Application of the Steric Directing Group Strategy to the Stereoselective Synthesis of the Octahydronaphthalene Substructure of Kijanolide and Tetronolide

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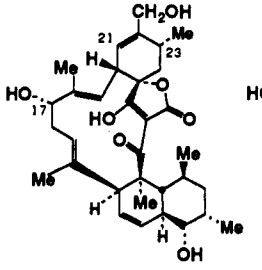
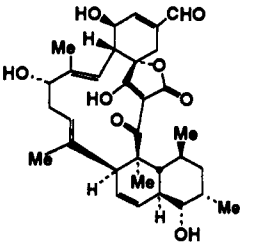
Abstract: A highly stereoselective synthesis of the kijanolide/tetronolide octahydronaphthalene substructure **4** has been completed. The synthesis proceeds in 16 steps from L-glyceraldehyde acetonide (**8**), with 88% stereoselectivity and in 11% overall yield. Key steps are the following: (1) the asymmetric crotylborations of **8** and **12** that introduce the C(5), C(6), and C(8) stereocenters of **4**; (2) the modified Suzuki coupling of vinylboronic acid **36** and dibromo olefin **31** that establishes the conjugated triene unit and introduces the C(9) Br steric directing group in a single operation; and (3) the highly stereoselective intramolecular Diels–Alder cycloaddition of tetraene **7**. Stereochemical information obtained from the intramolecular Diels–Alder reactions of **25** and **26** provides a framework for rationalizing the role of the C(5) acetoxy group and the C(9) Br substituent on the stereoselectivity of the intramolecular Diels–Alder reaction of **7**.

Introduction

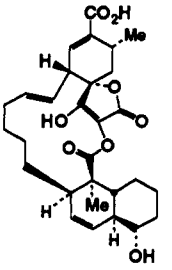
Kijanolide (**1**), tetronolide (**2**), and chlorothricolide (**3**) are the aglycones of a group of structurally related spirotetronate antibiotics. Kijanimicin (cf., kijanolide) is active against an unusual range of microorganisms, including the anaerobic bacterium *Propionibacterium acnes*. In vivo activity against *Plasmodium berghei* and *Plasmodium chabaudin* has also been demonstrated.[2] The tetrocarcins (cf., tetronolide) are antitumor antibiotics,[3] while chlorothricin (cf., chlorothricolide) has activity against Gram-positive bacteria.[4] The structural complexity and biological activity of these compounds have stimulated considerable interest in their synthesis.[5,6] Among a rapidly increasing list of synthetic efforts, the most notable contributions to date are the total syntheses of tetronolide[5m] and 24-*O*-methyl chlorothricolide[6r] completed by Yoshii and co-workers.



kijanolide (**1**)



tetronolide (**2**)



chlorothricolide (**3**)

(1) Taken in part from the Ph.D. Thesis of B. B. Brown, Indiana University, Bloomington, IN, 1992.

(2) (a) Structure: 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. (b) Biological activity: Waitz, J. A.; Horan, A. C.; Kalyanpur, M.; Lee, B. K.; Loebenberg, D.; Marquez, J. A.; Miller, G.; Patel, M. G. *J. Antibiot.* **1981**, *34*, 1101.

(3) (a) Structure: Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2984. (b) Biological activity: Tomita, F.; Tamaoki, T.; Shirahata, K.; Kasai, M.; Morimoto, M.; Ohkubo, S.; Mineura, K.; Ishii, S. *J. Antibiot.* **1980**, *33*, 668. Tomita, F.; Tamaoki, T. *J. Antibiot.* **1980**, *33*, 940. Tamaoki, T.; Kasai, M.; Shirahata, K.; Ohkubo, S.; Morimoto, M.; Mineura, K.; Ishii, S.; Tomita, F. *J. Antibiot.* **1980**, *33*, 946. Tamaoki, T.; Kasai, M.; Shirahata, K.; Tomita, F. *J. Antibiot.* **1982**, *35*, 979.

(4) (a) Structure: Muntwyler, R.; Keller-Schlierlein, W. *Helv. Chim. Acta* **1972**, *55*, 2071. Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Helv. Chim. Acta* **1972**, *55*, 2094. (b) Biological activity: Schindler, P. W. *Eur. J. Biochem.* **1975**, *51*, 579 and references cited therein.

(5) Studies on the synthesis of kijanolide and tetronolide: (a) Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1986**, 1197. (b) Marshall, J. A.; Grote, J.; Shearer, B. *J. Org. Chem.* **1986**, *51*, 1633. (c) Takeda, K.; Urahata, M.; Yoshii, E.; Takayanagi, H.; Ogura, H. *J. Org. Chem.* **1986**, *51*, 4735. (d) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135. (e) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186. (f) Takeda, K.; Kobayashi, T.; Saito, K.; Yoshii, E. *J. Org. Chem.* **1988**, *53*, 1092. (g) Takeda, K.; Yano, S.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951. (h) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. (i) Roush, W. R.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309. (j) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398. (k) Boeckman, R. K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091. (l) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. A. *Tetrahedron Lett.* **1991**, *32*, 4095. (m) Total synthesis of tetronolide: Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Tetrahedron Lett.* **1991**, *32*, 4925. (n) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987. (o) Roush, W. R.; Koyama, K. *Tetrahedron Lett.* **1992**, *33*, 6227.

(6) Studies on the synthesis of chlorothricolide: (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (b) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *J. Org. Chem.* **1981**, *46*, 4863. (c) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (d) Snider, B. B.; Burbaum, B. W. *J. Org. Chem.* **1983**, *48*, 4370. (e) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (f) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5277. (g) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421. (h) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (i) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (j) Marshall, J. A.; Audia, J. E.; Shearer, B. G. *J. Org. Chem.* **1986**, *51*, 1730. (k) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893. (l) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236. (m) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710. (n) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (o) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Tetrahedron Lett.* **1989**, *30*, 2233. (p) Poss, A. J.; Brodowski, M. H. *Tetrahedron Lett.* **1989**, *30*, 2505. (q) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949. (r) Total synthesis of (±)-24-*O*-methylchlorothricolide: Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431. (s) Schmidt, R. R.; Hirsenkorn, R. *Liebigs Ann. Chem.* **1990**, 883. (t) Hirsenkorn, R.; Haag-Zeino, B.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 4433. (u) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192. (v) Roush, W. R.; Sciotti, R. J. *Tetrahedron Lett.* **1992**, *33*, 4691.

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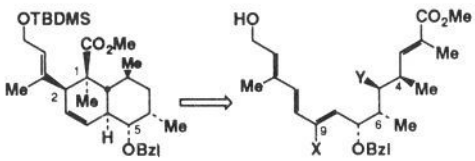
The groups of Yoshii, Marshall, and Boeckman as well as our own have utilized intramolecular Diels–Alder (IMDA) reactions for construction of the bottom half fragments of **1**–**3**.[5,6] Whereas Marshall[5b,e,j] and Yoshii[5c,m] employed Lewis acid catalyzed IMDA reactions of appropriately functionalized undeca-2,8,10-trienals to achieve stereochemical control, our strategy, and initially that of Boeckman as well,[6g] focused on the thermal cyclizations of undeca-2,8,10-trienoates with removable C(9) steric directing groups in order to enhance selectivity for the trans-fused octahydronaphthalene ring systems.[5h,6h,m,u] Boeckman recently reported a synthesis of the tetronolide bottom half substructure via the thermal IMDA reaction of a C(9)-unfunctionalized tetraene related to **5**.[5k]



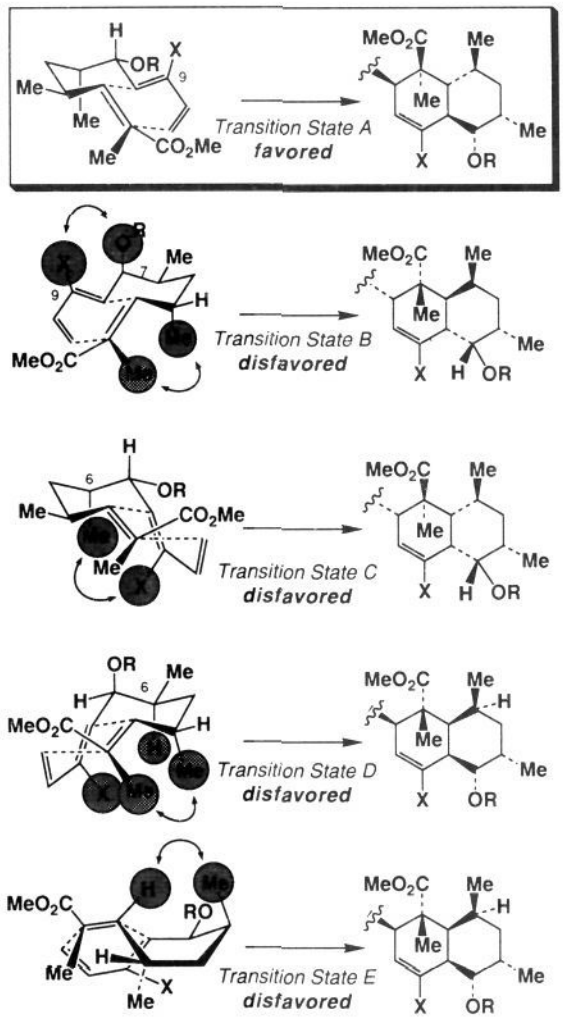
We initially targeted tetraenes **5** and **6** as substrates for IMDA reactions leading to the kijanolide/tetronolide octahydronaphthalene fragment **4**.[5h] Analysis of the chair-like transition states A–D available to **5** (X = H) reveals significant 1,3-allylic strain between the C(2) and C(4) methyl groups in transition states B and D (Scheme I).[7] Thus, transition states B and D should be substantially destabilized relative to A and C. Assuming that the bridging chain adopts a chair-like orientation in the transition state, the interactions indicated between C(9)-H and the axial C(6)-Me should significantly destabilize transition state C. Finally, boat-like transition state E, which has been implicated in the chlorothricolide series,[6u] should be destabilized by the flagpole interactions indicated between C(6)-Me and C(3)-H. We anticipated that, if cyclization were to occur via one of the undesired transition states B–E, these pathways would be further suppressed by application of the steric directing group strategy[6u] by using tetraene **6** with X = Br. An account of our development and application of this strategy to the synthesis of the chlorothricolide octahydronaphthalene unit has been published.[6u]

We provide herein the full details of our stereoselective synthesis of the kijanolide/tetronolide octahydronaphthalene subunit **4**. While we have not prepared the initial targets **5** and **6**, the more highly functionalized surrogate **7** has been synthesized and shown to be an excellent precursor to **4**. A preliminary account of this synthesis has appeared.[5h]

Results and Discussion

The synthesis of **7** commenced with the reaction of L-glyceraldehyde acetonide (**8**)[8] and (*R*,*R*)-tartrate (*E*)-crotylboronate **9**.[9] We have previously described the synthesis of the enantiomer

Scheme I. Analysis of Transition States Available to Trienes **5** and **6**

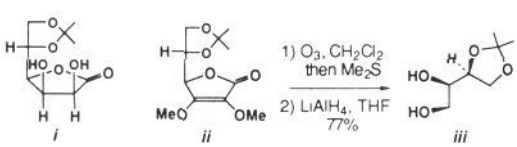


of **10** via the reaction of D-**8** and (*S*,*S*)-**9**.[9a,10] This reaction provided a 96:4 mixture of two diastereomers, from which **10** was obtained in 77% yield following chromatographic purification. Benzylation of **10** (BzlBr, NaH, DMF) provided benzyl ether **11** in 89% yield. Ozonolysis of **11** in MeOH and reduction of the intermediate α-methoxy hydroperoxide with Me_2S provided aldehyde **12**, which was treated with (*R*,*R*)-tartrate (*Z*)-crotylboronate **13** at −78 °C in toluene.[9] HPLC and ^1H NMR analyses of the crude reaction mixture established the presence of three diastereomers in a ratio of 94:5:1, as shown in Table I. The major 3,4-syn-4,5-anti-5,6-anti-6,7-syn diastereomer **14** was easily isolated by silica gel chromatography in 73% overall yield from **11**.

The minor diastereomers produced in the (*Z*)-crotylboronation of **12** were identified as **15** and **16**, respectively, by comparison of HPLC retention times with those of authentic samples prepared by the asymmetric crotylborations of **12** with (*S*,*S*)-**9** and (*S*,*S*)-**13**, respectively. The stereochemical assignments for **14** and **15** were confirmed subsequently by the stereochemical analyses of cycloadducts **37** and **44** obtained from the intramolecular Diels–Alder reactions of **7** and **26** (vide supra) and are in complete

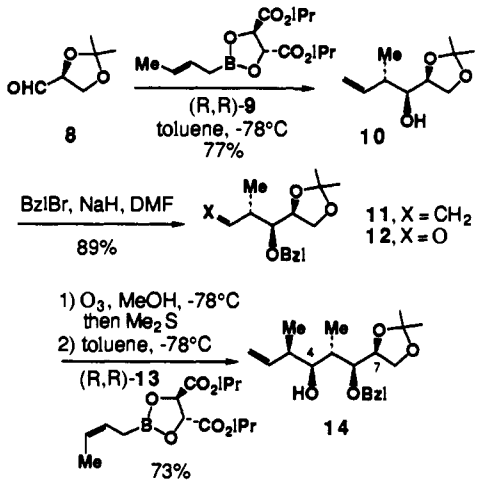
(7) Reviews of allylic strain: (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

(8) (*S*)-Glyceraldehyde acetonide **8** was prepared from L-ascorbic acid by two different routes. (a) L-Gulono-1,4-lactone **i** was synthesized from L-ascorbic acid according to Hubschwerlen's procedure (Hubschwerlen, C. *Synthesis* **1986**, 962), lactone **i** is now commercially available (Aldrich Chemical Co.). Cleavage of **i** with $NaIO_4$ as described provides (*S*)-glyceraldehyde acetonide. (b) (*S*)-Glyceraldehyde acetonide was also prepared by using Boeckman's modification of Jung's synthesis of (*S*)-glycerol acetonide (Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304). Thus, ozonolysis of **ii** followed by reduction of the resulting diester with $LiAlH_4$ provided **iii** in 77% yield. Cleavage of diol **iii** with $Pb(OAc)_4$ then provided **8**. We thank Prof. Boeckman for providing experimental details (Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. W.; Sato, R. I. *J. Org. Chem.* **1983**, *48*, 4152).



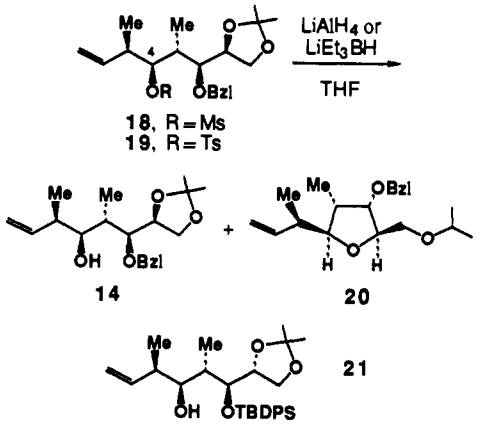
(9) (a) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117. (d) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339. (e) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(10) (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (b) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422.

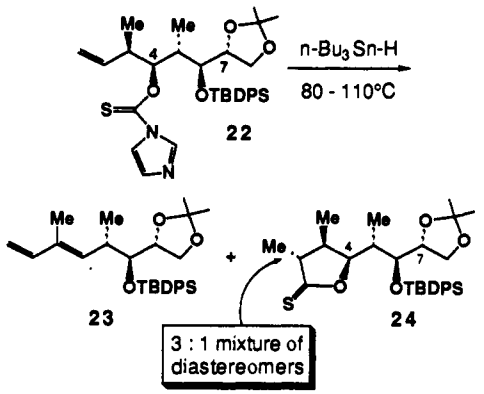


agreement with the known diastereo- and enantioselectivity of the tartrate crotylboronates **9** and **13**.[9]

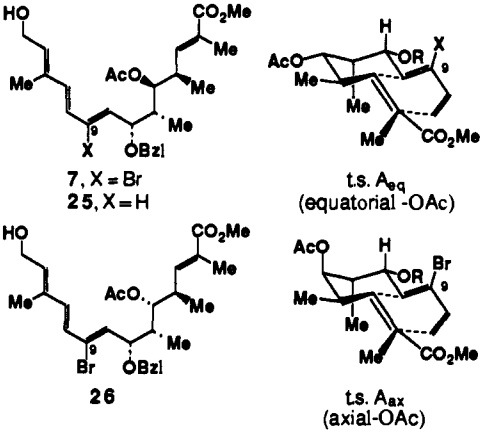
Our plan at this point was to remove the extraneous C(4) hydroxyl group from either **14** or **15**.[11] Mesylate (**18**) and tosylate (**19**) derivatives were prepared (only those deriving from **14** are shown) and subjected to various reducing reagents (i.e., $LiAlH_4$, SuperHydride[12]) under various experimental conditions. The reactions invariably provided mixtures of **14** via reductive cleavage of the sulfonate S–O bond, a 1,3-diene resulting from elimination of the sulfonate, and a compound tentatively identified as **20** that presumably derives from intramolecular displacement of the sulfonate by the C(7) oxygen and reduction of the resulting oxonium ion. Only minor amounts of the desired C(4)-H reduction product were observed. Similar problems were documented by Drozda in attempted reductions of tosylate or mesylate derivatives of **21**.[13]



Attempts to reduce **14**, **15**, and intermediates like **21** from a related series[13] via Barton-type radical deoxygenation procedures were also unsuccessful.[14] For example, treatment of the (alkoxythiocarbonyl)imidazolide derivative **22** (prepared by treatment of **21** with excess thiocarbonyldiimidazole in toluene at reflux)[15] with *n*-Bu_3SnH in toluene at reflux preferentially provided diene **23** via a Chugaev-like elimination.[16] When the reaction was performed with freshly prepared (distilled)[17] *n*-Bu_3SnH (1.0–2.5 equiv) in refluxing benzene (0.1 M), however, γ-thionolactone **24** was obtained in good yield as a 3:1 mixture of C(2) epimers. Addition of $Bu_3Sn^{\bullet}$ to the thiocarbonyl group generates a thioketyl stannyl ether that undergoes a 5-hexenyl radical type cyclization onto the double bond.[18] Related radical cyclization reactions have been described by Yamamoto and co-workers.[14b,19] Although the stereochemistry at C(2) of **24** has not been assigned rigorously, we presume that the trans diastereomer should predominate since interactions between the vinyl and C(3)-Me are minimized in the radical cyclization transition state leading to the trans diastereomer.[19] Radical cyclization products were observed in attempts to reduce thiocarbonyl derivatives of **14** and **15**, although the products in these cases were not rigorously characterized.



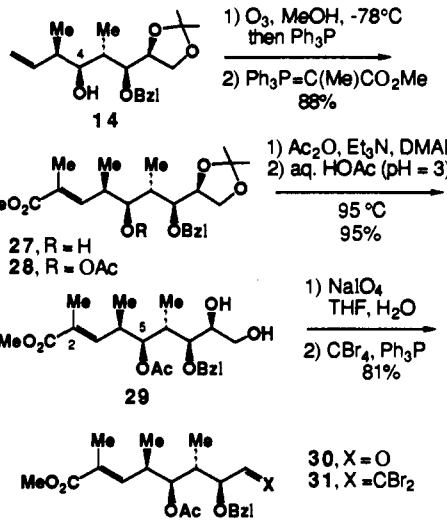
In view of the difficulties encountered in attempts to remove the C(4) hydroxyl group of **14**, **15**, and **21**,[13] we decided to postpone the deoxygenation step until after the intramolecular Diels–Alder reaction. This tactical maneuver, however, introduces additional stereochemical complexity into the synthesis, particularly since the alkoxy substituent could influence the stereoselectivity of the Diels–Alder step. Reexamination of IMDA transition states for tetraenes **7** and **26** reveals that **7**, which would be prepared from homoallylic alcohol **14**, can cyclize via transition state A_{eq} with the C(5) alkoxy group in an equatorial position. In contrast, cyclization of the C(5)-epimeric tetraene **26**, which would be accessible from **15**, would require the C(5) alkoxy group to occupy an axial position. We therefore elected to pursue tetraene **7** as the key intermediate of the modified approach.



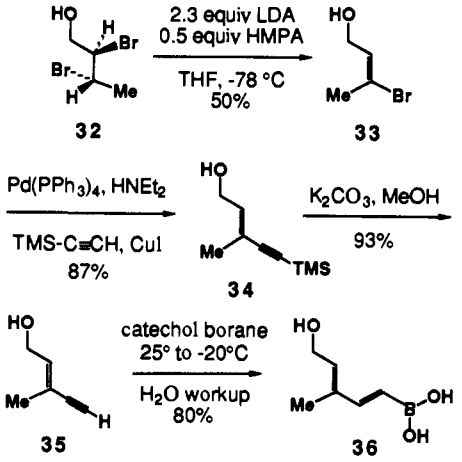
Ozonolysis of **14** provided a crude aldol that was immediately treated with $Ph_3P{=}C(Me)CO_2Me$ in toluene at 45 °C. This sequence provided unsaturated ester **27** in 88% yield. Acetate

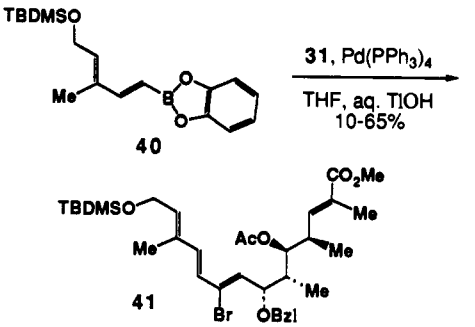
(11) For a review of deoxygenation procedures: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.
(12) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.
(13) These and related studies are described in the M.S. Thesis of S. E. Drozda, Massachusetts Institute of Technology, Cambridge, MA, 1987.
(14) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.
(15) Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.
(16) (a) Nace, H. R. *Org. React.* **1962**, *12*, 57. (b) Saunders, W. H.; Cockerill, A. F. *Mechanisms of Elimination Reactions*; Wiley-Interscience: London, 1973; p 105.
(17) Hayashi, K.; Iyoda, J.; Shiihara, I. *J. Organomet. Chem.* **1967**, *10*, 81.
(18) For recent reviews of radical cyclization reactions: (a) Curran, D. P. *Synlett* **1991**, 63. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.
(19) (a) Yamamoto, M.; Uruma, T.; Iwasa, S.; Kohmoto, S.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1265. (b) Iwasa, S.; Yamamoto, M.; Kohmoto, S.; Yamada, K. *J. Org. Chem.* **1991**, *56*, 2849.

28 was then prepared under standard conditions, and the acetonide was removed by hydrolysis in aqueous HOAc (pH 3) at 95 °C to give diol **29** in 95% yield. Oxidative cleavage of **29** with sodium periodate in aqueous THF afforded aldehyde **30**, which was then converted into dibromo olefin **31** by using the Corey–Fuchs procedure (Ph_3P, CBr_4, 85% yield).[20]



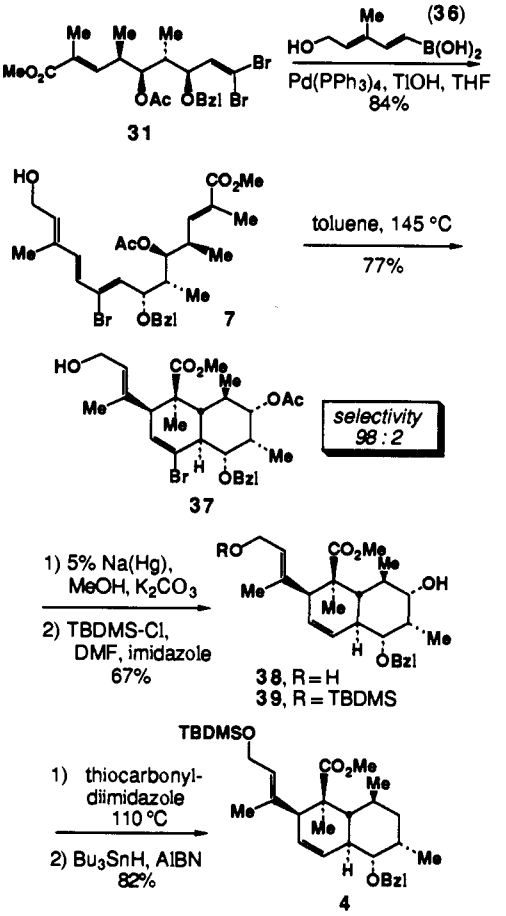
Introduction of the conjugated triene unit of **7** was accomplished by using the modified Suzuki cross-coupling technology[21] developed in our work on the synthesis of chlorothricolide.[6m,u,22] Vinylboronic acid **36** required for this sequence was prepared from *erythro*-2,3-dibromobutanol (**32**),[23] as summarized below. Treatment of **32** with 2.3 equiv of LDA and 0.5 equiv of HMPA in THF at −78 °C provided (*E*)-3-bromo-2-butenol (**33**) in 50% yield.[24] Coupling of **33** and (trimethylsilyl)acetylene provided **34** in 87% yield.[25] (*E*)-3-Methylpent-2-en-4-ynol (**35**), an intermediate in the large-scale synthesis of vitamin A and which is now commercially available (Aldrich),[26] was then obtained by treatment of **34** with catalytic K_2CO_3 in MeOH (93%). Finally, enyne **35** was treated with freshly distilled catecholborane (2.0





equiv) under N_2 at 0 °C. The viscous solution was stirred at room temperature until a light yellow precipitate formed (4 h) and then was stirred at −20 °C overnight before aqueous workup. This provided the sensitive vinylboronic acid **36** in 80% yield; the efficiency of the hydroboration decreased substantially if it was performed above room temperature.

Treatment of dibromo olefin **31** with 0.2 equiv of $Pd(PPh_3)_4$ and 1.4 equiv each of **36** and aqueous TlOH in THF for 5 min provided tetraene **7** in 75–84% yield. It should be noted that attempts to prepare tetraene **41** via the cross-coupling of dibromo olefin **31** and the TBDMS-protected catechol vinylboronate **40** (prepared from the TBDMS-protected **35**) gave poor results (10–65% yield). Vinylboronate **40** and the corresponding vinylboronic acid are more difficult to purify than **36**, and the variability of the yield of **41** reflects the quality of different batches of **40**. In addition, **41** was not easily separated from unreacted **31** since both compounds have comparable chromatographic properties. Therefore, it proved advantageous to perform the cross-coupling with vinylboronic acid **36** as described above.



The IMDA reaction was performed by heating a toluene solution of **7** in a resealable Carius tube at 145 °C under argon for 17 h. Careful analysis of the 300-MHz ^1H NMR spectrum of the crude reaction mixture indicated that the selectivity for **37**, subsequently isolated in 77% yield, was at least 98:2. A very small

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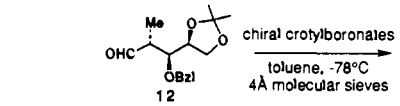
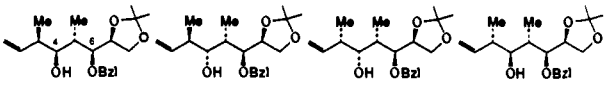
(22) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.
(23) Prepared in 92% yield by bromination of *trans*-crotyl alcohol: Schlosser, M.; Hammer, E. *Helv. Chim. Acta* **1974**, *57*, 2547.
(24) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipshutz, B. *Tetrahedron Lett.* **1978**, 1051.
(25) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.
(26) (a) Schwieter, U.; Saucy, G.; Montavon, M.; von Planta, C.; Rüegg, R.; Isler, O. *Helv. Chem. Acta* **1962**, *45*, 517. (b) von Planta, C.; Schwieter, U.; Chopard-dit-Jean, L.; Rüegg, R.; Kofler, M.; Isler, O. *Helv. Chem. Acta* **1962**, *45*, 548.

Table I. Asymmetric Crotylborations of **12**[a]



12

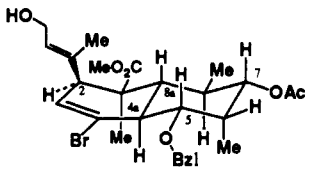


14 **15** **16** **17**

crotylboronate	14	15	16	17
(*R,R*)-**13** (matched case)	94	5	1	
(*S,S*)-**13** (mismatched)	82	3	15	
(*S,S*)-**9** (matched case)	3	86		11
(*R,R*)-**9** (mismatched)	2	57		41

[a] Diastereomer ratios determined by HPLC and ^{1}H NMR.

amount of what appears to be a second cycloadduct (ca. 2% of the total) was detected, but has not been isolated. The stereochemistry of **37** was assigned on the basis of the following coupling constants: $J_{4a,8a} = J_{4a,5} = J_{8,8a} = 10.5$ Hz; $J_{5,6} = 4.8$ Hz; $J_{6,7} = 4.5$ Hz; $J_{7,8} = 11.0$ Hz (see the accompanying three-dimensional structure).

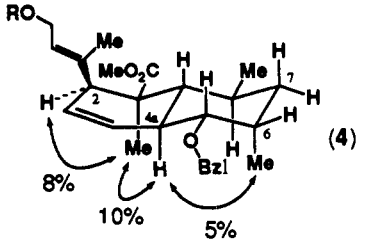


37

$J_{4a,8a}$	= 10.5 Hz
$J_{4a,5}$	= 10.5 Hz
$J_{5,6}$	= 4.8 Hz
$J_{6,7}$	= 4.5 Hz
$J_{7,8}$	= 11.0 Hz
$J_{8,8a}$	= 10.5 Hz

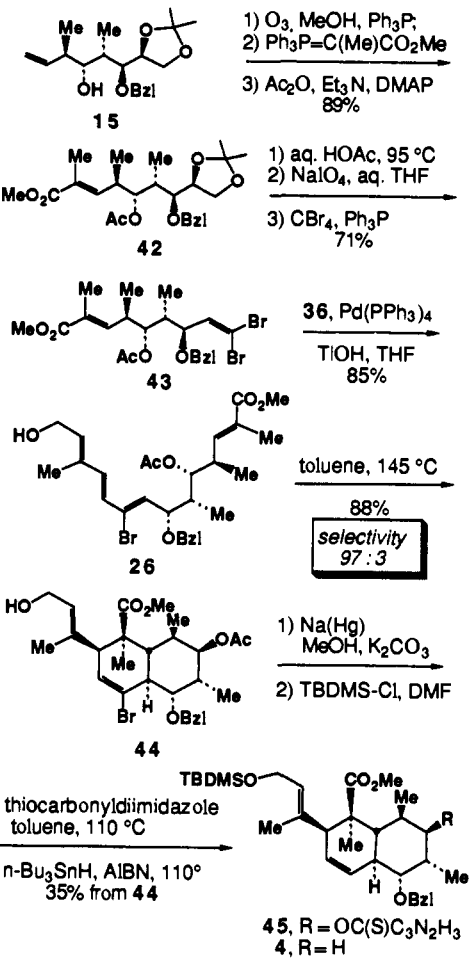
The elaborations of **37** to **4** proceeded without complication. First, **37** was treated with 5% Na(Hg) in methanol for 12 h. The mixture was then filtered and treated with catalytic K_2CO_3. This one-pot sequence provided diol **38** in 83% yield. The primary hydroxyl was then protected as a TBDMS ether (81%). Finally, the secondary hydroxyl group of **38** was removed by using the Rasmussen variant[15] of the Barton deoxygenation.[14] This provided the targeted kijanolide/tetronolide octahydronaphthalene fragment **4** in 55% overall yield from cycloadduct **37**. Overall, the synthesis proceeds in 11% yield for the 16-step sequence from L-glyceraldehyde acetonide (**8**), and the stereoselectivity is 88% d.s.

Although the stereochemistry of the five stereocenters at C(4a), C(5), C(6), C(8), and C(8a) had been assigned in cycloadduct **37**, it remained to verify the stereochemical assignments for the centers at C(1) and C(2). This was accomplished by a series of NOE experiments performed at 500 MHz on octahydronaphthalene **4**.[27] Irradiation of the C(1) methyl group produced an 8% NOE enhancement of the C(2) hydrogen and a 10% enhancement of the C(4a) hydrogen. Irradiation of the C(6) methyl group also led to a 5% enhancement of C(4a)-H. These data are in complete agreement with the assigned structure.

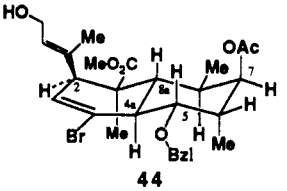


(4)

Although the IMDA reaction of tetraene **7** was highly stereoselective, questions remained as to the influence of the C(9) Br and C(5) acetoxy substituents on the outcome of this reaction. Tetraenes **25** and **26** were synthesized in order to probe these issues.



Tetraene **26**, the C(5) epimer of **7**, was synthesized in 52% overall yield from homoallylic alcohol **15** as summarized in the accompanying diagram. The IMDA reaction of **26** was highly stereoselective and provided cycloadduct **44** in 88% yield as the major component of a 97:3 mixture; we did not isolate the minor product for structural characterization. The stereochemistry of **44** was easily assigned on the basis of coupling constant analysis: $J_{4a,8a} = J_{8,8a} = 10.9$ Hz; $J_{4a,5} = 9.9$ Hz; $J_{5,6} = 5.1$ Hz; $J_{6,7} = J_{7,8} = 2.9$ Hz. Final proof of structure rested on the conversion of **44** to the kijanolide/tetronolide bottom half fragment **4**, which was identical in all respects to the samples prepared from **37**. Thus, the stereochemistry of the C(5) acetoxy substituent has no significant influence on the stereochemistry of these IMDA reactions.



44

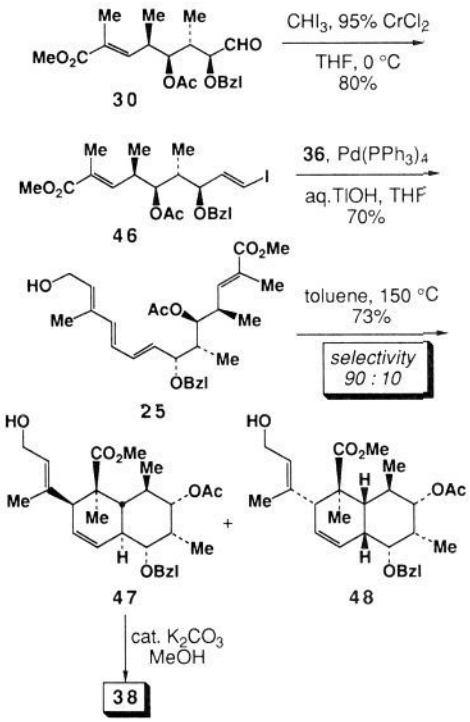
$J_{4a,8a}$	= 10.9 Hz
$J_{4a,5}$	= 9.9 Hz
$J_{5,6}$	= 5.1 Hz
$J_{6,7}$	= 2.9 Hz
$J_{7,8}$	= 2.9 Hz
$J_{8,8a}$	= 10.9 Hz

We next addressed the influence of the C(9) Br substituent on the stereochemistry of the IMDA reactions by synthesizing tetraene **25**. A premixed solution of aldehyde **30** and iodoform was slowly added via cannula to a solution of 95% $CrCl_2$ in THF at 0 °C.[28] This produced vinyl iodide **46** in 80% yield as a 98:2 mixture of olefin isomers. Coupling of **46** and vinylboronic acid **36** under standard conditions ($Pd(PPh_3)_4$, TlOH) yielded tetraene **25** in 70% yield. Thermal cyclization of **25** (150 °C, toluene) then provided a 9:1 mixture of cycloadducts **47** and **48**. The major diastereomer was easily purified and identified as the trans-fused

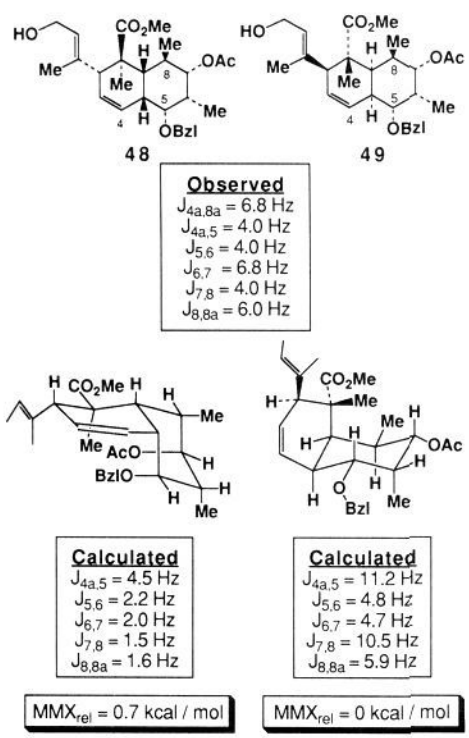
(27) We thank Dr. M. Hampdon-Smith for his assistance with these experiments.

(28) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

cycloadduct **47**, following deacetylation which provided diol **38**. The minor diastereomer, however, required HPLC purification and was assigned structure **48** by a combination of high-field NMR analysis and moelcular mechanics (MMX) calculations.[29]

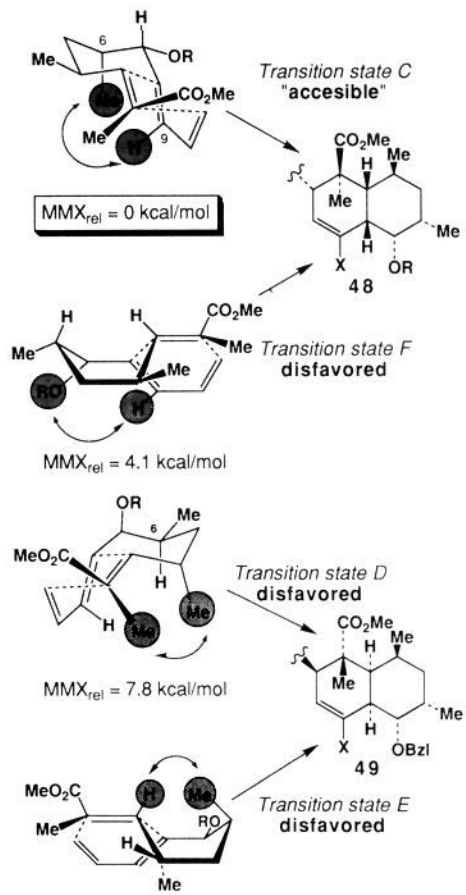


High-field ^{1}H NMR analysis of cycloadduct **48** revealed the following: $J_{4a,8a} = J_{6,7} = 6.8$ Hz; $J_{8a,8} = 6.0$ Hz; $J_{7,8} = J_{5,6} = J_{4a,5} = 4.0$ Hz. The 6.8-Hz coupling constant for $J_{4a,8a}$ defines the ring fusion to be cis. These data, however, did not permit the complete assignment of stereostructure, since Dreiding model analysis of cis-fused diastereomers **48** and **49** showed that each can adopt a conformation in reasonable agreement with the observed coupling constants. We therefore turned to Gajewski's MMX molecular modeling program for assistance with this analysis.[29]



Minimum steric energy structures generated for **48** and **49** are shown in the accompanying diagram. No other structures, including structures with boat conformations, were located within 3 kcal/mol of these minima. Since coupling constants for **48** generated via MMX correlate best with the experimentally determined values, the minor cycloadduct was tentatively assigned structure **48**.

As an alternative means of analysis, MMX steric energy calculations were performed on the four cis-fused transition states available to **25**. Transition states C and F conceivably can lead to **48**, while D and E can generate **49**. A bond order of 0.3 was used to define the C(3)–C(8) and C(2)–C(11) distances in the transition structures.[30] For simplicity, the C(5)–OAc substituent and the C(12)–C(14) segment were omitted. As shown in the accompanying diagram, these calculations suggested that chair-like transition state C is considerably lower in energy than the alternative transition structures D–F. This analysis therefore also supports the tentative assignment of **48** as the minor product of the IMDA reaction of **25**.



A transition state analogous to E has been implicated in the chlorothricolide IMDA series.[6u] The additional substituents on tetraene **25** evidently destabilize boat-like transition states E and F relative to the chair-like transition state C, such that they are

(29) Molecular mechanics calculations were performed by using the MMX PC modification of MM2: Gilbert, K. E.; Gajewski, J. J. Serena Software, P.O. Box 3076, Bloomington, IN, 47402-3076. MMX is derived from MM2 (1977 version QCPE 395) with the VESCF π subroutines from MMP1 (QCPE 318) and includes an internally defined set of transition state atoms for modeling pericyclic transition states.

(30) This value, inferred from Gajewski's Diels–Alder kinetic isotope effect data (Gajewski, J. J.; Peterson, K. B.; Kagel, J. R. *J. Am. Chem. Soc.* **1987**, *108*, 5545), was used because it reproduces Houk's 3-21G structure of the butadiene–ethylene Diels–Alder transition state (Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 4609). We thank Dr. Gajewski for providing these data prior to publication.

inaccessible in the kijanolide/tetronolide series. It is also to be expected on the basis of this analysis that transition state C will be further destabilized in the cyclizations of C(9)-Br-substituted tetraenes **7** and **26**, owing to interactions between the C(9)-Br and C(6)-Me groups. Thus, the C(9) Br steric directing group employed in the IMDA reactions of **7** and **26** evidently functions by shutting down transition state C, which is accessible, albeit marginally (ca. 10%), in the cyclization of **25**.

In summary, a highly stereoselective synthesis of the kijanolide/tetronolide octahydronaphthalene substructure **4** has been completed. Further progress toward the competion of total syntheses of these natural product targets 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 the 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 × 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 × 20 cm plates coated with a 0.25- or 0.5-mm thickness of silica gel containing PF-254 indicator (Analtech). Flash chromatography was performed as described by Still using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh).[31] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (by ^1H NMR analysis) for use in subsequent reactions.

(3*S*,4*S*,5*S*)-4-Hydroxy-5,6-(isopropylidenedioxy)-3-methylhex-1-ene (10). Crude (*R*,*R*)-diisopropyl tartrate (*E*)-crotylboronate **9** [24.6 g, theoretically 82.6 mmol; prepared via the (i-PrO)$_3$B sequence][9d] was dissolved in toluene (300 mL) and treated with powdered 4-Å molecular sieves (2.5 g) under N_2 for 30 min. This dispersion was cooled to −78 °C, and then freshly distilled L-glyceraldehyde acetonide (**8**)[8] (3.58 g, 27.5 mmol) was added as a solution in toluene (21 mL) via cannula over 30 min. The reaction was stirred for an additional 2 h at −78 °C and then allowed to warm to room temperature overnight (15 h). The white slurry was saponified by the addition of aqueous 0.5 N NaOH (200 mL) at 10 °C. The mixture was stirred for an additional 30 min at ambient temperature. The toluene layer was separated and washed with saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated (50 mmHg, 50 °C). The aqueous phase was extracted with Et_2O (4 × 100 mL). The combined ethereal extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), concentrated in vacuo, and combined with the toluene extracts. GC analysis of the crude reaction mixture revealed **10** as the major product (≥96% diastereomeric purity). The minor product (≤4%) was determined to be the 3,4-anti-4,5-anti diastereomer by comparison of GC retention times with those of authentic mixtures.[10b] Purification of the crude product by silica gel chromatography (4:1 hexane–ether) provided 3.95 g (77%) of alcohol **10** ($[\alpha]^{20}_D$ −17.6° (*c* = 2.1, CH_2CH_2)). The enantiomer of **10** has been fully characterized previously.[10]

(3*S*,4*S*,5*S*)-4-(Benzyloxy)-5,6-(isopropylidenedioxy)-3-methylhex-1-ene (11). To a 0 °C solution of **10** (3.0 g, 16.1 mmol) in dry DMF (40 mL) under N_2 was slowly added NaH (0.75 g of a 57% dispersion in oil, 18 mmol). Benzyl bromide (2.0 mL, 17 mmol) was then added over a 30-min period. The reaction mixture was stirred at ambient temeprature for 2 h and then was diluted with brine (50 mL) and extracted with 1:1 Et_2O–hexane (4 × 50 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) produced 3.96 g (89%) of benzyl ether **11** as an oil: R_f 0.31 (5:1 hexane–ether); $[\alpha]^{20}_D$ −13.8° (*c* = 2.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 5.91 (ddd, *J* = 16.5, 10.8, 8.5 Hz, 1 H), 5.01 (dd, *J* = 10.8, 1.6 Hz, 1 H), 4.97 (dd, *J* = 16.5, 1.6 Hz, 1 H), 4.90 (A of AB, J_{AB} = 11.7 Hz, 1 H), 4.64 (B of AB, J_{BA} = 11.7 Hz, 1 H), 4.19 (m, 1 H), 3.99 (dd, *J* = 7.8, 6.0 Hz, 1 H), 3.56 (dd, *J* = 7.8, 7.8 Hz, 1 H), 3.31 (dd, *J* = 7.8, 2.3 Hz, 1 H), 2.17 (m, 1 H), 1.44 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 1.08 (d, *J* = 7.2 Hz, 3 H); IR (neat) 3030, 3025, 1640, 1495 cm^{-1}; MS *m*/*z* 261 ($M^+ - CH_3$); HRMS for $C_{16}H_{21}O_3$ calcd 261.1485, found 261.1490. Anal. Calcd for $C_{17}H_{21}O_3$: C, 73.88; H, 8.75. Found: C, 74.17; H, 8.72.

(3*S*,4*R*,5*S*,6*S*,7*S*)-6-(Benzyloxy)-3,5-dimethyl-4-hydroxy-7,8-(isopropylidenedioxy)oct-1-ene (14). A −78 °C solution of **11** (2.50 g, 9.06 mmol) in dry MeOH (100 mL) was treated with a stream of O_3 in O_2 (by slowly bubbling the O_3/O_2 mixture through the solution) until **11** was no longer detected by TLC analysis (30 min), with care being taken not to oxidize the benzyl ether to the benzoate. The reaction mixture was allowed to warm to room temperature, and then 98% Me_2S (10 mL) was added. The mixture was stirred for 1.5 h and then was partitioned between CH_2Cl_2 (50 mL) and brine solution. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Crude aldehyde **12** so obtained was used in the next experiment without purification: R_f 0.20 (3:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, *J* = 2.3 Hz, 1 H), 7.33 (m, 5 H, aromatic), 4.79 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.64 (B of AB, J_{BA} = 11.3 Hz, 1 H), 4.32 (m, 1 H), 4.05 (dd, *J* = 7.8, 6.2 Hz, 1 H), 3.73 (dd, *J* = 7.8, 7.8 Hz, 1 H), 3.65 (dd, *J* = 6.4, 4.6 Hz, 1 H), 2.53 (m, 1 H), 1.44 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 1.18 (d, *J* = 7.1 Hz, 3 H); MS *m*/*z* 278 (parent ion); HRMS for $C_{16}H_{22}O_4$ calcd 278.1534, found 278.1530.

To a −78 °C solution of **12** (theoretically 9.06 mmol) and powdered 4-Å molecular sieves in dry toluene (20 mL; the mixture was stirred for 15 min at 25 °C) under N_2 was added a −78 °C solution of (*R*,*R*)-diisopropyl tartrate (*Z*)-crotylboronate **13** [2.84 g, theoretically 9.52 mmol; ca. 95% isomeric purity, prepared by the $(MeO)_2BF$ procedure][9c] in anhydrous toluene (125 mL) via cannula. The mixture was stirred for an additional 5 h at −78 °C before being allowed to warm to ambient temperature overnight. The mixture was then cooled to −50 °C, and $NaBH_4$ (1.08 g, 28.5 mmol) was slowly added. The reaction mixture was then brought to 0 °C and diluted with 1 N NaOH (150 mL). The solution was stirred for 2 h, and then the toluene layer was separated, washed with saturated $NaHCO_3$ (50 mL), dried ($MgSO_4$), and concentrated in vacuo (50 mmHg, 50 °C). The aqueous layers were combined and extracted with Et_2O (4 × 50 mL). The ethereal layers were dried (anhydrous $MgSO_4$), concentrated in vacuo, and combined with the toluene extract. HPLC analysis (1:5 ethyl acetate–hexane, 1 mL/min) of the crude product showed a 94:5:1 mixture of **14** (retention time 8.9 min), **15** (retention time 8.0 min), and **16** (retention time 10.1 min). Reference samples of **15** and **16** were prepared by the reactions of **12** with (*S*,*S*)-**9** and (*R*,*R*)-**13**, respectively. Purification of the reaction mixture by silica gel chromatography (4.5:1 hexane–ethyl acetate) provided 2.21 g (73%) of **14**: TLC R_f 0.23 (3:1 hexane–ether); $[\alpha]^{20}_D$ −3.5° (*c* = 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 5.91 (ddd, *J* = 17.2, 11.0, 6.0 Hz, 1 H), 5.11 (dd, *J* = 11.0, 2.0 Hz, 1 H), 5.09 (dd, *J* = 17.2, 2.0 Hz, 1 H), 4.87 (A of AB, J_{AB} = 11.9 Hz, 1 H), 4.66 (B of AB, J_{BA} = 11.9 Hz, 1 H), 4.54 (ddd, *J* = 6.8, 6.8, 6.8 Hz, 1 H), 4.06 (dd, *J* = 8.4, 6.8 Hz, 1 H), 3.68 (dd, *J* = 8.4, 6.8 Hz, 1 H), 3.61 (m, 1 H), 3.50 (dd, *J* = 6.8, 2.7 Hz, 1 H), 2.40 (d, *J* = 3.1 Hz, 1 H), 2.37 (m, 1 H), 1.72 (m, 1 H), 1.44 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 0.96 (d, *J* = 7.4 Hz, 3 H), 0.95 (d, *J* = 7.1 Hz, 3 H); IR (neat) 3500, 1645 cm^{-1}; MS *m*/*z* 335 (M^+ + H); HRMS for $C_{20}H_{31}O_4$ calcd 335.2136, found 335.2175. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.67; H, 8.81.

(3*S*,4*S*,5*S*,6*S*,7*S*)-6-(Benzyloxy)-3,5-dimethyl-4-hydroxy-7,8-(isopropylidenedioxy)oct-1-ene (15). To a −78 °C solution of (*S*,*S*)-diisopropyl tartrate (*E*)-crotylboronate **9** (2.41 g, 8.10 mmol; ca. 96% isomeric purity, prepared via the $FB(OMe)_2$ route)[9c] and powdered 4-Å molecular sieves (3 g) in dry toluene (50 mL) under N_2 was slowly added a solution of aldehyde **12** (theoretically 2.70 mmol; prepared by ozonolysis of **11**) in dry toluene (15 mL) via cannula (30 min). The reaction mixture was stirred for 4 h before being warmed to ambient temperature overnight. The solution was recooled to −50 °C, and $NaBH_4$ (0.2 g, 5.4 mmol) was added. This mixture was allowed to warm to ambient temperature and quenched with 1 N NaOH (14 mL). The toluene layer was separated, washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The combined aqueous layers were extracted with Et_2O (4 × 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. HPLC analysis (1:5 ethyl acetate–hexane, 1 mL/min) showed that the crude product contained an 86:11:3 mixture of **15**, **17**,[33] and **14**, respectively. Purification of this mixture by silica gel

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(33) Partial data for **17**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 5.84 (ddd, *J* = 17.7, 9.1, 6.4 Hz, 1 H), 5.12 (dd, *J* = 9.1, 1.6 Hz, 1 H), 5.09 (d, *J* = 17.7 Hz, 1 H), 4.87 (d, A of AB, J_{AB} = 11.7 Hz, 1 H), 4.66 (d, B of AB, J_{BA} = 11.7 Hz, 1 H), 4.71 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1 H), 4.06 (dd, *J* = 7.5, 7.5 Hz, 1 H), 3.68 (dd, *J* = 7.53, 7.5 Hz, 1 H), 3.61 (dt, *J* = 7.5, 3.3 Hz, 1 H), 3.50 (dd, *J* = 7.5, 2.7 Hz, 1 H), 2.40 (d, *J* = 3.3 Hz, 1 H), 2.37 (m, 1 H), 1.72 (m, 1 H), 1.45 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 0.97 (d, *J* = 1.6 Hz, 3 H), 0.94 (d, *J* = 2.3 Hz, 3 H).

chromatography (4:1 hexane–ether) provided 0.14 g (62%) of homoallylic alcohol **15**: R_f 0.21 (3:1 hexane–ether); $[\alpha]^{20}_D$ −19.2° (c = 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, aromatic), 5.81 (ddd, J = 17.2, 9.1, 7.6 Hz, 1 H), 5.09 (dd, J = 17.2, 1.6 Hz, 1 H), 5.04 (dd, J = 9.1, 1.6 Hz, 1 H), 4.92 (A of AB, J_{AB} = 11.1 Hz, 1 H), 4.60 (B of AB, J_{BA} = 11.1 Hz, 1 H), 4.42 (ddd, J = 7.2, 7.2, 7.2 Hz, 1 H), 3.99 (dd, J = 7.2, 7.2 Hz, 1 H), 3.60 (m, 2 H), 3.51 (dd, J = 7.2, 3.4 Hz, 1 H), 3.28 (s, 1 H), 2.24 (m, 1 H), 1.69 (m, 1 H), 1.46 (s, 3 H, acetonide), 1.40 (s, 3 H, acetonide), 1.01 (d, J = 7.0 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H); IR (neat) 3510, 1645 cm^{-1}; MS m/z 276 ($M^+ - C_3H_6O$); HRMS for $C_{17}H_{24}O_3$ ($M^+ - C_3H_6O$) calcd 276.1713, found 276.1696. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.08; H, 8.95.

(3*S*,4*R*,1′*R*,2′*S*,3′*R*)-4-[2′-[(*tert*-Butyldiphenylsilyl)oxy]-3′,4′-(isopropylidenedioxy)-1′-methylbutyl]-3,4-dimethyl-3-oxacyclopentane-2-thione (24). To a solution of alcohol **21** (120 mg, 0.24 mmol) in anhydrous toluene (4 mL) under N_2 was added thiocarbonyldiimidazole (0.46 g, 2.40 mmol). This mixture was heated to reflux for 14 h before being cooled to room temperature and concentrated in vacuo. Purification of **22** by silica gel chromatography (1:1 hexane–ether as eluent) yielded 90 mg (63%): R_f 0.33 (1:1 hexane–ether); $[\alpha]^{26}_D$ +5.3° (c = 2.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.65–7.60 (m, 5 H), 7.44–7.28 (m, 6 H), 6.95 (s, 1 H), 5.72–5.64 (m, 2 H), 4.91 (dd, J = 12.1, 2.0 Hz, 2 H), 4.17 (m, 1 H), 3.96–3.89 (m, 2 H), 3.62 (t, J = 7.8 Hz, 1 H), 2.62 (m, 1 H), 2.28 (m, 1 H), 1.26 (s, 3 H), 1.22 (s, 3 H), 1.05 (s, 9 H), 1.00 (d, J = 8.1 Hz, 3 H), 0.89 (d, J = 6.1 Hz, 3 H); IR (neat) 1639, 1585, 1525, 1410 (br), 1380 cm^{-1}; HRMS for $C_{33}H_{44}O_4N_2SSi$ (parent ion) calcd 592.2785, found 592.2817. Anal. Calcd for $C_{33}H_{44}O_4N_2SSi$: C, 66.85; H, 7.48. Found: C, 67.06; H, 7.29.

To a solution containing the above imidazolide **22** (30 mg, 0.05 mmol) and AIBN (2 mg, 0.01 mmol) in anhydrous benzene (0.8 mL) under N_2 was added n-Bu_3SnH (21 μL, 0.075 mmol). This mixture was heated to reflux for 3 h before being cooled to 25 °C and concentrated in vacuo. ^1H NMR analysis (400 MHz, $CDCl_3$) of the crude product showed a 3:1 mixture of two diastereomeric thionolactones. Purification of this mixture by silica gel chromatography (gradient elution: hexane → 10:1 hexane–ether) yielded 12 mg (46%) of the major isomer **24**. The minor diastereomer was not isolated. Data for **24**: R_f 0.47 (2:1 hexane–ether); $[\alpha]^{26}_D$ −7.4° (c = 0.8, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4 H), 7.41–7.36 (m, 6 H), 4.65 (dd, J = 11.5, 4.0 Hz, 1 H), 4.37 (dd, J = 8.0, 2.1 Hz, 1 H), 4.21 (q, J = 6.5 Hz, 1 H), 4.06 (dd, J = 8.0, 6.2 Hz, 1 H), 3.80 (dd, J = 8.0, 6.2 Hz, 1 H), 2.76 (m, 1 H), 2.35 (m, 1 H), 1.94 (m, 1 H), 1.30 (s, 3 H), 1.26 (s, 3 H), 1.19 (d, J = 7.0 Hz, 3 H), 1.08 (s, 9 H), 0.94 (d, J = 7.1 Hz, 3 H), 0.32 (d, J = 7.1 Hz, 3 H); IR (neat) 3062, 3041, 2989, 1720, 1592, 1466, 1423, 1378, 1310, 1255, 1212, 1162, 1101, 1054, 954, 922, 860, 829, 801, 733, 702, 605 cm^{-1}; high-resolution mass spectrum for $C_{30}H_{43}O_4SSi$ (M^+ + H) calcd 527.2626, found 527.2639. Anal. Calcd for $C_{30}H_{42}O_4SSi$: C, 68.39; H, 8.04. Found: C, 68.12; H, 8.07.

Methyl (*E*)-(4*S*,5*R*,6*S*,7*S*,8*S*)-7-(Benzyloxy)-5-hydroxy-8,9-(isopropylidenedioxy)-2,4,6-trimethylnon-2-enoate (27). A −78 °C solution of **14** (2.10 g, 6.3 mmol), in dry, degassed MeOH (125 mL) was treated with a stream of O_3 in O_2 until **14** could not be detected by TLC analysis. Care was taken not to oxidize the benzyl ether to the benzoate by letting the reaction proceed too long. The mixture was flushed with N_2 to remove residual O_3, and then triphenylphosphine (2.47 g, 9.4 mmol) was added. The solution was allowed to warm to ambient temperature and stirred for 2 h and then was concentrated in vacuo to give a slurry containing aldehyde, triphenylphosphine, and triphenylphosphine oxide. This mixture was triturated with cold hexane (2 × 50 mL). The combined organic layers were concentrated in vacuo to give the crude aldehyde, which was used directly in the next reaction: R_f 0.20 (1:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.50 (m, 5 H, aromatic), 4.87 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.66 (B of AB, J_{BA} = 11.6 Hz, 1 H), 4.47 (ddd, J = 6.7, 6.7, 6.7 Hz, 1 H), 4.25 (m, 1 H), 4.07 (dd, J = 8.3, 6.7 Hz, 1 H), 3.74 (dd, J = 8.3, 6.7 Hz, 1 H), 3.52 (dd, J = 6.7, 3.1 Hz, 1 H), 3.21 (s, 1 H), 2.43 (m, 1 H), 1.77 (m, 1 H), 1.45 (s, 3 H, acetonide), 1.38 (s, 3 H, acetonide), 1.11 (d, J = 7.0 Hz, 3 H), 0.92 (d, J = 7.2 Hz, 3 H); MS m/z 278 ($M^+ - C_3H_6O$); HRMS for $C_{16}H_{22}O_4$ calcd 278.1512, found 278.1514.

To a 25 °C solution of the aldehyde prepared above (theoretically 6.3 mmol) in dry toluene (50 mL) under N_2 was added [(methoxycarbonyl)ethylidene]triphenylphosphorane (4.37 g, 12.5 mmol) in dry CH_2Cl_2 (10 mL). This solution was warmed to 45 °C and stirred for 12 h. It was then concentrated in vacuo to give a slurry that was dissolved in hexanes (50 mL) and filtered through Celite. Concentration of the filtrate provided crude **27** as a 20:1 mixture of (*E*)- and (*Z*)-olefin isomers (^1H NMR analysis). Purification of this material by silica gel chromatography (4:1 hexane–ether) yielded 2.24 g (88%) of (*E*)-α,β-unsaturated ester **27**: R_f 0.24 (1:1 hexane–ether); $[\alpha]^{20}_D$ −20.2° (c = 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, aromatic), 6.80 (dd, J = 9.1, 1.7 Hz, 1 H), 4.85 (A of AB, J_{AB} = 11.7 Hz, 1 H), 4.64 (B of AB, J_{BA} = 11.7 Hz, 1 H), 4.46 (ddd, J = 6.7, 6.7, 6.7 Hz, 1 H), 4.03 (dd, J = 7.9, 6.7 Hz, 1 H), 3.73 (s, 3 H, ester), 3.69 (dd, J = 7.9, 6.7 Hz, 1 H), 3.54 (ddd, J = 7.6, 4.4, 4.0 Hz, 1 H), 3.47 (dd, J = 6.7, 2.8 Hz, 1 H), 3.02 (d, J = 4.4 Hz, 1 H), 2.64 (m, 1 H), 1.84 (s, 3 H), 1.71 (m, 1 H), 1.44 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 0.99 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 7.0 Hz, 3 H); IR (neat) 3495, 1715, 1645 cm^{-1}; MS m/z 305 ($M^+ - C_5H_9O_2$); HRMS for $C_{18}H_{25}O_4$ calcd 305.1746, found 305.1717. Anal. Calcd for $C_{23}H_{34}O_4$: C, 67.95; H, 8.43. Found: C, 67.91; H, 8.65.

Methyl (*E*)-(4*S*,5*R*,6*S*,7*S*,8*S*)-5-Acetoxy-7-(benzyloxy)-8,9-(isopropylidenedioxy)-2,4,6-trimethylnon-2-enoate (28). To a 25 °C solution of **27** (2.17 g, 5.3 mmol) in dry CH_2Cl_2 (60 mL) was added catalytic DMAP (65 mg, 0.5 mmol), triethylamine (3 mL, 22 mmol), and acetic anhydride (1 mL, 11 mmol). The reaction mixture was stirred for 16 h before being diluted with CH_2Cl_2 (70 mL) and washed with H_2O, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (2:1 hexane–ether) provided 2.28 g (95%) of acetate **28**: R_f 0.22 (2:1 hexane–ether); $[\alpha]^{26}_D$ −7.5° (c = 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 6.53 (dd, J = 9.9, 1.3 Hz, 1 H), 4.97 (dd, J = 6.1, 6.1 Hz, 1 H), 4.66 (s, 2 H), 4.25 (m, 1 H), 3.98 (dd, J = 8.0, 6.4 Hz, 1 H), 3.73 (dd, J = 8.0, 8.0 Hz, 1 H), 3.72 (s, 3 H, ester methyl), 3.30 (dd, J = 5.2, 5.2 Hz, 1 H), 2.95 (m, 1 H), 2.10 (m, 1 H), 2.09 (s, 3 H, acetate methyl), 1.75 (s, 3 H), 1.41 (s, 3 H, acetonide), 1.35 (s, 3 H, acetonide), 1.00 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H); IR (neat) 1740, 1715, 1650 cm^{-1}; MS m/z 433 ($M^+ - CH_3$); HRMS for $C_{24}H_{33}O_7$ calcd 433.2214, found 433.2216. Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.02; H, 8.10.

Methyl (*E*)-(4*S*,5*R*,6*S*,7*S*,8*S*)-5-Acetoxy-7-(benzyloxy)-8,9-dihydroxy-2,4,6-trimethylnon-2-enoate (29). A solution of **28** (2.23 g, 5.0 mmol) in MeOH (12 mL) and dilute aqueous HOAc (50 mL, pH 3.0) was heated to 95 °C for 25 h before being cooled, saturated with NaCl, and extracted with EtOAc (4 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), and filtered. Concentration of the filtrate in vacuo yielded 1.99 g (98%) of diol **29**, which was used in the next experiment without further purification: R_f 0.13 (7:1 ether–hexane); $[\alpha]^{26}_D$ +16.4° (c = 2.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 6.52 (d, J = 9.6 Hz, 1 H), 4.96 (dd, J = 6.1, 6.1 Hz, 1 H), 4.65 (A of AB, J_{AB} = 11.1 Hz, 1 H), 4.44 (B of AB, J_{BA} = 11.1 Hz, 1 H), 3.79 (m, 1 H), 3.71 (s, 3 H, ester methyl), 3.56 (m, 1 H), 3.47 (m, 1 H), 3.41 (dd, J = 6.0, 1.7 Hz, 1 H), 2.90 (m, 1 H), 2.45 (d, J = 9.0, 1 H), 2.24 (m, 1 H), 2.10 (s, 3 H, acetate methyl), 1.98 (dd, J = 8.2, 3.9 Hz, 1 H), 1.82 (s, 3 H), 1.09 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H); IR (neat) 3460, 1740, 1715, 1650 cm^{-1}; MS m/z 409 (M^+ + H); HRMS for $C_{22}H_{33}O_7$ calcd 409.2204, found 409.2235. Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.54; H, 8.05.

Methyl (*E*)-(4*S*,5*R*,6*S*,7*S*)-5-Acetoxy-7-(benzyloxy)-9,9-dibromo-2,4,6-trimethylnona-2,8-dienoate (31). A 25 °C solution of **29** (1.99 g, 4.87 mmol) and $NaIO_4$ (2.71 g, 12.7 mmol) in 10% aqueous THF (80 mL) was stirred for 4 h. The precipitated salts were then 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 1.76 g (95%) of crude aldehyde **30**, which was used in the next step without purification: R_f 0.31 (1:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 9.58 (d, J = 2.8 Hz, 1 H), 7.29 (m, 5 H, aromatic), 6.54 (d, J = 9.4 Hz, 1 H), 5.02 (dd, J = 6.1, 6.1 Hz, 1 H), 4.68 (A of AB, J_{AB} = 12.6 Hz, 1 H), 4.48 (B of AB, J_{BA} = 12.6 Hz, 1 H), 3.72 (s, 3 H, ester methyl), 3.63 (dd, J = 7.7 Hz, 3 H), 0.95 (d, J = 6.9 Hz, 3 H); IR (neat) 1730, 1710 cm^{-1}; mass spectrum m/z 361 ($M^+ - CH_3$).

A solution of aldehyde **30** (1.76 g, 4.7 mmol) in CH_2Cl_2 (9 mL) was dried over 4-Å molecular sieves (1.0 g) and then was slowly added via cannula (30 min) to a 0 °C solution of Ph_3P (15.4 g, 58 mmol) and CBr_4 (9.73 g, 29 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred for 30 min before being diluted with cold Et_2O (100 mL). The mixture was filtered through Celite, and the retained precipitiate was washed repeatedly with Et_2O. The combined filtrates were concentrated in vacuo, and the crude mixture was purified by silica gel chromatography (2:1 hexane–ether), giving 2.12 g (85% from **30**; 81% yield from diol **29**) of dibromo olefin **31** as a light yellow oil: R_f 0.44 (1:1 hexane–ether); $[\alpha]^{26}_D$ +12.4° (c = 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, aromatic), 6.53 (d, J = 10.3 Hz, 1 H), 6.33 (d, J = 8.9 Hz, 1 H), 5.01 (dd, J = 9.5, 3.2 Hz, 1 H), 4.54 (A of AB, J_{AB} = 11.7 Hz, 1 H), 4.45 (B of AB, J_{BA} = 11.7 Hz, 1 H), 4.11 (dd, J = 8.9, 6.8 Hz, 1 H), 3.71 (s, 3 H, ester methyl), 3.02 (m, 1 H), 2.07 (m, 1 H), 2.06 (s, 3 H), 1.75 (s, 3 H), 0.95 (d, J = 7.4 Hz, 3 H), 0.92 (d, J = 7.0 Hz, 3

H); IR (neat) 1735, 1715, 1650, 1615 cm^{-1}; MS m/z 364 ($M^+ - C_9H_9O_3$); HRMS for $C_{13}H_{19}O_2Br_2$ ($M^+ - C_9H_9O_3$) calcd 364.9728, found 364.9716. Anal. Calcd for $C_{22}H_{28}O_5Br_2$: C, 49.64; H, 5.30. Found: C, 49.55; H, 5.20.

(*E*)-3-Bromo-2-buten-1-ol (33).[24] A solution of racemic *erythro*-2,3-dibromobutanol (**32**) (3.0 g, 12.9 mmol) [mp 36 °C, bp 119 °C at 18 mmHg, prepared from *trans*-crotyl alcohol (1.0 g, 14.1 mmol) and bromine (0.72 mL, 14.1 mmol) in 92% yield][23] in anhydrous THF (25 mL) was slowly added via cannula to a −78 °C solution of LDA [prepared using 2.98 M *n*-BuLi in hexane (10.0 mL, 29.7 mmol) and diisopropylamine (4.2 mL, 29.8 mmol)] and 99% hexamethylphosphoric triamide (1.12 mL, 6.47 mmol) in anhydrous THF (45 mL). This mixture was stirred for 2 h before being quenched with H_2O (5.0 mL) and extracted with Et_2O (3 × 50 mL). The combined ethereal extracts were washed with brine and concentrated in vacuo. Purification of the crude product by silica gel chromatography (2:1 hexane–ether) provided 0.99 g (50%) of the known[24] (*E*)-3-bromo-2-buten-1-ol (**33**): bp 102–104 °C at 30 mmHg (lit.[24] bp 92–93 °C at 16 mmHg); R_f 0.13 (5:2 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 6.10, (t, 1 H), 4.11 (d, J = 7.5 Hz, 2 H), 2.31 (s, 3 H), 1.43 (s, 1 H).

(*E*)-5-(Trimethylsilyl)-3-methyl-2-buten-4-yn-1-ol (34). To a 0 °C solution of **33** (2.9 g, 19.2 mmol) in degassed, anhydrous benzene (1.0 M) under N_2 was added diethylamine (3.0 mL, 28.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.45 g, 0.38 mmol). This mixture was stirred for 45 min before 90% (trimethylsilyl)acetylene[32] (4.65 mL, 23.0 mmol; contaminated with 10% *n*-BuCl by ^1H NMR analysis) was added followed by CuI (0.585 g, 3.07 mmol) [purified via Soxhlet extraction with anhydrous THF]. When the exotherm had ceased, the cold bath was removed and the mixture stirred at ambient temperature for 16 h. The mixture was then diluted with Et_2O (100 mL) and washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and brine. The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (gradient elution: hexane → 3:1 hexane–ether) produced 0.72 g (66%; 87% based on recovered **33**) of enyne **34** along with 0.72 g (25%) of recovered **33**. Data for **34**: R_f 0.16 (3:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (qt, J = 6.6, 1.7 Hz, 1 H), 4.21 (t, 2 H), 1.83 (d, J = 1.7 Hz, 3 H), 1.69 (t, 1 H), 0.19 (s, 9 H); IR (neat) 3500 (br), 2145, 1630 cm^{-1}; MS m/z 153 ($M^+ - CH_3$); HRMS for $C_8H_{13}OSi$ calcd 153.0745, found 153.0745.

(*E*)-3-Methylpent-2-en-4-yn-1-ol (35).[26] A 40 °C solution of **34** (0.23 g, 1.33 mmol) and catalytic K_2CO_3 (2.0 mg, 0.02 mmol) in anhydrous MeOH (2 mL) was stirred for 5 h under N_2 before being cooled to room temperature and diluted with Et_2O (25 mL). The organic layer was separated, washed with H_2O and brine, and dried over anhydrous $MgSO_4$. Concentration of the filtrate in vacuo produced a crude product that was purified by silica gel chromatography (2:1 hexane–ether), yielding 0.12 g (93%) of the known alcohol[26] **35**: R_f 0.15 (2:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 6.07 (qt, J = 6.0, 1.6 Hz, 1 H), 4.22 (t, J = 6.0 Hz, 2 H), 2.83 (s, 1 H), 1.83 (d, J = 1.6 Hz, 3 H), 1.47 (t, J = 6.0 Hz, 1 H); MS m/z 96 (parent ion); HRMS for C_6H_8O calcd 96.0581, found 96.0564.

(*E,E*)-(5-Hydroxy-3-methylpenta-1,3-dienyl)boronic Acid (36). Neat acetylene **35** (0.5 g, 5.2 mmol) was placed on a resealable Carius tube and then cooled to 0 °C under Ar. Freshly double-distilled catecholborane (1.1 mL, 10.9 mmol, Aldrich) was then added slowly (25 min), allowing for H_2 evolution. The tube was sealed under Ar and stirred at 25 °C. A light yellow, viscous oil formed after 2 h, and a yellow solid precipitated at 4 h. The reaction was stored at −20 °C for 16 h, after which time **35** had been consumed according to TLC analysis. Addition of cold H_2O (10.0 mL) produced a milky white solution that was stirred for 1 h at 25 °C before being saturated with NaCl and extracted with EtOAc (5 × 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude product by silica gel chromatography (gradient elution: 1:1 hexane–ethyl acetate [to remove catechol] to 95:5 methylene chloride–methanol) provided 589 mg (80%) of the unstable vinylboronic acid **36**: R_f 0.11 (95:5 methylene chloride:methanol); ^1H NMR (300 MHz, CD_3OD) δ 5.41 (d, J = 17.5 Hz, 1 H), 4.19 (t, J = 6.5 Hz, 1 H), 4.15 (d, J = 17.5 Hz, 1 H), 2.67 (d, J = 6.5 Hz, 2 H), 0.23 (s, 3 H); IR ($CHCl_3$) 3400, 1600, 1480 cm^{-1}. The diethanolamine complex was prepared for further characterization: ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, J = 17.6 Hz, 1 H), 5.66 (d, J = 17.6 Hz, 1 H) superimposed on 5.66 (br t, J = 6.5 Hz, 1 H), 4.26 (d, J = 6.5 Hz, 2 H), 4.04 (m, 2 H), 3.94 (m, 2 H), 3.11 (m, 2 H), 2.93 (m, 2 H); HRMS for $C_{11}H_{20}O_3BN$ calcd 225.1526, found 225.1531.

Methyl (*E,Z,E,E*)-(4*S*,5*R*,6*S*,7*S*)-5-Acetoxy-7-(benzyloxy)-9-bromo-14-hydroxy-2,4,6,12-tetramethyltetradeca-2,8,10,12-tetraenoate (7). To a 25 °C solution of vinylboronic acid **36** (32 mg, 0.22 mmol) and 10% aqueous TlOH (0.50 mL) in anhydrous THF (0.1 mL) under N_2 was added a premixed (30–45 min) solution of dibromo olefin **31** (85 mg, 0.16 mmol) and tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.03 mmol) in degassed anhydrous THF (0.4 mL). The reaction mixture was stirred for 5 min and then was diluted with EtOAc (5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (2:1 hexane–ethyl acetate as eluent) yielded 73 mg (84%) of tetraene **7**: R_f 0.18 (1:1 hexane–ethyl acetate); $[\alpha]^{20}_D$ +30.1° (c = 1.6, $CHCl_3$): ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic), 6.70 (d, J = 14.8 Hz, 1 H), 6.58 (dd, J = 10.6, 1.6 Hz, 1 H), 6.22 (d, J = 14.8 Hz, 1 H), 5.87 (d, J = 8.5 Hz, 1 H), 5.85 (t, 1 H), 5.07 (dd, J = 8.9, 3.7 Hz, 1 H), 4.52 (A of AB, J_{AB} = 11.7 Hz, 1 H), 4.50 (dd, J = 8.5, 7.6 Hz, 1 H), 4.39 (B of AB, J_{BA} = 11.7 Hz, 1 H), 3.34 (m, 2 H), 3.72 (s, 3 H, ester methyl), 3.09 (m, 1 H), 2.11 (m, 1 H), 2.04 (s, 3 H, acetate methyl), 1.85 (s, 3 H), 1.80 (s, 3 H), 1.45 (t, 1 H), 0.94 (d, J = 6.8 Hz, 6 H); IR (neat) 3460, 1735, 1710, 1645, 1615 cm^{-1}; MS m/z 381 ($M^+ - C_9H_{12}O_3$); HRMS for $C_{19}H_{25}O_3{}^{79}Br$ ($M^+ - C_9H_{12}O_3$) calcd 381.1080, found 381.1065.

Intramolecular Diels–Alder Reaction of Tetraene 7: Preparation of Methyl 2β-[(*E*)-3-Hydroxy-1-methylprop-1-enyl]-7α-acetoxy-5α-(benzyloxy)-4-bromo-1α,6α,8β-trimethyl-1,2,4aα,5,6,7,8,8aβ-octahydronaphthalene-1β-carboxylate (37). A solution of tetraene **7** (71 mg, 0.13 mmol) in anhydrous toluene (3 mL) was transferred to a resealable Carius tube and purged with N_2 for 10 min. BHT (1.0 mg, 0.006 mmol) was then added, and the tube was sealed under N_2 and heated at 145 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature and then was concentrated in vacuo. ^1H NMR analysis (500 MHz, $CDCl_3$) of the crude product showed a 98:2 mixture of two cycloadducts. Purification of this mixture by silica gel chromatography (2:1 hexane–ethyl acetate) yielded 55 mg (77%) of **37**. The minor product is presumed to be a cycloadduct, but was not isolated. Data for **37**: R_f 0.17 (1:1 hexane–ethyl acetate); $[\alpha]^{20}_D$ −15.6° (c = 1.22, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 6.17 (dd, J = 4.6, 1.7 Hz, 1 H), 5.44 (t, 1 H), 4.63 (dd, J = 10.6, 4.6 Hz, 1 H), 4.60 (A of AB, J_{AB} = 10.5 Hz, 1 H), 4.53 (B of AB, J_{BA} = 10.5 Hz, 1 H), 4.15 (m, 2 H), 3.84 (dd, J = 10.3, 5.1 Hz, 1 H), 3.57 (s, 3 H, ester methyl), 2.73 (m, 1 H), 2.51 (d, J = 4.6 Hz, 1 H), 2.26 (ddd, J = 10.5, 10.3, 1.7 Hz, 1 H), 2.09 (s, 3 H, acetate methyl), 1.99 (dd, J = 10.9, 10.5 Hz, 1 H), 1.93 (m, 1 H), 1.62 (s, 3 H), 1.35 (t, 1 H), 1.25 (s, 3 H), 0.97 (d, J = 7.1 Hz, 3 H), 0.69 (d, J = 6.0 Hz, 3 H); ^1H NMR (300 MHz, C_6D_6) δ 7.25 (m, 5 H, aromatic), 6.21 (dd, J = 4.3, 2.4 Hz, 1 H), 5.32 (t, 1 H), 4.74 (dd, J = 11.0, 4.5 Hz, 1 H), 4.42 (A of AB, J_{AB} = 11.5 Hz, 1 H), 4.30 (B of AB, J_{BA} = 11.5 Hz, 1 H), 3.90 (m, 2 H), 3.77 (dd, J = 10.6, 4.8 Hz, 1 H), 3.21 (s, 3 H, ester methyl), 2.74 (m, 1 H), 2.20 (dd, J = 10.6, 10.5 Hz, 1 H), 2.14 (d, J = 4.3 Hz, 1 H), 2.07 (dd, J = 10.5, 10.5 Hz, 1 H), 1.82 (m, 1 H), 1.73 (s, 3 H, acetate methyl), 1.39 (s, 3 H), 1.08 (s, 3 H), 0.98 (d, J = 7.0 Hz, 3 H), 0.92 (t, 1 H), 0.76 (d, J = 6.4 Hz, 3 H); IR (neat) 3460, 1735, 1720, 1655, 1625 cm^{-1}; MS m/z 451 ($M^+ - H_2O - Br$); HRMS for $C_{28}H_{35}O_5$ ($M^+ - H_2O - Br$) calcd 451.2482, found 451.2482. Anal. Calcd for $C_{28}H_{37}O_6Br$: C, 61.20; H, 6.79. Found: C, 61.22; H, 6.74.

Methyl 2β-[(*E*)-3-Hydroxy-1-methylprop-1-enyl]-5α-(benzyloxy)-7α-hydroxy-1α,6α,8β-trimethyl-1,2,4aα,5,6,7,8,8aβ-octahydronaphthalene-1β-carboxylate (38). To a 25 °C solution of **37** (47 mg, 0.085 mmol) in dry MeOH (2 mL) under N_2 was added 5% Na(Hg) (780 mg, 1.7 mmol based on Na). This solution was stirred for 16 h before being filtered to remove Hg^0. K_2CO_3 (2 mg, 0.014 mmol) was then added, and the mixture was stirred for 1 h before being diluted with EtOAc (10 mL) and washed with H_2O. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by silica gel chromatography (2:1 ether–hexane as eluent) produced 30 mg (83%) of diol **38**: R_f 0.05 (2:1 ether–hexane); $[\alpha]^{26}_D$ −29.1° (c = 1.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 6.14 (d, J = 10.2 Hz, 1 H), 5.47 (m, 1 H), 5.39 (t, 1 H), 4.67 (A of AB, J_{AB} = 11.2 Hz, 1 H), 4.43 (B of AB, J_{BA} = 11.2 Hz, 1 H), 4.11 (m, 2 H), 3.55 (s, 3 H, ester methyl), 3.44 (m, 1 H), 3.32 (dd, J = 10.4, 4.8 Hz, 1 H), 2.70 (m, 1 H), 2.63 (dd, J = 2.0, 2.0 Hz, 1 H), 2.13 (ddd, J = 10.4, 10.0, 1.8 Hz, 1 H), 2.05 (s, 3 H), 1.73 (dd, J = 10.0, 10.0 Hz, 1 H), 1.63 (m, 2 H), 1.57 (s, 4 H), 1.23 (s, 3 H), 1.02 (d, J = 6.5 Hz, 3 H), 0.89 (t, 1 H), 0.80 (d, J = 6.2 Hz, 3 H); IR (neat) 3440, 1730, 1665, 1650, 1605 cm^{-1}; MS m/z 411 ($M^+ - H_2O$); HRMS for $C_{26}H_{35}O_4$ ($M^+ - H_2O$) calcd 411.2558, found 411.2539.

Methyl 2β-[(*E*)-1-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]-prop-1-enyl]-5α-benzyl-7α-hydroxy-1α,6α,8β-trimethyl-1,2,4aα,5,6,7,8,8aβ-octahydronaphthalene-1β-carboxylate (39). To a 25 °C solution of diol **38** (25 mg, 0.058 mmol) in anhydrous DMF (1.0 mL) under N_2 was added imiidazole (8.0 mg, 0.128 mmol) and 97% *tert*-butylchlorodimethylsilane (10 mg, 0.06 mmol). The reaction mixture was stirred for 1 h and then was diluted with 1:1 Et_2O–hexane (10 mL) and extracted with brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by silica gel chromatography (5:1 hexane–ether) produced 25 mg (81%) of **39**: R_f

0.13 (4:1 hexane–ether); $[\alpha]^{20}_D$ −45.6° (*c* = 1.10, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 6.12 (dd, *J* = 10.8, 2.4 Hz, 1 H), 5.46 (m, 1 H), 5.28 (t, 1 H), 4.67 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.42 (B of AB, J_{BA} = 11.3 Hz, 1 H), 4.13 (m, 2 H), 3.53 (s, 3 H, ester methyl), 3.43 (m, 1 H), 3.31 (dd, *J* = 10.9, 4.5 Hz, 1 H), 2.70 (m, 1 H), 2.62 (dd, *J* = 2.4, 1.3 Hz, 1 H), 2.12 (ddd, *J* = 10.9, 10.5, 1.6 Hz, 1 H), 1.74 (dd, *J* = 10.5, 10.5 Hz, 1 H), 1.63 (m, 1 H), 1.54 (d, *J* = 6.0 Hz, 1 H), 1.50 (s, 3 H), 1.22 (s, 3 H), 1.02 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.80 (d, *J* = 6.6 Hz, 3 H), 0.05 (s, 6 H); IR (neat) 3495, 1730, 1665, 1650 cm^{-1}; MS *m/z* 485 ($M^+ - C_4H_9$); HRMS for $C_{28}H_{41}O_5Si$ ($M^+ - C_4H_9$) calcd 485.2753, found 485.2739.

Preparation of the Kijanolide/Tetronolide Octahydronaphthalene Substructure: Methyl 2β-[(*E*)-1-Methyl-3-[(*tert*-butyldimethylsilyl)oxy]-prop-1-enyl]-5α-(benzyloxy)-1α,6α,8β-trimethyl-1,2,4aα,5,6,7,8,8aβ-octahydronaphthalene-1β-carboxylate (4). To a 25 °C solution of **39** (32 mg, 0.059 mmol) in anhydrous toluene (1 mL) under N_2 was added 97% thiocarbonyldiimidazole (63 mg, 0.35 mmol). This solution was heated at 100 °C for 16 h before the solvent was removed in vacuo. Purification of the crude mixture by silica gel chromatography (2:1 hexane–ether as eluent) gave 34 mg (87%) of the thiocarbonylimidazolide intermediate: R_f 0.25 (1:1 hexane–ether); $[\alpha]^{26}_D$ −44.1° (*c* = 1.40, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, *J* = 1.4 Hz, 1 H), 7.64 (dd, *J* = 1.1, 1.1 Hz, 1 H), 7.30 (m, 5 H, aromatic), 7.06 (d, *J* = 1.4 Hz, 1 H), 6.12 (d, *J* = 10.2 Hz, 1 H), 5.51 (m, 1 H), 5.40 (dd, *J* = 10.5, 5.4 Hz, 1 H), 5.31 (t, 1 H), 4.64 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.44 (B of AB, J_{BA} = 11.3 Hz, 1 H), 4.14 (m, 2 H), 3.53 (s, 3 H, ester methyl), 3.41 (dd, *J* = 10.9, 4.6 Hz, 1 H), 3.11 (m, 1 H), 2.66 (dd, *J* = 1.8, 1.8 Hz, 1 H), 2.20 (ddd, *J* = 10.9, 10.5, 1.6 Hz, 1 H), 2.13 (m, 1 H), 1.92 (dd, *J* = 10.5, 10.5 Hz, 1 H), 1.54 (s, 3 H), 1.29 (s, 3 H), 1.05 (d, *J* = 7.1 Hz, 3 H), 0.90 (s, 9 H), 0.76 (d, *J* = 6.6 Hz, 3 H), 0.05 (s, 6 H); IR (neat) 1730 cm^{-1}; MS *m/z* 652 (parent ion); HRMS for $C_{36}H_{52}O_5N_2SSi$ calcd 652.3375, found 652.3353. Anal. Calcd for $C_{36}H_{52}O_5N_2SSi$: C, 66.22; H, 8.03. Found: C, 66.40; H, 8.21.

To a solution of this intermediate (16 mg, 0.024 mmol) and AIBN (0.5 mg) in anhydrous toluene (2.0 mL) under N_2 was added freshly prepared *n*-Bu_3SnH[17] (10.5 μL, 0.04 mmol). The mixture was heated at 100 °C for 30 min before being cooled to ambient temperature and concentrated in vacuo. Purification of the crude product by silica gel chromatography (15:1 hexane–ether) provided 12 mg (92%) of the targeted kijanolide/tetronolide subunit **4**: R_f 0.44 (8:1 hexane–ether); $[\alpha]^{20}_D$ −21.1° (*c* = 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 (m, 5 H, aromatic), 6.09 (ddd, *J* = 10.2, 2.4, 1.5 Hz, 1 H), 5.39 (m, 1 H), 5.23 (t, 1 H), 4.60 (A of AB, J_{AB} = 11.4 Hz, 1 H), 4.35 (B of AB, J_{BA} = 11.4 Hz, 1 H), 4.08 (m, 2 H), 3.46 (s, 3 H, ester methyl), 3.37 (dd, *J* = 10.9, 5.2 Hz, 1 H), 2.51 (dd, *J* = 2.4, 2.4 Hz, 1 H), 2.37 (m, 1 H), 2.04 (ddd, *J* = 10.9, 10.2, 2.1 Hz, 1 H), 1.72 (dd, *J* = 10.2, 10.2 Hz, 1 H), 1.59 (m, 1 H), 1.48 (s, 3 H), 1.42 (m, 2 H), 1.16 (s, 3 H), 0.98 (d, *J* = 7.0 Hz, 3 H), 0.84 (s, 9 H), 0.64 (d, *J* = 6.7 Hz, 3 H), 0.01 (s, 6 H); IR (neat) 1730, 1650 cm^{-1}; MS *m/z* 469 ($M^+ - C_4H_9$); HRMS for $C_{28}H_{41}O_4Si$ ($M^+ - C_4H_9$) calcd 469.2804, found 469.2800. Anal. Calcd for $C_{32}H_{50}O_4Si$: C, 72.95; H, 9.60. Found: C, 73.01; H, 9.98.

Methyl (*E*)-(4*S*,5*S*,6*S*,7*S*,8*S*)-5-Acetoxy-7-(benzyloxy)-8,9-(isopropylidenedioxy)-2,4,6-trimethylnon-2-enoate (42). Homoallylic alcohol **15** (0.29 g, 0.87 mmol) was converted into acetate **42** (0.29 g, 89% yield) by using the reaction sequence described above for the conversion of **14** into **28**. Data for **42**: R_f 0.20 (2:1 hexane–ether); $[\alpha]^{20}_D$ −38.7° (*c* = 2.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 6.59 (dd, *J* = 10.3, 1.7 Hz, 1 H), 5.18 (dd, *J* = 7.8, 2.2 Hz, 1 H), 4.66 (A of AB, J_{AB} = 11.0 Hz, 1 H), 4.58 (B of AB, J_{BA} = 11.0 Hz, 1 H), 4.30 (m, 1 H), 4.01 (dd, *J* = 5.2, 4.6 Hz, 1 H), 3.75 (m, 1 H), 3.73 (s, 3 H, ester methyl), 3.24 (dd, *J* = 7.1, 5.1 Hz, 1 H), 2.82 (m, 1 H), 2.01 (m, 1 H), 1.92 (s, 3 H), 1.83 (s, 3 H), 1.44 (s, 3 H, acetonide), 1.37 (s, 3 H, acetonide), 1.01 (d, *J* = 7.0 Hz, 3 H), 0.96 (d, *J* = 6.5 Hz, 3 H); IR (neat) 1735, 1715, 1650 cm^{-1}; MS *m/z* 433 ($M^+ - CH_3$); HRMS for $C_{24}H_{33}O_7$ ($M^+ - CH_3$) calcd 433.2214, found 433.2230. Anal. Calcd for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.08; H, 8.14.

Methyl (*E*)-(4*S*,5*S*,6*S*,7*S*)-5-Acetoxy-7-(benzyloxy)-9,9-dibromo-2,4,6-trimethylnona-2,8-dienoate (43). Dibromo olefin **43** was prepared from **42** by using the sequence described for the preparation of dibromo olefin **31** from acetate **28**. Thus, acidic hydrolysis of the acetonide of **42** (0.18 g, 0.4 mmol) provided a crude diol (0.15 g, 91%) that was oxidized to the corresponding aldehyde with $NaIO_4$ and then converted to dibromo olefin **43** (0.15 g, 78%) by using the Corey–Fuchs procedure:[20] R_f 0.40 (1:1 hexane–ether); $[\alpha]^{20}_D$ +12.7° (*c* = 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 6.63 (dd, *J* = 10.1, 1.7 Hz, 1 H), 6.38 (d, *J* = 9.0 Hz, 1 H), 5.24 (dd, *J* = 7.8, 3.1 Hz, 1 H), 4.48 (A of AB, J_{AB} = 11.2 Hz, 1 H), 4.37 (B of AB, J_{BA} = 11.2 Hz, 1 H), 3.87 (dd, *J* = 9.0, 9.0 Hz, 1 H), 3.73 (s, 3 H, ester methyl), 2.84 (m, 1 H), 2.01 (m, 1 H), 1.98 (s, 3 H), 1.82 (s, 3 H), 0.97 (d, *J* = 6.0 Hz, 3 H), 0.95 (d, *J* = 7.1 Hz, 3 H); IR (neat) 1735, 1715, 1650, 1610 cm^{-1}; MS *m/z* 364 ($M^+ - C_9H_9O_3$). Anal. Calcd for $C_{22}H_{28}O_5Br_2$: C, 49.64; H, 5.30. Found: C, 49.63; H, 5.41.

Synthesis and Intramolecular Diels–Alder Reaction of Methyl (*E*,*Z*,*E*,*E*)-(4*S*,5*S*,6*S*,7*S*)-5-Acetoxy-7-(benzyloxy)-9-bromo-14-hydroxy-2,4,6,12-tetramethyltetradeca-2,8,10,12-tetraenoate (26). To a 25 °C solution of vinylboronic acid **36** (17 mg, 0.12 mmol) and 10% aqueous TlOH (0.27 mL, 0.12 mmol) in anhydrous THF (1 mL) under N_2 was added a premixed solution of dibromo olefin **43** (47 mg, 0.09 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) in anhydrous THF (2 mL). Subsequent workup and purification, using the procedure described for the preparation of **7**, yielded 40 mg (83%) of tetraene **26**: R_f 0.19 (1:1 hexane-ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5 H, aromatic), 6.72 (d, *J* = 14.8 Hz, 1 H), 6.65 (d, *J* = 10.2 Hz, 1 H), 6.27 (d, *J* = 14.8 Hz, 1 H), 5.97 (d, *J* = 8.9 Hz, 1 H), 5.88 (t, 1 H), 5.25 (dd, *J* = 7.4, 3.9 Hz, 1 H), 4.47 (A of AB, J_{AB} = 11.4 Hz, 1 H), 4.36 (m, 3 H, contains B of AB d), 4.27 (dd, *J* = 8.7, 8.7 Hz, 1 H), 3.75 (s, 3 H, ester methyl), 2.89 (m, 1 H), 2.03 (m, 1 H), 1.99 (s, 3 H), 1.87 (s, 3 H), 1.82 (s, 3 H), 1.35 (t, 1 H), 0.97 (d, *J* = 6.9 Hz, 6 H); MS *m/z* 381 ($M^+ - C_9H_{12}O_3$); HRMS for $C_{19}H_{26}O_3{}^{79}Br$ ($M^+ - C_9H_{12}O_3$) calcd 381.1080, found 381.1051.

A solution of tetraene **26** (17 mg) in degassed, dry toluene (2 mL) was heated to 140 °C in a sealed Carius tube in the presence of BHT for 16 h. ^1H NMR analysis of the crude reaction mixture showed a 97:3 mixture of cycloadducts. Purification of the major product by silica gel chromatography (2:1 hexane–ether as eluent) provided 15 mg (88%) of **44**: R_f 0.15 (1:1 hexane–ether); $[\alpha]^{26}_D$ −18.0° (*c* = 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 6.15 (dd, *J* = 4.7, 2.2 Hz, 1 H), 5.44 (t, 1 H), 4.90 (dd, *J* = 2.9, 2.9 Hz, 1 H), 4.62 (A of AB, J_{AB} = 11.2 Hz, 1 H), 4.50 (B of AB, J_{BA} = 11.2 Hz, 1 H), 4.16 (m, 2 H), 3.92 (dd, *J* = 9.9, 5.1 Hz, 1 H), 3.57 (s, 3 H), 2.56 (dd, *J* = 4.7, 1.5 Hz, 1 H), 2.48 (m, 1 H), 2.43 (dd, *J* = 10.9, 10.9 Hz, 1 H), 2.30 (dd, *J* = 10.9, 9.9 Hz, 1 H), 2.07 (s, 3 H), 1.92 (m, 1 H), 1.65 (s, 3 H), 1.24 (s, 3 H), 1.05 (d, *J* = 7.6 Hz, 3 H), 0.70 (d, *J* = 6.6 Hz, 3 H); MS *m/z* 531 ($M^+ - OH$); HRMS for $C_{28}H_{36}O_5Br$ ($M^+ - OH$) calcd 531.1772, found 531.1785.

Synthesis of the Kijanolide/Tetronolide Subunit 4 from Cycloadduct 44. Cycloadduct **44** (30 mg, 0.05 mmol) was reduced and deacylated using the conditions described for the conversion of **37** to **38** (5% NaHg in MeOH followed by the addition of K_2CO_3). The primary hydroxyl group of the resulting diol (20 mg, 87%) was protected as a *tert*-butyldimethylsilyl ether, and the secondary alcohol (22 mg, 86%) was then derivatized by treatment with thiocarbonyldiimidazole to give **45** (19 mg, 71%). Bu_3SnH reduction of **45** using the conditions described for the reduction of **39** provided 11 mg (75%) of the kijanolide/tetronolide octahydronaphthalene substructure **4** that was identical in all respects to samples of **4** prepared from **37**.

Data for the diol intermediate: R_f 0.10 (2:1 ether–hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5 H, aromatic), 6.14 (ddd, *J* = 10.1, 2.4, 2.0 Hz, 1 H), 5.43 (m, 1 H), 5.40 (t, 1 H), 4.66 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.44 (B of AB, J_{BA} = 11.3 Hz, 1 H), 4.08 (m, 2 H), 3.69 (dd, *J* = 10.8, 5.2 Hz, 1 H), 3.67 (m, 1 H), 3.56 (s, 3 H), 2.61 (dd, *J* = 2.4, 2.4 Hz, 1 H), 2.58 (m, 1 H), 2.43 (dd, *J* = 10.8, 10.8 Hz, 1 H), 2.11 (ddd, *J* = 10.8, 10.8, 2.0 Hz, 1 H), 1.81 (m, 1 H), 1.63 (s, 1 H), 1.60 (s, 3 H), 1.28 (m, 1 H), 1.24 (s, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 0.84 (d, *J* = 7.5 Hz, 3 H); MS *m/z* 411 ($M^+ - H_2O$); HRMS for $C_{26}H_{35}O_4$ ($M^+ - H_2O$) calcd 411.2561, found 411.2565.

Data for the intermediate TBDMS ether: R_f 0.13 (5:1 hexane–ethyl acetate); $[\alpha]^{26}_D$ +6.2° (*c* = 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5 H, aromatic), 6.11 (ddd, *J* = 10.0, 2.3, 2.2 Hz, 1 H), 5.45 (m, 1 H), 5.29 (t, 1 H), 4.64 (A of AB, J_{AB} = 11.3 Hz, 1 H), 4.43 (B of AB, J_{BA} = 11.3 Hz, 1 H), 4.13 (m, 2 H), 3.36 (m, 2 H), 3.53 (s, 3 H), 2.61 (dd, *J* = 2.3, 2.3 Hz, 1 H), 2.54 (m, 1 H), 2.41 (dd, *J* = 10.4, 10.4 Hz, 1 H), 2.10 (ddd, *J* = 10.4, 10.4, 2.2 Hz, 1 H), 1.81 (m, 1 H), 1.59 (s, 1 H), 1.55 (s, 3 H), 1.21 (s, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.89 (s, 9 H), 0.83 (d, *J* = 7.0 Hz, 3 H), 0.04 (s, 6 H); MS *m/z* 485 ($M^+ - C_4H_9$); HRMS for $C_{28}H_{41}O_5Si$ ($M^+ - C_4H_9$) calcd 485.2753, found 485.2743.

Data for **45**: R_f 0.22 (5:1 hexane–ethyl acetate); $[\alpha]^{26}_D$ +6.1° (*c* = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.66 (s, 1 H), 7.33 (m, 5 H, aromatic), 7.09 (s, 1 H), 6.13 (d, *J* = 10.1 Hz, 1 H), 5.52 (m, 1 H), 5.45 (s, 1 H), 5.35 (t, 1 H), 4.59 (A of AB, J_{AB} = 11.4 Hz, 1 H), 4.39 (B of AB, J_{BA} = 11.4 Hz, 1 H), 4.17 (m, 2 H), 3.53 (s, 3 H), 3.46 (dd, *J* = 11.2, 5.2 Hz, 1 H), 2.85 (m, 1 H), 2.69 (dd, *J* = 1.9, 1.9 Hz, 1 H), 2.51 (dd, *J* = 10.5, 10.5 Hz, 1 H), 2.19 (ddd, *J* = 11.2, 10.5, 1.2 Hz, 1 H), 2.07 (m, 1 H), 1.59 (s, 3 H), 1.27 (s, 3 H), 1.14 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.83 (d, *J* = 7.1 Hz, 3 H), 0.04 (s, 6 H); MS *m/z* 595 ($M^+ - C_4H_9$); HRMS for $C_{32}H_{43}O_5N_2S_1Si$ ($M^+ - C_4H_9$) calcd 595.2690, found 595.2681.

Methyl (*E*,*E*)-(4*S*,5*R*,6*S*,7*S*)-5-Acetoxy-7-(benzyloxy)-9-iodo-2,4,6-trimethylnona-2,8-dienoate (46). To a rapidly stirred solution of

aldehyde **30** (0.22 g, 0.58 mmol) and iodoform (0.60 g, 1.55 mmol) in dry THF (4.0 mL) at 0 °C under N_2 was added a solution of 95% $CrCl_2$ (0.57 g, 4.65 mmol) in dry THF (4 mL) via cannula. The reaction mixture was stirred for 3 h before it was quenched with H_2O and extracted with Et_2O (3 × 10 mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification of the resulting dark yellow oil by silica gel chromatography (5:1 hexane–ether) afforded 0.23 g (80%) of the vinyl iodide **46** as a 98:2 mixture of (*E*)- and (*Z*)-olefin isomers: R_f 0.48 (1:1 hexane–ether); $[\alpha]^{26}_D$ −24.0° (*c* = 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 5 H, aromatic), 6.50 (dd, *J* = 10.1, 1.0 Hz, 1 H), 6.44 (dd, *J* = 14.9, 7.7 Hz, 1 H), 6.29 (d, *J* = 14.9 Hz, 1 H), 4.91 (dd, *J* = 7.9, 5.2 Hz, 1 H), 4.54 (A of AB, J_{AB} = 11.8 Hz, 1 H), 4.31 (B of AB, J_{BA} = 11.8 Hz, 1 H), 3.71 (s, 3 H, ester methyl), 3.69 (m, 1 H), 2.92 (m, 1 H), 2.06 (m, 1 H), 2.01 (s, 3 H), 1.74 (d, *J* = 1.8 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 7.0 Hz, 3 H); IR (neat) 1730, 1715, 1650, 1605 cm^{-1}; MS *m/z* 393 ($M^+ - C_7H_7O$); HRMS for $C_{15}H_{22}O_4{}^{127}I$ ($M^+ - C_7H_7O$) calcd 393.0580, found 393.0579; HRMS for $C_{22}H_{29}O_5$ ($M^+ - {}^{127}I$) calcd 373.2036, found 373.2032.

Methyl (*E*,*E*,*E*,*E*)-(4*S*,5*R*,6*S*,7*S*)-5-Acetoxy-7-(benzyloxy)-14-hydroxy-2,4,6,12-tetramethyltetradeca-2,8,10,12-tetraenoate (25). To a 25 °C solution of vinylboronic acid **36** (25 mg, 0.16 mmol) and 10% TlOH (0.395 mL) in anhydrous THF (0.4 mL) under N_2 was added a premixed solution of vinyl iodide **46** (62 mg, 0.124 mmol) and $Pd(PPh_3)_4$ (32 mg, 0.025 mmol) in degassed THF (0.5 mL). After 4 min the light yellow reaction mixture was diluted with Et_2O (10 mL) and dried over anhydrous $MgSO_4$. The solution was filtered and concentrated in vacuo to give a crude product that was purified by silica gel chromatography (2:1 ether–hexane as eluent). In this way 44 mg (76%) of tetraene **25** was obtained: R_f 0.25 (1:1 hexane–EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 6.54 (dd, *J* = 10.1, 1.2 Hz, 1 H), 6.25 (m, 3 H), 5.69 (t, 1 H), 5.56 (dd, *J* = 14.5, 8.4 Hz, 1 H), 4.94 (dd, *J* = 7.2, 5.6 Hz, 1 H), 4.54 (A of AB, J_{AB} = 11.8 Hz, 1 H), 4.30 (m, 3 H, includes B of AB), 3.71 (m, 4 H), 2.97 (m, 1 H), 2.07 (m, 1 H), 2.00 (s, 3 H), 1.81 (s, 3 H), 1.77 (d, *J* = 1.2 Hz, 3 H), 1.33 (m, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 7.1 Hz, 3 H); MS *m/z* 361 ($M^+ - C_7H_7$).

Intramolecular Diels–Alder Reaction of Tetraene 25. A solution of **25** (44 mg, 0.094 mmol) and BHT (1.0 mg, 0.006 mmol) in anhydrous degassed toluene (3 mL) was transferred to a resealable Carius tube, sealed under N_2, and heated at 150 °C for 16 h. ^1H NMR analysis of the crude product showed a 90:10 mixture of two cycloadducts. Separation of this mixture by silica gel chromatography (2:1 hexane–ethyl acetate as eluent) provided 28 mg (64%) of cycloadduct **47** (64%) and 4 mg of a ca. 3:1 mixture of cycloadducts **47** and **48** (32 mg total; 73% combined yield). The minor cycloadduct **48** was isolated by preparative HPLC using a Waters system (1 mL/min) with a Magnum 9 Partisil (10 μm) silica column eluted with degassed 1.5:1 hexane–ethyl acetate. Retention times under these conditions were 67 (trans isomer **47**) and 79 min (cis isomer **48**).

Data for trans-fused cycloadduct **47**: R_f 0.23 (1:1 hexane–ethyl acetate); $[\alpha]^{26}_D$ −27.8° (*c* = 1.01, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (m, 5 H, aromatic), 6.11 (d, 10.3 Hz, 1 H), 5.46 (ddd, *J* = 10.3, 4.0,2.7 Hz, 1 H), 5.37 (t, 1 H), 4.69 (dd, *J* = 10.6 Hz, 1 H), 4.64 (A of AB, J_{AB} = 11.4 Hz, 1 H), 4.39 (B of AB, J_{BA} = 11.4 Hz, 1 H), 4.13 (m, 2 H), 3.51 (s, 3 H, ester methyl), 3.37 (dd, *J* = 11.0, 4.9 Hz, 1 H), 2.80 (m, 1 H), 2.62 (dd, *J* = 2.0, 2.0 Hz, 1 H), 2.13 (ddd, *J* = 11.0, 10.5, 4.0 Hz, 1 H), 2.08 (s, 3 H), 1.83 (m, 2 H), 1.56 (s, 3 H), 1.23 (s, 3 H), 0.99 (d, *J* = 7.0 Hz, 3 H), 0.68 (d, *J* = 6.2 Hz, 3 H); IR (neat) 3450, 1735, 1725, 1650 cm^{-1}; MS *m/z* 453 ($M^+ - H_2O$); HRMS for $C_{28}H_{36}O_5$ ($M^+ - H_2O$) calcd 453.2632, found 453.2635. Anal. Calcd for $C_{28}H_{38}O_6$: C, 71.46; H, 8.14. Found: C, 71.79; H, 7.91.

Data for cis-fused cycloadduct **48**: R_f 0.24 (1:1 hexane–ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 5.99 (ddd, *J* = 10.0, 3.0, 2.9 Hz, 1 H), 5.67 (dd, *J* = 10.0, 3.1, 2.5 Hz, 1 H), 5.42 (t, 1 H), 4.66 (A of AB, J_{AB} = 11.7 Hz, 1 H), 4.63 (B of AB, J_{BA} = 11.7 Hz, 1 H), 4.18 (m, 2 H), 3.65 (s, 3 H, ester methyl), 3.59 (dd, *J* = 4.0, 4.0 Hz, 1 H), 3.35 (m, 1 H), 2.56 (m, 1 H), 2.29 (dd, *J* = 6.9, 6.0 Hz, 1 H), 2.22 (m, 1 H), 2.05 (s, 3 H), 1.91 (m, 1 H), 1.84 (t, 1 H), 1.65 (s, 3 H), 1.19 (s, 3 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.96 (d, *J* = 7.0 Hz, 3 H); IR ($CHCl_3$) 3440, 1730, 1725 cm^{-1}; HRMS for $C_{28}H_{38}O_6$ (M^+) calcd 470.2660, found 470.2663.

Conversion of Cycloadduct 47 to Diol 39. Cycloadduct **47** (3 mg, 0.006 mmol) was dissolved in anhydrous MeOH (0.5 mL) and treated with K_2CO_3 (0.1 mg) for 30 min at room temperature. Standard workup provided diol **39** that was identical to the material previously prepared from cycloadduct **37**.

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Supplementary Material Available: Copies of ^1H NMR spectra of **7**, **25**, **26**, **34**, **36**, the *N*-methyldiethanolamine complex of **36**, **38**, **39**, **44**, **45**, **46**, and **48** (11 pages). This material is contained in many 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.

Molecular Harpoons. Membrane-Disruptive Surfactants That Can Recognize Osmotic Stress in Phospholipid Bilayers[1]

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Abstract: A series of wedge-shaped, nonionic surfactant molecules (molecular harpoons) have been synthesized and used to disrupt large unilamellar vesicles derived from 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC), POPC/cholesterol (2/1), and POPC/cholesterol (55/45), under isotonic and hypotonic (osmotically stressed) conditions. The activity of each surfactant has been defined by measuring its ability to release vesicle-encapsulated 5(6)-carboxyfluorescein (CF). Comparative studies have also been carried out, using Triton X-100 as the disruptive agent. The principal results of this study establish that it is possible for a disruptive surfactant to distinguish between osmotically stressed and nonstressed membranes and that such recognition is a sensitive function of the surfactant's composition, structure, and oligomeric state, as well as the compactness of the target membrane and its degree of osmotic stress. The implications of these findings for the rational design of membrane-disrupting antimicrobial agents are briefly discussed.

Introduction

The recent emergence of life-threatening microorganisms such as HIV and *Mycobacterium tuberculosis* and the growing problem of drug resistance provide considerable impetus for devising fundamentally new approaches toward drug design.[2-6] We believe that membrane-disrupting drugs are ideally suited as therapeutic agents because microbes should be less able to develop resistance

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