Studies on the Synthesis of Kijanolide: Synthesis of the 2-Acyl Spiro Tetronate and Investigations Concerning the Coupling of the Top and Bottom Half Fragments

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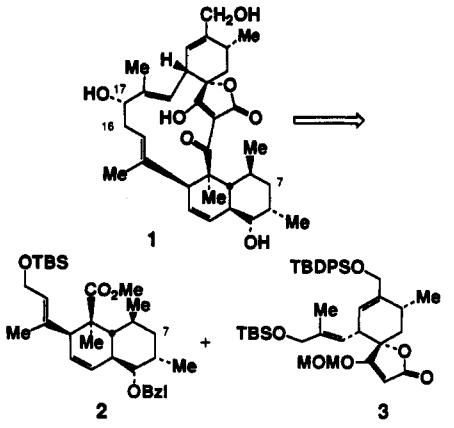
Several studies directed toward the synthesis of kijanolide are described. First, a method for synthesis of the 2-acyl spiro tetronate substructure (**15**, **52**) via a Dieckmann cyclization protocol was developed. Second, a 10-step synthesis of 7,7-dibromo-2,4-dimethyl-5-[(*tert*-butyldiphenylsilyl)oxy]heptenal **35** was developed, making possible the synthesis of a range of kijanolide bottom half precursors via olefination (e.g., **35** + **23** → **38**) and cross-coupling reactions (e.g., **38** → **19**). This solves the problems encountered due to the introduction of the C(7)-hydroxyl group in our previous synthesis of the kijanolide bottom half **2**.[2a] Third, a highly efficient procedure was developed for the coupling of kijanolide top half **8** and dioxinone **38** via an acyl ketene intermediate. This is the most efficient of several methods examined for acylating the hindered tertiary hydroxyl group of **8**. Attempts to perform the IMDA reaction of **46**, **47** or **9** (R = $SiEt_3$) generated in situ from coupling of **8** and the acyl ketene (**20**) derived from **42** were thwarted by the unexpected tendency of β-keto esters like **47** to fragment and decarboxylate via the acyl ketene intermediate at temperatures above 115 °C. 2-Acyl tetronates **53** and **54** were prepared, but these systems decomposed upon attempted IMDA cyclization at temperatures approaching 190 °C.

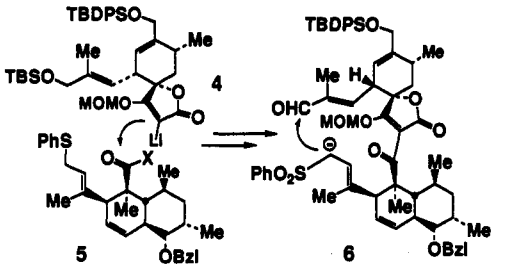
Introduction

In preceding papers we described syntheses of the bottom (**2**) and top (**3**) half fragments of kijanolide (**1**), the aglycon of the antibiotic kijanimicin.[2,3] We report herein further studies directed toward the synthesis of **1**, focusing specifically on attempts to couple precursors to fragments **2** and **3**. In connection with these investigations we have established a procedure for the synthesis of the 2-acyl spiro tetronate substructure of **1** and have also developed a second-generation synthesis of kijanolide bottom half precursors (e.g., **35** → **38** → **19**) that avoids the introduction and manipulation of the C(7) alkoxy group that complicated our synthesis of **2**.[2a]



Synthesis of the 2-Acyl Spiro Tetronate Substructure

Our plan at the conception of this synthesis called for the α-metalation of **3**[4-7] and addition of the resulting anion **4** to a suitably activated bottom half derivative **5**. Further elaboration of the coupled product would then set the stage for the closure of the macrocycle via anionic formation of the C(16)–C(17) bond as indicated in structure **6**.



The feasibility of this approach was demonstrated by Yoshii in a series of papers while our syntheses of **2** and **3** were in progress.[7] More recently, Yoshii successfully applied this strategy in the first total synthesis of tetronolide.[8] However, since Yoshii's model studies indicated that the efficiency of the addition of a kijanolide

(1) Taken in part from the 1992 Ph.D. Thesis of B. B. Brown.

(2) (a) Synthesis of **2**: Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.*, in press. (b) Synthesis of **3**: Roush, W. R.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309. Roush, W. R.; Brown, B. B. *J. Org. Chem.*, preceding paper in this issue. (c) A complete list of contributions from other laboratories directed toward the synthesis of kijanolide and the structurally related natural products tetronolide and chlorothricolide is provided in refs 5 and 6 in the full paper cited in ref 2a.

(3) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497.

(4) (a) Clemo, N. G.; Pattenden, G. *Tetrahedron Lett.* **1982**, *23*, 581. (b) Clemo, N. G.; Pattenden, G. *Ibid.* **1982**, *23*, 585. (c) Clemo, N. G.; Pattenden, G. *Ibid.* **1982**, *23*, 589.

(5) Miyata, O.; Schmidt, R. R. *Tetrahedron Lett.* **1982**, *23*, 1793.

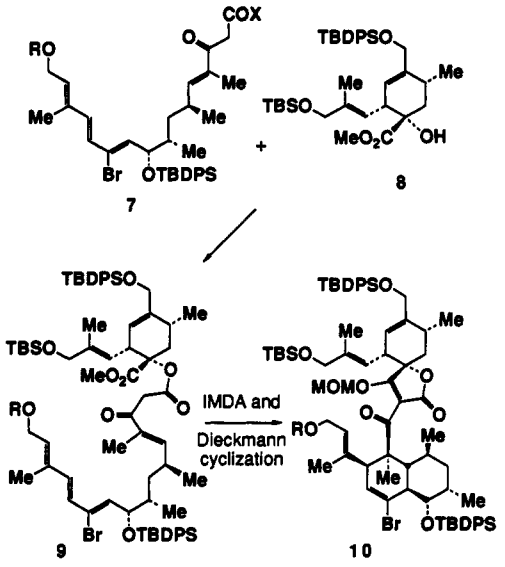
(6) (a) Takeda, K.; Kubo, H.; Koizumi, T.; Yoshii, E. *Tetrahedron Lett.* **1982**, *23*, 3175. (b) Nomura, K.; Hori, K.; Arai, M.; Yoshii, E. *Chem. Pharm. Bull.* **1986**, *34*, 5188.

(7) (a) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673. (b) Takeda, K.; Urahata, M.; Yoshii, E.; Takayanagi, H.; Ogura, H. *Ibid.* **1986**, *51*, 4735. (c) Takeda, K.; Yano, S.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951.

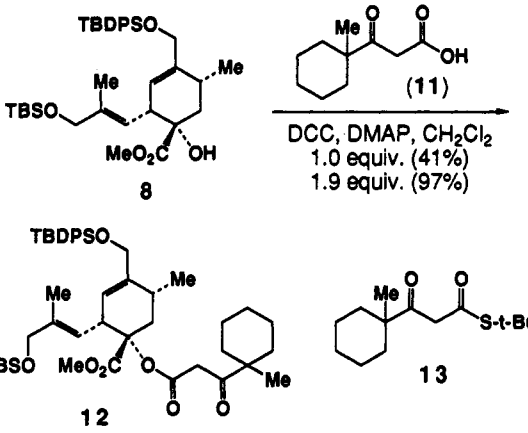
(8) Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925.

0022-3263/93/1958-2162$04.00/0

top half α-lithiotetronate to a model bottom half octahydronaphthalenecarboxaldehyde system lacking the equatorial C(6)-methyl group was poor (66% conversion),[7] we became concerned that the planned coupling of 4 and 5 would suffer from significant steric interactions involving the equatorial C(6)-methyl group that flanks the acyl unit of 5. These concerns prompted us to focus our efforts on alternative strategies in which acyclic precursors to the bottom half fragment (e.g., activated β-keto acid 7) are coupled to tertiary alcohol 8[2b] before construction of the 2-acyl tetronate[9] and IMDA closure of the bottom half.[10]



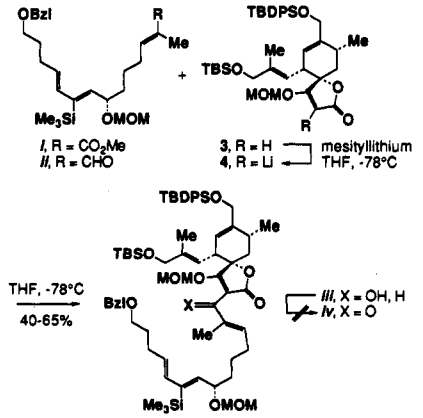
We began by initiating studies of 2-acyl spiro tetronate construction via Dieckmann cyclization of β-keto ester precursors.[13,14] Model β-keto ester 12 was prepared via DCC–DMAP coupling of 8[2b] and 11.[15-17] The yield of 12 was excellent (97%) when excess β-keto acid 11 was employed, but when stoichiometric β-keto acid was used (as would be required in the coupling of 8 and β-keto acid 7, X = OH), the yield of 12 was only 40–45%. The second equivalent of 11 is consumed in an unproductive decarboxylation reaction. Application of Yamaguchi's procedure[18] (trichlorobenzoyl chloride, DMAP, Et_3N, CH_2Cl_2) using stoichiometric 11 provided 12 in slightly better yield (45–55%). Application of the diethyl chlorophosphate[19] or the 2-chloropyridinium salt[20] acylation procedures failed to provide significant quantities of 12. Finally, attempts to prepare 12 by using β-keto thiol eter 13 according to the Masamune–Ley protocol were also unsuccessful.[14d,21]



The Dieckmann cyclization of 12 proved much more difficult than originally anticipated.[13,14] A variety of bases were examined (i.e., NaH, KOtBu, LHMDS, BrMgOEt, DBU, and mesityllithium), but most attempts failed to yield the 2-acyl tetronic acid 15. For example, an attempt to cyclize 12 by treatment with KOtBu in refluxing toluene provided tetronic acid 18 (deacylated!) in low yield (15–20%) as the only identifiable product. After considerable

(9) Reviews of tetronic acid syntheses: (a) Haynes, L. J.; Plimmer, J. R. *Q. Rev., Chem. Soc.* **1960**, *14*, 292. (b) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (c) Pattenden, G. *Fortschr. Chem. Org. Naturst.* **1978**, *35*, 133.

(10) We elected to pursue the acylation–IMDA–Dieckmann cyclization strategy for the synthesis of intermediate 10 since attempts to prepare the model acyl tetronate iv via the reaction of α-lithio tetronate 4 with unsaturated ester i[11] (or other activated acyl derivatives) were unsuccessful. While carbinol iii was obtained in 40–65% yield (unoptimized) from the reaction with aldehyde ii, all attempts to oxidize iii under a variety of conditions [DMSO–$(COCl)_2$, TFAA–DMSO, PCC, MnO_2, $BaMnO_4$, etc.)[12] were unsuccessful. Carbinol intermediate iii, like the subsequently prepared acyl tetronate system 54, decomposed upon attempted IMDA cyclization. Other methods (refs 6b, 13) for the synthesis of 2-acyl tetronates involving the direct acylation of 18 were also unsuccessful.



(11) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.

(12) For a review of DMSO-based oxidations: Tidwell, T. T. *Synthesis* **1990**, 857.

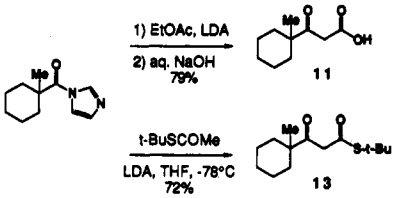
(13) (a) Bloomer, J. L.; Kappler, F. E. *J. Org. Chem.* **1974**, *39*, 113. (b) Bloomer, J. L.; Kappler, F. E. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1485 and references therein.

(14) (a) Lacey, R. N. *J. Chem. Soc.* **1954**, 832. (b) Haynes, L. J.; Stannes, A. N. *J. Chem. Soc* **1956**, 4103. (c) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (d) Booth, P. M.; Fox, C. M. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1987**, 121.

(15) For reviews of esterification methods: (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (c) Haslem, E. *Tetrahedron* **1980**, *36*, 2409. (d) Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1991**, *161*, 106.

(16) (a) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475. (b) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(17) β-Keto acid 11 and the β-keto thiol ester 13 were prepared as shown below.



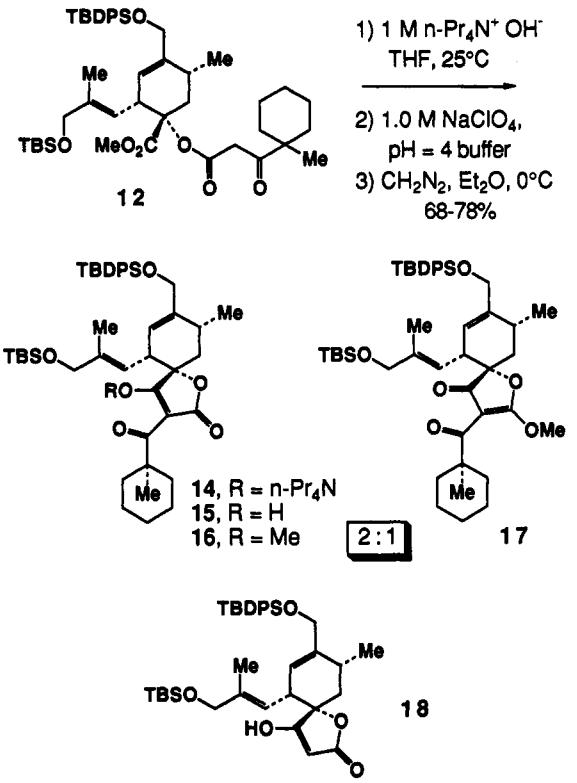
(18) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.

(19) (a) Masamune, S.; Kamata, S.; Diakur, J.; Sugihara, Y.; Bates, G. S. *Can. J. Chem.* **1975**, *53*, 3693. (b) Kaiho, T.; Masamune, S.; Toyoda, T. *J. Org. Chem.* **1982**, *47*, 1612.

(20) (a) Mukaiyama, T.; Usui, M.; Sagio, K. *Chem. Lett.* **1976**, 49. (b) Mukaiyama, T.; Narasaka, K.; Kikuchi, K. *Chem. Lett.* **1977**, 441. (c) Narasaka, K.; Masui, T.; Mukaiyama, T. *Chem. Lett.* **1977**, 763.

(21) (a) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513. (b) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. (c) Masamune, S.; Hayase, Y.; Schilling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.

experimentation we found that **15** can be prepared by treatment of β-keto ester **12** with $R_4N^+OH^-$ (R = *n*-Bu or *n*-Pr). While use of *n*-$Bu_4N^+F^-$ for such cyclizations has been reported previously by Ley,[14d] this reagent also deprotects the silyl ethers present in **12**. This problem is nicely avoided by using *n*-$Bu_4N^+OH^-$ or *n*-$Pr_4N^+OH^-$, since the facility of cyclization depends only on the counterion and not the base itself.



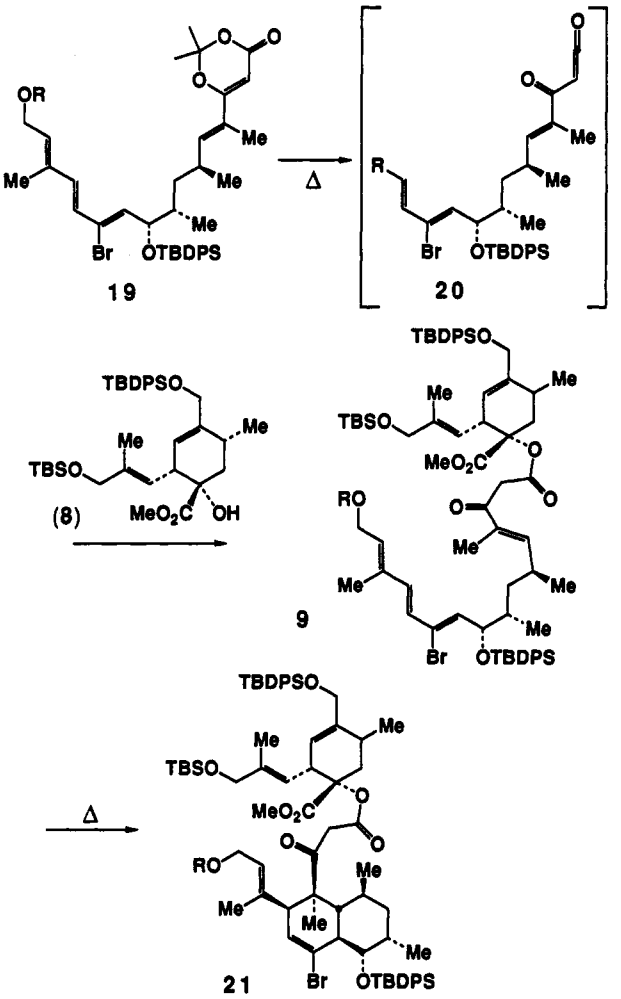
Thus, to a 25 °C solution of **12** in anhydrous THF (1 M) was added 2 equiv of a 1 M solution of *n*-$Pr_4N^+OH^-$ in H_2O. This mixture stirred for 16–24 h under N_2. Isolation of tetronic acid **15** was complicated, however, owing to the acidity of **15** and the difficulty of removing the tetra-*n*-propylammonium cation. Acidification of the reaction mixture with aqueous acid (1 N HCl or 40% HOAc) provided tetronic acid **15** in irreproducible yield and purity; mixtures containing **15**, the salt **14**, and/or an allylic alcohol resulting from the loss of the TBDMS protecting group were usually observed. A far superior workup involves the addition of 1 equiv of sodium perchlorate in sodium phosphate buffer solution (pH 4.0),[22] which causes the tetra-*n*-propylammonium cation to be precipitated as the perchlorate salt. Normal extractive workup then furnished **15** in good overall yield. Tetronate **15** was protected immediately following isolation, since it decomposed upon attempted purification by silica gel chromatography.

Treatment of **15** with diazomethane provided a 2:1 mixture of isomeric methyl ethers **16** and **17**. Tetronate **16** displays a characteristic IR band at 1745 cm^{-1}, and the methoxyl resonance appears at δ 3.80 in the ^1H NMR spectrum. In contrast, isomer **17** displays a weak IR stretch at 1695 cm^{-1} and a ^1H NMR singlet for the methoxyl at δ 4.10. These data are in reasonable agreement with literature values for closely related systems.[4-6]

(22) Craig, J. C.; Evenhart, E. T. *Synth. Commun.* **1990**, *20*, 2147.

The Acyl Ketene Coupling Strategy

Confident that a method for the synthesis of 2-acyl tetronates was in hand, we turned to the problem of coupling kijanolide top and bottom half precursors by way of a β-keto ester linkage. Reports that acyl ketenes, generated by the thermal decomposition of dioxinones,[23,24] are excellent acylating agents prompted us to pursue a sequence in which thermolysis of **19** in the presence of **8** would provide β-keto ester **9** by way of acyl ketene **20**. Ideally, continued heating of **9** would lead directly to **21** in a simple, one-pot tandem acylation–intramolecular Diels–Alder reaction sequence. An analogous strategy directed toward the synthesis of tetronolide was reported by Boeckman while our studies were in progress.[25]



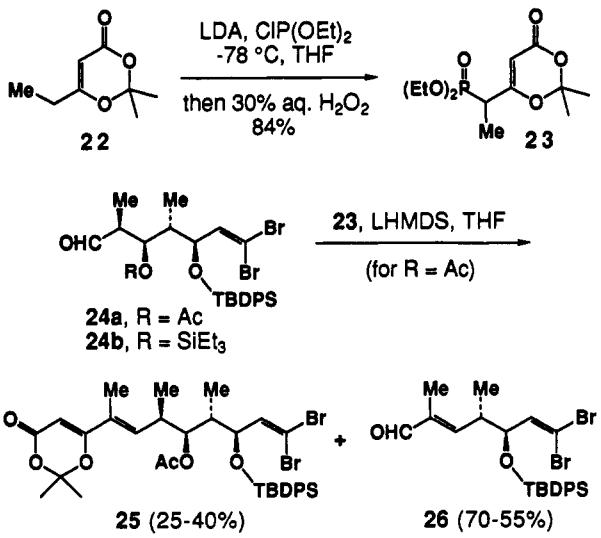
The Horner–Wadsworth–Emmons reagent **23** required for the synthesis of **19** was synthesized by treating the known dioxinone **22**[26a] with LDA in THF at 0 °C followed

(23) (a) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J. *J. Org. Chem.* 1984, *49*, 5105. (b) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431. (c) Sakaki, J.; Kobayashi, S.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, *38*, 2262 and references therein. (d) Freiermuth, B.; Wentrup, C. *J. Org. Chem.* **1991**, *56*, 2286.

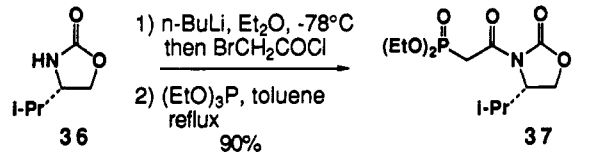
(24) (a) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (b) Paquette, L. A.; Macdonald, D.; Anderson, L. G.; Wright, J. *Ibid.* **1989**, *111*, 8037. (c) Boeckman, R. K., Jr.; Pruitt, J. R. *Ibid.* **1989**, *111*, 8286.

(25) Boeckman, R. K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091.

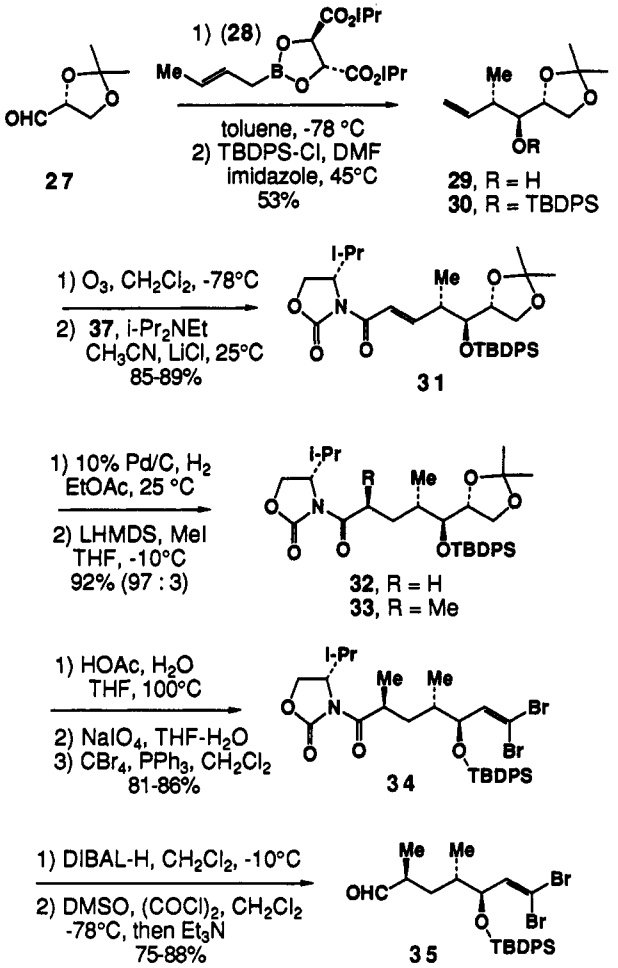
by diethyl chlorophosphite at −78 °C.[27] Oxidation of the crude product with H_2O_2 during workup then provided **23** in 84% yield.[28] Because attempts to condense **23** with aldehydes like **24** with β-alkoxy substituents resulted in substantial elimination (when R = Ac) or no reaction when R = $SiEt_3$, we developed a second-generation synthesis of bottom half precursors that avoided the introduction of the (now problematic!) C(3) hydroxyl group of **24**.[2a]



Rather than begin this revised synthesis with L-glyceraldehyde acetonide as in our previously described route,[2a] we elected to use the more available D-glyceraldehyde acetonide (**27**) as the starting material. Thus, treatment of the known homoallylic alcohol **29**[29,30] with TBDPS-Cl and imidazole in DMF at 45 °C provided TBDPS ether **30**. Ozonolysis of **30** in MeOH–CH_2Cl_2 at −78 °C (Ph_3P workup) provided a crude aldehyde that was immediately treated with the chiral Horner–Wadsworth–Emmons reagent **37** (prepared as shown from **36**).[31] This provided



α,β-unsaturated oxazolidinoine **31** with 10:1 selectivity in 85–89% overall yield. Hydrogenation of **31** with 10% Pd/C in EtOAc provided **32** in 95% yield. Treatment of the lithium enolate prepared from **32** ($LiN(TMS)_2$, 0.3 M in THF) with methyl iodide (5–10 equiv) at −78 to −10 °C then delivered **33** with 30:1 selectivity.[32] Hydrolysis of the isopropylidine group (aqueous HOAc, THF, 100 °C), periodate cleavage of the resulting diol, and then introduction of the dibromo olefin gave **34** in excellent yield. Reduction of **34** with DIBAL-H in CH_2Cl_2 provided a mixture of **35** and the primary alcohol that was oxidized via the Swern protocol[11] to give **35** in 75–88% yield from **34**.



Horner–Wadsworth–Emmons coupling[33,34] of aldehyde **35** and phosphonate **23** gave **38** in 88–95% yield as a 10–11:1 mixture of olefin isomers. Suzuki cross coupling[35] of **38** and vinyl boronic acid **39**[2a] then provided tetraene **19** (R = H) in 77–86% yield.

As an initial test of the viability of the tandem IMDA/acyl ketene trapping sequence, BOM ether **40** (prepared by treating **19** with BOM-Cl and i-Pr_2NEt, 74% yield) was heated in anhydrous xylene at 120 °C for 16 h in the presence of excess MeOH and 4-Å molecular sieves. This experiment provided β-keto ester **41** in 60% yield; the methyl ketone analogous to **43** was not detected (vide infra).

(26) (a) Sato, M.; Ogasawara, H.; Komatsu, S.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 3848. (b) For a review of applications of 1,3-dioxin-4-ones in synthesis, see: Kaneko, C.; Sato, M.; Sakaki, J.; Abe, Y. *J. Heterocycl. Chem.* **1990**, *27*, 25.

(27) (a) Leavitt, F. C.; Manuel, T. A.; Johnson, F.; Matternas, L. U. *J. Am. Chem. Soc.* **1960**, *82*, 5099. (b) Braye, E. H.; Hübel, W.; Coplier, I. *J. Am. Chem. Soc.* **1961**, *83*, 4406. (c) Meisenheimer, J.; Caspen, J.; Höring, M.; Lauter, W.; Lichtenstadt, L.; Samuel, W. *Ann. Chem.* **1926**, *315*, 43.

(28) An analogous synthesis of **23** was reported by Boeckman while our studies were in progress: Boeckman, R. K., Jr.; Kamenecka, T. M.; Nelson, S. G.; Pruitt, J. R.; Barta, T. E. *Tetrahedron Lett.* **1991**, *32*, 2581.

(29) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Roush, W. R.; Coe, J. W. *J. Org. Chem.* **1989**, *54*, 915.

(30) For the preparation of **28** and reactions with chiral and achiral aldehydes: (a) Roush, W. R.; Ando, K. A.; Powers, D. B.; Halterman, R. L.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. A. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

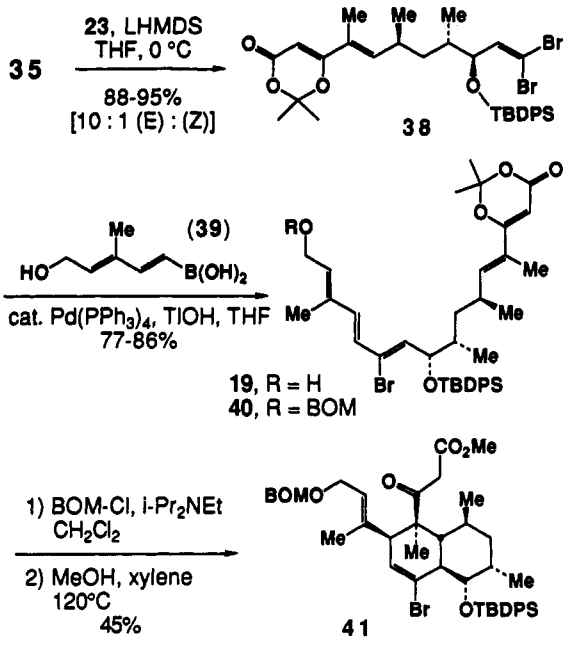
(31) Syntheses of the related phenylalaninol derived acylphosphorane and β-acyl phosphonate were reported while our work was in progress: (a) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 2260. (b) Shapiro, G.; Chengzhi, C. *Tetrahedron Lett.* **1992**, *33*, 2447.

(32) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

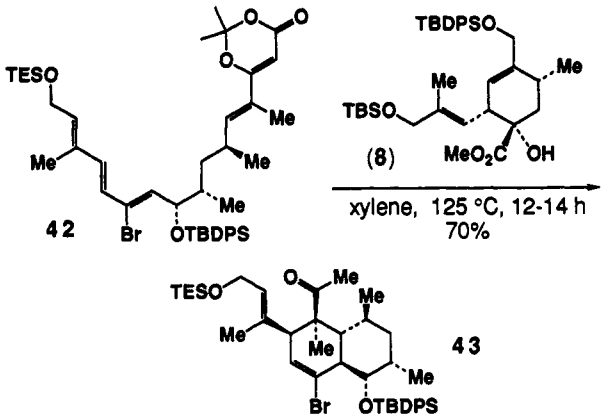
(33) (a) Wadsworth, W. S., Jr. *Org. React.* **1980**, *25*, 73. (b) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(34) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(35) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972 and references cited therein. (b) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756. (c) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.

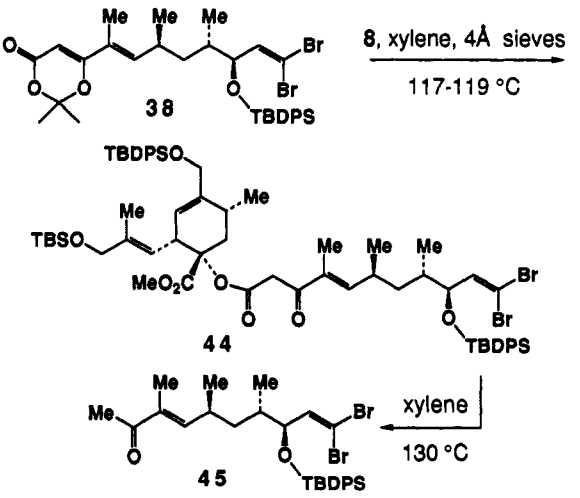


Surprisingly, attempts to extend this reaction to the coupling of 8 (3 equiv) and 19 (as the triethylsilyl ether derivative 42), or with related acyl ketene precursors,[36] in toluene or xylene at 120–130 °C provided *none* of the desired, coupled cycloadduct. Rather, in one experiment with 42, methyl ketone 43 was obtained in 70% yield along with 85% of recovered 8.



Two scenarios were considered for the formation of 43. First, it seemed possible that the rate of addition of 8 to the acyl ketene 20 generated from 42 might be retarded by steric hinderance of the tertiary alcohol, in which case the acyl ketene could be intercepted by adventitious H_2O. Subsequent decarboxylation and intramolecular cycloaddition would then provide 43. Second, 43 could arise via the thermal decomposition of the initially generated β-keto ester 9 (R = Et_3Si) or the targeted cycloadduct 21 (R = Et_3Si).[37] In order to clarify the timing of the formation of 43, we performed the following series of experiments leading to the synthesis and study of the thermal stability of tetraene β-keto ester 46 (i.e., 9, R = H).

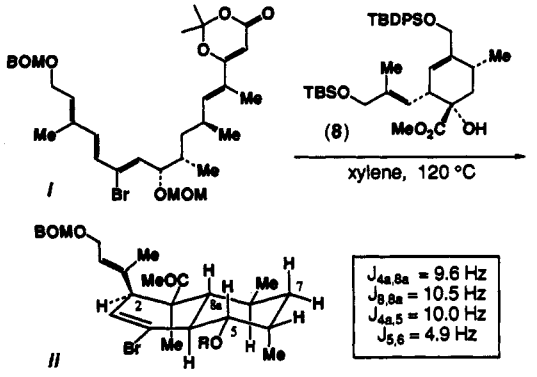
The reaction of dioxinone 38 and 8 provided a test of the ease of acyl ketene acylation of the tertiary hydroxyl group. Remarkably, this reaction provided β-keto ester 44 in up to 88% yield under carefully controlled conditions (1.8 equiv of 8, 115–118 °C, 1.5 h), indicating that steric problems were not responsible for the unsuccessful attempts to couple 42 and 8. If the reaction temperature was allowed to rise above 120 °C, a substantial amount of the methyl ketone 45 was obtained (45% of 45 at 125 °C for 1.5 h). This suggested to us that 44 is thermally unstable, a conclusion that was verified by heating 44 in xylene at 130 °C for 1 h. This control experiment provided a ca. 1:1:1 mixture of 8, 44 and 45. While 44 is more stable at lower temperatures, the coupling of 8 and 45 is unsuccessful if performed below 115 °C, presumably due to the slow rate of acyl ketene formation at this temperature. The ratio of 44 to 45 also depends on the reaction time (longer reaction times lead to increased amounts of methyl ketone 45) as well as on the amount of alcohol 8 used [76% yield with 1.8 equiv of 8 (3 h at 115–120 °C) vs 52% yield with 1.1 equiv of 8 (4 h at 115–120 °C)]. Use of excess 8 presents no problem since this intermediate is easily separated and may be recovered almost quantitatively from the reaction mixtures.



8	Temp.	Time	44	45
1.8 equiv.	115-118°C	1.5 h	88%	2%
1.8 equiv.	115-120°C	3 h	76%	4%
1.2 equiv.	115-120°C	5 h	64%	28%
1.1 equiv.	115-120°C	4 h	52%	38%
1.2 equiv.	125°C	1.5 h	46%	45%

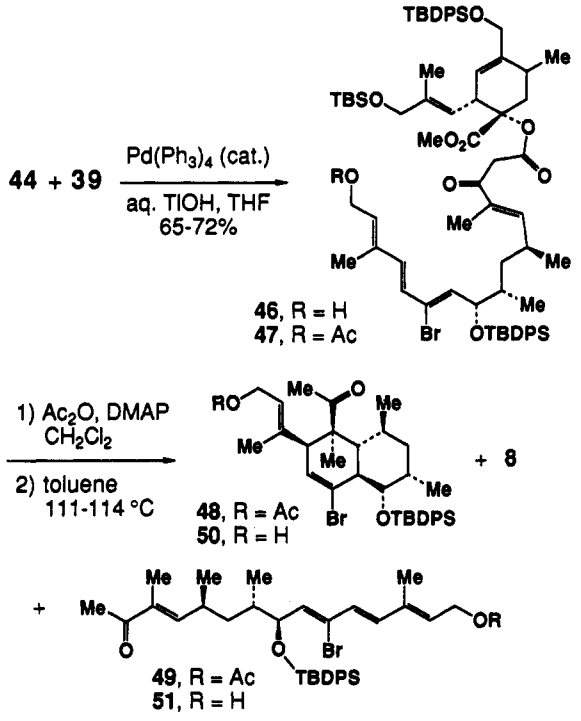
Tetraene 46 (i.e., 9, R = H) was synthesized via the standard Suzuki cross coupling of 44 and vinylboronic acid 39 (65–72% yield).[35] Acylation of 46 then provided

(36) Attempts to couple dioxinone i with 1.8 equiv of 8 at 120 °C similarly provided methyl ketone cycloadduct ii. The stereochemistry of ii was assigned by using the characteristic ^1H NMR data summarized below. The ^1H NMR data obtained for 43 (see text) were in excellent agreement with those for ii.



(37) (a) Clemens, R. J.; Witzeman, J. S. *J. Am. Chem. Soc.* **1989**, *111*, 2186. (b) Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401. (c) Witzeman, J. S.; Nottingham, W. D. *J. Org. Chem.* **1991**, *56*, 1713.

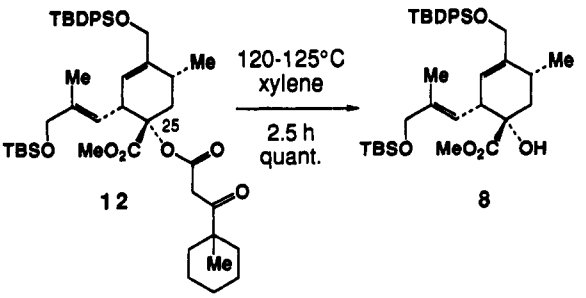
47 (Ac_2O, DMAP, CH_2Cl_2, 96%). Attempted protection of 46 as a BOM ether using BOMCl and Hunig's base was unsuccessful as a result of base-catalyzed decomposition.



A toluene solution of 47 was heated at 111–112 °C for 6 h, and then an aliquot was analyzed by ^1H NMR spectroscopy. This analysis indicated that a new product(s) had been formed (a methyl doublet at δ 0.5 characteristic of a cycloadduct was present), but that considerable 47 remained. The reaction mixture was then heated at 113–114 °C for an additional 14 h, at which time 47 had been completely consumed. Chromatographic separation of the reaction mixture yielded three compounds in a ratio of ca. 1:1:2 (88% combined yield): methyl ketone cycloadduct 48, tetraene methyl ketone 49, and tertiary alcohol 8. These data show conclusively that the rate of IMDA cyclization is slower than the rate of β-keto ester fragmentation and decarboxylation.

Thermal instability of tertiary β-keto esters is well known. Studies by Witzeman and co-workers have demonstrated that *tert*-butyl acetoacetate eliminates to the acyl ketene intermediate some 15 fold faster than ethyl acetoacetate at 106 °C.[23,27] In view of the difficulties we encountered with 42, 47, and related systems,[36] it is noteworthy that Boeckman recently successfully demonstrated a tandem acyl ketene acylation–intramolecular intramolecular Diels–Alder reaction sequence at 130 °C using methyl α-hydroxycyclohexanecarboxylate as the acyl ketene trapping agent.[25] However, we found that heating a xylene solution of model β-keto ester 12 at 120–125 °C for 2.5 h led to complete fragmentation to tertiary alcohol 8. Perhaps the greater steric congestion in the vicinity of the C(25)-oxygen atom of 12, 9 (R = $SiEt_3$), and 47 compared to Boeckman's less crowded model compound accounts for the greater thermal instability of our intermediates.

Several attempts were made to induce the IMDA cyclization of 46 in the presence of bis(trimethylsilyl)-acetamide (BSA, toluene, 120–140 °C) or TMSCl–$ZnCl_2$, in hope that the β-keto ester would be stabilized by silyl enol ether formation in situ. These attempts invariably



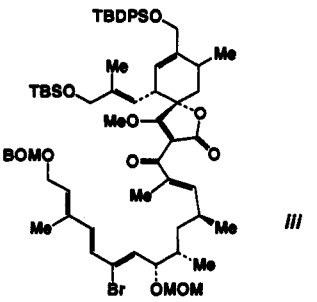
provided tertiary alcohol 8, methyl ketone cycloadduct 50, and/or acyclic tetraene methyl ketone 51; none of the targeted cycloadduct 21 (R = H or TMS) was ever detected. Attempted use of $Eu(fod)_2$ (45 → 110 °C, 12 h)[8,38] as a catalyst for the IMDA cyclization of 46 also failed to provide 21. Tertiary alcohol 8 was the only product that could be identified from this experiment.

Owing to our inability to effect the IMDA cyclization of 46 or 47 without deacylation and decarboxylation, we explored the possibility that the IMDA reaction could be performed on a substrate like 53 after closure of the spirotetronate system. Thus, β-keto ester 44 was treated with 2.0 equiv of *n*-$Pr_4N^+OH^-$ in THF. Standard workup with aqueous $NaClO_4$ yielded the tetronic acid that was protected by exposure to excess diazomethane in ether. This produced a separable 3:1 mixture of *O*-methyl tetronates 52 in 73–80% yield.

Tetraene 53 was then prepared in 60–65% yield by using the standard cross-coupling reaction with 39 ($Pd(PPh_3)_4$, TlOH, THF). Much to our considerable disappointment, heating solutions of 53 or the corresponding triethylsilyl ether 54 to temperatures approaching 190 °C failed to produce cycloadducts 55 or 56. Starting material was recovered at temperatures below 170 °C, even after 16–24-h reaction times, but decomposition pathways intervened at temperatures above 180 °C. We also investigated the use of Lewis acids to promote this cyclization, but no product was obtained upon exposure of 54 to Me_2AlCl (up to 3 equiv) in CH_2Cl_2 at temperatures ranging from −78 → 25 °C (16–32 h).[39] The lack of Diels–Alder reactivity of 53 and 54 is apparent upon inspection of molecular models, which indicate that the triene unit experiences severe nonbonded interactions with either the spirotetronate C(17)–C(19) side chain or the C(24) methylene in transition states leading to 55/56.

(38) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 3716. (b) Danishefsky, S.; Bednarski, M. *Tetrahedron Lett.* **1985**, *26*, 2507. (c) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, Y.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.

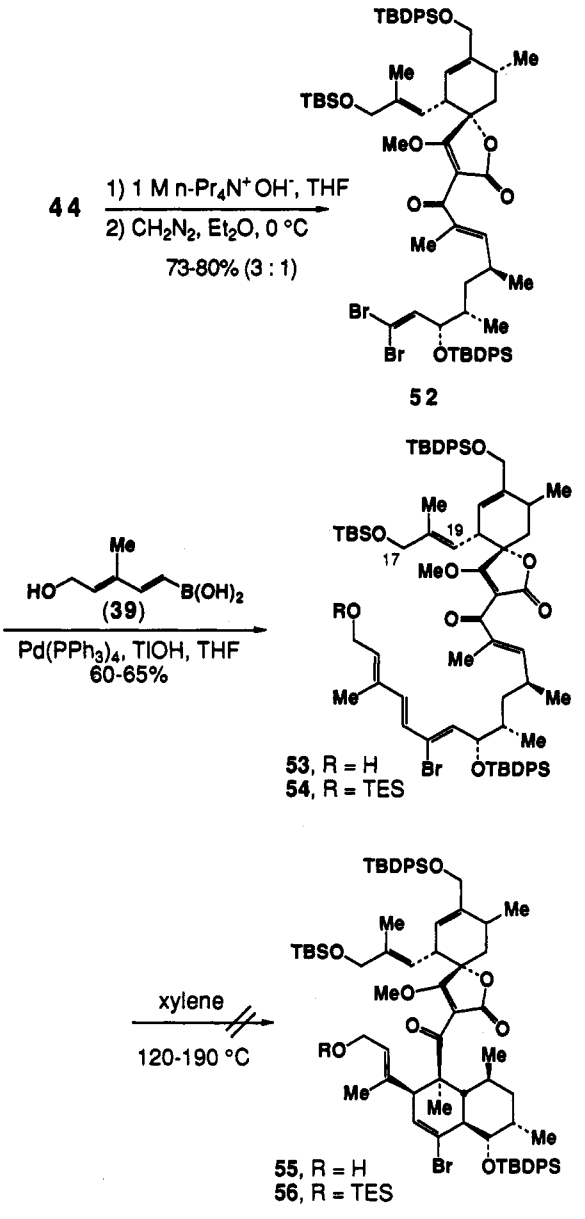
(39) Tetraene iii also failed to undergo thermal or Me_2AlCl-catalyzed intramolecular Diels–Alder cycloaddition.



iii

(40) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(41) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595.



Summary. The present study defines solutions to several important issues that are critical for further progress to be achieved towards the synthesis of kijanolide. First, a method for synthesis of the 2-acyl spiro tetronate substructure (**16**, **52**) via a Dieckmann cyclization protocol was established.

Second, a 10-step synthesis of 7,7-dibromo-2,4-dimethyl-5-[(*tert*-butyldiphenylsilyl)oxy]heptenal **35** was developed, thereby making possible the synthesis of a range of kijanolide bottom half precursors via olefination (e.g., **35** + **23** → **38**) and cross-coupling reactions (e.g., **38** → **19**).

Third, a highly efficient procedure was developed for the coupling of kijanolide top half **8** and dioxinone **38** via an acyl ketene intermediate. This is the most efficient of several methods examined for acylating the hindered tertiary alcohol of **8**.

Unfortunately, attempts to perform the IMDA reaction of **46**, or of the synthetically equivalent tetraene generated in situ from coupling of **8** and the acyl ketene derived from **42**, were thwarted owing to the tendency of hindered, tertiary β-keto esters like **12** and **47** to fragment and decarboxylate via the acyl ketene intermediate at temperatures above 115 °C. 2-Acyl tetronate **53** was synthesized, but this system decomposed upon attempted IMDA cyclization at temperatures approaching 190 °C.

These results strongly imply that if the acyl ketene strategy is to be incorporated into a successful total synthesis, the end game strategy must be modified such that the bottom half IMDA closure is completed before the connection with the top half tertiary alcohol **8**. Accordingly, we are currently exploring an alternative sequence involving the connection of precursors to the top and bottom half fragments about the C(17)–C(18) bond prior to the IMDA closure of the bottom half and the Dieckman closure of the spirotetronate system. Further progress toward completion of the total synthesis of kijanolide along these lines will be reported in due course.

Experimental Section

General. All reactions were conducted in oven-dried (125 °C) or flame-dried glassware under atmospheres of dry argon or nitrogen. All solvents were purified before use. Ether, THF, and toluene were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from CaH_2.

^1H NMR spectra were measured at 300, 400, and 500 MHz on commercially available instruments. Residual chloroform (δ 7.26 ppm) was used as internal reference for spectra measured in $CDCl_3$. Low- and high-resolution mass spectra were measured at 70 eV.

Analytical thin-layer chromatography (TLC) was performed by using 2.5-cm × 10-cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography was performed by using 20-cm × 20-cm plates coated with 0.25- or 0.5-mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh).[40] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (by ^1H NMR analysis) for use in subsequent reactions.

Synthesis of β-Keto Ester 12. To a 25 °C solution of alcohol **8**[2b] (55 mg, 0.09 mmol), β-keto acid **11**[17] (33 mg, 0.18 mmol), and DMAP (5 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (1 mL) under N_2 was added DCC (37 mg, 0.18 mmol). The reaction was stirred for 12 h before the resulting solid was removed by filtration, and the filtrate was concentrated in vacuo. Purification of the crude product by silica gel chromatography (15:1 hexane–acetone as eluent) yielded 67 mg (97%) of the desired β-keto ester **12**. This compound is a mixture of keto and enol tautomers: R_f 0.28 (10:1 hexane–acetone); $[\alpha]^{26}_D$ −95.6° (c = 1.6, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$), for keto tautomer, δ 7.73–7.65 (m, 4 H), 7.48–7.30 (m, 6 H), 5.46 (m, 1 H), 5.22 (m, 1 H), 4.17 (m, 1 H), 4.08–3.95 (m, 4 H), 3.74 (s, 3 H), 3.46 (A of AB d, J_{AB} = 15.1 Hz, 1 H), 3.38 (B of AB d, J_{AB} = 15.1 Hz, 1 H), 2.41 (m, 1 H), 2.24 (m, 1 H), 1.99–1.69 (m, 4 H), 1.61 (s, 3 H), 1.59–1.22 (m, 7 H), 1.09 (d, J = 7.8 Hz, 3 H), 1.03 (br s, 12 H), 0.90 (s, 9 H), 0.03 (s, 6 H); ^1H NMR data for enol tautomer, δ 7.73–7.65 (m, 4 H), 7.48–7.30 (m, 6 H), 5.46 (m, 1 H), 5.22 (m, 1 H), 5.02 (s, 1 H, enol CH), 4.17 (m, 1 H), 4.08–3.95 (m, 4 H), 3.71 (s, 3 H), 2.41 (m, 1 H), 2.24 (m, 1 H), 1.99–1.69 (m, 4 H), 1.57 (s, 3 H), 1.59–1.22 (m, 7 H), 1.07 (d, J = 7.8 Hz, 3 H), 1.03 (br s, 12 H), 0.90 (s, 9 H), 0.03 (br s, 6 H); IR (neat) 1755, 1704, 1676, 1611 cm^{-1}; HRMS for $C_{42}H_{59}O_7Si_2$ ($M^+ - C_4H_9$) calcd 731.3783, found 731.3800. Anal. Calcd for $C_{46}H_{68}Si_2O_7 \cdot H_2O$: C, 68.44; H, 8.74. Found: C, 68.35; H, 8.87.

Synthesis of Methyl Tetronate 16 from β-Keto Ester 12. To a 25 °C solution of β-keto ester **12** (18 mg, 0.022 mmol) in THF (0.12 mL) under N_2 was added a 1.0 M aqueous solution of tetra-*n*-propylammonium hydroxide (44 μL, 0.044 mmol). The reaction mixture was stirred for 22 h before it was diluted with pH 4 phosphate buffer (0.2 mL) and 1 M aqueous $NaClO_4$ (0.11 mL, 0.11 mmol). The mixture was stirred for 30 min, EtOAc (0.4 mL) was added, and the precipitate was filtered through glass wool. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Tetronic acid **15** (16 mg) so obtained was used in the next step without further purification.

To a 0 °C solution of tetronic acid **15** (16 mg, theoretically 0.022 mmol) in anhydrous Et_2O (0.20 mL) under N_2 was added

a 0 °C solution of diazomethane [generated from *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (10 mg, 0.07 mmol)] in anhydrous Et_2O (0.2 mL). After 30 min the reaction was allowed to warm to 25 °C, diluted with Et_2O (0.5 mL), and extracted with H_2O (0.30 mL). The aqueous layer was separated and extracted with Et_2O (2 × 0.50 mL). The combined ethereal layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. ^1H NMR analysis of this material revealed it to be a 2:1 mixture of methyl tetronates **16** and **17**. Purification of this mixture by silica gel chromatography (2:1 hexane–ether as eluent) yielded 7 mg (43%) of **16** and 4 mg (25%) of isomer **17**.

Data for major isomer **16**: R_f 0.41 (2:1 hexane–ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 4 H), 7.44–7.36 (m, 6 H), 5.37 (br s, 1 H), 5.18 (d, J = 10.7 Hz, 1 H), 4.21 (A of AB d, J_{AB} = 13.2 Hz, 1 H), 4.13 (B of AB d, J_{BA} = 13.2 Hz, 1 H), 3.95 (s, 2 H), 3.80 (s, 3 H), 3.48 (d, J = 10.7 Hz, 1 H), 2.61 (m, 1 H), 2.23 (dd, J = 14.0, 7.1 Hz, 1 H), 1.82–1.38 (m, 11 H), 1.61 (s, 3 H), 1.29 (s, 3 H), 1.14 (d, J = 7.4 Hz, 3 H), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.02 (s, 6 H); IR ($CHCl_3$) 1745, 1670, 1641 cm^{-1}; HRMS for $C_{46}H_{67}O_6Si_2$ (M^+ + H) calcd 771.4458, found 771.4527. Anal. Calcd for $C_{46}H_{66}O_6Si_2$: C, 71.64; H, 8.63. Found: C, 71.65; H, 8.63.

Data for minor isomer **17**: R_f 0.23 (2:1 hexane–ether); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 4 H), 7.44–7.36 (m, 6 H), 5.32 (br s, 1 H), 5.05 (d, J = 10.0 Hz, 1 H), 4.24 (A of AB d, J_{AB} = 14.0 Hz, 1 H), 4.14 (B of AB d, J_{BA} = 14.0 Hz, 1 H), 4.10 (s, 3 H), 3.91 (A of AB d, J_{AB} = 13.7 Hz, 1 H), 3.86 (B of AB d, J_{BA} = 13.7 Hz, 1 H), 3.60 (d, J = 10.0 Hz, 1 H), 2.61 (m, 1 H), 2.29 (dd, J = 14.6, 7.5 Hz, 1 H), 2.18–2.02 (m, 2 H), 1.68 (d, J = 14.6 Hz, 1 H), 1.62–1.31 (m, 8 H), 1.58 (s, 3 H), 1.26 (s, 3 H), 1.09 (d, J = 7.4 Hz, 3 H), 1.05 (s, 9 H), 0.87 (s, 9 H), 0.02 (s, 6 H); IR ($CHCl_3$) 1695 (weak), 1665 cm^{-1}; HRMS for $C_{46}H_{67}O_6Si_2$ (M^+ + H) calcd 771.4458, found 771.4523. Anal. Calcd for $C_{46}H_{66}O_6Si_2$: C, 71.64; H, 8.63. Found: C, 71.75; H, 8.44.

(3*S*,4*S*,5*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-5,6-*O*-isopropylidene-3-methylhex-1-ene (30). To a 40 °C solution of alcohol **29**[29] (3.0 g, 16.1 mmol; obtained in 64% yield from a 100-mmol-scale crotylboration)[30] in anhydrous DMF (25 mL) under N_2 was added 98% *tert*-butyldiphenylchlorosilane (10.7 g, 40 mmol, Aldrich) and imidazole (6.7 g, 97 mmol) in small portions over a 48-h period. The resulting slurry was stirred an additional 12 h before being diluted with brine (100 mL) and extracted with 1:1 Et_2O–hexane (4 × 150 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by silica gel chromatography (15:1 hexane–ether as eluent) produced 5.9 g (87%) of the desired silyl ether **30**: R_f 0.57 (5:1 hexane–ether); $[\alpha]^{26}_D$ −18.6° (c = 0.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.42 (m, 10 H), 5.75 (ddd, J = 17.2, 10.4, 7.3 Hz, 1 H), 4.92 (dd, J = 10.4, 1.3 Hz, 1 H), 4.82 (dd, J = 17.2, 1.3 Hz, 1 H), 4.05 (br dd, J = 13.1, 6.6 Hz, 1 H), 2.29 (m, 3 H), 1.28 (s, 3 H), 1.26 (s, 3 H), 1.06 (s, 9 H), 0.93 (6.9, 3 H); IR (neat) 3076, 3042, 1644, 1490 cm^{-1}; MS m/z 185 (M^+ − C_4H_9). Anal. Calcd for $C_{26}H_{36}O_3Si$: C, 73.53; H, 8.55. Found: C, 73.32; H, 8.29.

(+)-(4*S*)-3-[(Diethylphosphono)acetyl]-4-(1-methylethyl)-2-oxazolidinone (37). To a −78 °C solution of oxazolidinone **36**[32] (6.0 g, 46.4 mmol) in anhydrous Et_2O (200 mL) and anhydrous THF (30 mL) under N_2 was added 2.5 M hexane solution of *n*-BuLi (18.8 mL, 47.0 mmol). The resulting suspension was allowed to warm to −20 °C for 30 min and then was recooled to −78 °C. A solution of bromoacetyl chloride (7.31 g, 46.4 mmol) in anhydrous Et_2O (30 mL) was added, and the reaction mixture was allowed to warm to 25 °C (2 h) before being quenched with pH 7 phosphate buffer (150 mL) and extracted with Et_2O (4 × 150 mL). The combined ethereal extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Trituration of the crude product with hexane provided 10.9 g (94%) of the known[41] α-chloroacetyl oxazolidinone that was used directly in the next step: ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (A of AB d, J_{AB} = 11.8 Hz, 1 H), 4.46 (m, 1 H), 4.42 (B of AB d, J_{BA} = 11.8 Hz, 1 H), 4.34 (dd, J = 8.1 Hz, 8.1 Hz, 1 H), 4.26 (dd, J = 8.1, 3.2 Hz, 1 H), 2.41 (m, 1 H), 0.90 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H); MS m/z 250 (M^+ + H).

A solution of the (α-chloroacetyl)oxazolidinone (10.9 g, 43.6 mmol) and triethyl phosphite (7.84 g, 45.8 mmol) in anhydrous toluene (22 mL) was heated to reflux under N_2 for 3 h before being cooled and concentrated in vacuo. Purification of the crude product by silica gel chromatography (gradient elution: hexane → 1:1 hexane–ethyl acetate → ethyl acetate) yielded 13.2 g of **37** (90% from **37**): R_f 0.18 (ethyl acetate); $[\alpha]^{20}_D$ +41.6° (c = 5.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 4.43 (m, 1 H), 4.27–4.10 (m, 6 H), 3.86–3.63 (m, 2 H), 2.33 (m, 1 H), 1.29 (dt, J = 7.3, 2.0 Hz, 6 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 7.0 Hz, 3 H); IR (neat) 1781, 1701, 1261 cm^{-1}; HRMS for $C_{12}H_{23}O_6NP$ (M^+ + H) calcd 308.1263, found 308.1277. Anal. Calcd for $C_{12}H_{22}O_6NP$: C, 46.90; H, 7.22. Found: C, 47.02; H, 7.41.

(2′*E*,4*S*,4′*R*,5′*S*,6′*R*)-3-[5′-[(*tert*-Butyldiphenylsilyl)oxy]-6′,7′-*O*-isopropylidene-4′-methylhept-2′-enoyl]-4-isopropyl-1,3-oxazolidin-2-one (31). A −78 °C solution of **30** (1.0 g, 2.4 mmol) in dry MeOH (10 mL) and CH_2Cl_2 (10 mL) was treated with a stream of O_3 in O_2 until **30** could not be detected by TLC analysis. The reaction was flushed with N_2 to remove residual O_3, and then triphenylphosphine (0.93 g, 3.6 mmol) was added. The mixture was allowed to warm to ambient temperature and stirred for 2 h and then was concentrated in vacuo to give a slurry containing aldehyde and excess triphenylphosphine oxide. This mixture was triturated with hexane (2 × 40 mL) to remove Ph_3PO, and the hexane-soluble fraction was purified by silica gel chromatography (gradient elution: hexane → 3:1 hexane–ether) to give 1.0 g (99%) of aldehyde intermediate: R_f 0.27 (5:1 hexane–ether); $[\alpha]^{20}_D$ −14.3° (c = 1.19, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1 H), 7.72–7.37 (m, 10 H), 4.16 (m, 1 H), 4.05 (dd, J = 7.6, 2.6 Hz, 1 H), 3.94 (dd, J = 8.6, 6.4 Hz, 1 H), 3.54 (dd, J = 8.6, 5.3 Hz, 1 H), 2.48 (dq, J = 7.6, 2.6 Hz, 1 H), 1.23 (s, 3 H), 1.20 (d, J = 7.0 Hz, 3 H), 1.19 (s, 3 H), 1.07 (s, 9 H); IR (neat) 2715, 1726 cm^{-1}; MS m/z 426 (parent ion). Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.38; H, 8.03. Found: C, 70.09; H, 8.09.

To a 25 °C solution of the above aldehyde (1.0 g, 2.34 mmol) and phosphonate **37** (1.08 g, 3.51 mmol) in anhydrous CH_3CN (15 mL) under N_2 was added anhydrous LiCl (0.99 g, 23.4 mmol) and i-Pr_2NEt (0.45 mL, 2.60 mmol). The reaction mixture was stirred 48 h at 25 °C before being diluted with brine (45 mL) and extracted with Et_2O (4 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. This provided a crude product that included a 10:1 mixture of *E* and *Z* olefin isomers (^1H NMR analysis). Separation of this mixture by silica gel chromatography (2:1 hexane–ether as eluent) provided 1.21 g (89%) of α,β-unsaturated imide **31**: R_f 0.27 (2:1 hexane–ether); $[\alpha]^{26}_D$ +25.8° (c = 2.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4 H), 7.46–7.36 (m, 6 H), 7.15–7.11 (m, 2 H), 4.47 (m, 1 H), 4.26 (q, J = 8.2 Hz, 1 H), 4.19 (dd, J = 8.9, 3.3 Hz, 1 H), 4.04 (q, J = 6.3 Hz, 1 H), 3.82 (m, 2 H), 3.67 (dd, J = 8.9, 6.3 Hz, 1 H), 2.61 (m, 1 H), 2.38 (m, 1 H), 1.25 (s, 6 H), 1.08 (d, J = 7.3 Hz, 3 H), 1.06 (s, 9 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H); IR (neat) 1781, 1691, 1635 cm^{-1}; HRMS for $C_{29}H_{36}NO_6Si$ (M^+ − C_4H_9) calcd 522.2314, found 522.2301. Anal. Calcd for $C_{33}H_{45}NO_6Si$: C, 68.36; H, 7.82. Found: C, 68.14; H, 7.96.

(4*S*,4′*S*,5′*S*,6′*R*)-3-[5′-[(*tert*-Butyldiphenylsilyl)oxy]-6′,7′-*O*-isopropylidene-4′-methylheptanoyl]-4-isopropyl-1,3-oxazolidin-2-one (32). A 25 °C solution of **31** (1.6 g, 2.75 mmol) in EtOAc (28 mL) was hydrogenated under 1 atm of H_2 over 10% Pd/C (0.3 g). This mixture was stirred for 16 h under H_2 before being flushed with N_2 and filtered through a pad of sand and Celite with EtOAc as the eluent. The filtrate was concentrated in vacuo, and the crude product was purified by silica gel chromatography (2:1 hexane–ether as eluent). This yielded 1.60 g (99%) of imide **32**: R_f 0.19 (2:1 hexane–ether); $[\alpha]^{26}_D$ +30.9° (c = 3.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.44–7.33 (m, 6 H), 4.35 (m, 1 H), 4.24–4.10 (m, 3 H), 3.87 (dd, J = 8.0, 6.3 Hz, 1 H), 3.76 (dd, J = 5.9, 2.2 Hz, 1 H), 3.67 (dd, J = 8.0, 7.1 Hz, 1 H), 2.72 (m, 2 H), 2.32 (m, 1 H), 1.66 (m, 2 H), 1.52 (m, 1 H), 1.27 (s, 3 H), 1.24 (s, 3 H), 1.05 (s, 9 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H), 0.82 (d, J = 7.0 Hz, 3 H); IR (neat) 1783, 1701 cm^{-1}; HRMS for $C_{29}H_{38}NO_6Si$ (M^+ − C_4H_9) calcd 524.2471, found 524.2475. Anal. Calcd for $C_{33}H_{47}NO_6Si$: C, 68.12; H, 8.14. Found: C, 67.86; H, 8.31.

(2′*S*,4*S*,4′*S*,5′*S*,6′*R*)-3-[5′-[(*tert*-Butyldiphenylsilyl)oxy]-2′,4′-dimethyl-6′,7′-*O*-isopropylideneheptanoyl]-4-isopropyl-1,3-oxazolidin-2-one (33). To a −78 °C mixture of **32** (1.15 g, 1.97 mmol) and methyl iodide (1.97 g, 13.9 mmol) in dry THF (7 mL) under N_2 was added a 1.0 M solution of lithium hexamethyldisilazide (2.37 mL, 2.37 mmol) in THF over a 30-

min period. The reaction mixture was allowed to warm to 0°C over 3 h, diluted with brine, and extracted with Et_2O (3 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. ^1H NMR analysis of the crude product indicated **33** was the major product of a 97:3 mixture. Separation of this mixture by chromatography (3:1 hexane–ether as eluent) yielded 1.03 g (88%) of **33** along with 0.77 g (6%) of a ca. 1:1 mixture of **33** and the minor diastereomer: R_f 0.27 (2:1 hexane–ether); $[\alpha]^{26}_D$ +29.4° (*c* = 1.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4 H), 7.45–7.34 (m, 6 H), 4.30 (m, 1 H), 4.15 (d, *J* = 5.4 Hz, 2 H), 4.08 (q, *J* = 6.4 Hz, 1 H), 3.85 (dd, *J* = 8.1, 6.3 Hz, 1 H), 3.77 (dd, *J* = 5.6, 2.6 Hz, 1 H), 3.68 (dd, *J* = 8.1, 7.1 Hz, 1 H), 3.59 (m, 1 H), 2.29 (m, 1 H), 1.65 (m, 1 H), 1.54 (m, 1 H), 1.38 (m, 1 H), 1.27 (s, 6 H), 1.06 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 7.0 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H), 0.83 (d, *J* = 7.0 Hz, 3 H); IR (CH_2Cl_2) 1778, 1696 cm^{-1}; HRMS for $C_{27}H_{34}NO_5Si$ ($M^+ - C_7H_{15}O$) calcd 480.2210, found 480.2248. Anal. Calcd for $C_{34}H_{49}NO_6Si$: C, 68.53; H, 8.29. Found: C, 68.74; H, 8.48.

(2′*S*,4*S*,4′*S*,5′*S*)-3-[5′-[(*tert*-Butyldiphenylsilyl)oxy]-7′-dibromo-2′,4′-dimethylhept-6′-enoyl]-4-isopropyl-1,3-oxazolidin-2-one (34). A solution of **33** (1.90 g, 3.19 mmol) in 40% aqueous HOAc (16 mL) was heated to 98 °C for 20 min before THF (4 mL) was added. This solution was stirred 3 h before being cooled to room temperature and extracted with EtOAc (2 × 50 mL). The aqueous layer was cooled to 5 °C, neutralized to pH 7 with saturated aqueous $NaHCO_3$, and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to ca. 10% of the original volume. Purification of this crude mixture by silica gel chromatography (2-in. pad of 70–230 mesh) (gradient elution: 3:1 → 8:1 ether–hexane) gave 1.76 g (99%) of intermediate diol: R_f 0.09 (4:1 ether–hexane); $[\alpha]^{26}_D$ +36.2° (*c* = 4.7, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.65 (m, 4 H), 7.45–7.36 (m, 6 H), 4.32 (m, 1 H), 4.19–4.09 (m, 2 H), 3.73–3.57 (m, 5 H), 2.30 (m, 1 H), 2.22 (d, *J* = 5.9 Hz, 1 H), 1.76 (m, 1 H), 1.68–1.58 (br s, 2 H, OH), 1.54 (m, 1 H), 1.07 (s, 9 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 7.2 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H); IR (CH_2Cl_2) 3580, 1778, 1699 cm^{-1}; HRMS for $C_{29}H_{40}NO_4Si$ ($M^+ - C_2H_5O_2$) calcd 494.2722, found 494.2723. Anal. Calcd for $C_{31}H_{45}NO_6Si$: C, 66.99; H, 8.16. Found: C, 66.77; H, 8.21.

A mixture of the above diol (1.31 g, 2.36 mmol) and $NaIO_4$ (1.31 g, 6.14 mmol) in 10% aqueous THF (50 mL) was stirred at 25 °C for 16 h under N_2. The precipitated salts were filtered through Celite and washed with $CHCl_3$ (3 × 25 mL). The aqueous layer was separated and extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. This produced 1.18 g (96%) of a crude aldehyde that was used in the next step without purification: R_f 0.31 (2:1 hexane–ether); $[\alpha]^{26}_D$ +27.1° (*c* = 3.0, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.60 (d, *J* = 2.0 Hz, 1 H), 7.64–7.60 (m, 4 H), 7.46–7.35 (m, 6 H), 4.37 (m, 1 H), 4.23 (dd, *J* = 8.2, 8.2 Hz, 1 H), 4.16 (dd, *J* = 9.1, 2.9 Hz, 1 H), 3.87 (dd, *J* = 3.5, 1.6 Hz, 1 H), 3.63 (m, 1 H), 2.30 (m, 1 H), 1.94 (m, 1 H), 1.66 (m, 1 H), 1.49 (m, 1 H), 1.12 (s, 9 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H), 0.84 (d, *J* = 7.0 Hz, 3 H); IR (neat) 1778, 1731, 1695 cm^{-1}; HRMS for $C_{30}H_{42}NO_5Si$ (M^+ + H) calcd 524.2821, found 524.2815.

A solution of this aldehyde (1.18 g, theoretically 2.25 mmol) in CH_2Cl_2 (10 mL; the solution was predried over Linde 4-Å molecular sieves (1.0 g)) as slowly added via cannula (30 min) to a 0 °C solution of triphenylphosphine (7.43 g, 28.3 mmol) and carbon tetrabromide (4.78 g, 14.2 mmol) in CH_2Cl_2 (60 mL) under N_2. The mixture was stirred for 30 min before being diluted with cold EtOAc (100 mL). The resulting precipitate was filtered through Celite and washed repeatedly with EtOAc. The combined filtrates were concentrated in vacuo and the crude product was purified by silica gel chromatography (2:1 hexane–ether as eluent) giving 1.41 g (86% yield from **33**) of dibromo olefin **34**: R_f 0.41 (2:1 hexane–ether); $[\alpha]^{26}_D$ +27.4° (*c* = 2.7, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4 H), 7.44–7.35 (m, 6 H), 6.39 (d, *J* = 8.3 Hz, 1 H), 4.40 (m, 1 H), 4.25–4.16 (m, 3 H), 3.72 (m, 1 H), 2.34 (m, 1 H), 1.71 (m, 1 H), 1.45 (t, *J* = 7.1 Hz, 2 H), 1.08 (d, *J* = 6.8 Hz, 3 H), 1.06 (s, 9 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.85 (d, *J* = 7.0 Hz, 3 H); IR ($CHCl_3$) 1777, 1699 cm^{-1}; HRMS for $C_{27}H_{32}NO_4SiBr_2$ ($M^+ - C_4H_9$) calcd 620.0458, found 620.0443. Anal. Calcd for $C_{31}H_{41}NO_4SiBr_2$: C, 54.78; H, 6.08. Found: C, 54.38; H, 6.02.

(2*S*,4*S*,5*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-7-dibromo-2,4-dimethyl-6-heptenal (35). To a −50 °C solution of dibromo olefin **34** (0.80 g, 1.18 mmol) in anhydrous CH_2Cl_2 (14 mL) under N_2 was slowly added (2 h) a 1.0 M solution of DIBAL-H in CH_2Cl_2 (4.7 mL, 4.7 mmol). The solution was allowed to warm to −10 °C and stirred for 16 h before being diluted with EtOAc (100 mL) and saturated aqueous Rochelle's salt (50 mL). The aqueous layer was separated, saturated with NaCl, and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (1:1 hexane–ether as eluent) yielded 0.37 g (57%) of the desired aldehyde **35** along with 0.22 g (34%) of the corresponding primary alcohol that was oxidized via the Swern protocol described below.

To a −78 °C solution of oxalyl chloride (53 μL, 0.59 mmol) and DMSO (62 μL, 0.79 mmol) in anhydrous CH_2Cl_2 under N_2 was added a solution of the primary alcohol (0.22 g, 0.397 mmol) in anhydrous CH_2Cl_2 (1 mL). This mixture was stirred for 30 min at −78 °C before Et_3N (0.25 mL, 1.79 mmol) was added. The reaction mixture was allowed to warm to 25 °C over a 1-h period before being diluted with Et_2O (10 mL) and poured into 50% aqueous brine. The aqueous layer was extracted with Et_2O (3 × 10 mL). The combined ethereal layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (1:1 hexane–ether as eluent) produced 0.19 g (87%) of aldehyde **35**. Overall, 0.56 g of **35** was obtained for the two steps from **34** (86% overall yield): R_f 0.52 (2:1 hexane–ether); $[\alpha]^{26}_D$ −4.0° (*c* = 3.9, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 9.50 (d, *J* = 1.6 Hz, 1 H), 7.67–7.62 (m, 4 H), 7.46–7.36 (m, 6 H), 6.41 (d, *J* = 8.6 Hz, 1 H), 4.23 (dd, *J* = 8.6, 4.9 Hz, 1 H), 2.24 (m, 1 H), 1.74 (m, 1 H), 1.43 (m, 1 H), 1.25 (m, 1 H), 1.07 (s, 9 H), 0.96 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 7.0 Hz, 3 H); IR (neat) 2705, 1721, 1610 cm^{-1}; HRMS for $C_{21}H_{24}O_2SiBr_2$ ($M^+ - C_4H_9$) calcd 493.9905, found 493.9927.

Data for the intermediate primary alcohol: R_f 0.36 (1:1 hexane–ether); $[\alpha]^{26}_D$ −12.3° (*c* = 2.3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.62 (m, 4 H), 7.46–7.36 (m, 6 H), 6.42 (d, *J* = 8.6 Hz, 1 H), 4.19 (dd, *J* = 8.6, 4.8 Hz, 1 H), 3.30 (m, 2 H), 1.74 (m, 1 H), 1.59–1.52 (m, 2 H), 1.38 (br s, 1 H, OH), 1.18 (m, 1 H), 1.07 (s, 9 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 0.77 (d, *J* = 6.8 Hz, 3 H); HRMS for $C_{21}H_{25}O_2SiBr_2$ ($M^+ - C_4H_9$) calcd 494.9983, found 494.9972. Anal. Calcd for $C_{25}H_{34}O_2SiBr_2$: C, 54.15; H, 6.18. Found: C, 54.40; H, 6.32.

Synthesis of the Dioxinone–Phosphonate Reagent 23.[28] To a −20 °C of diisopropylamine (3.98 mL, 28.4 mmol) in anyydrous THF (50 mL) under N_2 was aded a 2.5 M solution of *n*-BuLi in THF (11.3 mL, 28.2 mmol). The reaction was allowed to warm to 0 °C and stirred for 30 min before being recooled to −78 °C. A solution of dioxinone **22**[26] (4.0 g, 25.6 mmol) in anhydrous THF (30 mL) was then added dropwise over a 30-min period. Diethoxy chloro phosphite (5.30 g, 30.7 mmol) was added 15 min later, and the reaction was allowed to warm to 25 °C over a 1-h period. Anhydrous benzene (100 mL) was then added, and the reaction mixture was concentrated in vacuo to ca. 20% of its original volume. This solution was recooled to 5 °C and treated with 30% aqueous H_2O_2 (20 mL) for 30 min. The aqueous layer was separated, saturated with NaCl, and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (gradient elution: 2:1 hexane–ethyl acetate → 2:1 ethyl acetate–hexane → ethyl acetate) provided 6.27 g (84%) of the known[28] phosphonate **23**: R_f 0.12 (4:1 ethyl acetate–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, *J* = 4.0 Hz, 1 H), 4.19–4.07 (m, 4 H), 2.76 (dq, *J* = 24.4, 7.5 Hz, 1 H), 1.70 (s, 6 H), 1.46–1.25 (m, 9 H).

(1′*E*,3′*S*,5′*S*,6′*S*)-6-[6′-[(*tert*-Butyldiphenylsilyl)oxy]-8′-dibromo-1′,3′,5′-trimethylocta-1′,7′-dienyl]-2,2-dimethyl-1,3-dioxin-4-one (38). To a 0 °C solution of phosphonate **23** (0.35 g, 0.99 mmol) in anhydrous THF (3 mL) under N_2 was added a 1.0 M solution of lithium hexamethyldisilazide in THF (0.96 mL, 0.96 mmol). This mixture was stirred for 10 min before a solution of aldehyde **35** (0.35 g, 0.63 mmol) in anhydrous THF (3 mL) was added dropwise via cannula. This mixture was stirred for 2 h at 0 °C before being diluted with Et_2O (25 mL) and 50%

aqueous brine. The aqueous layer was extracted with Et_2O (2 × 25 mL). The combined ethereal layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. This provided crude **38** as a 10–11:1 mixture of *E* and *Z* olefin isomers by ^1H NMR analysis. Purification of this material by silica gel chromatography (2:1 hexane–ether as eluent) yielded 0.41 g (94%) of the desired *E* unsaturated dioxinone **38**: R_f 0.37 (1:1 hexane–ether); $[\alpha]^{26}_D$ +30.8° (*c* = 1.9, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4 H), 7.45–7.34 (m, 6 H), 6.39 (d, *J* = 8.4 Hz, 1 H), 6.01 (d, *J* = 9.6 Hz, 1 H), 5.37 (s, 1 H), 4.20 (dd, *J* = 8.9, 4.5 Hz, 1 H), 2.51 (m, 1 H), 1.74 (m, 1 H), 1.67 (s, 3 H), 1.66 (s, 3 H), 1.70 (d, *J* = 3.2 Hz, 3 H), 1.37 (m, 1 H), 1.05 (s, 9 H), 1.02 (m, 1 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H); IR (neat) 1721 (br), 1635 cm^{-1}; HRMS for $C_{29}H_{33}O_4SiBr_2$ ($M^+ - C_4H_9$) calcd 631.0505, found 631.0495. Anal. Calcd for $C_{33}H_{42}O_4SiBr_2$: C, 57.39; H, 6.13. Found: C, 57.58; H, 6.16.

(1′*E*,7′*Z*,9′*E*,11′*E*)-(3′*S*,5′*S*,6′*S*)-6-[8′-Bromo-6′-[(*tert*-butyldiphenylsilyl)oxy]-13′-hydroxy-1′,3′,5′,11′-tetramethyltrideca-1′,7′,9′,11′-tetraenyl]-2,2-dimethyl-1,3-dioxin-4-one (19). To a 25 °C solution containing vinylboronic acid **39** (21 mg, 0.15 mmol) and 10% aqueous TlOH (0.30 mL) in anhydrous THF (0.1 mL) under N_2 was added a premixed solution (30–45 min) of dioxinone **38** (50 mg, 0.10 mmol) and tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) in degassed anhydrous THF (0.4 mL). The reaction mixture was stirred for 10 min, diluted with EtOAc (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (1:3 hexane–ether as eluent) yielded 49 mg (86%) of tetraene **19**: R_f 0.15 (1:3 hexane–ether); $[\alpha]^{26}_D$ −17.8° (*c* = 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.62 (m, 4 H), 7.41–7.28 (m, 6 H), 6.48 (d, *J* = 12.7 Hz, 1 H), 6.11 (d, *J* = 9.3 Hz, 1 H), 5.97 (d, *J* = 12.7 Hz, 1 H), 5.91 (d, *J* = 8.8 Hz, 1 H), 5.78 (t, *J* = 6.5 Hz, 1 H), 5.35 (s, 1 H), 4.62 (dd, *J* = 9.3, 4.2 Hz, 1 H), 4.31 (d, *J* = 6.5 Hz, 2 H), 2.58 (m, 1 H), 1.80 (s, 3 H), 1.69 (br s, 6 H), 1.66 (s, 3 H), 1.65 (m, 1 H), 1.42 (m, 2 H), 1.04 (s, 9 H), 0.96 (d, *J* = 7.0 Hz, 3 H), 0.85 (d, *J* = 7.3 Hz, 3 H); IR ($CHCl_3$) 3610, 3450 (broad), 1720, 1642, 1600 cm^{-1}; HRMS for $C_{35}H_{42}O_5SiBr$ ($M^+ - C_4H_9$) calcd 649.1985, found 649.1984. Anal. Calcd for $C_{39}H_{51}O_5SiBr \cdot H_2O$: C, 64.48; H, 7.30. Found: C, 64.16; H, 7.02.

Synthesis of Hydronaphthalene 41. To a 25 °C solution of dioxinone **19** (30 mg, 0.042 mmol) and chlorobenzyl methyl ether (12 μL, 2 equiv) in anhydrous CH_2Cl_2 (0.4 mL) under N_2 was added i-Pr_2NEt (15 μL, 0.08 mmol). The reaction mixture was stirred for 3 h before solvent was removed in vacuo. Purification of the crude product by silica gel chromatography (2:1 hexane–ether) provided 26 mg (74%) of the pentaene **40**: R_f 0.28 (2:1 hexane–ether); $[\alpha]^{26}_D$ −13.8° (*c* = 2.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.61 (m, 4 H), 7.42–7.28 (m, 11 H), 6.49 (d, *J* = 15.0 Hz, 1 H), 6.10 (d, *J* = 9.7 Hz, 1 H), 5.99 (d, *J* = 15.0 Hz, 1 H), 5.12 (d, *J* = 8.8 Hz, 1 H), 5.75 (t, *J* = 6.7 Hz, 1 H), 5.36 (s, 1 H), 4.78 (s, 2 H), 4.70 (br s, 1 H), 4.62 (s, 2 H), 4.28 (d, *J* = 6.7 Hz, 2 H), 2.56 (m, 1 H), 1.80 (s, 3 H), 1.70 (br s, 6 H), 1.66 (s, 3 H), 1.65–1.59 (m, 1 H), 1.41–1.38 (m, 1 H), 1.05 (s, 9 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.85 (d, *J* = 6.8 Hz, 3 H); IR ($CHCl_3$) 1720, 1645, 1600 cm^{-1}; HRMS for $C_{44}H_{55}O_6SiBr$ ($M^+ - C_3H_6O_2$) calcd 752.2896, found, 752.2838.

A solution of **40** (26 mg, 0.023 mmol) and a large excess of anhydrous methanol (5 μL, 0.11 mmol) in anhydrous toluene (300 μL) containing 4-Å molecular sieves was heated to 110–114 °C under N_2 for 16 h before being cooled to room temperature and concentrated in vacuo. Separation of the crude product by preparative TLC (silica gel, 1:1 hexane–ether) provided 14 mg (60%) of β-keto ester cycloadduct **41**: R_f 0.28 (1:1 hexane–ether); ^1H NMR (400 MHz, $CDCl_3$, a 3:1 mixture of keto and enol tautomers) δ 7.76–7.62 (m, 4 H), 7.42–7.27 (m, 11 H), 6.02 (br d, *J* = 5.6 Hz, 1 H), 5.40 (t, *J* = 7.3 Hz, 1 H), 4.74 (s, 2 H), 4.62 (s, 2 H), 4.26 (br s, 1 H), 4.15 (dd contains A of AB, *J* = 12.9, 7.1 Hz, 1 H), 4.00 (dd, contains B of AB, *J* = 12.9, 5.2 Hz, 1 H), 3.66 (s, 3 H), 3.58 (A′ of A′B′, *J* = 16.9 Hz, 1 H), 3.39 (B′ of A′B′, *J* = 16.9 Hz, 1 H), 2.42 (m, 2 H), 2.10 (t, *J* = 10.2 Hz, 1 H), 1.63–1.51 (m, 4 H), 1.51 (s, 3 H), 1.23 (s, 3 H), 1.11 (s, 9 H), 0.93 (br d, *J* = 7.0 Hz, 3 H), 0.53 (br d, *J* = 6.9 Hz, 3 H); ^1H NMR (400 MHz, $CDCl_3$) (enol) δ 7.76–7.62 (m, 4 H), 7.42–7.27 (m, 11 H), 6.04 (br d, *J* = 5.5 Hz, 1 H), 5.38 (t, *J* = 7.3 Hz, 1 H), 5.12 (s, 1 H), 4.70 (s, 2 H), 4.61 (s, 2 H), 4.26 (br s, 1 H), 4.15 (dd contains A of AB, *J* = 12.9, 7.1 Hz, 1 H), 4.00 (dd, contains B of AB, *J* = 12.9, 5.2 Hz, 1 H), 3.65 (s, 3 H), 2.61 (m, 1 H), 2.10 (t, *J* = 10.2 Hz, 1 H), 1.63–1.51 (m, 4 H), 1,51 (s, 3 H), 1.24 (s, 3 H), 1.11 (s, 9 H), 0.93 (br d, *J* = 7.0 Hz, 3 H), 0.72 (br d, *J* = 6.9 Hz, 3 H); IR 1745, 1709, 1610 cm^{-1}.

Coupling of Dioxinone 38 and Alcohol 8: Preparation of β-Keto Ester 44. To a 118 °C predried (4-Å sieves, 50 mg) solution of **8** (175 mg, 0.28 mmol) in anhydrous xylene (80 μL) under N_2 was added a solution of dioxinone **38** (108 mg, 0.156 mmol) in anhydrous xylene (50 μL) over a 30-min period. The reaction mixture was stirred an additional 1 h at 118 °C before being cooled to ambient temperature and purified by silica gel chromatography (8:1 hexane–ether). This produced 176 mg (88%) of β-keto ester **44** as well as 2 mg (2%) of methyl ketone **45** [R_f 0.47 (5:1 hexane–ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.61 (m, 4 H), 7.45–7.33 (m, 6 H), 6.39 (dd, *J* = 8.1, 1.0 Hz, 1 H), 6.31 (d, *J* = 8.6 Hz, 1 H), 4.22 (dd, *J* = 8.6, 4.8 Hz, 1 H), 2.54 (m, 1 H), 2.28 (d, *J* = 1.0 Hz, 3 H), 1.75–1.60 (m, 2 H), 1.67 (s, 3 H), 1.40 (m, 1 H), 1.06 (s, 9 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 0.90 (d, *J* = 7.1 Hz, 3 H); HRMS for $C_{25}H_{29}O_2SiBr_2$ ($M^+ - C_4H_9$) calcd 547.0303, found 547.0300]. Data for **44**, a ca. 3:1 mixture of keto and enol tautomers: R_f 0.51 (5:1 hexane–ethyl acetate); $[\alpha]^{26}_D$ +51.7° (*c* = 2.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.62–7.75 (m, 4 H), 7.35–7.50 (m, 6 H), 6.38 (d, *J* = 8.6 Hz, 1 H, keto), 6.37 (d, *J* = 8.6 Hz, 1 H, enol), 6.33 (br d, *J* = 9.6 Hz, 1 H, enol), 6.27 (br d, *J* = 9.4 Hz, 1 H, keto), 5.44 (br d, *J* = 5 Hz, 1 H), 5.28 (d, *J* = 10.2 Hz, 1 H, enol), 5.18 (d, *J* = 9.7 Hz, 1 H, keto), 5.10 (s, 1 H, enol C-H), 4.14–4.26 (m, 2 H), 3.93–4.09 (m, 3 H), 3.72 (s, 3 H, enol), 3.70 (s, 3 H, keto), 3.58 (s, 2 H, keto $OCCH_2CO$), 2.55 (m, 1 H), 2.39 (m, 1 H), 2.21 (m, 1 H), 1.86 (dd, *J* = 12.6, 10.5 Hz, 1 H), 1.68 (br s, 3 H), 1.59 (br s, 3 H), 1.06 (s, 9 H), 1.03 (s, 9 H), 0.96 (d, *J* = 6.7 Hz, 3 H, enol), 0.89 (d, *J* = 6 Hz, 3 H, keto); IR ($CHCl_3$) 1741, 1667 cm^{-1}. Anal. Calcd for $C_{66}H_{90}O_8Si_3Br_2$: C, 63.24; H, 7.08. Found: C, 63.33; H, 6.98.

Synthesis of 46 via Suzuki Coupling of 44 and Vinylboronic Acid 39. To a 25 °C solution of vinylboronic acid **39** (23 mg, 0.16 mmol) and 10% aqueous TlOH (0.26 mL) in anhydrous THF (0.1 mL) under N_2 was added a premixed solution (aged for 30–45 min) of dibromo olefin **44** (80 mg, 0.06 mmol) and tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.03 mmol) in degassed anhydrous THF (0.6 mL). The reaction mixture was stirred for 10 min, diluted with EtOAc (3 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (1:1 hexane–ether as eluent) yielded 53 mg (65%) of tetraene **46** as a mixture of keto and enol tautomers: R_f 0.11 (1:1 hexane–ether); $[\alpha]^{26}_D$ −51.4° (*c* = 1.4, CH_2Cl_2); ^1H NMR exists as a 2:1 mixture with enol (400 MHz, $CDCl_3$) δ 7.76–7.59 (m, 8 H), 7.41–7.29 (m, 12 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 6.26 (d, *J* = 9.4 Hz, 1 H), 5.97 (d, *J* = 16.0 Hz, 1 H), 5.91 (d, *J* = 8.9 Hz, 1 H), 5.77 (t, *J* = 6.7 Hz, 1 H), 5.42 (br s, 1 H), 5.18 (br d, *J* = 9.9 Hz, 1 H), 4.63 (m, 1 H), 4.36 (m, 2 H), 4.18 (m, contains A of AB, 1 H), 4.03 (m, contains B of AB, 1 H), 4.01 (br s, 2 H), 3.75 (s, 3 H), 3.58 (d, A′ of A′B′ d, *J* = 4.2 Hz, 1 H), 3.54 (d, B′ of A′B′, *J* = 4.2 Hz, 1 H), 2.63–1.99 (m, 4 H), 1.81 (br s, 3 H), 1.80–1.33 (m, 4 H), 1.67 (s, 3 H), 1.53 (br s, 3 H), 1.09 (s, 9 H), 1.06 (br s, 12 H), 0.99 (d, *J* = 6.9 Hz, 3 H, 0.89 (s, 9 H), 0.87 (d, *J* = 7.1 Hz, 3 H), 0.04 (s, 6 H); ^1H NMR (400 MHz, $CDCl_3$) (enol) δ 7.76–7.59 (m, 8 H), 7.41–7.29 (m, 12 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 6.26 (d, *J* = 9.4 Hz, 1 H), 5.97 (d, *J* = 16.0 Hz, 1 H), 5.91 (d, *J* = 8.9 Hz, 1 H), 5.77 (t, *J* = 6.7 Hz, 1 H), 5.42 (br s, 1 H), 5.29 (br d, *J* = 9.6 Hz, 1 H), 5.10 (s, 1 H), 4.36 (m, 3 H), 4.18 (m, contains A of AB, 1 H), 4.03 (m, contains B of AB, 1 H), 4.01 (br s, 2 H), 3.77 (s, 3 H), 2.63–1.99 (m, 4 H), 1.81 (br s, 3 H), 1.80–1.33 (m, 4 H), 1.69 (s, 3 H), 1.53 (br s, 3 H), 1.09 (s, 9 H), 1.06 (br s, 12 H), 0.96–0.89 (m, 15 H), 0.04 (s, 6 H); IR (neat) 3420 (br), 1741 (br), 1668 cm^{-1}; MS *m/z* 771 ($M^+ - C_{27}H_{34}BrO_2Si$; substantial fragmentation occurred owing to the molecular weight of **46**).

Attempted Intramolecular Diels–Alder Reaction of 47: Formation of 48 via a Fragmentation–Diels–Alder Sequence. A mixture of **46** (9 mg, 0.007 mmol), Ac_2O (2 μL, 3 equiv), and DMAP (2 mg, 1.5 equiv) in 100 μL of CH_2Cl_2 was stirred for 30 min and then was concentrated in vacuo. The crude product was purified by preparative TLC (2:1 hexane–ether; R_f 0.4) giving 9 mg (95%) of **47** as a mixture of keto and enol tautomers [^1H NMR ($CDCl_3$) δ 6.48 (d, *J* = 14.8 Hz, 1 H),

6.26 (d, J = 9.4 Hz, 1 H), 5.99 (d, J = 14.7 Hz, 1 H), 5.92 (d, J = 8.2 Hz, 1 H), 5.70 (t, J = 6.7 Hz, 1 H), 6.45 (m, 1 H), 5.28 (br d, J = 9.7 Hz, 1 H, enol tautomer), 5.18 (br d, J = 10.5 Hz, 1 H, keto tautomer), 5.10 (s, 1 H, CH of enol), 4.72 (d, J = 7 Hz, 2 H), 4.63 (dd, J = 8.3, 4.3 Hz, 1 H), 4.19 (m, 2 H), 3.95–4.09 (m, 3 H), 3.72 (s, 3 H, enol tautomer), 3.69 (s, 3 H, keto tautomer), 3.60, 3.54 (AB, J = 15 Hz, $COCH_2CO$, keto tautomer), 2.58 (m, 1 H), 2.39 (m, 1 H), 2.22 (m, 1 H), 2.09 (s, 3 H), 2.02 (m, 1 H), 1.87 (m, 1 H), 1.83 (s, 3 H), 1.70–1.80 (m, 2 H), 1.69 (s, 3 H, keto tautomer), 1.65 (s, 3 H, enol tautomer), 1.60 (s, 3 H), 1.05 (s, 9 H), 1.02 (s, 9 H), 0.96 (d, J = 6.7 Hz, 3 H, enol tautomer), 0.88 (d, J = 6.7 Hz, 3 H, keto tautomer)].

A solution of **47** (9 mg, 0.007 mmol) in toluene-d_8 (0.5 mL) in a sealed NMR tube was heated to 110–113 °C for 6 h. ^{1}H NMR analysis at this stage showed that a new product(s) had been formed (a methyl doublet at δ 0.5 characteristic of a cycloadduct was present, but that considerable **47** remained. The NMR tube was heated for an additional 20 h at 110–112 °C (oil bath temperature), at which point no **47** remained. Removal of solvent in vacuo and then separation of the resulting mixture by preparative TLC (2:1 hexane–ether) provided 4 mg (88%) of alcohol **8**, 2 mg (ca. 40%) of acyclic tetraene methyl ketone **49** [NMR (400 MHz, $CDCl_3$, partial listing) δ 7.6–7.7 (m, 4 H), 7.3–7.4 (m, 6 H), 6.45 (d, J = 15 Hz, 1 H), 6.30 (d, J = 9.4 Hz, 1 H), 5.95 (d, J = 15 Hz, 1 H), 5.90 (d, J = 8.3 Hz, 1 H), 5.68 (t, J = 6.7 Hz, 1 H), 4.72 (d, J = 6.7 Hz, 2 H), 4.62 (dd, J = 8.3, 4.6 Hz, 1 H), 2.55 (m, 1 H), 2.25 (s, 3 H), 2.05 (s, 3 H), 1.80 (s, 3 H), 1.65 (s, 3 H), 1.05 (s, 9 H), 0.96 (d, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 3 H); HRMS for $C_{33}H_{41}O_4BrSi$ ($M^+ - C_4H_8$) calcd 608.1957, found 608.1985], and the 3 mg (ca. 50%) of cycloadduct **48**: R_f 0.25 (2:1 hexane–ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.79 (m, 4 H), 7.35–7.45 (m, 6 H), 6.03 (br d, J = 5.6 Hz, 1 H), 5.34 (t, J = 6.2 Hz, 1 H), 4.50 (m, 2 H), 4.25 (m, 1 H), 2.56 (br dd, J = 5.9 Hz, 1 H), 2.41 (d, J = 8.3 Hz, 1 H), 1.07 (s, 3 H), 2.04 (s, 3 H), 2.02 (m, 1 H), 1.53 (s, 3 H), 1.25 (s, 3 H), 1.15 (m, 1 H), 1.11 (s, 9 H), 0.93 (d, J = 7.0 Hz, 3 H). 0.88 (m, 1 H), 0.50 (d, J = 6.5 Hz, 3 H); IR (neat) 1735, 1705 cm^{-1}; HRMS for $C_{37}H_{50}O_4BrSi$ (M^+ + H) calcd 665.2661, found 665.2698.

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Supplementary Material Available: ^{1}H NMR spectra of **35**, **40**, **41**, **46**, **47**, **48**, and **51** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.