Studies on the Synthesis of Nargenicin A_1: Highly Stereoselective Synthesis of the Complete Carbon Framework via the Transannular Diels−Alder Reaction of an 18-Membered Macrolide

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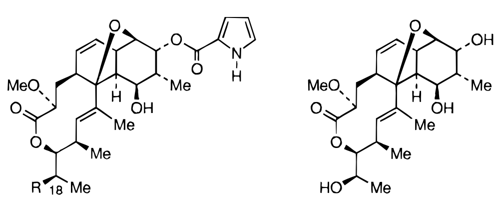
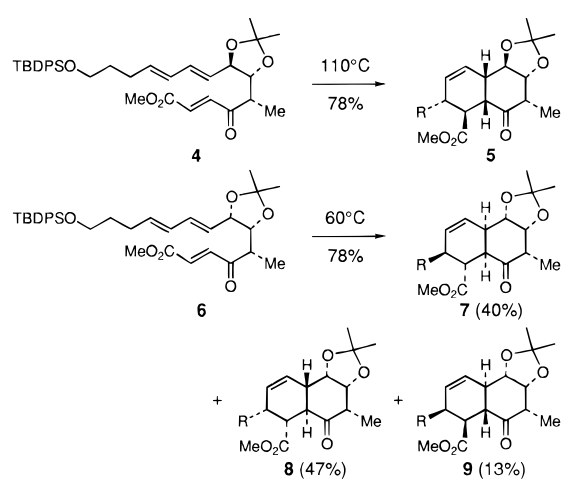
Abstract: A synthesis of the complete carbon skeleton of the nargenicins, represented by tricyclic lactone **45**, is described. The key step of the synthesis of **45** is the Yamaguchi macrolactonization of hydroxy acid **44** which is followed by the facile transannular Diels−Alder reaction of the 18-membered macrolide **22**. This sequence provides tricycle **45** in 66% yield, along with a 14% yield of tricycle **46** which is epimeric at C(10). Macrolide **22** was obtained in 38% yield when the macrolactonization was performed at 80 °C. The transannular Diels−Alder reaction of **22** at 80 °C provided tricycle **45** as the exclusive product (85% yield). In contrast, the intramolecular Diels−Alder reaction of seco ester **43** provided a mixture of trans-fused **47** in 56% yield and the desired cis-fused cycloadduct **48** in only 27% yield. Two independent stereochemical control features determine the success of the transannular Diels−Alder reaction of **22**: the C(6)−Br steric directing group that dictates that only one of the two faces of the diene is accessible to the dienophile in transition state **14** and allylic strain considerations involving the C(16)−Me substituent which enable only one face of the dienophile to be accessible to the diene in transition state **14**. The latter effect is operational only in the transannular cycloaddition mode as indicated by the results with **43**. An added benefit of this strategy is that the 10-membered lactone is established by a formal ring contraction of the more easily synthesized 18-membered lactone. Attempts to extend this strategy to the transannular Diels−Alder reaction of the C(13)-hydroxyl substituted macrolide **13** have not been successful.

Nargenicin A_1 (**1**) and nodusmicin (**2**) are structurally novel antibiotics isolated from *Nocardia argentineneas* and *Saccharopolyspora hirsuta*, respectively.[1−3] The stereostructure of nodusmicin was established by X-ray crystallographic studies,[2] while that of nargenicin A_1 was confirmed by its synthesis from nodusmicin.[3] The absolute configuration of the nargenicins, originally assigned by Cane by the nonempirical CD exciton method,[4] was subsequently verified via Kallmerten's enantioselective total synthesis of (+)-18-deoxynargenicin A_1 (**3**).[5] Several other approaches to the total synthesis of the nargenicins have been reported.[6,7]



1, R = OH, nargenicin A_1
3, R = H, 18-deoxynargenicin A_1
2, nodusmicin

We have previously described an approach to the decalin nucleus of **1** based on the intramolecular Diels−Alder reactions[8−10] of decatrienones **4** and **6**.[11] Unfortunately, while the intramolecular Diels−Alder reaction of **4** was exceptionally diastereoselective, the stereochemistry of the sole cycloadduct **5** was not suitable for its use in the projected total synthesis. Moreover, the stereoselectivity of the intramolecular Diels−Alder reactions of all other substrates examined, including **6**, was sufficiently poor that this conventional intramolecular Diels−Alder strategy for the synthesis of the nargenicins was abandoned.[12] An alternative approach to the nargenicins involving an intramolecular Diels−Alder reaction has also proven unsuccessful.[6]



[⊗] Abstract published in *Advance ACS Abstracts*, July 15, 1996.

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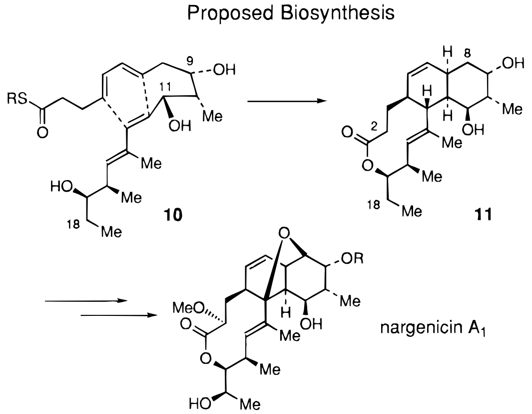
(9) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187.
(10) Roush, W. R. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550.
(11) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915.
(12) Coe, J. W. Ph. D. Thesis, Massachusetts Institute of Technology, 1988.

Cane has suggested that the nargenicin biosynthesis involves an intramolecular Diels−Alder reaction.[4,13,14] Feeding experiments with intact C(11)−C(19) and C(9)−C(19) acyclic fragments establish that the nargenicin carbon framework derives from the well established polypropionate-polyacetate biosynthetic pathway common to macrolide antibiotics.[13,14] Other studies have established that the oxygen atoms of the C(2) methoxy substituent, the C(8)−C(13) oxa bridge, and the C(18) hydroxyl group are derived from O_2, as determined by $^{18}O_2$ labeling studies.[4] This evidence supports the notion that **11** may be a late stage biosynthetic intermediate, the stereostructure of which logically implicates the acyclic tetraene **10** as a plausible precursor.[4,13,14]

Proposed Biosynthesis



Assuming that the biosynthesis does indeed involve an intramolecular Diels−Alder reaction of the type formulated in the proposed conversion of **10** to **11**, how is it that Nature is able to control the diastereoselectivity? The obvious answer is that the biosynthetic reaction is promoted by an enzyme catalyst.[15] A second possibility is that the functionality that we incorporated into the C(8)−C(14) segment of **4** and **6** is sufficiently different from that present in the putative biosynthetic Diels−Alder substrate that the reactions of **4**, **6**, and related trienes are poor mimics of the biosynthetic conversion. Although Diels−Alder reactions have been proposed as key steps in the biosyntheses of several families of natural products,[13,15,16] and while monoclonal antibodies have been developed that catalyze Diels−Alder reactions,[17] there are as yet no fully documented examples of naturally occurring "Diels−Alderases". To our knowledge, the closest example is the work of Oikawa and Ichihara who have demonstrated that a labeled, achiral triene precursor of the solanapyrones undergoes an enantioselective intramolecular Diels−Alder reaction when fed to *Alternaria solani*.[18] More recently, the same group has demonstrated that the stereoselectivity of the intramolecular Diels−Alder reaction performed in the presence of an *A. solani* cell-free extract is different from that of the thermal cycloaddition.[19] However, the presumed Diels−Alderase has not yet been isolated or characterized.

It is irrelevant for our purposes whether the putative nargenicin Diels−Alder biosynthetic step is enzyme catalyzed or not. Nevertheless, the conclusion that we reached is that if this key biosynthetic step is *not* enzyme catalyzed, then the triene substrate must have additional stereochemical control elements not present in **4** and **6** that serve to control the diastereoselectivity as well as functionality that causes the Diels−Alder reaction to occur rapidly under growth conditions of the microorganism. One final consideration that led to the approach described in this paper is that the "normal" products of the polypropionate biosynthetic pathway are macrocyclic lactones. Hence, we considered the possibility that the Diels−Alder reaction could be performed in the transannular mode,[20] with the conformational preferences of the 18-membered lactone serving to dictate the diastereoselectivity of the cycloaddition step.[21−24] We thus selected macrocyclic tetraenes **12** and **13** as targets for study.

Analysis of molecular models of **12** suggests that transition state **14** should be highly favored over the three other possibilities. We assume that the C(7)−C(12) unit will adopt the boat-like conformation indicated in **14**, which we have shown to be highly favored in the intramolecular Diels−Alder reactions of substituted 1,7,9-undecatrien-3-ones.[11] Furthermore, we have designed a C(6)-bromine steric directing group into **12** and **13**, which should induce the C(4−7) diene to react from a conformation in which C(6) is syn to C(8)−H, as is the case in **14**.[25] The alternate conformation of the diene, as in **15**, positions the bulky C(6)−Br substituent syn to the much more sterically demanding C(8,9)-acetonide unit; C(5)−H also interacts with C(2)−H in transition state **15**, but not in **14**. In both transition states **14** and **15**, the C(2)-methoxy group is equatorially positioned with respect to the macrocycle, the lactone is *s*-trans, and the C(16)−C(18) unit adopts staggered conformations with the C(16)-methyl group in an equatorial position on the macrocycle. Importantly, the proton at C(16) rather than C(16)−Me eclipses the C(14)−C(15) double bond, which minimizes allylic strain at this position.[26] Finally, as long as an *s*-trans conformation is adopted by the C(13)−C(14) single bond, then the conformation deduced for the C(1)−C(4) and C(13)−C(19) segments of the macrocycle are very close to the conformation of the ten membered ring of the natural product,[2] with the exception that the C(4)−C(13) bond that is developing in **14** is considerably longer than the fully formed bond at this position in the natural product.

The preceding analysis indicates that transition state **14** should be highly favored over the diastereomeric arrangement **15** owing to the interactions of the diene with C(2)−H and the C(8)−C(9) acetonide in **15**. There are two additional transition states (**16** and **17**) that should also be considered. These are obtained simply by reversing the face of the dienophile that is exposed to the diene in **14** and **15**. The consequences of this seemingly simple conformational change are profound. In order for the C(4)−C(7) diene and the C(12)−C(13) dienophile to achieve bonding interactions in these transition states, it is necessary for the macrocycle to adopt a conformation that has the C(16)−Me group eclipsing the C(14)−C(15) double bond, as indicated in **16** and **17**. We therefore anticipated from the outset that transition states **16** and **17** would be noncompetitive with **14** and that allylic strain considerations[26] involving the C(16)

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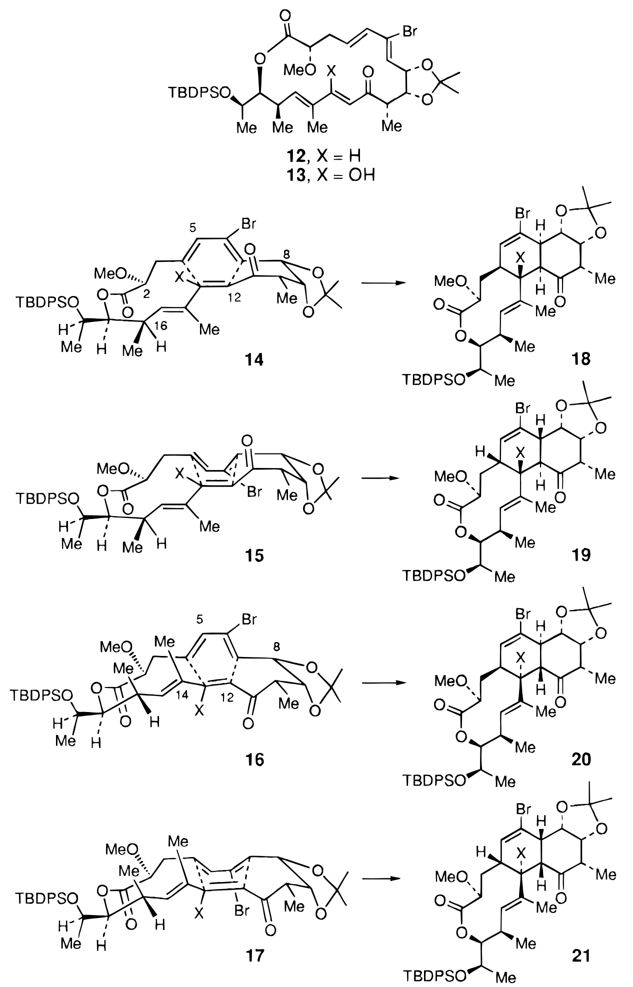
(14) Cane, D. E.; Luo, G. *J. Am. Chem. Soc.* **1995**, *117*, 6633.
(15) Laschat, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 289.
(16) Roush, W. R.; Myers, A. G. *J. Org. Chem.* **1981**, *46*, 1509.
(17) Hilvert, D. *Acc. Chem. Res.* **1993**, *26*, 552, and references cited therein.
(18) Oikawa, H.; Suzuki, Y.; Naya, A.; Katayama, K.; Ichihara, A. *J. Am. Chem. Soc.* **1994**, *116*, 3605.
(19) Oikawa, H.; Katayama, K.; Suzuki, Y.; Ichihara, A. *J. Chem. Soc., Chem. Commun.* **1995**, 1321.
(20) Deslongchamps, P. *Aldrichimica Acta* **1991**, *24*, 43.
(21) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.
(22) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148, and references cited therein.
(23) Schreiber, S. L.; Sammakia, T.; Hulin, B.; Schulte, G. *J. Am. Chem. Soc.* **1986**, *108*, 2106, and references cited therein.
(24) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. This paper describes a facile macrolactonization and transannular Diels−Alder reaction that proceeds with reversed regiochemistry compared to a related type II intramolecular Diels−Alder reaction.
(25) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.
(26) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.



stereocenter would play a major role in determining the conformational preferences of **12** and **13** in the cycloaddition transition states. *As will be shown subsequently, allylic interactions involving the C(16) stereocenter constitute the additional stereochemical control element required to control the diastereoselectivity of this key Diels–Alder reaction.*

Several additional strategic considerations also add to the attractiveness of this plan. First, one would anticipate that the transannular Diels–Alder reactions of tetraenes **12** and **13** will proceed at a much faster rate than the conventional intramolecular Diels–Alder reactions of analogously functionalized acyclic tetraenes.[20,27,28] Second, this approach constitutes a very simple ring contraction strategy for introducing the ten-membered lactone of the natural product. Ten membered lactones, in general, are difficult to prepare efficiently by conventional lactonization methods.[29,30] Kallmerten synthesized the 10-membered lactone in his 18-deoxynargenicin synthesis in 38% yield by macrolactonization of the seco acid.[5] However, Steliou was able to cyclize a seco acid prepared by degradation of natural nargenicin A_1 in only 8% yield.[31] Consequently, since 18-membered lactones are generally easier to synthesize than 10-membered ones,[30] this transannular Diels–Alder strategy seemed to be an ideal way to control the stereochemistry of the nargenicin nucleus as well as to introduce the highly problematic 10-membered lactone in a single operation.

(27) Bérubé, G.; Deslongchamps, P. *Tetrahedron Lett.* **1987**, *28*, 5255.
(28) Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674.
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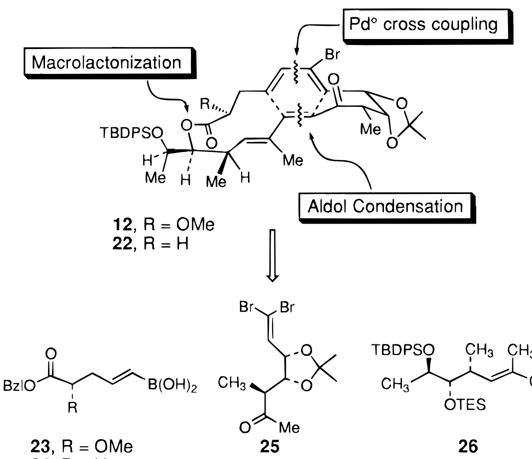
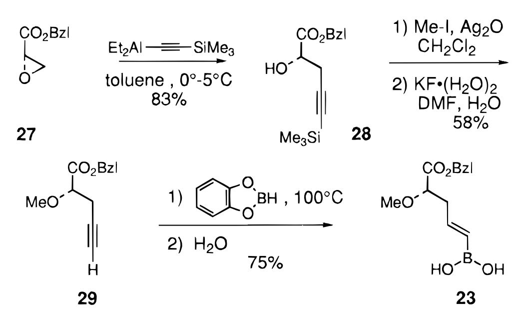
(30) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.
(31) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130.

Results and Discussion

Retrosynthetic Analysis of 13-Deoxymacrolide 12. Analysis of the structure of **12** suggested that this intermediate could be assembled from three precursors: vinylboronic acid **23**, corresponding to C(1)–C(5); methyl ketone **25**, corresponding to C(6)–C(12); and enal **26** corresponding to the C(13)–C(19) fragment of the macrolide target. We anticipated that the fragment assembly sequence would involve an aldol condensation of **25** and **26**, Suzuki cross coupling of the dibromoolefin unit of **25** with vinylboronic acid **23**[32,33] followed by a final macrolactonization step. However, at the time that this synthesis was undertaken, vinylboronic acid **23** was unavailable and the simpler vinylboronic acid **24** was used instead. Thus, the first macrolide that we discuss in this paper is **22**, and not **12**.



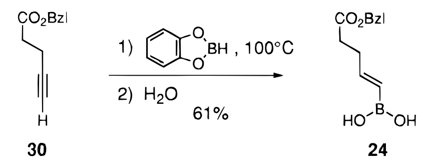
Synthesis of Vinylboronic Acids 23 and 24. Vinylboronic acid **23** was synthesized from benzyl (*S*)-glycidate (**27**),[34] which in turn was prepared from D-serine via potassium (*S*)-glycidate.[35] Thus, treatment of **27** with $Et_2AlC{\equiv}CSiMe_3$[36,37] provided **28** in 83% yield. Conversion of the alcohol to a methyl ether by using Ag_2O and MeI followed by cleavage of the acetylenic silane under mild conditions provided **29** in 58% yield. Finally, hydroboration of **29** with catecholborane provided the sensitive vinylboronic acid **23** in 75% yield.[38]



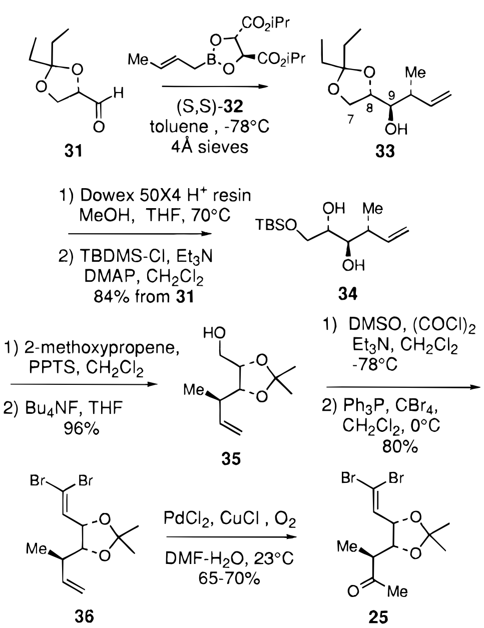
Vinylboronic acid **24** was similarly prepared in 61% yield by hydroboration of benzyl 4-pentynoate (**30**).

Synthesis of Methyl Ketone 25. Asymmetric (*E*)-crotylbo-

(32) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.
(33) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.
(34) Larcheveque, M.; Petit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.
(35) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380.
(36) Roush, W. R.; Blizzard, T. A.; Basha, F. Z. *Tetrahedron Lett.* **1982**, *23*, 2331.
(37) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.
(38) Kabalka, G. W.; Baker, J. D., Jr.; Neal, G. W. *J. Org. Chem.* **1977**, *42*, 512.



ration of L-glyceraldehyde pentylidene ketal **31**[39] with (*E*)-crotylboronate (*S*,*S*)-**32** provided **33** with excellent selectivity.[40,41] Removal of the ketal by heating a methanolic solution of **33** with Dowex 50 × 4-400 H^+ resin followed by selective silylation of the primary alcohol provided TBS ether **34** in 84% overall yield from **31**. The C(8,9) diol unit was then protected as an acetonide, and the TBS ether was cleaved to give primary alcohol **35** in 96% yield. It should be noted that it was not possible to transform **33** directly into **35** since the acetonide at the terminal C(7,8) position (as in **33**) is more stable than at the internal C(8,9) position in **35**.[11] Oxidation of **35** via the Swern protocol[42] and Corey−Fuchs olefination of the resulting aldehyde provided dibromodiene **36**.[43] Finally, subjection of **36** to standard Wacker oxidation conditions provided methyl ketone **25** in 65−70% yield.[44]



Synthesis of Enal 26. The synthesis of this fragment originated with the highly diastereoselective (*Z*)-crotylboration of (R)-lactaldehyde derivative **37**[45] and (*R*,*R*)-**38**,[40,41] which provided **39** with ≥99% diastereoselectivity (only one isomer detected).[46] Ozonolysis of **39**, treatment of the resulting β-hydroxy aldehyde with $Ph_3P{=}C(Me)CO_2Et$ provided enoate **40** in 79% yield. Finally, DIBAL-H reduction of the carboethoxy group and MnO_2 oxidation of the allylic alcohol provided the targeted enal **26**.

(39) Schmid, C. R.; Bradley, D. A. *Synthesis* **1992**, 587.
(40) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294.
(41) Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117.
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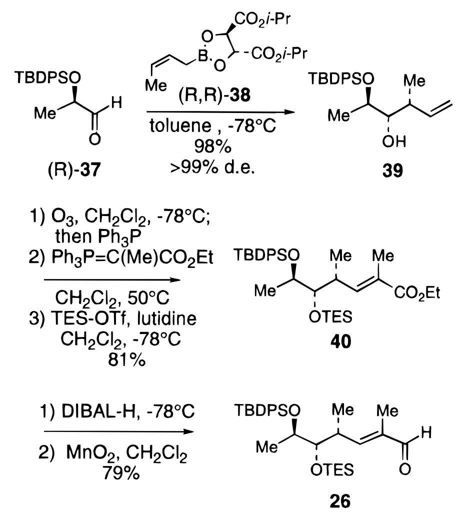
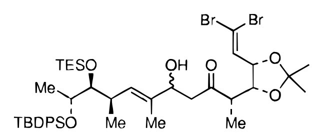
(44) Hegedus, L. S. In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 551.
(45) Soai, K.; Shimada, C.; Takeuchi, M.; Itabashi, M. *J. Chem. Soc., Chem. Commun.* **1994**, 567.
(46) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

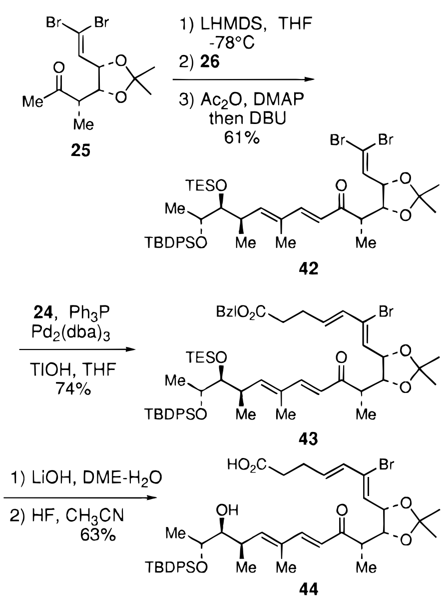


Synthesis and Transannular Diels−Alder Reaction of 13-Deoxymacrolide 22. We began the synthesis of macrolide **22** with the aldol coupling of methyl ketone **25** and enal **26**. Initial attempts to prepare aldol **41** via the addition of the lithium enolate of **25** to aldehyde **26** met with variable and poorly reproducible results (0−50%, depending on the reaction scale). Aldol **41** is very sensitive to retroaldol cleavage, which occurred even during silica gel chromatographic purification. It was possible to trap aldol **41** as the corresponding TBS ether in 69% yield by adding TBS-OTf before the reaction workup. Simple



41

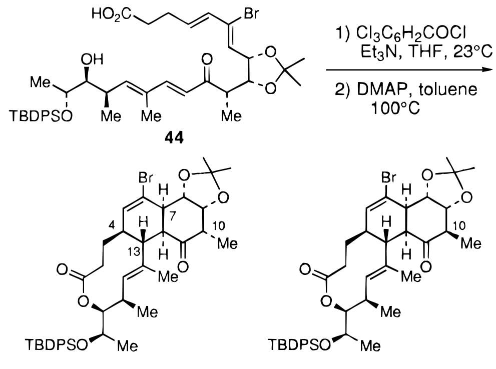
modification of this sequence involving treatment of the intermediate lithium aldolate with Ac_2O and DMAP followed by addition of DBU provided the desired trienone **42** in 61% yield. Suzuki coupling of **42** with vinylboronic acid **24** in the presence of $Pd_2(dba)_2$ and TlOH provided seco ester **43** in 74% yield.[33,47] Finally, deprotection of the benzyl ester and the C(17) triethylsilyl ether completed the synthesis of seco acid **44**.



Addition of the mixed anhydride generated by treatment of **44** with trichlorobenzoyl chloride and Et_3N in THF to a 100 °C

(47) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

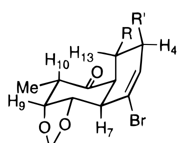
solution of DMAP in toluene provided a mixture of two tetracyclic products, **45** and **46**, in 79% combined yield.[48] The 18-membered macrolide **22** was not observed under these conditions. The stereochemistry of the major product, **45**, which was isolated in 66% yield, was assigned on the basis of ^{1}H NMR data. In addition to the *J* data summarized in the accompanying



45, 66% **46**, 13%

45	**46**
$J_{4,5}$ = 3.4 Hz	$J_{4,5}$ = 3.4 Hz
$J_{7,8}$ = 8.2 Hz	$J_{7,8}$ = 8.8 Hz
$J_{7,12}$ = 4.8 Hz	$J_{7,12}$ = 5.2 Hz
$J_{8,9}$ = 4.8 Hz	$J_{8,9}$ = 6.8 Hz
$J_{9,10}$ = 4.8 Hz	$J_{9,10}$ = 10.4 Hz
$J_{12,13}$ = 11.6 Hz	$J_{12,13}$ = 12.8 Hz
$J_{4,13}$ = 11.6 Hz	$J_{4,13}$ = 12.8 Hz

figure, strong NOEs observed between H_7–H_{12} (4.9%), H_9–H_{10} (4.6%), and H_{10}–H_{13} (3.7%) are uniquely consistent with the stereostructure depicted for **45**. *Interestingly, all stereo-*



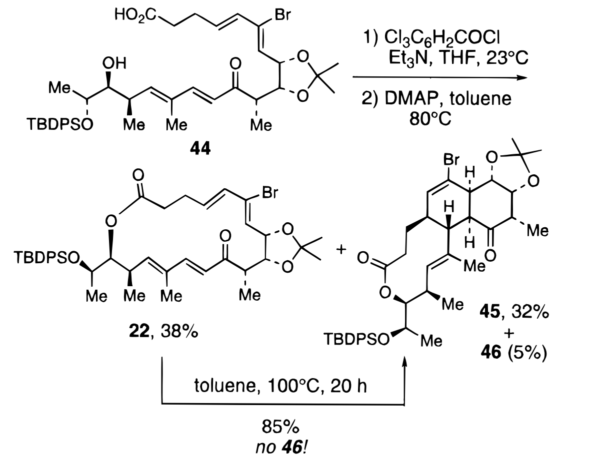
45

nOe Data
$H_{12} \rightarrow H_7$, 4.9%
$H_{10} \rightarrow H_9$, 4.6%
$H_{10} \rightarrow H_{13}$, 3.7%

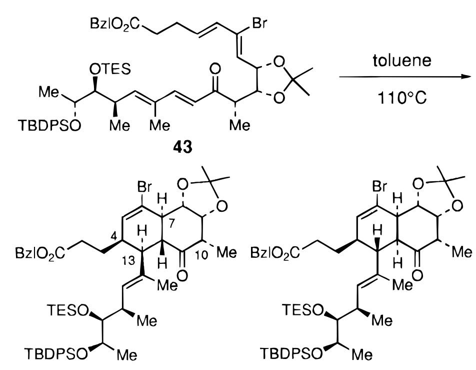
*centers of **45** except C(8) correspond exactly to the stereochemistry of the natural nargenicins*. The minor product, **46**, isolated in 13% yield, is the C(10) epimer of **45**. These results verified that the stereoselectivity of this transannular Diels–Alder reaction is strongly biased to produce cycloadduct **45**, exactly as predicted by our analysis of transition states **14-17**.

In an effort to minimize the extent of epimerization of **45**, the macrolactonization of **44** was performed at 80 °C. Under these conditions, macrolide **22** was obtained in 38% yield along with 32% of tetracycle **45** and only 5% of the C(10) epimer **46**. With a sample of **22** available, it was possible to assess the diastereoselectivity of the transannular Diels–Alder reaction. In the event, when a toluene solution of **22** was heated at 100 °C for 20 h, tetracycle **45** was obtained in 85% yield as the sole reaction product. Therefore, it is clear that the transannular Diels–Alder reaction of **22** is highly stereoselective, and that the C(10)-epimer **46** derives from epimerization of either **44** (or the corresponding mixed anhydride), **22**, or **45** under the weakly basic macrolactonization conditions.

In order to verify our prediction that the success of the synthesis of **45** depends on the conformational preferences of macrocycle **22** in the transannular cycloaddition transition states, and that a conventional intramolecular Diels–Alder (IMDA) reaction would not be very stereoselective in this series,[6,11,12] we examined the thermal cyclization of seco ester **43**. When a toluene solution of **43** was heated at 110 °C for 24 h, a ca. 2:1 mixture of cycloadducts **47** and **48** was obtained. As is clearly illustrated in the following diagram, the major product (**47**) of



this reaction possesses a trans ring fusion. This product arises from an acyclic transition state analogous to **14**. It is the minor product in this series, **48**, which derives from an acyclic transition state analogous to **16**, that has the correct nargenicin stereochemistry. Interestingly, both **47** and **48** possess the same relative stereochemistry at C(7)–C(8), indicating that the steric directing group functioned as intended in allowing only one face of the diene to interact with the dienophile in the reaction transition states.[25] The problem with the cyclization of **43** is that both faces of the dienophile interact with the diene, leading to the formation of two products with, unfortunately, the incorrect stereoisomer **47** predominating. This provides retrospective support for our original hypothesis that allylic interactions involving the C(16) stereocenter in the macrocyclic tetraene would serve as an important stereochemical control element and dictate the face of the dienophile that is presented to the diene in the transannular Diels–Alder reaction.



47, 56% **48**, 27%

47	**48**
$J_{4,5}$ = 5.2 Hz	$J_{4,5}$ = 3.2 Hz
$J_{7,8}$ = 9.6 Hz	$J_{7,8}$ = 7.2 Hz
$J_{7,12}$ = 12.0 Hz	$J_{7,12}$ = 5.2 Hz
$J_{8,9}$ = 5.0 Hz	$J_{8,9}$ = 5.2 Hz
$J_{9,10}$ = 5.0 Hz	$J_{9,10}$ = 5.2 Hz
$J_{12,13}$ = 12.0 Hz	$J_{12,13}$ = 9.6 Hz
	$J_{4,13}$ = 9.6 Hz

Synthesis of Macrolide 13. One problem not solved by the successful transannular Diels–Alder reaction of **22** concerns the introduction of the C(8)–C(13) oxa bridge present in the natural products. Unfortunately, repeated attempts to introduce the oxa bridge by application of remote oxidation procedures[49–51] on intermediates derived from **45** were not successful.[52] Accordingly, it was apparent that if the transannular Diels–Alder strategy was to yield a productive route to the naturally occurring

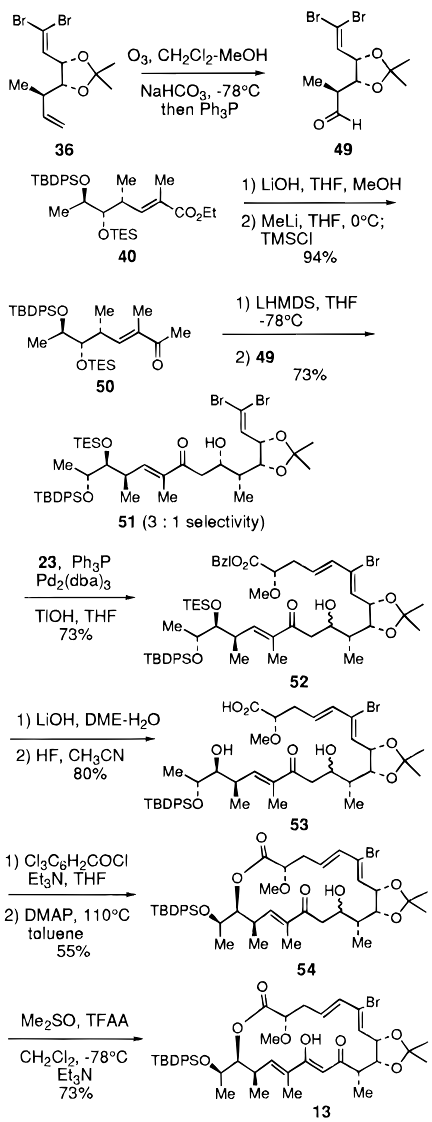
(48) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(49) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076.

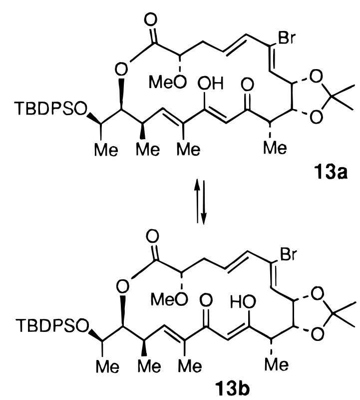
(50) Heusler, K.; Kalvoda, J. *Helv. Chim. Acta* **1963**, *46*, 2020.

(51) Mihailovic, M. L.; Gojkovic, S.; Konstantinovic, S. *Tetrahedron* **1973**, *29*, 3675.

nargenicins, it would be necessary to introduce an oxygen-containing functionality at C(13) prior to the Diels−Alder reaction. We therefore synthesized macrolide **13** in anticipation that it would undergo a facile transannular cycloaddition reaction to nargenicin precursor **18** (X = OH).



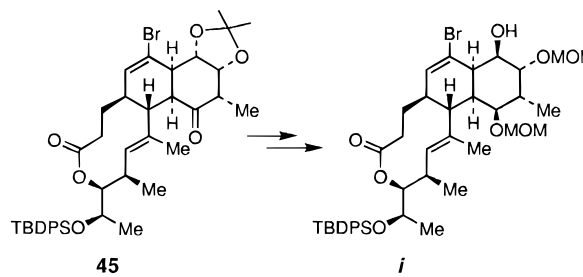
In view of the instability of aldol **41** (vide supra), the synthesis of **13** that we developed proceeds by way of aldol **51** that is considerably more stable. The required aldehyde component **49** was prepared by selective ozonolysis of the vinyl unit of **36**.[53] Aldehyde **49** was used without purification directly in the aldol reaction with methyl ketone **50**, which was prepared by standard procedures via the corresponding carboxylic acid.[54] The aldol coupling of **49** and **50** provided β-hydroxy ketone **51** in 73% yield as a 3:1 mixture of diastereomers. We presume that the major diastereomer is the Felkin isomer, as formulated in **51**, but this stereochemical assignment was not established rigorously. The diastereomeric mixture was not separated on a routine basis, since both isomers behaved similarly in subsequent transformations. Cross coupling of **51** (3:1 diastereomeric mixture) with vinylboronic acid **23** provided **52** in 73% yield. Standard deprotection of the benzyl ester and triethylsilyl ether provided the seco acid **53**, which when subjected to the Yamaguchi macrocyclization protocol provided macrolide **54** in 55% yield.[48] It is noteworthy that the potentially sensitive β-hydroxy ketone functionality survived the sequence of reactions from **51** to **54** without protection. Finally, oxidation of **54** with the Swern DMSO-trifluoroacetic anhydride reagent[42] provided macrocycle **13**, which exists exclusively as an enol tautomer. While **13** is probably a rapidly equilibrating mixture of the two isomeric enols, the regioisomer formulated as **13a** is expected to be the predominate one.[55,56]



Unfortunately, numerous attempts to induce **13** to undergo the desired transannular Diels−Alder reaction have not been successful. Macrocycle **13** was recovered unchanged when heated to 200 °C in toluene; at higher temperatures (>250 °C) substantial decomposition was observed. No reaction was observed when solutions of **13** were exposed to ultrasound at 50 °C,[57] or when **13** was dissolved in a 5 M solution of $LiClO_4$ in Et_2O.[58] Similarly, macrocycle **13** was recovered unchanged when treated with various Lewis acids including anhydrous $ZnCl_2$ in THF, Me_2AlCl in THF, $BF_3\cdot Et_2O$ in CH_2Cl_2 or $LiBF_4$ in CH_3CN at ambient temperature. Decomposition was observed when **13** was treated with Bu_3B and HOAc, in an attempt to generate a cyclic borate ester.[59]

It was clear from these results that the β-hydroxy enone unit in **13**, which can be thought of as an "acac" complex of a proton, is too electron rich to function as a dienophile in the transannular Diels−Alder reaction and that the anticipated entropic assistance of the transannular process is insufficient to overcome this electronic barrier.[27] However, the literature contains several examples of intramolecular Diels−Alder reactions of β-alkoxy and β-acetoxy enones.[60,61] Accordingly, many attempts were made to convert **13** or the analogous des-methoxy macrolide **55** into the corresponding enol acetate derivatives (e.g., **56** from **13**)

(52) Numerous attempts to introduce the oxa bridge by remote oxidation of alcohol *i*, which was prepared by an eight step sequence from **45**, were unsuccessful. Methods examined include $Pb(OAc)_4$, $CaCO_3$, benzene, 80 °C; $Pb(OAc)_4$, I_2, $CaCO_3$; Ag_2CO_3, Br_2; Ag_2CO_3, I_2; DDQ, CH_2Cl_2; and nitrite ester photolysis (see refs 49−51).



(53) Pryor, W. A.; Giamalva, D.; Church, D. F. *J. Am. Chem. Soc.* **1983**, *105*, 6858.

(54) Rubottom, G. M.; Kim, C. *J. Org. Chem.* **1983**, *48*, 1550.

(55) Bassetti, M.; Cerichelli, G.; Floris, B. *Tetrahedron* **1988**, *44*, 2997.

(56) Vila, A. J.; Lagier, C. M.; Oliveri, A. C. *J. Phys. Chem.* **1991**, *95*, 5069.

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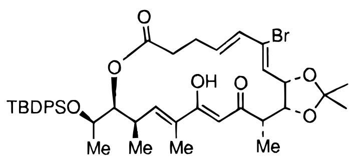
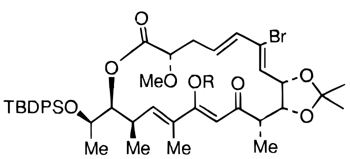
(59) Narasaka, K.; Pai, F. *Tetrahedron* **1984**, *40*, 2233.

by treatment with isopropenyl acetate or acetic anhydride in the presence of *p*-TsOH, or with acetyl chloride and Et_3N. However, no reaction occurred at ambient temperature to 90 °C, while substantial decomposition was observed above 100 °C. An enol acetate derivative of undetermined geometry was generated by treatment of **55** with $LiN(TMS)_2$ and Ac_2O, but this material decomposed when heated at 110 °C in toluene. Similarly, attempts to generate and cyclize enol diethyl phosphate (LHDMS, $(EtO)_2POCl$, THF) and enol sulfonate derivatives (MsCl, Et_3N) were unsuccessful. Attempts to generate enol ether derivatives by treatment of **13** or **55** with CH_2N_2, TsOH in MeOH, or MOM-Cl and *i*-Pr_2NEt in CH_2Cl_2 were similarly unproductive. A triethylsilyl enol ether (of undetermined regio- and stereochemistry) was obtained by treatment of **13** with Et_3SiOTf and lutidine at −78 °C, but this material also failed to undergo the desired transannular Diels−Alder reaction.



55



56, R = Ac
57, R = $PO(OEt)_2$
58, R = SO_2Me
59, R = Me
60, R = MOM
61, R = $SiEt_3$

Conclusions

We have established that the complete carbon skeleton of the nargenicins can be assembled with high stereoselectivity from subunits **24**, **25**, and **26** by a sequence involving the macrolactonization of seco acid **44** and the transannular Diels−Alder reaction of the derived 18-membered macrolide **22**. This sequence permits all of the stereochemical features of the nargenicin nucleus, represented by structure **45**, to be controlled. In contrast, stereocontrolled construction of the hydronaphthalene nucleus is not possible in the conventional intramolecular Diels−Alder mode as illustrated by the non-selective IMDA reaction of seco ester **43**. An added benefit of this strategy is that the troublesome 10-membered lactone is established by a formal ring contraction of the more easily synthesized 18-membered lactone.

Two independent stereochemical control features determine the success of the transannular Diels−Alder reaction of **22**. First, the C(6)−Br steric directing substituent dictates that only one of the two faces of the diene is accessible to the dienophile in transition state **14** (and potentially also in **16**).[25] Second, allylic strain considerations involving the C(16)−Me substituent dictate that only one face of the dienophile is accessible to the diene in transition state **14** (and possibly also **15**).[26] The latter effect is operational only in the transannular cycloaddition mode due to conformational constraints posed by the 18-membered macrocycle. The combination of these two effects lead to **14** being the most favorable of all the possible transition states, and as a result the transannular Diels−Alder reaction is highly stereoselective.

To the best of our knowledge, the tandem macrolactonization of **44** and transannular Diels−Alder reaction of **22** is the first fully documented example in which the transition state conformational preferences of the macrocycle play a decisive role in determining the stereoselectivity of the cycloaddition event.[24]

One hurdle remains to be solved in order for this strategy to be successfully applied to the total synthesis of the nargenicins, namely establishment of a method for introduction of the oxa bridge.[52] Studies addressing this issue are in progress, and will be the subject of future reports from our laboratory.

Experimental Section

General Methods. All reactions were conducted in flame-dried glassware under dry argon or nitrogen. All solvents except DMF were purified before use: diethyl ether, THF, and toluene were distilled from sodium benzophenone ketyl; dichloromethane and triethylamine were distilled from CaH_2, and methanol was distilled from magnesium turnings. DMF was used as received from commercial sources.

^1H NMR spectra were measured at 300 and 400 MHz on commericially available instruments. Chemical shifts are reported in δ units; coupling constants are reported in Hz. Residual chloroform (δ 7.26) and benzene (δ 7.15) were used as internal references for spectra measured in these solvents. ^{13}C NMR spectra were measured at 100.6 MHz, and residual chloroform (δ 77.0) and benzene (δ 128.0) were used as internal references. High resolution mass spectra were measured at 70 eV. Optical rotations were measured on a Rudolph Autopol III polarimeter using a quartz cell with 1 mL capacity and a 10 cm path length. Elemental analyses were performed by Robertson Laboratories, Florham Park, NJ.

Analytical thin layer chromatography (TLC) was performed with the use of plates coated with a 0.25 mm thickness of silica gel containing PF254 indicator (Analtech), and compounds were visualized with UV light, iodine, *p*-anisaldehyde, ceric ammonium molybdate, or ninhydrin stain. Preparative TLC was performed with the use of 20 cm × 20 cm plates coated with a 0.50 mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still with the use of Kieselgel 60 (230−400 mesh).[63]

Benzyl (2*S*)-2-hydroxy-5-(trimethylsilyl)-4-pentynoate (28). To a 0 °C solution of (trimethylsilyl)acetylene (20.3 mL, 144 mmol) in toluene (120 mL) was added *n*-BuLi (80 mL, 2.5 M in hexanes, 144 mmol) by syringe over 30 min. The resulting mixture was stirred for 30 min at which time diethylaluminum chloride (80 mL, 1.8 M in hexanes, 144 mmol) was added. The solution was warmed to room temperature, stirred for 2 h and recooled to 0 °C; a solution of benzyl (2*S*)-glycidate[34] (**27**, 12.8 g, 71.7 mmol) in 40 mL toluene was then added via cannula. The solution was stirred at 0 °C for 4 h at which time it was diluted with ether (200 mL), acidified with 1 M HCl (pH ∼ 4) and extracted with ether (4 × 100 mL). The combined organic layers were washed with water (100 mL), dried with $MgSO_4$, filtered and concentrated. Purification of the crude product by flash chromatography [silica gel, 10 × 15 cm, gradient elution: 5% ethyl acetate/hexanes (2 L); 10% ethyl acetate/hexanes (1 L); 15% ethyl acetate/hexanes (2 L)] gave alcohol **28** (16.5 g, 83%) as a colorless oil: $[\alpha]_D^{23}$ −71.5° (*c* 0.9, hexanes); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45−7.35 (m, 5 H), 5.27 and 5.21 (AB, J = 12.1 Hz, 2 H), 4.36 (m, J = 7.7, 4.9 Hz, 1 H), 3.05 (d, J = 6.9 Hz, 1 H), 2.7−2.8 (m, 2 H), 0.13 (s, 9 H); IR (neat) 3500, 2180, 1750 cm^{-1}; HRMS calcd for $C_{15}H_{20}O_3Si$ (M^+), 276.1182, found 276.1184. Anal. Calcd for $C_{15}H_{20}O_3Si$: C, 65.17; H, 7.31. Found: C, 65.00; H, 7.11.

Benzyl (2*S*)-2-methoxy-4-pentynoate (29). To a stirred solution of alcohol **28** (3.0 g, 11 mmol) in CH_2Cl_2 (15 mL) in a 50 mL round bottom flask with a screw cap seal was added silver(I) oxide (2.5 g, 11 mmol) and methyl iodide (2.0 mL, 32 mmol). The tube was sealed, placed in an oil bath at 50 °C and stirred for 12 h at which time additional silver(I) oxide (2.5 g, 22 mmol) and methyl iodide (2.0 mL, 65 mmol) were added. After being stirred for an additional 12 h at 50 °C the solution was cooled, filtered through Celite with CH_2Cl_2 and concentrated in a fume hood by aspirator vacuum. Purification of the crude product by flash chromatography (silica gel, 5 × 15 cm, 5% ethyl acetate/hexanes) gave the methyl ether (2.28 g, 72%) as a colorless

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(61) Shishido, K.; Takahashi, K.; Fukumoto, K.; Kametani, T.; Honda, T. *J. Org. Chem.* **1987**, *52*, 5704.

(62) For two other examples of transannular Diels−Alder reactions that are more selective than analogous intramolecular Diels−Alder reactions, see: (a) Roush, W. R.; Warmus, J. S.; Works, A. B. *Tetrahedron Lett.* **1993**, *34*, 4427. (b) Jung, S. H.; Lee, Y. S.; Park, H.; Kwon, D.-S. *Tetrahedron Lett.* **1995**, *36*, 1051.

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

oil: $[\alpha]_D^{23}$ −13.6° (*c* 0.5, hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5 H), 5.21 (s, 2 H), 3.95 (m, 1 H), 3.45 (s, 3 H), 2.75−2.65 (m, 2 H), 0.12 (s, 9 H); IR (neat) 2180, 1760 cm^{-1}; HRMS calcd for $C_{16}H_{22}O_3Si$ (M^+), 290.1339, found 290.1354. Anal. Calcd for $C_{16}H_{22}O_3Si$: C, 66.22; H, 7.65. Found: C, 65.82; H, 7.41.

To a stirred, 23 °C solution of the above methyl ether (1.74 g, 5.99 mmol) in *N,N*-dimethylformamide (20 mL) and water (7 mL) was added potassium fluoride dihydrate (2.82 g, 30.0 mmol) in one portion. The resulting mixture was stirred for 20 h at which time it was poured into brine solution (20 mL). The aqueous layer was extracted with ether (3 × 40 mL) and the combined organic layers were washed with brine (40 mL), dried with $MgSO_4$, filtered and concentrated. Purification of the crude product by flash chromatography (silica gel, 5 × 15 cm, 15% ethyl acetate/hexanes) gave alkyne **29** (1.06 g, 81%) as a colorless oil: $[\alpha]_D^{23}$ −29.0° (*c* 0.4, hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5 H), 5.26 and 5.20 (AB, *J* = 12 Hz, 2 H), 3.96 (t, *J* = 6.1 Hz, 1 H), 3.46 (s, 3 H), 2.8−2.6 (m, 2 H), 2.68 (t, *J* = 2.3 Hz, 1 H); IR (neat) 3300, 2220, 1750 cm^{-1}; HRMS calcd for $C_{13}H_{14}O_3$ (M^+), 218.0943, found 218.0939. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.28; H, 6.72.

(*E*)-(4*S*)-4-(Benzyloxycarbonyl)-4-methoxybut-1-enylboronic Acid (23). To a neat sample of alkyne **29** (800 mg, 3.66 mmol) in a tube equipped with a screw cap seal was added catechol borane (98 μL, 0.92 mmol) via syringe. The tube was flushed with argon, sealed and placed in an oil bath at 100 °C. After being stirred for 2.5 h the tube was cooled and placed under a positive pressure of argon; additional catechol borane (98 μL, 0.92 mmol) was added. This process was repeated until a total of 1.5 equiv of catechol borane (586 μL, 5.5 mmol total) had been added. After additional heating at 100 °C for 6 h the solution was cooled and carefully quenched with a 1:1 ethyl acetate/water mixture (4 mL). This mixture was stirred at room temperature for 12 h, diluted with 20 mL ethyl acetate and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated. Purification of the crude product by flash chromatography [silica gel, 3 × 15 cm, gradient elution: 50% ethyl acetate/hexanes (0.5 L); 5% methanol/dichloromethane (0.5 L)] gave boronic acid **23** (722 mg, 75%) which was stored as a 0.5 M solution in methanol: $[\alpha]_D^{23}$ −39.3° (*c* 1.2, methanol); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5 H), 6.44 (dt, *J* = 17.2, 7.0 Hz, 1 H), 5.59 (dt, *J* = 17.2, 1.4 Hz, 1 H), 5.17 (AB, *J* = 12.2 Hz, 2 H), 3.95 (dd, *J* = 6.6, 5.4 Hz, 1 H), 3.34 (s, 3 H), 2.7−2.5 (m, 2 H); IR (CCl_4) 3660, 3460, 1760, 1640 cm^{-1}. This compound was fully characterized as the pinacol ester, as described in the following procedure.

To a mixture of boronic acid **23** (132 mg, 0.50 mmol) and Na_2SO_4 (85 mg) in THF (2 mL) at 23 °C was added pinacol (60 mg, 0.50 mmol) in one portion. This mixture was stirred at room temperature for 1 h, filtered through a cotton plug and concentrated *in vacuo*. Purification of the crude product by flash chromatography (silica gel, 2 × 15 cm, 10% ethyl acetate/hexanes) gave the pinacol ester (111 mg, 67%) as a clear oil: $[\alpha]_D^{23}$ −24.6° (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.4−7.3 (m, 5 H), 6.57 (dt, *J* = 17.8, 6.6 Hz, 1 H), 5.52 (dd, *J* = 17.8, 1.4 Hz, 1 H), 5.18 (s, 2 H), 3.90 (t, *J* = 5.6 Hz, 1 H), 3.38 (s, 3 H), 2.65−2.55 (m, 2 H), 1.25 (s, 12 H); ^{11}B NMR (115 MHz, $CDCl_3$) δ 29.5; IR (CCl_4) 1760, 1640 cm^{-1}; HRMS calcd for $C_{19}H_{27}O_5B$ (M^+), 346.1951, found 346.1936.

Benzyl 4-Pentynoate (30). A solution of 4-pentynoic acid[64] (3.15 g, 30 mmol) in CH_3CN (100 mL) was treated with DBU (6.8 mL, 45 mmol) and benzyl bromide (9.5 mL, 80 mmol). This mixture was stirred at room temperature overnight under N_2. Et_2O (100 mL) and HCl (1 M, 50 mL) were added, the layers were separated, and the organic layer was washed with aqueous HCl (1 M, 3 × 20 mL). The combined aqueous layers were extracted with ether (3 × 20 mL). The organic phases were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Residual CH_3CN was removed by distillation, and the pot residue was purified by flash chromatography using 20:1 pentane-ether as eluant to yield **30** (4.63 g, 82%) as a yellow oil: R_f 0.76 (95:5 CH_2Cl_2-CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5 H), 5.15 (s, 2 H), 2.64−2.59 (m, 2 H), 2.55−2.51 (m, 2 H), 1.98 (t, *J* = 2.6 Hz, 1 H); IR (neat) 3290, 2120, 1740 (br), 1615 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{12}O_2$ (M^+) 188.0837, found 188.0833. Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.29; H, 6.66.

(*E*)-4-(Benzyloxycarbonyl)but-1-enylboronic Acid (24). To a flame-dried Carius tube was added benzyl 4-pentynoate (**30**) (686 mg, 3.65 mmol) and freshly distilled catecholborane (98 μL, 0.90 mmol). After gas evolution ceased, the tube was sealed and heated to 100 °C. An additional 3 aliquots of catecholborane (97 μL, 0.90 mmol, each) were added over 9.5 h (total volume for four additions of catecholborane was 390 μL, 3.68 mmol), and the mixture was stirred for an additional 20 h at 100 °C. The mixture was cooled to ambient temperature and diluted with brine (5 mL) and EtOAc (5 mL). The resulting mixture was vigorously stirred for 40 min. More EtOAc (10 mL) was added, and the two-phase system was separated. The aqueous phase was extracted with EtOAc (5 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo.* The residue was purified by flash chromatography on a short, wide column with 1:1 hexanes-ether to remove catechol, then quickly eluted with 95:5 CH_2Cl_2−CH_3OH to provide **24** (519 mg, 61%) as a very viscous clear oil: R_f 0.33 (95:5 CH_2Cl_2−CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.40−7.28 (m, 5 H), 6.5 (dt, *J* = 17.6, 5.8 Hz, 1 H), 5.6 (d, *J* = 17.6 Hz, 1 H), 5.1 (s, 2 H), 2.5−2.4 (m, 4 H); IR (neat) 3430 (br), 1760, 1660 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}O_3$ ($M^+ - B(OH)_2$) 189.0915, found 189.0899. This compound was fully characterized as the pinacol ester, which was prepared as described in the following procedure.

To a solution of vinyl boronic acid **24** (57 mg, 0.24 mmol) in dry THF (1 mL) was added pinacol (26 mg, 0.22 mmol) and Na_2SO_4 (20 mg, 0.10 mmol). After being stirred at room temperature under N_2 for 2 d, the mixture was filtered through a cotton plug and concentrated *in vacuo*. The crude product was purified by flash chromatography using 5:1 hexanes-ether as eluant to provide the pinacol ester (47 mg, 74%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5 H), 6.62 (m, 1 H), 5.47 (d, *J* = 18.0 Hz, 1 H), 5.10 (s, 2 H), 2.51−2.40 (m, 4 H), 1.26 (s, 12 H); ^{11}B NMR (115 MHz, $CDCl_3$) δ 29.9 (s); IR (neat) 1735, 1635 cm^{-1}; HRMS (CI) calcd for $C_{18}H_{25}O_4B$ (M^+), 315.1882, found 315.1858. Anal. Calcd for $C_{18}H_{25}O_4B$: C, 68.37; H, 7.97. Found: C, 68.41; H, 7.68.

(2*S*,3*R*,4*R*)-1-[(*tert*-Butyldimethylsilyl)oxy]-4-methylhex-5-en-2,3-diol (34). Chiral crotylboronate (*S*,*S*)-**32** (73.6 mL of a 0.93 M solution in toluene, 68 mmol)[65] was diluted with toluene (200 mL) and treated with powdered 4 Å molecular sieves (10 g, Aldrich) at room temperature for 30 min. This dispersion was then cooled to −78 °C. To this solution was then added a solution of 2,3-O-(3-pentylidene)-L-glyceraldehyde (**31**) (7.22 g, 45.6 mmol)[39] in toluene (10 mL) via syringe pump over a 30 min period. The reaction mixture was stirred for an additional 1.5 h at −78 °C at which time 1 M NaOH (135 mL) was added; the resulting mixture was then stirred at room temperature for 3 h. The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried with $MgSO_4$, filtered and concentrated via a distillation apparatus (3″ Vigreux column; 40 °C at 30 mm Hg). Purification of the resulting mixture of diastereomers (91:9 by GC analysis) by flash chromatography [silica gel, 7 × 15 cm, gradient elution: hexanes (1 L); 10% ethyl ether/hexanes (1 L); 20% ethyl ether/hexanes (1 L)] gave the desired homoallylic alcohol **33** as a colorless oil: $[\alpha]_D^{23}$ −15.6° (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.9−5.8 (m, 1 H), 5.2−5.1 (m, 2 H), 4.1−4.0 (m, 2 H), 3.9−3.8 (m, 1 H), 3.7−3.6 (m, 1 H), 2.45−2.35 (m, 1 H), 1.7−1.6 (m, 4 H), 1.09 (d, *J* = 7.2 Hz, 3 H), 0.90 (q, *J* = 7.2 Hz, 6 H); IR (CCl_4) 3600, 3500, 1640 cm^{-1}; HRMS calcd for $C_{10}H_{17}O_3$ ($M^+ - C_2H_5$), 185.1178, found 185.1182. Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.24; H, 10.37. Found: C, 67.40; H, 10.47.

This material was directly dissolved in a 2:1 mixture of methanol and tetrahydrofuran (30 mL) and heated at reflux in the presence of Dowex 50 × 4−400 H^+ resin for 8 h. The solution was filtered, then the solvent was removed *in vacuo* and the crude triol was purified by flash chromatography [silica gel, 3 × 15 cm, gradient elution: 50% ethyl ether/hexanes (0.5 L); 50% methanol/ethyl acetate (0.5 L)], which afforded (2*S*,3*R*,4*R*)-4-methylhex-5-en-1,2,3-triol (5.78 g, 86%) as a white solid (mp 69−71 °C): $[\alpha]_D^{23}$ +5.1° (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 18.0, 9.0, 8.0 Hz, 1 H), 5.18 (d, *J* = 12.0 Hz, 1 H), 5.17 (d, *J* = 16.0 Hz, 1 H), 3.7−3.9 (m, 2 H),

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3.7−3.6 (m, 1 H), 3.6−3.5 (m, 1 H), 2.5−2.4 (m, 1 H), 1.06 (d, J = 7.0 Hz, 3 H); IR (CH_2Cl_2) 3600, 1460 cm^{-1}; HRMS (CI, NH_3) calcd for $C_7H_{15}O_3$ (M^++1), 147.1021, found 147.1009. Anal. Calcd for $C_7H_{14}O_3Si$: C, 57.51; H, 9.65. Found: C, 57.21; H, 9.47. The antipode of this triol is a known compound.[11]

To a solution of the above triol (5.78 g, 39.3 mmol) in dry *N*,*N*-dimethylformamide (80 mL, Aldrich) at 0 °C was added *tert*-butyldimethylsilyl chloride (5.92 g, 39.3 mmol), triethylamine (6.37 mL, 45.7 mmol) and 4-dimethylaminopyridine (DMAP, 467 mg, 3.82 mmol). The resulting mixture was warmed to room temperature and stirred for 24 h at which time additional DMAP (467 mg, 3.82 mmol) was added. After being stirred for an additional 12 h the solution was poured into saturated $NaHCO_3$ (100 mL). The aqueous phase was extracted with diethyl ether (4 × 50 mL) and the combined organic layers were washed with water (100 mL), dried with $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography [silica gel, 5 × 15 cm, gradient elution: hexanes (0.5 L); 10% ethyl acetate/hexanes (0.5 L); 20% ethyl acetate/hexanes (1 L)] gave diol **34** (10.2 g, 98%) as a colorless oil: $[\alpha]_D^{23}$ +7.2° (*c* 1.0, hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.0−5.8 (m, 1 H), 5.2−5.0 (m, 2 H) 3.9−3.7 (m, 2 H), 3.6−3.5 (m, 1 H), 3.5−3.4 (m, 1 H), 2.6−2.5 (m, 1 H), 1.08 (d, J = 6.0 Hz, 3 H), 0.91 (s, 9 H), 0.09 (s, 6 H); IR (neat) 3440, 1640 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{13}H_{29}O_3Si$ (M^+ + 1), 261.1886, found 261.1877. The antipode of **34** is a known compound.[11]

(2*S*,3*R*,4*R*)-1-Hydroxy-2,3-(*O*-isopropylidene)-4-methylhex-5-ene (35). To 0 °C a solution of diol **34** (10.2 g, 38.8 mmol) and pyridinium *p*-toluenesulfonate (0.989, 3.9 mmol) in CH_2Cl_2 (100 mL) was added 2-methoxypropene (7.44 mL, 77.7 mmol) in one portion via syringe. The reaction mixture was allowed to warm to room temperature and stirred for 2 h, then it was poured into saturated $NaHCO_3$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated to afford the intermediate acetonide which was directly dissolved in THF (40 mL) and treated with tetra-*n*-butylammonium fluoride (38.8 mL, 1.0 M solution in THF, 38.8 mmol) at room temperature. After this mixture was stirred for 2 h, the solvent was removed *in vacuo* and the residue was purified by flash chromatography [silica gel, 5 × 15 cm, gradient elution: hexanes (0.5 L); 20% ethyl acetate/hexanes (0.5 L); 30% ethyl acetate/hexanes (1 L)] to afford alcohol **35** (6.92 g, 96%) as a colorless oil. Data for acetonide intermediate: $[\alpha]_D^{23}$ +12.5° (*c* 1.4, hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, J = 17.0, 10.0, 7.0 Hz, 1 H), 5.09 (d, J = 17.0 Hz, 1 H), 5.04 (d, J = 10.0 Hz, 1 H), 4.2−4.1 (m, 1 H), 3.89 (dd, J = 9.0, 5.5 Hz, 1 H), 3.78 (dd, J = 10.5, 7.5 Hz, 1 H), 3.54 (dd, J = 10.5, 5.0 Hz, 1 H), 2.6−2.5 (m, 1 H), 1.33 (s, 3 H), 1.41 (s, 3 H), 1.08 (d, J = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H); IR (neat) 1640, 1470, 1460 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{16}H_{33}O_3Si$ (M^+ + 1), 301.2200, found 301.2205. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.96; H, 10.73. Found: C, 63.98; H, 10.43.

Data for 35: $[\alpha]_D^{23}$ −47.1° (*c* 0.6, hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (ddd, J = 17.5, 10.2, 7.3 Hz, 1 H), 5.10 (d, J = 17.2 Hz, 1 H), 5.07 (d, J = 11.0 Hz, 1 H), 4.16 (apparent dd, J = 12.4, 5.5 Hz, 1 H), 3.94 (dd, J = 9.5, 5.5 Hz, 1 H), 3.7−3.6 (m, 2 H), 2.4−2.3 (m, 1 H), 1.37 (s, 3 H), 1.48 (s, 3 H), 1.04 (d, J = 6.7 Hz, 3 H); IR (neat) 3460, 1640, 1460 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_3$, 186.1256, found 186.1243. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.53; H, 9.77. Found: C, 64.45; H, 9.87.

(3*S*,4*R*,5*R*)-1,1-Dibromo-3,4-(*O*-isopropylidene)-5-methylhept-1,6-diene (36). Oxalyl chloride (1.03 mL, 11.8 mmol) was dissolved in CH_2Cl_2 (16 mL) and cooled to −78 °C. Dimethylsulfoxide (1.68 mL, 23.6 mmol) was added and the resulting mixture was stirred at −65 °C for 2 min at which time a solution of alcohol **35** (2.0 g, 11 mmol) in CH_2Cl_2 (10 mL) was added via cannula. The solution was stirred for 15 min; triethylamine (7.48 mL, 53.7 mmol) was added and the mixture was allowed to warm to room temperature over 1 h. The reaction mixture was poured into water (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with 1 M sodium thiosulfate (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and concentrated. The resulting residue was filtered through a plug of silica gel with 20% ethyl acetate/hexanes. Concentration of the eluant afforded the intermediate aldehyde that was used in the following experiment without any further purification.

To a solution of triphenylphosphine (11.2 g, 42.9 mmol) in CH_2Cl_2 (16 mL) cooled at 0 °C was added a solution of carbon tetrabromide (7.12 g, 21.5 mmol) in CH_2Cl_2 (8 mL) via cannula. After the solution was stirred for 1 h at 0 °C, a solution of freshly prepared aldehyde from the preceding experiment in CH_2Cl_2 (10 mL) was added via cannula. The mixture was stirred for 3 h at 0 °C at which time hexanes (40 mL) were added. The milky solution was filtered through a pad of silica gel/Celite with 20% ethyl acetate/hexanes as the eluent; the insoluble material left in the reaction flask was subjected to additional (3×) cycles of CH_2Cl_2 extraction and hexanes precipitation to remove any remaining product. Concentration of the filtrate followed by purification of the crude product by flash chromatography [silica gel, 5 × 15 cm, gradient elution: hexanes (1 L); 2% ethyl acetate/hexanes (1 L); 5% ethyl acetate/hexanes (1 L)] gave the dibromo diene **36** (2.93 g, 80%) as a colorless oil: $[\alpha]_D^{23}$ +4.1° (*c* 0.4, hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (d, J = 9.5 Hz, 1 H), 5.88 (ddd, J = 17.8, 10.8, 7.0 Hz, 1 H), 6.0−5.8 (m, 2 H), 4.74 (dd, J = 9.5, 5.4 Hz, 1 H), 3.97 (dd, J = 9.0, 5.4 Hz, 1 H), 2.2−2.4 (m, 1 H), 1.47 (s, 3 H), 1.36 (s, 3 H), 0.99 (d, J = 7.3 Hz, 3 H); IR (neat) 1640, 1620, 1460 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{10}H_{13}Br_2O_2$ (M^+ − CH_3), 323.9281, found 323.9277. Anal. Calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74. Found: C, 38.86; H, 4.65.

(3*S*,4*R*,5*R*)-1,1-Dibromo-3,4-(*O*-isopropylidene)-5-methylhept-1-en-6-one (25). A mixture of $PdCl_2$ (80 mg, 0.45 mmol), CuCl (450 mg, 4.5 mmol), and dibromodiene **36** (1.53 g, 4.5 mmol) in DMF (22 mL) and H_2O (3 mL) was stirred under an O_2 atmosphere for 24 h. The mixture was then poured into water (100 mL) and extracted with Et_2O (3 × 25 mL). The ethereal extracts were washed with brine solution, dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product by flash chromatography [silica gel, 5 × 15 cm, gradient elution: 5% Et_2O in hexanes (200 mL); 10% Et_2O in hexanes (200 mL); 15% Et_2O in hexanes (200 mL); 20% Et_2O in hexanes (200 mL); then 25% Et_2O in hexanes (200 mL)] provided methyl ketone **25** (1.04 g, 65%): R_f (0.3, 3:1 hexanes-Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.46 (d, J = 10 Hz, 1 H), 4.76 (dd, J = 9.3, 5.5 Hz, 1 H), 4.26 (dd, J = 10.6, 5.5 Hz, 1 H), 2.71−2.65 (m, 1 H), 2.24 (s, 3 H), 1.34 (s, 3 H), 1.02 (d, J = 7.1 Hz, 3 H); IR (neat) 1722, 1615, 1457 cm^{-1}; HRMS (CI, CH_4) calcd for $C_{10}H_{13}O_3Br_2$, 342.9192, found 342,9205.

(2*R*,3*S*,4*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-4-methylhex-5-en-3-ol (39). Crotylboronate (*R*,*R*)-**38** (37 mL of a 0.90 M solution in toluene, 33 mmol)[65] was diluted with toluene (50 mL) and treated with powdered 4-Å molecular sieves (10 g, Aldrich) at room temperature for 30 min. This dispersion was then cooled to −78 °C. A solution of (2*R*)-2-(*tert*-butyldiphenylsilyloxy)propanal (**37**)[45] (7.0 g, 22.4 mmol) in toluene (10 mL) was then added via syringe pump over a 30 min period. The reaction mixture was stirred for an additional 1.5 h at −78 °C at which time 1 M NaOH (135 mL) was added. The resulting mixture was then stirred at room temperature for 3 h. The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated. Filtration of the crude product through a 5 cm plug of silica gel with 5% ethyl acetate/hexanes afforded alcohol **39** (8.13 g, 98%) as a colorless oil: $[\alpha]_D^{23}$ +31.1° (*c* 0.5, hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.7−7.6 (m, 4 H), 7.5−7.3 (m, 6 H), 5.4−5.2 (m, 1 H), 5.0−4.8 (m, 2 H), 3.9−3.8 (m, 1 H), 3.30 (dd, J = 8.6, 3.4 Hz, 1 H), 2.2−2.1 (m, 1 H), 1.07 (s, 9 H), 1.04 (d, J = 5.2 Hz, 3 H), 1.01 (d, J = 4.9 Hz, 3 H); IR (neat) 3580, 3480, 1640, 1590, 1470, 1460 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{23}H_{33}O_2Si$ (M^+), 369.2251, found 369.2256. Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 74.8; H, 8.65.

Ethyl (*E*)-(4*R*,5*S*,6*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-2,4-dimethyl-5-[(triethylsilyl)oxy]hept-2-enoate (40). A −78 °C solution of homoallylic alcohol **39** (2.29 g, 6.22 mmol) in CH_2Cl_2 (15 mL) was treated with a stream of O_3 in O_2 until the solution turned blue; argon was then bubbled through the solution until the color disappeared. The resulting solution was treated with triphenylphosphine (3.26 g, 12.4 mmol), warmed to room temperature and stirred for 2 h. Removal of the solvent gave the aldehyde which was immediately dissolved in CH_2Cl_2 (15 mL) and transferred to a tube equipped with a screw cap seal. Ethyl 2-(triphenylphosphoranylidene)propionate (4.53 g, 12.4 mmol) was added, the tube was flushed with argon, sealed and heated in an oil bath at 50 °C for 26 h. The mixture was then triturated with hexanes, filtered through Celite and concentrated *in vacuo*. Purification of the crude product by flash chromatography [silica gel, 5 × 15 cm, gradient elution: 5% ethyl acetate/hexanes (1 L); 15% ethyl acetate/hexanes (1 L)] provided the intermediate hydroxy enoate (2.3 g, 82%) as a colorless oil: $[\alpha]_D^{23}$ −5.4° (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.7−7.6 (m, 4 H), 7.5−7.3 (m, 6 H), 6.23 (dd, *J* = 10.2, 1.4 Hz, 1 H), 4.14 (q, *J* = 7.2 Hz, 2 H), 3.8−3.7 (m, 1 H), 3.38 (dd, *J* = 9.0, 3.0 Hz, 1 H), 2.5−2.4 (m, 1 H), 1.75 (d, *J* = 1.4 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.07 (s, 9 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.97 (d, *J* = 6.4 Hz, 3 H); IR (neat) 3510, 1710 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{27}H_{38}O_4Si$ (M^+), 454.2540, found 454.2501.

To a solution of the hydroxy enoate (5.57 g, 12.2 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added 2,4-lutidine (2.84 mL, 24.5 mmol) followed by triethylsilyl trifluoromethanesulfonate (4.16 mL, 18.4 mmol). The resulting solution was stirred at −78 °C for 15 min and at 0 °C for 10 min at which time it was quenched with water (5 mL). The solution was then poured into water (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 5 × 15 cm, 5% ethyl acetate/hexanes) gave enoate **40** (6.95 g, 99%): $[\alpha]_D^{23}$ −8.1° (*c* 1.0, hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.7−7.6 (m, 4 H), 7.5−7.3 (m, 6 H), 6.54 (dd, *J* = 10.4, 1.2 Hz, 1 H), 4.1−4.3 (m, 2 H), 3.65−3.75 (m, 1 H), 3.56 (dd, *J* = 6.4, 6.0 Hz, 1 H), 2.7−2.6 (m, 1 H), 1.71 (d, *J* = 1.2 Hz, 3 H), 1.28 (t, *J* = 7.2 Hz, 3 H), 1.06 (s, 9 H), 1.0−0.9 (m, 15 H), 0.67 (q, *J* = 8.0 Hz, 4 H), 0.52 (q, *J* = 8.0 Hz, 2 H); IR (neat) 1720, 1650, 1460 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{33}H_{52}O_4Si_2$ (M^+), 568.3390, found 568.3396. Anal. Calcd for $C_{33}H_{52}O_4Si_2$: C, 69.74; H, 9.24. Found: C, 69.45; H, 9.41.

(*E*)-(4*R*,5*S*,6*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-2,4-dimethyl-5-[(triethylsilyl)oxy]hept-2-enal (26). To a −78 °C solution of enoate **40** (1.0 g, 1.8 mmol) in CH_2Cl_2 (10 mL) was added DIBAL-H (4.4 mL, 1 M in THF, 4.4 mmol). The mixture was stirred at −78 °C for 3 h, then was allowed to warm to ambient temperature. The solution was then diluted with MeOH (1 mL), aqueous Rochelle's salt solution (50 mL) and Et_2O (50 mL). The aqueous phase was separated and extracted with additional Et_2O (2 × 25 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude product by flash chromatography (30 mm silica gel column) using a gradient of 5%−30% Et_2O in hexanes provided the corresponding allylic alcohol (808 mg, 84%): $[\alpha]^{22}_D$ −31.6° (*c* = 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66−7.65 (m, 4 H), 7.45−7.43 (m, 2 H), 7.43−7.41 (m, 4 H), 4.92 (dd, *J* = 10.2, 0.8 Hz, 1 H), 3.74−3.70 (m, 3 H), 3.51 (dd, *J* = 8.2, 2.2 Hz, 1 H), 2.35−2.30 (m, 1 H), 1.45 (d, *J* = 1.2 Hz, 3 H), 1.06 (s, 9 H), 0.99 (t, *J* = 7.9 Hz, 9 H), 0.93 (d, 6.2 Hz, 3 H), 0.89 (d, 6.5 Hz, 3 H), 0.75−0.68 (m, 6 H); IR (neat) 3070, 1430, 1260 cm^{-1}; HRMS for $C_{31}H_{50}O_3Si_2$ (M^+) calcd 526.3298, found 526.3339. Anal. Calcd for $C_{31}H_{50}O_3Si_2$: C, 70.67; H, 9.56. Found: C, 70.63; H, 9.28.

A solution of the above allylic alcohol (436 mg, 0.83 mmol) in CH_2Cl_2 (3 mL) was treated with MnO_2 (1.43 g, 16.5 mmol; added in small portions over 1 h). The mixture was stirred at ambient temperature for 48 h, then was filtered through Celite (3 × 20 mL of CH_2Cl_2). Concentration of the filtrate *in vacuo*, and purification of the crude product by flash chromatography (silica gel, 5:1 hexanes−EtOAc) provided α,β-unsaturated aldehyde **26** (407 mg, 94%): R_f 0.7 (5:1 hexanes-EtOAc); $[\alpha]_D^{22}$ −19.8° (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.15 (s, 1 H), 7.65−7.60 (m, 4 H), 7.45−7.30 (m, 6 H), 5.98 (dd, *J* = 10.4, 1.2 Hz, 1 H), 3.56−3.60 (m, 2 H), 2.80−2.65 (m, 1 H), 1.58 (d, *J* = 1.2 Hz, 3 H), 1.06 (s, 9 H), 0.95−1.05 (m, 15 H), 0.75−0.65 (m, 6 H); IR ($CHCl_3$) 3020, 2880, 1685, 1640 cm^{-1}; HRMS calcd for $C_{27}H_{39}O_3Si_2$ (M^+ − ^{t}Bu), 467.2437, found 467.2423. Anal. Calcd for $C_{31}H_{48}O_3Si$: C,70.94; H, 9.22. Found: C, 70.80; H, 9.37.

(5*E*,7*E*)-(2*R*,3*S*,4*R*,10*S*,11*R*,12*S*)-14,14-Dibromo-2-[(*tert*-butyldiphenylsilyl)oxy]-11,12-(*O*-isopropylidene)-4,6,10-trimethyl-3-[(triethylsilyl)oxy]tetradec-5,7,13-trien-9-one (42). A 1 M THF solution of $LiN(TMS)_2$ (1.0 mL, 1.0 mmol) was added to a −78 °C solution of methyl ketone **25** (300 mg, 0.84 mmol) in THF (7 mL). The solution was stirred for 15 min at −78 °C, then a solution of enal **26** (402 mg, 0.77 mmol) in THF (2 mL) was added. The mixture was stirred for 15 min at −78 °C before addition of Ac_2O (160 μL, 1.7 mmol). The reaction mixture was then allowed to warm to room temperature and DMAP (100 mg, 0.82 mmol) was added. After the solution was stirred for 30 min at ambient temperature, DBU (625 μL, 4.2 mmol) was added. The mixture was stirred for an additional 30 min, then it was diluted with ether and poured into brine. The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with 0.5 N HCl, brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel chromatography (10% ether-hexanes) to give dienone **42** (402 mg, 61%): $[\alpha]_D^{20}$ +71.9° (*c* = 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.45−7.30 (m, 6 H), 7.07 (d, *J* = 15.6 Hz, 1 H), 6.54 (d, *J* = 9.2 Hz, 1 H), 6.09 (d, *J* = 15.6 Hz, 1 H), 5.45 (d, *J* = 10.0 Hz, 1 H), 4.80 (dd, *J* = 9.2, 5.2 Hz, 1 H), 4.48 (dd, *J* = 10.2, 5.2 Hz, 1 H), 3.63 (dq, *J* = 6.4, 2.2 Hz, 1 H), 3.51 (dd, *J* = 7.4, 2.2 Hz, 1 H), 2.93 (dq, *J* = 10.2, 6.4 Hz, 1 H), 2.64−2.50 (m, 1 H), 1.62 (s, 3 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.09 (d, *J* = 6.4 Hz, 3 H), 1.06 (s, 9 H), 0.99 (t, *J* = 7.6 Hz, 9 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.74−0.66 (q, *J* = 7.6 Hz, 6 H); IR ($CHCl_3$) 1680, 1660, 1620, 1590, 1460 cm^{-1}; HRMS calcd for $C_{38}H_{53}O_5Br_2Si_2$ (M^+ − ^{t}Bu), 805.1758, found 805.1751. Anal. Calcd for $C_{42}H_{62}O_5Br_2Si_2$: C, 58.46; H, 7.24. Found: C, 58.20; H, 7.38.

Benzyl (4*E*,6*Z*,12*E*,14*E*)-(8*S*,9*R*,10*S*,16*R*,17*S*,18*R*)-6-Bromo-18-[(*tert*-butyldiphenylsilyl)oxy]-8,9-(*O*-isopropylidene)-17-[(triethylsilyl)oxy]-10,14,16-trimethylnonadec-4,6,12,14-tetraen-11-onoate (43). An aqueous solution of TlOH (1.0 mL, 0.52 M, 0.52 mmol) was added to a solution of dibromide **42** (382 mg, 0.44 mmol), vinyl boronic acid **24** (165 mg, 0.71 mmol), $Pd_2(dba)_3$ (60 mg, 0.066 mmol) and Ph_3P (200 mg, 0.76 mmol) in THF (30 mL). After being stirred for 1 h at room temperature, the mixture was diluted with ether and filtered through Celite. Removal of the solvent in vacuo gave an oily residue, which was purified by silica gel chromatography (20% ether-hexanes as eluent) to afford tetraene **43** (318 mg, 74%): $[\alpha]_D^{20}$ +84.6° (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.50−7.30 (m, 11 H), 7.07 (d, *J* = 15.6 Hz, 1 H), 6.25−6.15 (m, 2 H), 6.10 (d, *J* = 15.6 Hz, 1 H), 5.95 (d, *J* = 9.4 Hz, 1 H), 5.43 (d, *J* = 10.4 Hz, 1 H), 5.15 (s, 2 H), 5.14 (dd, *J* = 9.4, 5.2 Hz, 1 H), 4.49 (dd, *J* = 10.2, 5.2 Hz, 1 H), 3.64 (dq, *J* = 6.4, 2.8 Hz, 1 H), 3.51 (dd, *J* = 8.0, 2.8 Hz, 1 H), 2.94 (dq, *J* = 10.2, 6.4 Hz, 1 H), 2.60−2.50 (m, 5 H), 1.62 (s, 3 H), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.07 (s, 9 H), 1.05 (d, *J* = 6.4 Hz, 3 H), 1.00 (t, *J* = 8.0 Hz, 9 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H), 0.69 (q, *J* = 8.0 Hz, 6 H); IR ($CHCl_3$) 1735, 1680, 1655, 1540, 1460 cm^{-1}; HRMS calcd for $C_{51}H_{69}O_5Si_2Br$ (M^+ − $C_3H_6O_2$), 896.3866, found 896.3846. Anal. Calcd for $C_{54}H_{75}O_7BrSi_2$: C, 66.71; H, 7.78. Found: C, 66.46; H, 8.00.

(4*E*,6*Z*,12*E*,14*E*)-(8*S*,9*R*,10*S*,16*R*,17*S*,18*R*)-6-Bromo-18-[(*tert*-butyldiphenylsilyl)oxy]-17-hydroxy-8,9-(*O*-isopropylidene)-10,14,16-trimethylnonadec-4,6,12,14-tetraen-11-onoic Acid (44). A solution of **43** (280 mg, 0.29 mmol) and LiOH (14 mg, 0.58 mmol) in DME (4 mL) and water (1 mL) was stirred for 3 h at room temperature. The reaction mixture was acidified with 0.5 N HCl, diluted with ether and poured into brine. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel chromatography (80% ether−hexanes as eluent) to afford the carboxylic acid (177 mg, 70%): $[\alpha]_D^{20}$ +93.3° (*c* 0.97, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.65−7.60 (m, 4 H), 7.50−7.30 (m, 6 H), 7.06 (d, *J* = 15.4 Hz, 1 H), 6.25−6.15 (m, 2 H), 6.09 (d, *J* = 15.4 Hz, 1 H), 5.96 (d, *J* = 9.4 Hz, 1 H), 5.42 (d, *J* =10.0 Hz, 1 H), 5.15 (dd, *J* = 9.4, 5.4 Hz, 1 H), 4.48 (dd, *J* = 10.2, 5.4 Hz, 1 H), 3.63 (dq, *J* = 6.6, 2.8 Hz, 1 H), 3.50 (dd, *J* = 7.6, 2.8 Hz, 1 H), 2.89 (dq, *J* = 10.2, 6.6 Hz, 1 H), 2.62−2.50 (m, 5 H), 1.61 (s, 3 H), 1.44 (s, 3 H), 1.37 (s, 3 H), 1.05 (s, 9 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 0.98 (t, *J* = 7.8 Hz, 9 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.69 (q, *J* = 7.8 Hz, 6 H); IR ($CHCl_3$) 3500, 1715, 1680, 1655, 1590 cm^{-1}. Anal. Calcd for $C_{47}H_{69}O_7BrSi_2$: C, 63.99; H, 7.88. Found: C, 64.07; H, 7.97.

A mixture of the above carboxylic acid (158 mg, 0.18 mmol) and 1M aq. HF (360 μL, 0.36 mmol) in acetonitrile (10 mL) was stirred in an ice bath for 5 h. The reaction mixture was diluted with ether and poured into brine. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (ether as eluent) to afford seco acid **44** (124 mg, 90%): $[\alpha]_D^{20}$ +79.6° (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60−7.65 (m, 4 H), 7.45−7.30 (m, 6 H), 7.00 (d, J = 15.6 Hz, 1 H), 6.25−6.15 (m, 2 H), 6.10 (d, J = 15.6 Hz, 1 H), 5.95 (d, J = 9.4 Hz, 1 H), 5.16 (d, J = 11.6 Hz, 1 H), 5.13 (dd, = 9.4, 5.2 Hz, 1 H), 4.46 (dd, J = 10.2, 5.2 Hz, 1 H), 3.69 (dq, J = 6.4, 2.8 Hz, 1 H), 3.28 (dd, J = 8.8, 2.8 Hz, 1 H), 2.85 (dq, J = 10.2, 6.4 Hz, 1 H), 2.62−2.40 (m, 5 H), 1.68 (s, 3 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.08 (s, 9 H), 1.02 (d, J = 6.4 Hz, 3 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H); IR ($CHCl_3$) 3500, 1715, 1680, 1655, 1625, 1595 cm^{-1}; HRMS calcd for $C_{37}H_{46}O_7BrSi$ (M^+ − ^tBu) 709.2196, found 709.2215. Anal. Calcd for $C_{41}H_{55}O_7BrSi$: C, 64.13; H, 7.22. Found: C, 63.91; H, 7.11.

Transannular Diels−Alder Reaction of 22 via Macrolactonization of 44: [1*E*,3*R*,4*S*(*R*),8a*R*,10a*R*,11*S*,12*R*,13*S,14*R*,14a*S*,14b*R*]-3,4,7,8,-8a,10a,11,12,13,14a,14b-Undecahydro-10-bromo-4-[1-[(1,1-dimethylethyl)diphenylsilyl]oxyethyl]-11,12-(*O*-isopropylidene)-1,3,13-trimethylnaphth[2,1-*e*]oxecin-6(7*H*),14-dione (45) and [1*E*,3*R*,4*S*(*R*),-8a*R*,10a*R*,11*S*,12*R*,13*R**,14*R*,14a*S*,14b*R*]-3,4,7,8,8a,10a,11,12,13,-14a,14b-Undecahydro-10-bromo-4-[1-[(1,1-dimethylethyl)diphenylsilyl]oxyethyl]-11,12-(*O*-isopropylidene)-1,3,13-trimethylnaphth[2,1-*e*]oxecin-6(7*H*),14-dione (46).** A mixture of seco acid **44** (50 mg, 0.065 mmol), trichlorobenzoyl chloride (33 μL, 0.21 mmol) and triethylamine (63 μL, 0.45 mmol) in THF (1.0 mL) was stirred for 3 h at room temperature. The solvent was removed *in vacuo*, and the residue was dissolved in toluene (20 mL). This solution was added over 15 h to a 100 °C solution of DMAP (50 mg, 0.41 mmol) in toluene (20 mL). The mixture was stirred for an additional 5 h, then was diluted with ether and poured into brine. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with 0.5 N HCl and brine, and dried over Na_2SO_4. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel chromatography (20% ether−hexanes as eluent) to afford **46** (6.5 mg, 13%). Further elution with 25% ether−hexanes afforded the desired transannular cycloadduct **45** (32.0 mg, 66%).

Data for 45: R_f 0.4 (2:1 hexanes−ether); $[\alpha]_D^{23}$ +41.6° (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, benzene-d_6) δ 7.65−7.85 (m, 4 H), 7.25−7.15 (m, 6 H), 5.72 (d, J = 3.4 Hz, 1 H, H-5), 5.35 (t, J = 6.8 Hz, 1 H, H-17), 4.97 (d, J = 6.8 Hz, 1 H, H-15), 4.13 (dd, J = 8.2, 4.8 Hz, 1 H, H-8), 4.07 (quint, J = 6.8 Hz, 1 H, H-18), 3.95 (t, J = 4.8 Hz, 1 H, H-9), 3.10 (sextet, J = 6.8 Hz, 1 H, H-16), 2.85 (dd, J = 8.2, 4.8 Hz, 1 H, H-7), 2.65 (dd, J = 11.6, 4.8 Hz, 1 H, H-12), 2.47 (dq, J = 6.8, 4.8 Hz, 1 H, H-10), 2.04 (ddd, J = 11.6, 5.2, 3.4 Hz, 1 H, H-4), 1.98 (t, J = 11.6 Hz, 1 H, H-13), 1.90 (m, 2 H, H-2), 1.84 (m, 2 H, H-3), 1.67 (s, 3 H), 1.43 (s, 3 H), 1.22 (d, J = 6.8 Hz, 3 H), 1.21 (s, 3 H), 1.20 (d, J = 6.8 Hz, 3 H), 1.13 (s, 9 H), 1.04 (d, J = 6.8 Hz, 3 H); nOe experiments in benzene-d_6: irradiation at H-10 caused a 4.6% enhancement of H-9 and a 3.7% enhancement of H-13; irradiation at H-12 resulted in a 4.9% enhancement of H-7; IR ($CHCl_3$) 3020, 2930, 2860, 1720, 1445, 1425, 1380, 1370, 1135, 1110, 1065, 995, 955, 860, 820 cm^{-1}; HRMS for $C_{37}H_{44}O_6BrSi$ (M^+ − ^tBu), calcd 693.2070, found 693.2109. Anal. Calcd for $C_{41}H_{53}O_6BrSi$: C, 65.67; H, 7.12. Found: C, 65.66; H 7.34.

Data for 46: R_f 0.5 (2:1 hexanes−ether); $[\alpha]_D^{23}$ −30.8° (*c* 0.51 $CHCl_3$); ^1H NMR (400 MHz, benzene-d_6) δ 7.85−7.65 (m, 4 H), 7.25−7.15 (m, 6 H), 5.77 (d, J = 3.4 Hz, 1 H, H-5), 5.42 (t, J = 6.6 Hz, 1 H, H-17), 4.82 (d, J = 6.6 Hz, 1 H, H-15), 4.20 (dd, J = 8.8, 6.8 Hz, 1 H, H-8), 4.90 (quint, J = 6.6 Hz, 1 H, H-18), 3.65 (dd, J = 10.4, 6.8 Hz, 1 H, H-9), 3.23 (sextet, J = 6.6 Hz, 1 H, H-16), 2.78 (dd, J = 8.8, 5.2 Hz, 1 H, H-7), 2.22 (dd, J = 12.8, 5.2 Hz, 1 H, H-12), 2.17 (dq, J = 10.4, 6.6 Hz, 1 H, H-10), 2.02 (ddd, J = 12.8, 5.2, 3.4 Hz, 1 H, H-4), 2.0−1.60 (m, 5 H, H-13, H-2, H-3), 1.85 (s, 3 H), 1.49 (s, 3 H), 1.23 (d, J = 6.6 Hz, 3 H), 1.21 (s, 3 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.15 (s, 9 H), 1.02 (d, J = 6.6 Hz, 3 H); IR ($CHCl_3$) 2960, 2930, 2850, 1720, 1455, 1425, 1375, 1260, 1250, 1165, 1105, 1070, 1050, 980, 950, 870, 830, 710 cm^{-1}; HRMS for $C_{37}H_{44}O_6BrSi$ (M^+ − ^tBu), calcd 693.2070, found 693.2059.

Synthesis of [5*E*,7*Z*,13*E*,15*E*,9*S*,10*R*,11*S*,17*R*,18*S*(*R*)]-7-Bromo-18-[1-[(1,1-dimethylethyl)diphenylsilyl]oxyethyl]-9,10-(*O*-isopropenyl)-11,15,17-trimethyloxacyclooctadec-5,7,13,15-tetraen-2,12-dione (Macrolide 22). The macrolactonization of **44** (40 mg) was performed as described in the preceding experiment, with the exception that the reaction temperature was 80 °C rather than 100 °C. The crude product was purified by silica gel chromatography (20−30% ether−hexanes), affording **46** (2.0 mg, 5%), **45** (12.4 mg, 32%), and macrolide **22** (14.8 mg, 38%): $[\alpha]_D^{22}$ +65.1° (*c* 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.760 (m, 4 H), 7.50−7.35 (m, 6 H), 6.90 (d, J = 15.8 Hz, 1 H, H-13), 6.20 (d, J = 15.8 Hz, 1 H, H-12), 5.95−6.09 (m, 3 H, H-4, H-5 and H-7), 5.46 (d, J = 10.0 Hz, 1 H, H-15), 5.07 (dd, J = 8.4, 5.4 Hz, 1 H, H-8), 4.98 (dd, J = 8.8, 6.4 Hz, 1 H, H-17), 4.39 (dd, J = 7.6, 5.4 Hz, 1 H, H-9), 3.84 (dq, J = 8.8, 6.8 Hz, 1 H, H-18), 3.38 (quint, J = 6.8 Hz, 1 H, H-10), 3.27 (m, 1 H, H-16), 2.20−2.70 (m, 4 H), 1.82 (s, 3 H), 1.51 (s, 3 H), 1.38 (s, 3 H), 1.21 (d, J = 6.8 Hz, 3 H), 1.06 (s, 9 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H); IR ($CHCl_3$) 2980, 2940, 2860, 1735, 1665, 1630, 1460, 1430, 1375, 1160, 1110, 1075, 1035, 910 cm^{-1}; HRMS for $C_{37}H_{44}O_6BrSi$ (M^+ − ^tBu), calcd 691.2092, found 691.2090.

Transannular Diels−Alder Reaction of 22. A solution of **22** (13.0 mg) in toluene was heated at 100 °C for 20 h. Removal of the solvent in vacuo gave an oily residue, which was purified by silica gel chromatography(25% ether−hexanes as eluent) to afford **45** (11.1 mg, 85%) as the only observed product.

Intramolecular Diels−Alder Reaction of Seco Ester 43: [1*S*,*-(1′*E*,3′*R*,4′*S*,5′*R*)-2*R*,4a*R*,5*S*,6*R*,7*S*,8a*R]-1,2,4a,5,6,7,8a-Heptahydro-2-(3″-benzyloxycabonylprop-1″-yl)-4-bromo-1-[5′-[(1,1-dimethylethyl)-diphenylsilyl]oxy-4′-(triethylsilyl)oxy-1′,3′-dimethyl-1′-hexenyl]-6,7-(*O*-isopropylidene)-naphthalen-8-one (47) and [1*R**(1′*E*,3′*R*,4′*S*,5′*R*)-2*R*,4a*R*,5*S*,6*R*,7*S*,8a*S**]-1,2,4a,5,6,7,8a-Heptahydro-2-(3″-benzyl-oxycabonylprop-1″-yl)-4-bromo-1-[5′-[(1,1-dimethylethyl)diphenyl-silyl]oxy-4′-(triethylsilyl)oxy-1′,3′-dimethyl-1′-hexenyl]-6,7-(*O*-iso-propylidene)naphthalen-8-one (48).** A solution of **43** (10.0 mg) in toluene (10 mL) was heated at 110 °C for 24 h. Removal of the solvent *in vacuo* gave an oily residue, which was purified by silica gel chromatography. Elution of the column with 10% ether−hexanes afforded **48** (2.7 mg, 27%), and elution with 12% ether−hexanes afforded **47** (5.6 mg, 56%).

Data for 47: $[\alpha]_D^{23}$ +29.3° (*c* 0 .92, $CHCl_3$); ^1H NMR (400 MHz, benzene-d_6) δ 7.85−7.80 (m, 4 H), 7.25−7.15 (m, 11 H), 6.21 (dd, J = 5.2, 1.8 Hz, 1 H, H-5), 5.02 (d, J = 12.4 Hz, 1 H, benzyl), 4.98 (d, J = 12.4 Hz, 1 H, benzyl), 4.56 (d, J = 9.2 Hz, 1 H, H-15), 4.23 (t, J = 5.0 Hz, 1 H, H-9), 4.18 (dd, J = 9.6, 5.0 Hz, 1 H, H-8), 4.09 (dq, J = 6.4, 2.2 Hz, 1 H, H-18), 3.67 (dd, J = 7.2, 2.2 Hz, 1 H, H-17), 2.69 (ddt, J = 12.0, 9.6, 1.8 Hz, 1 H, H-7), 2.58 (m, 1 H, H-16), 2.32 (t, J = 12.0 Hz, 1 H, H-12), 2.30−1.85 (m, 7 H, H-4, H-2, H-3, H-10 and H-13), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.30 (s, 3 H), 1.24 (d, J = 6.4 Hz, 3 H), 1.22 (d, J = 6.4 Hz, 3 H), 1.21 (s, 9 H), 1.10 (t, J = 7.6 Hz, 9 H), 1.04 (d, J = 6.4 Hz, 3 H), 0.83 (q, J = 7.6 Hz, 6 H); IR ($CHCl_3$) 1735, 1575, 1455 cm^{-1}; HRMS for $C_{50}H_{66}O_7BrSi_2$ (M^+ − ^tBu), calcd 915.3215, found 915.3526.

Data for 48: $[\alpha]_D^{23}$ +31.2° (*c* 0.42, $CHCl_3$); ^1H NMR (400 MHz, benzene-d_6) δ 7.85−7.80 (m, 4 H), 7.25−7.15 (m, 11 H), 6.01 (dd, J = 3.2, 0.8 Hz, 1 H, H-5), 5.01 (d, J = 12.4 Hz, 1 H, benzyl), 4.97 (d, J = 12.4 Hz, 1 H, benzyl), 4.72 (d, J = 9.2 Hz, 1 H, H-15), 4.54 (dd, J = 7.2, 5.2 Hz, 1 H, H-8), 4.21 (t, J = 5.2 Hz, 1 H, H-9), 3.98 (dq, J = 6.4, 2.8 Hz, 1 H, H-18), 3.64 (dd, J = 7.2, 2.8 Hz, 1 H, H-17), 2.99 (dd, J = 7.2, 5.2 Hz, 1 H, H-7), 2.62 (dd, J = 6.4, 5.2 Hz, 1 H, H-10), 2.58 (dd, J = 9.6, 5.2 Hz, 1 H, H-12), 2.55 (ddd, J = 9.6, 7.2, 3.2 Hz, 1 H, H-4), 2.18 (t, J = 9.6 Hz, 1 H, H-13), 2.15−1.80 (m, 5 H, H-2, H-3 and H-10), 1.43 (s, 3 H), 1.36 (s, 6 H, 2 Me's), 1.25 (d, J = 6.4 Hz, 3 H), 1.22 (d, J = 6.4 Hz, 3 H), 1.19 (s, 9 H), 1.09 (t, J = 7.6 Hz, 9 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.81 (q, J = 7.6 Hz, 6 H); IR ($CHCl_3$) 1720, 1455 cm^{-1}; HRMS for $C_{50}H_{66}O_7BrSi_2$ (M^+ − ^tBu), calcd 915.3215; found 915.3468.

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Supporting Information Available: Experimental procedures for the synthesis of macrolide **13** from precursors **36**, **40**, and **49** (9 pages). See any current masthead page for ordering and Internet access instructions.

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