JOC*Article*

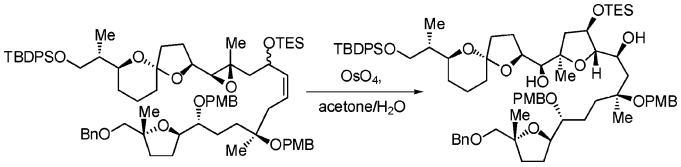
Pectenotoxin-2 Synthetic Studies. 3. Assessment of the Capacity for Stereocontrolled Cyclization To Form the Entire C1−C26 Subunit Based upon the Double Bond Geometry Across C15-C16

Patrick D. O'Connor, Christopher K. Knight, Dirk Friedrich,† Xiaowen Peng, and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210-1185

paquette.1@osu.edu

Received December 7, 2006



Second-generation synthetic routes to enantiopure sulfone **21** and aldehyde **24** are described. The union of these two intermediates by means of a Julia−Kocienski coupling gave rise to a series of *E*-configured building blocks that did not prove amenable to transannular cyclization. Alternatively, when the C15−C16 double bond was introduced with *Z*-geometry by Wittig olefination, spontaneous closure to generate a tetrahydrofuran culminated an ensuing direct dihydroxylation step. The structural assignment to **35**, undergirded by detailed ^{1}H and ^{13}C NMR studies, is consistent with proper transannular bonding so as to deliver the entire C1−C26 fragment of PTX2.

Introduction

The pectenotoxins (PTXs) comprise an important class of complex marine macrolides, the first members of which were isolated and identified in 1985.[1] They were of contemporary interest because of their role in promoting the onset of severe diarrhea, vomiting, and liver damage subsequent to the consumption of shellfish contaminated with the toxic dinoflagellates *Dinophysis fortii* and *Dinophysis accuminata*.[2] Subsequent studies have led to the structural characterization of as many as 15 PTXs[3] and to the discovery of their beneficial biological activity. For example, PTX2 (**1**) exhibits nanomolar cytotoxic capability against several human cancer cell lines[4] and has the impressive ability to interact with the acton skeleton at a unique site.[5]

The pectenotoxins are characterized by exquisitely complex structural features that consist of a pair of spiroacetals, 19 stereocenters (six are quaternary), and additional oxygenated rings that reside in a 33-carbon macrolide ring. The majority of the family members differ from each other in the spiro geometry at C7 and in the oxidation state of C43.[6] Following the assignment of absolute stereochemistry to PTX1 on the basis

† Present address: Sanofi-Aventis, 1041 U.S. Route 202/206, P.O. Box 6800, Bridgewater, NJ 08807-0800.

(1) (a) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, M.; Matsumoto, G. K.; Clardy, J. *Tetrahedron* **1985**, *41*, 1019. (b) Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475. (c) Daiguji, M.; Satake, M.; James, K. J.; Bishop, A.; Mackenzie, L.; Naoki, H.; Yasumoto, T. *Chem. Lett.* **1998**, 653.

(2) (a) Yasumoto, T.; Oshima, Y.; Yamaguchi, M. *Bull. Jpn. Soc. Sci. Fish.* **1978**, *44*, 1249. (b) Yasumoto, T.; Oshima, Y.; Sugawara, W.; Fukuyo, Y.; Oguri, H.; Igarashi, T.; Fujita, N. *Bull. Jpn. Soc. Sci. Fish.* **1980**, *46*, 1405. (c) *Toxic Dinoflagellate Blooms*; Kat, M., Anderson, D. M., White, A. W., Baden, D. G., Eds.; Elsevier: Amsterdam, 1985; p 215. (d) Kumagai, M.; Yanagi, T.; Murata, M.; Yasumoto, T.; Kat, M.; Lassus, P.; Rodriguez-Vazquez, J. A. *Agric. Biol. Chem.* **1986**, *40*, 2853. (e) Hu, T.; Doyle, J.; Jackson, D.; Marr, J.; Nixon, E.; Pleasance, S.; Quilliam, M. A.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1992**, 39. (f) *Toxic Phytoplankton Blooms in the Sea*; Boni, L., Poletti, A., Popei, M., Smayda, T. J., Shimizu, Y., Eds.; Elsevier: Amsterdam, 1993; p 475. (g) *Toxic Phytoplankton Blooms in the Sea*; Quilliam, M. A., Gilgan, M. W., Pleasance, S., Defreitas, A. S. W., Douglas, D., Fritz, L., Hu, T., Marr, J. C., Smyth, C., Wright, J. L. C., Smayda, T. J., Shimizu, Y., Eds.; Elsevier: Amsterdam, 1993; p 547. (h) Draisci, R.; Lucentini, L.; Giannetti, L.; Boria, P.; Poletti, R. *Toxicon* **1996**, *34*, 923.

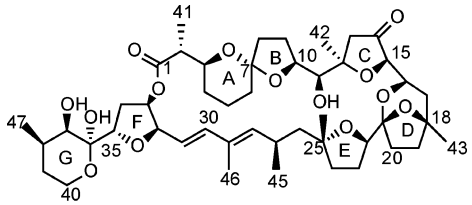
(3) (a) Miles, C. O.; Wilkins, A. L.; Samdal, I. A.; Sandvik, M.; Petersen, D.; Quilliam, M. A.; Naustvoll, L. J.; Rundberget, T.; Torgenson, T.; Hovgaard, P.; Jensen, D. J.; Cooney, J. M. *Chem. Res. Toxicol.* **2004**, *17*, 1423. (b) Miles, C. O.; Wilkins, A. L.; Hawkes, A. D.; Jensen, D. J.; Selwood, A. I.; Beuzenberg, V.; MacKenzie, A. L.; Cooney, J. M.; Holland, P. T. *Toxicon* **2006**, *48*, 152.

(4) Jung, J. H.; Sim, D. J.; Lee, C.-O. *J. Nat. Prod.* **1995**, *58*, 1722.

(5) (a) Spector, I.; Braet, F.; Shochet, N. R.; Bubb, M. R. *Microsc. Res. Tech.* **1999**, *47*, 18. (b) Leira, F.; Cabado, A. G.; Vieytes, M. R.; Roman, Y.; Alfonso, A.; Botana, L. M.; Yasumoto, T.; Malaguti, C.; Rossini, G. P. *Biochem. Pharm.* **2002**, *63*, 1979.

(6) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

10.1021/jo062513f CCC: $37.00 © 2007 American Chemical Society
Published on Web 02/02/2007



1

of X-ray crystallography,[1a] it has proven possible to deduce the structures of the remaining family members by NMR and MS techniques.

In light of the above, there have understandably been a number of efforts targeting several PTXs. Among the more notable achievements to date are Evans' asymmetric synthesis of pectenotoxins-4 and -8,[7] Brimble's targeting of the ABC segment of PTX7,[8] and Roush's preparation of the C11−C26 fragment of PTX2,[9] in addition to Murai's successful routes to the C8−C18 and C31−C40 components common to all members.[10−11] Our approach to the synthesis of **1** is based on the convergent coupling of either sulfonyl tetrazole **4**[11] or phosphonium iodide **5** to aldehyde **6**.[12] These key disconnections are illustrated in Scheme 1. Arrival at this pair of advanced intermediates requires that decisions be made with regard to three hydroxyl protecting groups. Subsequent to our initial effort that gave rise to **2** with R^1 = PMB and R^3 = TBS, it was recognized that modification of these masking functionalities was necessary. Similar modifications of the nature of R^2 were mandated en route to **4** and **5**. The integration of these changes into the synthesis plan is detailed herein. Beyond this, our attention was directed toward elucidating whether a *trans* or *cis* double bond as in **2** and **3**, respectively, was more ideally suited to the crafting of ring C following appropriate regioselective oxidation and intramolecular cyclization.

Results and Discussion

Second-Generation Route to Sulfone 21. The alternate route began with the known 4-methyl-4-penten-1-ol,[11] which was directly silylated to deliver **7** in advance of asymmetric dihydroxylation[13] with AD-mix-α[14] and conversion to PMP acetal **8** by reaction with *p*-methoxybenzaldehyde dimethyl acetal in the presence of pyridinium tosylate[15] (Scheme 2). The resulting mixture of diastereomers was subsequently modified to unmask the hydroxyl group as in **9** and allow for sequential implementation of Mitsunobu conditions involving 1-phenyl-1*H*-tetrazole-5-thiol[16] and peracid oxidation. This protocol provided access to sulfone **10**, thereby conveniently setting the stage for Julia−Kocienski coupling[17] to the previously reported aldehyde **11**.[11,18] These steps were followed by regiocontrolled cleavage of the acetal functionality with DIBAL-H[15,19] to provide the primary carbinol, which smoothly underwent oxidation to aldehyde **13** in the presence of the Dess−Martin periodinane reagent.[20]

Accommodation of **13** in the synthesis was accomplished by homologation with methoxymethylenetriphenyl phosphorane[21] in a conventional Wittig olefination. As expected, the response of the vinyl ether so formed to two-step oxymercuration−sodium borohydride reduction[21,22] satisfactorily gave **14** in >70% yield.

To position ourselves to produce the substituted tetrahydrofuran **18**, the time had arrived to introduce R^3, the second of the three requisite hydroxyl protecting groups. The robust requirements for R^3 prompted selection of the *tert*-butyldiphenylsilyl option. Advantage was immediately taken of its lowered hydrolytic reactivity, as reflected in the ensuing acetal cleavage under acidic conditions. With diol **15** in hand, we next explored the formation of epoxide **16** and ensuing implementation of asymmetric dihydroxylation. Both steps proceeded uneventfully to deliver **17** in a diastereomeric ratio of 4:1. Although the elevated polarity characteristics of this pair of compounds precluded their convenient separation, this was not the situation following stereocontrolled acid-catalyzed cyclization to install a tetrahydrofuran ring. The structural formulation of **18**, which was amenable to chromatographic purification, follows from detailed COSY and NOESY experiments.

This routing was followed by selective protection of the primary hydroxyl as the benzyl ether in advance of the introduction of a second PMB group and two-step generation of tetrazolyl sulfone **21**. A final molybdate oxidation[23] was particularly efficacious in this instance.

Studies Involving the (*E*)-Allylic Alcohol 26. Recourse to PMB protection at C18 in **21** required in turn that only a single minor modification be made in the C1−C15 fragment. This change, delineated in Scheme 3, consisted in conversion of the previously described α-hydroxy ester **22**[11] to its triethylsilyl ether **23**. The latter can be reproducibly reduced to aldehyde **24** with DIBAL-H *at low temperature* (−90 °C). Complications resulting from overreduction of the methyl ester functionality or the intrinsic instability of **24** could thereby be skirted. Fortunately, unchromatographed **24** proved to be pure enough for coupling studies.

In our original work, the configuration of C7 was assigned as *S* on the basis of anticipated stabilization arising from operation of the anomeric effect and the result of MM3

(7) (a) Evans, D. A.; Rajapakse, H. A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569. (b) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573.

(8) (a) Halim, R.; Brimble, A. M.; Merten, J. *Org. Lett.* **2005**, *7*, 2659. (b) Halim, R.; Brimble, M. A.; Merten, J. *Org. Biomol. Chem.* **2006**, *4*, 1387.

(9) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949.

(10) (a) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300. (b) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733. (c) Fujiwara, K.; Kobayashi, M.; Yamamoto, F.; Aki, Y.; Kawamura, M.; Awakura, D.; Amono, S.; Okano, A.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 5067.

(11) Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813.

(12) (a) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937. (b) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589.

(13) Kolb, H. C.; Van Nieuwenzhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(14) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

(15) Hale, K. J.; Cai, J. *Tetrahedron Lett.* **1996**, *37*, 4233.

(16) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Moreley, A. *Synlett* **1998**, 26.

(17) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856.

(18) Baker, R.; Brimble, M. A. *Tetrahedron Lett.* **1986**, *27*, 3311.

(19) Smith, A. B.; Hale, K. J.; Laasko, L. M.; Chen, K.; Riéka, A. *Tetrahedron Lett.* **1989**, *30*, 6960.

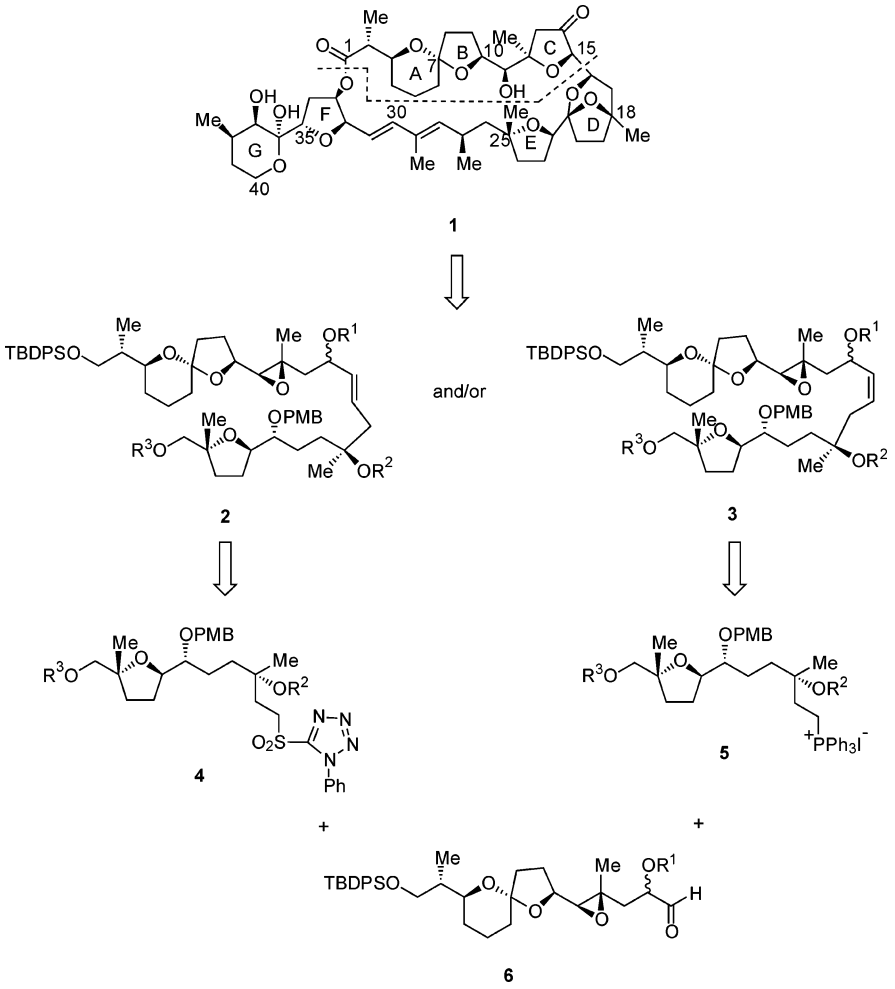
(20) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(21) Clark, J. S.; Freeman, R. P.; Cacho, M.; Thomas, A. W.; Swallow, S.; Wilson, C. *Tetrahedron Lett.* **2004**, *45*, 8639.

(22) Ator, M. A.; Schmidt, S. J.; Adams, J. L.; Dolle, R. E.; Kruse, L. I.; Frey, C. L.; Barone, J. M. *J. Med. Chem.* **1992**, *35*, 100.

(23) Pihko, P. M.; Aho, J. E. *Org. Lett.* **2004**, *6*, 3849.

SCHEME 1



calculations. The latter data suggested that the lack of anomeric stabilization in the C7*R* isomer amounted to approximately 5 kcal/mol. This conclusion has since been validated by experimental evidence from the Brimble group, who independently reported the synthesis of a common intermediate and assigned its structure on the basis of NOE studies.[8a] Although the C7*S* configuration is favored in the open chain or seco acid form, this is not necessarily the case when the spirokal is embedded in a macrocyclic framework. To this end, the observation by Sasaki et al. that PTX7 equilibrates under acidic conditions to a mixture rich in PTX6 with C7*R* configuration is relevant.[1b] The defining experiments reported by Pihko and Aho in which both AB ring anomers were separately synthesized under kinetic control also bear on this issue.[23]

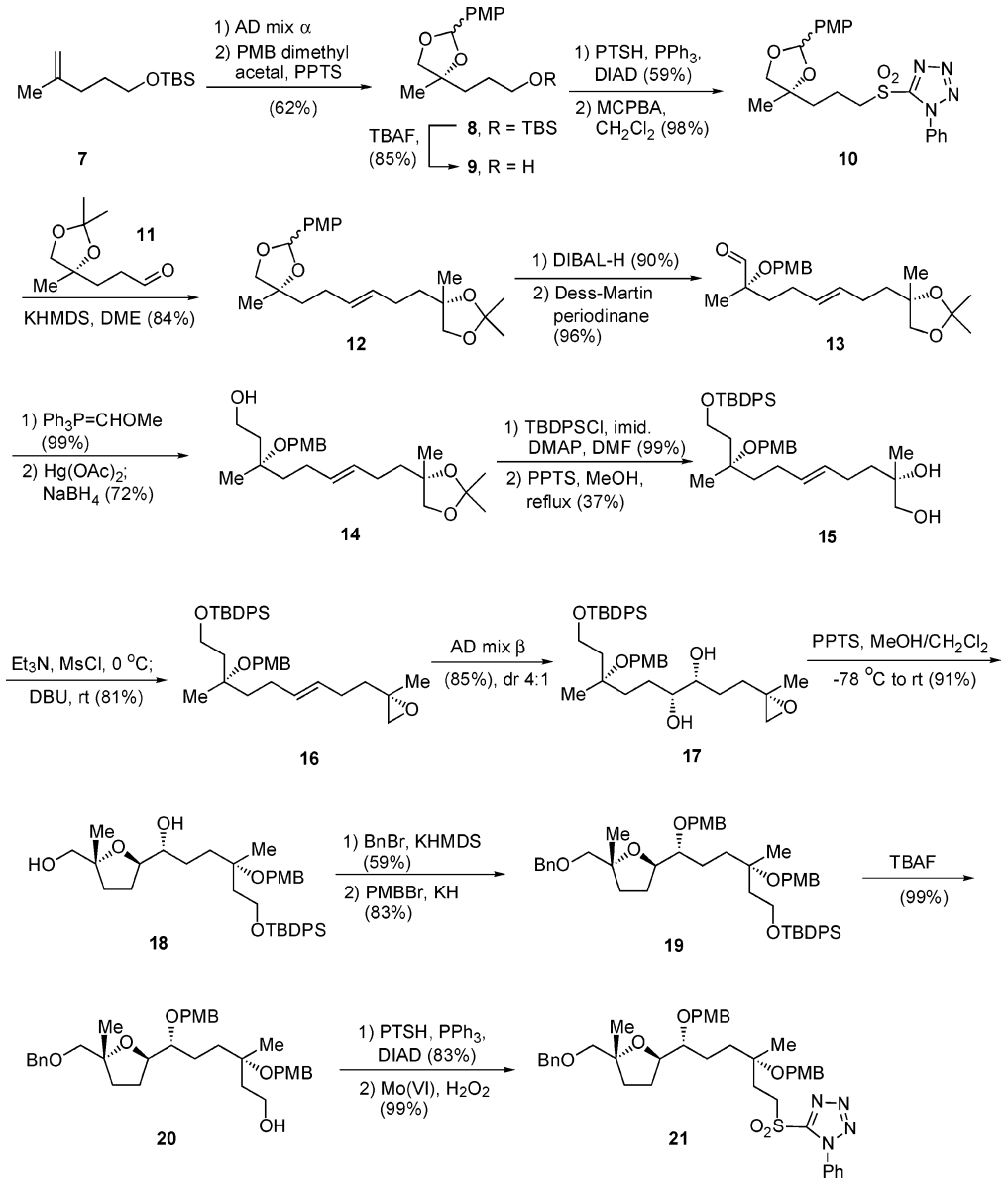
The union of aldehyde **24** with sulfone **21** through Julia olefination proceeded uneventfully to deliver the coupling product **25** in modest yield (Scheme 4). The relatively low efficiency of this step is attributed to the heightened sensitivity of **24**. Subsequent deprotection of the TES ether involved the use of acetic acid in aqueous THF. This step resulted in quantitative conversion to the pair of diastereomeric alcohols **26** and made possible further independent advancement to epoxy alcohol **27** and the (*E*)-enone **28**. Whereas the Dess−Martin periodinane can be effectively utilized in the **26** → **28** conversion, all attempts to bring about the epoxidation of **28** were to no avail. Alternate routing via **27** made it possible to access the desired epoxy ketone **29**, whose further chemical modification in a number of directions resulted either in decomposition or no reaction. Equally unproductive were our attempts to remove the PMB groups in **29** for the purpose of generating **30** as a prelude to the anticipated operation of hydroxyl-initiated transannular cyclization.

The above observations prompted subsequent consideration of an alternative route involving *Z*-unsaturation across C15−C16.

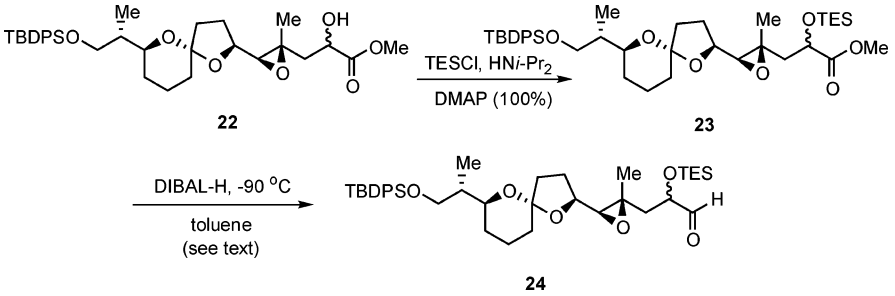
Ring Closure within the *Z*-Series with Generation of the C1−C26 Sector. The alternative synthetic program commenced with the preparation of phosphonium salt **32** via the primary iodide **31** (Scheme 5). Once the ylide had been generated from **32**, the much desired *Z*-configured coupling product **33** was furnished. Once again, the propensity of aldehyde **24** to degradation served to limit the yield of **33** to 40%. The dihydroxylation of **33** was not successful when performed via several methods. However, success was ultimately realized under forcing conditions involving the use of stoichiometric amounts of osmium tetroxide. This protocol gave rise in 37% yield to a diastereomeric mixture of diols. The isomer depicted as **34** was subject to spontaneous stereocontrolled transannular cyclization with deliverance of **35** as the only fully characterized product.

The LCMS (ESI^+)-derived spectrum of **35** showed one predominant peak in the total ion current trace, which produced no (quasi)-molecular ions. Instead, a $m/z = 1181$ base peak reconcilable with $[M + Na - C_6H_{14}Si]$ resulting from the facile loss of the TES protecting group was seen. Weaker ions

SCHEME 2



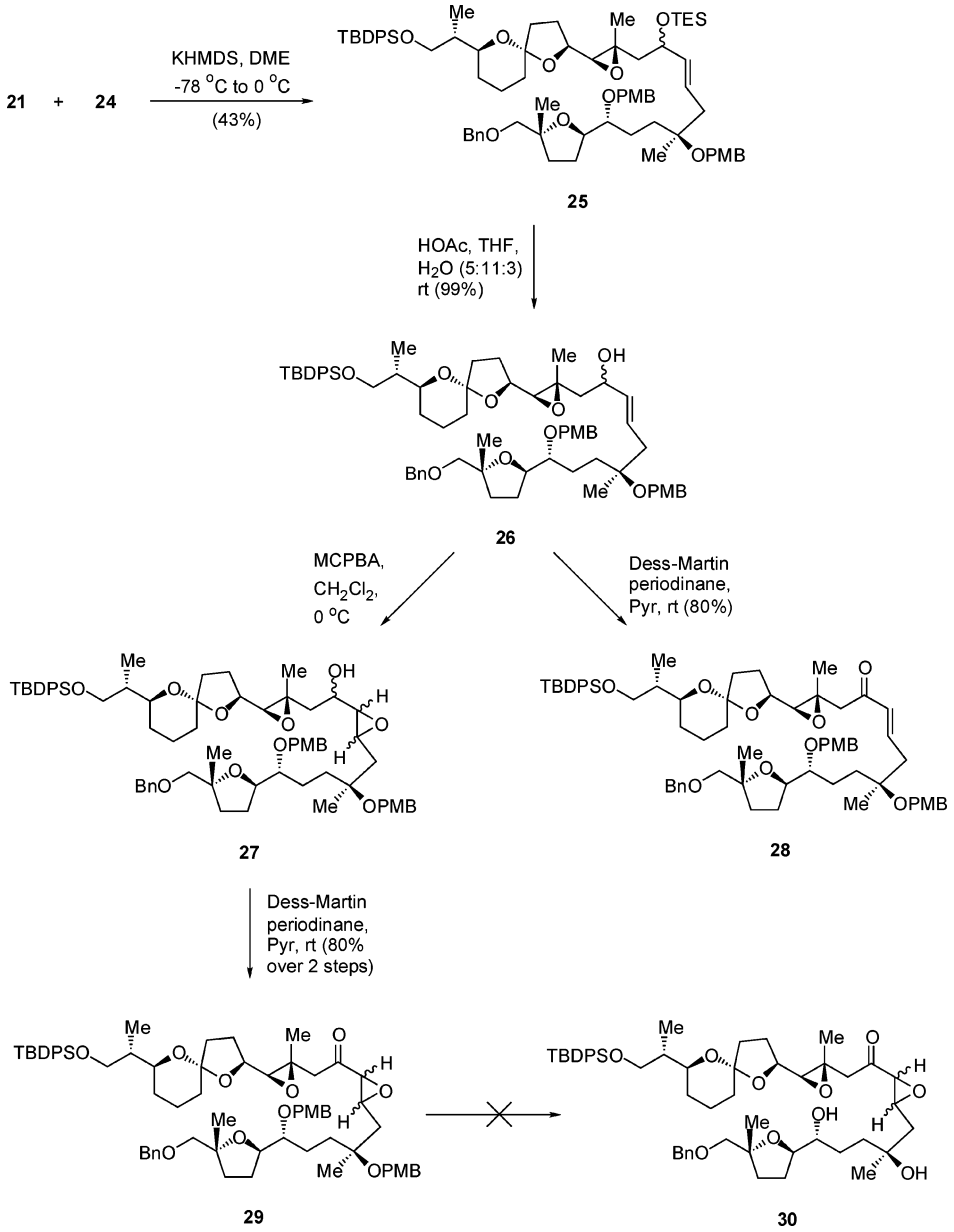
SCHEME 3



corresponding to $[M + NH_4 - C_6H_{14}Si]$ at $m/z = 1176$ and $[M + H - C_6H_{14}Si]$ at $m/z = 1159$ were also observed.

A number of key NMR observations proved to be diagnostic of structure. Thus, the ^1H and ^{13}C chemical shifts of C11 and C12 indicate that the epoxide ring has been opened. Beyond this, the ^{13}C shifts of C12 and C15 are not compatible with simple epoxide opening to produce an open-chain *vic*-diol or with either one of the two alternative modes of cyclization producing pyran rings. Instead, the ^{13}C chemical shifts of C12 and C15 strongly suggest that a tetrahydrofuran ring had been formed. This conclusion receives additional support from an HMBC correlation observed between H15 and C12 (3-bond correlation via oxygen). Importantly, the pattern of NOEs surrounding the C12 to C15 THF ring supports the indicated *relative* stereochemistry at C12/C14/C15. Last, appropriate HMBC correlations and/or NOEs confirm that all five protecting

SCHEME 4



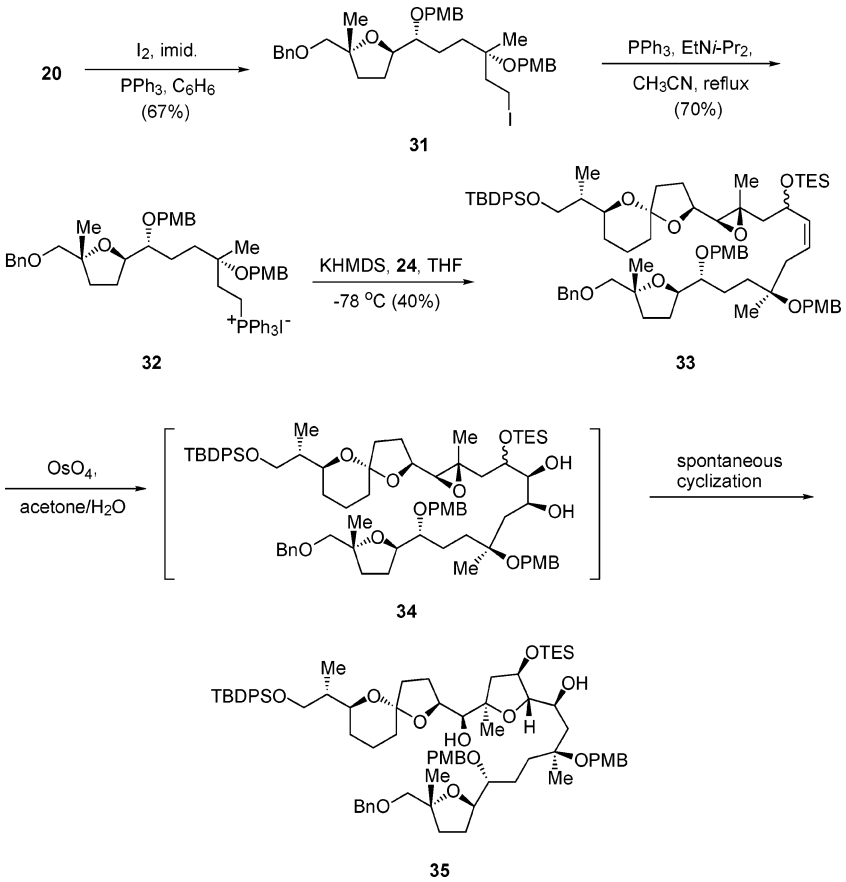
groups are in place. A compilation of these data is provided in Table 1 (Supporting Information).

Summary. To recapitulate, the linkage of intermediates **21** and **24** in a projected synthesis of pectenotoxin-2 was thwarted by an inability to induce **29** into transannular cyclization. In contrast, a key element of success was realized by replacing the Julia−Kocienski olefination with a Wittig alternative. The introduction of a *Z* double bond in this manner, when followed by proper dihydroxylation, resulted in the charting of a route to **35**. To arrive at the proper stereochemistry of PTX2 from **35** will require epimerization at C15 after generation of ketone functionality at C14. Studies intended to follow up this lead in addition to other avenues of molecular modification continue to be pursued.

Experimental Section

(3*R*,4*R*,7*S*)-7-(4-Methoxybenzyloxy)-9-(*tert*-butyldiphenylsilyloxy)-7-methyl-1-((*S*)-2-methyloxiran-2-yl)nonane-3,4-diol (17). $(DHQD)_2PHAL$ (0.035 g, 0.046 mmol), $K_3Fe(CN)_6$ (0.188 g, 0.575 mmol), K_2CO_3 (90.476 g, 3.45 mmol), potassium osmate dihydrate (0.004 g, 0.0115 mmol), $K_2S_2O_8$ (0.313 g, 1.16 mmol), methanesulfonamide (0.107 g, 1.127 mmol), and $NaHCO_3$ (0.290 g, 3.45 mmol) were suspended in *t*-BuOH/H_2O (1:1, 20 mL), cooled to 0 °C, and stirred for 30 min. A solution of **16** (0.675 g, 1.15 mmol) in *t*-BuOH (1 mL) was added by syringe pump over 1 h, and the mixture was stirred for 16 h. Hydrogen sulfoxide was bubbled through the mixture for 30 min or until no more precipitate was observed. The suspension was diluted with brine (10 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried, evaporated, and passed through a silica gel pad. Elution with EtOAc and removal of the solvent under reduced pressure provided a 4:1 mixture of diols (0.60 g, 85% combined) rich in **17**, which can be separated following cyclization to **18**. For **17**: colorless oil; IR (film, cm^{-1}) 3403, 1612, 1510, 1465; ^1H NMR (300 MHz, C_6D_6) δ 7.90−7.85 (m, 4H), 7.31−7.27 (m, 6H), 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.28−4.20 (m, 2H), 4.06−3.98 (m, 2H), 3.37 (s, 3H), 3.37−3.26 (m, 2H), 2.59 (br s, 1H) 2.38−2.21 (m, 2H), 2.08−2.00 (m, 2H), 1.86−1.31 (m, 9H), 1.26 (s, 9H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 136.0, 134.2, 131.8, 129.9, 129.1,

SCHEME 5



128.1, 127.7, 114.0, 76.0, 74.9, 74.0, 63.2, 60.7, 56.4, 54.7, 53.3, 41.9, 35.2, 32.7, 28.5, 27.9, 27.1, 24.0, 20.7, 19.4; HRMS (ES) calcd for *m*/*z* (M + Na)$^+$ 643.3431, obsd 643.3428.

(1*R*,4*S*)-4-(4-Methoxybenzyloxy)-6-(*tert*-butyldiphenylsilyloxy)-1-((2*R*,5*R*)-5-(hydroxymethyl)-5-methyl-tetrahydrofuran-2-yl)-4-methylhexan-1-ol (18). A solution of **17** (0.501 g, 0.807 mmol) in MeOH/CH_2Cl_2 1:1 (20 mL) was treated at −78 °C with pyridinium *p*-toluenesulfonate (0.052 g, 0.207 mmol), stirred for 5 min, and allowed to warm to room temperature for 2 h prior to being quenched with saturated sodium bicarbonate solution (50 mL). The aqueous layer was extracted (EtOAc, 3 × 40 mL), the combined organic phases were washed with brine, dried, and evaporated, and the residue was purified by silica gel chromatography (EtOAc/hexane 1:1) to afford pure **18** as a colorless oil (0.451 g, 91%): IR (film, cm^{-1}) 3405, 1610, 1510, 1465; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.80 (m, 4H), 7.22−7.20 (m, 8H), 6.80 (d, J = 8.6 Hz, 2H), 4.26−4.19 (m, 2H), 4.01 (t, J = 7.3 Hz, 2H), 3.58−3.54 (m, 1H), 3.31 (s, 3H), 3.24−3.16 (m, 3H), 2.37 (br s, 1H), 2.08−2.02 (m, 1H), 2.01−1.92 (m, 2H), 1.69−1.19 (series of m, 8H), 1.19 (s, 9H), 1.12 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.5 (2C), 1.33.8, 131.5, 129.5, 128.7, 127.6, 113.6, 83.6, 83.5, 76.1, 75.8, 75.0, 68.3, 62.7, 60.3, 60.2, 55.2, 45.0, 40.7, 34.3, 33.4, 28.3, 27.5, 26.8, 24.2, 23.7, 19.1; HRMS (ES) *m*/*z* calcd for (M + Na)$^+$ 643.3431, obsd 643.3431.

((3*S*,6*R*)-3,6-Bis(4-methoxybenzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)-5-methyl-tetrahydrofuran-2-yl)-3-methylhexyloxy)-(*tert*-butyl)diphenylsilane (19). Diol **18** (0.10 g, 0.16 mmol) was dissolved in THF (5 mL), cooled to −30 °C, and treated with KHMDS (0.5 M in toluene, 0.64 mL, 0.32 mmol). The solution was stirred for 45 min, warmed to −10 °C, and treated with benzyl bromide (0.02 mL, 0.17 mmol) via syringe pump over 16 h. The reaction mixture was quenched by the addition of saturated sodium bicarbonate solution, the aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed with brine, dried, and evaporated. The residue was chromatographed (SiO_2, elution with hexane/EtOAc 10:1) to afford the monobenzyl ether (0.067 g, 59%) as a colorless oil: IR (film, cm^{-1}) 3397, 1381, 1248; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.67 (m, 4H), 7.48−7.29 (m, 11H), 7.15 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 4.58 (s, 2H), 4.25−4.22 (m, 2H), 3.85−3.78 (m, 3H), 3.79 (s, 3H), 3.37−3.32 (m, 2H), 3.31−3.24 (m, 1H), 2.00−1.45 (m, 10H), 1.25 (s, 3H), 1.18 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 138.5, 135.5, 134.7, 133.9, 129.5, 128.8, 128.3, 127.6, 127.5, 127.4, 113.6, 83.0, 82.9, 76.3, 75.8, 74.8, 73.3, 62.7, 60.2, 55.2; HRMS (ES) *m*/*z* calcd for (M + Na)$^+$ 733.3900, obsd 733.3899.

The above alcohol (1.41 g, 198 mmol) and PMBBr (0.792 g, 3.96 mmol) were dissolved in THF (40 mL) and treated with KH (30% dispersion in mineral oil, 0.42 g, 3.17 mmol, 1.6 equiv) in one portion. The suspension was stirred for 2 h, cooled to 0 °C, and quenched by addition of MeOH (0.5 mL). The solution was diluted with saturated sodium bicarbonate solution, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried, evaporated, and chromatographed (SiO_2, elution with hexane/EtOAc 20:1) to afford **19** (1.36, 83%) as a colorless oil: IR (film, cm^{-1}) 1377, 1243, 1055; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.69 (m, 4H), 7.45−7.30 (m, 11H), 7.26 (d, J = 8.6 Hz, 2H), 7.13 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.6 Hz, 2H), 4.68 (d, J = 11.4 Hz, 1H), 4.62 (d, J = 2.1 Hz, 2H), 4.52 (d, J = 11.4 Hz, 1H), 4.23−4.08 (m, 2H), 3.86−3.75 (m, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.39 (s, 2H), 3.33−3.28 (m, 1H), 1.97−1.80 (m, 4H), 1.75−1.40 (m, 6H), 1.29 (s, 3H), 1.26 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.7, 138.7, 135.5, 133.9, 131.6, 131.3, 129.5, 129.4, 128.7, 128.2, 127.6, 127.4, 127.3, 113.6, 82.7, 81.8, 75.8, 73.3, 72.2, 65.8, 62.5, 60.2, 55.2, 40.7, 34.3, 29.6, 29.3, 27.8, 26.8, 24.8, 23.8, 19.1; HRMS (ES) *m*/*z* calcd for (M + Na)$^+$ 853.4476, obsd 853.4475.

(3*S*,6*R*)-3,6-Bis(4-methoxybenzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)-5-methyl-tetrahydrofuran-2-yl)-3-methylhexan-1-

ol (20). A solution of **19** (1.36 g, 1.20 mmol) in THF (20 mL) was cooled to 0 °C and treated with TBAF (1.0 M in THF, 2.52 mL) dropwise by syringe. The stirred solution was allowed to warm to room temperature and after 16 h was diluted with brine and extracted with EtOAc (3 × 20 mL) prior to drying and evaporation. The crude residue was chromatographed (SiO_2, hexanes/EtOAc 4:1) to afford the alcohol (0.96 g, 99%) as a colorless oil: IR (film, cm^{-1}) 3432, 1641, 1372, 1243; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 7H), 7.21 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 4H), 4.71 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 2.0 Hz, 2H) 4.54 (d, J = 11.4 Hz, 1H), 4.33 (d, J = 10.5 Hz, 1H), 4.29 (d, J = 10.5 Hz, 1H), 4.16−4.09 (m, 1H), 3.89−3.69 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.38 (s, 2H), 3.36−3.32 (m, 1H), 3.06−3.00 (m, 1H), 1.99−1.88 (m, 4H), 1.79−1.44 (m, 6H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 158.9, 138.6, 131.1, 130.9, 129.5 (2C), 128.9, 128.2 (2C), 127.4 (2C), 113.8 (2C), 82.8, 81.6, 81.4, 78.5, 76.5, 73.3, 63.0, 59.5, 55.2; HRMS (ES) *m*/*z* calcd for $(M + Na)^+$ 615.3298, obsd 615.3307.

5-((3*S*,6*R*)-3,6-Bis(4-methoxybenzyloxy)-6-((2*R*,5*R*)-5-(benzyloxymethyl)-5-methyl-tetrahydrofuran-2-yl)-3-methylhexylsulfonyl)-1-phenyl-1*H*-tetrazole (21). To a stirred solution of **20** (0.401 g, 0.675 mmol) in THF (10 mL) were added triphenylphosphine (0.193 g, 0.742 mmol) and 1-phenyl-1*H*-tetrazole-5-thiol (0.137 g, 0.773 mmol). After 5 min, the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (0.137 g, 0.681 mmol) was added dropwise via syringe, and the mixture was stirred for 1 h, allowed to warm to room temperature, stirred for 5 h, and quenched with saturated sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried, evaporated, and chromatographed (SiO_2, elution with hexane/EtOAc 20:1) to afford the sulfide (0.423 g, 83%) as a colorless oil: IR (film, cm^{-1}) 1730, 1611, 1512, 1457; ^1H NMR (300 MHz, $CDCl_3$) δ 7.87−7.50 (m, 5H), 7.35−7.25 (m, 9H), 6.87−6.83 (m, 4H), 4.71 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 1.9 Hz, 2H), 4.54 (d, J = 11.5 Hz, 1H), 4.33 (s, 2H), 4.16−4.09 (m, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.49−3.33 (m, 5H), 2.14−1.91 (m, 4H), 1.84−1.45 (m, 6H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.8, 154.5, 138.7, 133.7, 131.3, 131.2, 130.9 (2C), 129.7 (2C), 129.6, 129.1 (2C), 129.0, 128.3 (2C), 127.4 (2C), 123.7 (2C), 113.7 (2C), 113.6 (2C), 82.8, 81.8, 81.4, 76.5, 73.3, 72.4, 63.1, 55.2, 55.2, 38.0, 34.3, 33.9, 28.2, 28.1, 24.6, 23.1, 21.9; HRMS (ES) *m*/*z* calcd for $(M + Na)^+$ 775.3505, obsd 775.3510.

Ammonium molybdate trihydrate (0.018 g, 0.0148 mmol) was added to a stirred, 0 °C solution of hydrogen peroxide (0.042 mL, 30% in H_2O). After 15 min, the yellow solution was introduced dropwise by syringe to a solution of the above sulfide (0.112 g, 0.148 mmol) in absolute EtOH (2 mL) at room temperature. After 16 h, the reaction mixture was diluted with water (5 mL), the aqueous layer was extracted (EtOAc, 3 × 10 mL), and the combined organic layers were dried and evaporated. The crude residue was passed through a pad of silica (elution with 10% EtOAc in hexane) to afford **21** as a colorless oil (0.115 g, 99%): IR (film, cm^{-1}) 1729, 1609, 1515, 1457; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.55 (m, 5H), 7.37−7.20 (m, 9H), 6.86 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 4.70 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 1.4 Hz, 2H), 4.52 (d, J = 11.4 Hz, 1H), 4.29 (s, 2H), 4.16−4.08 (m, 1H), 3.82−3.75 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.38 (s, 2H), 3.34−3.31 (m, 1H), 2.24−1.90 (m, 4H), 1.80−1.39 (m, 6H), 1.27 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.9, 153.2, 138.6, 132.9, 131.3, 131.0, 130.6, 129.5 (2C), 129.4 (2C), 128.9, 128.8 (2C), 128.2 (2C), 127.4 (2C), 127.3 (2C), 113.7 (2C), 113.6 (2C), 82.8, 81.6, 81.0, 76.4, 73.2, 72.3, 63.0, 55.1, 55.1, 51.8, 34.2, 33.9, 30.4, 27.8; HRMS (ES) *m*/*z* calcd for $(M + Na)^+$ 807.3404, obsd 807.3398.

Silylation of 22. To a stirred solution of **22** (2.09 g, 3.50 mmol) in (50 mL) at 0 °C were added diisopropylamine (4.5 mL, 31 mmol) and triethylsilyl chloride (2.11 g, 14.0 mmol). The mixture was stirred until TLC showed complete consumption of the starting material, quenched with 1 M $NaHCO_3$ (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic fractions were pooled and dried, and the solvent was evaporated to leave an oil that was further purified by silica gel chromatography (hexane/EtOAc 10:1) to give **23** as a transparent oil (2.5 g, 100%): IR (film, cm^{-1}) 1759, 1460, 1428; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.63 (m, 4H), 7.45−7.34 (m, 6H), 4.42 (d, J = 4.3 Hz, 0.25H), 4.40 (d, J = 4.3 Hz, 0.25H), 4.33 (t, J = 6.3 Hz, 0.5H), 3.77−3.62 (m, 2H), 3.733 (s, 1.5H), 3.730 (s, 1.5H), 3.60 (d, J = 4.8 Hz, 1H), 3.55−3.49 (m, 1H), 2.75 (d, J = 8.0 Hz, 0.5H), 2.70 (d, J = 8.0 Hz, 0.5H), 2.22−1.99 (m, 2H), 1.90−1.51 (m, 11H), 1.34 (d, J = 5.8 Hz, 3H), 1.04 (s, 9H), 1.01−0.91 (m, 12H), 0.70−0.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 135.5 (2C), 133.9, 129.5, 127.6 (2C), 106.50, 106.46, 75.15, 75.08, 71.63, 71.60, 69.9, 69.6, 66.1, 65.3, 64.2, 59.4, 51.9, 44.0, 43.9, 40.8, 37.3, 32.78, 32.72, 28.14, 28.11, 26.9, 20.4, 19.3, 17.2, 12.98, 12.93, 6.8, 6.7, 4.6, 4.5; HRMS (ES) *m*/*z* calcd for $(M + Na)^+$ 733.3932, obsd 733.3929.

Controlled Reduction of 23. A stirred solution of **23** (208 mg, 293 μmol) in toluene (10 mL) was cooled to −90 °C, treated with a 1.1 M solution of DIBAL-H (1.5 mL, 1.7 mmol), and stirred for 1.5 h before being quenched with MeOH (1 mL, 24 mmol). A saturated solution of Rochelle's salt (20 mL) was added, and the mixture was allowed to warm to 0 °C, stirred for 0.5 h, and extracted with EtOAc (4 × 30 mL). The combined organic fractions were washed with brine, dried, and filtered through a short plug containing basic alumina (activity 1). The solvent was removed in vacuo to give **24** as an oil that was used without further purification: IR (film, cm^{-1}) 1736, 1454, 1108; ^1H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 1.3 Hz, 0.5H), 9.60 (d, J = 1.6 Hz, 0.5H), 7.66−7.63 (m, 4H), 7.45−7.35 (m, 6H), 4.18−4.12 (m, 1H), 3.77−3.35 (m, 4H), 2.81 (d, J = 8.0 Hz, 0.5H), 2.68 (d, J = 8.0 Hz, 0.5H), 2.24−2.16 (m, 1H), 2.03−1.44 (m, 12H), 1.35 (d, J = 2.7 Hz, 3H), 1.04 (s, 9H), 1.00−0.911 m, 12H), 0.69−0.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 135.6 (2C), 129.5 (2C), 127.6 (2C), 106.5, 75.7, 75.3, 75.1, 68.0, 65.2, 65.1, 59.4, 59.2, 41.8, 40.8, 37.3, 32.7, 28.2, 28.1, 26.8 (3C), 20.4, 19.3, 18.4, 17.7, 12.9, 6.7 (3C), 4.7 (3C); HRMS (ES) *m*/*z* calcd for $(M + Na)^+$ 703.3826, obsd 703.3815.

The aldehyde is exceptionally unstable, and upon standing overnight at room temperature will completely decompose.

Julia−Kocienski Coupling of 21 to 24. Sulfone **21** (0.095 g, 0.121 mmol) and aldehyde **24** (0.123 g, 0.181 mmol) were dissolved in DME (6 mL) and cooled to −70 °C. KHMDS (0.5 M in toluene, 0.256 mL, 0.128 mmol) was added dropwise via syringe. After 30 min, the mixture was warmed to 0 °C, stirred for an additional 30 min, quenched with saturated ammonium chloride solution, stirred for 10 min longer, and diluted with saturated sodium bicarbonate solution. The aqueous layer was extracted with EtOAc (3 × 30 mL), the combined organic extracts were washed with brine, dried, and evaporated, and the residue was chromatographed (SiO_2, elution with hexane/EtOAc 20:1) to afford **25** (0.065 g, 43%) as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.64 (m, 4H), 7.43−7.21 (m, 15H), 6.84 (d, J = 8.4 Hz, 4H), 5.66−5.56 (m, 2H), 4.69 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 1.9 Hz, 2H), 4.53 (d, J = 11.4 Hz, 1H), 4.29 (s, 2H), 4.12−4.08 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.78−3.51 (m, 5H), 3.37−3.29 (m, 3H), 2.68 (d, J = 8.0 Hz, 0.5H), 2.66 (d, J = 9.3 Hz, 0.5H), 2.35−1.39 (m, 22H), 1.32 (d, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.04 (s, 9H), 0.99−0.84 (m, 12H), 0.64−0.56 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 158.7, 138.7, 136.1, 135.6, 134.0, 133.9, 131.7, 131.3, 129.5, 129.4, 129.3, 128.8, 128.2, 127.5, 127.4, 127.3, 125.9, 125.7, 113.6, 113.5, 106.4, 106.3, 82.7, 81.8, 81.7, 81.6, 77.2, 76.6, 76.5, 75.4, 75.2, 73.3, 72.2, 71.6, 71.6, 71.1, 70.7, 66.0, 65.3, 64.4, 62.8, 59.9, 59.7, 55.2, 55.2, 47.7, 41.4, 41.3, 40.8, 37.3, 34.3, 33.6, 32.8, 32.7, 31.9, 29.7, 29.6, 29.3, 28.2, 28.1, 28.0, 27.9, 26.9 (3C), 24.8, 24.4, 23.5, 23.4, 22.6, 20.5, 20.4, 19.2, 17.8, 17.3, 6.9 (3C), 4.9 (3C); HRMS (ES) *m*/*z* calcd for $(M + Na)^+$ 1261.7171, obsd 1261.7125.

Desilylation of 25. A solution of **25** (0.005 g, 0.0043 mmol) in $THF/H_2O/AcOH$ (11:3:5, 1 mL) was stirred for 6 h and quenched

with saturated sodium bicarbonate solution. The aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was chromatographed (SiO_2, elution with hexane/EtOAc 20:1) to afford **26** (0.0045 mg, 99%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.63 (m, 6H), 7.45−7.22 (m, 13H), 6.85 (d, J = 8.5 Hz, 4H), 5.78−5.66 (m, 1H), 5.57−5.46 (m, 1H), 4.68 (d, J = 11.4 Hz, 1H), 4.60 (d, J = 2.1 Hz, 2H), 4.53 (d, J = 11.4 Hz, 1H), 4.30 (s, 2H), 4.13−4.07 (m, 1H), 3.784 (s, 3H), 3.777 (s, 3H), 3.79−3.65 (m, 3H), 3.62 (dd, J = 4.8, 10.1 Hz, 2H), 3.52 (dd, J = 6.1, 10.1 Hz, 2H), 3.37 (s, 2H), 3.37−3.30 (m, 1H), 2.92 (d, J = 8.1 Hz, 0.5H), 2.71 (d, J = 8.1 Hz, 0.5H), 2.36−2.14 (m, 2H), 1.98−0.90 (series of m, 21H), 1.26 (s, 6H), 1.25 (s, 3H), 1.04 (s, 9H), 0.97 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 158.8, 138.7, 136.1, 135.6, 134.0, 133.9, 131.3, 135.5 (4C), 135.2, 134.5, 133.9, 133.8, 131.6, 131.2, 129.4, 129.3, 128.8, 128.2, 127.6 (4C), 127.5, 127.4, 127.2, 126.8, 113.7, 113.6, 106.5, 106.4, 82.8, 81.7, 81.5, 77.2, 76.6, 75.5, 75.1, 73.3, 72.2, 71.6, 71.5, 69.9, 69.3, 66.0. 64.5, 63.4, 62.9, 62.8, 60.7, 60.3, 55.2, 55.2, 45.0, 44.2, 41.4, 41.3, 40.7, 37.4, 37.3, 34.3, 33.6, 32.8, 32.7, 31.9, 29.7, 22.7, 20.5, 19.2, 16.9; HRMS (ES) m/z calcd for $(M + Na)^+$ 1147.6307, obsd 1147.6289.

Epoxidation and Oxidation of 26. A solution of **26** (0.010 g, 0.0088 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 °C and treated with MCPBA (0.006 g, 0.035 mmol). After 3 h, the reaction mixture was quenched with saturated sodium bicarbonate and saturated sodium thiosulfate solutions. The mixture was stirred for 2 h and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue was dissolved in CH_2Cl_2 (1 mL), treated with pyridine (28 mg, 0.035 mmol) and Dess−Martin periodinane (0.011 g, 0.026 mmol), and stirred for 20 min. The suspension was diluted with CH_2Cl_2 (0.5 mL) and passed through a silica gel pad eluting with hexanes/EtOAc (20:1, 20 mL then 4:1, 100 mL). The latter fractions, which contained the epoxy ketone, were chromatographed (SiO_2, hexanes/EtOAc 20:1) to afford a 1:1 mixture of diastereomeric epoxy ketones **29** (6.0 mg, 59%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.60 (m, 4H), 7.46−7.22 (m, 15H), 6.87 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.72−4.65 (m, 1H), 4.59 (d, J = 2.0 Hz, 2H), 4.55−4.48 (m, 1H), 4.33−4.24 (m, 2H), 4.14−4.05 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.81−3.66 (m, 2H), 3.63 (dd, J = 4.8, 10.0 Hz, 1H), 3.52 (dd, J = 6.2, 10.0 Hz, 1H), 3.38 (s, 2H), 3.36−3.29 (m, 1H), 3.27−3.21 (m, 1H), 2.72−2.52 (m, 2H), 2.25−0.90 (m, 23H), 1.28 (s, 9H), 1.05 (s, 9H), 0.93 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 159.0, 158.9, 138.7, 135.6, 135.5, 134.4, 134.0, 133.9, 131.3, 131.2, 129.5, 129.4, 129.3, 128.9, 128.3, 127.6, 127.5, 127.4, 113.7, 113.6, 106.5, 82.8, 81.9, 81.5, 77.2, 76.6, 76.1, 75.1, 75.0, 73.3, 72.5, 71.6, 66.0, 64.0, 63.0, 59.3, 58.1, 58.0, 55.3, 55.2, 46.1, 41.0, 40.7, 37.2, 34.3, 34.0, 32.8, 31.9, 29.7, 29.6, 29.3, 28.1, 28.0, 26.8, 24.9, 23.8, 22.6, 20.4, 19.3, 17.5; HRMS (ES) m/z calcd for $(M + Na)^+$ 1161.6099, obsd 1161.6105.

Oxidation of 26. Alcohol **26** (10 mg, 8.8 μmol) was dissolved in CH_2Cl_2 (0.5 mL), treated with pyridine (28 mg, 0.035 mmol) and Dess−Martin periodinane (0.011 g, 0.026 mmol), and stirred for 20 min. The suspension was diluted with CH_2Cl_2 (0.5 mL) and passed through a silica gel pad eluting with hexane/EtOAc (20:1, 20 mL then 4:1, 100 mL). The latter fractions contained **28** (0.008 g, 80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65−7.62 (m, 4H), 7.41−7.21 (m, 15H), 6.93−6.86 (m, 1H), 6.844 (d, J = 8.4 Hz, 2H), 6.840 (d, J = 8.5 Hz, 2H), 6.21 (d, J = 15.8 Hz, 1H), 4.68 (d, J = 11.4 Hz, 1H), 4.59 (d, J = 1.8 Hz, 2H), 4.51 (d, J = 11.4 Hz, 1H), 4.13−4.07 (m, 2H), 3.784 (s, 3H), 3.779 (s, 3H), 3.78−3.65 (m, 3H), 3.61 (dd, J = 4.8, 10.0 Hz, 1H), 3.50 (dd, J = 6.2, 10.0 Hz, 1H), 3.36 (s, 2H), 3.35−3.30 (m, 1H), 2.73−2.69 (m, 3H), 2.52−0.90 (m, 21H), 1.25 (s, 6H), 1.24 (s, 3H), 1.03 (s, 9H), 0.96 (d, J = 6.7 Hz, 3H); HRMS (ES) m/z calcd for $(M + Na)^+$ 1145.6150, obsd 1145.6183.

Formation of Iodide 31. To a stirred solution of **20** (150 mg, 247 μmol) in benzene (5 mL) at 0 °C were added triphenylphosphine (129 mg, 494 μmol), imidazole (33 mg, 494 μmol), and iodine (125 mg, 494 μmol). The mixture was allowed to warm to room temperature, and stirring was continued for 1 h. The crude mixture was passed through a silica plug and eluted with hexane/EtOAc (1:1, 80 mL). The solvent was removed in vacuo to furnish **31** as a colorless oil (119 mg, 67%): IR (film, cm^{-1}) 1454, 1302, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.18 (m, 9H), 6.86 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.69 (d, J = 11.4 Hz, 1H), 4.61 (d, J = 1.6 Hz, 2H), 4.52 (d, J = 11.4 Hz, 2H), 4.29−4.191 (m, 2H), 4.14−4.06 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.37 (s, 2H), 3.36−3.28 (m, 1H), 3.22−3.13 (m, 2H), 2.29−1.38 (m, 10H), 1.26 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 158.9, 131.2, 129.5, 128.8 (2C), 128.3 (2C), 127.4 (2C), 113.6 (2C), 82.8, 81.6, 81.3, 78.1, 73.4, 72.4, 63.0, 55.3 (2C), 44.0, 34.3, 33.7, 27.8, 24.9, 24.5, 22.8, −0.23; HRMS (ES) m/z calcd for $(M + Na)^+$ 725.2315, obsd 725.2311; $[\alpha]^{20}_D$ +10.6 (c 1.7, $CHCl_3$).

Wittig Coupling of 24 with 32. The iodide (217.0 mg, 0.302 mmol) was dissolved in 3 mL of CH_3CN at room temperature. PPh_3 (793.0 mg, 3.02 mmol) and i-Pr_2NEt (111.0 mg, 0.902 mmol) were added. The mixture was heated at 90 °C for 48 h, and CH_3CN was removed by rotary evaporation. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) to afford **32** (207 mg, 70%), which was used directly.

To a stirred solution of **32** (207 mg, 211 μmol) in toluene (1.5 mL) at −78 °C was added a 0.6 M toluene solution of KHMDS (360 μL, 216 mmol), and the mixture was stirred at −78 °C for 0.5 h. A solution of **24** (216 mg, 317 μmol) was added slowly via syringe, and the mixture was stirred for 0.5 h prior to warming to room temperature and stirring for a further 1 h. The reaction mixture was quenched with 1 M NH_4Cl (20 mL) and extracted with ether (3 × 50 mL). The pooled organic fractions were washed with brine, dried, and concentrated in vacuo, giving a brown oil that was further purified by silica gel chromatography (hexane/EtOAc 6:1) to give **33** as a colorless oil (69 mg, 26%): IR (film, cm^{-1}) 1512, 1346, 1085; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.60 (m, 4H), 7.41−7.18 (m, 15H), 6.87−6.81 (m, 4H), 5.57−5.39 (m, 2H), 4.69 (d, J = 11.4 Hz, 1H), 4.60−4.48 (m, 3H), 4.28−4.21 (m, 3H), 4.14−4.06 (m, 1H), 3.79−3.77 (m, 6H), 3.76−3.60 (m, 2H), 3.56−3.48 (m, 1H), 3.38−3.28 (m, 3H), 3.22−3.13 (m, 1H), 2.77 (d, J = 8.0 Hz, 0.6H), 2.70 (d, J = 8.0 Hz, 0.4H), 2.40−0.90 (m, 38H), 0.63−0.55 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 138.7, 135.6, 134.0, 131.5, 131.2, 129.51, 129.49, 129.4, 128.91, 128.89, 128.8, 127.4, 113.6, 106.4, 81.3, 76.6, 75.4, 72.3, 66.1, 63.0, 60.0, 55.2, 40.8, 37.3, 34.4, 28.2, 28.12, 28.09, 27.9, 26.8, 24.9, 24.5, 23.7, 20.4, 19.3, 18.3, 13.0, 6.9; HRMS (ES) m/z calcd for $(M + Na)^+$ 1261.7171, obsd 1261.7229; $[\alpha]^{20}_D$ +9.2 (c 2.0, $CHCl_3$).

Dihydroxylation of 33 with Spontaneous Cyclization. To a stirred solution of **33** (26.0 mg, 0.021 mmol) in acetone (0.9 mL) and H_2O (0.3 mL) were added OsO_4 (10.3 mg, 0.0405 mmol) and NMO (20.0 mg, 0.148 mmol) at room temperature. The mixture was stirred for 24 h before being diluted with saturated $Na_2S_2O_3$ solution, stirred for 0.5 h, and extracted with EtOAc (4 × 20 mL). The combined organic layers were washed with brine, dried, and concentrated to give crude product (30 mg). The major component was purified by chromatography on silica gel (hexane/EtOAc 5:1 with 1% ethanol) to give pure **35** (5 mg) as a colorless oil. See text for spectral analysis.

Supporting Information Available: Experimental details for the preparation of **9**−**16** inclusive, table of partial NMR assignments for **35**, and ^{1}H NMR spectra for all new compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062513F