# Total Syntheses of Epothilones B and D

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Total syntheses of the microtubule stabilizing antitumor drugs epothilone B and D are described, starting from optically pure (*S*)-malic acid and methyl (*R*)-3-hydroxy-2-methylpropionate. The synthesis is highly convergent by coupling the three fragments C1−C6 (fragment **D**), C7−C10 (fragment **C**), and C11−C21 (fragment **B**). Key steps are two stereoselective Wittig type olefinations to generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama aldol addition to synthesize fragment **D**, and a sulfone anion allyl iodide alkylation to connect fragments **B** and **C**. Finally fragment **D** was attached to the **B** + **C** fragment via aldol addition.

## Introduction

Paclitaxel (Taxol) is clinically successful as a novel drug for the chemotherapy of ovarian carcinomas. It is also in clinical trials for the treatment of lung, head, neck, and other cancers. Unfortunately, paclitaxel is not an ideal drug for several reasons, e.g. multidrug resistance, poor bioavailability, and several serious side effects.[1] As a consequence, new anticancer agents that also function by microtubule stabilization but avoid some of the problems of taxol are currently of great interest. Of these potential post-paclitaxel agents (Figure 1), the epothilones A (**1**) and B (**2**) **(**Figure 2), first isolated and characterized by Höfle and co-workers, have advanced the furthest and several total syntheses of **1** and **2** as well as numerous derivatives thereof have been reported.[2]

The evaluation of a broad range of in vitro tests initially showed epothilone B (**2**) to be a potential paclitaxel successor. However, recent in vivo tests with nude mice have shown 12,13-desoxyepothilone B (=epothilone D, **4**) to be the best candidate of the epothilone family with respect to further development. For instance, the superiority of **4** over **2** is impressively borne out by the results of in vivo tests with normal athymic nude mice bearing human mammary adenocarcinoma MX-1 xenografts. When a daily dose of 0.6 mg/kg of **2** was applied intraperitonally (ip) to normal nude mice all the mice died within 7 days. When however 25 mg/kg of **4** was applied ip, all the mice survived. More importantly, **2** had only a marginal therapeutic effect, whereas **4** led to a drastic reduction of the tumor size, so that one out of six mice was without a detectable tumor after 35 days. When tumor therapy combined with low toxicity is considered, **4** is superior not only to **2** but also to paclitaxel and other antitumor drugs, such as adriamycin. It has also been demonstrated that, again in the nude mice test, **4** is curative for human tumor xenografts that are refractory to paclitaxel.[3]

In contrast to **2**, the desoxy compound **4** is not readily available from fermentation, nor can it be prepared in reasonable yield by partial synthesis from **2**, i.e., by deoxygenation of the epoxide.[4] This means that an efficient total synthesis of **4** is of the essence, which should be flexible enough to ensure a ready access to other interesting members of the epothilone family. In this paper we give a full account of our synthesis of **2** and **4** and we also attempt to outline the history how our approach has evolved.

## Results and Discussion

**First Generation Approach.** A strategy common to all syntheses reported so far is to dissect the carbon skeleton into two or three fragments. Our first synthetic plan envisaged disconnection at the C10−C11 bond to form the fragments **A** and **B** which could be connected by a sulfone alkylation with subsequent reductive desulfonylation (Figure 3). The preparation of fragment **A** (Scheme 1) was started with an aldol reaction between the known aldehyde **6**[5] **(**providing C7−C9**)** and Mori's ketone **5**[6] **(**providing C3−C6**)**, which should preferentially lead to a syn arrangement of the 6-Me and the 7-OH function. The relative stereochemistry of the 7-OH and the 8-Me was not clear at the beginning, but we hoped that by means of chelate formation in the transition state this would be anti as desired.[7,8] Indeed, alcohols **7a,b** were formed in a ratio of 4:1, and after chromatographic separation, the synthesis was continued with the main diastereoisomer **7a** whose 1,3-diol function was protected as PMP-acetal to form intermediate **8**. Carbons C1−C3 were introduced via ozonolysis of the terminal double bond to deliver the aldehyde, which was without isolation

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(1) Landino, L. M.; MacDonald, T. L. In *The Chemistry and Pharmacology of Taxol and its Derivatives*; Farin, V.; Ed.; Elsevier: New York, 1995; Chapter 7.

(2) Reviews: (a) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem.* **1998**, *110*, 2121−2153; *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2014−2045. (b) Mulzer, J. *Chem. Mon.* **2000**, *131*, 205−238.

(3) Chou, T. C.; Zhang, X. G.; Harris, C. R.; Kuduk, S.; Balog, A.; Savin, K. A.; Bertino, J. R.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15798.

(4) Bristol Myers Squibb Co., Int. Patent Application Number PCT/US98/12550, Int. Publication Number WO 99/02514, 1999.

(5) Walkup, R. D.; Boatman, P. D.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett.* **1990**, *31*, 7587−7590.

(6) Mori, I.; Ishihara, K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 1114−1117.

(7) Reetz, M. *Angew. Chem.* **1984**, *96*, 542−555; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556−569.

(8) This C6−C7 aldol type addition was first reported by our group[9a] and has been used in analogous[9b] and modified forms by others.[2]

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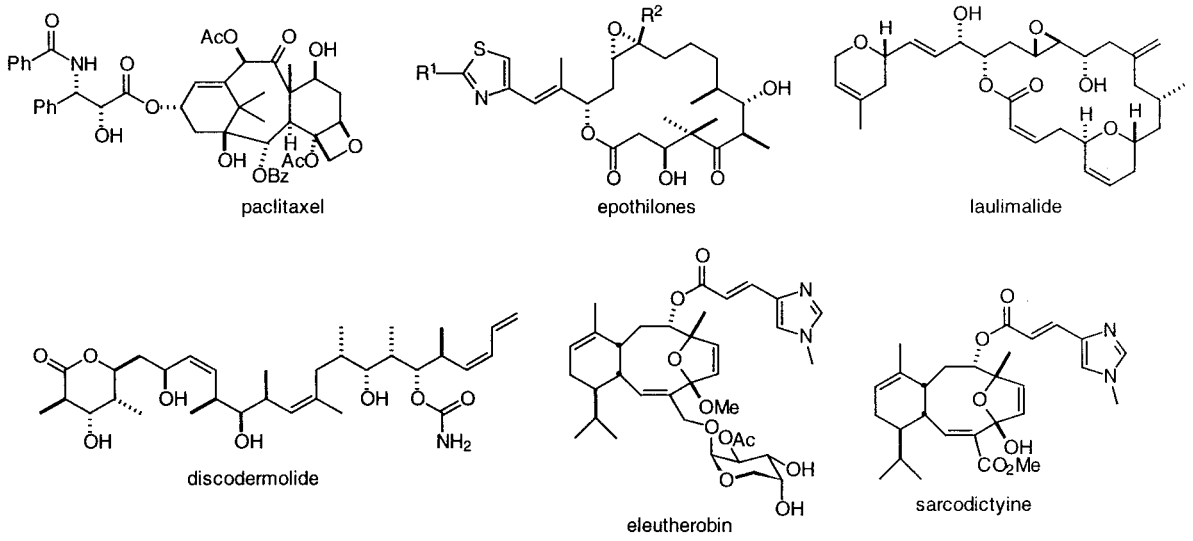
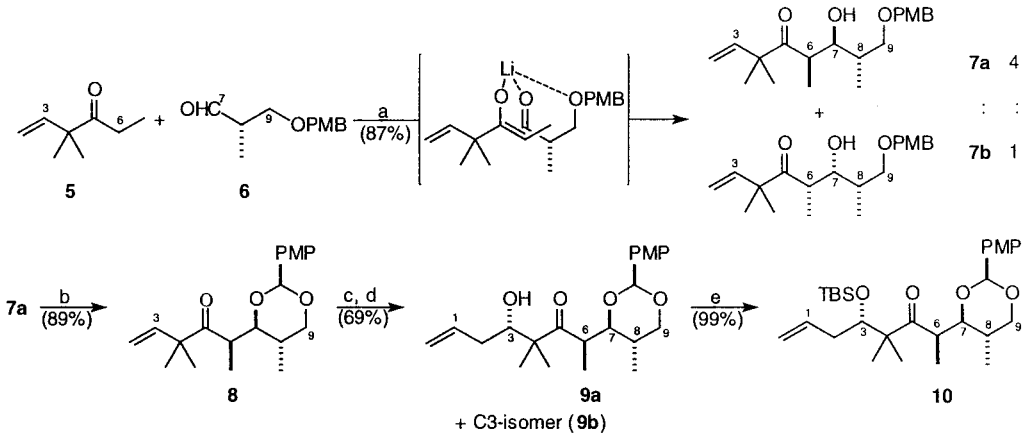



**Figure 1.**

**Scheme 1**




[a] Reagents and conditions: (a) **5**, LDA, −90 °C, 30 min, then **6**, 15 min, THF (87%, 4:1); (b) DDQ, 4 Å molecular sieves, −20 °C, rt (room temperature), 2 h, $CH_2Cl_2$ (89%); (c) $O_3$, −78 °C, rt, $Me_2S$ workup, $CH_2Cl_2$/MeOH (20:1) (93%); (d) (+)-Allyl-B(Ipc)$_2$, −78 °C, 1 h, $Et_2O$, oxidative workup (74%); (e) TBSOTf, 2,6-lutidine, 0 °C, 2 h, $CH_2Cl_2$ (99%).

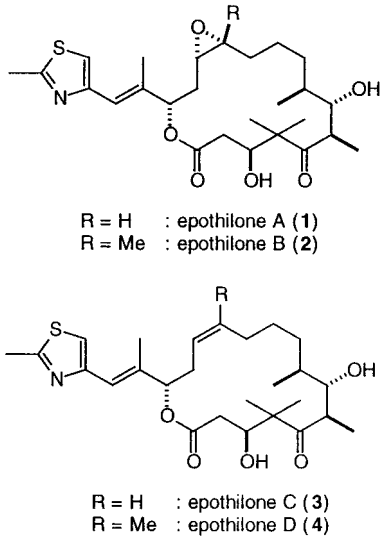



**Figure 2.**

subjected to an asymmetric Brown allylation to give the allylic alcohols **9a,b** in a 4:1 ratio. The main diastereoisomer **9a** was protected as the TBS-ether **10**.[9]

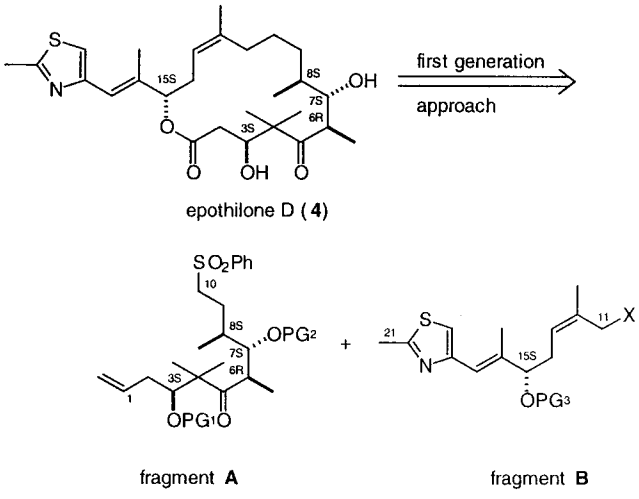
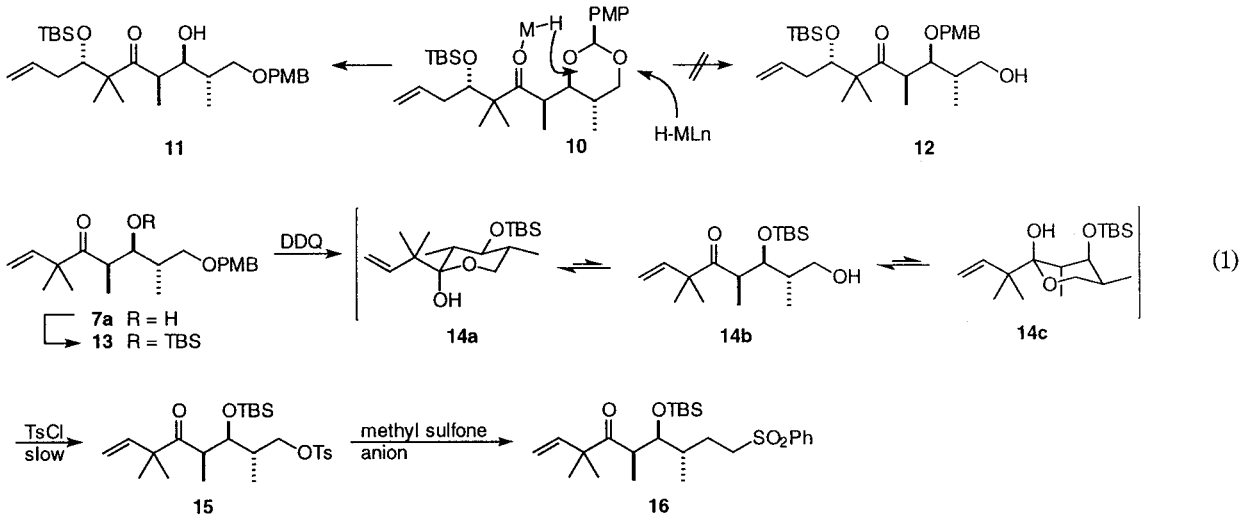
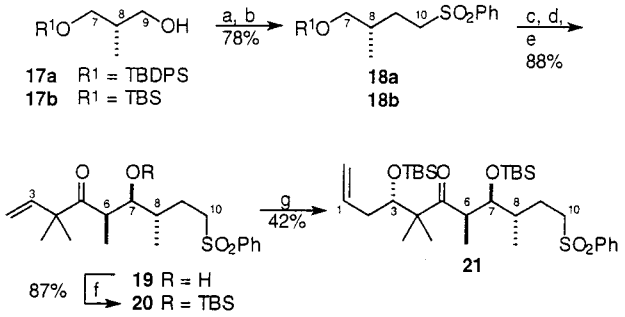



**Figure 3.**

Next we tried to selectively open the PMP acetal with DIBALH at the less hindered position to liberate the C9−OH group for further manipulation (eq 1). However, the reduction furnished regioisomer **11** exclusively, presumably due to an internal delivery of the hydride to C7−




**Scheme 2**

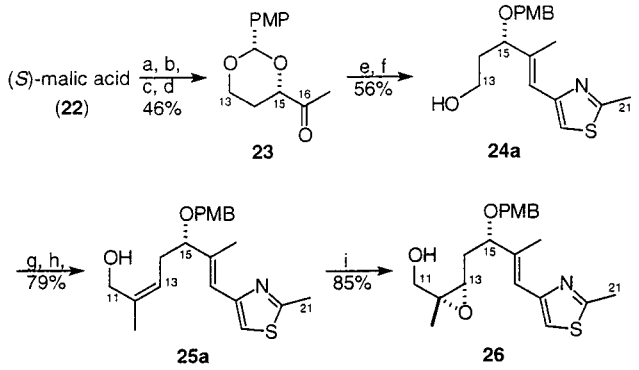



[a] Reagents and conditions: (a) TsCl (2 equiv), 0 °C, 1 h, pyridine; (b) methyl phenyl sulfone (1.5 equiv), *n*-BuLi, −20 °C, 12 h (96%); (c) TBAF, rt, 10 h, THF (88%); (d) Swern oxidation; (e) **5** (1.5 equiv), LDA, −78 °C, 25 min, then aldehyde, 5 min, THF (88%, 4:1 for the desired syn diastereoisomer **19**); (f) TBSOTf (2 equiv), 2,6-lutidine, −20 °C, 0 °C, 4 h, $CH_2Cl_2$ (87%); (g) (i) $O_3$, −78 °C, rt, $CH_2Cl_2$/MeOH (20:1), $Ph_3P$ workup (98%), (ii) (+)-Allyl-B(Ipc)$_2$, −78 °C, 1 h, $Et_2O$, oxidative workup (53%), (iii) TBSOTf (2 equiv), 2,6-lutidine, −20 °C, rt, 5 h, $CH_2Cl_2$ (96%).

OR via a carbonylaluminum complex. We therefore continued with alcohol **7a**, whose C7−OH was silylated to **13**, and the PMB protective group was removed oxidatively to furnish the alcohol **14**. Due to the fact that the open chain isomer **14b** coexisted as a minor component in an equilibrium mixture with cyclic hemiacetals **14a** and **14c**, tosylation of the primary OH function was extremely slow. So we abandoned this approach and restarted our synthesis with the known alcohol **17**[10] (Scheme 2), which was tosylated and alkylated with methyl phenyl sulfone anion to furnish sulfone **18** in 78% overall yield. Oxidation to the aldehyde and aldol addition with ketone **5** provided adduct **19** with 4:1-diastereoselectivity. Ozonolysis and Brown allylation followed by TBS protection led to the C1−C10 fragment **21**.

For the synthesis of the C11−C21 segment **B**, (*S*)-malic acid (**22**) was converted via the 1-methyl ester and (*S*)-(−)-methyl 2,4-dihydroxybutyrate[11] into ketone **23**. For the Wittig olefination we first tried (2-methylthiazol-4-yl)methyltriphenylphosphonium chloride, which afforded

**Scheme 3**




[a] Reagents and conditions: (a) TFAA, then MeOH; (b) $BH_3$·THF, (c) 4-$MeOC_6H_4CH(OMe)_2$, CSA, reflux, 6 h, toluene (53% yield for these three steps); (d) MeLi, −100 °C, 2 h, THF (86%); (e) (2-methylthiazol-4-yl)methyltriphenylphosphonium chloride, NaHMDS, −78 °C, then **23**, 40 °C, 1 h, THF (95%, *E*/*Z* = 3.6:1); (f) DIBALH (4 equiv), $CH_2Cl_2$, 4 h, −20 °C (89%, 5.6:1 for the desired regioisomer **24**); (g) (i) Swern oxidation, then (ii) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2Et$, KHMDS, 18-crown-6, −78 °C, 1 h, THF (86%, *Z*/*E* = 15:1); (h) DIBALH (3.5 equiv), −20 °C, 3 h, THF (98%); (i) D-(−)-diisopropyl tartrate, $Ti(OiPr)_4$, 4 Å molecular sieves, *tert*-BuOOH, −30 °C, 3 d, $CH_2Cl_2$ (95%, 8.5:1).

the desired (*E*)-olefin with a selectivity of 3.6:1. The cyclic acetal was regioselectively (5.6:1) opened to liberate the terminal hydroxyl group. Compound **24** was oxidized and immediately subjected to a (*Z*)-selective Wadsworth−Horner−Emmons olefination under Still−Gennari conditions[12] (86%, *Z*/*E* = 15:1). Reduction of the ester with DIBALH furnished the allylic alcohol **25a** which was used as a model system for asymmetric epoxidation under Sharpless conditions.[13] Although the compound **25a** bears a trisubstituted double bond with a *Z* configuration, the epoxide **26** was obtained in 95% yield and 8.5:1 diastereoselectivity (Scheme 3).[14]

(9) (a) Thomas, E. J.; Whitehead, J. W. F. *J. Chem Soc., Perkin Trans.1* **1989**, 507−518. (b) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *36*, 3455−3458.

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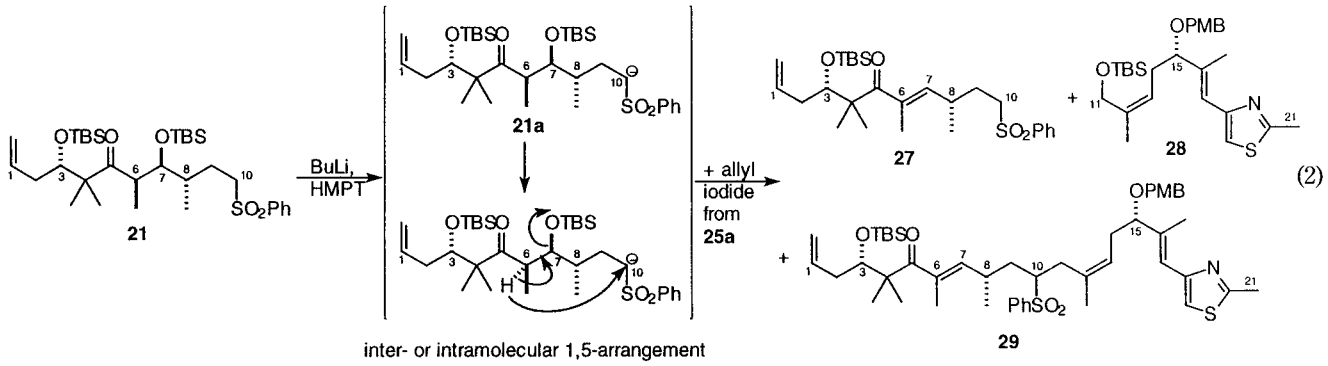



For the crucial C10−C11 coupling, the allylic alcohol **25a** was converted into the allyl iodide and treated with the lithium salt of **21** (eq 2). However, none of the desired diastereomeric coupling products were formed. Instead, we isolated a mixture of enone **27**, TBS ether **28**, and sulfone **29**. Obviously, anion **21a** had undergone an intramolecular proton shift followed by an E1cB elimination. In this way enone **27** was generated, and the liberated OTBS anion underwent a $S_N2$-displacement reaction with the allyl iodide to give **28**. With excess butyllithium, sulfone **27** was deprotonated and alkylated by the allylic iodide to form **29**. From these considerations it became clear that the presence of both the 5-carbonyl and the 10-sulfonyl functions in compound **21** were incompatible with the envisaged anionic alkylation.

**Second Generation Synthesis.** At this stage, an alternative retrosynthetic disconnection was envisaged (Figure 4). The C11−C21 fragment **B** remained unchanged; however, the sulfone moiety was now located in a smaller C7−C10 fragment **C**, which could be connected to **B** by sulfone alkylation. After that, the C1−C6 fragment **D** could be attached via the familiar C6−C7-aldol addition.

For the allyl iodide **B** a slightly modified preparation was developed, starting from hydroxylactone **31**, easily available in two steps from (*S*)-malic acid (**22**)[15] (Scheme 4). Two different protecting groups were tested for the later C15−OH function. Thus PMB protection of the 2-hydroxyl function furnished **32a**, which was treated with methyllithium to give **33** as a mixture of cyclic hemiacetals and hydroxy ketone. This mixture was subjected to a Wittig reaction with (2-methylthiazol-4-yl)methyltri-*n*-butylphosphonium chloride (**34**) to furnish the olefin **24a** in excellent yield and >95% (*E*)-selectivity.[16] Conversion of **24a** into the allyl iodide via (*Z*)-selective Horner−Wadworth−Emmons reaction[12] and reduction to the allylic alcohol was achieved as described above. An analogous sequence of operations was performed with C15−OTBS protection.

Furthermore, an extremely short and efficient synthesis was developed for the C1−C6 fragment (Scheme 5). Utilizing a protocol by Kiyooka,[17] the commercially available ketene acetal **36** was added to the aldehyde **35**[18] under mediation of the oxazaborolidinone prepared in situ from diborane and *N*-tosyl-D-valine. Hydroxy ester **37** was obtained with >90% ee, as determined by chiral HPLC. O-Silylation of **37** gave **38**, which was transformed to the desired ketone **41** by two alternative methods: (a) Ester **38** was treated with trimethylsilylmethyllithium to give, after methanolysis, methyl ketone **39**,[19] which was then deprotonated and methylated to furnish **41**. (b) Ethylmagnesium bromide was added to the aldehyde generated from **38** to deliver alcohol **40,** which was oxidized to **41**.

The connection of the fragments started from sulfone **18a** which was prepared from alcohol **17a** as shown in Scheme 2. Alkylation of **18a** with the iodide prepared from allylic alcohol **25a** proceeded smoothly to give the epimeric sulfones, which were desulfonated to **42a** and deprotected to form the C7-alcohol **43a** (Scheme 6). Swern oxidation and aldol addition with ketone **41** furnished the desired adduct **44a** with a diastereoselectivity of 4:1. Silyl protection of the C7−OH gave **45a**. The C1−OTBS protective group was removed selectively to give the primary alcohol **46a**, which was oxidized to carboxylic acid **47a**. However, all attempts to remove the C15−

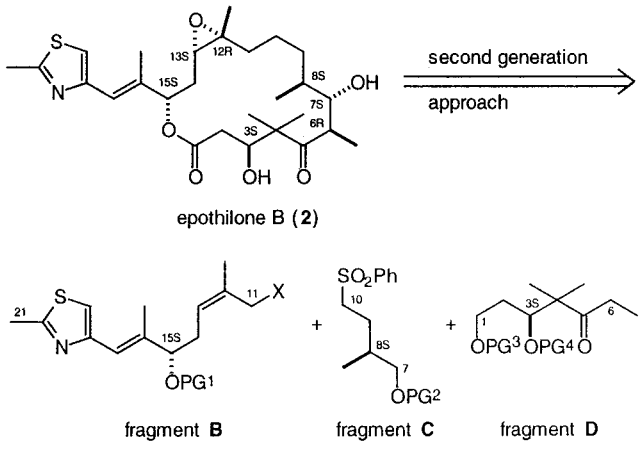



**Figure 4.**

(15) (a) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118−2120. (b) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865−2874.

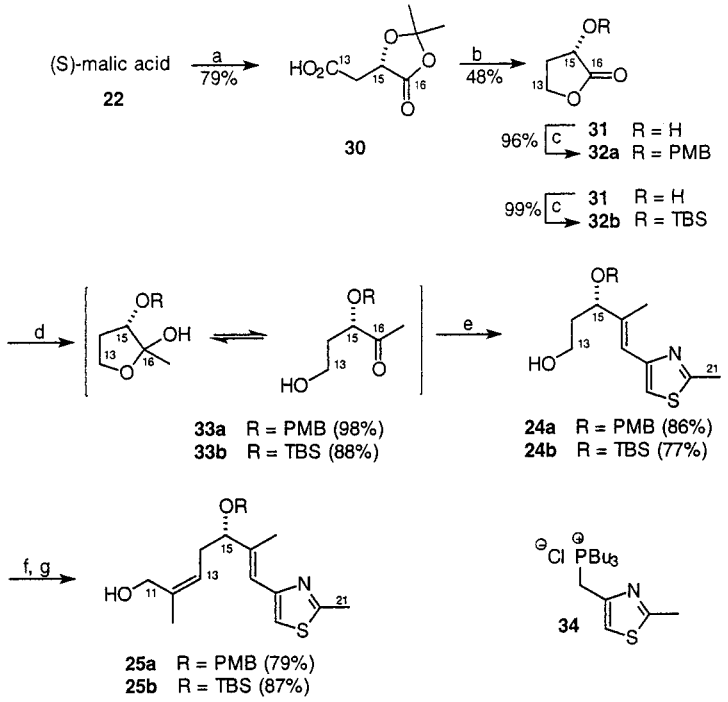
(16) Analogous substituted oxazolyltributylphosphonium salts have been investigated as olefination reagents in connection with synthetic studies on the calyculins,[a] ulapualides,[b] and phorboxazoles[c] and have been found to give excellent (*E*)-selectivities and better yields than the corresponding phosphonates. Thiazolylphosphonium salt **34** has independently been used by a Chinese group for the synthesis of the C7−C21 segment of epothilone A:[d] (a) Zhao, Z.; Scarlato, G. S.; Armstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 1609−1612. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Org. Chem.* **1992**, *57*, 1964−1966. (b) Celatka, C. A.; Liu, P. Panek, Y. S.; *Tetrahedron Lett.* **1997**, *38*, 5449−5452. (c) Paterson, I.; Arnott, E. A. *Tetrahedron Lett.* **1998**, *39*, 7185−7188. (d) Liu, Z. Y.; Yu, C.-Z.; Wang, R.-F.; Li, G. *Tetrahedron Lett.* **1998**, *39*, 5261−5264.

(17) Kiyooka, S.-I.; Kaneko, Y.; Komura, M., Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276−2278.

(18) (a) Jenmalm, A.; Berts, W.; Li, Y.-L.; Luthman, K.; Csõregh, I.; Hacksell, U. *J. Org. Chem.* **1994**, *59*, 1139−1148. (b) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388−3390.

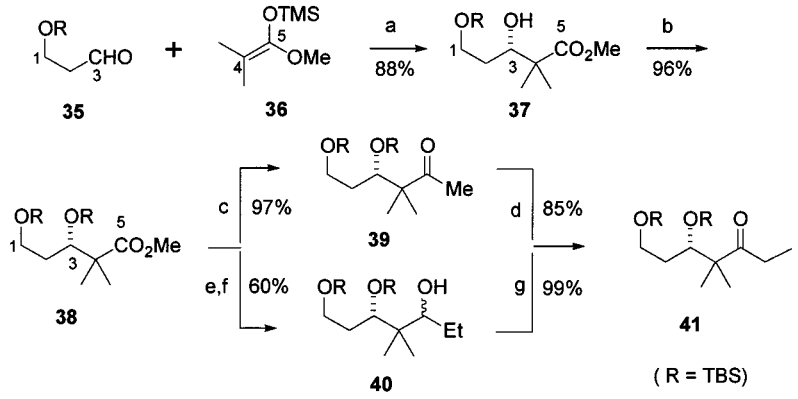
(19) Demuth, M. *Helv. Chim. Acta* **1978**, *61*, 3136−3138.

**Scheme 4**




[a] Reagents and conditions: (a) dimethoxypropane, cataalyst *p*TsOH, rt, 3 h (79%); (b) (i) $BH_3$·DMS (1.05 equiv), −78 °C, rt, 12 h, (ii) catalyst *p*TsOH, 65 °C, 1 h, toluene (48%). **Path a:** (for R = PMB): (c) PMBOC(=NH)$CCl_3$, catalyst CSA, rt, 12 h, $CH_2Cl_2$ (96%); (d) MeLi (1.02 equiv), −78 °C, 90 min, THF (98%); (e) **34**, KHMDS, −78 °C, 15 min, then **33a**, 50 °C, 30 min, THF (86% *E*-isomer, 5% *Z*-isomer); (f) (i) Swern oxidation, (ii) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2Et$, KHMDS, 18-crown-6, −78 °C, 1 h, THF (86%), *Z*:*E* = 5:1; (g) DIBALH (3.5 equiv), −20 °C, 3 h, THF (98%). **Path b:** (for R = TBS): (c) TBSCl (1.3 equiv), imidazole (2 equiv), 0 °C, 3 h, DMF (99%); (d) MeLi (1.2 equiv), −78 °C, 90 min, THF (88%); (e) **34**, LiHMDS, 0 °C, 40 min, then **33b**, 40−50 °C, 20 min, THF (77% *E*- and <1% Z-olefin); (f) (i) Swern oxidation, (ii) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2Et$, KHMDS, 18-crown-6, −78 °C, 1.5 h, THF (89%); (g) DIBALH (3 equiv), 0 °C, 2.5 h, THF (98%).

**Scheme 5**



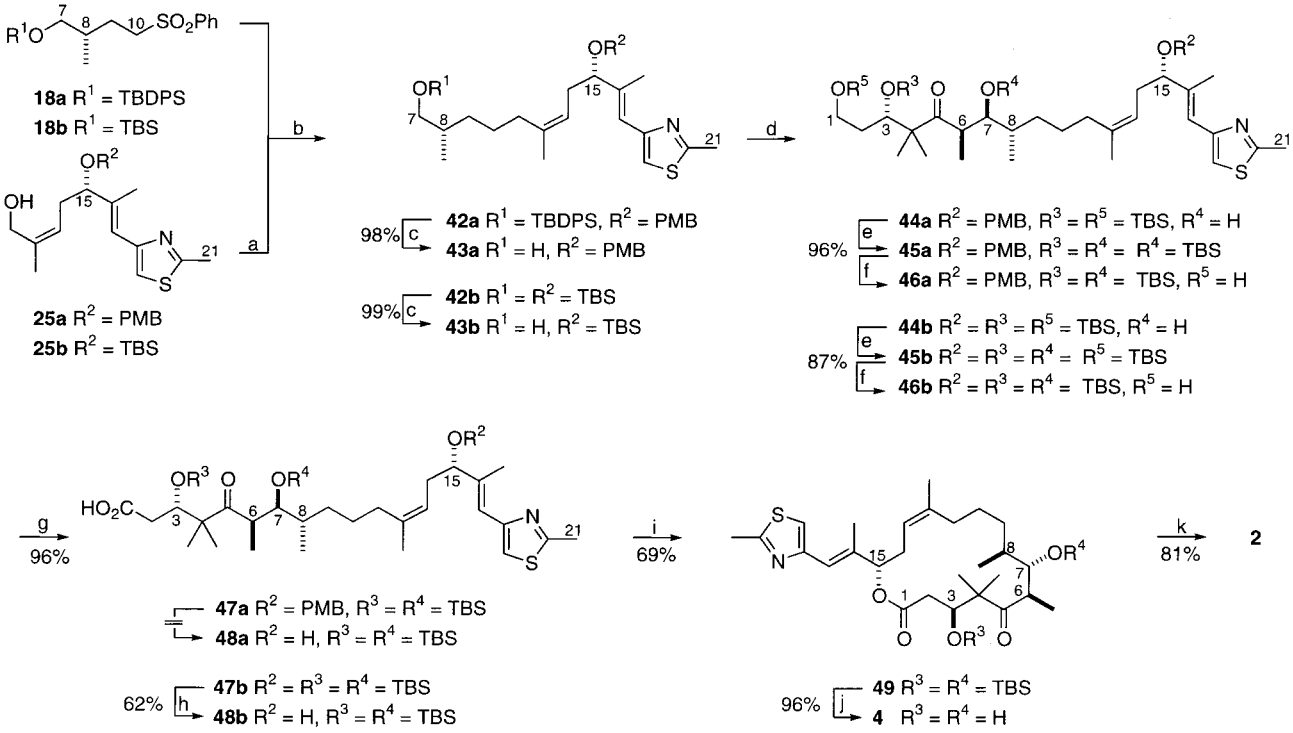

[a] Reagents and conditions: (a) N-Ts- D -valine (1 equiv), $BH_3$·THF (1 equiv), rt, 30 min, then **35** (1 equiv) and **36** (1 equiv), −78 °C, 4 h, $CH_2Cl_2$ (88%, >90% ee and 95% recovered N-Ts-D-valine); (b) TBSOTf (3 equiv), 2,6-lutidine, 0 °C, 3 h, $CH_2Cl_2$ (96%); (c) $TMSCH_2Li$, 0 °C, 4 h, pentane, then MeOH, 1 h, rt (97%); (d) LDA, −78 °C, 30 min, then MeI, −78 °C, rt, THF (85%); (e) DIBALH (3 equiv), −20 °C, 2 h, toluene (94%); (f) (i) Dess−Martin periodinane (1.3 equiv), 0 °C, 2 h, $CH_2Cl_2$, (ii) ethylmagnesium bromide (1.05 equiv), 0 °C, 2 h, $Et_2O$ (60% and 38.5% reduction product); (g) Dess−Martin periodinane (1.5 equiv), 0 °C, 2 h, $CH_2Cl_2$ (99%).

OPMB group failed. The only defined reaction we got was oxidation with DDQ, which led to the C15 ketone.

Therefore, the whole synthetic sequence was repeated with a C15−OTBS protecting group instead of the C15−OPMB. Thus, **18b** and the allylic iodide prepared from **25b** were connected to **42b** whose deprotection furnished **43b**, which was converted into **46b** in a sequence completely analogous to the one with the C15−OPMB protective group. Compound **46b** was identical with Nicolaou's intermediate in every respect ($^1H$ and $^{13}C$ NMR, etc.).[20] The synthesis was concluded with C1−OTBS deprotection, oxidation of C1 to the carboxylic acid, and C15−OTBS deprotection to generate seco acid **48b**, which gave lactone **49** via Keck macrolactonization. Global deprotection of **49** furnished **4** which was epoxidized with *m*-CPBA to **2** with a diastereoselectivity of 4−5:1. Our synthetic samples of **2** and **4** were identical with epothilones B and D with respect to all reported properties.

(20) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He. Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 7974−7991.

**Scheme 6**




[a] Reagents and conditions: **Path a** (for $R^1$ = TBDPS, $R^2$ = PMB): (a) (i) $Ph_3P$ (1.3 equiv), imidazole (1.35 equiv), $I_2$ (1.4 equiv), $CH_3CN/Et_2O$ (3:2), rt, 1 h, (ii) Li salt of **18a**, −78 °C, 1 h, then allylic iodide from **25a**, 1 h, THF (77%); (b) activated Mg, catalyst $HgCl_2$, controlled addition of MeOH, 40−50 °C, 2 h, EtOH (70% + 20% educt); (c) TBAF (2 equiv), rt, 3 h, THF (98%); (d) (i) Dess−Martin periodinane (1.3 equiv), rt, 2 h, $CH_2Cl_2$, (ii) lithium enolate from **41**, −90 °C, 30 min, THF (81% and recovered aldehyde, ca. 9:1 for the desired syn diastereoisomer **44a**); (e) TBSOTf (4 equiv), 2,6-lutidine, −15 °C, rt, 4 h, $CH_2Cl_2$ (98%); (f) CSA (1 equiv), 0 °C, 5 h, MeOH/$CH_2Cl_2$ (1:1) (98%); (g) (i) Dess−Martin periodinane (1.3 equiv), rt, 2 h, $CH_2Cl_2$, (ii) $NaClO_2$, $NaH_2PO_4$, 2,3-dimethyl-but-2-ene, 3 h, *tert*-butyl alcohol/water (96%). **Path b** (for $R^1 = R^2$ = TBS): (a) (i) $Ph_3P$ (1.3 equiv), imidazole (1.35 equiv), $I_2$ (1.4 equiv), $CH_3CN/Et_2O$ (3:2), rt, 1 h, (ii) **18b**, KHMDS, 18-crown-6, −78 °C, 1 h, then allylic iodide from **25b**, 1 h, THF (93%); (b) 5% Na/Hg, $Na_2HPO_4$, −15 °C, rt, 2 h, MeOH/THF (65%); (c) CSA (1 equiv), 0 °C, 5 h, MeOH/$CH_2Cl_2$ (1:1) (99%); (d) (i) Dess−Martin periodinane (1.3 equiv), rt, 4 h, $CH_2Cl_2$, (ii) lithium enolate from **41**, −95 °C, −85 °C, 90 min, THF (69%, 4:1 for the desired syn diastereoisomer **44b**); (e) TBSOTf (3 equiv), 2,6-lutidine, 0 °C, 3 h, $CH_2Cl_2$ (99%); (f) CSA (1 equiv), 0 °C, 4 h, MeOH/$CH_2Cl_2$ (1:1) (87%); (g) (i) Dess−Martin periodinane (1.3 equiv), rt, 2 h, $CH_2Cl_2$, (ii) $NaClO_2$, $NaH_2PO_4$, 2,3-dimethyl-but-2-ene, 3 h, *tert*-butyl alcohol/water (96%); (h) TBAF (5 equiv), rt, 10 h, THF (62%); (i) EDCI (2 equiv), DMAP (3 equiv), DMAP·HCl (2 equiv), reflux, 17 h, $CHCl_3$ (69%); (j) excess buffered HF·py, rt, 36 h, THF (96%); (k) *m*CPBA (1.5 equiv), −18 °C, 5 h, $CHCl_3$ (81%, with 4−5:1 diastereoselectivity for **2**).

## Conclusion

In conclusion, we have reported total syntheses of epothilones B and D in 18 (17) steps for the longest linear sequence and with about 8% overall yield. The stereogenic units (stereogenic centers and double bonds) were introduced with excellent to good stereoselectivity so that our synthesis compares very favorably with the ones that have been reported so far. A main advantage of our synthesis is that the two stereogenic centers at C8 and C15 are adapted from the chiral carbon pool with unambiguous configuration and reliable optical purity. The synthesis is modular and convergent, which means there is wide flexibility with respect to the individual subsections **B**−**D**. For instance, the construction of the 12,13-olefin moiety by Wittig type olefinations allows the introduction of almost any kind of a 13-substituent in an (*E*)- or (*Z*)-olefin geometry. The syntheses of other structurally interesting epothilone derivatives using this strategy will be disclosed soon.

## Experimental Section

**General Procedures.** Unless otherwise stated, solvents were dried by distillation under Ar, from sodium (PhMe), Na/K ($Et_2O$), potassium (THF), $CaH_2$ ($CH_2Cl_2$, DMF, MeCN, $Et_3N$, pentane), and Mg (MeOH, EtOH). All other commercially available reagents were used without further purification unless specified otherwise. All reactions were performed in oven-dried glassware under Ar. Chromatography and chromatographic refers to flash column chromatography on silica gel 60 (230−400 mesh with eluents given in parentheses). Analytical thin-layer chromatography (TLC) was performed on precoated glass-backed plates (Merck silica gel 60 $F_{254}$) and visualized by using either a UV lamp, ceric molybdate (CM), phosphomolybdic acid (PMA), sulfuric acidic/anisaldehyde (A), sulfuric acidic/vanilline (V), or potassium permanganate solution. Melting points (mp) are uncorrected. Optical rotations are reported in g/100 mL. Infrared spectra (IR) were measured as film on single-crystal silica plates and reported in wavenumbers ($cm^{-1}$) with broad signals denoted by (br). High-resolution mass spectra were obtained using electron ionization (EI), field ionization (FI), or fast atom bombardment (FAB).

**(+)-(2*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-2-methylpropan-1-ol (17a).[10a] (2*R*)-3-{[tert-Butyl(diphenyl)silyl]-oxy}-2-methylpropionate.** To a solution of (*R*)-methyl 3-hydroxy-2-methylpropionate (10 mL, 90.24 mmol) in dry DMF (200 mL) was added imidazole (12.3 g, 180.5 mmol) and *tert*-butyldiphenylsilyl chloride (TBDPSCl, 30.7 mL, 117.3 mmol). After being stirred overnight at room temperature, the mixture was quenched with ice water (200 mL). The aqueous DMF phase was extracted four times with $Et_2O$, and the organic solution was washed with saturated aqueous $NH_4Cl$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, elution with hexanes−EtOAc, 7:1) to give 38.34 g (>100%, contami-

nated with silanol) of the TBDPS ether as a colorless oil: $R_f$ 0.45 (hexanes−EtOAc, 10:1, CM: blue); IR (film) 1742, 1257, 1200 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.64 (m, 4H), 7.40 (m, 6H), 3.80 (dd, $J$ = 10.0, 7.5 Hz, 2H), 3.68 (s, 3H), 2.77 (sext, $J$ = 6.3 Hz, 1H), 1.20 (d, $J$ = 7.5 Hz, 3H), 1.09 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.3, 135.5, 133.5, 129.6, 127.6, 65.9, 51.5, 42.3, 26.7, 19.2, 13.4; MS(EI) *m/e* 341 $(M - CH_3)^+$.

**Alcohol 17a.** To a solution of the above crude ester in dry THF (1000 mL) was added dropwise DIBALH (270 mL, 1 M in toluene, 270 mmol) at 0 °C, and the mixture was stirred for 4 h, allowing to warm to room temperature. The cooled (0 °C) mixture was treated sequentially dropwise with MeOH (5 mL) and with saturated aqueous NaK tartrate (1000 mL). The cooling bath was removed, and after 3 h the phases were separated. The aqueous phase was extracted four times with $Et_2O$/hexanes (1:1). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, elution with hexanes−EtOAc, 5:1) to give 26.06 g (79.3 mmol, 88%) of the alcohol **17a** as a colorless oil: $R_f$ 0.40 (hexanes−EtOAc, 3:1, CM: blue; A, red brown); IR (film) 3350 br, 1260, 1188, 1112, 1087, 1041, 939, 740, $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.68 (m, 4H), 7.40 (m, 6H), 3.72 (ddd, $J$ = 20.0, 10.0, 5.0 Hz, 2H), 3.62 (dd, $J$ = 10.0, 2.0 Hz, 2H), 3.68 (s, 3H), 2.62 (br t, 1H), 1.99 (sext, $J$ = 6.3 Hz, 1H), 1.05 (s, 9H), 0.84 (d, $J$ = 7.5 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 135.5, 133.1, 129.8, 127.7, 68.6, 67.6, 37.3, 26.8, 19.1, 13.1; MS(EI) *m/e* 271 $(M - t\text{-}Bu)^+$.

**(2*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpropan-1-ol (17b).[10b] (−)-(2*R*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-2-methylpropionate.** To a solution of (*R*)-methyl 3-hydroxy-2-methylpropionate (10.76 g, 91.09 mmol) and imidazole (9.3 g, 136.6 mmol) in dry DMF (150 mL) was added TBSCl (17.85 g, 118.4 mmol) at 0 °C, and the mixture was stirred for 5 h allowing to reach room temperature. The mixture was quenched with saturated aqueous $NH_4Cl$, extracted with $Et_2O$, dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (12−18 mbar) at 90−100 °C to furnish 18.34 g (78.9 mmol, 86%) of the TBS ether as a colorless oil: $R_f$ 0.24 (hexanes−EtOAc, 3:1, A, violet); $[\alpha]^{20}_D$ −18.1 (*c* 3.03; $CHCl_3$); IR (film) 2955, 2858, 1744, 1257, 838, 777 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.76 (dd, $J$ = 9.5, 7.0 Hz, 1H), 3.66 (s, 3H), 3.63 (dd, $J$ = 9.5, 6.0 Hz, 1H), 2.63 (mc, 1H), 1.12 (d, $J$ = 7.0 Hz, 3H), 0.86 (s, 9H), 0.023 (s, 3H), 0.021 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.4, 65.2, 51.5, 42.5, 25.6, 18.2, 13.4, −5.5.

**Alcohol 17b.** To a solution of the above ester (15.2 g, 65.5 mmol) in dry THF (200 mL) was added dropwise DIBALH (197 mL, 1 M in toluene, 197 mmol) at −20 °C. After 2.5 h the reaction was quenched with MeOH (10 mL) at 0 °C and saturated aqueous NaK tartrate (200 mL) and $Et_2O$ (150 mL) were added, and the mixture was stirred for additional 45 min allowing to warm to room temperature. The layers were separated, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated to give 12.3 g (60.3 mmol, 92%) of the alcohol **17b** as a colorless oil: $R_f$ 0.6 (hexanes−EtOAc, 3:1, CM, blue); IR (film) 3065br, 1268, 1206, 1168, 1092 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.72 (dd, $J$ = 10.0, 4.5 Hz, 1H), 3.61 (m, 2H), 3.53 (dd, $J$ = 10.0, 8.0 Hz, 1H), 2.78 (dd, $J$ = 6.0, 4.5 Hz, 1H), 1.93 (mc, 1H), 0.89 (s, 9H), 0.83 (d, $J$ = 6.5 Hz, 3H), 0.06 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 68.8, 68.3, 37.0, 25.9, 18.2, 13.1, −5.56, −5.62.

**(−)-(3*S*)-4-{[*tert*-Butyl(diphenyl)silyl]oxy}-3-methylbutyl Phenyl Sulfone (18a).** To a solution of compound **17a** (6.57 g, 20 mmol) in dry pyridine (20 mL) was added tosyl chloride (6.94 g, 40 mmol) at 0 °C, and the mixture was stirred for 3.5 h. The reaction was quenched by addition of ice and stirred for 1 h. The aqueous phase was extracted with $Et_2O$ (3 × 50 mL), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was diluted with toluene and concentrated under reduced pressure to remove most of the pyridine by azeotropic distillation. The residue was purified by flash chromatography (silica gel, elution with hexanes−EtOAc, 10:1) to give 8.67 g (18.6 mmol, 93%) of the tosylate as a viscous colorless oil, which was used directly in the next step.

To a solution of methyl phenyl sulfone (4.34 g, 27.9 mmol) in THF (180 mL) was added dropwise *n*-BuLi (16.77 mL, 1.6 M in hexanes, 26.83 mmol) at −20 °C, the cooling bath was removed, and the reaction was allowed to warm to room temperature over a period of 30 min. To the solution of the Li salt was added the above-mentioned tosylate in dry THF (20 mL) at −20 °C, and the reaction was stirred overnight, allowing to warm to room temperature. The violet reaction mixture was quenched by addition of saturated aqueous $NH_4Cl$ and NaK tartrate. The phases were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic solutions were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Purification by chromatography (silica gel, elution with hexanes−EtOAc, 5:1) provided sequentially 630 mg unreacted tosylate and 7.69 g (82% or 89% with respect to the recovered tosylate, respectively) of the sulfone **18a** both as colorless oils: tosylate, $R_f$ 0.60 (hexanes−EtOAc, 3:1; PMA, blue; A, light blue); **18a,** $R_f$ 0.39 (hexanes−EtOAc, 3:1, PMA, light blue); $[\alpha]^{20}_D$ −5.8 (*c* 2.01, $CHCl_3$); IR (film) 1447, 1428, 1318, 1306, 1112, 1087 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.88 (mc, 2H), 7.63 (m, 1H), 7.55 (m, 6H), 7.37 (m, 6H), 3.44 (dd, $J$ = 9.8, 5.0 Hz, 1H), 3.36 (dd, $J$ = 9.8, 6.4 Hz, 1H), 3.09 (mc, 2H), 1.86 (dddd, $J$ = 12.8, 8.9, 7.9, 5.9 Hz, 1H), 1.70 (mc, 1H), 1.60 (ddt, $J$ = 12.8, 8.9, 7.4 Hz, 1H), 0.96 (s, 9H), 0.84 (d, $J$ = 6.4 Hz, 3H); $^{13}C$ NMR (62.5 MHz, $CDCl_3$) $\delta$ 135.54, 135.51, 133.6, 133.5, 129.7, 129.2, 128.1, 127.7, 68.0, 54.5, 34.7, 26.8, 26.4, 19.2, 16.4; MS (EI) *m/e* 468 $(M + H)^+$. Anal. Calcd for $C_{27}H_{34}O_3SSi$: C, 69.5; H, 7.3. Found: C, 69.39; H, 7.50.

**(−)-(3*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylbutyl Phenyl Sulfone (18b).** To a solution of (3*S*)-3-methyl-1-phenylsulfonylbutan-4-ol (prepared by desilylation of **18a** with 1.5 equiv of TBAF, rt, 10 h, THF (88%)) (5.55 g, 24.3 mmol) and imidazole (3.31 g, 48.6 mmol) in dry DMF (30 mL) was added TBSCl (4.75 g, 31.6 mmol) at 0 °C, and the mixture was stirred for 3 h, allowing to reach room temperature. The mixture was quenched by addition of saturated aqueous $NH_4Cl$ (50 mL) at 0 °C, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 5:1) furnished 8.2 g (24 mmol, 99%) of the TBS-protected sulfone **18b** as a colorless oil: $R_f$ 0.53 (hexanes−EtOAc, 3:1, PMA, blue); $[\alpha]^{20}_D$ −6.7 (*c* 2.64; $CHCl_3$); IR (film) 1447, 1389, 1306, 1106 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.90 (m, 2H), 7.64 (m, 1H), 7.55 (m, 2H), 3.42 (dd, $J$ = 10.0, 5.0 Hz, 1H), 3.31 (dd, $J$ = 10.0, 6.5 Hz, 1H), 3.14 (dd, $J$ = 9.0, 7.0 Hz, 2H), 1.79 (m, 1H), 1.65 (mc, 1H), 1.55 (m, 1H), 0.83 (d, $J$ = 6.5 Hz, 3H), 0.81 (s, 9H), −0.03 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 139.1, 133.5, 129.2, 128.1, 67.5, 54.6, 34.6, 26.4, 25.8, 18.2, 16.3, −5.5; MS (FI) *m/e* 343 $(M^+)$. Anal. Calcd for $C_{17}H_{30}O_3SSi$: C, 59.6; H, 8.8. Found: C, 59.38; H, 8.72.

**(−)-(3*S*,4*E*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methyl-5-(2-methyl-1,3-thiazol-4-yl)pent-4-en-1-ol (24b).** To a solution of **34** (31.95 g, 91.28 mmol), dried for 16 h (40 °C, 0.01 Torr), and **33b** (10.1 g, 43.48 mmol) in dry THF (200 mL) was added dropwise a solution of LiHMDS (101 mL, 1 M in THF, 101.0 mmol) at 0 °C over a period of 40 min. After 5 min the cooling bath was removed and the reaction mixture was heated to 55 °C for 40 min. After recooling, the mixture was diluted with $Et_2O$ (200 mL) and quenched by addition of saturated aqueous $NH_4Cl$, the phases were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and the residue was subjected twice to chromatography (silica gel, elution with hexanes−EtOAc, 5:1−3:1, and $CH_2Cl_2$–hexanes−EtOAc, 3:5:1, respectively) to give 10.95 g (33.48 mmol, 77%) of the *E*-olefin **24b**. Less polar byproducts were isolated in the following order: bissilylated *E*-olefin (600 mg, 3%), *Z*-olefin (122 mg, <1%), recovered **33b** (765 mg, 8%), and *E*-olefin

silylated at the primary hydroxy group (741 mg, 5%). **24b:** $R_f$ 0.21 (hexanes−EtOAc, 3:1, CM, blue); $[\alpha]^{20}_D$ −31.5 (*c* 2.81, $CHCl_3$); IR (film) 3385 br, 1472, 1255, 1098, 1005, 978 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.89 (s, 1H), 6.49 (s, 1H), 4.35 (dd, $J$ = 7.5, 4.5 Hz, 1H), 3.71 (m, 2H), 2.67 (s, 3H), 2.28 (t, $J$ = 5.0 Hz, 1H), 1.98 (s, 3H), 1.90−1.73 (m, 2H), 0.88 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.9, 153.4, 142.0, 119.2, 115.7, 77.7, 60.6, 38.7, 26.2, 19.6, 18.5, 14.7, −4.2, −4.8; MS (FI) *m/e* 327 ($M^+$).

**(−)-(2*Z*,5*S*,6*E*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,6-dimethyl-7-(2-methyl-1,3-thiazol-4-yl)hepta-2,6-dien-1-ol (25b). (3*S*,4*E*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-4-methyl-5-(2-methyl-1,3-thiazol-4-yl )pent-4-en-1-al.** To a solution of oxalyl chloride (1.57 mL, 17.95 mmol) in $CH_2Cl_2$ (150 mL) was added dropwise DMSO (2.66 mL, 37.4 mmol) at −78 °C. After the solution was stirred for 10 min, a solution of alcohol **24b** (4.9 g, 14.96 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise. The solution was stirred for additional 45 min before DIPEA (74.8 mmol) was added, and stirring was continued for 10 min at the same temperature and was then allowed to warm to room temperature within 60 min. The reaction mixture was diluted with $Et_2O$ (250 mL) and quenched by addition of saturated aqueous $NH_4Cl$ (100 mL). The phases were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration through a short pad of silica gel, the solvent was removed under reduced pressure and the crude aldehyde was subjected to the next reaction without further purification.

**Ethyl (2*Z*,5*S*,6*E*)-5-{[tert-Butyl(dimethyl)silyl]oxy}-2,6-dimethyl-7-(2-methyl-1,3-thiazol- 4-yl)hepta-2,6-dienoate.** To a solution of ethyl 2-[bis(2,2,2-trifluoroethyl)phosphono]-propionate (6.73 g, 19.46 mmol) and 18-crown-6 (11.9 g, 44.9 mmol) in dry THF (200 mL) was added a solution of KHMDS (3.62 g, 17.2 mmol) in dry THF (15 mL) at −78 °C. The cooling bath was removed, and the mixture was stirred for 15 min. Then a solution of the above crude aldehyde in dry THF (45 mL) was added at −78 °C over a period of 70 min, and the reaction was stirred for 30 min. The cooling bath was removed, and the mixture was quenched by addition of saturated aqueous $NH_4Cl$. The phases were separated, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After filtration through a short pad of silica gel the solvent was removed under reduced pressure and the residue was subjected to chromatography (silica gel, elution with hexanes−EtOAc, 15:1−10:1) to give 5.45 g (13.31 mmol, 89%) of the unsaturated ester as a single isomer: $R_f$ 0.46 (hexanes−EtOAc, 5:1, A, light blue); $[\alpha]^{20}_D$ −2.0 (*c* 3.38, $CH_2Cl_2$); IR (film) 1714, 1472, 1372, 1252, 1210, 1185, 1096, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.91 (s, 1H), 6.49 (s, 1H), 5.98 (td, $J$ = 7.3, 1.5 Hz, 1H), 4.21 (t, $J$ = 5.5 Hz, 1H), 4.18 (q, $J$ = 7.0 Hz, 2H), 2.75 (m, 2H), 2.70 (s, 3H), 2.00 (s, 3H), 1.88 (s, 3H), 1.28 (t, $J$ = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.0, 164.4, 153.2, 141.9, 139.0, 128.3, 118.8, 115.2, 77.9, 60.1, 36.6, 26.2, 20.7, 19.2, 18.2, 14.3, 14.1, −4.7, −5.1; MS (FI) *m/e* 410 ($M^+$). Anal. Calcd for $C_{21}H_{35}NO_3SSi$: C, 61.6; H, 8.6; N, 3.4. Found: C, 61.55; H, 8.53; N, 3.39.

**Reduction to 25b.** To a solution of the above unsaturated ester (5.43 g, 13.26 mmol) in dry THF (250 mL) was added dropwise DIBALH (40 mL, 1 M in heptanes, 40 mmol) at 0 °C, and stirring was continued for 2.5 h at the same temperature. The reaction was quenched by addition of MeOH (3 mL), diluted with $Et_2O$ (200 mL) and saturated aqueous NaK tartrate (200 mL), and stirred for 45 min allowing to reach room temperature. The phases were separated, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were washed with saturated aqueous $NH_4Cl$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by chromatography (silica gel, elution with hexanes−EtOAc, 5:1) provided 4.75 g (12.93 mmol, 98%) of the allylic alcohol **25b** as colorless crystals: $R_f$ 0.24 (hexanes−EtOAc, 3:1, A, violet); $[\alpha]^{20}_D$ −6.8 (*c* 2.20; $CHCl_3$); mp.: 58−60 °C; IR (film) 3333br, 1472, 1441, 1253, 1100, 1006 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.91 (s, 1H), 6.43 (s, 1H), 5.30 (td, $J$ = 8.0, 2.5 Hz, 1H), 4.13 (dd, $J$ = 11.0, 5.0 Hz, 1H), 4.12 (dd, $J$ = 12.0, 5.0 Hz, 1H), 4.00 (dd, $J$ = 12.0, 6.5 Hz, 1H), 2.69 (s, 3H), 2.46 (dt, $J$ = 14.1, 8.0 Hz, 1H), 2.22 (m, 1H), 2.20 (t, $J$ = 6.0 Hz, 1H), 2.00 (d, $J$ = 1.0 Hz, 3H), 1.79 (s, 3H), 0.88 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.6, 152.9, 142.2, 137.6, 124.3, 118.8, 115.2, 78.2, 61.9, 35.4, 25.8, 22.0, 19.2, 18.3, 14.2, −4.7, −4.9; MS (FI) *m/e* 368 (M + H)$^+$. Anal. Calcd for $C_{19}H_{33}NO_2SSi$: C, 62.1; H, 9.0; N, 3.8. Found: C, 61.64; H, 8.94; N, 3.79.

**[(4*S*)-2,2-Dimethyl-5-oxo-1,3-dioxolan-4-yl]acetic acid (30).**[15b] To a suspension of (*S*)-malic acid (**22**) (53.6 g, 0.4 mol) in 2,2-dimethoxypropane (250 mL) was added *p*-TsOH (500 mg, 2.63 mmol), and the mixture was stirred for 3 h. The solution was quenched by addition of a aqueous solution containing $NaHCO_3$ (220 mg, 2.63 mmol). The mixture was diluted with $CH_2Cl_2$ and slightly acidified, the phases were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure and the remaining solids were purified by recrystallization ($CHCl_3$–$CCl_4$, 1:1) to give 56.53 g (32.46 mmol, 79%) **30** as colorless crystals: IR (film) 3268, 1766, 1130, 1104 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 11.30 (br, ×bb1H), 4.69 (dd, $J$ = 6.5, 3.5 Hz, 1H), 2.97 (dd, $J$ = 17.6, 4.0 Hz, 1H), 2.83 (dd, $J$ = 17.6, 6.5 Hz, 1H), 1.59 (s, 3H), 1.54 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.1, 171.9, 111.4, 70.4, 35.9, 26.7, 25.7.

**(3*S*)-3-Hydroxydihydrofuran-2(3*H*)-one (31).**[15b] To a solution of **30** (41.8 g, 0.24 mol) in dry THF (250 mL) was added dropwise borane−dimethyl sulfide complex (25 mL, 10 M in DMS, 0.25 mol) at −78 °C. After being stirred overnight, allowing to reach room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, elution with acetone), and the volatiles were removed under reduced pressure. The remaining oil was dissolved in toluene (500 mL), a catalytic amount of *p*-TsOH was added, and the mixture was stirred for 1 h at 65 °C. After the mixture had cooled, pyridine (1 equiv with respect to used *p*-TsOH) was added and the mixture was concentrated under reduced pressure. The residue was purified by chromatography (silica gel, elution with hexanes−EtOAc, 2:1−1:2) and finally by Kugelrohr distillation (85 °C, 0.1 mbar) to give 12.0 g (118 mmol, 48%) of the lactone **31** as a colorless oil: $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 4.50 (dd, $J$ = 9.8, 8.4 Hz, 1H), 4.38 (ddd, $J$ = 10.8, 8.9, 2.0 Hz, 1H), 4.19 (ddd, $J$ = 10.3, 8.9, 5.9 Hz, 1H), 4.07 (br s, 1H), 2.55 (mc, 1H), 2.23 (mc, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 178.3, 67.2, 65.2, 30.7.

**(−)-(3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}dihydrofuran-2(3*H*)-one (32b).** To a solution of (*S*)-α-hydroxybutyrolactone **31 (**3.92 g, 38.4 mmol) and imidazole (5.23 g, 76.8 mmol) in dry DMF (50 mL) was added TBSCl (7.53 g, 49.92 mmol) at 0 °C, and the mixture was stirred for 2.5 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (100 mL), extracted with $Et_2O$, dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Chromatography (silica gel, elution with 3% $Et_2O$ in hexanes) afforded 8.27 g (38.2 mmol, 99%) of the TBS ether **32b** as a colorless oil, which crystallized at −20 °C: $R_f$ 0.51 (hexanes−EtOAc, 5:1, CM, blue); $[\alpha]^{20}_D$ −30.5 (*c* 5.82, $CHCl_3$); IR (film) 1788, 1254, 1220, 1154, 1022 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 4.43−4.34 (m, 2H), 4.19 (td, $J$ = 9.0, 6.6 Hz, 1H), 2.45 (m, 1H), 2.22 (dddd, $J$ = 12.8, 9.0, 9.0, 8.6 Hz, 1H), 0.91 (s, 9H), 0.017 (s, 3H), 0.014 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 175.8, 68.2, 64.7, 32.3, 25.9, 18.2, −4.2, −5.3; MS (FI) *m/e* 217 (M + H)$^+$.

**(3*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-hydroxypentan-2-one (33b).** To a solution of crude **32b** (5.27 g, from 24.34 mmol of (*S*)-α-hydroxybutyrolactone) in dry THF (100 mL) was added dropwise MeLi (18.3 mL, 1.6 M in $Et_2O$, 29.2 mmol) at −78 °C, and the reaction was stirred for 90 min at the same temperature. The cooling bath was removed, and saturated aqueous $NH_4Cl$ was added rapidly. The mixture was diluted with saturated aqueous NaK tartrate and $Et_2O$, the layers were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic solutions were dried over $MgSO_4$,

filtered, and concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, elution with hexanes− EtOAc, 10:1−5:1) affording 4.96 g (21.33 mmol, 88%) of **33b** as colorless crystals: $R_f$ 0.22 (hexanes− EtOAc, 5:1, A, green); mp 53−60 °C; IR (film) 3314 br, 1464, 1251, 1110, 1053, 1024 $cm^{-1}$; MS (FI) *m/e* 214 $(M - H_2O)^+$. Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.9; H, 10.4. Found: C, 57.15; H, 10.34.

**Tri-*n*-butyl[(2-methyl-1,3-thiazol-4-yl)methyl]phosphonium Chloride (34). 4-(Chloromethyl)-2-methyl-1,3-thiazole.** A solution of 1,3-dichloropropan-2-one (12.7 g, 0.1 mol) and thioacetamide (7.5 g, 0.1 mol) in dry ethanol (70 mL) was heated under Ar for 5.5 h and then concentrated under reduced pressure. The dark crystalline residue was dissolved in water (250 mL), and a pH ≈ 8 was achieved by addition of solid $NaHCO_3$. The mixture was extracted with $Et_2O$ (4 × 100 mL), and the combined organic solutions were dried over $MgSO_4$ and concentrated. The residue was purified by distillation (bp: 55 °C, 0.05 Torr) to obtain 11.9 g (80.7 mmol, 81%) of the thiazole as light yellow, skin-irritating oil, which was identical in every respect with the described compound.[21]

To a solution of 4-chloromethyl-2-methyl-1,3-thiazole (23 g, 156.0 mmol) in dry benzene (200 mL) was added tri-*n*-butylphosphane (38 mL, 156.0 mmol) under Ar, and the reaction was heated to reflux for 8 h. The mixture was concentrated under reduced pressure and the residue crystallized with dry $Et_2O$ to give 53 g (151.5 mmol, 97%) of the title compound as highly hygroscopic colorless crystals: mp 82−85 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.65 (d, $J$ = 3.5 Hz, 1H), 4.28 (d, $J$ = 14.6 Hz, 2H), 2.59 (s, 3H), 2.35 (mc, 6H), 1.35−1.50 (m, 12H), 0.86 (t, $J$ = 7.0 Hz, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 166.7 (d, $^4J$ = 1.5 Hz), 142.9 (d, $^2J$ = 9.9 Hz), 119.8 (d, $^3J$ = 9.2 Hz), 23.7 (d, $J$ = 15.3 Hz), 23.4 (d, $J$ = 5.4 Hz), 22.6 (d, $^1J$ = 47.4 Hz), 19.0 (d, $^1J$ = 46.8 Hz), 19.0 (s), 13.2 (s).

**(+)-Methyl (3*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-hydroxy-2,2-dimethylpentanoate (37).** To a solution of *N*-Ts-D-valine (1.36 g, 5.0 mmol) in dry $CH_2Cl_2$ (50 mL) was added dropwise at room temperature a solution of $BH_3$·THF (5 mL, 1 M in THF, 5.0 mmol) over a period of 30 min, and stirring was continued for 20 min. The reaction was cooled to −78 °C, and a solution of aldehyde **35**[18] **(**940 mg, 5.0 mmol) in dry $CH_2Cl_2$ (5 mL) was slowly added followed by a solution of freshly distilled ketene acetal **36** (960 mg, 5.5 mmol) in dry $CH_2Cl_2$ (5 mL). After being stirred for 4 h at the same temperature, the reaction mixture was quenched by addition of phosphate buffer (35 mL, pH = 6.9). The mixture was extracted with $CH_2Cl_2$ (3 × 20 mL), and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated. The residue was treated with cold hexane, and the precipitated *N*-Ts-D-valine was recovered by filtration (96%). The solution was again concentrated under reduced pressure and purified by flash column chromatography (silica gel, elution with hexanes−EtOAc, 5:1) to obtain 1.25 g (4.3 mmol, 88%) of the $\beta$-hydroxy ester **37** as a colorless oil: $R_f$ 0.39 (hexanes−EtOAc, 5:1, CM: blue); $[\alpha]^{20}_D$ +3.0 (*c* 1.88, $CHCl_3$); IR (film) 3630 br, 1733, 1472, 1257, 1193, 1138, 1099, $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.92 (m, 1H), 3.87 (dd, $J$ = 10.0, 5.0 Hz, 1H), 3.80 (m, 1H), 3.68 (s, 3H), 3.37 (d, $J$ = 3.5 Hz, 1H), 1.57 (ddd, $J$ = 11.0, 5.5, 1.0 Hz, 2H), 1.19 (s, 3H), 1.15 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.8, 76.0, 62.6, 51.8, 47.1, 33.7, 25.9, 21.3, 20.6, 18.2, −5.5; MS (FI) *m/e* 291 $(M^+)$. Anal. Calcd for $C_{14}H_{30}O_4Si$: C, 57.9; H, 10.4. Found: C, 58.26; H, 10.31.

**(−)-Methyl (3*S*)-3,5-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2,2-dimethylpentanoate (38).** To a solution of **37** (5.32 g, 18.3 mmol) in dry $CH_2Cl_2$ (100 mL) at 0 °C were added sequentially 2,6-lutidine (6.38 mL, 55.0 mmol) and then dropwise TBSOTf (5.05 mL, 22.0 mmol). The reaction was stirred for 3 h and then quenched with saturated aqueous $NH_4Cl$ (25 mL). The layers were separated, the aqueous phase was extracted twice with $CH_2Cl_2$, and the combined organic solutions were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Flash column chromatography (silica gel, elution with 3%−5% $Et_2O$ in hexane) furnished 7.1 g (17.6 mmol, 96%) of the protected ester **38** as a colorless oil: $R_f$ 0.33 (hexanes−EtOAc, 10:1, CM, blue); $[\alpha]^{20}_D$ −6.0 (*c* 3.91, $CHCl_3$); IR (film) 1736, 1472, 1464, 1257, 1135 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.05 (dd, $J$ = 7.5, 3.0 Hz, 1H), 3.64 (s, 3H), 3.62 (m, 2H), 1.59 (m, 2H), 1.15 (s, 3H), 1.08 (s, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.07 (s, 3H), 0.033 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 177.6, 73.4, 60.3, 51.6, 48.3, 36.9, 26.0, 25.9, 21.7, 20.4, 18.3, −3.9, −4.3, −5.3; MS (FI) *m/e* 405 $(M^+)$. Anal. Calcd for $C_{20}H_{44}O_4Si_2$: C, 59.4; H, 11.0. Found: C, 59.50; H, 10.74.

**(4*S*)-4,6-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3,3-dimethylhexan-2-one (39).** To a solution of **38 (**1.01 g, 2.5 mmol) in dry pentane (12 mL) was added ((trimethylsilyl)methyl)lithium (5.5 mL, 1 M in pentane, 5.5 mmol) at 0 °C, and the mixture was stirred for 4 h. To the suspension was added dry MeOH (2.5 mL), and the resulting emulsion was stirred for an additional 1 h at room temperature. The mixture was diluted with $Et_2O$ and water, the layers were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic solutions were dried over $NaSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, elution with 2% $Et_2O$ in hexanes) to obtain 470 mg (2.44 mmol, 97%) of **39** as a colorless oil: $R_f$ 0.4 (hexanes−EtOAc, 24:1, A, yellow brown); $[\alpha]^{20}_D$ −11.5 (*c* 0.71, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.00 (dd, $J$ = 8.0, 3.0 Hz, 1H), 3.64−3.54 (m, 2H), 2.10 (s, 3H), 1.39−1.59 (m, 2H), 1.06 (s, 3H), 1.01 (s, 3H), 0.85 (s, 18H), 0.06 (s, 3H), 0.02 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 213.7, 73.7, 60.4, 53.8, 37.6, 27.1, 26.4, 26.3, 22.3, 20.4, 18.7, 18.6, −3.6, −3.7, −4.9; MS (FI) *m/e* 389 $(M + H)^+$.

**(3*R*,5*S*)-5,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-4,4-dimethylheptan-3-ol (40a) and (3*S*,5*S*)-5,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-4,4-dimethylheptan-3-ol (40b). (3*S*)-3,5-Bis{[tert-butyl(dimethyl)silyl]oxy}-2,2-dimethylpentan-1-ol.** To a solution of **38 (**4.05 g, 10 mmol) in dry toluene (100 mL) at −20 °C was added dropwise DIBALH (30 mL, 1 M solution in hexanes, 30 mmol), and the reaction was stirred for 2 h. At 0 °C MeOH (5 mL) was added dropwise, and the mixture was diluted with $Et_2O$ (150 mL) and saturated aqueous NaK tartrate (250 mL). The layers were separated, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 10:1) furnished 3.53 g (9.36 mmol, 94%) of the alcohol as a colorless oil: $R_f$ 0.53 (hexanes−EtOAc, 5:1, CM, blue); $[\alpha]^{20}_D$ −12.4 (*c* 6.97, $CHCl_3$); IR (film) 3450 br, 1473, 1464, 1389, 1256, 1103, 1043 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 3.66 (m, 4H), 3.28 (dd, $J$ = 10.5, 7.0 Hz, 1H), 2.87 (dd, $J$ = 7.0, 4.0 Hz, 1H), 1.90 (m, 1H), 1.62 (m, 1H), 0.98 (s, 3H), 0.883 (s, 9H), 0.878 (s, 9H),); 0.79 (s, 3H), 0.084 (s, 3H), 0.078 (s, 3H), 0.04 (s, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 76.7, 70.2, 60.7, 39.3, 36.4, 26.0, 25.9, 22.8, 22.0, 18.3, 18.2, −4.0, −4.3, −5.30, −5.33; MS (EI) *m/e* 377 $(M^+)$. Anal. Calcd for $C_{19}H_{44}O_3Si_2$: C, 60.6; H, 11.8. Found: C, 60.82; H, 11.70.

**Alcohols 40.** To a solution of the above alcohol **(**820 mg, 2.18 mmol) in dry $CH_2Cl_2$ (100 mL) and dry pyridine (2 mL) was added DMP (1.21 g, 2.83 mmol), and the mixture was stirred for 2 h. At this time, TLC (hexanes−EtOAc, 10:1) indicated that the alcohol had been consumed and the aldehyde had been formed. The reaction mixture was diluted with $Et_2O$ (100 mL) and quenched with saturated aqueous $NaHCO_3$–$Na_2S_2O_3$ (1:1, 50 mL). The organic solution was washed with $NaHCO_3$–$Na_2S_2O_3$ (1:1, 2 × 50 mL), dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. The crude aldehyde was azeotropically dried from toluene and then directly used in the next step.

To a solution of the above crude aldehyde in dry $Et_2O$ (10 mL) was added dropwise ethylmagnesium bromide (0.76 mL, 3 M in $Et_2O$, 2.29 mmol) at 0 °C. The reaction was stirred for 2 h and then quenched with saturated aqueous $NH_4Cl$ (50 mL). The layers were separated, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were dried over

(21) (a) Gasteiger, J.; Herzig, C. *Tetrahedron* **1981**, *15*, 2607−2611. (b) Marzoni, G. *J. Heterocycl. Chem.* **1986**, *23*, 577−580.

$MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 25:1) furnished 530 mg (1.31 mmol, 60%) of a diastereomeric mixture of **40a,b**, as well as 316 mg (0.84 mmol, 38.5%) of educt alcohol, resulting from reduction of the aldehyde by the Grignard reagent. Aldehyde: $R_f$ 0.67 (hexanes−EtOAc, 10:1, CM, blue). **40a:** $R_f$ 0.53 (hexanes−EtOAc, 10:1, CM, blue); $[\alpha]^{20}_D$ −22.6 (*c* 2.32, $CHCl_3$); IR (film) 3500 br, 1472, 1464, 1389, 1362, 1256, 1101, 1048, 1004 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 4.29 (s, 1H), 3.71 (m, 1H), 3.63 (m, 2H), 1.92 (mc, 1H), 1.70 (mc, 1H), 1.35 (m, 2H), 1.00 (t, $J$ = 7.0 Hz, 3H), 0.97 (s, 3H), 0.90 (s, 9H), 0.88 (s, 9H), 0.73 (s, 3H), 0.112 (s, 3H), 0.11 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 80.5, 77.4, 60.1, 40.7, 36.0, 26.1, 25.9, 24.5, 23.5, 20.5, 18.24, 18.20, 11.3, −3.9, −4.3, −5.27, −5.31; MS (FI) *m/e* 405 ($M^+$). Anal. Calcd for $C_{21}H_{48}O_3Si_2$: C, 62.2; H, 12.0. Found: C, 62.57; H, 11.98. **40b:** $R_f$ 0.44 (hexanes−EtOAc, 10:1, CM, blue); IR (film) 3484 br, 1472, 1256, 1094 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 3.75 (m, 2H), 3.68 (td, $J$ = 9.5, 4.5 Hz, 1H), 3.33 (ddd, $J$ = 10.0, 4.5, 1.5 Hz, 1H), 2.74 (dd, $J$ = 4.5, 1.0 Hz, 1H), 2.00 (mc, 1H), 1.49 (m, 2H), 1.29 (mc, 1H), 0.98 (t, $J$ = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.85 (s, 3H), 0.74 (s, 3H), 0.07 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 78.0, 75.5, 61.9, 42.8, 36.5, 26.1, 26.0, 24.2, 18.7, 18.5, 18.4, 18.3, 11.7, −3.6, −4.4, −5.4; MS (FI) *m/e* 405 ($M^+$).

**(−)-(5*S*)-5,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-4,4-dimethylheptan-3-one (41). Method a.** To a solution of **40** (495 mg, 1.22 mmol) in dry $CH_2Cl_2$ (60 mL) and pyridine (1 mL) was added DMP (778 mg, 1.84 mmol) at 0 °C, and the suspension was stirred for 2 h. The mixture was diluted with cold $Et_2O$ (100 mL), filtered, and washed with saturated aqueous $NaHCO_3$−$Na_2S_2O_3$ (1:1). The organic solution was dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure to give 487 mg (1.21 mmol, 99%) of ketone **41** as a colorless oil.

**Method b.** To a solution of DIPA (110 $\mu$L, 0.78 mmol) in dry THF (4 mL) was added *n*-BuLi (0.3 mL, 2.5 M in hexanes, 0.75 mmol) at −78 °C, and stirring was continued for 40 min allowing to warm to room temperature. To the cooled solution (−78 °C) of LDA was added via syringe a solution of **39** (220 mg, 0.57 mmol) in dry THF (2 mL), and the reaction was stirred for 30 min. Then methyl iodide (0.5 mL, 9 mmol) was added, the cooling bath was removed, and the mixture was stirred for 90 min allowing to warm to 0 °C. The reaction was quenched with saturated aqueous $NH_4Cl$ (10 mL), the phases were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were dried over $NaSO_4$, filtered, and concentrated. Flash column chromatography (silica gel, elution with 3% $Et_2O$ in hexanes) afforded 195 mg (484 mmol, 85%) **41** as a colorless oil: $R_f$ 0.44 (hexanes−$CH_2Cl_2$, 1:1, A, violet blue); $[\alpha]^{20}_D$ −8.3 (*c* 2.1, $CHCl_3$), ref 20, $[\alpha]^{20}_D$ −7.3 (*c* 1.8, $CHCl_3$); IR (film) 1472, 1462, 1255, 1097 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 4.06 (dd, $J$ = 7.5, 3.0 Hz, 1H), 3.62 (m, 2H), 2.51 (m, 2H), 1.50 (m, 2H), 1.10 (s, 3H), 1.04 (s, 3H), 0.99 (t, $J$ = 7.3 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.6, 73.4, 60.1, 53.0, 37.3, 31.6, 26.1, 25.9, 22.2, 20.0, 18.3, 7.7, −4.1, −5.3; MS (FI) *m/e* 403 ($M^+$). Anal. Calcd for $C_{21}H_{46}O_3Si_2$: C, 62.6; H, 11.5. Found: C, 62.67; H, 11.29.

**(+)-4-((1*E*,3*S*,5*Z*,10*S*)-3,11-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-2,6,10-trimethyl undeca-1,5-dienyl)-2-methyl-1,3-thiazole (42b). 4-((1*E*,3*S*,5*Z*)-3-{[tert-Butyl(dimethyl)silyl]oxy}-7-iodo-2,6-dimethylhepta-1,5-dienyl)-2-methyl-1,3-thiazole.** To a solution of **25b** (4.66 g, 12.68 mmol) in dry $CH_3CN$−diethyl ether (3:2, 100 mL) were added sequentially $Ph_3P$ (4.33 g, 16.48 mmol), imidazole (1.16 g, 17.11 mmol), and iodine (4.63 g, 17.75 mmol). After 60 min of stirring at room temperature, $Et_2O$ (400 mL) was added. The precipitates were filtered off, and the filtrate was washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered through a small amount of silica gel, and concentrated under reduced pressure. The crude allylic iodide was dried in high vacuo under exclusion of light and then immediately used for the next step.

**4-[(1*E*,3*S*,5*Z*,8*R*/*S*,10*S*)-3,11-Bis{[tert-butyl(dimethyl)-silyl]oxy}-2,6,10-trimethyl-8-(phenylsulfonyl)undeca-1,5-dienyl]-2-methyl-1,3-thiazole.** To a solution of **18b** (5.65 g, 12.68 mmol) and 18-crown-6 (6.7 g, 25.35 mmol) in dry THF (350 mL) was added a solution of KHMDS (3.59 g, 17.11 mmol) in dry THF (50 mL) at −78 °C, and the mixture was stirred for 1 h. A solution of the above crude allylic iodide in dry THF (60 mL) was added dropwise at −78 °C, and the reaction mixture was stirred for 1 h. The cooling bath was removed, and the reaction was quenched by addition of saturated aqueous $NH_4Cl$ (250 mL) and extracted with $Et_2O$ (3 × 100 mL). The combined organic solutions were washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated. The residue was purified by two chromatographies (silica gel, (1) elution with hexanes−EtOAc, 10:1−5:1; (2) elution with hexanes−EtOAc, 10:1) to give 8.19 g of the sulfones as a diastereomeric mixture contaminated with **18b**. The latter was separated by a third chromatography (silica gel, elution with $CH_2Cl_2$): $R_f$ 0.54 (hexanes−EtOAc, 3:1, A, violet); IR (film) 1506, 1472, 1462, 1447, 1388, 1361, 1305, 1256 $cm^{-1}$; MS (FI) m/e 693 $(M + H)^+$.

**Desulfonation to 42b.** To a solution of the above diastereomeric sulfones (580 mg, 0.84 mmol) and $Na_2HPO_4$ (175 mg, 1.23 mmol) in MeOH−THF (2:1, 12 mL) was added 5% sodium−mercury amalgam (1.47 g, 3.19 mmol) at −15 °C. After 30 min the cooling bath was removed and the mixture was allowed to warm to room temperature over a period of 90 min. The mixture was filtered, the filter pad was washed $Et_2O$ and water, the layers of the filtrate were separated, and the organic phase was washed with $NH_4Cl$. The organic solution was dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 25:1) gave 300 mg (543.5 mmol, 65%) **42b** as a colorless oil: $R_f$ 0.74 (hexanes−EtOAc, 5:1, A, blue violet); $[\alpha]^{20}_D$ +8.4 (*c* 4.35; $CHCl_3$); IR (film) 1472, 1462, 1255, 1097 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.90 (s, 1H), 6.44 (s, 1H), 5.12 (dd, $J \approx$ 6.5, 6.4 Hz, 1H), 4.07 (dd, $J$ = 6.6, 6.5 Hz, 1H), 3.43 (dd, $J$ = 9.5, 5.5 Hz, 1H), 3.33 (dd, $J$ = 9.5, 6.5 Hz, 1H), 2.70 (s, 3H), 2.24 (m, 2H), 1.99 (s, 3H), 1.97 (m, 2H), 1.65 (s, 3H), 1.39−1.29 (m, 3H), 0.88 (s, 18H), 0.85 (d, $J$ = 6.5 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 6H), 0.008 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.3, 153.3, 142.6, 136.9, 121.4, 118.7, 114.9, 79.1, 68.4, 35.8, 35.3, 33.2, 32.3, 26.0, 25.9, 25.8, 23.5, 19.2, 18.6, 16.7, 13.9, −4.7, −5.4; MS (FI) *m/e* 553 $(M + H)^+$. Anal. Calcd for $C_{30}H_{57}NO_2SSi_2$: C, 65.3; H, 10.4; N, 2.5. Found: C, 65.51; H, 10.23; N, 2.58.

**(+)-(2*S*,6*Z*,9*S*,10*E*)-9-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,6,10-trimethyl-11-(2-methyl-1,3-thiazol-4-yl)undeca-6,10-dien-1-ol (43b).** To a solution of **42b** (1.39 g, 2.51 mmol) in MeOH−$CH_2Cl_2$ (1:1, 80 mL) was added CSA (583 mg, 2.51 mmol) at 0 °C. The mixture was stirred for 5 h allowing to warm to 10 °C and then poured into saturated aqueous $NaHCO_3$ (150 mL) and extracted with $Et_2O$. The combined organic solutions were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 5:1) provided 1.1 g (2.5 mmol, 99%) of **43b** as a colorless oil: $R_f$ 0.11 (hexanes−EtOAc, 5:1, CM, blue); $[\alpha]^{20}_D$ +9.5 (*c* 1.37; $CHCl_3$); IR (film) 3385 br, 1461, 1449, 1253, 1184, 1102, 1005 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.91 (s, 1H), 6.44 (s, 1H), 5.14 (dd, $J \approx$ 7.0, 6.9 Hz, 1H), 4.08 (dd, $J$ = 6.6, 6.5 Hz, 1H), 3.43 (m, 1H), 3.39 (m, 1H), 2.69 (s, 3H), 2.24 (m, 2H), 1.98 (d, $J$ = 1.0 Hz, 3H), 1.96 (m, 2H), 1.66 (d, $J$ = 1.0 Hz, 3H), 1.60 (m, 1H), 1.32−1.42 (m, 3H), 0.90 (d, $J$ = 6.5 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.3, 153.2, 142.7, 136.8, 121.7, 118.7, 114.8, 79.2, 68.1, 35.7, 35.5, 33.1, 32.1, 25.8, 25.3, 23.4, 19.1, 18.2, 16.2, 13.9, −4.7, −4.9; MS (FI) *m/e* 439 $(M + H)^+$. Anal. Calcd for $C_{24}H_{43}NO_2SSi$: C, 65.9; H, 9.9; N, 3.2. Found: C, 64.98; H, 9.79; N, 3.16.

**(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-1,3,15-Tris{[*tert*-butyl(dimethyl)silyl]oxy}-7-hydroxy-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)heptadeca-12,16-dien-5-one (44b).[20] (2*S*,6*Z*,9*S*,10*E*)-9-{[tert-Butyl(dimethyl)silyl]oxy}-2,6,10-**

**trimethyl-11-(2-methyl-1,3-thiazol-4-yl)undeca-6,10-dienal.** To a solution of **43b** (983 mg, 2.25 mmol) in dry $CH_2Cl_2$ (80 mL) and dry pyridine (2 mL) was added DMP (1.24 g, 2.92 mmol) at 0 °C. The mixture was stirred for 4 h and then diluted with $Et_2O$ (200 mL) and filtered through a short pad of silica gel. The organic solution was washed with saturated aqueous $NaHCO_3-Na_2S_2O_3$ (1:1, 100 mL), dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. The crude aldehyde was azeotropically dried from toluene and used without further purification in the next step: aldehyde, $R_f$ 0.26 ($CH_2Cl_2$, CM, blue); IR (film) 3385 br, 2956, 2927, 2856, 1461, 1449, 1253, 1184, 1102, 1005, 940, 888, 836, 776, 737 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 9.59 (d, $J$ = 1.5 Hz, 1H), 6.91 (s, 1H), 6.44 (s, 1H), 5.15 (dd, $J \approx$ 6.6, 6.5 Hz, 1H), 4.07 (t, $J$ = 6.5 Hz, 1H), 2.69 (s, 3H), 2.18−2.33 (m, 3H), 2.06−2.00 (m, 2H), 1.99 (d, $J$ = 1.0 Hz, 3H), 1.72−1.64 (m, 1H), 1.65 (d, $J$ = 1.5 Hz, 3H), 1.43−1.30 (m, 3H), 1.07 (d, $J$ = 6.5 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 205.1, 164.3, 153.2, 142.4, 136.0, 122.1, 118.7, 115.0, 78.9, 46.3, 35.4, 31.8, 30.4, 25.8, 25.2, 23.4, 19.2, 18.2, 14.0, 13.3, −4.7, −5.0.

**Aldol 44b.** To a solution of DIPA (441 mL, 3.14 mmol) in dry THF (10 mL) was added dropwise *n*-BuLi (1.26 mL, 2.5 M in hexanes, 3.14 mmol) at −78 °C, stirred for 15 min, and then allowed to warm to room temperature over a period of 30 min. To the cooled (−78 °C) LDA solution was added dropwise a solution of **41** (1.27 g, 3.14 mmol) in dry THF (10 mL). The reaction was stirred for 15 min and then allowed to warm to −35 °C over a period of 45 min and finally cooled to −95 °C. A solution of the above crude aldehyde in dry THF (5 mL) was added dropwise and the reaction stirred for 90 min allowing to warm to −80 °C. The cooling bath was removed, and the reaction was quenched with saturated aqueous $NH_4Cl$ (50 mL) and diluted with $Et_2O$ (50 mL). The layers were separated, the aqueous phase was extracted with $Et_2O$, and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 25:1) provided 1.31 g (1.56 mmol, 69%) of the syn aldol products as a diastereoisomeric mixture (∼4:1), which was separated by HPLC. **44b** (desired isomer): $R_f$ 0.14 ($CH_2Cl_2$, A, blue); IR (film) 1472, 1463, 1444, 1389, 1366, 1257, 1198, 1132, 1075, 1006 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.90 (s, 1H), 6.44 (s, 1H), 5.12 (t, $J \approx$ 7.6 Hz, 1H), 4.08 (t, $J$ = 6.5 Hz, 1H), 3.89 (dd, $J$ = 7.5, 3.0 Hz, 1H), 3.66 (m, 1H), 3.59 (m, 1H), 3.29 (m, 1H), 2.70 (s, 3H), 2.23 (m, 2H), 1.98 (s, 3H), 1.90−2.02 (m, 2H), 1.77−1.69 (m, 1H), 1.65 (s, 3H), 1.67−1.57 (m, 1H), 1.53−1.43 (m, 3H), 1.35−1.24 (m, 2H), 1.20 (s, 3H), 1.08 (s, 3H), 1.01 (d, $J$ = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87 (s, 18H), 0.81 (d, $J$ = 7.0 Hz, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 222.2, 164.3, 153.3, 142.6, 136.9, 121.5, 118.7, 114.9, 79.1, 74.9, 74.2, 60.5, 54.0, 41.4, 37.9, 35.5, 35.3, 33.0, 32.4, 26.1, 25.9, 25.2, 23.5, 22.9, 20.5, 19.2, 18.3, 15.4, 13.9, 9.6, −3.8, −4.1, −4.7, −4.9, −5.3. Undesired isomer: IR (film) 1472, 1462, 1255, 1183, 1104, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.90 (s, 1H), 6.45 (s, 1H), 5.14 (t, $J$ = 7.0 Hz, 1H), 4.08 (t, $J$ = 7.0 Hz, 1H), 4.03 (dd, $J$ = 7.0, 3.5 Hz, 1H), 3.69−3.58 (m, 2H), 3.47 (s, 1H), 3.40 (d, $J$ = 8.0 Hz, 1H), 3.22 (qd, $J$ = 7.0, 2.0 Hz, 1H), 2.70 (s, 3H), 2.18−2.30 (m, 2H), 1.99 (d, $J$ = 1.0 Hz, 3H), 2.00−1.90 (m, 2H), 1.67 (s, 3H), 1.58 (m, 1H), 1.51 (m, 3H), 1.41−1.29 (m, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.05 (d, $J$ = 6.5 Hz, 3H), 0.97 (d, $J$ = 6.5 Hz, 3H), 0.88 (s, 18H), 0.87 (s, 9H), 0.81 (d, $J$ = 7.0 Hz, 3H), 0.10 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), −0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 221.8, 164.3, 153.2, 142.5, 136.6, 121.7, 118.7, 114.9, 79.0, 75.1, 72.7, 60.2, 54.3, 41.4, 37.8, 35.5, 35.4, 32.9, 32.3, 26.2, 25.9, 25.8, 25.2, 23.6, 22.8, 19.6, 19.2, 18.4, 15.5, 13.9, 10.8, −3.7, −4.0, −4.7, −4.9, −5.3.

**(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-1,3,7,15-Tetrakis{[*tert*-butyl(dimethyl)silyl]oxy}-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)heptadeca-12,16-dien-5-one (45b).[20]** To a solution of **44b** (493 mg, 0.59 mmol) and 2,6-lutidine (250 mL, 1.76 mmol) in dry $CH_2Cl_2$ (15 mL) was added TBSOTf (203 $\mu$L, 0.88 mmol) at 0 °C. After 3 h at 0 °C the cooling bath was removed and the reaction was quenched with saturated aqueous $NH_4Cl$ (20 mL). The layers were separated, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic solutions were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Chromatography of the residue (silica gel, elution with hexanes−EtOAc, 25:1) provided 560 mg (588 mmol, quantitative) of **45b** as a colorless oil: $R_f$ 0.56 (hexanes−EtOAc, 10:1, V, blue); IR (film) 1256, 1102, 1005 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.90 (s, 1H), 6.44 (s, 1H), 5.12 (t, $J$ = 7.0 Hz, 1H), 4.07 (t, $J$ = 6.5 Hz, 1H), 3.87 (dd, $J$ = 7.5, 2.5 Hz, 1H), 3.75 (dd, $J$ = 7.0, 1.5 Hz, 1H), 3.66 (ddd, $J$ = 9.6, 9.0, 5.0 Hz, 1H), 3.56 (dd, $J$ = 7.5, 2.0 Hz, 1H), 3.13 (qd, $J$ = 6.5 Hz, 1H), 2.70 (s, 3H), 2.22 (m, 2H), 1.98 (d, $J$ = 1.0 Hz, 3H), 1.97−1.90 (m, 2H), 1.64 (s, 3H), 1.40−1.30 (m, 4H), 1.28−1.24 (m, 2H), 1.21 (s, 3H), 1.03 (d, $J$ = 7.0 Hz, 3H), 1.01 (s, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.875 (s, 3H), 0.876 (s, 9H), 0.871 (s, 9H), 0.08 (s, 3H), 0.053 (s, 3H), 0.047 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), 0.017 (s, 3H), −0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 218.2, 153.3, 142.5, 136.8, 121.6, 118.7, 114.9, 79.0, 77.5, 74.1, 61.0, 53.7, 45.0, 39.0, 38.1, 35.3, 32.6, 31.1, 26.2, 26.1, 26.0, 25.9, 24.9, 24.5, 23.5, 19.4, 19.2, 18.5, 18.3, 18.2, 17.5, 15.4, 13.9, −3.7, −3.8, −4.0, −4.7, −4.9, −5.3; MS (FI) *m/e* 953 ($M^+$).

**(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7,15-Tris{[*tert*-butyl(dimethyl)silyl]oxy}-1-hydroxy-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)heptadeca-12,16-dien-5-one (46b).[20]** To compound **45b** (540 mg, 0.57 mmol) dissolved in MeOH−$CH_2Cl_2$ (1:1, 20 mL) was added CSA (132 mg, 0.57 mmol) portionwise at 0 °C. The mixture was stirred for 4 h and then diluted with $CH_2Cl_2$ (20 mL) and quenched with saturated aqueous $NaHCO_3$ (25 mL). The layers were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure, and the residue was subjected to flash column chromatography (silica gel, elution with hexanes−EtOAc, 5:1) to afford 412 mg (0.49 mmol, 87%) of **46b** as a colorless oil: $R_f$ 0.32 (hexanes−EtOAc, 10:1, V, blue); IR (film) 3320 br, 1856, 1472, 1388, 1255, 1104, 1032 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.90 (s, 1H), 6.44 (s, 1H), 5.13 (t, $J$ = 7.5 Hz, 1H), 4.03−4.10 (m, 2H), 3.79 (dd, $J$ = 7.1, 1.3 Hz, 1H), 3.63 (dd, $J$ = 6.0, 5.6 Hz, 2H), 3.12 (qd, $J$ = 7.1, 6.7 Hz, 1H), 2.70 (s, 3H), 2.22 (m, 2H), 1.98 (d, $J$ = 0.9 Hz, 3H), 2.05−1.90 (m, 2H), 1.65 (s, 3H), 1.50−1.26 (m, 5H), 1.21 (s, 3H), 1.20−1.09 (m, 2H), 1.051 (s, 3H), 1.048 (d, $J$ = 6.9 Hz, 3H), 0.92−0.86 (m, 30H), 0.10 (s, 3H), 0.06 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 218.2, 164.3, 153.3, 142.5, 136.7, 121.6, 118.7, 114.9, 79.0, 77.5, 73.1, 60.2, 17.8, 17.6, 15.6, 14.2, 13.9, −3.6, −3.8, −3.91, −3.93, −4.7, −4.9; MS (FI) *m/e* 840 $(M + H)^+$.

**(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7,15-Tris{[*tert*-butyl(dimethyl)silyl]oxy}-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxoheptadeca-12,16-dienoic acid (47b).[20]** To a solution **46b** (389 mg, 0.46 mmol) and dry pyridine (1 mL) in dry $CH_2Cl_2$ (50 mL) was added DMP (258 mg, 0.60 mmol) at room temperature. The mixture was stirred for 2 h and then diluted with $Et_2O$ (150 mL); the precipitate was separated by filtration and washed with $Et_2O$. The filtrate was washed with saturated aqueous $NaHCO_3-Na_2S_2O_3$ (1:1, 100 mL), dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure to afford the crude aldehyde: $R_f$ 0.56 (hexanes−EtOAc, 5:1, A and V, blue).

To a solution of the above crude aldehyde in *tert*-butyl alcohol (10.3 mL) and 2,3-dimethyl-but-2-ene (10.3 mL) was added a solution of $NaClO_2$ (211 mg, 2.32 mmol) and $NaH_2PO_4$ (211 mg) in water (2.11 mL). The mixture was stirred for 40 min and then diluted with $CH_2Cl_2$/water (2:1, 150 mL) and slightly acidified with two drops of TFA. The layers were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel, elution with hexanes−EtOAc, 10:1−5:1−3:1) providing 380 mg (0.45 mmol, 96%) of the acid **47b** as a viscous colorless oil: $R_f$ 0.30 (hexanes−EtOAc, 5:1, A and V, violet blue); $[\alpha]^{20}_D$ −3.1 (*c* 1.37; $CHCl_3$); ref 20, −2.9 (*c* 0.8, $CHCl_3$); IR (film) 1714, 1472,

1255, 1102 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.92 (s, 1H), 6.63 (s, 1H), 5.17 (t, $J = 7.0$ Hz, 1H), 4.40 (dd, $J = 7.0$, 3.5 Hz, 1H), 4.12 (m, 1H), 3.74 (dd, $J = 5.5$, 2.0 Hz, 1H), 3.13 (qd, $J = 7.0$, 6.0 Hz, 1H), 2.70 (s, 3H), 2.43 (dd, $J = 16.6$, 3.5 Hz, 1H), 2.33 (dd, $J = 16.6$, 6.5 Hz, 1H), 2.22−2.12 (m, 2−3H), 1.94 (d, $J = 1.0$ Hz, 3H), 1.94−1.86 (m, 2H), 1.67 (s, 3H), 1.50−1.35 (m, 5H), 1.15 (s, 6H), 1.06 (d, $J = 7.0$ Hz, 3H), 0.89 (s, 9H), 0.885 (s, 3H), 0.88 (s, 18H), 0.12 (s, 3H), 0.08 (s, 9H), 0.07 (s, 3H), 0.03 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 218.2, 174.0, 165.3, 152.7, 143.7, 137.1, 121.7, 118.1, 114.4, 79.2, 76.7, 73.1, 63.7, 54.0, 44.2, 39.9, 39.5, 35.4, 33.9, 32.5, 31.7, 26.2, 26.1, 25.8, 25.6, 24.9, 23.5, 23.4, 18.7, 18.6, 18.5, 18.3, 16.4, 15.8, 14.0, −3.9, −4.0, 4.1, −4.5, −4.7, −5.0; MS (FI) *m/e* 854 $(M + H)^+$.

**(3*S*,6*R*,7*S*,8*S*,12*Z*,15*S*,16*E*)-3,7-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-15-hydroxy-4,4,6,8,12,16-hexamethyl-17-(2-methyl-1,3-thiazol-4-yl)-5-oxoheptadeca-12,16-dienoic acid (48b).**[20] To a solution of **47b** (365 mg, 0.45 mmol) in dry THF (10 mL) was added TBAF (2.23 mL, 1 M in THF, 2.23 mmol). The reaction mixture was stirred for 10 h at room temperature and then quenched by addition of saturated aqueous $NH_4Cl$ (70 mL) and extracted with $Et_2O$ (4 × 25 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, elution with $CH_2Cl_2$–hexanes−EtOAc, 6:5:1−4:3:1−2:1:1) providing 180 mg (0.244 mmol, 55%) of **48b** and 27 mg of recycled educt (**47b**) as colorless oils. **48b**: $R_f$ 0.47 (hexanes−EtOAc, 1:1, A and V, blue violet); $[\alpha]^{20}_D$ −10.9 (*c* 1.37; $CHCl_3$), ref 20, $[\alpha]^{20}_D$ −10.4 (*c* 0.4, $CHCl_3$); IR (film) 3357 br, 1696, 1472, 1387, 1255, 1186 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.94 (s, 1H), 6.63 (s, 1H), 5.17 (t, $J = 7.0$ Hz, 1H), 4.40 (dd, $J = 6.0$, 4.0 Hz, 1H), 4.14 (t, $J \approx 6.5$ Hz, 1H), 3.76 (dd, $J = 7.0$, 2.0 Hz, 1H), 3.14 (qd, $J = 7.0$, 6.5 Hz, 1H), 2.70 (s, 3H), 2.435 (dd, $J = 16.6$, 4.0 Hz, 1H), 2.33 (mc, 2H), 2.26 (dd, $J = 16.6$, 6.0 Hz, 1H), 2.14−2.04 (m, 1H), 2.01 (d, $J = 1.0$ Hz, 3H), 2.01−1.92 (m, 1H), 1.70 (s, 3H), 1.56−1.48 (mc, 3H), 1.50−1.34 (m, 2H), 1.19 (s, 3H), 1.10 (s, 3H), 1.05 (d, $J = 6.5$ Hz, 3H), 0.90 (d, $J \approx 7.0$ Hz, 3H), 0.89 (s, 9H), 0.865 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.055 (s, 3H), 0.04 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 217.9, 174.9, 165.0, 152.7, 142.2, 139.4, 120.3, 118.7, 115.1, 77.4, 77.3, 74.2, 53.8, 51.9, 44.8, 40.9, 39.2, 34.2, 32.5, 31.3, 26.4, 26.3, 26.2, 26.1, 23.6, 23.1, 19.9, 18.9, 18.5, 18.2, 17.1, 16.0, 14.6, 13.8, −3.8, −3.9, −4.1, −4.7; MS (FI) *m/e* 739 $(M + H)^+$.

**(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4,8-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)ethenyl]oxacyclohexadec-13-ene-2,6-dione (49).**[20] A solution of *N*-ethyl-*N*′-(3-(dimethylamino)propyl)-carbodiimide·HCl (EDCI, 65 mg, 0.34 mmol), DMAP (54 mg, 0.51 mmol), and DMAP·HCl (54 mg, 0.34 mmol) in dry $CHCl_3$ (100 mL) was warmed to reflux. A solution of **48b (**125 mg, 0.17 mmol) in dry $CHCl_3$ (8 mL) was added over a period of 17 h with a syringe pump at the same temperature. The reaction was cooled to room temperature and quenched with saturated aqueous $NH_4Cl$ (100 mL). The layers were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic extracts were dried over $MgSO_4$, filtered through a short pad of silica gel, and concentrated under reduced pressure. Flash column chromatography (silica gel, elution with hexanes−EtOAc, 25:1) provided 84 mg (0.12 mmol, 69%) of the macrolactone **49** as a light yellow oil: $R_f$ 0.37 (hexanes−EtOAc, 10:1, A and V, violet blue); $[\alpha]^{20}_D$ −12.5 (*c* 0.9, $CHCl_3$), ref 20, $[\alpha]^{20}_D$ −11.8 (*c* 0.8, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.95 (s, 1H), 6.55 (s, 1H), 5.15 (t, $J = 8.0$ Hz, 1H), 4.96 (d, $J = 9.6$ Hz, 1H), 4.02 (d, $J = 8.5$ Hz, 1H), 3.88 (d, $J = 9.0$ Hz, 1H), 3.01 (qd, $J = 7.0$, 6.5 Hz, 1H), 2.79 (dd, $J = 16.6$, 1.5 Hz, 1H), 2.69 (s, 3H), 2.71−2.62 (m, 2H), 2.49−2.41 (m, 1H), 2.09 (d, $J = 1.0$ Hz, 3H), 2.08−2.02 (m, 2H), 1.77−1.66 (m, 2H), 1.66 (s, 3H), 1.61−1.47 (m, 3H), 1.18 (s, 3H), 1.13 (s, 3H), 1.09 (d, $J = 6.5$ Hz, 3H), 0.97 (d, $J = 7.0$ Hz, 3H), 0.93 (s, 9H), 0.83 (s, 9H), 0.10 (s, 3H), 0.095 (s, 3H), 0.07 (s, 3H), −0.12 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.1, 171.2, 164.5, 152.5, 140.6, 138.8, 119.4, 119.2, 115.9, 79.9, 76.3, 53.4, 39.2, 32.5, 31.9, 31.4, 29.7, 27.4, 26.4, 26.2, 25.7, 24.5, 24.3, 23.1, 19.2, 18.7, 18.6, 17.8, 15.3, −3.3, −3.69, −3.70, −5.6.

**(4*S*,7*R*,8*S*,9*S*,13*Z*,16*S*)-4,8-Dihydroxy-5,5,7,9,13-pentamethyl-16-[(*E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)ethenyl]-oxacyclohexadec-13-ene-2,6-dione (Epothilone D, 4).** To a solution of **49** (75 mg, 0.104 mmol) in dry THF (5 mL) and dry pyridine (1.5 mL) was added HF·pyridine (1.5 mL) at 0 °C allowing to warm to room temperature over 18 h. To the mixture was added another 1 equiv of HF·pyridine (1.5 mL) at 0 °C and stirred for additional 18 h at room temperature. At 0 °C the mixture was quenched by slowly adding saturated aqueous $NaHCO_3$, diluted with $Et_2O$. The layers were separated, and the aqueous phase was extracted with $Et_2O$. The combined organic solutions were washed with aqueous $CuSO_4$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, elution with hexanes−EtOAc, 3:1) providing 49 mg (81 $\mu$mol, 78%) of a monodesilylated product ($R_f$ 0.19, hexanes−EtOAc, 3:1, V, blue) and 10 mg (19.6 $\mu$mol, 20%) of **4** (epothilone D). The former was again subjected to the above conditions to obtain all together 49 mg (99.7 $\mu$mol, 96%) of epothilone D (**4**): $R_f$ 0.11 (hexanes−EtOAc, 3:1, V, blue); $[\alpha]^{20}_D$ −89 (*c* 0.37; $CHCl_3$), ref 20, $[\alpha]^{20}_D$ −91.5 (*c* 0.3, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.94 (s, 1H), 6.57 (s, 1H), 5.21 (dd, $J = 10.0$, 1.5 Hz, 1H), 5.13 (dd, $J = 10.0$, 5.0 Hz, 1H), 4.28 (dd, $J = 11.0$, 2.5 Hz, 1H), 3.71 (dd, $J = 4.0$, 2.5 Hz, 1H), 3.45 (br s, 1H), 3.15 (qd, $J = 6.9$, 2.5 Hz, 1H), 3.02 (br s, 1H), 2.68 (s, 3H), 2.63 (dt, $J = 15.1$, 10.0 Hz, 1H), 2.45 (dd, $J = 14.6$, 11.0 Hz, 1H), 2.35−2.29 (m, 1H), 2.28 (dd, $J = 14.6$, 3.0 Hz, 1H), 2.22 (ddd, $J = 15.6$, 3.5, 2.0 Hz, 1H), 2.06 (d, $J = 1.0$ Hz, 3H), 1.89−1.83 (m, 1H), 1.78−1.68 (m, 2H), 1.65 (s, 3H), 1.33 (s, 3H), 1.31−1.24 (m, 4H), 1.18 (d, $J = 7.0$ Hz, 3H), 1.06 (s, 3H), 1.01 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 220.7, 170.4, 165.0, 152.0, 139.2, 138.4, 120.9, 119.2, 115.6, 78.9, 74.1, 72.3, 53.5, 41.7, 39.6, 38.4, 32.5, 31.9, 31.7, 31.6, 25.4, 22.9, 19.0, 18.0, 15.9, 15.7, 13.4.

**(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-Dihydroxy-8,8,10,12,16-pentamethyl-3-[( *E*)-1-methyl-2-(2-methyl-1,3-thiazol-4-yl)ethenyl]-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione (Epothilone B, 2).** To a solution of **4** (43 mg, 87.4 $\mu$mol) in dry $CHCl_3$ (3.5 mL) was added *m*-CPBA (32.5 mg, 0.13 mmol, 70% purity) at −18 °C. The reaction mixture was stirred for 5 h at the same temperature and then diluted with $CH_2Cl_2$ (14 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ (15 mL). The layers were separated, the aqueous phase was extracted with $CH_2Cl_2$, and the combined organic solutions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to chromatography (silica gel, elution with hexanes−EtOAc, 1:1) providing 36 mg (71 $\mu$mol, 81%) of epothilone B and its epoxide isomer as a 4−5:1 mixture, which were separated by HPLC (20% *i*-PrOH in hexanes): $R_f$ 0.32 (hexanes−EtOAc, 3:1, A, gray blue); $[\alpha]^{20}_D$ −36 (*c* 0.2, MeOH), ref 20, $[\alpha]^{20}_D$ −34.3 (*c* 0.2, MeOH); $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 6.96 (s, 1H), 6.58 (s, 1H), 5.41 (dd, $J = 8.0$, 3.0 Hz, 1H), 4.22 (br, 2H), 3.71 (t, $J = 4.0$ Hz, 1H), 3.29 (qd, $J = 7.0$, 4.0 Hz, 1H), 2.80 (dd, $J = 7.5$, 4.5 Hz, 1H), 2.69 (s, 3H), 2.65 (br, 1H), 2.53 (dd, $J = 14.1$, 10.0 Hz, 1H), 2.35 (dd, $J = 13.5$, 2.5 Hz, 1H), 2.13−2.06 (m, 1H), 2.08 (s, 3H), 1.91 (dd, $J = 15.6$, 8.0 Hz, 1H), 1.77−1.65 (m, 3H), 1.54−1.46 (m, 2H), 1.45−1.35 (m, 3H), 1.36 (s, 3H), 1.27 (s, 3H), 1.16 (d, $J = 7.0$ Hz, 3H), 1.07 (s, 3H), 0.99 (d, $J = 7.0$ Hz, 3H).

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**Supporting Information Available:** Text giving experimental procedures and complete characterization ($^1H$ and $^{13}C$ NMR and IR spectra and mass spectral data) for new compounds not included in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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