A Highly Diastereo- and Enantioselective Synthesis of the Top Half of Kijanolide

William R. Roush* and Bradley B. Brown[1]

Department of Chemistry, Indiana University, Bloomington, Indiana 47405

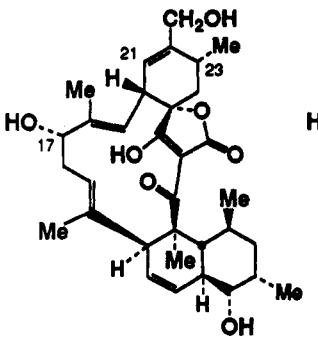
Received October 26, 1992

A highly diastereo- and enantioselective synthesis of spirotetronate 4 corresponding to the top half of kijanolide is reported. This synthesis features the novel exo-selective Diels–Alder reaction of triene 6 and the chiral, nonracemic dienophiles (*R*)-7 and (*R*)-8. The reaction of 6 and (*R*)-7 produced a mixture of the desired exo cycloadduct 28, the unexpected exo diastereofacial isomer 29, and a minor amount of the endo cycloadduct 30. However, the Diels–Alder reaction of 6 and dienophile (*R*)-8 with the more sterically demanding *tert*-butyl substituent provided a 13–14:1 mixture of exo cycloadduct 38 and endo isomer 39; the exo diastereofacial isomer corresponding to 29 was not observed. Elaboration of 28 and 38 to spirotetronate 4 proceeded by way of the Dieckmann cyclization of α-acetoxy ester 5.

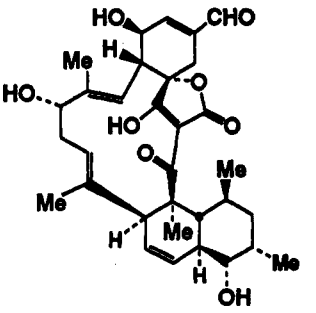
Introduction

Kijanolide (1), tetronolide (2), and chlorothricolide (3), the aglycons of the spirotetronate antibiotics kijanimicin, tetrocarcin A, and chlorothricin,[2] respectively, have attracted considerable attention as synthetic targets. Total syntheses of tetronolide[3] and 24-*O*-methylchlorothricolide[4] have been completed by Yoshii and co-workers, and synthetic approaches toward these structures have been pursued extensively in the laboratories of Ireland, Marshall, Schmidt, and Boeckmann, among others.[5,6] We have previously described a highly stereoselective synthesis of the hydronaphthalene subunit of kijanolide (1) and tetronolide (2)[6] and are pleased to report herein a highly enantio- and diastereoselective synthesis of the kijanolide top half spirotetronate substructure 4.[7]

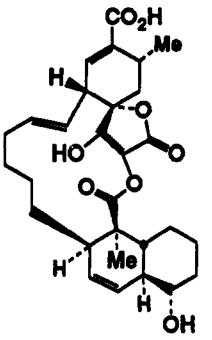
With one exception,[8g] all syntheses of the top half fragments (or of suitable top half precursors) of 1–3 have utilized Diels–Alder reactions.[7,8] Recognizing that the spirotetronate units of these antibiotics may be established by a Dieckmann cyclization of α-acetoxy esters,[8a] the synthetic problem reduces to the synthesis of a function-



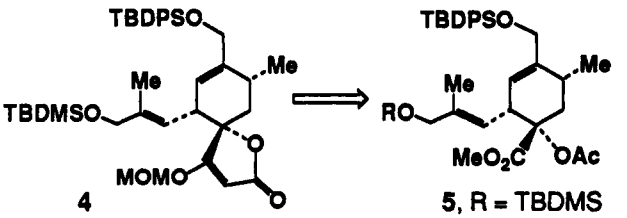
kijanolide (1)

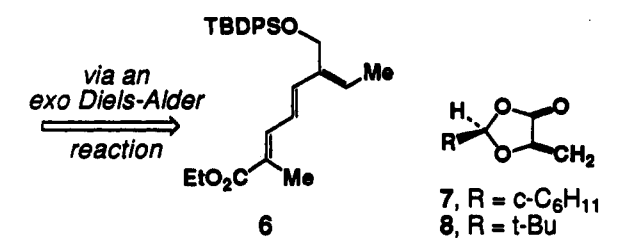


tetronolide (2)



chlorothricolide (3)





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

(2) (a) Kijanimicin: Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Mcfarlane, R. D.; Stephens, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1497. (b) Tetronolide: Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2984. (c) Chlorothricolide: Muntwyler, R.; Keller-Schlierlein, W. *Helv. Chim. Acta* **1972**, *55*, 2071. Brufani, M.; Cerrini, S.; Fedeli, W.; Mazza, F.; Muntwyler, R. *Ibid.* **1972**, *55*, 2094.

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

(4) Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431.

(5) A complete list of references to studies on the synthesis of kijanolide, tetronolide, and chlorothricolide is provided in ref 6b. For leading references (the most recent paper from each laboratory): (a) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (b) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *Ibid.* **1990**, *55*, 2398. (c) Hirsenkorn, R.; Haag-Zeino, B.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 4433. (d) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. S. *Ibid.* **1991**, *32*, 4095. (e) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192. (f) Snider, B. B.; Burbaum, B. W. *Ibid.* **1983**, *48*, 4370. (g) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (h) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Ibid.* **1989**, *30*, 2233. (i) Poss, A. J.; Brodowski, M. H. *Ibid.* **1989**, *30*, 2505. (j) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949.

(6) (a) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Tetrahedron Lett.* **1988**, *29*, 3541. (b) Roush, W. R.; Brown, B. B. *J. Am. Chem. Soc.*, in press.

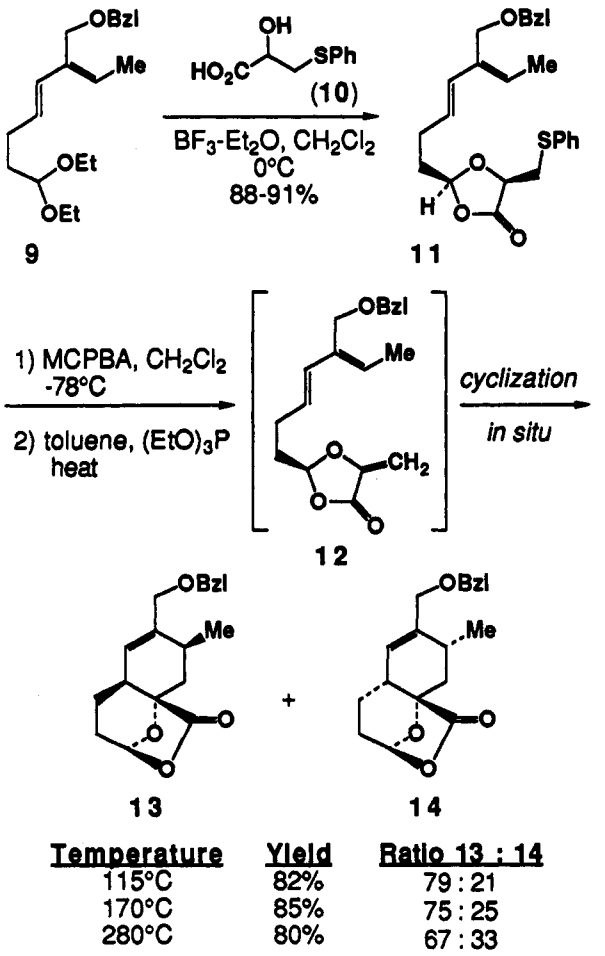
(7) A preliminary account of this work has appeared: Roush, W. R.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7309.

0022-3263/93/1958-2151$04.00/0

alized cyclohexene such as 5. However, *direct Diels–Alder* constructions of intermediates like 5 are complicated by the fact that the carbomethoxyl substituent is trans to the C(20) side chain (kijanolide numbering system), a stereochemical arrangement that requires an exo mode of cycloaddition. This stereochemical problem has been confronted several times,[4,8c,f,i] resulting in the development of indirect approaches in which the functionality in the cyclohexenyl ring is introduced and/or manipulated after the Diels–Alder step.[8a,b,d,e,h,k,m] Thus far, our synthesis of the kijanolide racemic top half fragment 4[7] and Boeckman's approach to the top half of tetronolide via an intramolecular Diels–Alder reaction[8l] are the only direct routes that have solved the diastereoselectivity issues associated with Diels–Alder constructions of these spirotetronate systems. Marshall recently reported an enantioselective synthesis of a kijanolide top half fragment by a route that involves inversion of configuration of C(25), the spiro stereocenter.[8m]

Our enantioselective synthesis of the kijanolide spirotetronate subunit 4 has its genesis in studies performed several years ago on the synthesis of chlorothricolide. Our original plan was to employ a Diels–Alder reaction of an α-(acyloxy)acrylate and a suitably functionalized triene. As initial studies along these lines were met with poor regio- and stereoselectivity,[9] we turned to approaches in which the Diels–Alder reaction was performed intramolecularly. The most fully developed sequence involved the intramolecular Diels–Alder reaction of 12 in which an enol pyruvate dienophile was tethered to the diene via an acetal linkage.[10,11] Unfortunately, the intramolecular Diels–Alder reaction of 12 also proceeded with poor exo/endo selectivity: 14 has the required exo stereochemistry but is the minor product of the reaction.[12]

Although this synthesis failed from the standpoint of exo/endo selectivity, we were intrigued by two key features: (i) the efficient, highly stereoselective synthesis of 12 via the condensation of acetal 9 and α-hydroxy ester 10 and (ii) the outstanding diastereofacial control exerted by the chiral acetal center (both 13 and 14 derived from cycloadditions to the same face of the chiral dienophile).[13] These observations prompted us to explore bimolecular



Temperature	Yield	Ratio 13 : 14
115°C	82%	79 : 21
170°C	85%	75 : 25
280°C	80%	67 : 33

Diels–Alder reactions of the 2-alkyl-1,3-dioxolan-4-one dienophiles 7 and 8.[14] *Remarkably, 7 and 8 undergo highly exo and diastereofacial selective Diels–Alder reactions with several dienes, a fortuitous result that provides the basis of the enantioselective synthesis of 4 reported herein.*[15] Full details concerning the enantioselective syntheses of 7 and 8, as well as speculation as to the basis of the exo selectivity of their Diels–Alder reactions, have been reported elsewhere.[16]

Results and Discussion

Synthesis of Triene 6. Triene 6 was synthesized starting from the readily available hydroxy ester 17. Treatment of a mixture of methyl acrylate (excess), acetaldehyde, and catalytic DABCO (1,4-diazabicyclo-[2.2.2]octane) provided the known[17] methyl 3-hydroxyl-2-methylenebutanoate 15 in 88% yield.[18] Allylic bromide 16 was obtained as a single isomer in 91% yield by treatment of 15 with NBS–dimethyl sulfide.[19,20] Assign-

(8) (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (b) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (c) Takeda, K.; Shibata, Y.; Sagawa, Y.; Urahata, M.; Funaki, K.; Hori, K.; Sasahara, H.; Yoshii, E. *J. Org. Chem.* **1985**, *50*, 4673. (d) Ireland, R. E.; Varney, M. D. *Ibid.* **1986**, *51*, 635. (e) Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1986**, 1197. (f) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *J. Org. Chem.* **1987**, *52*, 4135. (g) Matsuda, K.; Nomura, K.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1989**, 221. (h) Takeda, K.; Yano, S.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951. (i) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Ibid.* **1989**, *30*, 2233. (j) Poss, A. J.; Brodowski, M. H. *Ibid.* **1989**, *30*, 2505. (k) Schmidt, R. R.; Hirsenkorn, R. *Liebigs Ann. Chem.* **1990**, 883. (l) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. S. *Tetrahedron Lett.* **1991**, *32*, 4095. (m) Marshall, J. A.; Xie, S. *J. Org. Chem.* **1992**, *57*, 2987. (n) Roush, W. R.; Sciotti, R. J. *Tetrahedron Lett.* **1992**, *33*, 4691. (o) Roush, W. R.; Koyama, K. *Ibid.* **1992**, *33*, 6227.

(9) Roush, W. R.; Hall, S. E. Unpublished research, 1982.

(10) Research performed by Dr. M. Kageyama, 1984–5.

(11) For other examples of intramolecular Diels–Alder reactions of mixed acetals: ref 8l and (a) Boeckman, R. K., Jr.; Flann, C. J. *Tetrahedron Lett.* **1983**, *24*, 5035. (b) Jung, M. E.; Street, L. I. *J. Am. Chem. Soc.* **1984**, *106*, 8327.

(12) (a) A brief account of the synthesis of the top half of chlorothricolide via the intramolecular Diels–Alder reaction of 12 has been published: Roush, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1990; Vol. 2, p 91. (b) While not reported in the account cited in ref 12a, we also synthesized the chlorothricolide top half from 13 by a route involving inversion of configuration of the spiro center.

(13) For a review of synthetic applications of chiral 1,3-dioxalan-4-ones and related heterocycles: Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, p 125.

(14) (a) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305. (b) Dienophile 8 has also been studied by Mattay and co-workers: Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327.

(15) For a review of asymmetric Diels–Alder reactions: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.

(16) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380.

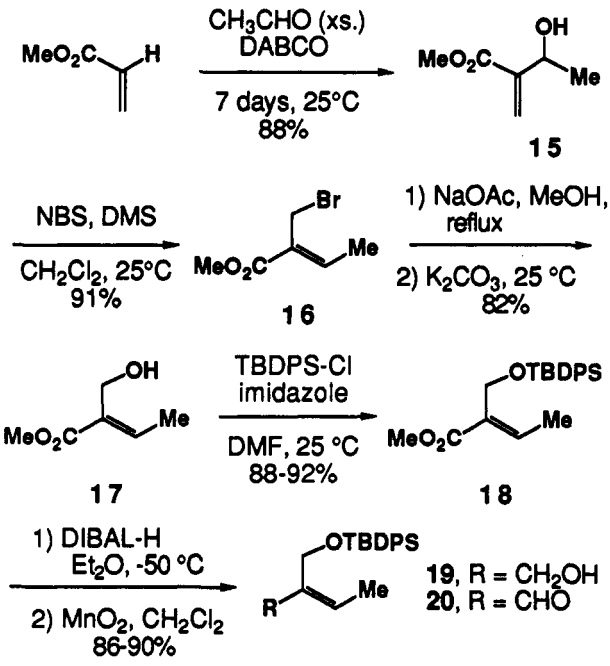
(17) (a) Hoffmann, H. M. R.; Rabe, J. J. *Org. Chem.* **1985**, *50*, 3849. (b) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795.

(18) For a recent review of the Baylis-Hillman reaction: Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(19) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.

(20) For modifications of the NBS-Me_2S procedure: (a) Depezay, J.-C.; Merrer, Y. L. *Tetrahedron Lett.* **1974**, 2751. (b) Goldberg, O.; Dreiding, A. S. *Helv. Chem. Acta* **1976**, *59*, 1904.

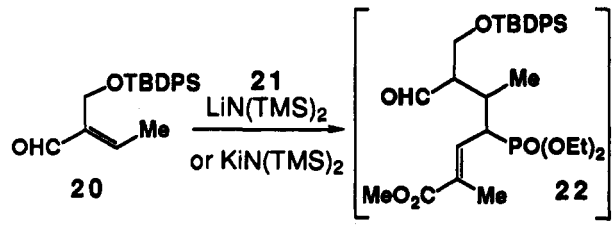
ment of the (*Z*) configuration in **16** is based on the ^{13}C chemical shift for the allylic methyl that appears at δ 23.9, compared to the corresponding signal for the (*E*)-isomer that appears at δ 36.8.[20b,21] Finally, exposure of **16** to excess sodium acetate in refluxing methanol followed by the addition of one equivalent of K_2CO_3 to affect acetate cleavage produced the known (2*E*)-2-(hydroxymethyl)-2-butenoate **17** in 82% yield.[22]

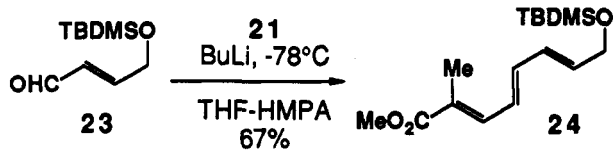


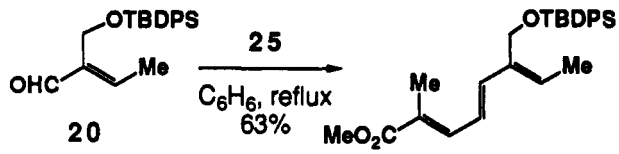
Protection of **17** as a *tert*-butyldiphenylsilyl ether **18** followed by DIBAL-H reduction of the ester function produced allylic alcohol **19** that was oxidized with excess MnO_2 in CH_2Cl_2. This provided enal **20** in 76–83% overall yield. Attempts to prepare **20** via Swern oxidations of **19** were complicated by the formation of the allylic chloride byproduct.[23]

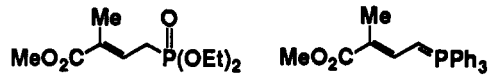
We initially hoped to prepare triene **6** via the reaction of **20** and γ-phosphonotiglate **21**, which is available by a standard Arbuzov reaction of methyl 4-bromo-2-methylcrotonate and triethyl phosphite.[21,24] In connection with work on the synthesis of streptovaricin D, we found this reagent provided (*E,E*)-dienes with *ca.* 20:1 selectivity using $KN(TMS)_2$ as base.[25] Attempts to apply this methodology to the synthesis of **6** using a variety of conditions [$KN(TMS)_2$ or $LiN(TMS)_2$ in THF (DMPU); NaOMe in DMF], however, were unsuccessful. We suspect that the anion of **21** undergoes a Michael reaction with **20** under these conditions, leading to **22**. Reagent **21** has been successfully utilized for the synthesis of triene **24**, an intermediate in our synthesis of the top half of tetronolide,[8o] and the Michael adduct analogous to **22** has been isolated from this reaction.[26]

The reaction of **20** and phosphorane **25**[27] was successful, but provided **6** in only 63% yield and as a 5:1 mixture of

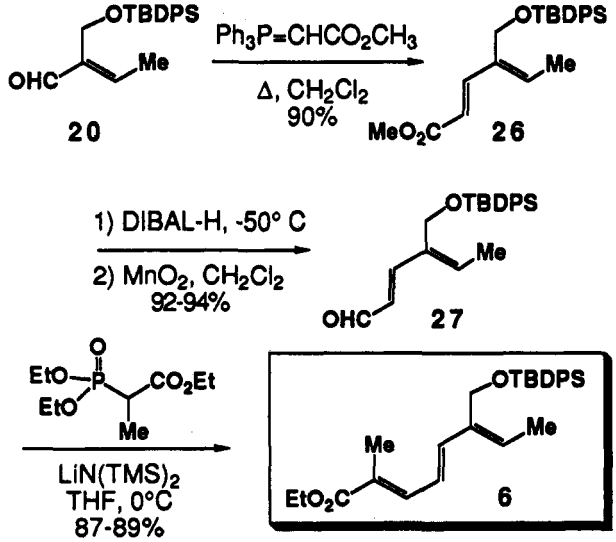








olefin isomers. This prompted us to elaborate **20** to **6** by the more efficient and more selective four-step procedure summarized below. α,β-Unsaturated aldehyde **20** was smoothly elaborated to the dienal **27** by sequential olefination with $Ph_3P{=}CHCO_2Me$ in CH_2Cl_2 (13:1 mixture of easily separable olefin isomers; 90% yield), reduction of the resulting unsaturated ester **26** with DIBAL-H in Et_2O at −50 °C (96% yield) and oxidation of the allylic alcohol by using MnO_2 (20 equiv, CH_2Cl_2, 95–98% yield). Finally, subjection of **27** to a Horner–Wadsworth–Emmons reaction with the lithium anion of $(EtO)_2POCH(Me)CO_2Et$ in THF at 0 °C provided trienoate **6** as a 28:1 mixture of olefin isomers in 87–89% yield.



Diels–Alder Reaction of 6 and (*R*)-7.[28] Dienophile **7** was used in our initial studies since **7** is less volatile and

(21) Löffler, A.; Pratt, R. J.; Rüesch, H. P.; Dreiding, A. *Helv. Chem. Acta* **1970**, *53*, 383.

(22) (a) Korte, F.; Behner, O. *Chem. Ber.* **1956**, *89*, 2675. (b) For related studies toward the synthesis of **17**, see: Ameer, F.; Drewes, S. E.; Emslie, N. D.; Kaye, P. T.; Mann, R. L. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2293.

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

(24) Pattenden, G.; Weedon, B. C. *J. Chem. Soc. C* **1968**, 1997.

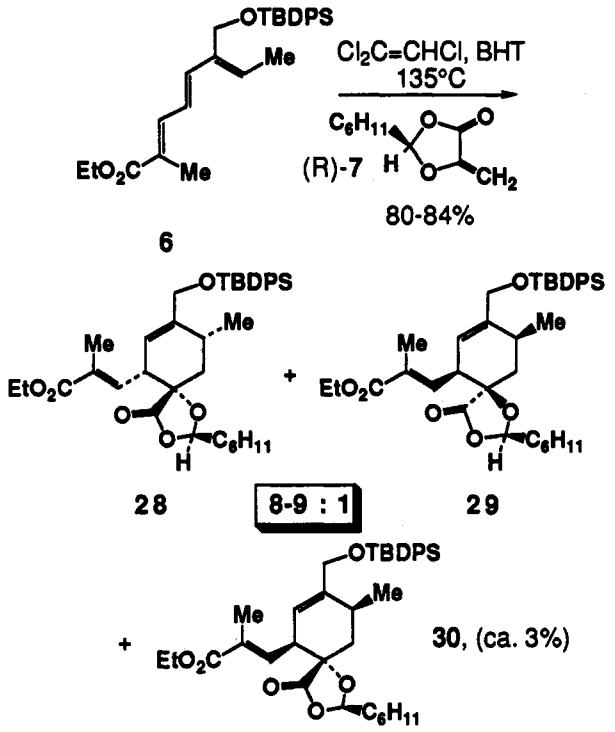
(25) These results are discussed in the 1989 Ph.D. Thesis of A. D. Palkowitz, MIT, Cambridge, MA 02139 (text pages 257–259).

(26) Roush, W. R.; Koyama, K. Unpublished research.

(27) Buchta, E.; Andree, F. *Chem. Ber.* **1960**, *93*, 1349.

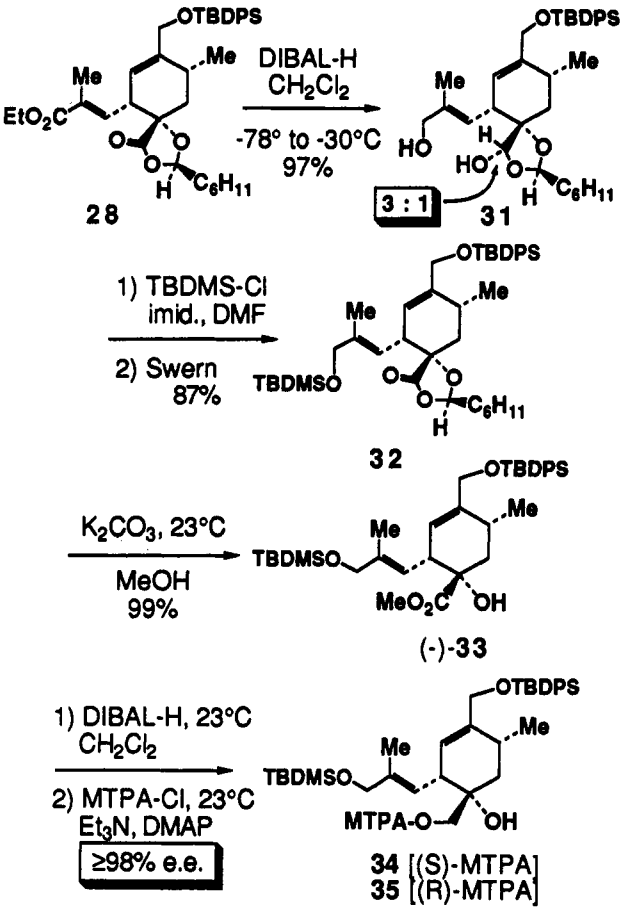
(28) For examples of bimolecular Diels–Alder reactions of trienes with the same substitution pattern as **6**: (a) Stork, G.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775. (b) Vedejs, E.; Reid, J. G. *Ibid.* **1984**, *106*, 4617. (c) Krafft, G. A.; Garcia, E. A.; Guram, A.; O'Shaughnessy, B.; Xu, X. *Tetrahedron Lett.* **1986**, *24*, 2691. (d) See also refs 8f and 8i.

is easier to purify than 8.[16] A mixture of 6 and (*R*)-7 (1.2–1.5 equiv) in trichloroethylene (1 M) was heated at 135 °C for 16 h in the presence of BHT as a radical inhibitor. Exo cycloadduct 28 was obtained as the major component of an 8–9:1 mixture with a diastereomeric cycloadduct whose structure was subsequently determined to be the exo diastereofacial isomer 29.[29] A small amount (ca. 3%) of a third cycloadduct, *endo*-30, was also obtained.[30] The yield of 28 isolated chromatographically was 73%, and the combined yield of cycloadducts was 80–84%.



Reduction of 28 with excess DIBAL-H in CH_2Cl_2 produced a 3:1 mixture of the unusual hemiacetal anomers 31 in 97% yield; attempts to selectively reduce the α,β-unsaturated ester of 28 were unsuccessful. The primary hydroxyl group of 31 was protected as a *tert*-butyldimethylsilyl ether (1.2 equiv of TBDMS-Cl, imidazole, DMF, 23 °C, 89% yield) and the hemiacetal reoxidized by using a standard Swern protocol to give 32 in 87% overall yield.

Treatment of 32 with K_2CO_3 in methanol at 0 °C provided hydroxy ester (−)-33 in 99% yield. The stereochemistry of this intermediate was established by a single-crystal X-ray analysis.[31] The enantiomeric purity of 33



was determined by Mosher ester analysis of the diol prepared by DIBAL-H reduction of 33.[32] The 400-MHz ^{1}H NMR spectrum of the (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) derivative 34 showed, among others, signals at δ 3.55 (s, 3 H) and 2.18 (m, 1 H). The (*R*)-(+)-MTPA ester 35 showed resonances only at δ 3.58 (s, 3 H) and 2.28 (m, 1 H), indicating the enantiomeric purity of (−)-33 to be ≥98% ee.

An alternative synthesis of lactone 32 involved the Diels–Alder reaction of triene 36 and (*R*)-7, which provided a 9:1 mixture of 32 and the exo diastereofacial isomer 37 in 80% yield. While this sequence is one step shorter than the synthesis by way of 28, it is less efficient since the DIBAL-H reduction of 6 and protection of the allylic alcohol provided 36 in only 44% yield.

The stereochemistry of the exo diastereofacial isomers 29 and 37 was determined as follows. Reduction of 29 with DIBAL-H in Et_2O produced an intermediate diol (ca. 3:1 mixture of hemiacetal anomers) that was converted into 37 via the selective monosilylation and hemiacetal oxidation sequence employed in the conversion of 31 to 32. *Methanolic hydrolysis of 37 then provided (+)-33, the enantiomer of the α-hydroxy ester prepared from 28 and 32.*

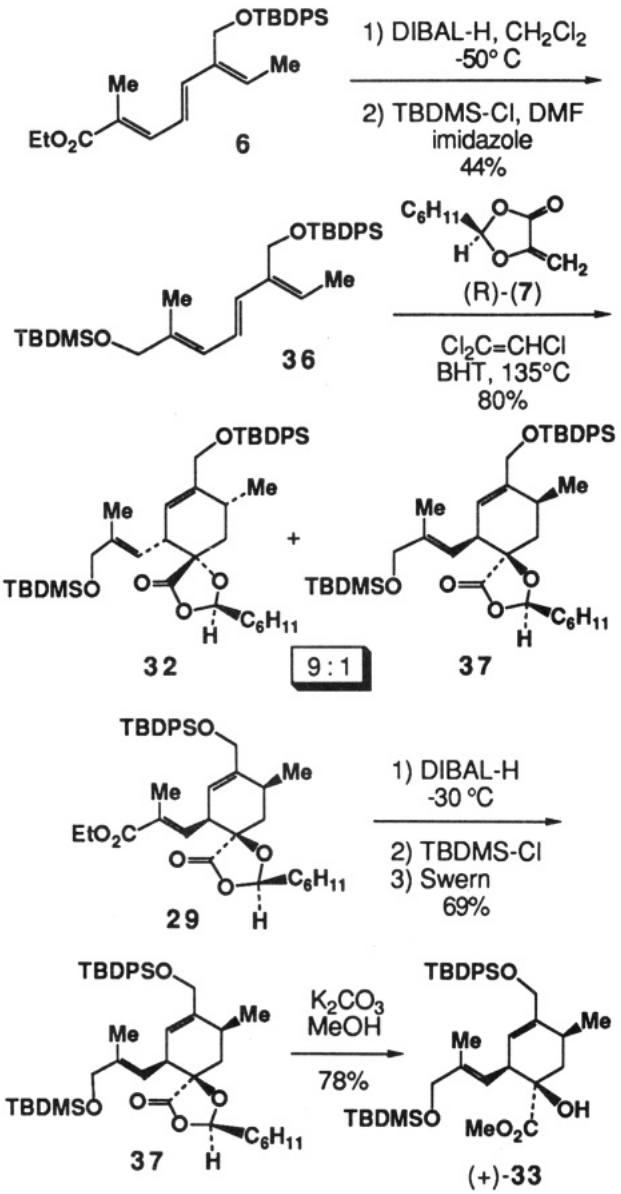
This result indicated that the diastereofacial selectivity of dienophile 7 was not as great as originally anticipated,[14a] since cycloadducts 29 and 32, which constitute 10–12% of the total Diels–Alder product mixtures, clearly arise via addition of the trienes to the more hindered *re* face of 7. This is in line with our observation that the Diels–Alder reaction of cyclopentadiene and (*R*)-7 also proceeds with ca. 5% stereochemical leakage of cycloaddition via the more hindered *re* face of 7.[16] This problem was easily

(29) We originally reported (ref 7) that the Diels–Alder reaction of triene 6 and racemic 7 provided an 8–9:1 mixture of 28 and an endo cycloadduct. In fact, however, the minor product is the second exo diastereomer 29.

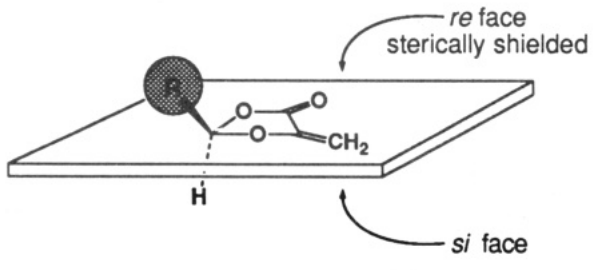
(30) We indicated in our preliminary communication (ref 7) that the ca. 3% product was a "regioisomer resulting from reversed orientation of the diene and dienophile". Only milligram quantities of 30 had been isolated at the time that our preliminary account was published, and the incorrect assignment was based on a preliminary ^{1}H NMR analysis which showed of H(20) of 30 as a doublet of doublets (J = 10.2, 5.3 Hz), while H(20) of 28 is a broad doublet (J = 10.5 Hz). The structure determination described in text, which establishes 30 as the correct structure, was performed after larger quantities were obtained upon scale-up of the reaction sequence.

(31) (a) Details of the X-ray determination of (−)-33 are provided in Report No. 91012 of the Indiana University Molecular Structure Center. Final residuals are $R(F)$ = 0.0462 and $R_w(F)$ = 0.0461. Copies of this report are available, on request, from Dr. John C. Huffman of the Indiana University Molecular Structure Center. (b) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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

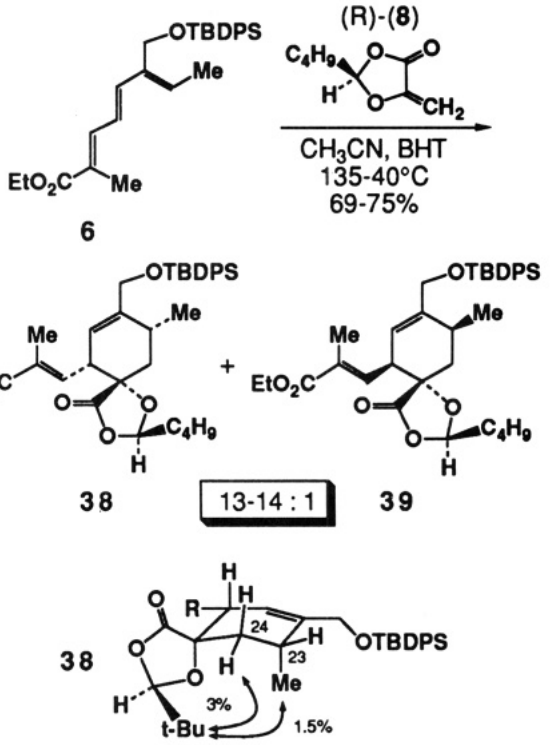


rectified by employing the more sterically demanding pivaldehyde derived chiral dienophile, (*R*)-8.

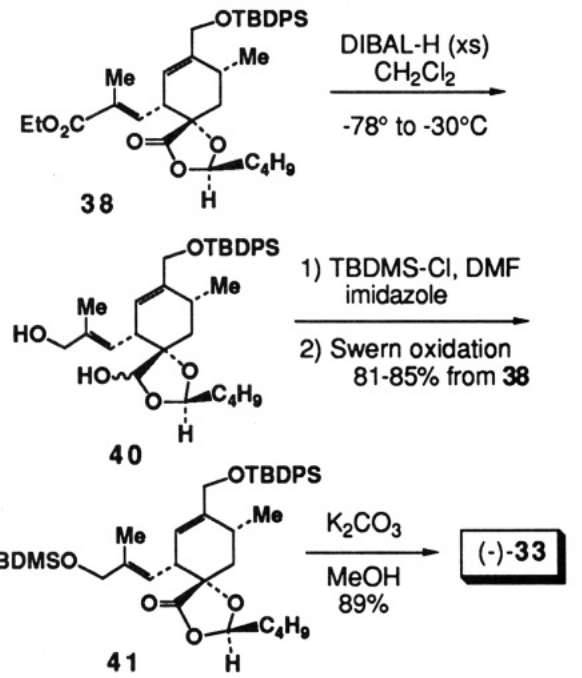


Diels-Alder Reaction of 6 and (*R*)-8. The Diels–Alder reaction of **6** and (*R*)-8 (CH_3CN, 135–140 °C, 16 h) provided a 13–14:1 mixture of exo cycloadduct **38** and the endo isomer **39** in 69–75% yield. No evidence for the presence of a second exo cycloadduct, analogous to **29**, was obtained. Therefore, the diastereofacial selectivity of the Diels–Alder reaction of (*R*)-**8** and **6** (≥13:1) is considerably greater than with (*R*)-**7** (8–9:1). This result is in agreement with our comparative study of the diastereofacial selectivity of the Diels–Alder reactions of **7** and **8** with cyclopentadiene.[16]

The stereochemistry of the acetal center of the major cycloadduct **38** was established by ^1H NOE studies: irradiation of the *tert*-butyl group led to a 3% enhancement

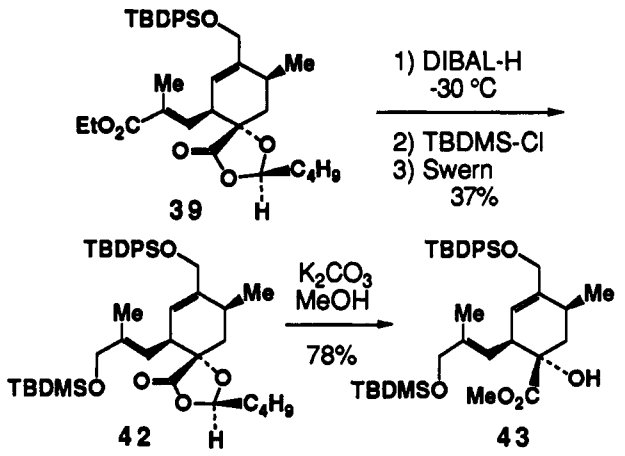


of H(24α) and a 1.5% enhancement of the C(23)-Me group. That **38** was indeed an exo cycloadduct was established by conversion to the previously described tertiary alcohol (−)-**33**. DIBAL-H reduction of **38** provided the expected diol **40** as a 3:1 mixture of hemiacetal anomers, along with ca. 30% of a hydroxy lactone resulting from the reduction of the side chain enoate. Treatment of this mixture with TBMDS-Cl and imidazole in DMF and oxidation of the hemiacetal via the Swern protocol provided lactone **41** in 81–85% yield from **38**. Methanolysis of **38** by treatment with K_2CO_3 in MeOH then gave alcohol (−)-**33** in 89% yield. This intermediate was identical in all aspects to samples previously prepared from cycloadduct **28**.

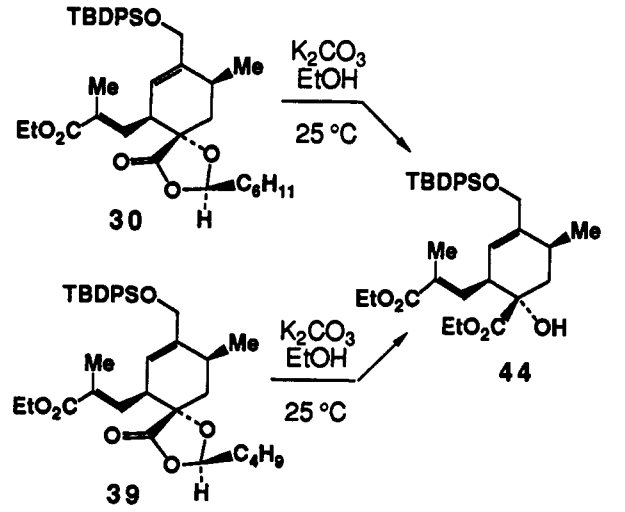


The stereochemistry of the minor cycloadduct **39** was assigned by conversion to α-hydroxy ester **43**, a diastereomer of the previously characterized intermediate **33**.

Since the exo stereochemistry of 28 and 38 has been verified by the X-ray structure analysis of 33,[31] it follows that 43 must derive from an endo cycloadduct. We assume that the absolute configuration of 39 is as shown, since this is the stereochemistry that would be obtained if the diene added to the most accessible *si* face of 8 via an endo transition state.



The stereochemistry of 30, the very minor product (3%) isolated from the Diels–Alder reaction of 6 and (*R*)-7,[30] was assigned by correlation with 39. As shown below, samples of 30 and 39 were treated with 1.1 equiv of K_2CO_3 in EtOH, and both reactions produced the same diethyl ester, 44.



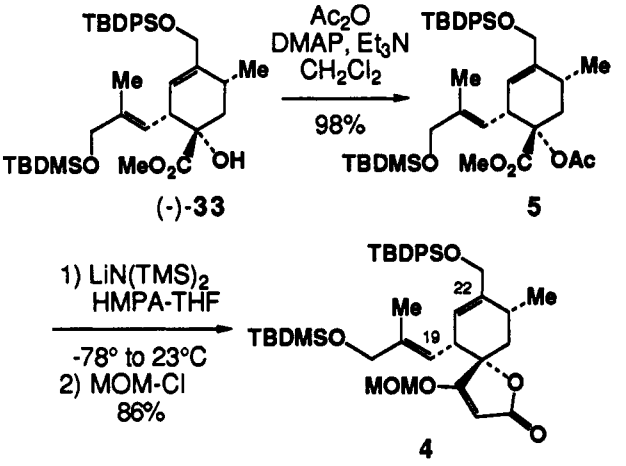
Synthesis of 4 via Dieckmann Closure of the Spiro Tetronate. Completion of the synthesis of the top half fragment 4 of kijanolide proceeded smoothly by using the Dieckmann technology introduced by Ireland in his pioneering synthesis of the top half of chlorothricolide.[8a] Acylation of (−)-33 with Ac_2O in the presence of DMAP and Et_3N provided 5 in 98% yield. A solution of 5 in THF containing 20 equiv of HMPA was treated with $LiN(TMS)_2$ at −78 °C to generate the enolate. This solution was allowed to warm to 23 °C over a 1-h period and then was treated with 2.5 equiv of chloromethyl methyl ether (MOM-Cl), giving the kijanolide top half fragment 4 with an easily removable tetronate protecting group. ^1H NMR data obtained for 4 were in very good agreement with data previously reported for 26,32-di-*O*-methylkijanolide (45, see Table I).[2a]

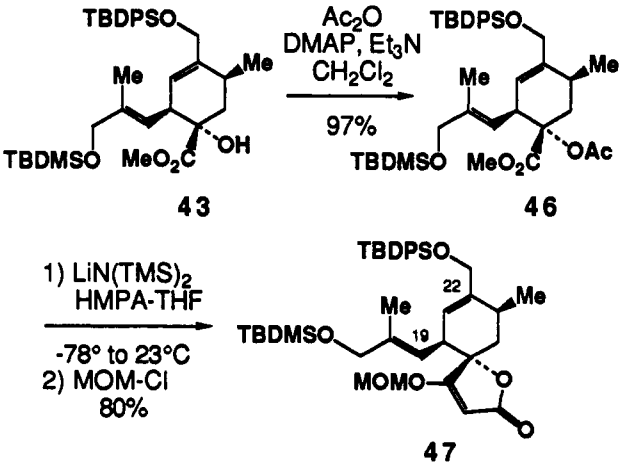
In contrast, the spectroscopic properties of the diastereomeric spiro tetronate 47 prepared from the endo alcohol 43 were significantly different than those of 4 (Table II). The spectroscopic properties of 47, however, are very similar to those reported by Yoshii for 48 which is in the same stereochemical series.[8f]

Table I. ^1H NMR Comparison of 4 and 26,32-Di-*O*-methylkijanolide (45)[a]

^1H resonance	4	45
H-20	3.45 (partially obscured)	3.42 (d, J = 9.7 Hz)
H-21	5.33 (br s)	5.47 (s)
H-23	2.62 (br dq, J = 7.4, 7.4 Hz)	2.61 (dq, J = 7.0, 7.5 Hz)
Me-C(23)	1.16 (d, J = 7.4 Hz)	1.28 (d, J = 7.5 Hz)
H-24α	1.67 (d, J = 14.1 Hz)	1.76 (d, J = 14.1 Hz)
H-24β	2.28 (dd, J = 14.1, 7.4 Hz)	2.33 (J = 14.1, 7.0 Hz)

[a] ^1H NMR spectra were measured in $CDCl_3$ and reported in δ units.

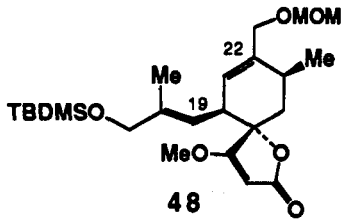




Summary. We have developed the first highly diastereo- and enantioselective synthesis of spirotetronate substructure (4) of kijanolide. This synthesis features the novel *exo*-selective Diels–Alder reaction of triene 6 and the chiral, nonracemic dienophiles (*R*)-7 and (*R*)-8. The reaction of 6 and dienophile (*R*)-7 produced a mixture of the desired exo cycloadduct 28, the unexpected exo diastereofacial isomer 29, and a minor amount of the endo cycloadduct 30. However, the Diels–Alder reaction of 6 and dienophile (*R*)-8 with a more sterically demanding *tert*-butyl substituent provided a 13–14:1 mixture of the desired exo cycloadduct 38 and the endo isomer 39; an exo diastereofacial isomer corresponding to 29 was not observed in this reaction.

We note in closing that this technology is also applicable to the enantioselective synthesis of the spiro tetronate

Table II. ^{1}H NMR Comparison of Spirotetronates 47 and 48[a]



^{1}H resonance	47	48
H-20	3.16 (dd, J = 9.8, 5.0 Hz)	3.17 (dd, J = 10.1, 4.9 Hz)
H-21	5.53 (dd, J = 5.0, 1.6 Hz)	5.53 (br d, J = 4.9 Hz)
H-23	2.65 (m)	2.64 (m)
Me-C(23)	1.02 (d, J = 7.0 Hz)	1.11 (d, J = 7.1 Hz)
H-24α	*b*	1.84 (dd, J = 13.9, 6.7 Hz)
H-24β	*b*	1.77 (dd, J = 13.9, 10.0 Hz)

[a] ^{1}H NMR spectra were measured in $CDCl_3$ and reported in δ units. [b] H-24α,β appear as a 2-proton doublet (J = 8.6 Hz) at δ 1.81.

fragments of tetronolide and chlorothricolide.[2b,c] Details of these synthetic studies will be reported elsewhere.[8n,o]

Experimental Section

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

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

Analytical thin-layer chromatography (TLC) was performed by using 2.5-cm × 10-cm plates coated with a 0.25-mm thickness of silica gel containing PF 254 indicator (Analtech). Preparative thin-layer chromatography was performed by using 20-cm × 20-cm plates coated with 0.25- or 0.5-mm thickness of silica gel containing PF254 indicator (Analtech). Flash chromatography was performed as described by Still using Kieselgel 60 (230–400 mesh) or Kieselgel 60 (70–230 mesh).[33] Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (by ^{1}H NMR analysis) for use in subsequent reactions.

Methyl 3-Hydroxy-2-methylenebutanoate (15).[17] A solution of acetaldehyde (10.0 mL, 0.18 mol), methyl acrylate (24.0 mL, 0.27 mol), and catalytic 1,4-diazabicyclo[2.2.2]octane (2.3 g, 0.02 mol) was stirred for 7 days at 25 °C under N_2 before being diluted with Et_2O (125 mL) and washed with H_2O (200 mL). The aqueous layer was separated, acidified to pH = 6 with 1 N HCl, and extracted with Et_2O (200 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by distillation (94–95 °C, 15 mmHg) produced 20.3 g (88%) of the known alcohol 15:[17] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, J = 1.4 Hz, 1 H), 5.80 (d, J = 1.2 Hz, 1 H), 4.57 (m, 1 H), 3.73 (s, 3 H), 3.00 (br d, J = 3.8 Hz, 1 H), 1.32 (d, J = 6.8 Hz, 3 H).

Methyl (2*Z*)-2-(Bromomethyl)-2-butenoate (16).[22] To a 0 °C solution of *N*-bromosuccinimide (15.2 g, 84.5 mmol) in CH_2Cl_2 (75 mL) was slowly added freshly distilled dimethyl sulfide (6.8 mL, 92.2 mmol) in dry CH_2Cl_2 (50 mL); the addition took 15 min on this scale, and a slight (ca. 5 °C) exotherm was observed. A solution of 15 (10.0 g, 76.8 mmol) in dry CH_2Cl_2 (45 mL) was then added dropwise over a 15-min period under N_2. This produced a clear yellow solution that was stirred for 16 h at 25 °C before being diluted with pentane (500 mL) and poured into a chilled mixture of H_2O and brine (1:1). The aqueous layer was separated and extracted with Et_2O (3 × 100 mL). The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo, and the resulting crude product was purified by silica gel chromatography (5:1 hexane–ether), giving 13.5 g (91%) of the known allylic bromide 16:[22] R_f 0.37 (5:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (q, J = 6.9 Hz, 1 H), 4.23 (s, 2 H), 3.79 (s, 3 H), 1.91 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 169.5, 143.3, 130.1, 52.1, 23.9, 14.5; IR (neat) 1725, 1645 cm^{-1}; MS m/z 193 (parent ion).

Methyl (2*E*)-2-(Hydroxymethyl)-2-butenoate (17).[22] A solution of 16 (8.20 g, 42.5 mmol) and sodium acetate (10.4 g, 125 mmol) in anhydrous MeOH (175 mL) was heated to reflux for 3.5 h under N_2. The mixture was cooled, and then anhydrous K_2CO_3 (5.87 g, 42.5 mmol) was added. The resulting slurry was stirred for 15 h at 25 °C before being filtered. The filtrate was concentrated to ca. 25% of the original volume, diluted with EtOAc (400 mL), and washed with H_2O (100 mL). The aqueous layer was separated, acidified to pH = 3 with 1 N HCl, and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Trituration of the crude material with hexane (10 mL) produced 4.53 g (82%) of a heavy oil composed of 17 and 7% of the methyl ether derived from methoxide displacement of bromide from 16. This mixture was used in the next step without purification. Data for 17:[22] R_f 0.11 (2:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (q, J = 6.9 Hz, 1 H), 4.33 (d, J = 6.2 Hz, 2 H), 3.75 (s, 3 H), 2.63 (t, J = 6.2 Hz, 1 H), 1.88 (d, J = 6.9 Hz, 3 H); IR (neat) 3420 (br), 1725 (br), 1650 cm^{-1}; MS m/z 131 (M^+ + H).

Methyl (2*E*)-2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-butenoate (18). To a 25 °C solution of 17 (4.5 g, 34 mmol; 93% purity) in anhydrous DMF (110 mL) was added imidazole (3.5 g, 51 mmol) and *tert*-butyldiphenylsilyl chloride (9.9 mL, 38 mmol) under N_2. This reaction was stirred for 16 h before being dissolved in 1:1 Et_2O–hexane (500 mL) and washed with 1:1 H_2O–brine (300 mL). The aqueous layer was separated and extracted with 1:1 Et_2O–hexane (3 × 300 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 12.5 g of crude ether 18 that was used directly in the next experiment without purification. Spectroscopic data obtained with purified 18: R_f 0.36 (5:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.69 (m, 4 H), 7.46–7.35 (m, 6 H), 6.96 (q, J = 6.9 Hz, 1 H), 4.42 (s, 2 H), 3.70 (s, 3 H), 1.77 (d, J = 6.9 Hz, 3 H), 1.03 (s, 9 H); IR (neat) 1723, 1653 cm^{-1}; MS m/z 311 ($M^+ - C_4H_9$). Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.70; H, 7.66. Found: C, 71.74; H, 7.71.

2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2(*Z*)-butenol (19). To a −50 °C solution of 18 (12.5 g, 34.0 mmol) in anhydrous Et_2O (135 mL, 0.25 M) under N_2 was added dropwise a 1.0 M solution of DIBAL-H (85 mL, 85 mmol) in hexanes over a 45-min period. One hour later, anhydrous methanol (30 mL) was added dropwise over a 10-min period. The resulting slurry was allowed to warm slowly to 5 °C before being poured into a 1:1 mixture of Et_2O (300 mL) and 50% aqueous Rochelle's salt (300 mL). This mixture was stirred for 1 h, and then the aqueous layer was separated and extracted with Et_2O (3 × 400 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, and the crude product was purified by silica gel chromatography (2:1 hexane–ether) to give 10.7 g (92%) of 19: R_f 0.23 (2:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73–7.69 (m, 4 H), 7.45–7.37 (m, 6 H), 5.57 (br q, J = 6.9 Hz, 1 H), 4.37 (s, 2 H), 4.23 (d, J = 6.1 Hz, 2 H), 2.41 (t, J = 6.1 Hz, 1 H), 1.44 (d, J = 6.9 Hz, 3 H), 1.06 (s, 9 H); IR (neat) 3380 (br), 1591 cm^{-1}; MS m/z 283 ($M^+ - C_4H_9$). Anal. Calcd for $C_{21}H_{26}O_2Si$: C, 74.07; H, 8.29. Found: C, 73.85; H, 8.33.

2-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2(*E*)-butenal (20). MnO_2 (76.5 g, 880 mmol, Aldrich) was added in small portions over a 48-h period to a vigorously stirred solution of 19 (15.0 g, 44.0 mmol) in dry CH_2Cl_2 (400 mL, 0.1 M). The resulting slurry was stirred for an additional 48 h before being filtered through a plug of sand and Celite. The filter pad was repeatedly washed with CH_2Cl_2. The filtrates were combined and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (5:1 hexane–ether) provided 14.3 g (96%) of enal 20: R_f 0.25 (5:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.38 (s, 1 H), 7.70–7.65 (m, 4 H), 7.46–7.36 (m, 6 H), 6.71 (q, J = 6.9 Hz, 1 H), 4.41 (s, 2 H), 2.02 (d, J = 6.9 Hz, 3 H), 1.03 (s, 9 H); IR (neat) 2859, 2715, 1691 cm^{-1}; HRMS for $C_{17}H_{17}O_2Si$ ($M^+ - C_4H_9$) calcd 281.1033, found 281.0984.

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

Methyl 4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2(*E*),4(*Z*)-hexadienoate (26). A solution of methyl (triphenylphosphoranylidene)acetate (14.8 g, 44.1 mmol) and **20** (5.0 g, 14.7 mmol) in dry CH_2Cl_2 (150 mL) was heated at reflux for 16 h under N_2. Concentration of the solution in vacuo produced a sticky yellow solid that was extracted with 10:1 hexane–Et_2O (3 × 25 mL). Concentration of the extracts produced crude **26** that was purified by silica gel chromatography (5:1 hexane–ether) to give 5.20 g (90%) of pure **26**: R_f 0.38 (4:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.47–7.36 (m, 6 H), 7.26 (d, J = 16.0 Hz, 1 H), 6.13 (d, J = 16.0 Hz, 1 H), 5.99 (q, J = 6.9 Hz, 1 H), 4.37 (s, 2 H), 3.77 (s, 3 H), 1.53 (d, J = 6.9 Hz, 3 H), 1.03 (s, 9 H); IR (neat) 1724, 1634, 1621 cm^{-1}; HRMS for $C_{24}H_{28}O_3Si$ calcd 394.1956, found 394.1967.

4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2(*E*),4(*Z*)-hexadienal (27). To a −50 °C solution of **26** (12.9 g, 32.7 mmol) in anhydrous Et_2O (150 mL, 0.2 M) under N_2 was slowly added a 1.0 M solution of DIBAL-H in hexanes (82 mL, 82 mmol). One hour later, anhydrous methanol (50 mL) was added and the reaction was allowed to warm to 5 °C before being poured into a 3:1 mixture of Et_2O and saturated aqueous Rochelle's salt (500 mL). This mixture was stirred 1 h, and then the aqueous layer was separated and extracted with Et_2O (3 × 200 mL). The combined ethereal layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (2:1 hexane–ether as eluent) produced 10.8 g (91%) of the intermediate dienol. This material was used directly in the next step without purification: R_f 0.20 (2:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4 H), 7.46–7.35 (m, 6 H), 6.15 (d, J = 16.0 Hz, 1 H), 5.97 (dt, J = 16.0, 5.8 Hz, 1 H), 5.62 (q, J = 7.0 Hz, 1 H), 4.36 (s, 2 H), 4.18 (br t, J = 5.8 Hz, 2 H), 1.53 (d, J = 7.0 Hz, 3 H), 1.21 (t, J = 5.6 Hz, 1 H, OH), 1.04 (s, 9 H); IR (neat) 3480 (br) cm^{-1}.

MnO_2 (51.2 g, 590 mmol, Aldrich) was added in small portions over a 32-h period to a vigorously stirred solution of the above dienol (10.8 g, 29.5 mmol) in dry CH_2Cl_2 (300 mL, 0.1 M) under N_2. The slurry was stirred an additional 48 h before being filtered through a plug of sand and Celite. The filter pad was repeatedly washed with CH_2Cl_2. The combined filtrate was concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (3:1 hexane–ether as eluent) produced 10.1 g (94%) of aldehyde **27** as a white solid: mp 97–98 °C; R_f 0.25 (4:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, J = 7.8 Hz, 1 H), 7.70–7.41 (m, 4 H), 7.39–7.36 (m, 6 H), 7.03 (d, J = 6.1 Hz, 1 H), 6.40 (dd, J = 7.8, 6.1 Hz, 1 H), 6.11 (q, J = 6.5 Hz, 1 H), 4.39 (s, 2 H), 1.59 (d, J = 6.5 Hz, 2 H), 1.03 (s, 9 H); HRMS for $C_{19}H_{19}O_2Si$ ($M^+ - C_4H_9$) calcd 307.1200, found 307.1141. Anal. Calcd for $C_{23}H_{28}O_2Si$: C, 75.73; H, 7.74. Found: C, 75.37; H, 7.83.

Ethyl 6-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2-methyl-2(*E*),4(*E*),6(*Z*)-octatrienoate (6). To a −50 °C solution of ethyl 2-(diethylphosphono)propionate (0.93 mL, 4.1 mmol) in anhydrous THF (15 mL) under N_2 was slowly added a 1.0 M solution of lithium hexamethyldisilazide (4.1 mL, 4.1 mmol) in THF. This mixture was stirred for 15 min before a solution of dienal **27** (1.0 g, 2.7 mmol) in anhydrous THF (10 mL) was added via cannula. The reaction mixture was allowed to warm to 0 °C over a 2-h period and stirred an additional 1 h before being diluted with anhydrous Et_2O (100 mL) and poured into saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with Et_2O (2 × 50 mL). The combined ethereal layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (5:1 hexane–ether) yielded 1.21 g (89%) of **6**: R_f 0.36 (4:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.69 (m, 4 H), 7.46–7.35 (m, 6 H), 7.25 (d, J = 11.3 Hz, 1 H), 6.76 (dd, J = 15.8, 11.3 Hz, 1 H), 6.47 (d, J = 15.8 Hz, 1 H), 5.79 (q, J = 6.9 Hz, 1 H), 4.42 (s, 2 H), 4.22 (q, J = 7.0 Hz, 2 H), 1.94 (s, 3 H), 1.56 (d, J = 6.9 Hz, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.04 (s, 9 H); IR (neat) 1712, 1641, 1615 cm^{-1}; HRMS for $C_{24}H_{27}O_3Si$ ($M^+ - C_4H_9$) calcd 391.1768, found 391.1717. Anal. Calcd for $C_{28}H_{36}O_3Si$: C, 74.95; H, 8.09. Found: C, 75.04; H, 7.95.

Diels–Alder Reaction of Triene 6 and (*R*)-7. A solution of triene **6** (0.45 g, 1.00 mmol) and freshly prepared dienophile (*R*)-**7**[16] (0.45 g, 2.50 mmol) in dry trichloroethylene (1.0 mL, 1.0 M; neutralized with basic alumina) in a presilylated Carius tube was degassed with a stream of N_2. A crystal of BHT was added and the tube sealed. The Carius tube was immersed in a 135 °C oil bath and stirred for 16 h. The mixture was cooled and then concentrated in vacuo. The crude product consisted of a 85:10:5 ratio of **28**:**29**:**30** as determined by analysis of the olefinic region of the ^1H NMR spectrum of the crude product. Separation of the isomers by silica gel chromatography (5:1 hexane–ether) yielded 440 mg (73%) of exo cycloadduct **28**, 51 mg (8%) of the diastereomeric exo cycloadduct **29**, and 16 mg (ca. 3%) of the endo isomer **30**.

Data for major exo cycloadduct 28: R_f 0.30 (5:1 hexane–ether); $[\alpha]^{26}_D$ −65.2° (c = 1.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.46–7.34 (m, 6 H), 6.61 (dd, J = 10.5, 1.6 Hz, 1 H), 5.30 (br s, 1 H), 5.24 (d, J = 4.3 Hz, 1 H), 4.25–4.12 (m, 4 H), 3.54 (br d, J = 10.5 Hz, 1 H), 2.63 (m, 1 H), 2.15 (dd, J = 14.0, 6.6 Hz, 1 H), 1.87 (s, 3 H), 1.82–1.60 (m, 8 H), 1.30 (t, J = 7.2 Hz, 3 H), 1.27–1.14 (m, 4 H), 1.13 (d, J = 7.5 Hz, 3 H), 1.05 (s, 9 H); IR (neat) 1798, 1718, 1652 cm^{-1}; MS m/z 573 ($M^+ - C_4H_9$). Anal. Calcd for $C_{38}H_{50}O_6Si$: C, 72.27; H, 7.99. Found: C, 72.11; H, 8.19.

Data for minor exo cycloadduct 29: R_f 0.28 (5:1 hexane–ether); $[\alpha]^{26}_D$ +46.5° (c = 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4 H), 7.43–7.36 (m, 6 H), 6.68 (dd, J = 10.5, 1.5 Hz, 1 H), 5.30 (d, J = 4.5 Hz, 1 H), 5.28 (br s, 1 H), 4.24–4.11 (m, 4 H), 3.59 (br d, J = 10.5 Hz, 1 H), 2.59 (m, 1 H), 1.94 (br d, J = 4.6 Hz, 2 H), 1.87 (d, J = 1.3 Hz, 3 H), 1.81–1.67 (m, 7 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.26–1.14 (m, 4 H), 1.10 (d, J = 7.4 Hz, 3 H), 1.05 (s, 9 H); IR (neat) 1796, 1710, 1650 cm^{-1}; HRMS for $C_{34}H_{41}O_6Si$ ($M^+ - C_4H_9$) calcd 573.2661, found 573.2626.

Data for endo cycloadduct 30: R_f 0.21 (5:1 hexane–ether); $[\alpha]^{26}_D$ +88.7° (c = 3.2, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.61 (m, 4 H), 7.41–7.34 (m, 6 H), 6.53 (dd, J = 10.2, 1.6 Hz, 1 H), 5.43 (br d, J = 5.3 Hz, 2 H), 4.24 (A of AB, J_{AB} = 13.2 Hz, 1 H), 4.19 (m, 2 H), 4.12 (B of AB, J_{BA} = 13.2 Hz, 1 H), 3.39 (dd, J = 10.2, 5.3 Hz, 1 H), 2.56 (m, 1 H), 1.86 (s, 3 H), 1.81–1.65 (m, 9 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.26–1.09 (m, 4 H), 1.06 (d, J = 7.5 Hz, 3 H), 1.05 (s, 9 H); IR (neat) 1791, 1716, 1682 cm^{-1}; HRMS for $C_{34}H_{41}O_6Si$ ($M^+ - C_4H_9$) calcd 573.2661, found 573.2690.

DIBAL Reduction of Cycloadduct 28. To a −60 °C solution of **28** (1.54 g, 2.44 mmol) in anhydrous CH_2Cl_2 (25 mL) under N_2 was slowly added a 1.0 M solution of DIBAL-H in CH_2Cl_2 (9.8 mL, 9.8 mmol). The mixture was stirred −30 °C for 2 h before being poured into a 1:1 mixture of aqueous Rochelle's salt and Et_2O. This mixture was stirred for 1 h at 25 °C. The aqueous layer was then separated, saturated with NaCl, and extracted with Et_2O (3 × 100 mL). The combined ethereal extracts were dried over $MgSO_4$ and concentrated in vacuo. This produced 1.44 g (97%) of diol **31** as a white, sticky solid, which proved to be 3:1 mixture of hemiacetals by ^1H NMR analysis: R_f 0.30 (1:1 hexane–ether); ^1H NMR (300 MHz, $CDCl_3$) (major hemiacetal) δ 7.74–7.65 (m, 4 H), 7.48–7.36 (m, 6 H), 5.49 (br s, 1 H), 5.30 (dd, J = 9.9, 1.4 Hz, 1 H), 4.94 (d, J = 8.6 Hz, 1 H, hemiacetal), 4.71 (d, J = 4.9 Hz, 1 H, acetal), 4.26 (m, 2 H), 4.03 (s, 2 H), 3.18 (m, 1 H), 2.52 (m, 1 H), 2.24 (d, J = 8.6 Hz, 1 H, OH), 1.78–1.65 (m, 10 H), 1.72 (s, 3 H), 1.33–1.09 (m, 4 H), 1.09 (d, J = 7.1 Hz, 3 H), 1.06 (s, 9 H); ^1H NMR (300 MHz, $CDCl_3$) (minor hemiacetal), 7.74–7.65 (m, 4 H), 7.48–7.36 (m, 6 H), 5.47 (br s, 1 H), 5.37 (dd, J = 9.5, 1.5 Hz, 1 H), 5.14 (d, J = 5.2 Hz, 1 H, hemiacetal), 4.98 (d, J = 4.9 Hz, 1 H, acetal), 4.25 (m, 2 H), 4.01 (s, 2 H), 3.56 (m, 1 H), 2.61 (d, J = 5.2 Hz, 1 H, OH), 2.46 (m, 1 H), 1.88 (dd, J = 12.8, 4.9 Hz, 1 H), 1.76–1.65 (m, 9 H), 1.74 (s, 3 H), 1.33–1.09 (m, 4 H), 1.06 (s, 9 H), 0.98 (d, J = 7.2 Hz, 3 H); IR (neat) 3450 (br), 1590 cm^{-1}; MS m/e 516 ($M^+ - C_4H_9 - H_2O$). Anal. Calcd for $C_{36}H_{50}O_5Si$: C, 73.18; H, 8.53. Found: C, 72.94; H, 8.67.

(2*R*,2*R*',4*S*,5*R*)-Spiro[1-[[(*tert*-butyldiphenylsilyl)oxy]methyl]-2-methyl-5-[3-[(*tert*-butyldimethylsilyl)oxy]-2-methylprop-1-enyl]cyclohex-1-ene-4,5'-2'-cyclohexyl-1',3'-dioxolan-4'-one] (32). To a 0 °C solution of diol **31** (1.44 g, 2.44 mmol) in anhydrous DMF (5.0 mL) under N_2 was added imidazole (0.43 g, 6.34 mmol) and *tert*-butyldimethylsilyl chloride (0.48 g, 3.2 mmol). This mixture was stirred for 16 h at 25 °C before being partitioned between 1:1 hexane–Et_2O (300 mL) and 50% aqueous brine (200 mL). The aqueous layer was separated and extracted with 1:1 hexane–Et_2O (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo and purified by silica gel chromatography (15:1 hexane–ether) to give 1.50 g (88%) of the monosilyl ether. This compound was also a 3:1 mixture of hemiacetal anomers: R_f 0.16 (15:1 hexane–

ether); ^{1}H NMR (300 MHz, $CDCl_3$) (major hemiacetal) δ 7.72–7.61 (m, 4 H), 7.44–7.31 (m, 6 H), 5.49 (br s, 1 H), 5.30 (dd, J = 9.8, 1.6 Hz, 1 H), 4.92 (d, J = 8.9 Hz, 1 H, hemiacetal), 4.71 (d, J = 4.8 Hz, 1 H, acetal), 4.23 (m, 2 H), 4.02 (s, 2 H), 3.14 (m, 1 H), 2.51 (m, 1 H), 2.22 (d, J = 8.9 Hz, 1 H, OH), 1.87 (dd, J = 12.1, 4.9 Hz, 1 H), 1.79–1.60 (m, 8 H), 1.65 (s, 3 H), 1.29–0.98 (m, 4 H), 1.06 (s, 9 H), 0.98 (d, J = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{1}H NMR (300 MHz, $CDCl_3$) (minor hemiacetal) δ 7.72–7.61 (m, 4 H), 7.44–7.31 (m, 6 H), 5.51 (br s, 1 H), 5.39 (dd, J = 10.1, 1.6 Hz, 1 H), 5.14 (d, J = 6.5 Hz, 1 H, hemiacetal), 4.97 (d, J = 4.8 Hz, 1 H, acetal), 4.23 (m, 2 H), 4.02 (s, 2 H), 3.53 (m, 1 H), 2.74 (d, J = 6.5 Hz, 1 H, OH), 2.51 (m, 1 H), 1.79–1.60 (m, 9 H), 1.68 (s, 3 H), 1.29–0.98 (m, 4 H), 1.06 (s, 9 H), 0.98 (d, J = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H); IR (neat) 3465 (broad), 1589 cm^{-1}; HRMS for $C_{38}H_{66}O_5Si_2$ ($M^+ - C_4H_9$) calcd 647.3573, found 647.3580.

To a −78 °C solution of oxalyl chloride (0.28 mL, 3.2 mmol) and DMSO (0.33 mL, 4.2 mmol) in anhydrous CH_2Cl_2 (20.0 mL) under N_2 was added the above hemiacetal (1.50 g, 2.13 mmol) as a solution in anhydrous CH_2Cl_2 (2.0 mL). This mixture was stirred for 30 min at −78 °C before Et_3N (1.34 mL, 9.6 mmol) was added. The reaction was allowed to warm to 25 °C over a 1-h period before being diluted with Et_2O (75 mL) and poured into 50% aqueous brine. The aqueous layer was separated and extracted with Et_2O (3 × 75 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (15:1 hexane–ether) produced 1.42 g (95%) of **32**: R_f 0.15 (20:1 hexane–ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4 H), 7.45–7.35 (m, 6 H), 5.38 (d, J = 10.0 Hz, 1 H), 5.32 (s, 1 H), 5.28 (d, J = 4.2 Hz, 1 H), 4.23 (A of AB, J_{AB} = 12.8 Hz, 1 H), 4.12 (B of AB, J_{BA} = 12.8 Hz, 1 H), 3.98 (s, 2 H), 3.47 (br d, J = 10.0 Hz, 1 H), 2.58 (m, 1 H), 2.17 (dd, J = 11.2, 7.8 Hz, 1 H), 1.82–1.61 (m, 8 H), 1.56 (s, 3 H), 1.32–1.06 (m, 4 H), 1.12 (d, J = 7.4 Hz, 3 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.03 (s, 6 H); IR ($CHCl_3$) 1781 cm^{-1}; HRMS for $C_{42}H_{62}O_5Si_2$ (parent ion) calcd 702.4119, found 702.4088.

Methyl (1*S*,2*S*,5*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]-1-hydroxy-5-methyl-2-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-3-cyclohexene-1-carboxylate (33). To a 0 °C solution of lactone **32** (1.40 g, 2.0 mmol) in anhydrous MeOH (20.0 mL, 0.1 M) under N_2 was added K_2CO_3 (0.27 g, 2.0 mmol). This mixture was stirred for 16 h at 25 °C before being diluted with EtOAc (75 mL) and washed with saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude material by silica gel chromatography (5:1 hexane–ether) produced 1.23 g of (−)-**33** as a white solid in 99% yield: mp 80–81 °C; R_f 0.16 (5:1 hexane–ether); $[\alpha]^{26}_D$ −37.8° (c = 4.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.45–7.34 (m, 6 H), 5.35 (br s, 1 H), 5.33 (br d, J = 10.2 Hz, 1 H), 4.24 (A of AB J_{AB} = 13.2 Hz, 1 H), 4.11 (B of AB, J_{BA} = 13.2 Hz, 1 H), 4.01 (s, 2 H), 3.74 (s, 3 H), 3.51 (br d, J = 10.2 Hz, 1 H), 2.78 (s, 1 H, OH), 2.54 (m, 1 H), 2.23 (dd, J = 13.5, 7.2 Hz, 1 H), 1.68 (dd, J = 13.5, 4.5 Hz, 1 H), 1.62 (s, 3 H), 1.13 (d, J = 7.4 Hz, 3 H), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); IR ($CHCl_3$) 3530, 1729, 1661 cm^{-1}; MS m/z 565 ($M^+ - C_4H_9$). Anal. Calcd for $C_{36}H_{54}O_5Si$: C, 69.40; H, 8.74. Found: C, 69.41; H, 8.80.

Enantiomeric Purity Determination of 33. To a 0 °C solution of **33** (50 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was slowly added a 1.0 M solution of DIBAL-H (0.24 mL, 0.24 mmol) in hexanes. This mixture was allowed to warm to 25 °C over a 1-h period before being poured into a 1:1 Et_2O and brine solution. The aqueous layer was separated and extracted with Et_2O (2 × 5 mL). The combined ethereal layers were dried over $MgSO_4$ and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (1:1 hexane–ether) provided 31 mg of the desired diol: R_f 0.10 (1:1 hexane–ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4 H), 7.44–7.36 (m, 6 H), 5.49 (dd, J = 5.4, 1.6 Hz, 1 H), 5.26 (dd, J = 10.1, 1.3 Hz, 1 H), 4.16 (A of AB, J_{AB} = 13.1 Hz, 1 H), 4.07 B of AB, J_{BA} = 13.1 Hz, 1 H, partially obscured), 4.07 (s, 2 H), 3.53 (s, 2 H), 3.24 (dd, J = 10.1, 5.4 Hz, 1 H), 2.32 (m, 1 H), 2.13 (br s, 1 H, OH), 1.97 (br s, 1 H, OH), 1.80 (dd, J = 13.1, 6.0 Hz, 1 H), 1.69 (s, 3 H), 1.42 (dd, J = 13.1, 11.0 Hz, 1 H), 1.04 (s, 9 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.91 (s, 9 H), 0.06 (s, 6 H). Solutions of this diol (25 mg, 0.04 mmol) in anhydrous CH_2Cl_2 (0.5 mL) under N_2 were treated with either (*S*)-(−)-MTPA-Cl or (*R*)-(+)-MTPA-Cl (13 μL, 0.06 mmol), Et_3N (18 μL, 0.13 mmol), and catalytic DMAP. The mixtures were diluted with Et_2O (2 mL) when judged complete by TLC analysis, and the resulting precipitates were filtered through glass wool. Concentration of the organic layers yielded the crude Mosher ester derivatives that were purified by preparative TLC (2:1 hexane–ether; the diastereomeric MTPA derivatives do not separate). The (*S*)-(−)-MTPA derivative **34** showed, among other, signals at δ 3.55 (s, 3 H), and 2.18 (m, 1 H). The (*R*)-(+)-MTPA derivative **35**, however, showed resonances only at δ 3.58 (s, 3 H), and 2.28 (m, 1 H), thus indicating the enantiomeric purity of optically active **115** to be ≥98% ee.

(2*S*,2*R*′,4*R*,5*S*)-Spiro[1-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2-methyl-5-[3-[(*tert*-butyldimethylsilyl)oxy]-2-methylprop-1-enyl]cyclohex-1-ene-4,5′-2′-cyclohexyl-1′,3′-dioxolan-4′-one] (37) from the Minor Exo Cycloadduct 29. A mixture of **29** (76 mg, 0.15 mmol) and DIBAL-H (0.60 mL, 0.60 mmol) in 1.5 mL of CH_2Cl_2 was stirred for 2 h at −30 °C. The reaction mixture was then diluted with saturated aqueous Rochelle's salt and extracted with Et_2O (3 × 10 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude diol (72 mg, 0.12 mmol) was treated with imidazole (21 mg, 0.31 mmol) and *tert*-butyldimethylsilyl chloride (25 mg, 0.17 mmol) in DMF (0.5 mL). After 16 h this mixture was dissolved in 1:1 hexane–Et_2O (10 mL) and washed with 50% aqueous brine (5 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by silica gel chromatography (15:1 hexane–ether as eluent: R_f 0.15) to give the intermediate silylated hemiacetal (57 mg, 0.08 mmol) as a 3:1 mixture of hemiacetal isomers. This material was added to a −78 °C solution of oxalyl chloride (11 μL, 0.12 mmol) and DMSO (12 μL, 0.16 mmol) in anhydrous CH_2Cl_2 (1.0 mL, 0.1 M). Et_3N (50 μL, 0.36 mmol) was added, and the reaction mixture was allowed to warm to 25 °C. The mixture was then diluted with 3:1 Et_2O and 50% aqueous brine (4 mL). The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (15:1 hexane–ether) produced 47 mg of **37**: R_f 0.27 (15:1 hexane–ether); +46.3° (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4 H), 7.45–7.35 (m, 6 H), 5.38 (br d, J = 10.2 Hz, 1 H), 5.34 (br s, 1 H), 5.23 (d, J = 5.6 Hz, 1 H), 4.22 (A of AB, J_{AB} = 12.9 Hz, 1 H), 4.10 (B of AB, J_{BA} = 12.9 Hz, 1 H), 3.99 (s, 2 H), 3.50 (br d, J = 10.2 Hz, 1 H), 2.54 (m, 1 H), 1.92 (d, J = 6.3 Hz, 2 H), 1.81–1.64 (m, 7 H), 1.62 (s, 3 H), 1.25–1.05 (m, 4 H), 1.08 (d, J = 7.3 Hz, 3 H), 1.05 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); IR ($CHCl_3$) 1793, 1588 cm^{-1}; HRMS for $C_{38}H_{53}O_5Si_2$ ($M^+ - C_4H_9$) calcd 645.3417, found 645.3428. Anal. Calcd for $C_{42}H_{62}O_5Si_2$: C, 71.74; H, 8.89. Found: C, 71.46; H, 8.73.

Methyl (1*R*,2*R*,5*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]-1-hydroxy-5-methyl-2-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-3-cyclohexene-1-carboxylate [(+)-33]. A 0 °C solution of lactone **37** (26 mg, 0.04 mmol) and K_2CO_3 (5 mg, 0.04 mmol) in anhydrous MeOH (0.5 mL, 0.1 M) was stirred for 16 h at 25 °C under N_2 and then was diluted with EtOAc (5 mL) and washed with saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude material by silica gel chromatography (5:1 hexane–ether) produced 18 mg (78%) of (+)-**33** ($[\alpha]^{26}_D$ +37.2° (c = 1.8, CH_2Cl_2)) which was identical in all respects except optical rotation to samples of (−)-**33** prepared from **28** as described above.

Diels–Alder Reaction of Triene 6 and (*R*)-8. A solution of **6** (2.75 g, 6.13 mmol) and freshly prepared dienophile (*R*)-**8**[16] (1.34 g, 8.58 mmol) in dry acetonitrile (6.0 mL, 1.0 M; neutralized with basic alumina) in a presilylated Carius tube was degassed with a stream of N_2. A crystal of BHT was added and the tube sealed. The tube was immersed in a 135–140 °C oil bath and stirred for 16 h. The cooled mixture was then concentrated in vacuo. The crude product consisted of a 92:8 ratio of **38**:**39** as determined by analysis of the olefinic region of the ^{1}H NMR spectrum. Separation of the mixture by silica gel chromatography (7:1 hexane–ether) yielded 2.38 g (64%) of exo cycloadduct **38** and 0.21 g (5%) of the endo isomer **39**.

Data for exo cycloadduct 38: R_f 0.25 (7:1 hexane–ether); $[\alpha]^{26}_D$ −79.0° (c = 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4 H), 7.47–7.38 (m, 6 H), 6.62 (dd, J = 10.9, 1.5 Hz, 1 H), 5.27 (br s, 1 H), 5.08 (s, 1 H), 4.24–4.15 (m, 4 H), 3.56 (br d, J = 10.9 Hz, 1 H), 2.62 (m, 1 H), 2.17 (dd, J = 14.5, 6.6 Hz, 1 H), 1.88 (s, 3 H), 1.82 (dd, J = 14.5, 2.2 Hz, 1 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.14 (d, J = 7.2 Hz, 3 H), 1.06 (s, 9 H), 0.94 (s, 9 H); IR (neat) 1792, 1721, 1645 cm^{-1}; HRMS for $C_{36}H_{48}O_6Si$ (parent ion) calcd 604.3207, found 604.3237. Anal. Calcd for $C_{36}H_{48}O_6Si$: C, 71.48; H, 8.00. Found: C, 71.74; H, 7.86.

Data for endo cycloadduct 39: R_f 0.21 (7:1 hexane–ether); $[\alpha]^{26}_D$ +145.7° (c = 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78–7.64 (m, 4 H), 7.46–7.31 (m, 6 H), 6.53 (dd, J = 10.4, 1.5 Hz, 1 H), 5.42 (dd, J = 5.1, 1.5 Hz, 1 H), 5.31 (s, 1 H), 4.26 (A of AB, J_{AB} = 13.7 Hz, 1 H), 4.20 (m, 2 H), 4.11 (B of AB, J_{BA} = 13.7 Hz, 1 H), 3.39 (dd, J = 10.4, 5.1 Hz, 1 H), 2.57 (m, 1 H), 1.86 (s, 3 H), 1.85 (d, J = 8.6 Hz, 2 H, partially obscured), 1.30 (t, J = 7.3 Hz, 3 H), 1.06 (d, J = 7.0 Hz, 3 H), 1.04 (s, 9 H), 0.98 (s, 9 H); IR (neat) 1790, 1718, 1681 cm^{-1}; HRMS for $C_{36}H_{48}O_6Si$ (parent ion) calcd 604.3207, found 604.3244. Anal. Calcd for $C_{36}H_{48}O_6Si$: C, 71.48; H, 8.00. Found: C, 71.19; H, 7.81.

DIBAL Reduction of Exo Cycloadduct 38: Preparation of (2*R*,2*R*′,4*S*,5*R*)-Spiro[1-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2-methyl-5-[3-[(*tert*-butyldimethylsilyl)oxy]-2-methylprop-1-enyl]cyclohex-1-ene-4,5′-2′-*tert*-butyl-1′,3′-dioxolan-4′-one] (41). A −50 °C solution of cycloadduct **38** (1.20 g, 1.98 mmol) in anhydrous CH_2Cl_2 (15 mL, 0.15 M) under N_2 was treated with a 1.0 M solution of DIBAL-H in CH_2Cl_2 (7.93 mL, 7.93 mmol). The mixture was stirred at −40 °C for 4 h before being poured into a 1:1 mixture of aqueous Rochelle's salt and Et_2O (50 mL). The reaction was then worked up by using the procedure described for the preparation of **31**. The crude product consisted of a 2.5:1 mixture (1.14 g) of diol **40** and a hydroxy lactone resulting from the selective reduction of the unsaturated ester unit of **38**. A small amount of this mixture (100 mg) was removed for purification and spectroscopic characterization of **40** (data obtained on a 3:1 hemiacetal mixture): R_f 0.23 (1:1 hexane–ether); $[\alpha]^{26}_D$ −87.7° (c = 0.9, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) (major hemiacetal) δ 7.73–7.64 (m, 4 H), 7.48–7.38 (m, 6 H), 5.48 (br s, 1 H), 5.38 (d, J = 10.4 Hz, 1 H), 5.27 (br s, 1 H, hemiacetal), 5.11 (s, 1 H, acetal), 4.24–4.10 (m, 2 H), 4.02 (s, 2 H), 3.48 (m, 1 H), 2.61 (m, 1 H), 2.16 (dd, J = 14.0, 7.1 Hz, 1 H), 1.81 (d, J = 14.0 Hz, 1 H), 1.69 (s, 3 H), 1.48 (br s, 2 H), 1.07 (d, J = 7.1 Hz, 3 H), 1.04 (s, 9 H), 0.98 (s, 9 H); ^1H NMR (400 MHz, $CDCl_3$) (minor hemiacetal), 7.73–7.64 (m, 4 H), 7.48–7.38 (m, 6 H), 5.50 (br s, 1 H), 5.32 (d, J = 9.9 Hz, 1 H), 4.96 (br s, 1 H, hemiacetal), 4.56 (s, 1 H, acetal), 4.24–4.10 (m, 2 H), 4.01 (s, 2 H), 3.18 (m, 1 H), 2.60 (m, 1 H), 1.87 (dd, J = 13.7, 3.7 Hz, 2 H), 1.77 (s, 3 H), 1.50 (br s, 2 H), 1.02 (s, 9 H), 1.00 (d, J = 7.0 Hz, 3 H), 0.98 (s, 9 H); IR (neat) 3445 (br) cm^{-1}; HRMS for $C_{34}H_{49}O_5Si$ (M^+ + H) calcd 565.3336, found 565.3390. Anal. Calcd for $C_{34}H_{48}O_5Si$: C, 72.30; H, 8.56. Found: C, 71.99; H, 8.29.

To a 0 °C solution of the above mixture containing diol **40** (1.04 g, 1.90 mmol) in anhydrous DMF (4.0 mL, 0.5 M) was added imidazole (0.32 g, 4.75 mmol) and *tert*-butyldimethylsilyl chloride (0.36 g, 2.37 mmol) under N_2. This mixture was stirred for 16 h at 25 °C before being diluted with 1:1 hexane–Et_2O (200 mL) and 50% aqueous brine (100 mL). The aqueous layer was separated and extracted with 1:1 hexane–Et_2O (2 × 75 mL). The combined organic extracts were dried over $MgSO_4$, concentrated in vacuo, and purified by silica gel chromatography (15:1 hexane–ether), giving 0.75 g (59%) of the intermediate hemiacetal mono-TBDMS ether and 0.42 g (33%) of lactone **41** (92% combined yield from **38**). Data for the mono-TBDMS ether intermediate (obtained on a 3:1 hemiacetal mixture): R_f 0.26 (5:1 hexane–ether); $[\alpha]^{26}_D$ −78.5° (c = 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) (major hemiacetal) δ 7.69–7.60 (m, 4 H), 7.48–7.31 (m, 6 H), 5.60 (br s, 1 H), 5.36 (d, J = 10.1 Hz, 1 H), 5.18 (br s, 1 H, hemiacetal), 5.01 (s, 1 H, acetal), 4.26 (m, 2 H), 4.01 (s, 2 H), 3.62 (m, 1 H), 2.64 (m, 1 H), 2.18 (dd, J = 14.1, 6.9 Hz, 1 H), 1.84–1.70 (m, 2 H), 1.69 (s, 3 H), 1.08 (s, 9 H), 1.01 (d, J = 7.1 Hz, 3 H), 0.92–0.90 (br s, 18 H), 0.02 (s, 6 H); ^1H NMR (300 MHz, $CDCl_3$) (minor hemiacetal) δ 7.69–7.60 (m, 4 H), 7.48–7.31 (m, 6 H), 5.62 (br s, 1 H), 5.40 (d, J = 10.1 Hz, 1 H), 4.98 (br s, 1 H, hemiacetal), 4.58 (s, 1 H, acetal), 4.26 (m, 2 H), 4.01 (s, 2 H), 3.18 (m, 1 H), 2.64 (m, 1 H), 1.84–1.70 (m, 3 H), 1.69 (s, 3 H), 1.08 (s, 9 H), 0.99 (d, J = 7.1 Hz, 3 H), 0.92–0.90 (br s, 18 H), 0.02 (s, 6 H); IR (neat) 3450 (br) cm^{-1}; HRMS for $C_{40}H_{62}O_5Si_2$ (parent ion) calcd 678.4119, found 678.4187.

To a −78 °C solution of oxalyl chloride (0.15 mL, 1.66 mmol) and DMSO (0.17 mL, 2.22 mmol) in anhydrous CH_2Cl_2 (12.0 mL, 0.1 M) under N_2 was added the above hemiacetal (0.73 g, 1.11 mmol) in anhydrous CH_2Cl_2 (1.0 mL). This mixture was stirred at −78 °C for 30 min before Et_3N (0.70 mL, 5.0 mmol) was added. The mixture was allowed to warm to 25 °C over a 1-h period and then was diluted with Et_2O (50 mL) and poured into 1:1 H_2O and brine. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (15:1 hexane–ether) produced 0.64 g (88%; total yield of 85% from **38**) of **41**: R_f 0.29 (15:1 hexane–ether); $[\alpha]^{26}_D$ −70.7° (c = 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.69 (m, 4 H), 7.44–7.38 (m, 6 H), 5.41 (dd, J = 10.9, 1.4 Hz, 1 H), 5.31 (br s, 1 H), 5.14 (s, 1 H), 4.23 (A of AB, J_{AB} = 12.8 Hz, 1 H), 4.11 (B of AB, J_{BA} = 12.8 Hz, 1 H), 3.99 (s, 2 H), 3.48 (d, J = 10.9 Hz, 1 H), 2.58 (m, 1 H), 2.16 (dd, J = 13.9, 7.2 Hz, 1 H), 1.77 (dd, J = 13.9, 1.3 Hz, 1 H), 1.60 (s, 3 H), 1.13 (d, J = 7.3 Hz, 3 H), 1.05 (s, 9 H), 0.92 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); IR ($CHCl_3$) 1792, 1588 cm^{-1}; HRMS for $C_{40}H_{61}O_5Si_2$ (M^+ + H) calcd 677.4041, found 677.4090.

Methyl (1*S*,2*S*,5*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]-1-hydroxy-5-methyl-2-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-3-cyclohexene-1-carboxylate [(−)-33] from 41. A solution of **41** (1.04 g, 1.6 mmol) and K_2CO_3 (0.22 g, 1.6 mmol) in anhydrous MeOH (16.0 mL, 0.1 M) was stirred under N_2 for 16 h at 25 °C, diluted with EtOAc (50 mL), and washed with saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude material by silica gel chromatography (5:1 hexane–ether) produced 0.88 g (89%) of (−)-**33** as a white solid.

Reduction of Endo Cycloadduct 39 and Preparation of (2*S*,2*R*′,4*S*,5*S*)-Spiro[1-[[(*tert*-butyldiphenylsilyl)oxy]-methyl]-2-methyl-5-[3-[(*tert*-butyldimethylsilyl)oxy]-2-methylprop-1-enyl]cyclohex-1-ene-4,5′-2′-*tert*-butyl-1′,3′-dioxolan-4′-one] (42). A mixture of **39** (0.30 g, 0.50 mmol) and DIBAL-H (1.24 mL, 1.24 mmol) in 3.3 mL of CH_2Cl_2 was stirred at −35 °C for 3 h before being quenched with saturated aqueous Rochelle's salt and extracted with Et_2O (3 × 25 mL). The combined ethereal extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude diol (0.27 g, 1.24 mmol) was then treated with imidazole (84 mg, 1.25 mmol) and *tert*-butyldimethylsilyl chloride (93 mg, 0.63 mmol) in DMF (1.5 mL). After 16 h this mixture was partitioned between 1:1 hexane–Et_2O (25 mL) and 50% aqueous brine (10 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo, and purified by silica gel chromatography (15:1 hexane–ether) to give the mono-TBDMS ether (145 mg, 45% from **39**) along with 71 mg (22%) of bis-TBDMS ether resulting from overprotection of the hemiacetal intermediate.

The mono-TBDMS ether (120 mg, 0.18 mmol) was added to a −78 °C solution of oxalyl chloride (25 μL, 0.27 mmol) and DMSO (28 μL, 0.37 mmol) in anhydrous CH_2Cl_2 (1.0 mL, 0.1 M). Et_3N (115 μL, 0.82 mmol) was added, and the reaction was warmed to 25 °C and partitioned between 3:1 Et_2O and 50% aqueous brine (8 mL). The aqueous layer was separated and extracted with Et_2O (3 × 5 mL). The combined ethereal layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (15:1 hexane–ether) produced 98 mg (83%) of **42**: R_f 0.42 (10:1 hexane–ether); $[\alpha]_D$ +86.7° (c = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4 H), 7.46–7.32 (m, 6 H), 5.44 (br d, J = 4.9 Hz, 1 H), 5.30 (s, 1 H), 5.22 (d, J = 10.2 Hz, 1 H), 4.25 (A of AB, J_{AB} = 13.2 Hz, 1 H), 4.07 (B of AB, J_{BA} = 13.2 Hz, 1 H), 4.01 (s, 2 H), 3.34 (dd, J = 10.2, 4.9 Hz, 1 H), 2.56 (m, 1 H), 1.82 (dd, J = 10.9, 6.2 Hz, 1 H), 1.76 (dd, J = 13.5, 10.9 Hz, 1 H), 1.62 (s, 3 H), 1.06 (d, J = 7.2 Hz, 3 H), 1.04 (s, 9 H), 0.97 (s, 9 H), 0.90 (s, 9 H), 0.05 (s, 6 H); IR ($CHCl_3$) 1796, 1589 cm^{-1}; HRMS for $C_{36}H_{51}O_5Si_2$ ($M^+ - C_4H_9$) calcd 619.3261, found 619.3327. Anal. Calcd for $C_{40}H_{60}O_5Si_2$: C, 70.95; H, 8.93. Found: C, 70.78; H, 8.86.

Methyl (1*S*,2*R*,5*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]-methyl]-1-hydroxy-5-methyl-2-[2′-methyl-3′-[(*tert*-butyl-

dimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-3-cyclohexene-1-carboxylate (43). A solution of endo lactone **42** (70 mg, 0.11 mmol) and K_2CO_3 (15 mg, 0.11 mmol) in anhydrous MeOH (1.0 mL, 0.1 M) was stirred under N_2 for 16 h at 25 °C and then was diluted with EtOAc (10 mL) and washed with saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification of the crude product by silica gel chromatography (5:1 hexane–ether) produced 56 mg (85%) of **43**: R_f 0.21 (3:1 hexane–ether); $[\alpha]^{26}_D$ +122.7 (*c* = 3.3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.66 (m, 4 H), 7.44–7.35 (m, 6 H), 5.51 (d, *J* = 5.1 Hz, 1 H), 5.04 (dd, *J* = 10.3, 1.4 Hz, 1 H), 4.22 (A of AB, J_{AB} = 13.4 Hz, 1 H), 4.13 (B of AB, J_{BA} = 13.4 Hz, 1 H), 3.95 (s, 2 H), 3.66 (s, 3 H), 3.14 (dd, *J* = 10.3, 5.1 Hz, 1 H), 2.71 (br s, 1 H, OH), 2.49 (m, 1 H), 1.92 (dd, *J* = 11.0, 5.8 Hz, 1 H), 1.75 (dd, *J* = 13.7, 11.0 Hz, 1 H), 1.61 (s, 3 H), 1.05 (s, 9 H), 1.01 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H); IR ($CHCl_3$) 3495, 1729, 1588 cm^{-1}; HRMS for $C_{36}H_{54}O_5Si_2$ (parent ion) calcd 622.3549, found 622.3537.

Methyl (1*S*,2*R*,5*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-hydroxy-5-methyl-2-[2′-methyl-2′-(methoxycarbonyl)-1′(*E*)-ethen-1′-yl]-3-cyclohexene-1-carboxylate (44). To a 25 °C solution of **30** (44 mg, 0.63 mmol) in anhydrous EtOH (0.5 mL) under N_2 was added K_2CO_3 (8 mg, 0.06 mmol). This mixture was stirred for 16 h before being diluted with EtOAc (10 mL) and washed with brine. The aqueous layer was separated and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude mixture by silica gel chromatography (2:1 hexane–ether) provided 18 mg (51%) of **44** along with recovered **30** (18 mg). Data for **44**: R_f 0.27 (2:1 hexane–ether); $[\alpha]^{26}_D$ +187.5° (*c* = 0.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4 H), 7.46–7.35 (m, 6 H), 6.40 (dd, *J* = 10.7, 1.3 Hz, 1 H), 5.46 (dd, *J* = 3.5, 1.6 Hz, 1 H), 4.23–4.08 (m, 6 H), 3.20 (dd, *J* = 10.2, 4.8 Hz, 1 H), 3.01 (br, 1 H, OH), 2.53 (m, 1 H), 1.92 (ddd, *J* = 10, 5.6, 1.1 Hz, 1 H), 1.85 (d, *J* = 1.3 Hz, 3 H), 1.82 (dd, *J* = 9.5, 2.4 Hz, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.22 (t, *J* = 7.0 Hz, 3 H), 1.04 (s, 9 H), 1.02 (d, *J* = 7.2 Hz, 3 H); IR (neat) 3500 (br), 1730 (shoulder), 1715, 1645 cm^{-1}; HRMS for $C_{33}H_{44}O_6Si$ (parent ion) calcd 564.3986, found 564.3931. Anal. Calcd for $C_{33}H_{44}O_6Si$: C, 70.17; H, 7.85. Found: C, 69.69; H, 7.75.

Methyl (1*S*,2*S*,5*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-acetoxy-5-methyl-2-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′yl]-3-cyclohexene-1-carboxylate (5). A 25 °C solution of (−)-**33** (110 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (1.0 mL, 0.2 M) under N_2 was treated with Et_3N (0.15 mL, 1.06 mmol), DMAP (0.005 g, 0.02 mmol), and acetic anhydride (0.07 mL, 0.70 mmol). The reaction mixture was stirred for 16 h before being diluted with Et_2O (25 mL) and H_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel chromatography (5:1 hexane–ether) to give 118 mg (98%) of **5**: R_f 0.22 (5:1 hexane–ether); $[\alpha]^{26}_D$ −100.2° (*c* = 2.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.72–7.66 (m, 4 H), 7.46–7.35 (m, 6 H), 5.44 (br d, *J* = 5.1 Hz, 1 H), 5.25 (dd, *J* = 11.8, 2.0 Hz, 1 H), 4.19 (A of AB, J_{AB} = 14.0 Hz, 1 H), 4.04 (B of AB, J_{BA} = 14.0 Hz, 1 H), 4.00 (m, 1 H), 3.99 (s, 2 H), 3.71 (s, 3 H), 2.36 (m, 1 H), 2.18 (dd, *J* = 12.8, 5.4 Hz, 1 H), 1.97 (s, 3 H), 1.91 (dd, *J* = 12.8, 10.2 Hz, 1 H), 1.56 (s, 3 H), 1.06 (br s, 12 H), 0.90 (s, 9 H), 0.05 (s, 6 H); IR (neat) 1751, 1738, 1589 cm^{-1}; MS *m/z* 607 ($M^+ - C_4H_9$). Anal. Calcd for $C_{38}H_{56}O_6Si_2$: C, 68.54; H, 8.49. Found: C, 68.12; H, 8.49.

(5*S*,6*S*,9*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(methoxymethoxy)-6-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-1-oxaspiro[4.5]deca-3,7-dien-2-one (4). To a −78 °C solution of **5** (63 mg, 0.095 mmol) and HMPA (0.33 mL, 1.90 mmol) in anhydrous THF (1.0 mL, 0.1 M) was slowly added a 1.0 M solution of lithium hexamethyldisilazide (0.22 mL, 0.22 mmol) in THF. This reaction mixture was allowed to warm to 23 °C over a 1-h period, stirred for 15 min, and then treated with MOM-Cl (0.02 mL, 0.24 mmol). This mixture was stirred for 30 min and then was diluted with Et_2O (10 mL) and saturated aqueous NH_4Cl. The aqueous layer was separated and extracted with Et_2O (2 × 10 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude product by silica gel chromatography (2:1 hexane–ether as eluent) produced 55 mg (86%) of **4**: R_f 0.28 (2:1 hexane–ether); $[\alpha]^{26}_D$ −23.9° (*c* = 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4 H), 7.48–7.36 (m, 6 H), 5.33 (br s, 1 H), 5.18 (br d, *J* = 10.4 Hz, 1 H), 5.12 (s, 1 H), 5.09 (t, *J* = 5.7 Hz, 2 H), 4.18 (q, *J* = 13.2 Hz, 2 H), 3.96 (s, 2 H), 3.46 (s, 3 H), 3.45 (br s, 1 H, partially obscured), 2.62 (br dq, *J* = 7.4, 7.4 Hz, 1 H), 2.28 (dd, *J* = 14.1, 7.4 Hz, 1 H), 1.67 (d, *J* = 14.1 Hz, 1 H), 1.56 (s, 3 H), 1.16 (d, *J* = 7.4 Hz, 3 H), 1.06 (s, 9 H), 0.86 (s, 9 H), 0.02 (s, 6 H); IR (neat) 1760, 1635, 1590 cm^{-1}; MS *m/z* 519 ($M^+ - C_4H_9$). Anal. Calcd for $C_{39}H_{56}O_6Si_2$: C, 69.11; H, 8.34. Found: C, 68.81; H, 8.42.

Methyl (1*S*,2*S*,5*R*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-1-acetoxy-5-methyl-2-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-3-cyclohexene-1-carboxylate (46). A 25 °C solution of endo cycloadduct derived alcohol **43** (33 mg, 0.05 mmol) in anhydrous CH_2Cl_2 (0.5 mL, 0.1 M) was treated with Et_3N (44 μL, 0.32 mmol), DMAP (1 mg, 0.005 mmol), and acetic anhydride (23 μL, 0.21 mmol). The mixture was stirred under N_2 for 16 h, diluted with Et_2O (5 mL), and washed with H_2O (1 mL). The aqueous layer was extracted with Et_2O (2 × 10 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by silica gel chromatography (5:1 hexane–ether), giving 35 mg (97%) of **46**: R_f 0.18 (5:1 hexane–ether); $[\alpha]^{26}_D$ +98.5° (*c* = 1.8, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4 H), 7.45–7.36 (m, 6 H), 5.40 (d, *J* = 5.0 Hz, 1 H), 5.02 (dd, *J* = 10.4, 1.1 Hz, 1 H), 4.26 (A of AB, J_{AB} = 12.9 Hz, 1 H), 4.06 (B of AB, J_{BA} = 12.9 Hz, 1 H), 3.94 (s, 2 H), 3.62 (s, 3 H), 3.35 (dd, *J* = 10.4, 5.0 Hz, 1 H), 2.59 (dd, *J* = 11.8, 5.6 Hz, 1 H), 2.27 (m, 1 H), 2.06 (s, 3 H), 1.76 (dd, *J* = 13.2, 11.8 Hz, 1 H), 1.58 (s, 3 H), 1.05 (d, *J* = 7.5 Hz, 3 H), 1.04 (s, 9 H), 0.89 (s, 9 H), 0.04 (s, 6 H); IR (neat) 1740 (br), 1588 cm^{-1}; HRMS for $C_{38}H_{56}O_6Si_2$ (parent ion) calcd 664.3600, found 664.3608. Anal. Calcd for $C_{38}H_{56}O_6Si_2$: C, 68.54; H, 8.49. Found: C, 68.33; H, 8.47.

(5*S*,6*R*,9*S*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(methoxymethoxy)-6-[2′-methyl-3′-[(*tert*-butyldimethylsilyl)oxy]-1′(*E*)-propen-1′-yl]-1-oxaspiro[4.5]deca-3,7-dien-2-one (47). A −78 °C solution of acetate **46** (20 mg, 0.03 mmol) and HMPA (105 μL, 0.60 mmol) in anhydrous THF (300 μL, 0.1 M) was treated with a 1.0 M THF solution of lithium hexamethyldisilazide (78 μL, 0.075 mmol). The mixture was allowed to warm to room temperature over 1 h, was stirred for an additional 15 min, and then was treated with MOM-Cl (7 μL, 0.09 mmol). This mixture was worked up by using the procedure described for the synthesis of **4**. Purification of the crude material by silica gel chromatography (2:1 hexane–ether) produced 16 mg (80%) of **47**: R_f 0.24 (1:1 hexane–ether); $[\alpha]^{26}_D$ +101.8° (*c* = 1.15, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.65 (m, 4 H), 7.45–7.37 (m, 6 H), 5.53 (dd, *J* = 5.0, 1.6 Hz, 1 H), 5.28 (dd, *J* = 9.8, 1.3 Hz, 1 H), 5.15 (s, 1 H), 5.03 (s, 2 H), 4.15 (q, *J* = 13.5 Hz, 2 H), 3.97 (s, 2 H), 3.40 (s, 3 H), 3.16 (dd, *J* = 9.8, 5.0 Hz, 1 H), 2.65 (m, 1 H), 1.81 (d, *J* = 8.6 Hz, 2 H), 1.57 (s, 3 H), 1.04 (s, 9 H), 1.02 (d, *J* = 7.0 Hz, 3 H), 0.90 (s, 9 H), 0.04 (s, 6 H); IR (neat) 1761, 1628, 1589 cm^{-1}; HRMS for $C_{39}H_{56}O_6Si_2$ (parent ion) calcd 676.3600, found 676.3669. Anal. Calcd for $C_{39}H_{56}O_6Si_2$: C, 69.11; H, 8.34. Found: C, 69.40; H, 8.09.

Acknowledgment. This research was supported by a grant from the National Institute of General Medical Sciences (GM 26782). We also thank Dr. John C. Huffman for performing the X-ray structure analysis of **33**.

Supplementary Material Available: Copies of the ^1H NMR spectra of **20**, **26**, **29**, **30**, **32**, **41**, and **43** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.