chromatography to afford hydroxy dithioketal **44** (242 mg, 87%). A solution of hydroxy dithioketal **44** (220 mg, 0.68 mmol) and Et_3N (2 mL) in DMSO (2 mL) and CH_2Cl_2 (4 mL) was treated with $SO_3 \cdot pyr$ (330 mg, 2.1 mmol) at 0 °C for 30 min. The reaction mixture was quenched by the addition of a saturated aqueous ammonium chloride solution (5 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford aldehyde **10** (194 mg, 89%). **10**: colorless oil; $R_f = 0.48$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2930, 2856, 1720, 1673, 1449, 1267, 1092\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 9.62$ (s, 1H, CH(O)), 4.01 (s, 1H), 3.81 (br d, $J = 11.0$ Hz, 1H), 3.25 (ddd, $J = 11.5$, 11.5, 3.0 Hz, 1H), 3.07 (dd, $J = 9.0$, 9.0 Hz, 1H), 2.94 (ddd, $J = 10.0$, 10.0, 4.0 Hz, 1H), 2.73–2.58 (m, 4H), 2.48–2.40 (m, 1H), 2.16 (br d, $J = 12.0$ Hz, 1H), 2.07–1.98 (m, 1H), 1.90–1.48 (m, 7H), 1.21 (t, $J = 7.5$ Hz, 3H, CH_3), 1.11 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 196.0, 91.2, 84.5, 80.9, 67.7, 60.9, 34.8, 33.2, 31.0, 25.8, 23.6, 22.6, 21.8, 13.8, 13.7$; HRMS (FAB) calcd for $C_{15}H_{26}O_3S_2$ ($[M + Cs^+]$) 451.0378, found 451.0381.

Olefin 45: A solution of phosphonium salt **9** (200 mg, 0.26 mmol) and HMPA (360 μL, 1.7 mmol) in THF (15 mL) was treated dropwise with *n*-butyllithium (178 μL, 1.6 M in hexanes, 0.29 mmol) at −78 °C and stirred for 20 min. A solution of aldehyde **10** (106 mg, 0.33 mmol) in THF (5 mL) was added at −78 °C, and the reaction mixture was stirred at this temperature for 30 min and at 25 °C for 20 min. It was quenched with a saturated aqueous ammonium chloride solution (5 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and the residue was purified by flash column chromatography (silica gel, 3:7, ether:hexanes) to afford olefin **45** (136 mg, 77%). **45**: colorless oil; $R_f = 0.8$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2931, 2849, 1729, 1453, 1280, 1156, 1100, 1027, 912, 733\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.48–7.44$ (m, 2H, ArH), 7.38–7.33 (m, 3H, ArH), 5.86–5.78 (m, 1H, =CH), 5.77–5.70 (m, 2H, =CH), 5.56–5.51 (m, 1H, =CH), 5.43 (s, 1H, PhCH), 4.81 (br m, 1H), 4.40 (d, $J = 9.0$ Hz, 1H), 4.37 (dd, $J = 10.0$, 4.5 Hz, 1H), 3.85 (br m, 1H), 3.75–3.70 (m, 1H), 3.67 (ddd, $J = 10.0$, 10.0, 4.5 Hz, 1H), 3.64–3.57 (m, 2H), 3.32–3.25 (m, 1H), 3.13 (dd, $J = 9.0$, 9.0 Hz, 1H), 3.07–3.00 (m, 1H), 2.79 (br m, 1H), 2.70–2.40 (m, 8H), 2.34–2.28 (m, 1H), 1.98 (br m, 4H), 1.82–1.75 (m, 2H), 1.70–1.62 (m, 3H), 1.50–1.41 (m, 1H), 1.24 (s, 9H, OC(O)*t*Bu), 1.19 (t, $J = 7.5$ Hz, 3H, CH_3), 1.18 (t, $J = 7.5$ Hz, 3H, CH_3); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 177.2, 137.6, 131.4, 128.8, 128.7, 128.2, 127.1, 126.5, 126.0, 101.2, 84.3, 83.1, 82.7, 80.9, 78.7, 77.8, 77.1, 75.7, 70.0, 67.7, 34.9, 33.9, 31.7, 30.9, 28.9, 27.0, 26.0, 23.7, 23.2, 21.0, 13.9, 13.9$; HRMS (FAB) calcd for $C_{38}H_{56}O_7S_2$ ($[M + Cs^+]$) 821.2522, found 821.2554.

Hydroxy dithioketal 46: A solution of olefin **45** (136 mg, 0.2 mmol) in CH_2Cl_2 (5 mL) was treated with DIBAL-H (0.21 mL, 1 M in CH_2Cl_2, 0.21 mmol) at −78 °C for 1 h. After addition of EtOAc (5 mL) and a saturated sodium potassium tartrate solution (2 mL) at −78 °C, the reaction mixture was stirred at 25 °C for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (silica gel, 1:1, ether:hexanes) to afford alcohol **46** (99.1 mg, 83%). **46**: colorless oil; $R_f = 0.3$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 3461, 2928, 2855, 1453, 1099, 699\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.48–7.43$ (m, 2H, ArH), 7.38–7.30 (m, 3H, ArH), 5.88–5.75 (m, 3H, =CH), 5.74-5.66 (m, 1H, =CH), 5.44 (s, 1H, PhCH), 4.48 (d, $J = 9.5$ Hz, 1H), 4.35–4.28 (m, 1H), 3.85 (br d, $J = 11.0$ Hz, 1H), 3.69 (br m, 2H), 3.66–3.59 (m, 2H), 3.48–3.42 (m, 1H), 3.31–3.26 (m, 1H), 3.15–3.06 (m, 2H), 2.74–2.40 (m, 12H), 1.98 (br m, 4H), 1.83–1.75 (m, 2H), 1.50–1.43 (m, 1H), 1.26 (br m, 2H), 1.22 (dd, $J = 7.5$, 7.5 Hz, 3H), 1.21 (dd, $J = 7.5$, 7.5 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$); $\delta = 137.6, 131.1, 129.4, 128.8, 128.2, 127.1, 126.8, 126.0, 101.2, 87.5, 83.0, 82.5, 81.0, 80.1, 78.5, 72.1, 70.5, 67.7, 67.5, 34.8, 33.7, 33.4, 31.7, 31.2, 26.0, 23.6, 21.0, 13.9, 13.6$; HRMS (FAB) calcd for $C_{33}H_{48}O_6S_2$ ($[M + Cs^+]$) 737.1947, found 737.1981.

Mixed thioketal 47: A heterogeneous mixture of hydroxy dithioketal **46** (20.0 mg, 0.033 mmol), powdered 4 Å molecular sieves (freshly activated, 200 mg), silica gel (dried under vacuum, 200 mg), sodium bicarbonate (28 mg, 0.33 mmol), and silver perchlorate (20.0 mg, 0.099 mmol) in dry nitromethane (3 mL) was stirred vigorously at 25 °C for 1 h. The reaction mixture was treated with Et_3N (20 mL), diluted with ether (20 mL), and filtered through a pad of celite. The filtrate was washed with a saturated aqueous ammonium chloride solution (3 × 3 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford mixed thioketal **47** (14.5 mg, 81%). $R_f = 0.70$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2931, 2857, 1453, 1392, 1294, 1104, 1023, 732, 698\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.49–7.41$ (m, 2H, ArH), 7.37–7.27 (m, 3H, ArH), 5.92–5.60 (m, 4H, CH=CH), 5.44 (s, 1H, PhCH), 4.36 (br m, 1H), 4.28 (br m, 1H), 4.17 (br m, 1H), 3.89 (br m, 1H), 3.82 (d, $J = 10.5$ Hz, 1H), 3.70–3.58 (m, 2H), 3.49 (br m, 1H), 3.32–3.23 (m, 1H), 3.20–3.07 (m, 2H), 2.84 (br m, 2H), 2.67 (br m, 1H), 2.56–2.48 (m, 2H), 2.33–2.20 (m, 2H), 2.13–1.87 (m, 6H), 1.82–1.75 (m, 2H), 1.60–1.48 (m, 3H), 1.26 (br m, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 137.5, 135.0, 129.3, 128.8, 128.2, 127.1, 126.0, 101.1, 97.2, 93.8, 87.1, 85.2, 83.5, 80.4, 77.2, 70.6, 69.7, 67.3, 42.5, 36.5, 34.2, 33.6, 31.9, 25.6, 21.2, 20.4, 13.5, 12.7$; HRMS (FAB), calcd for $C_{31}H_{42}O_6S$ ($[M + Cs^+]$): 675.1756, found 675.1730.

EFGH Ring system 8: A mixture of mixed thioketal **47** (65 mg, 0.12 mmol), AIBN (2.0 mg, 0.012 mmol) and triphenyltin hydride (420 mg, 1.2 mmol) in toluene (2 mL) was heated at 110 °C for 2 h. The reaction mixture was concentrated, and the residue was purified by flash column chromatography (silica gel, 1:1, ether:hexanes) to afford compound **8** (46.2 mg, 80%) as an amorphous solid. $R_f = 0.6$ (silica gel, 1:1, ether:hexanes); IR (thin film): $\tilde{\nu}_{max} = 2929, 2857, 1455, 1285, 1106, 1026, 731, 698\ cm^{-1}$; ^1H NMR (600 MHz, CD_3CN, 78 °C): $\delta = 7.41–7.32$ (m, 2H, ArH), 7.29–7.25 (m, 3H, ArH), 5.65 (ddd, $J = 11.1$, 5.3, 1.1 Hz, 1H), 5.63–5.55 (m, 2H), 5.52–5.46 (m, 1H), 5.40 (s, 1H, PhCH), 4.23–4.17 (m, 1H), 4.10–4.05 (m, 1H), 3.71–3.66 (m, 2H), 3.55–3.47 (m, 2H), 3.47–3.40 (m, 1H), 3.34–3.30 (m, 1H), 3.28 (br m, 1H), 3.18 (ddd, $J = 11.3$, 11.3, 3.2 Hz, 1H), 3.08 (ddd, $J = 10.7$, 9.1, 4.6, Hz, 1H), 2.99 (ddd, $J = 9.3$, 9.3, 2.8 Hz, 1H), 2.73–2.67 (m, 1H), 2.62 (br m, 1H), 2.23 (br m, 1H), 2.09–2.02 (m, 2H), 1.96–1.75 (m, 7H), 1.67–1.46 (m, 3H), 1.37–1.28 (m, 1H); ^{13}C NMR (150 MHz, CD_3CN, 78 °C): $\delta = 139.9, 139.2, 130.7, 129.9, 129.3, 128.2, 127.4, 125.9, 102.3, 85.9,$

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84.3, 83.8, 82.2, 80.3, 71.8, 68.3, 37.1, 35.5, 35.0, 33.2, 27.0, 21.3; HRMS (FAB), calcd for $C_{29}H_{38}O_6$ ($[M + Cs^+]$): 615.1723, found 615.1744.

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[1] See preceding paper: K. C. Nicolaou, M. E. Bunnage, D. G. McGarry, S. Shi, P. K. Somers, P. A. Wallace, X.-J. Chu, K. A. Agrios, J. L. Gunzner, Z. Yang, *Chem. Eur. J.* **1999**, *5*, 599 – 617.

[2] K. C. Nicolaou, Z. Yang, M. Ouellette, G.-Q. Shi, P. Gärtner, J. L. Gunzner, K. A. Agrios, R. Huber, R. Chadha, D. H. Huang, *J. Am. Chem. Soc.* **1997**, *119*, 8105 – 8106.

[3] K. C. Nicolaou, D. G. McGarry, P. K. Sommers, *J. Am. Chem. Soc.* **1990**, *112*, 3696 – 3697.

[4] K. C. Nicolaou, C. A. Veale, C.-K. Hwang, J. Hutchinson, C. V. C. Prasad, W. W. Ogilvie, *Angew. Chem.* **1991**, *103*, 304 – 308; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 299 – 303.

[5] K. C. Nicolaou, C. V. C. Prasad, C.-K. Hwang, M. E. Duggan, C. A. Veale, *J. Am. Chem. Soc.* **1989**, *111*, 5321 – 5330.

[6] K. C. Nicolaou, C. V. C. Prasad, W. W. Ogilvie, *J. Am. Chem. Soc.* **1990**, *112*, 4988 – 4989.

[7] a) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C.-K. Hwang, *J. Am. Chem. Soc.* **1989**, *111*, 5330 – 5334; b) K. C. Nicolaou, C. V. C. Prasad, P. K. Somers, C.-K. Hwang, *J. Am. Chem. Soc.* **1989**, *111*, 5335 – 5340.

[8] a) K. C. Nicolaou, D. G. McGarry, P. K. Somers, C. A. Veale, G. T. Furst, *J. Am. Chem. Soc.* **1987**, *109*, 2504 – 2506; b) K. C. Nicolaou, D. G. McGarry, P. K. Somers, B. H. Kim, W. W. Ogilvie, G. Yiannikouros, C. V. C. Prasad, C. A. Veale, R. R. Hark, *J. Am. Chem. Soc.* **1990**, *112*, 6223 – 6276.

[9] K. Tsushima, A. Murai, *Chem. Lett.* **1990**, 761 – 764.

[10] J. W. Burton, J. S. Clark, S. Derrer, T. C. Stork, J. G. Bendall, A. B. Holmes, *J. Am. Chem. Soc.* **1997**, *119*, 7483 – 7498.

[11] K. C. Nicolaou, E. A. Theodorakis, F. P. J. T. Rutjes, M. Sato, J. Tiebes, X.-Y. Xiao, C.-K. Hwang, M. E. Duggan, Z. Yang, E. A. Couladouros, F. Sato, J. Shin, H.-M. He, T. Bleckman, *J. Am. Chem. Soc.* **1995**, *117*, 10239 – 10251.

[12] J. Krüger, R. W. Hoffmann, *J. Am. Chem. Soc.* **1997**, *119*, 7499 – 7504; M. Isobe, S. Hosokawa, K. Kira, *Chem. Lett.* **1996**, 473 – 474; D. M. Grée, J. T. Martelli, R. L. Grée, *J. Org. Chem.* **1995**, *60*, 2316 – 2317; J. S. Clark, J. G. Kettle, *Tetrahedron Lett.* **1997**, *38*, 127 – 130; M. Bratz, W. H. Bullock, L. E. Overman, T. Takemoto, *J. Am. Chem. Soc.* **1995**, *117*, 5958 – 5966; G. S. Cockerill, P. Kocienski, R. Treadgold, *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093 – 2100; J. H. Udding, J. P. M. Giesseling, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1994**, *59*, 6671 – 6682; J. C. Heslin, C. J. Moody, A. M. Z. Slawin, D. J. Williams, *Tetrahedron Lett.* **1986**, *27*, 1403 – 1406; S. L. Schreiber, S. E. Kelly, *Tetrahedron Lett.* **1984**, *25*, 1757 – 1760.

[13] K. C. Nicolaou, G.-Q. Shi, J. L. Gunzner, P. Gärtner, Z. Yang, *J. Am. Chem. Soc.* **1997**, *119*, 5467 – 5468.

[14] a) E. Alvarez, M. T. Diaz, R. Perez, J. D. Martin, *Tetrahedron Lett.* **1991**, *32*, 2241 – 2244; b) W. Adam, O. Cueto, O. De Lucchi, K. Peters, E.-M. Peters, H. G. von Schnering, *J. Am. Chem. Soc.* **1981**, *103*, 5822 – 5828.

[15] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156.

[16] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989 – 1993.

[17] H. H. Wasserman, J. L. Ives, *Tetrahedron* **1981**, *37*, 1825 – 1852.

[18] H. Quast, T. Dietz, A. Witzel, *Liebigs Ann.* **1995**, 1495 – 501.

[19] S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639 – 666.

[20] W. S. Mahoney, D. M. Brestensky, J. M. Stryker, *J. Am. Chem. Soc.* **1997**, *119*, 8105 – 8106.

[21] J. Pawlak, M. S. Tempesta, J. Golik, M. G. Zagorski, M. S. Lee, K. Nakanishi, T. Iwashita, M. L. Gross, K. B. Tomer, *J. Am. Chem. Soc.* **1987**, *109*, 1144 – 1150.

[22] J. R. Parikh, W. Von E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505 – 5507.

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