Enantioselective Total Synthesis of (−)-Chlorothricolide via the Tandem Inter- and Intramolecular Diels−Alder Reaction of a Hexaenoate Intermediate

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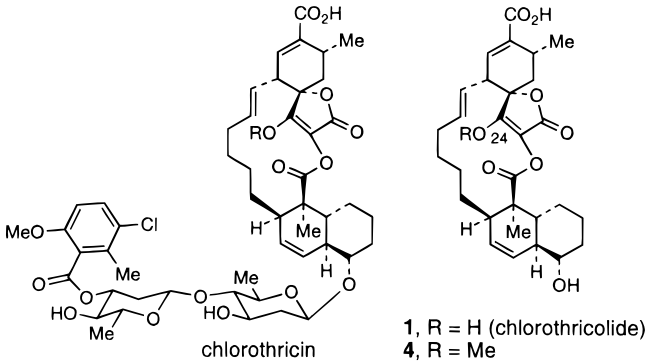
Received February 23, 1998

Abstract: An enantioselective total synthesis of (−)-chlorothricolide (**1**) has been completed via a route involving the tandem inter- and intramolecular Diels−Alder (IMDA) reaction of hexaenoate **19** and the chiral dienophile (*R*)-**12**. This reaction, which establishes seven asymmetric centers in a single operation, is feasible only by virtue of the high diastereofacial and exo selectivity of dienophile **12**. The C(9)-trimethylsilyl steric directing group of **19** also plays a key role by controlling the stereochemical course of the IMDA reaction leading to the bottom half octahydronaphthalene unit. Hexaenoate **19** was prepared in 32% overall yield by a 10-step sequence starting from the known acetylenic ketone **33**. Key steps include the asymmetric reduction of **33** using Alpine Borane (up to 94% ee), the Suzuki cross coupling of α-iodo vinylsilane **20** with vinylboronic acid **21**, and the Horner-type olefination of aldehyde **41** with dienylic phosphonate **22**. The key tandem inter-intramolecular Diels−Alder reaction was performed by heating a mixture of **19** and (*R*)-**12** (2 equiv) in toluene at 120 °C, which provided the targeted double cycloadduct **44** in 40−45% yield, along with 19% of other cycloadduct isomers and 25−20% of the IMDA adduct **24** with an (*E*,*E*,*E*)-C(16)−C(21) triene. The latter compound was recycled by treatment with additional (*R*)-**12** in trichloroethylene at 125 °C. The yield of **44** from hexaenoate **19** was 55−59% after one recycle of (*E*,*E*,*E*)-**24**. Elaboration of **44** to (−)-chlorothricolide was accomplished by a 9-step sequence in 26% overall yield, key steps of which included the construction of the spirotetronate subunit of **51** via the Dieckmann cyclization of **50**, deprotection of the two allyl units with Pd(0) catalysis, and the BOP-Cl-mediated macrolactonization of seco acid **52**. The vinyl trimethylsilane substituent was removed in the final step of the synthesis by treatment with EtSH and $BF_3 \cdot Et_2O$. Because an authentic sample of chlorothricolide was not available, synthetic (−)-chlorothricolide was treated with CH_2N_2 to give 24-*O*-methyl chlorothricolide methyl ester (**59**) [$[\alpha]^{25}_D$ −29.3° (*c* = 0.95, $CHCl_3$), mp 228.5−229 °C; lit.[1a] $[\alpha]_D^{20}$ −30° (*c* = 1, $CHCl_3$), lit.[1a] mp 230 °C)] which proved identical in all respects (except optical rotation and mp) with an authentic sample of racemic **59** provided by Professor Yoshii.

Chlorothricolide (**1**) is the aglycon of chlorothricin that was isolated from *Streptomyces antibioticus* by Keller-Schierlein and co-workers in 1969.[3,4] Chlorothricin is an inhibitor of pyruvate carboxylase and is active against Gram-positive bacteria.[5,6] Chlorothricolide methyl ester retains some antibiotic activity, although at concentrations 4 to 10-fold higher than the effective concentration of chlorothricin itself. The structure of chlorothricolide was originally assigned by using spectroscopic and degradation procedures[3] and, ultimately, was confirmed by single-crystal X-ray analysis of the cesium salt of chlorothricolide methyl ester.[4]

Interest in chlorothricolide as a synthetic target stems from the fact that it is the parent compound in a growing family of natural products possessing spirotetronic acid units. Other members of this family include kijanimicin,[7] tetrocarcin,[8] pyrrolosporin A,[9] PA-46101A and B,[10] the gastric ATP-ase



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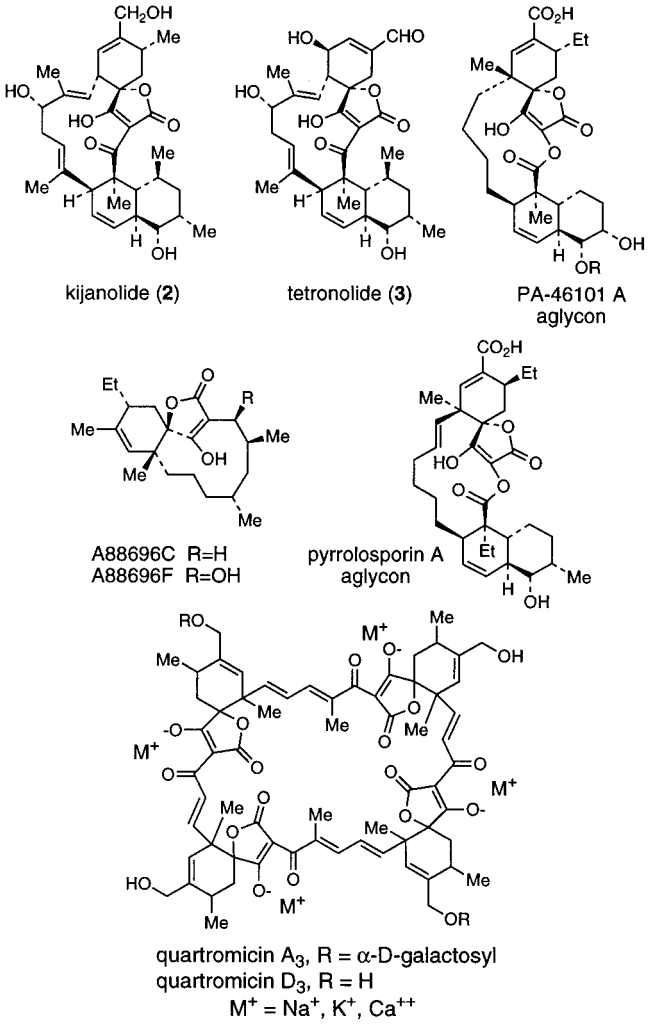
S0002-7863(98)00611-8 CCC: $15.00
Published on Web 07/21/1998

Chart 1



inhibitors A88696 C, D, and F,[11] and the quartromicins[12] (Chart 1). Virtually all of the published synthetic work in this area has focused on chlorothricolide,[13−37] kijanolide (**2**), the aglycon of kijanimicin, and tetronolide (**3**), the aglycon of the tetrocarcins.[38−56] Total syntheses of tetronolide[50] and 24-*O*-methyl chlorothricolide (**4**)[31] have been accomplished by Yoshii, and a formal synthesis of tetronolide[56] has been achieved in our laboratory. We report herein the full details of our enantioselective total synthesis of (−)-chlorothricolide, a preliminary report of which appeared in 1994.[36]

Synthetic Analysis

At the outset of our work on chlorothricolide, we planned to develop highly stereoselective syntheses of suitable top and bottom half units, and then to couple these fragments at a late stage of the synthesis. Toward this end, we established in 1988 that the intramolecular Diels−Alder (IMDA) reaction[57−59] of **5** provided the trans-fused perhydronaphthalene intermediate **6** with good selectivity and demonstrated that **6** is easily elaborated into the chlorothricolide bottom half fragment **9**.[26,34] The C(9)-TMS substituent plays a critical role in controlling the stereochemical course of this IMDA reaction, as the major product of cyclizations of related substrates lacking the C(9)-TMS substituent is a cis-fused cycloadduct analogous to **7**.[15] A full analysis of the steric directing group strategy has been published elsewhere.[34]

In 1992 we reported a highly enantio- and diastereoselective synthesis of the top half spirotetronate fragment **14**[35,37] via the highly exo, regio- and diastereofacially selective bimolecular Diels−Alder reaction of trienoate **11** and the chiral dienophile (*R*)-**12**.[60] We have used similar sequences to synthesize the spirotetronate units of kijanolide and tetronolide,[46,52,53,56] in all

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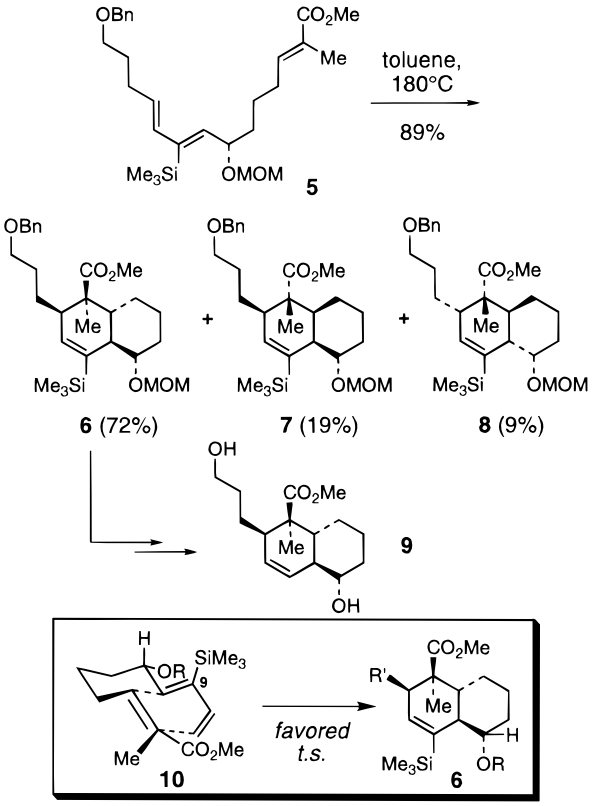
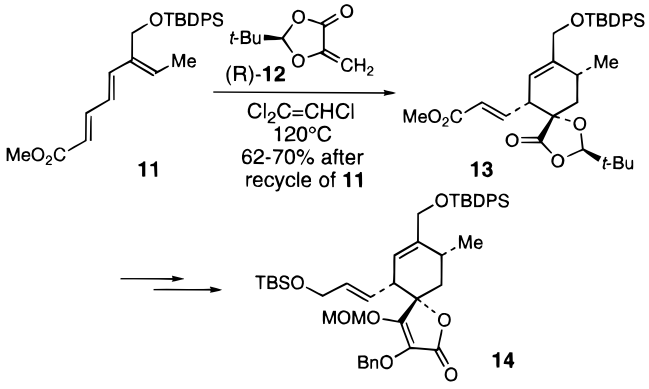


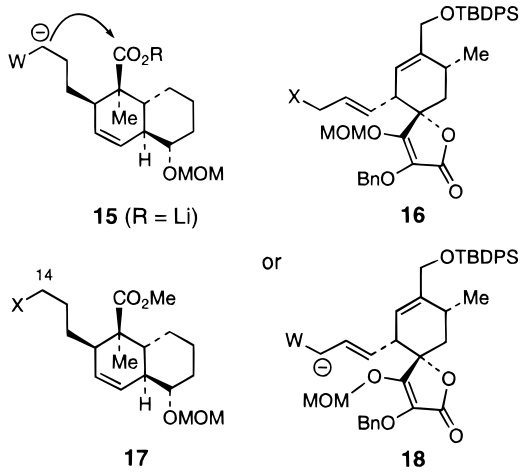
cases taking full advantage of the remarkable exo and diastereofacial selectivity of (*R*)-**12**.[60]

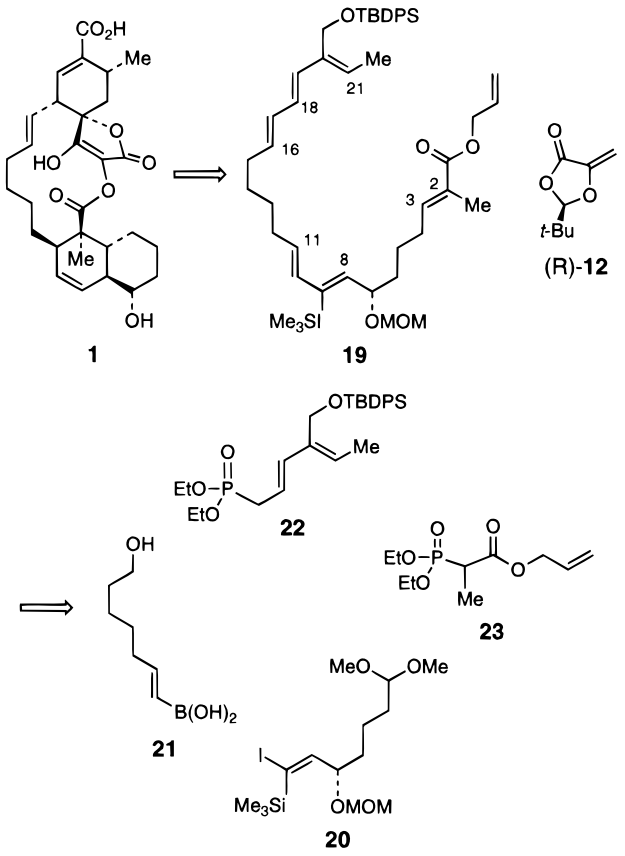


Having developed selective and efficient routes to **9** and **14**, we turned our attention to the coupling of these intermediates via formation of the C(14)−C(15) bond. It was readily apparent that this step would present a significant challenge.[22] If the bottom half fragment was used as the nucleophilic component (e.g., **15**, W = -SO_2Ar) in an alkylation reaction with a top half electrophile **16** (X = Br, I, etc.), it would be necessary to develop conditions to minimize addition of the C(14) carbanion to the C(1) carboxyl group (perhaps by using a carboxylate in the coupling sequence). While use of the top half fragment as the nucleophilic component (**18**, W = SO_2Ar) in an alkylation reaction with an electrophilic bottom half (**17**, X = leaving group) might pose fewer problems, we nevertheless were apprehensive about the prospects of performing this coupling on such highly functionalized intermediates.

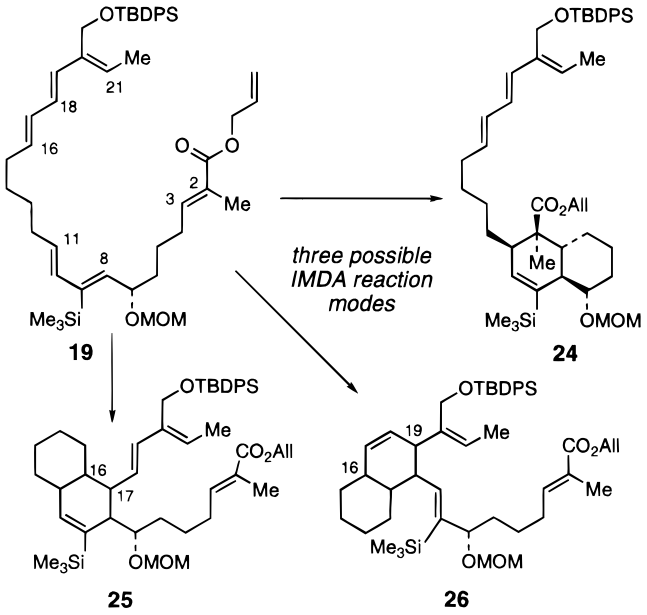
As an alternative, we recognized that coupling of precursors to the top and bottom half fragments—*prior to the two Diels−Alder reactions*—would pose relatively few complications. Hexaenoate **19** was thus identified as a key synthetic intermediate, which we imagined could be assembled in a straightforward manner from vinyl iodide **20**, vinylboronic acid **21**, dienylic phosphonate **22**, and β-keto phosphonate **23**.

bimolecular fragment coupling strategy:





However, use of **19** as a key synthetic intermediate raises questions about selectivity of the proposed tandem inter- and intramolecular Diels−Alder reaction. Three different modes of intramolecular Diels−Alder reactions are possible with this system: (i) addition of the C(2)−C(3) dienophile across the C(8)−C(11) diene, leading to **24**; (ii) addition of the C(16)−C(17) olefin across the C(8)−C(11) diene, leading to **25**; and (iii) participation of the C(10)−C(11) olefin as a dienophile in a IMDA reactions with the C(16)−C(19) diene, leading to **26**. There are also three different dienes that, in principle, can undergo bimolecular Diels−Alder reactions with dienophile (*R*)-

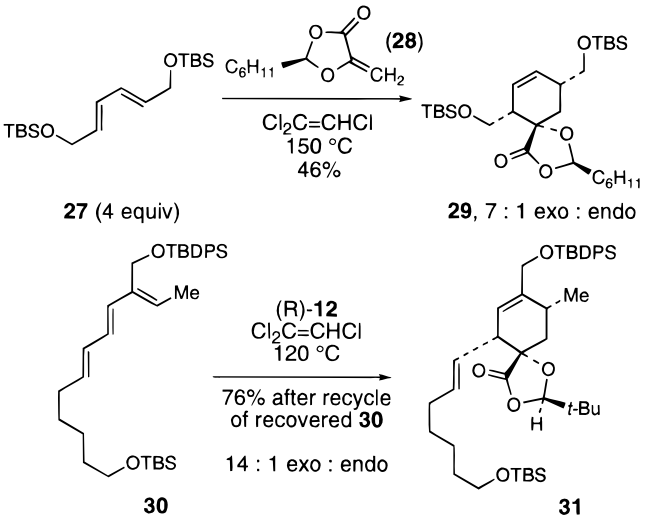


12.[61] Taking into account all possible endo, exo, diastereofacial (with respect to **12**), and regiochemical possibilities afforded by these diene−dienophile combinations, there are 96 distinct double Diels−Alder adducts that could be produced from **19** and (*R*)-**12** (assuming both components are enantiomerically pure).

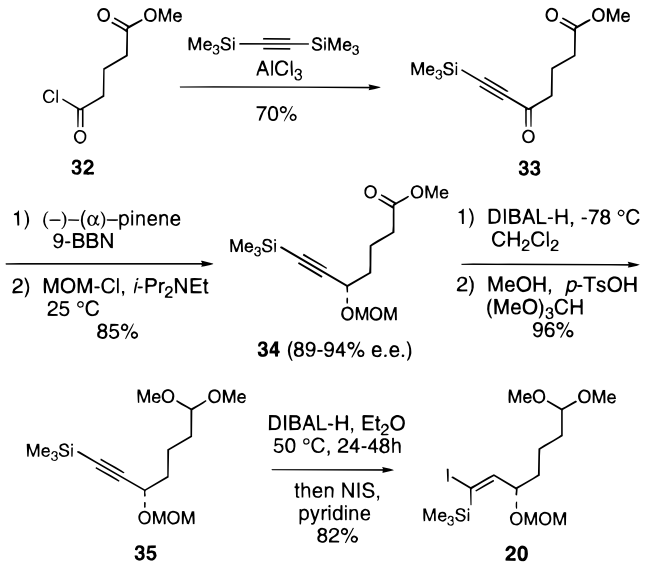
Fortunately, knowledge of the relative rates of the various Diels−Alder reactions enabled us to rule out all but the desired pathway as reasonable possibilities. Of the three potential modes of intramolecular Diels−Alder reactions, the C(2)−C(3) dienophile/C(8)−C(11) diene combination leading to **24** was expected to be the fastest since the C(2)−C(3) dienophile is the most activated of the three dienophiles.[57−59] Concerning the three bimolecular Diels−Alder combinations, previous studies in our laboratory indicated that the rates of Diels−Alder reactions of dienophiles (*R*)-**12** and **28** with acyclic dienes such as **27**[56,62] are considerably slower than their reactions with conjugated trienes such as **30**.[35,37] On this basis, we regarded the C(8)−C(11) diene unit of **19** as an unlikely reaction partner with (*R*)-**12**. In addition, the fact that the Diels−Alder reaction of **30** and (*R*)-**12** proceeds with exceptionally high exo, regio- and diastereofacial selectivity gave us confidence that the addition of (*R*)-**12** across the C(18)−C(21) unit of **19** would be comparably selective.[35,37]

Results and Discussion

Synthesis of Vinyl Iodide 20. The synthesis of vinyl iodide **20** was initiated by acylation of bis(trimethylsilyl)acetylene with commercially available acid chloride **32**, which provided the known acetylenic ketone **33** in 70% yield.[63] Asymmetric reduction of **33** with Alpine Borane,[64−66] generated in situ by heating a neat mixture of (−)-α-pinene and 9-BBN, afforded the optically active alcohol in 82% yield.[63] The enantiomeric purity of this intermediate from various runs was determined



to be 89−94% ee by Mosher ester analysis.[67] Protection of the secondary hydroxyl group as a MOM ether provided **34** in 85% yield for the two steps. This sequence introduces the only stereocenter of chlorothricolide that is not established in the tandem intra-intermolecular Diels−Alder reaction. Partial reduction of the carbomethoxyl unit of **34** with 1.05 equiv of DIBAL-H in CH_2Cl_2 at −78 °C and subsequent protection of the aldehyde as a dimethyl acetal afforded **35**. Hydroalumination of **35** using DIBAL-H in Et_2O at 50 °C in a sealed tube, followed by iodination of the resulting vinylalane intermediate provided vinyl iodide **20** in 82% yield.[68,69]



Synthesis of Dienylic Phosphonate 22. Phosphonate **22** was initially prepared from enal **36**[53] by way of the known dienylic alcohol **37**.[53] However, all attempts to convert **37** to the corresponding allylic bromide **38** provided a ca. 3:1 mixture of **38** and the isomeric dienylic bromide **39** that could not be separated.[70] Subjection of this mixture to an Arbuzov reaction[71,72] with triethyl phosphite gave phosphonate **22** in 60% overall yield, with no evidence that an allylic phosphonate

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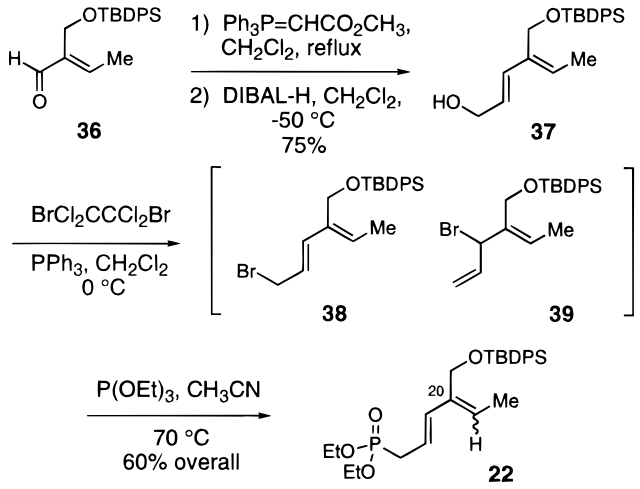
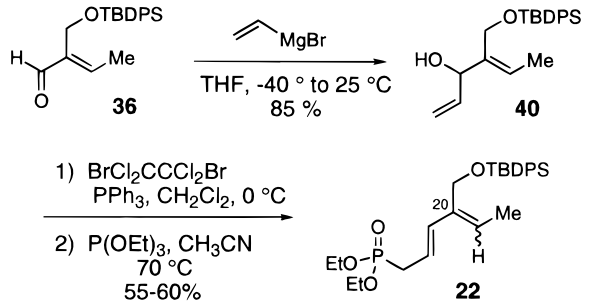


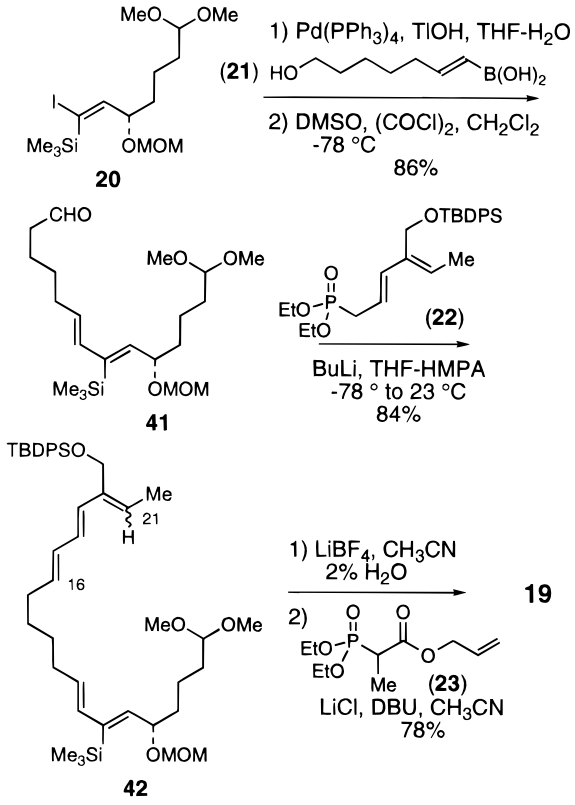
deriving from a S_N2 substitution of **39** was produced. This result suggested that dienylic alcohol **37** is not an obligatory intermediate and implied that **22** could be prepared more directly by way of allylic alcohol **40**. Indeed, bromination of **40** provided a mixture of **38** and **39** that was very comparable in composition to the mixture prepared from **37**. Arbuzov reaction of this mixture with triethyl phosphite then provided **22** in 55−60% overall yield from **40**.



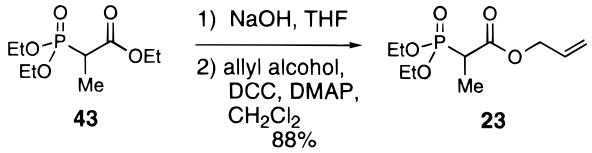
Phosphonate **22** prepared by this route was obtained as a ca. 5:1 mixture of C(20)-trisubstituted olefin isomers. This stereochemical imperfection was not viewed as a serious problem, since in previous studies we noted that this trisubstituted olefin isomerizes (reversibly) under the conditions of the Diels−Alder reaction with (*R*)-**12** and that only the (*Z*)-C(20) isomer undergoes the Diels−Alder reaction.[35,37]

Synthesis of Hexaenoate 19. The assembly of hexaenoate **19** began with the Suzuki cross-coupling[73] of vinyl iodide **20** and vinylboronic acid **21**[37] using Kishi's modified conditions.[74] Swern oxidation of the resulting primary alcohol then provided aldehyde **41** in 86% yield for the two steps.[75,76] The C(16)−C(21) triene unit was elaborated by olefination of aldehyde **41** with the lithium anion of dienylic phosphonate **22** (a ca. 5:1 mixture of C(20) (*Z*)- and (*E*)-olefin isomers).[77,78] Pentaene **42** was obtained in 84% yield, also as a 5:1 mixture of C(20) (*Z*)- and (*E*)-olefin isomers. However, only the (*E*)-isomer of the newly formed C(16)−C(17) olefin was detected.

Hydrolysis of the dimethyl acetal unit of **42** was surprisingly difficult. Use of standard hydrolysis conditions (oxalic acid, acetone; PPTs, wet acetone; HOAc, acetone; trifluoroacetic acid, acetone; trifluoroacetic acid, $CHCl_3$; or *p*-TsOH, acetone) resulted in recovery of **42** or considerable decomposition of **42** without product formation. Fortunately, deprotection of the



dimethyl acetal without decomposition of the pentaene could be accomplished by using $LiBF_4$ in wet CH_3CN.[79] Finally, the C(1)−C(3) dienophile unit was introduced via Horner−Wadsworth−Emmons olefination of the resulting aldehyde with *β*-keto phosphonate **23**, thereby providing hexaenoate **19** in 78% yield.[80] *β*-Keto phosphonate **23** was prepared in 88% overall yield by selective hydrolysis of the commercially available phosphonopropionate **43**, followed by DCC coupling[81] of the carboxylic acid with allyl alcohol. Overall, hexaenoate **19** was assembled by a highly convergent, 10-step synthesis that proceeds in 32% yield from the known acetylenic ketone **33**.



The Tandem Intra-Intermolecular Diels−Alder Reaction. The key tandem intra-intermolecular Diels−Alder reaction was performed by heating a 1 M solution of hexaenoate **19** and 2 equiv of dienophile (*R*)-**12**[60] in toluene at 120 °C for 20 h in the presence of a crystal of BHT as a radical inhibitor. This provided the desired adduct **44** in 40−45% yield as well as 19% of a mixture of other cycloadducts. In addition, 25−30%

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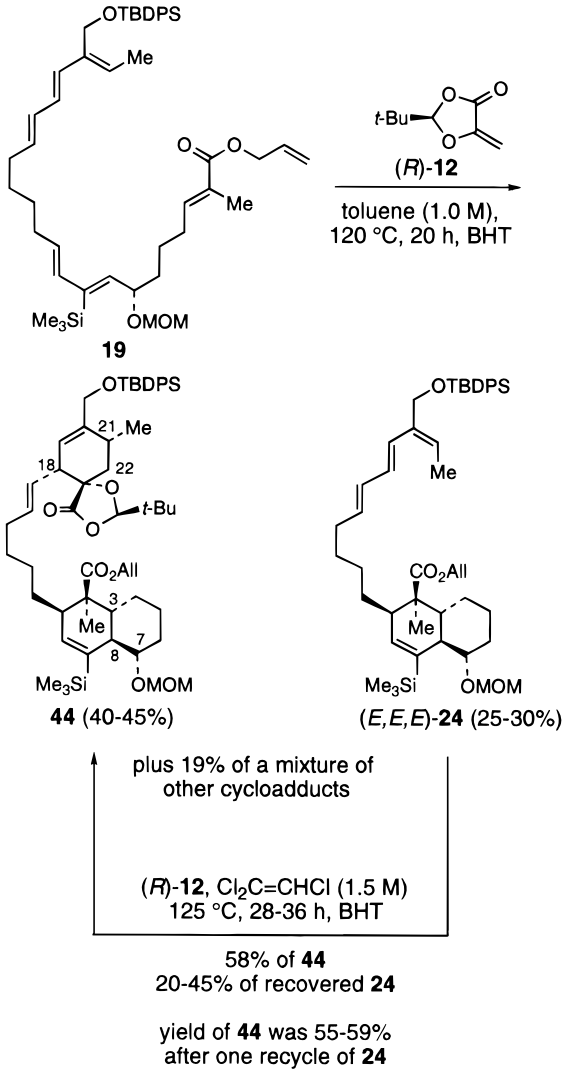
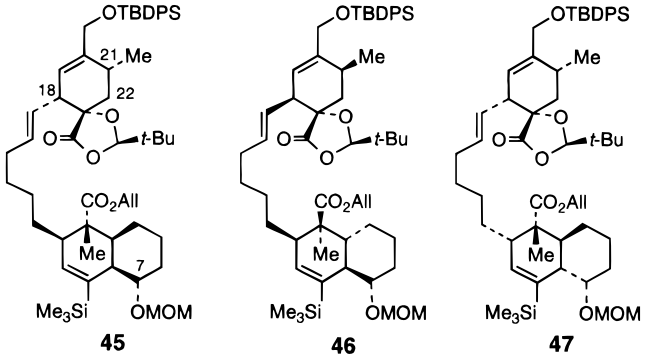
of the intramolecular Diels−Alder adduct (*E*,*E*,*E*)-**24** with an isomerized C(20)−C(21)-trisubstituted double bond was also obtained. Because we had already noticed that the C(20)−C(21)-trisubstituted olefin readily isomerizes under the conditions employed for this Diels−Alder reaction,[35,37] (*E*,*E*,*E*)-**24** was treated with additional dienophile (*R*)-**12** (2.0 equiv) in trichloroethylene (1.5 M) at 125 °C for 28−36 h in the presence of BHT as a radical inhibitor. This provided cycloadduct **44** in up to 58% yield, along with additional (*E*,*E*,*E*)-**24** (20−45%) that could be further recycled. The yield of the desired double Diels−Alder adduct **44** was 55−59% from **19** after one such recycle.



The stereostructures of **44** and **24** were assigned by correlation of ^{1}H NMR data with NMR data previously obtained for **6**[34] and **31**.[37] In particular, both **44** and **24** displayed $J_{3,8} = 8.8-9.4$ Hz and $J_{7,8} = 10$ Hz, characteristic of trans-fused octahydronaphthalenes with equatorial C(7) alkoxy substituents (δ 3.13 in both structures), while **44** displayed resonances for H(18) at δ 3.13 (d, $J = 8.4$ Hz), H(22_{ax}) at δ 2.11 (dd, $J = 14.0$, 7.2 Hz), and C(21)-Me at δ 1.13 (d, $J = 7.2$ Hz). The latter data are characteristic of a top half Diels−Alder adduct deriving from an exo transition state.[37,53,56]

This yield of **44** is remarkably close to the maximum yield (67%) anticipated on the assumption that the bimolecular Diels−Alder reaction of (*R*)-**12** and the C(16)−C(21) triene unit of **19** should proceed with 93:7 selectivity, as modeled by the reaction of (*R*)-**12** and **30**,[35,37] and that the intramolecular Diels−Alder reaction of the C(1)−C(11) undecatrienoate would proceed with 72:19:9 selectivity, as modeled by the IMDA cyclization of **5**.[34] That is, on the basis of these previously studied examples, one would anticipate that **44** should be the major product of a 67:18:8:5:1:1 mixture of double Diels−Alder adducts. In fact, HPLC analysis of the crude Diels−Alder reaction mixture indicated that four predominant double cycloadducts were obtained in the ratio of 67:13:5:5 (average of several runs). The HPLC trace also contained several other minor bands that presumably represent minor diastereomeric products expected from the Diels−Alder reaction of (*R*)-**12** and ent-**19** (present at the 3−5% level in **19**).

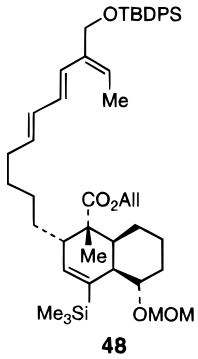
HPLC separation of the mixed fractions obtained from the initial double Diels−Alder reaction provided **45**, corresponding to the second most abundant double cycloadduct in the HPLC trace of the crude reaction mixture. This compound was assigned a cis-fused octahydronaphthalene nucleus by comparison if its ^{1}H NMR data with that previously obtained for **7**.[34] The resonance of H(7) (δ 4.10, $J = 2.8$ Hz) observed for **45** is characteristic of cis-fused octahydronaphthalenes bearing an axial C(7) alkoxy substituent.[15,34] Cycloadduct **45**, like **44**, displayed characteristic ^{1}H signals that define the top half cyclohexenyl unit as deriving from an exo transition state (e.g., H(18), δ 3.14 (d, $J = 8.8$ Hz); H(22_{ax}), δ 2.12 (dd, $J = 14.0$, 7.2 Hz); and C(21)−Me, δ 1.13 (d, $J = 7.2$ Hz)).



Further HPLC separation of mixed fractions provided very small amounts of an inseparable 1:1 mixture of two minor double cycloadducts. The ^{1}H NMR spectrum of this mixture contained a signal at δ 3.14 (d, $J = 8.8$ Hz) corresponding to H(18), characteristic of an exo top half and also a multiplet at δ 3.03 (apparent triplet) that is characteristic of H(18) of an endo-Diels−Alder derived top half.[37,53,56] The ^{1}H NMR spectrum of this mixture also exhibited a multiplet at δ 3.23 (dt, $J = 4.0$, 10.0 Hz) indicative of an equatorial MOM ether on a trans-fused octahydronaphthalene nucleus (as in **44**), as well as multiplets at δ 1.80−1.90 that have the same shape and appearance as those in the spectrum of the axial MOM trans-fused adduct **8**.[15,34] Accordingly, structures of the two cycloadducts in this minor 1:1 mixture have *tentatively* been assigned as **46** with an endo top half and a trans-fused bottom half with an equatorial MOM ether, and **47** with an exo top half and a trans-fused bottom half with an axial MOM ether. These assignments also correlate with the predicted product distribution based on earlier studies on the Diels−Alder reactions of **5** and **30**.

One additional (also inseparable) 1:1 mixture of two minor products was obtained. One of the products in this mixture was tentatively assigned (based on ^{1}H NMR data) as **48** containing a cis-fused bottom half and an intact C(16)−C(21)

triene unit.[82] The second component of this mixture contains



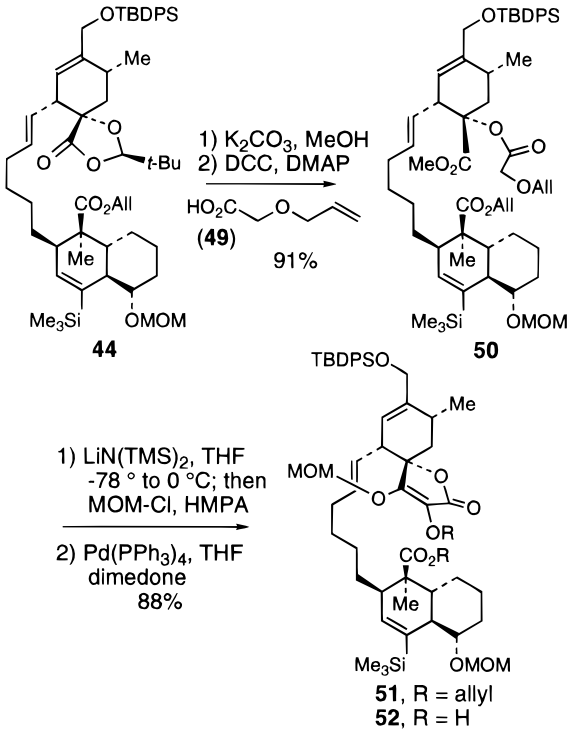
48

an exo top half, owing to the characteristic ^{1}H signal at δ 3.14 (d, J = 8.8 Hz) for H(18), but with an unknown stereochemistry of the bottom half. Attempts to separate these mixtures for further stereochemical analysis were unsuccessful.

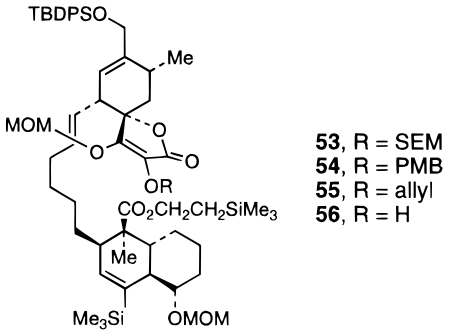
Considerable effort was devoted to the optimization of the tandem Diels−Alder reaction and the recycle of the intramolecular adduct (*E*,*E*,*E*)-**24**. The most consistent results were obtained when hexaenoate **19** was heated with 2 equiv of (*R*)-**12** at 120 °C in toluene (1 M). The yield and ratio of products were fairly constant when the reaction was performed at concentrations between 1.0 and 2.0 M. However, at higher reaction temperatures or concentrations, or when greater than 2 equiv of (*R*)-**12** was used, polymerization of the reaction mixture began to be a significant problem, leading to substantially reduced yields of product. Longer reaction times (>24 h) did not lead to improved yields of **44**, but did lead to reduced isolated yields of recovered (*E*,*E*,*E*)-**24**. These observations suggest that the stabilities of (*R*)-**12** and (*E*,*E*,*E*)-**24** are the factors that limit the overall efficiency of the tandem Diels−Alder reaction.

The recycle reaction of intramolecular cycloadduct (*E*,*E*,*E*)-**24** and dioxolanone (*R*)-**12** was performed most efficiently at 125 °C in trichloroethylene. This reaction required somewhat higher concentrations (1.5 M) and longer reaction times (28−48 h) to achieve maximum efficiency. Unfortunately, the recycle reaction was also constrained by a polymerization problem that resulted with increased reaction temperature (>130 °C) or when greater quantities (>2.0 equivalents) of dienophile were used. Nevertheless, under optimal conditions, the Diels−Alder reaction of (*E*,*E*,*E*)-**24** with 2 equiv of (*R*)-**12** in trichloroethylene provided **44** in up to 58% yield, along with recovered (*E*,*E*,*E*)-**24** (20−45%) that could be recycled further. As already noted, the yield of the double Diels−Alder adduct **44** was 55−59% from **19** after one such recycle.

Elaboration of 44 to (−)-Chlorothricolide. Intermediate **44** was elaborated to the seco acid **52** as summarized below. First, treatment of **44** with K_2CO_3 in MeOH provided the corresponding α-hydroxy methyl ester, which was then esterified with allyloxy acetic acid **49**[83] in the presence of DCC and DMAP,[81] thereby providing triester **50** in 91% overall yield. Dieckmann closure of the spiro tetronate was accomplished by treatment of **50** with $LiN(TMS)_2$ in THF at −78 °C. The enolate solution was allowed to warm to 0 °C and then MOM-Cl and HMPA were added to provide the fully protected tetronic ester **51** in 94% yield.[13,53] The two allyl protecting groups were then removed in a single step by treatment of **51** with catalytic $Ph(PPh_3)_4$ and dimedone in THF.[84] This provided the seco acid **52** in 94% yield (88% from **50**).



The simplicity of the four step conversion of **44** to **52** belies the considerable difficulty encountered in developing it. Prior to the identification of **51** as a suitable precursor to the seco acid, compounds **53**−**55** were also prepared. However, attempts



to deprotect the tetronate 2-(trimethylsilyl)ethoxymethyl (SEM) ether by treatment of **53** with TBAF in THF resulted in total decomposition of the starting material. Similarly, attempts to remove the *p*-methoxybenzyl (PMB) ether protecting group from the tetronate unit of **54** ((DDQ, wet CH_2Cl_2;[85] or CAN, wet CH_3CN[86]), were unsuccessful, owing to the instability of the product **56** toward these mild oxidants.[87] Ultimately, we identified the allyl ether protecting group[88] as the most appropriate for the enolic C(25) tetronate hydroxyl group, in

(82) Cycloadduct **48** was also obtained as the second most predominant product of the IMDA reaction of **19** performed (125 °C, 24 h, toluene, BHT inhibitor) in the *absence* of (*R*)-**12**. The major product of this reaction, **45**, was obtained in 40−47% yield following HPLC purification, while a mixture of **48** and a third IMDA product (presumably corresponding to **47**) was obtained in 13−17% yield.

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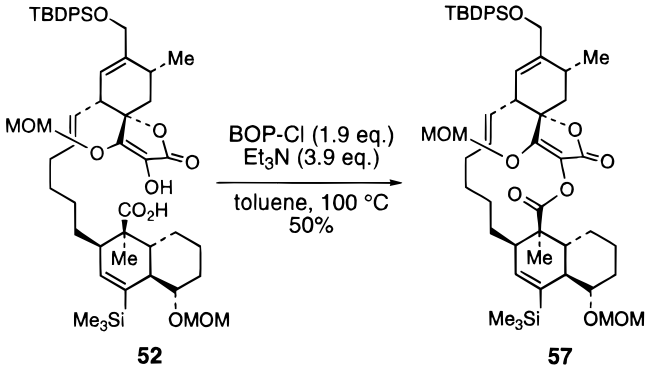
(86) Johansson, R.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

(87) A sample of **56**, prepared by deprotection of the allyl ether of **55**, decomposed when exposed to DDQ in wet CH_2Cl_2.

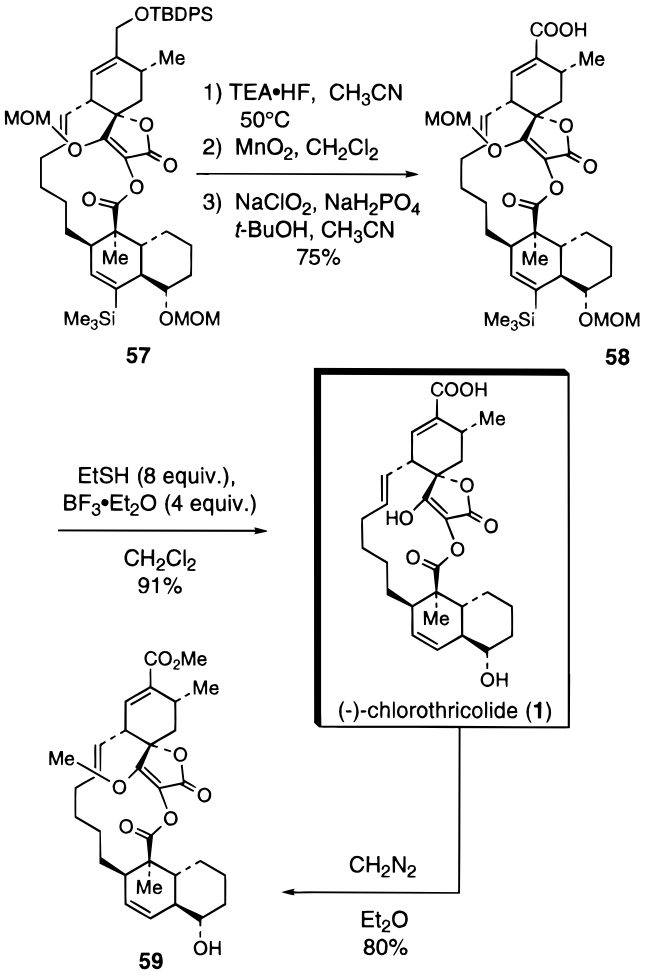
anticipation that this unit should be more acidic than most alcohols and have reactivity comparable to a phenol. The facility of the reaction of the C(25) allyl ether with Pd(0) and dimedone attests to the soundness of these arguments. Indeed, treatment of **55** with catalytic $Pd(PPh_3)_4$ and stoichiometric dimedone provided **56** in 83% yield. However, attempts to unmask the C(1) carboxylic acid unit of **56** also were thwarted. Treatment of **56** with a number of fluoride sources (e.g., KF in DMSO;[89] CsF in DMF;[90] or TBAF in THF, DMF, or CH_3CN[91]) resulted in decomposition or no reaction. Fortunately, the allyl unit that solved the tetronate C(25) OH protecting group problem also provided a workable solution to the C(1) acid protecting group issue (vide supra). An additional benefit to use of the allyl protecting group scheme for **51** is that both allyl groups could be removed simultaneously, thereby further simplifying the synthetic sequence.

With the seco acid **52** in hand, our attention turned to the macrolactonization reaction.[92] This transformation was best accomplished by treating **52** with bis(2-oxo-3-oxazolidinyl)-phosphonic chloride (BOP-Cl) (1.9 equiv) and Et_3N (3.9 equiv) at 100 °C for 1 h in toluene (0.01 M), which provided macrocycle **57** in 50% yield along with 31% of recovered seco acid **52**.[93] Attempts to improve the efficiency of this reaction by using additional equivalents of BOP−Cl (up to 8 equiv), lower reaction temperatures, longer reaction times, or by performing the macrolactonization in the presence of activated 4 Å molecular sieves were unsuccessful. Macrocycle **57** was obtained in low yield (10−20%) using the Yamaguchi lactonization (trichlorobenzoyl chloride, DMAP).[94,95] Use of DCC and DMAP gave the *N*-acyl urea rather than **57**, while use of DCC, DMAP, and DMAP·HCl gave a very low yield of the macrocycle.[96] Similarly, only traces of **57** were obtained from experiments performed using CDI[97] and DBU or trifluoroacetic anhydride and Et_3N[98] as the dehydrating agents.



52 **57**

The synthesis was completed by a simple four-step sequence, as follows. First, treatment of lactone **57** with Et_3N·HF in CH_3CN at 50 °C removed the primary TBDPS ether.[99] Oxidation of the allylic alcohol with MnO_2 and then oxidation of the aldehyde to the carboxylic acid by using $NaClO_2$ in aqueous *t*-BuOH in the presence of isobutylene provided **58** in 75% yield for the three steps.[100,101] Finally, simultaneous removal of the two MOM ethers and cleavage of the vinylsilane unit by treatment of **58** with EtSH and BF_3·Et_2O[102] provided synthetic (−)-chlorothricolide, (−)-(**1**) ($[\alpha]^{25}_D = -23°$ ($c = 0.2$, CH_2Cl_2)) in 91% yield. Because an authentic reference sample of (−)-chlorothricolide was not available, synthetic (−)-**1** was converted to 24-*O*-methylchlorothricolide methyl ester (**59**), a compound obtained in the original structural work on chlorothricin[3] and an intermediate in Yoshii's synthesis of racemic 24-*O*-methylchlorothricolide.[31] Thus, synthetic (−)-chlorothricolide was treated with excess diazomethane in diethyl ether to give 24-*O*-methylchlorothricolide methyl ester **59** [($[\alpha]^{25}_D$ −29.3° ($c = 0.95$, $CHCl_3$), mp 228.5−229 °C; lit.[3] $[\alpha]^{20}_D$ −30° ($c = 1$, $CHCl_3$); lit.[3] mp 230 °C)] in 80% yield. Synthetic (−)-**59** was identical in all respects (except optical rotation and melting point) with an authentic sample of racemic **59**.[31]



57 **58** **59**

Summary. This work constitutes the first total synthesis of (−)-chlorothricolide (**1**), the aglycon of the antibiotic chlorothricin. The synthesis proceeds in about 2% overall yield and 20 steps via the longest linear sequence originating from the known acetylenic ketone **33**. The synthesis features the tandem

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inter-intramolecular Diels−Alder reaction of hexaenoate **19** and the chiral dienophile (*R*)-**12** that establishes seven of the eight stereocenters of (−)-chlorothricolide in a single operation, with an overall stereoselectivity of ca. 67%. It is important to stress that the tandem Diels−Alder reaction strategy is feasible only by virtue of the exceptionally high diastereofacial and exo selectivity of the chiral dienophile **12**, which enables the relative and absolute stereochemistry of the three stereocenters of the top half fragment to be established independent of the five stereocenters in the bottom half perhydronaphthalene unit. The C(9)-trimethylsilyl substituent of **19** also plays a key strategic role by serving as the stereochemical control element for the IMDA reaction leading to the bottom half octahydronaphthalene unit.[103]

(103) Complete experimental details are provided in the Supporting Information.

Acknowledgment. This research was supported by a grant from the National Institute of General Medical Sciences (GM 26782). We also thank Professor Yoshii for providing a reference sample of racemic **59** for comparative purposes.

Supporting Information Available: Complete experimental procedures for the total synthesis of (−)-chlorothricolide, ^{1}H NMR spectra of (−)-**1**, **19**, **21**, **22**, (E,E,E)-**24**, **41**, **42**, **44**, **45**, **52**, **58**, and **59**, and ^{13}C NMR spectra of **59** (31 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA980611F