Enantioselective Synthesis of the Bottom Half of Chlorothricolide. 3. Studies of the Steric Directing Group Strategy for Stereocontrol in Intramolecular Diels-Alder Reactions[1]

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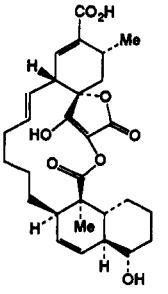
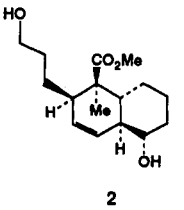
The intramolecular Diels-Alder reactions of a series of C(7)-alkoxy-substituted 2(*E*),8(*Z*),10(*E*)-undecatrienoates and trienals containing removable C(9)-Br or C(9)-$SiMe_3$ substituents (**11**, **12**, **13**, **33**, **42**, **43**, **44**, **45**) were studied as part of a program directed toward the total synthesis of the bottom half of chlorothricolide. The IMDA reaction of trienoate **3** that lacks a C(9) substituent had previously been shown to cyclize with poor stereoselectivity to a mixture of four cycloadducts. It was expected that the IMDA reactions of trienes containing C(9) substituents (i.e., steric directing groups) would proceed with substantially enhanced stereoselectivity via trans-fused transition state A owing to nonbonded interactions that the steric directing groups experience in the competitive transition states B-D. Cis-fused transition states C and D suffer from serious interactions between C(9)-X and the axial C(6)-H, while trans-fused transition state B is destabilized by a 1,3-eclipsing interaction with the C(7)-alkoxyl group. Only the desired transition state, trans-fused transition state A, suffers from no serious interactions involving the C(9) steric directing group. These predictions were verified experimentally: the trans-fused cycloadduct deriving from A was the major product in all cases. Stereoselectivity for trans-fused cycloadducts was consistently greater, using C(9)-TMS directing groups compared to C(9)-Br substituted systems (for IMDA reactions under analogous conditions), but the C(9)-Br group appeared to have a greater influence on the partition between transition states A and B (see Table I). A surprising aspect of this study, however, is that significant amounts of cis-fused cycloadducts were obtained from the thermal cyclizations of the above-named trienes (12-45%), and this pathway was not entirely suppressed even in the Lewis acid catalyzed cycloadditions of trienals **44** and **45** (5-9% of cis fused cycloadduct). The results with TMS-substituted trienes **33**, **42**, and **44** thus are in disagreement with an earlier report by Boeckman and Barta (ref 5f) that the IMDA reaction of **33** gives "a single cycloadduct (>100:1)." The cis-fused diastereomers most probably arise via boat-like transition state E rather than the chair-like transition state C. Cis-fused cycloadducts were not observed in the IMDA reaction of TMS-substituted triene **61** that lacks a C(7)-alkoxy substituent, suggesting that the C(7)-alkoxy groups electronically deactivate trans-fused transition state A such that boat-like transition state E is competitive only with substrates containing such C(7)-alkoxy substituents. Data are also presented that show that the C(9)-TMS substituents lead to an increase in reactivity (e.g., the IMDA reaction of **61** that proceeds at ambient temperature and the acid-catalyzed cyclocondensation of TMS diene aldehyde **63**). This study defines bromo trienoate **43** as the optimal precursor to the bottom half unit (**2**) of chlorothricolide, even though the IMDA reaction of **43** is less selective than that of TMS-substituted trienes **42** and **44**. The synthesis of **43** (Figure 4) involving the Pd^0-catalyzed cross-coupling reaction of dibromo olefin **35** and vinylboronate **37** is shorter and considerably more efficient than the syntheses of TMS trienes **42** and **44**, and this compensates for the fact that **43** is the least selective IMDA substrate. Syntheses that proceed by way of TMS trienoates like **42** or TMS trienals like **44** become competitive only if a more efficient triene synthesis is devised.

Chlorothricolide (**1**) is the structurally interesting aglycon of chlorothricin, an antibiotic with activity against gram-positive bacteria.[3,4] While chlorothricolide has attracted considerable attention as a synthetic target, no syntheses of **1** in unprotected form have yet appeared.[5,6] We report herein a full account of our enantioselective synthesis of the bottom-half fragment **2**[6a,b] and provide also a detailed analysis of the steric directing group strategy for stereocontrol of intramolecular Diels-Alder reactions that provides the basis of the present work.



chlorothricolide (**1**)



2

Our original plan called for **2** to be synthesized by the intramolecular Diels-Alder reaction of a suitably func-

(1) Portions of this research were performed at the Massachusetts Institute of Technology, Cambridge, MA 02139.

(2) M.I.T. Postdoctoral Research Associate, 1984-85.

(3) (a) Muntwyler, R.; Keller-Schleirlein, W. *Helv. Chim. Acta* **1972**, *55*, 2071. (b) Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Ibid.* **1972**, *55*, 2094.

(4) Schindler, P. W. *Eur. J. Biochem.* **1975**, *51*, 579 and references cited therein.

(5) (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. *Ibid.* **1981**, *46*, 4863. (c) Ireland, R. E.; Varney, M. D. *Ibid.* **1986**, *51*, 635. (d) Snider, B. B.; Burbaum, B. W. *Ibid.* **1983**, *48*, 4370. (e) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (f) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421. (g) Marshall, J. A.; Audia, J. E.; Grote, J. *Ibid.* **1984**, *49*, 5277. (h) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron* **1986**, *42*, 2893. (i) Marshall, J. A.; Audia, J. E.; Shearer, B. G. *J. Org. Chem.* **1986**, *51*, 1730. (j) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *Ibid.* **1987**, *52*, 1236. (k) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (l) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Ibid.* **1989**, *30*, 2233. (m) Poss, A. J.; Brodowski, M. H. *Ibid.* **1989**, *30*, 2505. (n) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949. (m) For a recent synthesis of (±)-24-*O*-methylchlorothricolide, see: Takeda, K.; Igharashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431. (n) Hirsenkorn, R.; Haag-Zeino, B.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 4433. (o) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949.

(6) (a) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710. (b) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (c) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611.

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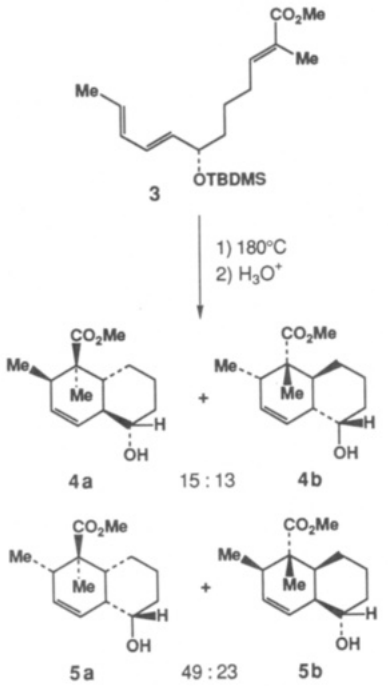
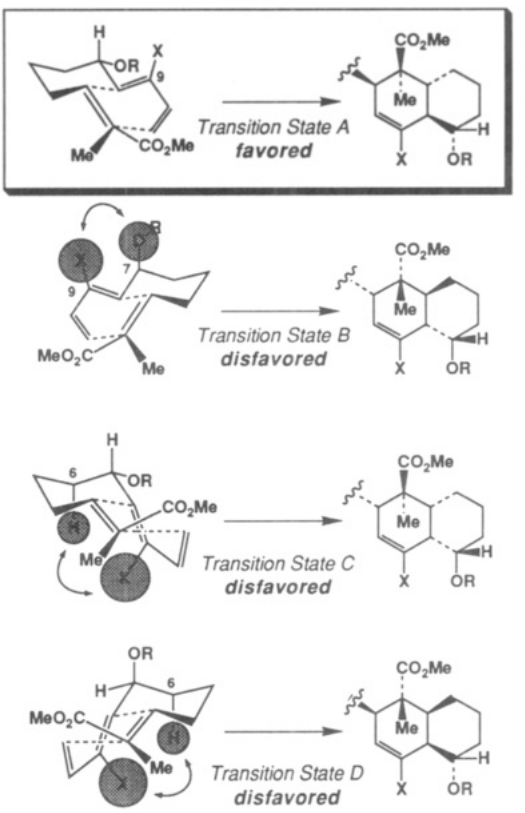
tionalized 2,8,10-undecatrienoate.[7] We found in preliminary studies with **3**, however, that trienes of this type cyclize preferentially to cis- rather than to trans-fused products.[8] In addition, diastereoselectivity in the trans-fused series was poor: the ratio of the desired diastereomer **4a** and its alkoxy epimer **4b** was roughly 1:1.



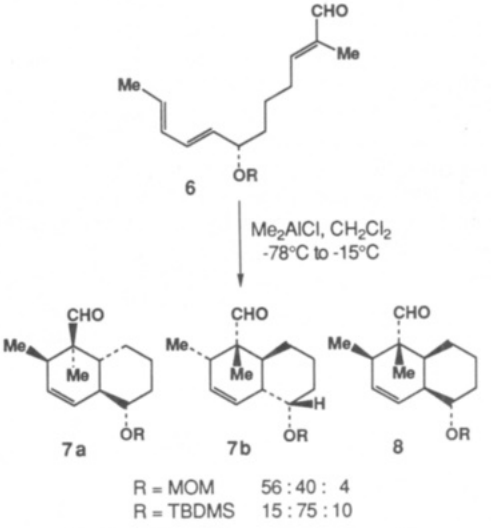
Thus, two independent problems required solution if an intramolecular Diels–Alder reaction was to be employed successfully in a stereocontrolled synthesis of **2**: (i) control of the trans-ring fusion stereochemistry and (ii) enhancement of the level of asymmetric induction from the allylic alkoxy unit in the triene precursor. The latter problem is especially pertinent when performing an enantioselective synthesis, since the "epimeric" products (cf. **4a** and **4b**) are enantiomeric at all centers except that bearing the original alkoxyl function. That is, utilization of the undesired epimer (e.g., **4b**) via an alkoxy inversion sequence is not an option when optically active intermediates are employed.

Attempts to improve the diastereoselectivity of the IMDA cyclization of **3** by using Lewis acid catalysis were unsuccessful owing to the instability and poor reactivity of the triene substrate: such systems decompose faster than they undergo Lewis acid catalyzed intramolecular cycloaddition.[8] Marshall, however, has made the important observation that the Lewis acid catalyzed cycloadditions of the corresponding trienals (e.g., **6**) occur readily at low temperatures with significant improvements in selectivity for the trans-fused product.[5g-j] In addition, as long as the allylic alkoxyl unit is introduced as a TBDMS ether, significant diastereoselectivity is realized for the axial alkoxyl epimer **7b**. Unfortunately, however,

Scheme I. Steric Directing Group Strategy



it is the equatorial epimer **7a** that is required for the chlorothricolide synthesis.



We pursued a totally different strategy for improving the stereoselectivity of these IMDA reactions. Based on an early study by Wilson, who established that the C-(8)-substituted triene **9** cyclized almost exclusively to the trans-fused decalin nucleus, while the C(8)-unsubstituted triene **10** provided a mixture of cis- and trans-fused cycloadducts,[9] we reasoned that placement of a heteroatom substituent, a so-called steric directing group,[10] at C(9) of

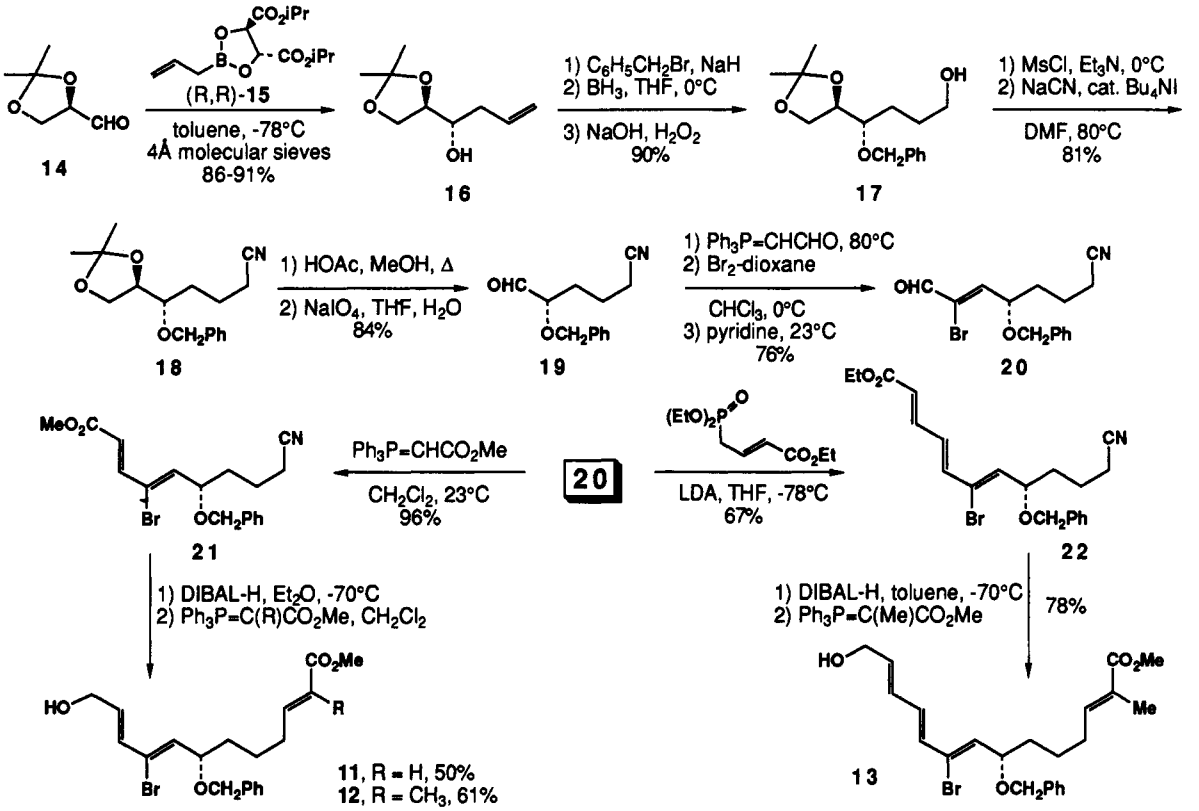
(7) Reviews of the intramolecular Diels–Alder reaction: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (b) Oppolzer, W. *Synthesis* **1978**, 793. (c) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63. (d) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (e) Ciganek, E. *Org. React.* **1984**, *32*, 1. (f) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183. (g) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer-Verlag: Berlin, 1984. (h) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (i) Roush, W. R. In *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; in press.

(8) Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

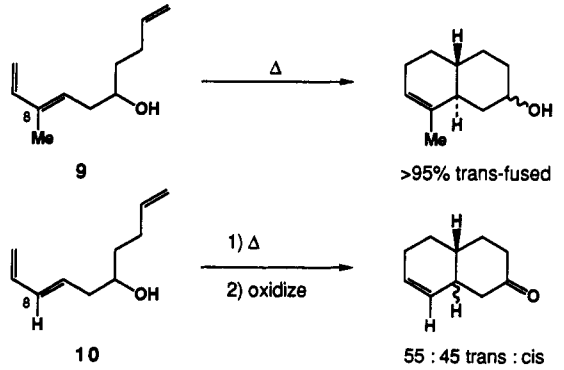
(9) (a) Wilson, S. R.; Huffman, J. C. *J. Org. Chem.* **1980**, *45*, 560. (b) Wilson, S. R.; Mao, D. T. *Ibid.* **1979**, *44*, 3093. (c) Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 6289.

(10) For several applications of steric directing groups in other classes of organic reactions, see: (a) Hasen, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229. (b) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, J. *Tetrahedron Lett.* **1982**, *23*, 3387. (c) Narula, A. S. *Ibid.* **1982**, *23*, 5579. (d) Wovkulich, P. M.; Barcelos, F.; Batcho, A. D.; Sereno, J. F.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R. *Tetrahedron* **1984**, *40*, 2283.

Scheme II



an appropriately functionalized triene would greatly enhance the preference for cyclization through trans-fused transition state A leading to the desired cycloadduct, since potentially serious nonbonded interactions would be created in the alternative chair-like transition states B–D (see Scheme I). Cis-fused transition states C and D were expected to suffer from an interaction between the axial H(6) and the C(9)-X substituent, while transition state B, that produces the undesired trans-fused axial alkoxyl epimer, would be destabilized by an eclipsing interaction between C(7)-OR and C(9)-X.



On the basis of this analysis we expected that diastereoselectivity via A would be greatest with the largest possible steric directing group X. A trimethylsilyl group was an obvious choice;[11] this group was employed by Boeckman and Barta, who were independently developing the steric directing group strategy in their laboratory.[5f] Difficulties encountered in our initial efforts to synthesize C(9)-TMS substituted trienes, however, prompted us to study first the intramolecular Diels–Alder reactions of a series of Br-containing trienes (**11**–**13**) that were easier to prepare.[6b]

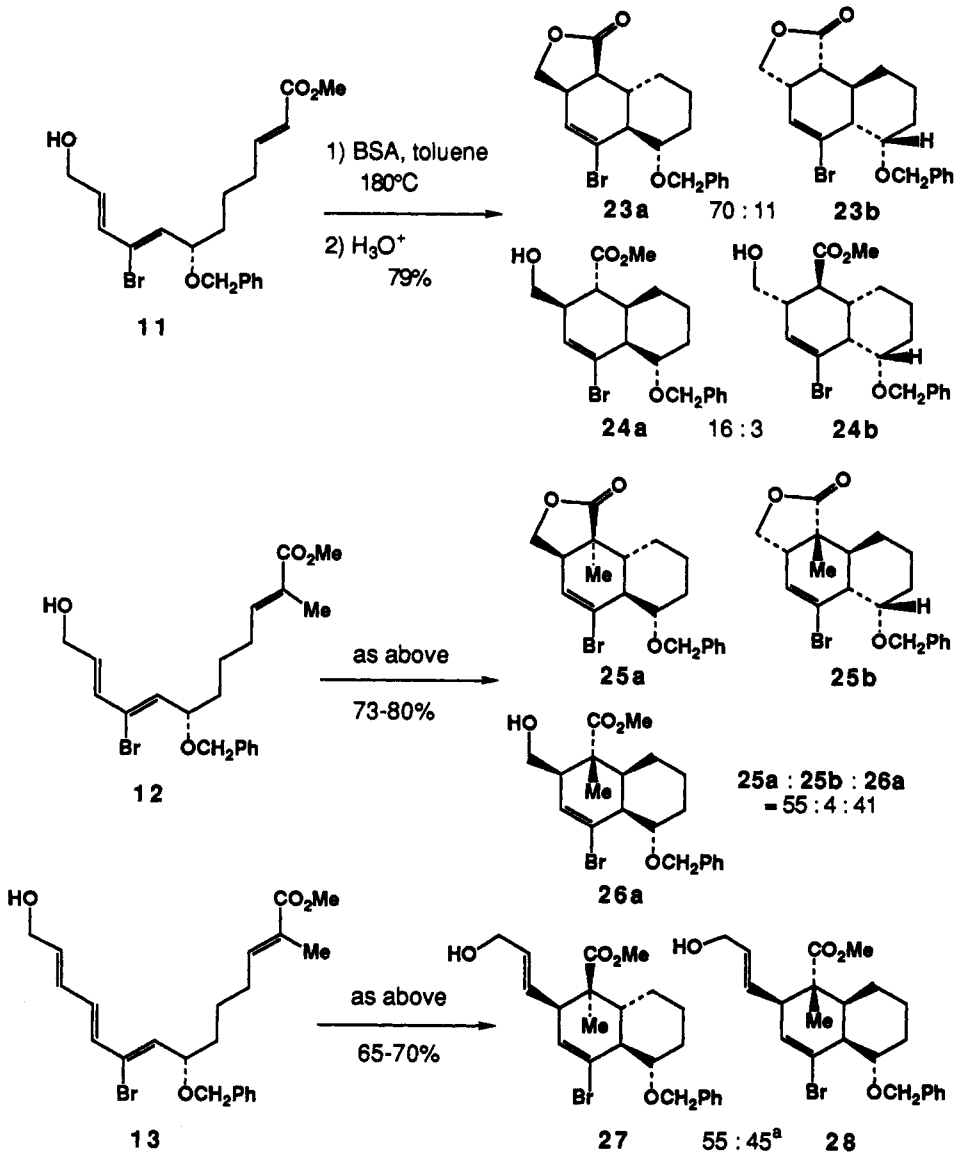
Trienes **11**–**13** were synthesized by the routes summarized in Scheme II. Thus, the well-known homoallylic alcohol **16**,[12] which we prepared by the matched double asymmetric reaction of D-glyceraldehyde acetonide (**14**) and tartrate allylboronate (*R,R*)-**15** that under fully optimized conditions proceeds with 98% diastereoselectivity,[13] was benzylated and then hydroborated by treatment with BH_3 in THF at 0 °C (standard NaOH, H_2O_2 workup) to afford primary alcohol **17** in 90% overall yield. Chain elongation via treatment of the corresponding mesylate with NaCN and catalytic Bu_4NI in DMF at 80 °C provided nitrile **18** in 81% yield, which upon acidic methanolysis and periodate cleavage of the diol intermediate provided aldehyde **19** in 84% yield. Condensation of **19** with a slight excess of $Ph_3P{=}CHCHO$ in benzene at 80 °C gave a 10:1 mixture of *E*- and *Z*-unsaturated aldehydes that, without separation, was treated with 1.2 equiv of the bromine–dioxane complex in $CHCl_3$ at 0 °C followed by excess pyridine to effect dehydrobromination. The yield of **20** for this three-step sequence was 76%. α-Bromo-α,β-unsaturated aldehyde **20**, which was essentially one olefin isomer (>95%), was elaborated to trienes **11**–**13** by straightforward olefination sequences. Thus, treatment of **20** with $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2 provided nitrile ester **21** (96%), while treatment of **20** with the lithium anion of trimethyl 4-phosphonocrotonate in THF (–78 °C)

(11) The *A* value of a trimethylsilyl group is 2.4–2.6 kcal mol^{-1}: Kitching, W.; Olszowy, H. A.; Drew, G. M.; Adcock, W. *J. Org. Chem.* **1982**, *47*, 5153.

(12) (a) Hoffmann, R. W.; Endesfelder, A.; Zeiss, H.-J. *Carbohydr. Res.* **1983**, *123*, 320. (b) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843.

(13) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (b) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109.

Scheme III[a]



[a] Only one alkoxyl epimer of each cycloadduct was detected.

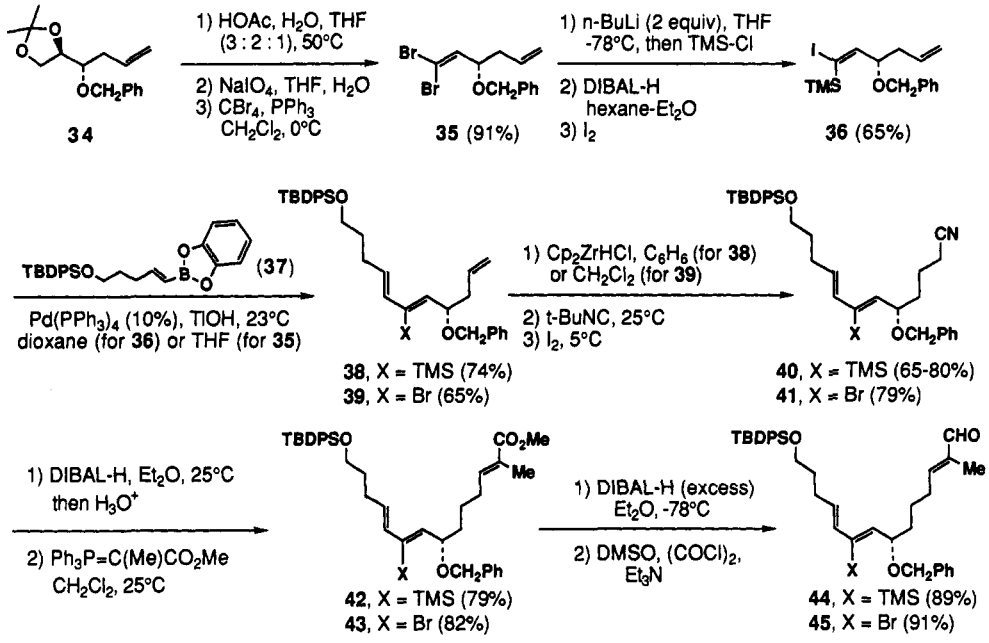
gave **22** in 67% yield. Reduction of these nitrile esters with an excess of DIBAL-H in Et_2O or toluene at −70 °C provided the corresponding hydroxy aldehydes, which were treated under standard conditions with $Ph_3P{=}CHCO_2Me$ or $Ph_3P{=}C(Me)CO_2Me$ to complete the syntheses of trienes **11**–**13**.

The results of the intramolecular Diels–Alder reactions of **11**–**13** are summarized in Scheme III. Following the procedure developed in our earlier studies, each triene was trimethylsilylated in situ by treatment with BSA in toluene.[8] The Diels–Alder reactions were then performed by heating these solutions at 170–180 °C typically for 24 h. The crude product mixtures were analyzed by ^1H NMR and GC to quantitate the various reaction products. Diastereomers were separated chromatographically following an acidic methanolysis step that hydrolyzed the TMS ethers.

It is interesting to note that selectivity of the IMDA reactions of **11**–**13** are improved relative to **3**, but not by as much as had been anticipated at the outset. The greatest selectivity was obtained with **11**, which provided an 81:19 mixture of trans-fused (**23**) to cis-fused (**24**) products; the ratio of alkoxyl epimers was roughly 7:1 in each series. The major product, **23a**, which comprised 70% of this mixture, was indeed generated by way of transition state A, consistent with the analysis presented earlier. Surprisingly, however, the trans/cis selectivity dropped with trienes **12** (59:41) and **13** (55:45), which have an additional methyl substituent on the dienophilic double bond. An analogous effect was not observed in our earlier studies of deca-2,8,10-trienoates lacking the C(9)-Br substituent.[8] Perhaps the Br substituent in **11**–**13** increases the contribution of the diene to the net dipole moment of the transition states, causing the cis-fused (C, D) transition states to become increasingly favored in the cases of **12** and **13** for the same reasons that the bimolecular Diels–Alder reactions of methyl methacrylate are generally more exo selective than those of methyl acrylate.[14] Alternatively, it may be that the Br substituent alters the polarization of the diene sufficiently that the timing of bond formation is slightly different in the cases of **12** and **13** relative to **11** (i.e., nonsynchronous transition state hypothesis).[15] In

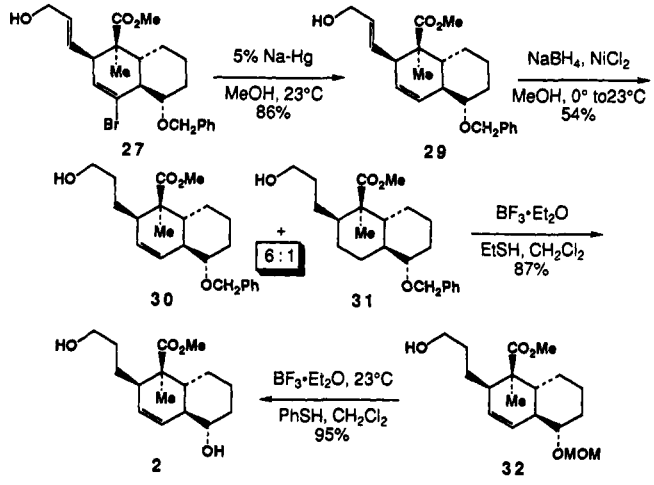
(14) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

Scheme IV



either event, it was clear that selectivity with the triene **13** targeted for our work on chlorothricolide was not as great as we had hoped to achieve and therefore that additional work on the development of this strategy was called for (vide infra).[16]

Cycloadduct **27** was elaborated to the bottom-half fragment **2** of chlorothricolide as follows. First, the Br substituent was removed in 86% yield by treatment with 5% Na/Hg in MeOH at 23 °C. The allylic alcohol unit of **29** was then reduced with moderate selectivity by treatment with $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ in MeOH.[17] The desired product **30** was obtained in 54% yield as a ca. 6:1 mixture with the fully saturated product **31** that could not be separated at this stage. A small amount of the product of allylic hydrogenolysis of the primary allylic alcohol was also identified. The mixture of **30** and **31** was then deprotected by using the methodology described by Fujita ($BF_3 \cdot Et_2O$, EtSH)[18] to give the corresponding mixture of diols from which the targeted chlorothricolide bottom-half fragment **2** was obtained in 87% yield. The enantiomeric purity of **2** was established to be >98% ee by comparison of the bis-MTPA derivative[19] with that prepared from a sample of racemic **2** obtained by deprotection ($BF_3 \cdot Et_2O$, PhSH)[20] of racemic **32**.[6c] Thus, the first enantioselective synthesis of a chlorothricolide synthetic intermediate had been accomplished.

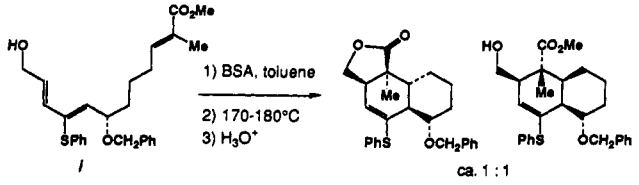


While these studies were in progress, we learned that Professor Boeckman had initiated studies on the steric directing group problem and had successfully synthesized triene **33** containing a C(9)-TMS unit.[5f] The Rochester group reported that **33** cyclized with >100:1 selectivity for the desired trans-fused cycloadduct (via transition state A), a result in accord with our original expectations. Because our efforts with the Br-containing trienes had not yielded a synthesis (cf., that via triene **13**) that we considered preparatively useful, we decided to reinvestigate routes to TMS-substituted trienes with expectations that, finally, a satisfactory synthetic solution to the chlorothricolide bottom-half problem had been found.

TMS-substituted triene **42** thus became the target of our revised approach (Scheme IV). Benzyl ether **34**, an in-

(15) (a) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S. *Tetrahedron Lett.* **1987**, *28*, 2447. (b) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297. For early applications of this hypothesis to the rationalization of IMDA diastereoselection, see: (c) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. (d) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273. (e) Taber, D. F.; Campbell, C.; Gunn, B. G.; Chiu, I.-C. *Tetrahedron Lett.* **1981**, *22*, 5141. (f) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696.

(16) The IMDA reaction of SPh substituted triene i was briefly explored, but since selectivity was poor this reaction was not fully developed. Attempts to accomplish IMDA cyclizations of the corresponding sulfoxide and sulfone derivatives failed to yield any products that resembled the desired cycloadducts.

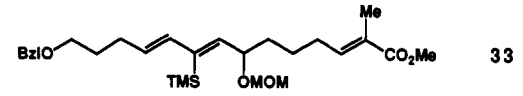


(17) (a) Grieco, P. A.; Inanaga, J.; Lin, N.-H.; Yanami, T. *J. Am. Chem. Soc.* **1982**, *104*, 5781. (b) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817.

(18) Fujita, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

(19) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(20) Kieczykowski, G. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 1938.

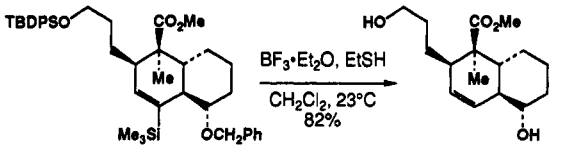


33

termediate in our earlier synthesis of **13**, was smoothly elaborated to dibromo diene **35**. After conversion of **35** to the corresponding TMS alkyne,[21] α-(iodovinyl)silane **36** was obtained via a hydroalumination–iodination sequence.[22] A critical step followed, namely, the palladium-catalyzed cross-coupling of **36** and vinylboronate **37** (prepared by hydroboration of the corresponding acetylene with catecholborane). Under standard Suzuki conditions (aqueous 2 N NaOH, C_6H_6),[23] we were able to prepare the desired TMS diene **38** in a maximum yield of only 55%. However, the efficiency of this reaction was improved to 74% by using the TlOH modification of the Suzuki cross-coupling reaction introduced by Kishi.[24] The TlOH protocol proved even more improtant in the cross-coupling of vinylboronate **37** and dibromo olefin **35** that provided bromo diene **39** as a single isomer in 65% yield,[25] versus a maximum of 36% under the original Suzuki conditions. The yield of **39** is improved even further (75%) if the cross-coupling of **35** is performed by using (5-hydroxy-(*E*)-pentenyl)boronic acid (**52**) in place of **37** (see Experimental Section).[25e] The vinyl unit of **38** underwent a selective zirconium-mediated hydrocyanation reaction using Buchwald's procedure (65–80%), and then nitrile **40** was smoothly elaborated to the targeted TMS triene **42** via DIBAL-H reduction and olefination using $Ph_3P{=}C(Me)CO_2Me$ (79% from **40**).

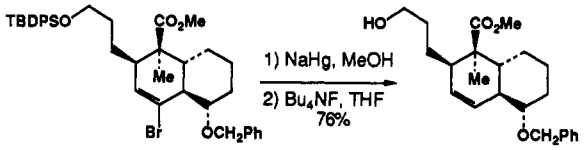
The intramolecular Diels–Alder reaction of **42** was performed at 160 °C as a 0.01 M solution in toluene in the presence of BHT as a radical inhibitor. *Much to our surprise, and in contrast to Boeckman's results, however, we found that the IMDA reaction of 42 provided a 78:14:8 mixture of three cycloadducts (**46a**, **48a**, and **47a**, respectively)*; see Table I, entry 1. The major product, **46a**, could not be separated from its trans-fused alkoxy epimer **47a**, and a 10:1 mixture of these isomers was obtained in 73% yield. A third product, the cis-fused diastereomer **48a**, was isolated in 12% yield. Treatment of the 10:1 mixture of **46a** and **47a** with a large excess of $BF_3{\cdot}Et_2O$ and EtSH provided enantiomerically pure **2** in 82% yield. Stereochemical assignments for the minor products follow from the observation of $J_{4a,8a}$ = 11.4 Hz for **47a** (defining the ring fusion to be trans) and $J_{4a,8a}$ = 3.8 Hz (defining the ring fusion to be cis) and $J_{1,8a}$ = 2.6 Hz for **48a**.

This unexpected result prompted us to braoden the scope of these investigations and examine the influence of both the steric directing group and the dienophile activating group on the stereoselectivity of this key IMDA reaction.[5g,h,j,15a] We were aware in particular of a report by Marshall that the Lewis acid mediated IMDA cyclization of a TMS-substituted trienal related to **44** provided a 10:1 mixture of trans-fused alkoxy epimers (cis-fused diastereomers were not detected)[5j] and remained optimistic that improved stereoselection might be achieved by simple modifications of our Diels–Alder substrate.



46a (containing 10% of **47a**) **2**

Trienes **43–45** were thus synthesized as outlined in Scheme IV, and their IMDA reactions were examined (see Table I). Surprisingly, mixtures of three cycloadducts were again obtained from each triene, even when the IMDA cyclizations of trienals **44** and **45** were performed with Lewis acid catalysts.[27] The stereochemistry of **46b** was assigned by conversion to **30**, an intermediate in our earlier synthesis of **2**. Stereostructural assignments for all other cycloadducts produced from **42–45** are based on detailed ^1H NMR analyses.



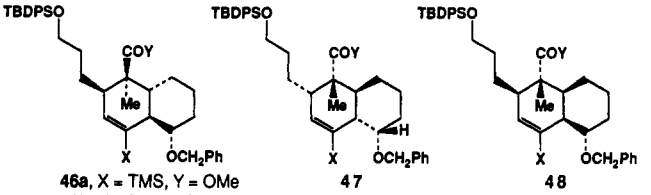
46b **30**

Our results show that the TMS substituent induces better trans selectivity than Br under all conditions examined (compare entries 1 vs 2, 3 vs 6, and 5 vs 7). The only area in which the Br substituent appears to outperform the TMS steric directing group is in the ability to induce equatorial configuration of the benzyloxy substituent in the cyclization transition states. That is, the ratio of alkoxyl epimers (**46**:**47**, from transition states A and B, respectively) was on the order of 9–10:1 in the thermal cyclizations of TMS trienes **42** and **44**, while in the Br series (trienes **43**, **45**) the diastereoselectivity was 15–18:1 for the thermal cyclizations. It should be noted, however, that the ratio of trans-fused alkoxyl diastereomers in the IMDA reactions of triene **11** was only 7:1, so the conclusion that the Br substituent has a greater influence than a TMS group on this stereocchemical issue may not be general.

Concerning the influence of the dienophile activating group, selectivity for the desired trans-fused cycloadduct **46** was better with CHO vs CO_2Me dienophile activation in the bromo triene series (**43** and **45**; entries 2, 6) but not in the thermal cyclizations of TMS trienes **42** and **44** (entries 1, 3). The latter result was surprising, particularly in view of earlier studies on the relationship of dienophile activation to intramolecular Diels–Alder stereoselection.[5g,h,j,15a] Significant improvement in trans stereoselectivity occurred, however, in the Lewis acid catalyzed cyclizations of trienals **44** and **45** (entries 4, 5, 7),[5g,h,j15a] but only the cyclization of TMS trienal **44** was preparatively useful. Thus, the Et_2AlCl-catalyzed cyclization of **44** provided a 89:5:6 mixture of **46c**:**47c**:**48c** in 77% combined yield (entry 4). This substrate is the most efficient IMDA precursor to the bottom half of **1** in terms of stereoselectivity and efficiency of cyclization.

(21) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(22) (a) Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229. (b) On, H. P.; Lewis, W.; Zwiefel, G. *Synthesis* **1981**, 999. (c) Zwiefel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.
(23) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972 and references therein.
(24) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4745.
(25) (a) The high stereoselectivity of this reaction was anticipated on the basis of the known rate difference for the palladium-catalyzed cross-couplings of (*E*)- vs (*Z*)-1-bromoolefins: Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 2529. (b) For other examples of selective cross-couplings of 1,1-dihaloolefins that were reported after our studies with **35** had been initiated, see: Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649. (c) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (d) Trost, B. M.; Walchli, R. *Ibid.* **1987**, *109*, 3487. (e) Additional examples of stereoselective syntheses of (*Z*,*E*)-2-bromo-1,3-dienes via this method have been reported: Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.
(26) Buchwald, S. L.; LaMaire, S. J. *Tetrahedron Lett.* **1987**, *28*, 295.
(27) We cannot rule out the possibility that the fourth cycloadduct (the alkoxyl epimer of **48**) may also have been produced at the <5% level, but inadvertently escaped our notice.

Table I. Intramolecular Diels–Alder Reactions of 42–45



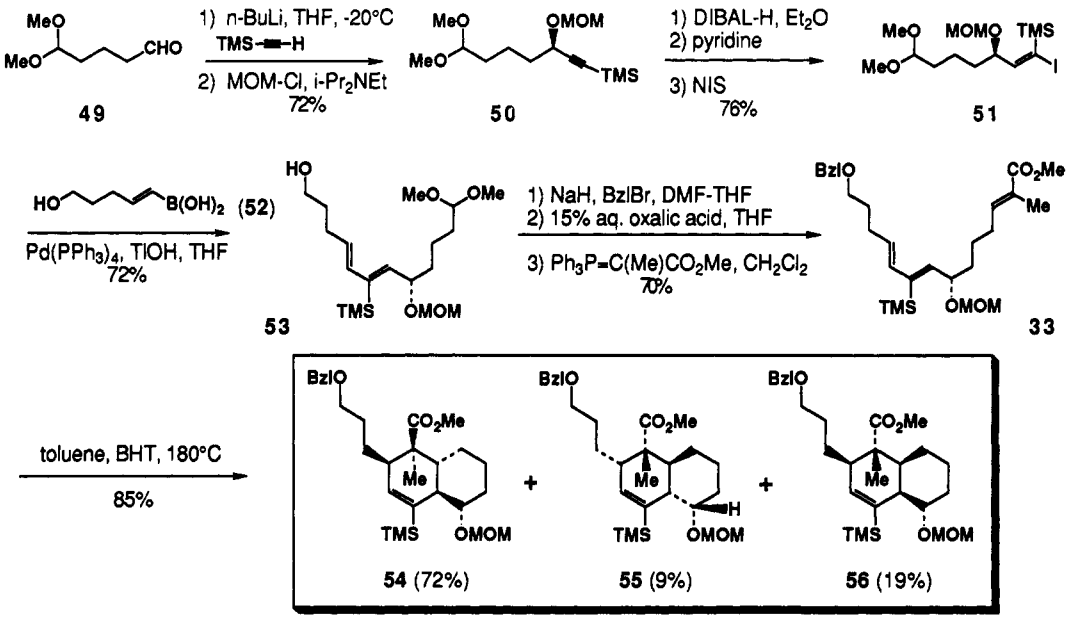
46a, X = TMS, Y = OMe
46b, X = Br, Y = OMe
46c, X = TMS, Y = H
46d, X = Br, Y = H

47 48

entry	triene	conditions[a]	46:47:48[b]	trans/cis[c]	eq:ax[d]	combined yield,[e] %	yield of 46[e], %
1	42	160 °C	78:8:14	86:14	10:1	85	66[f]
2	43	160 °C	62:4:34	66:34	15:1	80	50
3	44	160 °C	79:9:12	88:12	9:1	82	65[f]
4	44	Et_2AlCl, −15 °C	89:5:6	94:6	18:1	77	68[f]
5	44	$EtAlCl_2$, −40 °C	90:5:5	95:5	18:1	32	28[f]
6	45	160 °C	75:3:22	78:22	25:1	86	64
7	45	$EtAlCl_2$, −15 °C	90:1:9	91:9	90:1	24	22
8	45	Et_2AlCl, 23 °C		no reaction			

[a] Thermal reactions were performed in toluene (0.01 M) under N_2 at 160 °C in the presence of BHT. Lewis acid catalyzed reactions were performed in CH_2Cl_2 with 0.95 equiv of Lewis acid. [b] Product ratios were determined by ^1H NMR analysis of crude product mixtures or of partially purified samples (care being taken not to fractionate the diasteeomers). [c] Ratio of 46 + 47 versus 48. [d] Ratio of 46 to 47. [e] Yields of products purified by chromatography. [f] Yield corrected for the presence of 47 that is not separable from 46 under the chromatography conditions employed.

Scheme V



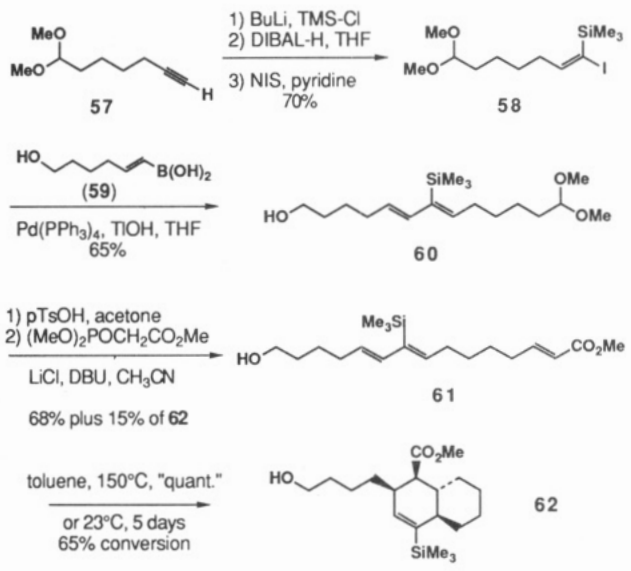
From the standpoint of defining the optimal precursor to **1**, issues other than the stereoselectivity and efficiency of the key IMDA reaction must also be considered. With dibromovinyl compound **35** as the point of reference, the syntheses of trienes **42–45** proceed as follows: **42**, six steps (27% overall yield); **43**, four steps (42%); **44**, eight steps (25%); and **45**, six steps (38%).[28] Thus, in terms of ease of triene synthesis (length and overall yield), yield of cycloadduct **46**, and ease of functional group manipulation following cyclization (an additional step(s) would be required to oxidize the aldehyde units present in **46c** and **46d**), and given the method of synthesis developed here, bromo triene **43** is in fact the optimal precursor to **1**. That is, the brevity and efficiency of the synthesis of **43** compensates for the fact that it is the least selective IMDA substrate. Syntheses that proceed by way of TMS trienoates like **42** or TMS trienals like **44** become competitive only if a much more efficient triene synthesis is devised.

The discrepancy between our results with **42** and those of Boeckman with **33** remained a matter of concern. We considered the possibility that the different set of protecting groups in the otherwise identical pair of trienes might have influenced the IMDA stereoselectivity[29] and decided to reexamine the intramolecular Diels–Alder re-

(28) Attempts to shorten the syntheses of TMS trienals **44** and **45** by using direct olefination methods for introducing the unsaturated aldehyde units gave considerably lower yields (43%) of less pure products than did the three-step sequences summarized in Figure 4 (e.g., (a) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391. (b) Corey, E. J.; Enders, P.; Bock, M. G. *Ibid.* **1976**, 7).

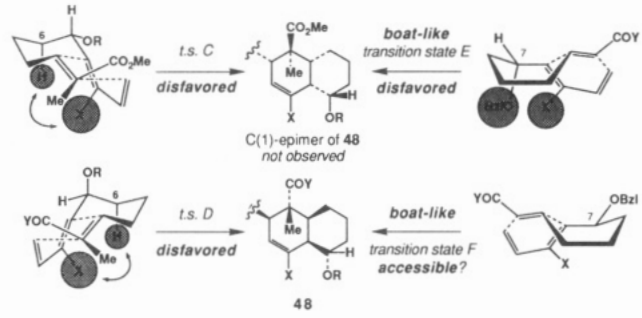
(29) Very significant differences in stereoselectivity have been observed in the Lewis acid catalyzed IMDA reactions of 7-alkoxy-2,8,10-decatrienals with allylic silyl vs allylic MOM ethers (cf. refs 5g,h,i) and we earlier noticed a modest dependence of stereoselectivity on the protecting group in the IMDA cyclizations of 6-alkoxy-2,7,9-nonatrienoates: Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008.

Scheme VI



action of **33**. Our synthesis of **33** (racemic) and the results of our reinvestigation of its thermal isomerization chemistry are summarized in Scheme V. In our hands, the IMDA reaction of **33** provided a mixture of three cycloadducts **54**, **55**, and **56** (corresponding to **46a–48a** for the cyclization of **42**) in the ratio 72:9:19, respectively. This product distribution is very similar to the ratio of products that we observed from **42** (Table I, entry 1). The cycloaddition of **33** was performed at concentrations ranging from 10^{-2} to 10^{-4} M with no apparent change in yield or product distribution. We found no evidence for the "bimolecular dimer" that Boeckman and Barta noted in their paper,[5f] and in our hands **33** did not appear to be significantly less reactive than trienes such as **3** that we had previously studied. Finally, the results of the IMDA reactions of **33** were not influenced by the way in which **33** had been purified or the way the glassware had been cleaned (base washed; base washed and pre-silylated; silylated in situ by using BSA): this suggests that our experiments were not compromised by the presence of an impurity that "catalyzed" the formation of diastereomers not observed by the Rochester group.[5f]

Our prediction that the IMDA diastereoselectivity of C(9)-substituted trienes would be greatest with the largest possible steric directing group X is correct, since diastereoselectivity is consistently greater with TMS- than Br-containing substrates.[11,30] Significantly more cis-fused product (12–45% for the thermal cyclization of trienes **11–13**, **33**, and **42–45**), however, was obtained than expected on the basis of the transition state analysis presented at the outset, which suggested that cis-fused, chair-like transition states C and D should be highly destabilized by the interaction between the C(9) steric directing group and the axial C(6) proton. While this prediction is undoubtedly correct, we failed to consider the possibility that boat-like transition states also might be accessible.[31] In this vein, we now attribute the production of cis-fused cycloadducts **48** in the thermal cyclizations of **42–45**, or of **56** in the IMDA reaction of **33**, etc., to the intervention of boat-like transition state F, which apparently is not significantly destabilized by interactions involving the C(9) steric directing group. Thus, while transition state F is probably minor relative to C or D in the cyclizations of trienes with X = H, when X = TMS transition states C and D are sufficiently destabilized that the boat-like arrangement F remains as a serious competitor for the desired pathway A. A greater amount of cis-fused diastereomer **48** (via F) is produced when X = Br than when X = TMS, however, since the Br group is only moderately sterically demanding,[11,30] and interactions with C(7)-H in F are expected to be less serious when X = Br than when X = TMS. That is, F is expected to be more accessible in the X = Br series. This analysis also accounts for the absence of the second cis-fused diastereomer (cf., the alkoxy epimer of **48**) in each of these reactions,[27] since boat-like transition state E is destabilized by a 1,3-interaction between the steric directing group X and the pseudo-axial C(7)-benzyloxy substituent.



In our earlier studies on the intramolecular Diels–Alder reactions of simple 2,8,10-undecatrienoates, we found that, in contrast to **3**, trienes lacking an alkoxy substituent at C(7) cyclized to roughly 1:1 mixtures of cis- and trans-fused products.[6c,32] We have suggested that C(7) alkoxy substituents destabilize the trans-fused transition state for steric reasons,[32] although electronic effects cannot be ruled out.[7i] In any event, this suggests that the C(7)-alkoxy substituents of **33**, **42–45**, and other trienes in this series cause the trans-fused transition states (cf., A, B) to be closer in energy to the cis-fused counterparts (C, D, and in particular transition state F that lacks the serious interactions involving X) than would be the case for substrates lacking the C(7)-alkoxyl group and therefore that trienes possessing C(9) steric directing groups but lacking C(7)-alkoxy substitution should exhibit exceptional selectivity for the trans-fused product.

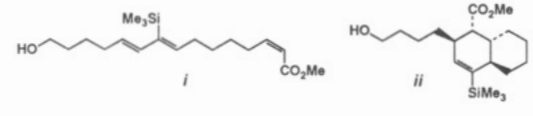
Triene **61** was synthesized to test this hypothesis (Scheme VI). This triene smoothly cyclized in toluene at 150 °C to give a single, trans-fused cycloadduct **62** in quantitative yield. No other stereoisomers were detected as long as **61** was isomerically pure.[33] Interestingly, this triene proved to be considerably more reactive than any other 2,8,10-undecatrienoate that we have examined. For example, cycloadduct **62** was obtained in 15% yield when the modified Horner–Wadsworth–Emmons reaction[34]

(30) The *A* value of Br is 0.4–0.5 kcal mol^{-1}: Hirsch, J. A. *Top. Stereochem.* **1967**, *1*, 199.

(31) For a detailed analysis of boat transition states in the IMDA reactions of substituted 1,7,9-decatrien-3-ones and 1,7,9-decatrienes, see: Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915.

(32) Roush, W. R.; Gillis, H. R. *J. Org. Chem.* **1982**, *47*, 4825.

(33) An inseparable 9:1 mixture of **61** and its (*Z*)-dienophile isomer (i) was obtained from the reaction of aldehyde **63** and $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2 (88% yield). Thermolysis of this mixture in toluene at 150 °C provided in quantitative yield a 9:1 mixture of **62** and its axial carbomethoxyl epimer, ii.

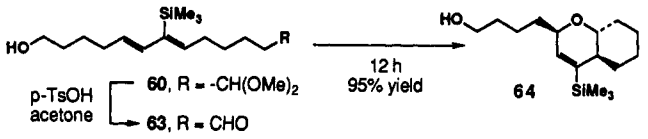


(34) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

leading to **61** was allowed to proceed overnight at 23 °C, and when an NMR sample of **61** was periodically examined, it was found that the IMDA cyclization had occurred to the extent of 65% after 5 days at room temperature. In our experience, triene **61** is the first member of the 2,8,10-undecatrienoate family to exhibit such pronounced reactivity.

Our results with **61** suggest that the TMS substituent increases the reactivity of the diene and therefore also the rate of the IMDA reaction, in contrast to previous implications that TMS-substituted trienes are less reactive than the parent systems.[5f] This thesis is supported also by our observation that aldehyde **63** underwent a novel acid-catalyzed intramolecular [4 + 2]-cycloaddition that provided **64** as a single stereoisomer. This reaction was first observed during attempts to deprotect acetal **60** under standard acid-catalyzed conditions. When such reactions are allowed to proceed for an overnight period, **64** is produced in essentially quantitative yield. The optimal conditions for the preparation of **63** and the minimization of its cyclization to **64** involve treatment of **60** with catalytic *p*-TsOH in acetone for 2–2.5 h at room temperature.

Previous attempts in our laboratory to accomplish the IMDA cyclizations of diene aldehydes lacking TMS substituents have failed. It is noteworthy therefore that the cyclization of **63** proceeds with such facility. Whether this is in fact a "hetero-Diels–Alder" reaction, however, is an open question. The trans-ring fusion of **64** was readily assigned by ^{1}H NMR methods, but the stereochemistry at the third center could not be assigned unambiguously. Since there is no evidence at present to argue otherwise, we have assigned the final stereocenter to be as shown, based on the assumption of the usual Diels–Alder paradigm.



In conclusion, results have been presented that suggest that boat-like transition state F is responsible for the production of cis-fused cycloadducts that are minor products of the IMDA reactions of C(9)-Br- and C(9)-TMS-substituted trienes **11–13**, **33**, and **42–45**. We have shown that the C(9)-TMS steric directing group is more effective than a C(9)-Br group in inducing a trans-ring fusion in the cycloaddition process, and maximal selectivity for cycloadducts possessing the stereochemistry required for the chlorothricolide bottom half occurs with TMS trienal substrates such as **44**. In terms of developing the most efficient synthesis of the bottom-half fragment **2**, however, C(9)-Br-substituted triene **43** is the best Diels–Alder substrate owing to the efficiency and brevity of its synthesis, as well as the ease of manipulation of all functionality following the IMDA cyclization. Additional progress on the completion of a total synthesis of chlorothricolide 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.

^{1}H NMR spectra were measured at 250, 300, 360, 400, and 500 MHz on commercially available instruments. Residual chloroform (δ 7.26) was used as internal reference for spectra measured in $CDCl_3$. ^{1}H NMR spectra measured in CD_3OD were referenced against the CHD_2OD (δ 3.30) or the HOD resonances (δ 4.80). ^{13}C NMR spectra were recorded at 75.4 MHz and were referenced with the δ 77.0 resonance of $CDCl_3$. 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 (PTLC) was performed by using 20 × 20 cm plates coated with a 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).[35] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (by ^{1}H NMR analysis) for use in subsequent reactions.

(2*R*,3*S*)-3-(Benzyloxy)hexane-1,2,6-triol 1,2-Acetonide (17). To a stirred suspension of 1.15 g of NaH (57% oil dispersion, pentane washed, 28 mmol) in 50 mL of dry DMF was added 4.7 g (27 mmol, 5 mL, neat) of **16** at 0 °C. The mixture was stirred at 0 °C for 15 min, and then 3.25 mL (27.3 mmol) of benzyl bromide was added. This mixture was stirred at 23 °C for 2 h and then partitioned between aqueous NH_4Cl (250 mL) and Et_2O. The aqueous phase was extracted with additional Et_2O. The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by chromatography on a silica gel (300 g, 4:1 hexane–ether), giving 6.59 g (92%) of the known benzyl ether **34** ($[\alpha]^{23}_D$ +35.4° (*c* 2.3, $CHCl_3$)).[12b] The small amount (ca. 2%) of the syn diastereomer was separated at this stage.

A solution of 3.67 g (14 mmol) of the above benzyl ether **34** in 30 mL of THF at 0 °C was treated with 14 mL of 1 M BH_3 in THF (14 mmol). This mixture was stirred for 2 h at 23 °C, then was cooled to 0 °C, and treated sequentially with 1.5 mL of water, 5 mL of 3 M NaOH, and 3.3 mL of 30% H_2O_2. This mixture was stirred for 2.3 h at 23 °C, diluted with water (150 mL), acidified with 10% HCl, extracted with ether, and washed with saturated $NaHCO_3$ and brine. The crude alcohol **17** (3.94 g, quantitative) so obtained was pure enough to use directly in the next reaction. A sample was purified chromatographically for analytical purposes: $[\alpha]^{25}_D$ +16.2° (*c* 2.1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.29 (m, 5 H), 4.64 (A of AB, 1 H, *J* = 11.7 Hz), 4.57 (B of AB, 1 H, *J* = 11.7 Hz), 4.05 (dd, 1 H, *J* = 15.7, 6.1 Hz), 4.09 (d, 1 H, *J* = 15.7 Hz), 3.86 (br dd, 1 H, *J* = 7.9, 6.4 Hz), 3.57 (m, 3 H), 1.76 (br s, 1 H, OH), 1.63 (m, 4 H), 1.40 (s, 3 H), 1.33 (s, 3 H); IR (neat) 3570–3120 (br, OH), 3040, 2980, 2940, 2860, 1450, 1380, 1200, 1050 cm^{-1}; mass spectrum *m/z* 265 ($M^+ - CH_3$). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H; 8.63. Found: C, 68.29; H; 8.37.

(5*S*,6*R*)-5-(Benzyloxy)-6,7-dihydroxyheptanenitrile 6,7-Acetonide (18). A mixture of 3.94 g (14 mmol, theoretically) of **17** and 2.9 mL of Et_3N (21 mmol) in 70 mL of CH_2Cl_2 was treated with 1.4 mL of CH_3SO_2Cl (18 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min, then was diluted with ether, and washed with water, 10% HCl, saturated $NaHCO_3$, and brine. The extracts were dried ($MgSO_4$) and concentrated in vacuo, and the crude mesylate (5.0 g) was used directly in the following reaction: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.63 (A of AB, 1 H, *J* = 11.4 Hz), 4.55 (B of AB, 1 H, *J* = 11.4 Hz), 4.19 (t, 2 H, *J* = 6.3 Hz), 4.06 (m, 2 H), 3.85 (m, 1 H), 3.53 (dt, 1 H, *J* = 8.5, 3.2 Hz), 2.96 (s, 3 H), 1.75 (m, 4 H), 1.40 (s, 3 H), 1.33 (s, 3 H); IR (neat) 2980, 2940, 1450, 1350, 1160 cm^{-1}.

The crude mesylate (5.0 g) was dissolved in 50 mL of DMF and treated with 892 mg (18 mmol) of NaCN and 74 mg (0.2 mmol) of *n*-Bu_4NI. This mixture was heated at 80 °C for 2 h and then was cooled and diluted with 250 mL of aqueous NH_4Cl. This mixture was extracted with ether (2 × 100 mL). The organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified chromatographically (200 g of silica gel, 4:1 hexane–ether), giving 3.26 g (80% yield) of **18**: $[\alpha]^{23}_D$ +51.3° (*c* 1.5, $CHCl_3$); ^{1}H NMR (250 MH_3, $CDCl_3$) δ 7.31 (m, 5 H), 4.63 (A of AB, 1 H, *J* = 11.4 Hz), 4.56 (B of AB, 1 H, *J* = 11.4 Hz), 4.06 (m, 2 H), 3.85 (m, 1 H), 3.51 (m, 1 H), 2.30 (m, 2 H), 1.73 (m, 4 H), 1.40 (s, 3 H), 1.33

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(s, 3 H); IR (neat) 3030, 2980, 2940, 2900, 2240, 1495, 1450, 1370, 1050 cm^{-1}; mass spectrum m/z 289 (parent ion). Anal. Calcd for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01. Found: C, 70.33; H, 8.07.

Aldehyde 19. A solution of 2.54 g of **18** (8.8 mmol) in 70 mL of 50% HOAc–MeOH was heated at reflux for 8 h. The reaction mixture was concentrated in vacuo, and the residue was chromatographed on a silica gel (50 g) using a gradient of ether–hexane to pure ether, giving 1.83 (84%) of diol: $[\alpha]^{23}_D$ −3.2° (*c* 1.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 4.58 (s, 2 H), 3.74 (m, 3 H), 3.52 (m, 1 H), 2.49 (br d, 1 H, OH), 2.29 (m, 2 H), 2.05 (br s, 1 H, OH), 1.76 (m, 4 H); IR (neat) 3400 (br), 2240, 1100 (br) cm^{-1}; mass spectrum m/z 249 (parent ion). Anal. Calcd for $C_{16}H_{19}O_3N$: C, 67.45; H, 7.68. Found: C, 67.37; H, 7.67.

A 5 °C solution of 1.73 g of the above diol (6.9 mmol) in 33 mL of THF and 33 mL of water was treated with 3.0 g of $NaIO_4$ (14 mmol) portion wise. After being stirred for 1 h at 23 °C, the mixture was diluted with water (120 mL), extracted with ether, and washed with brine. The extracts were dried ($MgSO_4$) and concentrated in vacuo to give 1.58 g (100%) of **19** that was used directly in the following reaction: $[\alpha]^{23}_D$ −77.8° (*c* 2.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.64 (d, 1 H, *J* = 2.0 Hz), 7.33 (m, 5 H), 4.69 (A of AB, 1 H, *J* = 11.2 Hz), 4.52 (B of AB, 1 H, *J* = 11.2 Hz), 3.78 (m, 1 H), 2.30 (t, 2 H, *J* = 6.6 Hz), 1.79 (m, 4 H); IR (neat) 3060, 3025, 2960, 2240, 1730, 1495, 1450, 1100 (br) cm^{-1}; mass spectrum m/z 188 (M^+ − CHO). Anal. Calcd for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96 Found: C, 71.54; H, 7.01.

α-Bromo-α,β-unsaturated Aldehyde 20. A mixture of 1.58 g (6.9 mmol) of **19** and 2.53 g (8.3 mmol) of $Ph_3P{=}CHCHO$ in 40 mL of benzene was heated at reflux for 3 h. The cooled mixture was then concentrated in vacuo. The crude product was purified by chromatography on silica gel (80 g) using ether–hexane (gradient) to give 1.40 g (83% yield) of the intermediate α,β-unsaturated aldehyde as a ca. 10:1 mixture of olefin isomers: $[\alpha]^{23}_D$ −52.7° (*c* 1.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.60 (d, 1 H, *J* = 7.8 Hz), 7.33 (m, 5 H), 6.71 (dd, 1 H, *J* = 15.8, 5.8 Hz), 6.30 (dd, 1 H, *J* = 15.9, 8.2 Hz), 4.59 (A of AB, 1 H, *J* = 11.7 Hz), 4.37 (B of AB, 1 H, *J* = 11.7 Hz), 4.11 (m, 1 H), 2.32 (t, 2 H, *J* = 6.5 Hz), 1.75 (m, 4 H); IR (neat) 2240, 1685, 1640 cm^{-1}; mass spectrum m/z 243 (parent ion). Anal. Calcd for $C_{15}H_{17}O_2N$: C, 74.05; H, 7.04. Found: C, 74.17; H, 7.25.

To a solution of 1.33 g of the above aldehyde (5.5 mmol) in 40 mL of $CHCl_3$ at 0 °C was added 1.63 g of dioxane dibromide (6.6 mmol) portionwise. The solution was stirred for 1 h at 0 °C; then 2.2 mL of pyridine (28 mmol) was added dropwise. This mixture was stirred for 30 min at 0 °C and 2 h at 23 °C. It was then diluted with water (15 mL), extracted with ether, and washed with 10% saturated $NaHCO_3$ and brine. The extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified on silica gel (50 g) using 1:1 ether–hexane as eluant to give 1.49 g (85% yield) of **20** that proved to be somewhat unstable to storage (as a result, an acceptable CH analysis was not obtained): $[\alpha]^{23}_D$ +4.7° (*c* 2.1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 7.32 (m, 5 H), 7.04 (d, 1 H, *J* = 7.9 Hz), 4.57 (A of AB, 1 H, *J* = 11.8 Hz), 4.51 (m, 1 H), 4.43 (B of AB, 1 H, *J* = 11.8 Hz), 2.34 (m, 2 H), 1.80 (m, 4 H); IR (neat) 3040, 3020, 2960, 2860, 2240, 1700 (br), 1620, 1080 cm^{-1}; mass spectrum m/z 321 (parent ion); high resolution mass spectrum for $C_{15}H_{16}NO_2Br$, calcd 323.0346, found 323.0359.

Diene Ester 21. A mixture of 966 mg of **20** (30 mmol) and 2.0 g of $Ph_3P{=}CHCO_2Me$ (60 mmol) in 10 mL of CH_2Cl_2 was stirred overnight at 23 °C. The reaction mixture was concentrated in vacuo, and the residue was purified on silica gel (30 g) using 1:1 ether–hexane, giving 1.09 g (96%) of **21**: $[\alpha]^{23}_D$ −40.7° (*c* 1.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 6.32 (d, 1 H, *J* = 7.3 Hz), 6.28 (d, 1 H, *J* = 14.3 Hz), 4.55 (A of AB, 1 H, *J* = 11.7 Hz), 4.41 (m, 1 H), 4.35 (B of AB, 1 H, *J* = 11.7 Hz), 3.77 (s, 3 H), 2.31 (t, 2 H, *J* = 6.5 Hz), 1.79 (m, 4 H); IR (neat) 3060, 3030, 2950, 2860, 2240, 1720 (br), 1630, 1600, 960, 915 cm^{-1}; mass spectrum m/z 377 (parent ion). Anal. Calcd for $C_{18}H_{20}O_3NBr$: C, 57.15; H, 5.33. Found: C, 56.87; H, 5.49.

Methyl (2*E*,7*S*,8*Z*,10*E*)-7-(Benzyloxy)-9-bromo-12-hydroxydodeca-2,8,10-trienoate (11). A solution of 113 mg of nitrile ester **21** (0.3 mmol) in 10 mL of ether at −78 °C was treated with 3 mL of 1 M DIBAL-H in hexane (3 mmol). The solution was stirred for 2 h; then excess DIBAL-H was quenched with water. The mixture was acidified with 10% HCl, allowed to warm to 23 °C, then extracted with ether, and washed with 10% HCl, 10% aqueous NaOH, water, and brine. The extracts were dried ($MgSO_4$) and concentrated in vacuo to give 96 mg (0.27 mmol) of crude hydroxy aldehyde. This material was dissolved in 5 mL of CH_2Cl_2 and treated with 180 mg (0.54 mmol) of $Ph_3P{=}CHCO_2Me$. This mixture was stirred overnight at 23 °C; then it was concentrated and the residue was purified by preparative TLC (2 mm silica gel, 1:1 ether–hexane), giving 61 mg (50%) of triene **11**: $[\alpha]^{23}_D$ −22.0° (*c* 1.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.91 (dt, 1 H, *J* = 15.6, 7.0 Hz), 6.32 (d, 1 H, *J* = 15.1 Hz), 6.24 (dt, 1 H, *J* = 14.8, 4.2 Hz), 5.92 (d, 1 H, *J* = 8.2 Hz), 5.78 (d, 1 H, *J* = 15.8 Hz), 4.54 (A of AB,1 H, *J* = 11.7 Hz), 4.41 (m, 1 H), 4.35 (B of AB, 1 H, *J* = 11.7 Hz), 4.30 (br s, 2 H), 3.70 (s, 3 H), 2.17 (m, 2 H), 1.50 (m, 5 H); IR (neat) 3440 (br), 2960, 2880, 1725, 1705 (sh), 1655, 1610, 980, 950 cm^{-1}; mass spectrum m/z 283 (no parent ion observed). Anal. Calcd for $C_{20}H_{25}O_4Br$: C, 58.81; H, 6.16. Found: C, 58.75; H, 6.24.

Methyl (2*E*,7*S*,8*Z*,10*E*)-7-(Benzyloxy)-9-bromo-12-hydroxy-2-methyldodeca-2,8,10-trienoate (12). Ester nitrile **21** (113 mg, 0.3 mmol) was reduced with excess DIBAL using the procedure described for the preparation of **11**. The crude aldehyde (89 mg, 0.25 mmol) so obtained was treated overnight with 174 mg (0.5 mmol) of $Ph_3P{=}C(Me)CO_2Me$ in 4 mL of CH_2Cl_2. The reaction mixture was concentrated in vacuo and the residue was purified by preparative TLC (2-mm silica gel plate, 2:1 ether–hexane), giving 64 mg (61%) of **12**: $[\alpha]^{23}_D$ −20.2° (*c* 2.2, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.71 (t, 1 H, *J* = 7.5 Hz), 6.33 (d, 1 H, *J* = 15.0 Hz), 6.24 (dt, 1 H, *J* = 14.8, 4.1 Hz), 5.92 (d, 1 H, *J* = 8.3 Hz), 4.54 (A of AB, 1 H, *J* = 11.7 Hz), 4.41 (m, 1 H), 4.36 (B of AB, 1 H, *J* = 11.7 Hz), 4.30 (br s, 2 H), 3.70 (s, 3 H), 2.15 (m, 2 H), 1.78 (s, 3 H), 1.60 (m, 5 H); IR (neat) 3440, 1710, 1690, 1645, 1080 (br), 945 cm^{-1}; mass spectrum m/z 283 (no parent ion observed). Anal. Calcd for $C_{21}H_{27}O_4Br$: C, 59.58; H, 6.43. Found: C, 59.28; H, 6.47.

Triene Ester 22. A solution of 0.34 mL of diisopropylamine in 5 mL of THF at −78 °C was treated with 0.95 mL of 2.1 M *n*-BuLi in hexane (2.4 mmol). This solution was stirred for 30 min at −78 °C; then 600 mg of triethyl phosphonocrotonate in 1 mL of THF was added. This mixture was stirred for 30 min at −78 °C; then 414 mg (1.3 mmol) of **20** in 1 mL of THF was added dropwise. This mixture was stirred for 30 min at −78 °C and 30 min at 23 °C before being quenched with aqueous NH_4Cl. The solution was extracted with ether. The extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified on silica gel (15 g) using 1:2 ether–hexane as eluant, giving 293 mg (54%) of **22**. The yield was 67% from smaller scale experiments: $[\alpha]^{23}_D$ −58.6° (*c* 1.6, $CHCl_3$): ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (dd, 1 H, *J* = 11.2, 14.4 Hz), 7.29 (m, 5 H), 6.71 (dd, H, *J* = 14.4, 11.2 Hz), 6.51 (d, 1 H, *J* = 14.4 Hz), 6.10 (d, 1 H, *J* = 8.1 Hz), 6.02 (d, 1 H, *J* = 15.3 Hz), 4.56 (A of AB, 1 H, *J* = 11.7 Hz), 4.41 (m, 1 H), 4.36 (B of AB, 1 H, *J* = 11.7 Hz), 4.21 (q, 2 H, *J* = 7.1 Hz), 2.31 (t, 2 H, *J* = 6.7 Hz), 1.76 (m, 4 H), 1.29 (t, 3 H, *J* = 7.1 Hz); IR (neat) 2240, 1715 (shoulder) 1700, 1625, 1590, 985, 930 cm^{-1}; mass spectrum m/z 417 (parent ion). Anal. Calcd for $C_{21}H_{24}O_3NBr$: C, 60.42; H, 5.78. Found: C, 60.54; H, 5.77.

Methyl (2*E*,7*S*,8*Z*,10*E*,12*E*)-7-(Benzyloxy)-9-bromo-14-hydroxy-2-methyltetradeca-2,7,8,10-tetraenoate (13). To a solution of 185 mg of **22** (0.44 mmol) in 8 mL of toluene at −78 °C was added 4.4 mL of 1 M DIBAL-H in hexane (4.4 mmol). After being stirred for 3 h at −78 °C, the mixture was quenched with water and acidified with 10% HCl. The cold solution was allowed to warm to 23 °C, then extracted with ether, and washed with 10% HCl, aqueous NaOH, water, and brine. The extracts were dried ($MgSO_4$), filtered, and concentrated to give 169 mg (100%) of hydroxy aldehyde that was used directly in the following reaction: ^1H NMR (250 MHz, $CDCl_3$) δ 9.72 (t, 1 H, *J* = 1.5 Hz), 7.29 (m, 5 H), 6.64 (dd, 1 H, *J* = 10.7, 14.4 Hz), 6.36 (dd, 1 H, *J* = 15.2, 10.7 Hz), 6.21 (d, 1 H, *J* = 14.4 Hz), 6.00 (dt, 1 H, *J* = 15.2, 5.5 Hz), 5.93 (d, 1 H, *J* = 8.4 Hz), 4.55 (A of AB, 1 H, *J* = 11.7 Hz), 4.41 (m, 1 H), 4.36 (B of AB, 1 H, *J* = 11.7 Hz), 4.24 (d, 2 H, *J* = 5.2 Hz), 2.40 (br t, 2 H, *J* = 6.5 Hz), 1.66 (m, 5 H); IR (neat) 3410 (br), 3020, 2920, 2860, 1725, 1620, 1605, 975 cm^{-1}.

A solution of the above hydroxy aldehyde (169 mg, 0.44 mmol) and 348 mg of $Ph_3P{=}C(Me)CO_2Me$ in 5 mL of CH_2Cl_2 was stirred overnight at 23 °C. The mixture was concentrated in vacuo, and

tetraene was purified by short column chromatography (silica gel, 1:1 ether–hexane), giving 155 mg (78%) of **13**: $[\alpha]^{23}_D$ −30.3° (*c* 1.8, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.71 (br t, 1 H, *J* = 7.4 Hz), 6.64 (dd, 1 H, *J* = 10.7, 14.4 Hz), 6.36 (dd, 1 H, *J* = 15.1, 10.7 Hz), 6.21 (d, 1 H, *J* = 14.4 Hz), 6.00 (dt, 1 H, *J* = 15.2, 5.5 Hz), 5.91 (d, 1 H, *J* = 8.3 Hz), 4.54 (A of AB, 1 H, *J* = 11.7 Hz), 4.38 (m, 1 H), 4.36 (B of AB, 1 H, *J* = 11.7 Hz), 4.24 (m, 2 H), 3.70 (s, 3 H), 2.15 (m, 2 H), 1.78 (s, 3 H), 1.59 (m, 5 H); IR (neat) 3420 (br), 3020, 2990, 2930, 2870, 1700, 1640 (sh), 1615 (sh) 975 cm^{-1}; mass spectrum *m/z* 448 (parent ion). Anal. Calcd for $C_{23}H_{29}BrO_4$: C, 61.47; H, 6.50. Found: C, 61.26; H, 6.62.

Intramolecular Diels–Alder Reaction of 11. 1α-(Benzyloxy)-8-bromo-6β-(hydroxymethyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylic Acid γ-Lactone (23a), 1α-(Benzyloxy)-8-bromo-6α-(hydroxymethyl)-1,2,3,4,4aα,5,6,8aβ-octahydronaphthalene-5α-carboxylic Acid γ-Lactone (23b), Methyl 1α-(Benzyloxy)-8-bromo-6β-(hydroxymethyl)-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (24a), and Methyl 1α-(Benzyloxy)-8-bromo-6α-(hydroxymethyl)-1,2,3,4,4aβ,5,6,8aβ-octahydronaphthalene-5β-carboxylate (24b). A mixture of 142 mg (0.35 mmol) of **11** and 0.22 mL of bis(trimethylsilyl)acetamide (BSA, 0.9 mmol) in 3 mL of toluene was flushed with Ar and transferred to a resealable Carius tube. After being allowed to stand for 1 h at 23 °C, the tube was placed in a 170 °C oil bath for 24 h. The reaction mixture was cooled and concentrated in vacuo. Analysis of this mixture by gas chromatography (10-ft SE 30 column, 210 °C) revealed four components in a ratio of 70:16:11:3, corresponding to **23a**, **24a**, **23b**, and **24b**, respectively. The crude product was dissolved in THF (5 mL) and treated with catalytic pTsOH at 23 °C for 2 days. The mixture was concentrated in vacuo and the reaction products were partially separated by preparative TLC (2-mm silica gel plate, 1:1 hexane–ether, two developments). This provided 10.5 mg (8%) of pure **23b** (R_f 0.77) and 108 mg (76%) of the mixture of **23a**, **24a**, and **24b** (R_f 0.4–0.7). The latter mixture was further fractionated by preparative TLC (two 0.5-mm silica gel plates, 4:1 CH_2Cl_2–hexane, two developments), giving 64 mg (49%) of **23a** (R_f 0.6), 2.4 mg (2%) of impure **24b** (R_f 0.4), and 20 mg (14%) of **24a** (R_f 0.2).

Data for **23a**: mp 107–108 °C; $[\alpha]^{23}_D$ +89.2° (*c* 1.3, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 6.09 (dd, 1 H, *J* = 2.9, 2.9 Hz), 4.63 (A of AB, 1 H, *J* = 10.6 Hz), 4.56 (B of AB, 1 H, *J* = 10.5 Hz), 4.42 (br dd, 1 H, *J* = 8.5 Hz), 4.04 (dd, 1 H, *J* = 6.8, 9.1 Hz), 3.44 (ddd, 1 H, *J* = 9.8, 9.8, 5.1 Hz, H_1), 3.11 (m, 1 H, H_6), 2.50 (dd, 1 H, *J* = 10.5, 9.3 Hz, H_5), 2.40 (m, 1 H), 2.21 (m, 2 H, includes H_{8a}, $J_{4a,8a}$ = 10.9 Hz), 1.82 (m, 1 H), 1.68 (qd, 1 H, *J* = 10.9, 3.8 Hz, H_{4a}), 1.40–1.07 (m, 4 H); IR ($CHCl_3$) 3000, 2925, 2860, 1780 (shoulder), 1770, 1165, 1145 cm^{-1}; mass spectrum *m/z* 376 (parent ion). Anal. Calcd for $C_{19}H_{21}O_3Br$: C, 60.49; H, 5.61. Found: C, 60.58; H. 5.81.

Data for **23b**: mp 126–127 °C; $[\alpha]^{23}_D$ −29.5° (*c* 0.93, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.09 (dd, 1 H, *J* = 4.9, 2.4 Hz, H_7), 4.57 (A of AB, 1 H, *J* = 11.3 Hz), 4.48 (B of AB, 1 H, *J* = 11.3 Hz), 4.42 (br dd, 1 H, *J* = 8.6 Hz), 4.26 (m, 1 H, $J_{1,8a}$ = 2 Hz, H_1), 3.95 (dd, 1 H, *J* = 11, 8.6 Hz), 3.13 (m, 1 H, H_6), 2.30 (m, 2 H, H_5 and H_{8a}), 2.17 (m, 3 H, includes H_{4a}), 1.40–1.09 (m, 4 H); IR ($CHCl_3$) 3000, 2940, 2850, 1775, 1765 (shoulder), 1160, 900 cm^{-1}; mass spectrum *m/z* 376 (parent ion). Anal. Calcd for $C_{19}H_{21}O_3Br$: C, 60.49; H, 5.61. Found: C, 60.29; H, 5.73.

Data for **24a**: mp 77–78 °C; $[\alpha]^{23}_D$ +77.8° (*c* 9.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.99 (d, 1 H, *J* = 3.0 Hz, H_7), 4.61 (A of AB, 1 H, *J* = 12.0 Hz), 4.53 (B of AB, 1 H, *J* = 12.0 Hz), 3.67 (s, 3 H), 3.43 (m, 3 H), 2.74 (m, 1 H, H_6), 2.68 (t, 1 H, *J* = 11 Hz, H_5), 2.51 (dd, 1 H, $J_{1,8a}$ = 9.8 Hz, $J_{4a,8a}$ = 4.2 Hz, H_{8a}), 2.40 (m, 1 H, H_{4a}), 2.09 (m, 1 H), 1.62–1.09 (m, 6 H): IR ($CHCl_3$) 3000, 2940, 2860, 1730, 1720 (shoulder), 1190, 1165 cm^{-1}; mass spectrum *m/z* 329 (M^+ − Br). Anal. Calcd for $C_{20}H_{25}O_4Br$: C, 58.69; H, 6.16. Found: C, 58.92; H, 6.26.

Partial data for **24b**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 6.03 (d, 1 H, *J* = 2.6 Hz, H_7), 4.58 (A of AB, 1 H, *J* = 11.3 Hz), 4.35 (B of AB, 1 H, *J* = 11.3 Hz), 3.98 (m, 1 H, includes $J_{1,8a}$ = 2–3 Hz, H_1), 3.66 (s, 3 H), 3.41 (t, 2 H, *J* = 5.4 Hz), 3.21 (dd, *J* = 12.3, 10.0 Hz, H_5), 2.75 (m, 1 H, H_6). The acetate derivative, prepared by the standard acylation procedure (Ac_2O, pyridine, CH_2Cl_2), was more fully characterized: ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.02 (br s, 1 H, H_7), 4.57 (A of AB, 1 H, *J* = 11.9 Hz), 4.38 (B of AB, 1 H, *J* = 11.9 Hz), 3.97 (m, 1 H, H_1), 3.86 (A of ABX, *J* = 10.8, 6.8 Hz, 1 H, $H_{1a'}$), 3.73 (B of ABX, *J* = 10.8, 7.2 Hz, 1 H, $H_{1b'}$), 3.67 (s, 3 H), 3.16 (dd, 1 H, *J* = 10, 11 Hz, H_5), 2.87 (m, 1 H, H_6), 2.36 (m, 1 H), 2.26 (m, 1 H), 2.07 (m, 1 H), 1.91 (s, 3 H); IR ($CHCl_3$) 2940, 2870, 1730, 1260, 1250, 1235, 1170 cm^{-1}; mass spectrum *m/z* 452 (M^+), 421 (M^+ − OMe).

Intramolecular Diels–Alder Reaction of 12. 1α-(Benzyloxy)-8-bromo-6β-(hydroxymethyl)-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylic Acid γ-Lactone (25a), 1α-(Benzyloxy)-8-bromo-6α-(hydroxymethyl)-5β-methyl-1,2,3,4,4aα,5,6,8aβ-octahydronaphthalene-5α-carboxylic Acid γ-Lactone (25b), and Methyl 1α-(Benzyloxy)-8-bromo-6α-(hydroxymethyl)-5β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (26a). A mixture of 111 mg (0.26 mmol) of **12** and 0.2 mL of BSA in 3 mL of toluene was subjected to the conditions specified for the IMDA reaction of **11**. Analysis of the crude product by GC (10-ft SE-30 column) indicated that three products were produced in the ratio of 55:41:4 (corresponding to **25a**, **26a**, and **25b**, respectively). This mixture was treated with catalytic pTsOH in THF as described for **11**. The crude product (a 54:40:6 mixture of three components by ^1H NMR analysis) was partially purified by preparative TLC (2-mm silica gel plate, 4:1 hexane-ether), giving 86 mg of the mixture of three products. This mixture was further purified by preparative TLC (two 0.5-mm plates, 2:1 CH_2Cl_2–hexane), giving 35 mg (34%) of **25a** (R_f 0.54), 3 mg (3%) of **25b** (R_f 0.8), and 29 mg (26%) **26a** (R_f 0.4).

Data for **25a**: mp 123–124 °C; $[\alpha]^{23}_D$ +151.2° (*c* 0.10, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 6.14 (dd, 1 H, *J* = 5.0, 2.4 Hz, H_7), 4.64 (A of AB, 1 H, *J* = 10.7 Hz), 4.52 (B of AB, 1 H, *J* = 10.7 Hz), 4.38 (t, 1 H, *J* = 8.7 Hz), 3.89 (dd, 1 H, *J* = 10.4, 9.1 Hz), 3.37 (ddd, 1 H, *J* = 9.6, 9.6, 5.0, H_1), 2.75 (m, 1 H), 2.42 (br t, 1 H, $J_{1,8a} \approx J_{4a,8a} \approx$ 10 Hz, H_{8a}), 2.34 (br d, 1 H, *J* = 12 Hz, $H_{2\beta}$), 1.84 (m, 2 H), 1.70 (br td, 1 H, *J* = 10–11, 3.0 Hz, H_{4a}), 1.35 (m, 3 H), 1.18 (s, 3 H); IR ($CHCl_3$) 3000, 2940, 2860, 1770, 1200, 1060, 1020 cm^{-1}; high resolution mass spectrum for $C_{20}H_{23}O_3{}^{78}Br$, calcd 390.0830, found 390.0803. Anal. Calcd for $C_{20}H_{23}O_3Br$: C, 61.39; H, 5.92. Found: C, 60.44; H, 5.87 (average of three attempts). It was subsequently discovered that **25a** hydrolyzes upon storage.

Data for **25b**: $[\alpha]^{23}_D$ −84.8° (*c* 0.51, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.29 (m, 5 H), 6.15 (dd, 1 H, *J* = 5.7, 2.3 Hz, H_7), 4.58 (A of AB, 1 H, *J* = 11.4 Hz), 4.48 (B of AB, 1 H, *J* = 11.4 Hz), 4.35 (br t, 1 H, *J* = 8.5 Hz), 4.33 (m, 1 H, H_1), 3.91 (dd, 1 H, *J* = 10.9, 8.9 Hz), 2.75 (m, 1 H, H_6), 2.38 (td, 1 H, *J* = 11, 2.6 Hz, H_{4a}), 2.21 (dd, 1 H, $J_{1,8a}$ = 1.9 Hz, $J_{4a,8a}$ = 10.9 Hz, H_{8a}), 2.12 (br d, 1 H, *J* = 12.6 Hz, $H_{2\alpha}$), 1.81 (br d, 1 H, *J* ≈ 13 Hz, $H_{4\alpha}$), 1.42–1.15 (m, 4 H), 1.13 (s, 3 H); IR ($CHCl_3$) 2940, 2860, 1770, 1450, 1070, 1010 cm^{-1}; mass spectrum *m/z* 311 (M^+ − Br). Anal. Calcd for $C_{20}H_{23}O_3Br$: C, 61.39; H, 5.92. Found: C, 61.66; H, 6.24.

Data for **26a**: $[\alpha]^{23}_D$ −80.8° (*c* 0.96, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.28 (dd, 1 H, *J* = 4.3, 3.0 Hz, H_7), 4.49 (s, 2 H), 4.11 (m, including $J_{1,8a}$ = 3.3 Hz, 1 H, H_1), 3.78 (dd, 1 H, *J* = 10.8, 6.3 Hz), 3.66 (t, 1 H, 6.3 Hz), 3.66 (s, 3 H), 3.12 (m, 1 H, H_6), 2.64 (m, including $J_{4a,8a}$ = 3.7 Hz, 1 H, H_{8a}), 2.53 (dt, 1 H, *J* = 12.8, 3.7 Hz, H_{4a}), 1.78 (br d, 1 H, *J* = 7.9 Hz), 1.68–1.32 (m, 6 H), 1.26 (s, 3 H); IR (neat) 3430 (br), 2940, 2860, 1720 (br), 1640, 1245, 1190 cm^{-1}; mass spectrum *m/z* 298 (no parent ion observed). Anal. Calcd for $C_{21}H_{27}O_4Br$: C, 59.58; H, 6.43. Found: C, 59.48; H, 6.57.

Intramolecular Diels–Alder Reaction of 13. Methyl 1α-(Benzyloxy)-8-bromo-6β-(3′-hydroxyprop-2′-en-1′-yl)-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (27) and Methyl 1α-(Benzyloxy)-8-bromo-6β-(3′-hydroxyprop-2′-en-1′-yl)-5β-methyl-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (28). A solution of 153 mg (0.34 mmol) of **13** in 3 mL of toluene was transferred to a resealable Carius tube and degassed with argon. BSA (0.21 mL, 0.85 mmol) was then added and the tube was sealed. Two hours later it was immersed in a 160 °C oil bath and heated for 24 h. The cooled solution was concentrated in vacuo and the residue was passed through a short column of Florisil using 9:1 hexane–Et_2O as solvent. The crude product was treated with catalytic pPTS in 2 mL of MeOH for 1 h at 23 °C. This mixture was concentrated in vacuo, and the product mixture was separated

by preparative TLC (2-mm silica gel plate, 1:1 ether–hexane), giving 56 mg (36%) of **27** (R_f 0.37) and 47 mg (31%) of **28** (R_f 0.63).

Data for **27**: $[\alpha]^{23}_D$ −120° (*c* 1.4, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 6.02 (dd, 1 H, *J* = 5.9, 2.0 Hz, H_7), 5.59 (dt, 1 H, *J* = 15.2, 5.0 Hz, $H_{2'}$), 5.48 (dd, 1 H, *J* = 15.2, 8.2 Hz, $H_{1'}$), 4.66 (A of AB, 1 H, *J* = 10.9 Hz), 4.50 (B of AB, 1 H, *J* = 10.9 Hz), 4.06 (m, 2 H, $H_{3'}$), 3.58 (s, 3 H), 3.43 (m, 1 H, H_1), 2.65 (br t, 1 H, *J* = 6.4 Hz, H_6), 2.24 (br t, 1 H, $J_{1a,8a} \approx J_{4a,8a} \approx 10$ Hz, H_{8a}), 1.94 (br td, 1 H, *J* = 10, 2.2 Hz, H_{4a}), 1.80–1.32 (m, 7 H), 1.20 (s, 3 H); IR (neat) 3450 (br), 3040, 3020, 2970, 2930, 2860, 1730, 1715, 1665, 1630, 1600 cm^{-1}; mass spectrum *m/z* 369 (M^+ − Br). Anal. Calcd for $C_{23}H_{29}O_4Br$: C, 61.47; H, 6.50. Found: C, 61.50; H, 6.80.

Data for **28**: $[\alpha]^{23}_D$ −169° (*c* 2.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 6.06 (dd, 1 H, *J* = 4.6, 3.0 Hz, H_7), 5.68 (m, 2 H), 4.49 (s, 2 H), 4.12 (m, 3 H, H_1 and $H_{3'}$), 3.67 (s, 3 H), 3.58 (m, 1 H, H_6), 2.64 (m, including $J_{4a,8a} \approx 3.5$ Hz, and $J_{1,8a} \approx$ 2–3 Hz, 1 H, H_{8a}), 2.56 (dm, 1 H, *J* = 12.9 Hz, H_{4a}), 1.81 (m, 1 H), 1.68–1.32 (m, 6 H), 1.16 (s, 3 H); IR (neat) 3420, 3020, 2940, 2860, 1730, 1710, 1665, 1635, 1610 cm^{-1}; mass spectrum *m/z* 341 ($M^+ - OC_7H_7$). Anal. Calcd for $C_{23}H_{29}O_4Br$: C, 61.47; H, 6.50. Found: C, 61.18; H, 6.50.

Methyl 1α-(Benzyloxy)-6β-(3′-hydroxyprop-2′-en-1′-yl)-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (29). A solution of 54 mg (0.12 mmol) of **27** in 5 mL of MeOH was treated with 4.5 g of 4–5% Na/Hg at 23 °C for 24 h. The mixture was then filtered through a Celite plug. The filtrate was concentrated, diluted with water, and extracted with Et_2O. The extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **29** that was purified by preparative TLC (0.5-mm silica gel plate, 3:1 ether–hexane). In this way 38 mg (86%) of **29** was obtained: $[\alpha]^{23}_D$ −104° (*c* 1.0, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 5 H), 6.07 (br d, 1 H, *J* = 9.8 Hz, H_8), 5.57 (dt, 1 H, *J* = 15, 5.3 Hz, $H_{2'}$), 5.47 (dd, 1 H, *J* = 15, 7.6 Hz, $H_{1'}$), 5.45 (m, 1 H, H_7), 4.65 (A of AB, 1 H, *J* = 11.3 Hz), 4.44 (B of AB, 1 H, *J* = 11.3 Hz), 4.03 (br d, 2 H, *J* = 5 Hz, $H_{3'}$), 3.57 (s, 3 H), 3.14 (ddd, 1 H, *J* = 10.2, 10.2, 4.2 Hz, H_1), 2.59 (br t, 1 H, *J* = 7 Hz, H_6), 2.26 (m, 1 H, $H_{2\beta}$), 1.18 (s, 3 H); IR (neat) 3450, 1730, 1715 (sh) cm^{-1}; mass spectrum *m/z* 352 ($M^+ - H_2O$). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.48; H, 8.06.

Methyl 6β-(3′-Hydroxyprop-1′-yl)-1α-hydroxy-5α-methyl-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (2). A. From 29. To a solution of 14.3 mg (0.039 mmol) of **29** in 1 mL of MeOH at 0 °C was added 0.4 mL of 1 M $NaBH_4$ in MeOH (0.4 mmol) and 5 mg (0.02 mmol) of $NiCl_2 \cdot 6H_2O$. This mixture was stirred for 30 min at 0 °C; then an additional 5 mg of $NiCl_2 \cdot 6H_2O$ and 0.4 mL of the $NaBH_4$–MeOH solution were added. This mixture was stirred for 1 h at 23 °C, then diluted with water, acidified with 10% HCl, and extracted with Et_2O. The organic extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated. The crude product was partially purified by chromatography (0.5-mm silica gel preparative plate, 3:1 Et_2O–hexane), giving 7.8 mg (54%) of a 6:1 mixture of **30** and **31**. This mixture could not be separated and was used as such in the next step. Data for **30**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 6.05 (br d, 1 H, *J* = 10.2 Hz, H_8), 5.70 (ddd, 1 H, *J* = 10.2, 4.9, 2.5 Hz, H_7), 4.66 (A of AB, 1 H, *J* = 12.1 Hz), 4.44 (B of AB, 1 H, *J* = 12.1 Hz), 3.67 (s, 3 H), 3.60 (t, 2 H, *J* = 7.2 Hz), 3.15 (ddd, 1 H, *J* = 10.1, 10.1, 4.5 Hz, H_1), 2.27 (br d, 1 H, *J* = 3.2 Hz), 1.88 (m, 1 H), 1.82 (m, 2 H), 1.64 (m, 3 H), 1.50–1.18 (m, 7 H), 1.16 (s, 3 H); IR ($CHCl_3$, of mixture) 3800–3140, 3020, 2940, 2860, 1730, 1460, 1250, 1060 cm^{-1}; high resolution mass spectrum for $C_{23}H_{32}O_4$ ($M^+ - CO_2Me$), calcd 313.2168, found 313.2173. Partial ^1H NMR data for **31**: δ 4.62 (d, 1 H, *J* = 11.2 Hz), 4.39 (d, *J* = 11.2 Hz, 1 H), 3.63 (s, 3 H), 3.03 (ddd, 1 H, H_1).

To a solution of 6.8 mg (0.018 mmol) of the above mixture in 2 mL of CH_2Cl_2 was added 150 μL of EtSH (2 mmol) and 45 μL (0.36 mmol) of $BF_2 \cdot Et_2O$. This mixture was stirred for 7 h at 23 °C, then diluted with ether, and washed with saturated $NaHCO_3$. The organic extracts were dried ($MgSO_4$), filtered, and concentrated, and the product mixture was separated by preparative TLC (0.25-mm silica gel plate, 4:1 ether–hexane, 3 developments), giving 4.4 mg (85%) of **2** (R_f 0.4) and 0.6 mg (10%) of the diol corresponding to **31** (R_f 0.25). Data for **2**: $[\alpha]^{23}_D$ −87.0° (*c* 0.44, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (*J* = 10.3 Hz, 1 H), 5.74 (ddd, *J* = 10.3, 4.9, 1.7 Hz, 1 H), 3.67 (s, 3 H), 3.59 (t, *J* = 6.5 Hz, 2 H), 3.33 (m, 1 H), 2.06 (m, 1 H), 1.97 (m, 1 H), 1.73–1.18 (m, 12 H), 1.78 (s, 3 H), 0.98 (m, 1 H); IR (neat) 3600, 3460, 3020, 2940, 1720, 1455, 1445, 1430, 1375, 1250, 1130, 1020 cm^{-1}; mass spectrum *m/z* 282 (parent ion); high resolution mass spectrum for $C_{16}H_{26}O_4$, calcd 282.1831, found 282.1830. Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 66.09, 66.12, 66.39; H, 8.86, 8.77, 9.03 (three independent determinations). These data are consistent with a partial hydrate. Calcd for $C_{16}H_{26}O_4 \cdot (H_2O)_{1/2}$: C, 65.95; H, 9.34.

B. From 32. To a solution of MOM ether **32** (15 mg, 0.046 mmol) in 2 mL of CH_2Cl_2 was added 100 μL of thiophenol (1 mmol) and 57 μL of $BF_3 \cdot Et_2O$ (0.46 mmol). This mixture was stirred at 23 °C for 1 h, then diluted with Et_2O, and extracted with aqueous NaOH. The crude product so obtained was purified by preparative TLC, as above, to give 14 mg (95%) of racemic **2**, the spectroscopic properties of which were identical with those reported for the optically active samples.

C. From 46a. A mixture of 21 mg of **46a** (0.031 mmol; a 9:1 mixture with **47a**) in 1 mL of dry CH_2Cl_2 was treated with 35 μL (0.67 mmol) of EtSH under N_2 at 23 °C for 20 h using the procedure previously above for the synthesis of **2** from **29** (via **30**). The reaction is easily monitored by TLC: the TBDPS ether is cleaved first followed by the vinyl-$SiMe_3$ group and then the benzyl ether. Additional $BF_3 \cdot Et_2O$ (50 μL, 0.4 mmol) and EtSH (80 μL, 1.1 mmol) were added after 20 h as the reaction was not complete. The mixture was stirred for an additional 10 h and then was worked up (in a hood!) as described in procedure A. The product mixture was separated by preparative TLC (0.5-mm silica gel plate, Et_2O) to give 7.1 mg (82%) of **2** (R_f 0.32, Et_2O; 92% based on the amount of **46a** present in the starting material) and 0.7 mg of the diol (R_f 0.15) corresponding to **47a**. The physical properties of **2** so obtained were identical with those described in A.

D. From 46b. A mixture of 22 mg (0.032 mmol) of **46b** in 3 mL of dry MeOH was treated with 300 mg of 5% Na–Hg under N_2. Additional 5% Na–Hg was added over several days until the reaction was complete; partial desilylation also occurred. The mixture was filtered through a Celite pad, diluted with brine, and extracted with Et_2O. The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was dissolved in 3 mL of THF and was treated with 0.10 mL (3.1 equiv) of a 1 M solution of Bu_4NF in THF under N_2. The reaction mixture was stirred for 2 h and then partitioned between Et_2O and saturated aqueous $NaHCO_3$. The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give crude **30**, which was purified by preparative TLC (1:1 hexane–Et_2O). In this way 9 mg (76%) of **30** ($[\alpha]^{23}_D$ −20.2° (*c* 0.9, $CHCl_3$)) was obtained; the spectroscopic properties were in complete agreement with those previously reported in procedure A. Deprotection of **30** as described previous for the **30**/**31** mixture (procedure A) provided **2**.

E. From 54. A solution of cycloadduct **54** (13 mg, 0.03 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was treated with ethanethiol (24 μL, 0.32 mmol) and $BF_2 \cdot Et_2O$ (20 μL, 0.16 mmol) for 16 h using the procedure described for the conversion of **29** to **2** (procedure A). The crude product was purified by chromatography on silica gel (230–450 mesh) using 2:1 ether–hexane, giving racemic **2** (6 mg, 80%).

Mosher Ester Analysis of 2. Samples of racemic and optically active **2** were treated with excess (*R*)-MTPA-Cl and DMAP in CH_2Cl_2 overnight at 23 °C. The conversions of **2** to the bis-MTPA esters was complete according to TLC analysis. The Mosher ester derivatives were purified by preparative TLC (4:1 hexane–Et_2O; the diastereomeric MTPA derivatives do not separate), and the purified esters (>95% yield from optically active **2**) were examined by high field NMR analysis. The MTPA derivative preparative from racemic **2** showed, among others, signals at δ 5.64 (dm, *J* = 10.3 Hz), 5.53 Hz (dm, *J* = 10 Hz), 5.56 (br d, *J* = 10.3 Hz), and 5.28 (br d, *J* = 10.3 Hz), of essentially equal intensity. The MTPA derivative of optically active **2**, however, showed only the resonances at δ 5.64 and 5.56, thus indicating the enantiomeric purity of optically active **2** to be >99%.

(*S*)-3-(Benzyloxy)-1,1-dibromohexa-1,5-diene (35). A solution of 6.59 g (25.1 mmol) of **34** in 25 mL of THF was treated

with 130 mL of 60% HOAc in H_2O, and the clear solution was stirred at 50 °C for 5 h. The crude mixture was concentrated in vacuo and excess HOAc was azeotropically removed with heptane. The oily residue was neutralized with 1 N NaOH and extracted several times with EtOAc. The combined organic layers were washed with brine, dried (Na_2OS_4), and concentrated in vacuo. The resulting (known)[12b] diol (6.19 g) was used without further purification in next step: R_f 0.13 (hexane–Et_2O 1:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.40 (m, 5 H), 5.88 (ddt, 1 H, J = 7.5, 10.4, 17.0 Hz), 5.17 (d, 1 H, J = 17.0 Hz), 5.12 (d, 1 H, J = 10.4 Hz), 4.69 (A of AB, J = 11.1 Hz, 1 H), 4.53 (B of AB, J = 11.1 Hz, 1 H), 3.40–3.85 (m, 4 H), 2.58 (br s, 1 H, OH), 2.30–2.55 (m, 2 H), 2.26 (br s, 1 H, OH).

The above crude diol (6.19 g, theoretically 25.1 mmol) was dissolved in 240 mL of a 1:1 mixture of THF–H_2O and cooled to 0 °C. Solid $NaIO_4$ (7 g, 32.71 mmol) was added and the suspension was vigorously stirred at 0 °C for 30 min and then 1 h at 23 °C. The mixture was diluted with 200 mL of H_2O, the pH was adjusted to 7 by addition of saturated aqueous $NaHCO_3$, and then the solution was extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo to give 5.63 g of the known (*S*)-2-(benzyloxy)pent-4-enal as a pale yellow oil that was used without purification in the next reaction:[12b] $[\alpha]^{23}_D$ –54.2° (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, 1 H, J = 3 Hz), 7.25–7.40 (m, 5 H), 5.82 (ddt, 1 H, J = 7.5, 10.3, 17.1 Hz), 5.10–5.20 (m, 2 H), 4.68 (A of AB, J = 11.7 Hz, 1 H), 4.60 (B of AB, J = 11.7 Hz, 1 H), 3.84 (dt, 1 H, J = 6.9, 2.0 Hz), 2.40–2.55 (m, 2 H).

A mixture of 26.4 g (101 mmol) of PPh_3 and 16.7 g (50.4 mmol) of CBr_4 in 150 mL of dry CH_2Cl_2 was cooled to 0 °C under nitrogen. The crude aldehyde (5.63 g, theoretically 25.1 mmol) from the preceding experiment was dissolved in 100 mL of dry CH_2Cl_2 and cooled to 0 °C. The chilled solution was added to the PPh_3–CBr_4 reagent via a cannula, and the resulting brown solution was stirred at 0 °C until complete (usually 30 min). The reaction mixture was concentrated in vacuo and then directly filtered through silica gel using Et_2O as solvent to remove Ph_3PO. The deep yellow oil obtained after evaporation of the filtrate was then chromatographed, using hexane/Et_2O 95:5 as eluant, yielding 7.96 g of dibromo olefin **35** (91%, three steps) as a pale yellow oil: R_f 0.39 (hexane–Et_2O 98:2); $[\alpha]^{23}_D$ –16.4° (*C* 0.97, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.36 (m, 5 H), 6.43 (d, 1 H, J = 8.1 Hz), 5.82 (ddt, 1 H, J = 7.5, 17.0, 10.3 Hz), 5.16 (d, 1 H, J = 10.3 Hz), 5.15 (d, 1 H, J = 17.0 Hz), 4.59 (A of AB, J = 11.7 Hz, 1 H), 4.42 (B of AB, J = 11.7 Hz, 1 H), 4.18 (dt, 1 H, J = 7.5, 6.3 Hz), 2.30–2.55 (m, 2 H); IR (neat) 3021, 2910, 2860, 1640, 1495, 1430, 1390, 1340, 1205, 1070, 1030, 1025, 990, 920 cm^{-1}; high resolution mass spectrum for $C_{13}H_{14}O^{81}Br_2$, calcd 306.8997, found 306.8993. Anal. Calcd for $C_{13}H_{14}OBr_2$: C, 45.12; H, 4.08. Found: C, 45.16; H, 4.23.

(*E*)-3(*S*)-(Benzyloxy)-1-iodo-1-(trimethylsilyl)hexa-1,5-diene (36). To a –78 °C solution of 3.98 g (11.5 mmol) of **35** in 100 mL of THF was added 14.4 mL of *n*-BuLi (1.6 M in hexane, 23 mmol) over a period of 15 min. The reaction was stirred at –78 °C for 1 h and at 23 °C for 1 h. The mixture was recooled to –78 °C and 2.2 mL (17.3 mmol) of distilled TMS-Cl was added dropwise via syringe (the solution turned to a pale yellow). This mixture was stirred for 1 h at –78 °C and at 23 °C for 4.5 h. The mixture was then diluted with brine, neutralized by careful addition of 1 N NaOH, and then extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed in vacuo to give a yellow oil that was chromatographed over silica gel using 98:2 hexane/Et_2O as eluant to give 2.52 g (85%) of the intermediate (trimethylsilyl)acetylene: $[\alpha]^{23}_D$ –103° (*c* 2.0, $CHCl_3$); NMR (300 MHz) δ 7.27–7.40 (m, 5 H), 5.80–5.96 (m, 1 H), 5.05–5.18 (m, 2 H), 4.80 (A of AB, J = 11.6 Hz, 1 H), 4.52 (B of AB, J = 11.6 Hz, 1 H), 4.11 (t, 1 H, J = 6.2 Hz), 2.40–2.60 (m, 2 H), 0.20 (s, 9 H); IR (neat) 3070, 3015, 2960, 2150, 1640, 1495, 1330, 1250, 1085, 1070, 990, 910; high resolution mass spectrum for $C_{13}H_{18}OSi$ (M^+ – allyl), calcd 217.1044, found 217.1048.

A mixture of 11.6 mL (11.6 mmol) of 1 M DIBAL in hexane and 1.22 mL (11.6 mmol) of Et_2O was cooled to 0 °C, and 2.0 g (7.75 mmol) of the above silylacetylene in 20 mL of dry Et_2O was added via syringe. After being stirred for 15 min at 0 °C, the mixture was stirred at 23 °C for 19 h. EtOAc (0.4 mL) was then added to quench the excess DIBAL and the colorless solution was cooled to –78 °C. A 1 M solution of iodine in THF (18 mL, 2.5 equiv) was added dropwise via an addition funnel. Initially, the color of iodine disappeared rapidly, but after the addition of 3–4 mL the iodine–aluminum exchange became slower and the reaction mixture remained brown. When the I_2 addition was complete the temperature was allowed to gradually rise to 23 °C, and the reaction mixture was stirred for 9.5 h. [The progress of the iodination step in a separate experiment was monitored by ^1H NMR. Conversions of >95% require at least 8 h; the vinylsilane resulting from protonolysis of the intermediate vinylalane is produced if the reaction is stopped at shorter reaction times.] Rochelle's salt solution (30 mL, saturated) was then added, followed by enough 10% Na_2SO_3 solution to reduce excess I_2. This mixture was extracted with Et_2O (3×) and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed in vacuo to give a yellow oil, which was chromatographed over silica gel using a gradient of hexane/Et_2O (98:2 to 9:1) as eluant. In this way, 2.28 g (76%) of vinyl iodide **36** was obtained, but was contaminated with ca. 5–10% of an unknown impurity that could not be separated. This mixture was used directly in the following cross-coupling experiments without additional purification: $[\alpha]^{23}_D$ –73.6° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5 H), 7.09 (d, 1 H, J = 9.0 Hz), 5.80 (ddt, 1 H, J = 7.5, 10.2, 17.0 Hz), 5.12 (d, 1 H, J = 10.2 Hz), 5.10 (d, 1 H, J = 17.0 Hz), 4.63 (A of AB, J = 12.3 Hz, 1 H), 4.40 (B of AB, J = 12.3 Hz, 1 H), 4.02 (dt, 1 H, J = 6.3, 9.0 Hz), 2.42 (dt, 1 H, J = 7.0, 13.5 Hz), 2.24 (dt, 1 H, J = 6.3, 13.5 Hz), 0.20 (s, 9 H); IR (neat) 3070, 3020, 2950, 2895, 2865, 1640, 1590, 1490, 1450, 1390, 1250, 1200, 1130, 1085, 1070, 1035, 990, 915, 840, 760, 730, 695 cm^{-1}; high resolution mass spectrum for $C_{13}H_{18}OSiI$ (M^+ – allyl), calcd 345.0166, found 345.0191.

4(*S*)-(Benzyloxy)-11-[(*tert*-butyldiphenylsilyl)oxy]-6-(trimethylsilyl)undeca-1,5,7-triene (38). A solution of 569 mg (1.47 mmol) of **36** in 10 mL of dry dioxane was treated with 170 mg (10%) of $Pd(PPh_3)_4$, 10 mL of a 0.3 M solution of crude **37** in dioxane, and 5.3 mL of 10% aqueous TlOH according to the procedure described for **39**. The reaction was complete in 5 min in this case. After standard workup (see **39**) and chromatography of the crude product (silica gel, 98:2 hexane–ether), R_f 0.26, 637 mg (74%) of **38** was obtained: $[\alpha]^{23}_D$ –22.5° (*c* 1.0, $CHCl_3$); NMR (300 MHz) δ 7.64–7.69 (m, 4 H), 7.30–7.44 (m, 11 H), 6.00–6.08 (m, 2 H), 5.87 (ddt, 1 H, J = 6.6, 10.4, 17.0 Hz), 5.57 (dt, 1 H, J = 6.7, 15.0 Hz), 5.10 (d, 1 H, J = 17.0 Hz), 5.05 (d, 1 H, J = 10.4 Hz), 4.58 (A of AB, J = 12.5 Hz, 1 H), 4.38 (B of AB, J = 12.5 Hz, 1 H), 4.10–4.20 (m, 1 H), 3.68 (t, 2 H, J = 6.8 Hz), 2.10–2.55 (m, 4 H), 1.60–1.75 (m, 2 H), 1.05 (s, 9 H), 0.11 (s, 9 H); IR (neat) 3075, 2960, 2935, 2860, 1640, 1590, 1495, 1470, 1453, 1440, 1390, 1250, 1110, 1090, 1070, 1025, 960, 910, 840, 735, 700; high resolution mass spectrum for $C_{33}H_{41}O_2Si_2$ (M^+ – *t*-Bu), calcd 525.2634, found 525.2679. Anal. Calcd for $C_{37}H_{50}O_2Si_2$: C, 76.24; H, 8.65. Found: C, 76.28; H, 8.45.

Triene **38** was also synthesized in 53% yield by treatment of **39** with *t*-BuLi (2.5 equiv) in THF at –78 °C followed by excess TMS-Cl. This experiment confirms the stereochemistry assigned to bromo triene **39**.

4(*S*)-(Benzyloxy)-6-bromo-11-[(*tert*-butyldiphenylsilyl)oxy]-undeca-1,5,7-triene (39). A mixture of 5.94 g of 5-[(*tert*-butyldiphenylsilyl)oxy]pent-1-yne (18.4 mmol) and 3 mL of distilled catechol borane (33.2 mmol) was heated at 95 °C for 3 h. Excess catechol borane was removed under high vacuum (0.5–1 mmHg, 23 °C, 3–4 h). The resulting thick colorless oil consisting of crude **37** (contains catechol from hydrolysis of catechol borane) was dissolved in THF [a dioxane solution is used for the cross-coupling with iodovinylsilane **36**, vide supra] to give a 0.3 M solution that was used directly in the next step. Vinylboronate **37** is unstable toward hydrolysis and oxidation: ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.69 (m, 4 H), 7.34–7.42 (m, 6 H), 6.95–7.30 (m, 4 H), 6.79–6.92 (m, 1 H), 5.79 (d, 1 H, J = 16.1 Hz), 3.71 (t, 2 H, J = 6.5 Hz), 2.40 (q, 2 H, J = 7.5 Hz), 1.75 (quint, 2 H, J = 7.0 Hz), 1.05 (s, 9 H); IR (neat) 3450, 3205, 2925, 2825, 1640, 1615, 1470, 1425, 1370, 1330, 1235, 1190, 1095, 740, 700.

A solution of 573 mg (1.66 mmol) of dibromide **35** and 192 mg (10%) of $Pd(PPh_3)_4$ in 10 mL of freshly distilled THF was stirred at 23 °C for 0.5 h; then 9.7 mL (2.9 mmol) of a 0.3 M solution of vinylboronate **37** in THF was added, followed by 5 mL (ca. 2.9

mmol) of 10% aqueous TlOH. A yellow-greenish precipitate formed immediately. The mixture was vigorously stirred at 23 °C, and after 10–15 min the reaction was complete. Aqueous NaOH (0.3 mL of 3 N solution) was added, and the mixture was stirred for an additional 2 h to decompose excess **37**. Inorganic salts were removed by filtration through a Celite pad. The filtrate was partitioned between Et_2O and brine and extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed in vacuo to give a deep yellow oil, which was supported on silica [by dissolving in CH_2Cl_2, treating with silica gel (2–3 times the weight of crude product, and evaporating to dryness] and then chromatographed using hexane/Et_2O 98:2 as eluant to give 641 mg (66%) of triene **39**: R_f 0.20; $[\alpha]^{23}_D$ −14.4° (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.70 (m, 4 H), 7.26–7.46 (m, 11 H), 6.02–6.23 (m, 2 H), 5.78–5.97 (m, 2 H), 5.11 (d, 1 H, *J* = 16.3 Hz), 5.07 (d, 1 H, *J* = 9.3 Hz), 4.35 (A of AB, *J* = 11.6 Hz, 1 H), 4.68 (B of AB, *J* = 11.6 Hz, 1 H), 4.40–4.55 (m, 1 H), 3.69 (t, 2 H, *J* = 5.5 Hz), 2.26–2.54 (m, 4 H), 1.65–1.77 (m, 2 H), 1.06 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 138.5 (s), 136.9 (d), 135.6 (d), 134.0 (s), 133.9 (s), 132.0 (d), 130.0 (d), 129.6 (d), 128.3 (d), 127.8 (d), 127.7 (d), 127.5 (d), 127.0 (d), 117.3 (t), 77.9 (d), 70.7 (t), 63.1 (t), 39.3 (t), 31.9 (t), 28.4 (t), 26.9 (q), 19.3 (s); IR (neat) 3065, 2945, 2855, 1430, 1390, 1105, 1090, 1065, 1025, 950, 913, 820, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{31}H_{36}O_2Si^{81}Br$ (M^+ − allyl), calcd 549.1638, found 549.1680. Anal. Calcd for $C_{34}H_{41}O_2SiBr$: C, 69.25; H, 7.01. Found: C, 69.44; H, 6.99.

Bromo triene **39** was also synthesized by using vinylboronic acid **59** in place of catechol vinylboronate **37** in the cross-coupling reaction. Thus, a mixture of 100 mg (0.29 mmol) of dibromide **35** and 75 mg (0.58 mmol) of vinylboronic acid **59** in 2 mL of THF under N_2 was treated with $Pd(Ph_3P)_4$ (33 mg, 0.029 mmol). The mixture was stirred for 10 min and then aqueous TlOH (0.73 mL of 0.4 M solution, 0.29 mmol) was added via syringe. A yellow-while solid (TlBr) immediately separated from the solution. The mixture was stirred for 10 min; then 5 mL of hexane was added followed by $MgSO_4$ to remove H_2O. This mixture was stirred for 1 h and then was filtered through Celite. The filtrate was concentrated in vacuo and the crude product was purified by flash chromatography on silica gel (2:1 Et_2O–hexane), yielding 20 mg of recovered **35** (20%) and 75 mg (73%; 92% based on consumed **35**) of the alcohol corresponding to **39**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.36 (m, 5 H), 6.08–6.18 (m, 2 H), 5.82–5.88 (m, 2 H), 5.11 (d, 1 H, *J* = 16.9 Hz), 5.08 (d, 1 H, *J* = 11.3 Hz), 4.57 (A of AB, *J* = 11.8 Hz, 1 H), 4.43 (B of AB, *J* = 11.8 Hz, 1 H), 4.46–4.51 (m, 1 H), 3.69 (t, 2 H, *J* = 6.5 Hz), 2.27–2.45 (m, 4 H), 1.70–1.76 (m, 2 H). A solution of this alcohol in dry DMF (6 mL) was treated with imidazole (28 mg, 0.42 mmol) and TBDPS-Cl (69 mg, 0.25 mmol). This mixture was stirred for 12 h at 23 °C and then was poured into 5 mL of H_2O and was extracted with Et_2O (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the crude product was purified by flash chromatography (5:1 hexane–EtOAc) to give 110 mg (89%) of the protected bromo triene **39**.

5(*S*)-(Benzyloxy)-12-[(*tert*-butyldiphenylsilyl)oxy]-7-(trimethylsilyl)undeca-6,8-dienenitrile (40). A solution of 1.19 g (2.04 mmol) of **38** was treated with Cp_2ZrHCl (1.7 g, 6.6 mmol) in 80 mL of CH_2Cl_2 according to the procedure described for the synthesis of **41**. The vinyl zirconcium intermediate was treated with *t*-BuNC (0.35 mL, 3.1 mmol) at 23 °C for 2 h, cooled to 0 °C, and quenched by the addition of 17.5 mL of a 0.35 M solution of I_2 in benzene (61.1 mmol). This mixture was stirred for 30 min and then was worked up by using the procedure described for the synthesis of **41**. Nitrile **40** (766 mg, 63%) was obtained following silica gel chromatography: R_f 0.35 (8:2 hexane–ether); $[\alpha]^{23}_D$ −29.6° (*c* 0.9, $CHCl_3$); NMR (300 MHz) δ 7.64–7.70 (m, 4 H), 7.26–7.46 (m, 11 H), 6.05 (d, 1 H, *J* = 15.8 Hz), 6.01 (d, 1 H, *J* = 8.9 Hz), 5.58 (dt, 1 H, *J* = 7.1, 15.8 Hz), 4.58 (A of AB, *J* = 11.6 Hz, 1 H), 4.33 (B of AB, *J* = 11.6 Hz, 1 H), 4.06–4.18 (m, 1 H), 3.68 (t, 2 H, *J* = 6.4 Hz), 2.36 (t, 2 H, *J* = 6.4 Hz), 2.17 (q, 2 H, *J* = 7.1 Hz), 1.50–2.00 (m, 6 H), 1.05 (s, 9 H), 0.13 (s, 9 H); IR (neat) 3060, 3020, 2950, 2930, 2840, 2240, 1590, 1495, 1470, 1455, 1425, 1390, 1360, 1250, 1110, 1090, 1025, 960, 840, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{34}H_{42}NO_2Si_2$ (M^+ − *t*-Bu), calcd 552.2743, found 552.2800. Anal. Calcd for $C_{38}H_{51}NO_2Si_2$: C, 74.82; H, 8.43. Found: C, 74.14; H, 8.21.

5(*S*)-(Benzyloxy)-7-bromo-12-[(*tert*-butyldiphenylsilyl)oxy]-dodeca-6,8-dienenitrile (41). A suspension of 460 mg (1.78 mmol) of Cp_2ZrHCl in 20 mL of dry CH_2Cl_2 was stirred for a few min at 23 °C under N_2. The solid was allowed to settle, and the supernatant was removed by syringe and was replaced by 20 mL of freshly distilled CH_2Cl_2. A solution of **39** (478 mg, 0.81 mmol) in CH_2Cl_2 (15 mL) was then added and the suspension stirred at 23 °C. After 10–15 min, a yellow solution was obtained. After 1 h, *t*-BuNC (140 μL, 1.24 mmol) was added and the resulting pale yellow or colorless solution was stirred for 1.5 h at 23 °C. It was then cooled to 0 °C and treated with a 0.33 M solution of iodine in benzene (8.2 mL, 2.43 mmol). After being stirred for 30 min at 5 °C, the deep brown solution was treated with 10% Na_2CO_3 and extracted with CH_2Cl_2. [Emulsions are very common during this extraction and it was occasionally necessary to filter the two-phase system through a Celite pad.] The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The crude mixture was supported on silica gel and chromatographed using 8:2 hexane/Et_2O as eluant to give mg 390 (79%) of **41**: R_f 0.25; $[\alpha]^{23}_D$ −21.1° (*c* 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.70 (m, 4 H), 7.26–7.46 (m, 11 H), 6.15 (dt, 1 H, *J* = 15.3, 7.1 Hz), 6.06 (d, 1 H, *J* = 15.3 Hz), 5.81 (d, 1 H, *J* = 8.3 Hz), 4.27 (A of AB, *J* = 11.6 Hz, 1 H), 4.68 (B of AB, *J* = 11.6 Hz, 1 H), 4.38–4.50 (m, 1 H), 3.70 (t, 2 H, *J* = 5.6 Hz), 2.24–2.37 (m, 4 H), 1.63–1.88 (m, 6 H), 1.06 (s, 9 H); IR (neat) 3065, 3019, 2930, 2860, 2240, 1645, 1610, 1585, 1495, 1470, 1450, 1430, 1390, 1360, 1225, 1185, 1110, 1025, 955, 820, 755, 700; high resolution mass spectrum for $C_{31}H_{33}BrNO_2Si$ (M^+ − *t*-Bu), calcd 558.1455, found 558.1436.

Methyl 7(*S*)-(Benzyloxy)-14-[(*tert*-butyldiphenylsilyl)oxy]-2-methyl-9-(trimethylsilyl)tetradeca-2,8,10-trienoate (42). Nitrile **40** (106 mg, 0.17 mmol) was converted into triene ester **42** (94 mg, 79%) by using the procedure described for the preparation of **43**: $[\alpha]^{23}_D$ −21.2° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.69 (m, 4 H), 7.26–7.46 (m, 11 H), 6.76 (t, 1 H, *J* = 6.5 Hz), 6.00–6.08 (m, 2 H), 5.58 (dt, 1 H, *J* = 6.8, 15.9 Hz), 4.57 (A of AB, *J* = 11.6 Hz, 1 H), 4.35 (B of AB, *J* = 11.6 Hz, 1 H), 2.12–2.22 (m, 4 H), 1.82 (s, 3 H), 1.40–1.80 (m, 6 H), 1.05 (s, 9 H), 0.12 (s, 9 H); IR (neat) 3060, 3020, 2940, 2825, 1712, 1645, 1425, 1385, 1250, 1190, 1105, 1090, 960, 835, 734, 700 cm^{-1}; high resolution mass spectrum for $C_{35}H_{51}O_4Si_2$ (M^+ − CH_2Ph), calcd 591.3312, found 591.3320. Anal. Calcd for $C_{42}H_{58}O_4Si_2$: C, 73.85; H, 8.56. Found: C, 73.21; H, 8.20.

Methyl 7(*S*)-(Benzyloxy)-9-bromo-14-[(*tert*-butyldiphenylsilyl)oxy]-2-methyltetradeca-2,8,10-trienoate (43). To a 0 °C solution of 412 mg (0.67 mmol) of **41** in 10 mL of dry Et_2O under N_2 was added 0.87 mL (0.87 mmol) of a 1.0 M DIBAL solution in hexane. The reaction was stirred at 23 °C for 4 h until complete. EtOAc (0.3 mL) was added to quench excess DIBAL; then 2 mL of 1 M H_2SO_4 was added. The mixture was vigorously stirred for 10 min and then the two clear layers were separated. The aqueous phase was extracted with additional Et_2O. The combined organic extracts were washed with 1 N NaOH and brine, dried ($MgSO_4$), and concentrated in vacuo. The crude aldehyde was used immediately in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 7.64–7.70 (m, 4 H), 7.26–7.46 (m, 11 H), 6.00–6.23 (m, 2 H), 5.81 (d, 1 H, *J* = 8.3 Hz), 4.28 (A of AB, *J* = 11.7 Hz, 1 H), 4.66 (B of AB, *J* = 11.7 Hz, 1 H), 4.34–4.42 (m, 1 H), 3.70 (t, 2 H, *J* = 5.8 Hz), 2.25–2.48 (m, 4 H), 1.50–1.90 (m, 6 H), 1.06 (s, 9 H); IR (neat) 3050, 3015, 2915, 2850, 2710, 1730, 1645, 1610, 1590, 1470, 1450, 1425, 1383, 1355, 1185, 1105, 1025, 950, 820, 735, 700 cm^{-1}.

The crude aldehyde (394 mg, theoretically 0.67 mmol) from the previous step was dissolved in 15 mL of CH_2Cl_2 and treated with 840 mg (2.41 mmol) of $Ph_3P{=}C(Me)CO_2Me$. The yellow solution was stirred for 3 h at 23 °C and then was concentrated in vacuo and directly chromatographed on silica gel (85:15 hexane–Et_2O) to remove Ph_3PO and other minor impurities. Triene **43** (379 mg) was obtained in 82% yield for the two steps: $[\alpha]^{23}_D$ −15.2° (*c* 2.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.70 (m, 4 H), 7.26–7.46 (m, 11 H), 6.74 (dt, 1 H, *J* = 1.6, 7.7 Hz), 6.15 (dt, 1 H, *J* = 6.5, 14.6 Hz), 6.06 (d, 1 H, *J* = 14.6 Hz), 5.80 (d, 1 H, *J* = 8.2 Hz), 4.29 (A of AB, *J* = 11.7 Hz, 1 H), 4.66 (B of AB, *J* = 11.7 Hz, 1 H), 4.30–4.45 (m, 1 H), 3.73 (s, 3 H), 3.70 (t, 2 H, *J* = 6.4 Hz), 2.31 (q, 2 H, *J* = 9.3 Hz), 1.45–1.80 (m, 6 H), 1.06 (s, 9 H); IR (neat) 3050, 3020, 2950, 2860, 1715, 1650, 1470, 1450, 1430, 1390, 1355, 1260, 1215, 1190, 1110, 1025, 950, 820, 755, 700

cm^{-1}; high resolution mass spectrum for $C_{35}H_{40}{}^{81}BrO_4Si$ (M^+ – *t*-Bu), calcd 633.1848, found 633.1826. Anal. Calcd for $C_{39}H_{49}BrO_4Si$: C, 67.90; H, 7.16. Found: C, 68.23; H, 7.14.

7(*S*)-(Benzyloxy)-14-[(*tert*-butyldiphenylsilyl)oxy]-2-methyl-9-(trimethylsilyl)tetradeca-2,8,10-trienal (44). A –78 °C solution of 302 mg (0.44 mmol) of **42** in 15 mL of dry Et_2O was treated with 1.15 mL of a 1 M solution of DIBAL-H in hexane (1.15 mmol). The mixture was stirred for 1.5 h at –78 °C and then was warmed to 23 °C and quenched by the addition of Rochelle salt solution. The mixture was extracted with Et_2O (3×). The extracts were dried (Na_2SO_4), filtered, and concentrated to give 310 mg of intermediate allylic alcohol that was used directly in the next step: ^1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.69 (m, 4 H), 7.26–7.46 (m, 11 H), 5.98–6.07 (m, 2 H), 5.57 (dt, 1 H, *J* = 7.6, 15.9 Hz), 5.39 (br t, 1 H), 4.56 (A of AB, *J* = 11.6 Hz, 1 H), 4.35 (B of AB, *J* = 11.6 Hz, 1 H), 4.04–4.12 (m, 1 H), 3.98 (br s, 2 H), 3.67 (t, 2 H, *J* = 6.3 Hz), 1.95–2.20 (m, 4 H), 1.64 (s, 3 H), 1.30–1.80 (m, 6 H), 1.05 (s, 9 H), 0.11 (s, 9 H); IR (neat) 3385, 3070, 2930, 2875, 1688, 1590, 1455, 1430, 1390, 1360, 1250, 1110, 1090, 1065, 965, 835, 735, 700 cm^{-1}.

A solution of the allylic alcohol prepared above (297 mg, theoretically 0.42 mmol) in 5 mL of CH_2Cl_2 was added dropwise to a –78 °C solution of the Swern reagent generated from 92 μL (1.05 mmol) of $(COCl)_2$ and 120 μL (1.7 mmol) of DMSO in 5 mL of CH_2Cl_2. This mixture was stirred for 15 min at –78 °C; then 0.30 mL (2.1 mmol) of Et_3N was added. The solution was allowed to warm to 0 °C over a 2-h period; then it was diluted with water and extracted with Et_2O (3×). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was then purified by chromatography on silica gel (8:2 hexane–Et_2O as eluant), giving 244 mg (89%) of triene **44**: ^1H NMR (300 MHz, $CDCl_3$) δ 9.39 (s, 1 H), 7.64–7.69 (m, 4 H), 7.26–7.46 (m, 11 H), 6.48 (t, 1 H, *J* = 6.8 Hz), 6.00–6.08 (m, 2 H), 5.58 (dt, 1 H, *J* = 6.8, 15.7 Hz), 4.59 (A of AB, *J* = 11.6 Hz, 1 H), 4.35 (B of AB, *J* = 11.6 Hz, 1 H), 4.07–4.18 (m, 1 H), 3.68 (t, 2 H, *J* = 6.3 Hz), 2.36 (q, 2 H, *J* = 7.3 Hz), 2.17 (q, 2 H, *J* = 6.8 Hz), 1.73 (s, 3 H), 1.40–1.80 (m, 6 H), 1.05 (s, 9 H), 0.12 (s, 9 H); IR (neat) 3070, 3015, 2930, 2830, 1690, 1645, 1440, 1390, 1360, 1250, 1110, 1030, 965, 835, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{37}H_{47}O_3Si_2$ (M^+ – *t*-Bu), calcd 595.3051, found 595.3055. Anal. Calcd for $C_{41}H_{56}O_3Si_2$: C, 75.40; H, 8.64. Found: C, 74.84; H, 8.26.

7(*S*)-(Benzyloxy)-9-bromo-14-[(*tert*-butyldiphenylsilyl)oxy]-2-methyltetradeca-2,8,10-trienal (45). Triene ester **43** (223 mg, 0.23 mmol) was converted into triene **45** (193 mg, 91%) by using the procedure described for the preparation of **44**. Aldehyde **45** was also prepared directly from nitrile **41** but in lower overall yield. Thus, 412 mg (0.67 mmol) of **41** was reduced with DIBAL as described in the preparation of **43**. A solution of the crude aldehyde (339 mg) in 6 mL of THF was then added dropwise to a –78 °C solution of the reagent generated by treatment of 0.83 mmol of α-(triethylsilyl)propionaldehyde *tert*-butylimine in 3 mL of THF with 0.84 mL of a 1.3 M solution of *sec*-BuLi in cyclohexane (1.1 mmol) at –78 °C for 30 min.[28] After the addition of aldehyde was complete, the solution was allowed to warm to –20 °C, and after 4.5 h at this temperature 3 mL of 20% NaH_2PO_4 was added. The pH was adjusted to 4.5 by the addition of 1 N HCl, and the two-phase mixture was stirred vigorously at 23 °C for 2 h. The organic phase was separated, washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography (silica gel, 8:2 hexane–ether), giving 159 mg of triene **45** (43% from **41**): ^1H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 7.64–7.70 (m, 4 H), 7.26–7.46 (m, 11 H), 6.45 (dt, 1 H, *J* = 1.8, 7.7 Hz), 6.16 (dt, 1 H, *J* = 6.5, 15.3 Hz), 6.06 (d, 1 H, *J* = 15.3 Hz), 5.81 (d, 1 H, *J* = 8.4 Hz), 4.58 (A of AB, *J* = 11.7 Hz, 1 H), 4.38 (B of AB, *J* = 11.7 Hz, 1 H), 4.36–4.46 (m, 1 H), 3.70 (t, 2 H, *J* = 5.6 Hz), 2.33 (m, 4 H), 1.72 (s, 3 H), 1.50–1.80 (m, 6 H), 1.06 (s, 9 H); IR (neat) 3075, 3030, 2935, 2860, 1965, 1650, 1475, 1460, 1430, 1390, 1360, 1110, 1030, 960, 825, 740, 700 cm^{-1}; high resolution mass spectrum for $C_{34}H_{38}{}^{81}BrO_3Si$ (M^+ – *t*-Bu), calcd 603.1743, found 603.1736. Anal. Calcd for $C_{38}H_{47}BrO_3Si$: C, 69.17; H, 7.18. Found: C, 69.17; H, 6.99.

Thermal Intramolecular Diels–Alder Reactions of Trienes 42–45. A 0.01 M solution of the substrate in toluene containing a crystal of BHT was transferred to a resealable Carius tube. The solutions were degassed with a stream of N_2 and then the tubes were sealed and heated in a 160 °C oil bath typically for 24–40 h. The cooled solutions were concentrated in vacuo and products were separated by using preparative TLC (silica gel, hexane–Et_2O solvent mixtures). Product ratios were determined by ^1H NMR analysis of crude or of partially purified product mixtures (care being taken not to fractionate product diastereomers). Results are summarized in Table I.

Lewis Acid Catalyzed IMDA Reactions of Trienals 44 and 45. The procedure described for the IMDA reaction of **44** is illustrative. A solution of 72 mg (0.11 mmol) of **44** in 2 mL of dry CH_2Cl_2 was cooled to –78 °C and treated with 0.11 mL of a 1 M solution of Et_2AlCl in hexane. After 1 h at –78 °C, the solution was allowed to warm to –15 °C, where it was maintained for 5 h until the cycloaddition was complete (TLC analysis). The mixture was then diluted with aqueous Rochelle's salt solution and extracted with Et_2O (3×). The extracts were then dried ($MgSO_4$), filtered, and concentrated in vacuo. The ratio of cycloadducts was determined by ^1H NMR analysis of the crude mixture and then cycloadducts were separated by preparative TLC (silica gel, 9:1 hexane–Et_2O, two developments). Results are summarized in Table I. Data for cycloadducts **46–48** follow.

Methyl 1α-(benzyloxy)-5α-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-8-(trimethylsilyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (46a): obtained as a 9:1 mixture with **47a**; R_f 0.45 (9:1 hexane–Et_2O); $[\alpha]^{23}_D$ –29.3° (*c* 2.4, $CHCl_3$) (of mixture); partial ^1H NMR (300 MHz, C_6D_6) δ 6.39 (br d, *J* = 5.3 Hz, 1 H), 4.28 (A of AB, *J* = 12.0 Hz, 1 H), 4.37 (B of AB, *J* = 12.0 Hz, 1 H), 3.65 (m, 2 H), 3.42 (s, 3 H), 3.13 (dt, *J* = 3.6, 9.8 Hz, H_1), 1.27 (s, 3 H), 1.20 (s, 9 H), 0.94 (m, 1 H), 0.28 (s, 9 H); IR (neat) 2940, 2860, 1730, 1605, 1590, 1455, 1430, 1380, 1360, 1260, 1245, 1260, 1130, 1110, 1055, 840, 740, 700 cm^{-1}; high resolution mass spectrum for $C_{38}H_{49}O_4Si$ (M^+ – *t*-Bu), calcd 625.3156, found 625.3178. Anal. Calcd for $C_{42}H_{58}O_4Si_2$: C, 73.85; H, 8.56. Found: C, 73.79; H, 8.85.

The stereostructure of **46a** was verified by conversion into **2** as described earlier in this paper.

Methyl 1α-(benzyloxy)-5β-methyl-6α-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-8-(trimethylsilyl)-1,2,3,4,4aα,5,6,8aβ-octahydronaphthalene-5α-carboxylate (47a): obtained as the minor component of a 9:1 mixture with **46a**; partial ^1H NMR data (300 MHz, C_6D_6) δ 6.15 (br dd, *J* = 5.3 Hz, H_7), 4.53 (A of AB, *J* = 14.3 Hz), 3.91 (B of AB, *J* = 14.3 Hz), 3.88 (br s, H_1), 2.88 (br t, *J* = 11.4 Hz, H_{4a}).

Methyl 1α-(benzyloxy)-5β-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-8-(trimethylsilyl)-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (48a): R_f 0.34 (9:1 hexane–Et_2O); ^1H NMR (300 MHz, C_6D_6) δ 6.40 (dd, *J* = 2.6, 3.9 Hz, 1 H), 4.57 (A of AB, *J* = 12.3 Hz), 4.51 (B of AB, *J* = 12.3 Hz), 4.01 (m, including $J_{1,8a}$ = 2.6 Hz, H_1), 3.68 (m, 2 H), 3.39 (s, 3 H), 3.08 (m, H_6), 2.82 (m, H_{8a}), 2.72 (m, including $J_{4a,8a}$ = 3.8 Hz, H_{4a}), 1.27 (s, 3 H), 1.21 (9 H, s), 0.14 (s, 9 H); IR (neat) 2940, 2860, 1730, 1600, 1455, 1430, 1390, 1250, 1190, 1110, 830, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{38}H_{49}O_4Si$ (M^+ – *t*-Bu), calcd 625.3156, found 625.3092. Anal. Calcd for $C_{42}H_{58}O_4Si_2$: C, 73.85; H, 8.56. Found: C, 73.41; H, 8.83.

Methyl 1α-(benzyloxy)-8-bromo-5α-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (46b): R_f 0.27 (9:1 hexane–Et_2O); $[\alpha]^{23}_D$ –43.8° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) δ 6.22 (dd, *J* = 4.1, 3.0 Hz, H_7), 4.25 (A of AB, *J* = 11.7 Hz, 1 H), 4.78 (B of AB, *J* = 11.7 Hz, 1 H), 3.58 (m, 2 H), 3.34 (s, 3 H), 3.31 (m, including $J_{1,8a}$ = 10.6 Hz, H_1), 2.26 (br t, *J* = 10.6 Hz, H_{8a}), 2.06 (br t, *J* = 10.6 Hz, H_{4a}), 1.19 (s, 9 H), 1.14 (s, 3 H); IR (neat) 2930, 2860, 1730, 1455, 1430, 1390, 1300, 1250, 1075, 1060, 820, 800, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{35}H_{40}{}^{79}BrO_4Si$ (M^+ – *t*-Bu), calcd 631.1868, found 631.1885. Anal. Calcd for $C_{39}H_{49}BrO_4Si$: C, 67.90; H, 7.16. Found: C, 68.07; H, 7.52.

The stereostructure of **46b** was verified by conversion into **2** as described earlier in this paper.

Methyl 1α-(benzyloxy)-8-bromo-5β-methyl-6α-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-1,2,3,4,4aα,5,6,8aβ-octahydronaphthalene-5α-carboxylate (47b): obtained as the minor component of a 9:1 mixture with **48b**; R_f 0.30 (9:1 hexane–Et_2O): partial ^1H NMR (300 MHz, C_6D_6) δ 6.05 (br s, H_7),

4.05 (br dd, J = 3.6 Hz, H_1), 2.11 (br t, J = 8 Hz, H_{4a}).

Methyl 1α-(benzyloxy)-8-bromo-5β-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxylate (48b): obtained as a 9:1 mixture with **47b**; ^{1}H NMR (300 MHz, C_6D_6) δ 6.35 (br t, H_7), 4.32 (A of AB, J = 12.7 Hz, 1 H), 4.42 (B of AB, J = 12.7 Hz, 1 H), 4.32 (br s, H_1), 3.59 (m, 2 H), 3.31 (s, CH_3), 3.07 (m, H_6), 2.97 (br s, H_{8a}), 2.73 (br dt, $J_{4a,4ax}$ = 11.2 Hz, H_{4a}), 1.20 (s, 9 H), 1.11 (s, 3 H); IR (neat) 2980, 2860, 1730, 1455, 1425, 1250, 1235, 1190, 1105, 1025, 820, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{35}H_{40}{}^{79}BrO_4Si$ (M^+ − t-Bu), calcd 631.1868, found 631.1862. Anal. Calcd for $C_{39}H_{49}BrO_4Si$: C, 67.90; H, 7.16. Found: C, 68.11; H, 7.46.

1α-(Benzyloxy)-5α-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-8-(trimethylsilyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxaldehyde (46c): obtained as a mixture with **47c**; R_f 0.42 (9:1 hexane–Et_2O); $[\alpha]^{23}_D$ −39.0° (c 1.46, $CHCl_3$); ^{1}H NMR (300 Hz, C_6D_6) δ 9.49 (s, 1 H), 6.29 (dd, J = 2.2, 4.4 Hz, H_7), 4.25 (A of AB, J = 12.7 Hz, 1 H), 4.41 ((B of AB, J = 12.7 Hz, 1 H), 3.59 (m, 2 H), 3.08 (dt, J = 3.9, 9.2 Hz, H_1), 2.04 (br t, $J_{4a,8a}$ = 9.3 Hz, H_{8a}), 1.88 (m, H_6), 1.76 (dt, H_{4a}), 1.21 (s, 9 H), 0.99 (s, 3 H), 0.82 (br dq, H_{4ax}), 0.26 (s, 9 H); IR (neat) 3070, 3030, 2935, 2860, 2700, 2280, 1725, 1590, 1495, 1475, 1455, 1430, 1390, 1360, 1240, 1105, 1025, 1000, 830, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{37}H_{47}O_3Si_2$ (M^+ − t-Bu), calcd 595.3051, found 595.3075. Anal. Calcd for $C_{41}H_{56}O_3Si_2$: C, 75.40; H, 8.64. Found: C, 74.83; H, 8.35.

1α-(Benzyloxy)-5β-methyl-6α-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-8-(trimethylsilyl)-1,2,3,4,4aα,5,6,8aβ-octahydronaphthalene-5α-carboxaldehyde (47c). This component is not separable from **46c**: partial ^{1}H NMR data (300 MHz, C_6D_6) δ 9.56 (s, 1 H), 6.13 (dd, J = 2.4 Hz, H_7), 4.42 (A of AB, J = 12 Hz, 1 H), 4.24 (B of AB, J = 12 Hz, 1 H), 3.93 (br s, H_1), 2.78 (dt, J = 2.11 Hz, H_{4a}), 0.13 (s, 9 H).

1α-(Benzyloxy)-5β-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-8-(trimethylsilyl)-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxaldehyde (48c): R_f 0.28 (9:1 hexane–Et_2O); ^{1}H NMR (300 MHz, C_6D_6) δ 9.22 (s, 1 H), 6.32 (dd, $J_{6,7}$ = 3.0 Hz, H_7), 4.42 (A of AB, J = 14.7 Hz, 1 H), 4.52 (B of AB, J = 14.7 Hz, 1 H), 3.98 (br s, $J_{1,8a}$ = 2.1 Hz, H_1), 3.67 (m, 2 H), 2.67 (m, H_6), 2.63 (m, H_{8a}), 2.27 (dt, $J_{4a,8a}$ = 2.9 Hz, $J_{4a,4ax}$ = 12 Hz, H_{4a}), 1.20 (s, 9 H), 0.77 (s, 3 H), 0.08 (s, 9 H); IR (neat) 2935, 2860, 2690, 1725, 1685, 1595, 1455, 1425, 1390, 1355, 1245, 1110, 1090, 1060, 995, 835, 740, 700 cm^{-1}; high resolution mass spectrum for $C_{37}H_{47}O_3Si_2$ (M^+ − t-Bu), calcd 595.3051, found 595.3062.

1α-(Benzyloxy)-8-bromo-5α-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxaldehyde (46d): R_f 0.45 (8:2 hexane–Et_2O); $[\alpha]^{23}_D$ −40.0° (c 2.1, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6) δ 9.25 (s, 1 H), 6.12 (dd, J = 5.3, 1.8 Hz, H_7), 4.27 (A of AB, J = 12 Hz, 1 H), 4.78 (B of AB, J = 11.9 Hz, 1 H), 3.52 (br t, 2 H), 3.25 (br dt, including $J_{1,8a}$ = 9 Hz, H_1), 2.18 (br t, J = 10 Hz, H_{8a}), 1.88 (m, H_2), 1.78 (dt, J = 2.8, 10.5 Hz, H_{4a}), 1.65 (m, H_6), 1.20 (s, 9 H), 1.06 (m, H_{3ax}), 0.85 (s, 3 H), 0.72 (dq, J = H_{4ax}); IR (neat) 3065, 2935, 2860, 1730, 1665, 1475, 1450, 1425, 1350, 1110, 820, 740, 700 cm^{-1}; high resolution mass spectrum for $C_{34}H_{38}{}^{81}BrO_3Si$ (M^+ − t-Bu), calcd 603.1743, found 603.1773. Anal. Calcd for $C_{38}H_{47}BrO_3Si$: C, 69.17; H, 7.18. Found: C, 68.89; H, 7.09.

1α-(Benzyloxy)-8-bromo-5β-methyl-6α-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-1,2,3,4,4aα,5,6,8aβ-octahydronaphthalene-5α-carboxaldehyde (47d). This structural assignment is tentative; this material was detected only in crude reaction mixtures. Partial ^{1}H NMR data: (300 MHz, C_6D_6) δ 9.06 (s, 1 H), 6.05 (dd, H_7).

1α-(Benzyloxy)-8-bromo-5β-methyl-6β-[3-[(*tert*-butyldiphenylsilyl)oxy]prop-1-yl]-1,2,3,4,4aα,5,6,8aα-octahydronaphthalene-5α-carboxaldehyde (48d): R_f (0.49, 8:2 hexane–Et_2O); ^{1}H NMR (300 MHz, C_6D_6) δ 9.00 (s, 1 H), 6.25 (br t, J = 4 Hz, H_7), 4.20 (A of AB, J = 11.7 Hz, 1 H), 4.31 (B of AB, J = 11.7 Hz, 1 H), 4.24 (m, H_1), 3.57 (m, 2 H), 2.73 (br s, including $J_{4a,8a}$ = 3.9 Hz), 2.57 (m, H_6), 2.23 (br dt, J = 8.2, 3.9 Hz, H_{4a}), 1.20 (s, 9 H), 0.59 (s, 3 H); IR (neat) 3070, 3025, 2930, 2856, 1725, 1470, 1450, 1425, 1390, 1355, 1110, 820, 735, 700 cm^{-1}; high resolution mass spectrum for $C_{34}H_{38}{}^{81}BrO_3Si$ (M^+ − t-Bu), calcd 603.1743, found 603.1779.

[7,7-Dimethoxy-3-(methoxymethoxy)hept-1-ynyl]trimethylsilane (50). A solution of the known aldehyde **49**[36] (4.0 g, 28.4 mmol) in anhydrous THF (10 mL) was added slowly to a −20 °C solution of $LiC{\equiv}CSiMe_3$ [prepared from 98% (trimethylsilyl)acetylene (4.9 mL, 34.1 mmol, Aldrich) and n-BuLi (13.6 mL, 34.1 mmol of a 2.5 M solution in THF) in THF (25 mL)]. After 15 min the solution was quenched with H_2O (10 mL) and diluted with ether (100 mL). The organic layer was separated and washed with H_2O and saturated aqueous NaCl, dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was chromatographed on silica gel (230–400 mesh) with 1:1 ether–hexane, giving (7,7-dimethoxy-3-hydroxyhept-1-ynyl)trimethylsilane (5.6 g, 82%) as a clear oil: R_f 0.35 (2:1 ether–hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (m, 2 H), 3.32 (s, 6 H), 1.90 (d, J = 5.5 Hz, 1 H), 1.69–1.63 (m, 6 H), 0.17 (s, 9 H); IR (neat) 3430, 2950, 2825, 2170, 1460, 1385, 1250, 1190, 1125, 1050, 845, 760, 695 cm^{-1}; mass spectrum m/z 181 (M^+ − $C_2H_7O_2$); high resolution mass spectrum for $C_{10}H_{17}OSi$, calcd 181.1059, found 181.1051. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.97; H, 9.90. Found: C, 58.80; H, 9.88.

A solution of the alcohol prepared in the preceding experiment (4.8 g, 19.6 mmol) in anhydrous CH_2Cl_2 (25 mL) was treated with $EtN(iPr)_2$ (6.8 mL, 39.2 mmol) and chloromethyl methyl ether (2.3 mL, 29.4 mmol) under Ar. The mixture was stirred for 16 h at 23 °C, then diluted with CH_2Cl_2 (50 mL), washed with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic extracts were dried (anhydrous Na_2SO_4) and concentrated in vacuo, and the crude product was chromatographed on silica gel (230–400 mesh) with 4:1 hexane–ether to give MOM ether **50** (5.0 g, 88%): R_f 0.36 (2:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (A of AB, J = 7.4 Hz, 1 H), 4.58 (B of AB, J = 7.4 Hz, 1 H), 4.38 (t, 1 H), 4.30 (t, 1 H), 3.37 (s, 3 H), 3.31 (s, 6 H), 1.73–1.62 (m, 6 H), 0.16 (s, 9 H); IR (neat) 2950, 2895, 2875, 2155, 1465, 1385, 1370, 1340, 1250, 1190, 1150, 1130, 1095, 1030, 920, 845, 760, 695 cm^{-1}; mass spectrum m/z 226 (M^+ − $C_2H_6O_2$); high resolution mass spectrum for $C_{12}H_{22}O_2Si$, calcd 226.1405, found 226.1404. Anal. Calcd for $C_{14}H_{28}O_4Si$: C, 58.29; H, 9.78. Found: C, 58.53; H, 10.00.

[(*E*)-7,7-Dimethoxy-1-iodo-3-(methoxymethoxy)hept-1-enyl]trimethylsilane (51). A solution of **50** (2.0 g, 6.9 mmol) in anhydrous ether (40 mL) was treated with DIBAL-H (9.0 mL, 9.0 mmol, 1.0 M in hexane) in a sealed Carius tube under Ar at 45 °C for 24–48 h. Pyridine (1.2 mL, 13.9 mmol) was then added at −20 °C, and the resulting mixture was stirred for 10 min.[37] The reaction mixture was then cooled to −50 °C, and 95% N-iodosuccinimide (3.2 g, 13.8 mmol) was added. This mixture stirred rapidly for 30 min while being allowed to warm slowly to −10 °C. The reaction mixture was then poured into cold 5% aqueous NaOH (50 mL) and stirred until the solution became clear (30 min). The aqueous layer was then diluted and extracted with ether (4 × 50 mL). The combined organic extracts were washed with H_2O and saturated aqueous NaCl, dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was chromatographed on silica gel (230–400 mesh) with 4:1 hexane–ether, giving (*E*)-vinyl iodide **51** (2.2 g, 76%) contaminated by ca. 10% of the trans-disubstituted vinylsilane resulting from protonolysis of the intermediate vinylalane. This mixture was not conveniently separated and therefore was used directly in the following reaction without additional purification: R_f 0.34 (2:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 9.7 Hz, 1 H), 4.66 (A of AB, J = 7.0 Hz, 1 H), 4.49 (B of AB, J = 7.0 Hz, 1 H), 4.35 (t, 1 H), 4.18 (m, 1 H), 3.34 (s, 3 H), 3.31 (s, 6 H), 1.67–1.41 (m, 6 H), 0.29 (s, 9 H); IR (neat) 2945, 2895, 2825, 1595, 1460, 1385, 1360, 1250, 1190, 1145, 1125, 1095, 1075, 1030, 920, 840, 760, 685, 625 cm^{-1}1; mass spectrum m/z 309 (M^+ − $C_4H_{11}O_3$); high resolution mass spectrum for $C_{10}H_{18}O_1SiI$, calcd 309.0123, found 309.0107.

(8*E*,6*Z*)-1,1-Dimethoxy-5-(methoxymethoxy)-7-(trimethylsilyl)undeca-6,8-dien-12-ol (53). Vinyl iodide **51** (110 mg, 0.26 mmol) was dissolved in anhydrous, degassed THF (1 mL) and treated with $Pd(PPh_3)_4$ (60 g, 0.05 mmol) for 15 min under Ar. This solution was then added dropwise, via cannula, to a

(36) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(37) Pyridine was added to suppress cleavage of the dimethyl acetal during the iodination step.

premixed 25 °C solution of boronic acid **52** (0.06 g, 0.45 mmol; prepared by treating 4-pentyn-1-ol with catecholborane at 100 °C for 16 h followed by aqueous hydrolysis and chromatographic purification) and 10% aqueous TlOH (1.0 mL, 0.45 mmol) in THF (0.5 mL). The reaction mixture was stirred for 4 min and then was diluted with ether (10 mL). The organic layer was separated, washed with H_2O, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and then dried ($MgSO_4$). Concentration of the organic extracts in vacuo followed by rapid purification by silica gel chromatography (230–400 mesh) using 1:1 hexane–ether provided diene **53** (72 mg, 73%): R_f 0.16 (2:1 ether–hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (dd, J = 15.2, 1.2 Hz, 1 H), 5.90 (dd, J = 9.7, 1.2 Hz, 1 H), 5.57 (td, J = 15.2, 7.2 Hz, 1 H), 4.67 (A of AB, J = 6.8 Hz, 1 H), 4.48 (B of AB, J = 6.8 Hz, 1 H), 4.36 (t, J = 5.3 Hz, 1 H), 4.28 (m, 1 H), 3.65 (q, 2 H), 3.35 (s, 3 H), 3.31 (s, 6 H), 2.15 (dq, J = 6.3, 1.2 Hz, 2 H), 1.69–1.40 (m, 8 H), 1.33 (t, 1 H), 0.18 (s, 9 H); IR (neat) 3440, 2950, 1465, 1455, 1390, 1250, 1195, 1155, 1130, 1090, 1040, 965, 915, 840, 760, 735, 690 cm^{-1}; mass spectrum m/z 297 ($M^+ - C_3H_9O_2$); high resolution mass spectrum for $C_{16}H_{29}O_3Si$, calcd 297.1907, found 297.1900. Anal. Calcd for $C_{19}H_{38}O_5Si$: C, 60.92; H, 10.22. Found: C, 60.68; H, 10.38.

Methyl (2*E*,8*Z*,10*E*)-14-(Benzyloxy)-7-(methoxymethoxy)-2-methyl-9-(trimethylsilyl)tetradeca-2,8,10-trienoate (33). A solution of alcohol **53** (500 mg, 1.3 mmol) in 3:1 DMF–THF (5 mL) under N_2 was treated with NaH (57% oil dispersion, 84 mg, 2.0 mmol) at 0 °C. The mixture was stirred for 15 min, and then benzyl bromide (0.2 mL, 1.6 mmol) was added. The reaction mixture was stirred at 23 °C for 16 h and then was poured into dilute aqueous NaCl and extracted with ether (4 × 20 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The crude product was chromatographed on silica gel (230–400 mesh) with 3:1 hexane–ether to provide the intermediate benzyl ether (540 mg, 87%): R_f 0.26 (2:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H, aromatic), 6.05 (dd, J = 15.2, 1.0 Hz, 1 H), 5.89 (dd, J = 9.8, 1.3 Hz, 1 H), 5.56 (td, J = 15.2, 7.2 Hz, 1 H), 4.67 (A of AB, J = 6.5 Hz, 1 H), 4.50 (s, 2 H), 4.48 (B of AB, J = 6.5 Hz, 1 H), 4.37 (t, 1 H), 4.29 (m, 1 H), 3.48 (t, 2 H), 3.36 (s, 3 H), 3.31 (s, 6 H), 2.14 (q, 2 H), 1.71 (m, 2 H), 1.67–1.42 (m, 6 H), 0.17 (s, 9 H); IR (neat) 3025, 2945, 1605, 1495, 1450, 1375, 1360, 1245, 1150, 1125, 1095, 1035, 960, 915, 835, 755, 730, 695 cm^{-1}; mass spectrum m/z 419 ($M^+ - C_2H_5O$); high resolution mass spectrum for $C_{24}H_{39}O_4Si$, calcd 419.2646, found 419.2662. Anal. Calcd for $C_{26}H_{44}O_5Si$: C, 67.20; H, 9.54. Found: C, 67.51; H, 9.49.

The benzyl ether prepared in the preceding experiment (420 mg, 0.93 mmol) was dissolved in a 2:1 mixture of THF and 15% aqueous oxalic acid solution (9 mL) and stirred at 23 °C under N_2 for 50 h. The reaction mixture was extracted with ether (4 × 30 mL). The organic layers were washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl and then dried ($MgSO_4$). Concentration of the filtered extracts in vacuo then gave the crude aldehyde that generally was used in the following experiment without purification: R_f 0.22 (2:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, J = 1.4 Hz, 1 H), 7.30 (m, 5 H, aromatic), 6.03 (dd, J = 15.2, 1.2 Hz, 1 H), 5.88 (dd, J = 10.2, 2.0 Hz, 1 H), 5.57 (dt, J = 15.2, 7.2 Hz, 1 H), 4.67 (A of AB, J = 6.7 Hz, 1 H), 4.50 (s, 2 H), 4.48 (B of AB, J = 6.7 Hz, 1 H), 4.32 (m, 1 H), 3.48 (t, 2 H), 3.36 (s, 3 H), 2.47 (dt, J = 6.8, 1.4 Hz, 2 H), 2.14 (q, 2 H), 1.71–1.48 (m, 6 H), 0.18 (s, 9 H); IR (neat) 3020, 2945, 2705, 1725, 1605, 1495, 1450, 1360, 1245, 1205, 1145, 1095, 1030, 960, 915, 835, 755, 735, 695 cm^{-1}; mass spectrum m/z 418 (parent ion); high resolution mass spectrum for $C_{24}H_{38}O_4Si$, calcd 418.2557, found 418.2520. Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15. Found: C, 69.18; H, 9.36.

The crude aldehyde prepared above (theoretically 0.93 mmol) was immediately dissolved in anhydrous CH_2Cl_2 (5 mL) and treated with methyl 2-(triphenylphosphoranylidene)propionate (0.64 g, 1.8 mmol, crystallized from acetone). The solution was stirred for 16 h under N_2; then hexane (10 mL) was added and the precipitated solids were filtered through Celite and washed with CH_2Cl_2 (3 × 10 mL). The combined filtrate was evaporated and the product was purified by silica gel chromatography (230–400 mesh) with 3:1 hexane–ether, giving the known[5f] (*E*,*Z*,*E*)-triene **33** (0.34 g, 75% for two steps): R_f 0.36 (2:1 hexane–ether); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic), 6.75 (t, 1 H), 6.03 (dd, J = 15.2, 1.3 Hz, 1 H), 5.87 (dd, J = 9.7, 1.3 Hz, 1 H), 5.57 (td, J = 15.2, 7.4 Hz, 1 H), 4.67 (A of AB, J = 6.7 Hz, 1 H), 4.50 (s, 2 H), 4.47 (B of AB, J = 6.7 Hz, 1 H), 4.28 (m, 1 H), 3.73 (s, 3 H), 3.48 (t, 2 H), 3.35 (s, 3 H), 2.21 (m, 2 H), 2.14 (q, 2 H), 1.83 (s, 3 H), 1.71 (m, 2 H), 1.63 (m, 2 H), 1.47 (m, 2 H), 0.17 (s, 9 H); IR (neat) 3025, 2945, 2850, 1720, 1650, 1495, 1455, 1435, 1360, 1250, 1190, 1150, 1095, 1030, 960, 915, 835, 730, 695 cm^{-1}; mass spectrum m/z 473 ($M^+ - CH_3$); high resolution mass spectrum for $C_{27}H_{41}O_5Si$, calcd 473.2733, found 473.2738. Anal. Calcd for $C_{28}H_{44}O_5Si$: C, 68.81; H, 9.07. Found: C, 68.64; H, 9.26.

Intramolecular Diels–Alder Reaction of 33. Preparation of Methyl 6β-[3-(Benzyloxy)prop-1-yl]-1α-(methoxymethoxy)-5α-methyl-8-(trimethylsilyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (54). A solution of triene **33** (37 mg, 0.07 mmol) in anhydrous toluene (7 mL, 0.01 M) was transferred to a resealable Carius tube and purged with Ar for 10 min. BHT (0.5 mg) was then added and the tube was sealed under Ar and heated at 180 °C for 16 h. The solution was allowed to cool to ambient and then was concentrated in vacuo. ^1H NMR analysis (500 MHz, C_6D_6) of the crude reaction mixture showed a 72:9:19 mixture of three cycloadducts. This mixture was partially purified by preparative TLC (0.5-mm silica gel preparative plate) with 1:1 hexane–ether, giving the mixture of three cycloadducts (33 mg, 89%) free of contaminants. This mixture was further purified by using 4:1 hexane–ether on a silica gel column (230–400 mesh) to give the major cycloadduct **54**[5f] (25 mg, 67%) and a 2:1 mixture of the minor cycloadducts (5 mg, 14%). This mixture was further fractionated on a 0.5-mm preparative TLC plate using 4:1 $CHCl_3$–CCl_4, giving reasonably pure samples (<1 mg) of cis-fused cycloadduct **56** and trans-fused epimer **55** that were used for spectroscopic characterization.

Data for major trans-fused cycloadduct **54**: R_f 0.42 (2:1 hexane–ether) and R_f 0.40 (4:1 $CHCl_3$–CCl_4, two elutions); ^1H NMR (500 MHz, C_6D_6) δ 7.18 (m, 5 H, aromatic), 6.37 (dd, J = 5.8, 1.8 Hz, 1 H), 4.55 (A of AB, J = 7.0 Hz, 1 H), 4.43 (B of AB, J = 7.0 Hz, 1 H), 4.28 (s, 2 H), 3.35 (s, 3 H), 3.26 (m, 2 H), 3.16 (s, 3 H), 3.11 (dt, J = 4.1, 10.1 Hz, 1 H), 2.41 (m, 1 H), 2.11 (q, 1 H), 2.02 (dd, J = 10.1, 10.1 Hz, 1 H), 1.90 (m, 2 H), 1.78–1.52 (m, 4 H), 1.31 (m, 2 H), 1.22 (s, 3 H), 0.87 (m, 2 H), 0.27 (s, 9 H); IR (neat) 3030, 2995, 2945, 2850, 1730, 1605, 1495, 1455, 1405, 1365, 1305, 1260, 1245, 1210, 1140, 1105, 1035, 995, 950, 920, 895, 835, 755, 695, 675 cm^{-1}; mass spectrum m/z 488 (parent ion); high resolution mass spectrum for $C_{28}H_{44}O_5Si$, calcd 488.2990, found 488.2978. Anal. Calcd for $C_{28}H_{44}O_5Si$: C, 68.81; H, 9.07. Found: C, 68.92; H, 9.06. The stereostructure of **54** was verified by conversion into **2** as previously described.

Data for trans-epi cycloadduct **55**: R_f 0.34 (2:1 hexane–ether) and R_f 0.24 (4:1 $CHCl_3$–CCl_4, two elutions); ^1H NMR (500 MHz, C_6D_6) δ 7.28 (m, 5 H, aromatic), 6.21 (dd, J = 5.8, 2.4 Hz, 1 H), 4.58 (A of AB, J = 6.7 Hz, 1 H), 4.49 (B of AB, J = 6.7 Hz, 1 H), 4.25 (s, 2 H), 4.10 (d, J = 2.1 Hz, 1 H), 3.38 (s, 3 H), 3.21 (m, 2 H), 3.17 (s, 3 H), 2.88 (ddd, $J_{4a,8a} = J_{4a,4ax}$ = 11.2 Hz, $J_{4a,4eq}$ = 2.1 Hz, 1 H), 2.15–1.97 (m, 3 H), 1.96–1.93 (dd, 11.2, 2.1 Hz, 1 H), 1.65–1.21 (m, 6 H), 1.20 (s, 3 H), 0.95 (m, 2 H), 0.41 (s, 9 H); IR ($CHCl_3$) 3020, 2995, 2950, 2850, 1730, 1605, 1495, 1460, 1420, 1365, 1260, 1105, 1090, 1035, 925, 835 cm^{-1}; mass spectrum m/z 473 ($M^+ - CH_3$); high resolution mass spectrum for $C_{27}H_{41}O_5Si$, calcd 473.2712, found 473.2709.

Data for cis-fused cycloadduct **56**: R_f 0.34 (2:1 hexane–ether) and R_f 0.33 (4:1 $CHCl_3$–CCl_4, two elutions); ^1H NMR (500 MHz, C_6D_6) δ 7.31 (m, 5 H, aromatic), 6.39 (dd, J = 4.5, 2.8 Hz, 1 H), 4.65 (A of AB, J = 6.9 Hz, 1 H), 4.61 (B of AB, J = 6.9 Hz, 1 H), 4.32 (s, 2 H), 4.27 (d, J = 2.6 Hz, 1 H), 3.34 (s, 3 H), 3.30 (dt, J = 6.3, 1.5 Hz, 2 H), 3.23 (s, 3 H), 3.04 (m, 1 H), 2.68 (m, 1 H), 2.61 (ddd, $J_{4a,4ax}$ = 12.4 Hz, $J_{4a,8a} = J_{4a,4eq}$ = 4.2 Hz, 1 H), 1.85–1.55 (m, 8 H), 1.21 (s, 3 H), 0.87 (m, 2 H), 0.40 (s, 9 H); IR ($CHCl_3$) 3025, 2995, 2945, 2850, 1730, 1600, 1495, 1455, 1415, 1365, 1260, 1140, 1105, 1035, 950, 920, 900, 835, 695 cm^{-1}; mass spectrum m/z 488 (parent ion); high resolution mass spectrum for $C_{28}H_{44}O_5Si$, calcd 488.2990, found 488.2990.

7,7-Dimethoxy-1-iodo-1-(trimethylsilyl)-1-heptene (58). To a solution of the known acetylenic acetal **57**[38] (5.06 g, 32.4 mmol)

(38) Semmelhack, M. F.; Wu, E. S. C. *J. Am. Chem. Soc.* **1976**, *88*, 3384.

in dry THF (60 mL) under Ar at 0 °C was added *n*-BuLi (1.0 M in hexanes, 14 mL, 36 mmol). The resulting dark brown solution was allowed to stir for 20 min at 0 °C. Chlorotrimethylsilane (3.9 g, 36 mmol) was added and the yellow mixture was allowed to stir for 20 min. The reaction diluted with Et_2O (30 mL) and washed with saturated ammonium chloride solution (50 mL). The aqueous layer was extracted 3× with Et_2O (30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was distilled (88–93 °C/1.5 mm) to afford 5.29 g (73%) of (7,7-dimethoxy-1-heptynyl)trimethylsilane a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 4.37 (t, J = 5.3 Hz, 1 H), 3.32 (s, 3 H), 2.23 (t, J = 7.1 Hz, 2 H), 1.63–1.44 (m, 6 H), 0.14 (s, 9 H); IR (thin film) 2940, 2820, 2165, 1455, 1245, 1130, 840 cm^{-1}; high resolution mass spectrum for $C_{11}H_{21}OSi$ ($M^+ - OCH_3$), calcd 197.1362, found 197.1402. Anal. Calcd for $C_{12}H_{24}O_2Si$: C, 63.11; H, 10.60. Found: C, 63.28; H, 10.31.

To a solution of the above (trimethylsilyl)acetylene (596 mg, 2.61 mmol) in 40 mL dry Et_2O (in a resealable Carius tube) was added DIBAL-H (1 M in hexane, 4.7 mL, 4.7 mmol) at room temperature. The reaction was heated to 40 °C for 12 h, after which it was cooled to −20 °C (dry ice/CCl_4) and dry pyridine (412 mg, 5.2 mmol, 0.42 mL) was added,[37] and the reaction was allowed to stir for 20 min at −20 °C. *N*-Iodosuccinimide (1.21 g, 5.2 mmol) was added in one portion, and the heterogeneous mixture was stirred vigorously at −20 °C for 1 h. The reaction mixture was poured into a cold 5% NaOH solution (50 mL) and Et_2O (20 mL) was added. This was stirred for 1 h until both layers became clear. The layers were separated and the aqueous phase was extracted with Et_2O (4 × 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude material by chromatography (9:1 hexane–Et_2O) gave 826 mg (89%) of **58** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 7.8 Hz, 1 H), 4.35 (t, J = 5.6 Hz, 1 H), 3.32 (s, 6 H), 2.08 (dt, J = 7.8, 6.5 Hz, 2 H), 1.60 (dt, J = 8.4, 5.6 Hz, 2 H), 1.38 (m, 4 H), 0.27 (s, 9 H); IR (thin film) 2940, 2855, 2820, 1583, 1457, 1245, 1120, 1050, 850 cm^{-1}; high resolution mass spectrum (EI) for $C_{11}H_{21}OSi$ ($M^+ - CH_3O$ – HI), calcd 197.1362, found 197.1402. Anal. Calcd for $C_{12}H_{25}O_2ISi$: C, 40.45; H, 7.02. Found: C, 40.56; H, 7.16.

(6-Hydroxy-1-hexenyl)boronic Acid (59). Freshly distilled catecholborane (887 mg, 7.4 mmol, 0.77 mL) was added slowly to 1-hydroxy-6-heptyne (345 mg, 3.52 mmol) in a Carius tube under Ar at 0 °C. After gas evolution ceased, the tube was sealed under Ar and heated to 80 °C for 12 h. The reaction was cooled to 0 °C and water was added slowly. The mixture was shaken until a homogeneous solution was obtained. This was allowed to stir for 3 h. Solid NaCl was added to saturate the solution, and the aqueous phase was extracted with EtOAc (5 × 20 mL). The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by rapid chromatography (SiO_2, 1:1 hexane–Et_2O) to remove catechol; then column was then washed with 95:5 CH_2Cl_2–MeOH to obtain 336 mg (67%) of **59** as a colorless foam: ^1H NMR (300 MHz, CD_3OD) δ 6.54 (dt, J = 17.6, 6.6 Hz, 1 H), 5.58 (dd, J = 17.6, 1.2 Hz, 1 H), 3.56 (t, J = 5.8 Hz, 2 H), 2.16 (dt, J = 6.6, 6.2 Hz, 2 H), 1.60–1.45 (m, 4 H). Boronic acid **59** was more fully characterized as the pinacol ester derivative: ^1H NMR (300 MHz, $CDCl_3$) δ 6.62 (dt, J = 17.8, 6.5 Hz, 1 H), 5.54 (dt, J = 17.8, 1.6 Hz, 1 H), 3.64 (br dt, J = 6.5, 4.6 Hz, 2 H), 2.19 (ddt, J = 6.5, 6.5, 1.6 Hz, 2 H), 1.62–1.43 (m, 4 H), 1.26 (s, 12 H); IR (thin film) 3680–3100, 2975, 2930, 2860, 1632, 1360, 1140, 990 cm^{-1}; high resolution mass spectrum (CI) for $C_{12}H_{24}BO_3$ ($M^+ + 1$), calcd 226.1855, found 226.1855. Anal. Calcd for $C_{12}H_{23}BO_3$: C, 63.74; H, 10.25. Found: C, 63.57; H, 9.96.

(*Z*,*E*)-1,1-Dimethoxy-13-hydroxy-7-(trimethylsilyl)-6,8-tridecadiene (60). A solution of boronic acid **59** (1.4 g, 10.2 mmol) and 10% (aqueous) TlOH (10.2 mmol, 23 mL) in 30 mL THF was degassed by passing Ar through the solution for 10 min. In a separate flask, iodide **58** (2.14 g, 6.01 mmol) and $(Ph_3P)_4Pd$ (1.4 g, 1.2 mmol) were combined in 20 mL of degassed THF under Ar at 23 °C. The boronic acid–TlOH mixture was added rapidly to the iodide/catalyst solution via cannula. A yellow solid formed immediately. The heterogeneous reaction was allowed to stir for 4 min, at which point the reaction was diluted with Et_2O (20 mL) and filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ solution (30 mL), and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (CH_2Cl_2, then 1:1 hexane–Et_2O) to afford 1.28 g (65%) of **60** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (t, J = 7.4 Hz, 1 H), 6.00 (d, J = 15.2 Hz, 1 H), 5.49 (dt, J = 15.2, 7.1 Hz, 1 H), 4.36 (t, J = 5.9 Hz, 1 H), 3.65 (br q, J = 5.9 Hz, 2 H), 3.32 (s, 6 H), 2.15 (dt, J = 7.4, 6.7 Hz, 2 H), 2.07 (ddt, 6.9, 7.0, 1.7 Hz, 2 H), 1.6 (m, 2 H), 1.50–1.40 (m, 6 H), 0.16 (s, 9 H); IR (CH_2Cl_2) 3600, 3550–3300, 2930, 2850, 2820, 1587, 1450, 1380, 1360, 1242, 1120, 1065, 1040, 835 cm^{-1}; high resolution mass spectrum (EI) for $C_{17}H_{33}O_2Si$ ($M^+ - CH_3O$), calcd 297.2249, found 297.2217. Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.85; H, 11.05. Found: C, 65.74; H, 11.20.

(*E*,*Z*,*E*)-Methyl 15-Hydroxy-9-(trimethylsilyl)-2,8,10-pentadecatrienoate (61). To a solution of diene **60** (51.2 mg, 0.156 mmol) in 1 mL of wet acetone was added a catalytic amount of pTsOH. The mixture was allowed to stir for 2.5 h at room temperature, at which point it was quenched with solid $NaHCO_3$ and Na_2SO_4. The reaction was filtered through a cotton plug and concentrated under reduced pressure to afford the crude aldehyde as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 1.4 Hz, 1 H), 6.08 (t, J = 7.2 Hz, 1 H), 6.00 (d, J = 15.2 Hz, 1 H), 5.48 (dt, J = 15.2, 7.0 Hz, 1 H), 3.65 (br dt, J = 6.3, 5.1 Hz, 2 H), 2.44 (dt, J = 7.5, 1.4 Hz, 2 H), 2.16 (dt, J = 7.6, 7.4 Hz, 2 H), 2.06 (dt, J = 7.5, 7.0 Hz, 2 H), 1.67–1.49 (m, 4 H), 1.47–1.25 (m, 4 H), 0.16 (s, 9 H); IR (thin film) 3600–3080, 2990, 2910, 2835, 2700, 1715, 1580, 1230, 950, 825 cm^{-1}; high resolution mass spectrum (EI) for $C_{16}H_{30}O_2Si$ (M^+), calcd 282.2015, found 282.1966. This material was dissolved in dry CH_3CN (0.15 mL) and was added to a solution of trimethyl phosphonoacetate (34 mg, 0.19 mmol), anhydrous LiCl (7.9 mg, 0.19 mL), and DBU (24 mg, 0.16 mmol) in 0.2 mL of dry CH_3CN at 23 °C under Ar. A precipitate formed after 10 min. The mixture was allowed to stir for 12 h at room temperature. The reaction was then diluted with Et_2O (2 mL) and was extracted with saturated NH_4Cl solution (3 mL). The phases were separated and the aqueous layer was extracted with Et_2O (4 × 5 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the crude product by chromatography (SiO_2, 1:1 hexane–Et_2O) yielded 36.6 g of **61** (69%) as a clear oil, which contained 15% of **62** as an inseparable mixture.

Data for **61**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (dt, J = 15.6, 6.7 Hz, 1 H), 6.08 (t, J = 7.4 Hz, 1 H), 6.00 (dd, J = 15.2, 1.6 Hz, 1 H), 5.82 (dt, J = 14.6, 1.6 Hz, 1 H), 5.49 (dt, J = 15.2, 6.8 Hz, 1 H), 3.73 (s, 3 H), 3.65 (dt, J = 6.4, 4.3 Hz, 2 H), 2.25–2.12 (m, 4 H), 2.07 (dt, J = 7.0, 6.6 Hz, 2 H), 1.61–1.55 (m, 2 H), 1.51–1.25 (m, 6 H), 0.16 (s, 9 H); IR (thin film) 3680–3120, 2930, 2860, 1728, 1660, 1595, 1435, 1247, 960, 835 cm^{-1}; high resolution mass spectrum (EI) for $C_{19}H_{34}O_3Si$ (M^+), calcd 338.2277, found 338.2276. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.13. Found: C, 67.58; H, 10.18.

Methyl 6β-(4-Hydroxybut-1-yl)-8-(trimethylsilyl)-1,2,3,4,4aβ,5,6,8aα-octahydronaphthalene-5β-carboxylate (62). A solution of triene **61** (82 mg, 0.24 mmol) in dry toluene (4 mL) was degassed with a stream of Ar for 15 min. The tube was sealed and heated to 150 °C for 20 h. The reaction was cooled, concentrated under reduced pressure, and purified by chromatography (SiO_2, 1:1 hexane–Et_2O) to give 80 mg (97%) of **62** as a single isomer.

A solution of triene **61** in degassed C_6D_6 was placed in a NMR tube and allowed to stand at 23 °C. The progress of the reaction was monitored by ^1H NMR. After 5 days, 65% of the adduct **62** was present as a single isomer. Data for **62**: ^1H NMR (400 MHz, C_6D_6) δ 6.13 (dd, J = 4.8, 2.4 Hz, 1 H), 3.39 (s, 3 H), 3.33 (m, 2 H), 2.63 (dd, J = 11.5, 5.9 Hz, 1 H), 2.44 (m, 1 H), 2.26 (dm, J ~ 13 Hz, 1 H), 2.05 (dm, J ~ 12.8 Hz, 1 H); 1.81 (m, 1 H), 1.68 (m, 3 H), 1.59 (m, 1 H), 1.47 (m, 2 H), 1.34 (m, 5 H), 1.08 (dq, J = 12.1, 3.5 Hz, 1 H), 0.86 (dq, J = 12.6, 3.5 Hz, 1 H), 0.16 (s, 9 H); IR (CH_2Cl_2) 3610, 3580–3320, 2940, 2855, 1730, 1605, 1455, 1445, 1433, 1245, 835 cm^{-1}; high resolution mass spectrum (EI) for $C_{19}H_{34}O_3Si$ (M^+), calcd 338.2277, found 338.2283. Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.41; H, 10.13. Found: C, 67.59; H, 10.06.

2α-(4-Hydroxybut-1-yl)-2,4aα,5,6,7,8-hexahydro-8aβ*H*-1-benzopyran (64). A solution of acetal **60** (22 mg, 0.067 mmol) in 0.5 mL of wet acetone was treated with a catalytic amount

pTsOH. The reaction was stirred at room temperature for 12 h. Solid $NaHCO_3$ and Na_2SO_4 were added. The mixture was filtered through a cotton plug and concentrated under reduced pressure. Purification of the crude product by chromatography (SiO_2, 1:1 hexane/Et_2O) afforded 18.3 mg (97%) of **64** as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (dd, J = 3.7, 2.7 Hz, 1 H), 4.10 (m, 1 H), 3.67 (br s, 2 H), 3.11 (m, 2 H), 2.03-1.94 (m, 2 H), 1.87-1.78 (m, 2 H), 1.74-1.24 (m, 11 H), 0.99 (dq, J = 12.1, 3.5 Hz, 1 H), 0.09 (s, 9 H); IR (thin film) 3550-3050, 2940, 2860, 1600, 1450, 1365, 1245, 1050, 835 cm^{-1}; high resolution mass spectrum (EI) for $C_{16}H_{30}O_2Si$ (M^+), calcd 282.2015, found 282.2009. Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.63. Found: C, 67.89; H, 10.73.

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Supplementary Material Available: ^1H NMR spectra of **2, 20**, acetate derivative of **24b, 25a, 36, 40, 41, 42, 44, 46c, 48c, 48d, 51, 55**, and **56** (15 pages). Ordering information is given on any current masthead page.

A New General Synthesis of Polycyclic Aromatic Compounds Based on Enamine Chemistry

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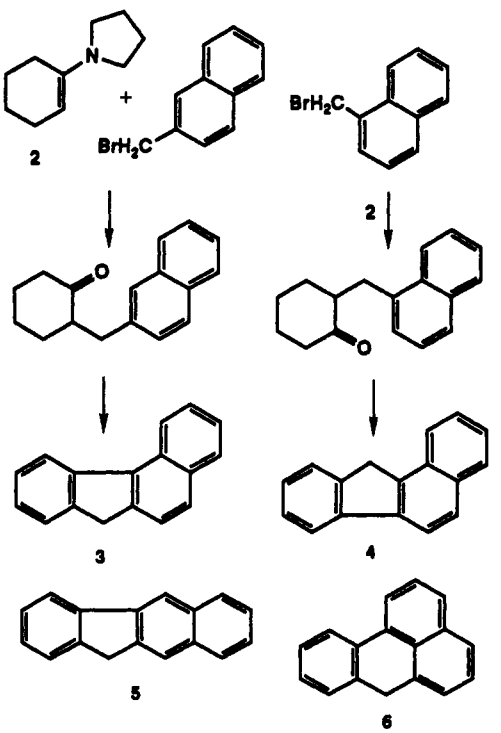
Alkylation of enamines and enamine salts by benzylic and (β-haloethyl)aryl halides, respectively, followed by acidic cyclodehydration and dehydrogenation provides an efficient synthetic approach to a wide range of polycyclic aromatic compounds of diverse structural types. Specific polycyclic hydrocarbons synthesized by this route include benzo[*a*]- and benzo[*c*]fluorene, 7*H*-dibenzo[*c,g*]-, 13*H*-dibenzo[*a,i*]-, and 13*H*-dibenzo[*a,g*]fluorene, 15*H*-tribenzo[*a,c,i*]fluorene, dibenzo[*b,def*]chrysene, benzo[*rst*]pentaphene, indeno[1,2-*b*]fluorene, fluoreno-[3,4-*c*]fluorene, octahydrodibenz[*a,j*]anthracene, dibenz[*a,j*]anthracene, octahydrodibenz[*a,h*]anthracene, dibenz[*a,h*]anthracene, picene, benzo[*c*]picene, 1*H*-benz[*bc*]aceanthrylene, and 4*H*-cyclopenta[*def*]chrysene. This method with appropriate modifications appears to be potentially broader in scope than established traditional methods of polycyclic hydrocarbon synthesis.

Development of methods for the synthesis of polycyclic aromatic hydrocarbons (polyarenes) has lagged behind expanding interest in their chemistry and biological properties. Polyarenes are widely distributed environmental contaminants formed by incomplete combustion of fossil fuels and other organic matter. Some polyarenes exhibit relatively potent carcinogenic activities.[1,2] The classical synthetic methods, which are still widely employed, were developed prior to the modern era of synthetic organic chemistry.[3] These methods frequently require harsh reagents and conditions, tend to furnish mixtures of isomeric products that are difficult to separate, and entail relatively large numbers of synthetic steps with relatively low overall yields.

This investigation is part of a program to devise novel, more efficient synthetic approaches to polycyclic aromatic molecules that do not suffer from these limitations. Specifically, we have investigated the alkylation of enamines and imine salts as the basis of potential synthetic routes to polycyclic aromatic compounds. The possible utility of this approach was suggested by prior studies[4] in which it was found that alkylation of the bromomagnesium salt of *N*-cyclopentenylcyclohexanimine with 2-(1-naphthyl)ethyl iodide, followed by acidic cyclization and dehydrogenation furnished 16,17-dihydro-15*H*-cyclopenta[*a*]phenanthrene (**1**), a key intermediate in the synthesis of the carcinogenic 17-keto derivatives of 1, previously available only by more complex multistep synthesis. We now report that this methodology with appropriate modifications provides convenient synthetic access to a wide range of polyarenes, nonalternant as well as alternant, including very large polycyclic ring systems and polyarenes relatively unobtainable by classical methods.

Scheme I



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